MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR TREATING DYSTROPHINOPATHIES

RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application Serial No. 63/220016, entitled "MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR TREATING DYSTROPHINOPATHIES", filed on July 9, 2021, and to U.S. Provisional Application Serial No. 63/316466, entitled "MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR TREATING DYSTROPHINOPATHIES", filed on March 4, 2022; the contents of each of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present application relates to targeting complexes for delivering molecular payloads (e.g., oligonucleotides) to cells and uses thereof, particularly uses relating to treatment of disease.

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING

[0003] The contents of the electronic sequence listing (D082470055WO00-SEQ-COB.xml; Size: 1,054,275 bytes; and Date of Creation: July 7, 2022) are herein incorporated by reference in their entirety.

BACKGROUND OF INVENTION

[0004] Dystrophinopathies are a group of distinct neuromuscular diseases that result from mutations in the gene encoding dystrophin. Dystrophinopathies include Duchenne muscular dystrophy, Becker muscular dystrophy, and X-linked dilated cardiomyopathy. The DMD gene ("DMD"), which encodes dystrophin, is a large gene, containing 79 exons and about 2.6 million total base pairs. Numerous mutations in DMD, including exonic frameshift, deletion, substitution, and duplicative mutations, are able to diminish the expression of functional dystrophin, leading to dystrophinopathies. Several agents that target exons of human DMD have been approved by the U.S. Food and Drug Administration (FDA), including casimersen, viltolarsen, golodirsen, and eteplirsen. Of these, viltolarsen and golodirsen target exon 53.

SUMMARY OF INVENTION

[0005] According to some aspects, the disclosure provides complexes that target muscle cells for purposes of delivering molecular payloads to those cells, as well as molecular payloads that can be used therein. In some embodiments, complexes provided herein are particularly useful for delivering molecular payloads that increase or restore expression or activity of functional dystrophin protein. In some embodiments, complexes comprise oligonucleotide based molecular payloads that promote expression of functional dystrophin protein through an in-frame exon skipping mechanism or suppression of stop codons, such as by facilitating skipping of DMD exon 53. In some embodiments, molecular payloads provided herein are useful for facilitating exon skipping in a DMD sequence, such as skipping of DMD exon 53. Accordingly, in some embodiments, complexes provided herein comprise muscle-targeting agents (e.g., muscle targeting antibodies) that specifically bind to receptors on the surface of muscle cells for purposes of delivering molecular payloads to the muscle cells. In some embodiments, the complexes are taken up into the cells via a receptor mediated internalization, following which the molecular payload may be released to perform a function inside the cells. For example, complexes engineered to deliver oligonucleotides may release the oligonucleotides such that the oligonucleotides can promote expression of functional dystrophin protein (e.g., through an exon skipping mechanism, such as by facilitating skipping of DMD exon 53) in the muscle cells. In some embodiments, the oligonucleotides are released by endosomal cleavage of covalent linkers connecting oligonucleotides and muscle-targeting agents of the complexes. Complexes and molecular payloads provided herein can be used for treating subjects having a mutated DMD gene, such as a mutated DMD gene that is amenable to exon 53 skipping.

[0006] According to some aspects, complexes comprising an anti-transferrin receptor 1 (TfR1) antibody covalently linked to an oligonucleotide configured for inducing skipping of exon 53 in a DMD pre-mRNA are provided herein, wherein the oligonucleotide comprises a region of complementarity that is complementary with at least 8 consecutive nucleotides of any one of SEQ ID NOs: 224, 206, 209, 212, 277, 214, 207, 208, 205, 160-204, 210, 211, 213, 215-223, 225-276, and 278-334.

[0007] In some embodiments, the oligonucleotide comprises a region of complementarity that is complementary with at least 8 consecutive nucleotides of any one of SEQ ID NOs: 212, 224, and 209.

[0008] In some embodiments, the oligonucleotide comprises a region of complementarity that is complementary with at least 8 consecutive nucleotides of any one of SEQ ID NOs: 206, 277, and 205.

[0009] In some embodiments, the oligonucleotide comprises a region of complementarity that is complementary with at least 8 consecutive nucleotides of any one of SEQ ID NOs: 206, 224, and 209.

[00010] In some embodiments, the oligonucleotide comprises a region of complementarity that is complementary with at least 8 consecutive nucleotides of any one of SEQ ID NOs: 214, 207, and 208.

[00011] In some embodiments, the oligonucleotide comprises a region of complementarity that is complementary with at least 8 consecutive nucleotides of any one of SEQ ID NOs: 212, 206, and 209.

[00012] In some embodiments, the oligonucleotide comprises a region of complementarity that is complementary with at least 8 consecutive nucleotides of any one of SEQ ID NOs: 214, 207, and 205.

[00013] In some embodiments, the oligonucleotide comprises a region of complementarity that is complementary with at least 8 consecutive nucleotides of any one of SEQ ID NOs: 277, 214, and 208.

[00014] In some embodiments, the anti-TfR1 antibody comprises:

(i) a heavy chain complementarity determining region 1 (CDR-H1) of SEQ ID NO: 33, a heavy chain complementarity determining region 2 (CDR-H2) of SEQ ID NO: 34, a heavy chain complementarity determining region 3 (CDR-H3) of SEQ ID NO: 35, a light chain complementarity determining region 1 (CDR-L1) of SEQ ID NO: 36, a light chain complementarity determining region 2 (CDR-L2) of SEQ ID NO: 37, and a light chain complementarity determining region 3 (CDR-L3) of SEQ ID NO: 32;

(ii) a CDR-H1 of SEQ ID NO: 7, a CDR-H2 of SEQ ID NO: 8, a CDR-H3 of SEQ ID NO: 9, a CDR-L1 of SEQ ID NO: 10, a CDR-L2 of SEQ ID NO: 11, and a CDR-L3 of SEQ ID NO: 6;

(iii) a CDR-H1 of SEQ ID NO: 7, a CDR-H2 of SEQ ID NO: 20, a CDR-H3 of SEQ ID NO: 9, a CDR-L1 of SEQ ID NO: 10, a CDR-L2 of SEQ ID NO: 11, and a CDR-L3 of SEQ ID NO: 6;

(iv) a CDR-H1 of SEQ ID NO: 7, a CDR-H2 of SEQ ID NO: 24, a CDR-H3 of SEQ ID NO: 9, a CDR-L1 of SEQ ID NO: 10, a CDR-L2 of SEQ ID NO: 11, and a CDR-L3 of SEQ ID NO: 6;

(v) a CDR-H1 of SEQ ID NO: 51, a CDR-H2 of SEQ ID NO: 52, a CDR-H3 of SEQ ID NO: 53, a CDR-L1 of SEQ ID NO: 54, a CDR-L2 of SEQ ID NO: 55, and a CDR-L3 of SEQ ID NO: 50;

(vi) a CDR-H1 of SEQ ID NO: 64, a CDR-H2 of SEQ ID NO: 52, a CDR-H3 of SEQ ID NO: 53, a CDR-L1 of SEQ ID NO: 54, a CDR-L2 of SEQ ID NO: 55, and a CDR-L3 of SEQ ID NO: 50; or

(vii) a CDR-H1 of SEQ ID NO: 67, a CDR-H2 of SEQ ID NO: 52, a CDR-H3 of SEQ ID NO: 53, a CDR-L1 of SEQ ID NO: 54, a CDR-L2 of SEQ ID NO: 55, and a CDR-L3 of SEQ ID NO: 50.

[00015] In some embodiments, the anti-TfR1 antibody comprises:

(i) a heavy chain variable region (VH) comprising an amino acid sequence at least 85% identical to SEQ ID NO: 76; and/or a light chain variable region (VL) comprising an amino acid sequence at least 85% identical to SEQ ID NO: 75;

(ii) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 69; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 70;

(iii) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 71; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 70;

(iv) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 72; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 70;

(v) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 73; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 74;

(vi) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 73; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 75;

(vii) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 76; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 74;

(viii) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 77; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 78;

(ix) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 79; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 80; or

(x) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 77; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 80.

[00016] In some embodiments, the anti-TfR1 antibody comprises:

(i) a VH comprising the amino acid sequence of SEQ ID NO: 76 and a VL comprising the amino acid sequence of SEQ ID NO: 75;

(ii) a VH comprising the amino acid sequence of SEQ ID NO: 69 and a VL comprising the amino acid sequence of SEQ ID NO: 70;

(iii) a VH comprising the amino acid sequence of SEQ ID NO: 71and a VL comprising the amino acid sequence of SEQ ID NO: 70;

(iv) a VH comprising the amino acid sequence of SEQ ID NO: 72 and a VL comprising the amino acid sequence of SEQ ID NO: 70;

(v) a VH comprising the amino acid sequence of SEQ ID NO: 73 and a VL comprising the amino acid sequence of SEQ ID NO: 74;

(vi) a VH comprising the amino acid sequence of SEQ ID NO: 73 and a VL comprising the amino acid sequence of SEQ ID NO: 75;

(vii) a VH comprising the amino acid sequence of SEQ ID NO: 76 and a VL comprising the amino acid sequence of SEQ ID NO: 74;

(viii) a VH comprising the amino acid sequence of SEQ ID NO: 77 and a VL comprising the amino acid sequence of SEQ ID NO: 78;

(ix) a VH comprising the amino acid sequence of SEQ ID NO: 79 and a VL comprising the amino acid sequence of SEQ ID NO: 80; or

(x) a VH comprising the amino acid sequence of SEQ ID NO: 77 and a VL comprising the amino acid sequence of SEQ ID NO: 80.

[00017] In some embodiments, the anti-TfR1 antibody is a Fab fragment, a Fab' fragment, a F(ab')2 fragment, an scFv, an Fv, or a full-length IgG.

[00018] In some embodiments, the anti-TfR1 antibody is a Fab fragment.

[00019] In some embodiments, the anti-TfR1 antibody comprises:

(i) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 101; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 90;

(ii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 97; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 85;

(iii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 98; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 85;

(iv) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 99; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 85;

(v) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 100; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 89;

(vi) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 100; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 90;

(vii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 101; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 89;

(viii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 102; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 93;

(ix) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 103; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 95; or

(x) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 102; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 95.

[00020] In some embodiments, the anti-TfR1 antibody comprises:

(i) a heavy chain comprising the amino acid sequence of SEQ ID NO: 101; and a light chain comprising the amino acid sequence of SEQ ID NO: 90;

(ii) a heavy chain comprising the amino acid sequence of SEQ ID NO: 97; and a light chain comprising the amino acid sequence of SEQ ID NO: 85;

(iii) a heavy chain comprising the amino acid sequence of SEQ ID NO: 98; and a light chain comprising the amino acid sequence of SEQ ID NO: 85;

(iv) a heavy chain comprising the amino acid sequence of SEQ ID NO: 99; and a light chain comprising the amino acid sequence of SEQ ID NO: 85;

(v) a heavy chain comprising the amino acid sequence of SEQ ID NO: 100; and a light chain comprising the amino acid sequence of SEQ ID NO: 89;

(vi) a heavy chain comprising the amino acid sequence of SEQ ID NO: 100; and a light chain comprising the amino acid sequence of SEQ ID NO: 90;

(vii) a heavy chain comprising the amino acid sequence of SEQ ID NO: 101; and a light chain comprising the amino acid sequence of SEQ ID NO: 89;

(viii) a heavy chain comprising the amino acid sequence of SEQ ID NO: 102; and a

light chain comprising the amino acid sequence of SEQ ID NO: 93;

(ix) a heavy chain comprising the amino acid sequence of SEQ ID NO: 103; and a light chain comprising the amino acid sequence of SEQ ID NO: 95; or

(x) a heavy chain comprising the amino acid sequence of SEQ ID NO: 102; and a light chain comprising the amino acid sequence of SEQ ID NO: 95.

[00021] In some embodiments, the anti-TfR1 antibody does not specifically bind to the transferrin binding site of the transferrin receptor 1 and/or the anti-TfR1 antibody does not inhibit binding of transferrin to the transferrin receptor 1.

[00022] In some embodiments, the oligonucleotide is complementary to at least 4 consecutive nucleotides of a splicing feature of the DMD pre-mRNA.

[00023] In some embodiments, the splicing feature is an exonic splicing enhancer (ESE) in exon 53 of the DMD pre-mRNA, optionally wherein the ESE comprises a sequence of any one of SEQ ID NOs: 689-715.

[00024] In some embodiments, the splicing feature is a branch point, a splice donor site, or a splice acceptor site, optionally wherein the splicing feature is across the junction of exon 52 and intron 52, in intron 52, across the junction of intron 52 and exon 53, across the junction of exon 53 and intron 53, in intron 53, or across the junction of intron 53 and exon 54 of the DMD pre-mRNA, and further optionally wherein the splicing feature comprises a sequence of any one of SEQ ID NOs: 685-688 and 716-718.

[00025] In some embodiments, the oligonucleotide comprises a sequence complementary to any one of SEQ ID NOs: 160-334 or comprises a sequence of any one of SEQ ID NOs: 335-684, wherein each thymine base (T) may independently and optionally be replaced with a uracil base (U), and each U may independently and optionally be replaced with a T.

[00026] In some embodiments, the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 574, 556, 559, 562, 627, 564, 557, 558, and 555, wherein each thymine base (T) may independently and optionally be replaced with a uracil base (U), and each U may independently and optionally be replaced with a T.

[00027] In some embodiments, the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 562, 574, and 559, wherein each T may independently and optionally be replaced with a U, and each U may independently and optionally be replaced with a T.

[00028] In some embodiments, the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 556, 627, and 555, wherein each T may independently and optionally be replaced with a U, and each U may independently and optionally be replaced with a T.

[00029] In some embodiments, the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 556, 574, and 559, wherein each T may independently and optionally be replaced with a U, and each U may independently and optionally be replaced with a T.

[00030] In some embodiments, the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 564, 557, and 558, wherein each T may independently and optionally be replaced with a U, and each U may independently and optionally be replaced with a T.

[00031] In some embodiments, the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 562, 556, and 559, wherein each T may independently and optionally be replaced with a U, and each U may independently and optionally be replaced with a T.

[00032] In some embodiments, the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 564, 557, and 555, wherein each T may independently and optionally be replaced with a U, and each U may independently and optionally be replaced with a T.

[00033] In some embodiments, the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 627, 564, and 558, wherein each T may independently and optionally be replaced with a U, and each U may independently and optionally be replaced with a T.

[00034] In some embodiments, the oligonucleotide comprises one or more phosphorodiamidate morpholinos, optionally wherein the oligonucleotide is a phosphorodiamidate morpholino oligomer (PMO).

[00035] In some embodiments, the anti-TfR1 antibody is covalently linked to the oligonucleotide via a cleavable linker, optionally wherein the cleavable linker comprises a valine-citrulline sequence.

[00036] In some embodiments, the anti-TfR1 antibody is covalently linked to the oligonucleotide via conjugation to a lysine residue or a cysteine residue of the antibody.

[00037] According to some aspects, oligonucleotides that target DMD are provided herein, wherein the oligonucleotide comprises a region of complementarity to any one of SEQ ID NOs: 160-334, optionally wherein the region of complementarity comprises at least 15 consecutive nucleosides complementary to any one of SEQ ID NOs: 160-334.

[00038] In some embodiments, the oligonucleotide comprises a region of complementarity to any one of SEQ ID NOs: 212, 224, and 209.

[00039] In some embodiments, the oligonucleotide comprises a region of complementarity to any one of SEQ ID NOs: 206, 277, and 205.

[00040] In some embodiments, the oligonucleotide comprises a region of complementarity to any one of SEQ ID NOs: 206, 224, and 209.

[00041] In some embodiments, the oligonucleotide comprises a region of complementarity to any one of SEQ ID NOs: 214, 207, and 208.

[00042] In some embodiments, the oligonucleotide comprises a region of complementarity to any one of SEQ ID NOs: 212, 206, and 209.

[00043] In some embodiments, the oligonucleotide comprises a region of complementarity to any one of SEQ ID NOs: 214, 207, and 205.

[00044] In some embodiments, the oligonucleotide comprises a region of complementarity to any one of SEQ ID NOs: 277, 214, and 208.

[00045] In some embodiments, the oligonucleotide comprises at least 15 consecutive nucleosides of any one of SEQ ID NOs: 335-684, optionally wherein the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 335-684, wherein each thymine base (T) may independently and optionally be replaced with a uracil base (U), and each U may independently and optionally be replaced with a T.

[00046] In some embodiments, the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 574, 556, 559, 562, 627, 564, 557, 558, and 555, wherein each thymine base (T) may independently and optionally be replaced with a uracil base (U), and each U may independently and optionally be replaced with a T.

[00047] In some embodiments, the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 562, 574, and 559, wherein each T may independently and optionally be replaced with a U, and each U may independently and optionally be replaced with a T.

[00048] In some embodiments, the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 556, 627, and 555, wherein each T may independently and optionally be replaced with a U, and each U may independently and optionally be replaced with a T.

[00049] In some embodiments, the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 556, 574, and 559, wherein each T may independently and optionally be replaced with a U, and each U may independently and optionally be replaced with a T.

[00050] In some embodiments, the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 564, 557, and 558, wherein each T may independently and optionally be replaced with a U, and each U may independently and optionally be replaced with a T.

[00051] In some embodiments, the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 562, 556, and 559, wherein each T may independently and optionally be replaced with a U, and each U may independently and optionally be replaced with a T.

[00052] In some embodiments, the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 564, 557, and 555, wherein each T may independently and optionally be replaced with a U, and each U may independently and optionally be replaced with a T.

[00053] In some embodiments, the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 627, 564, and 558, wherein each T may independently and optionally be replaced with a U, and each U may independently and optionally be replaced with a T.

[00054] According to some aspects, methods of delivering an oligonucleotide to a cell are provided herein, the method comprising contacting the cell with a complex disclosed herein or with an oligonucleotide disclosed herein.

[00055] According to some aspects, methods of promoting the expression or activity of a dystrophin protein in a cell are provided herein, the method comprising contacting the cell with a complex disclosed herein or with an oligonucleotide disclosed herein in an amount effective for promoting internalization of the oligonucleotide to the cell, optionally wherein the cell is a muscle cell.

[00056] In some embodiments, the cell comprises a DMD gene that is amenable to skipping of exon 53.

[00057] In some embodiments, the dystrophin protein is a truncated dystrophin protein.

BRIEF DESCRIPTION OF THE DRAWINGS

[00058] **FIG. 1** shows data illustrating that conjugates containing anti-TfR1 Fab (3M12 VH4/Vκ3) conjugated to a DMD exon-skipping oligonucleotide resulted in enhanced exon skipping compared to the naked DMD exon skipping oligo in Duchenne muscular dystrophy patient myotubes.

[00059] **FIG. 2** shows data illustrating that conjugates containing anti-TfR1 Fab (3M12 VH4/Vκ3) conjugated to DMD exon 53-skipping oligonucleotides facilitated skipping of exon 53 in Duchenne muscular dystrophy patient myotubes.

DETAILED DESCRIPTION OF INVENTION

[00060] Aspects of the disclosure relate to a recognition that while certain molecular payloads (*e.g.*, oligonucleotides, peptides, small molecules) can have beneficial effects in muscle cells, it has proven challenging to effectively target such cells. Accordingly, as described herein, the present disclosure provides complexes comprising muscle-targeting agents covalently linked to molecular payloads in order to overcome such challenges. In some embodiments, the complexes are particularly useful for delivering molecular payloads that

modulate (e.g., promote) the expression or activity of dystrophin protein (e.g., a truncated dystrophin protein) or DMD (*e.g.*, a mutated DMD allele). In some embodiments, complexes provided herein may comprise oligonucleotides that promote expression and activity of dystrophin protein or DMD, such as by facilitating in-frame exon skipping and/or suppression of premature stop codons. For example, complexes may comprise oligonucleotides that induce skipping of exon(s) of DMD RNA (*e.g.*, pre-mRNA), such as oligonucleotides that induce skipping of exon 53. In some embodiments, synthetic nucleic acid payloads (*e.g.*, DNA or RNA payloads) may be used that express one or more proteins that promote normal expression and activity of dystrophin protein or DMD.

[00061] Duchenne muscular dystrophy is an X-linked muscular disorder caused by one or more mutations in the DMD gene located on Xp21. Dystrophin protein typically forms the dystrophin-associated glycoprotein complex (DGC) at the sarcolemma, which links the muscle sarcomeric structure to the extracellular matrix and protects the sarcolemma from contraction-induced injury. In patients with Duchenne muscular dystrophy, the dystrophin protein is generally absent and muscle fibers typically become damaged due to mechanical overextension. Mutations in the DMD gene are associated with two types of muscular dystrophy, Duchenne muscular dystrophy and Becker muscular dystrophy, depending on whether the translational reading frame is lost or maintained. Becker muscular dystrophy is a clinically milder form of Duchenne muscular dystrophy, and is characterized by features similar to Duchenne muscular dystrophy. In some embodiments, exon skipping induced by oligonucleotides (e.g., delivered using complexes provided herein) can be used to restore the reading frame of a mutated DMD allele resulting in production of a truncated dystrophin protein that is sufficiently functional to improve muscle function. In some embodiments, such exon skipping converts a Duchenne muscular dystrophy phenotype into a milder Becker muscular dystrophy phenotype.

[00062] Further aspects of the disclosure, including a description of defined terms, are provided below.

I. Definitions

[00063] **Administering**: As used herein, the terms "administering" or "administration" means to provide a complex to a subject in a manner that is physiologically and/or (e.g., and) pharmacologically useful (*e.g.*, to treat a condition in the subject).

[00064] **Approximately:** As used herein, the term "approximately" or "about," as applied to one or more values of interest, refers to a value that is similar to a stated reference

value. In certain embodiments, the term "approximately" or "about" refers to a range of values that fall within 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[00065] **Antibody:** As used herein, the term "antibody" refers to a polypeptide that includes at least one immunoglobulin variable domain or at least one antigenic determinant, e.g., paratope that specifically binds to an antigen. In some embodiments, an antibody is a full-length antibody. In some embodiments, an antibody is a chimeric antibody. In some embodiments, an antibody is a humanized antibody. However, in some embodiments, an antibody is a Fab fragment, a Fab' fragment, a F(ab')2 fragment, a Fv fragment or a scFv fragment. In some embodiments, an antibody is a nanobody derived from a camelid antibody or a nanobody derived from shark antibody. In some embodiments, an antibody is a diabody. In some embodiments, an antibody comprises a framework having a human germline sequence. In another embodiment, an antibody comprises a heavy chain constant domain selected from the group consisting of IgG, IgG1, IgG2, IgG2A, IgG2B, IgG2C, IgG3, IgG4, IgA1, IgA2, IgD, IgM, and IgE constant domains. In some embodiments, an antibody comprises a heavy (H) chain variable region (abbreviated herein as VH), and/or (e.g., and) a light (L) chain variable region (abbreviated herein as VL). In some embodiments, an antibody comprises a constant domain, e.g., an Fc region. An immunoglobulin constant domain refers to a heavy or light chain constant domain. Human IgG heavy chain and light chain constant domain amino acid sequences and their functional variations are known. With respect to the heavy chain, in some embodiments, the heavy chain of an antibody described herein can be an alpha (α), delta (Δ), epsilon (ε), gamma (γ) or mu (μ) heavy chain. In some embodiments, the heavy chain of an antibody described herein can comprise a human alpha (α), delta (Δ), epsilon (ε), gamma (γ) or mu (μ) heavy chain. In a particular embodiment, an antibody described herein comprises a human gamma 1 CH1, CH2, and/or (e.g., and) CH3 domain. In some embodiments, the amino acid sequence of the VH domain comprises the amino acid sequence of a human gamma (γ) heavy chain constant region, such as any known in the art. Non-limiting examples of human constant region sequences have been described in the art, e.g., see U.S. Pat. No. 5,693,780 and Kabat E A et al., (1991) supra. In some embodiments, the VH domain comprises an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or at least 99% identical to any of the variable chain constant regions provided herein. In some embodiments, an antibody is modified, e.g., modified via glycosylation, phosphorylation,

sumoylation, and/or (e.g., and) methylation. In some embodiments, an antibody is a glycosylated antibody, which is conjugated to one or more sugar or carbohydrate molecules. In some embodiments, the one or more sugar or carbohydrate molecule are conjugated to the antibody via N-glycosylation, O-glycosylation, C-glycosylation, glypiation (GPI anchor attachment), and/or (e.g., and) phosphoglycosylation. In some embodiments, the one or more sugar or carbohydrate molecule are monosaccharides, disaccharides, oligosaccharides, or glycans. In some embodiments, the one or more sugar or carbohydrate molecule is a branched oligosaccharide or a branched glycan. In some embodiments, the one or more sugar or carbohydrate molecule includes a mannose unit, a glucose unit, an N-acetylglucosamine unit, an N-acetylgalactosamine unit, a galactose unit, a fucose unit, or a phospholipid unit. In some embodiments, an antibody is a construct that comprises a polypeptide comprising one or more antigen binding fragments of the disclosure linked to a linker polypeptide or an immunoglobulin constant domain. Linker polypeptides comprise two or more amino acid residues joined by peptide bonds and are used to link one or more antigen binding portions. Examples of linker polypeptides have been reported (see e.g., Holliger, P., et al. (1993) Proc. Natl. Acad. Sci. USA 90:6444-6448; Poljak, R. J., et al. (1994) Structure 2:1121-1123). Still further, an antibody may be part of a larger immunoadhesion molecule, formed by covalent or noncovalent association of the antibody or antibody portion with one or more other proteins or peptides. Examples of such immunoadhesion molecules include use of the streptavidin core region to make a tetrameric scFv molecule (Kipriyanov, S. M., et al. (1995) Human Antibodies and Hybridomas 6:93-101) and use of a cysteine residue, a marker peptide and a C-terminal polyhistidine tag to make bivalent and biotinylated scFv molecules (Kipriyanov, S. M., et al. (1994) Mol. Immunol. 31:1047-1058).

[00066] **Branch point:** As used herein, the term "branch point" or "branch site" refers to a nucleic acid sequence motif within an intron of a gene or pre-mRNA that is involved in splicing of pre-mRNA into mRNA (*i.e.*, removing introns from the pre-mRNA), and can be referred to as a splicing feature. A branch point is typically located 18 to 40 nucleotides from the 3' end of an intron, and contains an adenine but is otherwise relatively unrestricted in sequence. Common sequence motifs for branch points are YNYYRAY, YTRAC, and YNYTRAY, where Y is a pyrimidine, N is any nucleotide, R is any purine, and A is adenine. During splicing, the pre-mRNA is cleaved at the 5' end of the intron, which then attaches to the branch point region downstream through transesterification bonding between guanines and adenines from the 5' end and the branch point, respectively, to form a looped lariat structure.

[00067] **CDR:** As used herein, the term "CDR" refers to the complementarity determining region within antibody variable sequences. A typical antibody molecule comprises a heavy chain variable region (VH) and a light chain variable region (VL), which are usually involved in antigen binding. The VH and VL regions can be further subdivided into regions of hypervariability, also known as "complementarity determining regions" ("CDR"), interspersed with regions that are more conserved, which are known as "framework regions" ("FR"). Each VH and VL is typically composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The extent of the framework region and CDRs can be precisely identified using methodology known in the art, for example, by the Kabat definition, the IMGT definition, the Chothia definition, the AbM definition, and/or (e.g., and) the contact definition, all of which are well known in the art. See, e.g., Kabat, E.A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; IMGT®, the international ImMunoGeneTics information system® www.imgt.org, Lefranc, M.-P. et al., Nucleic Acids Res., 27:209-212 (1999); Ruiz, M. et al., Nucleic Acids Res., 28:219-221 (2000); Lefranc, M.-P., Nucleic Acids Res., 29:207-209 (2001); Lefranc, M.-P., Nucleic Acids Res., 31:307-310 (2003); Lefranc, M.-P. et al., In Silico Biol., 5, 0006 (2004) [Epub], 5:45-60 (2005); Lefranc, M.-P. et al., Nucleic Acids Res., 33:D593-597 (2005); Lefranc, M.-P. et al., Nucleic Acids Res., 37:D1006-1012 (2009); Lefranc, M.-P. et al., Nucleic Acids Res., 43:D413-422 (2015); Chothia et al., (1989) Nature 342:877; Chothia, C. et al. (1987) J. Mol. Biol. 196:901-917, Al-lazikani et al (1997) J. Molec. Biol. 273:927-948; and Almagro, J. Mol. Recognit. 17:132-143 (2004). See also bioinf.org.uk/abs. As used herein, a CDR may refer to the CDR defined by any method known in the art. Two antibodies having the same CDR means that the two antibodies have the same amino acid sequence of that CDR as determined by the same method, for example, the IMGT definition.

[00068] There are three CDRs in each of the variable regions of the heavy chain and the light chain, which are designated CDR1, CDR2 and CDR3, for each of the variable regions. The term "CDR set" as used herein refers to a group of three CDRs that occur in a single variable region capable of binding the antigen. The exact boundaries of these CDRs have been defined differently according to different systems. The system described by Kabat (Kabat *et al.,* Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md. (1987) and (1991)) not only provides an unambiguous residue numbering system applicable to any variable region of an antibody, but also provides precise residue boundaries

defining the three CDRs. These CDRs may be referred to as Kabat CDRs. Sub-portions of CDRs may be designated as L1, L2 and L3 or H1, H2 and H3 where the "L" and the "H" designates the light chain and the heavy chains regions, respectively. These regions may be referred to as Chothia CDRs, which have boundaries that overlap with Kabat CDRs. Other boundaries defining CDRs overlapping with the Kabat CDRs have been described by Padlan (FASEB J. 9:133-139 (1995)) and MacCallum (J Mol Biol 262(5):732-45 (1996)). Still other CDR boundary definitions may not strictly follow one of the above systems, but will nonetheless overlap with the Kabat CDRs, although they may be shortened or lengthened in light of prediction or experimental findings that particular residues or groups of residues or even entire CDRs do not significantly impact antigen binding. The methods used herein may utilize CDRs defined according to any of these systems. Examples of CDR definition systems are provided in Table 1.

Table 1. CDR Definitions

	IMGT[1]	Kabat[2]	Chothia[3]
CDR-H1	27-38	31-35	26-32
CDR-H2	56-65	50-65	53-55
CDR-H3	105-116/117	95-102	96-101
CDR-L1	27-38	24-34	26-32
CDR-L2	56-65	50-56	50-52
CDR-L3	105-116/117	89-97	91-96

[1] IMGT®, the international ImMunoGeneTics information system®, imgt.org, Lefranc, M.-P. et al., Nucleic Acids Res., 27:209-212 (1999)
[2] Kabat et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242
[3] Chothia et al., J. Mol. Biol. 196:901-917 (1987))

[00069] **CDR-grafted antibody:** The term "CDR-grafted antibody" refers to antibodies which comprise heavy and light chain variable region sequences from one species but in which the sequences of one or more of the CDR regions of VH and/or (e.g., and) VL are replaced with CDR sequences of another species, such as antibodies having murine heavy and light chain variable regions in which one or more of the murine CDRs (*e.g.*, CDR3) has been replaced with human CDR sequences.

[00070] **Chimeric antibody:** The term "chimeric antibody" refers to antibodies which comprise heavy and light chain variable region sequences from one species and constant region sequences from another species, such as antibodies having murine heavy and light chain variable regions linked to human constant regions.

[00071] **Complementary:** As used herein, the term "complementary" refers to the capacity for precise pairing between two nucleosides or two sets of nucleosides. In particular, complementary is a term that characterizes an extent of hydrogen bond pairing that brings

about binding between two nucleosides or two sets of nucleosides. For example, if a base at one position of an oligonucleotide is capable of hydrogen bonding with a base at the corresponding position of a target nucleic acid (e.g., an mRNA), then the bases are considered to be complementary to each other at that position. Base pairings may include both canonical Watson-Crick base pairing and non-Watson-Crick base pairing (e.g., Wobble base pairing and Hoogsteen base pairing). For example, in some embodiments, for complementary base pairings, adenosine-type bases (A) are complementary to thymidine-type bases (T) or uracil-type bases (U), that cytosine-type bases (C) are complementary to guanosine-type bases (G), and that universal bases such as 3-nitropyrrole or 5-nitroindole can hybridize to and are considered complementary to any A, C, U, or T. Inosine (I) has also been considered in the art to be a universal base and is considered complementary to any A, C, U or T.

[00072] **Conservative amino acid substitution:** As used herein, a "conservative amino acid substitution" refers to an amino acid substitution that does not alter the relative charge or size characteristics of the protein in which the amino acid substitution is made. Variants can be prepared according to methods for altering polypeptide sequence known to one of ordinary skill in the art such as are found in references which compile such methods, e.g. Molecular Cloning: A Laboratory Manual, J. Sambrook, et al., eds., Fourth Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 2012, or Current Protocols in Molecular Biology, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. Conservative substitutions of amino acids include substitutions made amongst amino acids within the following groups: (a) M, I, L, V; (b) F, Y, W; (c) K, R, H; (d) A, G; (e) S, T; (f) Q, N; and (g) E, D.

[00073] **Covalently linked:** As used herein, the term "covalently linked" refers to a characteristic of two or more molecules being linked together via at least one covalent bond. In some embodiments, two molecules can be covalently linked together by a single bond, e.g., a disulfide bond or disulfide bridge, that serves as a linker between the molecules. However, in some embodiments, two or more molecules can be covalently linked together via a molecule that serves as a linker that joins the two or more molecules together through multiple covalent bonds. In some embodiments, a linker may be a cleavable linker. However, in some embodiments, a linker may be a non-cleavable linker.

[00074] **Cross-reactive:** As used herein and in the context of a targeting agent (e.g., antibody), the term "cross-reactive," refers to a property of the agent being capable of specifically binding to more than one antigen of a similar type or class (e.g., antigens of multiple homologs, paralogs, or orthologs) with similar affinity or avidity. For example, in

some embodiments, an antibody that is cross-reactive against human and non-human primate antigens of a similar type or class (e.g., a human transferrin receptor and non-human primate transferrin receptor) is capable of binding to the human antigen and non-human primate antigens with a similar affinity or avidity. In some embodiments, an antibody is cross-reactive against a human antigen and a rodent antigen of a similar type or class. In some embodiments, an antibody is cross-reactive against a rodent antigen and a non-human primate antigen of a similar type or class. In some embodiments, an antibody is cross-reactive against a human antigen, a non-human primate antigen, and a rodent antigen of a similar type or class.

[00075] **DMD:** As used herein, the term "DMD" refers to a gene that encodes dystrophin protein, a key component of the dystrophin-glycoprotein complex, which bridges the inner cytoskeleton and the extracellular matrix in muscle cells, particularly muscle fibers. Deletions, duplications, and point mutations in DMD may cause dystrophinopathies, such as Duchenne muscular dystrophy, Becker muscular dystrophy, or cardiomyopathy. Alternative promoter usage and alternative splicing result in numerous distinct transcript variants and protein isoforms for this gene. In some embodiments, a dystrophin gene (DMD or DMD gene) may be a human (Gene ID: 1756), non-human primate (e.g., Gene ID: 465559), or rodent gene (e.g., Gene ID: 13405; Gene ID: 24907). In addition, multiple human transcript variants (e.g., as annotated under GenBank RefSeq Accession Numbers: NM_000109.3, NM_004006.2, NM_004009.3, NM_004010.3 and NM_004011.3) have been characterized that encode different protein isoforms.

[00076] **DMD allele:** As used herein, the term "DMD allele" refers to any one of alternative forms (e.g., wild-type or mutant forms) of a DMD gene. In some embodiments, a DMD allele may encode for dystrophin that retains its normal and typical functions. In some embodiments, a DMD allele may comprise one or more mutations that results in muscular dystrophy. Common mutations that lead to Duchenne muscular dystrophy involve frameshift, deletion, substitution, and duplicative mutations of one or more of 79 exons present in a dystrophin allele, *e.g.*, exon 8, exon 23, exon 41, exon 44, exon 45, exon 50, exon 51, exon 52, exon 53, or exon 55. Further examples of DMD mutations are disclosed, for example, in Flanigan KM, et al., *Mutational spectrum of DMD mutations in dystrophinopathy patients: application of modern diagnostic techniques to a large cohort.* Hum Mutat. 2009 Dec; 30 (12):1657-66, the contents of which are incorporated herein by reference in its entirety.

[00077] **Dystrophinopathy:** As used herein, the term "dystrophinopathy" refers to a muscle disease results from one or more mutated DMD alleles. Dystrophinopathies include a spectrum of conditions (ranging from mild to severe) that includes Duchenne muscular

dystrophy, Becker muscular dystrophy, and DMD-associated dilated cardiomyopathy (DCM). In some embodiments, at one end of the spectrum, dystrophinopathy is phenotypically associated with an asymptomatic increase in serum concentration of creatine phosphokinase (CK) and/or (e.g., and) muscle cramps with myoglobinuria. In some embodiments, at the other end of the spectrum, dystrophinopathy is phenotypically associated with progressive muscle diseases that are generally classified as Duchenne or Becker muscular dystrophy when skeletal muscle is primarily affected and as DMD-associated dilated cardiomyopathy (DCM) when the heart is primarily affected. Symptoms of Duchenne muscular dystrophy include muscle loss or degeneration, diminished muscle function, pseudohypertrophy of the tongue and calf muscles, higher risk of neurological abnormalities, and a shortened lifespan. Duchenne muscular dystrophy is associated with Online Mendelian Inheritance in Man (OMIM) Entry # 310200. Becker muscular dystrophy is associated with OMIM Entry # 300376. Dilated cardiomyopathy is associated with OMIM Entry X# 302045.

[00078] **Exonic splicing enhancer (ESE):** As used herein, the term "exonic splicing enhancer" or "ESE" refers to a nucleic acid sequence motif within an exon of a gene, pre-mRNA, or mRNA that directs or enhances splicing of pre-mRNA into mRNA, e.g., as described in Blencowe et al., Trends Biochem Sci 25, 106-10. (2000), incorporated herein by reference. ESEs can be referred to as splicing features. ESEs may direct or enhance splicing, for example, to remove one or more introns and/or one or more exons from a gene transcript. ESE motifs are typically 6-8 nucleobases in length. SR proteins (e.g., proteins encoded by the gene SRSF1, SRSF2, SRSF3, SRSF4, SRSF5, SRSF6, SRSF7, SRSF8, SRSF9, SRSF10, SRSF11, SRSF12, TRA2A or TRA2B) bind to ESEs through their RNA recognition motif region to facilitate splicing. ESE motifs can be identified through a number of methods, including those described in Cartegni et al., Nucleic Acids Research, 2003, Vol. 31, No. 13, 3568–3571, incorporated herein by reference.

[00079] **Framework:** As used herein, the term "framework" or "framework sequence" refers to the remaining sequences of a variable region minus the CDRs. Because the exact definition of a CDR sequence can be determined by different systems, the meaning of a framework sequence is subject to correspondingly different interpretations. The six CDRs (CDR-L1, CDR-L2, and CDR-L3 of light chain and CDR-H1, CDR-H2, and CDR-H3 of heavy chain) also divide the framework regions on the light chain and the heavy chain into four sub-regions (FR1, FR2, FR3 and FR4) on each chain, in which CDR1 is positioned between FR1 and FR2, CDR2 between FR2 and FR3, and CDR3 between FR3 and FR4. Without specifying the particular sub-regions as FR1, FR2, FR3 or FR4, a framework region, as

referred by others, represents the combined FRs within the variable region of a single, naturally occurring immunoglobulin chain. As used herein, a FR represents one of the four sub-regions, and FRs represents two or more of the four sub-regions constituting a framework region. Human heavy chain and light chain acceptor sequences are known in the art. In one embodiment, the acceptor sequences known in the art may be used in the antibodies disclosed herein.

[00080] **Human antibody:** The term "human antibody", as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies of the disclosure may include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.,* mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation *in vivo*), for example in the CDRs and in particular CDR3. However, the term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[00081] **Humanized antibody:** The term "humanized antibody" refers to antibodies which comprise heavy and light chain variable region sequences from a non-human species (*e.g.,* a mouse) but in which at least a portion of the VH and/or (e.g., and) VL sequence has been altered to be more "human-like", *i.e.,* more similar to human germline variable sequences. One type of humanized antibody is a CDR-grafted antibody, in which human CDR sequences are introduced into non-human VH and VL sequences to replace the corresponding non-human CDR sequences. In one embodiment, humanized anti-TfR1 antibodies and antigen binding portions are provided. Such antibodies may be generated by obtaining murine anti-TfR1 monoclonal antibodies using traditional hybridoma technology followed by humanization using *in vitro* genetic engineering, such as those disclosed in Kasaian et al PCT publication No. WO 2005/123126 A2.

[00082] **Internalizing cell surface receptor:** As used herein, the term, "internalizing cell surface receptor" refers to a cell surface receptor that is internalized by cells, e.g., upon external stimulation, e.g., ligand binding to the receptor. In some embodiments, an internalizing cell surface receptor is internalized by endocytosis. In some embodiments, an internalizing cell surface receptor is internalized by clathrin-mediated endocytosis. However, in some embodiments, an internalizing cell surface receptor is internalized by a clathrin-independent pathway, such as, for example, phagocytosis, macropinocytosis, caveolae- and raft-mediated uptake or constitutive clathrin-independent endocytosis. In some embodiments,

the internalizing cell surface receptor comprises an intracellular domain, a transmembrane domain, and/or (e.g., and) an extracellular domain, which may optionally further comprise a ligand-binding domain. In some embodiments, a cell surface receptor becomes internalized by a cell after ligand binding. In some embodiments, a ligand may be a muscle-targeting agent or a muscle-targeting antibody. In some embodiments, an internalizing cell surface receptor is a transferrin receptor.

[00083] **Isolated antibody:** An "isolated antibody", as used herein, is intended to refer to an antibody that is substantially free of other antibodies having different antigenic specificities (*e.g.*, an isolated antibody that specifically binds transferrin receptor is substantially free of antibodies that specifically bind antigens other than transferrin receptor). An isolated antibody that specifically binds transferrin receptor complex may, however, have cross-reactivity to other antigens, such as transferrin receptor molecules from other species. Moreover, an isolated antibody may be substantially free of other cellular material and/or (e.g., and) chemicals.

[00084] **Kabat numbering:** The terms "Kabat numbering", "Kabat definitions and "Kabat labeling" are used interchangeably herein. These terms, which are recognized in the art, refer to a system of numbering amino acid residues which are more variable (i.e. hypervariable) than other amino acid residues in the heavy and light chain variable regions of an antibody, or an antigen binding portion thereof (Kabat et al. (1971) Ann. NY Acad. Sci. 190:382-391 and, Kabat, E. A., *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). For the heavy chain variable region, the hypervariable region ranges from amino acid positions 31 to 35 for CDR1, amino acid positions 50 to 65 for CDR2, and amino acid positions 95 to 102 for CDR3. For the light chain variable region, the hypervariable region ranges from amino acid positions 24 to 34 for CDR1, amino acid positions 50 to 56 for CDR2, and amino acid positions 89 to 97 for CDR3.

[00085] **Molecular payload:** As used herein, the term "molecular payload" refers to a molecule or species that functions to modulate a biological outcome. In some embodiments, a molecular payload is linked to, or otherwise associated with a muscle-targeting agent. In some embodiments, the molecular payload is a small molecule, a protein, a peptide, a nucleic acid, or an oligonucleotide. In some embodiments, the molecular payload functions to modulate the transcription of a DNA sequence, to modulate the expression of a protein, or to modulate the activity of a protein. In some embodiments, the molecular payload is an oligonucleotide that comprises a strand having a region of complementarity to a target gene.

[00086] **Muscle-targeting agent:** As used herein, the term, "muscle-targeting agent," refers to a molecule that specifically binds to an antigen expressed on muscle cells. The antigen in or on muscle cells may be a membrane protein, for example an integral membrane protein or a peripheral membrane protein. Typically, a muscle-targeting agent specifically binds to an antigen on muscle cells that facilitates internalization of the muscle-targeting agent (and any associated molecular payload) into the muscle cells. In some embodiments, a muscle-targeting agent specifically binds to an internalizing, cell surface receptor on muscles and is capable of being internalized into muscle cells through receptor mediated internalization. In some embodiments, the muscle-targeting agent is a small molecule, a protein, a peptide, a nucleic acid (*e.g.*, an aptamer), or an antibody. In some embodiments, the muscle-targeting agent is linked to a molecular payload.

[00087] **Muscle-targeting antibody:** As used herein, the term, "muscle-targeting antibody," refers to a muscle-targeting agent that is an antibody that specifically binds to an antigen found in or on muscle cells. In some embodiments, a muscle-targeting antibody specifically binds to an antigen on muscle cells that facilitates internalization of the muscle-targeting antibody (and any associated molecular payment) into the muscle cells. In some embodiments, the muscle-targeting antibody specifically binds to an internalizing, cell surface receptor present on muscle cells. In some embodiments, the muscle-targeting antibody is an antibody that specifically binds to a transferrin receptor.

[00088] **Oligonucleotide:** As used herein, the term "oligonucleotide" refers to an oligomeric nucleic acid compound of up to 200 nucleotides in length. Examples of oligonucleotides include, but are not limited to, RNAi oligonucleotides (e.g., siRNAs, shRNAs), microRNAs, gapmers, mixmers, phosphorodiamidate morpholinos, peptide nucleic acids, aptamers, guide nucleic acids (e.g., Cas9 guide RNAs), etc. Oligonucleotides may be single-stranded or double-stranded. In some embodiments, an oligonucleotide may comprise one or more modified nucleosides (e.g., 2′-O-methyl sugar modifications, purine or pyrimidine modifications). In some embodiments, an oligonucleotide may comprise one or more modified internucleoside linkages. In some embodiments, an oligonucleotide may comprise one or more phosphorothioate linkages, which may be in the Rp or Sp stereochemical conformation.

[00089] **Recombinant antibody:** The term "recombinant human antibody", as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell (described in more details in this disclosure), antibodies isolated from a recombinant, combinatorial human antibody library (Hoogenboom H. R.,

(1997) TIB Tech. 15:62-70; Azzazy H., and Highsmith W. E., (2002) Clin. Biochem. 35:425-445; Gavilondo J. V., and Larrick J. W. (2002) BioTechniques 29:128-145; Hoogenboom H., and Chames P. (2000) Immunology Today 21:371-378), antibodies isolated from an animal (*e.g.,* a mouse) that is transgenic for human immunoglobulin genes (see e.g., Taylor, L. D., et al. (1992) Nucl. Acids Res. 20:6287-6295; Kellermann S-A., and Green L. L. (2002) Current Opinion in Biotechnology 13:593-597; Little M. et al (2000) Immunology Today 21:364-370) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to in vitro mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire in vivo. One embodiment of the disclosure provides fully human antibodies capable of binding human transferrin receptor which can be generated using techniques well known in the art, such as, but not limited to, using human Ig phage libraries such as those disclosed in Jermutus et al., PCT publication No. WO 2005/007699 A2.

[00090] **Region of complementarity:** As used herein, the term "region of complementarity" refers to a nucleotide sequence, e.g., of an oligonucleotide, that is sufficiently complementary to a cognate nucleotide sequence, e.g., of a target nucleic acid, such that the two nucleotide sequences are capable of annealing to one another under physiological conditions (e.g., in a cell). In some embodiments, a region of complementarity is fully complementary to a cognate nucleotide sequence of target nucleic acid. However, in some embodiments, a region of complementarity is partially complementary to a cognate nucleotide sequence of target nucleic acid (e.g., at least 80%, 90%, 95% or 99% complementarity). In some embodiments, a region of complementarity contains 1, 2, 3, or 4 mismatches compared with a cognate nucleotide sequence of a target nucleic acid.

[00091] **Specifically binds:** As used herein, the term "specifically binds" refers to the ability of a molecule to bind to a binding partner with a degree of affinity or avidity that enables the molecule to be used to distinguish the binding partner from an appropriate control in a binding assay or other binding context. With respect to an antibody, the term, "specifically binds", refers to the ability of the antibody to bind to a specific antigen with a degree of affinity or avidity, compared with an appropriate reference antigen or antigens, that

enables the antibody to be used to distinguish the specific antigen from others, e.g., to an extent that permits preferential targeting to certain cells, e.g., muscle cells, through binding to the antigen, as described herein. In some embodiments, an antibody specifically binds to a target if the antibody has a K_D for binding the target of at least about 10^{-4} M, 10^{-5} M, 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, 10^{-12} M, 10^{-13} M, or less. In some embodiments, an antibody specifically binds to the transferrin receptor, e.g., an epitope of the apical domain of transferrin receptor.

[00092] **Splice acceptor site:** As used herein, the term "splice acceptor site" or "splice acceptor" refers to a nucleic acid sequence motif at the 3' end of an intron or across an intron/exon junction of a gene or pre-mRNA that is involved in splicing of pre-mRNA into mRNA (*i.e.*, removing introns from the pre-mRNA), and can be referred to as a splicing feature. A splice acceptor site includes a terminal AG sequence at the 3' end of an intron, which is typically preceded (5'-ward) by a region high in pyrimidines (C/U). Upstream from the splice acceptor site is the branch point. Formation of a lariat loop intermediate structure by a transesterification reaction between the branch point and the splice donor site releases a 3'-OH of the 5' exon, which subsequently reacts with the first nucleotide of the 3' exon, thereby joining the exons and releasing the intron lariat. The AG sequence at the 3' end of the intron in the splice acceptor site is known to be critical for proper splicing, as changing one of these nucleotides results in inhibition of splicing. Rarely, alternative splice acceptor sites have an AC at the 3' end of the intron, instead of the more common AG. A common splice acceptor site motif has a sequence of or similar to [Y-rich region]-NCAGG or Y_xNYAGG, in which Y represents a pyrimidine, N represents any nucleotide, and x is a number from 4 to 20. The cut site follows the AG, which represent the 3'-terminal nucleotides of the excised intron.

[00093] **Splice donor site:** As used herein, the term "splice donor site" or "splice donor" refers to a nucleic acid sequence motif at the 5' end of an intron or across an exon/intron junction of a gene or pre-mRNA that is involved in splicing of pre-mRNA into mRNA (*i.e.*, removing introns from the pre-mRNA), and can be referred to as a splicing feature. A splice donor site includes a terminal GU sequence at the 5' end of the intron, within a larger and fairly unconstrained sequence. During splicing, the 2'-OH of a nucleotide within the branch point initiates a transesterification reaction via a nucleophilic attack on the 5' G of the intron within the splice donor site. The G is thereby cleaved from the pre-mRNA and bonds instead to the branch point nucleotide, forming a loop lariat structure. The 3' nucleotide of the upstream exon subsequently binds the splice acceptor site, joining the exons and excising the intron. A typical splice donor site has a sequence of or similar to GGGURAGU or AGGURNG, in which

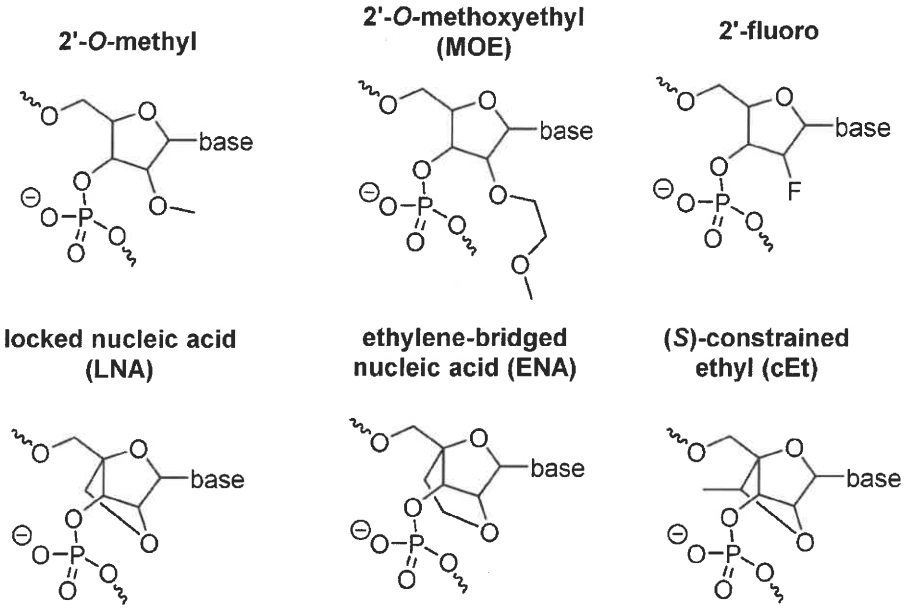
R represents a purine and N represents any nucleotide. The cut site precedes the first GU (*i.e.*, GG/GURAGU or AG/GURNG), which represent the 5'-terminal nucleotides of the excised intron.

