WHAT IS CLAIMED IS:

1. A conjugate of formula I:

$$P\text{-}(L\text{-}(X)_y)_n \qquad (I)$$

wherein,

each X is independently an oligonucleotide;

each L is independently a linking group;

P is a protein comprising (i) a modified CH3 constant domain that specifically binds to a transferrin receptor (TfR) with an affinity of 3nM to 600nM, and (ii) one or more non-targeting Fabs (NTFs) or non-binding variable regions (NBVRs);

each y is independently at least 1; and

n is at least 1;

wherein the modified CH3 domain comprises:

Trp, Tyr, Leu, Gln, or Glu at position 153;

Leu, Tyr, Met, Val, Phe or Trp at position 157;

Leu, Thr, His, Pro, or Phe at position 159;

Val, Pro, or an acidic amino acid at position 160;

Trp at position 161;

Val, Ser, Ala, or Gly at position 162;

Asn, Gly, His, Gln, Leu, Lys, Val, Phe, Ser, Ala, Asp, Thr or Glu at position 163;

Ser, Thr, Gln, Phe, Tyr or Val at position 164;

Gln, Phe, His, or Lys at position 165;

Glu, Ala, Ser, Leu, Thr, Pro or Asp at position 186;

Lys, Arg, Gly, or Pro at position 187;

Glu or Ser at position 188;

Thr, Asn or an acidic amino acid at position 189;

Trp, Tyr, His, or Phe at position 194;

Ser, Thr, Glu, Lys or Trp at position 197; and

Ser, Trp, Gly, Cys, Pro or Met at position 199;

as numbered with reference to SEQ ID NO:1.

2. The conjugate of claim 1, wherein the engineered binding site binds TfR with an affinity of 500nM to 3nM, 400nM to 20nM, 300nM to 30nM, 200nM to 40nM, 150nM to 50nM, or 130nM to 80nM.

3. The conjugate of claim 1 or 2, wherein P comprises one or more modified sites that facilitate the attachment of P to each L.

4. The conjugate of any one of claims 1-3, wherein P comprises:

(a) an Fc polypeptide comprising the modified CH3 constant domain; or

(b) an Fc polypeptide dimer, comprising a first Fc polypeptide comprising the modified CH3 constant domain; and a second Fc polypeptide dimerized to the first Fc polypeptide.

5. The conjugate of claim 4, wherein the Fc polypeptide is joined to the NTF or NBVR to produce a Fab-Fc fusion; or the first Fc polypeptide is joined to a first NTF or NVBR to produce a first Fab-Fc fusion and the second Fc polypeptide is joined to a second NTF or NVBR to produce a second Fab-Fc fusion

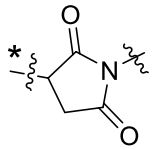
6. The conjugate of claim 4 or 5, wherein the modified site is an amino acid substitution.

7. The conjugate of claim 6, wherein the modified site is a cysteine substitution.

8. The conjugate of claim 7, wherein the cysteine substitution is selected from the group consisting of: S239C, S442C, A330C, K149C, and T289C, according to EU numbering and A114C according to Kabat numbering.

9. The conjugate of any one of claims 1-8, wherein the oligonucleotide is an antisense oligonucleotide (ASO) or a siRNA.

10. The conjugate of any one of claims 1-9, wherein the linking group L comprises a moiety having the structure:



wherein, * denotes the attachment point to a sulfur atom of a modified site within P.

11. The conjugate of any one of claims 1-10, wherein y is an integer from 1 to 4, optionally wherein y is 1.

12. The conjugate of any one of claims 1-11, wherein n is an integer from 1 to 6, optionally wherein n is 1.

13. A Fab-Fc dimer fusion, comprising:

(a) a first Fab-Fc fusion comprising a modified CH3 constant domain that specifically binds to a transferrin receptor with an affinity of 3nM to 600nM; and

wherein the modified CH3 domain comprises:

Trp, Tyr, Leu, Gln, or Glu at position 153;

Leu, Tyr, Met, Val, Phe or Trp at position 157;

Leu, Thr, His, Pro, or Phe at position 159;

Val, Pro, or an acidic amino acid at position 160;

Trp at position 161;

Val, Ser, Ala, or Gly at position 162;

Asn, Gly, His, Gln, Leu, Lys, Val, Phe, Ser, Ala, Asp, Thr or Glu at position 163;

Ser, Thr, Gln, Phe, Tyr or Val at position 164;

Gln, Phe, His, or Lys at position 165;

Glu, Ala, Ser, Leu, Thr, Pro or Asp at position 186;

Lys, Arg, Gly, or Pro at position 187;

Glu or Ser at position 188;

Thr, Asn or an acidic amino acid at position 189;

Trp, Tyr, His, or Phe at position 194;

Ser, Thr, Glu, Lys or Trp at position 197; and

Ser, Trp, Gly, Cys, Pro or Met at position 199;

as numbered with reference to SEQ ID NO:1;

(b) a second Fab-Fc fusion dimerized to the first Fab-Fc fusion;

wherein the Fab-Fc dimer fusion comprises one or more cysteine substitutions; and

wherein the first Fab-Fc fusion and/or the second Fab-Fc fusion comprises a NTF or NVBR.

14. The Fab-Fc dimer fusion of claim 13, wherein the one or more cysteine substitutions are selected from the group consisting of: S239C, S442C, A330C and T289C according to EU numbering, and A114C according to Kabat numbering.

15. The Fab-Fc dimer fusion of claim 13 or 14, the first Fab-Fc fusion and second Fab-Fc fusion each comprise a cysteine substitution.

16. The Fab-Fc dimer fusion of claim 15, wherein

(a) the first Fab-Fc fusion or the second Fab-Fc fusion comprises a cysteine substitution at S239C;

(b) the first Fab-Fc fusion and the second Fab-Fc fusion each comprises a cysteine substitution at S239C;

(c) the first Fab-Fc fusion or the second Fab-Fc fusion comprises two cysteine substitutions;

(d) the first Fab-Fc fusion and the second Fab-Fc fusion each comprises two cysteine substitutions;

(e) the first Fab-Fc fusion or the second Fab-Fc polypeptides comprises a cysteine substitution at S239C and A330C; or

(f) the first Fab-Fc fusion and second Fab-Fc fusions each comprises a cysteine substitution at S239C and A330C.

17. The Fab-Fc dimer fusion of claim 13 or 14, wherein the second Fab-Fc fusion comprises a cysteine substitution, optionally wherein the cysteine substitution is S239C.

