CLAIMS

1. A composition comprising a plurality of complexes, wherein each complex comprises an antibody covalently linked to one or more oligonucleotides, each oligonucleotide being covalently linked at a linkage site represented by a lysine (K) residue of the antibody,

wherein the antibody comprises a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region,

and wherein, at least 80% of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant region of each antibody.

2. The composition of claim 1, wherein at least 15% of the heavy chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant region of each antibody.

3. The composition of claim 1, wherein the complexes in the composition on average are covalently linked to 1-5 oligonucleotides, optionally wherein the complexes in the composition on average are covalently linked to about 2 oligonucleotides.

4. A composition comprising a plurality of complexes, wherein each complex comprises an antibody covalently linked to one or more oligonucleotides, each oligonucleotide being covalently linked at a linkage site represented by a lysine (K) residue of the antibody,

wherein the antibody comprises a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region,

wherein at least 80% of light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by a lysine (K) residue in a sequence motif DYEKHKVYA (SEQ ID NO: 53) of the light chain constant region of each antibody.

5. The composition of claim 4, wherein at least 15% of the heavy chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by the lysine (K) residue in a sequence motif VNHKPSN (SEQ ID NO: 58) of the heavy chain constant region of each antibody.

6. The composition of claim 4, wherein the complexes in the composition on average are covalently linked to 1-5 oligonucleotides, optionally wherein the complexes in the composition on average are covalently linked to about 2 oligonucleotides.

7. The composition of claim 1, wherein the antibody is an anti-transferrin receptor (TfR1) antibody comprising: a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14, a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NOs: 6 or 16.

8. The composition of claim 4, wherein the antibody is an anti-transferrin receptor (TfR1) antibody comprising: a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14, a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NOs: 6 or 16.

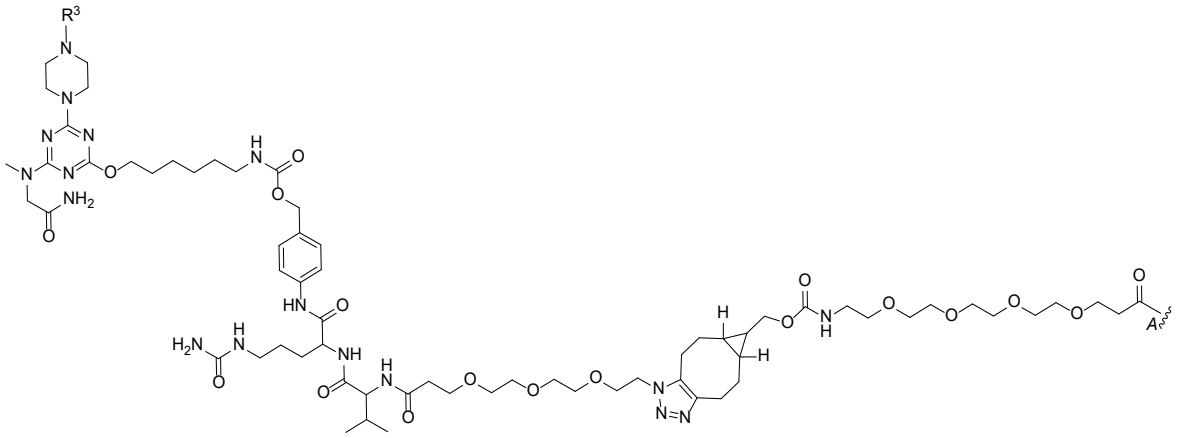
9. The composition of claim 1, wherein the oligonucleotide is a phosphorodiamidate morpholino oligomer (PMO).

10. The composition of claim 4, wherein the oligonucleotide is a phosphorodiamidate morpholino oligomer (PMO).

11. The composition of claim 1, wherein the oligonucleotide comprises a region of complementarity to a dystrophin (DMD) RNA.

