WHAT IS CLAIMED IS:

1. A peptide conjugated AON compound comprising at least two AON compounds comprising from 15 to 30 subunits of Formulas (I), (II), (III), (IV), (V), or (VI):

wherein B is a naturally occurring purine or pyrimidine nucleotide base selected from C, G, A, or T;

wherein said at least two AON compounds have a nucleotide base sequence that is complementary to at least 75% of the bases of a target pre-mRNA or mRNA;

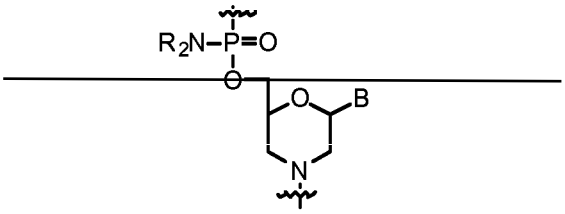
wherein said at least two AON compounds have from 0 to 3 repeating subunits where B is G;

wherein said at least two AON compounds have less than 60% of said subunits where B is C or G;

wherein said at least two AON compounds have a non-self-complimentary sequence; and

wherein said at least two AON compounds are conjugated to a polycationic peptide.

2. A peptide conjugated phosphorodiamidate morpholino compound comprising at least two phosphorodiamidate morpholino compounds comprising from 15 to 30 subunits of Formula (I):



(I)

wherein R is an alkyl group and B is a naturally occurring purine or pyrimidine nucleotide base selected from C, G, A, or T;

wherein said at least two phosphorodiamidate morpholino compounds have a nucleotide base sequence that is complementary to at least 8 contiguous bases of a target pre-mRNA or mRNA;

wherein said at least two phosphorodiamidate morpholino compounds have from 0 to 3 repeating subunits where B is G;

wherein said at least two phosphorodiamidate morpholino compounds have less than 60% of said subunits where B is C or G;

wherein said at least two phosphorodiamidate morpholino compounds have a non-self-complimentary sequence; and

wherein said at least two phosphorodiamidate morpholino compounds are conjugated to a polycationic peptide.

1. A peptide-antisense oligonucleotide (peptide-AON) conjugate comprising a polycationic peptide covalently conjugated to at least two antisense oligonucleotides (AONs), wherein each AON comprises:

(a) 15 to 30 subunits of a phosphorodiamidate morpholino (PMO), wherein each subunit comprises a naturally occurring purine or pyrimidine nucleotide base selected from the group consisting of C, G, A, and T;

(b) a nucleotide base sequence that is complementary to at least 8 contiguous bases of a target pre-mRNA, mRNA, microRNA, or long non-coding RNA of a gene;

(c) from 0 to 3 repeating subunits where the naturally occurring purine nucleotide base is G;

(d) less than 60% of said subunits where the naturally occurring purine or pyrimidine nucleotide base is C or G; and

(e) a non-self-complimentary sequence;

wherein the polycationic peptide is a cationic cell penetrating peptide (CPP), and wherein the peptide-AON conjugate comprises a cleavable linker containing a cleavage motif.

2. The peptide-AON conjugate of claim 1, wherein the cleavable linker comprises FK or FX at the P1/P1′ position, where X is any naturally occurring amino acid.

3. The peptide-AON conjugate of claim 1, wherein the cleavage motif is a hydrolytic enzyme cleavage motif.

4. The peptide-AON conjugate of claim 1, wherein the CPP comprises:

(a) RXRRXRRXRRXRXB (SEQ ID NO: 43), where R is D-arginine, X is 6-aminohexanoic acid, and B is β-alanine; or

(b) RXRRBRRXRRBRXB (SEQ ID NO: 44), wherein R is D-arginine, X is 6-aminohexanoic acid, and B is β-alanine.

5. The peptide-AON conjugate of claim 1, wherein the CPP comprises the formula: variable sequence-spacer-linker,

wherein the variable sequence is Ac—R(O)nR, wherein n≥7; wherein O is a sequence of residues selected from R, X, and Z; wherein R is L-arginine, X is 3-cis-aminocyclohexane, and Z is cis-2-aminocyclopentane-1-carbonyl, and

wherein the variable sequence:

(i) comprises an α-, β-, γ-, or δ-amino acid, or a cycloalkane structure;

(ii) causes the compound to be targeted to the nucleus;

(iii) causes the compound to be targeted to the cytosol; or

(iv) causes the compound to be targeted to the mitochondria.

6. The peptide-AON conjugate of claim 1, wherein the polycationic peptide comprises the formula: variable sequence-spacer-linker,

wherein the variable sequence is Ac—R(O)nR, wherein n≥7; wherein O is a sequence of residues selected from R, X, and Z; wherein R is L-arginine, X is 3-cis-aminocyclohexane, and Z is cis-2-aminocyclopentane-1-carbonyl, and

wherein the spacer:

(i) comprises an aminohexanoic acid (Ahx); or

(ii) comprises (Ahx)B, wherein B is selected from β-alanine or β-glycine.

7. The peptide-AON conjugate of claim 1, wherein the polycationic peptide comprises the formula variable sequence-spacer-linker,

wherein the variable sequence is Ac—R(O)nR, wherein n≥7; wherein O is a sequence of residues selected from R, X, and Z; wherein R is L-arginine, X is 3-cis-aminocyclohexane, and Z is cis-2-aminocyclopentane-1-carbonyl, and

wherein the linker:

(i) comprises the sequence FS;

(ii) comprises the sequence FSQ;

(iii) comprises the sequence FSQK; or

(iv) comprises the sequence FxyB, wherein F is phenylalanine, x is any amino acid and y is selected from glutamic acid (E), aspartic acid (D), lysine (K), serine (S), and threonine (T) or a non-natural analog of E, D, K, S or T, and B is β-alanine.

