an antisense strand which is complementary to a target gene; a sense strand which is complementary to said antisense strand; and one or more lipophilic moieties conjugated to one or more internal positions on at least one strand, optionally via a linker or carrier.

[0006a] In one aspect, the present disclosure refers to a double-stranded iRNA agent comprising: an antisense strand which is complementary to a target gene; a sense strand which is complementary to said antisense strand; and one or more lipophilic moieties conjugated to one or more internal positions on at least one strand, optionally via a linker or carrier wherein the lipophilic moiety comprises a saturated or unsaturated C_4-C_{18} hydrocarbon chain, and an optional functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne; wherein the one or more lipophilic moieties are conjugated to one or more of the following internal positions: 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; and wherein the double-stranded iRNA agent does not comprise a N- acetylgalactosamine (GalNAc) conjugate.

[0006b] In another aspect, provided herein is use of the double-stranded iRNA agent as described herein in the manufacture of a medicament for treating a subject having a CNS disorder or an ocular disorder, wherein the antisense strand of the double-stranded iRNA agent is complementary to a target gene in a CNS tissue associated with the CNS disorder or to a target gene in an ocular tissue associated with the ocular disorder.

[0007] In some examples, the lipophilicity of the lipophilic moiety, measured by octanol-water partition coefficient, $\log K_{ow}$, exceeds 0. The lipophilic moiety may possess a $\log K_{ow}$ exceeding 1, exceeding 1.5, exceeding 2, exceeding 3, exceeding 4, exceeding 5, or exceeding 10.

[0008] In some examples, the hydrophobicity of the double-stranded iRNA agent, measured by the unbound fraction in the plasma protein binding assay of the double-stranded iRNA agent, exceeds 0.2. In one example, the plasma protein binding assay determined is an electrophoretic mobility shift assay (EMSA) using human serum albumin protein. The hydrophobicity of the double-stranded iRNA 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.

[0009] In some examples, the lipophilic moiety is an aliphatic, cylic such as alicyclic, or polycyclic such as polyalicyclic compound, such as a steroid (e.g., sterol) or a linear or branched aliphatic hydrocarbon. Exemplary lipophilic moieties are lipid, cholesterol, retinoic acid, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-bis-O(hexadecyl)glycerol, geranyloxyhexyanol, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid, O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, ibuprofen, naproxen, dimethoxytrityl, or phenoxazine.

[0010] Suitable lipophilic moieties also include those containing a saturated or unsaturated C_4-C_{30} hydrocarbon chain (e.g., C_4-C_{30} alkyl or alkenyl), and an optional functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne. The functional groups are useful to attach the lipophilic moiety to the iRNA agent. In some examples, the lipophilic moiety contains a saturated or unsaturated C_6-C_{18} hydrocarbon chain (e.g., a linear C_6-C_{18} alkyl or alkenyl). In

one example, the lipophilic moiety contains a saturated or unsaturated C_{16} hydrocarbon chain (e.g., a linear C_{16} alkyl or alkenyl).

[0011] In some examples, the lipophilic moiety is a C_6-C_{30} acid (e.g., hexanoic acid, heptanoic acid, octanoic acid, nonanoic acid, decanoic acid, undecanoic acid, dodcanoic acid, tridecanoic acid, tetradecanoic acid, pentadecanoic acid, hexadecanoic acid, heptadecanoic acid, octadecanoic acid, oleic acid, linoleic acid, arachidonic acid, cis-4,7,10,13,16,19-

We claim:

1. A double-stranded iRNA agent comprising:

an antisense strand which is complementary to a target gene;

a sense strand which is complementary to said antisense strand; and

one or more lipophilic moieties conjugated to one or more internal positions on at least one strand, optionally via a linker or carrier

wherein the lipophilic moiety comprises a saturated or unsaturated C_4-C_{18} hydrocarbon chain, and an optional functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne;

wherein the one or more lipophilic moieties are conjugated to one or more of the following internal positions: 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; and

wherein the double-stranded iRNA agent does not comprise a N-acetylgalactosamine (GalNAc) conjugate.