[00094] **Subject:** As used herein, the term "subject" refers to a mammal. In some embodiments, a subject is non-human primate, or rodent. In some embodiments, a subject is a human. In some embodiments, a subject is a patient, e.g., a human patient that has or is suspected of having a disease. In some embodiments, the subject is a human patient who has or is suspected of having a disease resulting from a mutated DMD gene sequence, e.g., a mutation in an exon of a DMD gene sequence. In some embodiments, a subject has a dystrophinopathy, e.g., Duchenne muscular dystrophy. In some embodiments, a subject is a patient that has a mutation of the DMD gene that is amenable to exon 53 skipping.

[00095] **Transferrin receptor:** As used herein, the term, "transferrin receptor" (also known as TFRC, CD71, p90, or TFR1) refers to an internalizing cell surface receptor that binds transferrin to facilitate iron uptake by endocytosis. In some embodiments, a transferrin receptor may be of human (NCBI Gene ID 7037), non-human primate (e.g., NCBI Gene ID 711568 or NCBI Gene ID 102136007), or rodent (e.g., NCBI Gene ID 22042) origin. In addition, multiple human transcript variants have been characterized that encoded different isoforms of the receptor (e.g., as annotated under GenBank RefSeq Accession Numbers: NP_001121620.1, NP_003225.2, NP_001300894.1, and NP_001300895.1).

[00096] **2'-modified nucleoside**: As used herein, the terms "2'-modified nucleoside" and "2'-modified ribonucleoside" are used interchangeably and refer to a nucleoside having a sugar moiety modified at the 2' position. In some embodiments, the 2'-modified nucleoside is a 2'-4' bicyclic nucleoside, where the 2' and 4' positions of the sugar are bridged (e.g., via a methylene, an ethylene, or a (S)-constrained ethyl bridge). In some embodiments, the 2'-modified nucleoside is a non-bicyclic 2'-modified nucleoside, e.g., where the 2' position of the sugar moiety is substituted. Non-limiting examples of 2'-modified nucleosides include: 2'-deoxy, 2'-fluoro (2'-F), 2'-O-methyl (2'-O-Me), 2'-O-methoxyethyl (2'-MOE), 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), 2'-O-dimethylaminoethyloxyethyl (2'-O-DMAEOE), 2'-O-N-methylacetamido (2'-O-NMA), locked nucleic acid (LNA, methylene-bridged nucleic acid), ethylene-bridged nucleic acid (ENA), and (S)-constrained ethyl-bridged nucleic acid (cEt). In some embodiments, the 2'-modified nucleosides described herein are high-affinity modified nucleosides and oligonucleotides comprising the 2'-modified nucleosides have

increased affinity to a target sequences, relative to an unmodified oligonucleotide. Examples of structures of 2'-modified nucleosides are provided below:



These examples are shown with phosphate groups, but any internucleoside linkages are contemplated between 2'-modified nucleosides.

II. Complexes

[00097] Provided herein are complexes that comprise a targeting agent, e.g. an antibody, covalently linked to a molecular payload. In some embodiments, a complex comprises a muscle-targeting antibody covalently linked to an oligonucleotide. A complex may comprise an antibody that specifically binds a single antigenic site or that binds to at least two antigenic sites that may exist on the same or different antigens.

[00098] A complex may be used to modulate the activity or function of at least one gene, protein, and/or (e.g., and) nucleic acid. In some embodiments, the molecular payload present with a complex is responsible for the modulation of a gene, protein, and/or (e.g., and) nucleic acids. A molecular payload may be a small molecule, protein, nucleic acid, oligonucleotide, or any molecular entity capable of modulating the activity or function of a gene, protein, and/or (e.g., and) nucleic acid in a cell.

[00099] In some embodiments, a complex comprises a muscle-targeting agent, *e.g.*, an anti-transferrin receptor antibody, covalently linked to a molecular payload, *e.g.*, an antisense oligonucleotide that targets DMD to promote exon skipping, *e.g.*, in a transcript encoded from a mutated DMD allele. In some embodiments, the complex targets a DMD pre-mRNA to promote skipping of exon 53 in the DMD pre-mRNA.

A. Muscle-Targeting Agents

[000100] Some aspects of the disclosure provide muscle-targeting agents, *e.g.*, for delivering a molecular payload to a muscle cell. In some embodiments, such muscle-targeting agents are capable of binding to a muscle cell, *e.g.*, via specifically binding to an antigen on the muscle cell, and delivering an associated molecular payload to the muscle cell. In some embodiments, the molecular payload is bound (*e.g.*, covalently bound) to the muscle targeting agent and is internalized into the muscle cell upon binding of the muscle targeting agent to an antigen on the muscle cell, *e.g.*, via endocytosis. It should be appreciated that various types of muscle-targeting agents may be used in accordance with the disclosure. It should also be appreciated that any muscle targets (*e.g.*, muscle surface proteins) can be targeted by any type of muscle-targeting agent described herein. For example, the muscle-targeting agent may comprise, or consist of, a nucleic acid (*e.g.*, DNA or RNA), a peptide (*e.g.*, an antibody), a lipid (*e.g.*, a microvesicle), or a sugar moiety (*e.g.*, a polysaccharide). A muscle-targeting agent may comprise, or consist of, a small molecule. Exemplary muscle-targeting agents are described in further detail herein, however, it should be appreciated that the exemplary muscle-targeting agents provided herein are not meant to be limiting.

[000101] Some aspects of the disclosure provide muscle-targeting agents that specifically bind to an antigen on muscle, such as skeletal muscle, smooth muscle, or cardiac muscle. In some embodiments, any of the muscle-targeting agents provided herein bind to (*e.g.*, specifically bind to) an antigen on a skeletal muscle cell, a smooth muscle cell, and/or (e.g., and) a cardiac muscle cell.

[000102] By interacting with muscle-specific cell surface recognition elements (*e.g.*, cell membrane proteins), both tissue localization and selective uptake into muscle cells can be achieved. In some embodiments, molecules that are substrates for muscle uptake transporters are useful for delivering a molecular payload into muscle tissue. Binding to muscle surface recognition elements followed by endocytosis can allow even large molecules such as antibodies to enter muscle cells. As another example molecular payloads conjugated to transferrin or anti-TfR1 antibodies can be taken up by muscle cells via binding to transferrin receptor, which may then be endocytosed, *e.g.*, via clathrin-mediated endocytosis.

[000103] The use of muscle-targeting agents may be useful for concentrating a molecular payload (*e.g.*, oligonucleotide) in muscle while reducing toxicity associated with effects in other tissues. In some embodiments, the muscle-targeting agent concentrates a bound molecular payload in muscle cells as compared to another cell type within a subject. In some

embodiments, the muscle-targeting agent concentrates a bound molecular payload in muscle cells (*e.g.*, skeletal, smooth, or cardiac muscle cells) in an amount that is at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, or 100 times greater than an amount in non-muscle cells (*e.g.,* liver, neuronal, blood, or fat cells). In some embodiments, a toxicity of the molecular payload in a subject is reduced by at least 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 90%, or 95% when it is delivered to the subject when bound to the muscle-targeting agent.

[000104] In some embodiments, to achieve muscle selectivity, a muscle recognition element (*e.g.,* a muscle cell antigen) may be required. As one example, a muscle-targeting agent may be a small molecule that is a substrate for a muscle-specific uptake transporter. As another example, a muscle-targeting agent may be an antibody that enters a muscle cell via transporter-mediated endocytosis. As another example, a muscle targeting agent may be a ligand that binds to cell surface receptor on a muscle cell. It should be appreciated that while transporter-based approaches provide a direct path for cellular entry, receptor-based targeting may involve stimulated endocytosis to reach the desired site of action.

i. Muscle-Targeting Antibodies

[000105] In some embodiments, the muscle-targeting agent is an antibody. Generally, the high specificity of antibodies for their target antigen provides the potential for selectively targeting muscle cells (*e.g.,* skeletal, smooth, and/or (e.g., and) cardiac muscle cells). This specificity may also limit off-target toxicity. Examples of antibodies that are capable of targeting a surface antigen of muscle cells have been reported and are within the scope of the disclosure. For example, antibodies that target the surface of muscle cells are described in Arahata K., et al. "Immunostaining of skeletal and cardiac muscle surface membrane with antibody against Duchenne muscular dystrophy peptide" *Nature* 1988; 333: 861-3; Song K.S., et al. "Expression of caveolin-3 in skeletal, cardiac, and smooth muscle cells. Caveolin-3 is a component of the sarcolemma and co-fractionates with dystrophin and dystrophin-associated glycoproteins" *J Biol Chem* 1996; 271: 15160-5; and Weisbart R.H. et al., "Cell type specific targeted intracellular delivery into muscle of a monoclonal antibody that binds myosin IIb" *Mol Immunol.* 2003 Mar, 39(13):78309; the entire contents of each of which are incorporated herein by reference.

a. Anti-Transferrin Receptor (TfR) Antibodies

[000106] Some aspects of the disclosure are based on the recognition that agents binding to transferrin receptor, e.g., anti-transferrin-receptor antibodies, are capable of targeting muscle cell. Transferrin receptors are internalizing cell surface receptors that transport transferrin

across the cellular membrane and participate in the regulation and homeostasis of intracellular iron levels. Some aspects of the disclosure provide transferrin receptor binding proteins, which are capable of binding to transferrin receptor. Accordingly, aspects of the disclosure provide binding proteins (*e.g.,* antibodies) that bind to transferrin receptor. In some embodiments, binding proteins that bind to transferrin receptor are internalized, along with any bound molecular payload, into a muscle cell. As used herein, an antibody that binds to a transferrin receptor may be referred to interchangeably as an, transferrin receptor antibody, an anti-transferrin receptor antibody, or an anti-TfR1 antibody. Antibodies that bind, e.g. specifically bind, to a transferrin receptor may be internalized into the cell, e.g. through receptor-mediated endocytosis, upon binding to a transferrin receptor.

[000107] It should be appreciated that anti-TfR1 antibodies may be produced, synthesized, and/or (e.g., and) derivatized using several known methodologies, e.g. library design using phage display. Exemplary methodologies have been characterized in the art and are incorporated by reference (Díez, P. et al. "High-throughput phage-display screening in array format", Enzyme and microbial technology, 2015, 79, 34-41.; Christoph M. H. and Stanley, J.R. "Antibody Phage Display: Technique and Applications" J Invest Dermatol. 2014, 134:2.; Engleman, Edgar (Ed.) "Human Hybridomas and Monoclonal Antibodies." 1985, Springer.). In other embodiments, an anti-TfR1 antibody has been previously characterized or disclosed. Antibodies that specifically bind to transferrin receptor are known in the art (see, e.g. US Patent. No. 4,364,934, filed 12/4/1979, "Monoclonal antibody to a human early thymocyte antigen and methods for preparing same"; US Patent No. 8,409,573, filed 6/14/2006, "Anti-CD71 monoclonal antibodies and uses thereof for treating malignant tumor cells"; US Patent No. 9,708,406, filed 5/20/2014, "Anti-transferrin receptor antibodies and methods of use"; US 9,611,323, filed 12/19/2014, "Low affinity blood brain barrier receptor antibodies and uses therefor"; WO 2015/098989, filed 12/24/2014, "Novel anti-Transferrin receptor antibody that passes through blood-brain barrier"; Schneider C. et al. "Structural features of the cell surface receptor for transferrin that is recognized by the monoclonal antibody OKT9." J Biol Chem. 1982, 257:14, 8516-8522.; Lee et al. "Targeting Rat Anti-Mouse Transferrin Receptor Monoclonal Antibodies through Blood-Brain Barrier in Mouse" 2000, J Pharmacol. Exp. Ther., 292: 1048-1052.).

[000108] In some embodiments, the anti-TfR1 antibody described herein binds to transferrin receptor with high specificity and affinity. In some embodiments, the anti-TfR1 antibody described herein specifically binds to any extracellular epitope of a transferrin receptor or an epitope that becomes exposed to an antibody. In some embodiments, anti-TfR1

antibodies provided herein bind specifically to transferrin receptor from human, non-human primates, mouse, rat, *etc*. In some embodiments, anti-TfR1 antibodies provided herein bind to human transferrin receptor. In some embodiments, the anti-TfR1 antibody described herein binds to an amino acid segment of a human or non-human primate transferrin receptor, as provided in SEQ ID NOs: 105-108. In some embodiments, the anti-TfR1 antibody described herein binds to an amino acid segment corresponding to amino acids 90-96 of a human transferrin receptor as set forth in SEQ ID NO: 105, which is not in the apical domain of the transferrin receptor.

[000109] In some embodiments, the anti-TfR1 antibodies described herein (e.g., Anti-TfR clone 8 in Table 2 below) bind an epitope in TfR1, wherein the epitope comprises residues in amino acids 214-241 and/or amino acids 354-381 of SEQ ID NO: 105. In some embodiments, the anti-TfR1 antibodies described herein bind an epitope comprising residues in amino acids 214-241 and amino acids 354-381 of SEQ ID NO: 105. In some embodiments, the anti-TfR1 antibodies described herein bind an epitope comprising one or more of residues Y222, T227, K231, H234, T367, S368, S370, T376, and S378 of human TfR1 as set forth in SEQ ID NO: 105. In some embodiments, the anti-TfR1 antibodies described herein bind an epitope comprising residues Y222, T227, K231, H234, T367, S368, S370, T376, and S378 of human TfR1 as set forth in SEQ ID NO: 105.

[000110] In some embodiments, the anti-TfR1 antibody described herein (e.g., 3M12 in Table 2 below and its variants) bind an epitope in TfR1, wherein the epitope comprises residues in amino acids 258-291 and/or amino acids 358-381 of SEQ ID NO: 105. In some embodiments, the anti-TfR1 antibodies (e.g., 3M12 in Table 2 below and its variants) described herein bind an epitope comprising residues in amino acids amino acids 258-291 and amino acids 358-381 of SEQ ID NO: 105. In some embodiments, the anti-TfR1 antibodies described herein (e.g., 3M12 in Table 2 below and its variants) bind an epitope comprising one or more of residues K261, S273, Y282, T362, S368, S370, and K371 of human TfR1 as set forth in SEQ ID NO: 105. In some embodiments, the anti-TfR1 antibodies described herein (e.g., 3M12 in Table 2 below and its variants) bind an epitope comprising residues K261, S273, Y282, T362, S368, S370, and K371 of human TfR1 as set forth in SEQ ID NO: 105.

[000111] An example human transferrin receptor amino acid sequence, corresponding to NCBI sequence NP_003225.2 (transferrin receptor protein 1 isoform 1, homo sapiens) is as follows:

MMDQARSAFSNLFGGEPLSYTRFSLARQVDGDNSHVEMKLAVDEEENADNNTKANV
TKPKRCSGSICYGTIAVIVFFLIGFMIGYLGYCKGVEPKTECERLAGTESPVREEPGEDF

PAARRLYWDDLKRKLSEKLDSTDFTGTIKLLNENSYVPREAGSQKDENLALYVENQF
REFKLSKVWRDQHFVKIQVKDSAQNSVIIVDKNGRLVYLVENPGGYVAYSKAATVTG
KLVHANFGTKKDFEDLYTPVNGSIVIVRAGKITFAEKVANAESLNAIGVLIYMDQTKF
PIVNAELSFFGHAHLGTGDPYTPGFPSFNHTQFPPSRSSGLPNIPVQTISRAAAEKLFGN
MEGDCPSDWKTDSTCRMVTSESKNVKLTVSNVLKEIKILNIFGVIKGFVEPDHYVVVG
AQRDAWGPGAAKSGVGTALLLKLAQMFSDMVLKDGFQPSRSIIFASWSAGDFGSVG
ATEWLEGYLSSLHLKAFTYINLDKAVLGTSNFKVSASPLLYTLIEKTMQNVKHPVTGQ
FLYQDSNWASKVEKLTLDNAAFPFLAYSGIPAVSFCFCEDTDYPYLGTTMDTYKELIE
RIPELNKVARAAAEVAGQFVIKLTHDVELNLDYERYNSQLLSFVRDLNQYRADIKEM
GLSLQWLYSARGDFFRATSRLTTDFGNAEKTDRFVMKKLNDRVMRVEYHFLSPYVSP
KESPFRHVFWGSGSHTLPALLENLKLRKQNNGAFNETLFRNQLALATWTIQGAANAL
SGDVWDIDNEF (SEQ ID NO: 105).

[000112] An example non-human primate transferrin receptor amino acid sequence, corresponding to NCBI sequence NP_001244232.1(transferrin receptor protein 1, Macaca mulatta) is as follows:

MMDQARSAFSNLFGGEPLSYTRFSLARQVDGDNSHVEMKLGVDEEENTDNNTKPNG
TKPKRCGGNICYGTIAVIIFFLIGFMIGYLGYCKGVEPKTECERLAGTESPAREEPEEDFP
AAPRLYWDDLKRKLSEKLDTTDFTSTIKLLNENLYVPREAGSQKDENLALYIENQFRE
FKLSKVWRDQHFVKIQVKDSAQNSVIIVDKNGGLVYLVENPGGYVAYSKAATVTGK
LVHANFGTKKDFEDLDSPVNGSIVIVRAGKITFAEKVANAESLNAIGVLIYMDQTKFPI
VKADLSFFGHAHLGTGDPYTPGFPSFNHTQFPPSQSSGLPNIPVQTISRAAAEKLFGNM
EGDCPSDWKTDSTCKMVTSENKSVKLTVSNVLKETKILNIFGVIKGFVEPDHYVVVGA
QRDAWGPGAAKSSVGTALLLKLAQMFSDMVLKDGFQPSRSIIFASWSAGDFGSVGAT
EWLEGYLSSLHLKAFTYINLDKAVLGTSNFKVSASPLLYTLIEKTMQDVKHPVTGRSL
YQDSNWASKVEKLTLDNAAFPFLAYSGIPAVSFCFCEDTDYPYLGTTMDTYKELVERI
PELNKVARAAAEVAGQFVIKLTHDTELNLDYERYNSQLLLFLRDLNQYRADVKEMGL
SLQWLYSARGDFFRATSRLTTDFRNAEKRDKFVMKKLNDRVMRVEYYFLSPYVSPKE
SPFRHVFWGSGSHTLSALLESLKLRRQNNSAFNETLFRNQLALATWTIQGAANALSGD
VWDIDNEF

(SEQ ID NO: 106)

[000113] An example non-human primate transferrin receptor amino acid sequence, corresponding to NCBI sequence XP_005545315.1 (transferrin receptor protein 1, Macaca fascicularis) is as follows:

MMDQARSAFSNLFGGEPLSYTRFSLARQVDGDNSHVEMKLGVDEEENTDNNTKANG
TKPKRCGGNICYGTIAVIIFFLIGFMIGYLGYCKGVEPKTECERLAGTESPAREEPEEDFP
AAPRLYWDDLKRKLSEKLDTTDFTSTIKLLNENLYVPREAGSQKDENLALYIENQFRE
FKLSKVWRDQHFVKIQVKDSAQNSVIIVDKNGGLVYLVENPGGYVAYSKAATVTGK
LVHANFGTKKDFEDLDSPVNGSIVIVRAGKITFAEKVANAESLNAIGVLIYMDQTKFPI
VKADLSFFGHAHLGTGDPYTPGFPSFNHTQFPPSQSSGLPNIPVQTISRAAAEKLFGNM
EGDCPSDWKTDSTCKMVTSENKSVKLTVSNVLKETKILNIFGVIKGFVEPDHYVVVGA
QRDAWGPGAAKSSVGTALLLKLAQMFSDMVLKDGFQPSRSIIFASWSAGDFGSVGAT
EWLEGYLSSLHLKAFTYINLDKAVLGTSNFKVSASPLLYTLIEKTMQDVKHPVTGRSL
YQDSNWASKVEKLTLDNAAFPFLAYSGIPAVSFCFCEDTDYPYLGTTMDTYKELVERI
PELNKVARAAAEVAGQFVIKLTHDTELNLDYERYNSQLLLFLRDLNQYRADVKEMGL
SLQWLYSARGDFFRATSRLTTDFRNAEKRDKFVMKKLNDRVMRVEYYFLSPYVSPKE
SPFRHVFWGSGSHTLSALLESLKLRRQNNSAFNETLFRNQLALATWTIQGAANALSGD
VWDIDNEF (SEQ ID NO: 107).

[000114] An example mouse transferrin receptor amino acid sequence, corresponding to NCBI sequence NP_001344227.1 (transferrin receptor protein 1, mus musculus) is as follows:
MMDQARSAFSNLFGGEPLSYTRFSLARQVDGDNSHVEMKLAADEEENADNNMKASV
RKPKRFNGRLCFAAIALVIFFLIGFMSGYLGYCKRVEQKEECVKLAETEETDKSETMET
EDVPTSSRLYWADLKTLLSEKLNSIEFADTIKQLSQNTYTPREAGSQKDESLAYYIENQ
FHEFKFSKVWRDEHYVKIQVKSSIGQNMVTIVQSNGNLDPVESPEGYVAFSKPTEVSG
KLVHANFGTKKDFEELSYSVNGSLVIVRAGEITFAEKVANAQSFNAIGVLIYMDKNKF
PVVEADLALFGHAHLGTGDPYTPGFPSFNHTQFPPSQSSGLPNIPVQTISRAAAEKLFG
KMEGSCPARWNIDSSCKLELSQNQNVKLIVKNVLKERRILNIFGVIKGYEEPDRYVVV
GAQRDALGAGVAAKSSVGTGLLLKLAQVFSDMISKDGFRPSRSIIFASWTAGDFGAVG
ATEWLEGYLSSLHLKAFTYINLDKVVLGTSNFKVSASPLLYTLMGKIMQDVKHPVDG
KSLYRDSNWISKVEKLSFDNAAYPFLAYSGIPAVSFCFCEDADYPYLGTRLDTYEALT
QKVPQLNQMVRTAAEVAGQLIIKLTHDVELNLDYEMYNSKLLSFMKDLNQFKTDIRD
MGLSLQWLYSARGDYFRATSRLTTDFHNAEKTNRFVMREINDRIMKVEYHFLSPYVS
PRESPFRHIFWGSGSHTLSALVENLKLRQKNITAFNETLFRNQLALATWTIQGVANALS
GDIWNIDNEF
(SEQ ID NO: 108)

[000115] In some embodiments, an anti-TfR1 antibody binds to an amino acid segment of the receptor as follows:
FVKIQVKDSAQNSVIIVDKNGRLVYLVENPGGYVAYSKAATVTGKLVHANFGTKKDF

EDLYTPVNGSIVIVRAGKITFAEKVANAESLNAIGVLIYMDQTKFPIVNAELSFFGHAH LGTGDPYTPGFPSFNHTQFPPSRSSGLPNIPVQTISRAAAEKLFGNMEGDCPSDWKTDS TCRMVTSESKNVKLTVSNVLKE (SEQ ID NO: 109) and does not inhibit the binding interactions between transferrin receptors and transferrin and/or (e.g., and) human hemochromatosis protein (also known as HFE). In some embodiments, the anti-TfR1 antibody described herein does not bind an epitope in SEQ ID NO: 109.

[000116] Appropriate methodologies may be used to obtain and/or (e.g., and) produce antibodies, antibody fragments, or antigen-binding agents, e.g., through the use of recombinant DNA protocols. In some embodiments, an antibody may also be produced through the generation of hybridomas (see, e.g., Kohler, G and Milstein, C. "Continuous cultures of fused cells secreting antibody of predefined specificity" Nature, 1975, 256: 495-497). The antigen-of-interest may be used as the immunogen in any form or entity, e.g., recombinant or a naturally occurring form or entity. Hybridomas are screened using standard methods, e.g. ELISA screening, to find at least one hybridoma that produces an antibody that targets a particular antigen. Antibodies may also be produced through screening of protein expression libraries that express antibodies, e.g., phage display libraries. Phage display library design may also be used, in some embodiments, (see, e.g. U.S. Patent No 5,223,409, filed 3/1/1991, "Directed evolution of novel binding proteins"; WO 1992/18619, filed 4/10/1992, "Heterodimeric receptor libraries using phagemids"; WO 1991/17271, filed 5/1/1991, "Recombinant library screening methods"; WO 1992/20791, filed 5/15/1992, "Methods for producing members of specific binding pairs"; WO 1992/15679, filed 2/28/1992, and "Improved epitope displaying phage"). In some embodiments, an antigen-of-interest may be used to immunize a non-human animal, e.g., a rodent or a goat. In some embodiments, an antibody is then obtained from the non-human animal, and may be optionally modified using a number of methodologies, e.g., using recombinant DNA techniques. Additional examples of antibody production and methodologies are known in the art (see, e.g. Harlow et al. "Antibodies: A Laboratory Manual", Cold Spring Harbor Laboratory, 1988.).

[000117] In some embodiments, an antibody is modified, e.g., modified via glycosylation, phosphorylation, sumoylation, and/or (e.g., and) methylation. In some embodiments, an antibody is a glycosylated antibody, which is conjugated to one or more sugar or carbohydrate molecules. In some embodiments, the one or more sugar or carbohydrate molecule are conjugated to the antibody via N-glycosylation, O-glycosylation, C-glycosylation, glypiation (GPI anchor attachment), and/or (e.g., and) phosphoglycosylation. In some embodiments, the one or more sugar or carbohydrate molecules are monosaccharides, disaccharides,

oligosaccharides, or glycans. In some embodiments, the one or more sugar or carbohydrate molecule is a branched oligosaccharide or a branched glycan. In some embodiments, the one or more sugar or carbohydrate molecule includes a mannose unit, a glucose unit, an N-acetylglucosamine unit, an N-acetylgalactosamine unit, a galactose unit, a fucose unit, or a phospholipid unit. In some embodiments, there are about 1-10, about 1-5, about 5-10, about 1-4, about 1-3, or about 2 sugar molecules. In some embodiments, a glycosylated antibody is fully or partially glycosylated. In some embodiments, an antibody is glycosylated by chemical reactions or by enzymatic means. In some embodiments, an antibody is glycosylated in vitro or inside a cell, which may optionally be deficient in an enzyme in the N- or O- glycosylation pathway, e.g. a glycosyltransferase. In some embodiments, an antibody is functionalized with sugar or carbohydrate molecules as described in International Patent Application Publication WO2014065661, published on May 1, 2014, entitled, "*Modified antibody, antibody-conjugate and process for the preparation thereof*".

[000118] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VL domain and/or (e.g., and) a VH domain of any one of the anti-TfR1 antibodies selected from any one of Tables 2-7, and comprises a constant region comprising the amino acid sequences of the constant regions of an IgG, IgE, IgM, IgD, IgA or IgY immunoglobulin molecule, any class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2), or any subclass (e.g., IgG2a and IgG2b) of immunoglobulin molecule. Non-limiting examples of human constant regions are described in the art, *e.g.*, see Kabat E A et al., (1991) supra.

[000119] In some embodiments, agents binding to transferrin receptor, e.g., anti-TfR1 antibodies, are capable of targeting muscle cell and/or (e.g., and) mediate the transportation of an agent across the blood brain barrier. Transferrin receptors are internalizing cell surface receptors that transport transferrin across the cellular membrane and participate in the regulation and homeostasis of intracellular iron levels. Some aspects of the disclosure provide transferrin receptor binding proteins, which are capable of binding to transferrin receptor. Antibodies that bind, e.g. specifically bind, to a transferrin receptor may be internalized into the cell, e.g. through receptor-mediated endocytosis, upon binding to a transferrin receptor.

[000120] Provided herein, in some aspects, are humanized antibodies that bind to transferrin receptor with high specificity and affinity. In some embodiments, the humanized anti-TfR1 antibody described herein specifically binds to any extracellular epitope of a transferrin receptor or an epitope that becomes exposed to an antibody. In some embodiments, the humanized anti-TfR1 antibodies provided herein bind specifically to transferrin receptor from human, non-human primates, mouse, rat, *etc*. In some embodiments, the humanized anti-

TfR1 antibodies provided herein bind to human transferrin receptor. In some embodiments, the humanized anti-TfR1 antibody described herein binds to an amino acid segment of a human or non-human primate transferrin receptor, as provided in SEQ ID NOs: 105-108. In some embodiments, the humanized anti-TfR1 antibody described herein binds to an amino acid segment corresponding to amino acids 90-96 of a human transferrin receptor as set forth in SEQ ID NO: 105, which is not in the apical domain of the transferrin receptor. In some embodiments, the humanized anti-TfR1 antibodies described herein binds to TfR1 but does not bind to TfR2.

[000121] In some embodiments, an anti-TFR1 antibody specifically binds a TfR1 (e.g., a human or non-human primate TfR1) with binding affinity (e.g., as indicated by Kd) of at least about 10^{-4} M, 10^{-5} M, 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, 10^{-12} M, 10^{-13} M, or less. In some embodiments, the anti-TfR1 antibodies described herein bind to TfR1 with a KD of sub-nanomolar range. In some embodiments, the anti-TfR1 antibodies described herein selectively bind to transferrin receptor 1 (TfR1) but do not bind to transferrin receptor 2 (TfR2). In some embodiments, the anti-TfR1 antibodies described herein bind to human TfR1 and cyno TfR1 (e.g., with a Kd of 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, 10^{-12} M, 10^{-13} M, or less), but do not bind to a mouse TfR1. The affinity and binding kinetics of the anti-TfR1 antibody can be tested using any suitable method including but not limited to biosensor technology (e.g., OCTET or BIACORE). In some embodiments, binding of any one of the anti-TfR1 antibodies described herein does not complete with or inhibit transferrin binding to the TfR1. In some embodiments, binding of any one of the anti-TfR1 antibodies described herein does not complete with or inhibit HFE-beta-2-microglobulin binding to the TfR1.

[000122] Non-limiting examples of anti-TfR1 antibodies are provided in Table 2.

Table 2. Examples of Anti-TfR1 Antibodies

Ab	No. system	IMGT	Kabat	Chothia
3-A4	CDR-H1	GFNIKDDY (SEQ ID NO: 1)	DDYMY (SEQ ID NO: 7)	GFNIKDD (SEQ ID NO: 12)
	CDR-H2	IDPENGDT (SEQ ID NO: 2)	WIDPENGDTEYASKFQD (SEQ ID NO: 8)	ENG (SEQ ID NO: 13)
	CDR-H3	TLWLRRGLDY (SEQ ID NO: 3)	WLRRGLDY (SEQ ID NO: 9)	LRRGLD (SEQ ID NO: 14)
	CDR-L1	KSLLHSNGYTY (SEQ ID NO: 4)	RSSKSLLHSNGYTYLF (SEQ ID NO: 10)	SKSLLHSNGYTY (SEQ ID NO: 15)
	CDR-L2	RMS (SEQ ID NO: 5)	RMSNLAS (SEQ ID NO: 11)	RMS (SEQ ID NO: 5)
	CDR-L3	MQHLEYPFT (SEQ ID NO: 6)	MQHLEYPFT (SEQ ID NO: 6)	HLEYPF (SEQ ID NO: 16)

Ab	No. system	IMGT	Kabat	Chothia
	VH	EVQLQQSGAELVRPGASVKLSCTASGFNIKDDYMYWVKQRPEQGLEWIGWIDPENGDT EYASKFQDKATVTADTSSNTAYLQLSSLTSEDTAVYYCTLWLRRGLDYWGQGTSVTVS S (SEQ ID NO: 17)		
	VL	DIVMTQAAPSVPVTPGESVSISCRSSKSLLHSNGYTYLFWFLQRPGQSPQLLIYRMSNLA SGVPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPFTFGGGTKLEIK (SEQ ID NO: 18)		
3-A4 N54T*	CDR-H1	GFNIKDDY (SEQ ID NO: 1)	DDYMY (SEQ ID NO: 7)	GFNIKDD (SEQ ID NO: 12)
	CDR-H2	IDPETGDT (SEQ ID NO: 19)	WIDPETGDTEYASKFQD (SEQ ID NO: 20)	ETG (SEQ ID NO: 21)
	CDR-H3	TLWLRRGLDY (SEQ ID NO: 3)	WLRRGLDY (SEQ ID NO: 9)	LRRGLD (SEQ ID NO: 14)
	CDR-L1	KSLLHSNGYTY (SEQ ID NO: 4)	RSSKSLLHSNGYTYLF (SEQ ID NO: 10)	SKSLLHSNGYTY (SEQ ID NO: 15)
	CDR-L2	RMS (SEQ ID NO: 5)	RMSNLAS (SEQ ID NO: 11)	RMS(SEQ ID NO: 5)
	CDR-L3	MQHLEYPFT (SEQ ID NO: 6)	MQHLEYPFT (SEQ ID NO: 6)	HLEYPF (SEQ ID NO: 16)
	VH	EVQLQQSGAELVRPGASVKLSCTASGFNIKDDYMYWVKQRPEQGLEWIGWIDPETGDT EYASKFQDKATVTADTSSNTAYLQLSSLTSEDTAVYYCTLWLRRGLDYWGQGTSVTVS S (SEQ ID NO: 22)		
	VL	DIVMTQAAPSVPVTPGESVSISCRSSKSLLHSNGYTYLFWFLQRPGQSPQLLIYRMSNLA SGVPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPFTFGGGTKLEIK (SEQ ID NO: 18)		
3-A4 N54S*	CDR-H1	GFNIKDDY (SEQ ID NO: 1)	DDYMY (SEQ ID NO: 7)	GFNIKDD (SEQ ID NO: 12)
	CDR-H2	IDPESGDT (SEQ ID NO: 23)	WIDPESGDTEYASKFQD (SEQ ID NO: 24)	ESG (SEQ ID NO: 25)
	CDR-H3	TLWLRRGLDY (SEQ ID NO: 3)	WLRRGLDY (SEQ ID NO: 9)	LRRGLD (SEQ ID NO: 14)
	CDR-L1	KSLLHSNGYTY (SEQ ID NO: 4)	RSSKSLLHSNGYTYLF (SEQ ID NO: 10)	SKSLLHSNGYTY (SEQ ID NO: 15)
	CDR-L2	RMS (SEQ ID NO: 5)	RMSNLAS (SEQ ID NO: 11)	RMS (SEQ ID NO: 5)
	CDR-L3	MQHLEYPFT (SEQ ID NO: 6)	MQHLEYPFT (SEQ ID NO: 6)	HLEYPF (SEQ ID NO: 16)
	VH	EVQLQQSGAELVRPGASVKLSCTASGFNIKDDYMYWVKQRPEQGLEWIGWIDPESGDT EYASKFQDKATVTADTSSNTAYLQLSSLTSEDTAVYYCTLWLRRGLDYWGQGTSVTVS S (SEQ ID NO: 26)		
	VL	DIVMTQAAPSVPVTPGESVSISCRSSKSLLHSNGYTYLFWFLQRPGQSPQLLIYRMSNLA SGVPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPFTFGGGTKLEIK (SEQ ID NO: 18)		
3-M12	CDR-H1	GYSITSGYY (SEQ ID NO: 27)	SGYYWN (SEQ ID NO: 33)	GYSITSGY (SEQ ID NO: 38)
	CDR-H2	ITFDGAN (SEQ ID NO: 28)	YITFDGANNYNPSLKN (SEQ ID NO: 34)	FDG (SEQ ID NO: 39)
	CDR-H3	TRSSYDYDVLDY (SEQ ID NO: 29)	SSYDYDVLDY (SEQ ID NO: 35)	SYDYDVLD (SEQ ID NO: 40)
	CDR-L1	QDISNF (SEQ ID NO: 30)	RASQDISNFLN (SEQ ID NO: 36)	SQDISNF (SEQ ID NO: 41)
	CDR-L2	YTS (SEQ ID NO: 31)	YTSRLHS (SEQ ID NO: 37)	YTS (SEQ ID NO: 31)
	CDR-L3	QQGHTLPYT (SEQ ID NO: 32)	QQGHTLPYT (SEQ ID NO: 32)	GHTLPY (SEQ ID NO: 42)
	VH	DVQLQESGPGLVKPSQSLSLTCSVTGYSITSGYYWNWIRQFPGNKLEWMGYITFDGAN NYNPSLKNRISITRDTSKNQFFLKLTSVTTEDTATYYCTRSSYDYDVLDYWGQGTTLTV SS (SEQ ID NO: 43)		

Ab	No. system	IMGT	Kabat	Chothia
	VL	DIQMTQTTSSLSASLGDRVTISCRASQDISNFLNWYQQRPDGTVKLLIYYTSRLHSGVPS RFSGSGSGTDFSLTVSNLEQEDIATYFCQQGHTLPYTFGGGTKLEIK (SEQ ID NO: 44)		
5-H12	CDR-H1	GYSFTDYC (SEQ ID NO: 45)	DYCIN (SEQ ID NO: 51)	GYSFTDY (SEQ ID NO: 56)
	CDR-H2	IYPGSGNT (SEQ ID NO: 46)	WIYPGSGNTRYSERFKG (SEQ ID NO: 52)	GSG (SEQ ID NO: 57)
	CDR-H3	AREDYYPYHGMDY (SEQ ID NO: 47)	EDYYPYHGMDY (SEQ ID NO: 53)	DYYPYHGMD (SEQ ID NO: 58)
	CDR-L1	ESVDGYDNSF (SEQ ID NO: 48)	RASESVDGYDNSFMH (SEQ ID NO: 54)	SESVDGYDNSF (SEQ ID NO: 59)
	CDR-L2	RAS (SEQ ID NO: 49)	RASNLES (SEQ ID NO: 55)	RAS (SEQ ID NO: 49)
	CDR-L3	QQSSEDPWT (SEQ ID NO: 50)	QQSSEDPWT (SEQ ID NO: 50)	SSEDPW (SEQ ID NO: 60)
	VH	QIQLQQSGPELVRPGASVKISCKASGYSFTDYCINWVNQRPGQGLEWIGWIYPGSGNTR YSERFKGKATLTVDTSSNTAYMQLSSLTSEDSAVYFCAREDYYPYHGMDYWGQGTSV TVSS (SEQ ID NO: 61)		
	VL	DIVLTQSPTSLAVSLGQRATISCRASESVDGYDNSFMHWYQQKPGQPPKLLIFRASNLES GIPARFSGSGSRTDFTLTINPVEAADVATYYCQQSSEDPWTFGGGTKLEIK (SEQ ID NO: 62)		
5-H12 C33Y*	CDR-H1	GYSFTDYY (SEQ ID NO: 63)	DYYIN (SEQ ID NO: 64)	GYSFTDY (SEQ ID NO: 56)
	CDR-H2	IYPGSGNT (SEQ ID NO: 46)	WIYPGSGNTRYSERFKG (SEQ ID NO: 52)	GSG (SEQ ID NO: 57)
	CDR-H3	AREDYYPYHGMDY (SEQ ID NO: 47)	EDYYPYHGMDY (SEQ ID NO: 53)	DYYPYHGMD (SEQ ID NO: 58)
	CDR-L1	ESVDGYDNSF (SEQ ID NO: 48)	RASESVDGYDNSFMH (SEQ ID NO: 54)	SESVDGYDNSF (SEQ ID NO: 59)
	CDR-L2	RAS (SEQ ID NO: 49)	RASNLES (SEQ ID NO: 55)	RAS (SEQ ID NO: 49)
	CDR-L3	QQSSEDPWT (SEQ ID NO: 50)	QQSSEDPWT (SEQ ID NO: 50)	SSEDPW (SEQ ID NO: 60)
	VH	QIQLQQSGPELVRPGASVKISCKASGYSFTDYYINWVNQRPGQGLEWIGWIYPGSGNTR YSERFKGKATLTVDTSSNTAYMQLSSLTSEDSAVYFCAREDYYPYHGMDYWGQGTSV TVSS (SEQ ID NO: 65)		
	VL	DIVLTQSPTSLAVSLGQRATISCRASESVDGYDNSFMHWYQQKPGQPPKLLIFRASNLES GIPARFSGSGSRTDFTLTINPVEAADVATYYCQQSSEDPWTFGGGTKLEIK (SEQ ID NO: 62)		
5-H12 C33D*	CDR-H1	GYSFTDYD (SEQ ID NO: 66)	DYDIN (SEQ ID NO: 67)	GYSFTDY (SEQ ID NO: 56)
	CDR-H2	IYPGSGNT (SEQ ID NO: 46)	WIYPGSGNTRYSERFKG (SEQ ID NO: 52)	GSG (SEQ ID NO: 57)
	CDR-H3	AREDYYPYHGMDY (SEQ ID NO: 47)	EDYYPYHGMDY (SEQ ID NO: 53)	DYYPYHGMD (SEQ ID NO: 58)
	CDR-L1	ESVDGYDNSF (SEQ ID NO: 48)	RASESVDGYDNSFMH (SEQ ID NO: 54)	SESVDGYDNSF (SEQ ID NO: 59)
	CDR-L2	RAS (SEQ ID NO: 49)	RASNLES (SEQ ID NO: 55)	RAS (SEQ ID NO: 49)
	CDR-L3	QQSSEDPWT (SEQ ID NO: 50)	QQSSEDPWT (SEQ ID NO: 50)	SSEDPW (SEQ ID NO: 60)
	VH	QIQLQQSGPELVRPGASVKISCKASGYSFTDYDINWVNQRPGQGLEWIGWIYPGSGNTRY SERFKGKATLTVDTSSNTAYMQLSSLTSEDSAVYFCAREDYYPYHGMDYWGQGTSVTV SS (SEQ ID NO: 68)		
	VL	DIVLTQSPTSLAVSLGQRATISCRASESVDGYDNSFMHWYQQKPGQPPKLLIFRASNLES GIPARFSGSGSRTDFTLTINPVEAADVATYYCQQSSEDPWTFGGGTKLEIK (SEQ ID NO: 62)		
	CDR-H1	GYSFTSYW (SEQ ID NO: 138)	SYWIG (SEQ ID NO: 144)	GYSFTSY (SEQ ID NO: 149)

Ab	No. system	IMGT	Kabat	Chothia
Anti-TfR clone 8	CDR-H2	IYPGDSDT (SEQ ID NO: 139)	IIYPGDSDTRYSPSFQGQ (SEQ ID NO: 145)	GDS (SEQ ID NO: 150)
	CDR-H3	ARFPYDSSGYYSFDY (SEQ ID NO: 140)	FPYDSSGYYSFDY (SEQ ID NO: 146)	PYDSSGYYSFD (SEQ ID NO: 151)
	CDR-L1	QSISSY (SEQ ID NO: 141)	RASQSISSYLN (SEQ ID NO: 147)	SQSISSY (SEQ ID NO: 152)
	CDR-L2	AAS (SEQ ID NO: 142)	AASSLQS (SEQ ID NO: 148)	AAS (SEQ ID NO: 142)
	CDR-L3	QQSYSTPLT (SEQ ID NO: 143)	QQSYSTPLT (SEQ ID NO: 143)	SYSTPL (SEQ ID NO: 153)

** mutation positions are according to Kabat numbering of the respective VH sequences containing the mutations*

[000123] In some embodiments, the anti-TfR1 antibody of the present disclosure is a humanized variant of any one of the anti-TfR1 antibodies provided in Table 2. In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a CDR-H1, a CDR-H2, a CDR-H3, a CDR-L1, a CDR-L2, and a CDR-L3 that are the same as the CDR-H1, CDR-H2, and CDR-H3 in any one of the anti-TfR1 antibodies provided in Table 2, and comprises a humanized heavy chain variable region and/or (e.g., and) a humanized light chain variable region.

[000124] Examples of amino acid sequences of anti-TfR1 antibodies described herein are provided in Table 3.

Table 3. Variable Regions of Anti-TfR1 Antibodies

Antibody	Variable Region Amino Acid Sequence**
3A4 VH3 (N54T*)/Vκ4	V_H: EVQLVQSGSELKKPGASVKVSCTASGFNIK**DDYMY**WVRQPPGKGLEWIG**WID PETGDTEYASKFQD**RVTVTADTSTNTAYMELSSLRSEDTAVYYCTL**WLRRGL DY**WGQGTLVTVSS (SEQ ID NO: 69)
	V_L: DIVMTQSPLSLPVTPGEPASISC**RSSKSLLHSNGYTYLF**WFQQRPGQSPRLLIY**R MSNLAS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**MQHLEYPFT**FGGGT KVEIK (SEQ ID NO: 70)
3A4 VH3 (N54S*)/Vκ4	V_H: EVQLVQSGSELKKPGASVKVSCTASGFNIK**DDYMY**WVRQPPGKGLEWIG**WID PESGDTEYASKFQD**RVTVTADTSTNTAYMELSSLRSEDTAVYYCTL**WLRRGL DY**WGQGTLVTVSS (SEQ ID NO: 71)
	V_L: DIVMTQSPLSLPVTPGEPASISC**RSSKSLLHSNGYTYLF**WFQQRPGQSPRLLIY**R MSNLAS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**MQHLEYPFT**FGGGT KVEIK (SEQ ID NO: 70)
3A4 VH3 /Vκ4	VH: EVQLVQSGSELKKPGASVKVSCTASGFNIK**DDYMY**WVRQPPGKGLEWIG**WID PENGDTEYASKFQD**RVTVTADTSTNTAYMELSSLRSEDTAVYYCTL**WLRRGL DY**WGQGTLVTVSS (SEQ ID NO: 72)
	VL: DIVMTQSPLSLPVTPGEPASISC**RSSKSLLHSNGYTYLF**WFQQRPGQSPRLLIY**R MSNLAS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**MQHLEYPFT**FGGGT KVEIK (SEQ ID NO: 70)

Antibody	Variable Region Amino Acid Sequence**
3M12 VH3/Vκ2	VH: QVQLQESGPGLVKPSQTLSLTCSVTGYSIT**SGYYWN**WIRQPPGKGLEWMG**YIT FDGANNYNPSLKN**RVSISRDTSKNQFSLKLSSVTAEDTATYYCTR**SSYDYDVL DY**WGQGTTVTVSS (SEQ ID NO: 73)
	VL: DIQMTQSPSSLSASVGDRVTITC**RASQDISNFLN**WYQQKPGQPVKLLIY**YTSRL HS**GVPSRFSGSGSGTDFTLTISSLQPEDFATYFC**QQGHTLPYT**FGQGTKLEIK (SEQ ID NO: 74)
3M12 VH3/Vκ3	VH: QVQLQESGPGLVKPSQTLSLTCSVTGYSIT**SGYYWN**WIRQPPGKGLEWMG**YIT FDGANNYNPSLKN**RVSISRDTSKNQFSLKLSSVTAEDTATYYCTR**SSYDYDVL DY**WGQGTTVTVSS (SEQ ID NO: 73)
	VL: DIQMTQSPSSLSASVGDRVTITC**RASQDISNFLN**WYQQKPGQPVKLLIY**YTSRL HS**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQGHTLPYT**FGQGTKLEIK (SEQ ID NO: 75)
3M12 VH4/Vκ2	VH: QVQLQESGPGLVKPSQTLSLTCTVTGYSIT**SGYYWN**WIRQPPGKGLEWIG**YITF DGANNYNPSLKN**RVSISRDTSKNQFSLKLSSVTAEDTATYYCTR**SSYDYDVLD Y**WGQGTTVTVSS (SEQ ID NO: 76)
	VL: DIQMTQSPSSLSASVGDRVTITC**RASQDISNFLN**WYQQKPGQPVKLLIY**YTSRL HS**GVPSRFSGSGSGTDFTLTISSLQPEDFATYFC**QQGHTLPYT**FGQGTKLEIK (SEQ ID NO: 74)
3M12 VH4/Vκ3	VH: QVQLQESGPGLVKPSQTLSLTCTVTGYSIT**SGYYWN**WIRQPPGKGLEWIG**YITF DGANNYNPSLKN**RVSISRDTSKNQFSLKLSSVTAEDTATYYCTR**SSYDYDVLD Y**WGQGTTVTVSS (SEQ ID NO: 76)
	VL: DIQMTQSPSSLSASVGDRVTITC**RASQDISNFLN**WYQQKPGQPVKLLIY**YTSRL HS**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQGHTLPYT**FGQGTKLEIK (SEQ ID NO: 75)
5H12 VH5 (C33Y*)/Vκ3	VH: QVQLVQSGAEVKKPGASVKVSCKASGYSFT**DYYIN**WVRQAPGQGLEWMG**WI YPGSGNTRYSERFKG**RVTITRDTSASTAYMELSSLRSEDTAVYYCAR**EDYYPY HGMDY**WGQGTLVTVSS (SEQ ID NO: 77)
	VL: DIVLTQSPDSLAVSLGERATINC**RASESVDGYDNSFMH**WYQQKPGQPPKLLIF**R ASNLES**GVPDRFSGSGSRTDFTLTISSLQAEDVAVYYC**QQSSEDPWT**FGQGTK LEIK (SEQ ID NO: 78)
5H12 VH5 (C33D*)/Vκ4	VH: QVQLVQSGAEVKKPGASVKVSCKASGYSFT**DYDIN**WVRQAPGQGLEWMG**WI YPGSGNTRYSERFKG**RVTITRDTSASTAYMELSSLRSEDTAVYYCAR**EDYYPY HGMDY**WGQGTLVTVSS (SEQ ID NO: 79)
	VL: DIVMTQSPDSLAVSLGERATINC**RASESVDGYDNSFMH**WYQQKPGQPPKLLIF **RASNLES**GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**QQSSEDPWT**FGQGT KLEIK (SEQ ID NO: 80)
5H12 VH5 (C33Y*)/Vκ4	VH: QVQLVQSGAEVKKPGASVKVSCKASGYSFT**DYYIN**WVRQAPGQGLEWMG**WI YPGSGNTRYSERFKG**RVTITRDTSASTAYMELSSLRSEDTAVYYCAR**EDYYPY HGMDY**WGQGTLVTVSS (SEQ ID NO: 77)
	VL: DIVMTQSPDSLAVSLGERATINC**RASESVDGYDNSFMH**WYQQKPGQPPKLLIF **RASNLES**GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**QQSSEDPWT**FGQGT KLEIK (SEQ ID NO: 80)
Anti-TfR clone 8	VH: QVQLVQSGAEVKKPGESLKISCKGSGYSFT**SYWIG**WVRQMPGKGLEWMG**IIY PGDSDTRYSPSFQGQ**VTISADKSISTAYLQWSSLKASDTAMYYCAR**FPYDSSG YYSFDY**WGQGTLVTVSS (SEQ ID NO: 154)

Antibody	Variable Region Amino Acid Sequence**
	VL: DIQMTQSPSSLSASVGDRVTITC**RASQSISSYLN**WYQQKPGKAPKLLIY**AASSL** **QS**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQSYSTPLT**FGGGTKVEIK (SEQ ID NO: 155)

** mutation positions are according to Kabat numbering of the respective VH sequences containing the mutations*
*** CDRs according to the Kabat numbering system are bolded*

[000125] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VH comprising the CDR-H1, CDR-H2, and CDR-H3 of any one of the anti-TfR1 antibodies provided in Table 3 and comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) amino acid variations in the framework regions as compared with the respective VH provided in Table 3. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody of the present disclosure comprises a VL comprising the CDR-L1, CDR-L2, and CDR-L3 of any one of the anti-TfR1 antibodies provided in Table 3 and comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) amino acid variations in the framework regions as compared with the respective VL provided in Table 3. In some embodiments, the VH of the anti-TfR1 antibody is a humanized VH, and/or the VL of the anti-TfR1 antibody is a humanized VL.

