CLAIMS

1. A nucleic acid complex, comprising:

a first nucleic acid strand comprising 20-70 linked nucleosides;

a second nucleic acid strand binding to a central region of the first nucleic acid strand to form a first nucleic acid duplex; and

a third nucleic acid strand binding to a 5' region and a 3' region of the first nucleic acid strand to form a second nucleic acid duplex, wherein the third nucleic acid strand comprises an overhang, wherein the overhang is not complementary to the first nucleic acid strand and is capable of binding to an input nucleic acid strand to cause the displacement of the third nucleic acid strand from the first nucleic acid strand,

wherein the central region of the first nucleic acid strand comprises a sequence complementary to a target RNA, wherein the sequence is 10-35 nucleosides in length.

2. The nucleic acid complex of claim 1, wherein the sequence complementary to the target RNA is 10-21 nucleotides in length.

3. The nucleic acid complex of any one of claims 1-2, wherein the second nucleic acid strand binds to 19-25 linked nucleotides in the central region of the first nucleic acid strand to form the first nucleic acid duplex; and/or

wherein the first nucleic acid duplex does not comprise a Dicer cleavage site or wherein the nucleic acid complex does not comprise a Dicer cleavage site.

4. The nucleic acid complex of any one of claims 1-3, wherein the central region of the first nucleic acid strand is linked to the 5' region of the first nucleic acid strand via a 5' connector, the central region of the first nucleic acid strand is linked to the 3' region of the first nucleic acid strand via a 3' connector, or both; optionally

wherein the 5' connector, the 3' connector, or both comprise a C_3 3-carbon linker, a nucleotide, a modified nucleotide, or an exonuclease cleavage-resistant moiety, or a combination thereof; further optionally the modified nucleotide is a 2'-O-methyl nucleotide or a 2'-F nucleotide.

5. The nucleic acid complex of claim 4, wherein the 5' connector comprises, or is, a C_3 3-carbon linker, 2'-O-methyl nucleotide, 2'-F nucleotide, a nucleotide with a phosphodiester 5' and 3' connection cleavable by an exonuclease when in a single stranded form, or a combination thereof and/or wherein the 3' connector is a C_3 3-carbon linker; and/or

wherein the 3’ connector comprises a C_3 3-carbon linker, a nucleotide, a modified nucleotide, an exonuclease cleavage-resistant moiety when in a single stranded form, or a combination thereof; optionally the 3’ connector comprises, or is, a 2’-O-methyl nucleotide, and wherein the 2’-O-methyl nucleotide is optionally 2'-O-methyladenosine, 2'-O-methylguanosine, 2'-O-methyluridine, or 2'-O-methylcytidine.

6. The nucleic acid complex of any one of claims 1-5, wherein the second nucleic strand is fully complementary to the central region of the first nucleic acid strand, thereby forming blunt ends at the 5’ and 3’ termini of the second nucleic acid strand in the first nucleic acid duplex.

7. The nucleic acid complex of any one of claims 1-6, wherein the second nucleic acid strand does not have an overhand at 3’ terminus, or 5’ terminus, or both in the first nucleic acid duplex.

8. The nucleic acid complex of any one of claims 1-6, wherein the second nucleic acid strand has a 3’ overhang, a 5’ overhang, or both in the first nucleic acid duplex; optionally the second nucleic acid strand has an 3’ overhang and the 3’ overhang is one to five nucleosides in length.

9. The nucleic acid complex of any one of claims 1-8, wherein the 5’ terminus of the central region of the first nucleic acid strand, the 3’ terminus of the central region of the first nucleic acid strand, or both, comprises at least one phosphorothioate internucleoside linkage.

10. The nucleic acid complex of any one of claims 1-8, wherein each of the 5’ terminus of the central region of the first nucleic acid strand and the 3’ terminus of the central region of the first nucleic acid strand independently comprises one or more phosphorothioate internucleoside linkages.

11. The nucleic acid complex of any one of claims 1-8, wherein the central region of the first nucleic acid strand does not comprise phosphorothioate internucleoside linkages except for the internucleoside linkage(s) between two or three nucleosides at the 5’ terminus, 3’ terminus, or both, of the central region.

12. The nucleic acid complex of any one of claims 1-11, wherein at least 80%, at least 85%, at least 90%, or at least 95% of the nucleosides of one or more of (1) the central region of the first nucleic acid strand, (2) the 5’ region of the first nucleic strand, and (3) the 3’ region of the first nucleic strand are chemically modified; and/or wherein at least 80%, at least 85%, at least 90%, or at least 95% of the nucleosides of one or more of the first nucleic acid strand, the second nucleic strand and the third nucleic strand are chemically modified; optionally wherein at least

80%, at least 85%, at least 90%, at least 95%, or all of the nucleosides of the nucleic acid complex are chemically modified.