18. A Fab-Fc dimer fusion comprising:

(a) a first Fc polypeptide comprising a modified CH3 constant domain that specifically binds to a transferrin receptor with an affinity of 3nM to 600nM

wherein the modified CH3 domain comprises:

Trp, Tyr, Leu, Gln, or Glu at position 153;

Leu, Tyr, Met, Val, Phe or Trp at position 157;

Leu, Thr, His, Pro, or Phe at position 159;

Val, Pro, or an acidic amino acid at position 160;

Trp at position 161;

Val, Ser, Ala, or Gly at position 162;

Asn, Gly, His, Gln, Leu, Lys, Val, Phe, Ser, Ala, Asp, Thr or Glu at position 163;

Ser, Thr, Gln, Phe, Tyr or Val at position 164;

Gln, Phe, His, or Lys at position 165;

Glu, Ala, Ser, Leu, Thr, Pro or Asp at position 186;

Lys, Arg, Gly, or Pro at position 187;

Glu or Ser at position 188;

Thr, Asn or an acidic amino acid at position 189;

Trp, Tyr, His, or Phe at position 194;

Ser, Thr, Glu, Lys or Trp at position 197; and

Ser, Trp, Gly, Cys, Pro or Met at position 199;

as numbered with reference to SEQ ID NO:1; and

(b) a second Fc polypeptide dimerized to the first Fc polypeptide of (a);

wherein the first Fab-Fc fusion and/or the second Fab-Fc fusion comprises a NTF or NVBR; and

wherein the first Fab-Fc fusion and/or the second Fab-Fc fusion comprises one or more substitutions selected from the group consisting of: N297A and N297G, wherein the positions are according to EU numbering.

19. The conjugate of any one of claims 1-12 or the Fab-Fc dimer fusion of any one of claims 13-18, wherein the modified CH3 constant domain comprises:

Trp, Leu or Glu at position 153;

Tyr or Phe at position 157;

Thr at position 159;

Glu at position 160;

Trp at position 161;

Val, Ser, or Ala at position 162;

Asn or Ser at position 163;

Ser or Thr at position 186;

Glu or Ser at position 188;

Glu at position 189; and

Phe at position 194.

20. The conjugate of any one of claims 4-12 and 19 or the Fab-Fc dimer fusion of any one of claims 13-19, wherein:

(a) the first Fc polypeptide or Fab-Fc dimer fusion comprises a sequence having at least 85%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity to the sequence of any one of SEQ ID NOS:279, 281, 361-366, 491-494, 702-718, 632, 645-649, 738-746, 804, and

(b) the second Fc polypeptide or Fab-Fc dimer fusion comprises a sequence having at least 85%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity to the sequence of any one of SEQ ID NOS: 557-561, 627-631, 635-644, 719-723, 724-731, 733-737, and 810.

21. The conjugate or Fc dimer fusion of claim 20, wherein the first Fc polypeptide or the first Fab-Fc dimer fusion comprises a Glu at position 153, Tyr at position 157, Thr at position 159, Glu at position 160, Trp at position 161, Ser, or Ala at position 162, Asn at position 163, Thr or Ser at position 186, Glu at position 188, Glu at position 189, and Phe at position 194, as numbered with reference to SEQ ID NO:1.

22. The conjugate or Fc dimer fusion of claim 21, wherein:

the first Fc polypeptide or the first Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:362 and the second Fc polypeptide or the second Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:559;

the first Fc polypeptide or the first Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:702 and the second Fc polypeptide or the second Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:559;

the first Fc polypeptide or the first Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:708 and the second Fc polypeptide or the second Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:722;

the first Fc polypeptide or the first Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:718 and the second Fc polypeptide or the second Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:559;

the first Fc polypeptide or the first Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:362 and the second Fc polypeptide or the second Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:560;

the first Fc polypeptide or the first Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:362 and the second Fc polypeptide or the second Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:561; or

the first Fc polypeptide or the first Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:804 and the second Fc polypeptide or the second Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:810.

23. A conjugate of formula I:

$$P\text{-}(L\text{-}(X)_y)_n \qquad (I)$$

wherein,

each X is independently an oligonucleotide;

each L is independently a linking group;

P is a protein comprising (i) a modified CH3 constant domain that specifically binds to a transferrin receptor with an affinity of 3nM to 600nM, (ii) one or more NTFs or NVBRs, and (iii) one or more modified sites, wherein the one or more modified sites are amino acid substitutions that facilitate the attachment of P to each L;

each y is independently at least 1; and

n is at least 1;

wherein the modified CH3 domain comprises:

Trp, Tyr, Leu, Gln, or Glu at position 153;
Leu, Tyr, Met, Val, Phe or Trp at position 157;
Leu, Thr, His, Pro, or Phe at position 159;
Val, Pro, or an acidic amino acid at position 160;
Trp at position 161;
Val, Ser, Ala, or Gly at position 162;
Asn, Gly, His, Gln, Leu, Lys, Val, Phe, Ser, Ala, Asp, Thr or Glu at position 163;
Ser, Thr, Gln, Phe, Tyr or Val at position 164;
Gln, Phe, His, or Lys at position 165;
Glu, Ala, Ser, Leu, Thr, Pro or Asp at position 186;
Lys, Arg, Gly, or Pro at position 187;
Glu or Ser at position 188;
Thr, Asn or an acidic amino acid at position 189;
Trp, Tyr, His, or Phe at position 194;
Ser, Thr, Glu, Lys or Trp at position 197; and
Ser, Trp, Gly, Cys, Pro or Met at position 199;
as numbered with reference to SEQ ID NO:1.

24. The conjugate of claim 23, wherein P comprises a first Fc polypeptide comprising the modified CH3 constant domain.

25. The conjugate of claim 24, wherein P comprises an Fc polypeptide dimer, comprising the first Fc polypeptide and a second Fc polypeptide dimerized to the first Fc polypeptide.

26. The conjugate of claim25, wherein:

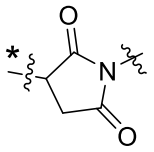
(a) the first Fc polypeptide or the second Fc polypeptide is joined to a a NTF or a NVBR to produce a Fab-Fc fusion; or

(b) the first Fc polypeptide is joined to a first NTF or NVBR to produce a first Fab-Fc fusion and the second Fc polypeptide is joined to a second NTF or NVBR to produce a

second Fab-Fc fusion, and wherein the first Fab-Fc fusion and the second Fab-Fc fusion form a Fab-Fc dimer fusion.

27. The conjugate of any one of claims 23-26, wherein the one or more modified sites comprises one or more cysteine substitution, optionally wherein the one or more cysteine substitutions are selected from the group consisting of: S239C, S442C, A330C, K149C, and T289C, according to EU numbering and A114C according to Kabat numbering.

28. The conjugate of any one of claims 23-27, wherein the linking group L comprises a moiety having the structure:



wherein, * denotes the attachment point to a sulfur atom of a modified site within P.

29. The conjugate of claim 28, wherein the modified site is an alanine or glycine substitution, optionally wherein the alanine or glycine substitution is N297A or N297G, according to EU numbering.