[000126] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VH comprising the CDR-H1, CDR-H2, and CDR-H3 of any one of the anti-TfR1 antibodies provided in Table 3 and comprising an amino acid sequence that is at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%) identical in the framework regions as compared with the respective VH provided in Table 3. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody of the present disclosure comprises a VL comprising the CDR-L1, CDR-L2, and CDR-L3 of any one of the anti-TfR1 antibodies provided in Table 3 and comprising an amino acid sequence that is at least 70% (e.g., at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%) identical in the framework regions as compared with the respective VL provided in Table 3. In some embodiments, the VH of the anti-TfR1 antibody is a humanized VH, and/or the VL of the anti-TfR1 antibody is a humanized VL.

[000127] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 69 and a VL comprising the amino acid sequence of SEQ ID NO: 70.

[000128] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 71 and a VL comprising the amino acid sequence of SEQ ID NO: 70.

[000129] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 72 and a VL comprising the amino acid sequence of SEQ ID NO: 70.

[000130] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 73 and a VL comprising the amino acid sequence of SEQ ID NO: 74.

[000131] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 73 and a VL comprising the amino acid sequence of SEQ ID NO: 75.

[000132] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 76 and a VL comprising the amino acid sequence of SEQ ID NO: 74.

[000133] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 76 and a VL comprising the amino acid sequence of SEQ ID NO: 75.

[000134] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 77 and a VL comprising the amino acid sequence of SEQ ID NO: 78.

[000135] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 79 and a VL comprising the amino acid sequence of SEQ ID NO: 80.

[000136] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 77 and a VL comprising the amino acid sequence of SEQ ID NO: 80.

[000137] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 154 and a VL comprising the amino acid sequence of SEQ ID NO: 155.

[000138] In some embodiments, the anti-TfR1 antibody described herein is a full-length IgG, which can include a heavy constant region and a light constant region from a human antibody. In some embodiments, the heavy chain of any of the anti-TfR1 antibodies as described herein may comprise a heavy chain constant region (CH) or a portion thereof (e.g., CH1, CH2, CH3, or a combination thereof). The heavy chain constant region can be of any suitable origin, e.g., human, mouse, rat, or rabbit. In one specific example, the heavy chain

constant region is from a human IgG (a gamma heavy chain), e.g., IgG1, IgG2, or IgG4. An example of a human IgG1 constant region is given below:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL
LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY
SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 81)

[000139] In some embodiments, the heavy chain of any of the anti-TfR1 antibodies described herein comprises a mutant human IgG1 constant region. For example, the introduction of LALA mutations (a mutant derived from mAb b12 that has been mutated to replace the lower hinge residues Leu234 Leu235 with Ala234 and Ala235) in the CH2 domain of human IgG1 is known to reduce Fcγ receptor binding (Bruhns, P., et al . (2009) and Xu, D. et al. (2000)). The mutant human IgG1 constant region is provided below (mutations bonded and underlined):

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE**A**
AGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY
SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 82)

[000140] In some embodiments, the light chain of any of the anti-TfR1 antibodies described herein may further comprise a light chain constant region (CL), which can be any CL known in the art. In some examples, the CL is a kappa light chain. In other examples, the CL is a lambda light chain. In some embodiments, the CL is a kappa light chain, the sequence of which is provided below:

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE
QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 83)

[000141] Other antibody heavy and light chain constant regions are well known in the art, e.g., those provided in the IMGT database (www.imgt.org) or at www.vbase2.org/vbstat.php, both of which are incorporated by reference herein.

[000142] In some embodiments, the anti-TfR1 antibody described herein comprises a heavy chain comprising any one of the VH as listed in Table 3 or any variants thereof and a

heavy chain constant region that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to SEQ ID NO: 81 or SEQ ID NO: 82. In some embodiments, the anti-TfR1 antibody described herein comprises a heavy chain comprising any one of the VH as listed in Table 3 or any variants thereof and a heavy chain constant region that contains no more than 25 amino acid variations (e.g., no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with SEQ ID NO: 81 or SEQ ID NO: 82. In some embodiments, the anti-TfR1 antibody described herein comprises a heavy chain comprising any one of the VH as listed in Table 3 or any variants thereof and a heavy chain constant region as set forth in SEQ ID NO: 81. In some embodiments, the anti-TfR1 antibody described herein comprises heavy chain comprising any one of the VH as listed in Table 3 or any variants thereof and a heavy chain constant region as set forth in SEQ ID NO: 82.

[000143] In some embodiments, the anti-TfR1 antibody described herein comprises a light chain comprising any one of the VL as listed in Table 3 or any variants thereof and a light chain constant region that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to SEQ ID NO: 83. In some embodiments, the anti-TfR1 antibody described herein comprises a light chain comprising any one of the VL as listed in Table 3 or any variants thereof and a light chain constant region contains no more than 25 amino acid variations (e.g., no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with SEQ ID NO: 83. In some embodiments, the anti-TfR1 antibody described herein comprises a light chain comprising any one of the VL as listed in Table 3 or any variants thereof and a light chain constant region set forth in SEQ ID NO: 83.

[000144] Examples of IgG heavy chain and light chain amino acid sequences of the anti-TfR1 antibodies described are provided in Table 4 below.

Table 4. Heavy chain and light chain sequences of examples of anti-TfR1 IgGs

Antibody	IgG Heavy Chain/Light Chain Sequences**
3A4 VH3 (N54T*)/Vκ4	Heavy Chain (with wild type human IgG1 constant region) EVQLVQSGSELKKPGASVKVSCTASGFNIK**DDYMY**WVRQPPGKGLEWIG**WIDP** **ETGDTEYASKFQD**RVTVTADTSTNTAYMELSSLRSEDTAVYYCTL**WLRRGLD** **Y**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK (SEQ ID NO: 84)

Antibody	IgG Heavy Chain/Light Chain Sequences**
	Light Chain (with kappa light chain constant region) DIVMTQSPLSLPVTPGEPASISC**RSSKSLLHSNGYTYLF**WFQQRPGQSPRLLIY**RM** **SNLAS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**MQHLEYPFT**FGGGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 85)
3A4 VH3 (N54S*)/Vκ4	Heavy Chain (with wild type human IgG1 constant region) EVQLVQSGSELKKPGASVKVSCTASGFNIK**DDYMY**WVRQPPGKGLEWIG**WIDP** **ESGDTEYASKFQD**RVTVTADTSTNTAYMELSSLRSEDTAVYYCTL**WLRRGLDY** WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK (SEQ ID NO: 86)
	Light Chain (with kappa light chain constant region) DIVMTQSPLSLPVTPGEPASISC**RSSKSLLHSNGYTYLF**WFQQRPGQSPRLLIY**RM** **SNLAS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**MQHLEYPFT**FGGGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 85)
3A4 VH3 /Vκ4	Heavy Chain (with wild type human IgG1 constant region) EVQLVQSGSELKKPGASVKVSCTASGFNIK**DDYMY**WVRQPPGKGLEWIG**WIDP** **ENGDTEYASKFQD**RVTVTADTSTNTAYMELSSLRSEDTAVYYCTL**WLRRGLD** **Y**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK (SEQ ID NO: 87)
	Light Chain (with kappa light chain constant region) DIVMTQSPLSLPVTPGEPASISC**RSSKSLLHSNGYTYLF**WFQQRPGQSPRLLIY**RM** **SNLAS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**MQHLEYPFT**FGGGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 85)
3M12 VH3/Vκ2	Heavy Chain (with wild type human IgG1 constant region) QVQLQESGPGLVKPSQTLSLTCSVTGYSIT**SGYYWN**WIRQPPGKGLEWMG**YITF** **DGANNYNPSLKN**RVSISRDTSKNQFSLKLSSVTAEDTATYYCTR**SSYDYDVLDY** WGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK (SEQ ID NO: 88)
	Light Chain (with kappa light chain constant region) DIQMTQSPSSLSASVGDRVTITC**RASQDISNFLN**WYQQKPGQPVKLLIY**YTSRLH** **S**GVPSRFSGSGSGTDFTLTISSLQPEDFATYFC**QQGHTLPYT**FGQGTKLEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 89)

Antibody	IgG Heavy Chain/Light Chain Sequences**
3M12 VH3/Vκ3	Heavy Chain (with wild type human IgG1 constant region) QVQLQESGPGLVKPSQTLSLTCSVTGYSIT**SGYYWN**WIRQPPGKGLEWMG**YITF** **DGANNYNPSLKN**RVSISRDTSKNQFSLKLSSVTAEDTATYYCTR**SSYDYDVLDY** WGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGK (SEQ ID NO: 88)
	Light Chain (with kappa light chain constant region) DIQMTQSPSSLSASVGDRVTITC**RASQDISNFLN**WYQQKPGQPVKLLIY**YTSRLH** **S**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQGHTLPYT**FGQGTKLEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 90)
3M12 VH4/Vκ2	Heavy Chain (with wild type human IgG1 constant region) QVQLQESGPGLVKPSQTLSLTCTVTGYSIT**SGYYWN**WIRQPPGKGLEWIG**YITFD** **GANNYNPSLKN**RVSISRDTSKNQFSLKLSSVTAEDTATYYCTR**SSYDYDVLDY**W GQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK (SEQ ID NO: 91)
	Light Chain (with kappa light chain constant region) DIQMTQSPSSLSASVGDRVTITC**RASQDISNFLN**WYQQKPGQPVKLLIY**YTSRLH** **S**GVPSRFSGSGSGTDFTLTISSLQPEDFATYFC**QQGHTLPYT**FGQGTKLEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 89)
3M12 VH4/Vκ3	Heavy Chain (with wild type human IgG1 constant region) QVQLQESGPGLVKPSQTLSLTCTVTGYSIT**SGYYWN**WIRQPPGKGLEWIG**YITFD** **GANNYNPSLKN**RVSISRDTSKNQFSLKLSSVTAEDTATYYCTR**SSYDYDVLDY**W GQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK (SEQ ID NO: 91)
	Light Chain (with kappa light chain constant region) DIQMTQSPSSLSASVGDRVTITC**RASQDISNFLN**WYQQKPGQPVKLLIY**YTSRLH** **S**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQGHTLPYT**FGQGTKLEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 90)
5H12 VH5 (C33Y*)/Vκ3	Heavy Chain (with wild type human IgG1 constant region) QVQLVQSGAEVKKPGASVKVSCKASGYSFT**DYYIN**WVRQAPGQGLEWMG**WIY** **PGSGNTRYSERFKG**RVTITRDTSASTAYMELSSLRSEDTAVYYCAR**EDYYPYH** **GMDY**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK (SEQ ID NO: 92)

Antibody	IgG Heavy Chain/Light Chain Sequences**
	Light Chain (with kappa light chain constant region) DIVLTQSPDSLAVSLGERATINC**RASESVDGYDNSFMH**WYQQKPGQPPKLLIF**RA SNLES**GVPDRFSGSGSRTDFTLTISSLQAEDVAVYYC**QQSSEDPWT**FGQGTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 93)
5H12 VH5 (C33D*)/Vκ4	Heavy Chain (with wild type human IgG1 constant region) QVQLVQSGAEVKKPGASVKVSCKASGYSFT**DYDIN**WVRQAPGQGLEWMG**WIY PGSGNTRYSERFKG**RVTITRDTSASTAYMELSSLRSEDTAVYYCAR**EDYYPYH GMDY**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK (SEQ ID NO: 94)
	Light Chain (with kappa light chain constant region) DIVMTQSPDSLAVSLGERATINC**RASESVDGYDNSFMH**WYQQKPGQPPKLLIF**R ASNLES**GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**QQSSEDPWTF**GQGTKLE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 95)
5H12 VH5 (C33Y*)/Vκ4	Heavy Chain (with wild type human IgG1 constant region) QVQLVQSGAEVKKPGASVKVSCKASGYSFT**DYYIN**WVRQAPGQGLEWMG**WIY PGSGNTRYSERFKG**RVTITRDTSASTAYMELSSLRSEDTAVYYCAR**EDYYPYH GMDY**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK (SEQ ID NO: 92)
	Light Chain (with kappa light chain constant region) DIVMTQSPDSLAVSLGERATINC**RASESVDGYDNSFMH**WYQQKPGQPPKLLIF**R ASNLES**GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**QQSSEDPWT**FGQGTKLE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 95)
Anti-TfR clone 8	VH: QVQLVQSGAEVKKPGESLKISCKGSGYSFT**SYWIG**WVRQMPGKGLEWMG**IIYP GDSDTRYSPSFQGQ**VTISADKSISTAYLQWSSLKASDTAMYYCAR**FPYDSSGYY SFDY**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE ALHNHYTQKSLSLSPGK (SEQ ID NO: 156)
	VL: DIQMTQSPSSLSASVGDRVTITC**RASQSISSYLN**WYQQKPGKAPKLLIY**AASSLQS** GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQSYSTPLT**FGGGTKVEIKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 157)

** mutation positions are according to Kabat numbering of the respective VH sequences containing the mutations*

*** CDRs according to the Kabat numbering system are bolded; VH/VL sequences underlined*

[000145] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain containing no more than 25 amino acid variations (e.g., no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the heavy chain as set forth in any one of SEQ ID NOs: 84, 86, 87, 88, 91, 92, 94, and 156. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody of the present disclosure comprises a light chain containing no more than 25 amino acid variations (e.g., no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the light chain as set forth in any one of SEQ ID NOs: 85, 89, 90, 93, 95, and 157.

[000146] In some embodiments, the anti-TfR1 antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 84, 86, 87, 88, 91, 92, 94, and 156. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody described herein comprises a light chain comprising an amino acid sequence that is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 85, 89, 90, 93, 95, and 157. In some embodiments, the anti-TfR1 antibody described herein comprises a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs: 84, 86, 87, 88, 91, 92, 94, and 156. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody described herein comprises a light chain comprising the amino acid sequence of any one of SEQ ID NOs: 85, 89, 90, 93, 95 and 157.

[000147] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 84 and a light chain comprising the amino acid sequence of SEQ ID NO: 85.

[000148] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 86 and a light chain comprising the amino acid sequence of SEQ ID NO: 85.

[000149] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 87 and a light chain comprising the amino acid sequence of SEQ ID NO: 85.

[000150] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 88 and a light chain comprising the amino acid sequence of SEQ ID NO: 89.

[000151] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 88 and a light chain comprising the amino acid sequence of SEQ ID NO: 90.

[000152] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 89.

[000153] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 90.

[000154] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 92 and a light chain comprising the amino acid sequence of SEQ ID NO: 93.

[000155] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 94 and a light chain comprising the amino acid sequence of SEQ ID NO: 95.

[000156] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 92 and a light chain comprising the amino acid sequence of SEQ ID NO: 95.

[000157] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 156 and a light chain comprising the amino acid sequence of SEQ ID NO: 157.

[000158] In some embodiments, the anti-TfR1 antibody is a Fab fragment, Fab' fragment, or $F(ab')_2$ fragment of an intact antibody (full-length antibody). Antigen binding fragment of an intact antibody (full-length antibody) can be prepared via routine methods (e.g., recombinantly or by digesting the heavy chain constant region of a full-length IgG using an enzyme such as papain). For example, $F(ab')_2$ fragments can be produced by pepsin or papain digestion of an antibody molecule, and Fab fragments that can be generated by reducing the disulfide bridges of $F(ab')_2$ fragments. In some embodiments, a heavy chain constant region in a Fab fragment of the anti-TfR1 antibody described herein comprises the amino acid sequence of:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 96)

[000159] In some embodiments, the anti-TfR1 antibody described herein comprises a heavy chain comprising any one of the VH as listed in Table 3 or any variants thereof and a heavy chain constant region that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to SEQ ID NO: 96. In some embodiments, the anti-TfR1 antibody described herein comprises a heavy chain comprising any one of the VH as listed in Table 3 or any variants thereof and a heavy chain constant region that contains no more than 25 amino acid variations (e.g., no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with SEQ ID NO: 96. In some embodiments, the anti-TfR1 antibody described herein comprises a heavy chain comprising any one of the VH as listed in Table 3 or any variants thereof and a heavy chain constant region as set forth in SEQ ID NO: 96.

[000160] In some embodiments, the anti-TfR1 antibody described herein comprises a light chain comprising any one of the VL as listed in Table 3 or any variants thereof and a light chain constant region that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to SEQ ID NO: 83. In some embodiments, the anti-TfR1 antibody described herein comprises a light chain comprising any one of the VL as listed in Table 3 or any variants thereof and a light chain constant region contains no more than 25 amino acid variations (e.g., no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with SEQ ID NO: 83. In some embodiments, the anti-TfR1 antibody described herein comprises a light chain comprising any one of the VL as listed in Table 3 or any variants thereof and a light chain constant region set forth in SEQ ID NO: 83.

[000161] Examples of Fab heavy chain and light chain amino acid sequences of the anti-TfR1 antibodies described are provided in Table 5 below.

Table 5. Heavy chain and light chain sequences of examples of anti-TfR1 Fabs

Antibody	Fab Heavy Chain/Light Chain Sequences**
3A4 VH3 (N54T*)/Vκ4	Heavy Chain (with partial human IgG1 constant region) EVQLVQSGSELKKPGASVKVSCTASGFNIK**DDYMY**WVRQPPGKGLEWIG**WIDP ETGDTEYASKFQD**RVTVTADTSTNTAYMELSSLRSEDTAVYYCTL**WLRRGLD** YWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHT (SEQ ID NO: 97)
	Light Chain (with kappa light chain constant region) DIVMTQSPLSLPVTPGEPASISC**RSSKSLLHSNGYTYLF**WFQQRPGQSPRLLIY**RM SNLAS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**MQHLEYPFT**FGGGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 85)

Antibody	Fab Heavy Chain/Light Chain Sequences**
3A4 VH3 (N54S*)/Vκ4	Heavy Chain (with partial human IgG1 constant region) EVQLVQSGSELKKPGASVKVSCTASGFNIK**DDYMY**WVRQPPGKGLEWIG**WIDP** **ESGDTEYASKFQD**RVTVTADTSTNTAYMELSSLRSEDTAVYYCTL**WLRRGLDY** WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSCDKTHT (SEQ ID NO: 98)
	Light Chain (with kappa light chain constant region) DIVMTQSPLSLPVTPGEPASISC**RSSKSLLHSNGYTYLF**WFQQRPGQSPRLLIY**RM** **SNLAS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**MQHLEYPFT**FGGGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 85)
3A4 VH3 /Vκ4	Heavy Chain (with partial human IgG1 constant region) EVQLVQSGSELKKPGASVKVSCTASGFNIK**DDYMY**WVRQPPGKGLEWIG**WIDP** **ENGDTEYASKFQD**RVTVTADTSTNTAYMELSSLRSEDTAVYYCTL**WLRRGLD** **Y**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHT (SEQ ID NO: 99)
	Light Chain (with kappa light chain constant region) DIVMTQSPLSLPVTPGEPASISC**RSSKSLLHSNGYTYLF**WFQQRPGQSPRLLIY**RM** **SNLAS**GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC**MQHLEYPFT**FGGGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 85)
3M12 VH3/Vκ2	Heavy Chain (with partial human IgG1 constant region) QVQLQESGPGLVKPSQTLSLTCSVTGYSIT**SGYYWN**WIRQPPGKGLEWMG**YITF** **DGANNYNPSLKN**RVSISRDTSKNQFSLKLSSVTAEDTATYYCTR**SSYDYDVLDY** WGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSCDKTHT (SEQ ID NO: 100)
	Light Chain (with kappa light chain constant region) DIQMTQSPSSLSASVGDRVTITC**RASQDISNFLN**WYQQKPGQPVKLLIY**YTSRLH** **S**GVPSRFSGSGSGTDFTLTISSLQPEDFATYFC**QQGHTLPYT**FGQGTKLEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 89)
3M12 VH3/Vκ3	Heavy Chain (with partial human IgG1 constant region) QVQLQESGPGLVKPSQTLSLTCSVTGYSIT**SGYYWN**WIRQPPGKGLEWMG**YITF** **DGANNYNPSLKN**RVSISRDTSKNQFSLKLSSVTAEDTATYYCTR**SSYDYDVLDY** WGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSCDKTHT (SEQ ID NO: 100)
	Light Chain (with kappa light chain constant region) DIQMTQSPSSLSASVGDRVTITC**RASQDISNFLN**WYQQKPGQPVKLLIY**YTSRLH** **S**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQGHTLPYT**FGQGTKLEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 90)
3M12 VH4/Vκ2	Heavy Chain (with partial human IgG1 constant region) QVQLQESGPGLVKPSQTLSLTCTVTGYSIT**SGYYWN**WIRQPPGKGLEWIG**YITFD** **GANNYNPSLKN**RVSISRDTSKNQFSLKLSSVTAEDTATYYCTR**SSYDYDVLDY**W GQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHT (SEQ ID NO: 101)
	Light Chain (with kappa light chain constant region) DIQMTQSPSSLSASVGDRVTITC**RASQDISNFLN**WYQQKPGQPVKLLIY**YTSRLH** **S**GVPSRFSGSGSGTDFTLTISSLQPEDFATYFC**QQGHTLPYT**FGQGTKLEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 89)

Antibody	Fab Heavy Chain/Light Chain Sequences**
3M12 VH4/Vκ3	Heavy Chain (with partial human IgG1 constant region) QVQLQESGPGLVKPSQTLSLTCTVTGYSIT**SGYYWN**WIRQPPGKGLEWIG**YITFD** **GANNYNPSLKN**RVSISRDTSKNQFSLKLSSVTAEDTATYYCTR**SSYDYDVLDY**W GQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP KSCDKTHT (SEQ ID NO: 101)
	Light Chain (with kappa light chain constant region) DIQMTQSPSSLSASVGDRVTITC**RASQDISNFLN**WYQQKPGQPVKLLIY**YTSRLH** **S**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQGHTLPYT**FGQGTKLEIKRTVA APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 90)
5H12 VH5 (C33Y*)/Vκ3	Heavy Chain (with partial human IgG1 constant region) QVQLVQSGAEVKKPGASVKVSCKASGYSFT**DYYIN**WVRQAPGQGLEWMG**WIY** **PGSGNTRYSERFKG**RVTITRDTSASTAYMELSSLRSEDTAVYYCAR**EDYYPYH** **GMDY**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHT (SEQ ID NO: 102)
	Light Chain (with kappa light chain constant region) DIVLTQSPDSLAVSLGERATINC**RASESVDGYDNSFMH**WYQQKPGQPPKLLIF**RA** **SNLES**GVPDRFSGSGSRTDFTLTISSLQAEDVAVYYC**QQSSEDPWT**FGQGTKLEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 93)
5H12 VH5 (C33D*)/Vκ4	Heavy Chain (with partial human IgG1 constant region) QVQLVQSGAEVKKPGASVKVSCKASGYSFT**DYDIN**WVRQAPGQGLEWMG**WIY** **PGSGNTRYSERFKG**RVTITRDTSASTAYMELSSLRSEDTAVYYCAR**EDYYPYH** **GMDY**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHT (SEQ ID NO: 103)
	Light Chain (with kappa light chain constant region) DIVMTQSPDSLAVSLGERATINC**RASESVDGYDNSFMH**WYQQKPGQPPKLLIF**R** **ASNLES**GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**QQSSEDPWT**FGQGTKLE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 95)
5H12 VH5 (C33Y*)/Vκ4	Heavy Chain (with partial human IgG1 constant region) QVQLVQSGAEVKKPGASVKVSCKASGYSFT**DYYIN**WVRQAPGQGLEWMG**WIY** **PGSGNTRYSERFKG**RVTITRDTSASTAYMELSSLRSEDTAVYYCAR**EDYYPYH** **GMDY**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSCDKTHT (SEQ ID NO: 102)
	Light Chain (with kappa light chain constant region) DIVMTQSPDSLAVSLGERATINC**RASESVDGYDNSFMH**WYQQKPGQPPKLLIF**R** **ASNLES**GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**QQSSEDPWT**FGQGTKLE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 95)
Anti-TfR clone 8 Version 1	VH: QVQLVQSGAEVKKPGESLKISCKGSGYSFT**SYWIG**WVRQMPGKGLEWMG**IIYP** **GDSDTRYSPSFQG**QVTISADKSISTAYLQWSSLKASDTAMYYCAR**FPYDSSGYY** **SFDY**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KKVEPKSCDKTHTCP (SEQ ID NO: 158)
	VL: DIQMTQSPSSLSASVGDRVTITC**RASQSISSYLN**WYQQKPGKAPKLLIY**AASSLQS** GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQSYSTPLT**FGGGTKVEIKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 157)

Antibody	Fab Heavy Chain/Light Chain Sequences**
Anti-TfR clone 8 Version 2	VH: QVQLVQSGAEVKKPGESLKISCKGSGYSFT**SYWIG**WVRQMPGKGLEWMG**IIYP GDSDTRYSPSFQGQ**VTISADKSISTAYLQWSSLKASDTAMYYCAR**FPYDSSGYY SFDY**WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KKVEPKSCDKTHT (SEQ ID NO: 159)
	VL: DIQMTQSPSSLSASVGDRVTITC**RASQSISSYLN**WYQQKPGKAPKLLIY**AASSLQS** GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QQSYSTPLT**FGGGTKVEIKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 157)

** mutation positions are according to Kabat numbering of the respective VH sequences containing the mutations*
*** CDRs according to the Kabat numbering system are bolded; VH/VL sequences underlined*

[000162] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain containing no more than 25 amino acid variations (e.g., no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the heavy chain as set forth in any one of SEQ ID NOs: 97-103, 158 and 159. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody of the present disclosure comprises a light chain containing no more than 25 amino acid variations (e.g., no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the light chain as set forth in any one of SEQ ID NOs: 85, 89, 90, 93, 95, and 157.

[000163] In some embodiments, the anti-TfR1 antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 97-103, 158 and 159. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody described herein comprises a light chain comprising an amino acid sequence that is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 85, 89, 90, 93, 95, and 157. In some embodiments, the anti-TfR1 antibody described herein comprises a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs: 97-103, 158 and 159. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody described herein comprises a light chain comprising the amino acid sequence of any one of SEQ ID NOs: 85, 89, 90, 93, 95, and 157.

[000164] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 97 and a light chain comprising the amino acid sequence of SEQ ID NO: 85.

[000165] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 98 and a light chain comprising the amino acid sequence of SEQ ID NO: 85.

[000166] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 99 and a light chain comprising the amino acid sequence of SEQ ID NO: 85.

[000167] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 100 and a light chain comprising the amino acid sequence of SEQ ID NO: 89.

[000168] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 100 and a light chain comprising the amino acid sequence of SEQ ID NO: 90.

[000169] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 101 and a light chain comprising the amino acid sequence of SEQ ID NO: 89.

[000170] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 101 and a light chain comprising the amino acid sequence of SEQ ID NO: 90.

[000171] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 102 and a light chain comprising the amino acid sequence of SEQ ID NO: 93.

[000172] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 103 and a light chain comprising the amino acid sequence of SEQ ID NO: 95.

[000173] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 102 and a light chain comprising the amino acid sequence of SEQ ID NO: 95.

[000174] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 158 and a light chain comprising the amino acid sequence of SEQ ID NO: 157.

[000175] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 159 and a light chain comprising the amino acid sequence of SEQ ID NO: 157.

Other known anti-TfR1 antibodies

[000176] Any other appropriate anti-TfR1 antibodies known in the art may be used as the muscle-targeting agent in the complexes disclosed herein. Examples of known anti-TfR1 antibodies, including associated references and binding epitopes, are listed in Table 6. In some embodiments, the anti-TfR1 antibody comprises the complementarity determining regions (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) of any of the anti-TfR1 antibodies provided herein, e.g., anti-TfR1 antibodies listed in Table 6.

Table 6 – List of anti-TfR1 antibody clones, including associated references and binding epitope information.

Antibody Clone Name	**Reference(s)**	**Epitope / Notes**
OKT9	US Patent. No. 4,364,934, filed 12/4/1979, entitled "MONOCLONAL ANTIBODY TO A HUMAN EARLY THYMOCYTE ANTIGEN AND METHODS FOR PREPARING SAME" Schneider C. et al. "Structural features of the cell surface receptor for transferrin that is recognized by the monoclonal antibody OKT9." J Biol Chem. 1982, 257:14, 8516-8522.	Apical domain of TfR1 (residues 305-366 of human TfR1 sequence XM_052730.3, available in GenBank)
(From JCR) Clone M11 Clone M23 Clone M27 Clone B84	• WO 2015/098989, filed 12/24/2014, "Novel anti-Transferrin receptor antibody that passes through blood-brain barrier" • US Patent No. 9,994,641, filed 12/24/2014, "Novel anti-Transferrin receptor antibody that passes through blood-brain barrier"	Apical domain (residues 230-244 and 326-347 of TfR1) and protease-like domain (residues 461-473)
(From Genentech) 7A4, 8A2, 15D2, 10D11, 7B10, 15G11, 16G5, 13C3, 16G4, 16F6, 7G7, 4C2, 1B12, and 13D4	• WO 2016/081643, filed 5/26/2016, entitled "ANTI-TRANSFERRIN RECEPTOR ANTIBODIES AND METHODS OF USE" • US Patent No. 9,708,406, filed 5/20/2014, "Anti-transferrin receptor antibodies and methods of use"	Apical domain and non-apical regions

Antibody Clone Name	Reference(s)	Epitope / Notes
(From Armagen) 8D3	• Lee et al. "Targeting Rat Anti-Mouse Transferrin Receptor Monoclonal Antibodies through Blood-Brain Barrier in Mouse" 2000, J Pharmacol. Exp. Ther., 292: 1048-1052. • US Patent App. 2010/077498, filed 9/11/2008, entitled "COMPOSITIONS AND METHODS FOR BLOOD-BRAIN BARRIER DELIVERY IN THE MOUSE"	
OX26	• Haobam, B. et al. 2014. Rab17-mediated recycling endosomes contribute to autophagosome formation in response to Group A Streptococcus invasion. Cellular microbiology. 16: 1806-21.	
DF1513	• Ortiz-Zapater E et al. Trafficking of the human transferrin receptor in plant cells: effects of tyrphostin A23 and brefeldin A. Plant J 48:757-70 (2006).	
1A1B2, 66IG10, MEM-189, JF0956, 29806, 1A1B2, TFRC/1818, 1E6, 66Ig10, TFRC/1059, Q1/71, 23D10, 13E4, TFRC/1149, ER-MP21, YTA74.4, BU54, 2B6, RI7 217	• Commercially available anti-transferrin receptor antibodies.	Novus Biologicals 8100 Southpark Way, A-8 Littleton CO 80120
(From INSERM) BA120g	• US Patent App. 2011/0311544A1, filed 6/15/2005, entitled "ANTI-CD71 MONOCLONAL ANTIBODIES AND USES THEREOF FOR TREATING MALIGNANT TUMOR CELLS"	Does not compete with OKT9
LUCA31	• US Patent No. 7,572,895, filed 6/7/2004, entitled "TRANSFERRIN RECEPTOR ANTIBODIES"	"LUCA31 epitope"
(Salk Institute) B3/25 T58/30	• Trowbridge, I.S. et al. "Anti-transferrin receptor monoclonal antibody and toxin–antibody conjugates affect growth of human tumour cells." Nature, 1981, volume 294, pages 171–173	

Antibody Clone Name	Reference(s)	Epitope / Notes
R17 217.1.3, 5E9C11, OKT9 (BE0023 clone)	• Commercially available anti-transferrin receptor antibodies.	BioXcell 10 Technology Dr., Suite 2B West Lebanon, NH 03784-1671 USA
BK19.9, B3/25, T56/14 and T58/1	• Gatter, K.C. et al. "Transferrin receptors in human tissues: their distribution and possible clinical relevance." J Clin Pathol. 1983 May;36(5):539-45.	

Anti-TfR1 antibody
CDRH1 (SEQ ID NO: 787)
CDRH2 (SEQ ID NO: 788)
CDRH3 (SEQ ID NO: 789)
CDRL1 (SEQ ID NO: 790)
CDRL2 (SEQ ID NO: 791)
CDRL3 (SEQ ID NO: 792)
VH (SEQ ID NO: 793)
VL (SEQ ID NO: 794)

Additional Anti-TfR1 antibody SEQ ID NOs

	VH/VL	CDR1	CDR2	CDR3
VH1	802	795	796	789
VH2	803	795	797	789
VH3	804	795	798	789
VH4	805	795	797	789
VL1	806	790	791	115
VL2	807	790	791	115
VL3	808	790	799	792
VL4	809	800	801	792

[000177] In some embodiments, anti-TfR1 antibodies of the present disclosure include one or more of the CDR-H (*e.g.*, CDR-H1, CDR-H2, and CDR-H3) amino acid sequences from any one of the anti-TfR1 antibodies selected from Table 6. In some embodiments, anti-TfR1 antibodies include the CDR-L1, CDR-L2, and CDR-L3 as provided for any one of the anti-TfR1 antibodies selected from Table 6. In some embodiments, anti-TfR1 antibodies include the CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 as provided for any one of the anti-TfR1 antibodies selected from Table 6.

[000178] In some embodiments, anti-TfR1 antibodies of the disclosure include any antibody that includes a heavy chain variable domain and/or (e.g., and) a light chain variable domain of any anti-TfR1 antibody, such as any one of the anti-TfR1 antibodies selected from Table 6. In some embodiments, anti-TfR1 antibodies of the disclosure include any antibody that includes the heavy chain variable and light chain variable pairs of any anti-TfR1 antibody, such as any one of the anti-TfR1 antibodies selected from Table 6.

[000179] Aspects of the disclosure provide anti-TfR1 antibodies having a heavy chain variable (VH) and/or (e.g., and) a light chain variable (VL) domain amino acid sequence homologous to any of those described herein. In some embodiments, the anti-TfR1 antibody comprises a heavy chain variable sequence or a light chain variable sequence that is at least 75% (*e.g.*, 80%, 85%, 90%, 95%, 98%, or 99%) identical to the heavy chain variable sequence and/ or any light chain variable sequence of any anti-TfR1 antibody, such as any one of the

anti-TfR1 antibodies selected from Table 6. In some embodiments, the homologous heavy chain variable and/or (e.g., and) a light chain variable amino acid sequences do not vary within any of the CDR sequences provided herein. For example, in some embodiments, the degree of sequence variation (*e.g.*, 75%, 80%, 85%, 90%, 95%, 98%, or 99%) may occur within a heavy chain variable and/or (e.g., and) a light chain variable sequence excluding any of the CDR sequences provided herein. In some embodiments, any of the anti-TfR1 antibodies provided herein comprise a heavy chain variable sequence and a light chain variable sequence that comprises a framework sequence that is at least 75%, 80%, 85%, 90%, 95%, 98%, or 99% identical to the framework sequence of any anti-TfR1 antibody, such as any one of the anti-TfR1 antibodies selected from Table 6.

[000180] An example of a transferrin receptor antibody that may be used in accordance with the present disclosure is described in International Application Publication WO 2016/081643, incorporated herein by reference. The amino acid sequences of this antibody are provided in Table 7.

Table 7. Heavy chain and light chain CDRs of an example of a known anti-TfR1 antibody

Sequence Type	Kabat	Chothia	Contact
CDR-H1	SYWMH (SEQ ID NO: 110)	GYTFTSY (SEQ ID NO: 116)	TSYWMH (SEQ ID NO: 118)
CDR-H2	EINPTNGRTNYIEKFKS (SEQ ID NO: 111)	NPTNGR (SEQ ID NO: 117)	WIGEINPTNGRTN (SEQ ID NO: 119)
CDR-H3	GTRAYHY (SEQ ID NO: 112)	GTRAYHY (SEQ ID NO: 112)	ARGTRA (SEQ ID NO: 120)
CDR-L1	RASDNLYSNLA (SEQ ID NO: 113)	RASDNLYSNLA (SEQ ID NO: 113)	YSNLAWY (SEQ ID NO: 121)
CDR-L2	DATNLAD (SEQ ID NO: 114)	DATNLAD (SEQ ID NO: 114)	LLVYDATNLA (SEQ ID NO: 122)
CDR-L3	QHFWGTPLT (SEQ ID NO: 115)	QHFWGTPLT (SEQ ID NO: 115)	QHFWGTPL (SEQ ID NO: 123)
Murine VH	QVQLQQPGAELVKPGASVKLSCKASGYTFTSYWMHWVKQRPGQGLEWIGEINPTNGRTNYIEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYCARGTRAYHYWGQGTSVTVSS (SEQ ID NO: 124)		
Murine VL	DIQMTQSPASLSVSVGETVTITCRASDNLYSNLAWYQQKQGKSPQLLVYDATNLADGVPSRFSGSGSGTQYSLKINSLQSEDFGTYYCQHFWGTPLTFGAGTKLELK (SEQ ID NO: 125)		
Humanized VH	EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMHWVRQAPGQRLEWIGEINPTNGRTNYIEKFKSRATLTVDKSASTAYMELSSLRSEDTAVYYCARGTRAYHYWGQGTMVTVSS (SEQ ID NO: 128)		
Humanized VL	DIQMTQSPSSLSASVGDRVTITCRASDNLYSNLAWYQQKPGKSPKLLVYDATNLADGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQHFWGTPLTFGQGTKVEIK (SEQ ID NO: 129)		

Sequence Type	Kabat	Chothia	Contact
HC of chimeric full-length IgG1	QVQLQQPGAELVKPGASVKLSCKASGYTFTSYWMHWVKQRPGQGLEWIGEINP TNGRTNYIEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYCARGTRAYHYW GQGTSVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK (SEQ ID NO: 132)		
LC of chimeric full-length IgG1	DIQMTQSPASLSVSVGETVTITCRASDNLYSNLAWYQQKQGKSPQLLVYDATNL ADGVPSRFSGSGSGTQYSLKINSLQSEDFGTYYCQHFWGTPLTFGAGTKLELKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 133)		
HC of fully human full-length IgG1	EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMHWVRQAPGQRLEWIGEIN PTNGRTNYIEKFKSRATLTVDKSASTAYMELSSLRSEDTAVYYCARGTRAYHY WGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK (SEQ ID NO: 134)		
LC of fully human full-length IgG1	DIQMTQSPSSLSASVGDRVTITCRASDNLYSNLAWYQQKPGKSPKLLVYDATNL ADGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQHFWGTPLTFGQGTKVEIKRT VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 135)		
HC of chimeric Fab	QVQLQQPGAELVKPGASVKLSCKASGYTFTSYWMHWVKQRPGQGLEWIGEINP TNGRTNYIEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYCARGTRAYHYW GQGTSVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSCDKTHTCP (SEQ ID NO: 136)		
HC of fully human Fab	EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMHWVRQAPGQRLEWIGEIN PTNGRTNYIEKFKSRATLTVDKSASTAYMELSSLRSEDTAVYYCARGTRAYHY WGQGTMVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCP (SEQ ID NO: 137)		

[000181] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a CDR-H1, a CDR-H2, and a CDR-H3 that are the same as the CDR-H1, CDR-H2, and CDR-H3 shown in Table 7. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody of the present disclosure comprises a CDR-L1, a CDR-L2, and a CDR-L3 that are the same as the CDR-L1, CDR-L2, and CDR-L3 shown in Table 7.

[000182] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a CDR-L3, which contains no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the CDR-L3 as shown in Table 7. In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a CDR-L3 containing one amino acid variation as compared with the CDR-L3 as shown in Table 7. In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a CDR-L3 of QHFAGTPLT (SEQ ID NO: 126) (according to the Kabat and Chothia definition system) or

QHFAGTPL (SEQ ID NO: 127) (according to the Contact definition system). In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a CDR-H1, a CDR-H2, a CDR-H3, a CDR-L1 and a CDR-L2 that are the same as the CDR-H1, CDR-H2, and CDR-H3 shown in Table 7, and comprises a CDR-L3 of QHFAGTPLT (SEQ ID NO: 126) (according to the Kabat and Chothia definition system) or QHFAGTPL (SEQ ID NO: 127) (according to the Contact definition system).

[000183] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises heavy chain CDRs that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, or 98%) identical to the heavy chain CDRs as shown in Table 7. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody of the present disclosure comprises light chain CDRs that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, or 98%) identical to the light chain CDRs as shown in Table 7.

[000184] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 124. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody of the present disclosure comprises a VL comprising the amino acid sequence of SEQ ID NO: 125.

[000185] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 128. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody of the present disclosure comprises a VL comprising the amino acid sequence of SEQ ID NO: 129.

[000186] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VH containing no more than 25 amino acid variations (e.g., no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VH as set forth in SEQ ID NO: 128. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody of the present disclosure comprises a VL containing no more than 15 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VL as set forth in SEQ ID NO: 129.

[000187] In some embodiments, the anti-TfR1 antibody of the present disclosure is a full-length IgG1 antibody, which can include a heavy constant region and a light constant region from a human antibody. In some embodiments, the heavy chain of any of the anti-TfR1 antibodies as described herein may comprises a heavy chain constant region (CH) or a portion thereof (e.g., CH1, CH2, CH3, or a combination thereof). The heavy chain constant region can of any suitable origin, e.g., human, mouse, rat, or rabbit. In one specific example, the heavy

chain constant region is from a human IgG (a gamma heavy chain), e.g., IgG1, IgG2, or IgG4. An example of human IgG1 constant region is given below:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 81)

[000188] In some embodiments, the light chain of any of the anti-TfR1 antibodies described herein may further comprise a light chain constant region (CL), which can be any CL known in the art. In some examples, the CL is a kappa light chain. In other examples, the CL is a lambda light chain. In some embodiments, the CL is a kappa light chain, the sequence of which is provided below:

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 83)

[000189] In some embodiments, the anti-TfR1 antibody described herein is a chimeric antibody that comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 132. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody described herein comprises a light chain comprising the amino acid sequence of SEQ ID NO: 133.

[000190] In some embodiments, the anti-TfR1 antibody described herein is a fully human antibody that comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 134. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody described herein comprises a light chain comprising the amino acid sequence of SEQ ID NO: 135.

[000191] In some embodiments, the anti-TfR1 antibody is an antigen binding fragment (Fab) of an intact antibody (full-length antibody). In some embodiments, the anti-TfR1 Fab described herein comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 136. Alternatively or in addition (e.g., in addition), the anti-TfR1 Fab described herein comprises a light chain comprising the amino acid sequence of SEQ ID NO: 133. In some embodiments, the anti-TfR1 Fab described herein comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 137. Alternatively or in addition (e.g., in addition), the anti-TfR1 Fab described herein comprises a light chain comprising the amino acid sequence of SEQ ID NO: 135.

[000192] The anti-TfR1 antibodies described herein can be in any antibody form, including, but not limited to, intact (i.e., full-length) antibodies, antigen-binding fragments thereof (such as Fab, Fab', F(ab')2, Fv), single chain antibodies, bi-specific antibodies, or nanobodies. In some embodiments, the anti-TfR1 antibody described herein is an scFv. In some embodiments, the anti-TfR1 antibody described herein is an scFv-Fab (e.g., scFv fused to a portion of a constant region). In some embodiments, the anti-TfR1 antibody described herein is an scFv fused to a constant region (e.g., human IgG1 constant region as set forth in SEQ ID NO: 81).

[000193] In some embodiments, conservative mutations can be introduced into antibody sequences (e.g., CDRs or framework sequences) at positions where the residues are not likely to be involved in interacting with a target antigen (e.g., transferrin receptor), for example, as determined based on a crystal structure. In some embodiments, one, two or more mutations (*e.g.,* amino acid substitutions) are introduced into the Fc region of an anti-TfR1 antibody described herein (*e.g.,* in a CH2 domain (residues 231-340 of human IgG1) and/or (e.g., and) CH3 domain (residues 341-447 of human IgG1) and/or (e.g., and) the hinge region, with numbering according to the Kabat numbering system (*e.g.,* the EU index in Kabat)) to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding and/or (e.g., and) antigen-dependent cellular cytotoxicity.

[000194] In some embodiments, one, two or more mutations (*e.g.,* amino acid substitutions) are introduced into the hinge region of the Fc region (CH1 domain) such that the number of cysteine residues in the hinge region are altered (*e.g.,* increased or decreased) as described in, e.g., U.S. Pat. No. 5,677,425. The number of cysteine residues in the hinge region of the CH1 domain can be altered to, *e.g.,* facilitate assembly of the light and heavy chains, or to alter (*e.g.,* increase or decrease) the stability of the antibody or to facilitate linker conjugation.

[000195] In some embodiments, one, two or more mutations (*e.g.,* amino acid substitutions) are introduced into the Fc region of a muscle-targeting antibody described herein (e.g., in a CH2 domain (residues 231-340 of human IgG1) and/or (e.g., and) CH3 domain (residues 341-447 of human IgG1) and/or (e.g., and) the hinge region, with numbering according to the Kabat numbering system (*e.g.,* the EU index in Kabat)) to increase or decrease the affinity of the antibody for an Fc receptor (*e.g.*, an activated Fc receptor) on the surface of an effector cell. Mutations in the Fc region of an antibody that decrease or increase the affinity of an antibody for an Fc receptor and techniques for introducing such mutations into the Fc receptor or fragment thereof are known to one of skill in the art. Examples of mutations in the

Fc receptor of an antibody that can be made to alter the affinity of the antibody for an Fc receptor are described in, e.g., Smith P et al., (2012) PNAS 109: 6181-6186, U.S. Pat. No. 6,737,056, and International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631, which are incorporated herein by reference.

[000196] In some embodiments, one, two or more amino acid mutations (*i.e.,* substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to alter (*e.g.,* decrease or increase) half-life of the antibody *in vivo*. See, e.g., International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631; and U.S. Pat. Nos. 5,869,046, 6,121,022, 6,277,375 and 6,165,745 for examples of mutations that will alter (*e.g.,* decrease or increase) the half-life of an antibody *in vivo*.

[000197] In some embodiments, one, two or more amino acid mutations (*i.e.,* substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to decrease the half-life of the anti-TfR1 antibody *in vivo*. In some embodiments, one, two or more amino acid mutations (*i.e.,* substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to increase the half-life of the antibody *in vivo*. In some embodiments, the antibodies can have one or more amino acid mutations (*e.g.,* substitutions) in the second constant (CH2) domain (residues 231-340 of human IgG1) and/or (e.g., and) the third constant (CH3) domain (residues 341-447 of human IgG1), with numbering according to the EU index in Kabat (Kabat E A et al., (1991) supra). In some embodiments, the constant region of the IgG1 of an antibody described herein comprises a methionine (M) to tyrosine (Y) substitution in position 252, a serine (S) to threonine (T) substitution in position 254, and a threonine (T) to glutamic acid (E) substitution in position 256, numbered according to the EU index as in Kabat. See U.S. Pat. No. 7,658,921, which is incorporated herein by reference. This type of mutant IgG, referred to as "YTE mutant" has been shown to display fourfold increased half-life as compared to wild-type versions of the same antibody (see Dall'Acqua W F et al., (2006) J Biol Chem 281: 23514-24). In some embodiments, an antibody comprises an IgG constant domain comprising one, two, three or more amino acid substitutions of amino acid residues at positions 251-257, 285-290, 308-314, 385-389, and 428-436, numbered according to the EU index as in Kabat.

[000198] In some embodiments, one, two or more amino acid substitutions are introduced into an IgG constant domain Fc region to alter the effector function(s) of the anti-TfR1 antibody. The effector ligand to which affinity is altered can be, for example, an Fc receptor or

the C1 component of complement. This approach is described in further detail in U.S. Pat. Nos. 5,624,821 and 5,648,260. In some embodiments, the deletion or inactivation (through point mutations or other means) of a constant region domain can reduce Fc receptor binding of the circulating antibody thereby increasing tumor localization. See, e.g., U.S. Pat. Nos. 5,585,097 and 8,591,886 for a description of mutations that delete or inactivate the constant domain and thereby increase tumor localization. In some embodiments, one or more amino acid substitutions may be introduced into the Fc region of an antibody described herein to remove potential glycosylation sites on Fc region, which may reduce Fc receptor binding (see, *e.g.*, Shields R L et al., (2001) J Biol Chem 276: 6591-604).

[000199] In some embodiments, one or more amino in the constant region of an anti-TfR1 antibody described herein can be replaced with a different amino acid residue such that the antibody has altered C1q binding and/or (e.g., and) reduced or abolished complement dependent cytotoxicity (CDC). This approach is described in further detail in U.S. Pat. No. 6,194,551 (Idusogie et al). In some embodiments, one or more amino acid residues in the N-terminal region of the CH2 domain of an antibody described herein are altered to thereby alter the ability of the antibody to fix complement. This approach is described further in International Publication No. WO 94/29351. In some embodiments, the Fc region of an antibody described herein is modified to increase the ability of the antibody to mediate antibody dependent cellular cytotoxicity (ADCC) and/or (e.g., and) to increase the affinity of the antibody for an Fcγ receptor. This approach is described further in International Publication No. WO 00/42072.

[000200] In some embodiments, the heavy and/or (e.g., and) light chain variable domain(s) sequence(s) of the antibodies provided herein can be used to generate, for example, CDR-grafted, chimeric, humanized, or composite human antibodies or antigen-binding fragments, as described elsewhere herein. As understood by one of ordinary skill in the art, any variant, CDR-grafted, chimeric, humanized, or composite antibodies derived from any of the antibodies provided herein may be useful in the compositions and methods described herein and will maintain the ability to specifically bind transferrin receptor, such that the variant, CDR-grafted, chimeric, humanized, or composite antibody has at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% or more binding to transferrin receptor relative to the original antibody from which it is derived.

[000201] In some embodiments, the antibodies provided herein comprise mutations that confer desirable properties to the antibodies. For example, to avoid potential complications due to Fab-arm exchange, which is known to occur with native IgG4 mAbs, the antibodies

provided herein may comprise a stabilizing 'Adair' mutation (Angal S., et al., "A single amino acid substitution abolishes the heterogeneity of chimeric mouse/human (IgG4) antibody," Mol Immunol 30, 105-108; 1993), where serine 228 (EU numbering; residue 241 Kabat numbering) is converted to proline resulting in an IgG1-like hinge sequence. Accordingly, any of the antibodies may include a stabilizing 'Adair' mutation.

