CLAIMS

WHAT IS CLAIMED IS:

1. A conjugate of Formula (I):

$$A\text{-}(X\text{-}B)_n$$

Formula (I)

wherein,

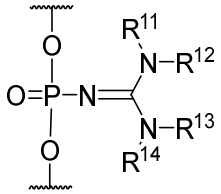
A is a binding moiety;

B is a double-stranded oligonucleotide comprising a guide strand and a passenger strand;

X is a bond or a linker;

n is a number ≥ 2; and

wherein the guide strand or the passenger strand comprises at least one modified internucleotide linkage comprising the structure of Formula (II):

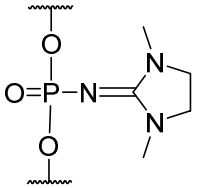


Formula (II);

wherein each R^{11}, R^{12}, R^{13}, and R^{14} is independently selected from -H, -C_{1-10} alkyl, -C_{2-10} alkenyl, -C_{2-10} alkynyl, or -C_{6-10} aryl;

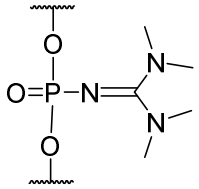
optionally, wherein R^{12} and R^{13}, together with an atom to which they are bound, form a 5-8 membered heterocyclic substituent moiety, selected from the group consisting of N-pyrrolidinyl, N-piperidinyl, N-azepanyl, N-azocanyl, and imidazolidine.

2. The conjugate of claim 1, wherein the internucleotide linkage has the structure of Formula (III):



Formula (III).

3. The conjugate of claim 1, wherein the internucleotide linkage has the structure of Formula (IV):



Formula (IV).

4. The conjugate of any one of claims 1-3, wherein the at least one modified internucleotide linkage of Formula (II) is located at an internal position or a terminus of the guide strand.

5. The conjugate of any one of claims 1-4, wherein the guide strand further comprises at least one phosphorothioate internucleotide linkage.

6. The conjugate of claim 5, wherein the at least one phosphorothioate internucleotide linkage and the at least one modified internucleotide linkage comprising the structure of Formula (II) are adjacent to one another.

7. The conjugate of any one of claims 1-6, wherein the passenger strand comprises the at least one modified internucleotide linkage of Formula (II).

8. The conjugate of any one of claims 1-7, wherein the at least one modified internucleotide linkage of Formula (II) is located at an internal position or a terminus of the passenger strand.

9. The conjugate of any one of claims 1-7, wherein the passenger strand comprises two modified internucleotide linkages of Formula (II) at the 3’ end and two modified internucleotide linkages of Formula (II) at the 5’ end.

10. The conjugate of any one of claims 1-7, wherein the passenger strand comprises four modified internucleotide linkages of Formula (II) at the 3’ end and four modified internucleotide linkages of Formula (II) at the 5’ end.

11. The conjugate of any one of claims 1-7, wherein the passenger strand comprises 18 modified internucleotide linkages of Formula (II).

12. The conjugate of any one of claims 1-11, wherein the passenger strand comprises two modified internucleotide linkages of Formula (II) at the 3’ end and two modified internucleotide linkages of Formula (II) at the 5’ end, and wherein the guide strand comprises two modified internucleotide linkages of Formula (II) at the 3’ end and two modified internucleotide linkages of Formula (II) at the 5’ end.

13. The conjugate of any one of claims 1-12, wherein the double-stranded oligonucleotide further comprises a modified internucleotide linkage selected from an alkylphosphonate, a triester, or a mesyl phosphoramidiate.

14. The conjugate of any one of claims 1-13, wherein the binding moiety is selected from the group consisting of a polypeptide, a protein, or an antibody or antigen binding fragment thereof.

15. The conjugate of claim 14, wherein the antibody or antigen binding fragment thereof comprises a humanized antibody or antigen binding fragment thereof, chimeric antibody or antigen binding fragment thereof, monoclonal antibody or antigen binding fragment thereof, monovalent Fab', divalent Fab2, single-chain variable fragment (scFv), diabody, minibody, nanobody, single-domain antibody (sdAb), or camelid antibody or antigen binding fragment thereof.

16. The conjugate of any one of claims 1-15, wherein the conjugate has a drug to antibody ratio (DAR) of about 2:1, 3:1 or 4:1.

17. The conjugate of any one of claims 1-16, wherein the modified internucleotide linkage of Formula (II) on the guide strand or the passenger strand increases activity of the conjugate of Formula (I).

18. The conjugate of any one of claims 1-17, wherein the modified internucleotide linkage of Formula (II) on the guide strand or the passenger strand of the siRNA increases the stability of the conjugate of Formula (I).

19. Use of the conjugate of any one of claims 1-18 in the manufacture of a medicament for modulating mRNA expression levels of a gene in a subject, wherein the conjugate is to be administered to the subject, wherein the conjugate decreases mRNA expression levels of the gene in the subject.

20. Use of the conjugate of any one of claims 1-18 in the manufacture of a medicament for treating muscle atrophy or myotonic dystrophy in a subject in need thereof, wherein the conjugate is to be administered to the subject, wherein the conjugate mediates RNA interference against a target mRNA in the subject, thereby treating muscle atrophy or mytonic dystrophy in the subject.

21. The conjugate of any one of claims 1-18 for use in therapy.