LEUCINE-RICH REPEAT KINASE 2 (*LRRK2*) iRNA AGENT COMPOSITIONS AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Application No. 63/216,119, filed on June 29, 2021, and U.S. Provisional Application No. 63/353,953, filed on June 21, 2022, each of which is incorporated herein by reference in its entirety.

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. The ASCII copy, created on June 28, 2022, is named A108868_1270WO_SL.txt and is 691,284 bytes in size.

BACKGROUND OF THE INVENTION

The leucine-rich repeat kinase 2 (LRRK2) gene encoding the protein LRRK2 is located in the chromosomal region 12q11.2-q13.1. LRRK2 belongs to the Roco protein family of the Ras/GTPase superfamily. The highly conserved LRRK2 protein is made up of 51 exons with a total of 2527 amino acids comprising enzymatic domains including a ROC (Ras of complex) GTPase domain and a serine/threonine kinase domain. Other protein-interacting domains in LRRK2 protein, include a leucine-rich repeat domain, a C-terminal WD40 repeat domain, and armadillo and ankyrin repeat domains

Mutations in the *LRRK2* gene have been implicated as causative for a dominantly inherited form of Parkinson's disease (PD), a progressively debilitating neurodegenerative syndrome. *LRRK2* mutations have been associated with phenotypic manifestations of frontotemporal lobar degeneration, corticobasal degeneration, degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), the presence of Lewy bodies (neuronal inclusions of aggregated α-synuclein and other ubiquitinated proteins) and associated motor neuron disease in patients. *LRRK2* mutations have also been found in sporadic PD cases having single nucleotide polymorphisms (SNPs) that confer increased *LRRK2* expression (about 2-fold increase), which may contribute to disease etiology due to an increased kinase activity established. Given the similarities in the clinical presentation of *LRRK2*-associated familial and sporadic PD it is likely that missense and/or deletion mutations in *LRRK2* play a critical role in the disease etiology of familial and sporadic PD.

There is currently no cure for Parkinson's disease, and treatments are only aimed at alleviating the symptoms and improving the patient's quality of life as the disease progresses. Accordingly, there is a need for agents that can selectively and efficiently inhibit the expression of the *LRRK2* gene such that subjects having a *LRRK2*-associated disorder, *e.g.*, Parkinson's disease, can be effectively treated.

SUMMARY OF THE INVENTION

The present disclosure provides RNAi compositions, which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a *LRRK2* gene. The *LRRK2* gene may be within a cell, *e.g.,* a cell within a subject, such as a human. The use of these iRNAs enables the targeted degradation of mRNAs of the corresponding gene (*LRRK2* gene) in mammals.

The iRNAs of the invention have been designed to target a *LRRK2* gene, *e.g.,* a *LRRK2* gene having a missense and/or deletion mutations in the exons of the gene, and having a combination of nucleotide modifications. The iRNAs of the invention inhibit the expression of the *LRRK2* gene by at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95%, relative to control levels. and reduce the level of sense- and antisense-containing foci. Without intending to be limited by theory, it is believed that a combination or sub-combination of the foregoing properties and the specific target sites, or the specific modifications in these iRNAs confer to the iRNAs of the invention improved efficacy, stability, potency, durability, and safety. In one aspect, the present invention provides double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of *LRRK2*, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 1808 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 1809.

In another aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of *LRRK2*, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding LRRK2, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO:1809.

In yet another aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of *LRRK2*, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding LRRK2, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 3-7.

In one embodiment, the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 1458-1478, 1484-1504, 1761-1781, 1950-1970, 2076-2096, 2094-2114, 2212-2232, 2213-2233, 2268-2288, 2431-2451, 2529-2549, 2565-2585, 2566-2586, 2569-2589, 2583-2603, 2605-2625, 2657-2677, 2764-2784, 2867-2887, 2881-2901, 2883-2903, 3022-3042, 3198-3218, 3330-3350, 3348-3368, 3395-3415, 3629-3649, 3630-3650, 3712-3732,

3713-3733, 3715-3735, 3717-3737, 3720-3740, 3727-3747, 3796-3816, 3800-3820, 3822-3842, 3829-3849, 3875-3895, 3971-3991, 4130-4150, 4443-4463, 4447-4467, 4449-4469, 4478-4498, 4488-4508, 4619-4639, 4652-4672, 4868-4888, 4950-4970, 4970-4990, 4971-4991, 4972-4992, 5092-5112, 5202-5222, 5226-5246, 5232-5252, 5233-5253, 5273-5293, 5318-5338, 5367-5387, 5368-5388, 5370-5390, 5373-5393, 5425-5445, 5443-5463, 5457-5477, 5461-5481, 5471-5491, 5475-5495, 5501-5521, 5557-5577, 5640-5660, 5646-5666, 5659-5679, 5674-5694, 5675-5695, 5676-5696, 5682-5702, 5684-5704, 5722-5742, 5725-5745, 5778-5798, 5779-5799, 5793-5813, 5964-5984, 5965-5985, 5984-6004, 6029-6049, 6092-6112, 6093-6113, 6094-6114, 6096-6116, 6127-6147, 6143-6163, 6165-6185, 6172-6192, 6173-6193, 6174-6194, 6175-6195, 6198-6218, 6319-6339, 6339-6359, 6418-6438, 6531-6551, 6536-6556, 6541-6561, 6573-6593, 6662-6682, 6730-6750, 6740-6760, 6742-6762, 6786-6806, 6791-6811, 6803-6823, 6804-6824, 6805-6825, 6807-6827, 6810-6830, 6811-6831, 6812-6832, 6818-6838, 6872-6892, 7004-7024, 7018-7038, 7020-7040, 7027-7047, 7028-7048, 7085-7105, 7103-7123, 7115-7135, 7121-7141, 7127-7147, 7242-7262, 7348-7368, 7397-7417, 7404-7424, 7405-7425, 7421-7441, 7443-7463, 7444-7464, 7445-7465, 7493-7513, 7535-7555, 7538-7558, 7539-7559, 7593-7613, 7629-7649, 7637-7657, 7638-7658, 7639-7659, 7671-7691, 7727-7747, 7729-7749, 8134-8154, 8135-8155, 1484-1504, 1488-1508, 1755-1775, 1761-1781, 1905-1925, 1945-1965, 1950-1970, 2029-2049, 2207-2227, 2212-2232, 2213-2233, 2431-2451, 2529-2549, 2565-2585, 2569-2589, 2648-2668, 2764-2784, 2874-2894, 2881-2901, 3051-3071, 3193-3213, 3198-3218, 3208-3228, 3330-3350, 3331-3351, 3350-3370, 3380-3400, 3390-3410, 3395-3415, 3573-3593, 3622-3642, 3632-3652, 3712-3732, 3715-3735, 3717-3737, 3718-3738, 3740-3760, 3795-3815, 3806-3826, 3829-3849, 3830-3850, 3938-3958, 3950-3970, 3971-3991, 4367-4387, 4376-4396, 4444-4464, 4446-4466, 4447-4467, 4551-4571, 4554-4574, 4704-4724, 4834-4854, 4839-4859, 4925-4945, 4970-4990, 4971-4991, 4972-4992, 5058-5078, 5092-5112, 5128-5148, 5196-5216, 5226-5246, 5275-5295, 5322-5342, 5349-5369, 5352-5372, 5365-5385, 5367-5387, 5368-5388, 5370-5390, 5373-5393, 5461-5481, 5475-5495, 5482-5502, 5515-5535, 5516-5536, 5541-5561, 5557-5577, 5607-5627, 5635-5655, 5641-5661, 5643-5663, 5644-5664, 5646-5666, 5655-5675, 5659-5679, 5660-5680, 5671-5691, 5674-5694, 5682-5702, 5683-5703, 5684-5704, 5721-5741, 5757-5777, 5763-5783, 5772-5792, 5773-5793, 5776-5796, 5777-5797, 5778-5798, 5779-5799, 5793-5813, 5794-5814, 5964-5984, 5965-5985, 5966-5986, 5980-6000, 5984-6004, 6029-6049, 6030-6050, 6071-6091, 6092-6112, 6093-6113, 6095-6115, 6129-6149, 6135-6155, 6136-6156 ,6142-6162, 6145-6165, 6171-6191, 6172-6192, 6174-6194, 6175-6195, 6178-6198, 6180-6200, 6196-6216, 6197-6217, 6198-6218, 6344-6364, 6355-6375, 6520-6540, 6536-6556, 6538-6558, 6539-6559, 6541-6561, 6723-6743, 6724-6744, 6729-6749, 6730-6750, 6737-6757, 6740-6760, 6742-6762, 6743-6763, 6786-6806, 6787-6807, 6791-6811, 6793-6813, 6794-6814, 6803-6823, 6805-6825, 6806-6826, 6807-6827, 6808-6828, 6810-6830, 6811-6831, 6812-6832, 6813-6833, 6814-6834, 6818-6838, 6828-6848, 6829-6849, 6834-6854, 6872-6892, 6918-6938, 6919-6939, 6920-6940, 6922-6942, 6989-7009, 7004-7024, 7012-7032, 7023-7043, 7035-7055, 7036-7056, 7041-7061, 7085-7105, 7103-7123, 7114-7134, 7116-7136, 7121-7141, 7129-7149, 7146-7166, 7149-7169, 7242-7262, 7247-7267, 7303-7323, 7348-7368, 7353-7373, 7397-7417, 7404-7424, 7405-7425, 7443-7463, 7493-7513, 7533-7553, 7538-7558, 7539-7559, 7593-7613,

7627-7647, 7629-7649, 7727-7747, 8005-8025, 8007-8027 and 8134-8154 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO: 2.

In one embodiment, the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 212-232, 238-258, 515-535, 704-724, 830-850, 848-868, 966-986, 967-987, 1022-1042, 1185-1205, 1283-1303, 1319-1339, 1320-1340, 1323-1343, 1337-1357, 1359-1379, 1411-1431, 1518-1538, 1621-1641, 1635-1655, 1637-1657, 1776-1796, 1952-1972, 2084-2104, 2102-2122, 2149-2169, 2383-2403, 2384-2404, 2466-2486, 2467-2487, 2469-2489, 2471-2491, 2474-2494, 2481-2501, 2550-2570, 2554-2574, 2576-2596, 2583-2603, 2629-2649, 2725-2745, 2884-2904, 3197-3217, 3201-3221, 3203-3223, 3232-3252, 3242-3262, 3373-3393, 3406-3426, 3622-3642, 3704-3724, 3724-3744, 3725-3745, 3726-3746, 3846-3866, 3956-3976, 3980-4000, 3986-4006, 3987-4007, 4027-4047, 4072-4092, 4121-4141, 4122-4142, 4124-4144, 4127-4147, 4179-4199, 4197-4217, 4211-4231, 4215-4235, 4225-4245, 4229-4249, 4255-4275, 4311-4331, 4394-4414, 4400-4420, 4413-4433, 4428-4448, 4429-4449, 4430-4450, 4436-4456, 4438-4458, 4476-4496, 4479-4499, 4532-4552, 4533-4553, 4547-4567, 4718-4738, 4719-4739, 4738-4758, 4783-4803, 4846-4866, 4847-4867, 4848-4868, 4850-4870, 4881-4901, 4897-4917, 4919-4939, 4926-4946, 4927-4947, 4928-4948, 4929-4949, 4952-4972, 5073-5093, 5093-5113, 5172-5192, 5285-5305, 5290-5310, 5295-5315, 5327-5347, 5416-5436, 5484-5504, 5494-5514, 5496-5516, 5540-5560, 5545-5565, 5557-5577, 5558-5578, 5559-5579, 5561-5581, 5564-5584, 5565-5585, 5566-5586, 5572-5592, 5626-5646, 5758-5778, 5772-5792, 5774-5794, 5781-5801, 5782-5802, 5839-5859, 5857-5877, 5869-5889, 5875-5895, 5881-5901, 5996-6016, 6102-6122, 6151-6171, 6158-6178, 6159-6179, 6175-6195, 6197-6217, 6198-6218, 6199-6219, 6247-6267, 6289-6309, 6292-6312, 6293-6313, 6347-6367, 6383-6403, 6391-6411, 6392-6412, 6393-6413, 6425-6445, 6481-6501, 6483-6503, 6888-6908 and 6889-6909 of SEQ ID NO: 1808, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO: 1809.

In one embodiment, the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1624152, AD-1624178, AD-1624412, AD-1624595, AD-1624721, AD-1624739, AD-1624856, AD-1624857, AD-1624894, AD-1625057, AD-1625155, AD-1625191, AD-1625192, AD-1625195, AD-1625209, AD-1625230, AD-1625282, AD-1625389, AD-1625485, AD-1625499, AD-1625501, AD-1625610, AD-1625786, AD-1625910, AD-1625928, AD-1625975, AD-1626183, AD-1626184, AD-1626265, AD-1626266, AD-1626268, AD-1626270, AD-1626273, AD-1626280, AD-1626349, AD-1626353, AD-1626375, AD-1626382, AD-1626428, AD-1626524, AD-1626636, AD-1626921, AD-1626925, AD-1626927, AD-1626936, AD-1626946, AD-1627077, AD-1627110, AD-1627308, AD-1627390, AD-1627410, AD-1627411, AD-1627412, AD-1627511, AD, 1627601, AD-1627625, AD-1627631, AD-1627632, AD-1627672, AD-1627717, AD-1627766, AD-1627767, AD-1627769, AD-1627772, AD-1627820, AD-1627838, AD-1627852, AD-1627856, AD-

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In some embodiments, the nucleotide sequence of the sense and antisense strand comprises any one of the sense strand nucleotide sequences in any one of Tables 3-7.

In one embodiment, the sense strand, the antisense strand, or both the sense strand and the antisense strand is conjugated to one or more lipophilic moieties.

In one embodiment, the lipophilic moiety is conjugated to one or more internal positions in the double stranded region of the dsRNA agent.

In one embodiment, the lipophilic moiety is conjugated via a linker or carrier.

In one embodiment, the lipophilicity of the lipophilic moiety, measured by logKow, exceeds 0.

In one embodiment, 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 one embodiment, the plasma protein binding assay is an electrophoretic mobility shift assay using human serum albumin protein.

In one embodiment, the sense strand, the antisense strand, or both the sense strand and the antisense strand of the dsRNA agent is conjugated to one or more Asialoglycoprotein receptor (ASGPR) ligands.

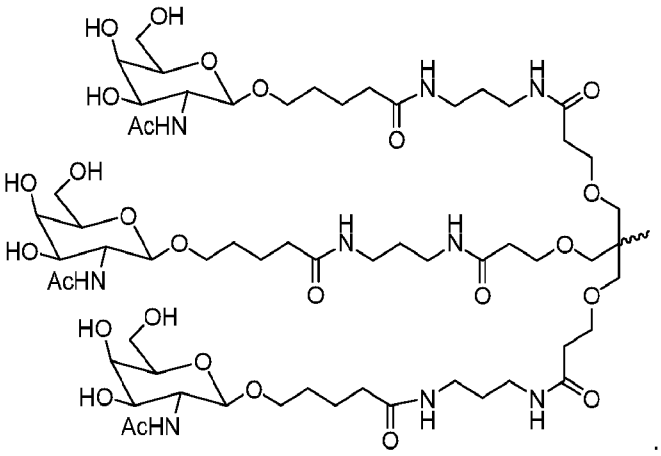
In one embodiment, the ASGPR ligand is attached to the 5' end or 3' end of the sense strand of the dsRNA agent.

In one embodiment, the ASGPR ligand is attached to the 5' end of the sense strand of the dsRNA agent.

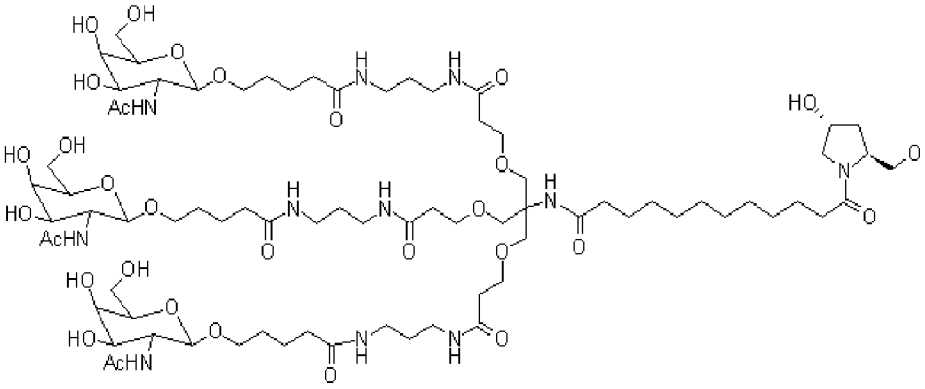
In one embodiment, the ASGPR ligand is attached to the 3' end of the sense strand of the dsRNA agent.

In one embodiment, the ASGPR ligand comprises one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

In one embodiment, the ASGPR ligand comprises:



In one embodiment, the ASGPR ligand is:



In various embodiments of the aforementioned dsRNA agents, the dsRNA agent targets a hotspot region of an mRNA encoding LRRK2. In one embodiment, the hotspot region comprises any one of SEQ ID NOs: 2260-2288 of SEQ ID NO: 1 or any one of nucleotides 3620-3652, 3794-3849, 5194-5222, 5366-5393, 5423-5463, 5674-5704, 5720-5745, 6090-6114, 6125-6156, 6518-6561, 6721-6750, 6740-6763, 7016-7061, 7083-7123, 7112-7136, 7125-7169, 7346-7373, 7441-7465, 7591-7659, 7636-7659, 8132-8155, 3627-3650, 5194-5222, 5674-5702, 5720-5745, 6091-6114, 6529-6559, 7034-7061, 7441-7465, and 7636-7659 of SEQ ID NO: 1. The dsRNA agent may be selected from the group consisting of AD-1627308, AD-1631049, AD-1631050, AD-1626349, AD-1626353, AD-1626375, AD-1626382, AD-1631080, AD-1807348, AD-1807393, AD-1631088, AD-1631089, AD-1631090, AD-1631108, AD-1807416, AD-

1807371, AD-1627767, AD-1627769, AD-1627772, AD-1631109, AD-1631110, AD-1631111, AD-1627820, AD-1627838, , AD-1628042, AD-1628043, AD-1628044, AD-1628050, AD-1628052,, AD-1628070, AD-1631108, AD-1631109, AD-1631110, AD-1631111, AD-1807397, AD-1807352, , AD-1628073, AD-1807374, AD-1807419, AD-1628381, AD-1628382, AD-1628383, AD-1631131, AD-1631132, AD-1631133, AD-1628396, AD-1807361, AD-1807406, AD-1631150, AD-1631151, AD-1631152, AD-1631153, AD-1631154, AD-1631155, AD-1631156, AD-1631157, AD-1631158, AD-1631160, AD-1631161, AD-1631162, AD-1807357, AD-1807402, AD-1628961, AD-1628963, AD-1629214, AD-1629216, AD-1629223, AD-1629224, AD-1629263, AD-1629280, AD-1631194, AD-1631195, AD-1631196, AD-1631197, AD-1807363, AD-1807408, AD-1629304, AD-1629524, AD-1631205, AD-1631206, AD-1807337, AD-1807354, AD-1807382, AD-1807399, AD-1629619, AD-1629620, AD-1629621, AD-1631210, AD-1807355, AD-1807377, AD-1807400, AD-1807422, AD-1629763, AD-1631215, AD-1631216, AD-1631217, AD-1807335, AD-1807336, AD-1807376, AD-1807380, AD-1807381, AD-1807421, AD-1630135, AD-1630136, AD-1631221, AD-1807369, AD-1807414, AD-1807364, AD-1807409, AD-1629808, and AD-1629809.

In another aspect, the present invention provides a dsRNA agent that targets a hotspot region of a leucine-rich repeat kinase 2 (*LRRK2*) mRNA.

In some embodiments, the dsRNA agent comprises at least one modified nucleotide.

In one embodiment, no more than five of the sense strand nucleotides and no more than five of the nucleotides of the antisense strand are unmodified nucleotides

In one embodiment, all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

In one embodiment, at least one of the modified nucleotides is selected from the group a deoxy-nucleotide, a 3'-terminal deoxythimidine (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, 2'-hydroxly-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 5'-phosphorothioate group, a nucleotide comprising a 5'-methylphosphonate group, a nucleotide comprising a 5' phosphate or 5' phosphate mimic, a nucleotide comprising vinyl phosphonate, a nucleotide comprising adenosine-glycol nucleic acid (GNA), a nucleotide comprising thymidine-glycol nucleic acid (GNA) S-Isomer, a nucleotide comprising 2-hydroxymethyl-tetrahydrofurane-5-phosphate, a nucleotide comprising 2'-deoxythymidine-3'phosphate, a nucleotide comprising 2'-deoxyguanosine-3'-

phosphate, and a terminal nucleotide linked to a cholesteryl derivative and a dodecanoic acid bisdecylamide group; and combinations thereof.

In one embodiment, the modified nucleotide is selected from the group consisting of a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, 3'-terminal deoxythimidine nucleotides (dT), a locked nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, and a non-natural base comprising nucleotide.

In one embodiment, the modified nucleotide comprises a short sequence of 3'-terminal deoxythimidine nucleotides (dT).

In one embodiment, the modifications on the nucleotides are 2'-O-methyl, GNA and 2'fluoro modifications.

In some embodiments, the dsRNA agent further comprises at least one phosphorothioate internucleotide linkage.

In one embodiment, the dsRNA agent comprises 6-8 phosphorothioate internucleotide linkages.

In one embodiment, each strand is no more than 30 nucleotides in length.

In one embodiment, at least one strand comprises a 3' overhang of at least 1 nucleotide. In another embodiment, at least one strand comprises a 3' overhang of at least 2 nucleotides.

The double stranded region may be 15-30 nucleotide pairs in length; 17-23 nucleotide pairs in length; 17-25 nucleotide pairs in length 23-27 nucleotide pairs in length; 19-21 nucleotide pairs in length; or 21-23 nucleotide pairs in length.

Each strand may have 19-30 nucleotides;19-23 nucleotides; or 21-23 nucleotides.

In one embodiment, one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand, such as via a linker or carrier.

In one embodiment, the internal positions include all positions except the terminal two positions from each end of the at least one strand.

In another embodiment, the internal positions include all positions except the terminal three positions from each end of the at least one strand.

In one embodiment, the internal positions exclude a cleavage site region of the sense strand.

In one embodiment, the internal positions include all positions except positions 9-12, counting from the 5'-end of the sense strand.

In another embodiment, the internal positions include all positions except positions 11-13, counting from the 3'-end of the sense strand.

In one embodiment, the internal positions exclude a cleavage site region of the antisense strand.

In one embodiment, the internal positions include all positions except positions 12-14, counting from the 5'-end of the antisense strand.

In one embodiment, 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 one embodiment, 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 another embodiment, 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 one embodiment, the internal positions in the double stranded region exclude a cleavage site region of the sense strand.

In one embodiment, 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 one embodiment, the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, or position 7 of the sense strand.

In another embodiment, the lipophilic moiety is conjugated to position 21, position 20, or position 15 of the sense strand.

In yet another embodiment, the lipophilic moiety is conjugated to position 20 or position 15 of the sense strand.

In one embodiment, the lipophilic moiety is conjugated to position 16 of the antisense strand.

In one embodiment, the lipophilic moiety is an aliphatic, alicyclic, or polyalicyclic compound.

In one embodiment, 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 one embodiment, 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 one embodiment, the lipophilic moiety contains a saturated or unsaturated C6-C18 hydrocarbon chain.

In one embodiment, the lipophilic moiety contains a saturated or unsaturated C16 hydrocarbon chain.

In one embodiment, the saturated or unsaturated C16 hydrocarbon chain is conjugated to position 6, counting from the 5'-end of the strand.

In one embodiment, 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 one embodiment, 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 one embodiment, 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 one embodiment, the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage.

In one embodiment, 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 one embodiment, 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 one embodiment, the dsRNA agent further comprises a targeting ligand that targets a liver tissue.

In one embodiment, the targeting ligand is a GalNAc conjugate.

In one embodiment, 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 another embodiment, 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 yet another embodiment, 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 another embodiment, 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 another embodiment, 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 one embodiment, the dsRNA agent further comprises a phosphate or phosphate mimic at the 5'-end of the antisense strand.

In one embodiment, the phosphate mimic is a 5'-vinyl phosphonate (VP).

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

In one embodiment, the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.

The present invention also provides cells and pharmaceutical compositions for inhibiting expression of a gene encoding LRRK2 comprising the dsRNA agents of the invention, such.

In one embodiment, the dsRNA agent is in an unbuffered solution, such as saline or water.

In another embodiment, the dsRNA agent is in a buffer solution, such as a buffer solution comprising acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof; or phosphate buffered saline (PBS).

In one aspect, the present invention provides a method of inhibiting expression of a *LRRK2* gene in a cell, the method comprising contacting the cell with a dsRNA agent of the invention, or a pharmaceutical composition of the invention, thereby inhibiting expression of the *LRRK2* gene in the cell.

In one embodiment, cell is within a subject.

In one embodiment, the subject is a human.

In one embodiment, the subject has a *LRRK2*-associated disorder.

In one embodiment, the *LRRK2*-associated disorder in the subject is a neurodegenerative disorder. In another embodiment, the *LRRK2*-associated disorder in the subject is an ocular disorder.

In one embodiment, the *LRRK2*-associated disorder is selected from the group consisting of Parkinson's disease or related disorders, and ocular disorders.

In some embodiments, contacting the cell with the dsRNA agent inhibits the expression of *LRRK2* by at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95%, relative to control levels.

In some embodiments, inhibiting expression of *LRRK2* decreases LRRK2 protein level in serum of the subject by at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95%, relative to control levels.

In one aspect, the present invention provides method of treating a subject having a disorder that would benefit from reduction in *LRRK2* expression, comprising administering to the subject a therapeutically effective amount of a dsRNA agent of the invention, or a pharmaceutical composition of the invention, thereby treating the subject having the disorder that would benefit from reduction in *LRRK2* expression.

In another aspect, the present invention provides a method of preventing at least one symptom in a subject having a disorder that would benefit from reduction in *LRRK2* expression, comprising administering to the subject a prophylactically effective amount of a dsRNA agent of the invention, or a pharmaceutical composition of the invention, thereby preventing at least one symptom in the subject having the disorder that would benefit from reduction in *LRRK2* expression.

In one embodiment, the disorder is a *LRRK2*-associated disorder.

In some embodiments, the *LRRK2*-associated disorder is selected from the group consisting of Parkinson's disease, Crohn's disease and ocular disorders.

In one embodiment, the subject is human.

In one embodiment, the administration of the agent to the subject causes a decrease in LRRK2 protein accumulation.

In one embodiment, the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.

In one embodiment, the dsRNA agent is administered to the subject subcutaneously.

In another embodiment, the dsRNA agent is administered to the subject intrathecally.

In yet another embodiment, the dsRNA agent is administered to the subject intracisternally. A non-limiting exemplary intracisternal administration comprises an injection into the cisterna magna (cerebellomedullary cistern) by suboccipital puncture.

In one embodiment, the methods of the invention further comprise determining the level of *LRRK2* in a sample(s) from the subject.

In one embodiment, the level of *LRRK2* in the subject sample(s) is a LRRK2 protein level in a blood, serum, or cerebrospinal fluid sample(s).

In one embodiment, the methods of the invention further comprise administering to the subject an additional therapeutic agent.

In one aspect, the present invention provides a kit comprising a dsRNA agent of the invention, or a pharmaceutical composition of the invention.

In another aspect, the present invention provides a vial comprising a dsRNA agent of the invention, or a pharmaceutical composition of the invention.

In yet another aspect, the present invention provides a syringe comprising a dsRNA agent of the invention, or a pharmaceutical composition of the invention.

In another aspect, the present invention provides an intrathecal pump comprising a dsRNA agent of the invention, or a pharmaceutical composition of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

FIG. 1 depicts the sequences and chemistry of exemplary LRRK2 siRNAs including AD-1807334, AD-1807336, AD-1807339, AD-1807344, AD-1807345, AD-1807349, AD-1807352, AD-1807364, AD-1807370, and AD-1807374. For each siRNA, "2-C16" refers to a 2'-O-hexadecyl modification, i.e., conjugation to a C16 ligand; "F" is a 2'-fluoro modification; "OMe" is a methoxy group; "GNA" refers to a glycol nucleic acid; and "PS" refers to a phosphorothioate linkage.

FIG. 2 is a graph depicting the percent LRRK2 message remaining relative to PBS in the brain tissue of mice on day 14 post-treatment with the exemplary duplexes indicated on the X-axis (from left to right: aCSF, AD-1807334, AD-1807336, AD-1807339, AD-1807344, AD-1807345, AD-1807349, AD-1807352, AD-1807364, AD-1807370, and AD-1807374).

DETAILED DESCRIPTION OF THE INVENTION

The present disclosure provides RNAi compositions, which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a *LRRK2* gene. The *LRRK2* gene may be within a cell, *e.g.*, a cell within a subject, such as a human. The use of these iRNAs enables the targeted degradation of mRNAs of the corresponding gene (*LRRK2* gene) in mammals.

The iRNAs of the invention have been designed to target a *LRRK2* gene, *e.g.*, a *LRRK2* gene either with or without nucleotide modifications. The iRNAs of the invention inhibit the expression of the *LRRK2* gene by at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%,

at least about 70%, at least about 80%, at least about 90%, or at least about 95%, relative to control levels, and reduce the level of sense- and antisense-containing foci. Without intending to be limited by theory, it is believed that a combination or sub-combination of the foregoing properties and the specific target sites, or the specific modifications in these iRNAs confer to the iRNAs of the invention improved efficacy, stability, potency, durability, and safety.

Accordingly, the present disclosure also provides methods of using the RNAi compositions of the disclosure for inhibiting the expression of a *LRRK2* gene or for treating a subject having a disorder that would benefit from inhibiting or reducing the expression of a *LRRK2* gene, *e.g.*, a *LRRK2*-associated disease, for example, a neurodegenerative disease such as Parkinson's disease, or an ocular disorder.

The RNAi agents of the disclosure include an RNA strand (the antisense strand) having a region which is about 30 nucleotides or less in length, *e.g.*, 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length, which region is substantially complementary to at least part of an mRNA transcript of a *LRRK2* gene, *e.g.*, an *LRRK2* exon. In certain embodiments, the RNAi agents of the disclosure include an RNA strand (the antisense strand) having a region which is about 21-23 nucleotides in length, which region is substantially complementary to at least part of an mRNA transcript of a *LRRK2* gene.

In certain embodiments, the RNAi agents of the disclosure include an RNA strand (the antisense strand) which can include longer lengths, for example up to 66 nucleotides, *e.g.*, 36-66, 26-36, 25-36, 31-60, 22-43, 27-53 nucleotides in length with a region of at least 19 contiguous nucleotides that is substantially complementary to at least a part of an mRNA transcript of a *LRRK2* gene. These RNAi agents with the longer length antisense strands preferably include a second RNA strand (the sense strand) of 20-60 nucleotides in length wherein the sense and antisense strands form a duplex of 18-30 contiguous nucleotides.

The use of these RNAi agents enables the targeted degradation and/or inhibition of mRNAs of a *LRRK2* gene in mammals. Thus, methods and compositions including these RNAi agents are useful for treating a subject who would benefit by a reduction in the levels or activity of a LRRK2 protein, such as a subject having a *LRRK2*-associated disease, such as Parkinson's disease, or an ocular disorder.

The following detailed description discloses how to make and use compositions containing RNAi agents to inhibit the expression of a *LRRK2* gene, as well as compositions and methods for treating subjects having diseases and disorders that would benefit from inhibition or reduction of the expression of the genes.

I. Definitions

In order that the present disclosure may be more readily understood, certain terms are first defined. In addition, it should be noted that whenever a value or range of values of a parameter are recited, it is

intended that values and ranges intermediate to the recited values are also intended to be part of this disclosure.

The articles “a” and “an” are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element, *e.g.*, a plurality of elements.

The term "including" is used herein to mean, and is used interchangeably with, the phrase "including but not limited to". The term "or" is used herein to mean, and is used interchangeably with, the term "and/or," unless context clearly indicates otherwise.

The term “about” is used herein to mean within the typical ranges of tolerances in the art. For example, “about” can be understood as about 2 standard deviations from the mean. In certain embodiments, about means ±10%. In certain embodiments, about means ±5%. When about is present before a series of numbers or a range, it is understood that “about” can modify each of the numbers in the series or 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 18 nucleotides of a 21 nucleotide nucleic acid molecule” means that 18, 19, 20, or 21 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 “or less” 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 an overhang of “no more than 2 nucleotides” has a 2, 1, or 0 nucleotide overhang. 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, the term “at least about”, when referring to a measurable value such as a parameter, an amount, and the like, is meant to encompass variations of +/-20%, preferably +/-10%, more preferably +/-5%, and still more preferably +/-1% from the specified value, insofar such variations are appropriate to perform in the disclosed invention. For example, the inhibition of expression of the *LRRK2* gene by “at least about 25%” means that the inhibition of expression of the *LRRK2* gene can be measured to be any value +/-20% of the specified 25%, i.e., 20%, 30 % or any intermediary value between 20-30%.

As used herein, “control level” refers to the levels of expression of a gene, or expression level of an RNA molecule or expression level of one or more proteins or protein subunits, in a non-modulated cell, tissue or a system identical to the cell, tissue or a system where the RNAi agents, described herein, are expressed. The cell, tissue or a system where the RNAi agents are expressed, have at least 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 2-fold, 3-fold, 4-fold, 5-fold or more expression of the gene, RNA and/or protein described above from that observed in the absence of the RNAi agent. The % and/or fold difference can be calculated relative to the control levels, for example,

$$\% \text{ difference} = \frac{[\text{expression with RNAi agent} - \text{expression without RNAi agent}]}{\text{expression without RNAi agent}} \times 100$$

As used herein, methods of detection can include determination that the amount of analyte present is below the level of detection of the method.

In the event of a conflict between an indicated target site and the nucleotide sequence for a sense or antisense strand, the indicated sequence takes precedence.

In the event of a conflict between a chemical structure and a chemical name, the chemical structure takes precedence.

The term "*LRRK2*" gene, also known as "DRDN," "RIPK7," "PARK8," "AURA17," "ROCO2", and "leucine-rich repeat kinase 2," refers to the gene encoding for a protein called Dardarin. The *LRRK2* gene is active in the brain and other tissues throughout the body. *LRRK2* is expressed in many regions of the brain, including microglia, oligodendrocytes, neurons and astrocytes. Expression in cells of both the innate and adaptive immune system have also been reported.

LRRK2 encodes for a protein known as Dardarin, which contains multiple functional domains, including a leucine-rich repeat (LRR) domain, a GTPase domain, a kinase domain, and a WD40 domain. Dardarin likely function as both an active GTPase and kinase. Being a large protein with several different functional and protein-interacting domains, LRRK2 may have different binding partners in different cell types. In support of multiple functions due to multiple protein-interacting domains, LRRK2 has been shown in vitro to influence regulation of autophagy, macroautophagy, ceramide metabolism, neurite outgrowth, vesicular trafficking, cytoskeletal components, and cell signaling pathways involving nuclear factor of activated T cells (NFAT), Wnt, and nuclear factor-κB. One of the domains of the dardarin protein is a leucine-rich region that appear to play a role in activities that require interactions with other proteins, such as transmitting signals or helping to assemble the cell's structural framework (cytoskeleton). Other parts of the Dardarin protein are also thought to be involved in protein-protein interactions. Dardarin has kinase and GTPase activity. Proteins with kinase activity assist in the transfer of a phosphate group (a cluster of oxygen and phosphorus atoms) from the energy molecule ATP to amino acids in certain proteins. This phosphorylation is an essential step in turning on and off many cell activities. Among the kinase substrates of LRRK2 are a subset of the Rab GTPases (guanosine triphosphatases), including Rab10, which has been implicated in the maintenance of endoplasmic reticulum, vesicle trafficking, and autophagy (Eguchi et al., Proc Nat Acad Sci 2018;15(39) E9115-E9124). LRRK2-induced phosphorylation of Rab10 likely inhibits its function by preventing binding to Rab GDP (guanosine diphosphate) dissociation inhibitor factors necessary for membrane delivery and recycling. Aberrantly enhanced LRRK2 kinase activity has been linked to the reduced activity of Rab10 and its effectors (Maio et al., Science Translational Medicine 25 Jul 2018: Vol. 10, Issue 451, eaar5429.) The GTPase activity of Dardarin is associated with a region of the protein

called the ROC domain. The ROC domain may help control the overall shape of the Dardarin protein. At least 20 different mutations in the *LRRK2* gene have been implicated as the cause of inherited and sporadic Parkinson's disease. Missense mutations in *LRRK2* cause familial Parkinson's disease. Additionally, genome-wide association studies involving scanning markers across the genomes of many patients with Parkinson's to associate specific genetic variations with Parkinson's point to the *LRRK2* locus as a risk factor for Parkinson's. Expression quantitative trait loci (eQTL) analysis to identify genetic variants that affect the expression of one or more genes suggest that the expression of *LRRK2* is increased about 2 fold in sporadic Parkinson's disease.

LRRK2 polymorphisms have been associated with inflammatory bowel disease (e.g., Crohn's disease) and leprosy, demonstrating a link to immune function. Recently, increased expression of *LRRK2* in monocytes following IFN-γ stimulation was reported, leading to a possible mechanism of *LRRK2* mediated pathophysiology in PD where *LRRK2* may play a role as a regulator of inflammatory and immune responses that modulates the risk for neurodegeneration. Although the mechanisms of *LRRK2* mediated pathology are still being investigated, increased expression of WT and/or mutated *LRRK2* in cells from PD patients, likely causes a dysregulation of function and activation in cells of both the innate and adaptive immune system, resulting in an undesirable inflammatory response and subsequent neurodegeneration in PD. Of note, a large proportion (e.g., about up to 30-40%) of people with IBD go on to develop PD.

Mutations in the *LRRK2* gene have also been associated in more peripheral processes, such as kidney functions, in rats and mice. Although LRRK2 knockout animals have a kidney defect, they are protected against AKI and CKD in rodent models. *LRRK2* knockdown in zebrafish is known to cause developmental perturbations such as axis curvature defects, ocular abnormalities, and edema in the eyes, lens, and otic vesicles (Prabhudesai, *et al.* (2016) *Neuroscience Research* Vol. 94, Issue 8:717-735)

Exemplary nucleotide and amino acid sequences of *LRRK2* can be found, for example, at GenBank Accession No. NM_198578.4 (Homo sapiens *LRRK2*, SEQ ID NO: 1, reverse complement, SEQ ID NO: 2); XM_024448833.1 (Homo sapiens *LRRK2* transcript variant X3, SEQ ID NO: 1808, reverse complement, SEQ ID NO: 1809); GenBank Accession No.: XM_015151449.2 (Macaca fascicularis *LRRK2*, SEQ ID NO: 3, reverse complement, SEQ ID NO: 4); GenBank Accession No. NM_025730.3 (Mus musculus *LRRK2*, SEQ ID NO: 5; reverse complement, SEQ ID NO: 6); and GenBank Accession No.: NM_001191789.1 (Rattus norvegicus *LRRK2*, SEQ ID NO: 7, reverse complement, SEQ ID NO: 8).

The nucleotide sequence of the genomic region of human chromosome harboring the *LRRK2* gene may be found in, for example, the Genome Reference Consortium Human Build 38 (also referred to as Human Genome build 38 or GRCh38) available at GenBank. The nucleotide sequence of the genomic region of human chromosome 12 harboring the *LRRK2* gene may also be found at, for example, GenBank Accession No. NC_000012.12, corresponding to nucleotides 40196744-40369285 of human chromosome 12. The nucleotide sequence of the human *LRRK2* gene may be found in, for example, GenBank Accession No. NG_011709.1

Further examples of *LRRK2* sequences can be found in publically available databases, for example, GenBank, OMIM, and UniProt.

Additional information on *LRRK2* can be found, for example, at the NCBI web site that refers to gene 120892.The term *LRRK2* as used herein also refers to variations of the *LRRK2* gene including variants provided in the clinical variant database, for example, at the NCBI clinical variants web site that refers to the term NM_198578.4.

The entire contents of each of the foregoing GenBank Accession numbers and the Gene database numbers are incorporated herein by reference as of the date of filing this application.

As used herein, "target sequence" refers to a contiguous portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a *LRRK2* gene, including both a primary transcription product and a mRNA that is a product of RNA processing of a primary transcription product. In one embodiment, the target portion of the sequence is at least long enough to serve as a substrate for RNAi-directed cleavage at or near that portion of the nucleotide sequence of an mRNA molecule formed during the transcription of a *LRRK2* gene.

The target sequence is about 15-30 nucleotides in length. For example, the target sequence can be from about 15-30 nucleotides, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length. In certain embodiments, the target sequence is 19-23 nucleotides in length, optionally 21-23 nucleotides in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

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. "G," "C," "A," "T", and "U" each generally stand for a nucleotide that contains guanine, cytosine, adenine, thymidine, and uracil as a base, respectively in the context of a modified or unmodified nucleotide. However, it will be understood that the term "ribonucleotide" or "nucleotide" can also refer to a modified nucleotide, as further detailed below, or a surrogate replacement moiety (see, *e.g.,* Table 2). The skilled person is well aware that guanine, cytosine, adenine, thymidine, and uracil can 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 can base pair with nucleotides containing adenine, cytosine, or uracil. Hence, nucleotides containing uracil, guanine, or adenine can 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.

The terms "iRNA", "RNAi agent," "iRNA agent," "RNA interference agent" as used interchangeably herein, refer to an agent that contains RNA as that term is defined herein, and which mediates the targeted cleavage of an RNA transcript *via* an RNA-induced silencing complex (RISC) pathway. RNA interference (RNAi) is a process that directs the sequence-specific degradation of mRNA. RNAi modulates, *e.g.*, inhibits, the expression of *LRRK2* in a cell, *e.g.*, a cell within a subject, such as a mammalian subject.

In one embodiment, an RNAi agent of the disclosure includes a single stranded RNAi that interacts with a target RNA sequence, *e.g.*, a *LRRK2* target mRNA sequence, to direct the cleavage of the target RNA. Without wishing to be bound by theory it is believed that long double stranded RNA introduced into cells is broken down into double-stranded short interfering RNAs (siRNAs) comprising a sense strand and an antisense strand by a Type III endonuclease known as Dicer (Sharp *et al.* (2001) *Genes Dev.* 15:485). Dicer, a ribonuclease-III-like enzyme, processes this dsRNA into 19-23 base pair short interfering RNAs with characteristic two base 3' overhangs (Bernstein, *et al.*, (2001) *Nature* 409:363). These 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 cleave the target to induce silencing (Elbashir, *et al.*, (2001) *Genes Dev.* 15:188). Thus, in one aspect the disclosure relates to a single stranded RNA (ssRNA) (the antisense strand of a siRNA duplex) generated within a cell and which promotes the formation of a RISC complex to effect silencing of the target gene, *i.e.*, a *LRRK2* gene. Accordingly, the term "siRNA" is also used herein to refer to an RNAi as described above.

In another embodiment, the RNAi agent may be a single-stranded RNA that is introduced into a cell or organism to inhibit a target mRNA. Single-stranded RNAi agents bind to the RISC endonuclease, Argonaute 2, which then cleaves the target mRNA. The single-stranded siRNAs are generally 15-30 nucleotides and are chemically modified. The design and testing of single-stranded RNAs 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 may be used as a single-stranded siRNA as described herein or as chemically modified by the methods described in Lima *et al.*, (2012) *Cell* 150:883-894.

In another embodiment, a "RNAi agent" for use in the compositions and methods of the disclosure is a double stranded RNA and is referred to herein as a "double stranded RNAi agent," "double stranded RNA (dsRNA) molecule," "dsRNA agent," or "dsRNA". The term "dsRNA" refers to a complex of ribonucleic acid molecules, having a duplex structure comprising two anti-parallel and substantially complementary nucleic acid strands, referred to as having "sense" and "antisense" orientations with respect to a target RNA, *i.e.*, a *LRRK2* gene. In some embodiments of the disclosure, a double stranded RNA

(dsRNA) triggers the degradation of a target RNA, *e.g.*, an mRNA, through a post-transcriptional gene-silencing mechanism referred to herein as RNA interference or RNAi.

In general, a dsRNA molecule can include ribonucleotides, but as described in detail herein, each or both strands can also include one or more non-ribonucleotides, *e.g.*, a deoxyribonucleotide, a modified nucleotide. In addition, as used in this specification, an "RNAi agent" may include ribonucleotides with chemical modifications; an RNAi agent may include substantial modifications at multiple nucleotides. As used herein, the term "modified nucleotide" refers to a nucleotide having, independently, a modified sugar moiety, a modified internucleotide linkage, or a modified nucleobase. Thus, the term modified nucleotide encompasses substitutions, additions or removal of, *e.g.*, a functional group or atom, to internucleoside linkages, sugar moieties, or nucleobases. The modifications suitable for use in the agents of the disclosure include all types of modifications disclosed herein or known in the art. Any such modifications, as used in a siRNA type molecule, are encompassed by "RNAi agent" for the purposes of this specification and claims.

In certain embodiments of the instant disclosure, inclusion of a deoxy-nucleotide if present within an RNAi agent can be considered to constitute a modified nucleotide.

The duplex region may be of any length that permits specific degradation of a desired target RNA through a RISC pathway, and may range from about 15-36 base pairs in length, for example, about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 base pairs in length, such as about 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs in length. In certain embodiments, the duplex region is 19-21 base pairs in length, *e.g.*, 21 base pairs in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

The two strands forming the duplex structure may be different portions of one larger RNA molecule, or they may be separate RNA molecules. Where the two strands are part of one larger molecule, they may be connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, with the connecting RNA chain is referred to as a "hairpin loop." A hairpin loop can comprise at least one unpaired nucleotide. In some embodiments, the hairpin loop can comprise 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 or nucleotides not directed to the target site of the dsRNA. In some embodiments, the hairpin loop can be 10 or fewer nucleotides. In some embodiments, the hairpin loop can be 8 or fewer unpaired nucleotides. In some embodiments, the hairpin loop can be 4-10 unpaired nucleotides. In some embodiments, the hairpin loop can be 4-8 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 certain embodiments where the two strands are connected covalently by means other than an uninterrupted chain of nucleotides between the

3'-end of one strand and the 5'-end of the respective other strand forming the duplex structure, the connecting structure is referred to as a "linker" (though it is noted that certain other structures defined elsewhere herein can also be referred to as a "linker"). The RNA strands may have the same or a different number of nucleotides. The maximum number of base pairs is the number of nucleotides in the shortest strand of the dsRNA minus any overhangs that are present in the duplex. In addition to the duplex structure, an RNAi may comprise one or more nucleotide overhangs. In one embodiment of the RNAi agent, at least one strand comprises a 3' overhang of at least 1 nucleotide. In another embodiment, at least one strand comprises a 3' overhang of at least 2 nucleotides, *e.g.*, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, or 15 nucleotides. In other embodiments, at least one strand of the RNAi agent comprises a 5' overhang of at least 1 nucleotide. In certain embodiments, at least one strand comprises a 5' overhang of at least 2 nucleotides, *e.g.*, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, or 15 nucleotides. In still other embodiments, both the 3' and the 5' end of one strand of the RNAi agent comprise an overhang of at least 1 nucleotide.

In one embodiment, an RNAi agent of the disclosure is a dsRNA, each strand of which independently comprises 19-23 nucleotides, that interacts with a target RNA sequence, *e.g.*, a *LRRK2* target mRNA sequence, to direct the cleavage of the target RNA.

In some embodiments, an iRNA of the invention is a dsRNA of 24-30 nucleotides that interacts with a target RNA sequence, *e.g.*, a *LRRK2* target mRNA sequence, to direct the cleavage of the target RNA.

As used herein, the term "nucleotide overhang" refers to at least one unpaired nucleotide that protrudes from the duplex structure of an RNAi agent, *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, 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) can 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 one embodiment, the antisense strand of a dsRNA has a 1-10 nucleotides, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides, overhang at the 3'-end or the 5'-end. In one embodiment, the sense strand of a dsRNA has a 1-10 nucleotide, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides, overhang at the 3'-end or the 5'-end. In another embodiment, one or more of the nucleotides in the overhang is replaced with a nucleoside thiophosphate.

In certain embodiments, the antisense strand of a dsRNA has a 1-10 nucleotide, *e.g.*, 0-3, 1-3, 2-4, 2-5, 4-10, 5-10, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides, overhang at the 3'-end or the 5'-end. In one embodiment, the sense strand of a dsRNA has a 1-10 nucleotide, *e.g.*, a 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides, overhang at the 3'-end or the 5'-end. In another embodiment, one or more of the nucleotides in the overhang is replaced with a nucleoside thiophosphate.

In certain embodiments, the overhang on the sense strand or the antisense strand, can include extended lengths longer than 10 nucleotides, *e.g.*, 1-30 nucleotides, 2-30 nucleotides, 10-30 nucleotides, or 10-15 nucleotides in length. In certain embodiments, an extended overhang is on the sense strand of the duplex. In certain embodiments, an extended overhang is present on the 3'end of the sense strand of the duplex. In certain embodiments, an extended overhang is present on the 5'end of the sense strand of the duplex. In certain embodiments, an extended overhang is on the antisense strand of the duplex. In certain embodiments, an extended overhang is present on the 3'end of the antisense strand of the duplex. In certain embodiments, an extended overhang is present on the 5'end of the antisense strand of the duplex. In certain embodiments, one or more of the nucleotides in the overhang is replaced with a nucleoside thiophosphate. In certain embodiments, the overhang includes a self-complementary portion such that the overhang is capable of forming a hairpin structure that is stable under physiological conditions.

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 is double stranded over its entire length.

The term "antisense strand" or "guide strand" refers to the strand of an RNAi agent, *e.g.*, a dsRNA, which includes a region that is substantially complementary to a target sequence, *e.g.*, a *LRRK2* mRNA.

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, *e.g.*, a *LRRK2* 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 molecule. 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 RNAi agent. In some embodiments, a double stranded RNA agent of the invention includes a nucleotide mismatch in the antisense strand. In some embodiments, the antisense strand of the double stranded RNA agent of the invention includes no more than 4 mismatches with the target mRNA, e.g., the antisense strand includes 4, 3, 2, 1, or 0 mismatches with the target mRNA. In some embodiments, the antisense strand double stranded RNA agent of the invention includes no more than 4 mismatches with the sense strand, *e.g.*, the antisense strand includes 4, 3, 2, 1, or 0 mismatches with the sense strand. In some embodiments, a double stranded RNA agent of the invention includes a nucleotide mismatch in the sense strand. In some embodiments, the sense strand of the double stranded RNA agent of the invention includes no more than 4 mismatches with the antisense strand, *e.g.*, the sense strand includes 4, 3, 2, 1, or 0 mismatches with the antisense strand. In some embodiments, the nucleotide mismatch is, for example, within 5, 4, 3 nucleotides from the 3'-end of the iRNA. In another embodiment, the nucleotide mismatch is, for example, in the 3'-terminal nucleotide of the iRNA agent. In some embodiments, the mismatch(s) is not in the seed region.

Thus, an RNAi agent as described herein can contain one or more mismatches to the target sequence. In one embodiment, an RNAi agent as described herein contains no more than 3 mismatches (*i.e.*, 3, 2, 1, or 0 mismatches). In one embodiment, an RNAi agent as described herein contains no more than 2 mismatches. In one embodiment, an RNAi agent as described herein contains no more than 1 mismatch. In one embodiment, an RNAi agent as described herein contains 0 mismatches. In certain embodiments, when the antisense strand of the RNAi agent contains mismatches to the target sequence, then the mismatch can optionally be restricted to be within the last 5 nucleotides from either the 5'- or 3'-end of the region of complementarity. For example, in such embodiments, for a 23 nucleotide RNAi agent, the strand which is complementary to a region of a *LRRK2* gene, 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 RNAi agent containing a mismatch to a target sequence is effective in inhibiting the expression of a *LRRK2* gene. For example, Jackson *et al.* (*Nat. Biotechnol.* 2003;21: 635–637) described an expression profile study where the expression of a small set of genes with sequence identity to the MAPK14 siRNA only at 12–18 nt of the sense strand, was down-regulated with similar kinetics to MAPK14. Similarly, Lin *et al.*, (*Nucleic Acids Res.* 2005; 33(14): 4527–4535) using qPCR and reporter assays, showed that a 7 nt complementation between a siRNA and a target is sufficient to cause mRNA degradation of the target. Consideration of the efficacy of RNAi agents with mismatches in inhibiting expression of a *LRRK2* gene is important, especially if the particular region of complementarity in a *LRRK2* gene is known to have polymorphic sequence variation within the population.

As used herein, "substantially all of the nucleotides are modified" are largely but not wholly modified and can include not more than 5, 4, 3, 2, or 1 unmodified nucleotide.

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

As used herein, the term "cleavage region" refers to a region that is located immediately adjacent to the cleavage site. The cleavage site is the site on the target at which cleavage occurs. In some embodiments, the cleavage region comprises three bases on either end of, and immediately adjacent to, the cleavage site. In some embodiments, the cleavage region comprises two bases on either end of, and immediately adjacent to, the cleavage site. In some embodiments, the cleavage site specifically occurs at the site bound by nucleotides 10 and 11 of the antisense strand, and the cleavage region comprises nucleotides 11, 12 and 13.

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 be, for example, "stringent conditions", including but not limited to, 400 mM NaCl, 40 mM PIPES pH 6.4, 1 mM EDTA, 50

°C or 70 °C for 12-16 hours followed by washing (see, *e.g.*, "Molecular Cloning: A Laboratory Manual, Sambrook, *et al.* (1989) Cold Spring Harbor Laboratory Press). As used herein, "stringent conditions" or "stringent hybridization conditions" refers to conditions under which an antisense compound hybridizes to its target sequence, but to a minimal number of other sequences. Stringent conditions are sequence-dependent and are different in different circumstances, and "stringent conditions" under which antisense compounds hybridize to a target sequence are determined by the nature and composition of the antisense compounds and the assays in which they are being investigated. Other conditions, such as physiologically relevant conditions as can be encountered inside an organism, can apply. The skilled person can 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 RNAi agent, *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 can 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. In some embodiments, the "substantially complementary" sequences disclosed herein comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the target *LRRK2* sequence, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary. 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, can yet be referred to as "fully complementary" for the purposes described herein.

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

The terms "complementary," "fully complementary" and "substantially complementary" herein can be used with respect to the base matching between two oligonucleotides or polynucleotides, such as the sense strand and the antisense strand of a dsRNA, or between the antisense strand of an RNAi agent and a target sequence, as is 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 LRRK2). For example, a polynucleotide is complementary to at least a part of a *LRRK2* mRNA if the sequence is substantially complementary to a non-interrupted portion of an mRNA encoding LRRK2.

Accordingly, in some embodiments, the antisense polynucleotides disclosed herein are fully complementary to the target *LRRK2* sequence. In other embodiments, the antisense polynucleotides disclosed herein are substantially complementary to the target *LRRK2* sequence and comprise a contiguous nucleotide sequence which is at least 80% complementary over its entire length to the equivalent region of the nucleotide sequence of any one of SEQ ID NOs:1, 3, 5, 7 and 1808, or a fragment of any one of SEQ ID NOs: 1, 3, 5, 7 and 1808, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary.

In some embodiments, the antisense polynucleotides disclosed herein are substantially complementary to a fragment of a target *LRRK2* sequence and comprise a contiguous nucleotide sequence which is at least 80% complementary over its entire length to a fragment of SEQ ID NO: 1 selected from the group of nucleotides 1458-1478, 1484-1504, 1761-1781, 1950-1970, 2076-2096, 2094-2114, 2212-2232, 2213-2233, 2268-2288, 2431-2451, 2529-2549, 2565-2585, 2566-2586, 2569-2589, 2583-2603, 2605-2625, 2657-2677, 2764-2784, 2867-2887, 2881-2901, 2883-2903, 3022-3042, 3198-3218, 3330-3350, 3348-3368, 3395-3415, 3629-3649, 3630-3650, 3712-3732, 3713-3733, 3715-3735, 3717-3737, 3720-3740, 3727-3747, 3796-3816, 3800-3820, 3822-3842, 3829-3849, 3875-3895, 3971-3991, 4130-4150, 4443-4463, 4447-4467, 4449-4469, 4478-4498, 4488-4508, 4619-4639, 4652-4672, 4868-4888, 4950-4970, 4970-4990, 4971-4991, 4972-4992, 5092-5112, 5202-5222, 5226-5246, 5232-5252, 5233-5253, 5273-5293, 5318-5338, 5367-5387, 5368-5388, 5370-5390, 5373-5393, 5425-5445, 5443-5463, 5457-5477, 5461-5481, 5471-5491, 5475-5495, 5501-5521, 5557-5577, 5640-5660, 5646-5666, 5659-5679, 5674-5694, 5675-5695, 5676-5696, 5682-5702, 5684-5704, 5722-5742, 5725-5745, 5778-5798, 5779-5799, 5793-5813, 5964-5984, 5965-5985, 5984-6004, 6029-6049, 6092-6112, 6093-6113, 6094-6114, 6096-6116, 6127-6147, 6143-6163, 6165-6185, 6172-6192, 6173-6193, 6174-6194, 6175-6195, 6198-6218, 6319-6339, 6339-6359, 6418-6438, 6531-6551, 6536-6556, 6541-6561, 6573-6593, 6662-6682, 6730-6750, 6740-6760, 6742-6762, 6786-6806, 6791-6811, 6803-6823, 6804-6824, 6805-6825, 6807-6827, 6810-6830, 6811-6831, 6812-6832, 6818-6838, 6872-6892, 7004-7024, 7018-7038, 7020-7040, 7027-7047, 7028-7048, 7085-7105, 7103-7123, 7115-7135, 7121-7141, 7127-7147, 7242-7262, 7348-7368, 7397-7417, 7404-7424, 7405-7425, 7421-7441, 7443-7463, 7444-7464, 7445-7465, 7493-7513, 7535-7555, 7538-7558, 7539-7559, 7593-7613, 7629-7649, 7637-7657, 7638-7658, 7639-7659, 7671-7691, 7727-7747, 7729-7749, 8134-8154, 8135-8155, 1484-1504, 1488-1508, 1755-1775, 1761-1781, 1905-1925, 1945-1965, 1950-1970, 2029-2049, 2207-2227, 2212-2232, 2213-2233, 2431-2451, 2529-2549, 2565-2585, 2569-2589, 2648-2668, 2764-2784, 2874-2894, 2881-2901, 3051-3071, 3193-3213, 3198-3218, 3208-3228, 3330-3350, 3331-3351, 3350-3370, 3380-3400, 3390-3410, 3395-3415, 3573-3593, 3622-3642,

3632-3652, 3712-3732, 3715-3735, 3717-3737, 3718-3738, 3740-3760, 3795-3815, 3806-3826, 3829-3849, 3830-3850, 3938-3958, 3950-3970, 3971-3991, 4367-4387, 4376-4396, 4444-4464, 4446-4466, 4447-4467, 4551-4571, 4554-4574, 4704-4724, 4834-4854, 4839-4859, 4925-4945, 4970-4990, 4971-4991, 4972-4992, 5058-5078, 5092-5112, 5128-5148, 5196-5216, 5226-5246, 5275-5295, 5322-5342, 5349-5369, 5352-5372, 5365-5385, 5367-5387, 5368-5388, 5370-5390, 5373-5393, 5461-5481, 5475-5495, 5482-5502, 5515-5535, 5516-5536, 5541-5561, 5557-5577, 5607-5627, 5635-5655, 5641-5661, 5643-5663, 5644-5664, 5646-5666, 5655-5675, 5659-5679, 5660-5680, 5671-5691, 5674-5694, 5682-5702, 5683-5703, 5684-5704, 5721-5741, 5757-5777, 5763-5783, 5772-5792, 5773-5793, 5776-5796, 5777-5797, 5778-5798, 5779-5799, 5793-5813, 5794-5814, 5964-5984, 5965-5985, 5966-5986, 5980-6000, 5984-6004, 6029-6049, 6030-6050, 6071-6091, 6092-6112, 6093-6113, 6095-6115, 6129-6149, 6135-6155, 6136-6156 ,6142-6162, 6145-6165, 6171-6191, 6172-6192, 6174-6194, 6175-6195, 6178-6198, 6180-6200, 6196-6216, 6197-6217, 6198-6218, 6344-6364, 6355-6375, 6520-6540, 6536-6556, 6538-6558, 6539-6559, 6541-6561, 6723-6743, 6724-6744, 6729-6749, 6730-6750, 6737-6757, 6740-6760, 6742-6762, 6743-6763, 6786-6806, 6787-6807, 6791-6811, 6793-6813, 6794-6814, 6803-6823, 6805-6825, 6806-6826, 6807-6827, 6808-6828, 6810-6830, 6811-6831, 6812-6832, 6813-6833, 6814-6834, 6818-6838, 6828-6848, 6829-6849, 6834-6854, 6872-6892, 6918-6938, 6919-6939, 6920-6940, 6922-6942, 6989-7009, 7004-7024, 7012-7032, 7023-7043, 7035-7055, 7036-7056, 7041-7061, 7085-7105, 7103-7123, 7114-7134, 7116-7136, 7121-7141, 7129-7149, 7146-7166, 7149-7169, 7242-7262, 7247-7267, 7303-7323, 7348-7368, 7353-7373, 7397-7417, 7404-7424, 7405-7425, 7443-7463, 7493-7513, 7533-7553, 7538-7558, 7539-7559, 7593-7613, 7627-7647, 7629-7649, 7727-7747, 8005-8025, 8007-8027 and 8134-8154 of SEQ ID NO: 1, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary. Ranges intermediate to the above recited ranges are also contemplated to be part of the disclosure.

In some embodiments, the antisense polynucleotides disclosed herein are substantially complementary to a fragment of a target *LRRK2* sequence and comprise a contiguous nucleotide sequence which is at least 80% complementary over its entire length to a fragment of SEQ ID NO: 1808 selected from the group of nucleotides 212-232, 238-258, 515-535, 704-724, 830-850, 848-868, 966-986, 967-987, 1022-1042, 1185-1205, 1283-1303, 1319-1339, 1320-1340, 1323-1343, 1337-1357, 1359-1379, 1411-1431, 1518-1538, 1621-1641, 1635-1655, 1637-1657, 1776-1796, 1952-1972, 2084-2104, 2102-2122, 2149-2169, 2383-2403, 2384-2404, 2466-2486, 2467-2487, 2469-2489, 2471-2491, 2474-2494, 2481-2501, 2550-2570, 2554-2574, 2576-2596, 2583-2603, 2629-2649, 2725-2745, 2884-2904, 3197-3217, 3201-3221, 3203-3223, 3232-3252, 3242-3262, 3373-3393, 3406-3426, 3622-3642, 3704-3724, 3724-3744, 3725-3745, 3726-3746, 3846-3866, 3956-3976, 3980-4000, 3986-4006, 3987-4007, 4027-4047, 4072-4092, 4121-4141, 4122-4142, 4124-4144, 4127-4147, 4179-4199, 4197-4217, 4211-4231, 4215-4235, 4225-4245, 4229-4249, 4255-4275, 4311-4331, 4394-4414, 4400-4420, 4413-4433, 4428-4448, 4429-4449, 4430-4450, 4436-4456, 4438-4458, 4476-4496, 4479-4499, 4532-4552, 4533-4553, 4547-4567, 4718-4738, 4719-4739, 4738-4758, 4783-4803, 4846-4866, 4847-4867, 4848-4868, 4850-4870, 4881-4901, 4897-4917, 4919-4939, 4926-4946, 4927-4947, 4928-

4948, 4929-4949, 4952-4972, 5073-5093, 5093-5113, 5172-5192, 5285-5305, 5290-5310, 5295-5315, 5327-5347, 5416-5436, 5484-5504, 5494-5514, 5496-5516, 5540-5560, 5545-5565, 5557-5577, 5558-5578, 5559-5579, 5561-5581, 5564-5584, 5565-5585, 5566-5586, 5572-5592, 5626-5646, 5758-5778, 5772-5792, 5774-5794, 5781-5801, 5782-5802, 5839-5859, 5857-5877, 5869-5889, 5875-5895, 5881-5901, 5996-6016, 6102-6122, 6151-6171, 6158-6178, 6159-6179, 6175-6195, 6197-6217, 6198-6218, 6199-6219, 6247-6267, 6289-6309, 6292-6312, 6293-6313, 6347-6367, 6383-6403, 6391-6411, 6392-6412, 6393-6413, 6425-6445, 6481-6501, 6483-6503, 6888-6908 and 6889-6909 of SEQ ID NO: 1808, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% complementary. Ranges intermediate to the above recited ranges are also contemplated to be part of the disclosure.

In other embodiments, the antisense polynucleotides disclosed herein are substantially complementary to the target *LRRK2* sequence and comprise a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the sense strand nucleotide sequences in any one of any one of Tables 3-7, or a fragment of any one of the sense strand nucleotide sequences in any one of Tables 3-7, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or 100% complementary.

In one embodiment, an RNAi agent of the disclosure includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is the same as a target *LRRK2* sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to the equivalent region of the nucleotide sequence of SEQ ID NOs: 1, 3, 5, 7 and 1808, or a fragment of any one of SEQ ID NOs: 1, 3, 5, 7 and 1808, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or 100% complementary.

In some embodiments, an iRNA of the invention includes a sense strand that is substantially complementary to an antisense polynucleotide which, in turn, is complementary to a target *LRRK2* sequence, and wherein the sense strand polynucleotide comprises a contiguous nucleotide sequence which is at least about 80% complementary over its entire length to any one of the antisense strand nucleotide sequences in any one of any one of Tables 3-7, or a fragment of any one of the antisense strand nucleotide sequences in any one of Tables 3-7, such as about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or 100% complementary.