[000202] In some embodiments, an antibody is modified, e.g., modified via glycosylation, phosphorylation, sumoylation, and/or (e.g., and) methylation. In some embodiments, an antibody is a glycosylated antibody, which is conjugated to one or more sugar or carbohydrate molecules. In some embodiments, the one or more sugar or carbohydrate molecule are conjugated to the antibody via N-glycosylation, O-glycosylation, C-glycosylation, glypiation (GPI anchor attachment), and/or (e.g., and) phosphoglycosylation. In some embodiments, the one or more sugar or carbohydrate molecules are monosaccharides, disaccharides, oligosaccharides, or glycans. In some embodiments, the one or more sugar or carbohydrate molecule is a branched oligosaccharide or a branched glycan. In some embodiments, the one or more sugar or carbohydrate molecule includes a mannose unit, a glucose unit, an N-acetylglucosamine unit, an N-acetylgalactosamine unit, a galactose unit, a fucose unit, or a phospholipid unit. In some embodiments, there are about 1-10, about 1-5, about 5-10, about 1-4, about 1-3, or about 2 sugar molecules. In some embodiments, a glycosylated antibody is fully or partially glycosylated. In some embodiments, an antibody is glycosylated by chemical reactions or by enzymatic means. In some embodiments, an antibody is glycosylated in vitro or inside a cell, which may optionally be deficient in an enzyme in the N- or O- glycosylation pathway, e.g. a glycosyltransferase. In some embodiments, an antibody is functionalized with sugar or carbohydrate molecules as described in International Patent Application Publication WO2014065661, published on May 1, 2014, entitled, "*Modified antibody, antibody-conjugate and process for the preparation thereof*".

[000203] In some embodiments, any one of the anti-TfR1 antibodies described herein may comprise a signal peptide in the heavy and/or (e.g., and) light chain sequence (e.g., a N-terminal signal peptide). In some embodiments, the anti-TfR1 antibody described herein comprises any one of the VH and VL sequences, any one of the IgG heavy chain and light chain sequences, or any one of the F(ab') heavy chain and light chain sequences described herein, and further comprises a signal peptide (e.g., a N-terminal signal peptide). In some embodiments, the signal peptide comprises the amino acid sequence of MGWSCIILFLVATATGVHS (SEQ ID NO: 104).

[000204] In some embodiments, an antibody provided herein may have one or more post-translational modifications. In some embodiments, N-terminal cyclization, also called pyroglutamate formation (pyro-Glu), may occur in the antibody at N-terminal Glutamate (Glu) and/or Glutamine (Gln) residues during production. As such, it should be appreciated that an antibody specified as having a sequence comprising an N-terminal glutamate or glutamine residue encompasses antibodies that have undergone pyroglutamate formation resulting from a post-translational modification. In some embodiments, pyroglutamate formation occurs in a heavy chain sequence. In some embodiments, pyroglutamate formation occurs in a light chain sequence.

b. Other Muscle-Targeting Antibodies

[000205] In some embodiments, the muscle-targeting antibody is an antibody that specifically binds hemojuvelin, caveolin-3, Duchenne muscular dystrophy peptide, myosin IIb or CD63. In some embodiments, the muscle-targeting antibody is an antibody that specifically binds a myogenic precursor protein. Exemplary myogenic precursor proteins include, without limitation, ABCG2, M-Cadherin/Cadherin-15, Caveolin-1, CD34, FoxK1, Integrin alpha 7, Integrin alpha 7 beta 1, MYF-5, MyoD, Myogenin, NCAM-1/CD56, Pax3, Pax7, and Pax9. In some embodiments, the muscle-targeting antibody is an antibody that specifically binds a skeletal muscle protein. Exemplary skeletal muscle proteins include, without limitation, alpha-Sarcoglycan, beta-Sarcoglycan, Calpain Inhibitors, Creatine Kinase MM/CKMM, eIF5A, Enolase 2/Neuron-specific Enolase, epsilon-Sarcoglycan, FABP3/H-FABP, GDF-8/Myostatin, GDF-11/GDF-8, Integrin alpha 7, Integrin alpha 7 beta 1, Integrin beta 1/CD29, MCAM/CD146, MyoD, Myogenin, Myosin Light Chain Kinase Inhibitors, NCAM-1/CD56, and Troponin I. In some embodiments, the muscle-targeting antibody is an antibody that specifically binds a smooth muscle protein. Exemplary smooth muscle proteins include, without limitation, alpha-Smooth Muscle Actin, VE-Cadherin, Caldesmon/CALD1, Calponin 1, Desmin, Histamine H2 R, Motilin R/GPR38, Transgelin/TAGLN, and Vimentin. However, it should be appreciated that antibodies to additional targets are within the scope of this disclosure and the exemplary lists of targets provided herein are not meant to be limiting.

c. Antibody Features/Alterations

[000206] In some embodiments, conservative mutations can be introduced into antibody sequences (e.g., CDRs or framework sequences) at positions where the residues are not likely to be involved in interacting with a target antigen (e.g., transferrin receptor), for example, as determined based on a crystal structure. In some embodiments, one, two or more mutations (*e.g.,* amino acid substitutions) are introduced into the Fc region of a muscle-targeting antibody

described herein (*e.g.*, in a CH2 domain (residues 231-340 of human IgG1) and/or (e.g., and) CH3 domain (residues 341-447 of human IgG1) and/or (e.g., and) the hinge region, with numbering according to the Kabat numbering system (*e.g.*, the EU index in Kabat)) to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding and/or (e.g., and) antigen-dependent cellular cytotoxicity.

[000207] In some embodiments, one, two or more mutations (*e.g.*, amino acid substitutions) are introduced into the hinge region of the Fc region (CH1 domain) such that the number of cysteine residues in the hinge region are altered (*e.g.*, increased or decreased) as described in, e.g., U.S. Pat. No. 5,677,425. The number of cysteine residues in the hinge region of the CH1 domain can be altered to, *e.g.*, facilitate assembly of the light and heavy chains, or to alter (*e.g.*, increase or decrease) the stability of the antibody or to facilitate linker conjugation.

[000208] In some embodiments, one, two or more mutations (*e.g.*, amino acid substitutions) are introduced into the Fc region of a muscle-targeting antibody described herein (e.g., in a CH2 domain (residues 231-340 of human IgG1) and/or (e.g., and) CH3 domain (residues 341-447 of human IgG1) and/or (e.g., and) the hinge region, with numbering according to the Kabat numbering system (*e.g.*, the EU index in Kabat)) to increase or decrease the affinity of the antibody for an Fc receptor (*e.g.*, an activated Fc receptor) on the surface of an effector cell. Mutations in the Fc region of an antibody that decrease or increase the affinity of an antibody for an Fc receptor and techniques for introducing such mutations into the Fc receptor or fragment thereof are known to one of skill in the art. Examples of mutations in the Fc receptor of an antibody that can be made to alter the affinity of the antibody for an Fc receptor are described in, e.g., Smith P et al., (2012) PNAS 109: 6181-6186, U.S. Pat. No. 6,737,056, and International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631, which are incorporated herein by reference.

[000209] In some embodiments, one, two or more amino acid mutations (*i.e.*, substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to alter (*e.g.*, decrease or increase) half-life of the antibody *in vivo*. See, e.g., International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631; and U.S. Pat. Nos. 5,869,046, 6,121,022, 6,277,375 and 6,165,745 for examples of mutations that will alter (*e.g.*, decrease or increase) the half-life of an antibody *in vivo*.

[000210] In some embodiments, one, two or more amino acid mutations (*i.e.*, substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-

binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to decrease the half-life of the anti-transferrin receptor antibody *in vivo*. In some embodiments, one, two or more amino acid mutations (*i.e.,* substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to increase the half-life of the antibody *in vivo*. In some embodiments, the antibodies can have one or more amino acid mutations (*e.g.,* substitutions) in the second constant (CH2) domain (residues 231-340 of human IgG1) and/or (e.g., and) the third constant (CH3) domain (residues 341-447 of human IgG1), with numbering according to the EU index in Kabat (Kabat E A et al., (1991) supra). In some embodiments, the constant region of the IgG1 of an antibody described herein comprises a methionine (M) to tyrosine (Y) substitution in position 252, a serine (S) to threonine (T) substitution in position 254, and a threonine (T) to glutamic acid (E) substitution in position 256, numbered according to the EU index as in Kabat. See U.S. Pat. No. 7,658,921, which is incorporated herein by reference. This type of mutant IgG, referred to as "YTE mutant" has been shown to display fourfold increased half-life as compared to wild-type versions of the same antibody (see Dall'Acqua W F et al., (2006) J Biol Chem 281: 23514-24). In some embodiments, an antibody comprises an IgG constant domain comprising one, two, three or more amino acid substitutions of amino acid residues at positions 251-257, 285-290, 308-314, 385-389, and 428-436, numbered according to the EU index as in Kabat.

[000211] In some embodiments, one, two or more amino acid substitutions are introduced into an IgG constant domain Fc region to alter the effector function(s) of the anti-transferrin receptor antibody. The effector ligand to which affinity is altered can be, for example, an Fc receptor or the C1 component of complement. This approach is described in further detail in U.S. Pat. Nos. 5,624,821 and 5,648,260. In some embodiments, the deletion or inactivation (through point mutations or other means) of a constant region domain can reduce Fc receptor binding of the circulating antibody thereby increasing tumor localization. See, e.g., U.S. Pat. Nos. 5,585,097 and 8,591,886 for a description of mutations that delete or inactivate the constant domain and thereby increase tumor localization. In some embodiments, one or more amino acid substitutions may be introduced into the Fc region of an antibody described herein to remove potential glycosylation sites on Fc region, which may reduce Fc receptor binding (see, *e.g.,* Shields R L et al., (2001) J Biol Chem 276: 6591-604).

[000212] In some embodiments, one or more amino in the constant region of a muscle-targeting antibody described herein can be replaced with a different amino acid residue such that the antibody has altered C1q binding and/or (e.g., and) reduced or abolished complement dependent cytotoxicity (CDC). This approach is described in further detail in U.S. Pat. No.

6,194,551 (Idusogie et al). In some embodiments, one or more amino acid residues in the N-terminal region of the CH2 domain of an antibody described herein are altered to thereby alter the ability of the antibody to fix complement. This approach is described further in International Publication No. WO 94/29351. In some embodiments, the Fc region of an antibody described herein is modified to increase the ability of the antibody to mediate antibody dependent cellular cytotoxicity (ADCC) and/or (e.g., and) to increase the affinity of the antibody for an Fcγ receptor. This approach is described further in International Publication No. WO 00/42072.

[000213] In some embodiments, the heavy and/or (e.g., and) light chain variable domain(s) sequence(s) of the antibodies provided herein can be used to generate, for example, CDR-grafted, chimeric, humanized, or composite human antibodies or antigen-binding fragments, as described elsewhere herein. As understood by one of ordinary skill in the art, any variant, CDR-grafted, chimeric, humanized, or composite antibodies derived from any of the antibodies provided herein may be useful in the compositions and methods described herein and will maintain the ability to specifically bind transferrin receptor, such that the variant, CDR-grafted, chimeric, humanized, or composite antibody has at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% or more binding to transferrin receptor relative to the original antibody from which it is derived.

[000214] In some embodiments, the antibodies provided herein comprise mutations that confer desirable properties to the antibodies. For example, to avoid potential complications due to Fab-arm exchange, which is known to occur with native IgG4 mAbs, the antibodies provided herein may comprise a stabilizing 'Adair' mutation (Angal S., et al., "A single amino acid substitution abolishes the heterogeneity of chimeric mouse/human (IgG4) antibody," Mol Immunol 30, 105-108; 1993), where serine 228 (EU numbering; residue 241 Kabat numbering) is converted to proline resulting in an IgG1-like hinge sequence. Accordingly, any of the antibodies may include a stabilizing 'Adair' mutation.

[000215] As provided herein, antibodies of this disclosure may optionally comprise constant regions or parts thereof. For example, a VL domain may be attached at its C-terminal end to a light chain constant domain like Cκ or Cλ. Similarly, a VH domain or portion thereof may be attached to all or part of a heavy chain like IgA, IgD, IgE, IgG, and IgM, and any isotype subclass. Antibodies may include suitable constant regions (see, for example, Kabat et al., Sequences of Proteins of Immunological Interest, No. 91-3242, National Institutes of Health Publications, Bethesda, Md. (1991)). Therefore, antibodies within the scope of this

may disclosure include VH and VL domains, or an antigen binding portion thereof, combined with any suitable constant regions.

ii. Muscle-Targeting Peptides

[000216] Some aspects of the disclosure provide muscle-targeting peptides as muscle-targeting agents. Short peptide sequences (e.g., peptide sequences of 5-20 amino acids in length) that bind to specific cell types have been described. For example, cell-targeting peptides have been described in Vines e., et al., A. "Cell-penetrating and cell-targeting peptides in drug delivery" *Biochim Biophys Acta* 2008, 1786: 126-38; Jarver P., et al., "In vivo biodistribution and efficacy of peptide mediated delivery" *Trends Pharmacol Sci* 2010; 31: 528-35; Samoylova T.I., et al., "Elucidation of muscle-binding peptides by phage display screening" *Muscle Nerve* 1999; 22: 460-6; U.S. Patent No. 6,329,501, issued on December 11, 2001, entitled "METHODS AND COMPOSITIONS FOR TARGETING COMPOUNDS TO MUSCLE"; and Samoylov A.M., et al., "Recognition of cell-specific binding of phage display derived peptides using an acoustic wave sensor." *Biomol Eng* 2002; 18: 269-72; the entire contents of each of which are incorporated herein by reference. By designing peptides to interact with specific cell surface antigens (*e.g.*, receptors), selectivity for a desired tissue, e.g., muscle, can be achieved. Skeletal muscle-targeting has been investigated and a range of molecular payloads are able to be delivered. These approaches may have high selectivity for muscle tissue without many of the practical disadvantages of a large antibody or viral particle. Accordingly, in some embodiments, the muscle-targeting agent is a muscle-targeting peptide that is from 4 to 50 amino acids in length. In some embodiments, the muscle-targeting peptide is 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 amino acids in length. Muscle-targeting peptides can be generated using any of several methods, such as phage display.

[000217] In some embodiments, a muscle-targeting peptide may bind to an internalizing cell surface receptor that is overexpressed or relatively highly expressed in muscle cells, e.g. a transferrin receptor, compared with certain other cells. In some embodiments, a muscle-targeting peptide may target, e.g., bind to, a transferrin receptor. In some embodiments, a peptide that targets a transferrin receptor may comprise a segment of a naturally occurring ligand, e.g., transferrin. In some embodiments, a peptide that targets a transferrin receptor is as described in US Patent No. 6,743,893, filed 11/30/2000, "RECEPTOR-MEDIATED UPTAKE OF PEPTIDES THAT BIND THE HUMAN TRANSFERRIN RECEPTOR". In some embodiments, a peptide that targets a transferrin receptor is as described in Kawamoto, M. et

al, "A novel transferrin receptor-targeted hybrid peptide disintegrates cancer cell membrane to induce rapid killing of cancer cells." BMC Cancer. 2011 Aug 18;11:359. In some embodiments, a peptide that targets a transferrin receptor is as described in US Patent No. 8,399,653, filed 5/20/2011, "TRANSFERRIN/TRANSFERRIN RECEPTOR-MEDIATED SIRNA DELIVERY".

[000218] As discussed above, examples of muscle targeting peptides have been reported. For example, muscle-specific peptides were identified using phage display library presenting surface heptapeptides. As one example a peptide having the amino acid sequence ASSLNIA (SEQ ID NO: 778) bound to C2C12 murine myotubes *in vitro*, and bound to mouse muscle tissue *in vivo*. Accordingly, in some embodiments, the muscle-targeting agent comprises the amino acid sequence ASSLNIA (SEQ ID NO: 778). This peptide displayed improved specificity for binding to heart and skeletal muscle tissue after intravenous injection in mice with reduced binding to liver, kidney, and brain. Additional muscle-specific peptides have been identified using phage display. For example, a 12 amino acid peptide was identified by phage display library for muscle targeting in the context of treatment for Duchenne muscular dystrophy. See, Yoshida D., et al., "Targeting of salicylate to skin and muscle following topical injections in rats." *Int J Pharm* 2002; 231: 177-84; the entire contents of which are hereby incorporated by reference. Here, a 12 amino acid peptide having the sequence SKTFNTHPQSTP (SEQ ID NO: 779) was identified and this muscle-targeting peptide showed improved binding to C2C12 cells relative to the ASSLNIA (SEQ ID NO: 778) peptide.

[000219] An additional method for identifying peptides selective for muscle (*e.g.*, skeletal muscle) over other cell types includes *in vitro* selection, which has been described in Ghosh D., et al., "Selection of muscle-binding peptides from context-specific peptide-presenting phage libraries for adenoviral vector targeting" *J Virol* 2005; 79: 13667-72; the entire contents of which are incorporated herein by reference. By pre-incubating a random 12-mer peptide phage display library with a mixture of non-muscle cell types, non-specific cell binders were selected out. Following rounds of selection the 12 amino acid peptide TARGEHKEEELI (SEQ ID NO: 780) appeared most frequently. Accordingly, in some embodiments, the muscle-targeting agent comprises the amino acid sequence TARGEHKEEELI (SEQ ID NO: 780).

[000220] A muscle-targeting agent may an amino acid-containing molecule or peptide. A muscle-targeting peptide may correspond to a sequence of a protein that preferentially binds to a protein receptor found in muscle cells. In some embodiments, a muscle-targeting peptide contains a high propensity of hydrophobic amino acids, e.g. valine, such that the peptide preferentially targets muscle cells. In some embodiments, a muscle-targeting peptide has not

been previously characterized or disclosed. These peptides may be conceived of, produced, synthesized, and/or (e.g., and) derivatized using any of several methodologies, e.g. phage displayed peptide libraries, one-bead one-compound peptide libraries, or positional scanning synthetic peptide combinatorial libraries. Exemplary methodologies have been characterized in the art and are incorporated by reference (Gray, B.P. and Brown, K.C. "Combinatorial Peptide Libraries: Mining for Cell-Binding Peptides" Chem Rev. 2014, 114:2, 1020–1081.; Samoylova, T.I. and Smith, B.F. "Elucidation of muscle-binding peptides by phage display screening." Muscle Nerve, 1999, 22:4. 460-6.). In some embodiments, a muscle-targeting peptide has been previously disclosed (see, e.g. Writer M.J. et al. "Targeted gene delivery to human airway epithelial cells with synthetic vectors incorporating novel targeting peptides selected by phage display." J. Drug Targeting. 2004;12:185; Cai, D. "BDNF-mediated enhancement of inflammation and injury in the aging heart." Physiol Genomics. 2006, 24:3, 191-7.; Zhang, L. "Molecular profiling of heart endothelial cells." Circulation, 2005, 112:11, 1601-11.; McGuire, M.J. et al. "In vitro selection of a peptide with high selectivity for cardiomyocytes in vivo." J Mol Biol. 2004, 342:1, 171-82.). Exemplary muscle-targeting peptides comprise an amino acid sequence of the following group: CQAQGQLVC (SEQ ID NO: 781), CSERSMNFC (SEQ ID NO: 782), CPKTRRVPC (SEQ ID NO: 783), WLSEAGPVVTVRALRGTGSW (SEQ ID NO: 784), ASSLNIA (SEQ ID NO: 778), CMQHSMRVC (SEQ ID NO: 785), and DDTRHWG (SEQ ID NO: 786). In some embodiments, a muscle-targeting peptide may comprise about 2-25 amino acids, about 2-20 amino acids, about 2-15 amino acids, about 2-10 amino acids, or about 2-5 amino acids. Muscle-targeting peptides may comprise naturally-occurring amino acids, e.g. cysteine, alanine, or non-naturally-occurring or modified amino acids. Non-naturally occurring amino acids include β-amino acids, homo-amino acids, proline derivatives, 3-substituted alanine derivatives, linear core amino acids, N-methyl amino acids, and others known in the art. In some embodiments, a muscle-targeting peptide may be linear; in other embodiments, a muscle-targeting peptide may be cyclic, e.g. bicyclic (see, e.g. Silvana, M.G. et al. Mol. Therapy, 2018, 26:1, 132–147.).

iii. Muscle-Targeting Receptor Ligands

[000221] A muscle-targeting agent may be a ligand, e.g. a ligand that binds to a receptor protein. A muscle-targeting ligand may be a protein, e.g. transferrin, which binds to an internalizing cell surface receptor expressed by a muscle cell. Accordingly, in some embodiments, the muscle-targeting agent is transferrin, or a derivative thereof that binds to a transferrin receptor. A muscle-targeting ligand may alternatively be a small molecule, e.g. a

lipophilic small molecule that preferentially targets muscle cells relative to other cell types. Exemplary lipophilic small molecules that may target muscle cells include compounds comprising cholesterol, cholesteryl, stearic acid, palmitic acid, oleic acid, oleyl, linolene, linoleic acid, myristic acid, sterols, dihydrotestosterone, testosterone derivatives, glycerine, alkyl chains, trityl groups, and alkoxy acids.

iv. Muscle-Targeting Aptamers

[000222] A muscle-targeting agent may be an aptamer, e.g. an RNA aptamer, which preferentially targets muscle cells relative to other cell types. In some embodiments, a muscle-targeting aptamer has not been previously characterized or disclosed. These aptamers may be conceived of, produced, synthesized, and/or (e.g., and) derivatized using any of several methodologies, e.g. Systematic Evolution of Ligands by Exponential Enrichment. Exemplary methodologies have been characterized in the art and are incorporated by reference (Yan, A.C. and Levy, M. "Aptamers and aptamer targeted delivery" RNA biology, 2009, 6:3, 316-20.; Germer, K. et al. "RNA aptamers and their therapeutic and diagnostic applications." Int. J. Biochem. Mol. Biol. 2013; 4: 27–40.). In some embodiments, a muscle-targeting aptamer has been previously disclosed (see, e.g. Phillippou, S. et al. "Selection and Identification of Skeletal-Muscle-Targeted RNA Aptamers." Mol Ther Nucleic Acids. 2018, 10:199-214.; Thiel, W.H. et al. "Smooth Muscle Cell-targeted RNA Aptamer Inhibits Neointimal Formation." Mol Ther. 2016, 24:4, 779-87.). Exemplary muscle-targeting aptamers include the A01B RNA aptamer and RNA Apt 14. In some embodiments, an aptamer is a nucleic acid-based aptamer, an oligonucleotide aptamer or a peptide aptamer. In some embodiments, an aptamer may be about 5-15 kDa, about 5-10 kDa, about 10-15 kDa, about 1-5 Da, about 1-3 kDa, or smaller.

v. Other Muscle-Targeting Agents

[000223] One strategy for targeting a muscle cell (e.g., a skeletal muscle cell) is to use a substrate of a muscle transporter protein, such as a transporter protein expressed on the sarcolemma. In some embodiments, the muscle-targeting agent is a substrate of an influx transporter that is specific to muscle tissue. In some embodiments, the influx transporter is specific to skeletal muscle tissue. Two main classes of transporters are expressed on the skeletal muscle sarcolemma, (1) the adenosine triphosphate (ATP) binding cassette (ABC) superfamily, which facilitate efflux from skeletal muscle tissue and (2) the solute carrier (SLC) superfamily, which can facilitate the influx of substrates into skeletal muscle. In some embodiments, the muscle-targeting agent is a substrate that binds to an ABC superfamily or an SLC superfamily of transporters. In some embodiments, the substrate that binds to the ABC or

SLC superfamily of transporters is a naturally-occurring substrate. In some embodiments, the substrate that binds to the ABC or SLC superfamily of transporters is a non-naturally occurring substrate, for example, a synthetic derivative thereof that binds to the ABC or SLC superfamily of transporters.

[000224] In some embodiments, the muscle-targeting agent is any muscle targeting agent described herein (e.g., antibodies, nucleic acids, small molecules, peptides, aptamers, lipids, sugar moieties) that target SLC superfamily of transporters. In some embodiments, the muscle-targeting agent is a substrate of an SLC superfamily of transporters. SLC transporters are either equilibrative or use proton or sodium ion gradients created across the membrane to drive transport of substrates. Exemplary SLC transporters that have high skeletal muscle expression include, without limitation, the SATT transporter (ASCT1; SLC1A4), GLUT4 transporter (SLC2A4), GLUT7 transporter (GLUT7; SLC2A7), ATRC2 transporter (CAT-2; SLC7A2), LAT3 transporter (KIAA0245; SLC7A6), PHT1 transporter (PTR4; SLC15A4), OATP-J transporter (OATP5A1; SLC21A15), OCT3 transporter (EMT; SLC22A3), OCTN2 transporter (FLJ46769; SLC22A5), ENT transporters (ENT1; SLC29A1 and ENT2; SLC29A2), PAT2 transporter (SLC36A2), and SAT2 transporter (KIAA1382; SLC38A2). These transporters can facilitate the influx of substrates into skeletal muscle, providing opportunities for muscle targeting.

[000225] In some embodiments, the muscle-targeting agent is a substrate of an equilibrative nucleoside transporter 2 (ENT2) transporter. Relative to other transporters, ENT2 has one of the highest mRNA expressions in skeletal muscle. While human ENT2 (hENT2) is expressed in most body organs such as brain, heart, placenta, thymus, pancreas, prostate, and kidney, it is especially abundant in skeletal muscle. Human ENT2 facilitates the uptake of its substrates depending on their concentration gradient. ENT2 plays a role in maintaining nucleoside homeostasis by transporting a wide range of purine and pyrimidine nucleobases. The hENT2 transporter has a low affinity for all nucleosides (adenosine, guanosine, uridine, thymidine, and cytidine) except for inosine. Accordingly, in some embodiments, the muscle-targeting agent is an ENT2 substrate. Exemplary ENT2 substrates include, without limitation, inosine, 2′,3′-dideoxyinosine, and calofarabine. In some embodiments, any of the muscle-targeting agents provided herein are associated with a molecular payload (e.g., oligonucleotide payload). In some embodiments, the muscle-targeting agent is covalently linked to the molecular payload. In some embodiments, the muscle-targeting agent is non-covalently linked to the molecular payload.

[000226] In some embodiments, the muscle-targeting agent is a substrate of an organic cation/carnitine transporter (OCTN2), which is a sodium ion-dependent, high affinity carnitine transporter. In some embodiments, the muscle-targeting agent is carnitine, mildronate, acetylcarnitine, or any derivative thereof that binds to OCTN2. In some embodiments, the carnitine, mildronate, acetylcarnitine, or derivative thereof is covalently linked to the molecular payload (e.g., oligonucleotide payload).

[000227] A muscle-targeting agent may be a protein that is protein that exists in at least one soluble form that targets muscle cells. In some embodiments, a muscle-targeting protein may be hemojuvelin (also known as repulsive guidance molecule C or hemochromatosis type 2 protein), a protein involved in iron overload and homeostasis. In some embodiments, hemojuvelin may be full length or a fragment, or a mutant with at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or at least 99% sequence identity to a functional hemojuvelin protein. In some embodiments, a hemojuvelin mutant may be a soluble fragment, may lack a N-terminal signaling, and/or (e.g., and) lack a C-terminal anchoring domain. In some embodiments, hemojuvelin may be annotated under GenBank RefSeq Accession Numbers NM_001316767.1, NM_145277.4, NM_202004.3, NM_213652.3, or NM_213653.3. It should be appreciated that a hemojuvelin may be of human, non-human primate, or rodent origin.

B. Molecular Payloads

[000228] Some aspects of the disclosure provide molecular payloads, e.g., for modulating a biological outcome, e.g., the transcription of a DNA sequence, the splicing and processing of a RNA sequence, the expression of a protein, or the activity of a protein. In some embodiments, a molecular payload is linked to, or otherwise associated with a muscle-targeting agent. In some embodiments, such molecular payloads are capable of targeting to a muscle cell, e.g., via specifically binding to a nucleic acid or protein in the muscle cell following delivery to the muscle cell by an associated muscle-targeting agent. It should be appreciated that various types of molecular payloads may be used in accordance with the disclosure. For example, the molecular payload may comprise, or consist of, an oligonucleotide (e.g., antisense oligonucleotide), a peptide (e.g., a peptide that binds a nucleic acid or protein associated with disease in a muscle cell), a protein (e.g., a protein that binds a nucleic acid or protein associated with disease in a muscle cell), or a small molecule (e.g., a small molecule that modulates the function of a nucleic acid or protein associated with disease in a muscle cell). In some embodiments, the molecular payload is an oligonucleotide that comprises a strand having

a region of complementarity to a mutated DMD allele. Exemplary molecular payloads are described in further detail herein, however, it should be appreciated that the exemplary molecular payloads provided herein are not meant to be limiting.

i. Oligonucleotides

[000229] Aspects of the disclosure relate to oligonucleotides configured to modulate (e.g., increase) expression of dystrophin, e.g., from a DMD allele. In some embodiments, oligonucleotides provided herein are configured to alter splicing of DMD pre-mRNA to promote expression of dystrophin protein (e.g., a functional truncated dystrophin protein). In some embodiments, oligonucleotides provided herein are configured to promote skipping of one or more exons in DMD, e.g., in a mutated DMD allele, in order to restore the reading frame. In some embodiments, the oligonucleotides allow for functional dystrophin protein expression (e.g., as described in Watanabe N, Nagata T, Satou Y, et al. NS-065/NCNP-01: an antisense oligonucleotide for potential treatment of exon 53 skipping in Duchenne muscular dystrophy. Mol Ther Nucleic Acids. 2018;13:442-449). In some embodiments, oligonucleotides provided are configured to promote skipping of exon 53 to produce a shorter but functional version of dystrophin (e.g., containing an in-frame deletion). In some embodiments, oligonucleotides are provided that promote exon 53 skipping (e.g., which may be relevant in a substantial number of patients, including, for example, patients amenable to exon 53 skipping, such as those having deletions in DMD exons 3-52, 4-52, 5-52, 6-52, 9-52, 10-52, 11-52, 13-52, 14-52, 16-52, 17-52, 19-52, 21-52, 23-52, 24-52, 25-52, 26-52, 27-52, 28-52, 29-52, 30-52, 31-52, 32-52, 33-52, 34-52, 35-52, 36-52, 37-52, 38-52, 39-52, 40-52, 41-52, 42-52, 43-52, 45-52, 47-52, 48-52, 49-52, 50-52, 52, 54-58, 54-61, 54-63, 54-64, 54-66, 54-76, or 54-77).

[000230] Table 8 provides non-limiting examples of sequences of oligonucleotides that are useful for targeting DMD, *e.g.,* for exon skipping, and for target sequences within DMD. In some embodiments, an oligonucleotide may comprise any antisense sequence provided in Table 8 or a sequence complementary to a target sequence provided in Table 8.

Table 8. Oligonucleotide sequences for targeting DMD.

SEQ ID NO	Target sequence† (5' to 3')	SEQ ID NO	Antisense Sequence† (5' to 3')	SEQ ID NO	Antisense Sequence† (5' to 3')	Target Site
160	GAGUCAUGGAAGG AGGGUCCCUAU	335	AUAGGGACCCUCC UUCCAUGACUC	510	ATAGGGACCCTCC TTCCATGACTC	Exon 53
161	GGAGGGUCCCUAU ACAGUAGAUG	336	CAUCUACUGUAUA GGGACCCUCC	511	CATCTACTGTATA GGGACCCTCC	Exon 53
162	AGGAGGGUCCCUA UACAGUAGAUG	337	CAUCUACUGUAUA GGGACCCUCCU	512	CATCTACTGTATA GGGACCCTCCT	Exon 53
163	GCUUGAGUCAUGG AAGGAGGG	338	CCCUCCUUCCAUG ACUCAAGC	513	CCCTCCTTCCATG ACTCAAGC	Exon 53

164	AGCUUGAGUCAUG GAAGGAGGG	339	CCCUCCUUCCAUG ACUCAAGCU	514	CCCTCCTTCCATG ACTCAAGCT	Exon 53
165	GCUUGAGUCAUGG AAGGAGG	340	CCUCCUUCCAUGA CUCAAGC	515	CCTCCTTCCATGA CTCAAGC	Exon 53
166	AGCUUGAGUCAUG GAAGGAGG	341	CCUCCUUCCAUGA CUCAAGCU	516	CCTCCTTCCATGA CTCAAGCT	Exon 53
167	CAACACAAUGGCU GGAAGCUAAGG	342	CCUUAGCUUCCAG CCAUUGUGUUG	517	CCTTAGCTTCCAG CCATTGTGTTG	Exon 53
168	UCAACACAAUGGC UGGAAGCUAAGG	343	CCUUAGCUUCCAG CCAUUGUGUUGA	518	CCTTAGCTTCCAG CCATTGTGTTGA	Exon 53
169	AGCUUGAGUCAUG GAAGGAG	344	CUCCUUCCAUGAC UCAAGCU	519	CTCCTTCCATGAC TCAAGCT	Exon 53
170	AUCAGUGGGAUGA AGUACAAG	345	CUUGUACUUCAUC CCACUGAU	520	CTTGTACTTCATC CCACTGAT	Exon 53
171	GAAUCAGUGGGAU GAAGUACAAG	346	CUUGUACUUCAUC CCACUGAUUC	521	CTTGTACTTCATC CCACTGATTC	Exon 53
172	UGAGUCAUGGAAG GAGGGUC	347	GACCCUCCUUCCA UGACUCA	522	GACCCTCCTTCCA TGACTCA	Exon 53
173	UUGAGUCAUGGAA GGAGGGUC	348	GACCCUCCUUCCA UGACUCAA	523	GACCCTCCTTCCA TGACTCAA	Exon 53
174	CUUGAGUCAUGGA AGGAGGGUC	349	GACCCUCCUUCCA UGACUCAAG	524	GACCCTCCTTCCA TGACTCAAG	Exon 53
175	GCUUGAGUCAUGG AAGGAGGGUC	350	GACCCUCCUUCCA UGACUCAAGC	525	GACCCTCCTTCCA TGACTCAAGC	Exon 53
176	GGGUCCCUAUACA GUAGAUGCAAUC	351	GAUUGCAUCUACU GUAUAGGGACCC	526	GATTGCATCTACT GTATAGGGACCC	Exon 53
177	GGAGGGUCCCUAU ACAGUAGAUGC	352	GCAUCUACUGUAU AGGGACCCUCC	527	GCATCTACTGTAT AGGGACCCTCC	Exon 53
178	AAGCAUGGGACAC ACAAAGC	353	GCUUUGUGUGUCC CAUGCUU	528	GCTTTGTGTGTCC CATGCTT	Intron 52
179	CAAGCAUGGGACA CACAAAGC	354	GCUUUGUGUGUCC CAUGCUUG	529	GCTTTGTGTGTCC CATGCTTG	Intron 52
180	ACAAGCAUGGGAC ACACAAAGC	355	GCUUUGUGUGUCC CAUGCUUGU	530	GCTTTGTGTGTCC CATGCTTGT	Intron 52
181	AACAAGCAUGGGA CACACAAAGC	356	GCUUUGUGUGUCC CAUGCUUGUU	531	GCTTTGTGTGTCC CATGCTTGTT	Intron 52
182	UAACAAGCAUGGG ACACACAAAGC	357	GCUUUGUGUGUCC CAUGCUUGUUA	532	GCTTTGTGTGTCC CATGCTTGTTA	Intron 52
183	GAGUCAUGGAAGG AGGGUCC	358	GGACCCUCCUUCC AUGACUC	533	GGACCCTCCTTCC ATGACTC	Exon 53
184	GGUCCCUAUACAG UAGAUGCAAUCC	359	GGAUUGCAUCUAC UGUAUAGGGACC	534	GGATTGCATCTAC TGTATAGGGACC	Exon 53
185	UGAGUCAUGGAAG GAGGGUCCC	360	GGGACCCUCCUUC CAUGACUCA	535	GGGACCCTCCTTC CATGACTCA	Exon 53
186	AAGUUUGUCCUGA AAGGUGGGUUAC	361	GUAACCCACCUUU CAGGACAAACUU	536	GTAACCCACCTTT CAGGACAAACTT	Intron 53
187	GAAUCAGUGGGAU GAAGUAC	362	GUACUUCAUCCCA CUGAUUC	537	GTACTTCATCCCA CTGATTC	Exon 53
188	GUUCAUCAUCCUA GCCAUAACAC	363	GUGUUAUGGCUAG GAUGAUGAAC	538	GTGTTATGGCTAG GATGATGAAC	Intron 52
189	CAGUGGGAUGAAG UACAAGA	364	UCUUGUACUUCAU CCCACUG	539	TCTTGTACTTCAT CCCACTG	Exon 53
190	UCAGUGGGAUGAA GUACAAGA	365	UCUUGUACUUCAU CCCACUGA	540	TCTTGTACTTCAT CCCACTGA	Exon 53
191	AUCAGUGGGAUGA AGUACAAGA	366	UCUUGUACUUCAU CCCACUGAU	541	TCTTGTACTTCAT CCCACTGAT	Exon 53
192	AAUCAGUGGGAUG AAGUACAAGA	367	UCUUGUACUUCAU CCCACUGAUU	542	TCTTGTACTTCAT CCCACTGATT	Exon 53
193	GAAUCAGUGGGAU GAAGUACAAGA	368	UCUUGUACUUCAU CCCACUGAUUC	543	TCTTGTACTTCAT CCCACTGATTC	Exon 53

194	AGAACACCUUCAG AACCGGAGGCA	369	UGCCUCCGGUUCU GAAGGUGUUCU	544	TGCCTCCGGTTCT GAAGGTGTTCT	Exon 53
195	AAGAACACCUUCA GAACCGGAGGCA	370	UGCCUCCGGUUCU GAAGGUGUUCUU	545	TGCCTCCGGTTCT GAAGGTGTTCTT	Exon 53
196	AGCAUGGGACACA CAAAGCA	371	UGCUUUGUGUGUC CCAUGCU	546	TGCTTTGTGTGTC CCATGCT	Intron 52
197	AAGCAUGGGACAC ACAAAGCA	372	UGCUUUGUGUGUC CCAUGCUU	547	TGCTTTGTGTGTC CCATGCTT	Intron 52
198	CAAGCAUGGGACA CACAAAGCA	373	UGCUUUGUGUGUC CCAUGCUUG	548	TGCTTTGTGTGTC CCATGCTTG	Intron 52
199	ACAAGCAUGGGAC ACACAAAGCA	374	UGCUUUGUGUGUC CCAUGCUUGU	549	TGCTTTGTGTGTC CCATGCTTGT	Intron 52
200	AACAAGCAUGGGA CACACAAAGCA	375	UGCUUUGUGUGUC CCAUGCUUGUU	550	TGCTTTGTGTGTC CCATGCTTGTT	Intron 52
201	UAACAAGCAUGGG ACACACAAAGCA	376	UGCUUUGUGUGUC CCAUGCUUGUUA	551	TGCTTTGTGTGTC CCATGCTTGTTA	Intron 52
202	GAAUCAGUGGGAU GAAGUACA	377	UGUACUUCAUCCC ACUGAUUC	552	TGTACTTCATCCC ACTGATTC	Exon 53
203	UAACAAGCAUGGG ACACACA	378	UGUGUGUCCCAUG CUUGUUA	553	TGTGTGTCCCATG CTTGTTA	Intron 52
204	GUUCAUCAUCCUA GCCAUAACACA	379	UGUGUUAUGGCUA GGAUGAUGAAC	554	TGTGTTATGGCTA GGATGATGAAC	Intron 52
205	AGUGGGAUGAAGU ACAAGAACA	380	UGUUCUUGUACUU CAUCCCACU	555	TGTTCTTGTACTT CATCCCACT	Exon 53
206	CAGUGGGAUGAAG UACAAGAACA	381	UGUUCUUGUACUU CAUCCCACUG	556	TGTTCTTGTACTT CATCCCACTG	Exon 53
207	UCAGUGGGAUGAA GUACAAGAACA	382	UGUUCUUGUACUU CAUCCCACUGA	557	TGTTCTTGTACTT CATCCCACTGA	Exon 53
208	AUCAGUGGGAUGA AGUACAAGAACA	383	UGUUCUUGUACUU CAUCCCACUGAU	558	TGTTCTTGTACTT CATCCCACTGAT	Exon 53
209	CAGUGGGAUGAAG UACAAGAA	384	UUCUUGUACUUCA UCCCACUG	559	TTCTTGTACTTCA TCCCACTG	Exon 53
210	UCAGUGGGAUGAA GUACAAGAA	385	UUCUUGUACUUCA UCCCACUGA	560	TTCTTGTACTTCA TCCCACTGA	Exon 53
211	AUCAGUGGGAUGA AGUACAAGAA	386	UUCUUGUACUUCA UCCCACUGAU	561	TTCTTGTACTTCA TCCCACTGAT	Exon 53
212	AAUCAGUGGGAUG AAGUACAAGAA	387	UUCUUGUACUUCA UCCCACUGAUU	562	TTCTTGTACTTCA TCCCACTGATT	Exon 53
213	GAAUCAGUGGGAU GAAGUACAAGAA	388	UUCUUGUACUUCA UCCCACUGAUUC	563	TTCTTGTACTTCA TCCCACTGATTC	Exon 53
214	GAAUCAGUGGGAU GAAGUACAA	389	UUGUACUUCAUCC CACUGAUUC	564	TTGTACTTCATCC CACTGATTC	Exon 53
215	UAACAAGCAUGGG ACACACAA	390	UUGUGUGUCCCAU GCUUGUUA	565	TTGTGTGTCCCAT GCTTGTTA	Intron 52
216	GUUCAUCAUCCUA GCCAUAACACAA	391	UUGUGUUAUGGCU AGGAUGAUGAAC	566	TTGTGTTATGGCT AGGATGATGAAC	Intron 52
217	ACAAGCAUGGGAC ACACAAA	392	UUUGUGUGUCCCA UGCUUGU	567	TTTGTGTGTCCCA TGCTTGT	Intron 52
218	AACAAGCAUGGGA CACACAAA	393	UUUGUGUGUCCCA UGCUUGUU	568	TTTGTGTGTCCCA TGCTTGTT	Intron 52
219	UAACAAGCAUGGG ACACACAAA	394	UUUGUGUGUCCCA UGCUUGUUA	569	TTTGTGTGTCCCA TGCTTGTTA	Intron 52
220	AUGUCUCCUCCAG ACUAGCAUUU	395	AAAUGCUAGUCUG GAGGAGACAU	570	AAATGCTAGTCTG GAGGAGACAT	Intron 52
221	AAUGUCUCCUCCA GACUAGCAUUU	396	AAAUGCUAGUCUG GAGGAGACAUU	571	AAATGCTAGTCTG GAGGAGACATT	Intron 52
222	AAAUGUCUCCUCC AGACUAGCAUUU	397	AAAUGCUAGUCUG GAGGAGACAUUU	572	AAATGCTAGTCTG GAGGAGACATTT	Intron 52
223	AAAGUUUGUCCUG AAAGGUGGGUU	398	AACCCACCUUUCA GGACAAACUUU	573	AACCCACCTTTCA GGACAAACTTT	Intron 53

224	CCUUCAGAACCGG AGGCAACAGUU	399	AACUGUUGCCUCC GGUUCUGAAGG	574	AACTGTTGCCTCC GGTTCTGAAGG	Exon 53
225	GAGUCAUGGAAGG AGGGUCCCU	400	AGGGACCCUCCUU CCAUGACUC	575	AGGGACCCTCCTT CCATGACTC	Exon 53
226	AGUCAUGGAAGGA GGGUCCCUAU	401	AUAGGGACCCUCC UUCCAUGACU	576	ATAGGGACCCTCC TTCCATGACT	Exon 53
227	GGAGGGUCCCUAU ACAGUAGAU	402	AUCUACUGUAUAG GGACCCUCC	577	ATCTACTGTATAG GGACCCTCC	Exon 53
228	AGGAGGGUCCCUA UACAGUAGAU	403	AUCUACUGUAUAG GGACCCUCCU	578	ATCTACTGTATAG GGACCCTCCT	Exon 53
229	ACCAAGGUUAGUA UCAAAGAU	404	AUCUUUGAUACUA ACCUUGGU	579	ATCTTTGATACTA ACCTTGGT	Exon 53/intron 53 junction
230	AACCAAGGUUAGU AUCAAAGAU	405	AUCUUUGAUACUA ACCUUGGUU	580	ATCTTTGATACTA ACCTTGGTT	Exon 53/intron 53 junction
231	UCAUCAUCCUAGC CAUAACACAAU	406	AUUGUGUUAUGGC UAGGAUGAUGA	581	ATTGTGTTATGGC TAGGATGATGA	Intron 52
232	CCUUCAGAACCGG AGGCAACAGUUG	407	CAACUGUUGCCUC CGGUUCUGAAGG	582	CAACTGTTGCCTC CGGTTCTGAAGG	Exon 53
233	AGAACACCUUCAG AACCGGAGG	408	CCUCCGGUUCUGA AGGUGUUCU	583	CCTCCGGTTCTGA AGGTGTTCT	Exon 53
234	AAGAACACCUUCA GAACCGGAGG	409	CCUCCGGUUCUGA AGGUGUUCUU	584	CCTCCGGTTCTGA AGGTGTTCTT	Exon 53
235	CAAGAACACCUUC AGAACCGGAGG	410	CCUCCGGUUCUGA AGGUGUUCUUG	585	CCTCCGGTTCTGA AGGTGTTCTTG	Exon 53
236	ACACAAUGGCUGG AAGCUAAGG	411	CCUUAGCUUCCAG CCAUUGUGU	586	CCTTAGCTTCCAG CCATTGTGT	Exon 53
237	AACACAAUGGCUG GAAGCUAAGG	412	CCUUAGCUUCCAG CCAUUGUGUU	587	CCTTAGCTTCCAG CCATTGTGTT	Exon 53
238	CAAGAACACCUUC AGAACCGGAG	413	CUCCGGUUCUGAA GGUGUUCUUG	588	CTCCGGTTCTGAA GGTGTTCTTG	Exon 53
239	UACAAGAACACCU UCAGAACCGGAG	414	CUCCGGUUCUGAA GGUGUUCUUGUA	589	CTCCGGTTCTGAA GGTGTTCTTGTA	Exon 53
240	CAACACAAUGGCU GGAAGCUAAG	415	CUUAGCUUCCAGC CAUUGUGUUG	590	CTTAGCTTCCAGC CATTGTGTTG	Exon 53
241	UCAACACAAUGGC UGGAAGCUAAG	416	CUUAGCUUCCAGC CAUUGUGUUGA	591	CTTAGCTTCCAGC CATTGTGTTGA	Exon 53
242	UCAGUGGGAUGAA GUACAAG	417	CUUGUACUUCAUC CCACUGA	592	CTTGTACTTCATC CCACTGA	Exon 53
243	AAUCAGUGGGAUG AAGUACAAG	418	CUUGUACUUCAUC CCACUGAUU	593	CTTGTACTTCATC CCACTGATT	Exon 53
244	AUACAGUAGAUGC AAUCCAAAAG	419	CUUUUGGAUUGCA UCUACUGUAU	594	CTTTTGGATTGCA TCTACTGTAT	Exon 53
245	GGUCCCUAUACAG UAGAUGCAAUC	420	GAUUGCAUCUACU GUAUAGGGACC	595	GATTGCATCTACT GTATAGGGACC	Exon 53
246	GAGGGUCCCUAUA CAGUAGAUGC	421	GCAUCUACUGUAU AGGGACCCUC	596	GCATCTACTGTAT AGGGACCCTC	Exon 53
247	AAUGUCUCCUCCA GACUAGC	422	GCUAGUCUGGAGG AGACAUU	597	GCTAGTCTGGAGG AGACATT	Intron 52
248	AAAUGUCUCCUCC AGACUAGC	423	GCUAGUCUGGAGG AGACAUUU	598	GCTAGTCTGGAGG AGACATTT	Intron 52
249	AAAAUGUCUCCUC CAGACUAGC	424	GCUAGUCUGGAGG AGACAUUUU	599	GCTAGTCTGGAGG AGACATTTT	Intron 52
250	UAAAAUGUCUCCU CCAGACUAGC	425	GCUAGUCUGGAGG AGACAUUUUA	600	GCTAGTCTGGAGG AGACATTTTA	Intron 52
251	UGAGUCAUGGAAG GAGGGUCC	426	GGACCCUCCUUCC AUGACUCA	601	GGACCCTCCTTCC ATGACTCA	Exon 53
252	UUGAGUCAUGGAA GGAGGGUCC	427	GGACCCUCCUUCC AUGACUCAA	602	GGACCCTCCTTCC ATGACTCAA	Exon 53
253	GUCCCUAUACAGU AGAUGCAAUCC	428	GGAUUGCAUCUAC UGUAUAGGGAC	603	GGATTGCATCTAC TGTATAGGGAC	Exon 53

254	AGUCAUGGAAGGA GGGUCCC	429	GGGACCCUCCUUC CAUGACU	604	GGGACCCTCCTTC CATGACT	Exon 53
255	UUGAGUCAUGGAA GGAGGGUCCC	430	GGGACCCUCCUUC CAUGACUCAA	605	GGGACCCTCCTTC CATGACTCAA	Exon 53
256	AACUUAAGUUCAU AUAUCCC	431	GGGAUAUAUGAAC UUAAGUU	606	GGGATATATGAAC TTAAGTT	Intron 52
257	AGUUUGUCCUGAA AGGUGGGUUACC	432	GGUAACCCACCUU UCAGGACAAACU	607	GGTAACCCACCTT TCAGGACAAACT	Intron 53
258	AGUUUGUCCUGAA AGGUGGGUUAC	433	GUAACCCACCUUU CAGGACAAACU	608	GTAACCCACCTTT CAGGACAAACT	Intron 53
259	UCAUCAUCCUAGC CAUAACAC	434	GUGUUAUGGCUAG GAUGAUGA	609	GTGTTATGGCTAG GATGATGA	Intron 52
260	UUCAUCAUCCUAG CCAUAACAC	435	GUGUUAUGGCUAG GAUGAUGAA	610	GTGTTATGGCTAG GATGATGAA	Intron 52
261	GUUCAUCAUCCUA GCCAUAAC	436	GUUAUGGCUAGGA UGAUGAAC	611	GTTATGGCTAGGA TGATGAAC	Intron 52
262	AUGUCUCCUCCAG ACUAGCAUUUA	437	UAAAUGCUAGUCU GGAGGAGACAU	612	TAAATGCTAGTCT GGAGGAGACAT	Intron 52
263	AAUGUCUCCUCCA GACUAGCAUUUA	438	UAAAUGCUAGUCU GGAGGAGACAUU	613	TAAATGCTAGTCT GGAGGAGACATT	Intron 52
264	AAGUUUGUCCUGA AAGGUGGGUUA	439	UAACCCACCUUUC AGGACAAACUU	614	TAACCCACCTTTC AGGACAAACTT	Intron 53
265	AAAGUUUGUCCUG AAAGGUGGGUUA	440	UAACCCACCUUUC AGGACAAACUUU	615	TAACCCACCTTTC AGGACAAACTTT	Intron 53
266	GAGUCAUGGAAGG AGGGUCCCUA	441	UAGGGACCCUCCU UCCAUGACUC	616	TAGGGACCCTCCT TCCATGACTC	Exon 53
267	ACCAAGGUUAGUA UCAAAGAUA	442	UAUCUUUGAUACU AACCUUGGU	617	TATCTTTGATACT AACCTTGGT	Exon 53/intron 53 junction
268	UACAGUAGAUGCA AUCCAAAAGA	443	UCUUUUGGAUUGC AUCUACUGUA	618	TCTTTTGGATTGC ATCTACTGTA	Exon 53
269	GUCCCUAUACAGU AGAUGCAAUCCA	444	UGGAUUGCAUCUA CUGUAUAGGGAC	619	TGGATTGCATCTA CTGTATAGGGAC	Exon 53
270	AAUCAGUGGGAUG AAGUACA	445	UGUACUUCAUCCC ACUGAUU	620	TGTACTTCATCCC ACTGATT	Exon 53
271	CAUCAUCCUAGCC AUAACACA	446	UGUGUUAUGGCUA GGAUGAUG	621	TGTGTTATGGCTA GGATGATG	Intron 52
272	UCAUCAUCCUAGC CAUAACACA	447	UGUGUUAUGGCUA GGAUGAUGA	622	TGTGTTATGGCTA GGATGATGA	Intron 52
273	UUCAUCAUCCUAG CCAUAACACA	448	UGUGUUAUGGCUA GGAUGAUGAA	623	TGTGTTATGGCTA GGATGATGAA	Intron 52
274	GUGGGAUGAAGUA CAAGAACA	449	UGUUCUUGUACUU CAUCCCAC	624	TGTTCTTGTACTT CATCCCAC	Exon 53
275	AGUGGGAUGAAGU ACAAGAA	450	UUCUUGUACUUCA UCCCACU	625	TTCTTGTACTTCA TCCCACT	Exon 53
276	AUCAGUGGGAUGA AGUACAA	451	UUGUACUUCAUCC CACUGAU	626	TTGTACTTCATCC CACTGAT	Exon 53
277	AAUCAGUGGGAUG AAGUACAA	452	UUGUACUUCAUCC CACUGAUU	627	TTGTACTTCATCC CACTGATT	Exon 53
278	AACAAGCAUGGGA CACACAA	453	UUGUGUGUCCCAU GCUUGUU	628	TTGTGTGTCCCAT GCTTGTT	Intron 52
279	UCAUCAUCCUAGC CAUAACACAA	454	UUGUGUUAUGGCU AGGAUGAUGA	629	TTGTGTTATGGCT AGGATGATGA	Intron 52
280	AAGUUUGUCCUGA AAGGUGGGUU	455	AACCCACCUUUCA GGACAAACUU	630	AACCCACCTTTCA GGACAAACTT	Intron 53
281	AAAAGUUUGUCCU GAAAGGUGGGUU	456	AACCCACCUUUCA GGACAAACUUUU	631	AACCCACCTTTCA GGACAAACTTTT	Intron 53
282	CCUAGCCAUAACA CAAUGAAUAAUU	457	AAUUAUUCAUUGU GUUAUGGCUAGG	632	AATTATTCATTGT GTTATGGCTAGG	Intron 52
283	AAGGAUUCAACAC AAUGGCU	458	AGCCAUUGUGUUG AAUCCUU	633	AGCCATTGTGTTG AATCCTT	Exon 53