30. The conjugate of any one of claims 23-26 and 29, wherein L is conjugated to P at Q295, optionally wherein L is conjugated to P by enzymatic conjugation,

optionally wherein the enzymatic conjugation uses a bacterial transglutaminase (BTG).

31. The conjugate of any one of claims 23-30, wherein the modified CH3 domain comprises:

Trp, Leu, or Glu at position 153;

Tyr or Phe at position 157;

Thr at position 159;

Glu at position 160;

Trp at position 161;

Val, Ser, or Ala at position 162;

Asn or Ser at position 163;

Ser or Thr at position 186;

Glu or Ser at position 188;

Glu at position 189; and

Phe at position 194.

32. The conjugate of any one of claims 24-31, wherein:

(a) the first Fc polypeptide or the first Fab-Fc fusion comprises a sequence having at least 85%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity to the sequence of any one of SEQ ID NOS:279, 281, 361-366, 491-494, 702-718, 632, 645-649, 738-746, 804; and

(b) the second Fc polypeptide or the second Fab-Fc dimer fusion comprises a sequence having at least 85%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity to the sequence of any one of SEQ ID NOS: 557-561, 627-631, 635-644, 719-723, 724-731, 733-737, and 810.

33. The conjugate of claim 32, wherein the first Fc polypeptide or the first Fab-Fc fusion comprises a Glu at position 153, Tyr at position 157, Thr at position 159, Glu at position 160, Trp at position 161, Ser, or Ala at position 162, Asn at position 163, Thr or Ser at position 186, Glu at position 188, Glu at position 189, and Phe at position 194, as numbered with reference to SEQ ID NO:1.

34. The conjugate of claim 32, wherein:

the first Fc polypeptide or the first Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:362 and the second Fc polypeptide or the second Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:559;

the first Fc polypeptide or the first Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:702 and the second Fc polypeptide or the second Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:559;

the first Fc polypeptide or the first Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:708 and the second Fc polypeptide or the second Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:722;

the first Fc polypeptide or the first Fab-Fc dimer fusion comprises the amino acid sequence of SEQ ID NO:718 and the second Fc polypeptide or the second Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:559;

the first Fc polypeptide or the first Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:362 and the second Fc polypeptide or the second Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:560;

the first Fc polypeptide or the first Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:362 and the second Fc polypeptide or the second Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:561; or

the first Fc polypeptide or the first Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:804 and the second Fc polypeptide or the second Fab-Fc fusion comprises the amino acid sequence of SEQ ID NO:810.

35. The conjugate of any one of claims 23-34, wherein the oligonucleotide comprises:

(a) an antisense oligonucleotide (ASO);

(b) a siRNA,

(c) a gapmer having a modification pattern of formula 5′-X_a-Y_a-Z_a-3′, wherein X_a and Z_a each comprise 3 LNA modified nucleotides, and wherein the gap region Y_a comprises PS linkages.

36. The conjugate of claim 35, wherein the oligonucleotide is an ASO, and

(a) each L is linked to the 5′ end of the ASO; or

(b) each L is linked to the 3′ end of the ASO.

37. The conjugate of any one of claims 23-36, wherein L comprises a C_6 amine group having the formula $-(CH_2)_6-NH-$.

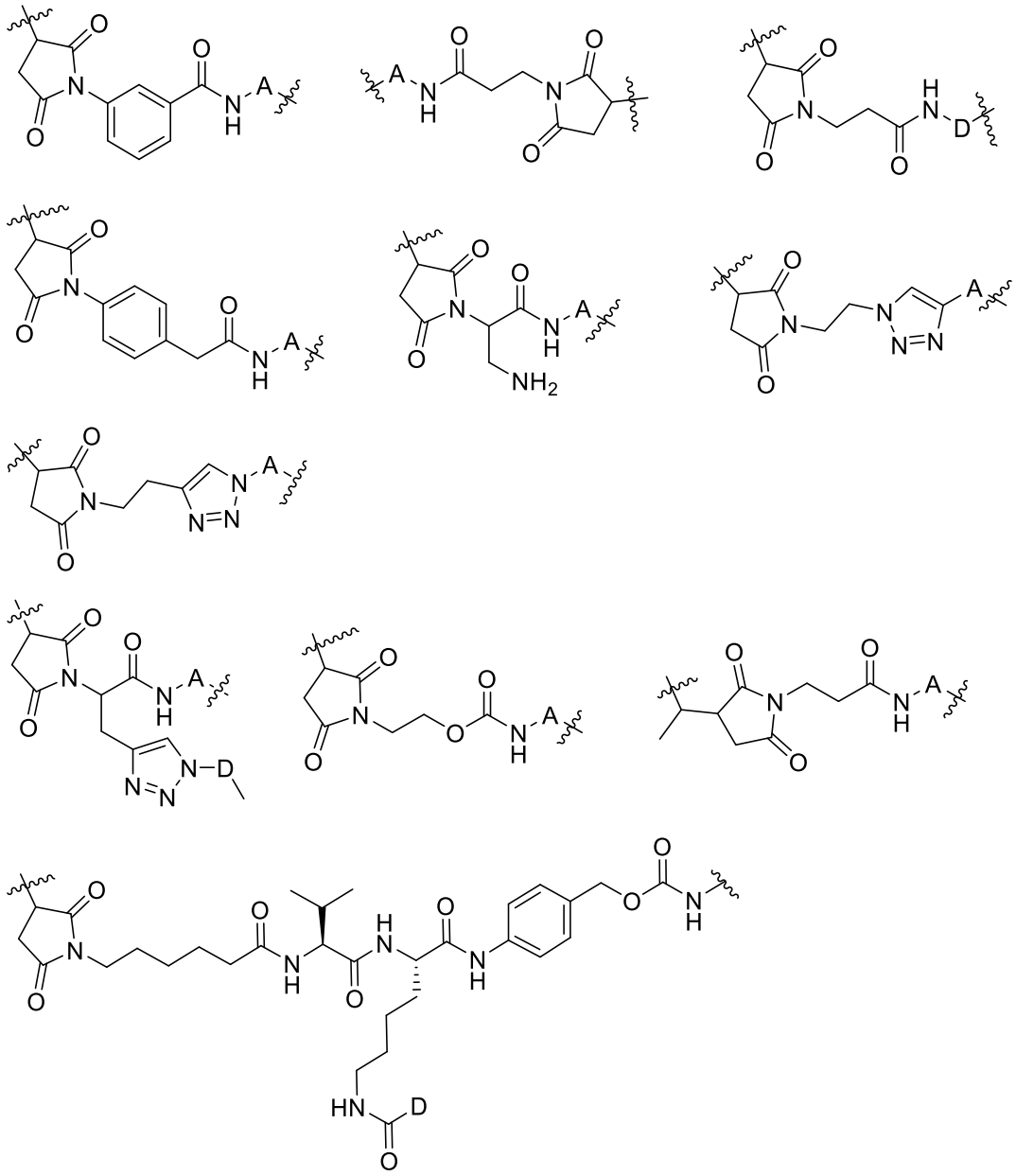
38. The conjugate of any one of claims 23-37, wherein P binds TfR with an affinity of 500nM to 10nM; 400nM to 20nM, 300nM to 30nM, 200nM to 40nM, 150nM to 50nM, or 100nM.