8. The peptide-AON conjugate of claim 1, wherein the CPP comprises the formula: variable sequence-spacer-linker,

wherein the variable sequence is Ac—R(O)nR, wherein n≥7; wherein O is a sequence of residues selected from R, X, and Z; wherein R is L-arginine, X is 3-cis-aminocyclohexane, and Z is cis-2-aminocyclopentane-1-carbonyl,
wherein the spacer comprises an aminohexanoic acid (Ahx) and
wherein the linker comprises FSQG-OH.

9. The peptide-AON conjugate of claim 1, wherein the CPP comprises the formula: variable sequence-spacer-linker,

wherein the variable sequence is Ac—R(O)nR, wherein n≥7; wherein O is a sequence of residues selected from R, X, and Z; wherein R is L-arginine, X is 3-cis-aminocyclohexane, and Z is cis-2-aminocyclopentane-1-carbonyl,
wherein the linker comprises the sequence FxyB, wherein F is phenylalanine, x is any amino acid and y is selected from glutamic acid (E), aspartic acid (D), lysine (K), serine (S), and threonine (T), and B is β-alanine; and wherein y is a non-natural analog of threonine; and wherein n is 7, and
wherein the spacer is (Ahx).

10. The peptide-AON conjugate of claim 1, wherein the CPP comprises a sequence selected from the group consisting of: SEQ ID NOs. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11.

11. The peptide-AON conjugate of claim 1, wherein the CPP is selected from the group consisting of:

(i) No. 1216: (SEQ ID NO.: 56) Ac-(RXRRBR)$_2$XFD(d-Glu)EG-OH; (ii) No. 1218: (SEQ ID NO.: 58) Ac-E(RXRRBR)$_2$XFKG-OH; (iii) No. 1219: (SEQ ID NO.: 59) Ac-E(RXRRBR)$_2$XFKEG-OH; (iv) No. 1220: (SEQ ID NO.: 60) Ac-E(RXRRBR)$_2$XFK(d-Glu)EG-OH; (v) No. 1221: (SEQ ID NO.: 61) Ac-(d-Glu)E(RXRRBR)$_2$XFKG-amide (vi) No. 1222: (SEQ ID NO.: 62) Ac-(dGlu)E(RXRRBR)$_2$XFKG-OH; (vii) No. 1223: (SEQ ID NO.: 63) Ac-(d-

Glu)E(RXRRBR)$_2$XFKEG-OH; or (viii) No. 1224: (SEQ ID NO.: 64) Ac-(d-Glu)E(RXRRBR)$_2$XFK((d-Glu)EG-OH,

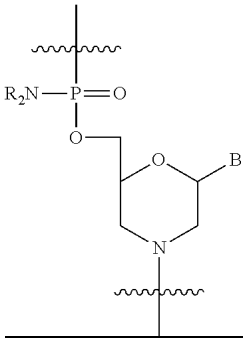
wherein Ac is acetyl, R is D-arginine, X is 6-aminohexanoic acid, B is β-alanine, F is phenylalanine, K is lysine, D is aspartic acid, E is glutamic acid, and G is glycine.

12. The peptide-AON conjugate of claim 1, wherein the peptide-AON conjugate is selected from the group consisting of:

(i) Ac-(RXR)$_4$XFKE-((PEG)$_2$-PMO)G-(PMO) (SEQ ID NO:81);
(ii) Ac-(RXRRBR)$_2$XFD(d-Glu)(PMO)E(PMO)G(PMO) (SEQ ID NO:70);
(iii) Ac-E(PMO)(RXRRBR)$_2$XFKG (SEQ ID NO:72);
(iv) Ac-E(PMO)(RXRRBR)$_2$XFKE(PMO)G(PMO) (SEQ ID NO:73);
(v) Ac-E(PMO)(RXRRBR)$_2$XFK(d-Glu)(PMO)E(PMO)G(PMO) (SEQ ID NO:74);
(vi) Ac-(d-Glu)(PMO)E(PMO)(RXRRBR)$_2$XFKG (SEQ ID NO:75);
(vii) Ac-(d-Glu)(PMO)E(PMO)(RXRRBR)$_2$XFKG(PMO) (SEQ ID NO:76);
(viii) Ac-(d-Glu)(PMO)E(PMO)(RXRRBR)$_2$XFKE(PMO)G(PMO) (SEQ ID NO:77);
(ix) Ac-(d-Glu)(PMO)E(PMO)(RXRRBR)$_2$XFK((d-Glu)(PMO)E(PMO)G(PMO) (SEQ ID NO:78);
(x) Ac-(RXRRBR)$_2$XFKE(PMO)G(PMO) (SEQ ID NO:69);
(xi) Ac-(RXR)$_4$XE((PEG)$_2$-PMO)G(PMO) (SEQ ID NO:87); and
(xii) Ac-(RXRRBR)$_2$XE(PMO)G(PMO) (SEQ ID NO:90),
where Ac is acetyl, R is D-arginine, X is 6-aminohexanoic acid, B is β-alanine, F is phenylalanine, K is lysine, D is aspartic acid, E is glutamic acid, and G is glycine.

13. The peptide-AON conjugate of claim 12, wherein the PMO is PMO23.

14. The peptide-AON conjugate of claim 1, wherein the PMO subunit is of Formula (I):



where R is an alkyl group and B is a naturally occurring purine or pyrimidine nucleotide base selected from cytosine (C), guanine (G), adenine (A), or thymine (T).