13. The nucleic acid complex of any one of claims 11-12, wherein the chemical modifications are to resist nuclease degradation, to increase melting temperature (Tm), or both, of the nucleic acid complex.

14. The nucleic acid complex of any one of claims 1-13, wherein less than 5%, less than 10%, less than 25%, or less than 50% of the internucleoside linkages in the first nucleic acid strand are phosphorothioate internucleoside linkages or wherein the first nucleic acid strand does not comprise phosphorothioate internucleoside linkages.

15. The nucleic acid complex of any one of claims 1-13, wherein the internucleoside linkages between (1) the one to three nucleotides adjacent to the 3' of the 5' connector, and/or (2) the one or two nucleotides adjacent to the 5' of the 3' connector, and/or (3) the one to three nucleotides adjacent to the 3' of the 3' connector, are phosphorothioate internucleoside linkages.

16. The nucleic acid complex of any one of claims 1-15, wherein the overhang of the third nucleic acid strand is capable of binding to the input nucleic acid strand to form a toehold, thereby causing the displacement of the third nucleic acid strand from the first nucleic acid strand; optionally the overhang of the third nucleic acid strand is 5 to 20 nucleosides in length, and further optionally 9 nucleotides in length; and/or

wherein all internucleoside linkages of the overhang of the third nucleic acid strand are phosphorothioate internucleoside linkages; optionally

wherein the 5' terminus, the 3' terminus, or both of the third nucleic acid strand comprises a terminal moiety; and further optionally the terminal moiety comprises a ligand, a fluorophore, an exonuclease, a fatty acid, a Cy3, an inverted dT attached to a tri-ethylene glycol, or a combination thereof.

17. An *in vitro* and/or *ex vivo* method of modulating a target RNA, comprising:

contacting a cell comprising a target RNA with the nucleic acid complex of any one of claims 1 to 16, wherein an input strand binds to the overhang of the third nucleic acid strand to cause displacement of the third nucleic acid strand from the first nucleic acid strand to release the sequence complementary to the target RNA into the cell, thereby modulating the target RNA.

18. The nucleic acid complex of any one of claims 1 to 16 for use in contacting a cell to modulate a target RNA, wherein an input strand binds to the overhang of the third nucleic acid strand to cause displacement of the third nucleic acid strand from the first nucleic acid strand to

release the sequence complementary to the target RNA into the cell, thereby modulating the target RNA.

19. The method of claim 17 or the nucleic acid complex for the use in claim 18, wherein the cell is a cancer cell; optionally, the cell is a neuron.

20. The nucleic acid complex of any one of claims 1 to 16 for use in treating a disease or a condition, wherein the nucleic acid complex is to be administered to a subject in need thereof, wherein the input strand binds to the overhang of the third nucleic acid strand to cause displacement of the third nucleic acid strand from the first nucleic acid strand to release the sequence complementary to a target RNA, thereby reducing the activity of the target RNA or protein expression from the target RNA in the subject to treat the disease or condition.

21. Use of the nucleic acid complex of any one of claims 1-16 in the preparation of a medicament for treating a central nervous system (CNS) disease or disorder or cancer.

22. The nucleic acid complex for use of claim 20, optionally wherein the disease or condition is a central nervous system (CNS) disease or disorder or cancer; or the use of claim 21; optionally wherein the target RNA is a mRNA or a miRNA; optionally

wherein the nucleic acid complex is to be administered to the subject via a lipid-mediated delivery system, optionally via liposomes, nanoparticles, or micelles; optionally wherein the nucleic acid complex is administered to the subject via nanoparticles, inorganic nanoparticles, nucleic acid lipid particles, polymeric nanoparticles, lipidoid nanoparticles (LNPs), chitosan and inulin nanoparticles, cyclodextrins nanoparticles, carbon nanotubes, liposomes, micellar structures, capsids, polymers, polymer matrices, hydrogels, dendrimers, nucleic acid nanostructure, exosomes, GalNAc-conjugated melittin-like peptides, or combinations thereof.

23. The nucleic acid complex for use or use of any one of claims 18-22, wherein the nucleic acid complex is to be administered to a subject in need thereof via a subcutaneous injection or an intravenous injection, optionally wherein the nucleic acid complex is administered to a subject in need thereof at a concentration about 0.1-10 nM, optionally about 0.1-1.0 nM.