In certain embodiments, the sense and antisense strands are selected from any one of duplexes AD-1624152, AD-1624178, AD-1624412, AD-1624595, AD-1624721, AD-1624739, AD-1624856, AD-1624857, AD-1624894, AD-1625057, AD-1625155, AD-1625191, AD-1625192, AD-1625195, AD-1625209, AD-1625230, AD-1625282, AD-1625389, AD-1625485, AD-1625499, AD-1625501, AD-1625610, AD-1625786, AD-1625910, AD-1625928, AD-1625975, AD-1626183, AD-1626184, AD-1626265, AD-1626266, AD-1626268, AD-1626270, AD-1626273, AD-1626280, AD-1626349, AD-

1626353, AD-1626375, AD-1626382, AD-1626428, AD-1626524, AD-1626636, AD-1626921, AD-1626925, AD-1626927, AD-1626936, AD-1626946, AD-1627077, AD-1627110, AD-1627308, AD-1627390, AD-1627410, AD-1627411, AD-1627412, AD-1627511, AD, 1627601, AD-1627625, AD-1627631, AD-1627632, AD-1627672, AD-1627717, AD-1627766, AD-1627767, AD-1627769, AD-1627772, AD-1627820, AD-1627838, AD-1627852, AD-1627856, AD-1627866, AD-1627870, AD-1627896, AD-1627952, AD-1628008, AD-1628014, AD-1628027, AD-1628042, AD-1628043, AD-1628044, AD-1628050, AD-1628052, AD-1628070, AD-1628073, AD-1628118, AD-1628119, AD-1628133, AD-1628253, AD-1628254, AD-1628273, AD-1628318, AD-1628381, AD-1628382, AD-1628383, AD-1628385, AD-1628396, AD-1628412, AD-1628434, AD-1628441, AD-1628442, AD-1628443, AD-1628444, AD-1628467, AD-1628570, AD-1628590, AD-1628668, AD-1628754, AD-1628759, AD-1628764, AD-1628794, AD-1628883, AD-1628951, AD-1628961, AD-1628963, AD-1629007, AD-1629012, AD-1629024, AD-1629025, AD-1629026, AD-1629028, AD-1629031, AD-1629032, AD-1629033, AD-1629039, AD-1629092, AD-1629200, AD-1629214, AD-1629216, AD-1629223, AD-1629224, AD-1629263, AD-1629280, AD-1629292, AD-1629298, AD-1629304, AD-1629419, AD-1629524, AD-1629573, AD-1629580, AD-1629581, AD-1629597, AD-1629619, AD-1629620, AD-1629621, AD-1629665, AD-1629707, AD-1629710, AD-1629711, AD-1629763, AD-1629799, AD-1629807, AD-1629808, AD-1629809, AD-1629838, AD-1629876, AD-1629878, AD-1630135, AD-1630136, AD-1631019, AD-1631020, AD-1631021, AD-1631022, AD-1631023, AD-1631024, AD-1631025, AD-1631026, AD-1631027, AD-1631028, AD-1631029, AD-1631030, AD-1631031, AD-1631032, AD-1631033, AD-1631034, AD-1631035, AD-1631036, AD-1631037, AD-1631038, AD-1631039, AD-1631040, AD-1631041, AD-1631042, AD-1631043, AD-1631044, AD-1631045, AD-1631046, AD-1631047, AD-1631048, AD-1631049, AD-1631050, AD-1631051, AD-1631052, AD-1631053, AD-1631054, AD-1631055, AD-1631056, AD-1631057, AD-1631058, AD-1631059, AD-1631060, AD-1631061, AD-1631062, AD-1631063, AD-1631064, AD-1631065, AD-1631066, AD-1631067, AD-1631068, AD-1631069, AD-1631070, AD-1631071, AD-1631072, AD-1631073, AD-1631074, AD-1631075, AD-1631076, AD-1631077, AD-1631078, AD-1631079, AD-1631080, AD-1631081, AD-1631082, AD-1631083, AD-1631084, AD-1631085, AD-1631086, AD-1631087, AD-1631088, AD-1631089, AD-1631090, AD-1631091, AD-1631092, AD-1631093, AD-1631094, AD-1631095, AD-1631096, AD-1631097, AD-1631098, AD-1631099, AD-1631100, AD-1631101, AD-1631102, AD-1631103, AD-1631104, AD-1631105, AD-1631106, AD-1631107, AD-1631108, AD-1631109, AD-1631110, AD-1631111, AD-1631112, AD-1631113, AD-1631114, AD-1631115, AD-1631116, AD-1631117, AD-1631118, AD-1631119, AD-1631120, AD-1631121, AD-1631122, AD-1631123, AD-1631124, AD-1631125, AD-1631126, AD-1631127, AD-1631128, AD-1631129, AD-1631130, AD-1631131, AD-1631132, AD-1631133, AD-1631134, AD-1631135, AD-1631136, AD-1631137, AD-1631138, AD-1631139, AD-1631140, AD-1631141, AD-1631142, AD-1631143, AD-1631144, AD-1631145, AD-1631146, AD-1631147, AD-1631148, AD-1631149, AD-

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In one embodiment, the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1624152, AD-1624178, AD-1624412, AD-1624595, AD-1624721, AD-1624739, AD-1624856, AD-1624857, AD-1624894, AD-1625057, AD-1625155, AD-1625191, AD-1625192, AD-1625195, AD-1625209, AD-1625230, AD-1625282, AD-1625389, AD-1625485, AD-1625499, AD-1625501, AD-1625610, AD-1625786, AD-1625910, AD-1625928, AD-1625975, AD-1626183, AD-1626184, AD-1626265, AD-1626266, AD-1626268, AD-1626270, AD-1626273, AD-1626280, AD-1626349, AD-1626353, AD-1626375, AD-1626382, AD-1626428, AD-1626524, AD-1626636, AD-1626921, AD-1626925, AD-1626927, AD-1626936, AD-1626946, AD-1627077, AD-1627110, AD-1627308, AD-1627390, AD-1627410, AD-1627411, AD-1627412, AD-1627511, AD, 1627601, AD-1627625, AD-1627631, AD-1627632, AD-1627672, AD-1627717, AD-1627766, AD-1627767, AD-1627769, AD-1627772, AD-1627820, AD-1627838, AD-1627852, AD-1627856, AD-

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In one embodiment, at least partial suppression of the expression of a *LRRK2* gene, is assessed by a reduction of the amount of *LRRK2* mRNA, *e.g.*, sense mRNA, antisense mRNA, total *LRRK2* mRNA, which can be isolated from or detected in a first cell or group of cells in which a *LRRK2* gene is transcribed and which has or have been treated such that the expression of a *LRRK2* gene is inhibited, 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). The degree of inhibition (e.g., percent remaining mRNA expression) may be expressed in terms of:

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

The phrase "contacting a cell with an RNAi agent," such as a dsRNA, as used herein, includes contacting a cell by any possible means. 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. The contacting may be done directly or indirectly. Thus, for example, the RNAi agent may be put into physical contact with the cell by the individual performing the method, or alternatively, the RNAi agent may be put into a situation that permits or causes 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.*, the central nervous system (CNS), optionally *via* intrathecal, intravitreal, intracisternal or other injection, or to the bloodstream (i.e., intravenous) or the subcutaneous space, such that the agent subsequently reaches the tissue where the cell to be contacted is located. 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, that directs or otherwise stabilizes the RNAi agent at a site of interest, *e.g.*, the CNS. 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.

In one embodiment, contacting a cell with an RNAi agent includes "introducing" or "delivering the RNAi agent into the cell" by facilitating or effecting uptake or absorption into the cell. Absorption or uptake of an RNAi agent can occur through unaided diffusive or active cellular processes, or by auxiliary agents or devices. Introducing an RNAi agent into a cell may be *in vitro* or *in vivo*. For example, for *in vivo* introduction, an RNAi agent can be injected into a tissue site or administered systemically. *In vitro* introduction into a cell includes methods known in the art such as electroporation and lipofection. Further approaches are described herein below or are known in the art.

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 one embodiment, 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. Briefly, duplexes were incubated with human serum albumin and the unbound fraction was determined. Exemplary assay protocol includes duplexes at a stock concentration of 10 μM, diluted to a final concentration of 0.5 μM (20 μL total volume) containing 0, 20, or 90% serum in 1x PBS. The samples can be mixed, centrifuged for 30 seconds, and subsequently incubated at room temperature for 10 minutes. Once incubation step is completed, 4 μL of 6x EMSA Gel-loading solution can be added to each sample, centrifuged for 30 seconds, and 12 μL of each sample can be loaded onto a 26 well BioRad 10% PAGE (polyacrylamide gel electrophoresis). The gel can be run for 1 hour at 100 volts. After completion of the run, the gel is removed from the casing and washed in 50 mL of 10% TBE (Tris base, boric acid and EDTA). Once washing is complete, 5 μL of SYBR Gold can be added to the gel, which is then allowed to incubate at room temperature for 10 minutes, and the gel-washed again in 50 mL of 10% TBE. In this exemplary assay, a Gel Doc XR+ gel documentation system may be used to read the gel using the following parameters: the imaging application set to SYBR Gold, the size set to Bio-Rad criterion gel, the exposure set to automatic for intense bands, the highlight saturated pixels may be turned one and the color is set to gray. The detection, molecular weight analysis, and output can all disabled. Once a clean photo of the gel is obtained Image Lab 5.2 may be used to process the image. The lanes and bands can be manually set to measure band intensity. Band intensities of each sample can be normalized to PBS to obtain the fraction of unbound siRNA. From this measurement relative hydrophobicity can determined. 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 improved 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 an 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, a "subject" is an animal, such as a mammal, including a primate (such as a human, a non-human primate, *e.g.*, a monkey, and a chimpanzee), or a non-primate (such as a rat, or a mouse). In a preferred embodiment, the subject is a human, such as a human being treated or assessed for a disease, disorder, or condition that would benefit from reduction in *LRRK2* expression; a human at risk for a disease,

disorder, or condition that would benefit from reduction in *LRRK2* expression; a human having a disease, disorder, or condition that would benefit from reduction in *LRRK2* expression; or human being treated for a disease, disorder, or condition that would benefit from reduction in *LRRK2* expression as described herein. In some embodiments, the subject is a female human. In other embodiments, the subject is a male human. In one embodiment, the subject is an adult subject. In one embodiment, the subject is a pediatric subject. In another embodiment, the subject is a juvenile subject, *i.e.*, a subject below 20 years of age.

As used herein, the terms "treating" or "treatment" refer to a beneficial or desired result including, but not limited to, alle*via*tion or amelioration of one or more signs or symptoms associated with *LRRK2* gene expression or LRRK2 protein production, *e.g.*, *LRRK2*-associated diseases, such as *LRRK2*-associated disease. "Treatment" can also mean prolonging survival as compared to expected survival in the absence of treatment.

The term "lower" in the context of the level of *LRRK2* in a subject or a disease marker or symptom refers to a statistically significant decrease in such level. The decrease can be, for example, at least 10%, 15%, 20%, 25%, 30%, %, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more. In certain embodiments, a decrease is at least 20%. In certain embodiments, the decrease is at least 50% in a disease marker, *e.g.*, the level of sense- or antisense-containing foci and/or the level of aberrant dipeptide repeat protein, *e.g.*, a decrease of 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more. In some embodiments, a decrease is at least about 25% in a disease marker, *e.g.*, LRRK2 protein and/or gene expression level is decreased by, *e.g.*, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95%. "Lower" in the context of the level of *LRRK2* in a subject is preferably down to a level accepted as within the range of normal for an individual without such disorder. In certain embodiments, "lower" is the decrease in the difference between the level of a marker or symptom for a subject suffering from a disease and a level accepted within the range of normal for an individual, *e.g.*, the level of decrease in bodyweight between an obese individual and an individual having a weight accepted within the range of normal.

As used herein, "prevention" or "preventing," when used in reference to a disease, disorder, or condition thereof, that would benefit from a reduction in expression of a *LRRK2* gene or production of a LRRK2 protein, refers to a reduction in the likelihood that a subject will develop a symptom associated with such a disease, disorder, or condition, *e.g.*, a symptom of a *LRRK2*-associated disease. The failure to develop a disease, disorder, or condition, or the reduction in the development of a symptom associated with such a disease, disorder, or condition (*e.g.*, by at least about 10% on a clinically accepted scale for that disease or disorder), or the exhibition of delayed symptoms delayed (*e.g.*, by days, weeks, months or years) is considered effective prevention.

As used herein, the term "*LRRK2*-associated disease" or "*LRRK2*-associated disorder" includes any disease or disorder that would benefit from reduction in the expression and/or activity of *LRRK2*. Exemplary *LRRK2*-associated diseases include those diseases in which subjects carry missense mutations and/or

deletions in the *LRRK2* gene, *e.g.,* Neurodegenerative disease such as Parkinson's disease (PD), Crohn's disease and ocular disorders. Neurodegenerative diseases include, but are not limited to, Parkinson's Disease, Amyotrophic Lateral Sclerosis (ALS), Alzheimer's Disease, Huntington's disease, Schizophrenia, progressive myoclonic epilepsy (Unver-Richt-Lundberg Lafora disease), Hallervorden-Spatz Disease, Retinitis Pigmentosa, Xeroderma Pigmentosum, and Melanin-related diseases. An "ocular disorder," or "ocular system disorder", as used herein referes to any disorder system of the eye and its visual system (*e.g.,* cornea, lens, and fluids). Non-limiting examples of ocular disorders include edema in the eyes, lens, and otic vesicles.

A *LRRK2* missense mutation, *e.g.,* G2019S, A2016T, may be found in subjects with either familial or sporadic Parkinson's disease. The mutations may lead to a two- or three-fold increase in kinase activity, which may result in activation of the neuronal death signaling pathway.

Subjects having missense mutations in the *LRRK2* gene can present as an autosomal dominant disease and is the most common form of familial PD, accounting for 1-2% of all PD cases. The common pathogenic mutations in *LRRK2* associated with PD reside in the GTPase and kinase domains with the most prevalent mutation, the G2019S mutation, in the kinase domain.

"Therapeutically effective amount," as used herein, is intended to include the amount of an RNAi agent that, when administered to a subject having a *LRRK2*-associated disease, is sufficient to effect treatment of the disease (*e.g.*, by diminishing, ameliorating, or maintaining the existing disease or one or more symptoms of disease). The "therapeutically effective amount" may vary depending on the RNAi agent, how the agent is administered, the disease and its severity and the history, age, weight, family history, genetic makeup, the types of preceding or concomitant treatments, if any, and other individual characteristics of the subject to be treated.

"Prophylactically effective amount," as used herein, is intended to include the amount of an RNAi agent that, when administered to a subject having a *LRRK2*-associated disorder, is sufficient to prevent or ameliorate the disease or one or more symptoms of the disease. Ameliorating the disease includes slowing the course of the disease or reducing the severity of later-developing disease. The "prophylactically effective amount" may vary depending on the RNAi agent, how the agent is administered, the degree of risk of disease, and the history, age, weight, family history, genetic makeup, the types of preceding or concomitant treatments, if any, and other individual characteristics of the patient to be treated.

A "therapeutically-effective amount" or "prophylactically effective amount" also includes an amount of an RNAi agent that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment. An RNAi agent employed in the methods of the present disclosure may be administered in a sufficient amount to produce a reasonable benefit/risk ratio applicable to such treatment.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, or dosage forms which are, within the scope of sound medical judgment, suitable

for use in contact with the tissues of human subjects and animal subjects without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (*e.g.*, lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject being treated. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) lubricating agents, such as magnesium state, sodium lauryl sulfate and talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates or polyanhydrides; (22) bulking agents, such as polypeptides and amino acids (23) serum component, such as serum albumin, HDL and LDL; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

The term "sample," as used herein, includes a collection of similar fluids, cells, or tissues isolated from a subject, as well as fluids, cells, or tissues present within a subject. Examples of biological fluids include blood, serum and serosal fluids, plasma, cerebrospinal fluid, ocular fluids, lymph, urine, saliva, and the like. Tissue samples may include samples from tissues, organs or localized regions. For example, samples may be derived from particular organs, parts of organs, or fluids or cells within those organs. In certain embodiments, samples may be derived from the brain (*e.g.*, whole brain or certain segments of brain, *e.g.*, striatum, or certain types of cells in the brain, such as, *e.g.*, neurons and glial cells (astrocytes, oligodendrocytes, microglial cells)). In some embodiments, a "sample derived from a subject" refers to blood drawn from the subject or plasma or serum derived therefrom. In further embodiments, a "sample derived from a subject" refers to brain tissue (or subcomponents thereof) or retinal tissue (or subcomponents thereof) derived from the subject.

The term "substituted" refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent including, but not limited to: alkyl, alkenyl, alkynyl, aryl, heterocyclyl, halo, thiol, alkylthio, arylthio, alkylthioalkyl, arylthioalkyl, alkylsulfonyl, alkylsulfonylalkyl, arylsulfonylalkyl, alkoxy, aryloxy, aralkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aryloxycarbonyl, haloalkyl, amino, trifluoromethyl, cyano, nitro, alkylamino, arylamino,

alkylaminoalkyl, arylaminoalkyl, aminoalkylamino, hydroxy, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, acyl, aralkoxycarbonyl, carboxylic acid, sulfonic acid, sulfonyl, phosphonic acid, aryl, heteroaryl, heterocyclic, and aliphatic. It is understood that the substituent can be further substituted.

The term "alkyl" refers to saturated and unsaturated non-aromatic hydrocarbon chains that may be a straight chain or branched chain, containing the indicated number of carbon atoms (these include without limitation propyl, allyl, or propargyl), which may be optionally inserted with N, O, or S. For example, "(C1-C6) alkyl" means a radical having from 1 6 carbon atoms in a linear or branched arrangement. "(C1-C6) alkyl" includes, for example, methyl, ethyl, propyl, iso-propyl, n-butyl, tert-butyl, pentyl and hexyl. In certain embodiments, a lipophilic moiety of the instant disclosure can include a C6-C18 alkyl hydrocarbon chain.

The term "alkylene" refers to an optionally substituted saturated aliphatic branched or straight chain divalent hydrocarbon radical having the specified number of carbon atoms. For example, "(C1-C6) alkylene" means a divalent saturated aliphatic radical having from 1-6 carbon atoms in a linear arrangement, e.g., $[(CH_2)_n]$, where n is an integer from 1 to 6. "(C1-C6) alkylene" includes methylene, ethylene, propylene, butylene, pentylene and hexylene. Alternatively, "(C1-C6) alkylene" means a divalent saturated radical having from 1-6 carbon atoms in a branched arrangement, for example: $[(CH_2CH_2CH_2CH_2CH(CH_3)]$, $[(CH_2CH_2CH_2CH_2C(CH_3)_2]$, $[(CH_2C(CH_3)_2CH(CH_3))]$, and the like. The term "alkylenedioxo" refers to a divalent species of the structure —O—R—O—, in which R represents an alkylene.

The term "mercapto" refers to an —SH radical. The term "thioalkoxy" refers to an —S— alkyl radical.

The term "halo" refers to any radical of fluorine, chlorine, bromine or iodine. "Halogen" and "halo" are used interchangeably herein.

As used herein, the term "cycloalkyl" means a saturated or unsaturated nonaromatic hydrocarbon ring group having from 3 to 14 carbon atoms, unless otherwise specified. For example, "(C3-C10) cycloalkyl" means a hydrocarbon radical of a (3-10)-membered saturated aliphatic cyclic hydrocarbon ring. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, etc. Cycloalkyls may include multiple spiro- or fused rings. Cycloalkyl groups are optionally mono-, di-, tri-, tetra-, or penta-substituted on any position as permitted by normal valency.

As used herein, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight or branched, containing at least one carbon-carbon double bond, and having from 2 to 10 carbon atoms unless otherwise specified. Up to five carbon-carbon double bonds may be present in such groups. For example, "C2-C6" alkenyl is defined as an alkenyl radical having from 2 to 6 carbon atoms. Examples of alkenyl groups include, but are not limited to, ethenyl, propenyl, butenyl, and cyclohexenyl. The straight, branched, or cyclic portion of the alkenyl group may contain double bonds and is optionally mono-, di-, tri-, tetra-, or

penta-substituted on any position as permitted by normal valency. The term "cycloalkenyl" means a monocyclic hydrocarbon group having the specified number of carbon atoms and at least one carbon-carbon double bond.

As used herein, the term "alkynyl" refers to a hydrocarbon radical, straight or branched, containing from 2 to 10 carbon atoms, unless otherwise specified, and containing at least one carbon-carbon triple bond. Up to 5 carbon-carbon triple bonds may be present. Thus, "C2-C6 alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Examples of alkynyl groups include, but are not limited to, ethynyl, 2-propynyl, and 2-butynyl. The straight or branched portion of the alkynyl group may contain triple bonds as permitted by normal valency, and may be optionally mono-, di-, tri-, tetra-, or penta-substituted on any position as permitted by normal valency.

As used herein, "alkoxyl" or "alkoxy" refers to an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. For example, "(C1-C3)alkoxy" includes methoxy, ethoxy and propoxy. For example, "(C1-C6)alkoxy", is intended to include C1, C2, C3, C4, C5, and C6 alkoxy groups. For example, "(C1-C8)alkoxy", is intended to include C1, C2, C3, C4, C5, C6, C7, and C8 alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, s-pentoxy, n-heptoxy, and n-octoxy. "Alkylthio" means an alkyl radical attached through a sulfur linking atom. The terms "alkylamino" or "aminoalkyl", means an alkyl radical attached through an NH linkage. "Dialkylamino" means two alkyl radical attached through a nitrogen linking atom. The amino groups may be unsubstituted, monosubstituted, or di-substituted. In some embodiments, the two alkyl radicals are the same (e.g., N,N-dimethylamino). In some embodiments, the two alkyl radicals are different (e.g., N-ethyl-N-methylamino).

As used herein, "aryl" or "aromatic" means any stable monocyclic or polycyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, anthracenyl, tetrahydronaphthyl, indanyl, and biphenyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring. Aryl groups are optionally mono-, di-, tri-, tetra-, or penta-substituted on any position as permitted by normal valency. The term "arylalkyl" or the term "aralkyl" refers to alkyl substituted with an aryl. The term "arylalkoxy" refers to an alkoxy substituted with aryl.

"Hetero" refers to the replacement of at least one carbon atom in a ring system with at least one heteroatom selected from N, S and O. "Hetero" also refers to the replacement of at least one carbon atom in an acyclic system. A hetero ring system or a hetero acyclic system may have, for example, 1, 2 or 3 carbon atoms replaced by a heteroatom.

As used herein, the term "heteroaryl" represents a stable monocyclic or polycyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Examples of heteroaryl groups include, but are not limited to, acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl,

benzofuranyl, benzimidazolonyl, benzoxazolonyl, quinolinyl, isoquinolinyl, dihydroisoindolonyl, imidazopyridinyl, isoindolonyl, indazolyl, oxazolyl, oxadiazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline. "Heteroaryl" is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring. Heteroaryl groups are optionally mono-, di-, tri-, tetra-, or penta-substituted on any position as permitted by normal valency.

As used herein, the term "heterocycle," "heterocyclic," or "heterocyclyl" means a 3- to 14-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, including polycyclic groups. As used herein, the term "heterocyclic" is also considered to be synonymous with the terms "heterocycle" and "heterocyclyl" and is understood as also having the same definitions set forth herein. "Heterocyclyl" includes the above mentioned heteroaryls, as well as dihydro and tetrahydro analogs thereof. Examples of heterocyclyl groups include, but are not limited to, azetidinyl, benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxooxazolidinyl, oxazolyl, oxazoline, oxopiperazinyl, oxopyrrolidinyl, oxomorpholinyl, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyridinonyl, pyrimidyl, pyrimidinonyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrahydrofuranyl, tetrahydrothiopyranyl, tetrahydroisoquinolinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, dioxidothiomorpholinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom. Heterocyclyl groups are optionally mono-, di-, tri-, tetra-, or penta-substituted on any position as permitted by normal valency.

"Heterocycloalkyl" refers to a cycloalkyl residue in which one to four of the carbons is replaced by a heteroatom such as oxygen, nitrogen or sulfur. Examples of heterocycles whose radicals are heterocyclyl groups include tetrahydropyran, morpholine, pyrrolidine, piperidine, thiazolidine, oxazole, oxazoline, isoxazole, dioxane, tetrahydrofuran and the like.

The term "heteroaryl" refers to an aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or

1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2, 3, or 4 atoms of each ring may be substituted by a substituent. Examples of heteroaryl groups include pyridyl, furyl or furanyl, imidazolyl, benzimidazolyl, pyrimidinyl, thiophenyl or thienyl, quinolinyl, indolyl, thiazolyl, and the like. The term "heteroarylalkyl" or the term "heteroaralkyl" refers to an alkyl substituted with a heteroaryl. The term "heteroarylalkoxy" refers to an alkoxy substituted with heteroaryl.

The term "cycloalkyl" as employed herein includes saturated and partially unsaturated cyclic hydrocarbon groups having 3 to 12 carbons, for example, 3 to 8 carbons, and, for example, 3 to 6 carbons, wherein the cycloalkyl group additionally may be optionally substituted. Cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

The term "acyl" refers to an alkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, or heteroarylcarbonyl substituent, any of which may be further substituted by substituents.

As used herein, "keto" refers to any alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, heteroaryl, or aryl group as defined herein attached through a carbonyl bridge.

Examples of keto groups include, but are not limited to, alkanoyl (e.g., acetyl, propionyl, butanoyl, pentanoyl, hexanoyl), alkenoyl (e.g., acryloyl) alkynoyl (e.g., ethynoyl, propynoyl, butynoyl, pentynoyl, hexynoyl), aryloyl (e.g., benzoyl), heteroaryloyl (e.g., pyrroloyl, imidazoloyl, quinolinoyl, pyridinoyl).

As used herein, "alkoxycarbonyl" refers to any alkoxy group as defined above attached through a carbonyl bridge (i.e., —C(O)O-alkyl). Examples of alkoxycarbonyl groups include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, iso-propoxycarbonyl, n-propoxycarbonyl, t-butoxycarbonyl, benzyloxycarbonyl or n-pentoxycarbonyl.

As used herein, "aryloxycarbonyl" refers to any aryl group as defined herein attached through an oxycarbonyl bridge (i.e., —C(O)O-aryl). Examples of aryloxycarbonyl groups include, but are not limited to, phenoxycarbonyl and naphthyloxycarbonyl.

As used herein, "heteroaryloxycarbonyl" refers to any heteroaryl group as defined herein attached through an oxycarbonyl bridge (i.e., —C(O)O-heteroaryl). Examples of heteroaryloxycarbonyl groups include, but are not limited to, 2-pyridyloxycarbonyl, 2-oxazolyloxycarbonyl, 4-thiazolyloxycarbonyl, or pyrimidinyloxycarbonyl.

The term "oxo" refers to an oxygen atom, which forms a carbonyl when attached to carbon, an N-oxide when attached to nitrogen, and a sulfoxide or sulfone when attached to sulfur.

The person of ordinary skill in the art would readily understand and appreciate that the compounds and compositions disclosed herein may have certain atoms (e.g., N, O, or S atoms) in a protonated or deprotonated state, depending upon the environment in which the compound or composition is placed. Accordingly, as used herein, the structures disclosed herein envisage that certain functional groups, such as, for example, OH, SH, or NH, may be protonated or deprotonated. The disclosure herein is intended to cover

the disclosed compounds and compositions regardless of their state of protonation based on the pH of the environment, as would be readily understood by the person of ordinary skill in the art.

II. RNAi Agents of the Disclosure

Described herein are RNAi agents that inhibit the expression of a *LRRK2* gene. In one embodiment, the RNAi agent includes double stranded ribonucleic acid (dsRNA) molecules for inhibiting the expression of a *LRRK2* gene in a cell, such as a cell within a subject, *e.g.*, a mammal, such as a human having a *LRRK2*-associated disease. 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 a *LRRK2* gene. The region of complementarity is about 15-30 nucleotides or less in length. Upon contact with a cell expressing the *LRRK2* gene, the RNAi agent inhibits the expression of the *LRRK2* gene (*e.g.*, a human gene, a primate gene, a non-primate gene) by at least 25%, or higher as described herein, when compared to a similar cell not contacted with the RNAi agent or an RNAi agent not complementary to the *LRRK2* gene. Expression of the *LRRK2* gene may be assayed by, for example, a PCR or branched DNA (bDNA)-based method, or by a protein-based method, such as by immunofluorescence analysis, using, for example, western blotting or flowcytometric techniques. In one embodiment, the level of knockdown is assayed in human A549 cells using an assay method provided in Example 1 below. In some embodiments, the level of knockdown is assayed in primary mouse hepatocytes. In another embodiment, the level of knockdown is assayed in Cos-7. In yet another embodiment, the level of knockdown is assayed in BE(2)-C cells. In some embodiments, the level of knockdown is assayed in Neuro-2a cells. In some embodiments, the level of knockdown is assayed in A549 cells.

A dsRNA includes two RNA strands that are complementary and hybridize to form a duplex structure under conditions in which the dsRNA is used. One strand of a dsRNA (the antisense strand) includes a region of complementarity that is substantially complementary, or fully complementary, to a target sequence. The target sequence can be derived from the sequence of an mRNA formed during the expression of a *LRRK2* gene. The other strand (the sense strand) 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. 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.

Generally, the duplex structure is 15 to 30 base pairs in length, *e.g.*, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs in length. In certain embodiments, the duplex structure is 18 to 25 base pairs in length, *e.g.*, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-25, 19-24, 19-23, 19-22, 19-21,

19-20, 20-25, 20-24,20-23, 20-22, 20-21, 21-25, 21-24, 21-23, 21-22, 22-25, 22-24, 22-23, 23-25, 23-24 or 24-25 base pairs in length, for example, 19-21 basepairs in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

Similarly, the region of complementarity to the target sequence is 15 to 30 nucleotides in length, *e.g.*, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 nucleotides in length, for example 19-23 nucleotides in length or 21-23 nucleotides in length. Ranges and lengths intermediate to the above recited ranges and lengths are also contemplated to be part of the disclosure.

In some embodiments, the duplex structure is 19 to 30 base pairs in length. Similarly, the region of complementarity to the target sequence is 19 to 30 nucleotides in length.

In some embodiments, the dsRNA is 15 to 23 nucleotides in length, 19 to 23 nucleotides in length, or 25 to 30 nucleotides in length. In general, the dsRNA is long enough to serve as a substrate for the Dicer enzyme. For example, it is well known in the art that dsRNAs longer than about 21-23 nucleotides can serve as substrates for Dicer. As the ordinarily skilled person also recognizes, the region of an RNA targeted for cleavage is 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 allow it to be a substrate for RNAi-directed cleavage (*i.e.*, cleavage through a RISC pathway).

One of skill in the art also recognizes that the duplex region is a primary functional portion of a dsRNA, *e.g.*, a duplex region of about 15 to 36 base pairs, *e.g.*, 15-36, 15-35, 15-34, 15-33, 15-32, 15-31, 15-30, 15-29, 15-28, 15-27, 15-26, 15-25, 15-24, 15-23, 15-22, 15-21, 15-20, 15-19, 15-18, 15-17, 18-30, 18-29, 18-28, 18-27, 18-26, 18-25, 18-24, 18-23, 18-22, 18-21, 18-20, 19-30, 19-29, 19-28, 19-27, 19-26, 19-25, 19-24, 19-23, 19-22, 19-21, 19-20, 20-30, 20-29, 20-28, 20-27, 20-26, 20-25, 20-24,20-23, 20-22, 20-21, 21-30, 21-29, 21-28, 21-27, 21-26, 21-25, 21-24, 21-23, or 21-22 base pairs, for example, 19-21 base pairs. Thus, in one embodiment, 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 recognizes that in one embodiment, a miRNA is a dsRNA. In another embodiment, a dsRNA is not a naturally occurring miRNA. In another embodiment, an RNAi agent useful to target *LRRK2* expression is not generated in the target cell by cleavage of a larger dsRNA.

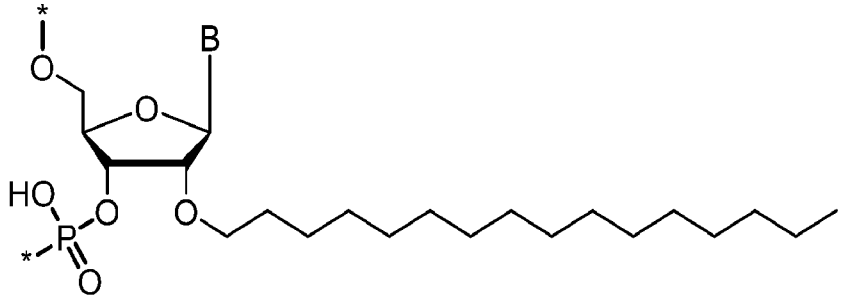
A dsRNA as described herein can further include one or more single-stranded nucleotide overhangs *e.g.*, 1, 2, 3, or 4 nucleotides. A nucleotide overhang can comprise or consist of a nucleotide/nucleoside analog, including a deoxynucleotide/nucleoside. The overhang(s) can be on the sense strand, the 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.

A dsRNA can be synthesized by standard methods known in the art. Double stranded RNAi compounds of the invention may be prepared using a two-step procedure. First, the individual strands of the double stranded RNA molecule are prepared separately. Then, the component strands are annealed. The individual strands of the dsRNA compound can be prepared using solution-phase or solid-phase organic synthesis or both. Organic synthesis offers the advantage that the oligonucleotide strands comprising unnatural or modified nucleotides can be easily prepared. Similarly, single-stranded oligonucleotides of the invention can be prepared using solution-phase or solid-phase organic synthesis or both.

In one aspect, a dsRNA of the disclosure includes at least two nucleotide sequences, a sense sequence and an antisense sequence. The sense strand sequence for *LRRK2* may be selected from the group of sequences provided in any one of Tables 3-7, and the corresponding nucleotide sequence of the antisense strand of the sense strand may be selected from the group of sequences of any one of Tables 3-7. In this aspect, 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 in the expression of a *LRRK2* gene. As such, in this aspect, a dsRNA includes two oligonucleotides, where one oligonucleotide is described as the sense strand (passenger strand) in any one of Tables 3-7, and the second oligonucleotide is described as the corresponding antisense strand (guide strand) of the sense strand in any one of Tables 3-7.

In one embodiment, the substantially complementary sequences of the dsRNA are contained on separate oligonucleotides. In another embodiment, the substantially complementary sequences of the dsRNA are contained on a single oligonucleotide.

It will be understood that, although the sequences in Table 5 and 7 are described as modified or conjugated sequences, the RNA of the RNAi agent of the disclosure *e.g.*, a dsRNA of the disclosure, may comprise any one of the sequences set forth in any one of Tables 3-4 and 6 that is un-modified, un-conjugated, or modified or conjugated differently than described therein. For example, although the sense strands of the agents of the invention may be conjugated to a GalNAc ligand, these agents may be conjugated to a moiety that directs delivery to the CNS, *e.g.*, a C16 ligand, as described herein. In one embodiment, the lipophilic moiety contains a saturated or unsaturated C16 hydrocarbon chain (e.g., a linear C16 alkyl or alkenyl). A lipophilic ligand can be included in any of the positions provided in the instant application. In some embodiments, the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage of the double-stranded iRNA agent. For example, a C16 ligand may be conjugated via the 2'-oxygen of a ribonucleotide as shown in the following structure:



where * denotes a bond to an adjacent nucleotide, and B is a nucleobase or a nucleobase analog, optionally where B is adenine, guanine, cytosine, thymine or uracil. Design and Synthesis of the ligands and monomers provided herein are described, for example, in PCT publication Nos. WO2019/217459, WO2020/132227, and WO2020/257194, contents of which are incorporated herein by reference in their entirety.

In some embodiments, the double-stranded iRNA agent further comprises a phosphate or phosphate mimic at the 5'-end of the antisense strand. In one embodiment, the phosphate mimic is a 5'-vinyl phosphonate (VP). In some embodiments, the 5'-end of the antisense strand of the double-stranded iRNA agent does not contain a 5'-vinyl phosphonate (VP).

The skilled person is well aware that dsRNAs having a duplex structure of about 20 to 23 base pairs, *e.g.,* 21, base pairs have been hailed as particularly effective in inducing RNA interference (Elbashir *et al.*, (2001) *EMBO J.*, 20:6877-6888). However, others have found that shorter or longer RNA duplex structures can also be effective (Chu and Rana (2007) *RNA* 14:1714-1719; Kim *et al.* (2005) *Nat Biotech* 23:222-226). In the embodiments described above, by virtue of the nature of the oligonucleotide sequences provided herein, dsRNAs described herein can include at least one strand of a length of minimally 21 nucleotides. It can be reasonably expected that shorter duplexes minus only a few nucleotides on one or both ends can be similarly effective as compared to the dsRNAs described above. Hence, dsRNAs having a sequence of at least 15, 16, 17, 18, 19, 20, or more contiguous nucleotides derived from one of the sequences provided herein, and differing in their ability to inhibit the expression of a *LRRK2* gene by at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95%inhibition relative to a control level, from a dsRNA comprising the full sequence using the *in vitro* assay with, *e.g.,* A549 cells and a 10 nM concentration of the RNA agent and the PCR assay as provided in the examples herein, are contemplated to be within the scope of the present disclosure. In some embodiments, inhibition from a dsRNA comprising the full sequence was measured using the *in vitro* assay with primary mouse hepatocytes.

In addition, the RNA agents described herein identify a site(s) in a *LRRK2* mRNA transcript that is susceptible to RISC-mediated cleavage. As such, the present disclosure further features RNAi agents that target within this site(s). As used herein, an RNAi agent is said to "target within" a particular site of an mRNA transcript if the RNAi agent promotes cleavage of the mRNA transcript anywhere within that particular site. Such an RNAi agent generally includes at least about 15 contiguous nucleotides, preferably

at least 19 nucleotides, from one of the sequences provided herein coupled to additional nucleotide sequences taken from the region contiguous to the selected sequence in a *LRRK2* gene.

An RNA target may have regions, or spans of the target RNA's nucleotide sequence, which are relatively more susceptible or amenable than other regions of the RNA target to mediating cleavage of the RNA target via RNA interference induced by the binding of an RNAi agent to that region. The increased susceptibility to RNA interference within such "hotspot regions" (or simply "hotspots") means that iRNA agents targeting the region will likely have higher efficacy in inducing iRNA interference than iRNA agents which target other regions of the target RNA. For example, without being bound by theory, the accessibility of a target region of a target RNA may influence the efficacy of iRNA agents which target that region, with some hotspot regions having increased accessibility. Secondary structures, for instance, that form in the RNA target (e.g., within or proximate to hotspot regions) may affect the ability of the iRNA agent to bind the target region and induce RNA interference.

According to certain aspects of the invention, an iRNA agent may be designed to target a hotspot region of any of the target RNAs described herein, including any identified portions of a target RNA (e.g., a particular exon). As used herein, a hotspot region may refer to an approximately 19-200, 19-150, 19-100, 19-75, 19-50, 21-200, 21-150, 21-100, 21-75, 21-50, 50-200, 50-150, 50-100, 50-75, 75-200, 75-150, 75-100, 100-200, or 100-150 nucleotide region of a target RNA sequence for which targeting using RNAi agents provides an observably higher probability of efficacious silencing relative to targeting other regions of the same target RNA. According to certain aspects of the invention, a hotspot region may comprise a limited region of the target RNA, and in some cases, a substantially limited region of the target, including for example, less than half of the length of the target RNA, such as about 5%, 10%, 15%, 20%, 25%, or 30% of the length of the target RNA. Conversely, the other regions against which a hotspot is compared may cumulatively comprise at least a majority of the length of the target RNA. For example, the other regions may cumulatively comprise at least about 60%, or at least about 70%, or at least about 80%, or at least about 90%, or at least about 95% of the length of the target RNA.

Compared regions of the target RNA may be empirically evaluated for identification of hotspots using efficacy data obtained from in vitro or in vivo screening assays. For example, RNAi agents targeting various regions that span a target RNA may be compared for frequency of efficacious iRNA agents (e.g., the amount by which target gene expression is inhibited, such as measured by mRNA expression or protein expression) that bind each region. In general, a hotspot can be recognized by observing clustering of multiple efficacious RNAi agents that bind to a limited region of the RNA target. A hotspot may be sufficiently characterized as such by observing efficacy of iRNA agents which cumulatively span at least about 60% of the target region identified as a hotspot, such as about 70%, about 80%, about 90%, or about 95% or more of the length of the region, including both ends of the region (i.e. at least about 60%, 70%, 80%, 90%, or 95% or more of

the nucleotides within the region, including the nucleotides at each end of the region, were targeted by an iRNA agent). According to some aspects of the invention, an iRNA agent which demonstrates at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% inhibition over the region (e.g., no more than about 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, or 5% mRNA remaining) may be identified as efficacious.

Amenability to targeting of RNA regions may also be assessed using quantitative comparison of inhibition measurements across different regions of a defined size (e.g., 25, 30, 40, 50, 60, 70, 80, 90, or 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, or 200 nts). For example, an average level of inhibition may be determined for each region and the averages of each region may be compared. The average level of inhibition within a hotspot region may be substantially higher than the average of averages for all evaluated regions. According to some aspects, the average level of inhibition in a hotspot region may be at least about 10%, 20%, 30%, 40%, or 50% higher than the average of averages. According to some aspects, the average level of inhibition in a hotspot region may be at least about 1.0, 1.1, 1.2, 1.3, 1.4, 1.5 1.6, 1.7, 1.8. 1.9, or 2.0 standard deviations above the average of averages. The average level of inhibition may be higher by a statistically significant (e.g., $p < 0.05$) amount. According to some aspects, each inhibition measurement within a hotspot region may be above a threshold amount (e.g., at or below a threshold amount of mRNA remaining). According to some aspects, each inhibition measurement within the region may be substantially higher than an average of all inhibition measurements across all the measured regions. For example, each inhibition measurement in a hotspot region may be at least about 10%, 20%, 30%, 40%, or 50% higher than the average of all inhibition measurements. According to some aspects, each inhibition measurement may be at least about 1.0, 1.1, 1.2, 1.3, 1.4, 1.5 1.6, 1.7, 1.8. 1.9, or 2.0 standard deviations above the average of all inhibition measurements. Each inhibition measurement may be higher by a statistically significant (e.g., $p < 0.05$) amount than the average of all inhibition measurements. A standard for evaluating a hotspot may comprise various combinations of the above standards where compatible (e.g., an average level of inhibition of at least about a first amount and having no inhibition measurements below a threshold level of a second amount, lesser than the first amount).

It is therefore expressly contemplated that any iRNA agent, including the specific exemplary iRNA agents described herein, which targets a hotspot region of a target RNA, may be preferably selected for inducing RNA interference of the target mRNA as targeting such a hotspot region is likely to exhibit a robust inhibitory response relative to targeting a region which is not a hotspot region. RNAi agents targeting target sequences that substantially overlap (e.g., by at least about 70%, 75%, 80%, 85%, 90%, 95% of the target sequence length) or, preferably, that reside fully within the hotspot region may be considered to target the hotspot region. Hotspot regions of the RNA target(s) of the instant invention may include any region for which the data disclosed herein demonstrates higher frequency of targeting by efficacious RNAi agents,

including by any of the standards described elsewhere herein, whether or not the range(s) of such hotspot region(s) are explicitly specified.

In various embodiments, a dsRNA agent of the present invention targets a hotspot region of an mRNA encoding LRRK2. In one embodiment, the hotspot region comprises nucleotides 3620-3652, 3794-3849, 5194-5222, 5366-5393, 5423-5463, 5674-5704, 5720-5745, 6090-6114, 6125-6156, 6518-6561, 6721-6750, 6740-6763, 7016-7061, 7083-7123, 7112-7136, 7125-7169, 7346-7373, 7441-7465, 7591-7659, 7636-7659, 8132-8155, 3627-3650, 5194-5222, 5674-5702, 5720-5745, 6091-6114, 6529-6559, 7034-7061, 7441-7465, and 7636-7659 of SEQ ID NO: 1. The dsRNA agent may be selected from the group consisting of AD-1627308, AD-1631049, AD-1631050, AD-1626349, AD-1626353, AD-1626375, AD-1626382, AD-1631080, AD-1807348, AD-1807393, AD-1631088, AD-1631089, AD-1631090, AD-1631108, AD-1807416, AD-1807371, AD-1627767, AD-1627769, AD-1627772, AD-1631109, AD-1631110, AD-1631111, AD-1627820, AD-1627838, , AD-1628042, AD-1628043, AD-1628044, AD-1628050, AD-1628052,, AD-1628070, AD-1631108, AD-1631109, AD-1631110, AD-1631111, AD-1807397, AD-1807352, , AD-1628073, AD-1807374, AD-1807419, AD-1628381, AD-1628382, AD-1628383, AD-1631131, AD-1631132, AD-1631133, AD-1628396, AD-1807361, AD-1807406, AD-1631150, AD-1631151, AD-1631152, AD-1631153, AD-1631154, AD-1631155, AD-1631156, AD-1631157, AD-1631158, AD-1631160, AD-1631161, AD-1631162, AD-1807357, AD-1807402, AD-1628961, AD-1628963, AD-1629214, AD-1629216, AD-1629223, AD-1629224, AD-1629263, AD-1629280, AD-1631194, AD-1631195, AD-1631196, AD-1631197, AD-1807363, AD-1807408, AD-1629304, AD-1629524, AD-1631205, AD-1631206, AD-1807337, AD-1807354, AD-1807382, AD-1807399, AD-1629619, AD-1629620, AD-1629621, AD-1631210, AD-1807355, AD-1807377, AD-1807400, AD-1807422, AD-1629763, AD-1631215, AD-1631216, AD-1631217, AD-1807335, AD-1807336, AD-1807376, AD-1807380, AD-1807381, AD-1807421, AD-1630135, AD-1630136, AD-1631221, AD-1807369, AD-1807414, AD-1807364, AD-1807409, AD-1629808, and AD-1629809.

III. Modified RNAi Agents of the Disclosure

In one embodiment, the RNA of the RNAi agent of the disclosure *e.g.*, a dsRNA, is un-modified, and does not comprise modified nucleotides, *e.g.*, chemical modifications or conjugations known in the art and described herein. In preferred embodiments, the RNA of an RNAi agent of the disclosure, *e.g.*, a dsRNA, is chemically modified to enhance stability or other beneficial characteristics. In certain embodiments of the disclosure, substantially all of the nucleotides of an RNAi agent of the disclosure are modified. In other embodiments of the disclosure, all of the nucleotides of an RNAi agent of the disclosure are modified. RNAi agents of the disclosure in which "substantially all of the nucleotides are modified" are largely but not wholly modified and can include not more than 5, 4, 3, 2, or unmodified nucleotides. In still other embodiments of the disclosure, RNAi agents of the disclosure can include not more than 5, 4, 3, 2 or 1 modified nucleotides.

The nucleic acids featured in the disclosure can be synthesized 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, end modifications, *e.g.*, 5'-end modifications (phosphorylation, conjugation, inverted linkages) or 3'-end modifications (conjugation, DNA nucleotides, inverted linkages, *etc.*); 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; sugar modifications (*e.g.*, at the 2'-position or 4'-position) or replacement of the sugar; or backbone modifications, including modification or replacement of the phosphodiester linkages. Specific examples of RNAi agents useful in the embodiments described herein 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 some embodiments, a modified RNAi agent has 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. In some embodiments of the invention, the dsRNA agents of the invention are in a free acid form. In other embodiments of the invention, the dsRNA agents of the invention are in a salt form. In one embodiment, the dsRNA agents of the invention are in a sodium salt form. In certain embodiments, when the dsRNA agents of the invention are in the sodium salt form, sodium ions are present in the agent as counterions for substantially all of the phosphodiester and/or phosphorothiotate groups present in the agent. Agents in which substantially all of the phosphodiester and/or phosphorothioate linkages have a sodium counterion include not more than 5, 4, 3, 2, or 1 phosphodiester and/or phosphorothioate linkages without a sodium counterion. In some embodiments, when the dsRNA agents of the invention are in the sodium salt form, sodium ions are present in the agent as counterions for all of the phosphodiester and/or phosphorothiotate groups present in the agent.

Representative U.S. patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S. Patent 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, the entire contents of each of which are hereby incorporated herein 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. Patent 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, the entire contents of each of which are hereby incorporated herein by reference.

In other embodiments, suitable RNA mimetics are contemplated for use in RNAi agents, in which both the sugar and the internucleoside linkage, *i.e.*, the backbone, of the nucleotide units are replaced with alternate groups. The nucleobase units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, a 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. Patent Nos. 5,539,082; 5,714,331; and 5,719,262, the entire contents of each of which are hereby incorporated herein by reference. Additional PNA compounds suitable for use in the RNAi agents of the disclosure are described in, 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-- of the above-referenced U.S. Patent No. 5,489,677, and the amide backbones of the above-referenced U.S. Patent No. 5,602,240. In some embodiments, the RNAs featured herein have morpholino backbone structures of the above-referenced US5,034,506. The native phosphodiester backbone can be represented as -O-P(O)(OH)-OCH_2-.

Modified RNAs can also contain one or more substituted sugar moieties. The RNAi agents, *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 can be substituted or unsubstituted C_1 to C_{10} alkyl or C_2 to C_{10} alkenyl and alkynyl. Exemplary suitable modifications include $O[(CH_2)_nO]_mCH_3$, $O(CH_2)_nOCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nONH_2$, 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} alkyl, substituted 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 RNAi agent, or a group for improving the pharmacodynamic properties of an RNAi agent, 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, as described in examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), *i.e.*, 2'-O--CH_2--O--CH_2--$N(CH_3)_2$. Further exemplary modifications include: 5'-Me-2'-F nucleotides, 5'-Me-2'-OMe nucleotides, 5'-Me-2'-deoxynucleotides, (both R and S isomers in these three families); 2'-alkoxyalkyl; and 2'-NMA (N-methylacetamide).

Other modifications include 2'-methoxy (2'-OCH_3), 2'-aminopropoxy (2'-$OCH_2CH_2CH_2NH_2$), 2'-O-hexadecyl, and 2'-fluoro (2'-F). Similar modifications can also be made at other positions on the RNA of an RNAi agent, 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. RNAi agents can 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. The entire contents of each of the foregoing are hereby incorporated herein by reference.

An RNAi agent of the disclosure can 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 modified 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.*, (1991) *Angewandte Chemie, International Edition*, 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 modified 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 O-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. Patent Nos. 3,687,808, 4,845,205; 5,130,302; 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; 5,750,692; 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, the entire contents of each of which are hereby incorporated herein by reference.

An RNAi agent of the disclosure can also be modified to include one or more bicyclic sugar moieties. 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 (LNA). A locked nucleic acid is a nucleotide having a modified ribose moiety in which the ribose moiety comprises an extra bridge connecting the 2' and 4' carbons. In other words, an LNA is a nucleotide comprising a bicyclic sugar moiety comprising a 4'-CH2-O-2' bridge. 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, 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′-(CH_2)—O-2′ (LNA); 4′-(CH_2)—S-2′; 4′-(CH_2)$_2$—O-2′ (ENA); 4′-CH(CH_3)—O-2′ (also referred to as "constrained ethyl" or "cEt") and 4′-CH(CH_2OCH_3)—O-2′ (and analogs thereof; see, *e.g.*, U.S. Pat. No. 7,399,845); 4′-C(CH_3)(CH_3)—O-2′ (and analogs thereof; see *e.g.*, US Patent No. 8,278,283); 4′-CH_2—N(OCH_3)-2′ (and analogs thereof; see *e.g.*, US Patent No. 8,278,425); 4′-CH_2—O—N(CH_3)-2′ (see, *e.g.*,U.S. Patent Publication No. 2004/0171570); 4′-CH_2—N(R)—O-2′, wherein R is H, C_1-C_{12} alkyl, or a protecting group (see, *e.g.*, U.S. Pat. No. 7,427,672); 4′-CH_2—C(H)(CH_3)-2′ (see, *e.g.*, Chattopadhyaya *et al., J. Org. Chem.*, 2009, 74, 118-134); and 4′-CH_2—C(=CH_2)-2′ (and analogs thereof; see, *e.g.*, US Patent No. 8,278,426). The entire contents of each of the foregoing are hereby incorporated herein by reference.

Additional representative US Patents and US Patent Publications that teach the preparation of locked nucleic acid nucleotides include, but are not limited to, the following: US Patent Nos. 6,268,490; 6,525,191; 6,670,461; 6,770,748; 6,794,499; 6,998,484; 7,053,207; 7,034,133;7,084,125; 7,399,845; 7,427,672; 7,569,686; 7,741,457; 8,022,193; 8,030,467; 8,278,425; 8,278,426; 8,278,283; US 2008/0039618; and US 2009/0012281, the entire contents of each of which are hereby incorporated herein by reference.

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).

An 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(CH_3)-O-2' bridge. In one embodiment, a constrained ethyl nucleotide is in the S conformation referred to herein as "S-cEt."

An 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 entire contents of each of which are hereby incorporated herein by reference.

In some embodiments, an 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 hereby incorporated by reference).

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 entire contents of each of which are hereby incorporated herein by reference.

An RNAi agent of the disclosure may also include one or more "cyclohexene nucleic acids" or ("CeNA"). CeNA are nucleotide analogs with a replacement of the furanose moiety of DNA by a cyclohexene ring. Incorporation of cylcohexenyl nucleosides in a DNA chain increases the stability of a DNA/RNA hybrid. CeNA is stable against degradation in serum and a CeNA/RNA hybrid is able to activate E. Coli RNase H, resulting in cleavage of the RNA strand. (see Wang et al., *Am. Chem. Soc. 2000, 122, 36, 8595–8602,* hereby incorporated by reference).

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 WO 2011/005861.

Other modifications of an 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 an RNAi agent. Suitable phosphate mimics are disclosed in, for example US 2012/0157511, the entire contents of which are incorporated herein by reference.

A. Modified RNAi agents Comprising Motifs of the Disclosure

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 entire contents of which are incorporated herein by reference. As shown herein and in WO 2013/075035, one or more motifs of three identical modifications on three consecutive nucleotides may be introduced 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 ligand, *e.g.,* a C16 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 may present improved gene silencing activity.

Accordingly, the disclosure provides double stranded RNAi agents capable of inhibiting the expression of a target gene (*i.e.,* a *LRRK2* gene) *in vivo*. The RNAi agent comprises a sense strand and an antisense strand. Each strand of the RNAi agent may be 15-30 nucleotides in length. For example, each strand may be 16-30 nucleotides in length, 17-30 nucleotides in length, 25-30 nucleotides in length, 27-30

nucleotides in length, 17-23 nucleotides in length, 17-21 nucleotides in length, 17-19 nucleotides in length, 19-25 nucleotides in length, 19-23 nucleotides in length, 19-21 nucleotides in length, 21-25 nucleotides in length, or 21-23 nucleotides in length. In certain embodiments, each strand is 19-23 nucleotides in length.

The sense strand and antisense strand typically form a duplex double stranded RNA ("dsRNA"), also referred to herein as an "RNAi agent." The duplex region of an RNAi agent may be 15-30 nucleotide pairs in length. For example, the duplex region can be 16-30 nucleotide pairs in length, 17-30 nucleotide pairs in length, 27-30 nucleotide pairs in length, 17 - 23 nucleotide pairs in length, 17-21 nucleotide pairs in length, 17-19 nucleotide pairs in length, 19-25 nucleotide pairs in length, 19-23 nucleotide pairs in length, 19- 21 nucleotide pairs in length, 21-25 nucleotide pairs in length, or 21-23 nucleotide pairs in length. In another example, the duplex region is selected from 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, and 27 nucleotides in length. In preferred embodiments, the duplex region is 19-21 nucleotide pairs in length.

In one embodiment, the RNAi agent may contain one or more overhang regions or capping groups at the 3'-end, 5'-end, or both ends of one or both strands. The overhang can be 1-6 nucleotides in length, for instance 2-6 nucleotides in length, 1-5 nucleotides in length, 2-5 nucleotides in length, 1-4 nucleotides in length, 2-4 nucleotides in length, 1-3 nucleotides in length, 2-3 nucleotides in length, or 1-2 nucleotides in length. In preferred embodiments, the nucleotide overhang region is 2 nucleotides in length. The overhangs can be the result of one strand being longer than the other, or the result of two strands of the same length being staggered. The overhang can form a mismatch with the target mRNA or it can be complementary to the gene sequences being targeted or can be another sequence. The first and second strands can also be joined, *e.g.*, by additional bases to form a hairpin, or by other non-base linkers.

In one embodiment, the nucleotides in the overhang region of the RNAi agent can each independently be a modified or unmodified nucleotide including, but no limited to 2'-sugar modified, such as, 2-F, 2'-O-methyl, thymidine (T), and any combinations thereof.

For example, TT can be an overhang sequence for either end on either strand. The overhang can form a mismatch with the target mRNA or it can be complementary to the gene sequences being targeted or can be another sequence.

The 5'- or 3'- overhangs at the sense strand, antisense strand or both strands of the RNAi agent may be phosphorylated. In some embodiments, the overhang region(s) contains two nucleotides having a phosphorothioate between the two nucleotides, where the two nucleotides can be the same or different. In one embodiment, the overhang is present at the 3'-end of the sense strand, antisense strand, or both strands. In one embodiment, this 3'-overhang is present in the antisense strand. In one embodiment, this 3'-overhang is present in the sense strand.

The RNAi agent may contain only a single overhang, which can strengthen the interference activity of the RNAi, without affecting its overall stability. For example, the single-stranded overhang may be located at the 3'-terminal end of the sense strand or, alternatively, at the 3'-terminal end of the antisense strand. The RNAi may also have a blunt end, located at the 5'-end of the antisense strand (i.e., the 3'-end of the sense

strand) or *vice versa*. Generally, the antisense strand of the RNAi has a nucleotide overhang at the 3'-end, and the 5'-end is blunt. While not wishing to be bound by theory, the asymmetric blunt end at the 5'-end of the antisense strand and 3'-end overhang of the antisense strand favor the guide strand loading into RISC process.

In one embodiment, the RNAi agent is double blunt-ended and 19 nucleotides in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 7, 8, and 9 from the 5'end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, and 13 from the 5'end.

In another embodiment, the RNAi agent is double blunt-ended and 20 nucleotides in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 8, 9, and 10 from the 5'end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, and 13 from the 5'end.

In yet another embodiment, the RNAi agent is double blunt-ended and 21 nucleotides in length, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 9, 10, and 11 from the 5'end. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, and 13 from the 5'end.

In one embodiment, the RNAi agent comprises a 21 nucleotide sense strand and a 23 nucleotide antisense strand, wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides at positions 9, 10, and 11 from the 5'end; the antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at positions 11, 12, and 13 from the 5'end, wherein one end of the RNAi agent is blunt, while the other end comprises a 2 nucleotide overhang.The 2 nucleotide overhang can be at the 3'-end of the antisense strand. When the 2 nucleotide overhang is at the 3'-end of the antisense strand, there may be two phosphorothioate internucleotide linkages between the terminal three 3'-nucleotides of the antisense strand, wherein two of the three nucleotides are the overhang nucleotides, and the third nucleotide is a paired nucleotide next to the overhang nucleotide. In one embodiment, the RNAi agent additionally has two phosphorothioate internucleotide linkages between the terminal three nucleotides at both the 5'-end of the sense strand and at the 5'-end of the antisense strand. In one embodiment, every nucleotide in the sense strand and the antisense strand of the RNAi agent, including the nucleotides that are part of the motifs are modified nucleotides. In one embodiment each residue is independently modified with a 2'-O-methyl or 2'-fluoro, *e.g.*, in an alternating motif. Optionally, the RNAi agent further comprises a ligand (*e.g.*, a lipophilic ligand, optionally a C16 ligand).

In one embodiment, the RNAi agent comprises a sense and an antisense strand, wherein the sense strand is 25-30 nucleotide residues in length, wherein starting from the 5' terminal nucleotide (position 1) positions 1 to 23 of the first strand comprise at least 8 ribonucleotides; the antisense strand is 36-66 nucleotide residues in length and, starting from the 3' terminal nucleotide, comprises at least 8 ribonucleotides in the positions paired with positions 1- 23 of sense strand to form a duplex; wherein at least

the 3 ' terminal nucleotide of antisense strand is unpaired with sense strand, and up to 6 consecutive 3' terminal nucleotides are unpaired with sense strand, thereby forming a 3' single stranded overhang of 1-6 nucleotides; wherein the 5' terminus of antisense strand comprises from 10-30 consecutive nucleotides which are unpaired with sense strand, thereby forming a 10-30 nucleotide single stranded 5' overhang; wherein at least the sense strand 5' terminal and 3' terminal nucleotides are base paired with nucleotides of antisense strand when sense and antisense strands are aligned for maximum complementarity, thereby forming a substantially duplexed region between sense and antisense strands; and antisense strand is sufficiently complementary to a target RNA along at least 19 ribonucleotides of antisense strand length to reduce target gene expression when the double stranded nucleic acid is introduced into a mammalian cell; and wherein the sense strand contains at least one motif of three 2'-F modifications on three consecutive nucleotides, where at least one of the motifs occurs at or near the cleavage site. The antisense strand contains at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at or near the cleavage site.

In one embodiment, the RNAi agent comprises sense and antisense strands, wherein the RNAi agent comprises a first strand having a length which is at least 25 and at most 29 nucleotides and a second strand having a length which is at most 30 nucleotides with at least one motif of three 2'-O-methyl modifications on three consecutive nucleotides at position 11, 12, and 13 from the 5' end; wherein the 3' end of the first strand and the 5' end of the second strand form a blunt end and the second strand is 1-4 nucleotides longer at its 3' end than the first strand, wherein the duplex region which is at least 25 nucleotides in length, and the second strand is sufficiently complementary to a target mRNA along at least 19 nucleotide of the second strand length to reduce target gene expression when the RNAi agent is introduced into a mammalian cell, and wherein dicer cleavage of the RNAi agent preferentially results in an siRNA comprising the 3' end of the second strand, thereby reducing expression of the target gene in the mammal. Optionally, the RNAi agent further comprises a ligand.

In one embodiment, the sense strand of the RNAi agent contains at least one motif of three identical modifications on three consecutive nucleotides, where one of the motifs occurs at the cleavage site in the sense strand.

In one embodiment, the antisense strand of the RNAi agent can also contain at least one motif of three identical modifications on three consecutive nucleotides, where one of the motifs occurs at or near the cleavage site in the antisense strand.

For an RNAi agent having a duplex region of 17-23 nucleotide in length, the cleavage site of the antisense strand is typically around the 10, 11 and 12 positions from the 5'-end. Thus the motifs of three identical modifications may occur at the 9, 10, and 11 positions; 10, 11, and 12 positions; 11, 12, and 13 positions; 12, 13, and 14 positions; or 13, 14, and 15 positions of the antisense strand, the count starting from the 1st nucleotide from the 5'-end of the antisense strand, or, the count starting from the 1st paired nucleotide within the duplex region from the 5'- end of the antisense strand. The cleavage site in the antisense strand may also change according to the length of the duplex region of the RNAi from the 5'-end.

The sense strand of the RNAi agent may contain at least one motif of three identical modifications on three consecutive nucleotides at the cleavage site of the strand; and the antisense strand may have at least one motif of three identical modifications on three consecutive nucleotides at or near the cleavage site of the strand. When the sense strand and the antisense strand form a dsRNA duplex, the sense strand and the antisense strand can be so aligned that one motif of the three nucleotides on the sense strand and one motif of the three nucleotides on the antisense strand have at least one nucleotide overlap, *i.e.*, at least one of the three nucleotides of the motif in the sense strand forms a base pair with at least one of the three nucleotides of the motif in the antisense strand. Alternatively, at least two nucleotides may overlap, or all three nucleotides may overlap.

In one embodiment, the sense strand of the RNAi agent may contain more than one motif of three identical modifications on three consecutive nucleotides. The first motif may occur at or near the cleavage site of the strand and the other motifs may be a wing modification. The term "wing modification" herein refers to a motif occurring at another portion of the strand that is separated from the motif at or near the cleavage site of the same strand. The wing modification is either adjacent to the first motif or is separated by at least one or more nucleotides. When the motifs are immediately adjacent to each other then the chemistry of the motifs are distinct from each other and when the motifs are separated by one or more nucleotide than the chemistries can be the same or different. Two or more wing modifications may be present. For instance, when two wing modifications are present, each wing modification may occur at one end relative to the first motif which is at or near cleavage site or on either side of the lead motif.

Like the sense strand, the antisense strand of the RNAi agent may contain more than one motif of three identical modifications on three consecutive nucleotides, with at least one of the motifs occurring at or near the cleavage site of the strand. This antisense strand may also contain one or more wing modifications in an alignment similar to the wing modifications that may be present on the sense strand.

In one embodiment, the wing modification on the sense strand or antisense strand of the RNAi agent typically does not include the first one or two terminal nucleotides at the 3'-end, 5'-end or both ends of the strand.

In another embodiment, the wing modification on the sense strand or antisense strand of the RNAi agent typically does not include the first one or two paired nucleotides within the duplex region at the 3'-end, 5'-end or both ends of the strand.

When the sense strand and the antisense strand of the RNAi agent each contain at least one wing modification, the wing modifications may fall on the same end of the duplex region, and have an overlap of one, two or three nucleotides.

When the sense strand and the antisense strand of the RNAi agent each contain at least two wing modifications, the sense strand and the antisense strand can be so aligned that two modifications each from one strand fall on one end of the duplex region, having an overlap of one, two or three nucleotides; two modifications each from one strand fall on the other end of the duplex region, having an overlap of one, two

or three nucleotides; two modifications one strand fall on each side of the lead motif, having an overlap of one, two, or three nucleotides in the duplex region.

In one embodiment, the RNAi agent comprises mismatch(es) with the target, within the duplex, or combinations thereof. The mismatch may occur in the overhang region or the duplex region. The base pair may 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 one embodiment, the RNAi agent 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 independently selected 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 one embodiment, 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.

In another embodiment, the nucleotide at the 3'-end of the sense strand is deoxythimidine (dT). In another embodiment, the nucleotide at the 3'-end of the antisense strand is deoxythimidine (dT). In one embodiment, there is a short sequence of deoxy-thymine nucleotides, for example, two dT nucleotides on the 3'-end of the sense or antisense strand.

In one embodiment, the sense strand sequence may be represented by formula (I):

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

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. Preferably YYY is all 2'-F modified nucleotides.

In one embodiment, the N_a or N_b comprise modifications of alternating pattern.

In one embodiment, 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 one embodiment, 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, 0-10, 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. Preferably, 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 one embodiment, the antisense strand sequence of the RNAi may be represented by formula (Ie):

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' (Ie)

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 motif of three identical modifications on three consecutive nucleotides.

In one embodiment, the N_a' or N_b' comprise modifications 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 17-23nucleotidein 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. Preferably, the Y'Y'Y' motif occurs at positions 11, 12, 13.

In one embodiment, Y'Y'Y' motif is all 2'-OMe modified nucleotides.

In one embodiment, k is 1 and l is 0, or k is 0 and l is 1, or both 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' (If);

5' n_q'-N_a'-Y'Y'Y'-N_b'-X'X'X'-n_p' 3' (Ig); or

5' n_q'-N_a'- Z'Z'Z'-N_b'-Y'Y'Y'-N_b'- X'X'X'-N_a'-n_p' 3' (Ih).

When the antisense strand is represented by formula (If), N_b' represents an oligonucleotide sequence comprising 0-10, 0-7, 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 (Ig), N_b' represents an oligonucleotide sequence comprising 0-10, 0-7, 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 (Ih), each N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 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. Preferably, 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 (Ie), each N_a' 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, UNA, CeNA, 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 one embodiment, 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 one embodiment the antisense strand may contain 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 a antisense strand being represented by any one of formulas (Ie), (If), (Ig), and (Ih), respectively.

Accordingly, the 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 (Ii):

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

antisense: $3'\ n_p'\text{-}N_a'\text{-}(X'X'X')_k\text{-}N_b'\text{-}Y'Y'Y'\text{-}N_b'\text{-}(Z'Z'Z')_l\text{-}N_a'\text{-}n_q'\ 5'$ (Ii)

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 modifications on three consecutive nucleotides.

In one embodiment, 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 another embodiment, 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 an RNAi duplex include the formulas below:

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

$3'\ n_p' - N_a' - Y'Y'Y' - N_a' n_q'\ 5'$ (Ij)

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

$3'\ n_p' - N_a' - Y'Y'Y' - N_b' - Z'Z'Z' - N_a' n_q'\ 5'$ (Ik)

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

$3'\ n_p' - N_a' - X'X'X' - N_b' - Y'Y'Y' - N_a' - n_q'\ 5'$ (Il)

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

$3'\ n_p' - N_a' - X'X'X' - N_b' - Y'Y'Y' - N_b' - Z'Z'Z' - N_a - n_q'\ 5'$ (Im)

When the RNAi agent is represented by formula (Ij), 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 (Ik), 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 (Il), each N_b, N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 0-10, 0-7, 0-5, 0-4, 0-2 or 0modified 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 (Im), each N_b, N_b' independently represents an oligonucleotide sequence comprising 0-10, 0-7, 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.

In one embodiment, when the RNAi agent is represented by formula (Im), the N_a modifications are 2′-O-methyl or 2′-fluoro modifications. In another embodiment, when the RNAi agent is represented by formula (Im), 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 yet another embodiment, when the RNAi agent is represented by formula (Im), 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 C16 (or related) moieties attached through a bivalent or trivalent branched linker (described below). In another embodiment, when the RNAi agent is represented by formula (IIIm), 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 lipophilic, *e.g.*, C16 (or related) moieties, optionally attached through a bivalent or trivalent branched linker.

In one embodiment, when the RNAi agent is represented by formula (Ij), 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 lipophilic, *e.g.*, C16 (or related) moieties attached through a bivalent or trivalent branched linker.

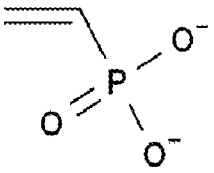
In one embodiment, the RNAi agent is a multimer containing at least two duplexes represented by formula (Ii), (Ij), (Ik), (Il), and (Im), wherein the duplexes are connected by a linker. The linker can be cleavable or non-cleavable. Optionally, the multimer further comprises a ligand. Each of the duplexes can target the same gene or two different genes; or each of the duplexes can target same gene at two different target sites.

In one embodiment, the RNAi agent is a multimer containing three, four, five, six or more duplexes represented by formula (Ii), (Ij), (Ik), (Il), and (Im), 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.