284	UAAAGGAUUCAAC ACAAUGGCU	459	AGCCAUUGUGUUG AAUCCUUUA	634	AGCCATTGTGTTG AATCCTTTA	Exon 53
285	ACCAAGGUUAGUA UCAAAGAUACCU	460	AGGUAUCUUUGAU ACUAACCUUGGU	635	AGGTATCTTTGAT ACTAACCTTGGT	Exon 53/intron 53 junction
286	GUCAUGGAAGGAG GGUCCCUAU	461	AUAGGGACCCUCC UUCCAUGAC	636	ATAGGGACCCTCC TTCCATGAC	Exon 53
287	AUAUAUGUAUUCU GACCUGAGGAU	462	AUCCUCAGGUCAG AAUACAUAUAU	637	ATCCTCAGGTCAG AATACATATAT	Intron 53
288	AAACCAAGGUUAG UAUCAAAGAU	463	AUCUUUGAUACUA ACCUUGGUUU	638	ATCTTTGATACTA ACCTTGGTTT	Exon 53/intron 53 junction
289	CUAGCCAUAACAC AAUGAAUAAU	464	AUUAUUCAUUGUG UUAUGGCUAG	639	ATTATTCATTGTG TTATGGCTAG	Intron 52
290	CCUAGCCAUAACA CAAUGAAUAAU	465	AUUAUUCAUUGUG UUAUGGCUAGG	640	ATTATTCATTGTG TTATGGCTAGG	Intron 52
291	UCCUAGCCAUAAC ACAAUGAAUAAU	466	AUUAUUCAUUGUG UUAUGGCUAGGA	641	ATTATTCATTGTG TTATGGCTAGGA	Intron 52
292	UUCAUCAUCCUAG CCAUAACACAAU	467	AUUGUGUUAUGGC UAGGAUGAUGAA	642	ATTGTGTTATGGC TAGGATGATGAA	Intron 52
293	AGCUGAAAUGAAC AGUAGACUUUG	468	CAAAGUCUACUGU UCAUUUCAGCU	643	CAAAGTCTACTGT TCATTTCAGCT	Intron 53
294	UAAAGGAUUCAAC ACAAUGGCUG	469	CAGCCAUUGUGUU GAAUCCUUUA	644	CAGCCATTGTGTT GAATCCTTTA	Exon 53
295	GAGGGUCCCUAUA CAGUAGAUG	470	CAUCUACUGUAUA GGGACCCUC	645	CATCTACTGTATA GGGACCCTC	Exon 53
296	UGAAAAGUUUGUC CUGAAAGGUGG	471	CCACCUUUCAGGA CAAACUUUUCA	646	CCACCTTTCAGGA CAAACTTTTCA	Intron 53
297	AGGAUUCAACACA AUGGCUGG	472	CCAGCCAUUGUGU UGAAUCCU	647	CCAGCCATTGTGT TGAATCCT	Exon 53
298	AAGGAUUCAACAC AAUGGCUGG	473	CCAGCCAUUGUGU UGAAUCCUU	648	CCAGCCATTGTGT TGAATCCTT	Exon 53
299	AAAGGAUUCAACA CAAUGGCUGG	474	CCAGCCAUUGUGU UGAAUCCUUU	649	CCAGCCATTGTGT TGAATCCTTT	Exon 53
300	UAAAGGAUUCAAC ACAAUGGCUGG	475	CCAGCCAUUGUGU UGAAUCCUUUA	650	CCAGCCATTGTGT TGAATCCTTTA	Exon 53
301	GAAAAGUUUGUCC UGAAAGGUGGG	476	CCCACCUUUCAGG ACAAACUUUUC	651	CCCACCTTTCAGG ACAAACTTTTC	Intron 53
302	UGAAAAGUUUGUC CUGAAAGGUGGG	477	CCCACCUUUCAGG ACAAACUUUUCA	652	CCCACCTTTCAGG ACAAACTTTTCA	Intron 53
303	CUUGAGUCAUGGA AGGAGGG	478	CCCUCCUUCCAUG ACUCAAG	653	CCCTCCTTCCATG ACTCAAG	Exon 53
304	AGAACACCUUCAG AACCGGAG	479	CUCCGGUUCUGAA GGUGUUCU	654	CTCCGGTTCTGAA GGTGTTCT	Exon 53
305	AAGAACACCUUCA GAACCGGAG	480	CUCCGGUUCUGAA GGUGUUCUU	655	CTCCGGTTCTGAA GGTGTTCTT	Exon 53
306	GGAUUCAACACAA UGGCUGGAAG	481	CUUCCAGCCAUUG UGUUGAAUCC	656	CTTCCAGCCATTG TGTTGAATCC	Exon 53
307	AGGAUUCAACACA AUGGCUGGAAG	482	CUUCCAGCCAUUG UGUUGAAUCCU	657	CTTCCAGCCATTG TGTTGAATCCT	Exon 53
308	AAGGAUUCAACAC AAUGGCUGGAAG	483	CUUCCAGCCAUUG UGUUGAAUCCUU	658	CTTCCAGCCATTG TGTTGAATCCTT	Exon 53
309	AGCUUGAGUCAUG GAAGGAGGGUC	484	GACCCUCCUUCCA UGACUCAAGCU	659	GACCCTCCTTCCA TGACTCAAGCT	Exon 53
310	GGGUCCCUAUACA GUAGAUGC	485	GCAUCUACUGUAU AGGGACCC	660	GCATCTACTGTAT AGGGACCC	Exon 53
311	UAAAGGAUUCAAC ACAAUGGC	486	GCCAUUGUGUUGA AUCCUUUA	661	GCCATTGTGTTGA ATCCTTTA	Exon 53
312	UUAAAAUGUCUCC UCCAGACUAGC	487	GCUAGUCUGGAGG AGACAUUUUAA	662	GCTAGTCTGGAGG AGACATTTTAA	Intron 52
313	GAUUCAACACAAU GGCUGGAAGC	488	GCUUCCAGCCAUU GUGUUGAAUC	663	GCTTCCAGCCATT GTGTTGAATC	Exon 53

314	GGAUUCAACACAA UGGCUGGAAGC	489	GCUUCCAGCCAUU GUGUUGAAUCC	664	GCTTCCAGCCATT GTGTTGAATCC	Exon 53
315	AGGAUUCAACACA AUGGCUGGAAGC	490	GCUUCCAGCCAUU GUGUUGAAUCCU	665	GCTTCCAGCCATT GTGTTGAATCCT	Exon 53
316	CUUGAGUCAUGGA AGGAGGGUCC	491	GGACCCUCCUUCC AUGACUCAAG	666	GGACCCTCCTTCC ATGACTCAAG	Exon 53
317	GCUUGAGUCAUGG AAGGAGGGUCC	492	GGACCCUCCUUCC AUGACUCAAGC	667	GGACCCTCCTTCC ATGACTCAAGC	Exon 53
318	AGCUUGAGUCAUG GAAGGAGGGUCC	493	GGACCCUCCUUCC AUGACUCAAGCU	668	GGACCCTCCTTCC ATGACTCAAGCT	Exon 53
319	CUUGAGUCAUGGA AGGAGGGUCCC	494	GGGACCCUCCUUC CAUGACUCAAG	669	GGGACCCTCCTTC CATGACTCAAG	Exon 53
320	GCUUGAGUCAUGG AAGGAGGGUCCC	495	GGGACCCUCCUUC CAUGACUCAAGC	670	GGGACCCTCCTTC CATGACTCAAGC	Exon 53
321	GUCUCCUCCAGAC UAGCAUUUAC	496	GUAAAUGCUAGUC UGGAGGAGAC	671	GTAAATGCTAGTC TGGAGGAGAC	Intron 52
322	GUAAGUUUUUUAA CAAGCAUGGGAC	497	GUCCCAUGCUUGU UAAAAAACUUAC	672	GTCCCATGCTTGT TAAAAAACTTAC	Intron 52
323	AGCUGAAAUGAAC AGUAGAC	498	GUCUACUGUUCAU UUCAGCU	673	GTCTACTGTTCAT TTCAGCT	Intron 53
324	CAUCAUCCUAGCC AUAACAC	499	GUGUUAUGGCUAG GAUGAUG	674	GTGTTATGGCTAG GATGATG	Intron 52
325	GAUUCAACACAAU GGCUGGAAGCUA	500	UAGCUUCCAGCCA UUGUGUUGAAUC	675	TAGCTTCCAGCCA TTGTGTTGAATC	Exon 53
326	AACCAAGGUUAGU AUCAAAGAUA	501	UAUCUUUGAUACU AACCUUGGUU	676	TATCTTTGATACT AACCTTGGTT	Exon 53/intron 53 junction
327	AGGAUUCAACACA AUGGCUGGA	502	UCCAGCCAUUGUG UUGAAUCCU	677	TCCAGCCATTGTG TTGAATCCT	Exon 53
328	AAGGAUUCAACAC AAUGGCUGGA	503	UCCAGCCAUUGUG UUGAAUCCUU	678	TCCAGCCATTGTG TTGAATCCTT	Exon 53
329	AAAGGAUUCAACA CAAUGGCUGGA	504	UCCAGCCAUUGUG UUGAAUCCUUU	679	TCCAGCCATTGTG TTGAATCCTTT	Exon 53
330	UAAAGGAUUCAAC ACAAUGGCUGGA	505	UCCAGCCAUUGUG UUGAAUCCUUUA	680	TCCAGCCATTGTG TTGAATCCTTTA	Exon 53
331	AUAUAUGUAUUCU GACCUGAGGA	506	UCCUCAGGUCAGA AUACAUAUAU	681	TCCTCAGGTCAGA ATACATATAT	Intron 53
332	GAACACCUUCAGA ACCGGAGGCA	507	UGCCUCCGGUUCU GAAGGUGUUC	682	TGCCTCCGGTTCT GAAGGTGTTC	Exon 53
333	GUUCAUCAUCCUA GCCAUAA	508	UUAUGGCUAGGAU GAUGAAC	683	TTATGGCTAGGAT GATGAAC	Intron 52
334	UUCAUCAUCCUAG CCAUAACACAA	509	UUGUGUUAUGGCU AGGAUGAUGAA	684	TTGTGTTATGGCT AGGATGATGAA	Intron 52

† Each thymine base (T) in any one of the oligonucleotides and/or target sequences provided in Table 8 may independently and optionally be replaced with a uracil base (U), and/or each U may independently and optionally be replaced with a T. Target sequences listed in Table 8 contain U's, but binding of a DMD-targeting oligonucleotide to RNA and/or DNA is contemplated.

[000231] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) targets a region of a DMD sequence. In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) targets a region of a DMD RNA (*e.g.*, the Dp427m transcript of SEQ ID NO: 130). In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a region of complementarity to a DMD RNA (*e.g.*, the Dp427m transcript of SEQ ID NO: 130). In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a region of

complementarity to an exon of a DMD RNA (*e.g.*, SEQ ID NO: 131, 762, or 777). In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a region of complementarity to an intron of a DMD RNA (*e.g.*, SEQ ID NO: 754 or 770). In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a region of complementarity to a portion of a DMD sequence (*e.g.*, a sequence provided by any one of SEQ ID NOs: 753, 755-761, 763-769, and 771-776). Examples of DMD sequences are provided below. Each of the DMD sequences provided below include thymine nucleotides (T's), but it should be understood that each sequence can represent a DNA sequence or an RNA sequence in which any or all of the T's would be replaced with uracil nucleotides (U's).

[000232] *Homo sapiens* dystrophin (DMD), transcript variant Dp427m, mRNA (NCBI Reference Sequence: NM_004006.2)

TCCTGGCATCAGTTACTGTGTTGACTCACTCAGTGTTGGGATCACTCACTTTCCCCCTACAGGACTCAGATCTGGG
AGGCAATTACCTTCGGAGAAAAACGAATAGGAAAAACTGAAGTGTTACTTTTTTTAAAGCTGCTGAAGTTTGTTGG
TTTCTCATTGTTTTTAAGCCTACTGGAGCAATAAAGTTTGAAGAACTTTTACCAGGTTTTTTTTATCGCTGCCTTG
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TTCACAAAATGGGTAAATGCACAATTTTCTAAGTTTGGGAAGCAGCATATTGAGAACCTCTTCAGTGACCTACAGG
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TCATGCCCTGAACAATGTCAACAAGGCACTGCGGGTTTTGCAGAACAATAATGTTGATTTAGTGAATATTGGAAGT
ACTGACATCGTAGATGGAAATCATAAACTGACTCTTGGTTTGATTTGGAATATAATCCTCCACTGGCAGGTCAAAA
ATGTAATGAAAAATATCATGGCTGGATTGCAACAAACCAACAGTGAAAAGATTCTCCTGAGCTGGGTCCGACAATC
AACTCGTAATTATCCACAGGTTAATGTAATCAACTTCACCACCAGCTGGTCTGATGGCCTGGCTTTGAATGCTCTC
ATCCATAGTCATAGGCCAGACCTATTTGACTGGAATAGTGTGGTTTGCCAGCAGTCAGCCACACAACGACTGGAAC
ATGCATTCAACATCGCCAGATATCAATTAGGCATAGAGAAACTACTCGATCCTGAAGATGTTGATACCACCTATCC
AGATAAGAAGTCCATCTTAATGTACATCACATCACTCTTCCAAGTTTTGCCTCAACAAGTGAGCATTGAAGCCATC
CAGGAAGTGGAAATGTTGCCAAGGCCACCTAAAGTGACTAAAGAAGAACATTTTCAGTTACATCATCAAATGCACT
ATTCTCAACAGATCACGGTCAGTCTAGCACAGGGATATGAGAGAACTTCTTCCCCTAAGCCTCGATTCAAGAGCTA
TGCCTACACACAGGCTGCTTATGTCACCACCTCTGACCCTACACGGAGCCCATTTCCTTCACAGCATTTGGAAGCT
CCTGAAGACAAGTCATTTGGCAGTTCATTGATGGAGAGTGAAGTAAACCTGGACCGTTATCAAACAGCTTTAGAAG
AAGTATTATCGTGGCTTCTTTCTGCTGAGGACACATTGCAAGCACAAGGAGAGATTTCTAATGATGTGGAAGTGGT
GAAAGACCAGTTTCATACTCATGAGGGGTACATGATGGATTTGACAGCCCATCAGGGCCGGGTTGGTAATATTCTA
CAATTGGGAAGTAAGCTGATTGGAACAGGAAAATTATCAGAAGATGAAGAAACTGAAGTACAAGAGCAGATGAATC
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TCTCCAGAATCAGAAACTGAAAGAGTTGAATGACTGGCTAACAAAAACAGAAGAAAGAACAAGGAAAATGGAGGAA
GAGCCTCTTGGACCTGATCTTGAAGACCTAAAACGCCAAGTACAACAACATAAGGTGCTTCAAGAAGATCTAGAAC
AAGAACAAGTCAGGGTCAATTCTCTCACTCACATGGTGGTGGTAGTTGATGAATCTAGTGGAGATCACGCAACTGC
TGCTTTGGAAGAACAACTTAAGGTATTGGGAGATCGATGGGCAAACATCTGTAGATGGACAGAAGACCGCTGGGTT
CTTTTACAAGACATCCTTCTCAAATGGCAACGTCTTACTGAAGAACAGTGCCTTTTTAGTGCATGGCTTTCAGAAA
AAGAAGATGCAGTGAACAAGATTCACACAACTGGCTTTAAAGATCAAAATGAAATGTTATCAAGTCTTCAAAAACT
GGCCGTTTTAAAAGCGGATCTAGAAAAGAAAAAGCAATCCATGGGCAAACTGTATTCACTCAAACAAGATCTTCTT
TCAACACTGAAGAATAAGTCAGTGACCCAGAAGACGGAAGCATGGCTGGATAACTTTGCCCGGTGTTGGGATAATT
TAGTCCAAAAACTTGAAAAGAGTACAGCACAGATTTCACAGGCTGTCACCACCACTCAGCCATCACTAACACAGAC
AACTGTAATGGAAACAGTAACTACGGTGACCACAAGGGAACAGATCCTGGTAAAGCATGCTCAAGAGGAACTTCCA
CCACCACCTCCCCAAAAGAAGAGGCAGATTACTGTGGATTCTGAAATTAGGAAAAGGTTGGATGTTGATATAACTG
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CCCAGCTGGTTGAGCATTGTCAAAAGCTAGAGGAGCAAATGAATAAACTCCGAAAAATTCAGAATCACATACAAAC
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TCTTCTCACAGTCAAAAGGAACTGGGTGGTTTGGTTTTTGTTGCTTTTTTAGATTTATTGTCCCATGTGGGATGAG
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ATCAGACTTCACCAAATATATGCCTTACTATTGTATTATAGTACTGCTTTACTGTGTATCTCAATAAAGCACGCAG
TTATGTTAC (SEQ ID NO: 130)

[000233] *Homo sapiens* dystrophin (DMD), transcript variant Dp427m, exon 52 (nucleotide positions 7787-7904 of NCBI Reference Sequence: NM_004006.2; nucleotide positions 1614862-1614979 of NCBI Reference Sequence: NG_012232.1)

GCAACAATGCAGGATTTGGAACAGAGGCGTCCCCAGTTGGAAGAACTCATTACCGCTGCCCAAAATTTGAAAAACA
AGACCAGCAATCAAGAGGCTAGAACAATCATTACGGATCGAA (SEQ ID NO: 131)

[000234] *Homo sapiens* dystrophin (DMD) exon 52/intron 52 junction (nucleotide positions 1614950-1615009 of NCBI Reference Sequence: NG_012232.1)

AAGAGGCTAGAACAATCATTACGGATCGAAGTAAGTTTTTTAACAAGCATGGGACACACA (SEQ ID NO: 753)

[000235] *Homo sapiens* dystrophin (DMD), intron 52 (nucleotide positions 1614980-1665023 of NCBI Reference Sequence: NG_012232.1)

GTAAGTTTTTTAACAAGCATGGGACACACAAAGCAAGATGCATGACAAGTTTCAATAAAAACTTAAGTTCATATAT
CCCCCTCACATTTATAAAAATAATGTGAAATAATTGTAAATGATAACAATTGTGCTGAGATTTTCAGTCCATAATG
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GCCGGGCGTGGTGGCGGGCGCCTGTAGTCCCAGCTACTTGGGAGGCTGAGGCAGGAGAATGGCGTGAACCCGGGAG
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ACAAGCAAAGAACAGAGCTTGGAATTTGTAAATGTCTCTTTCTGACTTGAAAATCTGCGCTCTTTCTAGTATGTTT

ACCATTTCCCATCTTGTTTTGTTGCTTTTGTTAATGACCTTAATCATTGTACTAAGACTAAATACTTCTTTTGTCT
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TTTACTACTATATATTTATTTTTCCTTTTATTCTAG (SEQ ID NO: 754)

[000236] *Homo sapiens* dystrophin (DMD), intron 52 target sequence 1 (nucleotide positions 1614980-1615029 of NCBI Reference Sequence: NG_012232.1)

GTAAGTTTTTTAACAAGCATGGGACACACAAAGCAAGATGCATGACAAGT (SEQ ID NO: 755)

[000237] *Homo sapiens* dystrophin (DMD), intron 52 target sequence 2 (nucleotide positions 1614980-1615024 of NCBI Reference Sequence: NG_012232.1)

GTAAGTTTTTTAACAAGCATGGGACACACAAAGCAAGATGCATGA (SEQ ID NO: 756)

[000238] *Homo sapiens* dystrophin (DMD), intron 52 target sequence 3 (nucleotide positions 1615029-1615068 of NCBI Reference Sequence: NG_012232.1)

TTTCAATAAAAACTTAAGTTCATATATCCCCCTCACATTT (SEQ ID NO: 757)

[000239] *Homo sapiens* dystrophin (DMD), intron 52 target sequence 4 (nucleotide positions 1664873-1664926 of NCBI Reference Sequence: NG_012232.1)

GAATCCTGTTGTTCATCATCCTAGCCATAACACAATGAATAATTTTTTAAATAA (SEQ ID NO: 758)

[000240] *Homo sapiens* dystrophin (DMD), intron 52 target sequence 5 (nucleotide positions 1664953-1665002 of NCBI Reference Sequence: NG_012232.1)

GAAGTTACATTTAAAATGTCTCCTCCAGACTAGCATTTACTACTATATAT (SEQ ID NO: 759)

[000241] *Homo sapiens* dystrophin (DMD), intron 52 target sequence 6 (nucleotide positions 1664774-1665023 of NCBI Reference Sequence: NG_012232.1)

TCAAGAATTGAGTTAAAATTTTATATATATGTTGATGTTCTATGTCACCTTCAGGAAAATAATTTAACAGAAACTA
ATATTTGCCATCAAAAAAGCAAAGAATCCTGTTGTTCATCATCCTAGCCATAACACAATGAATAATTTTTTAAATA
AGCAACATAAATGTGAGATAACGTTTGGAAGTTACATTTAAAATGTCTCCTCCAGACTAGCATTTACTACTATATA
TTTATTTTTCCTTTTATTCTAG (SEQ ID NO: 760)

[000242] *Homo sapiens* dystrophin (DMD) intron 52/exon 53 junction (nucleotide positions 1664994-1665053 of NCBI Reference Sequence: NG_012232.1)

ACTATATATTTATTTTTCCTTTTATTCTAGTTGAAAGAATTCAGAATCAGTGGGATGAAG (SEQ ID NO: 761)

[000243] *Homo sapiens* dystrophin (DMD), transcript variant Dp427m, exon 53 (nucleotide positions 7905-8116 of NCBI Reference Sequence: NM_004006.2; nucleotide positions 1665024-1665235 of NCBI Reference Sequence: NG_012232.1)

TTGAAAGAATTCAGAATCAGTGGGATGAAGTACAAGAACACCTTCAGAACCGGAGGCAACAGTTGAATGAAATGTT
AAAGGATTCAACACAATGGCTGGAAGCTAAGGAAGAAGCTGAGCAGGTCTTAGGACAGGCCAGAGCCAAGCTTGAG
TCATGGAAGGAGGGTCCCTATACAGTAGATGCAATCCAAAAGAAAATCACAGAAACCAAG (SEQ ID NO: 762)

[000244] *Homo sapiens* dystrophin (DMD), exon 53 target sequence 1 (nucleotide positions 1665027-1665073 of NCBI Reference Sequence: NG_012232.1)

AAAGAATTCAGAATCAGTGGGATGAAGTACAAGAACACCTTCAGAAC (SEQ ID NO: 763)

[000245] *Homo sapiens* dystrophin (DMD), exon 53 target sequence 2 (nucleotide positions 1665044-1665098 of NCBI Reference Sequence: NG_012232.1)

TGGGATGAAGTACAAGAACACCTTCAGAACCGGAGGCAACAGTTGAATGAAATGT (SEQ ID NO: 764)

[000246] *Homo sapiens* dystrophin (DMD), exon 53 target sequence 3 (nucleotide positions 1665089-1665141 of NCBI Reference Sequence: NG_012232.1)

AATGAAATGTTAAAGGATTCAACACAATGGCTGGAAGCTAAGGAAGAAGCTGA (SEQ ID NO: 765)

[000247] *Homo sapiens* dystrophin (DMD), exon 53 target sequence 4 (nucleotide positions 1665158-1665206 of NCBI Reference Sequence: NG_012232.1)

GCCAGAGCCAAGCTTGAGTCATGGAAGGAGGGTCCCTATACAGTAGATG (SEQ ID NO: 766)

[000248] *Homo sapiens* dystrophin (DMD), exon 53 target sequence 5 (nucleotide positions 1665173-1665228 of NCBI Reference Sequence: NG_012232.1)

GAGTCATGGAAGGAGGGTCCCTATACAGTAGATGCAATCCAAAAGAAAATCACAGA (SEQ ID NO: 767)

[000249] *Homo sapiens* dystrophin (DMD) exon 53/intron 53 junction (nucleotide positions 1665206-1665265 of NCBI Reference Sequence: NG_012232.1)

GCAATCCAAAAGAAAATCACAGAAACCAAGGTTAGTATCAAAGATACCTTTTTAAAATAA (SEQ ID NO: 768)

[000250] *Homo sapiens* dystrophin (DMD) exon 53/intron 53 junction target sequence 1 (nucleotide positions 1665218-1665264 of NCBI Reference Sequence: NG_012232.1)

AAAATCACAGAAACCAAGGTTAGTATCAAAGATACCTTTTTAAAATA (SEQ ID NO: 769)

[000251] *Homo sapiens* dystrophin (DMD), intron 53 (nucleotide positions 1665236-1716747 of NCBI Reference Sequence: NG_012232.1)

GTTAGTATCAAAGATACCTTTTTAAAATAAAATACTGGTTACATTTGATAAAATTATACCATAGATTGTAATTTAA
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CCCAATTGTAGCATTGAGATTCGTGGAGTTGTTGCAGTGGTTCTGAATTTTTCAAGCATGATACATAAAAAGATAA
ATGACTCTTTTGATATTTCTCCTTGCATTGATAGTTTGCCTGAAAACTAGATAAGCAGGGAGCCGGCAGTCCACGT
TAGCCCTTGAACTACATGAGGTTTAATTTATTTGCCCAACCAGAACCCTACACTACCTTTCAGCTGTGCAGTATTA
AAGTTTATTTAGGAGTTGATAAATAGCTTAGTGCAATGCTTCCTTTTTTCCAGTAGCTACATCCTCATAAACCTAT
TCTACCCTCCACCAGTTAATGCAGACAGAAGATTTTTATCCAGTATGAGCACTGAAACTCCACTGTGGAAGACTGT
GTGCTCAGCAAAAACCTCACCCATGATGAATAAACAGCTCTTCCGGGGGCTTTGCTGCCGCTGGCTCGGCAGGAGT
TGTTTATTGCCTGGTTTGCACATCCCATGATAAAGTTGCTGCTGAAATAAATTGCAGTTTTGCATAATTATTGACA
ATCACATCTTAACAAGCAATGTGTATCATATTCAAGTGTTCAATTTTTTAAAATCCATTTTTAGCTTATGTTTAAT
CCCAGAAAGTGTTTGTGTAGTAATAGAAGGCAAATAAGACATTTAAATAGAGTACTAATTTCCTCATTGCAGACAA
AGTTTACCTGAATCTTTTTCCATAGGACTGTTACTGCCTAAGGCAATTTTCCTTTCTAAGCTATTATTATATAGAT
ATTTGCTGAGGGCATATGTGTGTGTATCCACAATACATGCATTTTATATATATATATATATATATATATGATCA
AAAATATGAATACATTTTTAGAGTTTTTGTCATGAAAGAGTTTGTTTCATCTTTTTAAAATATTACAGGAATGGGG
AAATGGGATATGGGTAGAAGGAACTAATGTTTTTGAGTAACTGTAATGTATAACTGTATAACGTGGGGCACTCAAC
TTCACAGGAATTTTTTATTTTAATTCTCATCACAGCAATAGATATTGCAGATGAGAAACTGAGAATCAGAGAGGGA
ACTTGCCATATCACGTAAGTGGTAAAGAACACTGGGAATTGAACTCAGATCTGCCTAGTTTTTAAAACTCTACTCT
TTTTCATTACACATAACATTTTTATTTTGGAAAATGTTCTCAGTTGTATGATCAAGTAGTTAAATATGAAACTAAC
ACAATAATTATAACTGATGTCATGCAAAATGATAGTTTGCACAAAATGATAGTTTCTATGAAATGTTATTTCTTTA
CTTGTTAAGTCTTTCTTCCTTTGCCCTCCAATCCCCTTCTTTTTGTCTTTTCCTCTAGTCTTTTCCTTTTGATTCT
AGGTTTGTATTTTCTTGACTTTTCTCCTTGCATATCAAATCCTTGTTTTCTGCCTCAGAGCAGCATCAAAGACAAG
CATGGTACAGGGATTTTAGGGTTTTAACTATAAAGGTTTGTCTCAAATTTGGCAGTATATTAAAAATAAGCTTTCA
AAATTGACCAACAAAAACTACAAAATTGAAAAAAAGGTACTTTGAACTTTCACATGTTCAAATATATGTATATATA
TTTCACATATATATATGAAACCTCCTCTGTGGAGAGGGGTTTATAGAAATCTGTAATTGTCATTCTTGCATGCCTT
CCCCCATACAAACGCCTTTAAGTTAAATAAAAATGAAAGTAAATAGACTGCACAATATTATAGTTGTTGCTTAAAG
GAAGAGCTGTAGCAACAACTCACCCCATTGTTGGTATATTACAATTTAGTTCCTCCATCTTTCTCTTTTTATGGAG
TTCACTAGGTGCACCATTCTGATATTTAATAATTGCATCTGAACATTTGGTCCTTTGCAG (SEQ ID NO: 770)

[000252] *Homo sapiens* dystrophin (DMD), intron 53 target sequence 1 (nucleotide positions 1665236-1665285 of NCBI Reference Sequence: NG_012232.1)

GTTAGTATCAAAGATACCTTTTTAAAATAAAATACTGGTTACATTTGATA (SEQ ID NO: 771)

[000253] *Homo sapiens* dystrophin (DMD), intron 53 target sequence 2 (nucleotide positions 1665342-1665385 of NCBI Reference Sequence: NG_012232.1)

ATCACGTTAAAGCTGAAATGAACAGTAGACTTTGTATATTTATT (SEQ ID NO: 772)

[000254] *Homo sapiens* dystrophin (DMD), intron 53 target sequence 3 (nucleotide positions 1686260-1686309 of NCBI Reference Sequence: NG_012232.1)

ATGCTGCATTTGAAAAGTTTGTCCTGAAAGGTGGGTTACCTTATACTGTC (SEQ ID NO: 773)

[000255] *Homo sapiens* dystrophin (DMD), intron 53 target sequence 4 (nucleotide positions 1686339-1686382 of NCBI Reference Sequence: NG_012232.1)

AAGCAATCTAATATATGTATTCTGACCTGAGGATTCAGAAGCTG (SEQ ID NO: 774)

[000256] *Homo sapiens* dystrophin (DMD), intron 53 target sequence 5 (nucleotide positions 1716498-1716747 of NCBI Reference Sequence: NG_012232.1)

GTTTATAGAAATCTGTAATTGTCATTCTTGCATGCCTTCCCCCATACAAACGCCTTTAAGTTAAATAAAAATGAAA
GTAAATAGACTGCACAATATTATAGTTGTTGCTTAAAGGAAGAGCTGTAGCAACAACTCACCCCATTGTTGGTATA
TTACAATTTAGTTCCTCCATCTTTCTCTTTTTATGGAGTTCACTAGGTGCACCATTCTGATATTTAATAATTGCAT
CTGAACATTTGGTCCTTTGCAG (SEQ ID NO: 775)

[000257] *Homo sapiens* dystrophin (DMD), intron 53/exon 54 junction (nucleotide positions 1686464-1686495 of NCBI Reference Sequence: NG_012232.1)

AATTGCATCTGAACATTTGGTCCTTTGCAGCAGTTGGCCAAAGACCTCCGCCAGTGGCAG (SEQ ID NO: 776)

[000258] *Homo sapiens* dystrophin (DMD), transcript variant Dp427m, exon 54 (nucleotide positions 8117-8271 of NCBI Reference Sequence: NM_004006.2; nucleotide positions 1686466-1686620 of NCBI Reference Sequence: NG_012232.1)

CAGTTGGCCAAAGACCTCCGCCAGTGGCAGACAAATGTAGATGTGGCAAATGACTTGGCCCTGAAACTTCTCCGGG
ATTATTCTGCAGATGATACCAGAAAAGTCCACATGATAACAGAGAATATCAATGCCTCTTGGAGAAGCATTCATAA
AAG (SEQ ID NO: 777)

[000259] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) targets a splicing feature in a DMD sequence (*e.g.*, a DMD pre-mRNA). In some embodiments, a splicing feature in a DMD sequence is an exonic splicing enhancer (ESE), a branch point, a splice donor site, or a splice acceptor site in a DMD sequence. In some embodiments, an ESE is in exon 53 of a DMD sequence (*e.g.*, a DMD pre-mRNA). In some embodiments, a branch point is in intron 52 or intron 53 of a DMD sequence (*e.g.*, a DMD pre-mRNA). In some embodiments, a splice donor site is across the junction of exon 52 and intron 52, in intron 52, across the junction of exon 53 and intron 53, or in intron 53 of a DMD sequence (*e.g.*, a DMD pre-mRNA). In some embodiments, a splice acceptor site is in intron 52, across the junction of intron 52 and exon 53, in intron 53, or across the junction of intron 53 and exon 54 of a DMD sequence (*e.g.*, a DMD pre-mRNA). In some embodiments, the oligonucleotide useful for targeting DMD promotes skipping of exon 53, such as by targeting a splicing feature (*e.g.*, an ESE, a branch point, a splice donor site, or a splice acceptor site) in a

DMD sequence (*e.g.*, a DMD pre-mRNA). Examples of ESEs, branch points, splice donor sites, and splice acceptor sites are provided in Table 9.

[000260] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) targets an exonic splicing enhancer (ESE) in a DMD sequence. In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) targets an ESE in DMD exon 53 (e.g., an ESE listed in Table 9).

[000261] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping, such as for skipping exon 53) comprises a region of complementarity to a target sequence comprising one or more full or partial ESEs of a DMD transcript (e.g., one or more full or partial ESEs listed in Table 9). In some embodiments, the oligonucleotide comprises a region of complementarity to a target sequence comprising one or more full or partial ESEs of DMD exon 53. In some embodiments, the oligonucleotide comprises a region of complementarity to a target sequence comprising one or more full or partial ESEs as set forth in any one of SEQ ID NOs: 689-715. In some embodiments, the oligonucleotide comprises a region of complementarity to a target sequence comprising at least 4 (e.g., 4, 5, 6, 7, or 8) consecutive nucleotides of an ESE as set forth in any one of SEQ ID NOs: 689-715. In some embodiments, the oligonucleotide comprises at least 4 (e.g., 4, 5, 6, 7, or 8) consecutive nucleotides of an ESE antisense sequence as set forth in any one of SEQ ID NOs: 723-749.

[000262] In some embodiments, the oligonucleotide comprises a region of complementarity to a target sequence comprising at least 6 (e.g., 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) nucleotides of one or more ESEs (e.g., 2, 3, 4, or more adjacent ESEs) of DMD exon 53. In some embodiments, the oligonucleotide comprises a region of complementarity to a target sequence comprising at least 6 (e.g., 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) nucleotides of one or more ESEs (e.g., 2, 3, 4, or more adjacent ESEs) as set forth in any one of SEQ ID NOs: 689-715. In some embodiments, the oligonucleotide comprises at least 6 (e.g., 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more) nucleotides of one or more ESE antisense sequences (e.g., antisense sequences of 2, 3, 4, or more adjacent ESEs) as set forth in any one of SEQ ID NOs: 723-749.

[000263] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping, such as for skipping exon 53) is 18-35 nucleotides in length, and comprises a region of complementarity to a target sequence comprising at least 4 (e.g., 4, 5, 6, 7, or 8) consecutive nucleotides of an ESE as set forth in any one of SEQ ID NOs: 689-715. In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping, such as for skipping exon 53) is 20-30 (e.g., 20, 25, 30) nucleotides in length, and comprises a region of

complementarity to a target sequence comprising at least 4 (e.g., 4, 5, 6, 7, or 8) consecutive nucleotides of an ESE as set forth in any one of SEQ ID NOs: 689-715. In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping, such as for skipping exon 53) is 20-25 (*i.e.*, 20, 21, 22, 23, 24, or 25) nucleotides in length, and comprises a region of complementarity to a target sequence comprising at least 4 (e.g., 4, 5, 6, 7, or 8) consecutive nucleotides of an ESE as set forth in any one of SEQ ID NOs: 689-715. In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) is 30 nucleotides in length, and comprises a region of complementarity to a target sequence comprising at least 4 (e.g., 4, 5, 6, 7, or 8) consecutive nucleotides of an ESE as set forth in any one of SEQ ID NOs: 689-715.

[000264] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) targets a branch point in a DMD sequence. In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) targets a branch point in DMD intron 52 or intron 53 (e.g., a branch point listed in Table 9).

[000265] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping, such as for skipping exon 53) comprises a region of complementarity to a target sequence comprising a full or partial branch point of a DMD transcript (e.g., a full or partial branch point listed in Table 9). In some embodiments, the oligonucleotide comprises a region of complementarity to a target sequence comprising a full or partial branch point of DMD intron 52 or intron 53. In some embodiments, the oligonucleotide comprises a region of complementarity to a target sequence comprising a full or partial branch point as set forth in SEQ ID NO: 686, 687, or 717. In some embodiments, the oligonucleotide comprises a region of complementarity to a target sequence comprising at least 4 (e.g., 4, 5, 6, or 7) consecutive nucleotides of a branch point as set forth in SEQ ID NO: 686, 687, or 717. In some embodiments, the oligonucleotide comprises at least 4 (e.g., 4, 5, 6, or 7) consecutive nucleotides of a branch point antisense sequence as set forth in SEQ ID NO: 720, 721, or 751.

[000266] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping, such as for skipping exon 53) is 18-35 nucleotides in length, and comprises a region of complementarity to a target sequence comprising at least 4 (e.g., 4, 5, 6, or 7) consecutive nucleotides of a branch point as set forth in SEQ ID NO: 686, 687, or 717. In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping, such as for skipping exon 53) is 20-30 (e.g., 20, 25, 30) nucleotides in length, and comprises a region of complementarity to a target sequence comprising at least 4 (e.g., 4, 5, 6, or 7) consecutive nucleotides of a branch point as set forth in SEQ ID NO: 686, 687, or 717. In

some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping, such as for skipping exon 53) is 20-25 (*i.e.*, 20, 21, 22, 23, 24, or 25) nucleotides in length, and comprises a region of complementarity to a target sequence comprising at least 4 (e.g., 4, 5, 6, or 7) consecutive nucleotides of a branch point as set forth in SEQ ID NO: 686, 687, or 717. In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) is 30 nucleotides in length, and comprises a region of complementarity to a target sequence comprising at least 4 (e.g., 4, 5, 6, or 7) consecutive nucleotides of a branch point as set forth in SEQ ID NO: 686, 687, or 717.

[000267] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) targets a splice donor site in a DMD sequence. In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) targets a splice donor site across the junction of exon 52 and intron 52, in intron 52, across the junction of exon 53 and intron 53, or in intron 53 (e.g., a splice donor site listed in Table 9).

[000268] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping, such as for skipping exon 53) comprises a region of complementarity to a target sequence comprising a full or partial splice donor site of a DMD transcript (e.g., a full or partial splice donor site listed in Table 9). In some embodiments, the oligonucleotide comprises a region of complementarity to a target sequence comprising a full or partial splice donor site across the junction of exon 52 and intron 52, in intron 52, across the junction of exon 53 and intron 53, or in intron 53 of DMD. In some embodiments, the oligonucleotide comprises a region of complementarity to a target sequence comprising a full or partial splice donor site as set forth in SEQ ID NO: 685 or 716. In some embodiments, the oligonucleotide comprises a region of complementarity to a target sequence comprising at least 4 (*e.g.*, 4, 5, 6, 7, or 8) consecutive nucleotides of a splice donor site as set forth in SEQ ID NO: 685 or 716. In some embodiments, the oligonucleotide comprises at least 4 (*e.g.*, 4, 5, 6, 7, or 8) consecutive nucleotides of a splice donor site antisense sequence as set forth in SEQ ID NO: 719 or 750.

[000269] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping, such as for skipping exon 53) is 18-35 nucleotides in length, and comprises a region of complementarity to a target sequence comprising at least 4 (*e.g.*, 4, 5, 6, 7, or 8) consecutive nucleotides of a splice donor site as set forth in SEQ ID NO: 685 or 716. In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping, such as for skipping exon 53) is 20-30 (e.g., 20, 25, 30) nucleotides in length, and comprises a region of complementarity to a target sequence comprising at least 4 (*e.g.*, 4, 5, 6, 7, or 8) consecutive

nucleotides of a splice donor site as set forth in SEQ ID NO: 685 or 716. In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping, such as for skipping exon 53) is 20-25 (*i.e.*, 20, 21, 22, 23, 24, or 25) nucleotides in length, and comprises a region of complementarity to a target sequence comprising at least 4 (*e.g.*, 4, 5, 6, 7, or 8) consecutive nucleotides of a splice donor site as set forth in SEQ ID NO: 685 or 716. In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) is 30 nucleotides in length, and comprises a region of complementarity to a target sequence comprising at least 4 (*e.g.*, 4, 5, 6, 7, or 8) consecutive nucleotides of a splice donor site as set forth in SEQ ID NO: 685 or 716.

[000270] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) targets a splice acceptor site in a DMD sequence. In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) targets a splice acceptor site in intron 52, across the junction of intron 52 and exon 53, in intron 53, or across the junction of intron 53 and exon 54 (e.g., a splice acceptor site listed in Table 9).

[000271] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping, such as for skipping exon 53) comprises a region of complementarity to a target sequence comprising a full or partial splice acceptor site of a DMD transcript (e.g., a full or partial splice acceptor site listed in Table 9). In some embodiments, the oligonucleotide comprises a region of complementarity to a target sequence comprising a full or partial splice acceptor site in intron 52, across the junction of intron 52 and exon 53, in intron 53, or across the junction of intron 53 and exon 54 of DMD. In some embodiments, the oligonucleotide comprises a region of complementarity to a target sequence comprising a full or partial splice acceptor site as set forth in SEQ ID NO: 688 or 718. In some embodiments, the oligonucleotide comprises a region of complementarity to a target sequence comprising at least 4 (*e.g.*, 4, 5, 6, 7, 8, or 9) consecutive nucleotides of a splice acceptor site as set forth in SEQ ID NO: 688 or 718. In some embodiments, the oligonucleotide comprises at least 4 (*e.g.*, 4, 5, 6, 7, 8, or 9) consecutive nucleotides of a splice acceptor site antisense sequence as set forth in SEQ ID NO: 722 or 752.

[000272] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping, such as for skipping exon 53) is 18-35 nucleotides in length, and comprises a region of complementarity to a target sequence comprising at least 4 (*e.g.*, 4, 5, 6, 7, 8, or 9) consecutive nucleotides of a splice acceptor site as set forth in SEQ ID NO: 688 or 718. In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping, such as for skipping exon 53) is 20-30 (e.g., 20, 25, 30) nucleotides in length, and comprises a

region of complementarity to a target sequence comprising at least 4 (*e.g.*, 4, 5, 6, 7, 8, or 9) consecutive nucleotides of a splice acceptor site as set forth in SEQ ID NO: 688 or 718. In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping, such as for skipping exon 53) is 20-25 (*i.e.*, 20, 21, 22, 23, 24, or 25) nucleotides in length, and comprises a region of complementarity to a target sequence comprising at least 4 (*e.g.*, 4, 5, 6, 7, or 8) consecutive nucleotides of a splice acceptor site as set forth in SEQ ID NO: 688 or 718. In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) is 30 nucleotides in length, and comprises a region of complementarity to a target sequence comprising at least 4 (*e.g.*, 4, 5, 6, 7, 8, or 9) consecutive nucleotides of a splice acceptor site as set forth in SEQ ID NO: 688 or 718.

[000273] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a region of complementarity to a junction of an exon and an intron of a DMD RNA (*e.g.*, any one of the exon/intron junctions provided by SEQ ID NOs: 753, 761, 768, and 776). In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a region of complementarity to at least 10 (*e.g.*, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more) consecutive nucleosides of a junction of an exon and an intron of a DMD RNA (*e.g.*, any one of the exon/intron junctions provided by SEQ ID NOs: 753, 761, 768, and 776). In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) is complementary to any one of SEQ ID NOs: 753, 761, 768, and 776.

[000274] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a region of complementarity to a target sequence of a DMD RNA (*e.g.*, a target sequence provided by any one of SEQ ID NOs: 755-760, 763-767, 771-775, and 769). In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a region of complementarity to at least 10 (*e.g.*, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more) consecutive nucleosides of a target sequence of a DMD RNA (*e.g.*, a target sequence provided by any one of SEQ ID NOs: 755-760, 763-767, 771-775, and 769). In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) is complementary to any one of SEQ ID NOs: 755-760, 763-767, 771-775, and 769.

Table 9. Example target sequence motifs

Location in DMD	Type	SEQ ID NO:	Motif Sequence†	SEQ ID NO:	Motif Antisense Sequence†
Across exon 52/intron 52 junction	Splice Donor	685	AAGTAAGT	719	ACTTACTT

Location in DMD	Type	SEQ ID NO:	Motif Sequence†	SEQ ID NO:	Motif Antisense Sequence†
Intron 52	Branch Point	686	TTAAC	720	GTTAA
Intron 52	Branch Point	687	TGTTGAT	721	ATCAACA
Across intron 52/exon 53 junction	Splice Acceptor	688	TATTCTAGT	722	ACTAGAATA
Exon 53	ESE	689	GAATTCAG	723	CTGAATTC
Exon 53	ESE	690	TCAGTGG	724	CCACTGA
Exon 53	ESE	691	CAGTGGG	725	CCCACTG
Exon 53	ESE	692	GTACAAG	726	CTTGTAC
Exon 53	ESE	693	TCAGAAC	727	GTTCTGA
Exon 53	ESE	694	AACCGGA	728	TCCGGTT
Exon 53	ESE	695	CGGAGGC	729	GCCTCCG
Exon 53	ESE	696	TTAAAGG	730	CCTTTAA
Exon 53	ESE	697	GGATTCAA	731	TTGAATCC
Exon 53	ESE	698	ACAATGG	732	CCATTGT
Exon 53	ESE	699	GGCTGGAA	733	TTCCAGCC
Exon 53	ESE	700	CTAAGGA	734	TCCTTAG
Exon 53	ESE	701	CTGAGCA	735	TGCTCAG
Exon 53	ESE	702	AGCAGGT	736	ACCTGCT
Exon 53	ESE	703	TCTTAGG	737	CCTAAGA
Exon 53	ESE	704	CTTAGGA	738	TCCTAAG
Exon 53	ESE	705	GGACAGG	739	CCTGTCC
Exon 53	ESE	706	GACAGGC	740	GCCTGTC
Exon 53	ESE	707	GGCCAGAG	741	CTCTGGCC
Exon 53	ESE	708	CCAGAGC	742	GCTCTGG
Exon 53	ESE	709	TGAGTC	743	GACTCA
Exon 53	ESE	710	AGGAGGG	744	CCCTCCT
Exon 53	ESE	711	GGTCCCTA	745	TAGGGACC
Exon 53	ESE	712	ACAGTAG	746	CTACTGT
Exon 53	ESE	713	CCAAAAG	747	CTTTTGG
Exon 53	ESE	714	TCACAGA	748	TCTGTGA
Exon 53	ESE	715	CACAGA	749	TCTGTG
Across exon 53/intron 53 junction	Splice Donor	716	AGGTTAGT	750	ACTAACCT
Intron 53	Branch Point	717	TTCTGAT	751	ATCAGAA
Across intron 53/exon 54 junction	Splice Acceptor	718	TCCTTTGCAGC	752	GCTGCAAAG GA

† *Each thymine base (T) in any one of the sequences provided in Table 9 may independently and optionally be replaced with a uracil base (U). Motif sequences and antisense sequences listed in Table 9 contain T's, but binding of a motif sequence in RNA and/or DNA is contemplated.*

[000275] In some embodiments, any one of the oligonucleotides useful for targeting DMD (*e.g.*, for exon skipping) is a phosphorodiamidate morpholino oligomer (PMO).

[000276] In some embodiments, the oligonucleotide may have region of complementarity to a mutant DMD allele, for example, a DMD allele with at least one mutation in any of exons 1-79 of DMD in humans that leads to a frameshift and improper RNA splicing/processing.

[000277] In some embodiments, any one of the oligonucleotides can be in salt form, e.g., as sodium, potassium, or magnesium salts.

[000278] In some embodiments, the 5' or 3' nucleoside (e.g., terminal nucleoside) of any one of the oligonucleotides described herein is conjugated to an amine group, optionally via a spacer. In some embodiments, the spacer comprises an aliphatic moiety. In some embodiments, the spacer comprises a polyethylene glycol moiety. In some embodiments, a phosphodiester linkage is present between the spacer and the 5' or 3' nucleoside of the oligonucleotide. In some embodiments, the 5' or 3' nucleoside (e.g., terminal nucleoside) of any of the oligonucleotides described herein is conjugated to a spacer that is a substituted or unsubstituted aliphatic, substituted or unsubstituted heteroaliphatic, substituted or unsubstituted carbocyclylene, substituted or unsubstituted heterocyclylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene, -O-, -$N(R^A)$-, -S-, -C(=O)-, -C(=O)O-, -$C(=O)NR^A$-, -$NR^AC(=O)$-, -$NR^AC(=O)R^A$-, -$C(=O)R^A$-, -$NR^AC(=O)O$-, -$NR^AC(=O)N(R^A)$-, -OC(=O)-, -OC(=O)O-, -$OC(=O)N(R^A)$-, -$S(O)_2NR^A$-, -$NR^AS(O)_2$-, or a combination thereof; each R^A is independently hydrogen or substituted or unsubstituted alkyl. In certain embodiments, the spacer is a substituted or unsubstituted alkylene, substituted or unsubstituted heterocyclylene, substituted or unsubstituted heteroarylene, -O-, -$N(R^A)$-, or -$C(=O)N(R^A)_2$, or a combination thereof.