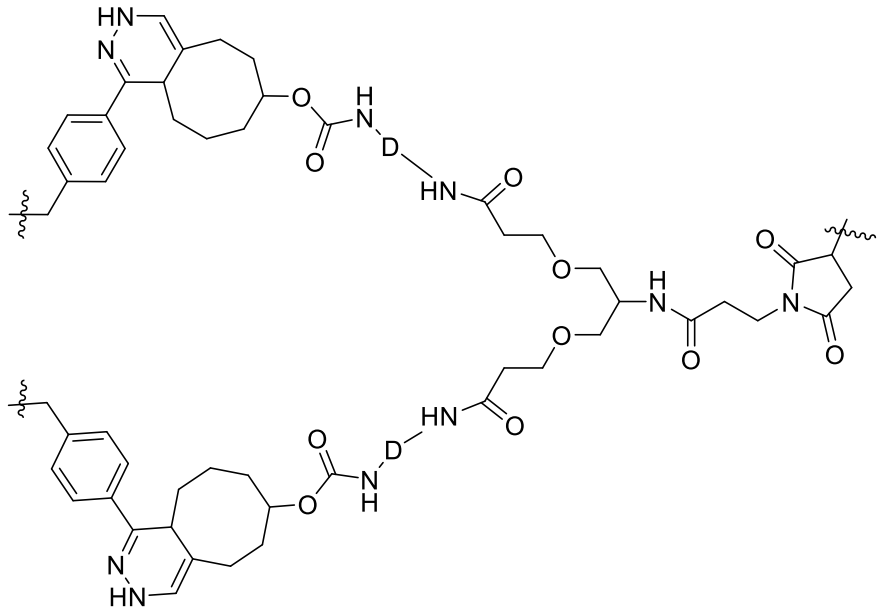
39. The conjugate of any one of claims 23-38, wherein y is an integer from 1 to 4, optionally wherein y is 1.

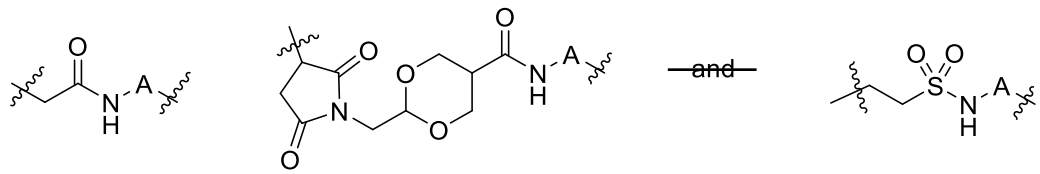
40. The conjugate of any one of claims 23-39, wherein n is an integer from 1 to 6, optionally wherein n is 1.

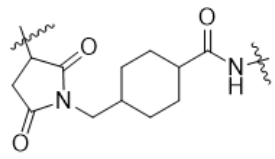
41. The conjugate of any one of claims 1-12 and 23-40, wherein

each L is a linking group independently selected from the group consisting of:









and

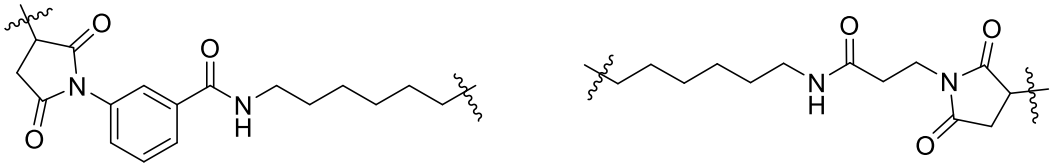
wherein,

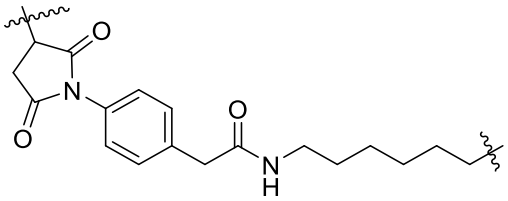
each A is independently (C_1-C_{15})alkylene;

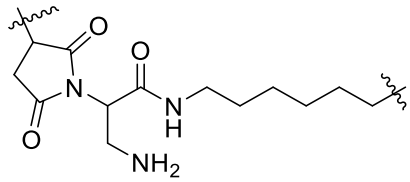
each D is $-(CH_2-CH_2-O)_m-$; and

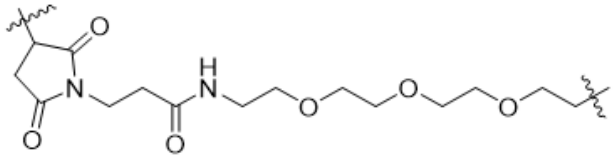
each m is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24.

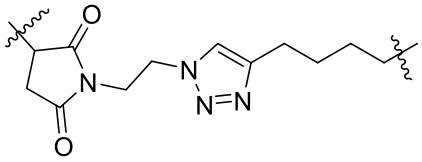
42. The conjugate of claim 41, wherein each L is a linking group independently selected from the group consisting of:

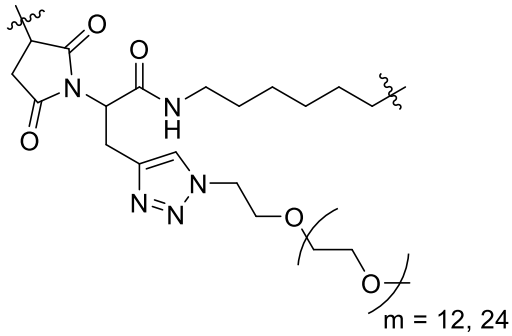


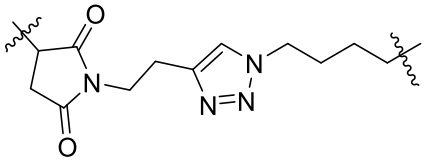


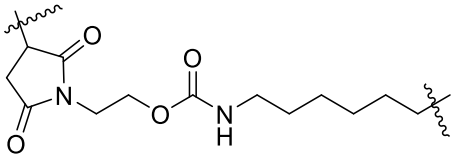


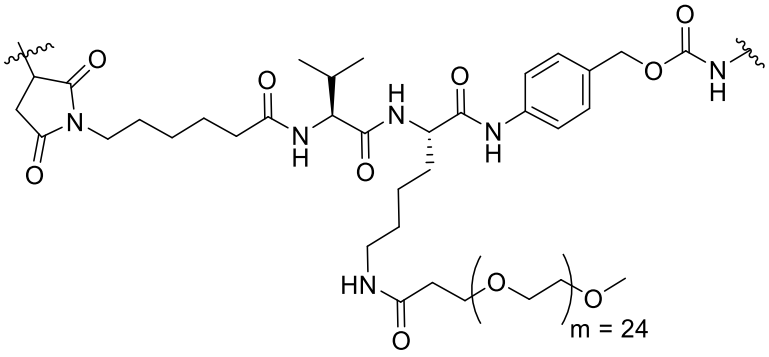


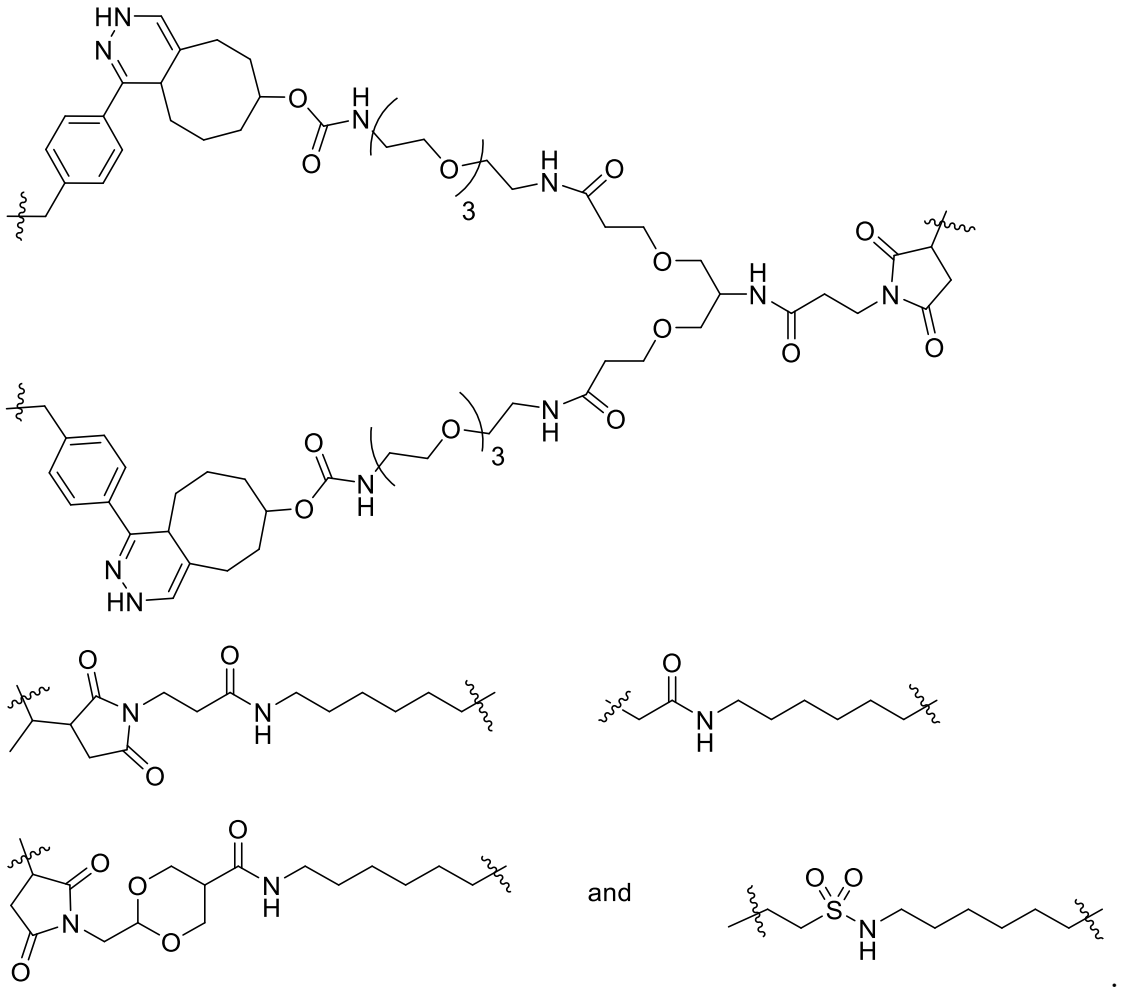



m = 12, 24






m = 24



43. A conjugate of formula I:

$$P\text{-}(L\text{-}(X)_y)_n \qquad (I)$$

wherein,

each X is independently an oligonucleotide;

each L is independently a linking group;

P is a protein comprising a modified CH3 constant domain that specifically binds to a transferrin receptor, wherein P does not comprise an antibody antigen-binding domain or antibody variable domain;

each y is independently 1 or more; and

n is 1 or more;

wherein the modified CH3 domain comprises:

Trp, Tyr, Leu, Gln, or Glu at position 153;
Leu, Tyr, Met, Val, Phe or Trp at position 157;
Leu, Thr, His, Pro, or Phe at position 159;
Val, Pro, or an acidic amino acid at position 160;
Trp at position 161;
Val, Ser, Ala, or Gly at position 162;
Asn, Gly, His, Gln, Leu, Lys, Val, Phe, Ser, Ala, Asp, Thr or Glu at position 163;
Ser, Thr, Gln, Phe, Tyr or Val at position 164;
Gln, Phe, His, or Lys at position 165;
Glu, Ala, Ser, Leu, Thr, Pro or Asp at position 186;
Lys, Arg, Gly, or Pro at position 187;
Glu or Ser at position 188;
Thr, Asn or an acidic amino acid at position 189;
Trp, Tyr, His, or Phe at position 194;
Ser, Thr, Glu, Lys or Trp at position 197; and
Ser, Trp, Gly, Cys, Pro or Met at position 199;
as numbered with reference to SEQ ID NO:1.

44. The conjugate of claim 43, wherein the oligonucleotide is an antisense oligonucleotide (ASO) or a siRNA.

45. The conjugate of claim 44, wherein the conjugate is greater than 50 kDa in size.

46. The conjugate of any one of claims 43-45, wherein P comprises an Fc polypeptide comprising the modified constant domain.

47. The conjugate of any one of claims 43-45, wherein P comprises an Fc polypeptide dimer, comprising a first Fc polypeptide comprising the modified constant domain; and a second Fc polypeptide dimerized to the first Fc polypeptide.

48. The conjugate of any one of claims 43-47, wherein P further comprises one or more modified sites, wherein the one or more modified site are amino acid substitutions that facilitate the attachment of P to each L.

49. The conjugate of claim 48, wherein the modified site is a cysteine substitution, optionally wherein the cysteine substitution is selected from the group consisting of: S239C, S442C, A330C, and T289C.