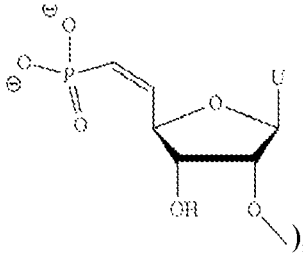
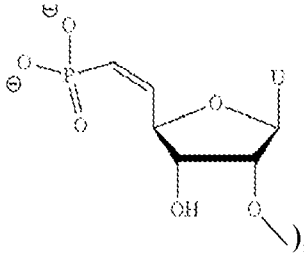
In one embodiment, two RNAi agents represented by formula (Ii), (Ij), (Ik), (Il), and (Im) are linked to each other at the 5' end, and one or both of the 3' ends and are optionally conjugated to to a ligand. Each of the agents can target the same gene or two different genes; or each of the agents can 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 entire contents of each of which are hereby incorporated herein by reference.

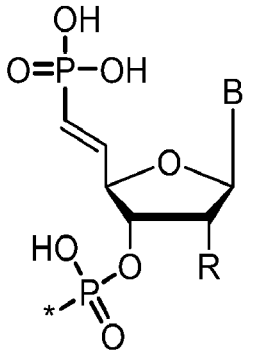
In certain embodiments, the compositions and methods of the disclosure include a vinyl phosphonate (VP) modification of an RNAi agent as described herein. In exemplary embodiments, a vinyl phosphonate of the disclosure has the following structure:



A vinyl phosphonate of the instant disclosure may be attached to either the antisense or the sense strand of a dsRNA of the disclosure. In certain 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. The dsRNA agent can comprise a phosphorus-containing group at the 5'-end of the sense strand or antisense strand. The 5'-end phosphorus-containing group can be 5'-end phosphate (5'-P), 5'-end phosphorothioate (5'-PS), 5'-end phosphorodithioate (5'-PS2), 5'-end vinylphosphonate (5'-VP), 5'-end methylphosphonate (MePhos), or 5'-deoxy-5'-C-malonyl. When the 5'-end phosphorus-containing group is 5'-end vinylphosphonate (5'-VP), the 5'-VP can be either 5'-E-VP isomer (i.e., trans-vinylphosphonate,


), 5′-Z-VP isomer (i.e., cis-vinylphosphonate, 
), or mixtures thereof.

For example, when the phosphate mimic is a 5'-E-vinyl phosphonate (VP), the 5'-terminal nucleotide can have the following structure,

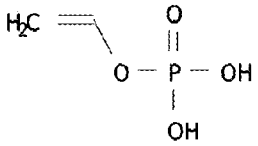


wherein * indicates the location of the bond to 5'-position of the adjacent nucleotide;

R is hydrogen, hydroxy, methoxy, or fluoro (e.g., methoxy), or another modification described herein; and

B is a nucleobase or a modified nucleobase, optionally where B is adenine, guanine, cytosine, thymine or uracil (e.g., uracil or adenine).

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



i. 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. As used herein "seed region" means at positions 2-9 of the 5'-end of the referenced strand. For example, thermally destabilizing modifications can be incorporated in the seed region of the antisense strand to reduce or inhibit off-target gene silencing.

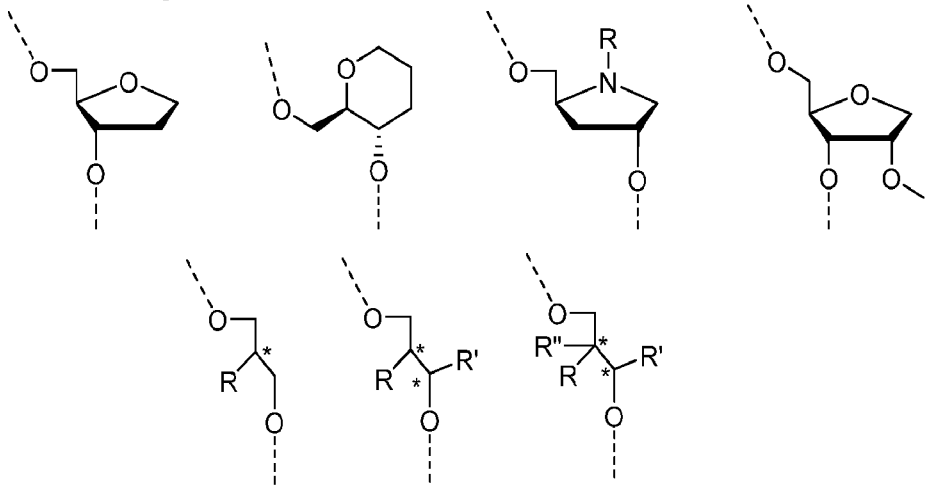
The term "thermally destabilizing modification(s)" includes modification(s) that would result with a dsRNA with a lower overall melting temperature (Tm) than the Tm of the dsRNA without having such modification(s). For example, the thermally destabilizing modification(s) can decrease the Tm of the dsRNA

by 1–4 °C, such as one, two, three or four degrees Celcius. And, the term "thermally destabilizing nucleotide" refers to a nucleotide containing one or more thermally destabilizing modifications.

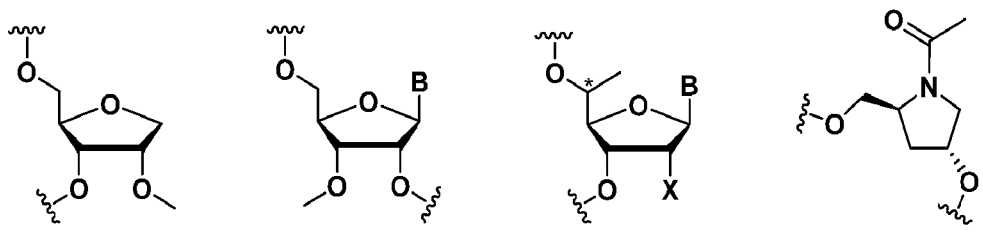
It has been discovered that dsRNAs with an antisense strand comprising at least one thermally destabilizing modification of the duplex within the first 9 nucleotide positions, counting from the 5' end, of the antisense strand have reduced off-target gene silencing activity. Accordingly, in some embodiments, 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, such as 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. 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)

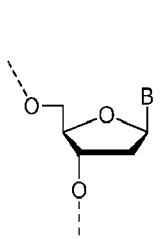
Mod4 (5'-Me)

X = OMe, F

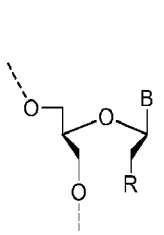
Mod5 (Hyp-spacer)

wherein B is a modified or unmodified nucleobase.

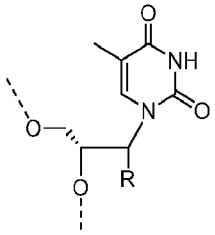
Exemplified sugar modifications include, but are not limited to the following:



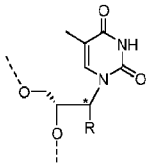
2'-deoxy



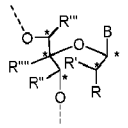
unlocked nucleic acid
R= H, OH, O-alkyl



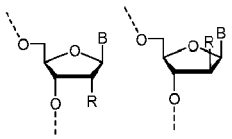
glycol nucleic acid
R= H, OH, O-alkyl



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



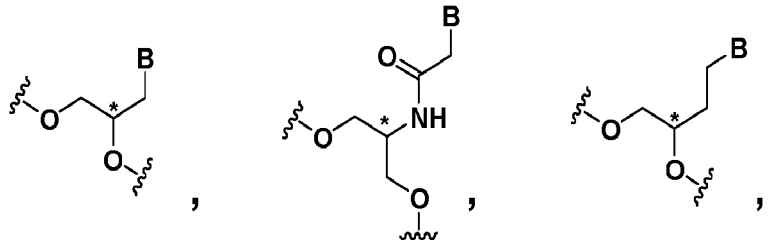
unlocked nucleic acid
R= H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2
R' = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2
R" = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2
R"' = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2
R"" = H, OH, CH_3, CH_2CH_3, O-alkyl, NH_2, NHMe, NMe_2



R = H, methyl, ethyl

wherein B is a modified or unmodified nucleobase.

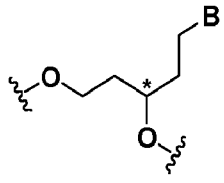
In some embodiments the thermally destabilizing modification of the duplex is selected from the group consisting of:



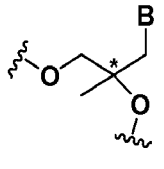
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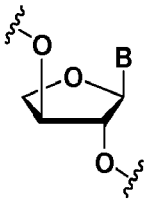
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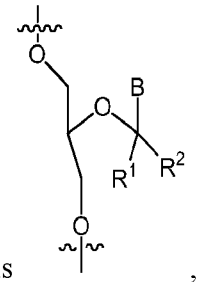


, and

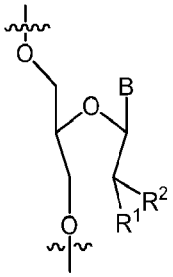
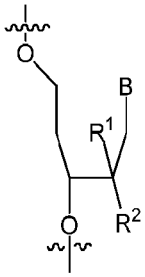
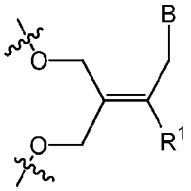
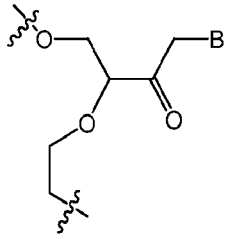


wherein B is a modified or unmodified nucleobase and the asterisk on each structure represents either *R*, *S* or *racemic*.

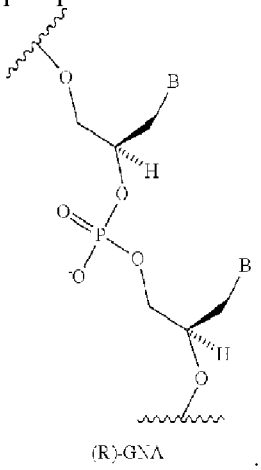
The term "acyclic nucleotide" refers to any nucleotide having an acyclic ribose sugar, for example, where any of bonds between the ribose carbons (*e.g.*, C1'-C2', C2'-C3', C3'-C4', C4'-O4', or C1'-O4') is absent or at least one of ribose carbons or oxygen (*e.g.*, C1', C2', C3', C4' or O4') are independently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



combination absent from the nucleotide. In some embodiments, acyclic nucleotide is ,

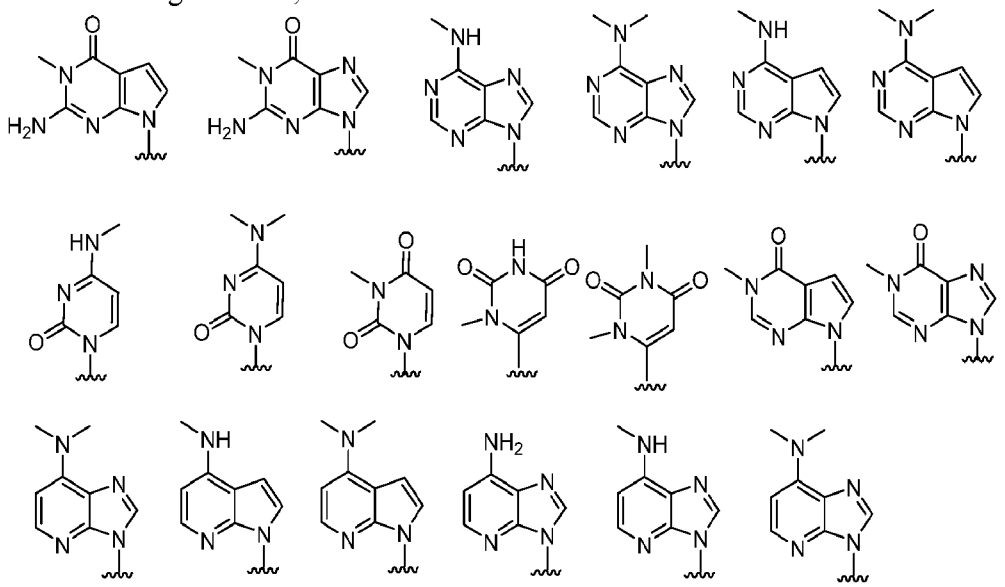

, 
, 
or 
, wherein B is a modified or unmodified nucleobase, R^1 and R^2 independently are H, halogen, OR_3, or alkyl; and R_3 is H, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl or sugar). The acyclic derivative provides greater backbone flexibility without affecting the Watson-Crick pairings. The acyclic 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 .

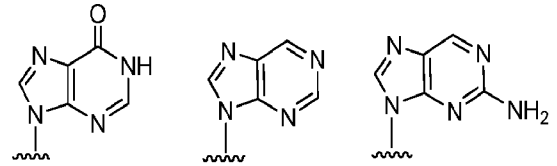
The thermally destabilizing modification of the duplex can be mismatches (*i.e.*, noncomplementary base pairs) between the thermally destabilizing nucleotide and the opposing nucleotide in the opposite strand within the dsRNA duplex. Exemplary mismatch base pairs include G:G, G:A, G:U, G:T, A:A, A:C, 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 Watson-Crick hydrogen-bonding to complementary base on the target mRNA, such as:

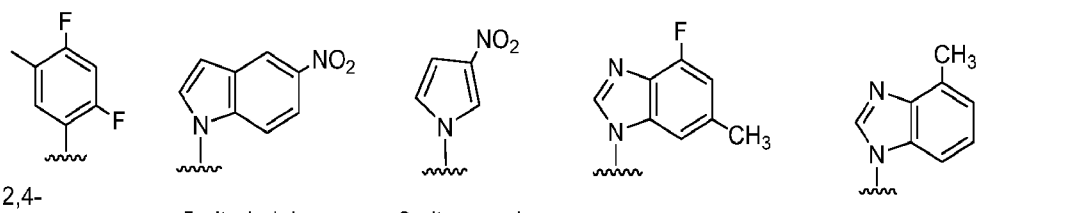


More examples of abasic nucleotide, acyclic nucleotide modifications (including UNA and GNA), and mismatch modifications have been described in detail in WO 2011/133876, which is herein incorporated by reference in its entirety. The thermally destabilizing modifications may also include universal base 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:

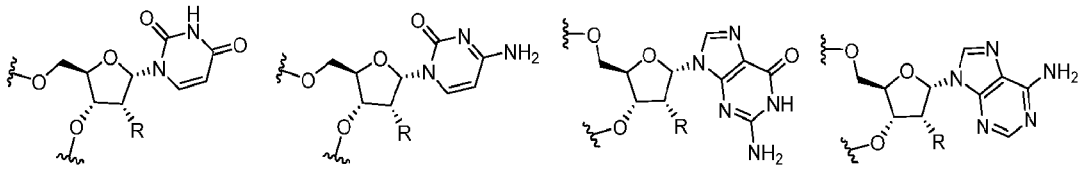


inosine nebularine 2-aminopurine



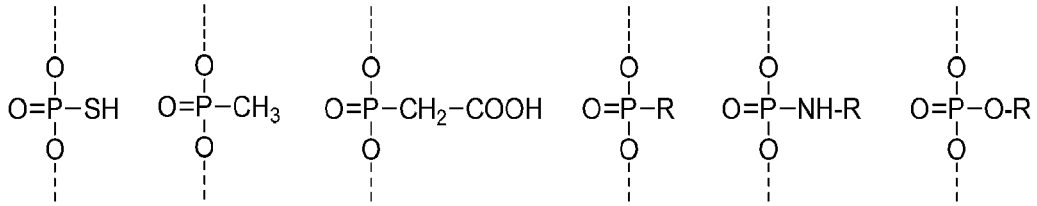
2,4-difluorotoluene 5-nitroindole 3-nitropyrrole 4-Fluoro-6-methylbenzimidazole 4-Methylbenzimidazole

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 recognizes, in view of the functional role of nucleobases is defining specificity of an 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 an 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 comprises stabilizing modifications at positions 2, 6, 8, 9, 14, and 16 from the 5'-end. In some other embodiments, the antisense comprises stabilizing modifications at positions 2, 6, 14, and 16 from the 5'-end. In still some other embodiments, the antisense 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 complementary 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 complementary 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 complementary 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 complementary 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 complementary 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 complementary 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, the dsRNA molecule of the disclosure comprising a sense and antisense strands, wherein: the sense strand is 25-30 nucleotide residues in length, wherein starting from the 5' terminal nucleotide (position 1), positions 1 to 23 of said sense strand comprise at least 8 ribonucleotides; antisense strand is 36-66 nucleotide residues in length and, starting from the 3' terminal nucleotide, at least 8 ribonucleotides in the positions paired with positions 1- 23 of sense strand to form a duplex; wherein at least the 3 ' terminal nucleotide of antisense strand is unpaired with sense strand, and up to 6 consecutive 3' terminal nucleotides are unpaired with sense strand, thereby forming a 3' single stranded overhang of 1-6 nucleotides; wherein the 5' terminus of antisense strand comprises from 10-30 consecutive nucleotides which are unpaired with sense strand, thereby forming a 10-30 nucleotide single stranded 5' overhang; wherein at least the sense strand 5' terminal and 3' terminal nucleotides are base paired with nucleotides of antisense strand when sense and antisense strands are aligned for maximum complementarity, thereby forming a substantially duplexed region between sense and antisense strands; and antisense strand is sufficiently complementary to a target RNA along at least 19 ribonucleotides of antisense strand length to reduce target gene expression when said double stranded nucleic acid is introduced into a mammalian cell; and wherein the antisense strand contains at least one thermally destabilizing nucleotide, where at least one thermally destabilizing nucleotide is in the seed region of the antisense strand (*i.e.* at position 2-9 of the 5'-end of the antisense strand). For example, the thermally destabilizing nucleotide occurs between positions opposite or complementary to positions 14-17 of the 5'-end of the sense strand, 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; and (vi) the dsRNA comprises at least four 2'-fluoro modifications; and (vii) the dsRNA comprises a duplex region of 12-30 nucleotide pairs in length.

In some embodiments, the dsRNA molecule of the disclosure comprises a sense and antisense strands, wherein said dsRNA molecule comprises a sense strand having a length which is at least 25 and at most 29 nucleotides and an antisense strand having a length which is at most 30 nucleotides with the sense

strand comprises a modified nucleotide that is susceptible to enzymatic degradation at position 11 from the 5'end, wherein the 3' end of said sense strand and the 5' end of said antisense strand form a blunt end and said antisense strand is 1-4 nucleotides longer at its 3' end than the sense strand, wherein the duplex region which is at least 25 nucleotides in length, and said antisense strand is sufficiently complementary to a target mRNA along at least 19 nt of said antisense strand length to reduce target gene expression when said dsRNA molecule is introduced into a mammalian cell, and wherein dicer cleavage of said dsRNA preferentially results in an siRNA comprising said 3' end of said antisense strand, thereby reducing expression of the target gene in the mammal, wherein the antisense strand contains at least one thermally destabilizing nucleotide, where the at least one thermally destabilizing nucleotide is in the seed region of the antisense strand (*i.e.* at position 2-9 of the 5'-end of the antisense strand), 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; and (vi) the dsRNA comprises at least four 2'-fluoro modifications; and (vii) the dsRNA has a duplex region of 12-29 nucleotide pairs in length.

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 occurs at all of the subject positions in the nucleic acid but in many cases it does 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 locked nucleic acid (LNA), unlocked nucleic acid (UNA), cyclohexene nucleic acid (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 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 1-10 nucleotides 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 or methylphosphonate internucleotide linkage at positions 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 1-10 nucleotides 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 modifications 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 positions 1-5 and one phosphorothioate or methylphosphonate internucleotide linkage modification within positions 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at position 1 or 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 positions 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at position 1 or 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 positions 1-5 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at position 1 or 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 positions 1-5 and two phosphorothioate internucleotide linkage modifications within positions 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at position 1 or 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 positions 1-5 and one phosphorothioate internucleotide linkage modification within positions 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 positions 1-5 and one within positions 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 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 position 1 or 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 positions 1-5 and one within positions 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 positions 1-5 and one phosphorothioate internucleotide linkage modification within positions 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 positions 1-5 and one phosphorothioate internucleotide linkage modification within positions 18-23 of the sense strand (counting from the 5'-end), and one phosphorothioate internucleotide linkage modification at position 1 or 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 positions 1 and 2, and two phosphorothioate internucleotide linkage modifications at positions 20 and 21 of the sense strand (counting from the 5'-end),

and one phosphorothioate internucleotide linkage modification at position 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 positions 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 position 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 positions 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 antisense strand comprises phosphorothioate internucleotide linkages between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23, wherein the antisense strand contains at least one thermally destabilizing modification of the duplex located in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand), and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six, seven or all eight) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5 or 6 2'-fluoro modifications; (ii) the antisense comprises 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; (vii) the dsRNA comprises a duplex region of 12-40 nucleotide pairs in length; and (viii) the dsRNA has a blunt end at 5'-end of the antisense strand.

In some embodiments, the antisense strand comprises phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23, wherein the antisense strand contains at least one thermally destabilizing modification of the duplex located in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand), and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six, seven or all eight) of the following characteristics: (i) the antisense comprises 2, 3, 4, 5 or 6 2'-fluoro modifications; (ii) the sense strand is conjugated with a ligand; (iii) the sense strand comprises 2, 3, 4 or 5 2'-fluoro modifications; (iv) the sense strand comprises 1, 2, 3, 4 or 5 phosphorothioate internucleotide linkages; (v) the dsRNA comprises at least four 2'-fluoro modifications; (vi) the dsRNA

comprises a duplex region of 12-40 nucleotide pairs in length; (vii) the dsRNA comprises a duplex region of 12-40 nucleotide pairs in length; and (viii) the dsRNA has a blunt end at 5'-end of the antisense strand.

In some embodiments, the sense strand comprises phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3, wherein the antisense strand contains at least one thermally destabilizing modification of the duplex located in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand), and wherein the dsRNA optionally further has at least one (*e.g.*, one, two, three, four, five, six, seven or all eight) 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 3, 4 or 5 phosphorothioate internucleotide linkages; (vi) the dsRNA comprises at least four 2'-fluoro modifications; (vii) the dsRNA comprises a duplex region of 12-40 nucleotide pairs in length; and (viii) the dsRNA has a blunt end at 5'-end of the antisense strand.

In some embodiments, the sense strand comprises phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3, the antisense strand comprises phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, between nucleotide positions 2 and 3, between nucleotide positions 21 and 22, and between nucleotide positions 22 and 23, wherein the antisense strand contains at least one thermally destabilizing modification of the duplex located in the seed region of the antisense strand (*i.e.*, at position 2-9 of the 5'-end of the antisense strand), 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 sense strand is conjugated with a ligand; (iii) the sense strand comprises 2, 3, 4 or 5 2'-fluoro modifications; (iv) the sense strand comprises 3, 4 or 5 phosphorothioate internucleotide linkages; (v) the dsRNA comprises at least four 2'-fluoro modifications; (vi) the dsRNA comprises a duplex region of 12-40 nucleotide pairs in length; and (vii) the dsRNA has a blunt end at 5'-end of the antisense strand.

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, the introduction of a 4'-modified or a 5'-modified nucleotide to the 3'-end of a PO, PS, or PS2 linkage of a dinucleotide modifies the second nucleotide in the dinucleotide pair. In other embodiments, the introduction of a 4'-modified or a 5'-modified nucleotide to the 3'-end of a PO, PS, or PS2 linkage of a dinucleotide modifies the nucleotide at the 3'-end of the dinucleotide pair.

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

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

In some embodiments, 5'-alkylated nucleotide 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 nucleotide is 5'-methyl nucleotide. The 5'-methyl can be either racemic or chirally pure *R* or *S* isomer.

In some embodiments, 4'-alkylated nucleotide 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 nucleotide is 4'-methyl nucleotide. The 4'-methyl can be either racemic or chirally pure *R* or *S* isomer.

In some embodiments, 4'-*O*-alkylated nucleotide 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 nucleotide is 4'-*O*-methyl nucleotide. 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.

As described in more detail below, the RNAi agent that contains conjugations of one or more carbohydrate moieties to an RNAi agent may improve one or more properties of the RNAi agent. In many cases, the carbohydrate moiety is 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 (e.g., 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," such as 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 may 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. The cyclic group can be selected from pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, [1,3]dioxolane, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, quinoxalinyl, pyridazinonyl, tetrahydrofuryl and and decalinyl.The acyclic group can be 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 3-7. These agents may further comprise a ligand.

IV. iRNAs Conjugated to Ligands

Another modification of the RNA of an iRNA of the invention involves chemically linking to the iRNA one or more ligands, moieties or conjugates that enhance the activity, cellular distribution or cellular uptake of the iRNA, *e.g.*, into a cell. 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 certain 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 do 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. Example 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-glucosamine 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. In certain embodiments, the ligand is a multivalent galactose, *e.g.*, an N-acetyl-galactosamine.

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, Eu(3+) 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 a cancer cell, endothelial cell, or bone 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, or intermediate filaments. The drug can be, for example, taxol, 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, polyethylene glycol (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 invention 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 iRNAs of the invention 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 invention 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 invention, 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 invention 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. Lipid Conjugates

In certain embodiments, the ligand or conjugate 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 distribution of the conjugate to a target tissue, *e.g.*, a non-kidney target tissue of the body. For example, the target tissue can be the liver, including parenchymal cells of the liver. Other molecules that can bind HSA can also be used as ligands. For example, naproxen 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, 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 is 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 certain 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 certain 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).

B. Cell Permeation Agents

In another aspect, the ligand is a cell-permeation agent, such as a helical cell-permeation agent. In certain 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: 9). An RFGF analogue (*e.g.*, amino acid sequence AALLPVLLAAP (SEQ ID NO: 10)) 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: 1806)) and the *Drosophila Antennapedia* protein (RQIKIWFQNRRMKWKK (SEQ ID NO: 1807)) 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 invention 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 peptidiomimemtics 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. Preferred 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 facilitates 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 an 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).

C. Carbohydrate Conjugates

In some embodiments of the compositions and methods of the invention, an iRNA 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 tri-saccharides include sugars having two or three monosaccharide units (*e.g.*, C5, C6, C7, or C8).

In certain embodiments, a carbohydrate conjugate comprises a monosaccharide. In certain embodiments, the monosaccharide is an N-acetylgalactosamine (GalNAc). GalNAc conjugates, which comprise one or more N-acetylgalactosamine (GalNAc) derivatives, are described, for example, in US 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 conjugated to the 5' end of the sense strand. In some embodiments, the GalNAc conjugate is conjugated to the iRNA agent (*e.g.*, to the 5' end of the sense strand) *via* a linker, *e.g.*, a linker as described herein.

In certain embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a monovalent linker. In some embodiments, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a bivalent linker. In yet other embodiments of the invention,

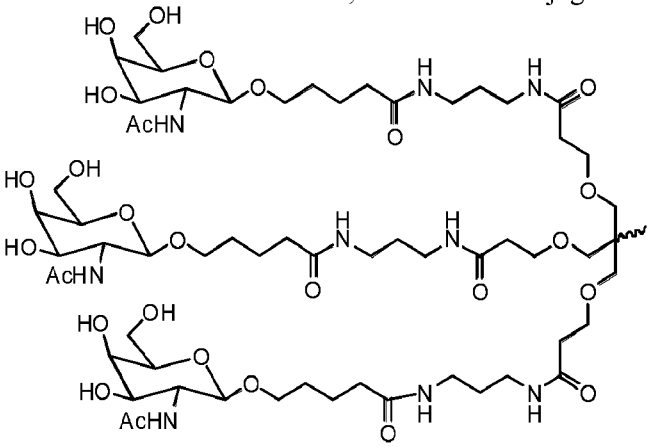
the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a trivalent linker. In other embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a tetravalent linker.

In certain embodiments, the double stranded RNAi agents of the invention comprise one GalNAc or GalNAc derivative attached to the iRNA agent. In certain embodiments, the double stranded RNAi agents of the invention comprise a plurality (*e.g.*, 2, 3, 4, 5, or 6) GalNAc or GalNAc derivatives, each independently attached to a plurality of nucleotides of the double stranded RNAi agent through a plurality of monovalent linkers.

In some embodiments, for example, when the two strands of an iRNA agent of the invention are part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality of unpaired nucleotides, each unpaired nucleotide within the hairpin loop may independently comprise a GalNAc or GalNAc derivative attached *via* a monovalent linker. The hairpin loop may also be formed by an extended overhang in one strand of the duplex.

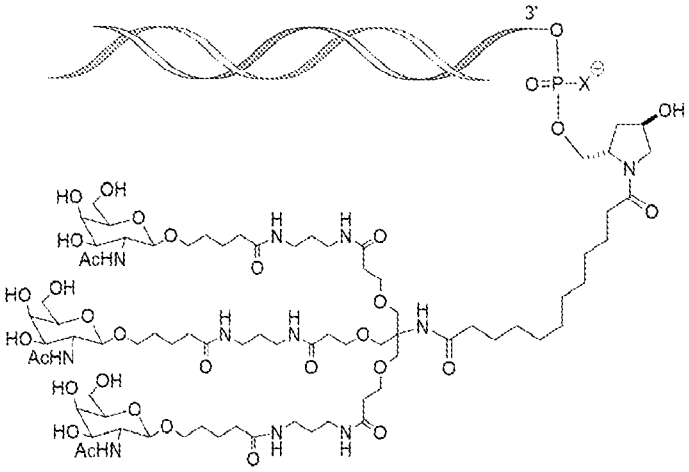
In some embodiments, for example, when the two strands of an iRNA agent of the invention are part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality of unpaired nucleotides, each unpaired nucleotide within the hairpin loop may independently comprise a GalNAc or GalNAc derivative attached *via* a monovalent linker. The hairpin loop may also be formed by an extended overhang in one strand of the duplex.

In some embodiments, the GalNAc conjugate is

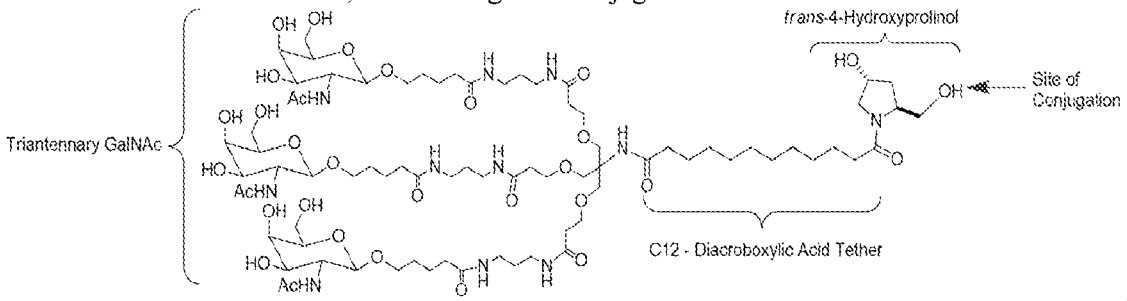


Formula II.

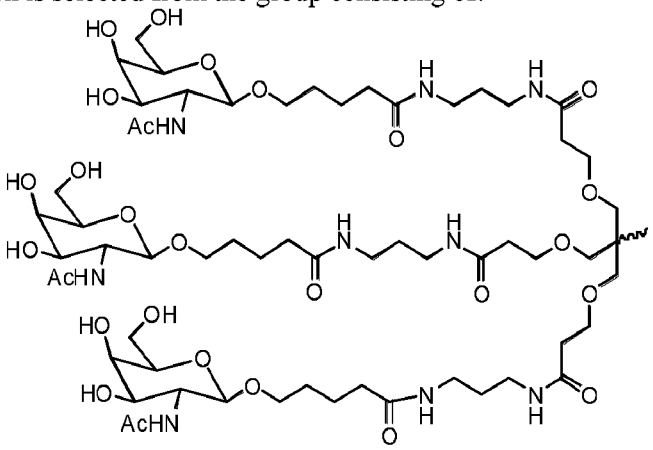
In some embodiments, the RNAi agent is attached to the carbohydrate conjugate *via* a linker as shown in the following schematic, wherein X is O or S



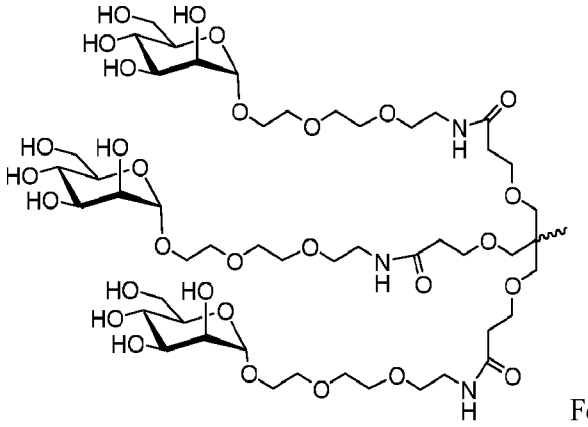
In some embodiments, the RNAi agent is conjugated to L96 as defined in Table 2 and shown below:



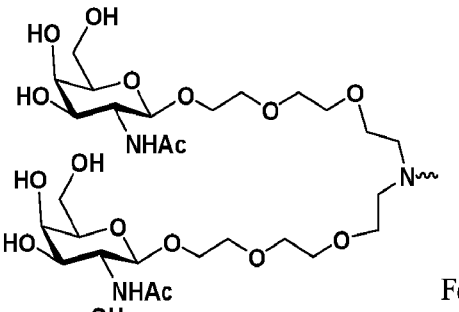
In certain embodiments, a carbohydrate conjugate for use in the compositions and methods of the invention is selected from the group consisting of:



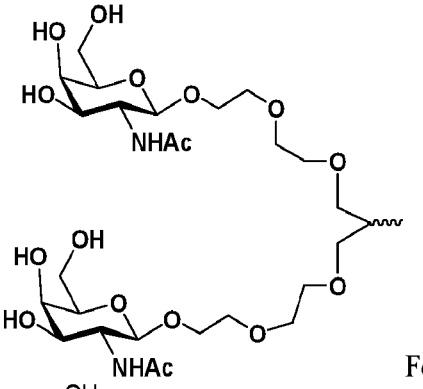
Formula II,



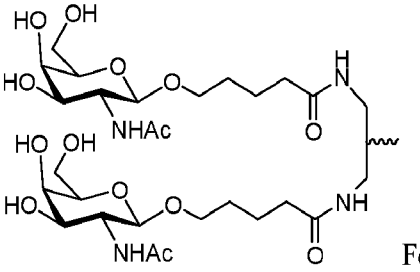
Formula III,



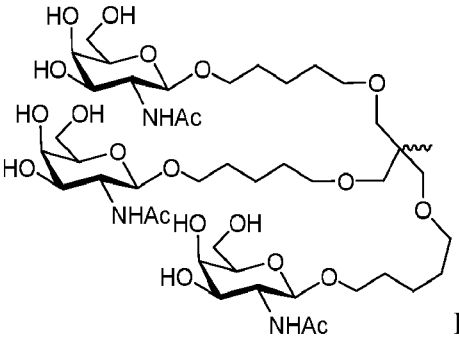
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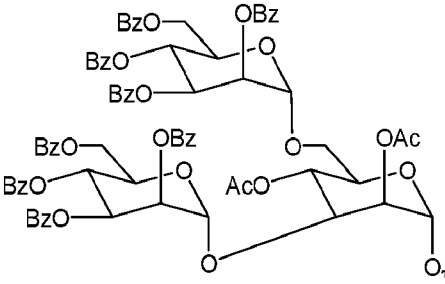
Formula V,



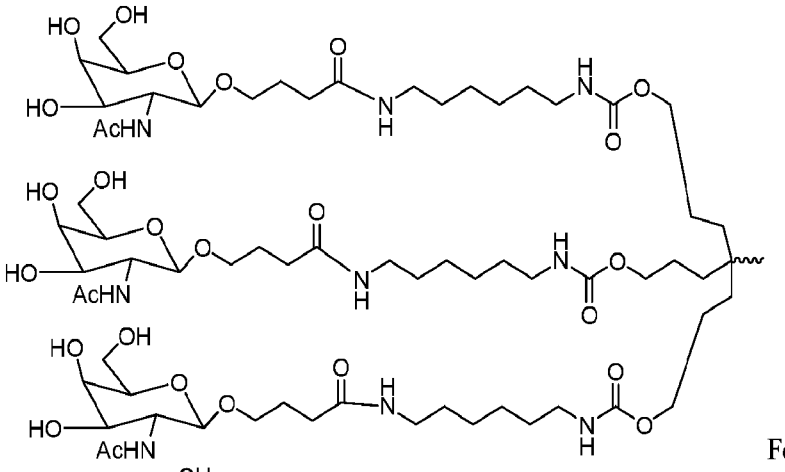
Formula VI,



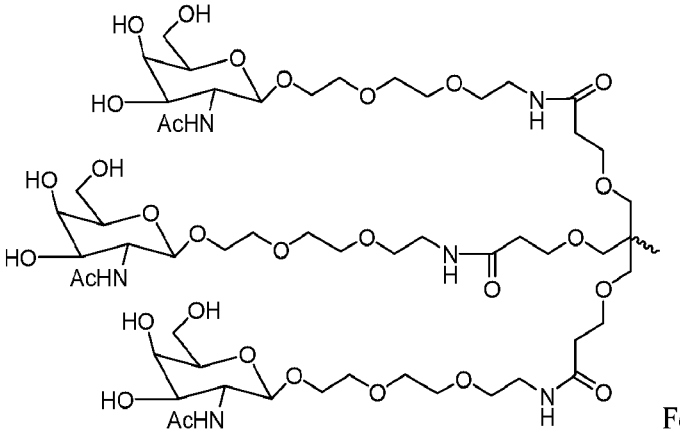
Formula VII,



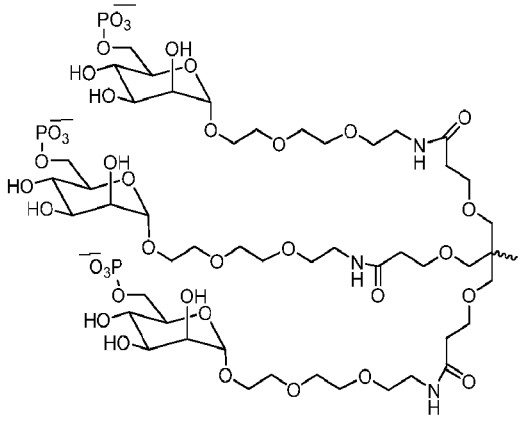
Formula VIII,



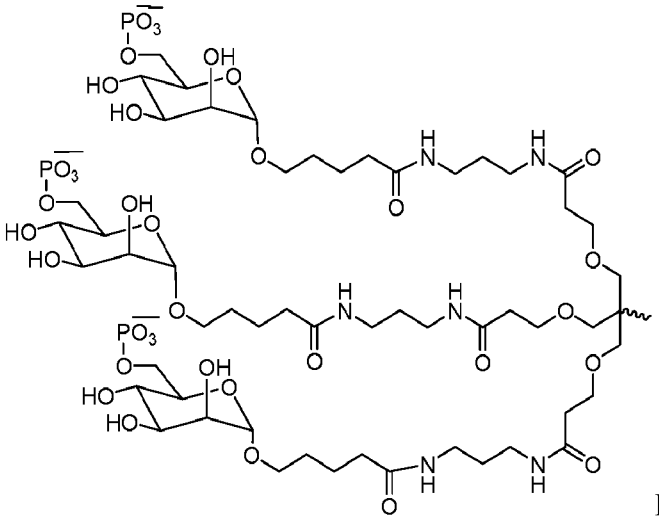
Formula IX,



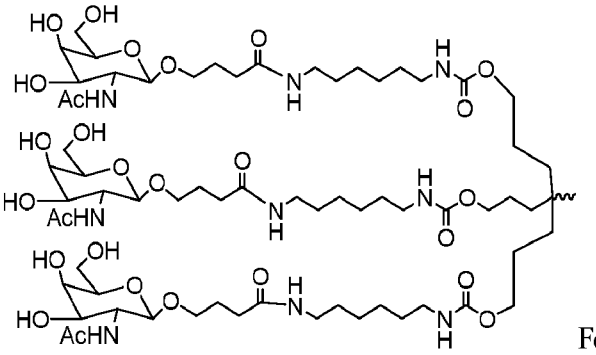
Formula X,



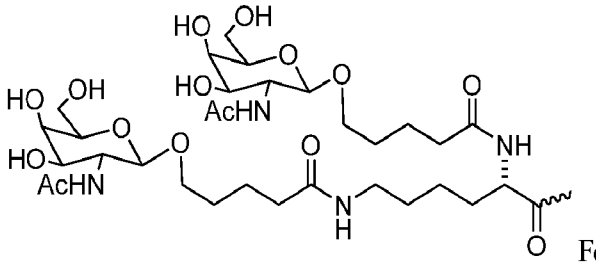
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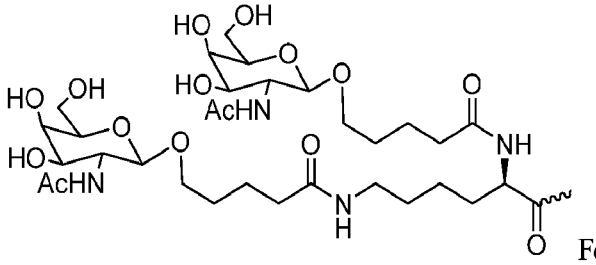
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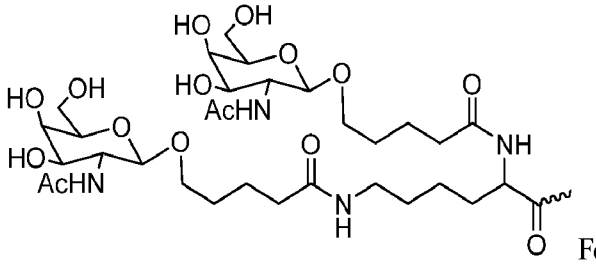
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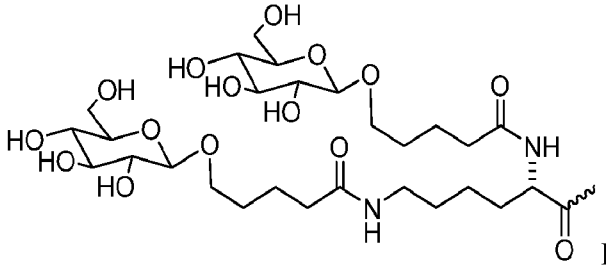
Formula XIV,



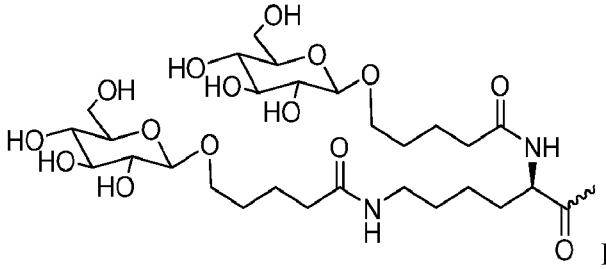
Formula XV,



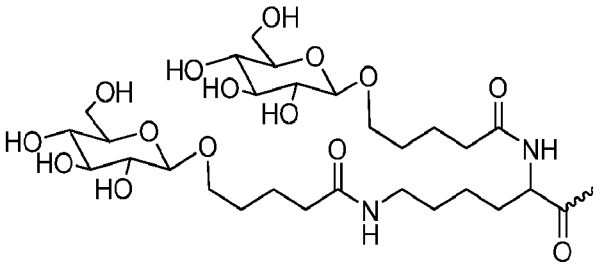
Formula XVI,



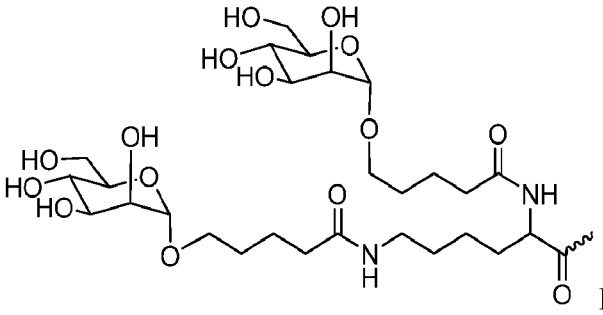
Formula XVII,



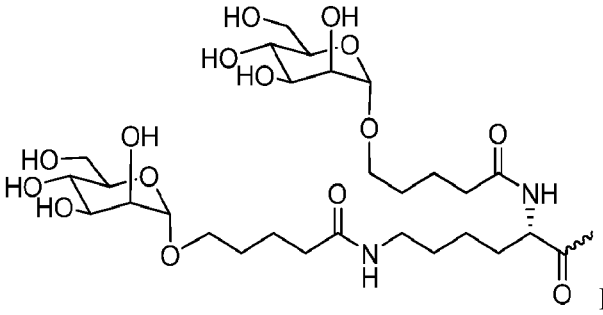
Formula XVIII,



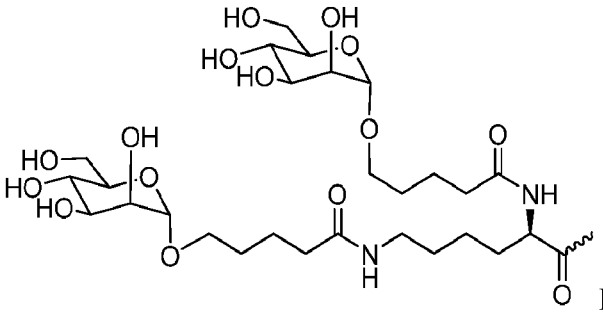
Formula XIX,



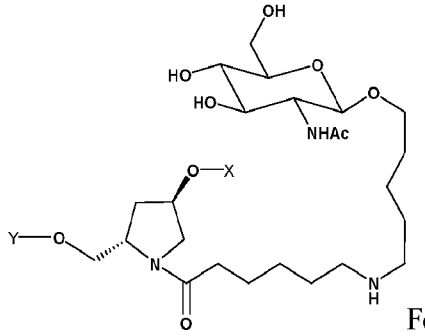
Formula XX,



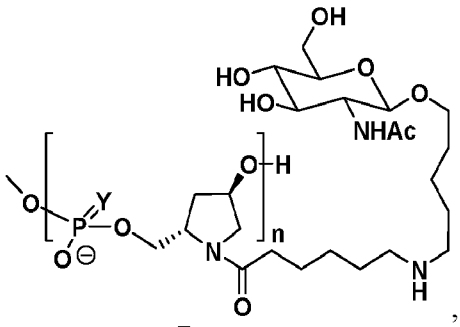
Formula XXI,



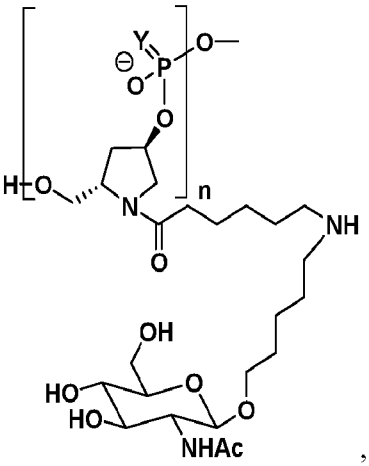
Formula XXII,



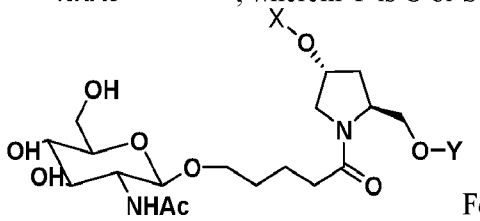
Formula XXIII;



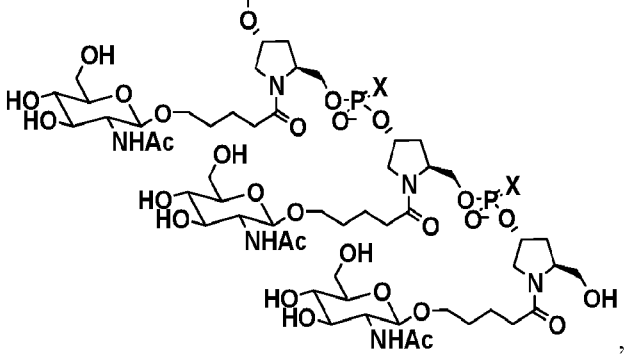
, wherein Y is O or S and n is 3 -6 (Formula XXIV);



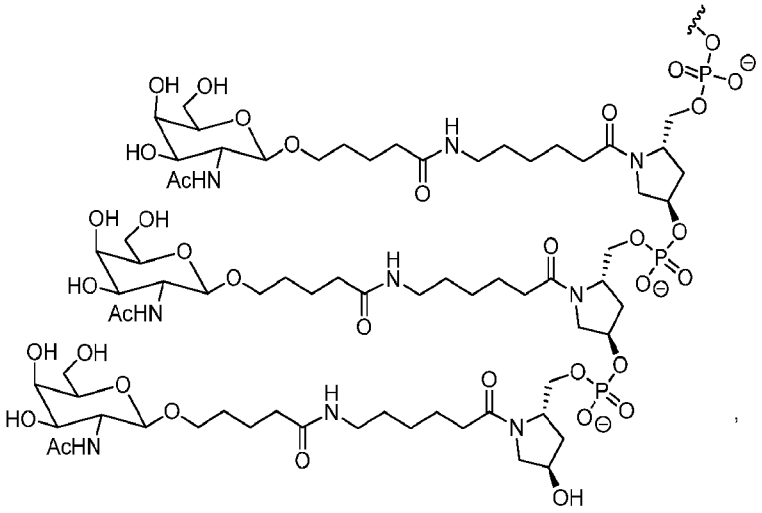
, wherein Y is O or S and n is 3-6 (Formula XXV);



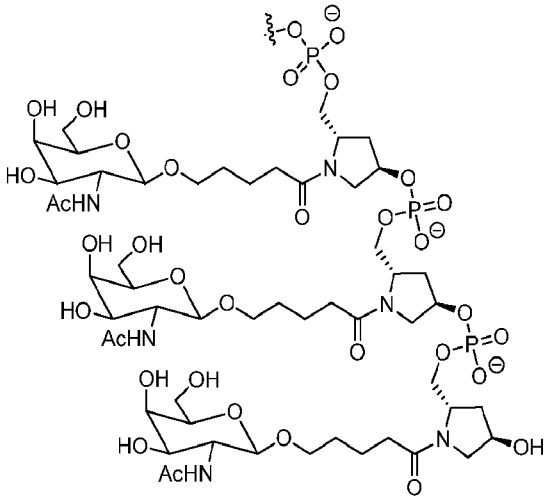
Formula XXVI;



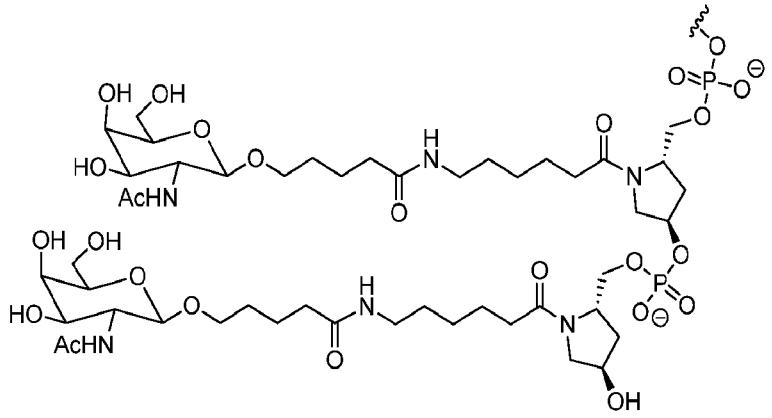
, wherein X is O or S (Formula XXVII);



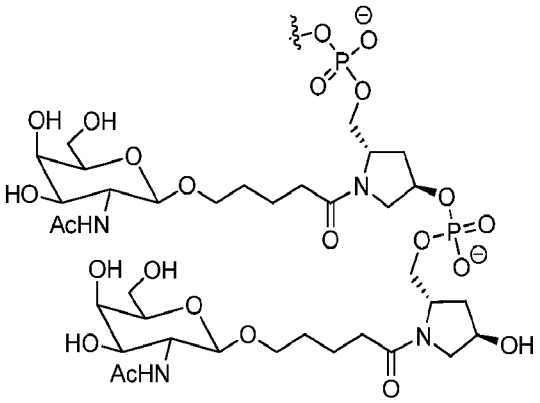
Formula XXVIII;



Formula XXIX;

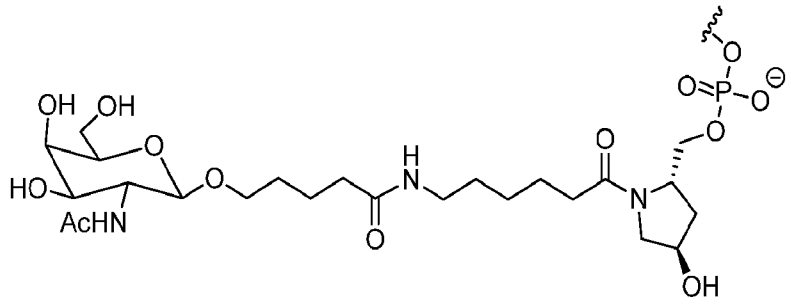


Formula XXX;

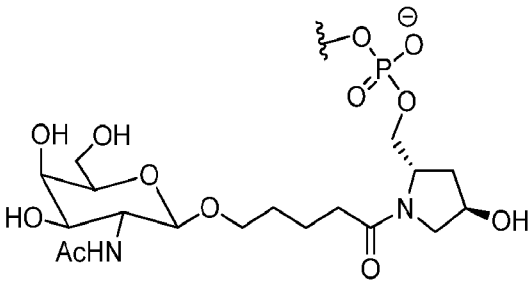


Formula XXXI;

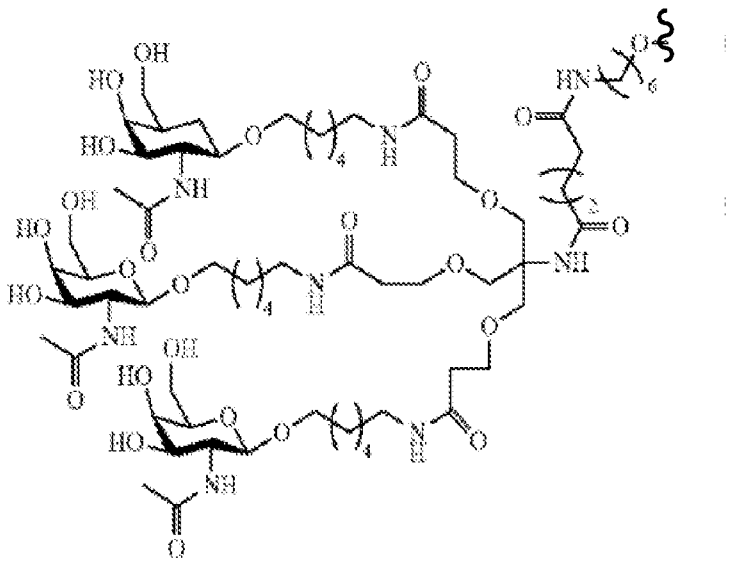
Formula XXXII;



, and

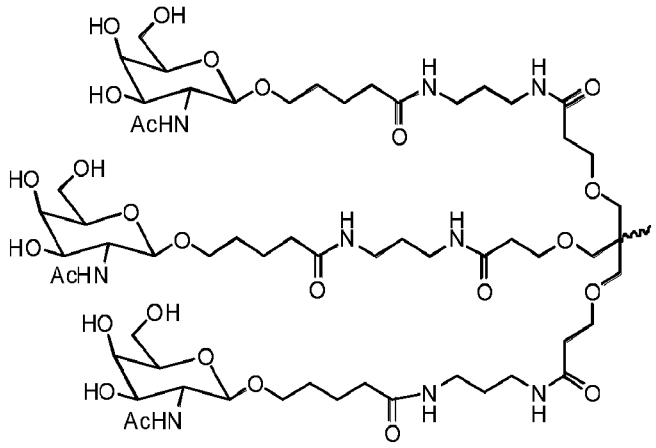


Formula XXXIII.



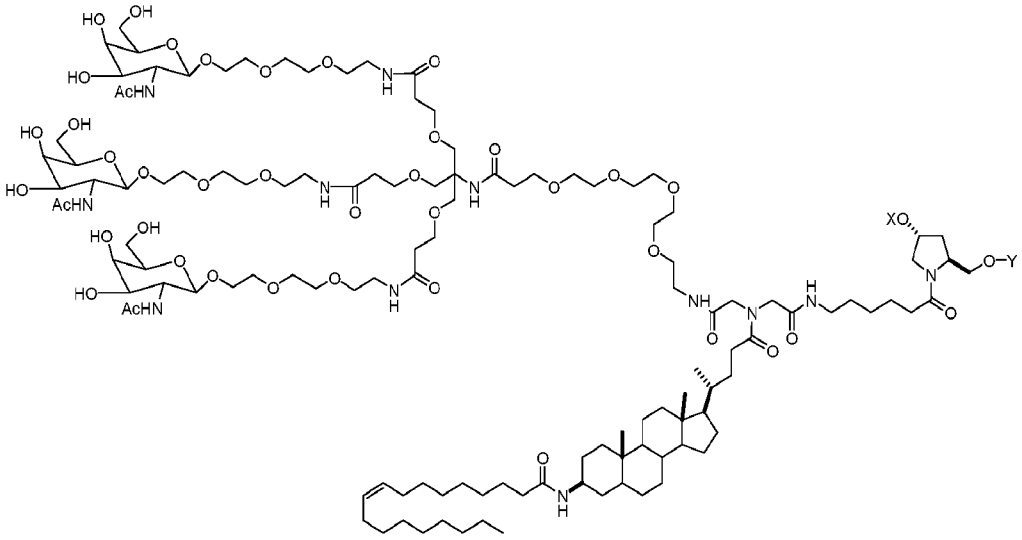
(Formula XXXIV)

In certain embodiments, a carbohydrate conjugate for use in the compositions and methods of the invention is a monosaccharide. In certain embodiments, the monosaccharide is an N-acetylgalactosamine, such as



Formula II.

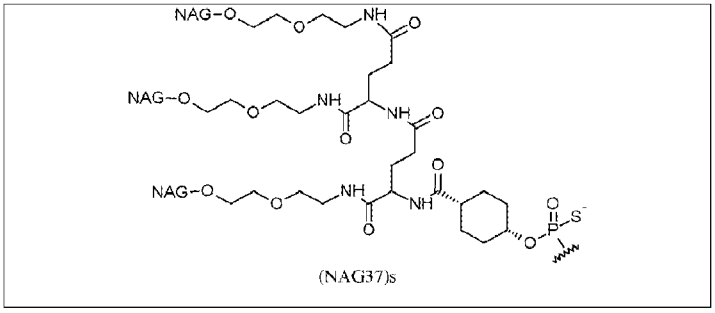
Another representative carbohydrate conjugate for use in the embodiments described herein includes, but is not limited to,



(Formula XXXV),

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

In some embodiments, a suitable ligand is a ligand disclosed in WO 2019/055633, the entire contents of which are incorporated herein by reference. In one embodiment the ligand comprises the structure below:



(Formula XXXVI).

In certain embodiments, the RNAi agents of the disclosure may include GalNAc ligands, even if such GalNAc ligands are currently projected to be of limited value for the preferred intrathecal/CNS delivery route(s) of the instant disclosure.

In certain embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a monovalent linker. In some embodiments, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a bivalent linker. In yet other embodiments of the invention, the GalNAc or GalNAc derivative is attached to an iRNA agent of the invention *via* a trivalent linker.

In one embodiment, the double stranded RNAi agents of the invention comprise one or more GalNAc or GalNAc derivative attached to the iRNA agent. The GalNAc may be attached to any nucleotide *via* a linker on the sense strand or antsisense strand. The GalNac may be attached to the 5'-end of the sense strand, the 3' end of the sense strand, the 5'-end of the antisense strand, or the 3' –end of the antisense strand. In one embodiment, the GalNAc is attached to the 3' end of the sense strand, *e.g.*, *via* a trivalent linker.

In other embodiments, the double stranded RNAi agents of the invention comprise a plurality (*e.g.*, 2, 3, 4, 5, or 6) GalNAc or GalNAc derivatives, each independently attached to a plurality of nucleotides of the double stranded RNAi agent through a plurality of linkers, *e.g.*, monovalent linkers.

In some embodiments, for example, when the two strands of an iRNA agent of the invention is part of one larger molecule connected by an uninterrupted chain of nucleotides between the 3'-end of one strand and the 5'-end of the respective other strand forming a hairpin loop comprising, a plurality of unpaired nucleotides, each unpaired nucleotide within the hairpin loop may independently comprise a GalNAc or GalNAc derivative attached *via* a monovalent linker.

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 or a cell permeation peptide.

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

D. 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.

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. 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 certain 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.

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 preferred embodiment,

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 have a cleavable linking group that is cleaved at a preferred 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. For example, a liver-targeting ligand can be linked to a cationic lipid through a linker that includes an ester group. Liver cells are rich in esterases, and therefore the linker is cleaved more efficiently in liver cells than in cell types that are not esterase-rich. Other cell-types rich in esterases include cells of the lung, renal cortex, and testis.

Linkers that contain peptide bonds can be used when targeting cell types rich in peptidases, such as liver cells and synoviocytes.

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 is also 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 preferred 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).

i. Redox cleavable linking groups

In certain 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.

ii. Phosphate-based cleavable linking groups

In certain 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-. Exemplary embodiments 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-, wherein Rk at each occurrence can be, independently, C1-C20 alkyl, C1-C20 haloalkyl, C6-C10 aryl, or C7-C12 aralkyl. In certain embodiments a phosphate-based linking group is -O-P(O)(OH)-O-. These candidates can be evaluated using methods analogous to those described above.

iii. Acid cleavable linking groups

In certain embodiments, a cleavable linker comprises an acid cleavable linking group. An acid cleavable linking group is a linking group that is cleaved under acidic conditions. In certain 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). One exemplary embodiment is when 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.

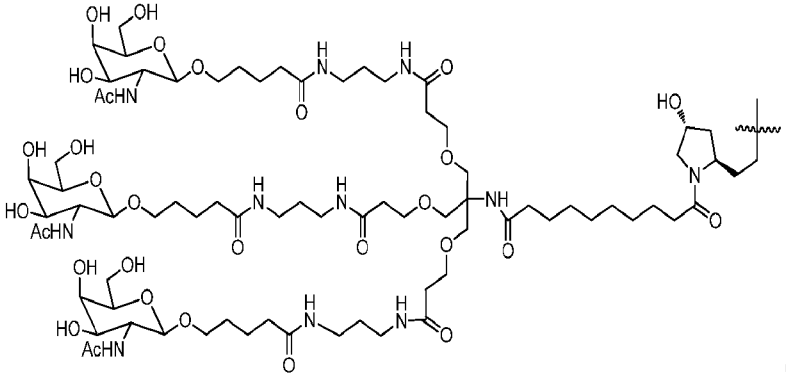
iv. Ester-based cleavable linking groups

In certain 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.

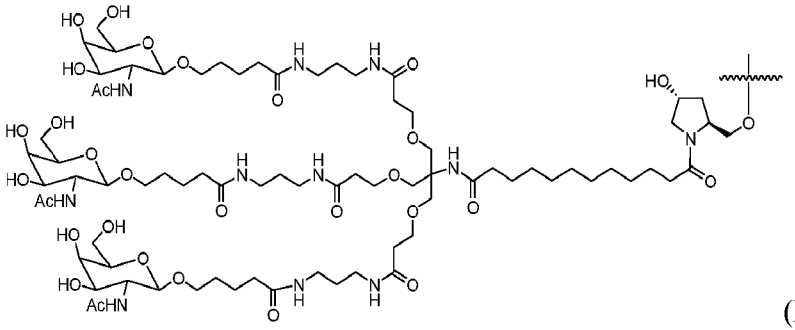
v. Peptide-based cleavable linking groups

In yet another embodiment, 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 – $NHCHR^ACO)NHCHR^BC(O)$- where R^A and R^B are the R groups of the two adjacent amino acids. These candidates can be evaluated using methods analogous to those described above.

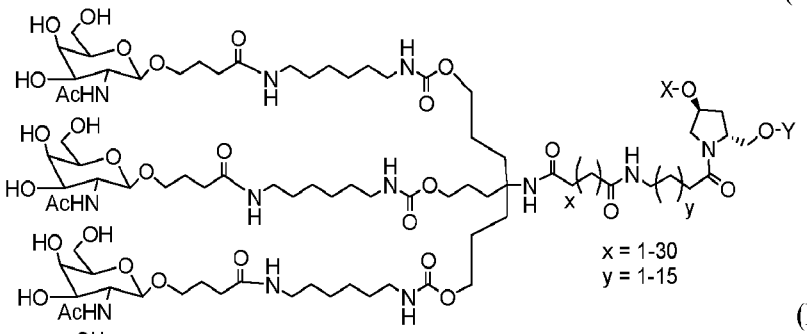
In some embodiments, an iRNA of the invention is conjugated to a carbohydrate through a linker. Non-limiting examples of iRNA carbohydrate conjugates with linkers of the compositions and methods of the invention include, but are not limited to,



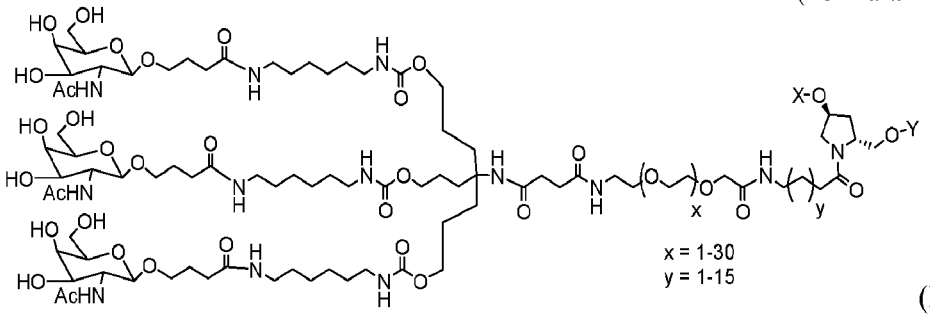
(Formula XXXVII),



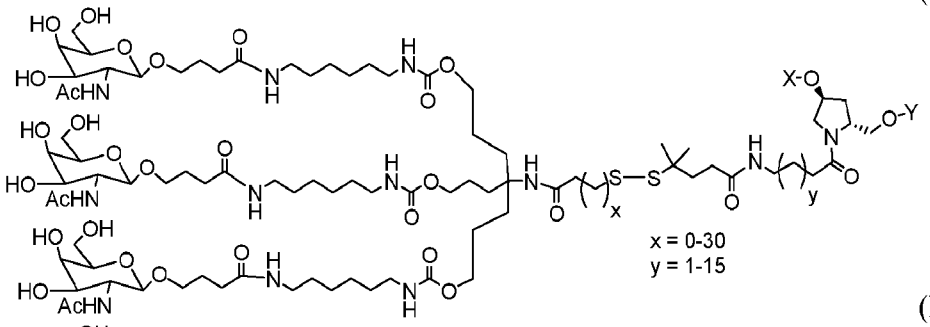
(Formula XXXVIII),



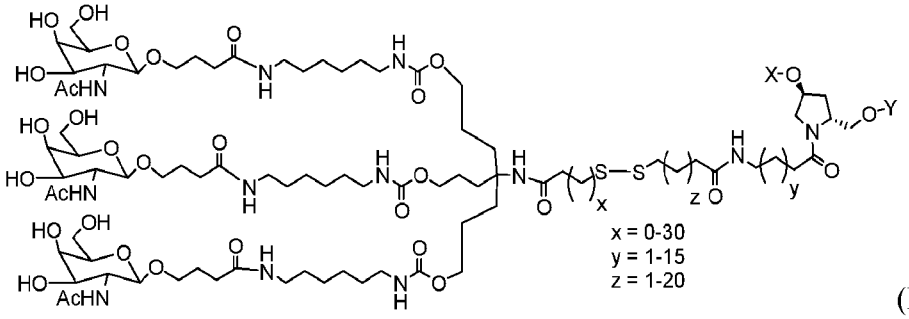
(Formula XXXIX),



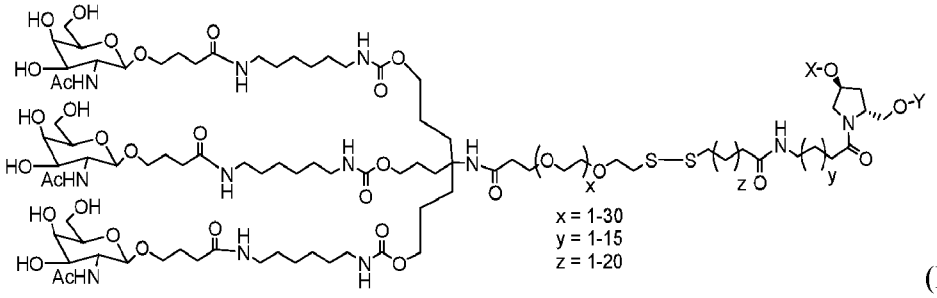
(Formula XL),



(Formula XLI),

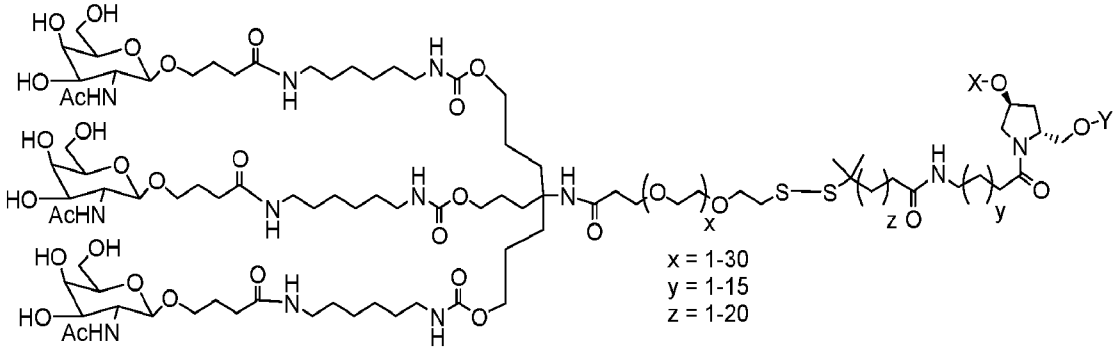


(Formula XLII),



(Formula XLIII),

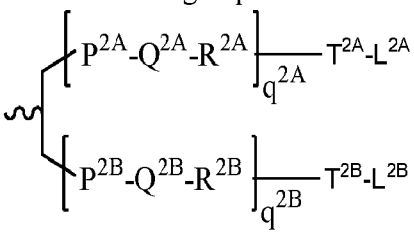
and



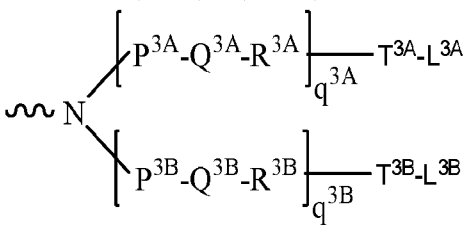
(Formula XLIV), when one of X or Y is an oligonucleotide, the other is a hydrogen.