2. The double-stranded iRNA agent of claim 1, wherein the lipophilic moiety is conjugated to a nucleobase or a sugar moiety.

3. The double-stranded iRNA agent of claim 2, wherein the lipophilic moiety is conjugated to a sugar moiety of a nucleotide via a 2'-O modification.

4. The double-stranded iRNA agent of any one of claims 1-3, wherein said sense and antisense strands are each 19 to 25 nucleotides in length, preferably each 21 to 23 nucleotides in length.

5. The double-stranded iRNA agent of any one of claims 1-4, wherein the lipophilic moiety contains a saturated or unsaturated C_6-C_{18} hydrocarbon chain, preferably a saturated or unsaturated C_{16} hydrocarbon chain.

6. The double-stranded iRNA agent of claim 5, wherein the lipophilic moiety consists of a saturated C_{16} hydrocarbon chain.

7. The double-stranded iRNA agent of claim 1, wherein the double-stranded iRNA agent comprises one lipophilic moiety directly bonded to a 2'-O of a sugar moiety at an internal position of the sense strand, and wherein:

the sense and antisense strands are each independently 19 to 25 nucleotides in length and form a double-stranded region 19-21 nucleotide pairs in length, having a blunt end at the 5'-end of the antisense strand; and

the lipophilic moiety is a linear C_{16} alkyl chain

8. The double-stranded iRNA agent of any one of claims 1-7, wherein one or more lipophilic moieties are conjugated to one or more of the following internal positions: 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.

9. The double-stranded iRNA agent of any one of claims 1-8, wherein said double-stranded iRNA agent comprises a single-stranded overhang on at least one of the termini; preferably wherein said single-stranded overhang is 1, 2 or 3 nucleotides in length.

10. The double-stranded iRNA agent of any one of claims 1-9, wherein the sense strand and antisense strand are characterized by one of the followings:

(i) the sense strand and antisense strand are each 19 nucleotides in length, wherein the sense strand contains 2'-F modifications on the nucleotides at positions 7, 8, and 9 from the 5'-end of the sense strand;

(ii) the sense strand and antisense strand are each 20 nucleotides in length, wherein the sense strand contains 2'-F modifications on the nucleotides at positions 8, 9, and 10 from the 5'-end of the sense strand; or

(iii) the sense strand and antisense strand are each 21 nucleotides in length, wherein the sense strand contains 2'-F modifications on the nucleotides at positions 9, 10, and 11 from the 5'-end of the sense strand.

11. The double-stranded iRNA agent of claim 10, wherein the antisense strand contains 2'-O-methyl modifications on the nucleotides at positions 11, 12, and 13 from the 5'-end of the antisense strand.

12. The double-stranded iRNA agent of any one of claims 1-9, wherein

the sense strand is 21 nucleotides in length, and

the antisense strand is 23 nucleotides in length and has a two nucleotide overhang at the 3'-end of the antisense strand, wherein:

the sense strand contains 2'-F modifications on the nucleotides at positions 9, 10, and 11 from the 5'-end of the sense strand; and

the antisense strand contains 2'-O-methyl modifications on the nucleotides at positions 11, 12, and 13 from the 5'-end of the antisense strand.

13. The double-stranded iRNA agent of any one of claims 1-12, wherein the double-stranded iRNA agent comprises:

(i) at least one phosphorothioate or methylphosphonate internucleotide linkage;

(ii) at least two phosphorothioate internucleotide linkages at the first five nucleotides on the antisense strand, counting from the 5'-end of the antisense strand;

(iii) 8 phosphorothioate internucleotide linkages;

(iv) an overhang region containing two nucleotides at the 3'-end of the antisense strand and a phosphorothioate or methylphosphonate internucleotide linkage between the two overhang nucleotides; and/or

(v) an overhang region at the 3'-end of the antisense strand and two phosphorothioate internucleotide linkages between the terminal three nucleotides at the 3'-end of the antisense strand, in which two of the three terminal nucleotides are the overhang nucleotides, and the third nucleotide is a paired nucleotide next to the overhang nucleotides.