12. The composition of claim 4, wherein the oligonucleotide comprises a region of complementarity to a dystrophin (DMD) RNA.

13. A composition comprising a plurality of complexes of the formula (I): $[R^1]_{n1}$-R^2, wherein each R^1 independently comprises a group of the formula (Ia):



(Ia),

wherein R^2 comprises an anti-transferrin receptor (TfR1) antibody comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region; and wherein the anti-TfR1 antibody comprises: a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14, a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as

set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NOs: 6 or 16;

wherein R^3 comprises a phosphorodiamidate morpholino oligomer (PMO) comprising a nucleobase sequence of CTCCAACATCAAGGAAGATGGCATTTCTAG (SEQ ID NO: 21);

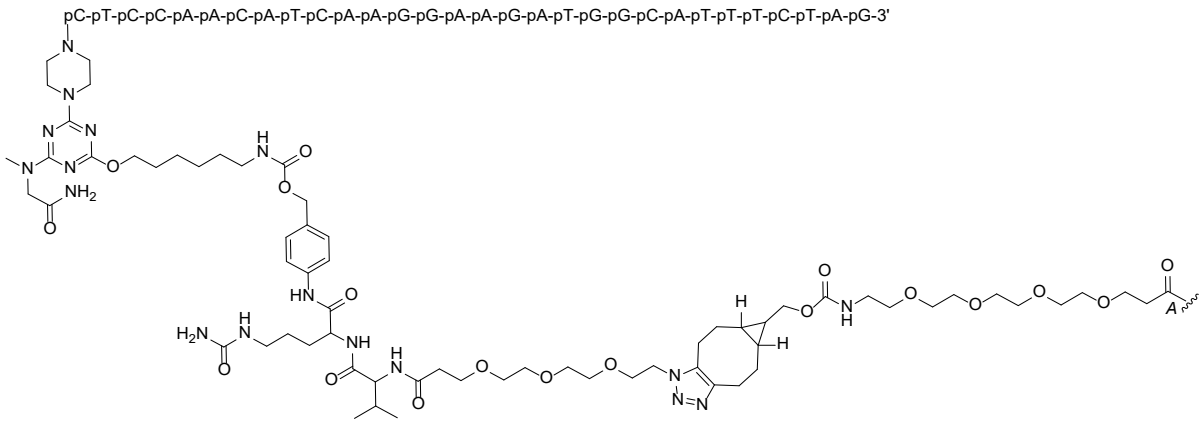
wherein each R^1 is covalently linked at attachment point *A* to R^2 via a linkage site represented by a lysine (K) residue of the anti-TfR1 antibody, and wherein, at least 80% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant region of each antibody; and

wherein in each complex, n1 is independently an integer of one or greater representing the number of instances of R^1, optionally wherein the average value of n1 of complexes in the composition is in the range of 1 to 5.

14. The composition of claim 13, wherein 85%-95% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant region of each antibody, and/or
wherein at least 15% of the heavy chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant region of each antibody.

15. The composition of claim 13, wherein the average value of n1 of complexes in the composition is 2 or approximately 2.

16. A composition comprising a plurality of complexes of the formula (I): $[R^1]_{n1}$-R^2, wherein each R^1 independently comprises a group of the formula (Ib):



(Ib),

in which -p is a phosphorodiamidate linkage of a phosphorodiamidate morpholino oligomer (PMO), and wherein the PMO comprises a base sequence of CTCCAACATCAAGGAAGATGGCATTTCTAG (SEQ ID NO: 21);

wherein R^2 comprises an anti-transferrin receptor (TfR1) antibody comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region; and wherein the anti-TfR1 antibody comprises: a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14, a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NOs: 6 or 16; and