In certain embodiments of the compositions and methods of the invention, a ligand is one or more "GalNAc" (N-acetylgalactosamine) derivatives attached through a bivalent or trivalent branched linker.

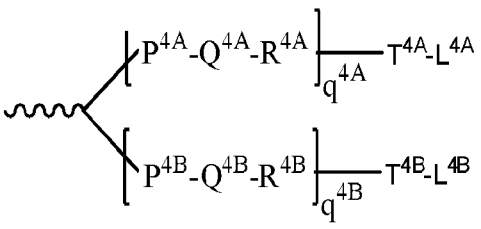
In certain embodiments, a dsRNA of the invention is conjugated to a bivalent or trivalent branched linker selected from the group of structures shown in any of formula (XLV) – (XLVI):



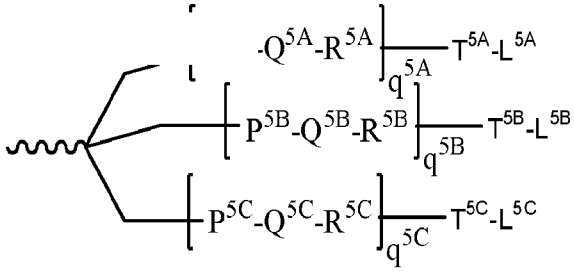
Formula XLV ,



Formula XLVI ,

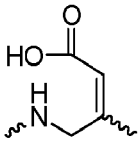
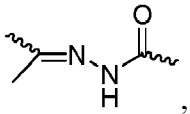
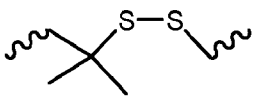
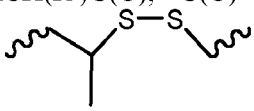
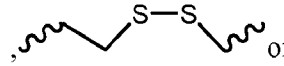


Formula XLVII,

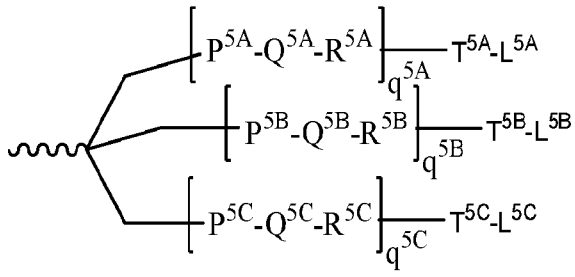


Formula XLVIII,

B, 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 wherin 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; andR^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 (XLIX):



(Formula XLIX),

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.

Representative U.S. Patents that teach the preparation of RNA conjugates include, but are not limited to, U.S. Patent 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;5,688,941; 6,294,664; 6,320,017; 6,576,752; 6,783,931; 6,900,297; 7,037,646; and 8,106,022, the entire contents of each of which are hereby incorporated herein 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 can be incorporated in a single compound or even at a single nucleoside within an iRNA. The present invention also includes iRNA compounds that are chimeric compounds.

"Chimeric" iRNA compounds or "chimeras," in the context of this invention, are iRNA compounds, preferably dsRNA agents, 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, or increased binding affinity for the target nucleic acid. An additional region of the iRNA can 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 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 can 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.

V. Delivery of an RNAi Agent of the Disclosure

The delivery of an RNAi agent of the disclosure to a cell *e.g.*, a cell within a subject, such as a human subject (*e.g.*, a subject in need thereof, such as a subject having a *LRRK2*-associated disorder, *e.g.*, *LRRK2*-associated disease, can be achieved in a number of different ways. For example, delivery may be performed by contacting a cell with an RNAi agent of the disclosure either *in vitro* or *in vivo*. *In vivo* delivery may also be performed directly by administering a composition comprising an RNAi agent, *e.g.*, a dsRNA, to a subject. Alternatively, *in vivo* delivery may be performed indirectly by administering one or more vectors that encode and direct the expression of the RNAi agent. These alternatives are discussed further below.

In general, any method of delivering a nucleic acid molecule (*in vitro* or *in vivo*) can be adapted for use with an RNAi agent of the disclosure (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). For *in vivo* delivery, factors to consider in order to deliver an RNAi agent include, for example, biological stability of the delivered agent, prevention of non-specific effects, and accumulation of the delivered agent in the target tissue. The non-specific effects of an RNAi agent can be minimized by local administration, for example, by direct injection or implantation into a tissue 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 can otherwise be harmed by the agent or that can degrade the agent, and permits a lower total dose of the RNAi agent to be administered. Several studies have shown successful knockdown of gene products when an RNAi agent 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 a.l* (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 RNAi agent 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 RNAi agent to the target tissue and avoid undesirable off-target effects (*e.g.*, without wishing to be bound by theory, use of GNAs as described herein has been identified to destabilize the seed region of a dsRNA, resulting in enhanced preference of such dsRNAs for

on-target effectiveness, relative to off-target effects, as such off-target effects are significantly weakened by such seed region destabilization). RNAi agents can be modified by chemical conjugation to lipophilic groups such as cholesterol to enhance cellular uptake and prevent degradation. For example, an RNAi agent 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 RNAi agent 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 RNAi agent 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 molecule RNAi agent (negatively charged) and also enhance interactions at the negatively charged cell membrane to permit efficient uptake of an RNAi agent by the cell. Cationic lipids, dendrimers, or polymers can either be bound to an RNAi agent, 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 RNAi agent. The formation of vesicles or micelles further prevents degradation of the RNAi agent when administered systemically. Methods for making and administering cationic- RNAi agent 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 RNAi agents 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 RNAi agent forms a complex with cyclodextrin for systemic administration. Methods for administration and pharmaceutical compositions of RNAi agents and cyclodextrins can be found in U.S. Patent No. 7, 427, 605, which is herein incorporated by reference in its entirety.

Certain aspects of the instant disclosure relate to a method of reducing the expression of a *LRRK2* target gene in a cell, comprising contacting said cell with the double-stranded RNAi agent of the disclosure. In one embodiment, the cell is an extraheptic cell, optionally a CNS cell, such as a brain cell. In other embodiment, the cell is an extraheptic cell, optionally an ocular cell.

Another aspect of the disclosure relates to a method of reducing the expression of a *LRRK2* target gene in a subject, comprising administering to the subject the double-stranded RNAi agent of the disclosure.

Another aspect of the disclosure relates to a method of treating a subject having a CNS disorder (neurodegenerative disorder), comprising administering to the subject a therapeutically effective amount of

the double-stranded *LRRK2*-targeting RNAi agent of the disclosure, thereby treating the subject. Exemplary CNS disorders that can be treated by the method of the disclosure include *LRRK2*-associated disease CNS disorder such as Parkinson's disease.

Another aspect of the disclosure relates to a method of treating a subject having an ocular system disorder, comprising administering to the subject a therapeutically effective amount of the double-stranded *LRRK2*-targeting RNAi agent of the disclosure, thereby treating the subject. Exemplary ocular disorders that can be treated by the method of the disclosure include *LRRK2*-associated ocular diseases such as edema in the eyes, lens, and otic vesicles.

Non-limiting Exemplary CNS disorders that can be treated by the method of the disclosure include CNS disorder such as tauopathy, Alzheimer disease, frontotemporal dementia (FTD), behavioral variant frontotemporal dementia (bvFTD), nonfluent variant primary progressive aphasia (nfvPPA), primary progressive aphasia - semantic (PPA-S), primary progressive aphasia - logopenic (PPA-L), frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), Pick's disease (PiD), argyrophilic grain disease (AGD), multiple system tauopathy with presenile dementia (MSTD), white matter tauopathy with globular glial inclusions (FTLD with GGIs), FTLD with MAPT mutations, neurofibrillary tangle (NFT) dementia, FTD with motor neuron disease, amyotrophic lateral sclerosis (ALS), corticobasal syndrome (CBS), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), Parkinson's disease, postencephalitic Parkinsonism, Niemann-Pick disease, Huntington disease, type 1 myotonic dystrophy, and Down syndrome (DS), Crohn's disease.

In one embodiment, the double-stranded RNAi agent is administered intrathecally. By intrathecal administration of the double-stranded RNAi agent, the method can reduce the expression of a *LRRK2* target gene in a brain (*e.g.*, striatum) or spine tissue, for instance, cortex, cerebellum, cervical spine, lumbar spine, and thoracic spine, immune cells such as monocytes and T-cells.

For ease of exposition the formulations, compositions and methods in this section are discussed largely with regard to modified siRNA compounds. It may be understood, however, that these formulations, compositions and methods can be practiced with other siRNA compounds, *e.g.*, unmodified siRNA compounds, and such practice is within the disclosure. A composition that includes an RNAi agent can be delivered to a subject by a variety of routes. Exemplary routes include: intrathecal, intravenous, topical, rectal, anal, vaginal, nasal, pulmonary, and ocular.

The RNAi agents of the disclosure can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically include one or more species of RNAi agent and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the

compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

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 topical (including ophthalmic, vaginal, rectal, intranasal, transdermal), intrathecal, oral, or parenteral. Parenteral administration includes intravenous drip, subcutaneous, intraperitoneal or intramuscular injection, or intrathecal or intraventricular administration.

The route and site of administration may be chosen to enhance targeting. For example, to target neural or spinal tissue, intrathecal injection would be a logical choice. Lung cells might be targeted by administering the RNAi agent in aerosol form. The vascular endothelial cells could be targeted by coating a balloon catheter with the RNAi agent and mechanically introducing the RNA.

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.

Compositions for oral administration include powders or granules, suspensions or solutions in water, syrups, elixirs or non-aqueous media, tablets, capsules, lozenges, or troches. In the case of tablets, carriers that can be used include lactose, sodium citrate and salts of phosphoric acid. Various disintegrants such as starch, and lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc, are commonly used in tablets. For oral administration in capsule form, useful diluents are lactose and high molecular weight polyethylene glycols. When aqueous suspensions are required for oral use, the nucleic acid compositions can be combined with emulsifying and suspending agents. If desired, certain sweetening or flavoring agents can be added.

Compositions for intrathecal or intraventricular administration may include sterile aqueous solutions which may also contain buffers, diluents, and other suitable additives.

Formulations for parenteral administration may include sterile aqueous solutions which may also contain buffers, diluents, and other suitable additives. Intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir. For intravenous use, the total concentration of solutes may be controlled to render the preparation isotonic.

In one embodiment, the administration of the siRNA compound, *e.g.*, a double-stranded siRNA compound, or ssiRNA compound, composition is parenteral, *e.g.*, intravenous (*e.g.*, as a bolus or as a diffusible infusion), intradermal, intraperitoneal, intramuscular, intrathecal, intraventricular, intracranial, subcutaneous, transmucosal, buccal, sublingual, endoscopic, rectal, oral, vaginal, topical, pulmonary, intranasal, urethral, or ocular. Administration can be provided by the subject or by another person, *e.g.*, a health care provider. The medication can be provided in measured doses or in a dispenser which delivers a metered dose. Selected modes of delivery are discussed in more detail below.

A. Intrathecal Administration.

In one embodiment, the double-stranded RNAi agent is delivered by intrathecal injection (*i.e.*, injection into the spinal fluid which bathes the brain and spinal cord tissue). Intrathecal injection of RNAi agents into the spinal fluid can be performed as a bolus injection or *via* minipumps which can be implanted beneath the skin, providing a regular and constant delivery of siRNA into the spinal fluid. The circulation of the spinal fluid from the choroid plexus, where it is produced, down around the spinal chord and dorsal root ganglia and subsequently up past the cerebellum and over the cortex to the arachnoid granulations, where the fluid can exit the CNS, that, depending upon size, stability, and solubility of the compounds injected, molecules delivered intrathecally could hit targets throughout the entire CNS.

In some embodiments, the intrathecal administration is *via* a pump. The pump may be a surgically implanted osmotic pump. In one embodiment, the osmotic pump is implanted into the subarachnoid space of the spinal canal to facilitate intrathecal administration.

In some embodiments, the intrathecal administration is *via* an intrathecal delivery system for a pharmaceutical including a reservoir containing a volume of the pharmaceutical agent, and a pump configured to deliver a portion of the pharmaceutical agent contained in the reservoir. More details about this intrathecal delivery system may be found in WO 2015/116658, which is incorporated by reference in its entirety.

The amount of intrathecally injected RNAi agents may vary from one target gene to another target gene and the appropriate amount that has to be applied may have to be determined individually for each target gene. Typically, this amount ranges from 10 μg to 2 mg, preferably 50 μg to 1500 μg, more preferably 100 μg to 1000 μg.

B. Vector encoded RNAi agents of the Disclosure

RNAi agents targeting the *LRRK2* gene can be expressed from transcription units inserted into DNA or RNA vectors (see, *e.g.*, Couture, A, *et al.*, *TIG.* (1996), 12:5-10; WO 00/22113, WO 00/22114, and US 6,054,299). Expression is preferably sustained (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.*, (1995) *Proc. Natl. Acad. Sci. USA* 92:1292).

The individual strand or strands of an RNAi agent 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 one embodiment, a dsRNA is expressed as inverted repeat polynucleotides joined by a linker polynucleotide sequence such that the dsRNA has a stem and loop structure.

RNAi agent expression vectors are generally DNA plasmids or viral vectors. Expression vectors compatible with eukaryotic cells, preferably those compatible with vertebrate cells, can be used to produce recombinant constructs for the expression of an RNAi agent as described herein. Delivery of RNAi agent 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.

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) SV 40 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 may or may not become incorporated into the cells' genome. The constructs can include viral sequences for transfection, if desired. Alternatively, the construct can be incorporated into vectors capable of episomal replication, *e.g.* EPV and EBV vectors. Constructs for the recombinant expression of an RNAi agent generally require regulatory elements, *e.g.*, promoters, enhancers, *etc.*, to ensure the expression of the RNAi agent in target cells. Other aspects to consider for vectors and constructs are known in the art.

VI. Pharmaceutical Compositions of the Invention

The present disclosure also includes pharmaceutical compositions and formulations which include the RNAi agents of the disclosure. In one embodiment, provided herein are pharmaceutical compositions containing an RNAi agent, as described herein, and a pharmaceutically acceptable carrier. The pharmaceutical compositions containing the RNAi agent are useful for treating a disease or disorder associated with the expression or activity of *LRRK2*, *e.g.*, *LRRK2*-associated disease.

In some embodiments, the pharmaceutical compositions of the invention are sterile. In another embodiment, the pharmaceutical compositions of the invention are pyrogen free.

Such pharmaceutical compositions are formulated based on the mode of delivery. One example is compositions that are formulated for systemic administration *via* parenteral delivery, *e.g.*, by intravenous (IV), intramuscular (IM), or for subcutaneous (subQ) delivery. Another example is compositions that are formulated for direct delivery into the CNS, *e.g.*, by intrathecal or intravitreal routes of injection, optionally by infusion into the brain (*e.g.*, striatum), such as by continuous pump infusion.

The pharmaceutical compositions of the disclosure may be administered in dosages sufficient to inhibit expression of a *LRRK2* gene. In general, a suitable dose of an RNAi agent of the disclosure is in the range of about 0.001 to about 200.0 milligrams per kilogram body weight of the recipient per day, generally in the range of about 1 to 50 mg per kilogram body weight per day.

A repeat-dose regimen may include administration of a therapeutic amount of an RNAi agent on a regular basis, such as monthly to once every six months. In certain embodiments, the RNAi agent is administered about once per quarter (*i.e.*, about once every three months) to about twice per year.

After an initial treatment regimen (*e.g.*, loading dose), the treatments can be administered on a less frequent basis.

In other embodiments, a single dose of the pharmaceutical compositions can be long lasting, such that subsequent doses are administered at not more than 1, 2, 3, or 4 or more month intervals. In some embodiments of the disclosure, a single dose of the pharmaceutical compositions of the disclosure is administered once per month. In other embodiments of the disclosure, a single dose of the pharmaceutical compositions of the disclosure is administered once per quarter to twice per year.

The skilled artisan will appreciate that certain factors can 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 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.

Advances in mouse genetics have generated a number of mouse models for the study of various human diseases, such as Parkinson's disease that would benefit from reduction in the expression of *LRRK2*. Such models can be used for *in vivo* testing of RNAi agents, as well as for determining a therapeutically effective dose. Suitable rodent models are known in the art and include, for example, those described in, for example, Cepeda, *et al.* (*ASN Neuro* (2010) 2(2):e00033) and Pouladi, *et al.* (*Nat Reviews* (2013) 14:708).

The pharmaceutical compositions of the present disclosure can be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration can be topical (*e.g.*, by a transdermal patch), pulmonary, *e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal, oral 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.

The RNAi agents can be delivered in a manner to target a particular tissue, such as the CNS (*e.g.*, neuronal, glial or vascular tissue of the brain).

Pharmaceutical compositions and formulations for topical administration can 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 can be necessary or desirable. Coated condoms, gloves and the like can also be useful. Suitable topical formulations include those in which the RNAi agents 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). RNAi agents featured in the disclosure can be encapsulated within liposomes or can form complexes thereto, in particular to cationic liposomes. Alternatively, RNAi agents can 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 US 6,747,014, which is incorporated herein by reference.

A. RNAi Agent Formulations Comprising Membranous Molecular Assemblies

An RNAi agent for use in the compositions and methods of the disclosure can be formulated for delivery in a membranous molecular assembly, *e.g.*, a liposome or a micelle. As used herein, the term "liposome" refers to a vesicle composed of amphiphilic lipids arranged in at least one bilayer, *e.g.*, one bilayer or a plurality of bilayers. Liposomes include unilamellar and multilamellar vesicles that have a membrane formed from a lipophilic material and an aqueous interior. The aqueous portion contains the RNAi agent composition. The lipophilic material isolates the aqueous interior from an aqueous exterior, which typically does not include the RNAi agent composition, although in some examples, it may. 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 liposomal bilayer fuses with bilayer of the cellular membranes. As the merging of the liposome and cell progresses, the internal aqueous contents that include the RNAi agent are delivered into the cell where the RNAi agent can specifically bind to a target RNA and can mediate RNAi. In some embodiments, the liposomes are also specifically targeted, *e.g.*, to direct the RNAi agent to particular cell types.

A liposome containing an RNAi agent can be prepared by a variety of methods. In one example, the lipid component of a liposome is dissolved in a detergent so that micelles are formed with the lipid component. For example, the lipid component can be an amphipathic cationic lipid or lipid conjugate. The detergent can have a high critical micelle concentration and may be nonionic. Exemplary detergents include cholate, CHAPS, octylglucoside, deoxycholate, and lauroyl sarcosine. The RNAi agent preparation is then added to the micelles that include the lipid component. The cationic groups on the lipid interact with the RNAi agent and condense around the RNAi agent to form a liposome. After condensation, the detergent is removed, *e.g.*, by dialysis, to yield a liposomal preparation of RNAi agent.

If necessary a carrier compound that assists in condensation can be added during the condensation reaction, *e.g.*, by controlled addition. For example, the carrier compound can be a polymer other than a nucleic acid (*e.g.*, spermine or spermidine). pH can also be adjusted to favor condensation.

Methods for producing stable polynucleotide delivery vehicles, which incorporate a polynucleotide/cationic lipid complex as structural components of the delivery vehicle, are further described in, *e.g.*, WO 96/37194, the entire contents of which are incorporated herein by reference. Liposome formation can also include one or more aspects of exemplary methods described in Felgner, P. L. *et al.*, (1987) *Proc. Natl. Acad. Sci. USA* 8:7413-7417; United States Patent No. 4,897,355; United States Patent No. 5,171,678; Bangham *et al.*, (1965) *M. Mol. Biol.* 23:238; Olson *et al.*, (1979) *Biochim. Biophys. Acta* 557:9; Szoka *et al.*, (1978) *Proc. Natl. Acad. Sci.* 75: 4194; Mayhew *et al.*, (1984) *Biochim. Biophys. Acta* 775:169; Kim *et al.*, (1983) *Biochim. Biophys. Acta* 728:339; and Fukunaga *et al.*, (1984) *Endocrinol.* 115:757. Commonly used techniques for preparing lipid aggregates of appropriate size for use as delivery vehicles include sonication and freeze-thaw plus extrusion (see, *e.g.*, Mayer *et al.*, (1986) *Biochim. Biophys. Acta* 858:161. Microfluidization can be used when consistently small (50 to 200 nm) and relatively uniform aggregates are desired (Mayhew *et al.*, (1984) *Biochim. Biophys. Acta* 775:169. These methods are readily adapted to packaging RNAi agent preparations into liposomes.

Liposomes fall into two broad classes. Cationic liposomes are positively charged liposomes which interact with the negatively charged nucleic acid molecules to form a stable complex. The positively charged nucleic acid/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.* (1987) *Biochem. Biophys. Res. Commun.*, 147:980-985).

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

Examples of other methods to introduce liposomes into cells *in vitro* and *in vivo* include United States Patent No. 5,283,185; United States Patent No. 5,171,678; WO 94/00569; WO 93/24640; WO 91/16024; Felgner, (1994) *J. Biol. Chem.* 269:2550; Nabel, (1993) *Proc. Natl. Acad. Sci.* 90:11307; Nabel, (1992) *Human Gene Ther.* 3:649; Gershon, (1993) *Biochem.* 32:7143; and Strauss, (1992) *EMBO J.* 11:417.

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 cyclosporine A into different layers of the skin (Hu *et al.*, (1994) *S.T.P.Pharma. Sci.*, 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.*, (1987) *FEBS Letters,* 223:42; Wu *et al.*, (1993) *Cancer Research,* 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). United States Patent 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. United States Patent 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*).

In one embodiment, cationic liposomes are used. Cationic liposomes possess the advantage of being able to fuse to the cell membrane. Non-cationic liposomes, although not able to fuse as efficiently with the plasma membrane, are taken up by macrophages in vivo and can be used to deliver RNAi agents to macrophages.

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 RNAi agents in their internal compartments from metabolism and degradation (Rosoff, in "Pharmaceutical Dosage Forms," Lieberman, Rieger and Banker (Eds.), 1988, 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.

A positively charged synthetic cationic lipid, N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA) can be used to form small liposomes that interact spontaneously with nucleic acid to form lipid-nucleic acid complexes which are capable of fusing with the negatively charged lipids of the cell membranes of tissue culture cells, resulting in delivery of RNAi agent (see, *e.g.*, Felgner, P. L. *et al.*, (1987) *Proc. Natl. Acad. Sci. USA* 8:7413-7417, and United States Patent No.4,897,355 for a description of DOTMA and its use with DNA).

A DOTMA analogue, 1,2-bis(oleoyloxy)-3-(trimethylammonia)propane (DOTAP) can be used in combination with a phospholipid to form DNA-complexing vesicles. Lipofectin™ Bethesda Research Laboratories, Gaithersburg, Md.) is an effective agent for the delivery of highly anionic nucleic acids into living tissue culture cells that comprise positively charged DOTMA liposomes which interact spontaneously with negatively charged polynucleotides to form complexes. When enough positively charged liposomes are used, the net charge on the resulting complexes is also positive. Positively charged complexes prepared in this way spontaneously attach to negatively charged cell surfaces, fuse with the plasma membrane, and efficiently deliver functional nucleic acids into, for example, tissue culture cells. Another commercially available cationic lipid, 1,2-bis(oleoyloxy)-3,3-(trimethylammonia)propane ("DOTAP") (Boehringer Mannheim, Indianapolis, Indiana) differs from DOTMA in that the oleoyl moieties are linked by ester, rather than ether linkages.

Other reported cationic lipid compounds include those that have been conjugated to a variety of moieties including, for example, carboxyspermine which has been conjugated to one of two types of lipids and includes compounds such as 5-carboxyspermylglycine dioctaoleoylamide ("DOGS") (Transfectam™, Promega, Madison, Wisconsin) and dipalmitoylphosphatidylethanolamine 5-carboxyspermyl-amide ("DPPES") (see, *e.g.*, United States Patent No. 5,171,678).

Another cationic lipid conjugate includes derivatization of the lipid with cholesterol ("DC-Chol") which has been formulated into liposomes in combination with DOPE (See, Gao, X. and Huang, L., (1991) *Biochim. Biophys. Res. Commun.* 179:280). Lipopolylysine, made by conjugating polylysine to DOPE, has been reported to be effective for transfection in the presence of serum (Zhou, X. *et al.*, (1991) *Biochim. Biophys. Acta* 1065:8). For certain cell lines, these liposomes containing conjugated cationic lipids, are said to exhibit lower toxicity and provide more efficient transfection than the DOTMA-containing compositions. Other commercially available cationic lipid products include DMRIE and DMRIE-HP (Vical, La Jolla, California) and Lipofectamine (DOSPA) (Life Technology, Inc., Gaithersburg, Maryland). Other cationic lipids suitable for the delivery of oligonucleotides are described in WO 98/39359 and WO 96/37194.

Liposomal formulations are particularly suited for topical administration with liposomes presenting 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 RNAi agent into the skin. In some implementations, liposomes are used for delivering RNAi agent to epidermal cells and also to enhance the penetration of RNAi agent into dermal

tissues, *e.g.*, into skin. For example, the liposomes can be applied topically. Topical delivery of drugs formulated as liposomes to the skin has been documented (see, *e.g.*, Weiner *et al.*, (1992) *Journal of Drug Targeting*, vol. 2,405-410 and du Plessis *et al.*, (1992) *Antiviral Research*, 18:259-265; Mannino, R. J. and Fould-Fogerite, S., (1998) *Biotechniques* 6:682-690; Itani, T. *et al.*, (1987) *Gene* 56:267-276; Nicolau, C. *et al.* (1987) *Meth. Enzymol.* 149:157-176; Straubinger, R. M. and Papahadjopoulos, D. (1983) *Meth. Enzymol.* 101:512-527; Wang, C. Y. and Huang, L., (1987) *Proc. Natl. Acad. Sci. USA* 84:7851-7855).

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 a drug into the dermis of mouse skin. Such formulations with RNAi agent are useful for treating a dermatological disorder.

Liposomes that include RNAi agents can be made highly deformable. Such deformability can enable the liposomes to penetrate through pore that are smaller than the average radius of the liposome. For example, transfersomes are a type of deformable liposomes. Transferosomes can be made by adding surface edge activators, usually surfactants, to a standard liposomal composition. Transfersomes that include RNAi agent can be delivered, for example, subcutaneously by infection in order to deliver RNAi agent to keratinocytes in the skin. In order to cross 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. In addition, due to the lipid properties, these transferosomes can be self-optimizing (adaptive to the shape of pores, *e.g.*, in the skin), self-repairing, and can frequently reach their targets without fragmenting, and often self-loading.

Other formulations amenable to the present disclosure are described in United States provisional application serial Nos. 61/018,616, filed January 2, 2008; 61/018,611, filed January 2, 2008; 61/039,748, filed March 26, 2008; 61/047,087, filed April 22, 2008 and 61/051,528, filed May 8, 2008. PCT application number PCT/US2007/080331, filed October 3, 2007, also describes formulations that are amenable to the present disclosure.

Transfersomes, yet another type of liposomes, are highly deformable lipid aggregates which are attractive candidates for drug delivery vehicles. Transfersomes can 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 those described herein, particularlay in 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).

The RNAi agent for use in the methods of the disclosure can also be provided as micellar formulations. “Micelles” are defined herein as a particular type of molecular assembly in which amphipathic molecules are arranged in a spherical structure such that all the hydrophobic portions of the molecules are directed inward, leaving the hydrophilic portions in contact with the surrounding aqueous phase. The converse arrangement exists if the environment is hydrophobic.

A mixed micellar formulation suitable for delivery through transdermal membranes may be prepared by mixing an aqueous solution of the siRNA composition, an alkali metal C_8 to C_{22} alkyl sulphate, and a micelle forming compounds. Exemplary micelle forming compounds include lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, glycolic acid, lactic acid, chamomile extract,

cucumber extract, oleic acid, linoleic acid, linolenic acid, monoolein, monooleates, monolaurates, borage oil, evening of primrose oil, menthol, trihydroxy oxo cholanyl glycine and pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, polylysine, triolein, polyoxyethylene ethers and analogues thereof, polidocanol alkyl ethers and analogues thereof, chenodeoxycholate, deoxycholate, and mixtures thereof. The micelle forming compounds may be added at the same time or after addition of the alkali metal alkyl sulphate. Mixed micelles will form with substantially any kind of mixing of the ingredients but vigorous mixing in order to provide smaller size micelles.

In one method a first micellar composition is prepared which contains the siRNA composition and at least the alkali metal alkyl sulphate. The first micellar composition is then mixed with at least three micelle forming compounds to form a mixed micellar composition. In another method, the micellar composition is prepared by mixing the siRNA composition, the alkali metal alkyl sulphate and at least one of the micelle forming compounds, followed by addition of the remaining micelle forming compounds, with vigorous mixing.

Phenol or m-cresol may be added to the mixed micellar composition to stabilize the formulation and protect against bacterial growth. Alternatively, phenol or m-cresol may be added with the micelle forming ingredients. An isotonic agent such as glycerin may also be added after formation of the mixed micellar composition.

For delivery of the micellar formulation as a spray, the formulation can be put into an aerosol dispenser and the dispenser is charged with a propellant. The propellant, which is under pressure, is in liquid form in the dispenser. The ratios of the ingredients are adjusted so that the aqueous and propellant phases become one, *i.e.*, there is one phase. If there are two phases, it is necessary to shake the dispenser prior to dispensing a portion of the contents, *e.g.*, through a metered valve. The dispensed dose of pharmaceutical agent is propelled from the metered valve in a fine spray.

Propellants may include hydrogen-containing chlorofluorocarbons, hydrogen-containing fluorocarbons, dimethyl ether and diethyl ether. In certain embodiments, HFA 134a (1,1,1,2 tetrafluoroethane) may be used.

The specific concentrations of the essential ingredients can be determined by relatively straightforward experimentation. For absorption through the oral cavities, it is often desirable to increase, *e.g.*, at least double or triple, the dosage for through injection or administration through the gastrointestinal tract.

B. Lipid particles

RNAi agents, *e.g.*, dsRNAs of in the disclosure may be fully encapsulated in a lipid formulation, *e.g.*, a LNP, or other nucleic acid-lipid particle.

As used herein, the term "LNP" refers to a stable nucleic acid-lipid particle. LNPs typically contain a cationic lipid, a non-cationic lipid, and a lipid that prevents aggregation of the particle (*e.g.*, a PEG-lipid conjugate). LNPs 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). LNPs include "pSPLP," which include an encapsulated condensing agent-nucleic acid complex as set forth in 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; United States Patent Publication No. 2010/0324120 and WO 96/40964.

In one embodiment, 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. Ranges intermediate to the above recited ranges are also contemplated to be part of the disclosure.

Certain specific LNP formulations for delivery of RNAi agents have been described in the art, including, *e.g.*, "LNP01" formulations as described in, *e.g.*, WO 2008/042973, which is hereby incorporated by reference.

Additional exemplary lipid-dsRNA formulations are identified in the Table 1 below.

Table 1. Additional Exemplary Lipid-dsRNA Formulations

	Ionizable/Cationic Lipid	**cationic lipid/non-cationic lipid/cholesterol/PEG-lipid conjugate Lipid:siRNA ratio**
SNALP-1	1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)	DLinDMA/DPPC/Cholesterol/PEG-cDMA (57.1/7.1/34.4/1.4) lipid:siRNA ~ 7:1
2-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

	Ionizable/Cationic Lipid	**cationic lipid/non-cationic lipid/cholesterol/PEG-lipid conjugate Lipid:siRNA ratio**
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 (Tech G1)	Tech G1/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

	Ionizable/Cationic Lipid	cationic lipid/non-cationic lipid/cholesterol/PEG-lipid conjugate Lipid:siRNA ratio
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) and SNALP (l,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA)) comprising formulations are described in WO 2009/127060, which is hereby incorporated by reference.

XTC comprising formulations are described in WO 2010/088537, the entire contents of which are hereby incorporated herein by reference.

MC3 comprising formulations are described, *e.g.*, in United States Patent Publication No. 2010/0324120, the entire contents of which are hereby incorporated by reference.

ALNY-100 comprising formulations are described in WO 2010/054406, the entire contents of which are hereby incorporated herein by reference.

C12-200 comprising formulations are described in WO 2010/129709, the entire contents of which are hereby incorporated herein by reference.

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 can 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 enhancer surfactants and chelators. Suitable surfactants include fatty acids or esters or salts thereof, bile acids 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 can 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, U.S. 2003/0027780, 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, intraventricular or intrahepatic administration can include sterile aqueous solutions which can 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 can be generated from a variety of components that include, but are not limited to, preformed liquids, self-emulsifying solids and self-emulsifying semisolids. Particularly preferred are formulations that target the brain when treating *LRRK2*-associated diseases or disorders.

The pharmaceutical formulations of the present disclosure, which can conveniently be presented in unit dosage form, can 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 of the present disclosure can 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 of the present disclosure can also be formulated as suspensions in aqueous, non-aqueous or mixed media. Aqueous suspensions can further contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol or dextran. The suspension can also contain stabilizers.

C. Additional Formulations

i. Emulsions

The compositions of the present disclosure can 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 can 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 can contain additional components in addition to the

dispersed phases, and the active drug which can be present as a solution in either aqueous phase, oily phase or itself as a separate phase. Pharmaceutical excipients such as emulsifiers, stabilizers, dyes, and anti-oxidants can also be present in emulsions as needed. Pharmaceutical emulsions can 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 can 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 can be incorporated into either phase of the emulsion. Emulsifiers can 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 can 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 can 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 can 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.

ii. Microemulsions

In one embodiment of the present disclosure, the compositions of RNAi agents and nucleic acids are formulated as microemulsions. A microemulsion can 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, isotropically 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 can, however, be prepared without the use of cosurfactants and alcohol-free self-emulsifying microemulsion systems are known in the art. The aqueous phase can 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 can 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 can form spontaneously when their components are brought together at ambient temperature. This can be particularly advantageous when formulating thermolabile drugs, peptides or RNAi agents. 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 RNAi agents and nucleic acids from the gastrointestinal tract, as well as improve the local cellular uptake of RNAi agents and nucleic acids.

Microemulsions of the present disclosure can 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 RNAi agents and nucleic acids of the present disclosure. Penetration enhancers used in the microemulsions of the present disclosure can 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.

iii. Microparticles

An RNAi agent of the disclosure may be incorporated into a particle, *e.g.*, a microparticle. Microparticles can be produced by spray-drying, but may also be produced by other methods including lyophilization, evaporation, fluid bed drying, vacuum drying, or a combination of these techniques.

iv. Penetration Enhancers

In one embodiment, the present disclosure employs various penetration enhancers to effect the efficient delivery of nucleic acids, particularly RNAi agents, 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 can 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 can 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 (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 RNAi agents 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).

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).

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, 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 RNAi agents 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 beta-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).

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 RNAi agents through the alimentary mucosa (see *e.g.*, Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). This class of penetration enhancers includes, 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 RNAi agents at the cellular level can 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 (WO 97/30731), are also known to enhance the cellular uptake of dsRNAs.

Other agents can 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.

v. Excipients

In contrast to a carrier compound, a "pharmaceutical carrier" or "excipient" is a pharmaceutically acceptable solvent, suspending agent or any other pharmacologically inert vehicle for delivering one or more nucleic acids to an animal. The excipient can 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 can 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 can 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.

vi. Other Components

The compositions of the present disclosure can additionally contain other adjunct components conventionally found in pharmaceutical compositions, at their art-established usage levels. Thus, for example, the compositions can contain additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, local anesthetics or anti-inflammatory agents, or can 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 or aromatic substances and the like which do not deleteriously interact with the nucleic acid(s) of the formulation.

Aqueous suspensions can contain substances which increase the viscosity of the suspension including, for example, sodium carboxymethylcellulose, sorbitol or dextran. The suspension can also contain stabilizers.

In some embodiments, pharmaceutical compositions featured in the disclosure include (a) one or more RNAi agents and (b) one or more agents which function by a non-RNAi mechanism and which are useful in treating a *LRRK2*-associated disorder. Examples of such agents include, but are not lmited to, monoamine inhibitors, reserpine, anticonvulsants, antipsychotic agents, and antidepressants.

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 LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (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 LD_{50}/ED_{50}. Compounds that exhibit high therapeutic indices are preferred.

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 herein in the disclosure lies generally within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage can 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 can 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 IC_{50} (*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 can be measured, for example, by high performance liquid chromatography.

In addition to their administration, as discussed above, the RNAi agents featured in the disclosure can be administered in combination with other known agents effective in treatment of pathological processes mediated by nucleotide repeat expression. In any event, the administering physician can adjust the amount and timing of RNAi agent administration on the basis of results observed using standard measures of efficacy known in the art or described herein.

VII. Kits

In certain aspects, the instant disclosure provides kits that include a suitable container containing a pharmaceutical formulation of a siRNA compound, *e.g.*, a double-stranded siRNA compound, or ssiRNA compound, (*e.g.*, a precursor, *e.g.*, a larger siRNA compound which can be processed into a ssiRNA compound, or a DNA which encodes an siRNA compound, *e.g.*, a double-stranded siRNA compound, or ssiRNA compound, or precursor thereof).

Such kits include one or more dsRNA agent(s) and instructions for use, e.g., instructions for administering a prophylactically or therapeutically effective amount of a dsRNA agent(s). The dsRNA agent may be in a vial or a pre-filled syringe. The kits may optionally further comprise means for administering the dsRNA agent (*e.g.*, an injection device, such as a pre-filled syringe or an intrathecal pump), or means for measuring the inhibition of C3 (*e.g.*, means for measuring the inhibition of *LRRK2* mRNA, LRRK2 protein, and/or *LRRK2* activity). Such means for measuring the inhibition of *LRRK2* may comprise a means for obtaining a sample from a subject, such as, *e.g.*, a CSF and/or plasma sample. The kits of the invention may optionally further comprise means for determining the therapeutically effective or prophylactically effective amount.

In certain embodiments the individual components of the pharmaceutical formulation may be provided in one container. Alternatively, it may be desirable to provide the components of the pharmaceutical formulation separately in two or more containers, *e.g.*, one container for a siRNA compound preparation, and at least another for a carrier compound. The kit may be packaged in a number of different configurations such as one or more containers in a single box. The different components can be combined, *e.g.*, according to instructions provided with the kit. The components can be combined according to a method described herein, *e.g.*, to prepare and administer a pharmaceutical composition. The kit can also include a delivery device.

VIII. Methods for Inhibiting *LRRK2* Expression

The present disclosure also provides methods of inhibiting expression of a *LRRK2* gene in a cell. The methods include contacting a cell with an RNAi agent, *e.g.*, double stranded RNAi agent, in an amount effective to inhibit expression and/or activity of *LRRK2* in the cell, thereby inhibiting expression and/or activity of *LRRK2* in the cell. In certain embodiments of the disclosure, *LRRK2* expression and/or activity is inhibited by at leat 30% preferentially in CNS (*e.g.*, brain) cells. In specific embodiments, *LRRK2* expression and/or activity is inhibited by at least 30%. In other embodiments of the disclosure, *LRRK2* expression and/or activity is inhibited preferentially by at least 30% in ocular (*e.g.*, eye) cells. In certain other embodiments of the disclosure, *LRRK2* expression and/or activity is inhibited by at least 30% preferentially in hepatocytes.

Contacting of a cell with an RNAi agent, *e.g.*, a double stranded RNAi agent, may be done *in vitro* or *in vivo*. Contacting a cell *in vivo* with the RNAi agent includes contacting a cell or group of cells within

a subject, *e.g.*, a human subject, with the RNAi agent. Combinations of *in vitro* and *in vivo* methods of contacting a cell are also possible.

Contacting a cell may be direct or indirect, as discussed above. Furthermore, contacting a cell may be accomplished *via* a targeting ligand, including any ligand described herein or known in the art. In some embodiments, the targeting ligand is a carbohydrate moiety, *e.g.*, a GalNAc ligand, or any other ligand that directs the RNAi agent to a site of interest.

The term "inhibiting," as used herein, is used interchangeably with "reducing," "silencing," "downregulating," "suppressing" and other similar terms, and includes any level of inhibition. In certain embodiments, a level of inhibition, *e.g.*, for an RNAi agent of the instant disclosure, can be assessed in cell culture conditions, *e.g.*, wherein cells in cell culture are transfected *via* Lipofectamine™-mediated transfection at a concentration in the vicinity of a cell of 10 nM or less, 1 nM or less, *etc.* Knockdown of a given RNAi agent can be determined *via* comparison of pre-treated levels in cell culture versus post-treated levels in cell culture, optionally also comparing against cells treated in parallel with a scrambled or other form of control RNAi agent. Knockdown in cell culture of, *e.g.*, at least about 30%, can thereby be identified as indicative of "inhibiting" or "reducing", "downregulating" or "suppressing", *etc.* having occurred. It is expressly contemplated that assessment of targeted mRNA or encoded protein levels (and therefore an extent of "inhibiting", *etc.* caused by an RNAi agent of the disclosure) can also be assessed in *in vivo* systems for the RNAi agents of the instant disclosure, under properly controlled conditions as described in the art.

The phrase "inhibiting *LRRK2*," "inhibiting expression of a *LRRK2* gene" or "inhibiting expression of *LRRK2*," as used herein, includes inhibition of expression of any *LRRK2* gene (such as, *e.g.*, a mouse *Lrrk2* gene, a rat *LRRK2* gene, a monkey *LRRK2* gene, or a human *LRRK2* gene) as well as variants or mutants of a *LRRK2* gene that encode a LRRK2 protein. Thus, the *LRRK2* gene may be a wild-type *LRRK2* gene, a mutant *LRRK2* gene, or a transgenic *LRRK2* gene in the context of a genetically manipulated cell, group of cells, or organism.

"Inhibiting expression of a *LRRK2* gene" includes any level of inhibition of a *LRRK2* gene, *e.g.*, at least partial suppression of the expression of a *LRRK2* gene, such as an inhibition by at least about 25%. In certain embodiments, inhibition is at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95%, or at least about 99%, relative to a control level. *LRRK2* inhibition can be measured using the *in vitro* assay with, *e.g.*, A549 cells and a 10 nM concentration of the RNA agent and the PCR assay as provided in the examples herein, are contemplated to be within the scope of the present disclosure. In some embodiments, *LRRK2* inhibition can be measured using the *in vitro* assay with human A549 cells. In some embodiments, *LRRK2* inhibition can be measured using the *in vitro* assay with primary mouse hepatocytes. In another embodiment, *LRRK2* inhibition can be measured using the *in vitro* assay with Cos-7 (Dual-Luciferase psiCHECK2 vector). In yet another embodiment, *LRRK2* inhibition can be measured using the *in vitro* assay

with BE(2)-C cells. In some embodiments, *LRRK2* inhibition can be measured using the *in vitro* assay with Neuro-2a cells.

The expression of a *LRRK2* gene may be assessed based on the level of any variable associated with *LRRK2* gene expression, *e.g.*, *LRRK2* mRNA level (*e.g.*, sense mRNA, antisense mRNA, total *LRRK2* mRNA, sense *LRRK2* repeat-containing mRNA, and/or antisense *LRRK2* repeat-containing mRNA) or LRRK2 protein level (*e.g.*, total LRRK2 protein, wild-type LRRK2 protein, or expanded repeat-containing protein), or, for example, the level of sense- or antisense-containing foci and/or the level of aberrant dipeptide repeat protein.

Inhibition may be assessed by a decrease in an absolute or relative level of one or more of these variables compared with a control level. The control level may be any type of control level that is utilized in the art, *e.g.*, a pre-dose baseline level, or a level determined from a similar subject, cell, or sample that is untreated or treated with a control (such as, *e.g.*, buffer only control or inactive agent control).

For example, in some embodiments of the methods of the disclosure, expression of a *LRRK2* gene (*e.g.*, as assessed by sense- or antisense-containing foci and/or aberrant dipeptide repeat protein level) is inhibited by at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, or 95%, relative to a control level, or to below the level of detection of the assay. In other embodiments of the methods of the disclosure, expression of a *LRRK2* gene (*e.g.*, as assessed by mRNA or protein expression level) is inhibited by at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95% relative to a control level. In certain embodiments, the methods include a clinically relevant inhibition of expression of *LRRK2*, *e.g.* as demonstrated by a clinically relevant outcome after treatment of a subject with an agent to reduce the expression of *LRRK2*.

Inhibition of the expression of a *LRRK2* gene may be manifested by a reduction of the amount of mRNA expressed by a first cell or group of cells (such cells may be present, for example, in a sample derived from a subject) in which a *LRRK2* gene is transcribed and which has or have been treated (*e.g.*, by contacting the cell or cells with an RNAi agent of the disclosure, or by administering an RNAi agent of the disclosure to a subject in which the cells are or were present) such that the expression of a *LRRK2* gene is inhibited, as compared to a second cell or group of cells substantially identical to the first cell or group of cells but which has not or have not been so treated (control cell(s) not treated with an RNAi agent or not treated with an RNAi agent targeted to the gene of interest). The degree of inhibition may be expressed in terms of:

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

In other embodiments, inhibition of the expression of a *LRRK2* gene may be assessed in terms of a reduction of a parameter that is functionally linked to a *LRRK2* gene expression, *e.g.*, LRRK2 protein expression, sense- or antisense-containing foci and/or the level of aberrant dipeptide repeat protein. *LRRK2*

gene silencing may be determined in any cell expressing *LRRK2*, either endogenous or heterologous from an expression construct, and by any assay known in the art.

Inhibition of the expression of a LRRK2 protein may be manifested by a reduction in the level of the LRRK2 protein (or functional parameter, *e.g.*, kinase and/or GTPase activity) that is expressed by a cell or group of cells (*e.g.*, the level of protein expressed in a sample derived from a subject). As explained above, for the assessment of mRNA suppression, the inhibiton of protein expression levels in a treated cell or group of cells may similarly be expressed as a percentage of the level of protein in a control cell or group of cells. In some embodiments, the phrase "inhibiting *LRRK2*", can also refer to the inhibition of the kinase and/or GTPase activity of *LRRK2*, *e.g.*, at least partial suppression of the *LRRK2* kinase and/or GTPase activity, such as an inhibition by at least about 25%. In certain embodiments, inhibition of the *LRRK2* kinase and/or GTPase activity is by at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95%,, or at least about 99% relative to a control level. *LRRK2* kinase activity can be measured using the *in vitro* assay with, *e.g.*, the assay described in (Smith *et al.* (2006) *Nature Neuroscience* 9(10):1231-3). *LRRK2* GTPase activity can be measured using the *in vitro* assay with, *e.g.*, the assay described in (Xiong *et al.* (2010) *Plos Genet* 6(4): e1000902).

A control cell or group of cells that may be used to assess the inhibition of the expression of a *LRRK2* gene includes a cell or group of cells that has not yet been contacted with an RNAi agent of the disclosure. For example, the control cell or group of cells may be derived from an individual subject (*e.g.*, a human or animal subject) prior to treatment of the subject with an RNAi agent.

The level of *LRRK2* mRNA that is expressed by a cell or group of cells may be determined using any method known in the art for assessing mRNA expression. In one embodiment, the level of expression of *LRRK2* in a sample is determined by detecting a transcribed polynucleotide, or portion thereof, *e.g.*, mRNA of the *LRRK2* gene. RNA may be extracted from cells using RNA extraction techniques including, for example, using acid phenol/guanidine isothiocyanate extraction (RNAzol B; Biogenesis), RNeasy™ RNA preparation kits (Qiagen®) or PAXgene (PreAnalytix, Switzerland). Typical assay formats utilizing ribonucleic acid hybridization include nuclear run-on assays, RT-PCR, RNase protection assays, northern blotting, *in situ* hybridization, and microarray analysis. Strand specific *LRRK2* mRNAs may be detected using the quantitative RT-PCR and or droplet digital PCR methods described in, for example, Jiang, *et al. supra*, Lagier-Tourenne, *et al.*, *supra* and Jiang, *et al.*, *supra*. Circulating *LRRK2* mRNA may be detected using methods the described in WO2012/177906, the entire contents of which are hereby incorporated herein by reference.

In some embodiments, the level of expression of *LRRK2* is determined using a nucleic acid probe. The term "probe", as used herein, refers to any molecule that is capable of selectively binding to a specific *LRRK2* nucleic acid or protein, or fragment thereof. Probes can be synthesized by one of skill in the art, or derived from appropriate biological preparations. Probes may be specifically designed to be labeled.

Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic molecules.

Isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or northern analyses, polymerase chain reaction (PCR) analyses and probe arrays. One method for the determination of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to *LRRK2* mRNA. In one embodiment, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative embodiment, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix® gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in determining the level of *LRRK2* mRNA.

An alternative method for determining the level of expression of *LRRK2* in a sample involves the process of nucleic acid amplification or reverse transcriptase (to prepare cDNA) of for example mRNA in the sample, *e.g.*, by RT-PCR (the experimental embodiment set forth in Mullis, 1987, US Patent No. 4,683,202), ligase chain reaction (Barany (1991) *Proc. Natl. Acad. Sci. USA* 88:189-193), self sustained sequence replication (Guatelli *et al.* (1990) *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi *et al.* (1988) *Bio/Technology* 6:1197), rolling circle replication (Lizardi *et al.*, US Patent No. 5,854,033) or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. In particular aspects of the disclosure, the level of expression of *LRRK2* is determined by quantitative fluorogenic RT-PCR (*i.e.*, the TaqMan™ System), by a Dual-Glo® Luciferase assay, or by other art-recognized method for measurement of *LRRK2* expression or mRNA level.

The expression level of *LRRK2* mRNA may be monitored using a membrane blot (such as used in hybridization analysis such as northern, Southern, dot, and the like), or microwells, sample tubes, gels, beads or fibers (or any solid support comprising bound nucleic acids). See US Patent Nos. 5,770,722, 5,874,219, 5,744,305, 5,677,195 and 5,445,934, which are incorporated herein by reference. The determination of *LRRK2* expression level may also comprise using nucleic acid probes in solution.

In some embodiments, the level of mRNA expression is assessed using branched DNA (bDNA) assays or real time PCR (qPCR). The use of this PCR method is described and exemplified in the Examples presented herein. Such methods can also be used for the detection of *LRRK2* nucleic acids.

The level of LRRK2 protein expression may be determined using any method known in the art for the measurement of protein levels. Such methods include, for example, electrophoresis, capillary electrophoresis, high performance liquid chromatography (HPLC), thin layer chromatography (TLC), hyperdiffusion chromatography, fluid or gel precipitin reactions, absorption spectroscopy, a colorimetric

assays, spectrophotometric assays, flow cytometry, immunodiffusion (single or double), immunoelectrophoresis, western blotting, radioimmunoassay (RIA), enzyme-linked immunosorbent assays (ELISAs), immunofluorescent assays, electrochemiluminescence assays, and the like. The level of LRRK protein expression can be measured by exosome extraction followed by either ELISA/MSD/SIMOA or LC-MS. Such assays can also be used for the detection of proteins indicative of the presence or replication of LRRK2 proteins.

The level of sense- or antisense-containing foci and the level of aberrant dipeptide repeat protein may be assessed using methods well-known to one of ordinary skill in the art, including, for example, fluorescent *in situ* hybridization (FISH), immunohistochemistry and immunoassay (see, *e.g.,* Jiang, *et al. supra*).In some embodiments, the efficacy of the methods of the disclosure in the treatment of a *LRRK2*-associated disease is assessed by a decrease in *LRRK2* mRNA level (*e.g*, by assessment of a CSF sample and/or plasma sample for *LRRK2* level, by brain biopsy, or otherwise).

In some embodiments of the methods of the disclosure, the RNAi agent is administered to a subject such that the RNAi agent is delivered to a specific site within the subject. The inhibition of expression of *LRRK2* may be assessed using measurements of the level or change in the level of *LRRK2* mRNA (*e.g.,* sense mRNA, antisense mRNA, total *LRRK2* mRNA), LRRK2 protein (*e.g.,* total LRRK2 protein, wild-type LRRK2 protein), sense-containing foci, antisense-containing foci, aberrant dipeptide repeat protein in a sample derived from a specific site within the subject, *e.g.*, CNS cells or ocular cells. In certain embodiments, the methods include a clinically relevant inhibition of expression of *LRRK2*, *e.g.* as demonstrated by a clinically relevant outcome after treatment of a subject with an agent to reduce the expression of *LRRK2*, suchas, for example, stabilization or inhibition of caudate atrophy (*e.g.,* as assessed by volumetric MRI (vMRI)), a stabilization or reduction in neurofilament light chain (Nfl) levels in a CSF sample from a subject, a reduction in mutant *LRRK2* mRNA or a cleaved mutant LRRK2 protein, *e.g.,* full-length mutant *LRRK2* mRNA or protein and a cleaved mutant *LRRK2* mRNA or protein, and a stabilization or improvement in Unified *LRRK2*-associated disease Rating Scale (UHDRS) score.

As used herein, the terms detecting or determining a level of an analyte are understood to mean performing the steps to determine if a material, *e.g.*, protein, RNA, is present. As used herein, methods of detecting or determining include detection or determination of an analyte level that is below the level of detection for the method used.

IX. Methods of Treating or Preventing *LRRK2*-Associated Diseases

The present disclosure also provides methods of using an RNAi agent of the disclosure or a composition containing an RNAi agent of the disclosure to reduce or inhibit *LRRK2* expression in a cell. The methods include contacting the cell with a dsRNA of the disclosure and maintaining the cell for a time sufficient to obtain degradation of the mRNA transcript of a *LRRK2* gene, thereby inhibiting expression of the *LRRK2* gene in the cell.

In addition, the present disclosure also provides methods of using an RNAi agent of the disclosure or a composition containing an RNAi agent of the disclosure to reduce the level and/or inhibit formation of sense- and antisense-containing foci in a cell. The methods include contacting the cell with a dsRNA of the disclosure, thereby reducing the level of the *LRRK2* sense- and antisense-containing foci in the cell.

The present disclosure also provides methods of using an RNAi agent of the disclosure or a composition containing an RNAi agent of the disclosure to reduce the level and/or inhibit formation of aberrant dipeptide repeat protein in a cell. The methods include contacting the cell with a dsRNA of the disclosure, thereby reducing the level of the aberrant dipeptide repeat protein in the cell.

Reduction in gene expression, the level of *LRRK2* sense- and antisense-containing foci, and/or aberrant dipeptide repeat protein can be assessed by any methods known in the art. For example, a reduction in the expression of *LRRK2* may be determined by determining the mRNA expression level of *LRRK2* using methods routine to one of ordinary skill in the art, *e.g.,* northern blotting, qRT-PCR; by determining the protein level of *LRRK2* using methods routine to one of ordinary skill in the art, such as western blotting, immunological techniques.

In the methods of the disclosure the cell may be contacted *in vitro* or *in vivo, i.e.,* the cell may be within a subject.

A cell suitable for treatment using the methods of the disclosure may be any cell that expresses a *LRRK2* gene. A cell suitable for use in the methods of the disclosure may be a mammalian cell, *e.g.,* a primate cell (such as a human cell or a non-human primate cell, *e.g.*, a monkey cell or a chimpanzee cell), a non-primate cell (such as a rat cell, or a mouse cell). In one embodiment, the cell is a human cell, *e.g.,* a human CNS cell, or a human ocular cell.

LRRK2 expression (*e.g.,* as assessed by sense mRNA, antisense mRNA, total *LRRK2* mRNA, total LRRK2 protein) is inhibited in the cell by about 20%, 25%, 30%, 35%, 40%, 45%, or 50% relative to the expression in a control cell. In certain embodiments, *LRRK2* expression is inhibited by at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 95% relative to a control level.

Inhibition, as assessed by sense- or antisense-containing foci and/or aberrant dipeptide repeat protein level) is inhibited in the cell by at least 20%, 30%, 40%, preferably at least 50%, 60%, 70%, 80%, 85%, 90%, or 95%, or to below the level of detection of the assay.

The *in vivo* methods of the disclosure may include administering to a subject a composition containing an RNAi agent, where the RNAi agent includes a nucleotide sequence that is complementary to at least a part of an RNA transcript of the *LRRK2* gene of the mammal to be treated. When the organism to be treated is a mammal such as a human, the composition can be administered by any means known in the art including, but not limited to oral, intraperitoneal, or parenteral routes, including intracranial (*e.g.*, intraventricular, intraparenchymal, and intrathecal), intravenous, intramuscular, intravitreal, subcutaneous, transdermal, airway (aerosol), nasal, rectal, and topical (including buccal and sublingual) administration. In

certain embodiments, the compositions are administered by intravenous infusion or injection. In certain embodiments, the compositions are administered by subcutaneous injection. In certain embodiments, the compositions are administered by intrathecal injection.

In some embodiments, the administration is *via* a depot injection. A depot injection may release the RNAi agent in a consistent way over a prolonged time period. Thus, a depot injection may reduce the frequency of dosing needed to obtain a desired effect, *e.g.*, a desired inhibition of *LRRK2*, or a therapeutic or prophylactic effect. A depot injection may also provide more consistent serum concentrations. Depot injections may include subcutaneous injections or intramuscular injections. In preferred embodiments, the depot injection is a subcutaneous injection.

In some embodiments, the administration is *via* a pump. The pump may be an external pump or a surgically implanted pump. In certain embodiments, the pump is a subcutaneously implanted osmotic pump. In other embodiments, the pump is an infusion pump. An infusion pump may be used for intracranial, intravenous, subcutaneous, arterial, or epidural infusions. In preferred embodiments, the infusion pump is a subcutaneous infusion pump. In other embodiments, the pump is a surgically implanted pump that delivers the RNAi agent to the CNS.

The mode of administration may be chosen based upon whether local or systemic treatment is desired and based upon the area to be treated. The route and site of administration may be chosen to enhance targeting.

In one aspect, the present disclosure also provides methods for inhibiting the expression of a *LRRK2* gene in a mammal. The methods include administering to the mammal a composition comprising a dsRNA that targets a *LRRK2* gene in a cell of the mammal, thereby inhibiting expression of the *LRRK2* gene in the cell. Reduction in gene expression can be assessed by any methods known it the art and by methods, *e.g.* qRT-PCR, described herein. Reduction in protein production can be assessed by any methods known it the art and by methods, *e.g.* ELISA, described herein. In one embodiment, a CNS biopsy sample or a cerebrospinal fluid (CSF) sample serves as the tissue material for monitoring the reduction in *LRRK2* gene or protein expression (or of a proxy therefore).

The present disclosure further provides methods of treatment of a subject in need thereof. The treatment methods of the disclosure include administering an RNAi agent of the disclosure to a subject, *e.g.*, a subject that would benefit from inhibition of *LRRK2* expression, such as a subject having missense mutations in the *LRRK2* gene, in a therapeutically effective amount of an RNAi agent targeting a *LRRK2* gene or a pharmaceutical composition comprising an RNAi agent targeting a *LRRK2* gene.

In addition, the present disclosure provides methods of preventing, treating or inhibiting the progression of a *LRRK2*-associated disease or disorder (*e.g.*, a *LRRK2*-associated disorder), in a subject. The methods include administering to the subject a therapeutically effective amount of any of the RNAi agent, *e.g.*, dsRNA agents, or the pharmaceutical composition provided herein, thereby preventing, treating or inhibiting the progression of a *LRRK2*-associated disease or disorder in the subject.

An RNAi agent of the disclosure may be administered as a "free RNAi agent." A free RNAi agent is administered in the absence of a pharmaceutical composition. The naked RNAi agent may be in a suitable buffer solution. The buffer solution may comprise acetate, citrate, prolamine, carbonate, or phosphate, or any combination thereof. In one embodiment, the buffer solution is phosphate buffered saline (PBS). The pH and osmolarity of the buffer solution containing the RNAi agent can be adjusted such that it is suitable for administering to a subject.

Alternatively, an RNAi agent of the disclosure may be administered as a pharmaceutical composition, such as a dsRNA liposomal formulation.

Subjects that would benefit from a reduction or inhibition of *LRRK2* gene expression are those having a *LRRK2*-associated disease, *e.g.*, *LRRK2*-associated disease. Exemplary *LRRK2*-associated diseases include, but are not limited to, PD, Crohn's disease, immune disorders and ocular disorders.

The disclosure further provides methods for the use of an RNAi agent or a pharmaceutical composition thereof, *e.g.*, for treating a subject that would benefit from reduction or inhibition of *LRRK2* expression, *e.g.*, a subject having a *LRRK2*-associated disorder, in combination with other pharmaceuticals or other therapeutic methods, *e.g.*, with known pharmaceuticals or known therapeutic methods, such as, for example, those which are currently employed for treating these disorders. For example, in certain embodiments, an RNAi agent targeting *LRRK2* is administered in combination with, *e.g.*, an agent useful in treating a *LRRK2*-associated disorder as described elsewhere herein or as otherwise known in the art. For example, additional agents suitable for treating a subject that would benefit from reducton in *LRRK2* expression, *e.g.*, a subject having a *LRRK2*-associated disorder, may include agents currently used to treat symptoms of *LRRK2*-associated diseases. The RNAi agent and additional therapeutic agents may be administered at the same time or in the same combination, *e.g.*, intrathecally, or the additional therapeutic agent can be administered as part of a separate composition or at separate times or by another method known in the art or described herein.

Exemplary additional therapeutics include, for example, a monoamine inhibitor, *e.g.*, tetrabenazine (Xenazine), deutetrabenazine (Austedo), and reserpine, an anticonvulsant, *e.g.*, valproic acid (Depakote, Depakene, Depacon), and clonazepam (Klonopin), an antipsychotic agent, *e.g.*, risperidone (Risperdal), and haloperidol (Haldol), and an antidepressant, *e.g.*, paroxetine (Paxil).

In one embodiment, the method includes administering a composition featured herein such that expression of the target *LRRK2* gene is decreased, for at least one month. In preferred embodiments, expression is decreased for at least 2 months, 3 months, or 6 months.

Preferably, the RNAi agents useful for the methods and compositions featured herein specifically target RNAs (primary or processed) of the target *LRRK2* gene. Compositions and methods for inhibiting the expression of these genes using RNAi agents can be prepared and performed as described herein.

Administration of the dsRNA according to the methods of the disclosure may result in a reduction of the severity, signs, symptoms, or markers of such diseases or disorders in a patient with a *LRRK2*-

associated disorder. By "reduction" in this context is meant a statistically significant or clinically significant decrease in such level. The reduction can be, for example, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100% relative to a control level.

Efficacy of treatment or prevention of disease can be assessed, for example by measuring disease progression, disease remission, symptom severity, reduction in pain, quality of life, dose of a medication required to sustain a treatment effect, level of a disease marker or any other measurable parameter appropriate for a given disease being treated or targeted for prevention. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. For example, efficacy of treatment of a *LRRK2*-associated disorder may be assessed, for example, by periodic monitoring of a subject's. Comparisons of the later readings with the initial readings provide a physician an indication of whether the treatment is effective. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. In connection with the administration of an RNAi agent targeting *LRRK2* or pharmaceutical composition thereof, "effective against" a *LRRK2*-associated disorder indicates that administration in a clinically appropriate manner results in a beneficial effect for at least a statistically significant fraction of patients, such as an improvement of symptoms, a cure, a reduction in disease, extension of life, improvement in quality of life, or other effect generally recognized as positive by medical doctors familiar with treating *LRRK2*-associated disorders and the related causes.

A treatment or preventive effect is evident when there is a statistically significant improvement in one or more parameters of disease status, or by a failure to worsen or to develop symptoms where they would otherwise be anticipated. As an example, a favorable change of at least 10% in a measurable parameter of disease, and preferably at least 20%, 30%, 40%, 50% or more can be indicative of effective treatment. Efficacy for a given RNAi agent drug or formulation of that drug can also be judged using an experimental animal model for the given disease as known in the art. When using an experimental animal model, efficacy of treatment is evidenced when a statistically significant reduction in a marker or symptom is observed.

Alternatively, the efficacy can be measured by a reduction in the severity of disease as determined by one skilled in the art of diagnosis based on a clinically accepted disease severity grading scale. Any positive change resulting in *e.g.*, lessening of severity of disease measured using the appropriate scale, represents adequate treatment using an RNAi agent or RNAi agent formulation as described herein.

In certain embodiments, subjects can be administered a therapeutic amount of dsRNA, such as about 0.01 mg/kg to about 200 mg/kg. In other embodiments, subjects can be administered a therapeutic amount of dsRNA, such as about 0.01 mg/kg to about 500 mg/kg. In yet other embodiments, subjects can be administered a therapeutic amount of dsRNA of about 500 mg/kg or more.

The RNAi agent can be administered intrathecally, *via* intravitreal injection, or by intravenous infusion over a period of time, on a regular basis. In certain embodiments, after an initial treatment regimen, the treatments can be administered on a less frequent basis. Administration of the RNAi agent can reduce *LRRK2* levels, *e.g.*, in a cell, tissue, blood, CSF sample or other compartment of the patient. In one embodiment, administration of the RNAi agent can reduce *LRRK2* levels, *e.g.*, in a cell, tissue, blood, CSF sample or other compartment of the patient by at least about 25%, such as about 25%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or about 95% relative to a control level.

Before administration of a full dose of the RNAi agent, patients can be administered a smaller dose, such as a 5% infusion reaction, and monitored for adverse effects, such as an allergic reaction. In another example, the patient can be monitored for unwanted immunostimulatory effects, such as increased cytokine (*e.g.*, TNF-alpha or INF-alpha) levels.

Alternatively, the RNAi agent can be administered subcutaneously, *i.e.*, by subcutaneous injection. One or more injections may be used to deliver the desired, *e.g.*, monthly dose of RNAi agent to a subject. The injections may be repeated over a period of time. The administration may be repeated on a regular basis. In certain embodiments, after an initial treatment regimen, the treatments can be administered on a less frequent basis. A repeat-dose regimine may include administration of a therapeutic amount of RNAi agent on a regular basis, such as monthly or extending to once a quarter, twice per year, once per year. In certain embodiments, the RNAi agent is administered about once per month to about once per quarter (*i.e.*, about once every three months).