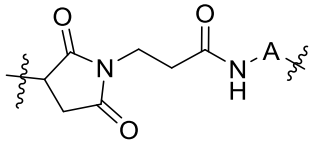
50. A conjugate of formula I:

$$P\text{-}(L\text{-}(X)_y)_n \qquad (I)$$

wherein,

each X is independently an oligonucleotide;

each L is independently



wherein A is $(C_1\text{-}C_{15})$alkylene;

P is a protein comprising a Fab-Fc dimer fusion, comprising (i) a modified CH3 constant domain that specifically binds to a transferrin receptor with an affinity of 100nm, (ii) one or more NTFs or NVBRs, and (iii) one or more modified sites, which facilitate the attachment of P to each L, and wherein the one or more modified sites are selected from the group consisting of S239C, S442C, A330C, K149C, and T289C, according to EU numbering and A114C according to Kabat numbering;

each y is independently at least 1; and

n is at least 1;

wherein the modified CH3 domain comprises:

Trp, Tyr, Leu, Gln, or Glu at position 153;

Leu, Tyr, Met, Val, Phe or Trp at position 157;

Leu, Thr, His, Pro, or Phe at position 159;

Val, Pro, or an acidic amino acid at position 160;

Trp at position 161;

Val, Ser, Ala, or Gly at position 162;

Asn, Gly, His, Gln, Leu, Lys, Val, Phe, Ser, Ala, Asp, Thr or Glu at position 163;

Ser, Thr, Gln, Phe, Tyr or Val at position 164;

Gln, Phe, His, or Lys at position 165;

Glu, Ala, Ser, Leu, Thr, Pro or Asp at position 186;

Lys, Arg, Gly, or Pro at position 187;

Glu or Ser at position 188;

Thr, Asn or an acidic amino acid at position 189;

Trp, Tyr, His, or Phe at position 194;

Ser, Thr, Glu, Lys or Trp at position 197; and

Ser, Trp, Gly, Cys, Pro or Met at position 199;

as numbered with reference to SEQ ID NO:1.

51. The conjugate of claim 50, wherein y is an integer from 1 to 4, optionally wherein y is 1.

52. The conjugate of claim 50 or 51, wherein n is an integer from 1 to 6, optionally wherein n is 1.

53. A pharmaceutical composition comprising a conjugate of formula (I) of any one of claims 1-12 and 23-52 and a pharmaceutically acceptable excipient.

54. The pharmaceutical composition of claim 53, comprising a plurality of conjugates of formula (I), optionally wherein the ratio of oligonucleotide to protein in the composition is 1:1 to 4:1, 1:1 to 2:1, or 1.23.

55. The pharmaceutical composition of claim 54, wherein the ratio of oligonucleotide to protein in the composition is 2:1 to 3:1, or 2.5.

56. The conjugate according to any one of claims 1-12 and 23-52 or the pharmaceutical composition of any one of claims 53-55 suitable for use in delivering an oligonucleotide to muscle tissue and/or brain tissue in a patient.

57. The pharmaceutical composition of any one of claims 53-55 suitable for use in modulating gene expression in a brain cell or a plurality of brain cells.

58. The pharmaceutical composition for use according to claim 57, wherein the modulating target gene expression is gene knockdown or gene knockout.

59. The pharmaceutical composition for use according to claim 57 or 58, wherein administration of the pharmaceutical composition decreases mean cell volume by less than 2 femtoliters.

60. The pharmaceutical composition for use according to any one of claims 57-59, wherein administration of the pharmaceutical composition decreases TfR protein levels in the brain vasculature by less than 10%, 15%, 20%, 25%, 30%, 40%, 50%, or 60%.

61. The pharmaceutical composition for use according to any one of claims 57-60, wherein the brain cell is a neuron, an endothelial cell, an oligodendrocyte, an astrocyte, or a microglia.

62. The pharmaceutical composition for use according to any one of claims 57-60, wherein the plurality of cells comprises at least two, three, four, or five cell types selected from the group consisting of: a neuron, an endothelial cell, an oligodendrocyte, an astrocyte, and a microglia, optionally wherein the neuron is an excitatory neuron or inhibitory neuron.

63. The pharmaceutical composition for use according to any one of claims57-62, wherein the conjugate is formulated for intravenous administration.

64. A pharmaceutical composition of any one of claims 53-57 suitable for use in delivering an oligonucleotide to deep brain regions.

65. The pharmaceutical composition for use according to claim 64, wherein the deep brain regions comprise at least one of: cortex, brainstem, hippocampus, striatum, cerebellum, or thalamus.

66. The pharmaceutical composition of any one of claims 53-57 suitable for use in delivering the oligonucleotide to spinal cord, optionally wherein the spinal cord is a cervical spinal cord and/or a lumbar spinal cord.

67. A pharmaceutical composition of any one of claims 53-57 suitable suitable for use in delivering an antisense oligonucleotide across brain regions.

68. A pharmaceutical composition of any one of claims 53-57 suitable for use in transporting an oligonucleotide across the BBB and delivering the oligonucleotide to a neuron cell, thereby generating a neuron cell with decreased target gene expression.

69. A pharmaceutical composition of any one of claims 53-57 suitable for use in transporting an oligonucleotide across the BBB and delivering the oligonucleotide to a neuron cell, thereby modifying a neuron cell to decrease target gene expression in the neuron cell.

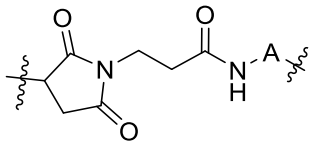
70. A conjugate suitable for use in transporting an oligonucleotide across the blood brain barrier (BBB) of a patient, wherein the conjugate comprises a conjugate of formula I:

$$P\text{-}(L\text{-}(X)_y)_n \qquad (I)$$

wherein,

each X is independently an oligonucleotide;

each L is independently



wherein A is $(C_1\text{-}C_{15})$alkylene;

P is a protein comprising a Fab-Fc dimer fusion, comprising (i) a modified CH3 constant domain that specifically binds to a transferrin receptor with an affinity of 100nm, (ii) one or more NTFs or NBVRs, and (iii) one or more modified sites that facilitate the attachment of P to each L, wherein the one or more modified sites are selected from the group consisting of: S239C, S442C, A330C, K149C, and T289C, according to EU numbering and A114C according to Kabat numbering;

each y is independently at least 1; and

n is at least 1;

wherein the modified CH3 domain comprises:

Trp or Glu at position 153;

Tyr at position 157;

Thr at position 159;

Glu at position 160;

Trp at position 161;

Ser or Ala at position 162;

Asn or Ser at position 163;

Tyr at position 164;

Lys at position 165;

Thr at position 186;

Lys at position 187;

Glu at position 188;

Glu at position 189;

Phe at position 194;

Ser at position 197; and

Ser at position 199;

as numbered with reference to SEQ ID NO:1.

