

CLAIMS

What is claimed is:

1. A complex comprising an anti-transferrin receptor antibody covalently linked, via a protease-sensitive linker, to an oligonucleotide that targets a DMPK RNA, wherein the complex is configured for delivering the oligonucleotide into muscle cells,
wherein the oligonucleotide is 15, 16, 17, or 18 nucleotides in length and comprises a region of complementarity that is fully complementary, along a length of at least 14 contiguous nucleotides, to a coding region of a DMPK sequence as set forth in SEQ ID NO: 15,
wherein the oligonucleotide is configured to bring about degradation of the DMPK RNA via RNase H mediated degradation, wherein the oligonucleotide comprises a 5'-X-Y-Z-3' formula, wherein X and Z are flanking regions comprising one or more 2'-modified nucleosides selected from the group consisting of: 2'-O-methyl, 2'-fluoro, 2'-O-methoxyethyl, and 2',4'-bridged nucleosides, wherein Y is a gap region and each nucleoside in Y is a 2'-deoxyribonucleoside, and wherein the oligonucleotide comprises one or more phosphorothioate internucleoside linkages; and
wherein the anti-transferrin receptor antibody binds an extracellular domain of a transferrin receptor protein 1 (TfR1).
2. The complex of claim 1, wherein the 5' end of the oligonucleotide is covalently linked to a lysine in the anti-transferrin receptor antibody via the protease-sensitive linker.
3. The complex of claim 1 or 2, wherein the protease-sensitive linker comprises a cleavage site of a lysosomal and/or endosomal protease.
4. The complex of claim 3, wherein the lysosomal and/or endosomal protease is a cathepsin protease.
5. The complex of any one of claims 1-4, wherein the protease-sensitive linker comprises a valine-citrulline sequence.

6. The complex of any one of claims 1-5, wherein the protease sensitive linker comprises a triazole obtained by a cycloaddition reaction between an azide and an alkyne.
7. The complex of claim 6, wherein prior to the cycloaddition reaction, the azide is located on the protease sensitive linker that is covalently linked to the 5' end of the oligonucleotide and the alkyne is provided in a bicyclononyne moiety, and wherein the protease-sensitive linker further covalently links to the anti-transferrin receptor antibody.
8. The complex of claim 6 or 7, wherein the protease-sensitive linker further comprises one or more polyethylene glycol units.
9. The complex of any one of claims 1-8, wherein each nucleotide in X and Z is a 2'-modified nucleoside.
10. The complex of any one of claims 1-9, wherein each internucleoside linkage in the oligonucleotide is a phosphorothioate linkage.
11. The complex of any one of claims 1-10, wherein the oligonucleotide is 16, 17 or 18 nucleotides in length.
12. The complex of any one of claims 1-11, wherein the region of complementarity is fully complementary, along a length of at least 16 contiguous nucleotides, to the coding region of the DMPK sequence.
13. The complex of any one of claims 1-12, wherein the anti-transferrin receptor antibody is in the form of a ScFv, Fab fragment, Fab' fragment, F(ab')₂ fragment, or Fv fragment.
14. The complex of any one of claims 1-13, wherein the anti-transferrin receptor antibody is in the form of a Fab fragment.

15. The complex of any one of claims 1-14, wherein the DMPK RNA comprises 38 to 200 repeating CUG units.
16. The complex of any one of claims 1-15, wherein administration of the complex to a subject results in reduction of DMPK RNA level by at least 50% in muscle cells of the subject.
17. The complex of any one of claims 1-16, wherein administration of the complex to a subject rescues splicing defects in muscle cells of the subject.
18. The complex of any one of claims 1-17, wherein the muscle cells are skeletal muscle cells, cardiac muscle cells, or smooth muscle cells.
19. The complex of any one of claims 16-18, wherein the subject is human.
20. The complex of any one of claims 16-18, wherein the subject is cynomolgus.
21. The complex of any one of claims 1-20, wherein the DMPK RNA contains a disease-associated repeat sequence in the 3'-UTR that is associated with myotonic dystrophy type 1 (DM1).
22. The complex of any one of claims 1-21 for use as a medicament for reducing expression levels of DMPK in muscle cells of a subject.
23. The complex of any one of claims 1-21 for use as a medicament for treating myotonic dystrophy type 1 (DM1) in a subject.
24. The complex of claim 22 or 23, wherein the complex is formulated for intravenous administration.
25. Use of the complex of any one of claims 1-21 for the manufacture of a medicament for reducing expression levels of DMPK in muscle cells of a subject.

26. Use of the complex of any one of claims 1-21 for the manufacture of a medicament for treating myotonic dystrophy type 1 (DM1) in a subject.

27. The use of claim 25 or 26, wherein the complex is formulated for intravenous administration.