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 invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the RNAi agents and methods featured in the invention, 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 addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

An inforrmal Sequence Listing is filed herewith and forms part of the specification as filed.

EXAMPLES

Example 1. RNAi Agent Design, Synthesis, Selection, and *In Vitro* Evaluation

Source of reagents

Where the source of a reagent is not specifically given herein, such reagent can be obtained from any supplier of reagents for molecular biology at a quality/purity standard for application in molecular biology.

Bioinformatics

siRNAs targeting the human *LRRK2* transcript (Homo sapiens leucine rich repeat kinase 2 (*LRRK2*) mRNA, NCBI refseqID NG_011709.1; NCBI GeneID: 120892) were designed using custom R and Python scripts. The human *LRRK2* mRNA (NM_198578.4) has a length of 9239 bases. The human *LRRK2* transcript variant X3 (XM_024448833.1) mRNA has a length of 7989 bases.

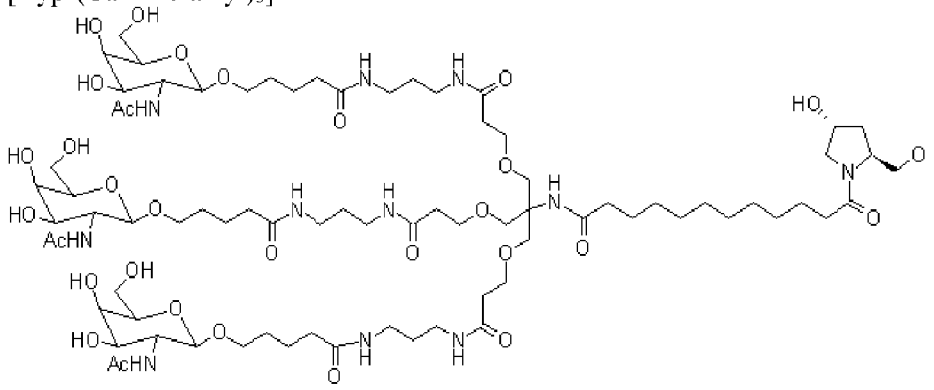
Detailed lists of the unmodified *LRRK2* sense and antisense strand nucleotide sequences are shown in Tables 3, 4, and 6. Detailed lists of the modified *LRRK2* sense and antisense strand nucleotide sequences are shown in Table 5 and 7. Tables 6 and 7 include *LRRK2* sense and antisense strand nucleotide sequences for C16 ligand conjugation.

It is to be understood that, throughout the application, a duplex name without a decimal is equivalent to a duplex name with a decimal which merely references the batch number of the duplex. For example, AD-1631035 is equivalent to AD-1631035.1.

Table 2. 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; and it is understood that when the nucleotide contains a 2'-fluoro modification, then the fluoro replaces the hydroxy at that position of the parent nucleotide (i.e., it is a 2'-deoxy-2'-fluoronucleotide).

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
As	adenosine-3'-phosphorothioate
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
Cs	cytidine-3'-phosphorothioate
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
Gs	guanosine-3'-phosphorothioate
T	5'-methyluridine-3'-phosphate
Tf	2'-fluoro-5-methyluridine-3'-phosphate
Tfs	2'-fluoro-5-methyluridine-3'-phosphorothioate
Ts	5-methyluridine-3'-phosphorothioate

Abbreviation	Nucleotide(s)
U	Uridine-3'-phosphate
Uf	2'-fluorouridine-3'-phosphate
Ufs	2'-fluorouridine -3'-phosphorothioate
Us	uridine -3'-phosphorothioate
N	any nucleotide, modified or unmodified
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
s	phosphorothioate linkage
L96	N-[tris(GalNAc-alkyl)-amido-dodecanoyl)]-4-hydroxyprolinol [Hyp-(GalNAc-alkyl)$_3$] 
(A2p)	Adenosine-2'-phosphate
(A2ps)	Adenosine-2'-phosphorothioate
(C2p)	Cytidine-2'-phosphate
(C2ps)	Cytidine-2'-phosphorothioate
(G2p)	Guanosine-2'-phosphate
(G2ps)	Guanosine-2'-phosphorothioate
(T2p)	Thymidine 2'-phosphate
(T2ps)	Thymidine 2'-phosphorothioate
(U2p)	Uridine-2'-phosphate
(U2ps)	uridine-2'-phosphorothioate
(Agn)	Adenosine-glycol nucleic acid (GNA)
(Cgn)	Cytidine-glycol nucleic acid (GNA)
(Ggn)	Guanosine-glycol nucleic acid (GNA)
(Tgn)	Thymidine-glycol nucleic acid (GNA) S-Isomer
P	Phosphate
VP	Vinyl-phosphonate
dA	2`-deoxyadenosine-3`-phosphate
dAs	2`-deoxyadenosine-3`-phosphorothioate
dC	2`-deoxycytidine-3`-phosphate
dCs	2`-deoxycytidine-3`-phosphorothioate

Abbreviation	Nucleotide(s)
dG	2`-deoxyguanosine-3`-phosphate
dGs	2`-deoxyguanosine-3`-phosphorothioate
dT	2`-deoxythymidine-3`-phosphate
dTs	2`-deoxythymidine-3`-phosphorothioate
dU	2`-deoxyuridine
dUs	2`-deoxyuridine-3`-phosphorothioate
(Ahd)	2'-O-hexadecyl-adenosine-3'-phosphate
(Ahds)	2'-O-hexadecyl-adenosine-3'-phosphorothioate
(Chd)	2'-O-hexadecyl-cytidine-3'-phosphate
(Chds)	2'-O-hexadecyl-cytidine-3'-phosphorothioate
(Ghd)	2'-O-hexadecyl-guanosine-3'-phosphate
(Ghds)	2'-O-hexadecyl-guanosine-3'-phosphorothioate
(Uhd)	2'-O-hexadecyl-uridine-3'-phosphate
(Uhds)	2'-O-hexadecyl-uridine-3'-phosphorothioate

Table 3. Unmodified Sense and Antisense Strand Sequences of Human *LRRK2* dsRNA Agents

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in XM_024448833.1	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in XM_024448833.1	Range in NM_198578.4
AD-1624152	ACACCUGAAUGUUUUGGAGUA	11	212-232	1458-1478	UACUCCAAAACAUUCAGGUGUAU	167	210-232	1456-1478
AD-1624178	AGAAGCAUAUACAUUCUCCUA	12	238-258	1484-1504	UAGGAGAAUGUAUAUGCUUCUGC	168	236-258	1482-1504
AD-1624412	UCACAAACUGGUCCUAGCAGA	13	515-535	1761-1781	UCUGCUAGGACCAGUUUGUGAAU	169	513-535	1759-1781
AD-1624595	GGGUUUAAGUCUUAUAGGAUA	14	704-724	1950-1970	UAUCCUAUAAGACUUAAACCCAG	170	702-724	1948-1970
AD-1624721	AGGAUUUCAGACAAUCUUAGA	15	830-850	2076-2096	UCUAAGAUUGUCUGAAAUCCUUU	171	828-850	2074-2096
AD-1624739	AGCAAUCCUCAAAUUGUCAGA	16	848-868	2094-2114	UCUGACAAUUUGAGGAUUGCUAA	172	846-868	2092-2114
AD-1624856	AACCUCUGUUGCAAGUGUUUA	17	966-986	2212-2232	UAAACACUUGCAACAGAGGUUUA	173	964-986	2210-2232
AD-1624857	ACCUCUGUUGCAAGUGUUUUA	18	967-987	2213-2233	UAAAACACUUGCAACAGAGGUUU	174	965-987	2211-2233
AD-1624894	GAUGCUAGAGAGAGCGUGUGA	19	1022-1042	2268-2288	UCACACGCUCUCUCUAGCAUCAC	175	1020-1042	2266-2288
AD-1625057	UCUCGUGAACAAGAUGUACGA	20	1185-1205	2431-2451	UCGUACAUCUUGUUCACGAGAUC	176	1183-1205	2429-2451
AD-1625155	GGCCAACAAUAGCAUUUGCCA	21	1283-1303	2529-2549	UGGCAAAUGCUAUUGUUGGCCAC	177	1281-1303	2527-2549
AD-1625191	AGGAAAAGUUGAACCUUCUUA	22	1319-1339	2565-2585	UAAGAAGGUUCAACUUUUCCUAU	178	1317-1339	2563-2585
AD-1625192	GGAAAAGUUGAACCUUCUUGA	23	1320-1340	2566-2586	UCAAGAAGGUUCAACUUUUCCUA	179	1318-1340	2564-2586
AD-1625195	AAAGUUGAACCUUCUUGGCUA	24	1323-1343	2569-2589	UAGCCAAGAAGGUUCAACUUUUC	180	1321-1343	2567-2589
AD-	UUGGCUUGGUCC	25	1337-1357	2583-2603	UGAAAUAAAGGAC	181	1335-1357	2581-2603

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in XM_024448833.1	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in XM_024448833.1	Range in NM_198578.4
1625209	UUUAUUUCA				CAAGCCAAGA			
AD-1625230	GAUAAGACUUC UAAUUUAAGA	26	1359-1379	2605-2625	UCUUAAAUUAGAA GUCUUAUCUG	182	1357-1379	2603-2625
AD-1625282	GAAUGGUGAUC AGAUAUCAGA	27	1411-1431	2657-2677	UCUGAUAUCUGAU CACCAUUCUU	183	1409-1431	2655-2677
AD-1625389	UUUAUUCCUGAC UCUUCUAUA	28	1518-1538	2764-2784	UAUAGAAGAGUCA GGAAUAAAGG	184	1516-1538	2762-2784
AD-1625485	UUAGUGUAGGA GAAUUUUACA	29	1621-1641	2867-2887	UGUAAAAUUCUCC UACACUAAUU	185	1619-1641	2865-2887
AD-1625499	UUUUACCGAGA UGCCGUAUUA	30	1635-1655	2881-2901	UAAUACGGCAUCU CGGUAAAAUU	186	1633-1655	2879-2901
AD-1625501	UUACCGAGAUGC CGUAUUACA	31	1637-1657	2883-2903	UGUAAUACGGCAU CUCGGUAAAA	187	1635-1657	2881-2903
AD-1625610	AAACUUCAAUCC CAUAUGAGA	32	1776-1796	3022-3042	UCUCAUAUGGGAU UGAAGUUUUG	188	1774-1796	3020-3042
AD-1625786	UGCACUCACGAG CUUUCCACA	33	1952-1972	3198-3218	UGUGGAAAGCUCG UGAGUGCAUU	189	1950-1972	3196-3218
AD-1625910	CUCUCGAAAUGA CAUUGGACA	34	2084-2104	3330-3350	UGUCCAAUGUCAU UUCGAGAGAC	190	2082-2104	3328-3350
AD-1625928	ACCCUCAGUGGU UUUAGAUCA	35	2102-2122	3348-3368	UGAUCUAAAACCA CUGAGGGUCC	191	2100-2122	3346-3368
AD-1625975	AGUUUAACCUG UCAUAUAACA	36	2149-2169	3395-3415	UGUUAUAUGACAG GUUAAACUGU	192	2147-2169	3393-3415
AD-1626183	UUGCUGCUAUGC CUUUCUUGA	37	2383-2403	3629-3649	UCAAGAAAGGCAU AGCAGCAAGA	193	2381-2403	3627-3649
AD-1626184	UGCUGCUAUGCC UUUCUUGCA	38	2384-2404	3630-3650	UGCAAGAAAGGCA UAGCAGCAAG	194	2382-2404	3628-3650
AD-1626265	UUAAAUCUUCCA CACUUGCGA	39	2466-2486	3712-3732	UCGCAAGUGUGGA AGAUUUAAAA	195	2464-2486	3710-3732
AD-1626266	UAAAUCUUCCAC ACUUGCGGA	40	2467-2487	3713-3733	UCCGCAAGUGUGG AAGAUUUAAA	196	2465-2487	3711-3733
AD-1626268	AAUCUUCCACAC UUGCGGUCA	41	2469-2489	3715-3735	UGACCGCAAGUGU GGAAGAUUUA	197	2467-2489	3713-3735
AD-1626270	UCUUCCACACUU GCGGUCUUA	42	2471-2491	3717-3737	UAAGACCGCAAGU GUGGAAGAUU	198	2469-2491	3715-3737
AD-1626273	UCCACACUUGCG GUCUUUAGA	43	2474-2494	3720-3740	UCUAAAGACCGCA AGUGUGGAAG	199	2472-2494	3718-3740
AD-1626280	UUGCGGUCUUU AGAUAUGAGA	44	2481-2501	3727-3747	UCUCAUAUCUAAA GACCGCAAGU	200	2479-2501	3725-3747
AD-1626349	AACUUAAGGGA ACUCUUAUUA	45	2550-2570	3796-3816	UAAUAAGAGUUCC CUUAAGUUCA	201	2548-2570	3794-3816
AD-1626353	UAAGGGAACUC UUAUUUAGCA	46	2554-2574	3800-3820	UGCUAAAUAAGAG UUCCCUUAAG	202	2552-2574	3798-3820
AD-1626375	UAAUCAGAUCA GCAUCUUGGA	47	2576-2596	3822-3842	UCCAAGAUGCUGA UCUGAUUAUG	203	2574-2596	3820-3842
AD-1626382	AUCAGCAUCUUG GACUUGAGA	48	2583-2603	3829-3849	UCUCAAGUCCAAG AUGCUGAUCU	204	2581-2603	3827-3849

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in XM_024448833.1	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in XM_024448833.1	Range in NM_198578.4
AD-1626428	UAGAGAAACUGCAUCUUUCUA	49	2629-2649	3875-3895	UAGAAAGAUGCAGUUUCUCUACU	205	2627-2649	3873-3895
AD-1626524	UGGAACUAAGAUCCUUUCCCA	50	2725-2745	3971-3991	UGGGAAAGGAUCUUAGUUCCAAG	206	2723-2745	3969-3991
AD-1626636	AUAACCGAAUGAAACUUAUGA	51	2884-2904	4130-4150	UCAUAAGUUUCAUUCGGUUAUAA	207	2882-2904	4128-4150
AD-1626921	CAAUAUAAAGGCUCGCGCUUA	52	3197-3217	4443-4463	UAAGCGCGAGCCUUUAUAUUGAA	208	3195-3217	4441-4463
AD-1626925	AUAAAGGCUCGCGCUUCUUCA	53	3201-3221	4447-4467	UGAAGAAGCGCGAGCCUUUAUAU	209	3199-3221	4445-4467
AD-1626927	AAAGGCUCGCGCUUCUUCUUA	54	3203-3223	4449-4469	UAAGAAGAAGCGCGAGCCUUUAU	210	3201-3223	4447-4469
AD-1626936	UUCUCGUUGGCACACAUUUGA	55	3232-3252	4478-4498	UCAAAUGUGUGCCAACGAGAAUC	211	3230-3252	4476-4498
AD-1626946	CACACAUUUGGAUGUUUCUGA	56	3242-3262	4488-4508	UCAGAAACAUCCAAAUGUGUGCC	212	3240-3262	4486-4508
AD-1627077	AUGCUUUGGCAAAACUUCGGA	57	3373-3393	4619-4639	UCCGAAGUUUUGCCAAAGCAUCA	213	3371-3393	4617-4639
AD-1627110	ACGAGAGCCUUAAUUUCAAGA	58	3406-3426	4652-4672	UCUUGAAAUUAAGGCUCUCGUUU	214	3404-3426	4650-4672
AD-1627308	AAUCAGGAGUCCUUCUUCAUA	59	3622-3642	4868-4888	UAUGAAGAAGGACUCCUGAUUCA	215	3620-3642	4866-4888
AD-1627390	AAUCAUGGCACAGAUUUUGAA	60	3704-3724	4950-4970	UTCAAAAUCUGTGCCAUGAUUUU	216	3702-3724	4948-4970
AD-1627410	CAGUGAAAGUGGAAGGUUGUA	61	3724-3744	4970-4990	UACAACCUUCCACUUUCACUGUC	217	3722-3744	4968-4990
AD-1627411	AGUGAAAGUGGAAGGUUGUCA	62	3725-3745	4971-4991	UGACAACCUUCCACUUUCACUGU	218	3723-3745	4969-4991
AD-1627412	GUGAAAGUGGAAGGUUGUCCA	63	3726-3746	4972-4992	UGGACAACCUUCCACUUUCACUG	219	3724-3746	4970-4992
AD-1627511	CUAGAAAAAUUCCAGAUUGCA	64	3846-3866	5092-5112	UGCAAUCUGGAAUUUUUCUAGGA	220	3844-3866	5090-5112
AD-1627601	AAUUAUCAUCCGACUAUAUGA	65	3956-3976	5202-5222	UCAUAUAGUCGGAUGAUAAUUUC	221	3954-3976	5200-5222
AD-1627625	GCCUUAUUUUCCAAUGGGAUA	66	3980-4000	5226-5246	UAUCCCAUUGGAAAAUAAGGCAU	222	3978-4000	5224-5246
AD-1627631	UUUUCCAAUGGGAUUUUGGUA	67	3986-4006	5232-5252	UACCAAAAUCCCAUUGGAAAAUA	223	3984-4006	5230-5252
AD-1627632	UUUCCAAUGGGAUUUUGGUCA	68	3987-4007	5233-5253	UGACCAAAAUCCCAUUGGAAAAU	224	3985-4007	5231-5253
AD-1627672	UUGAGAUUUCACCUUACAUGA	69	4027-4047	5273-5293	UCAUGUAAGGUGAAAUCUCAAGU	225	4025-4047	5271-5293
AD-1627717	GCCCAAACAGAAUGUAUUGGA	70	4072-4092	5318-5338	UCCAAUACAUUCUGUUUGGGCGA	226	4070-4092	5316-5338
AD-1627766	UGAAGCUUAUUGUCUGGUAGA	71	4121-4141	5367-5387	UCUACCAGACAAUAAGCUUCAGG	227	4119-4141	5365-5387
AD-	GAAGCUUAUUG	72	4122-4142	5368-5388	UCCUACCAGACAA	228	4120-4142	5366-5388

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in XM_024448833.1	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in XM_024448833.1	Range in NM_198578.4
1627767	UCUGGUAGGA				UAAGCUUCAG			
AD-1627769	AGCUUAUUGUCUGGUAGGAUA	73	4124-4144	5370-5390	UAUCCUACCAGACAAUAAGCUUC	229	4122-4144	5368-5390
AD-1627772	UUAUUGUCUGGUAGGAUCUGA	74	4127-4147	5373-5393	UCAGAUCCUACCAGACAAUAAGC	230	4125-4147	5371-5393
AD-1627820	AAAAUUACAGUUCCUUCUUGA	75	4179-4199	5425-5445	UCAAGAAGGAACUGUAAUUUUUA	231	4177-4199	5423-5445
AD-1627838	UGUAGAAAAGGCUGUAUUCUA	76	4197-4217	5443-5463	UAGAAUACAGCCUUUUCUACAAG	232	4195-4217	5441-5463
AD-1627852	UAUUCUUUUGGGCCAAGUUGA	77	4211-4231	5457-5477	UCAACUTGGCCCAAAAGAAUACA	233	4209-4231	5455-5477
AD-1627856	CUUUUGGGCCAAGUUGUGGAA	78	4215-4235	5461-5481	UTCCACAACUUGGCCCAAAAGAA	234	4213-4235	5459-5481
AD-1627866	AAGUUGUGGACCACAUUGAUA	79	4225-4245	5471-5491	UAUCAATGUGGTCCACAACUUGG	235	4223-4245	5469-5491
AD-1627870	UGUGGACCACAUUGAUUCUCA	80	4229-4249	5475-5495	UGAGAATCAAUGUGGUCCACAAC	236	4227-4249	5473-5495
AD-1627896	AAGAAUGGUUUCCUGGGUUGA	81	4255-4275	5501-5521	UCAACCCAGGAAACCAUUCUUCC	237	4253-4275	5499-5521
AD-1627952	UUGAAGAAAUGGGCAUUAUAA	82	4311-4331	5557-5577	UTAUAATGCCCAUUUCUUCAACA	238	4309-4331	5555-5577
AD-1628008	GGAAGGAGAUCUCUUAGUAAA	83	4394-4414	5640-5660	UTUACUAAGAGAUCUCCUUCCUC	239	4392-4414	5638-5660
AD-1628014	AGAUCUCUUAGUAAAUCCAGA	84	4400-4420	5646-5666	UCUGGATUUACTAAGAGAUCUCC	240	4398-4420	5644-5666
AD-1628027	AAUCCAGAUCAACCAAGGCUA	85	4413-4433	5659-5679	UAGCCUTGGUUGAUCUGGAUUUA	241	4411-4433	5657-5679
AD-1628042	AGGCUCACCAUUCCAAUAUCA	86	4428-4448	5674-5694	UGAUAUTGGAATGGUGAGCCUUG	242	4426-4448	5672-5694
AD-1628043	GGCUCACCAUUCCAAUAUCUA	87	4429-4449	5675-5695	UAGATATUGGAAUGGUGAGCCUU	243	4427-4449	5673-5695
AD-1628044	GCUCACCAUUCCAAUAUCUCA	88	4430-4450	5676-5696	UGAGAUAUUGGAAUGGUGAGCCU	244	4428-4450	5674-5696
AD-1628050	CAUUCCAAUAUCUCAGAUUGA	89	4436-4456	5682-5702	UCAATCTGAGATAUUGGAAUGGU	245	4434-4456	5680-5702
AD-1628052	UUCCAAUAUCUCAGAUUGCCA	90	4438-4458	5684-5704	UGGCAATCUGAGAUAUUGGAAUG	246	4436-4458	5682-5704
AD-1628070	GACCUGCCUAGAAAUAUUAUA	91	4476-4496	5722-5742	UAUAAUAUUUCTAGGCAGGUCAG	247	4474-4496	5720-5742
AD-1628073	CUGCCUAGAAAUAUUAUGUUA	92	4479-4499	5725-5745	UAACAUAAUAUTUCUAGGCAGGU	248	4477-4499	5723-5745
AD-1628118	AGAGUUUCUCCUAGGUGAUGA	93	4532-4552	5778-5798	UCAUCACCUAGGAGAAACUCUGG	249	4530-4552	5776-5798
AD-1628119	GAGUUUCUCCUAGGUGAUGGA	94	4533-4553	5779-5799	UCCATCACCUAGGAGAAACUCUG	250	4531-4553	5777-5799
AD-1628133	UGAUGGCAGUUUUGGAUCAGA	95	4547-4567	5793-5813	UCUGAUCCAAAACUGCCAUCACC	251	4545-4567	5791-5813

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in XM_024448833.1	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in XM_024448833.1	Range in NM_198578.4
AD-1628253	GAUGUUGGUGAUGGAGUUAGA	96	4718-4738	5964-5984	UCUAACTCCAUCACCAACAUCCG	252	4716-4738	5962-5984
AD-1628254	AUGUUGGUGAUGGAGUUAGCA	97	4719-4739	5965-5985	UGCUAACUCCATCACCAACAUCC	253	4717-4739	5963-5985
AD-1628273	CCUCCAAGGGUUCCUUGGAUA	98	4738-4758	5984-6004	UAUCCAAGGAACCCUUGGAGGCU	254	4736-4758	5982-6004
AD-1628318	GCCUCACUAGAACCCUACAGA	99	4783-4803	6029-6049	UCUGTAGGGUUCUAGUGAGGCUG	255	4781-4803	6027-6049
AD-1628381	ACUCAGCCAUGAUUAUAUACA	100	4846-4866	6092-6112	UGUATATAAUCAUGGCUGAGUGG	256	4844-4866	6090-6112
AD-1628382	CUCAGCCAUGAUUAUAUACCA	101	4847-4867	6093-6113	UGGUAUAUAAUCAUGGCUGAGUG	257	4845-4867	6091-6113
AD-1628383	UCAGCCAUGAUUAUAUACCGA	102	4848-4868	6094-6114	UCGGTATAUAATCAUGGCUGAGU	258	4846-4868	6092-6114
AD-1628385	AGCCAUGAUUAUAUACCGAGA	103	4850-4870	6096-6116	UCUCGGTAUAUAAUCAUGGCUGA	259	4848-4870	6094-6116
AD-1628396	CACAAUGUGCUGCUUUUCACA	104	4881-4901	6127-6147	UGUGAAAAGCAGCACAUUGUGGG	260	4879-4901	6125-6147
AD-1628412	UCACACUGUAUCCCAAUGCUA	105	4897-4917	6143-6163	UAGCAUTGGGATACAGUGUGAAA	261	4895-4917	6141-6163
AD-1628434	CAUCAUUGCAAAGAUUGCUGA	106	4919-4939	6165-6185	UCAGCAAUCUUTGCAAUGAUGGC	262	4917-4939	6163-6185
AD-1628441	GCAAAGAUUGCUGACUACGGA	107	4926-4946	6172-6192	UCCGTAGUCAGCAAUCUUUGCAA	263	4924-4946	6170-6192
AD-1628442	CAAAGAUUGCUGACUACGGCA	108	4927-4947	6173-6193	UGCCGUAGUCAGCAAUCUUUGCA	264	4925-4947	6171-6193
AD-1628443	AAAGAUUGCUGACUACGGCAA	109	4928-4948	6174-6194	UTGCCGTAGUCAGCAAUCUUUGC	265	4926-4948	6172-6194
AD-1628444	AAGAUUGCUGACUACGGCAUA	110	4929-4949	6175-6195	UAUGCCGUAGUCAGCAAUCUUUG	266	4927-4949	6173-6195
AD-1628467	UCAGUACUGCUGUAGAAUGGA	111	4952-4972	6198-6218	UCCATUCUACAGCAGUACUGAGC	267	4950-4972	6196-6218
AD-1628570	CUACUCUAUGACAUUUUGACA	112	5073-5093	6319-6339	UGUCAAAAUGUCAUAGAGUAGUA	268	5071-5093	6317-6339
AD-1628590	AACUGGAGGUAGAAUAGUAGA	113	5093-5113	6339-6359	UCUACUAUUCUACCUCCAGUUGU	269	5091-5113	6337-6359
AD-1628668	CCAGUUAAAGAAUAUGGUUGA	114	5172-5192	6418-6438	UCAACCAUAUUCUUUAACUGGAU	270	5170-5192	6416-6438
AD-1628754	GAAUUCAGCUGAAUUAGUCUA	115	5285-5305	6531-6551	UAGACUAAUUCAGCUGAAUUCAA	271	5283-5305	6529-6551
AD-1628759	CAGCUGAAUUAGUCUGUCUGA	116	5290-5310	6536-6556	UCAGACAGACUAAUUCAGCUGAA	272	5288-5310	6534-6556
AD-1628764	GAAUUAGUCUGUCUGACGAGA	117	5295-5315	6541-6561	UCUCGUCAGACAGACUAAUUCAG	273	5293-5315	6539-6561
AD-1628794	ACCUAAAAACGUAAUUGUUGA	118	5327-5347	6573-6593	UCAACAAUUACGUUUUUAGGUAA	274	5325-5347	6571-6593
AD-	GAGGACAGCUCU	119	5416-5436	6662-6682	UAAGAAAUGAGA	275	5414-5436	6660-6682

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in XM_024448833.1	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in XM_024448833.1	Range in NM_198578.4
1628883	CAUUUCUUA				GCUGUCCUCUG			
AD-1628951	AUAUUGUGCUUAGCCUUGGUA	120	5484-5504	6730-6750	UACCAAGGCUAAGCACAAUAUUC	276	5482-5504	6728-6750
AD-1628961	UAGCCUUGGUGCAUCUUCCUA	121	5494-5514	6740-6760	UAGGAAGAUGCACCAAGGCUAAG	277	5492-5514	6738-6760
AD-1628963	GCCUUGGUGCAUCUUCCUGUA	122	5496-5516	6742-6762	UACAGGAAGAUGCACCAAGGCUA	278	5494-5516	6740-6762
AD-1629007	UGGGACACAGUCUGGUACUCA	123	5540-5560	6786-6806	UGAGTACCAGACUGUGUCCCAGA	279	5538-5560	6784-6806
AD-1629012	CACAGUCUGGUACUCUCCUGA	124	5545-5565	6791-6811	UCAGGAGAGUACCAGACUGUGUC	280	5543-5565	6789-6811
AD-1629024	CUCUCCUGGUCAUCAAUACCA	125	5557-5577	6803-6823	UGGUAUTGAUGACCAGGAGAGUA	281	5555-5577	6801-6823
AD-1629025	UCUCCUGGUCAUCAAUACCGA	126	5558-5578	6804-6824	UCGGTATUGAUGACCAGGAGAGU	282	5556-5578	6802-6824
AD-1629026	CUCCUGGUCAUCAAUACCGAA	127	5559-5579	6805-6825	UTCGGUAUUGATGACCAGGAGAG	283	5557-5579	6803-6825
AD-1629028	CCUGGUCAUCAAUACCGAAGA	128	5561-5581	6807-6827	UCUUCGGUAUUGAUGACCAGGAG	284	5559-5581	6805-6827
AD-1629031	GGUCAUCAAUACCGAAGAUGA	129	5564-5584	6810-6830	UCAUCUTCGGUAUUGAUGACCAG	285	5562-5584	6808-6830
AD-1629032	GUCAUCAAUACCGAAGAUGGA	130	5565-5585	6811-6831	UCCATCTUCGGTAUUGAUGACCA	286	5563-5585	6809-6831
AD-1629033	UCAUCAAUACCGAAGAUGGGA	131	5566-5586	6812-6832	UCCCAUCUUCGGUAUUGAUGACC	287	5564-5586	6810-6832
AD-1629039	AUACCGAAGAUGGGAAAAAGA	132	5572-5592	6818-6838	UCUUTUTCCCATCUUCGGUAUUG	288	5570-5592	6816-6838
AD-1629092	CUUGUUUGUAUUGCAAUUCCA	133	5626-5646	6872-6892	UGGAAUTGCAATACAAACAAGUG	289	5624-5646	6870-6892
AD-1629200	UACUAAAUAUAGGAAAUGUCA	134	5758-5778	7004-7024	UGACAUTUCCUAUAUUUAGUAUC	290	5756-5778	7002-7024
AD-1629214	AAUGUCAGUACUCCAUUGAUA	135	5772-5792	7018-7038	UAUCAATGGAGTACUGACAUUUC	291	5770-5792	7016-7038
AD-1629216	UGUCAGUACUCCAUUGAUGUA	136	5774-5794	7020-7040	UACATCAAUGGAGUACUGACAUU	292	5772-5794	7018-7040
AD-1629223	ACUCCAUUGAUGUGUUUGAGA	137	5781-5801	7027-7047	UCUCAAACACATCAAUGGAGUAC	293	5779-5801	7025-7047
AD-1629224	CUCCAUUGAUGUGUUUGAGUA	138	5782-5802	7028-7048	UACUCAAACACAUCAAUGGAGUA	294	5780-5802	7026-7048
AD-1629263	GAGGAUGUGGCACAAAGAUUA	139	5839-5859	7085-7105	UAAUCUTUGUGCCACAUCCUCCC	295	5837-5859	7083-7105
AD-1629280	UUUUCUCCUUUUCUAAUGAUA	140	5857-5877	7103-7123	UAUCAUTAGAAAAGGAGAAAAUC	296	5855-5877	7101-7123
AD-1629292	CUAAUGAUUUCACCAUUCAGA	141	5869-5889	7115-7135	UCUGAATGGUGAAAUCAUUAGAA	297	5867-5889	7113-7135
AD-1629298	AUUUCACCAUUCAGAAACUCA	142	5875-5895	7121-7141	UGAGTUTCUGAAUGGUGAAAUCA	298	5873-5895	7119-7141

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in XM_024448833.1	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in XM_024448833.1	Range in NM_198578.4
AD-1629304	CCAUUCAGAAACUCAUUGAGA	143	5881-5901	7127-7147	UCUCAATGAGUTUCUGAAUGGUG	299	5879-5901	7125-7147
AD-1629419	UAGCCCUGUUGUGGAAGUGUA	144	5996-6016	7242-7262	UACACUTCCACAACAGGGCUAUU	300	5994-6016	7240-7262
AD-1629524	AAACACAAAAUGUCUUAUUCA	145	6102-6122	7348-7368	UGAATAAGACATUUUGUGUUUUG	301	6100-6122	7346-7368
AD-1629573	AGAACACUGCUCUUUGGAUAA	146	6151-6171	7397-7417	UTAUCCAAAGAGCAGUGUUCUUC	302	6149-6171	7395-7417
AD-1629580	UGCUCUUUGGAUAGGAACUGA	147	6158-6178	7404-7424	UCAGTUCCUAUCCAAAGAGCAGU	303	6156-6178	7402-7424
AD-1629581	GCUCUUUGGAUAGGAACUGGA	148	6159-6179	7405-7425	UCCAGUTCCUATCCAAAGAGCAG	304	6157-6179	7403-7425
AD-1629597	CUGGAGGAGGCCAUAUUUUAA	149	6175-6195	7421-7441	UTAAAATAUGGCCUCCUCCAGUU	305	6173-6195	7419-7441
AD-1629619	CCUGGAUCUUUCAACUCGUCA	150	6197-6217	7443-7463	UGACGAGUUGAAAGAUCCAGGAG	306	6195-6217	7441-7463
AD-1629620	CUGGAUCUUUCAACUCGUCGA	151	6198-6218	7444-7464	UCGACGAGUUGAAAGAUCCAGGA	307	6196-6218	7442-7464
AD-1629621	UGGAUCUUUCAACUCGUCGAA	152	6199-6219	7445-7465	UTCGACGAGUUGAAAGAUCCAGG	308	6197-6219	7443-7465
AD-1629665	AUUCGGUCAGAGUCAUGAUGA	153	6247-6267	7493-7513	UCAUCATGACUCUGACCGAAUUA	309	6245-6267	7491-7513
AD-1629707	AAAAUGUCAUGCUGGUAUUGA	154	6289-6309	7535-7555	UCAATACCAGCAUGACAUUUUUA	310	6287-6309	7533-7555
AD-1629710	AUGUCAUGCUGGUAUUGGGCA	155	6292-6312	7538-7558	UGCCCAAUACCAGCAUGACAUUU	311	6290-6312	7536-7558
AD-1629711	UGUCAUGCUGGUAUUGGGCUA	156	6293-6313	7539-7559	UAGCCCAAUACCAGCAUGACAUU	312	6291-6313	7537-7559
AD-1629763	GAAAGAGAUACAAUCUUGCUA	157	6347-6367	7593-7613	UAGCAAGAUUGTAUCUCUUUCUG	313	6345-6367	7591-7613
AD-1629799	CAAUCUUCCACAUGAAGUGCA	158	6383-6403	7629-7649	UGCACUTCAUGTGGAAGAUUGAU	314	6381-6403	7627-7649
AD-1629807	CACAUGAAGUGCAAAAUUUAA	159	6391-6411	7637-7657	UTAAAUTUUGCACUUCAUGUGGA	315	6389-6411	7635-7657
AD-1629808	ACAUGAAGUGCAAAAUUUAGA	160	6392-6412	7638-7658	UCUAAATUUUGCACUUCAUGUGG	316	6390-6412	7636-7658
AD-1629809	CAUGAAGUGCAAAAUUUAGAA	161	6393-6413	7639-7659	UTCUAAAUUUUGCACUUCAUGUG	317	6391-6413	7637-7659
AD-1629838	AGUGAGAAAAGAAUUAGCUGA	162	6425-6445	7671-7691	UCAGCUAAUUCTUUUCUCACUUC	318	6423-6445	7669-7691
AD-1629876	AUAGGAAUUGUCUUUGGAUAA	163	6481-6501	7727-7747	UTAUCCAAAGACAAUUCCUAUUU	319	6479-6501	7725-7747
AD-1629878	AGGAAUUGUCUUUGGAUAGGA	164	6483-6503	7729-7749	UCCUAUCCAAAGACAAUUCCUAU	320	6481-6503	7727-7749
AD-1630135	AAAAUAUUAAGACAGUUUCCA	165	6888-6908	8134-8154	UGGAAACUGUCTUAAUAUUUUCA	321	6886-6908	8132-8154
AD-	AAAUAUUAAGA	166	6889-6909	8135-8155	UGGGAAACUGUCU	322	6887-6909	8133-8155

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in XM_024448833.1	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in XM_024448833.1	Range in NM_198578.4
1630136	CAGUUUCCCA				UAAUAUUUUC			

Table 4. Unmodified Sense and Antisense Strand Sequences of Human Reactive *LRRK2* dsRNA Agents

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4
AD-1631019	AGAAGCAUAUACAUUCUCCUA	323	1484-1504	UAGGAGAAUGUAUAUGCUUCUGC	526	1482-1504
AD-1631020	GCAUAUACAUUCUCCUGAAGA	324	1488-1508	UCUUCAGGAGAAUGUAUAUGCUU	527	1486-1508
AD-1631021	UGAUAUUCACAAACUGGUCCA	325	1755-1775	UGGACCAGUUUGUGAAUAUCAUU	528	1753-1775
AD-1631022	UCACAAACUGGUCCUAGCAGA	326	1761-1781	UCUGCUAGGACCAGUUUGUGAAU	529	1759-1781
AD-1631023	UCACACACUGCAGAUGUAUCA	327	1905-1925	UGAUACAUCUGCAGUGUGUGAAG	530	1903-1925
AD-1631024	UGUCUGGGUUUAAGUCUUAUA	328	1945-1965	UAUAAGACUUAAACCCAGACACU	531	1943-1965
AD-1631025	GGGUUUAAGUCUUAUAGGAUA	329	1950-1970	UAUCCUAUAAGACUUAAACCCAG	532	1948-1970
AD-1631026	GUUUCCAGCUUAUACCGAUUA	330	2029-2049	UAAUCGGUAUAAGCUGGAAACCA	533	2027-2049
AD-1631027	UUCUAAACCUCUGUUGCAAGA	331	2207-2227	UCUUGCAACAGAGGUUUAGAAAC	534	2205-2227
AD-1631028	AACCUCUGUUGCAAGUGUUUA	332	2212-2232	UAAACACUUGCAACAGAGGUUUA	535	2210-2232
AD-1631029	ACCUCUGUUGCAAGUGUUUUA	333	2213-2233	UAAAACACUUGCAACAGAGGUUU	536	2211-2233
AD-1631030	UCUCGUGAACAAGAUGUACGA	334	2431-2451	UCGUACAUCUUGUUCACGAGAUC	537	2429-2451
AD-1631031	GGCCAACAAUAGCAUUUGCCA	335	2529-2549	UGGCAAAUGCUAUUGUUGGCCAC	538	2527-2549
AD-1631032	AGGAAAAGUUGAACCUUCUUA	336	2565-2585	UAAGAAGGUUCAACUUUUCCUAU	539	2563-2585
AD-1631033	AAAGUUGAACCUUCUUGGCUA	337	2569-2589	UAGCCAAGAAGGUUCAACUUUUC	540	2567-2589
AD-1631034	CACUAGCAAGAAUGGUGAUCA	338	2648-2668	UGAUCACCAUUCUUGCUAGUGUA	541	2646-2668
AD-1631035	UUUAUUCCUGACUCUUCUAUA	339	2764-2784	UAUAGAAGAGUCAGGAAUAAAGG	542	2762-2784
AD-1631036	AGGAGAAUUUUACCGAGAUGA	340	2874-2894	UCAUCUCGGUAAAAUUCUCCUAC	543	2872-2894
AD-1631037	UUUUACCGAGAUGCCGUAUUA	341	2881-2901	UAAUACGGCAUCUCGGUAAAAUU	544	2879-2901
AD-1631038	CAGCAUUUCUUCUCUGGCUUA	342	3051-3071	UAAGCCAGAGAAGAAAUGCUGUC	545	3049-3071

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4
AD-1631039	CAGAAUGCACUCACG AGCUUA	343	3193-3213	UAAGCUCGUGAGUG CAUUCUGGU	546	3191-3213
AD-1631040	UGCACUCACGAGCUU UCCACA	344	3198-3218	UGUGGAAAGCUCGU GAGUGCAUU	547	3196-3218
AD-1631041	AGCUUUCCACAACAGC UAUGA	345	3208-3228	UCAUAGCUGUUGUG GAAAGCUCG	548	3206-3228
AD-1631042	CUCUCGAAAUGACAU UGGACA	346	3330-3350	UGUCCAAUGUCAUU UCGAGAGAC	549	3328-3350
AD-1631043	UCUCGAAAUGACAUU GGACCA	347	3331-3351	UGGUCCAAUGUCAU UUCGAGAGA	550	3329-3351
AD-1631044	CCUCAGUGGUUUUAG AUCCUA	348	3350-3370	UAGGAUCUAAAACC ACUGAGGGU	551	3348-3370
AD-1631045	GUCCAACUCUGAAAC AGUUUA	349	3380-3400	UAAACUGUUUCAGA GUUGGACAU	552	3378-3400
AD-1631046	GAAACAGUUUAACCU GUCAUA	350	3390-3410	UAUGACAGGUUAAA CUGUUUCAG	553	3388-3410
AD-1631047	AGUUUAACCUGUCAU AUAACA	351	3395-3415	UGUUAUAUGACAGG UUAAACUGU	554	3393-3415
AD-1631048	GAACUUUCUUGAGGC UUGUCA	352	3573-3593	UGACAAGCCUCAAG AAAGUUCUC	555	3571-3593
AD-1631049	AAUUUUCUUGCUGCU AUGCCA	353	3622-3642	UGGCAUAGCAGCAA GAAAAUUCA	556	3620-3642
AD-1631050	CUGCUAUGCCUUUCU UGCCUA	354	3632-3652	UAGGCAAGAAAGGC AUAGCAGCA	557	3630-3652
AD-1631051	UUAAAUCUUCCACAC UUGCGA	355	3712-3732	UCGCAAGUGUGGAA GAUUUAAAA	558	3710-3732
AD-1631052	AAUCUUCCACACUUGC GGUCA	356	3715-3735	UGACCGCAAGUGUG GAAGAUUUA	559	3713-3735
AD-1631053	UCUUCCACACUUGCGG UCUUA	357	3717-3737	UAAGACCGCAAGUG UGGAAGAUU	560	3715-3737
AD-1631054	CUUCCACACUUGCGGU CUUUA	358	3718-3738	UAAAGACCGCAAGU GUGGAAGAU	561	3716-3738
AD-1631055	AUAUGAGCAGCAAUG AUAUUA	359	3740-3760	UAAUAUCAUUGCUG CUCAUAUCU	562	3738-3760
AD-1631056	GAACUUAAGGGAACU CUUAUA	360	3795-3815	UAUAAGAGUUCCCU UAAGUUCAA	563	3793-3815
AD-1631057	AACUCUUAUUUAGCC AUAAUA	361	3806-3826	UAUUAUGGCUAAAU AAGAGUUCC	564	3804-3826
AD-1631058	AUCAGCAUCUUGGAC UUGAGA	362	3829-3849	UCUCAAGUCCAAGA UGCUGAUCU	565	3827-3849
AD-1631059	UCAGCAUCUUGGACU UGAGUA	363	3830-3850	UACUCAAGUCCAAG AUGCUGAUC	566	3828-3850
AD-1631060	AAAAUCUGACAUCUC UGGAUA	364	3938-3958	UAUCCAGAGAUGUC AGAUUUUCA	567	3936-3958
AD-1631061	CUCUGGAUGUCAGUU ACAACA	365	3950-3970	UGUUGUAACUGACA UCCAGAGAU	568	3948-3970
AD-1631062	UGGAACUAAGAUCCU UUCCCA	366	3971-3991	UGGGAAAGGAUCUU AGUUCCAAG	569	3969-3991

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4
AD-1631063	AGCGAGCAUUGUACCUUGCUA	367	4367-4387	UAGCAAGGUACAAUGCUCGCUGC	570	4365-4387
AD-1631064	UGUACCUUGCUGUCUAUGACA	368	4376-4396	UGUCAUAGACAGCAAGGUACAAU	571	4374-4396
AD-1631065	AAUAUAAAGGCUCGCGCUUCA	369	4444-4464	UGAAGCGCGAGCCUUUAUAUUGA	572	4442-4464
AD-1631066	UAUAAAGGCUCGCGCUUCUUA	370	4446-4466	UAAGAAGCGCGAGCCUUUAUAUU	573	4444-4466
AD-1631067	AUAAAGGCUCGCGCUUCUUCA	371	4447-4467	UGAAGAAGCGCGAGCCUUUAUAU	574	4445-4467
AD-1631068	ACUCCUGAAUAAGCGAGGGUA	372	4551-4571	UACCCUCGCUUAUUCAGGAGUUC	575	4549-4571
AD-1631069	CCUGAAUAAGCGAGGGUUCCA	373	4554-4574	UGGAACCCUCGCUUAUUCAGGAG	576	4552-4574
AD-1631070	UCCAGACUGCUAUGUAGAACA	374	4704-4724	UGUUCUACAUAGCAGUCUGGAAU	577	4702-4724
AD-1631071	AAUGAGCUUCCUCACGCAGUA	375	4834-4854	UACUGCGUGAGGAAGCUCAUUUU	578	4832-4854
AD-1631072	GCUUCCUCACGCAGUUCACUA	376	4839-4859	UAGUGAACUGCGUGAGGAAGCUC	579	4837-4859
AD-1631073	UUGUGGAACCCAAGUGGCUUA	377	4925-4945	UAAGCCACUUGGGUUCCACAAAG	580	4923-4945
AD-1631074	CAGUGAAAGUGGAAGGUUGUA	378	4970-4990	UACAACCUUCCACUUUCACUGUC	581	4968-4990
AD-1631075	AGUGAAAGUGGAAGGUUGUCA	379	4971-4991	UGACAACCUUCCACUUUCACUGU	582	4969-4991
AD-1631076	GUGAAAGUGGAAGGUUGUCCA	380	4972-4992	UGGACAACCUUCCACUUUCACUG	583	4970-4992
AD-1631077	UCCAAAGAACUACAUGUCACA	381	5058-5078	UGUGACAUGUAGUUCUUUGGAAA	584	5056-5078
AD-1631078	CUAGAAAAAUUCCAGAUUGCA	382	5092-5112	UGCAAUCUGGAAUUUUUCUAGGA	585	5090-5112
AD-1631079	GAAUAUUUGCUGGUUCCAAGA	383	5128-5148	UCUUGGAACCAGCAAAUAUUCUU	586	5126-5148
AD-1631080	CUCUGAAAUUAUCAUCCGACA	384	5196-5216	UGUCGGAUGAUAAUUUCAGAGUU	587	5194-5216
AD-1631081	GCCUUAUUUUCCAAUGGGAUA	385	5226-5246	UAUCCCAUUGGAAAAUAAGGCAU	588	5224-5246
AD-1631082	GAGAUUUCACCUUACAUGCUA	386	5275-5295	UAGCAUGUAAGGUGAAAUCUCAA	589	5273-5295
AD-1631083	AAACAGAAUGUAUUGGCGACA	387	5322-5342	UGUCGCCAAUACAUUCUGUUUGG	590	5320-5342
AD-1631084	UUACUUAAAUUGGUCUCCUGA	388	5349-5369	UCAGGAGACCAAUUUAAGUAAAU	591	5347-5369
AD-1631085	CUUAAAUUGGUCUCCUGAAGA	389	5352-5372	UCUUCAGGAGACCAAUUUAAGUA	592	5350-5372
AD-1631086	CCUGAAGCUUAUUGUCUGGUA	390	5365-5385	UACCAGACAAUAAGCUUCAGGAG	593	5363-5385

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4
AD-1631087	UGAAGCUUAUUGUCUGGUAGA	391	5367-5387	UCUACCAGACAAUAAGCUUCAGG	594	5365-5387
AD-1631088	GAAGCUUAUUGUCUGGUAGGA	392	5368-5388	UCCUACCAGACAAUAAGCUUCAG	595	5366-5388
AD-1631089	AGCUUAUUGUCUGGUAGGAUA	393	5370-5390	UAUCCUACCAGACAAUAAGCUUC	596	5368-5390
AD-1631090	UUAUUGUCUGGUAGGAUCUGA	394	5373-5393	UCAGAUCCUACCAGACAAUAAGC	597	5371-5393
AD-1631091	CUUUUGGGCCAAGUUGUGGAA	395	5461-5481	UUCCACAACUUGGCCCAAAAGAA	598	5459-5481
AD-1631092	UGUGGACCACAUUGAUUCUCA	396	5475-5495	UGAGAATCAAUGUGGUCCACAAC	599	5473-5495
AD-1631093	CACAUUGAUUCUCUCAUGGAA	397	5482-5502	UUCCAUGAGAGAAUCAAUGUGGU	600	5480-5502
AD-1631094	GGGUUGCUGGAGAUUGAUAUA	398	5515-5535	UAUAUCAAUCUCCAGCAACCCAG	601	5513-5535
AD-1631095	GGUUGCUGGAGAUUGAUAUUA	399	5516-5536	UAAUAUCAAUCUCCAGCAACCCA	602	5514-5536
AD-1631096	UGAAGGAGAAACUCUGUUGAA	400	5541-5561	UUCAACAGAGUUUCUCCUUCACC	603	5539-5561
AD-1631097	UUGAAGAAAUGGGCAUUAUAA	401	5557-5577	UUAUAATGCCCAUUUCUUCAACA	604	5555-5577
AD-1631098	AAUCUUACUUGAUGACUUGAA	402	5607-5627	UUCAAGTCAUCAAGUAAGAUUUU	605	5605-5627
AD-1631099	GCAGAGGAAGGAGAUCUCUUA	403	5635-5655	UAAGAGAUCUCCUUCCUCUGCUU	606	5633-5655
AD-1631100	GAAGGAGAUCUCUUAGUAAAA	404	5641-5661	UUUUACTAAGAGAUCUCCUUCCU	607	5639-5661
AD-1631101	AGGAGAUCUCUUAGUAAAUCA	405	5643-5663	UGAUUUACUAAGAGAUCUCCUUC	608	5641-5663
AD-1631102	GGAGAUCUCUUAGUAAAUCCA	406	5644-5664	UGGAUUTACUAAGAGAUCUCCUU	609	5642-5664
AD-1631103	AGAUCUCUUAGUAAAUCCAGA	407	5646-5666	UCUGGATUUACUAAGAGAUCUCC	610	5644-5666
AD-1631104	AGUAAAUCCAGAUCAACCAAA	408	5655-5675	UUUGGUTGAUCUGGAUUUACUAA	611	5653-5675
AD-1631105	AAUCCAGAUCAACCAAGGCUA	409	5659-5679	UAGCCUTGGUUGAUCUGGAUUUA	612	5657-5679
AD-1631106	AUCCAGAUCAACCAAGGCUCA	410	5660-5680	UGAGCCTUGGUUGAUCUGGAUUU	613	5658-5680
AD-1631107	CCAAGGCUCACCAUUCCAAUA	411	5671-5691	UAUUGGAAUGGUGAGCCUUGGUU	614	5669-5691
AD-1631108	AGGCUCACCAUUCCAAUAUCA	412	5674-5694	UGAUAUTGGAAUGGUGAGCCUUG	615	5672-5694
AD-1631109	CAUUCCAAUAUCUCAGAUUGA	413	5682-5702	UCAAUCTGAGAUAUUGGAAUGGU	616	5680-5702
AD-1631110	AUUCCAAUAUCUCAGAUUGCA	414	5683-5703	UGCAAUCUGAGAUAUUGGAAUGG	617	5681-5703

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4
AD-1631111	UUCCAAUAUCUCAGAUUGCCA	415	5684-5704	UGGCAATCUGAGAUAUUGGAAUG	618	5682-5704
AD-1631112	UGACCUGCCUAGAAAUAUUAA	416	5721-5741	UUAAUATUUCUAGGCAGGUCAGC	619	5719-5741
AD-1631113	GUUGGAAUUUGAACAAGCUCA	417	5757-5777	UGAGCUTGUUCAAAUUCCAACUC	620	5755-5777
AD-1631114	AUUUGAACAAGCUCCAGAGUA	418	5763-5783	UACUCUGGAGCUUGUUCAAAUUC	621	5761-5783
AD-1631115	AGCUCCAGAGUUUCUCCUAGA	419	5772-5792	UCUAGGAGAAACUCUGGAGCUUG	622	5770-5792
AD-1631116	GCUCCAGAGUUUCUCCUAGGA	420	5773-5793	UCCUAGGAGAAACUCUGGAGCUU	623	5771-5793
AD-1631117	CCAGAGUUUCUCCUAGGUGAA	421	5776-5796	UUCACCTAGGAGAAACUCUGGAG	624	5774-5796
AD-1631118	CAGAGUUUCUCCUAGGUGAUA	422	5777-5797	UAUCACCUAGGAGAAACUCUGGA	625	5775-5797
AD-1631119	AGAGUUUCUCCUAGGUGAUGA	423	5778-5798	UCAUCACCUAGGAGAAACUCUGG	626	5776-5798
AD-1631120	GAGUUUCUCCUAGGUGAUGGA	424	5779-5799	UCCAUCACCUAGGAGAAACUCUG	627	5777-5799
AD-1631121	UGAUGGCAGUUUUGGAUCAGA	425	5793-5813	UCUGAUCCAAAACUGCCAUCACC	628	5791-5813
AD-1631122	GAUGGCAGUUUUGGAUCAGUA	426	5794-5814	UACUGATCCAAAACUGCCAUCAC	629	5792-5814
AD-1631123	GAUGUUGGUGAUGGAGUUAGA	427	5964-5984	UCUAACTCCAUCACCAACAUCCG	630	5962-5984
AD-1631124	AUGUUGGUGAUGGAGUUAGCA	428	5965-5985	UGCUAACUCCAUCACCAACAUCC	631	5963-5985
AD-1631125	UGUUGGUGAUGGAGUUAGCCA	429	5966-5986	UGGCUAACUCCAUCACCAACAUC	632	5964-5986
AD-1631126	UUAGCCUCCAAGGGUUCCUUA	430	5980-6000	UAAGGAACCCUUGGAGGCUAACU	633	5978-6000
AD-1631127	CCUCCAAGGGUUCCUUGGAUA	431	5984-6004	UAUCCAAGGAACCCUUGGAGGCU	634	5982-6004
AD-1631128	GCCUCACUAGAACCCUACAGA	432	6029-6049	UCUGUAGGGUUCUAGUGAGGCUG	635	6027-6049
AD-1631129	CCUCACUAGAACCCUACAGCA	433	6030-6050	UGCUGUAGGGUUCUAGUGAGGCU	636	6028-6050
AD-1631130	CUGAUGGUUUGAGAUACCUCA	434	6071-6091	UGAGGUAUCUCAAACCAUCAGCU	637	6069-6091
AD-1631131	ACUCAGCCAUGAUUAUAUACA	435	6092-6112	UGUAUATAAUCAUGGCUGAGUGG	638	6090-6112
AD-1631132	CUCAGCCAUGAUUAUAUACCA	436	6093-6113	UGGUAUAUAAUCAUGGCUGAGUG	639	6091-6113
AD-1631133	CAGCCAUGAUUAUAUACCGAA	437	6095-6115	UUCGGUAUAUAAUCAUGGCUGAG	640	6093-6115
AD-1631134	CAAUGUGCUGCUUUUCACACA	438	6129-6149	UGUGUGAAAAGCAGCACAUUGUG	641	6127-6149

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4
AD-1631135	GCUGCUUUUCACACUGUAUCA	439	6135-6155	UGAUACAGUGUGAAAAGCAGCAC	642	6133-6155
AD-1631136	CUGCUUUUCACACUGUAUCCA	440	6136-6156	UGGAUACAGUGUGAAAAGCAGCA	643	6134-6156
AD-1631137	UUCACACUGUAUCCCAAUGCA	441	6142-6162	UGCAUUGGGAUACAGUGUGAAAA	644	6140-6162
AD-1631138	ACACUGUAUCCCAAUGCUGCA	442	6145-6165	UGCAGCAUUGGGAUACAGUGUGA	645	6143-6165
AD-1631139	UGCAAAGAUUGCUGACUACGA	443	6171-6191	UCGUAGUCAGCAAUCUUUGCAAU	646	6169-6191
AD-1631140	GCAAAGAUUGCUGACUACGGA	444	6172-6192	UCCGUAGUCAGCAAUCUUUGCAA	647	6170-6192
AD-1631141	AAAGAUUGCUGACUACGGCAA	445	6174-6194	UUGCCGUAGUCAGCAAUCUUUGC	648	6172-6194
AD-1631142	AAGAUUGCUGACUACGGCAUA	446	6175-6195	UAUGCCGUAGUCAGCAAUCUUUG	649	6173-6195
AD-1631143	AUUGCUGACUACGGCAUUGCA	447	6178-6198	UGCAAUGCCGUAGUCAGCAAUCU	650	6176-6198
AD-1631144	UGCUGACUACGGCAUUGCUCA	448	6180-6200	UGAGCAAUGCCGUAGUCAGCAAU	651	6178-6200
AD-1631145	GCUCAGUACUGCUGUAGAAUA	449	6196-6216	UAUUCUACAGCAGUACUGAGCAA	652	6194-6216
AD-1631146	CUCAGUACUGCUGUAGAAUGA	450	6197-6217	UCAUUCUACAGCAGUACUGAGCA	653	6195-6217
AD-1631147	UCAGUACUGCUGUAGAAUGGA	451	6198-6218	UCCAUUCUACAGCAGUACUGAGC	654	6196-6218
AD-1631148	GAGGUAGAAUAGUAGAGGGUA	452	6344-6364	UACCCUCUACUAUUCUACCUCCA	655	6342-6364
AD-1631149	GUAGAGGGUUUGAAGUUUCCA	453	6355-6375	UGGAAACUUCAAACCCUCUACUA	656	6353-6375
AD-1631150	UUUGACAUUUUGAAUUCAGCA	454	6520-6540	UGCUGAAUUCAAAAUGUCAAAGA	657	6518-6540
AD-1631151	CAGCUGAAUUAGUCUGUCUGA	455	6536-6556	UCAGACAGACUAAUUCAGCUGAA	658	6534-6556
AD-1631152	GCUGAAUUAGUCUGUCUGACA	456	6538-6558	UGUCAGACAGACUAAUUCAGCUG	659	6536-6558
AD-1631153	CUGAAUUAGUCUGUCUGACGA	457	6539-6559	UCGUCAGACAGACUAAUUCAGCU	660	6537-6559
AD-1631154	GAAUUAGUCUGUCUGACGAGA	458	6541-6561	UCUCGUCAGACAGACUAAUUCAG	661	6539-6561
AD-1631155	UAGUAGAAUAUUGUGCUUAGA	459	6723-6743	UCUAAGCACAAUAUUCUACUAUC	662	6721-6743
AD-1631156	AGUAGAAUAUUGUGCUUAGCA	460	6724-6744	UGCUAAGCACAAUAUUCUACUAU	663	6722-6744
AD-1631157	AAUAUUGUGCUUAGCCUUGGA	461	6729-6749	UCCAAGGCUAAGCACAAUAUUCU	664	6727-6749
AD-1631158	AUAUUGUGCUUAGCCUUGGUA	462	6730-6750	UACCAAGGCUAAGCACAAUAUUC	665	6728-6750

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4
AD-1631159	GCUUAGCCUUGGUGCAUCUUA	463	6737-6757	UAAGAUGCACCAAGGCUAAGCAC	666	6735-6757
AD-1631160	UAGCCUUGGUGCAUCUUCCUA	464	6740-6760	UAGGAAGAUGCACCAAGGCUAAG	667	6738-6760
AD-1631161	GCCUUGGUGCAUCUUCCUGUA	465	6742-6762	UACAGGAAGAUGCACCAAGGCUA	668	6740-6762
AD-1631162	CCUUGGUGCAUCUUCCUGUUA	466	6743-6763	UAACAGGAAGAUGCACCAAGGCU	669	6741-6763
AD-1631163	UGGGACACAGUCUGGUACUCA	467	6786-6806	UGAGUACCAGACUGUGUCCCAGA	670	6784-6806
AD-1631164	GGGACACAGUCUGGUACUCUA	468	6787-6807	UAGAGUACCAGACUGUGUCCCAG	671	6785-6807
AD-1631165	CACAGUCUGGUACUCUCCUGA	469	6791-6811	UCAGGAGAGUACCAGACUGUGUC	672	6789-6811
AD-1631166	CAGUCUGGUACUCUCCUGGUA	470	6793-6813	UACCAGGAGAGUACCAGACUGUG	673	6791-6813
AD-1631167	AGUCUGGUACUCUCCUGGUCA	471	6794-6814	UGACCAGGAGAGUACCAGACUGU	674	6792-6814
AD-1631168	CUCUCCUGGUCAUCAAUACCA	472	6803-6823	UGGUAUTGAUGACCAGGAGAGUA	675	6801-6823
AD-1631169	CUCCUGGUCAUCAAUACCGAA	473	6805-6825	UUCGGUAUUGAUGACCAGGAGAG	676	6803-6825
AD-1631170	UCCUGGUCAUCAAUACCGAAA	474	6806-6826	UUUCGGTAUUGAUGACCAGGAGA	677	6804-6826
AD-1631171	CCUGGUCAUCAAUACCGAAGA	475	6807-6827	UCUUCGGUAUUGAUGACCAGGAG	678	6805-6827
AD-1631172	CUGGUCAUCAAUACCGAAGAA	476	6808-6828	UUCUUCGGUAUUGAUGACCAGGA	679	6806-6828
AD-1631173	GGUCAUCAAUACCGAAGAUGA	477	6810-6830	UCAUCUTCGGUAUUGAUGACCAG	680	6808-6830
AD-1631174	GUCAUCAAUACCGAAGAUGGA	478	6811-6831	UCCAUCTUCGGUAUUGAUGACCA	681	6809-6831
AD-1631175	UCAUCAAUACCGAAGAUGGGA	479	6812-6832	UCCCAUCUUCGGUAUUGAUGACC	682	6810-6832
AD-1631176	CAUCAAUACCGAAGAUGGGAA	480	6813-6833	UUCCCATCUUCGGUAUUGAUGAC	683	6811-6833
AD-1631177	AUCAAUACCGAAGAUGGGAAA	481	6814-6834	UUUCCCAUCUUCGGUAUUGAUGA	684	6812-6834
AD-1631178	AUACCGAAGAUGGGAAAAAGA	482	6818-6838	UCUUUUTCCCAUCUUCGGUAUUG	685	6816-6838
AD-1631179	UGGGAAAAAGAGACAUACCCA	483	6828-6848	UGGGUATGUCUCUUUUUCCCAUC	686	6826-6848
AD-1631180	GGGAAAAAGAGACAUACCCUA	484	6829-6849	UAGGGUAUGUCUCUUUUUCCCAU	687	6827-6849
AD-1631181	AAAGAGACAUACCCUAGAAAA	485	6834-6854	UUUUCUAGGGUAUGUCUCUUUUU	688	6832-6854
AD-1631182	CUUGUUUGUAUUGCAAUUCCA	486	6872-6892	UGGAAUTGCAAUACAAACAAGUG	689	6870-6892

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4
AD-1631183	UUUUCUUUUGGUUGGAACCGA	487	6918-6938	UCGGUUCCAACCAAAAGAAAAUU	690	6916-6938
AD-1631184	UUUCUUUUGGUUGGAACCGCA	488	6919-6939	UGCGGUTCCAACCAAAAGAAAAU	691	6917-6939
AD-1631185	UUCUUUUGGUUGGAACCGCUA	489	6920-6940	UAGCGGTUCCAACCAAAAGAAAA	692	6918-6940
AD-1631186	CUUUUGGUUGGAACCGCUGAA	490	6922-6942	UUCAGCGGUUCCAACCAAAAGAA	693	6920-6942
AD-1631187	CUGCUCCUUUGAAGAUACUAA	491	6989-7009	UUAGUATCUUCAAAGGAGCAGCU	694	6987-7009
AD-1631188	UACUAAAUAUAGGAAAUGUCA	492	7004-7024	UGACAUTUCCUAUAUUUAGUAUC	695	7002-7024
AD-1631189	AUAGGAAAUGUCAGUACUCCA	493	7012-7032	UGGAGUACUGACAUUUCCUAUAU	696	7010-7032
AD-1631190	CAGUACUCCAUUGAUGUGUUA	494	7023-7043	UAACACAUCAAUGGAGUACUGAC	697	7021-7043
AD-1631191	GAUGUGUUUGAGUGAAUCCAA	495	7035-7055	UUGGAUTCACUCAAACACAUCAA	698	7033-7055
AD-1631192	AUGUGUUUGAGUGAAUCCACA	496	7036-7056	UGUGGATUCACUCAAACACAUCA	699	7034-7056
AD-1631193	UUUGAGUGAAUCCACAAAUUA	497	7041-7061	UAAUUUGUGGAUUCACUCAAACA	700	7039-7061
AD-1631194	GAGGAUGUGGCACAAAGAUUA	498	7085-7105	UAAUCUTUGUGCCACAUCCUCCC	701	7083-7105
AD-1631195	UUUUCUCCUUUUCUAAUGAUA	499	7103-7123	UAUCAUTAGAAAAGGAGAAAAUC	702	7101-7123
AD-1631196	UCUAAUGAUUUCACCAUUCAA	500	7114-7134	UUGAAUGGUGAAAUCAUUAGAAA	703	7112-7134
AD-1631197	UAAUGAUUUCACCAUUCAGAA	501	7116-7136	UUCUGAAUGGUGAAAUCAUUAGA	704	7114-7136
AD-1631198	AUUUCACCAUUCAGAAACUCA	502	7121-7141	UGAGUUTCUGAAUGGUGAAAUCA	705	7119-7141
AD-1631199	AUUCAGAAACUCAUUGAGACA	503	7129-7149	UGUCUCAAUGAGUUUCUGAAUGG	706	7127-7149
AD-1631200	GACAAGAACAAGCCAACUGUA	504	7146-7166	UACAGUTGGCUUGUUCUUGUCUC	707	7144-7166
AD-1631201	AAGAACAAGCCAACUGUUUUA	505	7149-7169	UAAAACAGUUGGCUUGUUCUUGU	708	7147-7169
AD-1631202	UAGCCCUGUUGUGGAAGUGUA	506	7242-7262	UACACUTCCACAACAGGGCUAUU	709	7240-7262
AD-1631203	CUGUUGUGGAAGUGUGGGAUA	507	7247-7267	UAUCCCACACUUCCACAACAGGG	710	7245-7267
AD-1631204	GUGCACUUUUUAAGGGAGGUA	508	7303-7323	UACCUCCCUUAAAAAGUGCACGC	711	7301-7323
AD-1631205	AAACACAAAAUGUCUUAUUCA	509	7348-7368	UGAAUAAGACAUUUUGUGUUUUG	712	7346-7368
AD-1631206	CAAAAUGUCUUAUUCUGGGAA	510	7353-7373	UUCCCAGAAUAAGACAUUUUGUG	713	7351-7373

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4
AD-1631207	AGAACACUGCUCUUUGGAUAA	511	7397-7417	UUAUCCAAAGAGCAGUGUUCUUC	714	7395-7417
AD-1631208	UGCUCUUUGGAUAGGAACUGA	512	7404-7424	UCAGUUCCUAUCCAAAGAGCAGU	715	7402-7424
AD-1631209	GCUCUUUGGAUAGGAACUGGA	513	7405-7425	UCCAGUTCCUAUCCAAAGAGCAG	716	7403-7425
AD-1631210	CCUGGAUCUUUCAACUCGUCA	514	7443-7463	UGACGAGUUGAAAGAUCCAGGAG	717	7441-7463
AD-1631211	AUUCGGUCAGAGUCAUGAUGA	515	7493-7513	UCAUCATGACUCUGACCGAAUUA	718	7491-7513
AD-1631212	UAAAAAUGUCAUGCUGGUAUA	516	7533-7553	UAUACCAGCAUGACAUUUUUAAG	719	7531-7553
AD-1631213	AUGUCAUGCUGGUAUUGGGCA	517	7538-7558	UGCCCAAUACCAGCAUGACAUUU	720	7536-7558
AD-1631214	UGUCAUGCUGGUAUUGGGCUA	518	7539-7559	UAGCCCAAUACCAGCAUGACAUU	721	7537-7559
AD-1631215	GAAAGAGAUACAAUCUUGCUA	519	7593-7613	UAGCAAGAUUGUAUCUCUUUCUG	722	7591-7613
AD-1631216	AUCAAUCUUCCACAUGAAGUA	520	7627-7647	UACUUCAUGUGGAAGAUUGAUGU	723	7625-7647
AD-1631217	CAAUCUUCCACAUGAAGUGCA	521	7629-7649	UGCACUTCAUGUGGAAGAUUGAU	724	7627-7649
AD-1631218	AUAGGAAUUGUCUUUGGAUAA	522	7727-7747	UUAUCCAAAGACAAUUCCUAUUU	725	7725-7747
AD-1631219	UACUAAAAUUUAUAAGGCCGA	523	8005-8025	UCGGCCTUAUAAAUUUUAGUAUG	726	8003-8025
AD-1631220	CUAAAAUUUAUAAGGCCGAUA	524	8007-8027	UAUCGGCCUUAUAAAUUUUAGUA	727	8005-8027
AD-1631221	AAAAUAUUAAGACAGUUUCCA	525	8134-8154	UGGAAACUGUCUUAAUAUUUUCA	728	8132-8154

