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 the double-stranded iRNA agent as described herein for use in therapy.

[0006c] 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, 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.

[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 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.

3. The double-stranded iRNA agent of claim 1 or 2, wherein said sense and antisense strands are each 19 to 25 nucleotides in length.

4. The double-stranded iRNA agent of claim 1, wherein the lipophilic moiety contains a saturated or unsaturated C_6-C_{18} hydrocarbon chain.

5. The double-stranded iRNA agent of claim 4, wherein the lipophilic moiety contains a saturated or unsaturated C_{16} hydrocarbon chain.

6. The double-stranded iRNA agent of any one of claims 1-5, wherein the lipophilic moiety is conjugated via a carrier that replaces one or more nucleotide(s) in the internal position(s).

7. The double-stranded iRNA agent of claim 6, 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.

8. The double-stranded iRNA agent of any one of claims 1-7, 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.

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.

10. The double-stranded iRNA agent of any one of claims 1-9, wherein the lipophilic moiety is conjugated to a nucleobase or a sugar moiety.

11. The double-stranded iRNA agent of any one of claims 1-10, 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.

12. The double stranded iRNA agent of any one of claims 1-11, 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.

13. The double-stranded iRNA agent of any one of claims 1-12 for use in therapy.

14. 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 1-12.

15. Use of the double-stranded iRNA agent of any one of claims 1-12 in the manufacture of a medicament for treating a subject having a CNS 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.

16. The use of claim 15, wherein the CNS disorder is selected from the group of alzheimer, amyotrophic lateral schlerosis (ALS), frontotemporal dementia, huntington, Parkinson, spinocerebellar, prion, and lafora.

17. The use of claim 15, 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.

18. The use of claim 15, 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.