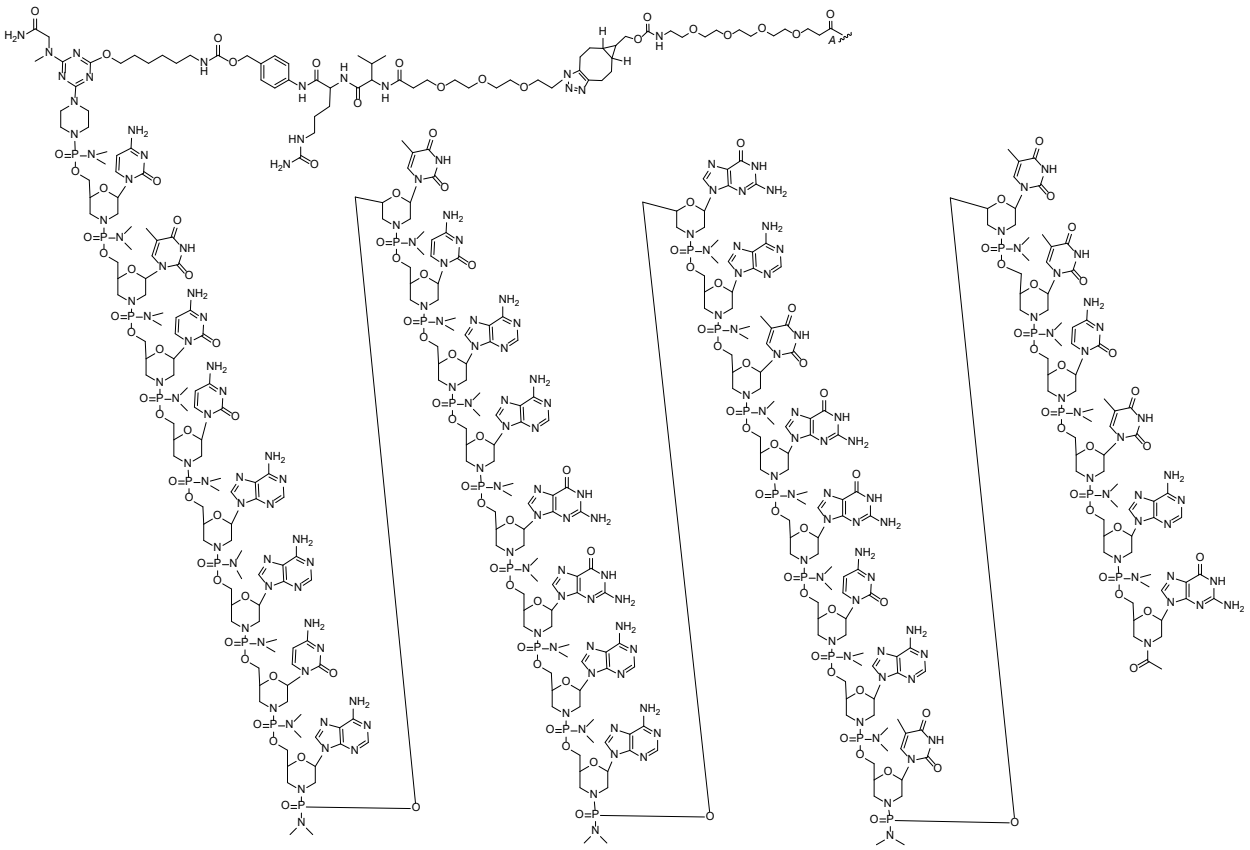
wherein each R^1 is covalently linked at attachment point *A* to R^2 via a linkage site represented by a lysine (K) residue of the anti-TfR1 antibody, and wherein, at least 80% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant region of each antibody; and

wherein in each complex, n1 is independently an integer of one or greater representing the number of instances of R^1, and optionally wherein the average value of n1 of the complexes of the composition is in the range of 1 to 5.

17. The composition of claim 16, wherein 85%-95% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant region of each antibody, and/or
wherein at least 15% of the heavy chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant region of each antibody.

18. The composition of claim 16, wherein the average value of n1 of complexes in the composition is 2 or approximately 2.