Table 5. Modified Sense and Antisense Strand Sequences of Human *LRRK2* dsRNA Agents

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1631035	ususuau(Uhd)CfcUfGfAfcucuucuauaL96	729	VPusAfsuaga(Agn)gagucaGfgAfauaaasgsg	1088	CCUUUAUUCCUGACUCUUCUAUG	1447
AD-1625389	ususuau(Uhd)ccUfGfAfcucuucuauaL96	730	VPusdAsuadGadAgagudCaGfgaauaaasgsg	1089	CCUUUAUUCCUGACUCUUCUAUG	1448
AD-1628570	csusacu(Chd)uaUfGfAfcauuuugacaL96	731	VPusdGsucdAadAaugudCaUfagaguagsusa	1090	UACUACUCUAUGACAUUUUGACA	1449
AD-1631151	csasgcu(Ghd)AfaUfUfAfgucugucugaL96	732	VPusCfsagac(Agn)gacuaaUfuCfagcugsasa	1091	UUCAGCUGAAUUAGUCUGUCUGA	1450
AD-1628759	csasgcu(Ghd)aaUfUfAfgucugucugaL96	733	VPusdCsagdAcdAgacudAaUfucagcugsasa	1092	UUCAGCUGAAUUAGUCUGUCUGA	1451
AD-1631205	asasaca(Chd)AfaAfAfUfgucuuauucaL96	734	VPusGfsaaua(Agn)gacauuUfuGfuguuususg	1093	CAAAACACAAAAUGUCUUAUUCU	1452

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1629524	asasaca(Chd)aaAfAfUf gucuuauucaL96	735	VPusdGsaadTadAgacadTu Ufuguguuususg	1094	CAAAACACAAAAU GUCUUAUUCU	1453
AD-1631045	gsuscca(Ahd)CfuCfUf Gfaaacaguuua L96	736	VPusAfsaacu(G2p)uuucag AfgUfuggacsasu	1095	AUGUCCAACUCUG AAACAGUUUA	1454
AD-1631077	uscscaa(Ahd)GfaAfCfU facaugucacaL96	737	VPusGfsugac(Agn)uguagu UfcUfuuggasasa	1096	UUUCCAAAGAACU ACAUGUCACA	1455
AD-1631109	csasuuc(Chd)AfaUfAf Ufcucagauuga L96	738	VPusCfsaauc(Tgn)gagaua UfuGfgaaugsgsu	1097	ACCAUUCCAAUAU CUCAGAUUGC	1456
AD-1628050	csasuuc(Chd)aaUfAfUf cucagauuga L96	739	VPusdCsaadTcdTgagadTa Ufuggaaugsgsu	1098	ACCAUUCCAAUAU CUCAGAUUGC	1457
AD-1628073	csusgcc(Uhd)agAfAfAf uauuauguua L96	740	VPusdAsacdAudAauaudT uCfuaggcagsgsu	1099	ACCUGCCUAGAAA UAUUAUGUUG	1458
AD-1631135	gscsugc(Uhd)UfuUfCf Afcacuguauca L96	741	VPusGfsauac(Agn)guguga AfaAfgcagcsasc	1100	GUGCUGCUUUUCA CACUGUAUCC	1459
AD-1631061	csuscug(Ghd)AfuGfUf Cfaguuacaaca L96	742	VPusGfsuugu(Agn)acugac AfuCfcagagsasu	1101	AUCUCUGGAUGUC AGUUACAACU	1460
AD-1631063	asgscga(Ghd)CfaUfUf Gfuaccuugcua L96	743	VPusAfsgcaa(G2p)guacaa UfgCfucgcusgsc	1102	GCAGCGAGCAUUG UACCUUGCUG	1461
AD-1631093	csascau(Uhd)GfaUfUfC fucucauggaaL96	744	VPusUfsccau(G2p)agagaa UfcAfaugugsgsu	1103	ACCACAUUGAUUC UCUCAUGGAA	1462
AD-1631190	csasgua(Chd)UfcCfAfU fugauguguua L96	745	VPusAfsacac(Agn)ucaaug GfaGfuacugsasc	1104	GUCAGUACUCCAU UGAUGUGUUU	1463
AD-1631196	uscsuaa(Uhd)GfaUfUf Ufcaccauucaa L96	746	VPusUfsgaau(G2p)gugaaa UfcAfuuagasasa	1105	UUUCUAAUGAUUU CACCAUUCAG	1464
AD-1629292	csusaau(Ghd)auUfUfCf accauucagaL96	747	VPusdCsugdAadTggugdA aAfucauuagsasa	1106	UUCUAAUGAUUUC ACCAUUCAGA	1465
AD-1629304	cscsauu(Chd)agAfAfAf cucauugagaL96	748	VPusdCsucdAadTgagudT uCfugaauggsusg	1107	CACCAUUCAGAAA CUCAUUGAGA	1466
AD-1631210	cscsugg(Ahd)UfcUfUf Ufcaacucguca L96	749	VPusGfsacga(G2p)uugaaa GfaUfccaggsasg	1108	CUCCUGGAUCUUU CAACUCGUCG	1467
AD-1629619	cscsugg(Ahd)ucUfUfUf caacucgucaL96	750	VPusdGsacdGadGuugadA aGfauccaggsasg	1109	CUCCUGGAUCUUU CAACUCGUCG	1468
AD-1631216	asuscaa(Uhd)CfuUfCfC facaugaaguaL96	751	VPusAfscuuc(Agn)ugugga AfgAfuugausgsu	1110	ACAUCAAUCUUCC ACAUGAAGUG	1469
AD-1631042	csuscuc(Ghd)AfaAfUf Gfacauuggaca L96	752	VPusGfsucca(Agn)ugucau UfuCfgagagsasc	1111	GUCUCUCGAAAUG ACAUUGGACC	1470
AD-1625910	csuscuc(Ghd)aaAfUfGf acauuggacaL96	753	VPusdGsucdCadAugucdA uUfucgagagsasc	1112	GUCUCUCGAAAUG ACAUUGGACC	1471
AD-1626273	uscscac(Ahd)cuUfGfCf ggucuuuagaL96	754	VPusdCsuadAadGaccgdC aAfguguggasasg	1113	CUUCCACACUUGC GGUCUUUAGA	1472
AD-1626353	usasagg(Ghd)aaCfUfCf uuauuuagcaL96	755	VPusdGscudAadAuaagdA gUfucccuuasasg	1114	CUUAAGGGAACUC UUAUUUAGCC	1473
AD-1626428	usasgag(Ahd)aaCfUfGf caucuuucuaL96	756	VPusdAsgadAadGaugcdA gUfuucucuascsu	1115	AGUAGAGAAACUG CAUCUUUCUC	1474
AD-1631060	asasaau(Chd)UfgAfCfA fucucuggauaL96	757	VPusAfsucca(G2p)agaugu CfaGfauuuuscsa	1116	UGAAAAUCUGACA UCUCUGGAUG	1475
AD-1631078	csusaga(Ahd)AfaAfUf Ufccagauugca L96	758	VPusGfscaau(C2p)uggaau UfuUfucuagsgsa	1117	UCCUAGAAAAAUU CCAGAUUGCU	1476

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1627511	csusaga(Ahd)aaAfUfUfUfccagauugcaL96	759	VPusdGscadAudCuggadAuUfuuucuagsgsa	1118	UCCUAGAAAAAUUCCAGAUUGCU	1477
AD-1627672	ususgag(Ahd)uuUfCfAfAfccuuacaugaL96	760	VPusdCsaudGudAaggudGaAfaucucaasgsu	1119	ACUUGAGAUUUCACCUUACAUGC	1478
AD-1631100	gsasagg(Ahd)GfaUfCfUfcuuaguaaaaL96	761	VPusUfsuuac(Tgn)aagagaUfcUfccuucscsu	1120	AGGAAGGAGAUCUCUUAGUAAAU	1479
AD-1631101	asgsgag(Ahd)UfcUfCfUfuaguaaaucaL96	762	VPusGfsauuu(Agn)cuaagaGfaUfcuccususc	1121	GAAGGAGAUCUCUUAGUAAAUCC	1480
AD-1631111	ususcca(Ahd)UfaUfCfUfcagauugccaL96	763	VPusGfsgcaa(Tgn)cugagaUfaUfuggaasusg	1122	CAUUCCAAUAUCUCAGAUUGCCC	1481
AD-1628052	ususcca(Ahd)uaUfCfUfUfcagauugccaL96	764	VPusdGsgcdAadTcugadGaUfauuggaasusg	1123	CAUUCCAAUAUCUCAGAUUGCCC	1482
AD-1631117	cscsaga(Ghd)UfuUfCfUfccuaggugaaL96	765	VPusUfscacc(Tgn)aggagaAfaCfucuggsasg	1124	CUCCAGAGUUUCUCCUAGGUGAU	1483
AD-1629214	asasugu(Chd)agUfAfCfUfuccauugauaL96	766	VPusdAsucdAadTggagdTaCfugacauususc	1125	GAAAUGUCAGUACUCCAUUGAUG	1484
AD-1631193	ususuga(Ghd)UfgAfAfUfccacaaauuaL96	767	VPusAfsauuu(G2p)uggauuCfaCfucaaascsa	1126	UGUUUGAGUGAAUCCACAAAUUC	1485
AD-1631195	ususuuc(Uhd)CfcUfUfUfucuaaugauaL96	768	VPusAfsucau(Tgn)agaaaaGfgAfgaaaasusc	1127	GAUUUUCUCCUUUUCUAAUGAUU	1486
AD-1629280	ususuuc(Uhd)ccUfUfUfUfucuaaugauaL96	769	VPusdAsucdAudTagaadAaGfgagaaaasusc	1128	GAUUUUCUCCUUUUCUAAUGAUU	1487
AD-1631197	usasaug(Ahd)UfuUfCfAfccauucagaaL96	770	VPusUfscuga(Agn)uggugaAfaUfcauuasgsa	1129	UCUAAUGAUUUCACCAUUCAGAA	1488
AD-1631198	asusuuc(Ahd)CfcAfUfUfcagaaacucaL96	771	VPusGfsaguu(Tgn)cugaauGfgUfgaaauscsa	1130	UGAUUUCACCAUUCAGAAACUCA	1489
AD-1629298	asusuuc(Ahd)ccAfUfUfUfcagaaacucaL96	772	VPusdGsagdTudTcugadAuGfgugaaauscsa	1131	UGAUUUCACCAUUCAGAAACUCA	1490
AD-1631201	asasgaa(Chd)AfaGfCfCffaacuguuuuaL96	773	VPusAfsaaac(Agn)guuggcUfuGfuucuusgsu	1132	ACAAGAACAAGCCAACUGUUUUC	1491
AD-1629620	csusgga(Uhd)cuUfUfCfUfaacucgucgaL96	774	VPusdCsgadCgdAguugdAaAfgauccagsgsa	1133	UCCUGGAUCUUUCAACUCGUCGA	1492
AD-1631026	gsusuuc(Chd)AfgCfUfUfufauaccgauuaL96	775	VPusAfsaucg(G2p)uauaagCfuGfgaaacscsa	1134	UGGUUUCCAGCUUAUACCGAUUU	1493
AD-1631027	ususcua(Ahd)AfcCfUfCfuguugcaagaL96	776	VPusCfsuugc(Agn)acagagGfuUfuagaasasc	1135	GUUUCUAAACCUCUGUUGCAAGU	1494
AD-1631028	asasccu(Chd)UfgUfUfGfcaaguguuuaL96	777	VPusAfsaaca(C2p)uugcaaCfaGfagguususa	1136	UAAACCUCUGUUGCAAGUGUUUU	1495
AD-1624856	asasccu(Chd)ugUfUfGfcaaguguuuaL96	778	VPusdAsaadCadCuugcdAaCfagagguususa	1137	UAAACCUCUGUUGCAAGUGUUUU	1496
AD-1631041	asgscuu(Uhd)CfcAfCfAfacagcuaugaL96	779	VPusCfsauag(C2p)uguuguGfgAfaagcuscsg	1138	CGAGCUUUCCACAACAGCUAUGU	1497
AD-1631051	ususaaa(Uhd)CfuUfCfCffacacuugcgaL96	780	VPusCfsgcaa(G2p)ugugga AfgAfuuuaasasa	1139	UUUUAAAUCUUCCACACUUGCGG	1498
AD-1626265	ususaaa(Uhd)cuUfCfCfacacuugcgaL96	781	VPusdCsgcdAadGugugdGaAfgauuuaasasa	1140	UUUUAAAUCUUCCACACUUGCGG	1499
AD-1631057	asascuc(Uhd)UfaUfUfUfagccauaauaL96	782	VPusAfsuuau(G2p)gcuaaaUfaAfgaguuscsc	1141	GGAACUCUUAUUUAGCCAUAAUC	1500

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1631082	gsasgau(Uhd)UfcAfCf CfuuacaugcuaL96	783	VPusAfsgcau(G2p)uaaggu GfaAfaucucsasa	1142	UUGAGAUUUCACC UUACAUGCUU	1501
AD-1631110	asususcc(Ahd)AfuAfUf CfucagauugcaL96	784	VPusGfscaau(C2p)ugagau AfuUfggaausgsg	1143	CCAUUCCAAUAUC UCAGAUUGCC	1502
AD-1631136	csusgcu(Uhd)UfuCfAf CfacuguauccaL96	785	VPusGfsgaua(C2p)agugug AfaAfagcagscsa	1144	UGCUGCUUUUCAC ACUGUAUCCC	1503
AD-1628754	gsasauu(Chd)agCfUfGf aauuagucuaL96	786	VPusdAsgadCudAauucdA gCfugaauucsasa	1145	UUGAAUUCAGCUG AAUUAGUCUG	1504
AD-1628794	ascscua(Ahd)aaAfCfGf uaauuguugaL96	787	VPusdCsaadCadAuuacdG uUfuuuaggusasa	1146	UUACCUAAAAACG UAAUUGUUGA	1505
AD-1629216	usgsuca(Ghd)uaCfUfCf cauugauguaL96	788	VPusdAscadTcdAauggdA gUfacugacasusu	1147	AAUGUCAGUACUC CAUUGAUGUG	1506
AD-1631199	asususca(Ghd)AfaAfCf UfcauugagacaL96	789	VPusGfsucuc(Agn)augagu UfuCfugaausgsg	1148	CCAUUCAGAAACU CAUUGAGACA	1507
AD-1629621	usgsgau(Chd)uuUfCfAf acucgucgaaL96	790	VPusdTscgdAcdGaguudG aAfagauccasgsg	1149	CCUGGAUCUUUCA ACUCGUCGAC	1508
AD-1629809	csasuga(Ahd)guGfCfAf aaauuuagaaL96	791	VPusdTscudAadAuuuudG cAfcuucaugsusg	1150	CACAUGAAGUGCA AAAUUUAGAA	1509
AD-1624739	asgscaa(Uhd)ccUfCfAf aauugucagaL96	792	VPusdCsugdAcdAauuudG aGfgauugcusasa	1151	UUAGCAAUCCUCA AAUUGUCAGC	1510
AD-1631029	ascscuc(Uhd)GfuUfGf CfaaguguuuuaL96	793	VPusAfsaaac(Agn)cuugca AfcAfgaggususu	1152	AAACCUCUGUUGC AAGUGUUUUG	1511
AD-1624857	ascscuc(Uhd)guUfGfCf aaguguuuuaL96	794	VPusdAsaadAcdAcuugdC aAfcagaggususu	1153	AAACCUCUGUUGC AAGUGUUUUG	1512
AD-1625209	ususggc(Uhd)ugGfUfCf cuuuauuucaL96	795	VPusdGsaadAudAaaggdA cCfaagccaasgsa	1154	UCUUGGCUUGGUC CUUUAUUUCC	1513
AD-1625230	gsasuaa(Ghd)acUfUfCf uaauuuaagaL96	796	VPusdCsuudAadAuuagdA aGfucuuaucsusg	1155	CAGAUAAGACUUC UAAUUUAAGG	1514
AD-1631043	uscsucg(Ahd)AfaUfGf AfcauuggaccaL96	797	VPusGfsgucc(Agn)auguca UfuUfcgagasgsa	1156	UCUCUCGAAAUGA CAUUGGACCC	1515
AD-1631046	gsasaac(Ahd)GfuUfUf AfaccugucauaL96	798	VPusAfsugac(Agn)gguuaa AfcUfguuucsasg	1157	CUGAAACAGUUUA ACCUGUCAUA	1516
AD-1631019	asgsaag(Chd)AfuAfUf AfcauucuccuaL96	799	VPusAfsggag(Agn)auguau AfuGfcuucusgsc	1158	GCAGAAGCAUAUA CAUUCUCCUG	1517
AD-1624178	asgsaag(Chd)auAfUfAf cauucuccuaL96	800	VPusdAsggdAgdAaugudA uAfugcuucusgsc	1159	GCAGAAGCAUAUA CAUUCUCCUG	1518
AD-1626183	ususgcu(Ghd)cuAfUfGf ccuuucuugaL96	801	VPusdCsaadGadAaggcdA uAfgcagcaasgsa	1160	UCUUGCUGCUAUG CCUUUCUUGC	1519
AD-1626375	usasauc(Ahd)gaUfCfAf gcaucuuggaL96	802	VPusdCscadAgdAugcudG aUfcugauuasusg	1161	CAUAAUCAGAUCA GCAUCUUGGA	1520
AD-1631080	csuscug(Ahd)AfaUfUf AfucauccgacaL96	803	VPusGfsucgg(Agn)ugauaa UfuUfcagagsusu	1162	AACUCUGAAAUUA UCAUCCGACU	1521
AD-1631102	gsgsaga(Uhd)CfuCfUf UfaguaaauccaL96	804	VPusGfsgauu(Tgn)acuaag AfgAfucuccsusu	1163	AAGGAGAUCUCUU AGUAAAUCCA	1522
AD-1631103	asgsauc(Uhd)CfuUfAf GfuaaauccagaL96	805	VPusCfsugga(Tgn)uuacua AfgAfgaucuscsc	1164	GGAGAUCUCUUAG UAAAUCCAGA	1523
AD-1628014	asgsauc(Uhd)cuUfAfGf uaaauccagaL96	806	VPusdCsugdGadTuuacdTa Afgagaucuscsc	1165	GGAGAUCUCUUAG UAAAUCCAGA	1524

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1631108	asgsgcu(Chd)AfcCfAf UfuccaauaucaL96	807	VPusGfsauau(Tgn)ggaaug GfuGfagccususg	1166	CAAGGCUCACCAU UCCAAUAUCU	1525
AD-1628042	asgsgcu(Chd)acCfAfUf uccaauaucaL96	808	VPusdGsaudAudTggaadT gGfugagccususg	1167	CAAGGCUCACCAU UCCAAUAUCU	1526
AD-1628043	gsgscuc(Ahd)ccAfUfUf ccaauaucuaL96	809	VPusdAsgadTadTuggadA uGfgugagccsusu	1168	AAGGCUCACCAUU CCAAUAUCUC	1527
AD-1628044	gscsuca(Chd)caUfUfCf caauaucucaL96	810	VPusdGsagdAudAuuggdA aUfggugagcscsu	1169	AGGCUCACCAUUC CAAUAUCUCA	1528
AD-1628383	uscsagc(Chd)auGfAfUf uauauaccgaL96	811	VPusdCsggdTadTauaadTc Afuggcugasgsu	1170	ACUCAGCCAUGAU UAUAUACCGA	1529
AD-1631134	csasaug(Uhd)GfcUfGf Cfuuuucacacal96	812	VPusGfsugug(Agn)aaagca GfcAfcauugsusg	1171	CACAAUGUGCUGC UUUUCACACU	1530
AD-1628412	uscsaca(Chd)ugUfAfUf cccaaugcuaL96	813	VPusdAsgcdAudTgggadT aCfagugugasasa	1172	UUUCACACUGUAU CCCAAUGCUG	1531
AD-1631145	gscsuca(Ghd)UfaCfUf Gfcuguagaaual96	814	VPusAfsuucu(Agn)cagcag UfaCfugagcsasa	1173	UUGCUCAGUACUG CUGUAGAAUG	1532
AD-1631147	uscsagu(Ahd)CfuGfCf Ufguagaauggal96	815	VPusCfscauu(C2p)uacagc AfgUfacugasgsc	1174	GCUCAGUACUGCU GUAGAAUGGG	1533
AD-1628467	uscsagu(Ahd)cuGfCfUf guagaauggaL96	816	VPusdCscadTudCuacadGc Afguacugasgsc	1175	GCUCAGUACUGCU GUAGAAUGGG	1534
AD-1631150	ususuga(Chd)AfuUfUf Ufgaauucagcal96	817	VPusGfscuga(Agn)uucaaa AfuGfucaaasgsa	1176	UCUUUGACAUUUU GAAUUCAGCU	1535
AD-1631152	gscsuga(Ahd)UfuAfGf Ufcugucugacal96	818	VPusGfsucag(Agn)cagacu AfaUfucagcsusg	1177	CAGCUGAAUUAGU CUGUCUGACG	1536
AD-1631173	gsgsuca(Uhd)CfaAfUf Afccgaagaugal96	819	VPusCfsaucu(Tgn)cgguau UfgAfugaccsasg	1178	CUGGUCAUCAAUA CCGAAGAUGG	1537
AD-1629031	gsgsuca(Uhd)caAfUfAf ccgaagaugaL96	820	VPusdCsaudCudTcggudA uUfgaugaccsasg	1179	CUGGUCAUCAAUA CCGAAGAUGG	1538
AD-1631187	csusgcu(Chd)CfuUfUf Gfaagauacuaal96	821	VPusUfsagua(Tgn)cuucaa AfgGfagcagscsu	1180	AGCUGCUCCUUUG AAGAUACUAA	1539
AD-1631217	csasauc(Uhd)UfcCfAfC faugaagugcaL96	822	VPusGfscacu(Tgn)caugug GfaAfgauugsasu	1181	AUCAAUCUUCCAC AUGAAGUGCA	1540
AD-1629799	csasauc(Uhd)ucCfAfCf augaagugcaL96	823	VPusdGscadCudTcaugdTg Gfaagauugsasu	1182	AUCAAUCUUCCAC AUGAAGUGCA	1541
AD-1631025	gsgsguu(Uhd)AfaGfUf Cfuuauaggaual96	824	VPusAfsuccu(Agn)uaagac UfuAfaacccsasg	1183	CUGGGUUUAAGUC UUAUAGGAUA	1542
AD-1624595	gsgsguu(Uhd)aaGfUfCf uuauaggauaL96	825	VPusdAsucdCudAuaagdA cUfuaaacccsasg	1184	CUGGGUUUAAGUC UUAUAGGAUA	1543
AD-1631030	uscsucg(Uhd)GfaAfCf Afagauguacgal96	826	VPusCfsguac(Agn)ucuugu UfcAfcgagasusc	1185	GAUCUCGUGAACA AGAUGUACGA	1544
AD-1625057	uscsucg(Uhd)gaAfCfAf agauguacgaL96	827	VPusdCsgudAcdAucuudG uUfcacgagasusc	1186	GAUCUCGUGAACA AGAUGUACGA	1545
AD-1631032	asgsgaa(Ahd)AfgUfUf Gfaaccuucuual96	828	VPusAfsagaa(G2p)guucaa CfuUfuuccusasu	1187	AUAGGAAAAGUU GAACCUUCUUG	1546
AD-1625191	asgsgaa(Ahd)agUfUfGf aaccuucuuaL96	829	VPusdAsagdAadGguucdA aCfuuuuccusasu	1188	AUAGGAAAAGUU GAACCUUCUUG	1547
AD-1625192	gsgsaaa(Ahd)guUfGfAf accuucuugaL96	830	VPusdCsaadGadAgguudC aAfcuuuuccsusa	1189	UAGGAAAAGUUG AACCUUCUUGG	1548

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1631033	asasagu(Uhd)GfaAfCfC fuucuuggcuaL96	831	VPusAfsgcca(Agn)gaaggu UfcAfacuuususc	1190	GAAAAGUUGAACC UUCUUGGCUU	1549
AD-1625195	asasagu(Uhd)gaAfCfCf uucuuggcuaL96	832	VPusdAsgcdCadAgaagdG uUfcaacuuususc	1191	GAAAAGUUGAACC UUCUUGGCUU	1550
AD-1625485	ususagu(Ghd)uaGfGfAf gaauuuuacaL96	833	VPusdGsuadAadAuucudC cUfacacuaasusu	1192	AAUUAGUGUAGG AGAAUUUUACC	1551
AD-1625610	asasacu(Uhd)caAfUfCf ccauaugagaL96	834	VPusdCsucdAudAugggdA uUfgaaguuususg	1193	CAAAACUUCAAUC CCAUAUGAGG	1552
AD-1631038	csasgca(Uhd)UfuCfUf UfcucuggcuuaL96	835	VPusAfsagcc(Agn)gagaag AfaAfugcugsusc	1194	GACAGCAUUUCUU CUCUGGCUUC	1553
AD-1624152	ascsacc(Uhd)gaAfUfGf uuuuggaguaL96	836	VPusdAscudCcdAaaacdA uUfcaggugusasu	1195	AUACACCUGAAUG UUUUGGAGUU	1554
AD-1631044	cscsuca(Ghd)UfgGfUf UfuuagauccuaL96	837	VPusAfsggau(C2p)uaaaac CfaCfugaggsgsu	1196	ACCCUCAGUGGUU UUAGAUCCUA	1555
AD-1631020	gscsaua(Uhd)AfcAfUf UfcuccugaagaL96	838	VPusCfsuuca(G2p)gagaau GfuAfuaugcsusu	1197	AAGCAUAUACAUU CUCCUGAAGU	1556
AD-1631056	gsasacu(Uhd)AfaGfGf GfaacucuuauaL96	839	VPusAfsuaag(Agn)guuccc UfuAfaguucsasa	1198	UUGAACUUAAGGG AACUCUUAUU	1557
AD-1631059	uscsagc(Ahd)UfcUfUf GfgacuugaguaL96	840	VPusAfscuca(Agn)guccaa GfaUfgcugasusc	1199	GAUCAGCAUCUUG GACUUGAGUG	1558
AD-1631062	usgsgaa(Chd)UfaAfGf AfuccuuucccaL96	841	VPusGfsggaa(Agn)ggaucu UfaGfuuccasasg	1200	CUUGGAACUAAGA UCCUUUCCCA	1559
AD-1626524	usgsgaa(Chd)uaAfGfAf uccuuucccaL96	842	VPusdGsggdAadAggaudC uUfaguuccasasg	1201	CUUGGAACUAAGA UCCUUUCCCA	1560
AD-1627632	ususucc(Ahd)auGfGfGf auuuuggucaL96	843	VPusdGsacdCadAaaucdCc Afuuggaaasasu	1202	AUUUUCCAAUGGG AUUUUGGUCA	1561
AD-1631087	usgsaag(Chd)UfuAfUf UfgucugguagaL96	844	VPusCfsuacc(Agn)gacaau AfaGfcuucasgsg	1203	CCUGAAGCUUAUU GUCUGGUAGG	1562
AD-1627766	usgsaag(Chd)uuAfUfUf gucugguagaL96	845	VPusdCsuadCcdAgacadA uAfagcuucasgsg	1204	CCUGAAGCUUAUU GUCUGGUAGG	1563
AD-1628008	gsgsaag(Ghd)agAfUfCf ucuuaguaaaL96	846	VPusdTsuadCudAagagdA uCfuccuuccsusc	1205	GAGGAAGGAGAUC UCUUAGUAAA	1564
AD-1631104	asgsuaa(Ahd)UfcCfAf GfaucaaccaaaL96	847	VPusUfsuggu(Tgn)gaucug GfaUfuuacusasa	1206	UUAGUAAAUCCAG AUCAACCAAG	1565
AD-1631116	gscsucc(Ahd)GfaGfUf UfucuccuaggaL96	848	VPusCfscuag(G2p)agaaac UfcUfggagcsusu	1207	AAGCUCCAGAGUU UCUCCUAGGU	1566
AD-1631129	cscsuca(Chd)UfaGfAfA fcccuacagcaL96	849	VPusGfscugu(Agn)ggguuc UfaGfugaggscsu	1208	AGCCUCACUAGAA CCCUACAGCA	1567
AD-1631130	csusgau(Ghd)GfuUfUf GfagauaccucaL96	850	VPusGfsaggu(Agn)ucucaa AfcCfaucagscsu	1209	AGCUGAUGGUUUG AGAUACCUCC	1568
AD-1631133	csasgcc(Ahd)UfgAfUf UfauauaccgaaL96	851	VPusUfscggu(Agn)uauaau CfaUfggcugsasg	1210	CUCAGCCAUGAUU AUAUACCGAG	1569
AD-1631139	usgscaa(Ahd)GfaUfUf GfcugacuacgaL96	852	VPusCfsguag(Tgn)cagcaa UfcUfuugcasasu	1211	AUUGCAAAGAUUG CUGACUACGG	1570
AD-1631153	csusgaa(Uhd)UfaGfUf CfugucugacgaL96	853	VPusCfsguca(G2p)acagac UfaAfuucagscsu	1212	AGCUGAAUUAGUC UGUCUGACGA	1571
AD-1628883	gsasgga(Chd)agCfUfCf ucauuucuuaL96	854	VPusdAsagdAadAugagdA gCfuguccucsusg	1213	CAGAGGACAGCUC UCAUUUCUUG	1572

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1631170	uscscug(Ghd)UfcAfUfCfaauaccgaaaL96	855	VPusUfsucgg(Tgn)auugauGfaCfcaggasgsa	1214	UCUCCUGGUCAUCAAUACCGAAG	1573
AD-1631189	asusagg(Ahd)AfaUfGfUfcaguacuccaL96	856	VPusGfsgagu(Agn)cugacaUfuUfccuausasu	1215	AUAUAGGAAAUGUCAGUACUCCA	1574
AD-1629224	csuscca(Uhd)ugAfUfGfUguuugaguaL96	857	VPusdAscudCadAacacdAuCfaauggagsusa	1216	UACUCCAUUGAUGUGUUUGAGUG	1575
AD-1631192	asusgug(Uhd)UfuGfAfGfugaauccacaL96	858	VPusGfsugga(Tgn)ucacucAfaAfcacauscsa	1217	UGAUGUGUUUGAGUGAAUCCACA	1576
AD-1631200	gsascaa(Ghd)AfaCfAfAfgccaacuguaL96	859	VPusAfscagu(Tgn)ggcuugUfuCfuugucsusc	1218	GAGACAAGAACAAGCCAACUGUU	1577
AD-1631207	asgsaac(Ahd)CfuGfCfUfcuuuggauaaL96	860	VPusUfsaucc(Agn)aagagcAfgUfguucususc	1219	GAAGAACACUGCUCUUUGGAUAG	1578
AD-1629573	asgsaac(Ahd)cuGfCfUfcuuuggauaaL96	861	VPusdTsaudCcdAaagadGcAfguguucususc	1220	GAAGAACACUGCUCUUUGGAUAG	1579
AD-1629807	csascau(Ghd)aaGfUfGfcaaaauuuaaL96	862	VPusdTsaadAudTuugcdAcUfucaugugsgsa	1221	UCCACAUGAAGUGCAAAAUUUAG	1580
AD-1631218	asusagg(Ahd)AfuUfGfUfcuuuggauaaL96	863	VPusUfsaucc(Agn)aagacaAfuUfccuaususu	1222	AAAUAGGAAUUGUCUUUGGAUAG	1581
AD-1629876	asusagg(Ahd)auUfGfUfcuuuggauaaL96	864	VPusdTsaudCcdAaagadCaAfuuccuaususu	1223	AAAUAGGAAUUGUCUUUGGAUAG	1582
AD-1631023	uscsaca(Chd)AfcUfGfCfagauguaucaL96	865	VPusGfsauac(Agn)ucugcaGfuGfugugasasg	1224	CUUCACACACUGCAGAUGUAUCC	1583
AD-1631024	usgsucu(Ghd)GfgUfUfUfaagucuuauaL96	866	VPusAfsuaag(Agn)cuuaaaCfcCfagacascsu	1225	AGUGUCUGGGUUUAAGUCUUAUA	1584
AD-1624721	asgsgau(Uhd)ucAfGfAfcaaucuuagaL96	867	VPusdCsuadAgdAuugudCuGfaaauccususu	1226	AAAGGAUUUCAGACAAUCUUAGC	1585
AD-1625501	ususacc(Ghd)agAfUfGfccguauuacaL96	868	VPusdGsuadAudAcggcdAuCfucgguaasasa	1227	UUUUACCGAGAUGCCGUAUUACA	1586
AD-1625928	ascsccu(Chd)agUfGfGfuuuuagaucaL96	869	VPusdGsaudCudAaaacdCaCfugagggcscsc	1228	GGACCCUCAGUGGUUUUAGAUCC	1587
AD-1631047	asgsuuu(Ahd)AfcCfUfGfucauauaacaL96	870	VPusGfsuuau(Agn)ugacagGfuUfaaacusgsu	1229	ACAGUUUAACCUGUCAUAUAACC	1588
AD-1625975	asgsuuu(Ahd)acCfUfGfucauauaacaL96	871	VPusdGsuudAudAugacdAgGfuuaaacusgsu	1230	ACAGUUUAACCUGUCAUAUAACC	1589
AD-1626184	usgscug(Chd)uaUfGfCfcuuucuugcaL96	872	VPusdGscadAgdAaaggdCaUfagcagcasasg	1231	CUUGCUGCUAUGCCUUUCUUGCC	1590
AD-1631050	csusgcu(Ahd)UfgCfCfUfuucuugccuaL96	873	VPusAfsggca(Agn)gaaaggCfaUfagcagscsa	1232	UGCUGCUAUGCCUUUCUUGCCUC	1591
AD-1626266	usasaau(Chd)uuCfCfAfcacuugcggaL96	874	VPusdCscgdCadAgugudGgAfagauuuasasa	1233	UUUAAAUCUUCCACACUUGCGGU	1592
AD-1626349	asascuu(Ahd)agGfGfAfacucuuauuaL96	875	VPusdAsaudAadGaguudCcCfuuaaguuscsa	1234	UGAACUUAAGGGAACUCUUAUUU	1593
AD-1631058	asuscag(Chd)AfuCfUfUfggacuugagaL96	876	VPusCfsucaa(G2p)uccaagAfuGfcugauscsu	1235	AGAUCAGCAUCUUGGACUUGAGU	1594
AD-1626382	asuscag(Chd)auCfUfUfUfggacuugagaL96	877	VPusdCsucdAadGuccadAgAfugcugauscsu	1236	AGAUCAGCAUCUUGGACUUGAGU	1595
AD-1626636	asusaac(Chd)gaAfUfGfaaacuuaugaL96	878	VPusdCsaudAadGuuucdAuUfcgguuausasa	1237	UUAUAACCGAAUGAAACUUAUGA	1596

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1626946	csascac(Ahd)uuUfGfGfGfauguuucugaL96	879	VPusdCsagdAadAcaucdCaAfaugugugscsc	1238	GGCACACAUUUGGAUGUUUCUGA	1597
AD-1627077	asusgcu(Uhd)ugGfCfAfaaacuucggaL96	880	VPusdCscgdAadGuuuudGcCfaaagcauscsa	1239	UGAUGCUUUGGCAAAACUUCGGA	1598
AD-1631070	uscscag(Ahd)CfuGfCfUfauguagaacaL96	881	VPusGfsuucu(Agn)cauagcAfgUfcuggasasu	1240	AUUCCAGACUGCUAUGUAGAACU	1599
AD-1627308	asasuca(Ghd)gaGfUfCfcuucuucauaL96	882	VPusdAsugdAadGaaggdAcUfccugauuscsa	1241	UGAAUCAGGAGUCCUUCUUCAUU	1600
AD-1631081	gscscuu(Ahd)UfuUfUfCfcaaugggauaL96	883	VPusAfsuccc(Agn)uuggaaAfaUfaaggcsasu	1242	AUGCCUUAUUUUCCAAUGGGAUU	1601
AD-1627625	gscscuu(Ahd)uuUfUfCfcaaugggauaL96	884	VPusdAsucdCcdAuuggdAaAfauaaggcsasu	1243	AUGCCUUAUUUUCCAAUGGGAUU	1602
AD-1627820	asasaau(Uhd)acAfGfUfuccuucuugaL96	885	VPusdCsaadGadAggaadCuGfuaauuuususa	1244	UAAAAAUUACAGUUCCUUCUUGU	1603
AD-1631098	asasucu(Uhd)AfcUfUfGfaugacuugaaL96	886	VPusUfscaag(Tgn)caucaaGfuAfagauususu	1245	AAAAUCUUACUUGAUGACUUGAU	1604
AD-1631113	gsusugg(Ahd)AfuUfUfGfaacaagcucaL96	887	VPusGfsagcu(Tgn)guucaaAfuUfccaacsusc	1246	GAGUUGGAAUUUGAACAAGCUCC	1605
AD-1631115	asgscuc(Chd)AfgAfGfUfuucuccuagaL96	888	VPusCfsuagg(Agn)gaaacuCfuGfgagcususg	1247	CAAGCUCCAGAGUUUCUCCUAGG	1606
AD-1631118	csasgag(Uhd)UfuCfUfCfcuaggugauaL96	889	VPusAfsucac(C2p)uaggagAfaAfcucugsgsa	1248	UCCAGAGUUUCUCCUAGGUGAUG	1607
AD-1631128	gscscuc(Ahd)CfuAfGfAfacccuacagaL96	890	VPusCfsugua(G2p)gguucuAfgUfgaggcsusg	1249	CAGCCUCACUAGAACCCUACAGC	1608
AD-1628318	gscscuc(Ahd)cuAfGfAfacccuacagaL96	891	VPusdCsugdTadGgguudCuAfgugaggcsusg	1250	CAGCCUCACUAGAACCCUACAGC	1609
AD-1631131	ascsuca(Ghd)CfcAfUfGfauuauauacaL96	892	VPusGfsuaua(Tgn)aaucauGfgCfugagusgsg	1251	CCACUCAGCCAUGAUUAUAUACC	1610
AD-1628381	ascsuca(Ghd)ccAfUfGfauuauauacaL96	893	VPusdGsuadTadTaaucdAuGfgcugagusgsg	1252	CCACUCAGCCAUGAUUAUAUACC	1611
AD-1631132	csuscag(Chd)CfaUfGfAfuuauauaccaL96	894	VPusGfsguau(Agn)uaaucaUfgGfcugagsusg	1253	CACUCAGCCAUGAUUAUAUACCG	1612
AD-1628382	csuscag(Chd)caUfGfAfuuauauaccaL96	895	VPusdGsgudAudAuaaudCaUfggcugagsusg	1254	CACUCAGCCAUGAUUAUAUACCG	1613
AD-1631161	gscscuu(Ghd)GfuGfCfAfucuuccuguaL96	896	VPusAfscagg(Agn)agaugcAfcCfaaggcsusa	1255	UAGCCUUGGUGCAUCUUCCUGUU	1614
AD-1628963	gscscuu(Ghd)guGfCfAfucuuccuguaL96	897	VPusdAscadGgdAagaudGcAfccaaggcsusa	1256	UAGCCUUGGUGCAUCUUCCUGUU	1615
AD-1631162	cscsuug(Ghd)UfgCfAfUfcuuccuguuaL96	898	VPusAfsacag(G2p)aagaugCfaCfcaaggscsu	1257	AGCCUUGGUGCAUCUUCCUGUUG	1616
AD-1631177	asuscaa(Uhd)AfcCfGfAfagaugggaaaL96	899	VPusUfsuccc(Agn)ucuucgGfuAfuugausgsa	1258	UCAUCAAUACCGAAGAUGGGAAA	1617
AD-1631182	csusugu(Uhd)UfgUfAfUfugcaauuccaL96	900	VPusGfsgaau(Tgn)gcaauaCfaAfacaagsusg	1259	CACUUGUUUGUAUUGCAAUUCCU	1618
AD-1629092	csusugu(Uhd)ugUfAfUfugcaauuccaL96	901	VPusdGsgadAudTgcaadTaCfaaacaagsusg	1260	CACUUGUUUGUAUUGCAAUUCCU	1619
AD-1629223	ascsucc(Ahd)uuGfAfUfguguuugagaL96	902	VPusdCsucdAadAcacadTcAfauggagusasc	1261	GUACUCCAUUGAUGUGUUUGAGU	1620

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1631215	gsasaag(Ahd)GfaUfAfCfaaucuugcuaL96	903	VPusAfsgcaa(G2p)auuguaUfcUfcuuucsusg	1262	CAGAAAGAGAUACAAUCUUGCUU	1621
AD-1629763	gsasaag(Ahd)gaUfAfCfaaucuugcuaL96	904	VPusdAsgcdAadGauugdTaUfcucuuucsusg	1263	CAGAAAGAGAUACAAUCUUGCUU	1622
AD-1631034	csascua(Ghd)CfaAfGfAfauggugaucaL96	905	VPusGfsauca(C2p)cauucuUfgCfuagugsusa	1264	UACACUAGCAAGAAUGGUGAUCA	1623
AD-1631053	uscsuuc(Chd)AfcAfCfUfugcggucuuaL96	906	VPusAfsagac(C2p)gcaaguGfuGfgaagasusu	1265	AAUCUUCCACACUUGCGGUCUUU	1624
AD-1626270	uscsuuc(Chd)acAfCfUfugcggucuuaL96	907	VPusdAsagdAcdCgcaadGuGfuggaagasusu	1266	AAUCUUCCACACUUGCGGUCUUU	1625
AD-1631054	csusucc(Ahd)CfaCfUfUfgcggucuuuaL96	908	VPusAfsaaga(C2p)cgcaagUfgUfggaagsasu	1267	AUCUUCCACACUUGCGGUCUUUA	1626
AD-1626280	ususgcg(Ghd)ucUfUfUfUfagauaugagaL96	909	VPusdCsucdAudAucuadAaGfaccgcaasgsu	1268	ACUUGCGGUCUUUAGAUAUGAGC	1627
AD-1631064	usgsuac(Chd)UfuGfCfUfgucuaugacaL96	910	VPusGfsucau(Agn)gacagcAfaGfguacasasu	1269	AUUGUACCUUGCUGUCUAUGACC	1628
AD-1631072	gscsuuc(Chd)UfcAfCfGfcaguucacuaL96	911	VPusAfsguga(Agn)cugcguGfaGfgaagcsusc	1270	GAGCUUCCUCACGCAGUUCACUU	1629
AD-1631074	csasgug(Ahd)AfaGfUfGfgaagguuguaL96	912	VPusAfscaac(C2p)uuccacUfuUfcacugsusc	1271	GACAGUGAAAGUGGAAGGUUGUC	1630
AD-1627410	csasgug(Ahd)aaGfUfGfgaagguuguaL96	913	VPusdAscadAcdCuuccdAcUfuucacugsusc	1272	GACAGUGAAAGUGGAAGGUUGUC	1631
AD-1631122	gsasugg(Chd)AfgUfUfUfuggaucaguaL96	914	VPusAfscuga(Tgn)ccaaaaCfuGfccaucsasc	1273	GUGAUGGCAGUUUUGGAUCAGUU	1632
AD-1631137	ususcac(Ahd)CfuGfUfAfucccaaugcaL96	915	VPusGfscauu(G2p)ggauacAfgUfgugaasasa	1274	UUUUCACACUGUAUCCCAAUGCU	1633
AD-1628434	csasuca(Uhd)ugCfAfAfAfagauugcugaL96	916	VPusdCsagdCadAucuudTgCfaaugaugsgsc	1275	GCCAUCAUUGCAAAGAUUGCUGA	1634
AD-1631146	csuscag(Uhd)AfcUfGfCfuguagaaugaL96	917	VPusCfsauuc(Tgn)acagcaGfuAfcugagscsa	1276	UGCUCAGUACUGCUGUAGAAUGG	1635
AD-1631154	gsasauu(Ahd)GfuCfUfGfucugacgagaL96	918	VPusCfsucgu(C2p)agacagAfcUfaauucsasg	1277	CUGAAUUAGUCUGUCUGACGAGA	1636
AD-1628764	gsasauu(Ahd)guCfUfGfucugacgagaL96	919	VPusdCsucdGudCagacdAgAfcuaauucsasg	1278	CUGAAUUAGUCUGUCUGACGAGA	1637
AD-1631155	usasgua(Ghd)AfaUfAfUfugugcuuagaL96	920	VPusCfsuaag(C2p)acaauaUfuCfuacuasusc	1279	GAUAGUAGAAUAUUGUGCUUAGC	1638
AD-1631164	gsgsgac(Ahd)CfaGfUfCfugguacucuaL96	921	VPusAfsgagu(Agn)ccagacUfgUfgucccsasg	1280	CUGGGACACAGUCUGGUACUCUC	1639
AD-1631165	csascag(Uhd)CfuGfGfUfacucuccugaL96	922	VPusCfsagga(G2p)aguaccAfgAfcugugsusc	1281	GACACAGUCUGGUACUCUCCUGG	1640
AD-1629012	csascag(Uhd)cuGfGfUfacucuccugaL96	923	VPusdCsagdGadGaguadCcAfgacugugsusc	1282	GACACAGUCUGGUACUCUCCUGG	1641
AD-1631174	gsuscau(Chd)AfaUfAfCfcgaagauggaL96	924	VPusCfscauc(Tgn)ucgguaUfuGfaugacscsa	1283	UGGUCAUCAAUACCGAAGAUGGG	1642
AD-1629032	gsuscau(Chd)aaUfAfCfcgaagauggaL96	925	VPusdCscadTcdTucggdTaUfugaugacscsa	1284	UGGUCAUCAAUACCGAAGAUGGG	1643
AD-1631180	gsgsgaa(Ahd)AfaGfAfGfacauacccuaL96	926	VPusAfsgggu(Agn)ugucucUfuUfuucccsasu	1285	AUGGGAAAAAGAGACAUACCCUA	1644

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1631181	asasaga(Ghd)AfcAfUf Afcccuagaaaa L96	927	VPusUfsuucu(Agn)ggguau GfuCfucuuususu	1286	AAAAAGAGACAUA CCCUAGAAAA	1645
AD-1631188	usascua(Ahd)AfuAfUf Afggaaaauguca L96	928	VPusGfsacau(Tgn)uccuau AfuUfuaguasusc	1287	GAUACUAAAUAUA GGAAAUGUCA	1646
AD-1629200	usascua(Ahd)auAfUfAf ggaaaugucaL96	929	VPusdGsacdAudTuccudA uAfuuuaguasusc	1288	GAUACUAAAUAUA GGAAAUGUCA	1647
AD-1631191	gsasugu(Ghd)UfuUfGf Afgugaauccaa L96	930	VPusUfsggau(Tgn)cacuca AfaCfacaucsasa	1289	UUGAUGUGUUUG AGUGAAUCCAC	1648
AD-1629808	ascsaug(Ahd)agUfGfCf aaaauuuagaL96	931	VPusdCsuadAadTuuugdC aCfuucaugusgsg	1290	CCACAUGAAGUGC AAAAUUUAGA	1649
AD-1629838	asgsuga(Ghd)aaAfAfGf aauuagcugaL96	932	VPusdCsagdCudAauucdT uUfucucacususc	1291	GAAGUGAGAAAA GAAUUAGCUGA	1650
AD-1631049	asasuuu(Uhd)CfuUfGf Cfugcuaugcca L96	933	VPusGfsgcau(Agn)gcagca AfgAfaaauuscsa	1292	UGAAUUUUCUUGC UGCUAUGCCU	1651
AD-1631079	gsasaua(Uhd)UfuGfCf Ufgguuccaaga L96	934	VPusCfsuugg(Agn)accagc AfaAfuauucsusu	1293	AAGAAUAUUUGCU GGUUCCAAGC	1652
AD-1627631	ususuuc(Chd)aaUfGfGf gauuuuggua L96	935	VPusdAsccdAadAauccdC aUfuggaaaasusa	1294	UAUUUUCCAAUGG GAUUUUGGUC	1653
AD-1631095	gsgsuug(Chd)UfgGfAf Gfauugauauua L96	936	VPusAfsauau(C2p)aaucuc CfaGfcaaccscsa	1295	UGGGUUGCUGGAG AUUGAUAUUU	1654
AD-1631096	usgsaag(Ghd)AfgAfAf Afcucuguugaa L96	937	VPusUfscaac(Agn)gaguuu CfuCfcuucascsc	1296	GGUGAAGGAGAA ACUCUGUUGAA	1655
AD-1631121	usgsaug(Ghd)CfaGfUf Ufuuggaucaga L96	938	VPusCfsugau(C2p)caaaac UfgCfcaucascsc	1297	GGUGAUGGCAGUU UUGGAUCAGU	1656
AD-1628133	usgsaug(Ghd)caGfUfUf uuggaucagaL96	939	VPusdCsugdAudCcaaadA cUfgccaucascsc	1298	GGUGAUGGCAGUU UUGGAUCAGU	1657
AD-1631140	gscsaaa(Ghd)AfuUfGf Cfugacuacgga L96	940	VPusCfscgua(G2p)ucagca AfuCfuuugcsasa	1299	UUGCAAAGAUUGC UGACUACGGC	1658
AD-1628441	gscsaaa(Ghd)auUfGfCf ugacuacggaL96	941	VPusdCscgdTadGucagdCa Afucuuugcsasa	1300	UUGCAAAGAUUGC UGACUACGGC	1659
AD-1631166	csasguc(Uhd)GfgUfAf Cfucuccuggua L96	942	VPusAfsccag(G2p)agagua CfcAfgacugsusg	1301	CACAGUCUGGUAC UCUCCUGGUC	1660
AD-1631169	csusccu(Ghd)GfuCfAf Ufcaauaccgaa L96	943	VPusUfscggu(Agn)uugaug AfcCfaggagsasg	1302	CUCUCCUGGUCAU CAAUACCGAA	1661
AD-1629026	csusccu(Ghd)guCfAfUf caauaccgaaL96	944	VPusdTscgdGudAuugadT gAfccaggagsasg	1303	CUCUCCUGGUCAU CAAUACCGAA	1662
AD-1631171	cscsugg(Uhd)CfaUfCf Afauaccgaaga L96	945	VPusCfsuucg(G2p)uauuga UfgAfccaggsasg	1304	CUCCUGGUCAUCA AUACCGAAGA	1663
AD-1629028	cscsugg(Uhd)caUfCfAf auaccgaagaL96	946	VPusdCsuudCgdGuauudG aUfgaccaggsasg	1305	CUCCUGGUCAUCA AUACCGAAGA	1664
AD-1631172	csusggu(Chd)AfuCfAf Afuaccgaagaa L96	947	VPusUfscuuc(G2p)guauug AfuGfaccagsgsa	1306	UCCUGGUCAUCAA UACCGAAGAU	1665
AD-1631178	asusacc(Ghd)AfaGfAf Ufgggaaaaga L96	948	VPusCfsuuuu(Tgn)cccauc UfuCfgguaususg	1307	CAAUACCGAAGAU GGGAAAAAGA	1666
AD-1629039	asusacc(Ghd)aaGfAfUf gggaaaaagaL96	949	VPusdCsuudTudTcccadTc Ufucgguaususg	1308	CAAUACCGAAGAU GGGAAAAAGA	1667
AD-1631209	gscsucu(Uhd)UfgGfAf Ufaggaacugga L96	950	VPusCfscagu(Tgn)ccuauc CfaAfagagcsasg	1309	CUGCUCUUUGGAU AGGAACUGGA	1668

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1629581	gscsucu(Uhd)ugGfAfUfaggaacuggaL96	951	VPusdCscadGudTccuadTcCfaaagagcsasg	1310	CUGCUCUUUGGAUAGGAACUGGA	1669
AD-1631221	asasaau(Ahd)UfuAfAfGfacaguuuccaL96	952	VPusGfsgaaa(C2p)ugucuuAfaUfauuuuscsa	1311	UGAAAAUAUUAAGACAGUUUCCC	1670
AD-1630135	asasaau(Ahd)uuAfAfGfacaguuuccaL96	953	VPusdGsgadAadCugucdTuAfauauuuuscsa	1312	UGAAAAUAUUAAGACAGUUUCCC	1671
AD-1625282	gsasaug(Ghd)ugAfUfCfagauaucagaL96	954	VPusdCsugdAudAucugdAuCfaccauucsusu	1313	AAGAAUGGUGAUCAGAUAUCAGA	1672
AD-1631036	asgsgag(Ahd)AfuUfUfUfaccgagaugaL96	955	VPusCfsaucu(C2p)gguaaaAfuUfcuccusasc	1314	GUAGGAGAAUUUUACCGAGAUGC	1673
AD-1631037	ususuua(Chd)CfgAfGfAfugccguauuaL96	956	VPusAfsauac(G2p)gcaucuCfgGfuaaaasusu	1315	AAUUUUACCGAGAUGCCGUAUUA	1674
AD-1625499	ususuua(Chd)cgAfGfAfugccguauuaL96	957	VPusdAsaudAcdGgcaudCuCfgguaaaasusu	1316	AAUUUUACCGAGAUGCCGUAUUA	1675
AD-1631039	csasgaa(Uhd)GfcAfCfUfcacgagcuuaL96	958	VPusAfsagcu(C2p)gugaguGfcAfuucugsgsu	1317	ACCAGAAUGCACUCACGAGCUUU	1676
AD-1631048	gsasacu(Uhd)UfcUfUfGfaggcuugucaL96	959	VPusGfsacaa(G2p)ccucaaGfaAfaguucsusc	1318	GAGAACUUUCUUGAGGCUUGUCC	1677
AD-1631052	asasucu(Uhd)CfcAfCfAfcuugcggucaL96	960	VPusGfsaccg(C2p)aaguguGfgAfagauususa	1319	UAAAUCUUCCACACUUGCGGUCU	1678
AD-1626268	asasucu(Uhd)ccAfCfAfcuugcggucaL96	961	VPusdGsacdCgdCaagudGuGfgaagauususa	1320	UAAAUCUUCCACACUUGCGGUCU	1679
AD-1626927	asasagg(Chd)ucGfCfGfcuucuucuuaL96	962	VPusdAsagdAadGaagcdGcGfagccuuusasu	1321	AUAAAGGCUCGCGCUUCUUCUUC	1680
AD-1626936	ususcuc(Ghd)uuGfGfCfacacauuugaL96	963	VPusdCsaadAudGugugdCcAfacgagaasusc	1322	GAUUCUCGUUGGCACACAUUUGG	1681
AD-1627601	asasuua(Uhd)caUfCfCfgacuauaugaL96	964	VPusdCsaudAudAgucgdGaUfgauaauususc	1323	GAAAUUAUCAUCCGACUAUAUGA	1682
AD-1631084	ususacu(Uhd)AfaAfUfUfggucuccugaL96	965	VPusCfsagga(G2p)accaauUfuAfaguaasasu	1324	AUUUACUUAAAUUGGUCUCCUGA	1683
AD-1631090	ususauu(Ghd)UfcUfGfGfuaggaucugaL96	966	VPusCfsagau(C2p)cuaccaGfaCfaauaasgsc	1325	GCUUAUUGUCUGGUAGGAUCUGA	1684
AD-1627772	ususauu(Ghd)ucUfGfGfuaggaucugaL96	967	VPusdCsagdAudCcuacdCaGfacaauaasgsc	1326	GCUUAUUGUCUGGUAGGAUCUGA	1685
AD-1627838	usgsuag(Ahd)aaAfGfGfcuguauucuaL96	968	VPusdAsgadAudAcagcdCuUfuucuacasasg	1327	CUUGUAGAAAAGGCUGUAUUCUU	1686
AD-1631092	usgsugg(Ahd)CfcAfCfAfuugauucucaL96	969	VPusGfsagaa(Tgn)caauguGfgUfccacasasc	1328	GUUGUGGACCACAUUGAUUCUCU	1687
AD-1627870	usgsugg(Ahd)ccAfCfAfuugauucucaL96	970	VPusdGsagdAadTcaaudGuGfguccacasasc	1329	GUUGUGGACCACAUUGAUUCUCU	1688
AD-1631094	gsgsguu(Ghd)CfuGfGfAfgauugauauaL96	971	VPusAfsuauc(Agn)aucuccAfgCfaacccsasg	1330	CUGGGUUGCUGGAGAUUGAUAUU	1689
AD-1631112	usgsacc(Uhd)GfcCfUfAfgaaauauuaaL96	972	VPusUfsaaua(Tgn)uucuagGfcAfggucasgsc	1331	GCUGACCUGCCUAGAAAUAUUAU	1690
AD-1631138	ascsacu(Ghd)UfaUfCfCfcaaugcugcaL96	973	VPusGfscagc(Agn)uuggaUfaCfagugusgsa	1332	UCACACUGUAUCCCAAUGCUGCC	1691
AD-1631142	asasgau(Uhd)GfcUfGfAfcuacggcauaL96	974	VPusAfsugcc(G2p)uagucaGfcAfaucuususg	1333	CAAAGAUUGCUGACUACGGCAUU	1692

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1628444	asasgau(Uhd)gcUfGfAfcuacggcauaL96	975	VPusdAsugdCcdGuagudCaGfcaaucuususg	1334	CAAAGAUUGCUGACUACGGCAUU	1693
AD-1628590	asascug(Ghd)agGfUfAfgaauaguagaL96	976	VPusdCsuadCudAuucudAcCfuccaguusgsu	1335	ACAACUGGAGGUAGAAUAGUAGA	1694
AD-1631149	gsusaga(Ghd)GfgUfUfUfgaaguuuccaL96	977	VPusGfsgaaa(C2p)uucaaaCfcCfucuacsusa	1336	UAGUAGAGGGUUUGAAGUUUCCA	1695
AD-1631156	asgsuag(Ahd)AfuAfUfUfgugcuuagcaL96	978	VPusGfscuaa(G2p)cacaauAfuUfcuacusasu	1337	AUAGUAGAAUAUUGUGCUUAGCC	1696
AD-1631163	usgsgga(Chd)AfcAfGfUfcugguacucaL96	979	VPusGfsagua(C2p)cagacuGfuGfucccasgsa	1338	UCUGGGACACAGUCUGGUACUCU	1697
AD-1629007	usgsgga(Chd)acAfGfUfcugguacucaL96	980	VPusdGsagdTadCcagadCuGfugucccasgsa	1339	UCUGGGACACAGUCUGGUACUCU	1698
AD-1629025	uscsucc(Uhd)ggUfCfAfucaauaccgaL96	981	VPusdCsggdTadTugaudGaCfcaggagasgsu	1340	ACUCUCCUGGUCAUCAAUACCGA	1699
AD-1631206	csasaaa(Uhd)GfuCfUfUfUfauucugggaaL96	982	VPusUfsccca(G2p)aauaagAfcAfuuuugsusg	1341	CACAAAAUGUCUUAUUCUGGGAG	1700
AD-1631040	usgscac(Uhd)CfaCfGfAfgcuuuccacaL96	983	VPusGfsugga(Agn)agcucgUfgAfgugcasusu	1342	AAUGCACUCACGAGCUUUCCACA	1701
AD-1625786	usgscac(Uhd)caCfGfAfgcuuuccacaL96	984	VPusdGsugdGadAagcudCgUfgagugcasusu	1343	AAUGCACUCACGAGCUUUCCACA	1702
AD-1631055	asusaug(Ahd)GfcAfGfCfaaugauauuaL96	985	VPusAfsauau(C2p)auugcuGfcUfcauauscsu	1344	AGAUAUGAGCAGCAAUGAUAUUC	1703
AD-1627110	ascsgag(Ahd)gcCfUfUfaauuucaagaL96	986	VPusdCsuudGadAauuadAgGfcucucgususu	1345	AAACGAGAGCCUUAAUUUCAAGA	1704
AD-1631071	asasuga(Ghd)CfuUfCfCfucacgcaguaL96	987	VPusAfscugc(G2p)ugaggaAfgCfucauususu	1346	AAAAUGAGCUUCCUCACGCAGUU	1705
AD-1631075	asgsuga(Ahd)AfgUfGfGfaagguugucaL96	988	VPusGfsacaa(C2p)cuuccaCfuUfucacusgsu	1347	ACAGUGAAAGUGGAAGGUUGUCC	1706
AD-1627411	asgsuga(Ahd)agUfGfGfaagguugucaL96	989	VPusdGsacdAadCcuucdCaCfuuucacusgsu	1348	ACAGUGAAAGUGGAAGGUUGUCC	1707
AD-1627717	gscscca(Ahd)acAfGfAfauguauuggaL96	990	VPusdCscadAudAcauudCuGfuuugggcsgsa	1349	UCGCCCAAACAGAAUGUAUUGGC	1708
AD-1631086	cscsuga(Ahd)GfcUfUfAfuugucugguaL96	991	VPusAfsccag(Agn)caauaaGfcUfucaggsasg	1350	CUCCUGAAGCUUAUUGUCUGGUA	1709
AD-1631088	gsasagc(Uhd)UfaUfUfGfucugguaggaL96	992	VPusCfscuac(C2p)agacaaUfaAfgcuucsasg	1351	CUGAAGCUUAUUGUCUGGUAGGA	1710
AD-1627767	gsasagc(Uhd)uaUfUfGfucugguaggaL96	993	VPusdCscudAcdCagacdAaUfaagcuucsasg	1352	CUGAAGCUUAUUGUCUGGUAGGA	1711
AD-1628070	gsasccu(Ghd)ccUfAfGfaaauauuauaL96	994	VPusdAsuadAudAuuucdTaGfgcaggucsasg	1353	CUGACCUGCCUAGAAAUAUUAUG	1712
AD-1631127	cscsucc(Ahd)AfgGfGfUfuccuuggauaL96	995	VPusAfsucca(Agn)ggaaccCfuUfggaggscsu	1354	AGCCUCCAAGGGUUCCUUGGAUC	1713
AD-1628273	cscsucc(Ahd)agGfGfUfuccuuggauaL96	996	VPusdAsucdCadAggaadCcCfuuggaggscsu	1355	AGCCUCCAAGGGUUCCUUGGAUC	1714
AD-1628396	csascaa(Uhd)guGfCfUfUfgcuuuucacaL96	997	VPusdGsugdAadAagcadGcAfcauugugsgsg	1356	CCCACAAUGUGCUGCUUUUCACA	1715
AD-1631148	gsasggu(Ahd)GfaAfUfAfguagaggguaL96	998	VPusAfscccu(C2p)uacuauUfcUfaccucscsa	1357	UGGAGGUAGAAUAGUAGAGGGUU	1716

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1628668	cscsagu(Uhd)aaAfGfAfauaugguugaL96	999	VPusdCsaadCcdAuauudCuUfuaacuggsasu	1358	AUCCAGUUAAAGAAUAUGGUUGU	1717
AD-1631160	usasgcc(Uhd)UfgGfUfGfcaucuuccuaL96	1000	VPusAfsggaa(G2p)augcacCfaAfggcuasasg	1359	CUUAGCCUUGGUGCAUCUUCCUG	1718
AD-1628961	usasgcc(Uhd)ugGfUfGfcaucuuccuaL96	1001	VPusdAsggdAadGaugcdAcCfaaggcuasasg	1360	CUUAGCCUUGGUGCAUCUUCCUG	1719
AD-1631167	asgsucu(Ghd)GfuAfCfUfcuccuggucaL96	1002	VPusGfsacca(G2p)gagaguAfcCfagacusgsu	1361	ACAGUCUGGUACUCUCCUGGUCA	1720
AD-1631176	csasuca(Ahd)UfaCfCfGfaagaugggaaL96	1003	VPusUfsccca(Tgn)cuucggUfaUfugaugsasc	1362	GUCAUCAAUACCGAAGAUGGGAA	1721
AD-1631185	ususcuu(Uhd)UfgGfUfUfggaaccgcuaL96	1004	VPusAfsgcgg(Tgn)uccaacCfaAfaagaasasa	1363	UUUUCUUUUGGUUGGAACCGCUG	1722
AD-1631203	csusguu(Ghd)UfgGfAfAfgugugggauaL96	1005	VPusAfsuccc(Agn)cacuucCfaCfaacagsgsg	1364	CCCUGUUGUGGAAGUGUGGGAUA	1723
AD-1631208	usgscuc(Uhd)UfuGfGfAfuaggaacugaL96	1006	VPusCfsaguu(C2p)cuauccAfaAfgagcasgsu	1365	ACUGCUCUUUGGAUAGGAACUGG	1724
AD-1629580	usgscuc(Uhd)uuGfGfAfuaggaacugaL96	1007	VPusdCsagdTudCcuaudCcAfaagagcasgsu	1366	ACUGCUCUUUGGAUAGGAACUGG	1725
AD-1631211	asusucg(Ghd)UfcAfGfAfgucaugaugaL96	1008	VPusCfsauca(Tgn)gacucuGfaCfcgaaususa	1367	UAAUUCGGUCAGAGUCAUGAUGA	1726
AD-1629665	asusucg(Ghd)ucAfGfAfgucaugaugaL96	1009	VPusdCsaudCadTgacudCuGfaccgaaususa	1368	UAAUUCGGUCAGAGUCAUGAUGA	1727
AD-1631219	usascua(Ahd)AfaUfUfUfauaaggccgaL96	1010	VPusCfsggcc(Tgn)uauaaaUfuUfuaguasusg	1369	CAUACUAAAAUUUAUAAGGCCGA	1728
AD-1631220	csusaaa(Ahd)UfuUfAfUfaaggccgauaL96	1011	VPusAfsucgg(C2p)cuuauaAfaUfuuuagsusa	1370	UACUAAAAUUUAUAAGGCCGAUA	1729
AD-1631031	gsgscca(Ahd)CfaAfUfAfgcauuugccaL96	1012	VPusGfsgcaa(Agn)ugcuauUfgUfuggccsasc	1371	GUGGCCAACAAUAGCAUUUGCCU	1730
AD-1625155	gsgscca(Ahd)caAfUfAfgcauuugccaL96	1013	VPusdGsgcdAadAugcudAuUfguuggccsasc	1372	GUGGCCAACAAUAGCAUUUGCCU	1731
AD-1631068	ascsucc(Uhd)GfaAfUfAfagcgaggguaL96	1014	VPusAfscccu(C2p)gcuuauUfcAfggagususc	1373	GAACUCCUGAAUAAGCGAGGGUU	1732
AD-1631085	csusuaa(Ahd)UfuGfGfUfcuccugaagaL96	1015	VPusCfsuuca(G2p)gagaccAfaUfuuaagsusa	1374	UACUUAAAUUGGUCUCCUGAAGC	1733
AD-1631089	asgscuu(Ahd)UfuGfUfCfugguaggauaL96	1016	VPusAfsuccu(Agn)ccagacAfaUfaagcususc	1375	GAAGCUUAUUGUCUGGUAGGAUC	1734
AD-1627769	asgscuu(Ahd)uuGfUfCfugguaggauaL96	1017	VPusdAsucdCudAccagdAcAfauaagcususc	1376	GAAGCUUAUUGUCUGGUAGGAUC	1735
AD-1631097	ususgaa(Ghd)AfaAfUfGfggcauuauaaL96	1018	VPusUfsauaa(Tgn)gcccauUfuCfuucaascsa	1377	UGUUGAAGAAAUGGGCAUUAUAU	1736
AD-1627952	ususgaa(Ghd)aaAfUfGfggcauuauaaL96	1019	VPusdTsaudAadTgcccdAuUfucuucaascsa	1378	UGUUGAAGAAAUGGGCAUUAUAU	1737
AD-1631099	gscsaga(Ghd)GfaAfGfGfgagaucucuuaL96	1020	VPusAfsagag(Agn)ucuccuUfcCfucugcsusu	1379	AAGCAGAGGAAGGAGAUCUCUUA	1738
AD-1631105	asasucc(Ahd)GfaUfCfAfaccaaggcuaL96	1021	VPusAfsgccu(Tgn)gguugaUfcUfggauususa	1380	UAAAUCCAGAUCAACCAAGGCUC	1739
AD-1628027	asasucc(Ahd)gaUfCfAfaccaaggcuaL96	1022	VPusdAsgcdCudTgguudGaUfcuggauususa	1381	UAAAUCCAGAUCAACCAAGGCUC	1740