[000279] In some embodiments, the 5' or 3' nucleoside of any one of the oligonucleotides described herein is conjugated to a compound of the formula -NH_2-$(CH_2)_n$-, wherein n is an integer from 1 to 12. In some embodiments, n is 6, 7, 8, 9, 10, 11, or 12. In some embodiments, a phosphodiester linkage is present between the compound of the formula NH_2-$(CH_2)_n$- and the 5' or 3' nucleoside of the oligonucleotide. In some embodiments, a compound of the formula NH_2-$(CH_2)_6$- is conjugated to the oligonucleotide via a reaction between 6-amino-1-hexanol (NH_2-$(CH_2)_6$-OH) and the 5' phosphate of the oligonucleotide.

[000280] In some embodiments, the oligonucleotide is conjugated to a targeting agent, e.g., a muscle targeting agent such as an anti-TfR1 antibody, e.g., via the amine group.

a. Oligonucleotide Size/Sequence

[000281] Oligonucleotides may be of a variety of different lengths, e.g., depending on the format. In some embodiments, an oligonucleotide is 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 75, or more nucleotides in length. In some embodiments, the oligonucleotide is 8 to 50 nucleotides in length, 8 to 40 nucleotides in length, 8 to 30 nucleotides in length, 10 to 15 nucleotides in length, 10 to 20 nucleotides in length, 15 to 25 nucleotides in length, 21 to 23 nucleotides in lengths, 20 to 25 nucleotides in length, etc.

[000282] In some embodiments, a nucleic acid sequence of an oligonucleotide for purposes of the present disclosure is "complementary" to a target nucleic acid when it is specifically hybridizable to the target nucleic acid. In some embodiments, an oligonucleotide hybridizing to a target nucleic acid (e.g., an mRNA or pre-mRNA molecule) results in modulation of activity or expression of the target (e.g., decreased mRNA translation, altered pre-mRNA splicing, exon skipping, target mRNA degradation, etc.). In some embodiments, a nucleic acid sequence of an oligonucleotide has a sufficient degree of complementarity to its target nucleic acid such that it does not hybridize non-target sequences under conditions in which avoidance of non-specific binding is desired, *e.g.*, under physiological conditions. Thus, in some embodiments, an oligonucleotide may be at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% complementary to the consecutive nucleotides of a target nucleic acid. In some embodiments a complementary nucleotide sequence need not be 100% complementary to that of its target to be specifically hybridizable or specific for a target nucleic acid. In certain embodiments, oligonucleotides comprise one or more mismatched nucleobases relative to the target nucleic acid. In certain embodiments, activity relating to the target is reduced by such mismatch, but activity relating to a non-target is reduced by a greater amount (*i.e.*, selectivity for the target nucleic acid is increased and off-target effects are decreased).

[000283] In some embodiments, an oligonucleotide comprises region of complementarity to a target nucleic acid that is in the range of 8 to 15, 8 to 30, 8 to 40, or 10 to 50, or 5 to 50, 15 to 20, 20 to 25, or 5 to 40 nucleotides in length. In some embodiments, a region of complementarity of an oligonucleotide to a target nucleic acid is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 nucleotides in length. In some embodiments, the region of complementarity is complementary with at least 8 consecutive nucleotides of a target nucleic acid. In some embodiments, an oligonucleotide may contain 1, 2 or 3 base mismatches compared to the portion of the consecutive nucleotides of target nucleic acid. In some embodiments the oligonucleotide may have up to 3 mismatches over 15 bases, or up to 2 mismatches over 10 bases.

[000284] In some embodiments, the oligonucleotide is complementary (e.g., at least 85% at least 90%, at least 95%, or 100%) to a target sequence of the any one of the oligonucleotides described herein (e.g., the oligonucleotides listed in Table 8). In some embodiments, the oligonucleotide is complementary (e.g., at least 85% at least 90%, at least 95%, or 100%) to a

target sequence of the any one of the oligonucleotides provided by SEQ ID NO: 335-684. In some embodiments, such target sequence is 100% complementary to an oligonucleotide listed in Table 8. In some embodiments, such target sequence is 100% complementary to an oligonucleotide provided by SEQ ID NO: 335-684. In some embodiments, the oligonucleotide is complementary (e.g., at least 85% at least 90%, at least 95%, or 100%) to a target sequence provided herein (e.g., a target sequence listed in Table 8). In some embodiments, the oligonucleotide is complementary (e.g., at least 85% at least 90%, at least 95%, or 100%) to any one of SEQ ID NO: 160-334.

[000285] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a region of complementarity to a target sequence of a DMD RNA (*e.g.*, a target sequence provided by any one of SEQ ID NOs: 160-334). In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a region of complementarity to at least 8 (*e.g.*, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more) consecutive nucleosides of a target sequence of a DMD RNA (*e.g.*, a target sequence provided by any one of SEQ ID NOs: 160-334). In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) is complementary to any one of SEQ ID NOs: 160-334.

[000286] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a sequence comprising at least 8 (e.g., 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more) consecutive nucleobases of a DMD-targeting sequence provided herein (e.g., an antisense sequence listed in Table 8). In some embodiments, the oligonucleotide comprises a sequence comprising at least 8 (e.g., 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more) consecutive nucleobases of any one of SEQ ID NOs: 335-684. In some embodiments, the oligonucleotide comprises the sequence of any one of SEQ ID NOs: 335-684.

[000287] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a region of complementarity to a target sequence of a DMD RNA (*e.g.*, a target sequence provided by any one of SEQ ID NOs: 212, 206, 224, 277, 214, 209, 207, 208, and 205). In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a region of complementarity to at least 8 (*e.g.*, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more) consecutive nucleosides of a target sequence of a DMD RNA (*e.g.*, a target sequence provided by any one of SEQ ID NOs: 212, 206, 224, 277, 214, 209, 207, 208, and 205). In some embodiments, an oligonucleotide useful

for targeting DMD (*e.g.*, for exon skipping) is complementary to any one of SEQ ID NOs: 212, 206, 224, 277, 214, 209, 207, 208, and 205.

[000288] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a region of complementarity to a target sequence of a DMD RNA provided by any one of SEQ ID NOs: 212, 224, and 209.

[000289] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a region of complementarity to a target sequence of a DMD RNA provided by any one of SEQ ID NOs: 206, 277, and 205.

[000290] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a region of complementarity to a target sequence of a DMD RNA provided by any one of SEQ ID NOs: 206, 224, and 209.

[000291] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a region of complementarity to a target sequence of a DMD RNA provided by any one of SEQ ID NOs: 214, 207, and 208.

[000292] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a region of complementarity to a target sequence of a DMD RNA provided by any one of SEQ ID NOs: 212, 206, and 209.

[000293] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a region of complementarity to a target sequence of a DMD RNA provided by any one of SEQ ID NOs: 214, 207, and 205.

[000294] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a region of complementarity to a target sequence of a DMD RNA provided by any one of SEQ ID NOs: 277, 214, and 208.

[000295] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a sequence comprising at least 8 (e.g., 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more) contiguous nucleobases of a DMD-targeting sequence provided herein (e.g., a sequence of any one of SEQ ID NOs: 562, 556, 574, 627, 564, 559, 557, 558, and 555). In some embodiments, the oligonucleotide comprises at least 8 (*e.g.*, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or more) consecutive nucleosides of a DMD-targeting sequence provided herein (*e.g.*, a sequence of any one of SEQ ID NOs: 562, 556, 574, 627, 564, 559, 557, 558, and 555). In some embodiments, the oligonucleotide comprises the sequence of any one of SEQ ID NOs: 562, 556, 574, 627, 564, 559, 557, 558, and 555.

[000296] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a sequence of any one of SEQ ID NOs: 562, 574, and 559.

[000297] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a sequence of any one of SEQ ID NOs: 556, 627, and 555.

[000298] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a sequence of any one of SEQ ID NOs: 556, 574, and 559.

[000299] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a sequence of any one of SEQ ID NOs: 564, 557, and 558.

[000300] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a sequence of any one of SEQ ID NOs: 562, 556, and 559.

[000301] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a sequence of any one of SEQ ID NOs: 564, 557, and 555.

[000302] In some embodiments, an oligonucleotide useful for targeting DMD (*e.g.*, for exon skipping) comprises a sequence of any one of SEQ ID NOs: 627, 564, and 558.

[000303] In some embodiments, it should be appreciated that methylation of the nucleobase uracil at the C5 position forms thymine. Thus, in some embodiments, a nucleotide or nucleoside having a C5 methylated uracil (or 5-methyl-uracil) may be equivalently identified as a thymine nucleotide or nucleoside.

[000304] In some embodiments, any one or more of the thymine bases (T's) in any one of the oligonucleotides provided herein (e.g., the oligonucleotides listed in Table 8) may independently and optionally be uracil bases (U's), and/or any one or more of the U's in the oligonucleotides provided herein may independently and optionally be T's. In some embodiments, any one or more of the thymine bases (T's) in any one of the oligonucleotides provided by SEQ ID NOs: 510-684 or in an oligonucleotide complementary to any one of SEQ ID NOs: 160-334 may optionally be uracil bases (U's), and/or any one or more of the U's in the oligonucleotides may optionally be T's. In some embodiments, any one or more of the uracil bases (U's) in any one of the oligonucleotides provided by SEQ ID NOs: 335-509 or in an oligonucleotide complementary to any one of SEQ ID NOs: 160-334 may optionally be thymine bases (T's), and/or any one or more of the T's in the oligonucleotides may optionally be U's.

b. Oligonucleotide Modifications:

[000305] The oligonucleotides described herein may be modified, e.g., comprise a modified sugar moiety, a modified internucleoside linkage, a modified nucleotide or nucleoside and/or (e.g., and) combinations thereof. In addition, in some embodiments,

oligonucleotides may exhibit one or more of the following properties: do not mediate alternative splicing; are not immune stimulatory; are nuclease resistant; have improved cell uptake compared to unmodified oligonucleotides; are not toxic to cells or mammals; have improved endosomal exit internally in a cell; minimizes TLR stimulation; or avoid pattern recognition receptors. Any of the modified chemistries or formats of oligonucleotides described herein can be combined with each other. For example, one, two, three, four, five, or more different types of modifications can be included within the same oligonucleotide.

[000306] In some embodiments, certain nucleotide or nucleoside modifications may be used that make an oligonucleotide into which they are incorporated more resistant to nuclease digestion than the native oligodeoxynucleotide or oligoribonucleotide molecules; these modified oligonucleotides survive intact for a longer time than unmodified oligonucleotides. Specific examples of modified oligonucleotides include those comprising modified backbones, for example, modified internucleoside linkages such as phosphorothioates, phosphotriesters, methyl phosphonates, short chain alkyl or cycloalkyl intersugar linkages or short chain heteroatomic or heterocyclic intersugar linkages. Accordingly, oligonucleotides of the disclosure can be stabilized against nucleolytic degradation such as by the incorporation of a modification, e.g., a nucleotide or nucleoside modification.

[000307] In some embodiments, an oligonucleotide may be of up to 50 or up to 100 nucleotides in length in which 2 to 10, 2 to 15, 2 to 16, 2 to 17, 2 to 18, 2 to 19, 2 to 20, 2 to 25, 2 to 30, 2 to 40, 2 to 45, or more nucleotides or nucleosides of the oligonucleotide are modified nucleotides/nucleosides. The oligonucleotide may be of 8 to 30 nucleotides in length in which 2 to 10, 2 to 15, 2 to 16, 2 to 17, 2 to 18, 2 to 19, 2 to 20, 2 to 25, 2 to 30 nucleotides or nucleosides of the oligonucleotide are modified nucleotides/nucleosides. The oligonucleotide may be of 8 to 15 nucleotides in length in which 2 to 4, 2 to 5, 2 to 6, 2 to 7, 2 to 8, 2 to 9, 2 to 10, 2 to 11, 2 to 12, 2 to 13, 2 to 14 nucleotides or nucleosides of the oligonucleotide are modified nucleotides/nucleosides. Optionally, the oligonucleotides may have every nucleotide or nucleoside except 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides/nucleosides modified. Oligonucleotide modifications are described further herein.

c. Modified Nucleosides

[000308] In some embodiments, the oligonucleotide described herein comprises at least one nucleoside modified at the 2' position of the sugar. In some embodiments, an oligonucleotide comprises at least one 2'-modified nucleoside. In some embodiments, all of the nucleosides in the oligonucleotide are 2'-modified nucleosides.

[000309] In some embodiments, the oligonucleotide described herein comprises one or more non-bicyclic 2'-modified nucleosides, e.g., 2'-deoxy, 2'-fluoro (2'-F), 2'-O-methyl (2'-O-Me), 2'-O-methoxyethyl (2'-MOE), 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), 2'-O-dimethylaminoethyloxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA) modified nucleoside.

[000310] In some embodiments, the oligonucleotide described herein comprises one or more 2'-4' bicyclic nucleosides in which the ribose ring comprises a bridge moiety connecting two atoms in the ring, *e.g.*, connecting the 2'-O atom to the 4'-C atom via a methylene (LNA) bridge, an ethylene (ENA) bridge, or a (S)-constrained ethyl (cEt) bridge. Examples of LNAs are described in International Patent Application Publication WO/2008/043753, published on April 17, 2008, and entitled "*RNA Antagonist Compounds For The Modulation Of PCSK9*", the contents of which are incorporated herein by reference in its entirety. Examples of ENAs are provided in International Patent Publication No. WO 2005/042777, published on May 12, 2005, and entitled "*APP/ENA Antisense*"; Morita et al., Nucleic Acid Res., Suppl 1:241-242, 2001; Surono et al., Hum. Gene Ther., 15:749-757, 2004; Koizumi, Curr. Opin. Mol. Ther., 8:144-149, 2006 and Horie et al., Nucleic Acids Symp. Ser (Oxf), 49:171-172, 2005; the disclosures of which are incorporated herein by reference in their entireties. Examples of cEt are provided in US Patents 7,101,993; 7,399,845 and 7,569,686, each of which is herein incorporated by reference in its entirety.

[000311] In some embodiments, the oligonucleotide comprises a modified nucleoside disclosed in one of the following United States Patent or Patent Application Publications: US Patent 7,399,845, issued on July 15, 2008, and entitled "6-*Modified Bicyclic Nucleic Acid Analogs*"; US Patent 7,741,457, issued on June 22, 2010, and entitled "*6-Modified Bicyclic Nucleic Acid Analogs*"; US Patent 8,022,193, issued on September 20, 2011, and entitled "*6-Modified Bicyclic Nucleic Acid Analogs*"; US Patent 7,569,686, issued on August 4, 2009, and entitled "*Compounds And Methods For Synthesis Of Bicyclic Nucleic Acid Analogs*"; US Patent 7,335,765, issued on February 26, 2008, and entitled "*Novel Nucleoside And Oligonucleotide Analogues*"; US Patent 7,314,923, issued on January 1, 2008, and entitled "*Novel Nucleoside And Oligonucleotide Analogues*"; US Patent 7,816,333, issued on October 19, 2010, and entitled "*Oligonucleotide Analogues And Methods Utilizing The Same*" and US Publication Number 2011/0009471 now US Patent 8,957,201, issued on February 17, 2015, and entitled "*Oligonucleotide Analogues And Methods Utilizing The Same*", the entire contents of each of which are incorporated herein by reference for all purposes.

[000312] In some embodiments, the oligonucleotide comprises at least one modified nucleoside that results in an increase in Tm of the oligonucleotide in a range of 1°C, 2 °C, 3°C, 4 °C, or 5°C compared with an oligonucleotide that does not have the at least one modified nucleoside. The oligonucleotide may have a plurality of modified nucleosides that result in a total increase in Tm of the oligonucleotide in a range of 2 °C, 3 °C, 4 °C, 5 °C, 6 °C, 7 °C, 8 °C, 9 °C, 10 °C, 15 °C, 20 °C, 25 °C, 30 °C, 35 °C, 40 °C, 45 °C or more compared with an oligonucleotide that does not have the modified nucleoside.

[000313] The oligonucleotide may comprise a mix of nucleosides of different kinds. For example, an oligonucleotide may comprise a mix of 2'-deoxyribonucleosides or ribonucleosides and 2'-fluoro modified nucleosides. An oligonucleotide may comprise a mix of deoxyribonucleosides or ribonucleosides and 2'-O-Me modified nucleosides. An oligonucleotide may comprise a mix of 2'-fluoro modified nucleosides and 2'-O-Me modified nucleosides. An oligonucleotide may comprise a mix of 2'-4' bicyclic nucleosides and 2'-MOE, 2'-fluoro, or 2'-O-Me modified nucleosides. An oligonucleotide may comprise a mix of non-bicyclic 2'-modified nucleosides (e.g., 2'-MOE, 2'-fluoro, or 2'-O-Me) and 2'-4' bicyclic nucleosides (e.g., LNA, ENA, cEt).

[000314] The oligonucleotide may comprise alternating nucleosides of different kinds. For example, an oligonucleotide may comprise alternating 2'-deoxyribonucleosides or ribonucleosides and 2'-fluoro modified nucleosides. An oligonucleotide may comprise alternating deoxyribonucleosides or ribonucleosides and 2'-O-Me modified nucleosides. An oligonucleotide may comprise alternating 2'-fluoro modified nucleosides and 2'-O-Me modified nucleosides. An oligonucleotide may comprise alternating 2'-4' bicyclic nucleosides and 2'-MOE, 2'-fluoro, or 2'-O-Me modified nucleosides. An oligonucleotide may comprise alternating non-bicyclic 2'-modified nucleosides (e.g., 2'-MOE, 2'-fluoro, or 2'-O-Me) and 2'-4' bicyclic nucleosides (e.g., LNA, ENA, cEt).

[000315] In some embodiments, an oligonucleotide described herein comprises a 5′-vinylphosphonate modification, one or more abasic residues, and/or one or more inverted abasic residues.

d. Internucleoside Linkages / Backbones

[000316] In some embodiments, oligonucleotide may contain a phosphorothioate or other modified internucleoside linkage. In some embodiments, the oligonucleotide comprises phosphorothioate internucleoside linkages. In some embodiments, the oligonucleotide comprises phosphorothioate internucleoside linkages between at least two nucleosides. In some embodiments, the oligonucleotide comprises phosphorothioate internucleoside linkages

between all nucleosides. For example, in some embodiments, oligonucleotides comprise modified internucleoside linkages at the first, second, and/or (e.g., and) third internucleoside linkage at the 5' or 3' end of the nucleotide sequence.

[000317] Phosphorus-containing linkages that may be used include, but are not limited to, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates comprising 3'alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates comprising 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'; see US patent nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5, 177,196; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455, 233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,306; 5,550,111; 5,563, 253; 5,571,799; 5,587,361; and 5,625,050.

[000318] In some embodiments, oligonucleotides may have heteroatom backbones, such as methylene(methylimino) or MMI backbones; amide backbones (see De Mesmaeker et al. Ace. Chem. Res. 1995, 28:366-374); morpholino backbones (see Summerton and Weller, U.S. Pat. No. 5,034,506); or peptide nucleic acid (PNA) backbones (wherein the phosphodiester backbone of the oligonucleotide is replaced with a polyamide backbone, the nucleotides being bound directly or indirectly to the aza nitrogen atoms of the polyamide backbone, see Nielsen et al., Science 1991, 254, 1497).

e. Stereospecific Oligonucleotides

[000319] In some embodiments, internucleotidic phosphorus atoms of oligonucleotides are chiral, and the properties of the oligonucleotides by adjusted based on the configuration of the chiral phosphorus atoms. In some embodiments, appropriate methods may be used to synthesize P-chiral oligonucleotide analogs in a stereocontrolled manner (e.g., as described in Oka N, Wada T, Stereocontrolled synthesis of oligonucleotide analogs containing chiral internucleotidic phosphorus atoms. Chem Soc Rev. 2011 Dec;40(12):5829-43.) In some embodiments, phosphorothioate containing oligonucleotides comprise nucleoside units that are joined together by either substantially all Sp or substantially all Rp phosphorothioate intersugar linkages are provided. In some embodiments, such phosphorothioate oligonucleotides having substantially chirally pure intersugar linkages are prepared by enzymatic or chemical synthesis, as described, for example, in US Patent 5,587,261, issued on December 12, 1996, the contents

of which are incorporated herein by reference in their entirety. In some embodiments, chirally controlled oligonucleotides provide selective cleavage patterns of a target nucleic acid. For example, in some embodiments, a chirally controlled oligonucleotide provides single site cleavage within a complementary sequence of a nucleic acid, as described, for example, in US Patent Application Publication 20170037399 A1, published on February 2, 2017, entitled "CHIRAL DESIGN", the contents of which are incorporated herein by reference in their entirety.

f. Morpholinos

[000320] In some embodiments, the oligonucleotide may be a morpholino-based compounds. Morpholino-based oligomeric compounds are described in Dwaine A. Braasch and David R. Corey, Biochemistry, 2002, 41(14), 4503-4510); Genesis, volume 30, issue 3, 2001; Heasman, J., Dev. Biol., 2002, 243, 209-214; Nasevicius et al., Nat. Genet., 2000, 26, 216-220; Lacerra et al., Proc. Natl. Acad. Sci., 2000, 97, 9591-9596; and U.S. Pat. No. 5,034,506, issued Jul. 23, 1991. In some embodiments, the morpholino-based oligomeric compound is a phosphorodiamidate morpholino oligomer (PMO) (e.g., as described in Iverson, Curr. Opin. Mol. Ther., 3:235-238, 2001; and Wang et al., J. Gene Med., 12:354-364, 2010; the disclosures of which are incorporated herein by reference in their entireties).

g. Peptide Nucleic Acids (PNAs)

[000321] In some embodiments, both a sugar and an internucleoside linkage (the backbone) of the nucleotide units of an oligonucleotide are replaced with novel groups. In some embodiments, the base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an oligonucleotide mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar-backbone of an oligonucleotide is replaced with an amide containing backbone, for example, an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative publication that report the preparation of PNA compounds include, but are not limited to, US patent nos. 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference. Further teaching of PNA compounds can be found in Nielsen *et al.*, Science, 1991, 254, 1497-1500.

h. Mixmers

[000322] In some embodiments, an oligonucleotide described herein may be a mixmer or comprise a mixmer sequence pattern. In general, mixmers are oligonucleotides that comprise both naturally and non-naturally occurring nucleosides or comprise two different types of non-

naturally occurring nucleosides typically in an alternating pattern. Mixmers generally have higher binding affinity than unmodified oligonucleotides and may be used to specifically bind a target molecule, *e.g.*, to block a binding site on the target molecule. Generally, mixmers do not recruit an RNase to the target molecule and thus do not promote cleavage of the target molecule. Such oligonucleotides that are incapable of recruiting RNase H have been described, for example, see WO2007/112754 or WO2007/112753.

[000323] In some embodiments, the mixmer comprises or consists of a repeating pattern of nucleoside analogues and naturally occurring nucleosides, or one type of nucleoside analogue and a second type of nucleoside analogue. However, a mixmer need not comprise a repeating pattern and may instead comprise any arrangement of modified nucleoside s and naturally occurring nucleoside s or any arrangement of one type of modified nucleoside and a second type of modified nucleoside. The repeating pattern, may, for instance be every second or every third nucleoside is a modified nucleoside, such as LNA, and the remaining nucleoside s are naturally occurring nucleosides, such as DNA, or are a 2′ substituted nucleoside analogue such as 2′-MOE or 2′ fluoro analogues, or any other modified nucleoside described herein. It is recognized that the repeating pattern of modified nucleoside, such as LNA units, may be combined with modified nucleoside at fixed positions—*e.g.* at the 5′ or 3′ termini.

[000324] In some embodiments, a mixmer does not comprise a region of more than 5, more than 4, more than 3, or more than 2 consecutive naturally occurring nucleosides, such as DNA nucleosides. In some embodiments, the mixmer comprises at least a region consisting of at least two consecutive modified nucleosides, such as at least two consecutive LNAs. In some embodiments, the mixmer comprises at least a region consisting of at least three consecutive modified nucleoside units, such as at least three consecutive LNAs.

[000325] In some embodiments, the mixmer does not comprise a region of more than 7, more than 6, more than 5, more than 4, more than 3, or more than 2 consecutive nucleoside analogues, such as LNAs. In some embodiments, LNA units may be replaced with other nucleoside analogues, such as those referred to herein.

[000326] Mixmers may be designed to comprise a mixture of affinity enhancing modified nucleosides, such as in non-limiting example LNA nucleosides and 2'-O-Me nucleosides. In some embodiments, a mixmer comprises modified internucleoside linkages (*e.g.*, phosphorothioate internucleoside linkages or other linkages) between at least two, at least three, at least four, at least five or more nucleosides.

[000327] A mixmer may be produced using any suitable method. Representative U.S. patents, U.S. patent publications, and PCT publications that teach the preparation of mixmers

include U.S. patent publication Nos. US20060128646, US20090209748, US20090298916, US20110077288, and US20120322851, and U.S. patent No. 7687617.

[000328] In some embodiments, a mixmer comprises one or more morpholino nucleosides. For example, in some embodiments, a mixmer may comprise morpholino nucleosides mixed (*e.g.*, in an alternating manner) with one or more other nucleosides (*e.g.*, DNA, RNA nucleosides) or modified nucleosides (*e.g.*, LNA, 2'-O-Me nucleosides).

[000329] In some embodiments, mixmers are useful for splice correcting or exon skipping, for example, as reported in Touznik A., et al., *LNA/DNA mixmer-based antisense oligonucleotides correct alternative splicing of the SMN2 gene and restore SMN protein expression in type 1 SMA fibroblasts* Scientific Reports, volume 7, Article number: 3672 (2017), Chen S. et al., *Synthesis of a Morpholino Nucleic Acid (MNA)-Uridine Phosphoramidite, and Exon Skipping Using MNA/2'-O-Methyl Mixmer Antisense Oligonucleotide*, Molecules 2016, 21, 1582, the contents of each which are incorporated herein by reference.

i. Multimers

[000330] In some embodiments, molecular payloads may comprise multimers (e.g., concatemers) of 2 or more oligonucleotides connected by a linker. In this way, in some embodiments, the oligonucleotide loading of a complex can be increased beyond the available linking sites on a targeting agent (e.g., available thiol sites on an antibody) or otherwise tuned to achieve a particular payload loading content. Oligonucleotides in a multimer can be the same or different (e.g., targeting different genes or different sites on the same gene or products thereof).

[000331] In some embodiments, multimers comprise 2 or more oligonucleotides linked together by a cleavable linker. However, in some embodiments, multimers comprise 2 or more oligonucleotides linked together by a non-cleavable linker. In some embodiments, a multimer comprises 2, 3, 4, 5, 6, 7, 8, 9, 10 or more oligonucleotides linked together. In some embodiments, a multimer comprises 2 to 5, 2 to 10 or 4 to 20 oligonucleotides linked together.

[000332] In some embodiments, a multimer comprises 2 or more oligonucleotides linked end-to-end (in a linear arrangement). In some embodiments, a multimer comprises 2 or more oligonucleotides linked end-to-end via an oligonucleotide based linker (e.g., poly-dT linker, an abasic linker). In some embodiments, a multimer comprises a 5' end of one oligonucleotide linked to a 3' end of another oligonucleotide. In some embodiments, a multimer comprises a 3' end of one oligonucleotide linked to a 3' end of another oligonucleotide. In some embodiments, a multimer comprises a 5' end of one oligonucleotide linked to a 5' end of

another oligonucleotide. Still, in some embodiments, multimers can comprise a branched structure comprising multiple oligonucleotides linked together by a branching linker.

[000333] Further examples of multimers that may be used in the complexes provided herein are disclosed, for example, in US Patent Application Number 2015/0315588 A1, entitled *Methods of delivering multiple targeting oligonucleotides to a cell using cleavable linkers*, which was published on November 5, 2015; US Patent Application Number 2015/0247141 A1, entitled *Multimeric Oligonucleotide Compounds*, which was published on September 3, 2015, US Patent Application Number US 2011/0158937 A1, entitled *Immunostimulatory Oligonucleotide Multimers*, which was published on June 30, 2011; and US Patent Number 5,693,773, entitled *Triplex-Forming Antisense Oligonucleotides Having Abasic Linkers Targeting Nucleic Acids Comprising Mixed Sequences Of Purines And Pyrimidines,* which issued on December 2, 1997, the contents of each of which are incorporated herein by reference in their entireties.

C. Linkers

[000334] Complexes described herein generally comprise a linker that covalently links any one of the anti-TfR1 antibodies described herein to a molecular payload. A linker comprises at least one covalent bond. In some embodiments, a linker may be a single bond, e.g., a disulfide bond or disulfide bridge, that covalently links an anti-TfR1 antibody to a molecular payload. However, in some embodiments, a linker may covalently link any one of the anti-TfR1 antibodies described herein to a molecular payload through multiple covalent bonds. In some embodiments, a linker may be a cleavable linker. However, in some embodiments, a linker may be a non-cleavable linker. A linker is typically stable *in vitro* and *in vivo*, and may be stable in certain cellular environments. Additionally, typically a linker does not negatively impact the functional properties of either the anti-TfR1 antibody or the molecular payload. Examples and methods of synthesis of linkers are known in the art (see, e.g. Kline, T. et al. "Methods to Make Homogenous Antibody Drug Conjugates." Pharmaceutical Research, 2015, 32:11, 3480–3493.; Jain, N. et al. "Current ADC Linker Chemistry" Pharm Res. 2015, 32:11, 3526–3540.; McCombs, J.R. and Owen, S.C. "Antibody Drug Conjugates: Design and Selection of Linker, Payload and Conjugation Chemistry" AAPS J. 2015, 17:2, 339–351.).

[000335] A linker typically will contain two different reactive species that allow for attachment to both the anti-TfR1 antibody and a molecular payload. In some embodiments, the two different reactive species may be a nucleophile and/or an electrophile. In some

embodiments, a linker contains two different electrophiles or nucleophiles that are specific for two different nucleophiles or electrophiles. In some embodiments, a linker is covalently linked to an anti-TfR1 antibody via conjugation to a lysine residue or a cysteine residue of the anti-TfR1 antibody. In some embodiments, a linker is covalently linked to a cysteine residue of an anti-TfR1 antibody via a maleimide-containing linker, wherein optionally the maleimide-containing linker comprises a maleimidocaproyl or maleimidomethyl cyclohexane-1-carboxylate group. In some embodiments, a linker is covalently linked to a cysteine residue of an anti-TfR1 antibody or thiol functionalized molecular payload via a 3-arylpropionitrile functional group. In some embodiments, a linker is covalently linked to a lysine residue of an anti-TfR1 antibody. In some embodiments, a linker is covalently linked to an anti-TfR1 antibody and/or (e.g., and) a molecular payload, independently, via an amide bond, a carbamate bond, a hydrazide, a triazole, a thioether, and/or a disulfide bond.

i. Cleavable Linkers

[000336] A cleavable linker may be a protease-sensitive linker, a pH-sensitive linker, or a glutathione-sensitive linker. These linkers are typically cleavable only intracellularly and are preferably stable in extracellular environments, e.g., extracellular to a muscle cell.

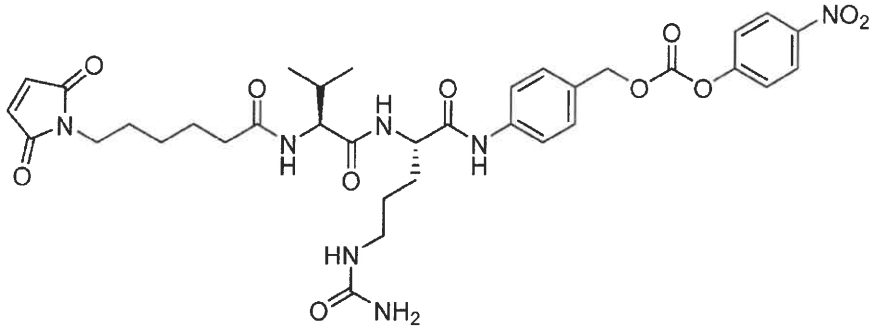
[000337] Protease-sensitive linkers are cleavable by protease enzymatic activity. These linkers typically comprise peptide sequences and may be 2-10 amino acids, about 2-5 amino acids, about 5-10 amino acids, about 10 amino acids, about 5 amino acids, about 3 amino acids, or about 2 amino acids in length. In some embodiments, a peptide sequence may comprise naturally-occurring amino acids, e.g. cysteine, alanine, or non-naturally-occurring or modified amino acids. Non-naturally occurring amino acids include β-amino acids, homo-amino acids, proline derivatives, 3-substituted alanine derivatives, linear core amino acids, N-methyl amino acids, and others known in the art. In some embodiments, a protease-sensitive linker comprises a valine-citrulline or alanine-citrulline sequence. In some embodiments, a protease-sensitive linker can be cleaved by a lysosomal protease, e.g. cathepsin B, and/or (e.g., and) an endosomal protease.

[000338] A pH-sensitive linker is a covalent linkage that readily degrades in high or low pH environments. In some embodiments, a pH-sensitive linker may be cleaved at a pH in a range of 4 to 6. In some embodiments, a pH-sensitive linker comprises a hydrazone or cyclic acetal. In some embodiments, a pH-sensitive linker is cleaved within an endosome or a lysosome.

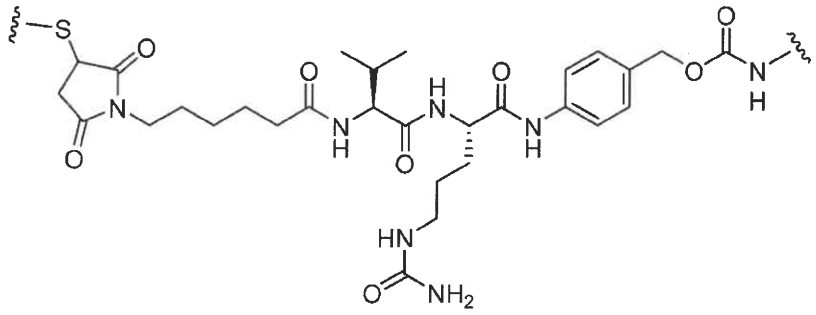
[000339] In some embodiments, a glutathione-sensitive linker comprises a disulfide moiety. In some embodiments, a glutathione-sensitive linker is cleaved by a disulfide

exchange reaction with a glutathione species inside a cell. In some embodiments, the disulfide moiety further comprises at least one amino acid, e.g., a cysteine residue.

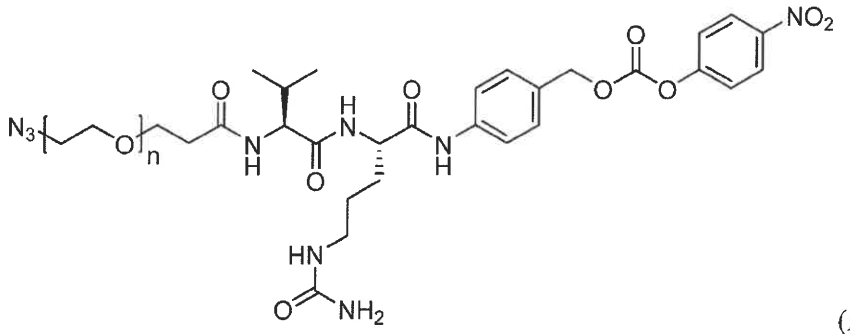
[000340] In some embodiments, a linker comprises a valine-citrulline sequence (e.g., as described in US Patent 6,214,345, incorporated herein by reference). In some embodiments, before conjugation, a linker comprises a structure of:



[000341] In some embodiments, after conjugation, a linker comprises a structure of:



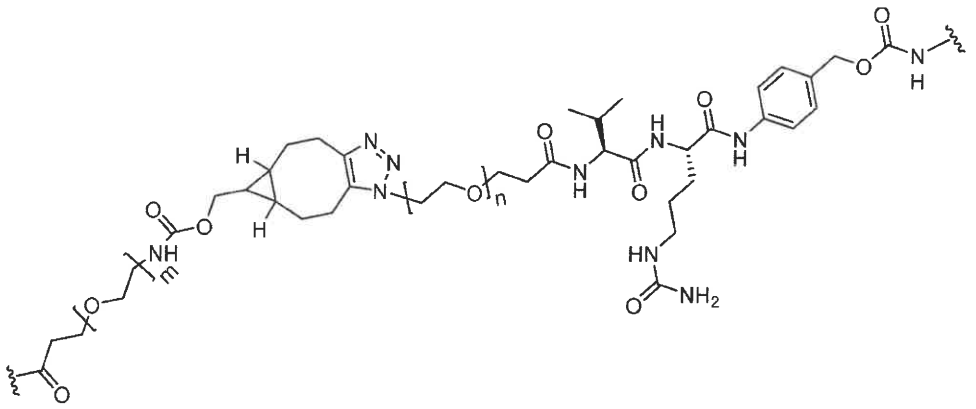
[000342] In some embodiments, before conjugation, a linker comprises a structure of:



(A)

wherein n is any number from 0-10. In some embodiments, n is 3.

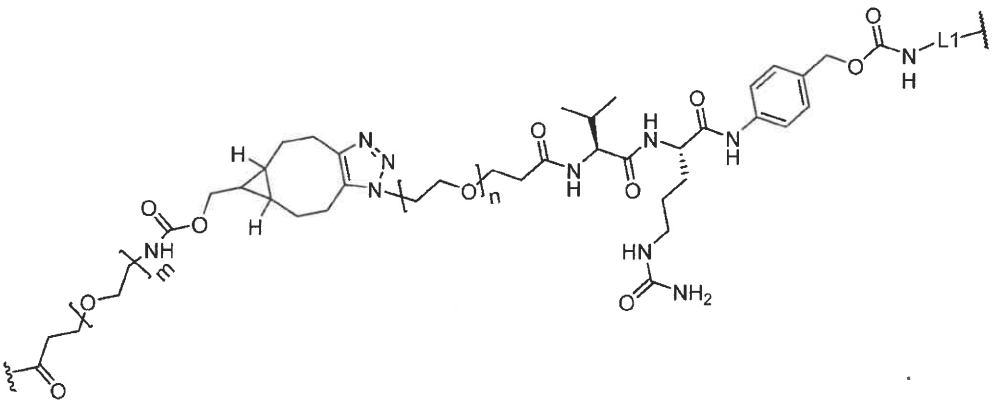
[000343] In some embodiments, a linker comprises a structure of:



(H),

wherein n is any number from 0-10, wherein m is any number from 0-10. In some embodiments, n is 3 and/or (e.g., and) m is 4.

[000344] In some embodiments, a linker comprises a structure of:



(I),

wherein n is any number from 0-10, wherein m is any number from 0-10. In some embodiments, n is 3 and/or (e.g., and) m is 4.

ii. Non-cleavable Linkers

[000345] In some embodiments, non-cleavable linkers may be used. Generally, a non-cleavable linker cannot be readily degraded in a cellular or physiological environment. In some embodiments, a non-cleavable linker comprises an optionally substituted alkyl group, wherein the substitutions may include halogens, hydroxyl groups, oxygen species, and other common substitutions. In some embodiments, a linker may comprise an optionally substituted alkyl, an optionally substituted alkylene, an optionally substituted arylene, a heteroarylene, a peptide sequence comprising at least one non-natural amino acid, a truncated glycan, a sugar or sugars that cannot be enzymatically degraded, an azide, an alkyne-azide, a peptide sequence comprising a LPXT sequence, a thioether, a biotin, a biphenyl, repeating units of polyethylene glycol or equivalent compounds, acid esters, acid amides, sulfamides, and/or an alkoxy-amine linker. In some embodiments, sortase-mediated ligation can be utilized to covalently link an anti-TfR1 antibody comprising a LPXT sequence to a molecular payload comprising a $(G)_n$

sequence (see, e.g. Proft T. Sortase-mediated protein ligation: an emerging biotechnology tool for protein modification and immobilization. Biotechnol Lett. 2010, 32(1):1-10.).

[000346] In some embodiments, a linker may comprise a substituted alkylene, an optionally substituted alkenylene, an optionally substituted alkynylene, an optionally substituted cycloalkylene, an optionally substituted cycloalkenylene, an optionally substituted arylene, an optionally substituted heteroarylene further comprising at least one heteroatom selected from N, O, and S,; an optionally substituted heterocyclylene further comprising at least one heteroatom selected from N, O, and S, an imino, an optionally substituted nitrogen species, an optionally substituted oxygen species O, an optionally substituted sulfur species, or a poly(alkylene oxide), e.g. polyethylene oxide or polypropylene oxide. In some embodiments, a linker may be a non-cleavable N-gamma-maleimidobutyryl-oxysuccinimide ester (GMBS) linker.

iii. Linker conjugation

[000347] In some embodiments, a linker is covalently linked to an anti-TfR1 antibody and/or (e.g., and) molecular payload via a phosphate, thioether, ether, carbon-carbon, carbamate, or amide bond. In some embodiments, a linker is covalently linked to an oligonucleotide through a phosphate or phosphorothioate group, e.g. a terminal phosphate of an oligonucleotide backbone. In some embodiments, a linker is covalently linked to an anti-TfR1 antibody, through a lysine or cysteine residue present on the anti-TfR1 antibody.

[000348] In some embodiments, a linker, or a portion thereof is covalently linked to an anti-TfR1 antibody and/or (e.g., and) molecular payload by a cycloaddition reaction between an azide and an alkyne to form a triazole, wherein the azide or the alkyne may be located on the anti-TfR1 antibody, molecular payload, or the linker. In some embodiments, an alkyne may be a cyclic alkyne, *e.g.*, a cyclooctyne. In some embodiments, an alkyne may be bicyclononyne (also known as bicyclo[6.1.0]nonyne or BCN) or substituted bicyclononyne. In some embodiments, a cyclooctyne is as described in International Patent Application Publication WO2011136645, published on November 3, 2011, entitled, "*Fused Cyclooctyne Compounds And Their Use In Metal-free Click Reactions*". In some embodiments, an azide may be a sugar or carbohydrate molecule that comprises an azide. In some embodiments, an azide may be 6-azido-6- deoxygalactose or 6-azido-N-acetylgalactosamine. In some embodiments, a sugar or carbohydrate molecule that comprises an azide is as described in International Patent Application Publication WO2016170186, published on October 27, 2016, entitled, "*Process For The Modification Of A Glycoprotein Using A Glycosyltransferase That Is Or Is Derived From A β(1,4)-N-Acetylgalactosaminyltransferase*". In some embodiments, a

cycloaddition reaction between an azide and an alkyne to form a triazole, wherein the azide or the alkyne may be located on the anti-TfR1 antibody, molecular payload, or the linker is as described in International Patent Application Publication WO2014065661, published on May 1, 2014, entitled, "*Modified antibody, antibody-conjugate and process for the preparation thereof*"; or International Patent Application Publication WO2016170186, published on October 27, 2016, entitled, "*Process For The Modification Of A Glycoprotein Using A Glycosyltransferase That Is Or Is Derived From A β(1,4)-N-Acetylgalactosaminyltransferase*".

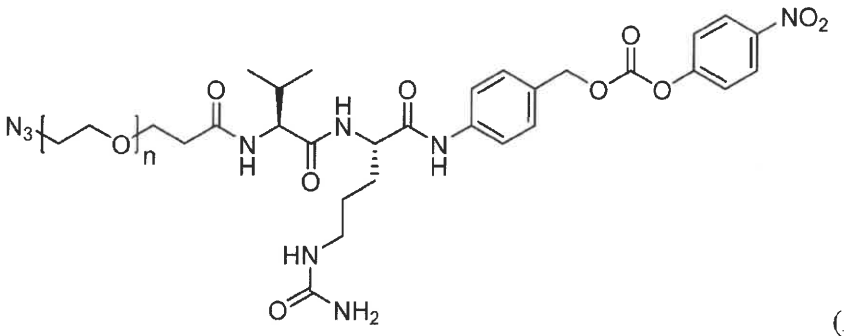
[000349] In some embodiments, a linker comprises a spacer, *e.g.*, a polyethylene glycol spacer or an acyl/carbomoyl sulfamide spacer, *e.g.*, a HydraSpace™ spacer. In some embodiments, a spacer is as described in Verkade, J.M.M. et al., "*A Polar Sulfamide Spacer Significantly Enhances the Manufacturability, Stability, and Therapeutic Index of Antibody-Drug Conjugates*", Antibodies, 2018, 7, 12.

[000350] In some embodiments, a linker is covalently linked to an anti-TfR1 antibody and/or (e.g., and) molecular payload by the Diels-Alder reaction between a dienophile and a diene/hetero-diene, wherein the dienophile or the diene/hetero-diene may be located on the anti-TfR1 antibody, molecular payload, or the linker. In some embodiments a linker is covalently linked to an anti-TfR1 antibody and/or (e.g., and) molecular payload by other pericyclic reactions such as an ene reaction. In some embodiments, a linker is covalently linked to an anti-TfR1 antibody and/or (e.g., and) molecular payload by an amide, thioamide, or sulfonamide bond reaction. In some embodiments, a linker is covalently linked to an anti-TfR1 antibody and/or (e.g., and) molecular payload by a condensation reaction to form an oxime, hydrazone, or semicarbazide group existing between the linker and the anti-TfR1 antibody and/or (e.g., and) molecular payload.

[000351] In some embodiments, a linker is covalently linked to an anti-TfR1 antibody and/or (e.g., and) molecular payload by a conjugate addition reaction between a nucleophile, e.g. an amine or a hydroxyl group, and an electrophile, e.g. a carboxylic acid, carbonate, or an aldehyde. In some embodiments, a nucleophile may exist on a linker and an electrophile may exist on an anti-TfR1 antibody or molecular payload prior to a reaction between a linker and an anti-TfR1 antibody or molecular payload. In some embodiments, an electrophile may exist on a linker and a nucleophile may exist on an anti-TfR1 antibody or molecular payload prior to a reaction between a linker and an anti-TfR1 antibody or molecular payload. In some embodiments, an electrophile may be an azide, pentafluorophenyl, a silicon centers, a carbonyl, a carboxylic acid, an anhydride, an isocyanate, a thioisocyanate, a succinimidyl ester, a sulfosuccinimidyl ester, a maleimide, an alkyl halide, an alkyl pseudohalide, an epoxide, an

episulfide, an aziridine, an aryl, an activated phosphorus center, and/or an activated sulfur center. In some embodiments, a nucleophile may be an optionally substituted alkene, an optionally substituted alkyne, an optionally substituted aryl, an optionally substituted heterocyclyl, a hydroxyl group, an amino group, an alkylamino group, an anilido group, and/or a thiol group.

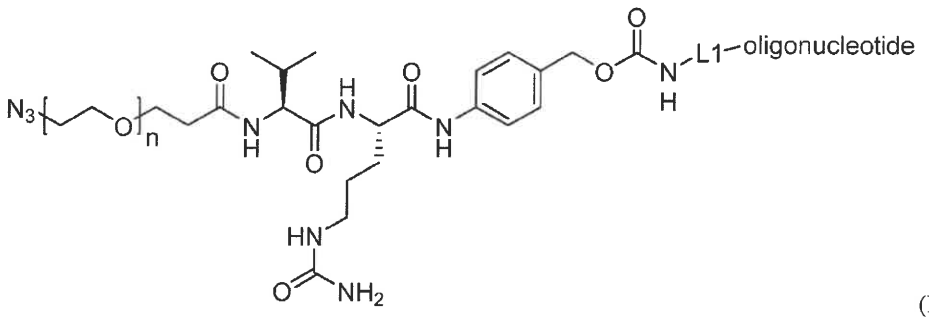
[000352] In some embodiments, a linker comprises a valine-citrulline sequence covalently linked to a reactive chemical moiety (e.g., an azide moiety or a BCN moiety for click chemistry). In some embodiments, a linker comprising a valine-citrulline sequence covalently linked to a reactive chemical moiety (e.g., an azide moiety for click chemistry) comprises a structure of:



(A)

wherein n is any number from 0-10. In some embodiments, n is 3.

[000353] In some embodiments, a linker comprising the structure of Formula (A) is covalently linked (e.g., optionally via additional chemical moieties) to a molecular payload (e.g., an oligonucleotide). In some embodiments, a linker comprising the structure of Formula (A) is covalently linked to an oligonucleotide, e.g., through a nucleophilic substitution with amine-L1-oligonucleotides forming a carbamate bond, yielding a compound comprising a structure of:

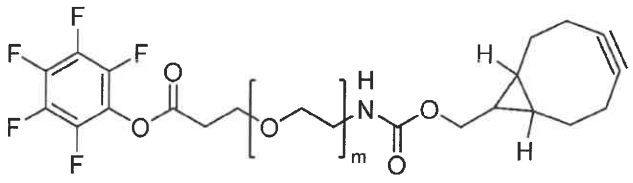


(B)

wherein n is any number from 0-10. In some embodiments, n is 3.

[000354] In some embodiments, the compound of Formula (B) is further covalently linked via a triazole to additional moieties, wherein the triazole is formed by a click reaction

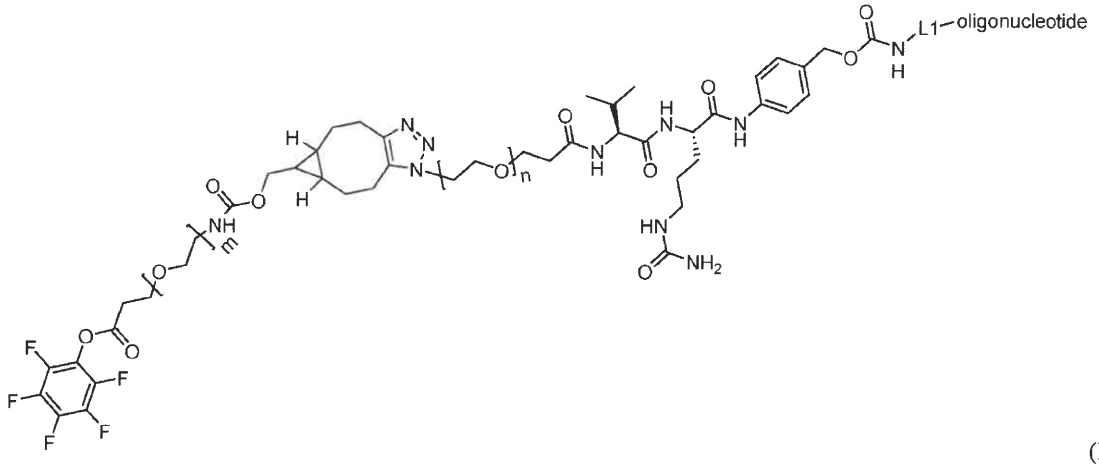
between the azide of Formula (A) or Formula (B) and an alkyne provided on a bicyclononyne. In some embodiments, a compound comprising a bicyclononyne comprises a structure of:



(C)

wherein m is any number from 0-10. In some embodiments, m is 4.