14. The double-stranded iRNA agent of any one of claims 1-8, comprising

(a) a sense strand having:

(i) a length of 21 nucleotides;

(ii) 2'-OMe modifications at positions 1 to 6, 8, and 12 to 21, and 2'-F modifications at positions 7, and 9 to 11; and

(iii) phosphorothioate internucleotide linkages between nucleotide positions 1 and 2, and between nucleotide positions 2 and 3, counting from the 5'-end of the sense strand; and

(b) an antisense strand having:

(i) a length of 23 nucleotides;

(ii) (1) 2’-OMe modifications at positions 1, 3 to 5, 7, 8, 10 to 13, 15, and 17 to 23, and 2’-F modifications at positions 2, 6, 9, 14, and 16, counting from the 5’-end of the antisense strand; or

(2) 2’-OMe modifications at positions 1, 3 to 5, 7, 10 to 13, 15, and 17 to 23, and 2’-F modifications at positions 2, 6, 8, 9, 14, and 16, counting from the 5’-end of the antisense strand; and

(iii) 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, counting from the 5’-end of the antisense strand;

wherein the double-stranded iRNA agent has a two-nucleotide overhang at the 3’-end of the antisense strand, and a blunt end at the 5’-end of the antisense strand.

15. The double-stranded iRNA agent of any one of claims 1-14, wherein the double-stranded iRNA agent has one or more of the following characteristics:

(i) the first base pair at the 5’-end of the antisense strand is an AU base pair;

(ii) each of the sense and antisense strands contains at least two different modifications;

(iii) the double-stranded iRNA agent comprises:

a mismatch to the target RNA within the duplex region; and/or

one or more modification is acyclic nucleotide modification, and the acyclic nucleotide is an UNA or a GNA; or

a 2’-5’ internucleotide linkage; and/or

(iv) each of the sense and antisense strands is independently modified with one or more modifications selected from the group consisting of an acyclic nucleotide, LNA, HNA, CeNA, 2’-methoxyethyl, 2’ O-methyl, 2’-O-allyl, 2’-C-allyl, 2’-deoxy, 2’-fluoro, 2'-O-N-methylacetamido (2'-O-NMA), a 2'-O-dimethylaminoethoxyethyl (2'-O-DMAEOE), 2'-O-aminopropyl (2'-O-AP), and 2'-ara-F.

16. The double-stranded iRNA agent as claimed in any one of claims 1-15, wherein one or more lipophilic moieties are conjugated only to one or more internal positions selected from the group consisting of: positions 4-8 and 13-18 on the sense strand, counting from the 5'-end of the sense strand.

17. The double-stranded iRNA agent as claimed in any one of claims 1-15, wherein the double-stranded iRNA agent comprises one lipophilic moiety comprising a saturated or unsaturated C_6-C_{18} hydrocarbon chain, and an optional functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne, conjugated only to one internal position selected from the group consisting of: positions 4-8 and 13-18 on the sense strand, counting from the 5' end of the sense strand, optionally via a linker or carrier.

18. The double-stranded iRNA agent of claim 17, wherein the one lipophilic moiety consists of a saturated C_{16} hydrocarbon chain, and an optional functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne.

19. The double-stranded iRNA agent of claim 18, wherein:
the one lipophilic moiety consists of a saturated C_{16} hydrocarbon chain having a hydroxyl functional group, or
the one lipophilic moiety consists of a saturated C_{16} hydrocarbon chain.

20. The double-stranded iRNA agent of any one of claims 17-19, wherein the sense and antisense strands are each independently 21 to 23 nucleotides in length, and the internal position is position 5, 6, 7, or 13, counting from the 5'-end of the sense strand.

21. The double-stranded iRNA agent of any one of claims 1-20, wherein the lipophilic moiety is conjugated via a carrier that replaces one or more nucleotide(s) in the internal position(s).