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1631106	asuscca(Ghd)AfuCfAf AfccaaggcucaL96	1023	VPusGfsagcc(Tgn)ugguug AfuCfuggaususu	1382	AAAUCCAGAUCAA CCAAGGCUCA	1741
AD-1631119	asgsagu(Uhd)UfcUfCf CfuaggugaugaL96	1024	VPusCfsauca(C2p)cuagga GfaAfacucusgsg	1383	CCAGAGUUUCUCC UAGGUGAUGG	1742
AD-1628118	asgsagu(Uhd)ucUfCfCf uaggugaugaL96	1025	VPusdCsaudCadCcuagdG aGfaaacucusgsg	1384	CCAGAGUUUCUCC UAGGUGAUGG	1743
AD-1631157	asasuau(Uhd)GfuGfCf UfuagccuuggaL96	1026	VPusCfscaag(G2p)cuaagc AfcAfauauuscsu	1385	AGAAUAUUGUGCU UAGCCUUGGU	1744
AD-1631158	asusauu(Ghd)UfgCfUf UfagccuugguaL96	1027	VPusAfsccaa(G2p)gcuaag CfaCfaauaususc	1386	GAAUAUUGUGCUU AGCCUUGGUG	1745
AD-1628951	asusauu(Ghd)ugCfUfUf agccuugguaL96	1028	VPusdAsccdAadGgcuadA gCfacaauaususc	1387	GAAUAUUGUGCUU AGCCUUGGUG	1746
AD-1631183	ususuuc(Uhd)UfuUfGf GfuuggaaccgaL96	1029	VPusCfsgguu(C2p)caacca AfaAfgaaaasusu	1388	AAUUUUCUUUUGG UUGGAACCGC	1747
AD-1631186	csusuuu(Ghd)GfuUfGf GfaaccgcugaaL96	1030	VPusUfscagc(G2p)guucca AfcCfaaaagsasa	1389	UUCUUUUGGUUGG AACCGCUGAU	1748
AD-1631202	usasgcc(Chd)UfgUfUf GfuggaaguguaL96	1031	VPusAfscacu(Tgn)ccacaa CfaGfggcuasusu	1390	AAUAGCCCUGUUG UGGAAGUGUG	1749
AD-1629419	usasgcc(Chd)ugUfUfGf uggaaguguaL96	1032	VPusdAscadCudTccacdAa Cfagggcuasusu	1391	AAUAGCCCUGUUG UGGAAGUGUG	1750
AD-1629878	asgsgaa(Uhd)ugUfCfUf uuggauaggaL96	1033	VPusdCscudAudCcaaadG aCfaauuccusasu	1392	AUAGGAAUUGUCU UUGGAUAGGA	1751
AD-1627852	usasuuc(Uhd)uuUfGfGf gccaaguugaL96	1034	VPusdCsaadCudTggccdCa Afaagaauascsa	1393	UGUAUUCUUUUGG GCCAAGUUGU	1752
AD-1631124	asusguu(Ghd)GfuGfAf UfggaguuagcaL96	1035	VPusGfscuaa(C2p)uccauc AfcCfaacauscsc	1394	GGAUGUUGGUGA UGGAGUUAGCC	1753
AD-1628254	asusguu(Ghd)guGfAfU fggaguuagcaL96	1036	VPusdGscudAadCuccadTc Afccaacauscsc	1395	GGAUGUUGGUGA UGGAGUUAGCC	1754
AD-1631143	asusugc(Uhd)GfaCfUf AfcggcauugcaL96	1037	VPusGfscaau(G2p)ccguag UfcAfgcaauscsu	1396	AGAUUGCUGACUA CGGCAUUGCU	1755
AD-1631021	usgsaua(Uhd)UfcAfCf AfaacugguccaL96	1038	VPusGfsgacc(Agn)guuugu GfaAfuaucasusu	1397	AAUGAUAUUCACA AACUGGUCCU	1756
AD-1631184	ususucu(Uhd)UfuGfGf UfuggaaccgcaL96	1039	VPusGfscggu(Tgn)ccaacc AfaAfagaaasasu	1398	AUUUUCUUUUGGU UGGAACCGCU	1757
AD-1631212	usasaaa(Ahd)UfgUfCf AfugcugguauaL96	1040	VPusAfsuacc(Agn)gcauga CfaUfuuuuasasg	1399	CUUAAAAAUGUCA UGCUGGUAUU	1758
AD-1629707	asasaau(Ghd)ucAfUfGf cugguauugaL96	1041	VPusdCsaadTadCcagcdAu Gfacauuuususa	1400	UAAAAAUGUCAUG CUGGUAUUGG	1759
AD-1630136	asasaua(Uhd)uaAfGfAf caguuucccaL96	1042	VPusdGsggdAadAcugudC uUfaauauuususc	1401	GAAAAUAUUAAG ACAGUUUCCCA	1760
AD-1624894	gsasugc(Uhd)agAfGfAf gagcgugugaL96	1043	VPusdCsacdAcdGcucudC uCfuagcaucsasc	1402	GUGAUGCUAGAGA GAGCGUGUGA	1761
AD-1626921	csasaua(Uhd)aaAfGfGf cucgcgcuuaL96	1044	VPusdAsagdCgdCgagcdC uUfuauauugsasa	1403	UUCAAUAUAAAGG CUCGCGCUUC	1762
AD-1631067	asusaaa(Ghd)GfcUfCfG fcgcuucuucaL96	1045	VPusGfsaaga(Agn)gcgcga GfcCfuuuausasu	1404	AUAUAAAGGCUCG CGCUUCUUCU	1763
AD-1626925	asusaaa(Ghd)gcUfCfGf cgcuucuucaL96	1046	VPusdGsaadGadAgcgcdG aGfccuuuausasu	1405	AUAUAAAGGCUCG CGCUUCUUCU	1764

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1631076	gsusgaa(Ahd)GfuGfGfAfagguuguccaL96	1047	VPusGfsgaca(Agn)ccuuccAfcUfuucacsusg	1406	CAGUGAAAGUGGAAGGUUGUCCA	1765
AD-1627412	gsusgaa(Ahd)guGfGfAfagguuguccaL96	1048	VPusdGsgadCadAccuudCcAfcuuucacsusg	1407	CAGUGAAAGUGGAAGGUUGUCCA	1766
AD-1631083	asasaca(Ghd)AfaUfGfUfauuggcgacaL96	1049	VPusGfsucgc(C2p)aauacaUfuCfuguuusgsg	1408	CCAAACAGAAUGUAUUGGCGACA	1767
AD-1631120	gsasguu(Uhd)CfuCfCfUfaggugauggaL96	1050	VPusCfscauc(Agn)ccuaggAfgAfaacucsusg	1409	CAGAGUUUCUCCUAGGUGAUGGC	1768
AD-1628119	gsasguu(Uhd)cuCfCfUfaggugauggaL96	1051	VPusdCscadTcdAccuadGgAfgaaacucsusg	1410	CAGAGUUUCUCCUAGGUGAUGGC	1769
AD-1631123	gsasugu(Uhd)GfgUfGfAfuggaguuagaL96	1052	VPusCfsuaac(Tgn)ccaucaCfcAfacaucscsg	1411	CGGAUGUUGGUGAUGGAGUUAGC	1770
AD-1628253	gsasugu(Uhd)ggUfGfAfuggaguuagaL96	1053	VPusdCsuadAcdTccaudCaCfcaacaucscsg	1412	CGGAUGUUGGUGAUGGAGUUAGC	1771
AD-1631144	usgscug(Ahd)CfuAfCfGfgcauugcucaL96	1054	VPusGfsagca(Agn)ugccguAfgUfcagcasasu	1413	AUUGCUGACUACGGCAUUGCUCA	1772
AD-1631022	uscsaca(Ahd)AfcUfGfGfuccuagcagaL96	1055	VPusCfsugcu(Agn)ggaccaGfuUfugugasasu	1414	AUUCACAAACUGGUCCUAGCAGC	1773
AD-1624412	uscsaca(Ahd)acUfGfGfuccuagcagaL96	1056	VPusdCsugdCudAggacdCaGfuuugugasasu	1415	AUUCACAAACUGGUCCUAGCAGC	1774
AD-1631159	gscsuua(Ghd)CfcUfUfGfgugcaucuuaL96	1057	VPusAfsagau(G2p)caccaaGfgCfuaagcsasc	1416	GUGCUUAGCCUUGGUGCAUCUUC	1775
AD-1631168	csuscuc(Chd)UfgGfUfCfaucaauaccaL96	1058	VPusGfsguau(Tgn)gaugacCfaGfgagagsusa	1417	UACUCUCCUGGUCAUCAAUACCG	1776
AD-1629024	csuscuc(Chd)ugGfUfCfaucaauaccaL96	1059	VPusdGsgudAudTgaugdAcCfaggagagsusa	1418	UACUCUCCUGGUCAUCAAUACCG	1777
AD-1631179	usgsgga(Ahd)AfaAfGfAfgacauacccaL96	1060	VPusGfsggua(Tgn)gucucuUfuUfucccasusc	1419	GAUGGGAAAAAGAGACAUACCCU	1778
AD-1631204	gsusgca(Chd)UfuUfUfUfaagggagguaL96	1061	VPusAfsccuc(C2p)cuuaaaAfaGfugcacsgsc	1420	GCGUGCACUUUUUAAGGGAGGUA	1779
AD-1631213	asusguc(Ahd)UfgCfUfGfguauugggcaL96	1062	VPusGfsccca(Agn)uaccagCfaUfgacaususu	1421	AAAUGUCAUGCUGGUAUUGGGCU	1780
AD-1629710	asusguc(Ahd)ugCfUfGfguauugggcaL96	1063	VPusdGsccdCadAuaccdAgCfaugacaususu	1422	AAAUGUCAUGCUGGUAUUGGGCU	1781
AD-1631066	usasuaa(Ahd)GfgCfUfCfgcgcuucuuaL96	1064	VPusAfsagaa(G2p)cgcgagCfcUfuuauasusu	1423	AAUAUAAAGGCUCGCGCUUCUUC	1782
AD-1631073	ususgug(Ghd)AfaCfCfCfaaguggcuuaL96	1065	VPusAfsagcc(Agn)cuugggUfuCfcacaasasg	1424	CUUUGUGGAACCCAAGUGGCUUU	1783
AD-1627866	asasguu(Ghd)ugGfAfCfcacauugauaL96	1066	VPusdAsucdAadTguggdTcCfacaacuusgsg	1425	CCAAGUUGUGGACCACAUUGAUU	1784
AD-1631107	cscsaag(Ghd)CfuCfAfCfcauuccaauaL96	1067	VPusAfsuugg(Agn)auggugAfgCfcuuggsusu	1426	AACCAAGGCUCACCAUUCCAAUA	1785
AD-1631126	ususagc(Chd)UfcCfAfAfggguuccuuaL96	1068	VPusAfsagga(Agn)cccuugGfaGfgcuaascsu	1427	AGUUAGCCUCCAAGGGUUCCUUG	1786
AD-1631141	asasaga(Uhd)UfgCfUfGfacuacggcaaL96	1069	VPusUfsgccg(Tgn)agucagCfaAfucuuusgsc	1428	GCAAAGAUUGCUGACUACGGCAU	1787
AD-1628443	asasaga(Uhd)ugCfUfGfacuacggcaaL96	1070	VPusdTsgcdCgdTagucdAgCfaaucuuusgsc	1429	GCAAAGAUUGCUGACUACGGCAU	1788

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1631175	uscsauc(Ahd)AfuAfCf CfgaagaugggaL96	1071	VPusCfsccau(C2p)uucggu AfuUfgaugascsc	1430	GGUCAUCAAUACC GAAGAUGGGA	1789
AD-1629033	uscsauc(Ahd)auAfCfCf gaagaugggaL96	1072	VPusdCsccdAudCuucgdG uAfuugaugascsc	1431	GGUCAUCAAUACC GAAGAUGGGA	1790
AD-1629597	csusgga(Ghd)gaGfGfCf cauauuuuaaL96	1073	VPusdTsaadAadTauggdCc Ufccuccagsusu	1432	AACUGGAGGAGGC CAUAUUUUAC	1791
AD-1631214	usgsuca(Uhd)GfcUfGf GfuauugggcuaL96	1074	VPusAfsgccc(Agn)auacca GfcAfugacasusu	1433	AAUGUCAUGCUGG UAUUGGGCUA	1792
AD-1629711	usgsuca(Uhd)gcUfGfGf uauugggcuaL96	1075	VPusdAsgcdCcdAauacdC aGfcaugacasusu	1434	AAUGUCAUGCUGG UAUUGGGCUA	1793
AD-1631065	asasuau(Ahd)AfaGfGf CfucgcgcuucaL96	1076	VPusGfsaagc(G2p)cgagcc UfuUfauauusgsa	1435	UCAAUAUAAAGGC UCGCGCUUCU	1794
AD-1631069	cscsuga(Ahd)UfaAfGf CfgaggguuccaL96	1077	VPusGfsgaac(C2p)cucgcu UfaUfucaggsasg	1436	CUCCUGAAUAAGC GAGGGUUCCC	1795
AD-1627390	asasuca(Uhd)ggCfAfCf agauuuugaaL96	1078	VPusdTscadAadAucugdT gCfcaugauususu	1437	AAAAUCAUGGCAC AGAUUUUGAC	1796
AD-1631091	csusuuu(Ghd)GfgCfCf AfaguuguggaaL96	1079	VPusUfsccac(Agn)acuugg CfcCfaaaagsasa	1438	UUCUUUUGGGCCA AGUUGUGGAC	1797
AD-1627856	csusuuu(Ghd)ggCfCfAf aguuguggaaL96	1080	VPusdTsccdAcdAacuudG gCfccaaaagsasa	1439	UUCUUUUGGGCCA AGUUGUGGAC	1798
AD-1627896	asasgaa(Uhd)ggUfUfUf ccuggguugaL96	1081	VPusdCsaadCcdCaggadAa Cfcauucuuscsc	1440	GGAAGAAUGGUU UCCUGGGUUGC	1799
AD-1631114	asusuug(Ahd)AfcAfAf GfcuccagaguaL96	1082	VPusAfscucu(G2p)gagcuu GfuUfcaaaususc	1441	GAAUUUGAACAAG CUCCAGAGUU	1800
AD-1631125	usgsuug(Ghd)UfgAfUf GfgaguuagccaL96	1083	VPusGfsgcua(Agn)cuccau CfaCfcaacasusc	1442	GAUGUUGGUGAU GGAGUUAGCCU	1801
AD-1628385	asgscca(Uhd)gaUfUfAf uauaccgagaL96	1084	VPusdCsucdGgdTauaudA aUfcauggcusgsa	1443	UCAGCCAUGAUUA UAUACCGAGA	1802
AD-1628442	csasaag(Ahd)uuGfCfUf gacuacggcaL96	1085	VPusdGsccdGudAgucadG cAfaucuuugscsa	1444	UGCAAAGAUUGCU GACUACGGCA	1803
AD-1631194	gsasgga(Uhd)GfuGfGf CfacaaagauuaL96	1086	VPusAfsaucu(Tgn)ugugcc AfcAfuccucscsc	1445	GGGAGGAUGUGGC ACAAAGAUUU	1804
AD-1629263	gsasgga(Uhd)guGfGfCf acaaagauuaL96	1087	VPusdAsaudCudTugugdC cAfcauccucscsc	1446	GGGAGGAUGUGGC ACAAAGAUUU	1805

Table 6. Unmodified Sense and Antisense Strand Sequences of Human *LRRK2* dsRNA Agents That Use C16 Ligand or Unconjugated to a Ligand

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4
AD-1807334	CUUGUUUGUAUUGC AAUUCCA	1810	6872-6892	UGGAAUTGCAAUA CAAACAAGUG	1900	6870-6892
AD-1807335	GAAAGAGAUACAAU CUUGCUA	1811	7593-7613	UAGCAAGAUUGTA UCUCUUUCUG	1901	7591-7613
AD-1807336	CAUGAAGUGCAAAA UUUAGAA	1812	7639-7659	UTCUAAAUUUUGC ACUUCAUGUG	1902	7637-7659
AD-1807337	AAACACAAAAUGUC UUAUUCA	1813	7348-7368	UGAATAAGACATU UUGUGUUUUG	1903	7346-7368

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4
AD-1807338	ACUCCAUUGAUGUGUUUGAGA	1814	7027-7047	UCUCAAACACATCAAUGGAGUAC	1904	7025-7047
AD-1807339	UAAAUCUUCCACACUUGCGGA	1815	3713-3733	UCCGCAAGUGUGGAAGAUUUAAA	1905	3711-3733
AD-1807340	GCUGAAUUAGUCUGUCUGACA	1816	6538-6558	UGUCAGACAGACUAAUUCAGCUG	1906	6536-6558
AD-1807341	CUCAGCCAUGAUUAUAUACCA	1817	6093-6113	UGGUAUAUAAUCAUGGCUGAGUG	1907	6091-6113
AD-1807342	CUCAGCCAUGAUUAUAUACCA	1818	6093-6113	UGGUAUAUAAUCAUGGCUGAGUG	1908	6091-6113
AD-1807343	UCCAAAGAACUACAUGUCACA	1819	5058-5078	UGUGACAUGUAGUUCUUUGGAAA	1909	5056-5078
AD-1807344	UGGAUCUUUCAACUCGUCGAA	1820	7445-7465	UTCGACGAGUUGAAAGAUCCAGG	1910	7443-7465
AD-1807345	CUGCCUAGAAAUAUUAUGUUA	1821	5725-5745	UAACAUAAUAUTUCUAGGCAGGU	1911	5723-5745
AD-1807346	UAAGGGAACUCUUAUUUAGCA	1822	3800-3820	UGCUAAAUAAGAGUUCCCUUAAG	1912	3798-3820
AD-1807347	CUGGAUCUUUCAACUCGUCGA	1823	7444-7464	UCGACGAGUUGAAAGAUCCAGGA	1913	7442-7464
AD-1807348	CUCUGAAAUUAUCAUCCGACA	1824	5196-5216	UGUCGGAUGAUAAUUUCAGAGUU	1914	5194-5216
AD-1807349	CAGCUGAAUUAGUCUGUCUGA	1825	6536-6556	UCAGACAGACUAAUUCAGCUGAA	1915	6534-6556
AD-1807350	CUUGUUUGUAUUGCAAUUCCA	1826	6872-6892	UGGAAUTGCAATACAAACAAGUG	1916	6870-6892
AD-1807351	AAUCAGGAGUCCUUCUUCAUA	1827	4868-4888	UAUGAAGAAGGACUCCUGAUUCA	1917	4866-4888
AD-1807352	GCUCACCAUUCCAAUAUCUCA	1828	5676-5696	UGAGAUAUUGGAAUGGUGAGCCU	1918	5674-5696
AD-1807353	CAAUCUUCCACAUGAAGUGCA	1829	7629-7649	UGCACUTCAUGTGGAAGAUUGAU	1919	7627-7649
AD-1807354	AAACACAAAAUGUCUUAUUCA	1830	7348-7368	UGAAUAAGACAUUUUGUGUUUUG	1920	7346-7368
AD-1807355	CCUGGAUCUUUCAACUCGUCA	1831	7443-7463	UGACGAGUUGAAAGAUCCAGGAG	1921	7441-7463
AD-1807356	CUACUCUAUGACAUUUUGACA	1832	6319-6339	UGUCAAAAUGUCAUAGAGUAGUA	1922	6317-6339
AD-1807357	GCCUUGGUGCAUCUUCCUGUA	1833	6742-6762	UACAGGAAGAUGCACCAAGGCUA	1923	6740-6762
AD-1807358	UUGCUGCUAUGCCUUUCUUGA	1834	3629-3649	UCAAGAAAGGCAUAGCAGCAAGA	1924	3627-3649
AD-1807359	AGUGAGAAAAGAAUUAGCUGA	1835	7671-7691	UCAGCUAAUUCTUUUCUCACUUC	1925	7669-7691
AD-1807360	AGAUCUCUUAGUAAAUCCAGA	1836	5646-5666	UCUGGATUUACTAAGAGAUCUCC	1926	5644-5666
AD-1807361	CACAAUGUGCUGCUUUUCACA	1837	6127-6147	UGUGAAAAGCAGCACAUUGUGGG	1927	6125-6147

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4
AD-1807362	GAAUUCAGCUGAAUUAGUCUA	1838	6531-6551	UAGACUAAUUCAGCUGAAUUCAA	1928	6529-6551
AD-1807363	CCAUUCAGAAACUCAUUGAGA	1839	7127-7147	UCUCAATGAGUTUCUGAAUGGUG	1929	7125-7147
AD-1807364	ACAUGAAGUGCAAAAUUUAGA	1840	7638-7658	UCUAAATUUUGCACUUCAUGUGG	1930	7636-7658
AD-1807365	UGCUGCUAUGCCUUUCUUGCA	1841	3630-3650	UGCAAGAAAGGCAUAGCAGCAAG	1931	3628-3650
AD-1807366	GGGAAAAAGAGACAUACCCUA	1842	6829-6849	UAGGGUAUGUCUCUUUUUCCCAU	1932	6827-6849
AD-1807367	CAUUCCAAUAUCUCAGAUUGA	1843	5682-5702	UCAATCTGAGATAUUGGAAUGGU	1933	5680-5702
AD-1807368	AUGUGUUUGAGUGAAUCCACA	1844	7036-7056	UGUGGATUCACUCAAACACAUCA	1934	7034-7056
AD-1807369	AAAAUAUUAAGACAGUUUCCA	1845	8134-8154	UGGAAACUGUCTUAAUAUUUUCA	1935	8132-8154
AD-1807370	CAUUCCAAUAUCUCAGAUUGA	1846	5682-5702	UCAAUCTGAGAUAUUGGAAUGGU	1936	5680-5702
AD-1807371	GAAGCUUAUUGUCUGGUAGGA	1847	5368-5388	UCCUACCAGACAAUAAGCUUCAG	1937	5366-5388
AD-1807372	CAGUACUCCAUUGAUGUGUUA	1848	7023-7043	UAACACAUCAAUGGAGUACUGAC	1938	7021-7043
AD-1807373	AGUUUAACCUGUCAUAUAACA	1849	3395-3415	UGUUAUAUGACAGGUUAAACUGU	1939	3393-3415
AD-1807374	GACCUGCCUAGAAAUAUUAUA	1850	5722-5742	UAUAAUAUUUCTAGGCAGGUCAG	1940	5720-5742
AD-1807375	GUAGAGGGUUUGAAGUUUCCA	1851	6355-6375	UGGAAACUUCAAACCCUCUACUA	1941	6353-6375
AD-1807376	GAAAGAGAUACAAUCUUGCUA	1852	7593-7613	UAGCAAGAUUGUAUCUCUUUCUG	1942	7591-7613
AD-1807377	CCUGGAUCUUUCAACUCGUCA	1853	7443-7463	UGACGAGUUGAAAGAUCCAGGAG	1943	7441-7463
AD-1807378	UUUGAGUGAAUCCACAAAUUA	1854	7041-7061	UAAUUUGUGGAUUCACUCAAACA	1944	7039-7061
AD-1807379	CUUGUUUGUAUUGCAAUUCCA	1855	6872-6892	UGGAAUTGCAAUACAAACAAGUG	1945	6870-6892
AD-1807380	GAAAGAGAUACAAUCUUGCUA	1856	7593-7613	UAGCAAGAUUGTAUCUCUUUCUG	1946	7591-7613
AD-1807381	CAUGAAGUGCAAAAUUUAGAA	1857	7639-7659	UTCUAAAUUUUGCACUUCAUGUG	1947	7637-7659
AD-1807382	AAACACAAAAUGUCUUAUUCA	1858	7348-7368	UGAATAAGACATUUUGUGUUUUG	1948	7346-7368
AD-1807383	ACUCCAUUGAUGUGUUUGAGA	1859	7027-7047	UCUCAAACACATCAAUGGAGUAC	1949	7025-7047
AD-1807384	UAAAUCUUCCACACUUGCGGA	1860	3713-3733	UCCGCAAGUGUGGAAGAUUUAAA	1950	3711-3733
AD-1807385	GCUGAAUUAGUCUGUCUGACA	1861	6538-6558	UGUCAGACAGACUAAUUCAGCUG	1951	6536-6558

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4
AD-1807386	CUCAGCCAUGAUUAUAUACCA	1862	6093-6113	UGGUAUAUAAUCAUGGCUGAGUG	1952	6091-6113
AD-1807387	CUCAGCCAUGAUUAUAUACCA	1863	6093-6113	UGGUAUAUAAUCAUGGCUGAGUG	1953	6091-6113
AD-1807388	UCCAAAGAACUACAUGUCACA	1864	5058-5078	UGUGACAUGUAGUUCUUUGGAAA	1954	5056-5078
AD-1807389	UGGAUCUUUCAACUCGUCGAA	1865	7445-7465	UTCGACGAGUUGAAAGAUCCAGG	1955	7443-7465
AD-1807390	CUGCCUAGAAAUAUUAUGUUA	1866	5725-5745	UAACAUAAUAUTUCUAGGCAGGU	1956	5723-5745
AD-1807391	UAAGGGAACUCUUAUUUAGCA	1867	3800-3820	UGCUAAAUAAGAGUUCCCUUAAG	1957	3798-3820
AD-1807392	CUGGAUCUUUCAACUCGUCGA	1868	7444-7464	UCGACGAGUUGAAAGAUCCAGGA	1958	7442-7464
AD-1807393	CUCUGAAAUUAUCAUCCGACA	1869	5196-5216	UGUCGGAUGAUAAUUUCAGAGUU	1959	5194-5216
AD-1807394	CAGCUGAAUUAGUCUGUCUGA	1870	6536-6556	UCAGACAGACUAAUUCAGCUGAA	1960	6534-6556
AD-1807395	CUUGUUUGUAUUGCAAUUCCA	1871	6872-6892	UGGAAUTGCAATACAAACAAGUG	1961	6870-6892
AD-1807396	AAUCAGGAGUCCUUCUUCAUA	1872	4868-4888	UAUGAAGAAGGACUCCUGAUUCA	1962	4866-4888
AD-1807397	GCUCACCAUUCCAAUAUCUCA	1873	5676-5696	UGAGAUAUUGGAAUGGUGAGCCU	1963	5674-5696
AD-1807398	CAAUCUUCCACAUGAAGUGCA	1874	7629-7649	UGCACUTCAUGTGGAAGAUUGAU	1964	7627-7649
AD-1807399	AAACACAAAAUGUCUUAUUCA	1875	7348-7368	UGAAUAAGACAUUUUGUGUUUUG	1965	7346-7368
AD-1807400	CCUGGAUCUUUCAACUCGUCA	1876	7443-7463	UGACGAGUUGAAAGAUCCAGGAG	1966	7441-7463
AD-1807401	CUACUCUAUGACAUUUUGACA	1877	6319-6339	UGUCAAAAUGUCAUAGAGUAGUA	1967	6317-6339
AD-1807402	GCCUUGGUGCAUCUUCCUGUA	1878	6742-6762	UACAGGAAGAUGCACCAAGGCUA	1968	6740-6762
AD-1807403	UUGCUGCUAUGCCUUUCUUGA	1879	3629-3649	UCAAGAAAGGCAUAGCAGCAAGA	1969	3627-3649
AD-1807404	AGUGAGAAAAGAAUUAGCUGA	1880	7671-7691	UCAGCUAAUUCTUUUCUCACUUC	1970	7669-7691
AD-1807405	AGAUCUCUUAGUAAAUCCAGA	1881	5646-5666	UCUGGATUUACTAAGAGAUCUCC	1971	5644-5666
AD-1807406	CACAAUGUGCUGCUUUUCACA	1882	6127-6147	UGUGAAAAGCAGCACAUUGUGGG	1972	6125-6147
AD-1807407	GAAUUCAGCUGAAUUAGUCUA	1883	6531-6551	UAGACUAAUUCAGCUGAAUUCAA	1973	6529-6551
AD-1807408	CCAUUCAGAAACUCAUUGAGA	1884	7127-7147	UCUCAATGAGUTUCUGAAUGGUG	1974	7125-7147
AD-1807409	ACAUGAAGUGCAAAAUUUAGA	1885	7638-7658	UCUAAATUUUGCACUUCAUGUGG	1975	7636-7658

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4	Antisense Sequence 5' to 3'	SEQ ID NO:	Range in NM_198578.4
AD-1807410	UGCUGCUAUGCCUUUCUUGCA	1886	3630-3650	UGCAAGAAAGGCAUAGCAGCAAG	1976	3628-3650
AD-1807411	GGGAAAAAGAGACAUACCCUA	1887	6829-6849	UAGGGUAUGUCUCUUUUUCCCAU	1977	6827-6849
AD-1807412	CAUUCCAAUAUCUCAGAUUGA	1888	5682-5702	UCAATCTGAGATAUUGGAAUGGU	1978	5680-5702
AD-1807413	AUGUGUUUGAGUGAAUCCACA	1889	7036-7056	UGUGGATUCACUCAAACACAUCA	1979	7034-7056
AD-1807414	AAAAUAUUAAGACAGUUUCCA	1890	8134-8154	UGGAAACUGUCTUAAUAUUUUCA	1980	8132-8154
AD-1807415	CAUUCCAAUAUCUCAGAUUGA	1891	5682-5702	UCAAUCTGAGAUAUUGGAAUGGU	1981	5680-5702
AD-1807416	GAAGCUUAUUGUCUGGUAGGA	1892	5368-5388	UCCUACCAGACAAUAAGCUUCAG	1982	5366-5388
AD-1807417	CAGUACUCCAUUGAUGUGUUA	1893	7023-7043	UAACACAUCAAUGGAGUACUGAC	1983	7021-7043
AD-1807418	AGUUUAACCUGUCAUAUAACA	1894	3395-3415	UGUUAUAUGACAGGUUAAACUGU	1984	3393-3415
AD-1807419	GACCUGCCUAGAAAUAUUAUA	1895	5722-5742	UAUAAUAUUUCTAGGCAGGUCAG	1985	5720-5742
AD-1807420	GUAGAGGGUUUGAAGUUUCCA	1896	6355-6375	UGGAAACUUCAAACCCUCUACUA	1986	6353-6375
AD-1807421	GAAAGAGAUACAAUCUUGCUA	1897	7593-7613	UAGCAAGAUUGUAUCUCUUUCUG	1987	7591-7613
AD-1807422	CCUGGAUCUUUCAACUCGUCA	1898	7443-7463	UGACGAGUUGAAAGAUCCAGGAG	1988	7441-7463
AD-1807423	UUUGAGUGAAUCCACAAAUUA	1899	7041-7061	UAAUUUGUGGAUUCACUCAAACA	1989	7039-7061

Table 7. Modified Sense and Antisense Strand Sequences of Human *LRRK2* dsRNA Agents That Use C16 Ligand or Unconjugated to a Ligand

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1807334	csusugu(Uhd)UfgUfAfUfugcaauucscsa	1990	VPusGfsgadAu(Tgn)gcaauaCfaAfacaagsusg	2080	CACUUGUUUGUAUUGCAAUUCCU	2170
AD-1807335	gsasaag(Ahd)gaUfAfCfaaucuugcsusa	1991	VPusdAsgcdAadGauugdTaUfcucuuucsusg	2081	CAGAAAGAGAUACAAUCUUGCUU	2171
AD-1807336	csasuga(Ahd)guGfCfAfaaauuuagsasa	1992	VPusdTscudAadAuuuudGcAfcuucaugsusg	2082	CACAUGAAGUGCAAAAUUUAGAA	2172
AD-1807337	asasaca(Chd)aaAfAfUfgucuuauuscsa	1993	VPusdGsaadTadAgacadTuUfuguguuususg	2083	CAAAACACAAAAUGUCUUAUUCU	2173
AD-1807338	ascsucc(Ahd)uuGfAfUfguguuugasgsa	1994	VPusdCsucdAadAcacadTcAfauggagusasc	2084	GUACUCCAUUGAUGUGUUUGAGU	2174
AD-1807339	usasaau(Chd)uuCfCfAfcacuugcgsgsa	1995	VPusdCscgdCadAgugudGgAfagauuuasasa	2085	UUUAAAUCUUCCACACUUGCGGU	2175
AD-1807340	gscsuga(Ahd)UfuAfGfUfcugucugascsa	1996	VPusGfsucdAg(Agn)cagacuAfaUfucagcsusg	2086	CAGCUGAAUUAGUCUGUCUGACG	2176

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1807341	csuscag(Chd)caUfGfAfuuauauacscsa	1997	VPusdGsgudAudAuaaudCaUfggcugagsusg	2087	CACUCAGCCAUGAUUAUAUACCG	2177
AD-1807342	csuscag(Chd)CfaUfGfAfuuauauacscsa	1998	VPusGfsgudAu(Agn)uaaucaUfgGfcugagsusg	2088	CACUCAGCCAUGAUUAUAUACCG	2178
AD-1807343	uscscaa(Ahd)GfaAfCfUfacaugucascsa	1999	VPusGfsugdAc(Agn)uguaguUfcUfuuggasasa	2089	UUUCCAAAGAACUACAUGUCACA	2179
AD-1807344	usgsgau(Chd)uuUfCfAfacucgucgsasa	2000	VPusdTscgdAcdGaguudGaAfagauccasgsg	2090	CCUGGAUCUUUCAACUCGUCGAC	2180
AD-1807345	csusgcc(Uhd)agAfAfAfAfuauuaugususa	2001	VPusdAsacdAudAauaudTuCfuaggcagsgsu	2091	ACCUGCCUAGAAAUAUUAUGUUG	2181
AD-1807346	usasagggaaCfUfCfuuau(Uhd)uagscsa	2002	VPusdGscudAadAuaagdAgUfucccuuasasg	2092	CUUAAGGGAACUCUUAUUUAGCC	2182
AD-1807347	csusgga(Uhd)cuUfUfCfaacucgucsgsa	2003	VPusdCsgadCgdAguugdAaAfgauccagsgsa	2093	UCCUGGAUCUUUCAACUCGUCGA	2183
AD-1807348	csuscug(Ahd)AfaUfUfAfucauccgascsa	2004	VPusGfsucdGg(Agn)ugauaaUfuUfcagagsusu	2094	AACUCUGAAAUUAUCAUCCGACU	2184
AD-1807349	csasgc(Uhd)gaaUfUfAfgucugucusgsa	2005	VPusdCsagdAcdAgacudAaUfucagcugsasa	2095	UUCAGCUGAAUUAGUCUGUCUGA	2185
AD-1807350	csusugu(Uhd)ugUfAfUfugcaauucscsa	2006	VPusdGsgadAudTgcaadTaCfaaacaagsusg	2096	CACUUGUUUGUAUUGCAAUUCCU	2186
AD-1807351	asasucaggaGfUfCfcuuc(Uhd)ucasusa	2007	VPusdAsugdAadGaaggdAcUfccugauuscsa	2097	UGAAUCAGGAGUCCUUCUUCAUU	2187
AD-1807352	gscsuca(Chd)caUfUfCfcaauaucuscsa	2008	VPusdGsagdAudAuuggdAaUfggugagcscsu	2098	AGGCUCACCAUUCCAAUAUCUCA	2188
AD-1807353	csasauc(Uhd)ucCfAfCfaugaagugscsa	2009	VPusdGscadCudTcaugdTgGfaagauugsasu	2099	AUCAAUCUUCCACAUGAAGUGCA	2189
AD-1807354	asasaca(Chd)AfaAfAfUfgucuuauuscsa	2010	VPusGfsaadTa(Agn)gacauuUfuGfuguuususg	2100	CAAAACACAAAAUGUCUUAUUCU	2190
AD-1807355	cscsugg(Ahd)ucUfUfUfUfcaacucguscsa	2011	VPusdGsacdGadGuugadAaGfauccaggsasg	2101	CUCCUGGAUCUUUCAACUCGUCG	2191
AD-1807356	csusacu(Chd)uaUfGfAfcauuuugascsa	2012	VPusdGsucdAadAaugudCaUfagaguagsusa	2102	UACUACUCUAUGACAUUUUGACA	2192
AD-1807357	gscscu(Uhd)gGfuGfCfAfucuuccugsusa	2013	VPusAfscadGg(Agn)agaugcAfcCfaaggcsusa	2103	UAGCCUUGGUGCAUCUUCCUGUU	2193
AD-1807358	ususgcug(Chd)uAfUfGfccuuucuusgsa	2014	VPusdCsaadGadAaggcdAuAfgcagcaasgsa	2104	UCUUGCUGCUAUGCCUUUCUUGC	2194
AD-1807359	asgsugagaaAfAfGfaau(Uhd)agcusgsa	2015	VPusdCsagdCudAauucdTuUfucucacususc	2105	GAAGUGAGAAAAGAAUUAGCUGA	2195
AD-1807360	asgsauc(Uhd)cuUfAfGfuaaauccasgsa	2016	VPusdCsugdGadTuuacdTaAfgagaucuscsc	2106	GGAGAUCUCUUAGUAAAUCCAGA	2196
AD-1807361	csascaa(Uhd)guGfCfUfgcuuuucascsa	2017	VPusdGsugdAadAagcadGcAfcauugugsgsg	2107	CCCACAAUGUGCUGCUUUUCACA	2197
AD-1807362	gsasauu(Chd)agCfUfGfaauuagucsusa	2018	VPusdAsgadCudAauucdAgCfugaauucsasa	2108	UUGAAUUCAGCUGAAUUAGUCUG	2198
AD-1807363	cscsauu(Chd)agAfAfAfAfcucauugasgsa	2019	VPusdCsucdAadTgagudTuCfugaauggsusg	2109	CACCAUUCAGAAACUCAUUGAGA	2199
AD-1807364	ascsaug(Ahd)agUfGfCfaaaauuuasgsa	2020	VPusdCsuadAadTuuugdCaCfuucaugusgsg	2110	CCACAUGAAGUGCAAAAUUUAGA	2200

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1807365	usgscug(Chd)uaUfGfCfcuuucuugscsa	2021	VPusdGscadAgdAaaggdCaUfagcagcasasg	2111	CUUGCUGCUAUGCCUUUCUUGCC	2201
AD-1807366	gsgsgaa(Ahd)AfaGfAfGfacauacccsusa	2022	VPusAfsggdGu(Agn)ugucucUfuUfuucccsasu	2112	AUGGGAAAAAGAGACAUACCCUA	2202
AD-1807367	csasuuc(Chd)aaUfAfUfcucagauusgsa	2023	VPusdCsaadTcdTgagadTaUfuggaaugsgsu	2113	ACCAUUCCAAUAUCUCAGAUUGC	2203
AD-1807368	asusgug(Uhd)UfuGfAfGfugaauccascsa	2024	VPusGfsugdGa(Tgn)ucacucAfaAfcacauscsa	2114	UGAUGUGUUUGAGUGAAUCCACA	2204
AD-1807369	asasaau(Ahd)uuAfAfGfacaguuucscsa	2025	VPusdGsgadAadCugucdTuAfauauuuuscsa	2115	UGAAAAUAUUAAGACAGUUUCCC	2205
AD-1807370	csasuuc(Chd)AfaUfAfUfcucagauusgsa	2026	VPusCfsaadTc(Tgn)gagauaUfuGfgaaugsgsu	2116	ACCAUUCCAAUAUCUCAGAUUGC	2206
AD-1807371	gsasagc(Uhd)uaUfUfGfucugguagsgsa	2027	VPusdCscudAcdCagacdAaUfaagcuucsasg	2117	CUGAAGCUUAUUGUCUGGUAGGA	2207
AD-1807372	csasgua(Chd)UfcCfAfUfugaugugususa	2028	VPusAfsacdAc(Agn)ucaaugGfaGfuacugsasc	2118	GUCAGUACUCCAUUGAUGUGUUU	2208
AD-1807373	asgsuuu(Ahd)acCfUfGfucauauaascsa	2029	VPusdGsuudAudAugacdAgGfuuaaacusgsu	2119	ACAGUUUAACCUGUCAUAUAACC	2209
AD-1807374	gsasccug(Chd)cUfAfGfaaauauuasusa	2030	VPusdAsuadAudAuuucdTaGfgcaggucsasg	2120	CUGACCUGCCUAGAAAUAUUAUG	2210
AD-1807375	gsusagagGfgUfUfUfgaag(Uhd)uucscsa	2031	VPusGfsgadAa(C2p)uucaaaCfcCfucuacsusa	2121	UAGUAGAGGGUUUGAAGUUUCCA	2211
AD-1807376	gsasaag(Ahd)GfaUfAfCfaaucuugcsusa	2032	VPusAfsgcdAa(G2p)auuguaUfcUfcuuucsusg	2122	CAGAAAGAGAUACAAUCUUGCUU	2212
AD-1807377	cscsugg(Ahd)UfcUfUfUfcaacucguscsa	2033	VPusGfsacdGa(G2p)uugaaaGfaUfccaggsasg	2123	CUCCUGGAUCUUUCAACUCGUCG	2213
AD-1807378	ususugag(Uhd)gAfAfUfccacaaaususa	2034	VPusAfsaudTu(G2p)uggauuCfaCfucaaascsa	2124	UGUUUGAGUGAAUCCACAAAUUC	2214
AD-1807379	csusuguuUfgUfAfUfugcaauucscsa	2035	VPusGfsgadAu(Tgn)gcaauaCfaAfacaagsusg	2125	CACUUGUUUGUAUUGCAAUUCCU	2215
AD-1807380	gsasaagagaUfAfCfaaucuugcsusa	2036	VPusdAsgcdAadGauugdTaUfcucuuucsusg	2126	CAGAAAGAGAUACAAUCUUGCUU	2216
AD-1807381	csasugaaguGfCfAfaaauuuagsasa	2037	VPusdTscudAadAuuuudGcAfcuucaugsusg	2127	CACAUGAAGUGCAAAAUUUAGAA	2217
AD-1807382	asasacacaaAfAfUfgucuuauuscsa	2038	VPusdGsaadTadAgacadTuUfuguguuususg	2128	CAAAACACAAAAUGUCUUAUUCU	2218
AD-1807383	ascsuccauuGfAfUfgguuuugasgsa	2039	VPusdCsucdAadAcacadTcAfauggagusasc	2129	GUACUCCAUUGAUGUGUUUGAGU	2219
AD-1807384	usasaaucuuCfCfAfcacuugcgsgsa	2040	VPusdCscgdCadAgugudGgAfagauuuasasa	2130	UUUAAAUCUUCCACACUUGCGGU	2220
AD-1807385	gscsugaaUfuAfGfUfcugucugascsa	2041	VPusGfsucdAg(Agn)cagacuAfaUfucagcsusg	2131	CAGCUGAAUUAGUCUGUCUGACG	2221
AD-1807386	csuscagccaUfGfAfuuauauacscsa	2042	VPusdGsgudAudAuaaudCaUfggcugagsusg	2132	CACUCAGCCAUGAUUAUAUACCG	2222
AD-1807387	csuscagcCfaUfGfAfuuauauacscsa	2043	VPusGfsgudAu(Agn)uaaucaUfgGfcugagsusg	2133	CACUCAGCCAUGAUUAUAUACCG	2223
AD-1807388	uscscaaaGfaAfCfUfacaugucascsa	2044	VPusGfsugdAc(Agn)uguaguUfcUfuuggasasa	2134	UUUCCAAAGAACUACAUGUCACA	2224

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1807389	usgsgaucuuUfCfAfacu cgucgsasa	2045	VPusdTscgdAcdGaguud GaAfagauccasgsg	2135	CCUGGAUCUUUCAAC UCGUCGAC	2225
AD-1807390	csusgccuagAfAfAfuau uaugususa	2046	VPusdAsacdAudAauaud TuCfuaggcagsgsu	2136	ACCUGCCUAGAAAU AUUAUGUUG	2226
AD-1807391	usasagggaaCfUfCfuua uuuagscsa	2047	VPusdGscudAadAuaagd AgUfucccuuasasg	2137	CUUAAGGGAACUCU UAUUUAGCC	2227
AD-1807392	csusggaucuUfUfCfaac ucgucsgsa	2048	VPusdCsgadCgdAguugd AaAfgauccagsgsa	2138	UCCUGGAUCUUUCA ACUCGUCGA	2228
AD-1807393	csuscugaAfaUfUfAfuc auccgascsa	2049	VPusGfsucdGg(Agn)uga uaaUfuUfcagagsusu	2139	AACUCUGAAAUUAU CAUCCGACU	2229
AD-1807394	csasgcugaaUfUfAfguc ugucusgsa	2050	VPusdCsagdAcdAgacud AaUfucagcugsasa	2140	UUCAGCUGAAUUAG UCUGUCUGA	2230
AD-1807395	csusuguuugUfAfUfugc aauucscsa	2051	VPusdGsgadAudTgcaadT aCfaaacaagsusg	2141	CACUUGUUUGUAUU GCAAUUCCU	2231
AD-1807396	asasucaggaGfUfCfcuu cuucasusa	2052	VPusdAsugdAadGaaggd AcUfccugauuscsa	2142	UGAAUCAGGAGUCC UUCUUCAUU	2232
AD-1807397	gscsucaccaUfUfCfcaa uaucuscsa	2053	VPusdGsagdAudAuuggd AaUfggugagcscsu	2143	AGGCUCACCAUUCCA AUAUCUCA	2233
AD-1807398	csasaucuucCfAfCfaug aagugscsa	2054	VPusdGscadCudTcaugdT gGfaagauugsasu	2144	AUCAAUCUUCCACAU GAAGUGCA	2234
AD-1807399	asasacacAfaAfAfUfgu cuuauuscsa	2055	VPusGfsaadTa(Agn)gaca uuUfuGfuguuususg	2145	CAAAACACAAAAUG UCUUAUUCU	2235
AD-1807400	cscsuggaucUfUfUfcaa cucguscsa	2056	VPusdGsacdGadGuugad AaGfauccaggsasg	2146	CUCCUGGAUCUUUCA ACUCGUCG	2236
AD-1807401	csusacucuaUfGfAfcau uuugascsa	2057	VPusdGsucdAadAaugud CaUfagaguagsusa	2147	UACUACUCUAUGAC AUUUUGACA	2237
AD-1807402	gscscuugGfuGfCfAfuc uuccugsusa	2058	VPusAfscadGg(Agn)agau gcAfcCfaaggcsusa	2148	UAGCCUUGGUGCAU CUUCCUGUU	2238
AD-1807403	ususgcugcuAfUfGfccu uucuusgsa	2059	VPusdCsaadGadAaggcd AuAfgcagcaasgsa	2149	UCUUGCUGCUAUGCC UUUCUUGC	2239
AD-1807404	asgsugagaaAfAfGfaau uagcusgsa	2060	VPusdCsagdCudAauucdT uUfucucacususc	2150	GAAGUGAGAAAAGA AUUAGCUGA	2240
AD-1807405	asgsaucucuUfAfGfuaa auccasgsa	2061	VPusdCsugdGadTuuacdT aAfgagaucuscsc	2151	GGAGAUCUCUUAGU AAAUCCAGA	2241
AD-1807406	csascaauguGfCfUfgcu uuucascsa	2062	VPusdGsugdAadAagcad GcAfcauugugsgsg	2152	CCCACAAUGUGCUGC UUUUCACA	2242
AD-1807407	gsasauucagCfUfGfaau uagucsusa	2063	VPusdAsgadCudAauucd AgCfugaauucsasa	2153	UUGAAUUCAGCUGA AUUAGUCUG	2243
AD-1807408	cscsauucagAfAfAfcuc auugasgsa	2064	VPusdCsucdAadTgagudT uCfugaauggsusg	2154	CACCAUUCAGAAACU CAUUGAGA	2244
AD-1807409	ascsaugaagUfGfCfaaa auuuasgsa	2065	VPusdCsuadAadTuuugd CaCfuucaugusgsg	2155	CCACAUGAAGUGCA AAAUUUAGA	2245
AD-1807410	usgscugcuaUfGfCfcuu ucuugscsa	2066	VPusdGscadAgdAaaggd CaUfagcagcasasg	2156	CUUGCUGCUAUGCCU UUCUUGCC	2246
AD-1807411	gsgsgaaaAfaGfAfGfac auacccsusa	2067	VPusAfsggdGu(Agn)ugu cucUfuUfuucccsasu	2157	AUGGGAAAAAGAGA CAUACCCUA	2247
AD-1807412	csasuuccaaUfAfUfcuc agauusgsa	2068	VPusdCsaadTcdTgagadT aUfuggaaugsgsu	2158	ACCAUUCCAAUAUCU CAGAUUGC	2248

Duplex ID	Sense Sequence 5' to 3'	SEQ ID NO:	Antisense Sequence 5' to 3'	SEQ ID NO:	mRNA Target Sequence 5' to 3'	SEQ ID NO:
AD-1807413	asusguguUfuGfAfGfugaauccascsa	2069	VPusGfsugdGa(Tgn)ucacucAfaAfcacauscsa	2159	UGAUGUGUUUGAGUGAAUCCACA	2249
AD-1807414	asasaauauuAfAfGfacaguuucscsa	2070	VPusdGsgadAadCugucdTuAfauauuuuscsa	2160	UGAAAAUAUUAAGACAGUUUCCC	2250
AD-1807415	csasuuccAfaUfAfUfcucagauusgsa	2071	VPusCfsaadTc(Tgn)gagauaUfuGfgaaugsgsu	2161	ACCAUUCCAAUAUCUCAGAUUGC	2251
AD-1807416	gsasagcuuaUfUfGfucugguagsgsa	2072	VPusdCscudAcdCagacdAaUfaagcuucsasg	2162	CUGAAGCUUAUUGUCUGGUAGGA	2252
AD-1807417	csasguacUfcCfAfUfugaugugususa	2073	VPusAfsacdAc(Agn)ucaaugGfaGfuacugsasc	2163	GUCAGUACUCCAUUGAUGUGUUU	2253
AD-1807418	asgsuuuaacCfUfGfucauauaascsa	2074	VPusdGsuudAudAugacdAgGfuuaaacusgsu	2164	ACAGUUUAACCUGUCAUAUAACC	2254
AD-1807419	gsasccugccUfAfGfaaauauuasusa	2075	VPusdAsuadAudAuuucdTaGfgcaggucsasg	2165	CUGACCUGCCUAGAAAUAUUAUG	2255
AD-1807420	gsusagagGfgUfUfUfgaaguuucscsa	2076	VPusGfsgadAa(C2p)uucaaaCfcCfucuacsusa	2166	UAGUAGAGGGUUUGAAGUUUCCA	2256
AD-1807421	gsasaagaGfaUfAfCfaaucuugcsusa	2077	VPusAfsgcdAa(G2p)auuguaUfcUfcuuucsusg	2167	CAGAAAGAGAUACAAUCUUGCUU	2257
AD-1807422	cscsuggaUfcUfUfUfcaacucguscsa	2078	VPusGfsacdGa(G2p)uugaaaGfaUfccaggsasg	2168	CUCCUGGAUCUUUCAACUCGUCG	2258
AD-1807423	ususugagugAfAfUfccacaaaususa	2079	VPusAfsaudTu(G2p)uggauuCfaCfucaaascsa	2169	UGUUUGAGUGAAUCCACAAAUUC	2259

Example 2. *In Vitro* Evaluation of *LRRK2* siRNA

Experimental Methods

i. Lung epithelial cell culture and transfections:

Human Lung Epithelial cells A549 (ATCC) were transfected by adding approximately 5µl of 1 ng/µl, diluted in Opti-MEM, 4.9µl of Opti-MEM plus 0.1µl of Lipofectamine 2000 per well (Invitrogen, Carlsbad CA. cat #11668-019) to 5 µl of siRNA duplexes per well, with approximately 4 replicates of each siRNA duplex, into a 384-well plate, and the cells were then incubated at room temperature for about 15 minutes. siRNA duplexes without a ligand, as well as siRNA duplexes with a C16 ligand were tested. Three dose experiments were performed at 10nM, 1nM, and 0.1nM.

ii. Hepatocyte cell culture and transfections:

Primary mouse hepatocytes (PMH) were transfected by adding 5 µl of 1 ng/µl, diluted in Opti-MEM, 4.9µl of Opti-MEM plus 0.1µl of Lipofectamine 2000 per well (Invitrogen, Carlsbad CA. cat #11668-019) to 5µl of siRNA duplexes per well, with approximately 4 replicates of each siRNA duplex, into a 384-well plate, and the cells were then incubated at room temperature for 15 minutes. Thirty-five µl of Dulbecco's Modified Eagle Medium (ThermoFisher) containing ~5 x10^3 cells was then added to the siRNA mixture. Three dose experiments were performed at 10nM, 1nM, and 0.1nM.

iii. *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 is 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 the supernatant removed. The plates were loaded to the BioTek for RNA purification.

iv. *cDNA synthesis using ABI High capacity cDNA reverse transcription kit (Applied Biosystems, Foster City, CA, Cat #4368813):*

Ten µl of a master mix containing 1µl 10X Buffer, 0.4ul 25X dNTPs, 1 µl 10x Random primers, 0.5µl Reverse Transcriptase, 0.5 µl RNase inhibitor and 6.6 µl of H2O per reaction were added to the isolated RNA. Plates were then sealed, mixed, and incubated on an electromagnetic shaker for 10 minutes at room temperature, followed by 2h 37°C. The plate was stored in -20 °C until it is ready for qPCR.

v. *Real time PCR:*

Two µl of cDNA and 5µl Lightcycler 480 probe master mix (Roche Cat # 04887301001) were added to either 0.5-1 µl of Human GAPDH TaqMan Probe (4326317E) and 0.5-1 µl human *LRRK2* probe (Hs01115057_m1, Hs00968198, or Hs00411197, Thermo) or 0.5-1 µl Mouse GAPDH TaqMan Probe (4352339E) and 0.5-1µl mouse *Lrrk2* probe (Mm00481934_m1) per well in 384 well plates (Roche cat # 04887301001). Real time PCR was performed using a LightCycler480 Real Time PCR system (Roche). Each duplex was tested at least two times and data was normalized to cells transfected with a non-targeting control siRNA. To calculate relative fold change, real time data was analyzed using the ΔΔCt method and was normalized to assays performed with cells transfected with a non-targeting control siRNA.

Results

i. *Dose Screen of LRRK dsRNA Agents*

The results of the dose screen 1 in A549 cells with exemplary *LRRK2* siRNAs of Tables 3 and 4 are shown in Table 8. The results of the dose screen 2 in A549 cells with exemplary *LRRK2* siRNAs of Table 6, conjugated to a C16-ligand or unconjugated to a ligand, are shown in Tables 9 and 10, respectively. The results in Tables 9 and 10, expressed as average % *LRRK2* mRNA remaining, were obtained during an RNAseq analysis at a duplex concentration of 10 nM. In Table 9, the parent (i.e., L96-conjugated) dsRNA data were calculated based on the *in vitro* data in Table 8. The data are expressed as percent message remaining relative to the non-targeting control.

Table 8. Dose Screens of *LRRK2* dsRNA Agents (L96-Conjugated) in A549 Cells

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % *LRRK2* mRNA Remaining	SD	Avg % *LRRK2* mRNA Remaining	SD	Avg % *LRRK2* mRNA Remaining	SD
AD-1624152	40	4	94	8	95	2
AD-1624178	36	2	62	5	80	5
AD-1631019	93	3	83	10	95	5
AD-1631020	57	6	85	2	86	6
AD-1631021	65	7	98	12	101	7
AD-1624412	51	1	94	7	103	12
AD-1631022	58	3	93	7	93	3
AD-1631023	88	12	111	6	120	10
AD-1631024	93	13	100	13	111	15
AD-1631025	37	5	63	4	84	7
AD-1624595	42	5	70	12	77	15
AD-1631026	61	2	108	6	110	11
AD-1624721	45	8	102	13	102	13
AD-1624739	45	1	84	3	89	6
AD-1631027	54	6	115	15	105	8
AD-1624856	45	7	98	9	107	6
AD-1631028	64	10	100	7	119	6
AD-1624857	44	8	79	6	95	8
AD-1631029	75	5	99	6	91	6
AD-1624894	57	5	111	8	95	6
AD-1631030	34	5	71	7	104	21
AD-1625057	35	4	87	2	93	17
AD-1625155	73	9	99	4	106	11
AD-1631031	78	14	104	6	107	8
AD-1625191	59	8	101	12	93	12
AD-1631032	77	14	92	7	95	7
AD-1625192	44	12	98	18	95	18
AD-1631033	49	4	89	6	98	8
AD-1625195	49	6	105	21	111	10
AD-1625209	40	3	78	10	88	8
AD-1625230	33	5	76	8	81	7
AD-1631034	43	5	67	7	76	8
AD-1625282	40	5	125	18	92	18
AD-1625389	29	5	95	30	103	14
AD-1631035	42	4	102	19	112	12
AD-1625485	31	5	61	6	75	2
AD-1631036	41	5	117	12	119	19
AD-1625499	30	3	103	10	103	20

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % *LRRK2* mRNA Remaining	SD	Avg % *LRRK2* mRNA Remaining	SD	Avg % *LRRK2* mRNA Remaining	SD
AD-1631037	35	4	116	14	106	7
AD-1625501	51	8	93	10	104	9
AD-1625610	40	4	76	7	79	12
AD-1631038	58	10	108	20	92	11
AD-1631039	44	3	106	16	100	9
AD-1625786	38	5	84	9	84	13
AD-1631040	62	7	91	8	93	16
AD-1631041	65	11	111	13	113	9
AD-1625910	58	4	93	2	100	12
AD-1631042	73	7	97	8	105	6
AD-1631043	83	7	95	8	99	13
AD-1625928	51	9	94	6	102	5
AD-1631044	43	7	93	7	89	4
AD-1631045	46	6	106	13	94	10
AD-1631046	44	3	85	3	88	11
AD-1625975	29	2	90	16	99	9
AD-1631047	52	9	97	2	114	9
AD-1631048	45	5	116	7	97	9
AD-1631049	37	2	100	6	99	13
AD-1626183	28	4	67	6	85	7
AD-1626184	25	6	119	17	102	19
AD-1631050	31	5	86	8	98	7
AD-1626265	48	7	99	13	126	19
AD-1631051	50	7	100	9	116	10
AD-1626266	24	4	63	12	87	10
AD-1626268	61	13	119	19	137	20
AD-1631052	61	10	124	11	105	11
AD-1631053	37	5	73	0	93	16
AD-1626270	39	8	92	10	84	10
AD-1631054	40	12	72	3	77	9
AD-1626273	41	5	110	27	96	7
AD-1626280	42	4	113	5	93	10
AD-1631055	55	5	99	4	88	8
AD-1631056	89	17	85	10	93	10
AD-1626349	38	7	80	5	85	2
AD-1626353	26	2	69	7	96	27
AD-1631057	40	5	90	10	100	3
AD-1626375	34	5	83	6	92	4
AD-1626382	33	3	75	10	88	6

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % *LRRK2* mRNA Remaining	SD	Avg % *LRRK2* mRNA Remaining	SD	Avg % *LRRK2* mRNA Remaining	SD
AD-1631058	39	2	86	4	85	9
AD-1631059	101	12	89	7	96	2
AD-1626428	74	7	92	6	116	25
AD-1631060	91	2	93	7	106	8
AD-1631061	93	14	99	10	103	4
AD-1631062	41	3	87	4	80	8
AD-1626524	54	7	140	24	103	12
AD-1626636	44	4	75	6	96	7
AD-1631063	62	3	91	3	108	12
AD-1631064	66	9	107	7	108	12
AD-1626921	51	5	93	6	110	7
AD-1631065	37	6	75	5	93	11
AD-1631066	64	6	99	4	98	10
AD-1626925	40	5	94	6	100	9
AD-1631067	70	6	104	6	107	8
AD-1626927	90	13	112	10	108	7
AD-1626936	38	3	106	4	101	5
AD-1626946	54	10	93	6	81	8
AD-1631068	89	12	100	6	107	11
AD-1631069	54	3	93	4	103	15
AD-1627077	49	6	95	4	94	5
AD-1627110	49	5	105	9	87	10
AD-1631070	38	10	76	3	100	10
AD-1631071	27	3	81	5	94	17
AD-1631072	85	6	105	17	107	10
AD-1627308	26	2	70	5	79	13
AD-1631073	72	5	91	9	98	6
AD-1627390	31	4	77	3	97	10
AD-1631074	38	3	95	9	111	18
AD-1627410	47	5	86	8	116	13
AD-1631075	40	3	91	8	88	14
AD-1627411	72	2	88	9	99	19
AD-1631076	39	3	88	7	89	11
AD-1627412	77	6	87	5	94	12
AD-1631077	24	1	80	3	106	9
AD-1627511	30	3	97	8	110	4
AD-1631078	35	1	85	5	109	9
AD-1631079	44	4	108	14	103	9
AD-1631080	25	2	73	6	79	6

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % *LRRK2* mRNA Remaining	SD	Avg % *LRRK2* mRNA Remaining	SD	Avg % *LRRK2* mRNA Remaining	SD
AD-1627601	29	4	108	9	89	7
AD-1627625	33	5	79	6	86	5
AD-1631081	44	6	74	8	91	6
AD-1627631	44	9	105	18	108	8
AD-1627632	46	6	112	7	110	8
AD-1627672	37	3	82	6	85	12
AD-1631082	40	4	87	4	90	4
AD-1627717	38	1	87	5	104	12
AD-1631083	63	6	103	6	109	3
AD-1631084	67	3	109	6	94	7
AD-1631085	38	5	97	9	96	8
AD-1631086	41	3	97	7	93	12
AD-1627766	38	3	89	8	100	15
AD-1631087	54	8	99	13	92	5
AD-1627767	26	3	92	11	74	11
AD-1631089	38	5	92	12	94	5
AD-1627769	42	5	82	5	104	10
AD-1627772	32	4	96	11	87	6
AD-1631090	35	2	94	4	87	7
AD-1627820	37	4	77	9	77	4
AD-1627838	32	3	87	8	86	6
AD-1627852	61	4	94	7	114	4
AD-1627856	46	5	88	7	95	5
AD-1631091	88	5	86	11	110	11
AD-1627866	35	6	88	8	87	4
AD-1627870	40	3	105	10	90	7
AD-1631092	84	6	90	10	100	12
AD-1631093	40	5	99	10	109	10
AD-1627896	41	7	77	5	104	6
AD-1631094	32	2	106	11	79	13
AD-1631095	58	5	111	10	105	17
AD-1631096	41	8	90	6	102	9
AD-1627952	44	4	90	9	105	10
AD-1631097	61	6	100	6	112	8
AD-1631098	84	5	81	10	77	4
AD-1631099	54	8	100	9	105	5
AD-1628008	71	26	90	7	85	4
AD-1631100	38	3	96	8	104	9
AD-1631101	67	2	102	11	115	10

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % *LRRK2* mRNA Remaining	SD	Avg % *LRRK2* mRNA Remaining	SD	Avg % *LRRK2* mRNA Remaining	SD
AD-1631102	54	5	95	11	93	4
AD-1628014	28	2	70	4	86	3
AD-1631103	37	3	86	3	97	10
AD-1631104	80	4	101	10	98	8
AD-1631105	42	7	97	4	113	10
AD-1628027	55	9	89	5	103	9
AD-1631106	55	9	95	4	100	9
AD-1631107	48	5	86	10	99	12
AD-1628042	31	2	85	2	91	7
AD-1631108	43	2	87	7	91	6
AD-1628043	46	11	82	9	93	4
AD-1628044	27	1	64	6	76	6
AD-1628050	28	3	86	7	98	6
AD-1631109	29	2	82	3	99	3
AD-1631110	40	5	94	11	91	8
AD-1628052	32	4	97	11	102	8
AD-1631111	36	4	95	6	116	17
AD-1631112	88	7	84	1	85	6
AD-1628070	28	4	77	4	73	7
AD-1628073	25	3	72	7	89	14
AD-1631113	43	7	69	8	82	4
AD-1631114	70	20	87	3	104	8
AD-1631115	45	6	77	3	84	11
AD-1631116	54	9	79	8	85	9
AD-1631117	40	1	100	12	108	11
AD-1631118	33	1	79	2	79	3
AD-1628118	49	3	100	8	100	5
AD-1631119	63	7	92	10	98	8
AD-1631120	57	10	100	5	96	6
AD-1628119	62	1	103	9	106	6
AD-1631121	37	8	80	7	104	16
AD-1628133	38	8	98	4	106	7
AD-1631122	49	4	97	15	106	16
AD-1628253	52	11	90	5	99	13
AD-1631123	58	8	96	4	101	5
AD-1631124	47	3	99	11	103	7
AD-1628254	52	10	98	11	106	11
AD-1631125	62	5	102	15	102	6
AD-1631126	97	13	92	4	97	12

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % *LRRK2* mRNA Remaining	SD	Avg % *LRRK2* mRNA Remaining	SD	Avg % *LRRK2* mRNA Remaining	SD
AD-1628273	81	3	109	3	83	13
AD-1631127	81	13	91	8	91	10
AD-1631128	41	6	82	6	81	9
AD-1628318	54	6	82	1	82	2
AD-1631129	40	3	128	8	112	10
AD-1631130	53	6	103	5	110	8
AD-1628381	38	3	71	3	81	2
AD-1631131	109	12	78	4	87	4
AD-1631132	25	8	63	3	75	8
AD-1628382	25	4	63	4	81	9
AD-1628383	29	1	78	12	83	6
AD-1631133	101	10	94	8	96	12
AD-1628385	37	5	79	5	95	9
AD-1628396	26	1	86	6	83	8
AD-1631134	32	6	85	4	88	15
AD-1631135	36	1	81	10	93	5
AD-1631136	30	4	78	5	90	4
AD-1631137	57	13	94	11	115	26
AD-1628412	36	4	119	26	94	3
AD-1631138	44	6	103	4	83	3
AD-1628434	35	5	91	5	118	16
AD-1631139	59	5	102	10	96	7
AD-1631140	44	5	122	0	106	5
AD-1628441	56	6	108	10	116	11
AD-1628442	48	4	78	1	88	5
AD-1628443	63	1	93	10	90	12
AD-1631141	73	6	89	3	92	5
AD-1631142	51	7	91	9	83	8
AD-1628444	55	10	94	8	84	7
AD-1631143	65	6	100	5	121	17
AD-1631144	74	8	98	6	98	4
AD-1631145	82	1	84	6	80	2
AD-1631146	57	0	134	7	116	19
AD-1628467	33	4	87	4	81	2
AD-1631147	36	2	86	4	84	7
AD-1628570	26	3	80	8	90	8
AD-1628590	45	4	85	6	93	10
AD-1631148	35	4	84	10	74	7
AD-1631149	20	2	66	5	78	13

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % *LRRK2* mRNA Remaining	SD	Avg % *LRRK2* mRNA Remaining	SD	Avg % *LRRK2* mRNA Remaining	SD
AD-1628668	49	9	111	23	110	14
AD-1631150	37	4	84	6	77	4
AD-1628754	28	4	71	12	82	1
AD-1628759	25	3	84	6	103	6
AD-1631151	52	8	98	8	92	11
AD-1631152	23	2	69	6	73	8
AD-1631153	28	2	99	8	87	6
AD-1631154	39	3	102	12	133	5
AD-1628764	40	2	107	7	99	9
AD-1628794	35	9	67	5	90	12
AD-1628883	40	4	94	9	98	9
AD-1631155	40	4	71	1	97	0
AD-1631156	27	1	93	7	82	5
AD-1631157	30	6	61	1	86	1
AD-1631158	36	2	97	9	111	4
AD-1628951	38	7	87	4	97	6
AD-1631159	78	9	103	13	100	11
AD-1628961	78	5	100	7	111	15
AD-1631160	81	0	102	5	129	21
AD-1631161	27	4	70	1	81	7
AD-1628963	33	7	89	7	82	6
AD-1631162	34	4	97	11	90	7
AD-1631163	43	6	94	9	82	10
AD-1629007	48	4	95	5	78	9
AD-1631164	75	10	97	6	97	6
AD-1631165	67	3	99	8	92	10
AD-1629012	76	17	93	6	108	10
AD-1631166	49	2	119	13	99	0
AD-1631167	43	5	100	5	112	9
AD-1629024	39	4	92	6	94	8
AD-1631168	80	12	99	10	94	11
AD-1629025	43	6	85	6	88	9
AD-1629026	33	1	106	6	93	12
AD-1631169	60	4	124	16	102	7
AD-1631170	118	4	99	5	89	7
AD-1631171	37	8	116	13	105	10
AD-1629028	60	17	108	16	117	21
AD-1631172	40	4	105	11	99	8
AD-1629031	48	3	90	11	107	8