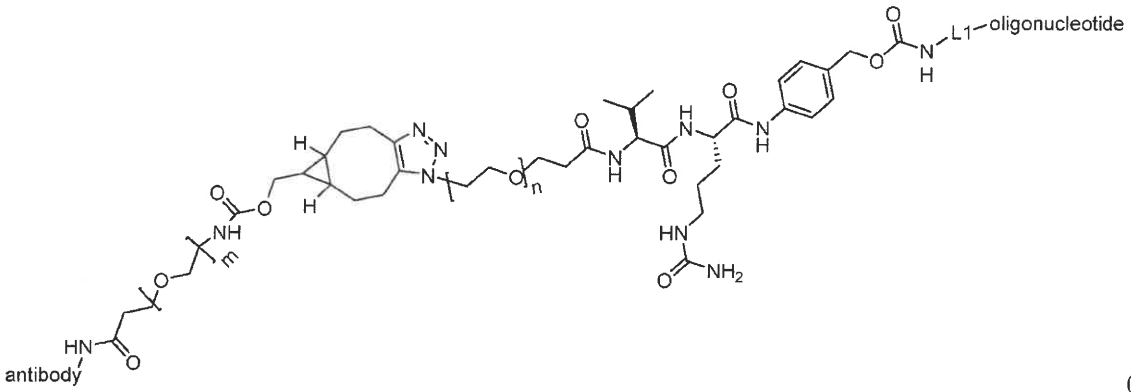
[000355] In some embodiments, the azide of the compound of structure (B) forms a triazole via a click reaction with the alkyne of the compound of structure (C), forming a compound comprising a structure of:



(D),

wherein n is any number from 0-10, and wherein m is any number from 0-10. In some embodiments, n is 3 and m is 4.

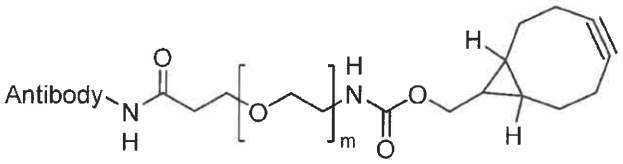
[000356] In some embodiments, the compound of structure (D) is further covalently linked to a lysine of the anti-TfR1 antibody, forming a complex comprising a structure of:



(E),

wherein n is any number from 0-10, wherein m is any number from 0-10. In some embodiments, n is 3 and/or (e.g., and) m is 4. It should be understood that the amide shown adjacent the anti-TfR1 antibody in Formula (E) results from a reaction with an amine of the anti-TfR1 antibody, such as a lysine epsilon amine.

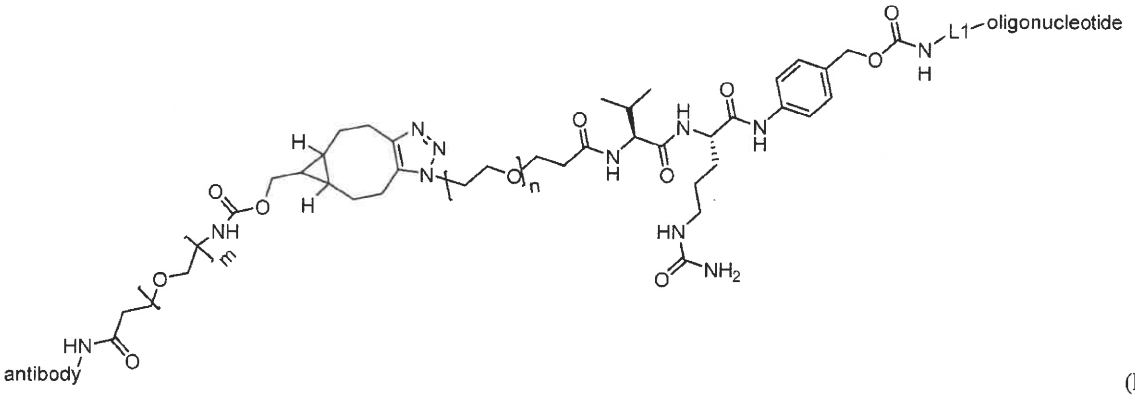
[000357] In some embodiments, the compound of Formula (C) is further covalently linked to a lysine of the anti-TfR1 antibody, forming a compound comprising a structure of:



(F),

wherein m is 0-15 (e.g., 4). It should be understood that the amide shown adjacent the anti-TfR1 antibody in Formula (F) results from a reaction with an amine of the anti-TfR1 antibody, such as a lysine epsilon amine.

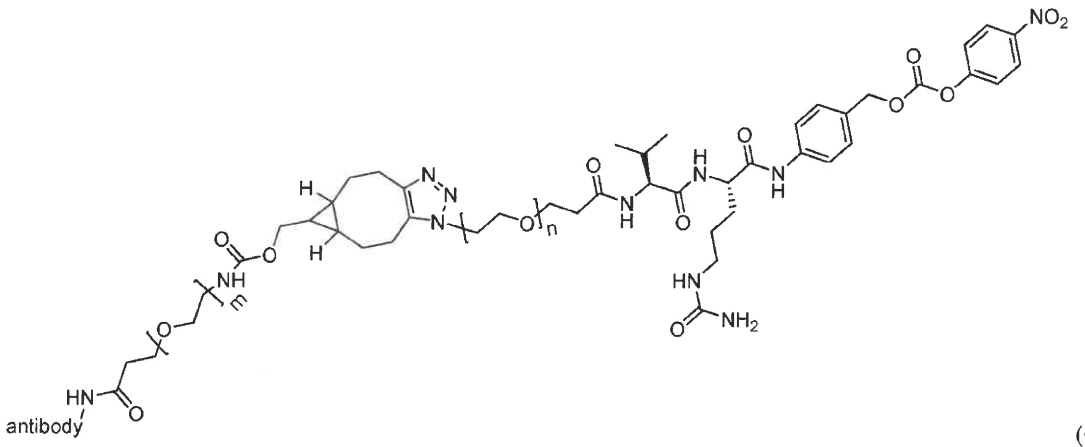
[000358] In some embodiments, the azide of the compound of structure (B) forms a triazole via a click reaction with the alkyne of the compound of structure (F), forming a complex comprising a structure of:



(E),

wherein n is any number from 0-10, wherein m is any number from 0-10. In some embodiments, n is 3 and/or (e.g., and) m is 4. It should be understood that the amide shown adjacent the anti-TfR1 antibody in Formula (E) results from a reaction with an amine of the anti-TfR1 antibody, such as a lysine epsilon amine.

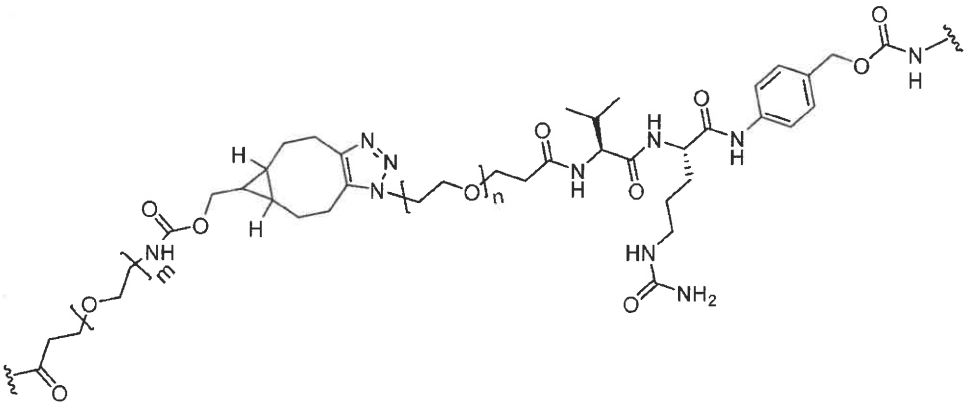
[000359] In some embodiments, the azide of the compound of structure (A) forms a triazole via a click reaction with the alkyne of the compound of structure (F), forming a compound comprising a structure of:



(G),

wherein n is any number from 0-10, wherein m is any number from 0-10. In some embodiments, n is 3 and/or (e.g., and) m is 4. In some embodiments, an oligonucleotide is covalently linked to a compound comprising a structure of formula (G), thereby forming a complex comprising a structure of formula (E). It should be understood that the amide shown adjacent the anti-TfR1 antibody in Formula (G) results from a reaction with an amine of the anti-TfR1 antibody, such as a lysine epsilon amine.

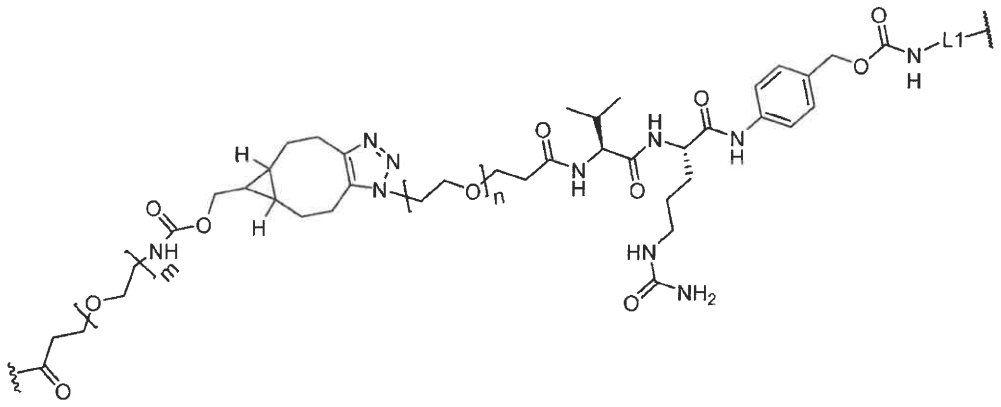
[000360] In some embodiments, in any one of the complexes described herein, the anti-TfR1 antibody is covalently linked via a lysine of the anti-TfR1 antibody to a molecular payload (e.g., an oligonucleotide) via a linker comprising a structure of:



(H),

wherein n is any number from 0-10, wherein m is any number from 0-10. In some embodiments, n is 3 and/or (e.g., and) m is 4.

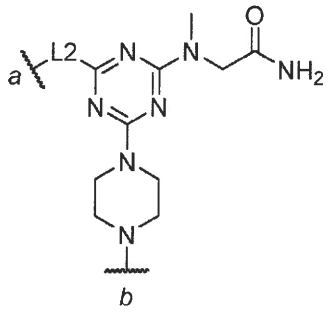
[000361] In some embodiments, in any one of the complexes described herein, the anti-TfR1 antibody is covalently linked via a lysine of the anti-TfR1 antibody to a molecular payload (e.g., an oligonucleotide) via a linker comprising a structure of:

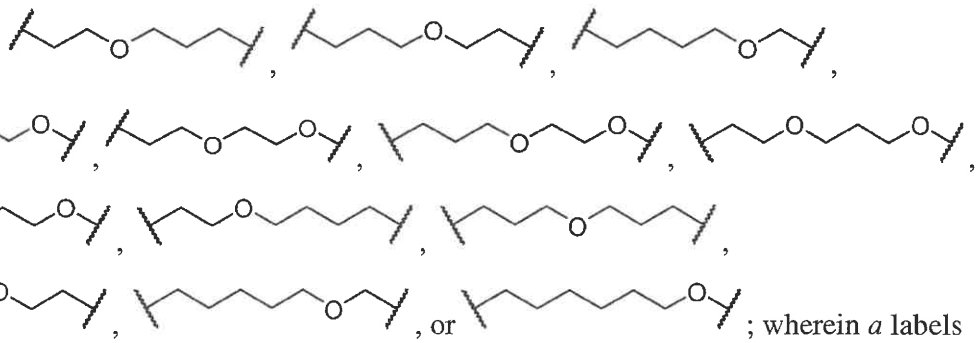


(I),

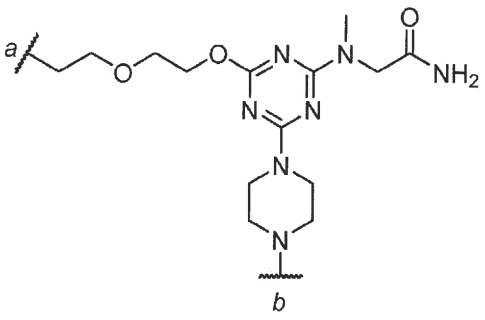
wherein n is any number from 0-10, wherein m is any number from 0-10. In some embodiments, n is 3 and/or (e.g., and) m is 4.

[000362] In some embodiments, in formulae (B), (D), (E), and (I), L1 is a spacer that is a substituted or unsubstituted aliphatic, substituted or unsubstituted heteroaliphatic, substituted or unsubstituted carbocyclylene, substituted or unsubstituted heterocyclylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene, -O-, -$N(R^A)$-, -S-, -C(=O)-, -C(=O)O-, -C(=O)NR^A-, -NR^AC(=O)-, -NR^AC(=O)R^A-, -C(=O)R^A-, -NR^AC(=O)O-, -NR^AC(=O)$N(R^A)$-, -OC(=O)-, -OC(=O)O-, -OC(=O)$N(R^A)$-, -$S(O)_2NR^A$-, -$NR^AS(O)_2$-, or a combination thereof, wherein each R^A is independently hydrogen or substituted or unsubstituted alkyl. In some embodiments, L1 is

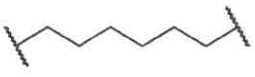


wherein L2 is ; wherein *a* labels the site directly linked to the carbamate moiety of formulae (B), (D), (E), and (I); and *b* labels the site covalently linked (directly or via additional chemical moieties) to the oligonucleotide.

[000363] In some embodiments, L1 is:



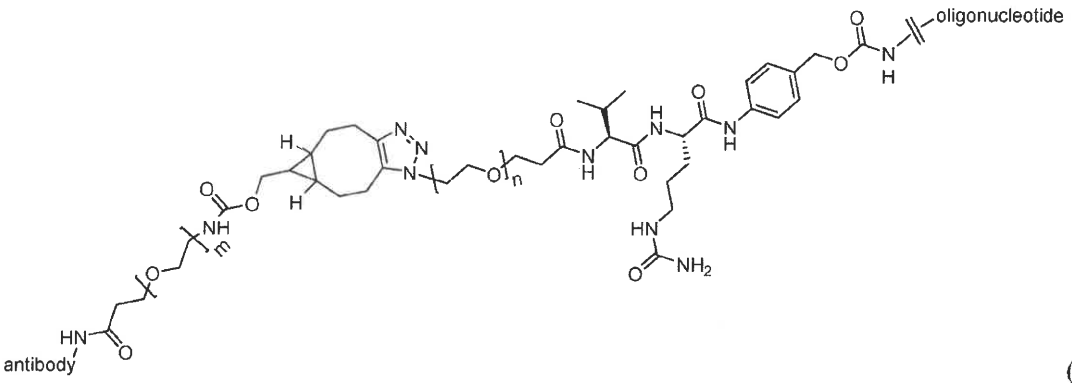
wherein *a* labels the site directly linked to the carbamate moiety of formulae (B), (D), (E), and (I); and *b* labels the site covalently linked (directly or via additional chemical moieties) to the oligonucleotide.

[000364] In some embodiments, L1 is .

[000365] In some embodiments, L1 is linked to a 5' phosphate of the oligonucleotide. In some embodiments, the phosphate is a phosphodiester. In some embodiments, L1 is linked to a 5' phosphorothioate of the oligonucleotide. In some embodiments, L1 is linked to a 5' phosphonoamidate of the oligonucleotide. In some embodiments, L1 is linked via a phosphorodiamidate linkage to the 5' end of the oligonucleotide.

[000366] In some embodiments, L1 is optional (e.g., need not be present).

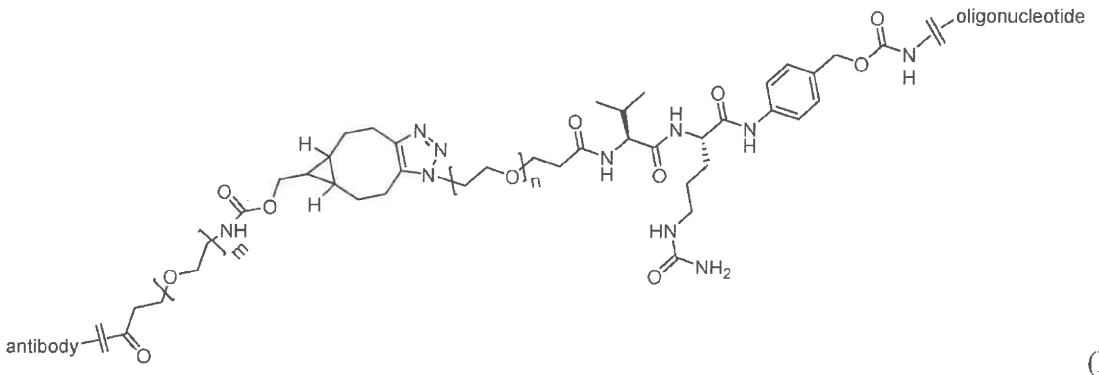
[000367] In some embodiments, any one of the complexes described herein has a structure of:



(J),

wherein n is 0-15 (e.g., 3) and m is 0-15 (e.g., 4). It should be understood that the amide shown adjacent the anti-TfR1 antibody in Formula (J) results from a reaction with an amine of the anti-TfR1 antibody, such as a lysine epsilon amine.

[000368] In some embodiments, any one of the complexes described herein has a structure of:



(K),

wherein n is 0-15 (e.g., 3) and m is 0-15 (e.g., 4).

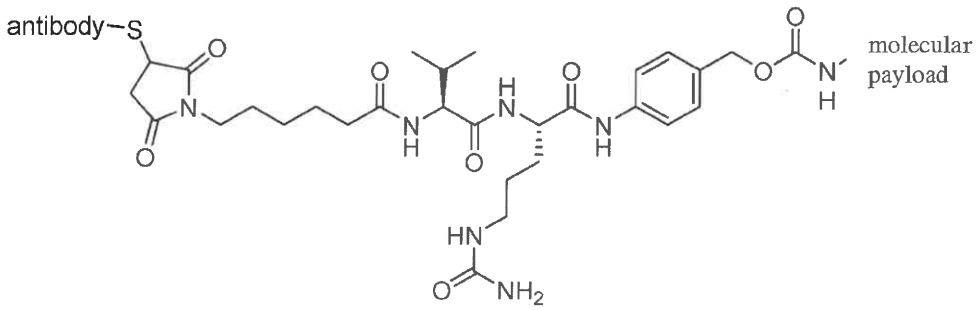
[000369] In some embodiments, the oligonucleotide is modified to comprise an amine group at the 5' end, the 3' end, or internally (e.g., as an amine functionalized nucleobase), prior to linking to a compound, e.g., a compound of formula (A) or formula (G).

[000370] Although linker conjugation is described in the context of anti-TfR1 antibodies and oligonucleotide molecular payloads, it should be understood that use of such linker conjugation on other muscle-targeting agents, such as other muscle-targeting antibodies, and/or on other molecular payloads is contemplated.

D. Examples of Antibody-Molecular Payload Complexes

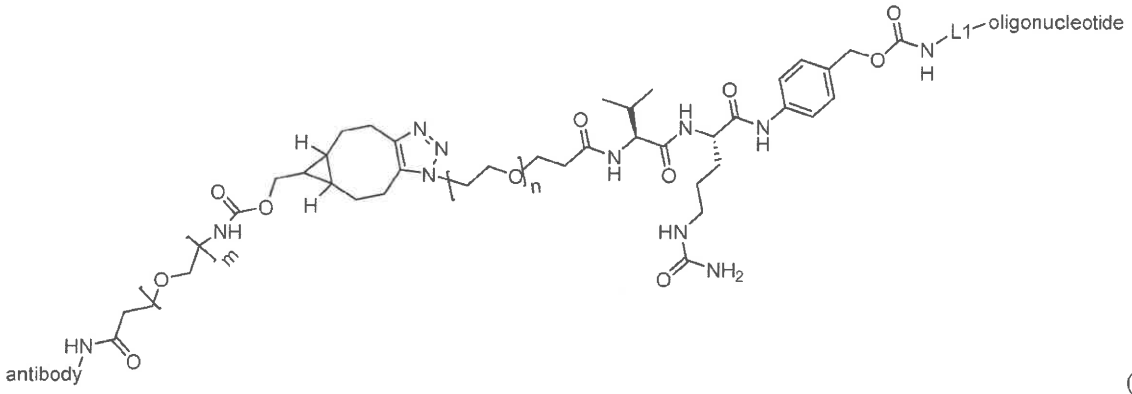
[000371] Further provided herein are non-limiting examples of complexes comprising any one the anti-TfR1 antibodies described herein covalently linked to any of the molecular payloads (e.g., an oligonucleotide) described herein. In some embodiments, the anti-TfR1 antibody (e.g., any one of the anti-TfR1 antibodies provided in Tables 2-7) is covalently linked to a molecular payload (e.g., an oligonucleotide such as the oligonucleotides provided in Table 8) via a linker. Any of the linkers described herein may be used. In some embodiments, if the molecular payload is an oligonucleotide, the linker is linked to the 5′ end of the oligonucleotide, the 3′ end of the oligonucleotide, or to an internal site of the oligonucleotide. In some embodiments, the linker is linked to the anti-TfR1 antibody via a thiol-reactive linkage (e.g., via a cysteine in the anti-TfR1 antibody). In some embodiments, the linker (e.g., a linker comprising a valine-citrulline sequence) is linked to the antibody (e.g., an anti-TfR1 antibody described herein) via an amine group (e.g., via a lysine in the antibody). In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000372] An example of a structure of a complex comprising an anti-TfR1 antibody covalently linked to a molecular payload via a linker is provided below:



wherein the linker is linked to the antibody via a thiol-reactive linkage (e.g., via a cysteine in the antibody). In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000373] Another example of a structure of a complex comprising an anti-TfR1 antibody covalently linked to a molecular payload via a linker is provided below:



(E)

wherein n is a number between 0-10, wherein m is a number between 0-10, wherein the linker is linked to the antibody via an amine group (e.g., on a lysine residue), and/or (e.g., and) wherein the linker is linked to the oligonucleotide (e.g., at the 5' end, 3' end, or internally). In some embodiments, the linker is linked to the antibody via a lysine, the linker is linked to the oligonucleotide at the 5' end, n is 3, and m is 4. In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334). It should be understood that the amide shown adjacent the anti-TfR1 antibody in Formula (E) results from a reaction with an amine of the anti-TfR1 antibody, such as a lysine epsilon amine.

[000374] It should be appreciated that antibodies can be linked to molecular payloads with different stoichiometries, a property that may be referred to as a drug to antibody ratios (DAR) with the "drug" being the molecular payload. In some embodiments, one molecular payload is linked to an antibody (DAR = 1). In some embodiments, two molecular payloads

are linked to an antibody (DAR = 2). In some embodiments, three molecular payloads are linked to an antibody (DAR = 3). In some embodiments, four molecular payloads are linked to an antibody (DAR = 4). In some embodiments, a mixture of different complexes, each having a different DAR, is provided. In some embodiments, an average DAR of complexes in such a mixture may be in a range of 1 to 3, 1 to 4, 1 to 5 or more. An average DAR of complexes in a mixture need not be an integer value. DAR may be increased by conjugating molecular payloads to different sites on an antibody and/or (e.g., and) by conjugating multimers to one or more sites on antibody. For example, a DAR of 2 may be achieved by conjugating a single molecular payload to two different sites on an antibody or by conjugating a dimer molecular payload to a single site of an antibody.

[000375] In some embodiments, the complex described herein comprises an anti-TfR1 antibody described herein (e.g., the antibodies provided in Tables 2-7) covalently linked to a molecular payload. In some embodiments, the complex described herein comprises an anti-TfR1 antibody described herein (e.g., the antibodies provided in Tables 2-7) covalently linked to molecular payload via a linker (e.g., a linker comprising a valine-citrulline sequence). In some embodiments, the linker (e.g., a linker comprising a valine-citrulline sequence) is linked to the antibody (e.g., an anti-TfR1 antibody described herein) via a thiol-reactive linkage (e.g., via a cysteine in the antibody). In some embodiments, the linker (e.g., a linker comprising a valine-citrulline sequence) is linked to the antibody (e.g., an anti-TfR1 antibody described herein) via an amine group (e.g., via a lysine in the antibody). In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000376] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to a molecular payload, wherein the anti-TfR1 antibody comprises a CDR-H1, a CDR-H2, a CDR-H3, a CDR-L1, a CDR-L2, and a CDR-L3 of any one of the antibodies listed in Table 2. In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000377] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to a molecular payload, wherein the anti-TfR1 antibody comprises a VH comprising the amino acid sequence of SEQ ID NO: 69, SEQ ID NO: 71, or SEQ ID NO: 72, and a VL comprising the amino acid sequence of SEQ ID NO: 70. In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting

oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000378] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to a molecular payload, wherein the anti-TfR1 antibody comprises a VH comprising the amino acid sequence of SEQ ID NO: 73 or SEQ ID NO: 76, and a VL comprising the amino acid sequence of SEQ ID NO: 74. In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000379] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to a molecular payload, wherein the anti-TfR1 antibody comprises a VH comprising the amino acid sequence of SEQ ID NO: 73 or SEQ ID NO: 76, and a VL comprising the amino acid sequence of SEQ ID NO: 75. In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000380] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to a molecular payload, wherein the anti-TfR1 antibody comprises a VH comprising the amino acid sequence of SEQ ID NO: 77, and a VL comprising the amino acid sequence of SEQ ID NO: 78. In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000381] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to a molecular payload, wherein the anti-TfR1 antibody comprises a VH comprising the amino acid sequence of SEQ ID NO: 77 or SEQ ID NO: 79, and a VL comprising the amino acid sequence of SEQ ID NO: 80. In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000382] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to a molecular payload, wherein the anti-TfR1 antibody comprises a VH comprising the amino acid sequence of SEQ ID NO: 154, and a VL comprising the amino acid sequence of SEQ ID NO: 155. In some embodiments, the molecular payload is a DMD-

targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000383] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to a molecular payload, wherein the anti-TfR1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 84, SEQ ID NO: 86 or SEQ ID NO: 87 and a light chain comprising the amino acid sequence of SEQ ID NO: 85. In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000384] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to a molecular payload, wherein the anti-TfR1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 88 or SEQ ID NO: 91, and a light chain comprising the amino acid sequence of SEQ ID NO: 89. In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000385] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to a molecular payload, wherein the anti-TfR1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 88 or SEQ ID NO: 91, and a light chain comprising the amino acid sequence of SEQ ID NO: 90. In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000386] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to a molecular payload, wherein the anti-TfR1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 92 or SEQ ID NO: 94, and a light chain comprising the amino acid sequence of SEQ ID NO: 95. In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000387] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to a molecular payload, wherein the anti-TfR1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 92, and a light chain comprising the amino acid sequence of SEQ ID NO: 93. In some embodiments, the molecular

payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000388] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to a molecular payload, wherein the anti-TfR1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 156, and a light chain comprising the amino acid sequence of SEQ ID NO: 157. In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000389] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to a molecular payload, wherein the anti-TfR1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 97, SEQ ID NO: 98, or SEQ ID NO: 99 and a light chain comprising the amino acid sequence of SEQ ID NO: 85. In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000390] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to a molecular payload, wherein the anti-TfR1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 100 or SEQ ID NO: 101 and a light chain comprising the amino acid sequence of SEQ ID NO: 89. In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000391] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to a molecular payload, wherein the anti-TfR1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 100 or SEQ ID NO: 101 and a light chain comprising the amino acid sequence of SEQ ID NO: 90. In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

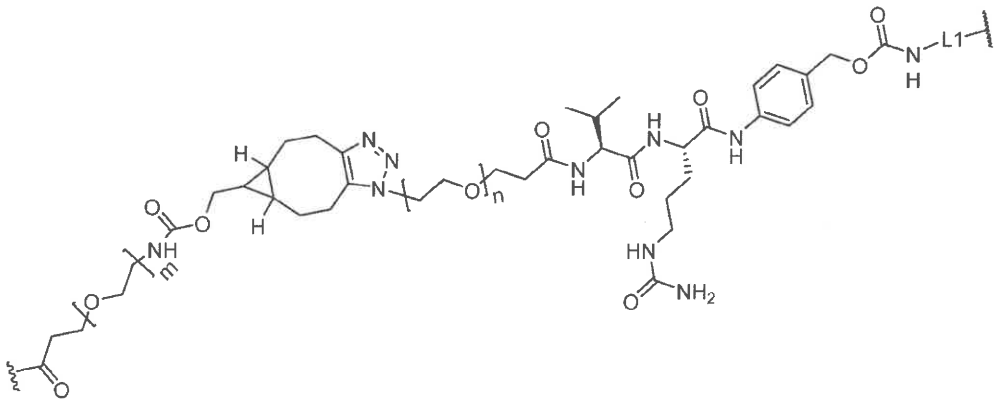
[000392] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to a molecular payload, wherein the anti-TfR1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 102 and a light chain

comprising the amino acid sequence of SEQ ID NO: 93. In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000393] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to a molecular payload, wherein the anti-TfR1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 102 or SEQ ID NO: 103 and a light chain comprising the amino acid sequence of SEQ ID NO: 95. In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000394] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to a molecular payload, wherein the anti-TfR1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 158 or SEQ ID NO: 159 and a light chain comprising the amino acid sequence of SEQ ID NO: 157. In some embodiments, the molecular payload is a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334).

[000395] In any of the example complexes described herein, in some embodiments, the anti-TfR1 antibody is covalently linked to the molecular payload via a linker comprising a structure of:

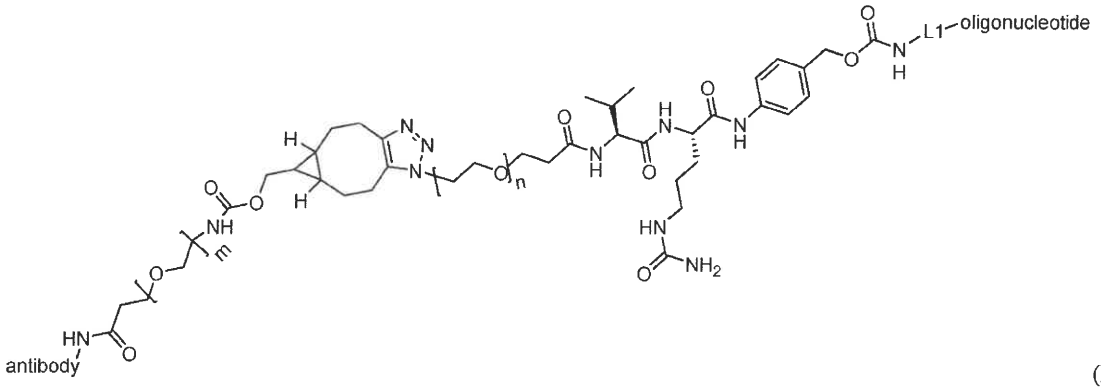


(I)

wherein n is 3, m is 4.

[000396] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to the 5' end of a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334) via a lysine in the anti-TfR1 antibody,

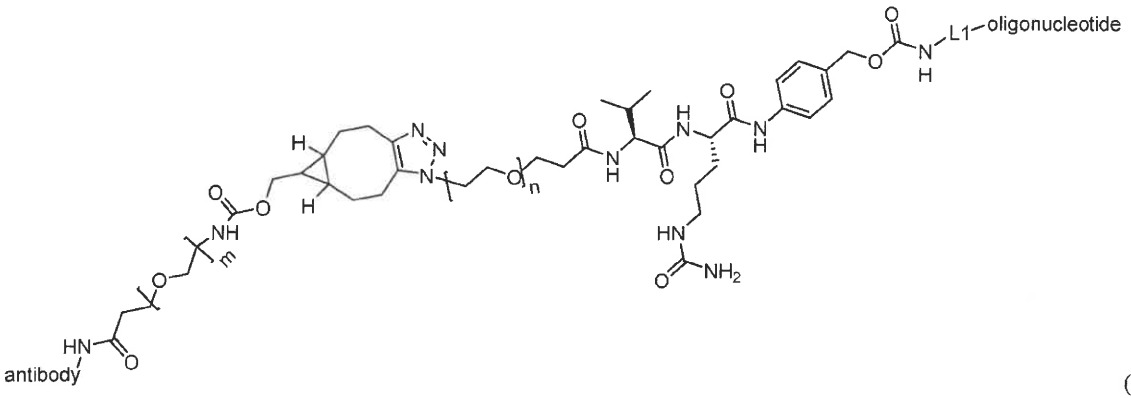
wherein the anti-TfR1 antibody comprises a CDR-H1, a CDR-H2, a CDR-H3, a CDR-L1, a CDR-L2, and a CDR-L3 of any one of the antibodies listed in Table 2, wherein the complex has a structure of:



(E)

wherein n is 3 and m is 4. It should be understood that the amide shown adjacent the anti-TfR1 antibody in Formula (E) results from a reaction with an amine of the anti-TfR1 antibody, such as a lysine epsilon amine.

[000397] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to the 5' end of a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334) via a lysine in the anti-TfR1 antibody, wherein the anti-TfR1 antibody comprises a VH and VL of any one of the antibodies listed in Table 3, wherein the complex has a structure of:

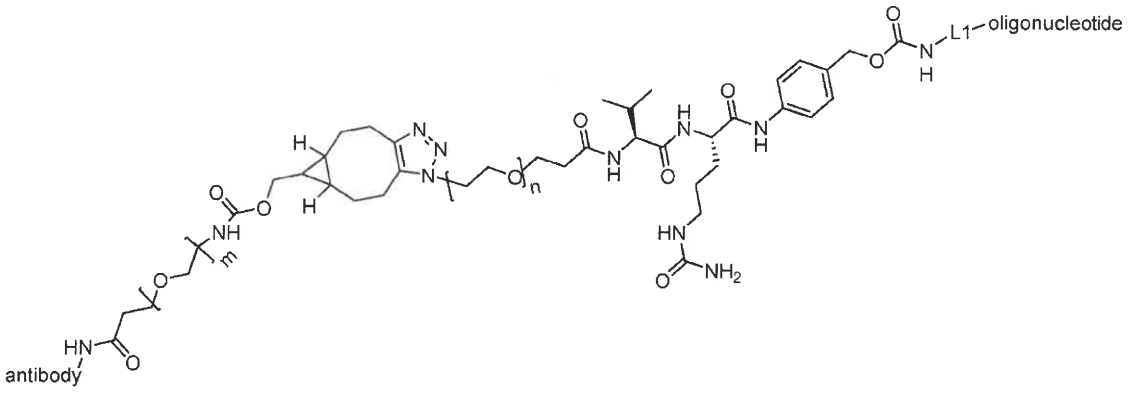


(E)

wherein n is 3 and m is 4. It should be understood that the amide shown adjacent the anti-TfR1 antibody in Formula (E) results from a reaction with an amine of the anti-TfR1 antibody, such as a lysine epsilon amine.

[000398] In some embodiments, the complex described herein comprises an anti-TfR1 antibody covalently linked to the 5' end of a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334) via a lysine in the anti-TfR1 antibody,

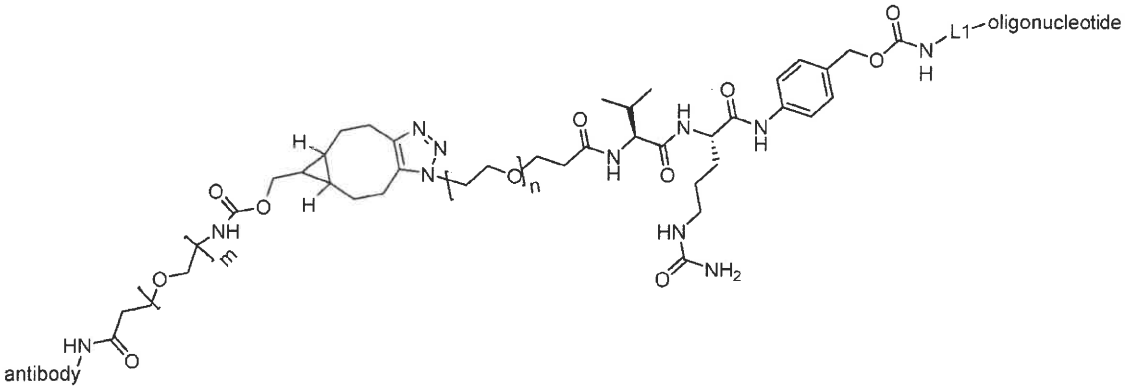
wherein the anti-TfR1 antibody comprises a heavy chain and light chain of any one of the antibodies listed in Table 4, wherein the complex has a structure of:



(E)

wherein n is 3 and m is 4. It should be understood that the amide shown adjacent the anti-TfR1 antibody in Formula (E) results from a reaction with an amine of the anti-TfR1 antibody, such as a lysine epsilon amine.

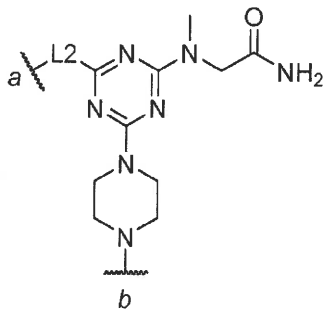
[000399] In some embodiments, the complex described herein comprises an anti-TfR1 Fab covalently linked to the 5' end of a DMD-targeting oligonucleotide (e.g., a DMD-targeting oligonucleotide listed in Table 8, provided by any one of SEQ ID NO: 335-684, or complementary to any one of SEQ ID NO: 160-334) via a lysine in the anti-TfR1 antibody, wherein the anti-TfR1 Fab comprises a heavy chain and light chain of any one of the antibodies listed in Table 5, wherein the complex has a structure of:

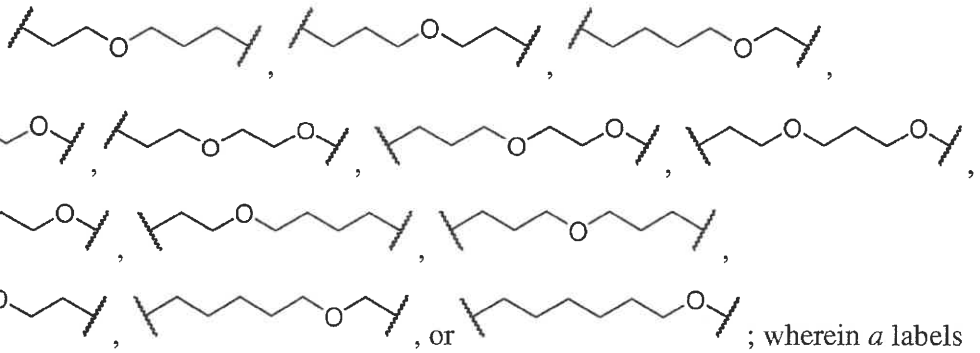


(E)

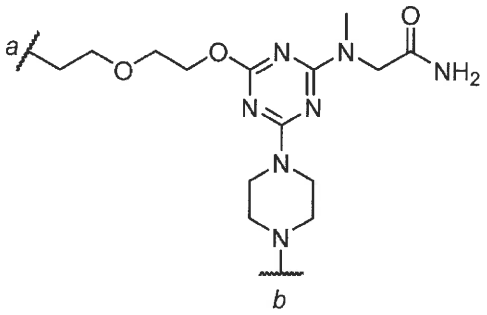
wherein n is 3 and m is 4. It should be understood that the amide shown adjacent the anti-TfR1 antibody in Formula (E) results from a reaction with an amine of the anti-TfR1 antibody, such as a lysine epsilon amine.

[000400] In some embodiments, in any one of the examples of complexes described herein, L1 is:



wherein L2 is ; wherein *a* labels the site directly linked to the carbamate moiety of formulae (B), (D), (E), and (I); and *b* labels the site covalently linked (directly or via additional chemical moieties) to the oligonucleotide.

[000401] In some embodiments, L1 is:



wherein *a* labels the site directly linked to the carbamate moiety of formulae (B), (D), (E), and (I); and *b* labels the site covalently linked (directly or via additional chemical moieties) to the oligonucleotide.

[000402] In some embodiments, L1 is linked to a 5' phosphate of the oligonucleotide. In some embodiments, the phosphate is a phosphodiester. In some embodiments, L1 is linked to a 5' phosphorothioate of the oligonucleotide. In some embodiments, L1 is linked to a 5' phosphonoamidate of the oligonucleotide. In some embodiments, L1 is linked via a phosphorodiamidate linkage to the 5' end of the oligonucleotide.

[000403] In some embodiments, L1 is optional (e.g., need not be present).

III. Formulations

[000404] Complexes provided herein may be formulated in any suitable manner. Generally, complexes provided herein are formulated in a manner suitable for pharmaceutical use. For example, complexes can be delivered to a subject using a formulation that minimizes degradation, facilitates delivery and/or (e.g., and) uptake, or provides another beneficial property to the complexes in the formulation. In some embodiments, provided herein are compositions comprising complexes and pharmaceutically acceptable carriers. Such compositions can be suitably formulated such that when administered to a subject, either into the immediate environment of a target cell or systemically, a sufficient amount of the complexes enter target muscle cells. In some embodiments, complexes are formulated in buffer solutions such as phosphate-buffered saline solutions, liposomes, micellar structures, and capsids.

[000405] It should be appreciated that, in some embodiments, compositions may include separately one or more components of complexes provided herein (e.g., muscle-targeting agents, linkers, molecular payloads, or precursor molecules of any one of them).

[000406] In some embodiments, complexes are formulated in water or in an aqueous solution (e.g., water with pH adjustments). In some embodiments, complexes are formulated in basic buffered aqueous solutions (e.g., PBS). In some embodiments, formulations as disclosed herein comprise an excipient. In some embodiments, an excipient confers to a composition improved stability, improved absorption, improved solubility and/or (e.g., and) therapeutic enhancement of the active ingredient. In some embodiments, an excipient is a buffering agent (*e.g.*, sodium citrate, sodium phosphate, a tris base, or sodium hydroxide) or a vehicle (*e.g.*, a buffered solution, petrolatum, dimethyl sulfoxide, or mineral oil).

[000407] In some embodiments, a complex or component thereof (e.g., oligonucleotide or antibody) is lyophilized for extending its shelf-life and then made into a solution before use (*e.g.*, administration to a subject). Accordingly, an excipient in a composition comprising a complex, or component thereof, described herein may be a lyoprotectant (*e.g.*, mannitol, lactose, polyethylene glycol, or polyvinyl pyrolidone), or a collapse temperature modifier (*e.g.*, dextran, ficoll, or gelatin).

[000408] In some embodiments, a pharmaceutical composition is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, administration. Typically, the route of administration is intravenous or subcutaneous.

[000409] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous

preparation of sterile injectable solutions or dispersions. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. In some embodiments, formulations include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, and sodium chloride in the composition. Sterile injectable solutions can be prepared by incorporating the complexes in a required amount in a selected solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization.

[000410] In some embodiments, a composition may contain at least about 0.1% of the complex, or component thereof, or more, although the percentage of the active ingredient(s) may be between about 1% and about 80% or more of the weight or volume of the total composition. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

IV. Methods of Use / Treatment

[000411] Complexes comprising a muscle-targeting agent covalently linked to a molecular payload as described herein are effective in treating a subject having a dystrophinopathy, e.g., Duchenne muscular dystrophy. In some embodiments, complexes comprise a molecular payload that is an oligonucleotide, *e.g.*, an antisense oligonucleotide that facilitates exon skipping of a pre-mRNA expressed from a mutated DMD allele.

[000412] In some embodiments, a subject may be a human subject, a non-human primate subject, a rodent subject, or any suitable mammalian subject. In some embodiments, a subject may have Duchenne muscular dystrophy or other dystrophinopathy. In some embodiments, a subject has a mutated DMD allele, which may optionally comprise at least one mutation in a DMD exon that causes a frameshift mutation and leads to improper RNA splicing/processing. In some embodiments, a subject is suffering from symptoms of a severe dystrophinopathy, e.g. muscle atrophy or muscle loss. In some embodiments, a subject has an asymptomatic increase in serum concentration of creatine phosphokinase (CK) and/or (e.g., and) muscle cramps with myoglobinuria. In some embodiments, a subject has a progressive muscle disease, such as Duchenne or Becker muscular dystrophy or DMD-associated dilated cardiomyopathy (DCM). In some embodiments, a subject is not suffering from symptoms of a dystrophinopathy.

[000413] In some embodiments, a subject has a mutation in a DMD gene that is amenable to exon 53 skipping. In some embodiments, a complex comprising a muscle-targeting agent covalently linked to a molecular payload as described herein is effective in treating a subject having a mutation in a DMD gene that is amenable to exon 53 skipping. In some embodiments, a complex comprises a molecular payload that is an oligonucleotide, *e.g.*, an antisense oligonucleotide that facilitates skipping of exon 53 of a pre-mRNA, such as in a pre-mRNA encoded from a mutated DMD gene (*e.g.*, a mutated DMD gene that is amenable to exon 53 skipping).

[000414] An aspect of the disclosure includes methods involving administering to a subject an effective amount of a complex as described herein. In some embodiments, an effective amount of a pharmaceutical composition that comprises a complex comprising a muscle-targeting agent covalently linked to a molecular payload can be administered to a subject in need of treatment. In some embodiments, a pharmaceutical composition comprising a complex as described herein may be administered by a suitable route, which may include intravenous administration, e.g., as a bolus or by continuous infusion over a period of time. In some embodiments, administration may be performed by intramuscular, intraperitoneal, intracerebrospinal, subcutaneous, intra-articular, intrasynovial, or intrathecal routes. In some embodiments, a pharmaceutical composition may be in solid form, aqueous form, or a liquid form. In some embodiments, an aqueous or liquid form may be nebulized or lyophilized. In some embodiments, a nebulized or lyophilized form may be reconstituted with an aqueous or liquid solution.

[000415] Compositions for intravenous administration may contain various carriers such as vegetable oils, dimethylactamide, dimethyformamide, ethyl lactate, ethyl carbonate, isopropyl myristate, ethanol, and polyols (glycerol, propylene glycol, liquid polyethylene glycol, and the like). For intravenous injection, water soluble antibodies can be administered by the drip method, whereby a pharmaceutical formulation containing the antibody and a physiologically acceptable excipients is infused. Physiologically acceptable excipients may include, for example, 5% dextrose, 0.9% saline, Ringer's solution or other suitable excipients. Intramuscular preparations, e.g., a sterile formulation of a suitable soluble salt form of the antibody, can be dissolved and administered in a pharmaceutical excipient such as Water-for-Injection, 0.9% saline, or 5% glucose solution.

[000416] In some embodiments, a pharmaceutical composition that comprises a complex comprising a muscle-targeting agent covalently linked to a molecular payload is administered via site-specific or local delivery techniques. Examples of these techniques include implantable

depot sources of the complex, local delivery catheters, site specific carriers, direct injection, or direct application.

[000417] In some embodiments, a pharmaceutical composition that comprises a complex comprising a muscle-targeting agent covalently linked to a molecular payload is administered at an effective concentration that confers therapeutic effect on a subject. Effective amounts vary, as recognized by those skilled in the art, depending on the severity of the disease, unique characteristics of the subject being treated, e.g., age, physical conditions, health, or weight, the duration of the treatment, the nature of any concurrent therapies, the route of administration and related factors. These related factors are known to those in the art and may be addressed with no more than routine experimentation. In some embodiments, an effective concentration is the maximum dose that is considered to be safe for the patient. In some embodiments, an effective concentration will be the lowest possible concentration that provides maximum efficacy.

[000418] Empirical considerations, e.g., the half-life of the complex in a subject, generally will contribute to determination of the concentration of pharmaceutical composition that is used for treatment. The frequency of administration may be empirically determined and adjusted to maximize the efficacy of the treatment.

[000419] The efficacy of treatment may be assessed using any suitable methods. In some embodiments, the efficacy of treatment may be assessed by evaluation of observation of symptoms associated with a dystrophinopathy, e.g., muscle atrophy or muscle weakness, through measures of a subject's self-reported outcomes, e.g., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, or by quality-of-life indicators, e.g., lifespan.

[000420] In some embodiments, a pharmaceutical composition that comprises a complex comprising a muscle-targeting agent covalently linked to a molecular payload described herein is administered to a subject at an effective concentration sufficient to modulate activity or expression of a target gene by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% or at least 95% relative to a control, e.g. baseline level of gene expression prior to treatment.

ADDITIONAL EMBODIMENTS

1. A complex comprising an anti-transferrin receptor 1 (TfR1) antibody covalently linked to a molecular payload configured for inducing skipping of exon 53 in a DMD pre-mRNA, wherein the anti-TfR1 antibody is an antibody identified in any one of Tables 2-7.

2. The complex of embodiment 1, wherein the anti-TfR1 antibody comprises:

(i) a heavy chain complementarity determining region 1 (CDR-H1) of SEQ ID NO: 33, a heavy chain complementarity determining region 2 (CDR-H2) of SEQ ID NO: 34, a heavy chain complementarity determining region 3 (CDR-H3) of SEQ ID NO: 35, a light chain complementarity determining region 1 (CDR-L1) of SEQ ID NO: 36, a light chain complementarity determining region 2 (CDR-L2) of SEQ ID NO: 37, and a light chain complementarity determining region 3 (CDR-L3) of SEQ ID NO: 32;

(ii) a CDR-H1 of SEQ ID NO: 7, a CDR-H2 of SEQ ID NO: 8, a CDR-H3 of SEQ ID NO: 9, a CDR-L1 of SEQ ID NO: 10, a CDR-L2 of SEQ ID NO: 11, and a CDR-L3 of SEQ ID NO: 6;

(iii) a CDR-H1 of SEQ ID NO: 7, a CDR-H2 of SEQ ID NO: 20, a CDR-H3 of SEQ ID NO: 9, a CDR-L1 of SEQ ID NO: 10, a CDR-L2 of SEQ ID NO: 11, and a CDR-L3 of SEQ ID NO: 6;

(iv) a CDR-H1 of SEQ ID NO: 7, a CDR-H2 of SEQ ID NO: 24, a CDR-H3 of SEQ ID NO: 9, a CDR-L1 of SEQ ID NO: 10, a CDR-L2 of SEQ ID NO: 11, and a CDR-L3 of SEQ ID NO: 6;

(v) a CDR-H1 of SEQ ID NO: 51, a CDR-H2 of SEQ ID NO: 52, a CDR-H3 of SEQ ID NO: 53, a CDR-L1 of SEQ ID NO: 54, a CDR-L2 of SEQ ID NO: 55, and a CDR-L3 of SEQ ID NO: 50;

(vi) a CDR-H1 of SEQ ID NO: 64, a CDR-H2 of SEQ ID NO: 52, a CDR-H3 of SEQ ID NO: 53, a CDR-L1 of SEQ ID NO: 54, a CDR-L2 of SEQ ID NO: 55, and a CDR-L3 of SEQ ID NO: 50; or

(vii) a CDR-H1 of SEQ ID NO: 67, a CDR-H2 of SEQ ID NO: 52, a CDR-H3 of SEQ ID NO: 53, a CDR-L1 of SEQ ID NO: 54, a CDR-L2 of SEQ ID NO: 55, and a CDR-L3 of SEQ ID NO: 50.

3. The complex of embodiment 1 or embodiment 2, wherein the anti-TfR1 antibody comprises:

(i) a heavy chain variable region (VH) comprising an amino acid sequence at least 85% identical to SEQ ID NO: 76; and/or a light chain variable region (VL) comprising an amino acid sequence at least 85% identical to SEQ ID NO: 75;

(ii) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 69; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 70;

(iii) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 71; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 70;

(iv) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 72; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 70;

(v) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 73; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 74;

(vi) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 73; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 75;

(vii) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 76; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 74;

(viii) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 77; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 78;

(ix) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 79; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 80; or

(x) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 77; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 80.

