CLAIMS

What is claimed is:

1. A complex comprising a muscle-targeting agent covalently linked to a molecular payload configured to modulate expression or activity of a muscle disease gene that encodes a non-secreted product that functions within muscle cells,

wherein the muscle-targeting agent specifically binds to an internalizing cell surface receptor on muscle cells,

wherein the muscle-targeting agent is a muscle-targeting antibody, wherein the muscle-targeting antibody specifically binds to an extracellular epitope of a transferrin receptor,

wherein the extracellular epitope of the transferrin receptor comprises an epitope of the apical domain of the transferrin receptor.

2. The complex of claim 1, wherein the muscle-targeting antibody specifically binds to an epitope of a sequence within amino acids C89 to F760 of SEQ ID NO: 1-3.

3. The complex of claim 1 or claim 2, wherein the muscle-targeting agent is covalently linked to the molecular payload via a linker, wherein the linker is covalently linked to the muscle-targeting agent and/or the molecular payload by a cycloaddition reaction between an azide and an alkyne to form a triazole, wherein the azide or the alkyne is located on the muscle-targeting agent, the molecular payload, or the linker and wherein the alkyne is a bicyclononyne or a substituted bicyclononyne.

4. The complex of any one of claims 1 to 3, wherein the equilibrium dissociation constant (Kd) of binding of the muscle-targeting antibody to the transferrin receptor is in a range from 10^{-11} M to 10^{-6} M.

5. The complex of any one of claims 1 to 4, wherein the muscle targeting antibody is a humanized antibody.

6. The complex of any one of claims 1 to 5, wherein the complex is configured to promote transferrin receptor mediated internalization of the molecular payload into a muscle cell.

7. The complex of any one of 1 to 6, wherein the muscle-targeting antibody is in the form of a ScFv, a Fab fragment, Fab' fragment, $F(ab')_2$ fragment, or Fv fragment.

8. The complex of any one of claims 1 to 7, wherein the muscle-targeting antibody is a Fab fragment.

9. The complex of any one of claims 1 to 8, wherein the muscle disease gene is DMPK.

10. The complex of any one of claims 1 to 8, wherein the muscle disease gene is DMD.

11. The complex of any one of claims 1 to 8, wherein the muscle disease gene is DUX4.

12. The complex of any one of claims 1 to 11, wherein the molecular payload comprises an oligonucleotide.

13. The complex of claim 12, wherein the oligonucleotide is an antisense oligonucleotide or an siRNA.

14. The complex of claim 12 or claim 13, wherein the oligonucleotide comprises a region of complementarity to an RNA encoded by the muscle disease gene.

15. The complex of any one of claims 12 to 14, wherein the oligonucleotide is 15 to 35 nucleotides in length.

16. The complex of any one of claims 12 to 15, wherein the oligonucleotide is 16 to 30 nucleotides in length.

17. The complex of any one of claims 14 to 16, wherein the region of complementarity is at least 12 nucleotides in length.

18. The complex of any one of claims 14 to 17, wherein the region of complementarity is at least 16 nucleotides in length.

19. The complex of any one of claims 12 to 18, wherein the oligonucleotide comprises one or more modified nucleosides.

20. The complex of claim 19, wherein the one or more modified nucleosides comprise 2′-modified nucleosides.

21. The complex of claim 20, wherein the 2′-modified nucleosides are selected from the group consisting of: 2′-O-methyl, 2′-fluoro, 2′-O-methoxyethyl, 2′, 4′-bridged nucleosides, and combinations thereof.

22. The complex of any one of claims 12 to 21, wherein the oligonucleotide comprises at least one modified internucleoside linkage.

23. The complex of claim 22, wherein the at least one modified internucleoside linkage is a phosphorothioate linkage.

24. The complex of any one of claims 12 to 23, wherein the oligonucleotide comprises one or more phosphorodiamidate morpholinos.

25. The complex of any one of claims 12 to 19 and 22, wherein the oligonucleotide is a phosphorodiamidate morpholino oligomer (PMO).

26. The complex of any one of claims 1 to 25, wherein the muscle-targeting agent is covalently linked to the molecular payload via a cleavable linker.

27. The complex of claim 26, wherein the cleavable linker comprises a protease-sensitive linker.

28. The complex of claim 27, wherein the protease-sensitive linker comprises a sequence cleavable by a lysosomal protease and/or an endosomal protease.

29. The complex of claim 28, wherein the protease-sensitive linker comprises a valine-citrulline sequence.

30. The complex of any one of claims 1 to 25, wherein the muscle-targeting agent is covalently linked to the molecular payload via a non-cleavable linker.

31. The complex of claim 30, wherein the non-cleavable linker comprises an optionally substituted alkyl group.

32. The complex of any one of claims 26 to 31, wherein the cleavable linker or the non-cleavable linker comprises a polyethylene glycol spacer.

33. The complex of any one of claims 1 to 32, wherein the muscle-targeting agent is covalently linked to the molecular payload via conjugation to a lysine residue of the muscle-targeting agent.

34. The complex of any one of claims 1 to 32, wherein the muscle-targeting agent is covalently linked to the molecular payload via conjugation to a cysteine residue of the muscle-targeting agent.

35. The complex of any one of claims 1 to 34 for use in therapy.

36. The complex of any one of claims 1 to 34 for use in treating a subject having a muscle disease, wherein an effective amount of the complex is to be administered to the subject.

37. The complex for use of claim 36, wherein the muscle disease is a disease selected from the group consisting of: Adult Pompe Disease, Centronuclear myopathy (CNM), Duchenne Muscular Dystrophy, Facioscapulohumeral Muscular Dystrophy (FSHD), Familial Hypertrophic Cardiomyopathy, Fibrodysplasia Ossificans Progressiva (FOP), Friedreich's Ataxia (FRDA), Inclusion Body Myopathy 2, Laing Distal Myopathy, Myofibrillar Myopathy, Myotonia Congenita (autosomal dominant form, Thomsen Disease), Myotonic Dystrophy Type I, Myotonic Dystrophy Type II, Myotubular Myopathy, Oculopharyngeal Muscular Dystrophy, and Paramyotonia Congenita.

38. The complex for use of claim 36, wherein the muscle disease is Duchenne Muscular Dystrophy.

39. The complex for use of claim 36, wherein the muscle disease is Myotonic Dystrophy Type I.

40. The complex for use of claim 36, wherein the muscle disease is Facioscapulohumeral Muscular Dystrophy (FSHD).

41. The complex for use of any one of claims 36-40, wherein the complex is to be intravenously administered to the subject.

42. The complex of any one of claims 12 to 34 for use in delivering an oligonucleotide to a cell in a subject.

43. The complex for use of claim 42, wherein the cell is skeletal muscle cell, cardiac muscle cell, or smooth muscle cell.

44. The complex for use of claim 42 or claim 43, wherein the subject is human.

45. The complex for use of claim 42 or claim 43, wherein the subject is cynomolgus.