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % *LRRK2* mRNA Remaining	SD	Avg % *LRRK2* mRNA Remaining	SD	Avg % *LRRK2* mRNA Remaining	SD
AD-1631173	72	19	94	10	94	0
AD-1629032	44	4	111	10	100	15
AD-1631174	69	16	90	9	106	10
AD-1631175	62	6	88	7	88	5
AD-1629033	62	6	97	6	110	12
AD-1631176	38	4	94	4	114	14
AD-1631177	54	11	87	7	94	10
AD-1631178	39	2	108	7	122	18
AD-1629039	41	6	125	12	105	9
AD-1631179	43	3	93	7	103	12
AD-1631180	27	3	96	7	101	5
AD-1631181	101	14	112	18	119	14
AD-1631182	18	2	62	9	69	3
AD-1629092	26	5	65	5	72	13
AD-1631183	55	9	107	12	109	4
AD-1631184	47	4	83	6	101	3
AD-1631185	103	7	112	15	124	12
AD-1631186	42	6	93	8	97	13
AD-1631187	40	14	78	7	77	0
AD-1631188	33	7	106	15	94	16
AD-1629200	34	2	93	10	122	20
AD-1631189	60	12	123	14	93	3
AD-1629214	30	1	96	5	106	4
AD-1629216	37	2	66	3	90	10
AD-1631190	30	12	86	5	109	5
AD-1629223	23	4	66	7	83	5
AD-1629224	34	3	98	12	111	9
AD-1631191	32	7	89	5	93	10
AD-1631192	28	7	91	3	104	10
AD-1631193	24	1	70	9	89	8
AD-1631194	33	1	84	5	96	4
AD-1629263	35	3	84	11	89	7
AD-1629280	31	4	88	8	95	8
AD-1631195	86	5	106	5	102	6
AD-1631196	23	1	90	6	89	2
AD-1629292	36	7	93	8	100	15
AD-1631197	38	4	103	7	103	11
AD-1629298	53	5	96	1	101	6
AD-1631198	88	8	108	13	113	6

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % *LRRK2* mRNA Remaining	SD	Avg % *LRRK2* mRNA Remaining	SD	Avg % *LRRK2* mRNA Remaining	SD
AD-1629304	28	3	81	5	96	5
AD-1631199	35	4	88	3	97	5
AD-1631200	37	5	96	15	100	9
AD-1631201	36	5	91	20	105	10
AD-1629419	53	6	92	5	105	7
AD-1631202	68	11	102	9	102	2
AD-1631203	61	9	111	9	111	8
AD-1631204	41	7	83	2	95	13
AD-1629524	20	3	77	9	100	6
AD-1631205	26	4	82	9	97	3
AD-1631206	30	5	88	9	84	4
AD-1629573	34	6	89	8	91	6
AD-1631207	43	2	89	4	100	7
AD-1631208	39	7	102	4	118	14
AD-1629580	46	5	97	8	113	7
AD-1629581	54	11	111	4	104	5
AD-1631209	88	7	129	11	107	4
AD-1629597	70	3	103	10	114	14
AD-1631210	23	2	78	6	93	6
AD-1629619	26	2	85	8	102	10
AD-1629620	25	3	75	3	84	3
AD-1629621	24	5	75	5	81	4
AD-1629665	54	8	104	5	96	7
AD-1631211	75	12	111	16	113	11
AD-1631212	42	8	84	8	101	7
AD-1629707	57	7	99	4	107	10
AD-1629710	56	9	94	10	95	7
AD-1631213	82	7	99	12	94	8
AD-1629711	72	2	96	8	95	12
AD-1631214	85	8	89	6	106	9
AD-1629763	22	2	52	7	80	9
AD-1631215	24	2	63	7	72	5
AD-1631216	37	3	84	7	99	11
AD-1629799	26	2	79	5	91	8
AD-1631217	96	16	82	1	114	11
AD-1629807	34	2	84	4	93	12
AD-1629808	28	7	73	7	82	12
AD-1629809	22	3	57	3	70	4
AD-1629838	26	4	84	10	87	18

	10 nM Dose		1 nM Dose		0.1 nM Dose	
Duplex	Avg % *LRRK2* mRNA Remaining	SD	Avg % *LRRK2* mRNA Remaining	SD	Avg % *LRRK2* mRNA Remaining	SD
AD-1629876	33	4	110	20	103	1
AD-1631218	50	4	85	9	92	7
AD-1629878	41	7	78	6	89	9
AD-1631219	39	7	89	6	99	6
AD-1631220	33	2	82	9	91	6
AD-1630135	28	3	81	10	88	12
AD-1631221	29	3	96	15	84	5
AD-1630136	35	8	69	4	72	7

Table 9. IC70 of *LRRK2* Parent dsRNA Agents and Dose Screen of C16-Conjugated Corresponding dsRNA Agents

Parent Duplex ID	Parent *in vitro* IC70 (nM)	C16 Duplex ID	C16 Duplex (10 nM) Avg% *LRRK2* mRNA Remaining
AD-1631182	3.31	AD-1807334	37%
AD-1629763	4.27	AD-1807335	43%
AD-1629809	4.78	AD-1807336	33%
AD-1629524	5.26	AD-1807337	34%
AD-1629223	6.31	AD-1807338	40%
AD-1626266	6.60	AD-1807339	36%
AD-1631152	6.93	AD-1807340	35%
AD-1628382	7.60	AD-1807341	38%
AD-1631132	7.86	AD-1807342	31%
AD-1631077	8.06	AD-1807343	31%
AD-1629621	8.40	AD-1807344	43%
AD-1628073	8.61	AD-1807345	36%
AD-1626353	8.82	AD-1807346	41%
AD-1629620	9.34	AD-1807347	42%
AD-1631080	9.35	AD-1807348	35%
AD-1628759	9.55	AD-1807349	38%
AD-1629092	9.67	AD-1807350	42%
AD-1627308	10.08	AD-1807351	34%
AD-1628044	10.45	AD-1807352	35%
AD-1629799	10.71	AD-1807353	45%
AD-1631205	10.74	AD-1807354	40%
AD-1629619	10.84	AD-1807355	50%
AD-1628570	10.95	AD-1807356	32%
AD-1631161	11.30	AD-1807357	48%

Parent Duplex ID	Parent *in vitro* IC70 (nM)	C16 Duplex ID	C16 Duplex (10 nM) Avg% *LRRK2* mRNA Remaining
AD-1626183	11.65	AD-1807358	35%
AD-1629838	11.94	AD-1807359	35%
AD-1628014	12.25	AD-1807360	41%
AD-1628396	12.80	AD-1807361	50%
AD-1628754	13.05	AD-1807362	33%
AD-1629304	13.47	AD-1807363	41%
AD-1629808	13.58	AD-1807364	34%
AD-1626184	14.03	AD-1807365	32%
AD-1631180	14.06	AD-1807366	39%
AD-1628050	14.25	AD-1807367	36%
AD-1631192	14.47	AD-1807368	40%
AD-1630135	14.61	AD-1807369	37%
AD-1631109	14.99	AD-1807370	41%
AD-1627767	15.79	AD-1807371	39%
AD-1631190	16.25	AD-1807372	34%
AD-1625975	16.84	AD-1807373	21%
AD-1628070	16.84	AD-1807374	36%
AD-1631149	4.53	AD-1807375	42%
AD-1631215	7.02	AD-1807376	41%
AD-1631210	7.40	AD-1807377	41%
AD-1631193	7.42	AD-1807378	33%

Table 10. Parent dsRNA Agents and Dose Screen of Unconjugated Corresponding dsRNA Agents

Parent Duplex ID	Unconjugated Duplex ID	Unconjugated Duplex (10 nM) Avg% *LRRK2* mRNA Remaining
AD-1631182	AD-1807379	33%
AD-1629763	AD-1807380	34%
AD-1629809	AD-1807381	39%
AD-1629524	AD-1807382	34%
AD-1629223	AD-1807383	37%
AD-1626266	AD-1807384	27%
AD-1631152	AD-1807385	37%
AD-1628382	AD-1807386	34%
AD-1631132	AD-1807387	31%
AD-1631077	AD-1807388	35%
AD-1629621	AD-1807389	40%
AD-1628073	AD-1807390	32%
AD-1626353	AD-1807391	26%

Parent Duplex ID	Unconjugated Duplex ID	Unconjugated Duplex (10 nM) Avg% *LRRK2* mRNA Remaining
AD-1629620	AD-1807392	41%
AD-1631080	AD-1807393	32%
AD-1628759	AD-1807394	37%
AD-1629092	AD-1807395	29%
AD-1627308	AD-1807396	35%
AD-1628044	AD-1807397	47%
AD-1629799	AD-1807398	40%
AD-1631205	AD-1807399	33%
AD-1629619	AD-1807400	41%
AD-1628570	AD-1807401	37%
AD-1631161	AD-1807402	39%
AD-1626183	AD-1807403	33%
AD-1629838	AD-1807404	41%
AD-1628014	AD-1807405	36%
AD-1628396	AD-1807406	34%
AD-1628754	AD-1807407	35%
AD-1629304	AD-1807408	47%
AD-1629808	AD-1807409	34%
AD-1626184	AD-1807410	20%
AD-1631180	AD-1807411	37%
AD-1628050	AD-1807412	38%
AD-1631192	AD-1807413	33%
AD-1630135	AD-1807414	41%
AD-1631109	AD-1807415	40%
AD-1627767	AD-1807416	44%
AD-1631190	AD-1807417	35%
AD-1625975	AD-1807418	21%
AD-1628070	AD-1807419	39%
AD-1631149	AD-1807420	38%
AD-1631215	AD-1807421	37%
AD-1631210	AD-1807422	39%
AD-1631193	AD-1807423	39%
AD-1631182	AD-1807379	33%
AD-1629763	AD-1807380	34%
AD-1629809	AD-1807381	39%
AD-1629524	AD-1807382	34%
AD-1629223	AD-1807383	37%
AD-1626266	AD-1807384	27%
AD-1631152	AD-1807385	37%
AD-1628382	AD-1807386	34%
AD-1631132	AD-1807387	31%

Parent Duplex ID	Unconjugated Duplex ID	Unconjugated Duplex (10 nM) Avg% *LRRK2* mRNA Remaining
AD-1631077	AD-1807388	35%
AD-1629621	AD-1807389	40%
AD-1628073	AD-1807390	32%
AD-1626353	AD-1807391	26%
AD-1629620	AD-1807392	41%
AD-1631080	AD-1807393	32%
AD-1628759	AD-1807394	37%
AD-1629092	AD-1807395	29%
AD-1627308	AD-1807396	35%
AD-1628044	AD-1807397	47%
AD-1629799	AD-1807398	40%
AD-1631205	AD-1807399	33%
AD-1629619	AD-1807400	41%
AD-1628570	AD-1807401	37%
AD-1631161	AD-1807402	39%
AD-1626183	AD-1807403	33%
AD-1629838	AD-1807404	41%
AD-1628014	AD-1807405	36%
AD-1628396	AD-1807406	34%
AD-1628754	AD-1807407	35%
AD-1629304	AD-1807408	47%
AD-1629808	AD-1807409	34%
AD-1626184	AD-1807410	20%
AD-1631180	AD-1807411	37%
AD-1628050	AD-1807412	38%
AD-1631192	AD-1807413	33%
AD-1630135	AD-1807414	41%
AD-1631109	AD-1807415	40%
AD-1627767	AD-1807416	44%
AD-1631190	AD-1807417	35%
AD-1625975	AD-1807418	21%
AD-1628070	AD-1807419	39%
AD-1631149	AD-1807420	38%
AD-1631215	AD-1807421	37%
AD-1631210	AD-1807422	39%
AD-1631193	AD-1807423	39%

i. *Hotspot analysis*

Based on the *in vitro* data provided in Tables 8-10, *LRRK2* mRNA target sequences which, upon binding of a dsRNA agent, were associated with decrease in *LRRK2* mRNA to a remaining message level of ≤ 40% and ≤ 30%, were identified in Tables 11 and 12, respectively.

Table 11. *LRRK2* mRNA target sequences having ≤ 40% message remaining as measured in Example 2

Target Start	Target End	mRNA Target Sequence (NM_198578.4)	SEQ ID NO:
3620	3652	UGAAUUUUCUUGCUGCUAUGCCUUUCUUGCCUC	2260
3794	3849	UGAACUUAAGGGAACUCUUAUUUAGCCAUAAUCAGAUCAGCAUCUUGGACUUGAGU	2261
5194	5222	AACUCUGAAAUUAUCAUCCGACUAUAUGA	2262
5366	5393	CUGAAGCUUAUUGUCUGGUAGGAUCUGA	2263
5423	5463	UAAAAAUUACAGUUCCUUCUUGUAGAAAAGGCUGUAUUCUU	2264
5674	5704	AGGCUCACCAUUCCAAUAUCUCAGAUUGCCC	2265
5720	5745	CUGACCUGCCUAGAAAUAUUAUGUUG	2266
6090	6114	CCACUCAGCCAUGAUUAUAUACCGA	2267
6125	6156	CCCACAAUGUGCUGCUUUUCACACUGUAUCCC	2268
6518	6561	UCUUUGACAUUUUGAAUUCAGCUGAAUUAGUCUGUCUGACGAGA	2269
6721	6750	GAUAGUAGAAUAUUGUGCUUAGCCUUGGUG	2270
6740	6763	UAGCCUUGGUGCAUCUUCCUGUUG	2271
7016	7061	GAAAUGUCAGUACUCCAUUGAUGUGUUUGAGUGAAUCCACAAAUUC	2272
7083	7123	GGGAGGAUGUGGCACAAAGAUUUUCUCCUUUUCUAAUGAUU	2273
7112	7136	UUUCUAAUGAUUUCACCAUUCAGAA	2274
7125	7169	CACCAUUCAGAAACUCAUUGAGACAAGAACAAGCCAACUGUUUUC	2275

Target Start	Target End	mRNA Target Sequence (NM_198578.4)	SEQ ID NO:
7346	7373	CAAAACACAAAAUGUCUUAUUCUGGGAG	2276
7441	7465	CUCCUGGAUCUUUCAACUCGUCGAC	2277
7591	7659	CAGAAAGAGAUACAAUCUUGCUUGACCGUUUGGGACAUCAAUCUUCCACAUGAAGUGCAAAAUUUAGAA	2278
8132	8155	UGAAAAUAUUAAGACAGUUUCCCA	2279

Table 12. *LRRK2* mRNA target sequences having ≤ 30% message remaining as measured in Example 2

Target Start	Target End	mRNA Target Sequence (NM_198578.4)	SEQ ID NO.:
3627	3650	UCUUGCUGCUAUGCCUUUCUUGCC	2280
5194	5222	AACUCUGAAAUUAUCAUCCGACUAUAUGA	2281
5674	5702	AGGCUCACCAUUCCAAUAUCUCAGAUUGC	2282
5720	5745	CUGACCUGCCUAGAAAUAUUAUGUUG	2283
6091	6114	CACUCAGCCAUGAUUAUAUACCGA	2284
6529	6559	UUGAAUUCAGCUGAAUUAGUCUGUCUGACGA	2285
7034	7061	UGAUGUGUUUGAGUGAAUCCACAAAUUC	2286
7441	7465	CUCCUGGAUCUUUCAACUCGUCGAC	2287
7636	7659	CCACAUGAAGUGCAAAAUUUAGAA	2288

It is expressly contemplated that nucleotides 3620-3652, 3794-3849, 5194-5222, 5366-5393, 5423-5463, 5674-5704, 5720-5745, 6090-6114, 6125-6156, 6518-6561, 6721-6750, 6740-6763, 7016-7061, 7083-7123, 7112-7136, 7125-7169, 7346-7373, 7441-7465, 7591-7659, 7636-7659, 8132-8155, 3627-3650, 5194-5222, 5674-5702, 5720-5745, 6091-6114, 6529-6559, 7034-7061, 7441-7465, and 7636-7659 of NM_001276.4 comprise hotspot regions, set forth as SEQ ID NOs: 2260-2288, which is targeted by AD-1627308, AD-1631049, AD-1631050, AD-1626349, AD-1626353, AD-1626375, AD-1626382, AD-1631080, AD-1807348, AD-1807393, AD-1631088, AD-1631089, AD-1631090, AD-1631108, AD-1807416, AD-1807371, AD-1627767, AD-1627769, AD-1627772, AD-1631109, AD-1631110, AD-1631111, AD-1627820, AD-1627838, , AD-1628042, AD-1628043, AD-1628044, AD-1628050, AD-1628052,, AD-1628070, AD-1631108, AD-1631109, AD-1631110, AD-1631111, AD-1807397, AD-1807352, , AD-1628073, AD-1807374, AD-1807419, AD-1628381, AD-1628382, AD-1628383, AD-1631131, AD-1631132, AD-1631133, AD-1628396, AD-1807361, AD-1807406, AD-1631150, AD-1631151, AD-1631152, AD-1631153, AD-1631154, AD-1631155, AD-1631156, AD-1631157, AD-1631158, AD-1631160, AD-1631161, AD-1631162, AD-1807357, AD-1807402, AD-1628961, AD-1628963, AD-1629214, AD-1629216, AD-1629223, AD-1629224, AD-1629263, AD-1629280, AD-1631194, AD-1631195, AD-1631196, AD-1631197, AD-1807363, AD-1807408, AD-1629304, AD-1629524, AD-1631205, AD-1631206, AD-1807337, AD-1807354, AD-1807382, AD-1807399, AD-1629619, AD-1629620, AD-1629621, AD-1631210, AD-1807355, AD-1807377, AD-1807400, AD-1807422, AD-1629763, AD-1631215, AD-1631216, AD-1631217, AD-1807335, AD-1807336, AD-1807376, AD-1807380, AD-1807381, AD-1807421, AD-1630135, AD-1630136, AD-1631221, AD-1807369, AD-1807414, AD-1807364, AD-1807409, AD-1629808, and AD-1629809.

Example 3. *In Vivo* Evaluation of *LRRK2* mRNA Suppression in Mice

This Example describes methods for the *in vivo* evaluation of *LRRK2* RNAi agents in mice expressing human *Lrrk2* RNAs.

Experimental Methods

To assess the efficacy of the RNAi agents described herein, these agents are administered to mice that express mouse *Lrrk2* or human *LRRK2*. In some experiments, the RNAi agents (in buffer such as aCSF) or aCSF control is administered to female C57BL/6 mice that are about 6-8 weeks old.

In other experiments, the RNAi agents (in buffer such as aCSF) or aCSF control was administered in a randomized manner to humanized female C57BL/6J-Tg(LRRK2*G2019S)2AMjff/J mice ("MJFF mice") that were about 10-16 weeks old. The MJFF mice are hemizygous for the human BAC *LRRK2* (G2019S) transgene that expresses a mutant form of *LRRK2* (G2019S) associated with autosomal dominant, late-onset Parkinson's disease directed by the human *LRRK2* promoter/enhancer regions on the BAC transgene. These mice represent an *in vivo* model for studying the dominant toxic effects of mutant *LRRK2**G2019S expression. Mouse age was staggered across treatments to controls for assay expression differences with age, although age was not expected to impact baseline variability during the experimental time course, and functional data of 6- and 12-month old mice did not show an age-related difference.

The control group included 4 animals and each of the RNAi agents of interest (described in Tables 7 and 13, and FIG. 1) is administered to a group of 4 animals. The administration was through a single intracerebroventricular injection (free-hand ICV injection) administered at a dose of 150 μg in 10 μl (15 mg/ml stock). Plasma was collected at day fourteen (14) post-administration and stored at -80 °C until assaying. At fourteen (14) days post-administration, mice were euthanized. Plasma was isolated and stored at -80 °C until assaying. Brain (right hemisphere), liver tissue, lung (left lobe), and kidney (left) are collected, flash-frozen and stored at -80 °C until processing. The study design is summarized in Table 14.

Table 13. Exemplary LRRK2 Duplexes and Corresponding Chemistry

Duplex ID	Strand	Modified Sequence	SEQ ID NO:
AD-1807334	sense	csusugu(Uhd)UfgUfAfUfugcaauucscsa	1990
	antisense	VPusGfsgadAu(Tgn)gcaauaCfaAfacaagsusg	2080
AD-1807336	sense	csasuga(Ahd)guGfCfAfaaauuuagsasa	1992
	antisense	VPusdTscudAadAuuuudGcAfcuucaugsusg	2082
AD-1807339	sense	usasaau(Chd)uuCfCfAfcacuugcgsgsa	1995
	antisense	VPusdCscgdCadAgugudGgAfagauuuasasa	2085
AD-1807344	sense	usgsgau(Chd)uuUfCfAfacucgucgsasa	2000
	antisense	VPusdTscgdAcdGaguudGaAfagauccasgsg	2090
AD-1807345	sense	csusgcc(Uhd)agAfAfAfuauuaugususa	2001
	antisense	VPusdAsacdAudAauaudTuCfuaggcagsgsu	2091

AD-1807349	sense	csasgc(Uhd)gaaUfUfAfgucugucusgsa	2005
	antisense	VPusdCsagdAcdAgacudAaUfucagcugsasa	2095
AD-1807352	sense	gscsuca(Chd)caUfUfCfcaauaucuscsa	2008
	antisense	VPusdGsagdAudAuuggdAaUfggugagcscsu	2098
AD-1807364	sense	ascsaug(Ahd)agUfGfCfaaaauuuasgsa	2020
	antisense	VPusdCsuadAadTuuugdCaCfuucaugusgsg	2110
AD-1807370	sense	csasuuc(Chd)AfaUfAfUfcucagauusgsa	2026
	antisense	VPusCfsaadTc(Tgn)gagauaUfuGfgaaugsgsu	2116
AD-1807374	sense	gsasccug(Chd)cUfAfGfaaauauuasusa	2030
	antisense	VPusdAsuadAudAuuucdTaGfgcaggucsasg	2120

Table 14. Study Design for Intracerebroventricular Dosing of dsRNA Agents in Humanized Mice

Group #	Animal #	Treatment	Dose (μg)	Timepoint	Tissue
1	1-4	aCSF	-	Day 14	**Terminal plasma** **Post-perfusion frozen (qPCR):** Right hemibrain (cerebellum and olfactory bulbs removed), Liver, Lung, Kidney **Post-perfusion frozen (protein):** Left brain hemisphere **Post-perfusion fixed (histology):** Lung, Kidney
2	5-8	AD-1807334	150 (150 mg/ml in 10 μl)		
3	9-12	AD-1807336			
4	13-16	AD-1807339			
5	17-20	AD-1807344			
6	21-24	AD-1807345			
7	25-28	AD-1807349			
8	29-32	AD-1807352			
9	33-36	AD-1807364			
10	37-40	AD-1807370			
11	41-44	AD-1807374			

Efficacy of the RNAi agents was evaluated by the measurement of *LRRK2* mRNA in brain, liver, lung and kidney tissues at 14 days post-dose. *LRRK2* brain mRNA levels were assayed utilizing RT-qPCR. Mouse brain (right hemisphere) samples were ground and tissue lysates were prepared. The mRNA levels in the brain lysates (and CSF as an endogenous control) was assayed by RT-qPCR using mouse Xpnpep1 probe (Applied Biosystems) as the control probe and a suitable *LRRK2* probe (e.g., Hs00968198), and mRNA levels were determined (see, e.g., above and Jiang, *supra*). The mRNA levels in the liver, lung, and kidney tissue are assayed by RT-qPCR using mouse Xpnpep1 probe (Applied Biosystems) as the control probe and a suitable *LRRK2* probe (e.g., Hs01115057_m1, Hs00968198, Hs00411197, Mm00481934_m1, experimental probe).

Efficacy of the RNAi agents is also evaluated by the measurement of LRRK2 protein and the histological assessment in the 14-day post-dose brain, liver, lung, or kidney tissues.

Results

The results of the *in vivo* evaluation of LRRK2-targeting dsRNA agents in Tables 7, 13, and FIG. 1 are shown in Table 15 and FIG. 2. The results demonstrate the ability of the exemplary dsRNA agents to reduce the LRRK2 mRNA levels *in vivo* in the brain.

Table 15. *In Vivo* Evaluation of LRRK2 dsRNA Agents

Tissue	**Brain**	
	Avg % LRRK2 mRNA Remaining	**SD**
aCSF	100.0	22.1
AD-1807334	68.2	14.8
AD-1807336	71.1	4.8
AD-1807339	82.2	10.0
AD-1807344	68.8	10.5
AD-1807345	88.8	10.9
AD-1807349	83.6	19.3
AD-1807352	82.5	15.7
AD-1807364	88.0	15.1
AD-1807370	86.8	16.8
AD-1807374	73.6	13.1

Example 4. Evaluation of *LRRK2* RNAi Agents *in vivo* in Mice

This Example describes methods to evaluate high performing dsRNA agents at a higher dose.

To assess the efficacy of the RNAi agent of interest, the agent is administered to the MJFF mice that has the human *LRRK2* gene with the pathogenic G2019S mutation. There are a total of 5 groups including to a control (aCSF) group had 4 other groups corresponding to 4 different RNAi agents (e.g., AD-1807334, AD-1807336, AD-1807344, and AD-1807374) at 300 µg as shown below in Table 16 with an exemplary study plan. Each group has 4 animals. The administration is through a single intracerebroventricular injection (free-hand ICV injection) administered into the brain right hemisphere in 10µl (30 mg/ml stock). Fourteen (14) days post-administration, mice are euthanized and perfused with saline prior to tissue collection. Whole blood and plasma are isolated and stored at -80 °C until assaying. Brain (right hemisphere), liver tissue, lung (left lobe) and kidney (left) are collected, flash-frozen and stored at -80 °C. until processing. Tissue samples and terminal blood are also collected for future protein analysis. An exemplary study design is shown in Table 14.

Table 16. Study Design for *LRRK2* RNAi Agents *in vivo* Evaluation

Group	Treatment	Dose (μg)	Dosing	Injection	Timepoint	(n)
1	aCSF	-				
2	AD-1807334					
3	AD-1807336					
4	AD-1807344		Single	Freehand		
5	AD-1807374	300	dose D0	ICV	D14	4

Efficacy and dose response of the RNAi agent are evaluated by the measurement of the percentage of *LRRK2* mRNA remaining in brain, liver, lung and kidney tissues at 14 days post-dose of the RNAi agent. *LRRK2* brain mRNA levels are assayed utilizing RT-qPCR. Mouse brain (right hemisphere) samples are ground and tissue lysates are prepared. The brain lysate sample is incubated with a suitable *LRRK2* probe (e.g., Hs01115057_m1, Hs00968198, Hs00411197, Mm00481934_m1) and CSF as an endogenous control. mRNA levels are determined in brain samples by RT-qPCR (see, e.g., above and Jiang, *supra*). The mRNA levels in the liver, lung, and kidney tissues are assayed by RT-qPCR using mouse Xpnpep1 probe (Applied Biosystems) as the control probe and *LRRK2* probe (e.g., Hs01115057_m1, Hs00968198, Hs00411197, Mm00481934_m1 as the experimental probe).

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments and methods described herein. Such equivalents are intended to be encompassed by the scope of the following claims.

LRRK2 SEQUENCES

SEQ ID NO:1

> NM_198578.4 Homo sapiens leucine rich repeat kinase 2 (*LRRK2*), mRNA

GGGGCCCGCGGGGAGCGCTGGCTGCGGGCGGTGAGCTGAGCTCGCCCCCGGGGAGCTGTGGCCGGCGCCCC
TGCCGGTTCCCTGAGCAGCGGACGTTCATGCTGGGAGGGCGGCGGGTTGGAAGCAGGTGCCACCATGGCTA
GTGGCAGCTGTCAGGGGTGCGAAGAGGACGAGGAAACTCTGAAGAAGTTGATAGTCAGGCTGAACAATGTC
CAGGAAGGAAAACAGATAGAAACGCTGGTCCAAATCCTGGAGGATCTGCTGGTGTTCACGTACTCCGAGCG
CGCCTCCAAGTTATTTCAAGGCAAAAATATCCATGTGCCTCTGTTGATCGTCTTGGACTCCTATATGAGAG
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CAGGTAAAATCACCTTGCTGATATTGGATGAAGAAAGTGATATTTTCATGTTAATTTTTGATGCCATGCAC
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AACTTTAAA

SEQ ID NO:2
>Reverse Complement of SEQ ID NO:1

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SEQ ID NO:8

>Reverse Complement of SEQ ID NO:7

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SEQ ID NO:1808

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CLAIMS

We claim:

1. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of *LRRK2*, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a region of complementarity to an mRNA encoding LRRK2, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 3-7.

2. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of *LRRK2*, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 1 or 1808 and the antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 2 or 1809.

3. A double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of *LRRK2*, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region,

wherein the antisense strand comprises a region of complementarity to an mRNA encoding LRRK2, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 2 or 1809.

4. The dsRNA agent of any one of claims 1-3, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 1458-1478, 1484-1504, 1761-1781, 1950-1970, 2076-2096, 2094-2114, 2212-2232, 2213-2233, 2268-2288, 2431-2451, 2529-2549, 2565-2585, 2566-2586, 2569-2589, 2583-2603, 2605-2625, 2657-2677, 2764-2784, 2867-2887, 2881-2901, 2883-2903, 3022-3042, 3198-3218, 3330-3350, 3348-3368, 3395-3415, 3629-3649, 3630-3650, 3712-3732, 3713-3733, 3715-3735, 3717-3737, 3720-3740, 3727-3747, 3796-3816, 3800-3820, 3822-3842, 3829-3849, 3875-3895, 3971-3991, 4130-4150, 4443-4463, 4447-4467, 4449-4469, 4478-4498, 4488-4508, 4619-4639, 4652-4672, 4868-4888, 4950-4970, 4970-4990, 4971-4991, 4972-4992, 5092-5112, 5202-5222, 5226-5246, 5232-5252, 5233-5253, 5273-5293, 5318-5338, 5367-5387, 5368-5388, 5370-5390, 5373-5393, 5425-5445, 5443-5463, 5457-5477, 5461-5481, 5471-5491, 5475-5495, 5501-5521, 5557-5577, 5640-5660, 5646-5666, 5659-5679, 5674-5694, 5675-5695, 5676-5696, 5682-5702, 5684-5704, 5722-5742, 5725-5745, 5778-5798, 5779-5799, 5793-5813, 5964-5984, 5965-5985, 5984-6004, 6029-6049, 6092-6112, 6093-6113, 6094-6114, 6096-6116, 6127-6147, 6143-6163, 6165-6185, 6172-6192, 6173-

6193, 6174-6194, 6175-6195, 6198-6218, 6319-6339, 6339-6359, 6418-6438, 6531-6551, 6536-6556, 6541-6561, 6573-6593, 6662-6682, 6730-6750, 6740-6760, 6742-6762, 6786-6806, 6791-6811, 6803-6823, 6804-6824, 6805-6825, 6807-6827, 6810-6830, 6811-6831, 6812-6832, 6818-6838, 6872-6892, 7004-7024, 7018-7038, 7020-7040, 7027-7047, 7028-7048, 7085-7105, 7103-7123, 7115-7135, 7121-7141, 7127-7147, 7242-7262, 7348-7368, 7397-7417, 7404-7424, 7405-7425, 7421-7441, 7443-7463, 7444-7464, 7445-7465, 7493-7513, 7535-7555, 7538-7558, 7539-7559, 7593-7613, 7629-7649, 7637-7657, 7638-7658, 7639-7659, 7671-7691, 7727-7747, 7729-7749, 8134-8154, 8135-8155, 1484-1504, 1488-1508, 1755-1775, 1761-1781, 1905-1925, 1945-1965, 1950-1970, 2029-2049, 2207-2227, 2212-2232, 2213-2233, 2431-2451, 2529-2549, 2565-2585, 2569-2589, 2648-2668, 2764-2784, 2874-2894, 2881-2901, 3051-3071, 3193-3213, 3198-3218, 3208-3228, 3330-3350, 3331-3351, 3350-3370, 3380-3400, 3390-3410, 3395-3415, 3573-3593, 3622-3642, 3632-3652, 3712-3732, 3715-3735, 3717-3737, 3718-3738, 3740-3760, 3795-3815, 3806-3826, 3829-3849, 3830-3850, 3938-3958, 3950-3970, 3971-3991, 4367-4387, 4376-4396, 4444-4464, 4446-4466, 4447-4467, 4551-4571, 4554-4574, 4704-4724, 4834-4854, 4839-4859, 4925-4945, 4970-4990, 4971-4991, 4972-4992, 5058-5078, 5092-5112, 5128-5148, 5196-5216, 5226-5246, 5275-5295, 5322-5342, 5349-5369, 5352-5372, 5365-5385, 5367-5387, 5368-5388, 5370-5390, 5373-5393, 5461-5481, 5475-5495, 5482-5502, 5515-5535, 5516-5536, 5541-5561, 5557-5577, 5607-5627, 5635-5655, 5641-5661, 5643-5663, 5644-5664, 5646-5666, 5655-5675, 5659-5679, 5660-5680, 5671-5691, 5674-5694, 5682-5702, 5683-5703, 5684-5704, 5721-5741, 5757-5777, 5763-5783, 5772-5792, 5773-5793, 5776-5796, 5777-5797, 5778-5798, 5779-5799, 5793-5813, 5794-5814, 5964-5984, 5965-5985, 5966-5986, 5980-6000, 5984-6004, 6029-6049, 6030-6050, 6071-6091, 6092-6112, 6093-6113, 6095-6115, 6129-6149, 6135-6155, 6136-6156 ,6142-6162, 6145-6165, 6171-6191, 6172-6192, 6174-6194, 6175-6195, 6178-6198, 6180-6200, 6196-6216, 6197-6217, 6198-6218, 6344-6364, 6355-6375, 6520-6540, 6536-6556, 6538-6558, 6539-6559, 6541-6561, 6723-6743, 6724-6744, 6729-6749, 6730-6750, 6737-6757, 6740-6760, 6742-6762, 6743-6763, 6786-6806, 6787-6807, 6791-6811, 6793-6813, 6794-6814, 6803-6823, 6805-6825, 6806-6826, 6807-6827, 6808-6828, 6810-6830, 6811-6831, 6812-6832, 6813-6833, 6814-6834, 6818-6838, 6828-6848, 6829-6849, 6834-6854, 6872-6892, 6918-6938, 6919-6939, 6920-6940, 6922-6942, 6989-7009, 7004-7024, 7012-7032, 7023-7043, 7035-7055, 7036-7056, 7041-7061, 7085-7105, 7103-7123, 7114-7134, 7116-7136, 7121-7141, 7129-7149, 7146-7166, 7149-7169, 7242-7262, 7247-7267, 7303-7323, 7348-7368, 7353-7373, 7397-7417, 7404-7424, 7405-7425, 7443-7463, 7493-7513, 7533-7553, 7538-7558, 7539-7559, 7593-7613, 7627-7647, 7629-7649, 7727-7747, 8005-8025, 8007-8027 and 8134-8154 of SEQ ID NO: 1, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO: 2.

5. The dsRNA agent of any one of claims 1-4, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1624152, AD-1624178, AD-1624412, AD-1624595, AD-1624721, AD-1624739, AD-1624856, AD-1624857, AD-1624894, AD-

1625057, AD-1625155, AD-1625191, AD-1625192, AD-1625195, AD-1625209, AD-1625230, AD-1625282, AD-1625389, AD-1625485, AD-1625499, AD-1625501, AD-1625610, AD-1625786, AD-1625910, AD-1625928, AD-1625975, AD-1626183, AD-1626184, AD-1626265, AD-1626266, AD-1626268, AD-1626270, AD-1626273, AD-1626280, AD-1626349, AD-1626353, AD-1626375, AD-1626382, AD-1626428, AD-1626524, AD-1626636, AD-1626921, AD-1626925, AD-1626927, AD-1626936, AD-1626946, AD-1627077, AD-1627110, AD-1627308, AD-1627390, AD-1627410, AD-1627411, AD-1627412, AD-1627511, AD, 1627601, AD-1627625, AD-1627631, AD-1627632, AD-1627672, AD-1627717, AD-1627766, AD-1627767, AD-1627769, AD-1627772, AD-1627820, AD-1627838, AD-1627852, AD-1627856, AD-1627866, AD-1627870, AD-1627896, AD-1627952, AD-1628008, AD-1628014, AD-1628027, AD-1628042, AD-1628043, AD-1628044, AD-1628050, AD-1628052, AD-1628070, AD-1628073, AD-1628118, AD-1628119, AD-1628133, AD-1628253, AD-1628254, AD-1628273, AD-1628318, AD-1628381, AD-1628382, AD-1628383, AD-1628385, AD-1628396, AD-1628412, AD-1628434, AD-1628441, AD-1628442, AD-1628443, AD-1628444, AD-1628467, AD-1628570, AD-1628590, AD-1628668, AD-1628754, AD-1628759, AD-1628764, AD-1628794, AD-1628883, AD-1628951, AD-1628961, AD-1628963, AD-1629007, AD-1629012, AD-1629024, AD-1629025, AD-1629026, AD-1629028, AD-1629031, AD-1629032, AD-1629033, AD-1629039, AD-1629092, AD-1629200, AD-1629214, AD-1629216, AD-1629223, AD-1629224, AD-1629263, AD-1629280, AD-1629292, AD-1629298, AD-1629304, AD-1629419, AD-1629524, AD-1629573, AD-1629580, AD-1629581, AD-1629597, AD-1629619, AD-1629620, AD-1629621, AD-1629665, AD-1629707, AD-1629710, AD-1629711, AD-1629763, AD-1629799, AD-1629807, AD-1629808, AD-1629809, AD-1629838, AD-1629876, AD-1629878, AD-1630135, AD-1630136, AD-1631019, AD-1631020, AD-1631021, AD-1631022, AD-1631023, AD-1631024, AD-1631025, AD-1631026, AD-1631027, AD-1631028, AD-1631029, AD-1631030, AD-1631031, AD-1631032, AD-1631033, AD-1631034, AD-1631035, AD-1631036, AD-1631037, AD-1631038, AD-1631039, AD-1631040, AD-1631041, AD-1631042, AD-1631043, AD-1631044, AD-1631045, AD-1631046, AD-1631047, AD-1631048, AD-1631049, AD-1631050, AD-1631051, AD-1631052, AD-1631053, AD-1631054, AD-1631055, AD-1631056, AD-1631057, AD-1631058, AD-1631059, AD-1631060, AD-1631061, AD-1631062, AD-1631063, AD-1631064, AD-1631065, AD-1631066, AD-1631067, AD-1631068, AD-1631069, AD-1631070, AD-1631071, AD-1631072, AD-1631073, AD-1631074, AD-1631075, AD-1631076, AD-1631077, AD-1631078, AD-1631079, AD-1631080, AD-1631081, AD-1631082, AD-1631083, AD-1631084, AD-1631085, AD-1631086, AD-1631087, AD-1631088, AD-1631089, AD-1631090, AD-1631091, AD-1631092, AD-1631093, AD-1631094, AD-1631095, AD-1631096, AD-1631097, AD-1631098, AD-1631099, AD-1631100, AD-1631101, AD-1631102, AD-1631103, AD-1631104, AD-1631105, AD-1631106, AD-1631107, AD-1631108, AD-1631109, AD-1631110, AD-1631111, AD-1631112, AD-1631113, AD-1631114, AD-1631115, AD-1631116, AD-1631117, AD-1631118, AD-1631119, AD-1631120, AD-1631121, AD-1631122, AD-1631123, AD-

1631124, AD-1631125, AD-1631126, AD-1631127, AD-1631128, AD-1631129, AD-1631130, AD-1631131, AD-1631132, AD-1631133, AD-1631134, AD-1631135, AD-1631136, AD-1631137, AD-1631138, AD-1631139, AD-1631140, AD-1631141, AD-1631142, AD-1631143, AD-1631144, AD-1631145, AD-1631146, AD-1631147, AD-1631148, AD-1631149, AD-1631150, AD-1631151, AD-1631152, AD-1631153, AD-1631154, AD-1631155, AD-1631156, AD-1631157, AD-1631158, AD-1631159, AD-1631160, AD-1631161, AD-1631162, AD-1631163, AD-1631164, AD-1631165, AD-1631166, AD-1631167, AD-1631168, AD-1631169, AD-1631170, AD-1631171, AD-1631172, AD-1631173, AD-1631174, AD-1631175, AD-1631176, AD-1631177, AD-1631178, AD-1631179, AD-1631180, AD-1631181, AD-1631182, AD-1631183, AD-1631184, AD-1631185, AD-1631186, AD-1631187, AD-1631188, AD-1631189, AD-1631190, AD-1631191, AD-1631192, AD-1631193, AD-1631194, AD-1631195, AD-1631196, AD-1631197, AD-1631198, AD-1631199, AD-1631200, AD-1631201, AD-1631202, AD-1631203, AD-1631204, AD-1631205, AD-1631206, AD-1631207, AD-1631208, AD-1631209, AD-1631210, AD-1631211, AD-1631212, AD-1631213, AD-1631214, AD-1631215, AD-1631216, AD-1631217, AD-1631218, AD-1631219, AD-1631220, AD-1631221, AD-1807334, AD-1807335, AD-1807336, AD-1807337, AD-1807338, AD-1807339, AD-1807340, AD-1807341, AD-1807342, AD-1807343, AD-1807344, AD-1807345, AD-1807346, AD-1807347, AD-1807348, AD-1807349, AD-1807350, AD-1807351, AD-1807352, AD-1807353, AD-1807354, AD-1807355, AD-1807356, AD-1807357, AD-1807358, AD-1807359, AD-1807360, AD-1807361, AD-1807362, AD-1807363, AD-1807364, AD-1807365, AD-1807366, AD-1807367, AD-1807368, AD-1807369, AD-1807370, AD-1807371, AD-1807372, AD-1807373, AD-1807374, AD-1807375, AD-1807376, AD-1807377, AD-1807378, AD-1807379, AD-1807380, AD-1807381, AD-1807382, AD-1807383, AD-1807384, AD-1807385, AD-1807386, AD-1807387, AD-1807388, AD-1807389, AD-1807390, AD-1807391, AD-1807392, AD-1807393, AD-1807394, AD-1807395, AD-1807396, AD-1807397, AD-1807398, AD-1807399, AD-1807400, AD-1807401, AD-1807402, AD-1807403, AD-1807404, AD-1807405, AD-1807406, AD-1807407, AD-1807408, AD-1807409, AD-1807410, AD-1807411, AD-1807412, AD-1807413, AD-1807414, AD-1807415, AD-1807416, AD-1807417, AD-1807418, AD-1807419, AD-1807420, AD-1807421, AD-1807422, and AD-1807423.

6. The dsRNA agent of any one of claims 2-3, wherein the sense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the nucleotide sequence of nucleotides 212-232, 238-258, 515-535, 704-724, 830-850, 848-868, 966-986, 967-987, 1022-1042, 1185-1205, 1283-1303, 1319-1339, 1320-1340, 1323-1343, 1337-1357, 1359-1379, 1411-1431, 1518-1538, 1621-1641, 1635-1655, 1637-1657, 1776-1796, 1952-1972, 2084-2104, 2102-2122, 2149-2169, 2383-2403, 2384-2404, 2466-2486, 2467-2487, 2469-2489, 2471-2491, 2474-2494, 2481-2501, 2550-2570, 2554-2574, 2576-2596, 2583-2603, 2629-2649, 2725-2745, 2884-2904, 3197-3217, 3201-3221, 3203-3223, 3232-3252, 3242-3262, 3373-3393, 3406-3426, 3622-3642, 3704-3724, 3724-3744, 3725-3745, 3726-3746, 3846-3866,

3956-3976, 3980-4000, 3986-4006, 3987-4007, 4027-4047, 4072-4092, 4121-4141, 4122-4142, 4124-4144, 4127-4147, 4179-4199, 4197-4217, 4211-4231, 4215-4235, 4225-4245, 4229-4249, 4255-4275, 4311-4331, 4394-4414, 4400-4420, 4413-4433, 4428-4448, 4429-4449, 4430-4450, 4436-4456, 4438-4458, 4476-4496, 4479-4499, 4532-4552, 4533-4553, 4547-4567, 4718-4738, 4719-4739, 4738-4758, 4783-4803, 4846-4866, 4847-4867, 4848-4868, 4850-4870, 4881-4901, 4897-4917, 4919-4939, 4926-4946, 4927-4947, 4928-4948, 4929-4949, 4952-4972, 5073-5093, 5093-5113, 5172-5192, 5285-5305, 5290-5310, 5295-5315, 5327-5347, 5416-5436, 5484-5504, 5494-5514, 5496-5516, 5540-5560, 5545-5565, 5557-5577, 5558-5578, 5559-5579, 5561-5581, 5564-5584, 5565-5585, 5566-5586, 5572-5592, 5626-5646, 5758-5778, 5772-5792, 5774-5794, 5781-5801, 5782-5802, 5839-5859, 5857-5877, 5869-5889, 5875-5895, 5881-5901, 5996-6016, 6102-6122, 6151-6171, 6158-6178, 6159-6179, 6175-6195, 6197-6217, 6198-6218, 6199-6219, 6247-6267, 6289-6309, 6292-6312, 6293-6313, 6347-6367, 6383-6403, 6391-6411, 6392-6412, 6393-6413, 6425-6445, 6481-6501, 6483-6503, 6888-6908 and 6889-6909 of SEQ ID NO: 1808, and the antisense strand comprises at least 15 contiguous nucleotides from the corresponding nucleotide sequence of SEQ ID NO: 1809.

7. The dsRNA agent of any one of claims 2-3 or 6, wherein the antisense strand comprises at least 15 contiguous nucleotides differing by no more than three nucleotides from any one of the antisense strand nucleotide sequences of a duplex selected from the group consisting of AD-1624152, AD-1624178, AD-1624412, AD-1624595, AD-1624721, AD-1624739, AD-1624856, AD-1624857, AD-1624894, AD-1625057, AD-1625155, AD-1625191, AD-1625192, AD-1625195, AD-1625209, AD-1625230, AD-1625282, AD-1625389, AD-1625485, AD-1625499, AD-1625501, AD-1625610, AD-1625786, AD-1625910, AD-1625928, AD-1625975, AD-1626183, AD-1626184, AD-1626265, AD-1626266, AD-1626268, AD-1626270, AD-1626273, AD-1626280, AD-1626349, AD-1626353, AD-1626375, AD-1626382, AD-1626428, AD-1626524, AD-1626636, AD-1626921, AD-1626925, AD-1626927, AD-1626936, AD-1626946, AD-1627077, AD-1627110, AD-1627308, AD-1627390, AD-1627410, AD-1627411, AD-1627412, AD-1627511, AD, 1627601, AD-1627625, AD-1627631, AD-1627632, AD-1627672, AD-1627717, AD-1627766, AD-1627767, AD-1627769, AD-1627772, AD-1627820, AD-1627838, AD-1627852, AD-1627856, AD-1627866, AD-1627870, AD-1627896, AD-1627952, AD-1628008, AD-1628014, AD-1628027, AD-1628042, AD-1628043, AD-1628044, AD-1628050, AD-1628052, AD-1628070, AD-1628073, AD-1628118, AD-1628119, AD-1628133, AD-1628253, AD-1628254, AD-1628273, AD-1628318, AD-1628381, AD-1628382, AD-1628383, AD-1628385, AD-1628396, AD-1628412, AD-1628434, AD-1628441, AD-1628442, AD-1628443, AD-1628444, AD-1628467, AD-1628570, AD-1628590, AD-1628668, AD-1628754, AD-1628759, AD-1628764, AD-1628794, AD-1628883, AD-1628951, AD-1628961, AD-1628963, AD-1629007, AD-1629012, AD-1629024, AD-1629025, AD-1629026, AD-1629028, AD-1629031, AD-1629032, AD-1629033, AD-1629039, AD-1629092, AD-1629200, AD-1629214, AD-1629216, AD-1629223, AD-1629224, AD-1629263, AD-1629280, AD-1629292, AD-1629298, AD-1629304, AD-1629419, AD-1629524, AD-

1629573, AD-1629580, AD-1629581, AD-1629597, AD-1629619, AD-1629620, AD-1629621, AD-1629665, AD-1629707, AD-1629710, AD-1629711, AD-1629763, AD-1629799, AD-1629807, AD-1629808, AD-1629809, AD-1629838, AD-1629876, AD-1629878, AD-1630135 and AD-1630136.

8. The dsRNA agent of claim 2 or 3, wherein the nucleotide sequence of the sense and antisense strand comprise any one of the sense and antisense strand nucleotide sequences in any one of Tables 3-7.

9. The dsRNA agent of any one of claims 1-8, wherein the sense strand, the antisense strand, or both the sense strand and the antisense strand is conjugated to one or more lipophilic moieties.

10. The dsRNA agent of claim 9, wherein the lipophilic moiety is conjugated to one or more internal positions in the double stranded region of the dsRNA agent.

11. The dsRNA agent of claim 9 or 10, wherein the lipophilic moiety is conjugated via a linker or carrier.

12. The dsRNA agent of any one of claims 9-11, wherein lipophilicity of the lipophilic moiety, measured by logKow, exceeds 0.

13. The dsRNA agent of any one of claims 1-12, wherein the hydrophobicity of the double-stranded RNA agent, measured by the unbound fraction in a plasma protein binding assay of the double-stranded RNA agent, exceeds 0.2.

14. The dsRNA agent of claim 13, wherein the plasma protein binding assay is an electrophoretic mobility shift assay using human serum albumin protein.

15. The dsRNA agent of any one of claims 1-14, wherein the sense strand, the antisense strand, or both the sense strand and the antisense strand is conjugated to one or more Asialoglycoprotein receptor (ASGPR) ligands.

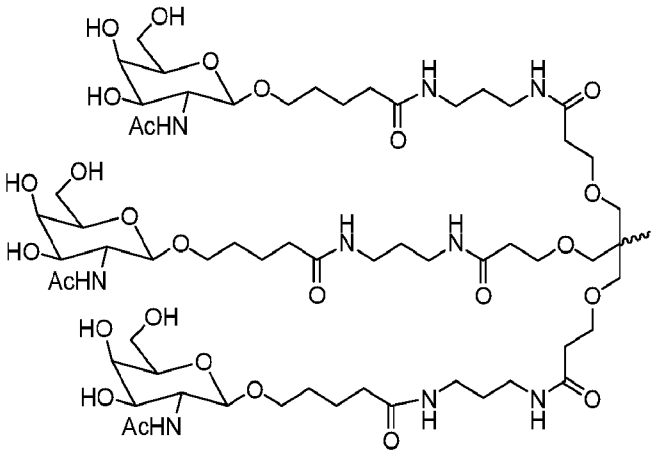
16. The dsRNA agent of claim 15, wherein the ASGPR ligand is attached to the 5' end or 3' end of the sense strand.

17. The dsRNA agent of claim 15, wherein the ASGPR ligand is attached to the 5' end of the sense strand.

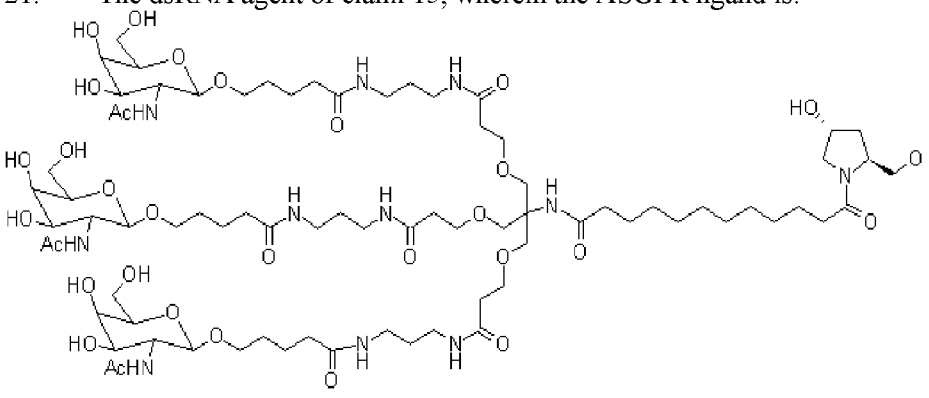
18. The dsRNA agent of claim 15, wherein the ASGPR ligand is attached to the 3' end of the sense strand.

19. The dsRNA agent of any one of claims 15-18, wherein the ASGPR ligand comprises one or more GalNAc derivatives attached through a bivalent or trivalent branched linker.

20. The dsRNA agent of any one of claims 15-19, wherein the ASGPR ligand comprises:



21. The dsRNA agent of claim 15, wherein the ASGPR ligand is:



22. The dsRNA agent of any one of claims 1-14, wherein the dsRNA agent comprises at least one modified nucleotide.

23. The dsRNA agent of claim 22, wherein no more than five of the sense strand nucleotides and no more than five of the nucleotides of the antisense strand are unmodified nucleotides

24. The dsRNA agent of claim 22, wherein all of the nucleotides of the sense strand and all of the nucleotides of the antisense strand are modified nucleotides.

25. The dsRNA agent of any one of claims 22-24, wherein at least one of the modified nucleotides is selected from the group a deoxy-nucleotide, a 3'-terminal deoxythimidine (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, 2'-hydroxy-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 5'-phosphorothioate group, a nucleotide comprising a 5'-methylphosphonate group, a nucleotide comprising a 5' phosphate or 5' phosphate mimic, a nucleotide comprising vinyl phosphonate, a nucleotide comprising adenosine-glycol nucleic acid (GNA), a nucleotide comprising thymidine-glycol nucleic acid (GNA) S-Isomer, a nucleotide comprising 2-hydroxymethyl-tetrahydrofurane-5-phosphate, a nucleotide comprising 2'-deoxythymidine-3'phosphate, a nucleotide comprising 2'-deoxyguanosine-3'-phosphate, and a terminal nucleotide linked to a cholesteryl derivative and a dodecanoic acid bisdecylamide group; and combinations thereof.

26. The dsRNA agent of claim 25, wherein the modified nucleotide is selected from the group consisting of a 2'-deoxy-2'-fluoro modified nucleotide, a 2'-deoxy-modified nucleotide, 3'-terminal deoxythimidine nucleotides (dT), a locked nucleotide, an abasic nucleotide, a 2'-amino-modified nucleotide, a 2'-alkyl-modified nucleotide, a morpholino nucleotide, a phosphoramidate, and a non-natural base comprising nucleotide.

27. The dsRNA agent of claim 25, wherein the modified nucleotide comprises a short sequence of 3'-terminal deoxythimidine nucleotides (dT).

28. The dsRNA agent of claim 25, wherein the modifications on the nucleotides are 2'-O-methyl, GNA and 2'fluoro modifications.

29. The dsRNA agent of any one of claims 1-28, further comprising at least one phosphorothioate internucleotide linkage.

30. The dsRNA agent of claim 29, wherein the dsRNA agent comprises 6-8 phosphorothioate internucleotide linkages.

31. The dsRNA agent of any one of claims 1-30, wherein each strand is no more than 30 nucleotides in length.

32. The dsRNA agent of any one of claims 1-31, wherein at least one strand comprises a 3' overhang of at least 1 nucleotide.

33. The dsRNA agent of any one of claims 1-32, wherein at least one strand comprises a 3' overhang of at least 2 nucleotides.

34. The dsRNA agent of any one of claims 1-33, wherein the double stranded region is 15-30 nucleotide pairs in length.

35. The dsRNA agent of claim 34, wherein the double stranded region is 17-23 nucleotide pairs in length.

36. The dsRNA agent of claim 34, wherein the double stranded region is 17-25 nucleotide pairs in length.

37. The dsRNA agent of claim 34, wherein the double stranded region is 23-27 nucleotide pairs in length.

38. The dsRNA agent of claim 34, wherein the double stranded region is 19-21 nucleotide pairs in length.

39. The dsRNA agent of claim 34, wherein the double stranded region is 21-23 nucleotide pairs in length.

40. The dsRNA agent of any one of claims 1-39, wherein each strand has 19-30 nucleotides.

41. The dsRNA agent of any one of claims 1-39, wherein each strand has 19-23 nucleotides.

42. The dsRNA agent of any one of claims 1-39, wherein each strand has 21-23 nucleotides.

43. The dsRNA agent of any one of claims 10-42, wherein one or more lipophilic moieties are conjugated to one or more internal positions on at least one strand.

44. The dsRNA agent of claim 43, 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.

45. The dsRNA agent of claim 44, wherein the internal positions include all positions except the terminal two positions from each end of the at least one strand.

46. The dsRNA agent of claim 44, wherein the internal positions include all positions except the terminal three positions from each end of the at least one strand.

47. The dsRNA agent of claim 44-46, wherein the internal positions exclude a cleavage site region of the sense strand.

48. The dsRNA agent of claim 47, wherein the internal positions include all positions except positions 9-12, counting from the 5'-end of the sense strand.

49. The dsRNA agent of claim 47, wherein the internal positions include all positions except positions 11-13, counting from the 3'-end of the sense strand.

50. The dsRNA agent of claim 44-46, wherein the internal positions exclude a cleavage site region of the antisense strand.

51. The dsRNA agent of claim 50, wherein the internal positions include all positions except positions 12-14, counting from the 5'-end of the antisense strand.

52. The dsRNA agent of claim 44-46, 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.

53. The dsRNA agent of any one of claims 10-52, 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.

54. The dsRNA agent of claim 53, 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.

55. The dsRNA agent of claim 10, wherein the internal positions in the double stranded region exclude a cleavage site region of the sense strand.

56. The dsRNA agent of any one of claims 9-55, 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.

57. The dsRNA agent of claim 56, wherein the lipophilic moiety is conjugated to position 21, position 20, position 15, position 1, or position 7 of the sense strand.

58. The dsRNA agent of claim 56, wherein the lipophilic moiety is conjugated to position 21, position 20, or position 15 of the sense strand.

59. The dsRNA agent of claim 56, wherein the lipophilic moiety is conjugated to position 20 or position 15 of the sense strand.

60. The dsRNA agent of claim 56, wherein the lipophilic moiety is conjugated to position 16 of the antisense strand.

61. The dsRNA agent of any one of claims 9-60, wherein the lipophilic moiety is an aliphatic, alicyclic, or polyalicyclic compound.

62. The dsRNA agent of claim 61, 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.

63. The dsRNA agent of claim 61, 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.

64. The dsRNA agent of claim 63, wherein the lipophilic moiety contains a saturated or unsaturated C6-C18 hydrocarbon chain.

65. The dsRNA agent of claim 63, wherein the lipophilic moiety contains a saturated or unsaturated C16 hydrocarbon chain.

66. The dsRNA agent of claim 65, wherein the saturated or unsaturated C16 hydrocarbon chain is conjugated to position 6, counting from the 5'-end of the strand.

67. The dsRNA agent of any one of claims 9-66, 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.

68. The dsRNA agent of claim 67, 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.

69. The dsRNA agent of any one of claims 9-66, 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.

70. The double-stranded iRNA agent of any one of claims 9-69, wherein the lipophilic moiety is conjugated to a nucleobase, sugar moiety, or internucleosidic linkage.

71. The dsRNA agent of any one of claims 9-70, wherein the lipophilic moeity or targeting ligand is conjugated via a bio-clevable linker selected from the group consisting of DNA, RNA, disulfide, amide, funtionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, mannose, and combinations thereof.

72. The dsRNA agent of any one of claims 9-71, 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.

73. The dsRNA agent of any one of claims 9-70, further comprising a targeting ligand that targets a liver tissue.

74. The dsRNA agent of any one of claims 9-70, further comprising a targeting ligand that targets a neuronal cell.

75. The dsRNA agent of any one of claims 9-70, further comprising a targeting ligand that targets any ocular cell.

76. The dsRNA agent of claim 73, wherein the targeting ligand is a GalNAc conjugate.

77. The dsRNA agent of any one of claims 1-76 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.

78. The dsRNA agent of any one of claims 1-76 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.

79. The dsRNA agent of any one of claims 1-76 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.

80. The dsRNA agent of any one of claims 1-76 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.

81. The dsRNA agent of any one of claims 1-76 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.

82. The dsRNA agent of any one of claims 1-81, further comprising a phosphate or phosphate mimic at the 5'-end of the antisense strand.

83. The dsRNA agent of claim 82, wherein the phosphate mimic is a 5'-vinyl phosphonate (VP).

84. The dsRNA agent of any one of claims 1-81, wherein the base pair at the 1 position of the 5′-end of the antisense strand of the duplex is an AU base pair.

85. The dsRNA agent of any one of claims 1-81, wherein the sense strand has a total of 21 nucleotides and the antisense strand has a total of 23 nucleotides.

86. The dsRNA of any one of claims 1-89, wherein the dsRNA agent targets a hotspot region of an mRNA encoding LRRK2.

87. The dsRNA agent of claim 86, wherein the hotspot region comprises any one of SEQ ID NOs: 2260-2288 of SEQ ID NO: 1 or any one of nucleotides 3620-3652, 3794-3849, 5194-5222, 5366-5393, 5423-5463, 5674-5704, 5720-5745, 6090-6114, 6125-6156, 6518-6561, 6721-6750, 6740-6763, 7016-7061, 7083-7123, 7112-7136, 7125-7169, 7346-7373, 7441-7465, 7591-7659, 7636-7659, 8132-8155, 3627-3650, 5194-5222, 5674-5702, 5720-5745, 6091-6114, 6529-6559, 7034-7061, 7441-7465, and 7636-7659 of SEQ ID NO: 1.

88. The dsRNA agent of claim 87, wherein the dsRNA agent is selected from the group consisting of AD-1627308, AD-1631049, AD-1631050, AD-1626349, AD-1626353, AD-1626375, AD-1626382, AD-1631080, AD-1807348, AD-1807393, AD-1631088, AD-1631089, AD-1631090, AD-1631108, AD-1807416, AD-1807371, AD-1627767, AD-1627769, AD-1627772, AD-1631109, AD-1631110, AD-1631111, AD-1627820, AD-1627838, , AD-1628042, AD-1628043, AD-1628044, AD-1628050, AD-1628052,, AD-1628070, AD-1631108, AD-1631109, AD-1631110, AD-1631111, AD-1807397, AD-1807352, , AD-1628073, AD-1807374, AD-1807419, AD-1628381, AD-1628382, AD-1628383, AD-1631131, AD-1631132, AD-1631133, AD-1628396, AD-1807361, AD-1807406, AD-1631150, AD-1631151, AD-1631152, AD-1631153, AD-1631154, AD-1631155, AD-1631156, AD-1631157, AD-1631158, AD-1631160, AD-1631161, AD-1631162, AD-1807357, AD-1807402, AD-1628961, AD-1628963, AD-1629214, AD-1629216, AD-1629223, AD-1629224, AD-1629263, AD-1629280, AD-1631194, AD-1631195, AD-1631196, AD-1631197, AD-1807363, AD-1807408, AD-1629304, AD-1629524, AD-1631205, AD-1631206, AD-1807337, AD-1807354, AD-1807382, AD-1807399, AD-1629619, AD-1629620, AD-1629621, AD-1631210, AD-1807355, AD-1807377, AD-1807400, AD-1807422, AD-1629763, AD-1631215, AD-1631216, AD-1631217, AD-1807335, AD-1807336, AD-1807376, AD-1807380, AD-1807381, AD-1807421, AD-1630135, AD-1630136, AD-1631221, AD-1807369, AD-1807414, AD-1807364, AD-1807409, AD-1629808, and AD-1629809.

89. A dsRNA agent that targets a hotspot region of a myosin regulatory light chain interacting protein (*LRRK2*) mRNA.

90. A cell containing the dsRNA agent of any one of claims 1-89.

91. A pharmaceutical composition for inhibiting expression of a gene encoding LRRK2, comprising the dsRNA agent of any one of claims 1-89.

92. A pharmaceutical composition comprising the dsRNA agent of any one of claims 1-89 and a lipid formulation.

93. The pharmaceutical composition of claim 91 or 92, wherein dsRNA agent is in an unbuffered solution.

94. The pharmaceutical composition of claim 91, wherein the unbuffered solution is saline or water.

95. The pharmaceutical composition of claim 91 or 92, wherein said dsRNA agent is in a buffer solution.

96. The pharmaceutical composition of claim 95, wherein the buffer solution comprises acetate, citrate, prolamine, carbonate, or phosphate or any combination thereof.

97. The pharmaceutical composition of claim 95, wherein the buffer solution is phosphate buffered saline (PBS).

98. A method of inhibiting expression of a *LRRK2* gene in a cell, the method comprising contacting the cell with the dsRNA agent of any one of claims 1-89, or the pharmaceutical composition of any one of claims 91-97, thereby inhibiting expression of the *LRRK2* gene in the cell.

99. The method of claim 98, wherein the cell is within a subject.

100. The method of claim 99, wherein the subject is a human.

101. The method of claim 100, wherein the subject has a *LRRK2*-associated disorder.

102. The method of claim 101, wherein the *LRRK2*-associated disorder is a neurodegenerative disorder.

103. The method of claim 102, wherein the neurodegenerative disorder is a familial disorder.

104. The method of claim 102, wherein the neurodegenerative disorder is a sporadic disorder.

105. The method of claim 103 or 104, wherein the neurodegenerative disorder is Parkinson's disease.

106. The method of claim 101, wherein the *LRRK2*-associated disorder is an ocular disorder.

107. The method of any one of claims 98-106, wherein contacting the cell with the dsRNA agent inhibits the expression of *LRRK2* by at least about 25%.

108. The method of any one of claims 98-107, wherein inhibiting expression of *LRRK2* decreases LRRK2 protein level in serum of the subject by at least about 25%.

109. A method of treating a subject having a disorder that would benefit from reduction in *LRRK2* expression, comprising administering to the subject a therapeutically effective amount of the dsRNA agent of any one of claims 1-89, or the pharmaceutical composition of any one of claims 91-97, thereby treating the subject having the disorder that would benefit from reduction in *LRRK2* expression.

110. A method of preventing at least one symptom in a subject having a disorder that would benefit from reduction in *LRRK2* expression, comprising administering to the subject a prophylactically effective amount of the dsRNA agent of any one of claims 1-89, or the pharmaceutical composition of any one of claims 91-97, thereby preventing at least one symptom in the subject having the disorder that would benefit from reduction in *LRRK2* expression.

111. The method of claim 109 or 110, wherein the disorder is a *LRRK2*-associated disorder.

112. The method of claim 111, wherein the *LRRK2*-associated disorder is selected from the group consisting of Parkinson's disease, and ocular disorders.

113. The method of any one of claims 110-112, wherein the subject is human.

114. The method of claim 113, wherein the administration of the agent to the subject causes a decrease in LRRK2 protein accumulation.

115. The method of any one of claims 109-114, wherein the dsRNA agent is administered to the subject at a dose of about 0.01 mg/kg to about 50 mg/kg.

116. The method of any one of claims 109-115, wherein the dsRNA agent is administered to the subject intrathecally.

117. The method of any one of claims 109-116, further comprising determining the level of *LRRK2* in a sample(s) from the subject.

118. The method of claim 117, wherein the level of *LRRK2* in the subject sample(s) is a LRRK2 protein level in a blood, serum, or cerebrospinal fluid sample(s).

119. The method of any one of claims 109-118, further comprising administering to the subject an additional therapeutic agent.

120. A kit comprising the dsRNA agent of any one of claims 1-89 or the pharmaceutical composition of any one of claims 91-97.

121. A vial comprising the dsRNA agent of any one of claims 1-89 or the pharmaceutical composition of any one of claims 91-97.

122. A syringe comprising the dsRNA agent of any one of claims 1-89 or the pharmaceutical composition of any one of claims 91-97.

123. An intrathecal pump comprising the dsRNA agent of any one of claims 1-89 or the pharmaceutical composition of any one of claims 91-97.