CLAIMS

What is claimed is:

1. A complex comprising an anti-transferrin receptor antibody covalently linked to a 5′ end or a 3′ end of an oligonucleotide,

wherein the anti-transferrin receptor antibody binds in the range of C89 to F760 of human transferrin receptor protein 1 (TfR1) having an amino acid sequence as set forth in SEQ ID NO: 1;

wherein the oligonucleotide comprises one or more modifications and a region of complementarity of at least 15 nucleotides in length to the nucleotide sequence as set forth in SEQ ID NO: 52, wherein the oligonucleotide is in the range of 15-30 nucleotides in length;

wherein the one or more modifications comprise a 2′-modified nucleoside selected from the group consisting of: 2′-O-methyl nucleoside, a 2′-fluoro nucleoside, a 2′-O-methoxyethyl nucleoside, and 2′,4′-bridged nucleosides, and combinations thereof, and/or comprise a modified backbone selected from a backbone comprising one or more phosphorothioate linkages and a phosphorodiamidate morpholino backbone.

2. The complex of claim 1, wherein the region of complementarity is at least 16 nucleotides in length.

3. The complex of claim 1 or 2, wherein the region of complementarity is at least 17 nucleotides in length.

4. The complex of any one of claims 1-3, wherein the region of complementarity is at least 18 nucleotides in length.

5. The complex of any one of claims 1-4, wherein the region of complementarity is at least 19 nucleotides in length.

6. The complex of any one of claims 1-5, wherein the region of complementarity is at least 20 nucleotides in length.

7. The complex of any one of claims 1-6, wherein the oligonucleotide is a phosphorodiamidate morpholino oligomer (PMO).

8. The complex of any one of claims 1-7, wherein the oligonucleotide comprises a modified backbone comprising one or more phosphorothioate linkages.

9. The complex of any one of claims 1-8, wherein the anti-transferrin receptor antibody further comprises one or more sugar or carbohydrate molecules.

10. The complex of claim 9, wherein the one or more sugar or carbohydrate molecules comprise a mannose unit, a glucose unit, an N-acetylglucosamine unit, an N-acetylgalactosamine unit, a galactose unit, a fucose unit, a phospholipid unit, or combinations thereof.

11. The complex of any one of claims 1-10, wherein the oligonucleotide is covalently linked to a lysine in the anti-transferrin receptor antibody via a cleavable linker.

12. The complex of claim 11, wherein the cleavable linker comprises a valine-citrulline sequence.

13. The complex of claim 12, wherein the complex is obtained by a cycloaddition reaction between an azide and an alkyne to form a triazole.

14. The complex of claim 13, wherein, prior to the cycloaddition reaction, the azide is covalently linked to the valine-citrulline sequence of the cleavable linker that is covalently linked to the oligonucleotide and the alkyne is provided in a bicyclononyne moiety that further covalently links to the anti-transferrin receptor antibody.

15. The complex of any one of claims 11-14, wherein the cleavable linker further comprises one or more polyethylene glycol units.

16. The complex of any one of claims 1-15, wherein the anti-transferrin receptor antibody is in the form of a ScFv, Fab fragment, Fab′ fragment, F(ab′)2 fragment, or Fv fragment.

17. The complex of any one of claims 1-16, wherein the anti-transferrin receptor antibody is in the form of a Fab fragment.

18. The complex of any one of claims 1-17, wherein the oligonucleotide is a double-stranded molecule comprising the single strand hybridized to a complementary strand.

19. A complex comprising an anti-transferrin receptor antibody covalently linked to a 5′ end or a 3′ end of an oligonucleotide,

wherein the anti-transferrin receptor antibody binds in the range of C89 to F760 of human transferrin receptor protein 1 (TfR1) having an amino acid sequence as set forth in SEQ ID NO: 1;

wherein the oligonucleotide comprises one or more modifications and comprises a region of complementarity of at least 15 nucleotides in length to an RNA encoded by a gene associated with a disease associated with muscle weakness, wherein the oligonucleotide is in the range of 15-30 nucleotides in length;

wherein the one or more modifications comprise a 2′-modified nucleoside selected from the group consisting of: 2′-O-methyl nucleoside, a 2′-fluoro nucleoside, a 2′-O-methoxyethyl nucleoside, and 2′,4′-bridged nucleosides, and combinations thereof, and/or comprise a modified backbone selected from a backbone comprising one or more phosphorothioate linkages and a phosphorodiamidate morpholino backbone.

20. The complex of claim 19, wherein the anti-transferrin receptor antibody comprises a CDRH1, a CDRH2, a CDRH3, a CDRL1, a CDRL2, and a CDRL3 of an antibody selected from the group consisting of: OKT9, M11, M23, M27, B84, 7A4, 8A2, 15D2, 10D11, 7B10, 15G11, 16G5, 13C3, 16G4, 16F6, 7G7, 4C2, 1B12, 13D4, 8D3, OX26, DF1513, 1A1B2, 66IG10, MEM-189, JF0956, 29806, TFRC/1818, 1E6, 66Ig10, TFRC/1059, Q1/71, 23D10, 13E4, TFRC/1149, ER-MP21, YTA74.4, BU54, 2B6, RI7 217, BA120g, LUCA31, B3/25, T58/30, R17 217.1.3, 5E9C11, BE0023, BK19.9, B3/25, T56/14, and T58/1.

21. The complex of claim 19 or 20, wherein the oligonucleotide comprises a modified backbone comprising one or more phosphorothioate linkages.

22. The complex of any one of claims 19-21, wherein the anti-transferrin receptor antibody further comprises one or more sugar or carbohydrate molecules.

23. The complex of claim 22, wherein the one or more sugar or carbohydrate molecules comprise a mannose unit, a glucose unit, an N-acetylglucosamine unit, an N-acetylgalactosamine unit, a galactose unit, a fucose unit, a phospholipid unit, or combinations thereof.

24. The complex of any one of claims 19-23, wherein the oligonucleotide is single stranded.

25. The complex of any one of claims 19-23, wherein the oligonucleotide is double stranded.

26. The complex of any one of claims 19-25, wherein the gene associated with a disease associated with muscle weakness is DUX4.

27. The complex of any one of claims 19-25, wherein the gene associated with a disease associated with muscle weakness is Murf1.

28. The complex of any one of claims 19-25, wherein the disease associated with muscle weakness is a muscular dystrophy.

29. The complex of any one of claims 1-28 for use as a medicament for reducing expression levels of DUX4 in muscle cells of a subject.

30. The complex of claim 29, wherein the muscle cells are skeletal muscle cells, cardiac muscle cells, or smooth muscle cells.

31. The complex of any one of claims 1-28 for use as a medicament for treating facioscapulohumeral muscular dystrophy (FSHD) in a subject.

32. The complex of any one of claims 29-31, wherein the complex is formulated for intravenous administration.

33. The complex of any one of claims 29-32, wherein the subject is human.

34. Use of the complex of any one of claims 1-28 for the manufacture of a medicament for reducing expression levels of DUX4 in muscle cells of a subject.

35. The use of claim 34, wherein the muscle cells are skeletal muscle cells, cardiac muscle cells, or smooth muscle cells.

36. Use of the complex of any one of claims 1-28 for the manufacture of a medicament for treating facioscapulohumeral muscular dystrophy (FSHD) in a subject.

37. The use of any one of claims 34-36, wherein the complex is formulated for intravenous administration.

38. The use of any one of claims 34-37, wherein the subject is human.