22. The double-stranded iRNA agent of claim 21, 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.

23. The double-stranded iRNA agent of any one of claims 1-22, wherein the lipophilic moiety is conjugated via a bio-clevable linker selected from the group consisting of DNA, RNA, disulfide, amide, functionalized monosaccharides or oligosaccharides of galactosamine, glucosamine, glucose, galactose, mannose, and combinations thereof.

24. The double-stranded iRNA agent of any one of claims 1-23, 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.

25. The double-stranded iRNA agent of claim 24, wherein the lipophilic moiety is conjugated to the double-strand iRNA agent via a linker comprising an amide or a disulfide.

26. The double-stranded iRNA agent of claim 24, wherein the lipophilic moiety is conjugated to the double-strand iRNA agent via a linker comprising a formula of: TAP-$(CH_2)_n$NH-; TAP-$(CH_2)_n$-C(O)-; TAP-$(CH_2)_n$-C(O)O-; TAP-$(CH_2)_n$-; or TAP-$(CH_2)_n$-NH-C(O)-; wherein TAP represents the attachment point to the double-stranded iRNA agent and n is 1-20.

27. The double-stranded iRNA agent of claim 26, wherein the linker of the formula further comprises one or more of additional linking groups selected from the group consisting of -O-$(CH_2)_n$-, -$(CH_2)_n$-SS-, -$(CH_2)_n$-, and -(CH=CH)-; preferably the additional linking group is $(CH_2)_n$-SS-.

28. The double-stranded iRNA agent of claim 27, wherein the lipophilic moiety is TAP-$(CH_2)_n$NH(LIGAND) or TAP-$(CH_2)_n$-NH-C(O)(LIGAND), wherein

LIGAND consists of a saturated or unsaturated C_6-C_{18} hydrocarbon chain and an optional functional group selected from the group consisting of hydroxyl, amine, carboxylic acid, sulfonate, phosphate, thiol, azide, and alkyne.

29. The double-stranded iRNA agent of any one of claims 1-28, further comprising a phosphate or phosphate mimic at the 5'-end of the antisense strand; preferably the phosphate mimic is a 5'-vinyl phosphonate (VP).

30. The double stranded iRNA agent of any one of claims 1-29, 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.

31. An *in vitro* method of reducing the expression of a target gene in a cell, comprising contacting said cell with a double-stranded iRNA agent of any one of claims 1-30.

32. Use of the double-stranded iRNA agent of any one of claims 1-30 in the manufacture of a medicament for treating a subject having a CNS disorder or an ocular disorder, wherein the antisense strand of the double-stranded iRNA agent is complementary to a target gene in a CNS tissue associated with the CNS disorder or to a target gene in an ocular tissue associated with the ocular disorder.

33. The use of claim 32, wherein:
the CNS disorder is selected from the group of alzheimer, amyotrophic lateral schlerosis (ALS), frontotemporal dementia, huntington, Parkinson, spinocerebellar, prion, and lafora; and/or
the ocular disorder is selected from the group of age-related macular degeneration (AMD), birdshot chorioretinopathy, dominant retinitis pigmentosa 4, Fuch's dystrophy, hATTR amyloidosis, cataract, glaucoma, dry eye syndrome, and stargardt's disease.

34. The use of claim 32, wherein the CNS tissue is a brain or spine tissue selected from the group consisting of cortex, cerebellum, cervical spine, lumbar spine, and thoracic spine.

35. The use of claim 32, wherein the target gene is selected from the group consisiting of APP, ATXN2, C9orf72, TARDBP, MAPT(Tau), HTT, SNCA, FUS, ATXN3, ATXN1, SCA1, SCA7, SCA8, MeCP2, PRNP, SOD1, DMPK, and TTR; or
the target gene is selected from the group consisiting of VEGF, C3, CFB, MYOC, ROCK2, ADRB2, CA2, CRYGC, PPP3CB, CTNNB1, and TTR.