4. The complex of any one of embodiments 1 to 3, wherein the anti-TfR1 antibody comprises:

(i) a VH comprising the amino acid sequence of SEQ ID NO: 76 and a VL comprising the amino acid sequence of SEQ ID NO: 75;

(ii) a VH comprising the amino acid sequence of SEQ ID NO: 69 and a VL comprising the amino acid sequence of SEQ ID NO: 70;

(iii) a VH comprising the amino acid sequence of SEQ ID NO: 71and a VL comprising the amino acid sequence of SEQ ID NO: 70;

(iv) a VH comprising the amino acid sequence of SEQ ID NO: 72 and a VL comprising the amino acid sequence of SEQ ID NO: 70;

(v) a VH comprising the amino acid sequence of SEQ ID NO: 73 and a VL comprising the amino acid sequence of SEQ ID NO: 74;

(vi) a VH comprising the amino acid sequence of SEQ ID NO: 73 and a VL comprising the amino acid sequence of SEQ ID NO: 75;

(vii) a VH comprising the amino acid sequence of SEQ ID NO: 76 and a VL comprising the amino acid sequence of SEQ ID NO: 74;

(viii) a VH comprising the amino acid sequence of SEQ ID NO: 77 and a VL comprising the amino acid sequence of SEQ ID NO: 78;

(ix) a VH comprising the amino acid sequence of SEQ ID NO: 79 and a VL comprising the amino acid sequence of SEQ ID NO: 80; or

(x) a VH comprising the amino acid sequence of SEQ ID NO: 77 and a VL comprising the amino acid sequence of SEQ ID NO: 80.

5. The complex of any one of embodiments 1 to 4, wherein the anti-TfR1 antibody is a Fab fragment, a Fab' fragment, a F(ab')2 fragment, an scFv, an Fv, or a full-length IgG.

6. The complex of embodiment 5, wherein the anti-TfR1 antibody is a Fab fragment.

7. The complex of embodiment 6, wherein the anti-TfR1 antibody comprises:

(i) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 101; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 90;

(ii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 97; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 85;

(iii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 98; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 85;

(iv) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 99; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 85;

(v) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 100; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 89;

(vi) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 100; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 90;

(vii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 101; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 89;

(viii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 102; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 93;

(ix) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 103; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 95; or

(x) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 102; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 95.

8. The complex of embodiment 6 or embodiment 7, wherein the anti-TfR1 antibody comprises:

(i) a heavy chain comprising the amino acid sequence of SEQ ID NO: 101; and a light chain comprising the amino acid sequence of SEQ ID NO: 90;

(ii) a heavy chain comprising the amino acid sequence of SEQ ID NO: 97; and a light chain comprising the amino acid sequence of SEQ ID NO: 85;

(iii) a heavy chain comprising the amino acid sequence of SEQ ID NO: 98; and a light chain comprising the amino acid sequence of SEQ ID NO: 85;

(iv) a heavy chain comprising the amino acid sequence of SEQ ID NO: 99; and a light chain comprising the amino acid sequence of SEQ ID NO: 85;

(v) a heavy chain comprising the amino acid sequence of SEQ ID NO: 100; and a light chain comprising the amino acid sequence of SEQ ID NO: 89;

(vi) a heavy chain comprising the amino acid sequence of SEQ ID NO: 100; and a light chain comprising the amino acid sequence of SEQ ID NO: 90;

(vii) a heavy chain comprising the amino acid sequence of SEQ ID NO: 101; and a light chain comprising the amino acid sequence of SEQ ID NO: 89;

(viii) a heavy chain comprising the amino acid sequence of SEQ ID NO: 102; and a light chain comprising the amino acid sequence of SEQ ID NO: 93;

(ix) a heavy chain comprising the amino acid sequence of SEQ ID NO: 103; and a light chain comprising the amino acid sequence of SEQ ID NO: 95; or

(x) a heavy chain comprising the amino acid sequence of SEQ ID NO: 102; and a light chain comprising the amino acid sequence of SEQ ID NO: 95.

9. The complex of any one of embodiments 1 to 8, wherein the anti-TfR1 antibody does not specifically bind to the transferrin binding site of the transferrin receptor 1 and/or wherein the anti-TfR1 antibody does not inhibit binding of transferrin to the transferrin receptor 1.

10. The complex of any one of embodiments 1 to 9, wherein the molecular payload comprises an oligonucleotide.

11. The complex of embodiment 10, wherein the oligonucleotide promotes antisense-mediated exon skipping in the DMD pre-RNA.

12. The complex of embodiment 10 or 11, wherein the oligonucleotide comprises a region of complementarity to a splicing feature of the DMD pre-mRNA.

13. The complex of embodiment 12, wherein the splicing feature is an exonic splicing enhancer (ESE) of the DMD pre-mRNA.

14. The complex of embodiment 13, wherein the splicing feature is in exon 53 of the DMD pre-mRNA, optionally wherein the ESE comprises a sequence of any one of SEQ ID NOs: 689-715.

15. The complex of embodiment 12, wherein the splicing feature is a branch point, a splice donor site, or a splice acceptor site.

16. The complex of embodiment 15, wherein the splicing feature is across the junction of exon 52 and intron 52, in intron 52, across the junction of intron 52 and exon 53, across the junction of exon 53 and intron 53, in intron 53, or across the junction of intron 53 and exon 54 of the DMD pre-mRNA, optionally wherein the splicing feature comprises a sequence of any one of SEQ ID NOs: 685-688 and 716-718.

17. The complex of any one of embodiments 12 to 16, wherein the region of complementarity comprises at least 4 consecutive nucleosides complementary to the splicing feature.

18. The complex of any one of embodiments 1 to 9, wherein the molecular payload comprises an oligonucleotide comprising a sequence complementary to any one of SEQ ID NOs: 160-334 or comprising a sequence of any one of SEQ ID NOs: 335-684, wherein each thymine base (T) may independently and optionally be replaced with a uracil base (U), and each U may independently and optionally be replaced with a T.

19. The complex of any one of embodiments 1 to 9, wherein the molecular payload comprises an oligonucleotide comprising a sequence of any one of SEQ ID NOs: 627, 562, 521, 559, 557, 558, 556, 555, and 574, wherein each thymine base (T) may independently and optionally be replaced with a uracil base (U), and each U may independently and optionally be replaced with a T.

20. The complex of any one of embodiments 10 to 19, wherein the oligonucleotide comprises at least one modified internucleoside linkage.

21. The complex of embodiment 20, wherein the at least one modified internucleoside linkage is a phosphorothioate linkage.

22. The complex of any one of embodiments 10 to 21, wherein the oligonucleotide comprises one or more modified nucleosides.

23. The complex of embodiment 22, wherein the one or more modified nucleosides are 2'-modified nucleosides.

24. The complex of any one of embodiments 10 to 19, wherein the oligonucleotide comprises one or more phosphorodiamidate morpholinos, optionally wherein the oligonucleotide is a phosphorodiamidate morpholino oligomer (PMO).

25. The complex of any one of embodiments 1 to 24, wherein the anti-TfR1 antibody is covalently linked to the molecular payload via a cleavable linker.

26. The complex of embodiment 25, wherein the cleavable linker comprises a valine-citrulline sequence.

27. The complex of any one of embodiments 1 to 26, wherein the anti-TfR1 antibody is covalently linked to the molecular payload via conjugation to a lysine residue or a cysteine residue of the antibody.

28. A complex comprising an anti-TfR1 antibody covalently linked to an oligonucleotide configured for inducing skipping of exon 53 in a DMD pre-mRNA, wherein the oligonucleotide comprises a region of complementarity to any one of SEQ ID NOs: 160-334.

29. The complex of embodiment 28, wherein the anti-TfR1 antibody is an antibody identified in any one of Tables 2-7.

30. A complex comprising an anti-TfR1 antibody covalently linked to an oligonucleotide configured for inducing skipping of exon 53 in a DMD pre-mRNA, wherein the oligonucleotide comprises a region of complementarity to a splicing feature of the DMD pre-mRNA.

31. An oligonucleotide that targets DMD, wherein the oligonucleotide comprises a region of complementarity to any one of SEQ ID NOs: 160-334.

32. The oligonucleotide of embodiment 31, wherein the region of complementarity comprises at least 15 consecutive nucleosides complementary to any one of SEQ ID NOs: 160-334.

33. The oligonucleotide of embodiment 31 or 32, wherein the oligonucleotide comprises at least 15 consecutive nucleosides of any one of SEQ ID NOs: 335-684, optionally wherein the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 335-684, wherein each thymine base (T) may independently and optionally be replaced with a uracil base (U), and each U may independently and optionally be replaced with a T.

34. The oligonucleotide of embodiment 33, wherein the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 627, 562, 521, 559, 557, 558, 556, 555, and 574, wherein each thymine base (T) may independently and optionally be replaced with a uracil base (U), and each U may independently and optionally be replaced with a T.

35. A method of delivering a molecular payload to a cell, the method comprising contacting the cell with the complex of any one of embodiments 1 to 27.

36. A method of delivering an oligonucleotide to a cell, the method comprising contacting the cell with the complex of any one of embodiments 28 to 30.

37. A method of promoting the expression or activity of a dystrophin protein in a cell, the method comprising contacting the cell with the complex of any one of embodiments 1 to 27 in an amount effective for promoting internalization of the molecular payload to the cell, optionally wherein the cell is a muscle cell.

38. A method of promoting the expression or activity of a dystrophin protein in a cell, the method comprising contacting the cell with the complex of any one of embodiments 28 to 30 in an amount effective for promoting internalization of the oligonucleotide to the cell, optionally wherein the cell is a muscle cell.

39. The method of embodiment 37 or 38, wherein the cell is *in vitro*.

40. The method of embodiment 37 or 38, wherein the cell is in a subject.

41. The method of embodiment 40, wherein the subject is a human.

42. The method of embodiment 41, wherein the subject has a DMD gene that is amenable to skipping of exon 53.

43. The method of any one of embodiments 37 to 42, wherein the dystrophin protein is a truncated dystrophin protein.

44. A method of treating a subject having a mutated DMD allele that is associated with a dystrophinopathy, the method comprising administering to the subject an effective amount of the complex of any one of embodiments 1 to 30.

45. A method of promoting skipping of exon 53 of a DMD pre-mRNA transcript in a cell, the method comprising contacting the cell with an effective amount of the complex of any one of embodiments 1 to 30.

46. A method of treating a subject having a mutated DMD allele that is associated with a dystrophinopathy, the method comprising administering to the subject an effective amount of the complex of any one of embodiments 1 to 30.

EXAMPLES

Example 1. Exon-skipping activity of anti-TfR1 antibody conjugates in Duchenne muscular dystrophy patient myotubes

[000421] In this study, the exon-skipping activities of anti-TfR1 antibody conjugates comprising an anti-TfR1 Fab (3M12 VH4/Vκ3) covalently linked to a DMD exon 51-skipping antisense oligonucleotide (ASO) were evaluated. The DMD exon 51-skipping ASO is a phosphorodiamidate morpholino oligomer (PMO) of 30 nucleotides in length and targets an ESE in DMD exon 51 having the sequence TGGAGGT (SEQ ID NO: 778). Immortalized human myoblasts bearing an exon 52 deletion in the DMD gene were thawed and seeded at a density of 1e6 cell/flask in Promocell Skeletal Cell Growth Media (with 5% FBS and 1x Pen-Strep) and allowed to grow to confluency. Once confluent, cells were trypsinized and pelleted via centrifugation and resuspended in fresh Promocell Skeletal Cell Growth Media. The cell number was counted and cells were seeded into Matrigel-coated 96-well plates at a density of 50,000 cells/well. Cells were allowed to recover for 24 hours. Cells were induced to differentiate into myotubes by aspirating the growth media and replacing with differentiation media with no serum. Cells were then treated with the DMD exon 51-skipping oligonucleotide (not covalently linked to an antibody – "naked") at 10 μM ASO or the anti-TfR1 Fab (3M12 VH4/Vκ3) covalently linked to the DMD exon 51-skipping oligonucleotide at 10 μM ASO equivalent. Cells were incubated with test articles for ten days then total RNA was harvested from the 96 well plates. cDNA synthesis was performed on 75 ng of total RNA, and mutation specific PCRs were performed to evaluate the degree of exon 51 skipping in the cells. Mutation-specific PCR products were run on a 4% agarose gel and visualized using SYBR gold. Densitometry was used to calculate the relative amounts of the skipped and unskipped amplicon and exon skipping was determined as a ratio of the Exon 51 skipped amplicon divided by the total amount of amplicon present:

$$\%Exon\ Skipping = \frac{Skipped\ Amplicon}{(Skipped\ Amplicon + Unskipped\ Amplicon)} * 100.$$

[000422] The results demonstrate that the conjugate resulted in enhanced exon skipping compared to the naked DMD exon 51-skipping oligonucleotide in patient myotubes (FIG. 1). This indicates that anti-TfR1 Fab 3M12 VH4/Vκ3 enabled cellular internalization of the conjugate into muscle cells resulting in activity of the exon 51-skipping oligonucleotide in the muscle cells. Similarly, an anti-TfR1 antibody (*e.g.*, anti-TfR1 Fab 3M12 VH4/Vκ3) can enable internalization of a conjugate comprising the anti-TfR1 antibody covalently linked to other exon skipping oligonucleotides (*e.g.*, an exon skipping oligonucleotide provided herein, such as an exon 53 skipping oligonucleotide) into muscle cells and facilitate activity of the exon skipping oligonucleotide in the muscle cells.

Example 2. Exon skipping activity of anti-TfR1 Fab-ASO conjugate in vivo in cynomolgus monkeys

[000423] Anti-TfR1 Fab 3M12 VH4/Vκ3 was covalently linked to the DMD exon 51-skipping antisense oligonucleotide (ASO) that was used in Example 1. The exon skipping activity of the conjugate was tested in vivo in healthy non-human primates. Naïve male cynomolgus monkeys (n= 4-5 per group) were administered two doses of vehicle, 30 mg/kg naked ASO (*i.e.*, not covalently linked to an antibody), or 122 mg/kg anti-TfR1 Fab (3M12 VH4/Vκ3) covalently linked to the DMD exon 51-skipping oligonucleotide (30 mg/kg ASO equivalent) via intravenous infusion on days 1 and 8. Animals were sacrificed and tissues harvested either 2 weeks or 4 weeks after the first dose was administered. Total RNA was collected from tissue samples using a Promega Maxwell® RSC instrument and cDNA synthesis was performed using qScript cDNA SuperMix. Assessment of exon 51 skipping was performed using end-point PCR.

[000424] Capillary electrophoresis of the PCR products was used to assess exon skipping, and % exon 51 skipping was calculated using the following formula:

$$\%\ Exon\ Skipping = \frac{Molarity\ of\ Skipped\ Band}{Molarity\ of\ Skipped\ Band + Molarity\ of\ Unskipped\ Band} * 100.$$

Calculated exon 51 skipping results are shown in Table 10.

Table 10. % Exon 51 skipping of DMD mRNA in cynomolgus monkey

Time	2 weeks			4 weeks	
Group	**Vehicle**	**Naked ASO[a]**	**Conjugate**	**Naked ASO[a]**	**Conjugate**
Conjugate dose[b]	0	n/a	122	n/a	122
ASO Dose[c]	0	30	30	30	30
Quadriceps[d]	0.00 (0.00)	1.216 (1.083)	4.906 (3.131)	0.840 (1.169)	1.708 (1.395)
Diaphragm[d]	0.00 (0.00)	1.891 (2.911)	7.315 (1.532)	0.717 (1.315)	9.225 (4.696)
Heart[d]	0.00 (0.00)	0.043 (0.096)	3.42 (1.192)	0.00 (0.00)	4.525 (1.400)

Biceps [d]	0.00 (0.00)	0.607 (0.615)	3.129 (0.912)	1.214 (1.441)	4.863 (3.881)
Tibialis anterior [d]	0.00 (0.00)	0.699 (0.997)	1.042 (0.685)	0.384 (0.615)	0.816 (0.915)
Gastrocnemius [d]	0.00 (0.00)	0.388 (0.573)	2.424 (2.329)	0.00 (0.00)	5.393 (2.695)

[a]ASO = antisense oligonucleotide.

[b]Conjugate doses are listed as mg/kg of anti-TfR1 Fab 3M12 VH4/Vκ3-ASO conjugate.

[c]ASO doses are listed as mg/kg ASO or ASO equivalent of the anti-TfR1 Fab 3M12 VH4/Vκ3-ASO dose.

[d]Exon skipping values are mean % exon 51 skipping with standard deviations (n=5) in parentheses.

[000425] Tissue ASO accumulation was also quantified using a hybridization ELISA with a probe complementary to the ASO sequence. A standard curve was generated and ASO levels (in ng/g) were derived from a linear regression of the standard curve. The ASO was distributed to all tissues evaluated at a higher level following the administration of the anti-TfR1 Fab VH4/Vκ3-ASO conjugate as compared to the administration of naked ASO. Intravenous administration of naked ASO resulted in levels of ASO that were close to background levels in all tissues evaluated at 2 and 4 weeks after the first does was administered. Administration of anti-TfR1 Fab VH4/Vκ3-ASO conjugate resulted in distribution of ASO through the tissues evaluated with a rank order of heart>diaphragm>bicep>quadriceps>gastrocnemius>tibialis anterior 2 weeks after first dosing. The duration of tissue concentration was also assessed. Concentrations of the ASO in quadriceps, bicep and diaphragm decreased by less than 50% over the time period evaluated (2 to 4 weeks), while levels of ASO in the heart, tibialis anterior, and gastrocnemius remained virtually unchanged (Table 11). This indicates that anti-TfR1 Fab 3M12 VH4/Vκ3 enabled cellular internalization of the conjugate into muscle cells *in vivo*, resulting in activity of the exon skipping oligonucleotide in the muscle cells. Similarly, an anti-TfR1 antibody (*e.g.*, anti-TfR1 Fab 3M12 VH4/Vκ3) *in vivo* can enable internalization of a conjugate comprising the anti-TfR1 antibody covalently linked to other exon skipping oligonucleotides (*e.g.*, an exon skipping oligonucleotide provided herein, such as an exon 53 skipping oligonucleotide) into muscle cells and facilitate activity of the exon skipping oligonucleotide in the muscle cells.

Table 11. Tissue distribution of DMD exon 51 skipping ASO in cynomolgus monkeys

Time	**2 weeks**			**4 weeks**	
Group	**Vehicle**	**Naked ASO[a]**	**Conjugate**	**Naked ASO[a]**	**Conjugate**
Conjugate Dose[b]	0	n/a	122	n/a	122
ASO Dose[c]	0	30	30	30	30
Quadriceps [d]	0 (59.05)	696.8 (868.15)	2436 (954.0)	197 (134)	682 (281)
Diaphragm [d]	0± (144.3)	580.02 (360.11)	6750 (2256)	60 (120)	3131 (1618)
Heart [d]	0 (396.03)	1449 (1337)	27138 (6315)	943 (1803)	30410 (9247)

Biceps [d]	0 (69.58)	615.63 (335.17)	2840 (980.31)	130 (80)	1326 (623)
Tibialis anterior [d]	0 (76.31)	564.71 (327.88)	1591 (253.50)	169 (110)	1087 (514)
Gastrocnemius [d]	0 (41.15)	705.47 (863.75)	2096 (474.04)	170 (69)	1265 (272)

[a]ASO = Antisense oligonucleotide.

[b]Conjugate doses are listed as mg/kg of anti-TfR1 Fab 3M12 VH4/Vκ3-ASO conjugate.

[c]ASO doses are listed as mg/kg ASO or ASO equivalent of the anti-TfR1 Fab 3M12 VH4/Vκ3-ASO conjugate dose.

[d]ASO values are mean concentrations of ASO in tissue as ng/g with standard deviations (n=5) in parentheses.

Example 3. Exon-skipping activity of antisense oligonucleotides in Duchenne muscular dystrophy patient myotubes

[000426] In this study, the exon-skipping activity of a panel of DMD exon 53-skipping antisense oligonucleotides (ASO) was evaluated. Each DMD exon 53-skipping ASO tested is a phosphorodiamidate morpholino oligomer (PMO) of 20-25 nucleotides in length and may target various splicing features in DMD exon 53 and the immediately preceding and following introns.

[000427] Immortalized human myoblasts bearing an exon 52 deletion were thawed and seeded at a density of 1 x 10^6 cells/flask in Promocell Skeletal Cell Growth Media (with 5% FBS and 1x Pen-Strep) and allowed to grow to confluency. Once confluent, cells were trypsinized and pelleted via centrifugation and resuspended in fresh Promocell Skeletal Cell Growth Media. The cells were counted and seeded into Matrigel-coated wells of 96-well plates at a density of 50,000 cells/well. Cells were allowed to recover for 24 hours. Cells were induced to differentiate into myotubes by replacing the growth media with differentiation media containing no serum. Cells were then treated with each DMD exon 53-skipping oligonucleotide at a final concentration of 10 μM ASO, with each ASO tested in three replicates across three wells. Cells were incubated with ASO for ten days, then total RNA was harvested from the 96 well plates. cDNA synthesis was performed using 75 ng of total RNA, and mutation specific PCRs were performed to evaluate the degree of exon 53 skipping in the cells. Mutation-specific PCR products were run on a 4% agarose gel and visualized using SYBR gold. Densitometry was used to calculate the relative amounts of the skipped and unskipped amplicon and exon skipping was determined as a ratio of the Exon 53 skipped amplicon divided by the total amount of amplicon present:

$$\%Exon\ Skipping = \frac{Skipped\ Amplicon}{(Skipped\ Amplicon + Unskipped\ Amplicon)} * 100.$$

[000428] The results shown in Table 12 demonstrate that treatment with certain of the ASOs tested resulted in enhanced exon skipping.

Table 12. Exon 53 skipping antisense oligonucleotides

ASO ID	ASO Sequence	SEQ ID NO:	% Exon 53 Skipping	
			Mean	St.Dev.
ASO001	TTTGTGTGTCCCATGCTTGTTA	569	2.26	0.16
ASO002	TTTGTGTGTCCCATGCTTGTT	568	2.34	0.50
ASO003	TTGTGTGTCCCATGCTTGTT	628	1.50	0.32
ASO004	TTGTACTTCATCCCACTGATT	627	47.64	4.44
ASO005	TTGTGTTATGGCTAGGATGATGA	629	0.72	0.45
ASO006	TTGTACTTCATCCCACTGAT	626	9.10	2.10
ASO007	TTCTTGTACTTCATCCCACTGATT	562	73.55	6.92
ASO008	TTGTGTGTCCCATGCTTGTTA	565	2.04	0.44
ASO009	TTGTGTTATGGCTAGGATGATGAAC	566	1.13	0.09
ASO010	TTGTACTTCATCCCACTGATTC	564	53.11	3.97
ASO011	TTGTGTTATGGCTAGGATGATGAA	684	0.85	0.25
ASO012	TTTGTGTGTCCCATGCTTGT	567	1.48	0.47
ASO013	TTCTTGTACTTCATCCCACTGAT	561	61.72	4.24
ASO014	TTCTTGTACTTCATCCCACTGA	560	18.09	10.96
ASO015	TTCTTGTACTTCATCCCACTG	559	52.26	9.47
ASO016	TTCTTGTACTTCATCCCACT	625	35.53	2.96
ASO017	TGTTCTTGTACTTCATCCCACTGA	557	45.01	6.11
ASO018	TTATGGCTAGGATGATGAAC	683	1.91	0.36
ASO019	TGTTCTTGTACTTCATCCCACTGAT	558	59.56	16.00
ASO020	TGTTCTTGTACTTCATCCCACTG	556	81.55	2.95
ASO021	TGTTCTTGTACTTCATCCCAC	624	2.51	0.15
ASO022	TGTTCTTGTACTTCATCCCACT	555	67.30	3.26
ASO023	TGTGTTATGGCTAGGATGATGAAC	554	1.23	1.27
ASO024	ATCTTTGATACTAACCTTGGTT	580	4.30	2.19
ASO025	ATTATTCATTGTGTTATGGCTAGG	640	0.81	0.31
ASO026	ATTATTCATTGTGTTATGGCTAG	639	0.93	0.32
ASO027	ATCTTTGATACTAACCTTGGTTT	638	3.46	1.65
ASO028	ATTATTCATTGTGTTATGGCTAGGA	641	0.58	0.58
ASO029	AACCCACCTTTCAGGACAAACTTT	573	2.26	0.69
ASO030	AAATGCTAGTCTGGAGGAGACATTT	572	2.21	0.95
ASO031	AACCCACCTTTCAGGACAAACTT	630	4.67	1.67
ASO032	AAATGCTAGTCTGGAGGAGACATT	571	3.73	2.90
ASO033	ATAGGGACCCTCCTTCCATGACTC	510	15.76	8.08
ASO034	AGGTATCTTTGATACTAACCTTGGT	635	6.25	1.21
ASO035	ATCTACTGTATAGGGACCCTCC	577	2.42	2.03
ASO036	ATAGGGACCCTCCTTCCATGACT	576	48.79	38.26
ASO037	AGCCATTGTGTTGAATCCTT	633	16.87	4.47
ASO038	ATCTTTGATACTAACCTTGGT	579	2.43	0.34
ASO039	ATCCTCAGGTCAGAATACATATAT	637	1.31	0.50
ASO040	AGGGACCCTCCTTCCATGACTC	575	15.89	2.64
ASO041	AATTATTCATTGTGTTATGGCTAGG	632	0.38	0.17
ASO042	AACCCACCTTTCAGGACAAACTTTT	631	1.32	0.41

ASO043	ATCTACTGTATAGGGACCCTCCT	578	2.11	0.37
ASO044	ATAGGGACCCTCCTTCCATGAC	636	16.70	2.50
ASO045	AGCCATTGTGTTGAATCCTTTA	634	16.56	1.07
ASO046	AACTGTTGCCTCCGGTTCTGAAGG	574	91.78	2.46
ASO047	AAATGCTAGTCTGGAGGAGACAT	570	8.38	5.76
ASO048	GCCATTGTGTTGAATCCTTTA	661	22.22	1.27
ASO049	GTACTTCATCCCACTGATTC	537	52.90	18.27
ASO050	GTCTACTGTTCATTTCAGCT	673	0.87	0.61
ASO051	GACCCTCCTTCCATGACTCAA	523	11.25	2.38
ASO052	TCTTGTACTTCATCCCACTGAT	541	51.15	5.02
ASO053	TCTTGTACTTCATCCCACTGATT	542	62.64	9.05
ASO054	TCCAGCCATTGTGTTGAATCCTT	678	31.57	3.71
ASO055	TCCAGCCATTGTGTTGAATCCTTT	679	26.62	6.68
ASO056	CATCTACTGTATAGGGACCCTCC	511	4.69	3.83
ASO057	CATCTACTGTATAGGGACCCTCCT	512	3.75	1.31
ASO058	CCTCCGGTTCTGAAGGTGTTCTTG	585	89.21	1.52
ASO059	CTTCCAGCCATTGTGTTGAATCC	656	44.29	4.59
ASO060	CTTCCAGCCATTGTGTTGAATCCTT	658	63.55	27.70
ASO061	GCATCTACTGTATAGGGACCC	660	4.13	1.03
ASO062	CTCCGGTTCTGAAGGTGTTCTT	655	79.38	9.80
ASO063	CTCCGGTTCTGAAGGTGTTCTTG	588	88.63	1.84
ASO064	CTCCGGTTCTGAAGGTGTTCTTGTA	589	84.93	6.15
ASO065	CTCCTTCCATGACTCAAGCT	519	3.05	1.00
ASO066	GCTTCCAGCCATTGTGTTGAATCCT	665	32.20	12.34
ASO067	TGCCTCCGGTTCTGAAGGTGTTCT	544	93.40	1.75
ASO068	TGCCTCCGGTTCTGAAGGTGTTCTT	545	79.58	18.76
ASO069	TGTGTTATGGCTAGGATGATG	621	1.27	0.90
ASO070	TGTGTTATGGCTAGGATGATGA	622	0.92	0.44
ASO071	TGTGTTATGGCTAGGATGATGAA	623	0.87	0.73
ASO072	TGTACTTCATCCCACTGATT	620	50.15	4.67
ASO073	CCTCCGGTTCTGAAGGTGTTCT	583	87.82	3.64
ASO074	CCCTCCTTCCATGACTCAAGCT	514	11.09	6.70
ASO075	CCCTCCTTCCATGACTCAAG	653	3.15	1.87
ASO076	CATCTACTGTATAGGGACCCTC	645	3.44	0.62
ASO077	TCCAGCCATTGTGTTGAATCCTTTA	680	59.05	20.32
ASO078	TCCAGCCATTGTGTTGAATCCT	677	55.73	12.25
ASO079	CTTGTACTTCATCCCACTGATTC	521	92.61	2.02
ASO080	CTTGTACTTCATCCCACTGATT	593	77.61	10.11
ASO081	CTTGTACTTCATCCCACTGAT	520	62.03	0.97
ASO082	CTTGTACTTCATCCCACTGA	592	67.71	10.26
ASO083	CTCCGGTTCTGAAGGTGTTCT	654	86.47	5.84
ASO084	CCTTAGCTTCCAGCCATTGTGTTGA	518	41.65	11.35
ASO085	CCTTAGCTTCCAGCCATTGTGTTG	517	58.30	8.49
ASO086	CCTTAGCTTCCAGCCATTGTGT	586	18.78	4.58
ASO087	CCAGCCATTGTGTTGAATCCTTTA	650	39.06	8.29

ASO088	CCAGCCATTGTGTTGAATCCTTT	649	38.87	3.99
ASO089	CCAGCCATTGTGTTGAATCCTT	648	52.62	7.79
ASO090	TCTTGTACTTCATCCCACTGATTC	543	79.70	2.54
ASO091	TCTTGTACTTCATCCCACTGA	540	49.66	6.71
ASO092	TCTTGTACTTCATCCCACTG	539	66.75	6.16
ASO093	GGGACCCTCCTTCCATGACTCAAG	669	3.18	2.25
ASO094	GGGACCCTCCTTCCATGACT	604	8.01	2.02
ASO095	GCTTTGTGTGTCCCATGCTTGTTA	532	2.44	1.95
ASO096	GCTTTGTGTGTCCCATGCTT	528	16.63	18.02
ASO097	GCTAGTCTGGAGGAGACATTTTA	600	18.15	6.20
ASO098	GACCCTCCTTCCATGACTCAAGCT	659	1.83	1.83
ASO099	GACCCTCCTTCCATGACTCAAG	524	3.13	0.00
ASO100	GACCCTCCTTCCATGACTCA	522	15.94	15.94
ASO101	TGCTTTGTGTGTCCCATGCTTG	548	1.82	1.54
ASO102	TGCTTTGTGTGTCCCATGCTT	547	2.74	0.72
ASO103	TGCTTTGTGTGTCCCATGCT	546	5.60	4.56
ASO104	GGACCCTCCTTCCATGACTCAAGCT	668	21.61	8.35
ASO105	GGACCCTCCTTCCATGACTCAAGC	667	1.98	2.80
ASO106	GGACCCTCCTTCCATGACTCAA	602	6.27	6.32
ASO107	GGACCCTCCTTCCATGACTC	533	13.82	7.50
ASO108	TTCTTGTACTTCATCCCACTGATTC	563	83.98	5.29
ASO109	GGACCCTCCTTCCATGACTCA	601	19.19	4.91
ASO110	TGCTTTGTGTGTCCCATGCTTGTTA	551	5.83	0.76
ASO111	GACCCTCCTTCCATGACTCAAGC	525	28.29	13.82
ASO112	GCTAGTCTGGAGGAGACATTTTAA	662	3.49	0.84
ASO113	GGGACCCTCCTTCCATGACTCAA	605	10.71	11.45
ASO114	GGGACCCTCCTTCCATGACTCAAGC	670	67.65	32.35
ASO115	CCAGCCATTGTGTTGAATCCT	647	58.35	10.19
ASO116	CCCTCCTTCCATGACTCAAGC	513	11.02	0.00
ASO117	CCTCCGGTTCTGAAGGTGTTCTT	584	94.25	1.82
ASO118	CTTCCAGCCATTGTGTTGAATCCT	657	56.75	14.87
ASO119	GCATCTACTGTATAGGGACCCTC	596	0.00	0.00
ASO120	GCATCTACTGTATAGGGACCCTCC	527	3.50	1.57
ASO121	GCTTCCAGCCATTGTGTTGAATC	663	26.42	0.00
ASO122	GCTTCCAGCCATTGTGTTGAATCC	664	43.43	17.09
ASO123	TGCCTCCGGTTCTGAAGGTGTTC	682	96.86	2.25
ASO124	ATTGTGTTATGGCTAGGATGATGA	581	0.00	0.00
ASO125	ATTGTGTTATGGCTAGGATGATGAA	642	7.29	10.31
ASO126	CCCACCTTTCAGGACAAACTTTTCA	652	7.14	3.82
ASO127	CCTCCTTCCATGACTCAAGC	515	7.17	5.08
ASO128	CCTCCTTCCATGACTCAAGCT	516	8.37	1.63
ASO129	CTTAGCTTCCAGCCATTGTGTTG	590	51.44	23.31
ASO130	CTTAGCTTCCAGCCATTGTGTTGA	591	40.09	2.77
ASO131	GATTGCATCTACTGTATAGGGACC	595	1.85	1.85
ASO132	GGATTGCATCTACTGTATAGGGACC	534	3.57	3.57

ASO133	GTAACCCACCTTTCAGGACAAACT	608	1.52	2.14
ASO134	GTAACCCACCTTTCAGGACAAACTT	536	2.38	1.09
ASO135	TAAATGCTAGTCTGGAGGAGACAT	612	4.40	1.74
ASO136	TAAATGCTAGTCTGGAGGAGACATT	613	5.78	1.05
ASO137	TAACCCACCTTTCAGGACAAACTT	614	0.90	0.69
ASO138	TAACCCACCTTTCAGGACAAACTTT	615	1.63	2.30
ASO139	TATCTTTGATACTAACCTTGGT	617	6.31	1.18
ASO140	TATCTTTGATACTAACCTTGGTT	676	4.40	2.19
ASO141	CAAAGTCTACTGTTCATTTCAGCT	643	35.59	45.59
ASO142	CAGCCATTGTGTTGAATCCTTTA	644	68.26	13.46
ASO143	CCACCTTTCAGGACAAACTTTTCA	646	2.94	2.70
ASO144	CTTTTGGATTGCATCTACTGTAT	594	9.99	9.93
ASO145	GTAAATGCTAGTCTGGAGGAGAC	671	0.00	0.00
ASO146	GTCCCATGCTTGTTAAAAAACTTAC	672	1.60	1.15
ASO147	TAGCTTCCAGCCATTGTGTTGAATC	675	58.00	17.17
ASO148	TAGGGACCCTCCTTCCATGACTC	616	14.29	14.29
ASO149	TCCTCAGGTCAGAATACATATAT	681	1.19	0.84
ASO150	TCTTTTGGATTGCATCTACTGTA	618	2.17	1.03
ASO151	GGACCCTCCTTCCATGACTCAAG	666	2.20	1.71
ASO152	TGCTTTGTGTGTCCCATGCTTGTT	550	2.20	0.75
ASO153	GCTAGTCTGGAGGAGACATT	597	14.24	7.06
ASO154	GCTAGTCTGGAGGAGACATTT	598	28.85	14.86
ASO155	GCTAGTCTGGAGGAGACATTTT	599	4.88	1.11
ASO156	GCTTTGTGTGTCCCATGCTTG	529	0.84	0.35
ASO157	GGGACCCTCCTTCCATGACTCA	535	24.78	10.92
ASO158	CCTTAGCTTCCAGCCATTGTGTT	587	77.55	16.31
ASO159	GTGTTATGGCTAGGATGATGA	609	3.03	1.90
ASO160	GTGTTATGGCTAGGATGATGAA	610	12.82	2.73
ASO161	GTGTTATGGCTAGGATGATGAAC	538	40.33	28.42
ASO162	GATTGCATCTACTGTATAGGGACCC	526	17.32	9.95
ASO163	GGATTGCATCTACTGTATAGGGAC	603	18.00	1.60
ASO164	CAACTGTTGCCTCCGGTTCTGAAGG	582	91.41	7.19

Example 4. Exon-skipping activity of anti-TfR1 antibody conjugates in Duchenne muscular dystrophy patient myotubes

[000429] In this study, the exon-skipping activities of anti-TfR1 antibody conjugates comprising an anti-TfR1 Fab (3M12 VH4/Vκ3) covalently linked to a DMD exon 53-skipping antisense oligonucleotide (ASO) were evaluated. The DMD exon 53-skipping ASOs tested in this Example are a subset of those tested in Example 3. They are phosphorodiamidate morpholino oligomers (PMOs) of 21-25 nucleotides in length and may target various splicing features in DMD exon 53 and the immediately preceding and following introns. ASO007, ASO020, ASO046, ASO004, ASO010, ASO015, ASO017, ASO019, and ASO022 listed in

Table 12 were covalently linked via a cleavable linker to anti-TfR1 Fab (3M12 VH4/Vκ3). Attempted linkage of ASO013, ASO016, and ASO036 to the anti-TfR1 Fab was unsuccessful.

[000430] Immortalized human myoblasts bearing an exon 52 deletion were thawed and seeded at a density of 1 x 10^6 cells/flask in Promocell Skeletal Cell Growth Media (with 5% FBS and 1x Pen-Strep) and allowed to grow to confluency. Once confluent, cells were trypsinized and pelleted via centrifugation and resuspended in fresh Promocell Skeletal Cell Growth Media. The cells were counted and seeded into Matrigel-coated wells of 96-well plates at a density of 50,000 cells/well. Cells were allowed to recover for 24 hours. Cells were induced to differentiate into myotubes by replacing the growth media with differentiation media containing no serum. Cells were then treated with conjugates comprising DMD exon 53-skipping oligonucleotide covalently linked to anti-TfR1 Fab (3M12 VH4/Vk3) at a final concentration of 0.15625 μM, 0.625 μM, 2.5 μM, and a higher dose of either 5 μM or 10 μM ASO equivalent. Cells were incubated with conjugates for ten days, then total RNA was harvested from the 96 well plates. cDNA synthesis was performed using 75 ng of total RNA, and mutation specific PCRs were performed to evaluate the degree of exon 53 skipping in the cells. Mutation-specific PCR products were run on a 4% agarose gel and visualized using SYBR gold. Densitometry was used to calculate the relative amounts of the skipped and unskipped amplicon and exon skipping was determined as a ratio of the Exon 53 skipped amplicon divided by the total amount of amplicon present:

$$\%Exon\ Skipping = \frac{Skipped\ Amplicon}{(Skipped\ Amplicon + Unskipped\ Amplicon)} * 100.$$

[000431] The results shown in FIG. 2 demonstrate that treatment with certain of the anti-TfR1-ASO conjugates tested resulted in enhanced exon skipping. Five of the conjugates tested (comprising ASO007, ASO046, ASO010, ASO015, and ASO017 listed in Table 12, respectively) achieved exon 53 skipping in excess of 75% at the highest dose.

EQUIVALENTS AND TERMINOLOGY

[000432] The disclosure illustratively described herein suitably can be practiced in the absence of any element or elements, limitation or limitations that are not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of", and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the disclosure. Thus, it should be

understood that although the present disclosure has been specifically disclosed by preferred embodiments, optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this disclosure.

[000433] In addition, where features or aspects of the disclosure are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

[000434] It should be appreciated that, in some embodiments, sequences presented in the sequence listing may be referred to in describing the structure of an oligonucleotide or other nucleic acid. In such embodiments, the actual oligonucleotide or other nucleic acid may have one or more alternative nucleotides or nucleosides (e.g., an RNA counterpart of a DNA nucleoside or a DNA counterpart of an RNA nucleoside) and/or (e.g., and) one or more modified nucleotides/nucleosides and/or (e.g., and) one or more modified internucleoside linkages and/or (e.g., and) one or more other modification compared with the specified sequence while retaining essentially same or similar complementary properties as the specified sequence.

[000435] The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (*i.e.*, meaning "including, but not limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*e.g.*, "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[000436] Embodiments of this invention are described herein. Variations of those embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description.

[000437] The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

CLAIMS

What is claimed is:

1. A complex comprising an anti-transferrin receptor 1 (TfR1) antibody covalently linked to an oligonucleotide configured for inducing skipping of exon 53 in a DMD pre-mRNA, wherein the oligonucleotide comprises a region of complementarity that is complementary with at least 8 consecutive nucleotides of any one of SEQ ID NOs: 224, 206, 209, 212, 277, 214, 207, 208, 205, 160-204, 210, 211, 213, 215-223, 225-276, and 278-334.

2. The complex of claim 1, wherein the anti-TfR1 antibody comprises:

(i) a heavy chain complementarity determining region 1 (CDR-H1) of SEQ ID NO: 33, a heavy chain complementarity determining region 2 (CDR-H2) of SEQ ID NO: 34, a heavy chain complementarity determining region 3 (CDR-H3) of SEQ ID NO: 35, a light chain complementarity determining region 1 (CDR-L1) of SEQ ID NO: 36, a light chain complementarity determining region 2 (CDR-L2) of SEQ ID NO: 37, and a light chain complementarity determining region 3 (CDR-L3) of SEQ ID NO: 32;

(ii) a CDR-H1 of SEQ ID NO: 7, a CDR-H2 of SEQ ID NO: 8, a CDR-H3 of SEQ ID NO: 9, a CDR-L1 of SEQ ID NO: 10, a CDR-L2 of SEQ ID NO: 11, and a CDR-L3 of SEQ ID NO: 6;

(iii) a CDR-H1 of SEQ ID NO: 7, a CDR-H2 of SEQ ID NO: 20, a CDR-H3 of SEQ ID NO: 9, a CDR-L1 of SEQ ID NO: 10, a CDR-L2 of SEQ ID NO: 11, and a CDR-L3 of SEQ ID NO: 6;

(iv) a CDR-H1 of SEQ ID NO: 7, a CDR-H2 of SEQ ID NO: 24, a CDR-H3 of SEQ ID NO: 9, a CDR-L1 of SEQ ID NO: 10, a CDR-L2 of SEQ ID NO: 11, and a CDR-L3 of SEQ ID NO: 6;

(v) a CDR-H1 of SEQ ID NO: 51, a CDR-H2 of SEQ ID NO: 52, a CDR-H3 of SEQ ID NO: 53, a CDR-L1 of SEQ ID NO: 54, a CDR-L2 of SEQ ID NO: 55, and a CDR-L3 of SEQ ID NO: 50;

(vi) a CDR-H1 of SEQ ID NO: 64, a CDR-H2 of SEQ ID NO: 52, a CDR-H3 of SEQ ID NO: 53, a CDR-L1 of SEQ ID NO: 54, a CDR-L2 of SEQ ID NO: 55, and a CDR-L3 of SEQ ID NO: 50; or

(vii) a CDR-H1 of SEQ ID NO: 67, a CDR-H2 of SEQ ID NO: 52, a CDR-H3 of SEQ ID NO: 53, a CDR-L1 of SEQ ID NO: 54, a CDR-L2 of SEQ ID NO: 55, and a CDR-L3 of SEQ ID NO: 50.

3. The complex of claim 1 or claim 2, wherein the anti-TfR1 antibody comprises:

(i) a heavy chain variable region (VH) comprising an amino acid sequence at least 85% identical to SEQ ID NO: 76; and/or a light chain variable region (VL) comprising an amino acid sequence at least 85% identical to SEQ ID NO: 75;

(ii) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 69; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 70;

(iii) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 71; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 70;

(iv) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 72; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 70;

(v) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 73; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 74;

(vi) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 73; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 75;

(vii) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 76; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 74;

(viii) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 77; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 78;

(ix) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 79; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 80; or

(x) a VH comprising an amino acid sequence at least 85% identical to SEQ ID NO: 77; and/or a VL comprising an amino acid sequence at least 85% identical to SEQ ID NO: 80.

4. The complex of any one of claims 1 to 3, wherein the anti-TfR1 antibody comprises:

(i) a VH comprising the amino acid sequence of SEQ ID NO: 76 and a VL comprising the amino acid sequence of SEQ ID NO: 75;

(ii) a VH comprising the amino acid sequence of SEQ ID NO: 69 and a VL comprising the amino acid sequence of SEQ ID NO: 70;

(iii) a VH comprising the amino acid sequence of SEQ ID NO: 71and a VL comprising the amino acid sequence of SEQ ID NO: 70;

(iv) a VH comprising the amino acid sequence of SEQ ID NO: 72 and a VL comprising the amino acid sequence of SEQ ID NO: 70;

(v) a VH comprising the amino acid sequence of SEQ ID NO: 73 and a VL comprising the amino acid sequence of SEQ ID NO: 74;

(vi) a VH comprising the amino acid sequence of SEQ ID NO: 73 and a VL comprising the amino acid sequence of SEQ ID NO: 75;

(vii) a VH comprising the amino acid sequence of SEQ ID NO: 76 and a VL comprising the amino acid sequence of SEQ ID NO: 74;

(viii) a VH comprising the amino acid sequence of SEQ ID NO: 77 and a VL comprising the amino acid sequence of SEQ ID NO: 78;

(ix) a VH comprising the amino acid sequence of SEQ ID NO: 79 and a VL comprising the amino acid sequence of SEQ ID NO: 80; or

(x) a VH comprising the amino acid sequence of SEQ ID NO: 77 and a VL comprising the amino acid sequence of SEQ ID NO: 80.

5. The complex of any one of claims 1 to 4, wherein the anti-TfR1 antibody is a Fab fragment, a Fab' fragment, a F(ab')2 fragment, an scFv, an Fv, or a full-length IgG.

6. The complex of claim 5, wherein the anti-TfR1 antibody is a Fab fragment.

7. The complex of claim 6, wherein the anti-TfR1 antibody comprises:

(i) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 101; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 90;

(ii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 97; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 85;

(iii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 98; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 85;

(iv) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 99; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 85;

(v) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 100; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 89;

(vi) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 100; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 90;

(vii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 101; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 89;

(viii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 102; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 93;

(ix) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 103; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 95; or

(x) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 102; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 95.

8. The complex of claim 6 or claim 7, wherein the anti-TfR1 antibody comprises:

(i) a heavy chain comprising the amino acid sequence of SEQ ID NO: 101; and a light chain comprising the amino acid sequence of SEQ ID NO: 90;

(ii) a heavy chain comprising the amino acid sequence of SEQ ID NO: 97; and a light chain comprising the amino acid sequence of SEQ ID NO: 85;

(iii) a heavy chain comprising the amino acid sequence of SEQ ID NO: 98; and a light chain comprising the amino acid sequence of SEQ ID NO: 85;

(iv) a heavy chain comprising the amino acid sequence of SEQ ID NO: 99; and a light chain comprising the amino acid sequence of SEQ ID NO: 85;

(v) a heavy chain comprising the amino acid sequence of SEQ ID NO: 100; and a light chain comprising the amino acid sequence of SEQ ID NO: 89;

(vi) a heavy chain comprising the amino acid sequence of SEQ ID NO: 100; and a light chain comprising the amino acid sequence of SEQ ID NO: 90;

(vii) a heavy chain comprising the amino acid sequence of SEQ ID NO: 101; and a light chain comprising the amino acid sequence of SEQ ID NO: 89;

(viii) a heavy chain comprising the amino acid sequence of SEQ ID NO: 102; and a light chain comprising the amino acid sequence of SEQ ID NO: 93;

(ix) a heavy chain comprising the amino acid sequence of SEQ ID NO: 103; and a light chain comprising the amino acid sequence of SEQ ID NO: 95; or

(x) a heavy chain comprising the amino acid sequence of SEQ ID NO: 102; and a light chain comprising the amino acid sequence of SEQ ID NO: 95.

9. The complex of any one of claims 1 to 8, wherein the anti-TfR1 antibody does not specifically bind to the transferrin binding site of the transferrin receptor 1 and/or wherein the anti-TfR1 antibody does not inhibit binding of transferrin to the transferrin receptor 1.

10. The complex of any one of claims 1 to 9, wherein the oligonucleotide is complementary to at least 4 consecutive nucleotides of a splicing feature of the DMD pre-mRNA.

11. The complex of claim 10, wherein the splicing feature is an exonic splicing enhancer (ESE) in exon 53 of the DMD pre-mRNA, optionally wherein the ESE comprises a sequence of any one of SEQ ID NOs: 689-715.

12. The complex of claim 10, wherein the splicing feature is a branch point, a splice donor site, or a splice acceptor site, optionally wherein the splicing feature is across the junction of exon 52 and intron 52, in intron 52, across the junction of intron 52 and exon 53, across the junction of exon 53 and intron 53, in intron 53, or across the junction of intron 53 and exon 54 of the DMD pre-mRNA, and further optionally wherein the splicing feature comprises a sequence of any one of SEQ ID NOs: 685-688 and 716-718.

13. The complex of any one of claims 1 to 12, wherein the oligonucleotide comprises a sequence complementary to any one of SEQ ID NOs: 160-334 or comprises a sequence of any one of SEQ ID NOs: 335-684, wherein each thymine base (T) may independently and optionally be replaced with a uracil base (U), and each U may independently and optionally be replaced with a T.

14. The complex of any one of claims 1 to 12, wherein the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 574, 556, 559, 562, 627, 564, 557, 558, and 555, wherein each thymine base (T) may independently and optionally be replaced with a uracil base (U), and each U may independently and optionally be replaced with a T.

15. The complex of any one of claims 1 to 14, wherein the oligonucleotide comprises one or more phosphorodiamidate morpholinos, optionally wherein the oligonucleotide is a phosphorodiamidate morpholino oligomer (PMO).

16. The complex of any one of claims 1 to 15, wherein the anti-TfR1 antibody is covalently linked to the oligonucleotide via a cleavable linker, optionally wherein the cleavable linker comprises a valine-citrulline sequence.

17. The complex of any one of claims 1 to 16, wherein the anti-TfR1 antibody is covalently linked to the oligonucleotide via conjugation to a lysine residue or a cysteine residue of the antibody.

18. An oligonucleotide that targets DMD, wherein the oligonucleotide comprises a region of complementarity to any one of SEQ ID NOs: 160-334, optionally wherein the region of complementarity comprises at least 15 consecutive nucleosides complementary to any one of SEQ ID NOs: 160-334.

19. The oligonucleotide of claim 18, wherein the oligonucleotide comprises at least 15 consecutive nucleosides of any one of SEQ ID NOs: 335-684, optionally wherein the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 335-684, wherein each thymine base (T) may independently and optionally be replaced with a uracil base (U), and each U may independently and optionally be replaced with a T.

20. The oligonucleotide of claim 19, wherein the oligonucleotide comprises a sequence of any one of SEQ ID NOs: 574, 556, 559, 562, 627, 564, 557, 558, and 555, wherein each thymine base (T) may independently and optionally be replaced with a uracil base (U), and each U may independently and optionally be replaced with a T.

21. A method of delivering an oligonucleotide to a cell, the method comprising contacting the cell with the complex of any one of claims 1 to 17 or with the oligonucleotide of any one of claims 18-20.

22. A method of promoting the expression or activity of a dystrophin protein in a cell, the method comprising contacting the cell with the complex of any one of claims 1 to 17 or with the oligonucleotide of any one of claims 18-20 in an amount effective for promoting internalization of the oligonucleotide to the cell, optionally wherein the cell is a muscle cell.