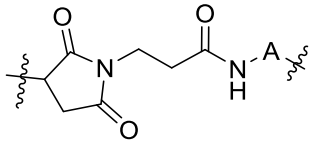
71. A conjugate suitable for use in modulating the expression of a target gene in a cell within the brain of a patient, wherein the conjugate comprises a conjugate of formula I:

$$P\text{-}(L\text{-}(X)_y)_n \qquad (I)$$

wherein,

each X is independently an oligonucleotide;

each L is independently



wherein A is $(C_1\text{-}C_{15})$alkylene;

P is a protein comprising a Fab-Fc dimer fusion, comprising (i) a modified CH3 constant domain that specifically binds to a transferrin receptor with an affinity of 100nm, (ii) one or more NTFs or NBVRs, and (iii) one or more modified sites that facilitate the attachment of P to each L, wherein the one or more modified sites are selected from the group consisting of: S239C, S442C, A330C, K149C, and T289C, according to EU numbering and A114C according to Kabat numbering;

each y is independently at least 1; and

n is at least 1;

wherein the modified CH3 domain comprises:

Trp, Tyr, Leu, Gln, or Glu at position 153;

Leu, Tyr, Met, Val, Phe or Trp at position 157;

Leu, Thr, His, Pro, or Phe at position 159;

Val, Pro, or an acidic amino acid at position 160;

Trp at position 161;

Val, Ser, Ala, or Gly at position 162;

Asn, Gly, His, Gln, Leu, Lys, Val, Phe, Ser, Ala, Asp, Thr or Glu at position 163;

Ser, Thr, Gln, Phe, Tyr or Val at position 164;

Gln, Phe, His, or Lys at position 165;

Glu, Ala, Ser, Leu, Thr, Pro or Asp at position 186;

Lys, Arg, Gly, or Pro at position 187;

Glu or Ser at position 188;

Thr, Asn or an acidic amino acid at position 189;

Trp, Tyr, His, or Phe at position 194;

Ser, Thr, Glu, Lys or Trp at position 197; and

Ser, Trp, Gly, Cys, Pro or Met at position 199;

as numbered with reference to SEQ ID NO:1.

72. The conjugate for use according to claim 71, wherein the modulation of target gene expression is gene knockdown or gene knockout.

73. A conjugate suitable for use in modulating the expression of a target gene in cells within the brain of a patient, wherein the conjugate comprises a conjugate of formula I:

$$P\text{-}(L\text{-}(X)_y)_n \qquad (I)$$

wherein,

each X is independently an oligonucleotide;

each L is independently a linking group;

P is a protein comprising 1) a modified CH3 constant domain that specifically binds to a transferrin receptor with an affinity of 3nM to 600nM, (ii) one or more NTFs or NBVRs, and (iii) one or more modified sites that facilitate the attachment of P to each L;

each y is independently at least 1; and

n is at least 1;

wherein the modified CH3 domain comprises:

Trp, Tyr, Leu, Gln, or Glu at position 153;

Leu, Tyr, Met, Val, Phe or Trp at position 157;

Leu, Thr, His, Pro, or Phe at position 159;

Val, Pro, or an acidic amino acid at position 160;

Trp at position 161;

Val, Ser, Ala, or Gly at position 162;

Asn, Gly, His, Gln, Leu, Lys, Val, Phe, Ser, Ala, Asp, Thr or Glu at position 163;

Ser, Thr, Gln, Phe, Tyr or Val at position 164;

Gln, Phe, His, or Lys at position 165;

Glu, Ala, Ser, Leu, Thr, Pro or Asp at position 186;

Lys, Arg, Gly, or Pro at position 187;

Glu or Ser at position 188;

Thr, Asn or an acidic amino acid at position 189;

Trp, Tyr, His, or Phe at position 194;

Ser, Thr, Glu, Lys or Trp at position 197; and

Ser, Trp, Gly, Cys, Pro or Met at position 199;

as numbered with reference to SEQ ID NO:1.

74. The conjugate for use according to claim 73, wherein the cells comprise at least two, three, four, or five cell types selected from the group consisting of: a neuron, an endothelial cell, an oligodendrocyte, an astrocyte, and a microglia, optionally wherein the neuron is an excitatory neuron or inhibitory neuron.

75. The conjugate for use according to claim 73 or 74, wherein the modulation of target gene expression is gene knockdown or gene knockout.

76. A conjugate suitable for use in transporting oligonucleotides across the blood brain barrier (BBB) of a patient and delivering the oligonucleotides to cells distributed throughout brain regions or the central nervous system, wherein the conjugate comprises a conjugate of formula I:

$$P\text{-}(L\text{-}(X)_y)_n \qquad (I)$$

wherein,

each X is independently an oligonucleotide;

each L is independently a linking group;

P is a protein comprising (i) a modified CH3 constant domain that specifically binds to a transferrin receptor with an affinity of 3nM to 600nM , (ii) one or more NTFs or NBVRs, and (iii) one or more modified sites that facilitate the attachment of P to each L;

each y is independently at least 1; and

n is at least 1;

wherein the modified CH3 domain comprises:

Trp, Tyr, Leu, Gln, or Glu at position 153;

Leu, Tyr, Met, Val, Phe or Trp at position 157;

Leu, Thr, His, Pro, or Phe at position 159;

Val, Pro, or an acidic amino acid at position 160;

Trp at position 161;

Val, Ser, Ala, or Gly at position 162;

Asn, Gly, His, Gln, Leu, Lys, Val, Phe, Ser, Ala, Asp, Thr or Glu at position 163;

Ser, Thr, Gln, Phe, Tyr or Val at position 164;

Gln, Phe, His, or Lys at position 165;

Glu, Ala, Ser, Leu, Thr, Pro or Asp at position 186;

Lys, Arg, Gly, or Pro at position 187;

Glu or Ser at position 188;

Thr, Asn or an acidic amino acid at position 189;

Trp, Tyr, His, or Phe at position 194;

Ser, Thr, Glu, Lys or Trp at position 197; and

Ser, Trp, Gly, Cys, Pro or Met at position 199;

as numbered with reference to SEQ ID NO:1.

77. The conjugate for use according to claim 76, wherein brain regions comprise at least one deep brain region.

78. The conjugate for use according to claim 76 or 77, wherein the oligonucleotide modulates the expression of a target gene.

79. The conjugate for use according to claim 78, wherein the modulation of target gene expression is gene knockdown or gene knockout.