19. A composition comprising a plurality of complexes of the formula (I): $[R^1]_{n1}$-R^2, wherein: each R^1 comprises a group of the formula (Ic):



(Ic),

wherein R^2 comprises an anti-transferrin receptor (TfR1) antibody comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region; and wherein the anti-TfR1 antibody comprises: a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14, a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NOs: 6 or 16; and

wherein each R^1 is covalently linked at attachment point *A* to R^2 via a linkage site represented by a lysine (K) residue of the anti-TfR1 antibody, and wherein, at least 80% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant region of each antibody; and

wherein in each complex, n1 is independently an integer of one or greater representing the number of instances of R^1, and optionally wherein the average value of n1 of the complexes of the composition is in the range of 1 to 5.

20. The composition of claim 19, wherein 85%-95% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant region of each antibody, and/or

wherein at least 15% of the heavy chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant region of each antibody.

21. The composition of claim 19, wherein the average value of n1 of complexes in the composition is 2 or approximately 2.

22. The composition of any one of claims 1-21, wherein the antibody is a Fab fragment, a full-length IgG, a Fab' fragment, or a F(ab')2 fragment.

23. The composition of any one of claims 1-21, wherein the antibody is a Fab fragment.

24. The composition of any one of claims 1-21, wherein the VH comprises an amino acid sequence at least 85% identical to SEQ ID NO: 17; and/or wherein the VL comprises an amino acid sequence at least 85% identical to SEQ ID NO: 18, optionally wherein the VH comprises the amino acid sequence of SEQ ID NO: 17 and the VL comprises the amino acid sequence of SEQ ID NO: 18.

25. The composition of claim 24, wherein the antibody is a Fab fragment.

26. The composition of claim 24, wherein the heavy chain comprises an N-terminal pyroglutamate.

27. The composition of any one of claims 1-21, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 19 and the light chain comprises the amino acid sequence of SEQ ID NO: 20.

28. The composition of claim 27, wherein the antibody is a Fab fragment.

29. The composition of claim 27, wherein the heavy chain comprises an N-terminal pyroglutamate.

30. The composition of any one of claims 1-21 for use in promoting expression or activity of a dystrophin protein in a subject.

31. The composition for use of claim 30, wherein the subject has a mutated dystrophin allele, optionally wherein the mutated dystrophin allele comprises a mutation amenable to

exon 51 skipping, or wherein the mutated dystrophin allele comprises a frameshift mutation in exon 51.

32. The composition for use of claim 30, wherein the complexes promote expression or activity of dystrophin protein in the subject, optionally wherein the dystrophin protein is a truncated dystrophin protein.

33. The composition for use of claim 30, wherein the subject is a human.

34. The composition of any one of claims 1-21 for use in treating Duchenne Muscular Dystrophy (DMD) in a subject.

35. The composition for use of claim 34, wherein the subject has a mutated dystrophin allele, optionally wherein the mutated dystrophin allele comprises a mutation amenable to exon 51 skipping, or wherein the mutated dystrophin allele comprises a frameshift mutation in exon 51.

36. The composition for use of claim 34, wherein the complexes promote expression or activity of dystrophin protein in the subject, optionally wherein the dystrophin protein is a truncated dystrophin protein.

37. The composition for use of claim 34, wherein the subject is a human.

38. The composition of claim 27 for use in treating Duchenne Muscular Dystrophy (DMD) in a subject, optionally wherein the subject is a human.

39. The composition for use of claim 38, wherein the subject has a mutated dystrophin allele, optionally wherein the mutated dystrophin allele comprises a mutation amenable to exon 51 skipping, or wherein the mutated dystrophin allele comprises a frameshift mutation in exon 51.

40. The composition for use of claim 38, wherein the complexes promote expression or activity of dystrophin protein in the subject, optionally wherein the dystrophin protein is a truncated dystrophin protein.