80. A conjugate suitable for use in delivering oligonucleotides to the CNS cells of a patient, wherein the conjugate comprises a conjugate of formula I:

$$P\text{-}(L\text{-}(X)_y)_n \qquad (I)$$

wherein,

each X is independently an oligonucleotide;

each L is independently a linking group;

P is a protein comprising (i) a modified CH3 constant domain that specifically binds to a transferrin receptor with an affinity of 3nM to 600nM, and (ii) one or more NTFs or NBVRs;

each y is independently at least 1; and

n is at least 1; and,

wherein the modified CH3 domain comprises:

Trp, Tyr, Leu, Gln, or Glu at position 153;

Leu, Tyr, Met, Val, Phe or Trp at position 157;

Leu, Thr, His, Pro, or Phe at position 159;

Val, Pro, or an acidic amino acid at position 160;

Trp at position 161;

Val, Ser, Ala, or Gly at position 162;

Asn, Gly, His, Gln, Leu, Lys, Val, Phe, Ser, Ala, Asp, Thr or Glu at position 163;

Ser, Thr, Gln, Phe, Tyr or Val at position 164;

Gln, Phe, His, or Lys at position 165;

Glu, Ala, Ser, Leu, Thr, Pro or Asp at position 186;

Lys, Arg, Gly, or Pro at position 187;

Glu or Ser at position 188;

Thr, Asn or an acidic amino acid at position 189;

Trp, Tyr, His, or Phe at position 194;

Ser, Thr, Glu, Lys or Trp at position 197; and

Ser, Trp, Gly, Cys, Pro or Met at position 199;

as numbered with reference to SEQ ID NO:1; and

wherein delivery of the oligonucleotides to the CNS modulates gene expression throughout brain regions or the central nervous system.

81. The conjugate for use according to claim 80, wherein the brain regions comprise at least one deep brain region, optionally wherein the at least one deep brain region is selected from: striatum, thalamus, caudate putamen, substantia nigra, and brainstem.

82. The conjugate for use according to claim 80 or 81, wherein the cells within the brain regions comprise endothelial cells, neurons, astrocytes, oligodendrocytes, and microglia.

83. The conjugate for use according to claim 82, wherein the oligonucleotide modulates gene expression in the endothelial cells, neurons, astrocytes,

oligodendrocytes, and/or microglia, optionally wherein the oligonucleotide reduces gene expression in the cells by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99% or 100%, as compared to the expression without administering the oligonucleotide.

84. The conjugate for use according to any one of claims70-83, wherein the conjugate is formulated for intravenous administration.

85. The Fab-Fc dimer of any one of claims 13-22 or the conjugate of any one of claims 1-12, 19-42, and 50-52, wherein each NTF or NBVR comprises a heavy chain variable region and a light change variable region, does not specifically bind to a naturally occurring epitope in a subject, and comprises three heavy chain CDRs and three light chain CDRs, wherein:

(a) CDR-H1 comprises SEQ ID NO: 825,
CDR-H2 comprises SEQ ID NO: 827,
CDR-H3 comprises SEQ ID NO: 829,
CDR-L1 comprises SEQ ID NO: 819,
CDR-L2 comprises SEQ ID NO: 821, and
CDR-L3 comprises SEQ ID NO: 823; or

(b) CDR-H1 comprises SEQ ID NO: 826,
CDR-H2 comprises SEQ ID NO: 828 or 869,
CDR-H3 comprises SEQ ID NO: 829,
CDR-L1 comprises SEQ ID NO: 820,
CDR-L2 comprises SEQ ID NO: 822, and
CDR-L3 comprises SEQ ID NO: 824.

86. The Fab-Fc dimer or the conjugate of claim 85, wherein

(a) the heavy chain variable region comprises an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% identity to the amino acid sequence of SEQ ID NO: 837 and the light chain variable region comprises an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% identity to the amino acid sequence of SEQ ID NO: 832; or

(b) the heavy chain variable region comprises an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% identity to the amino acid sequence of SEQ ID NO: 853 and the light chain variable region comprises an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% identity to the amino acid sequence of SEQ ID NO: 851.

87. The Fab-Fc dimer or the conjugate of claim 86, wherein:

(a) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 837 and the light chain variable region comprises the amino acid sequence of SEQ ID NO: 832; or

(b) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 853 and the light chain variable region comprises the amino acid sequence of SEQ ID NO: 851.

88. The Fab-Fc dimer or the conjugate of claim 85, wherein the NTF comprises:

(a) a heavy chain comprising an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% identity to the amino acid sequence of any one of SEQ ID NOs: 838, 839, 840, 841, 844, 845, 846, and 847, and a light chain comprising an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% identity to the amino acid sequence of any one of SEQ ID NOs: 833 and 835; or

(b) a heavy chain comprising an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% identity to the amino acid sequence of any one of SEQ ID NOs: 854, 855, 856, 857, 859, 860, 861, and 862, and a light chain comprising an amino acid sequence having at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% identity to the amino acid sequence of any one of SEQ ID NOs: 850 and 852.

89. The Fab-Fc dimer or the conjugate of claim 88, wherein:

(a) the heavy chain comprises the amino acid sequence of any one of SEQ ID NO: 838, 839, 840, 841, 844, 845, 846, and 847, and the light chain comprises the amino acid sequence of any one of SEQ ID NO: 833 and 835; or

(b) the heavy chain comprises the amino acid sequence of any one of SEQ ID NOs: 854, 855, 856, 857, 859, 860, 861, and 862, and the light chain comprises the amino acid sequence of any one of SEQ ID NO: 850 and 852.

90. The Fab-Fc dimer or the conjugate of claim 89, wherein:

(a) the heavy chain comprises the amino acid sequence of SEQ ID NO: 838, 839, 840, or 841, and the light chain comprises the amino acid sequence of SEQ ID NO: 833;

(b) the heavy chain comprises the amino acid sequence of SEQ ID NO: 844, 845, 846, or 847, and the light chain comprises the amino acid sequence of SEQ ID NO: 833;

(c) the heavy chain comprises the amino acid sequence of SEQ ID NO: 838, 839, 840, or 841, and the light chain comprises the amino acid sequence of SEQ ID NO: 835;

(d) the heavy chain comprises the amino acid sequence of SEQ ID NO: 844, 845, 846, or 847, and the light chain comprises the amino acid sequence of SEQ ID NO: 835;

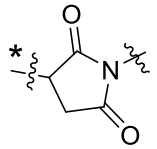
(e) the heavy chain comprises the amino acid sequence of SEQ ID NO: 854, 855, 856, or 857, and the light chain comprises the amino acid sequence of SEQ ID NO: 850;

(f) the heavy chain comprises the amino acid sequence of SEQ ID NO: 859, 860, 861, or 862, and the light chain comprises the amino acid sequence of SEQ ID NO: 850;

(g) the heavy chain comprises the amino acid sequence of SEQ ID NO: 854, 855, 856, or 857, and the light chain comprises the amino acid sequence of SEQ ID NO: 852; and,

(h) the heavy chain comprises the amino acid sequence of SEQ ID NO: 859, 860, 861, or 862, and the light chain comprises the amino acid sequence of SEQ ID NO: 852.

91. The pharmaceutical composition for use according to any one of claims 57-69, wherein the oligonucleotide is conjugated to the protein via a linker having the structure:



wherein, * denotes the attachment point to a sulfur atom of a modified site within P.