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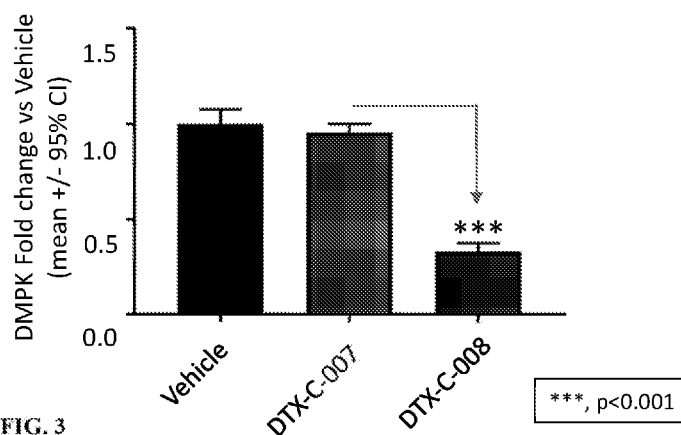


FIG. 3

(57) Abstract: Aspects of the disclosure relate to complexes comprising a muscle-targeting agent covalently linked to a molecular payload. In some embodiments, the muscle-targeting agent specifically binds to an internalizing cell surface receptor on muscle cells. In some embodiments, the molecular payload inhibits expression or activity of a DMPK allele comprising a disease-associated-repeat. In some embodiments, the molecular payload is an oligonucleotide, such as an antisense oligonucleotide or RNAi oligonucleotide.

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MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR TREATING MYOTONIC DYSTROPHY

RELATED APPLICATIONS

[0001] This application claims the benefit of the filing date of U.S. Provisional Application No. 62/713,914, entitled “MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR TREATING MYOTONIC DYSTROPHY”, filed August 2, 2018; U.S. Provisional Application No. 62/779,161, entitled “MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR TREATING MYOTONIC DYSTROPHY”, filed December 13, 2018; U.S. Provisional Application No. 62/855,761, entitled “MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR TREATING MYOTONIC DYSTROPHY”, filed May 31, 2019; U.S. Provisional Application No. 62/858,888, entitled “MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR TREATING MYOTONIC DYSTROPHY”, filed June 7, 2019; and U.S. Provisional Application No. 62/859,672, entitled “MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR TREATING MYOTONIC DYSTROPHY”, filed June 10, 2019; 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 THE SEQUENCE LISTING

[0003] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled D082470000WO00-SEQ.txt created on July 25, 2019 which is 155 kilobytes in size. The information in electronic format of the sequence listing is incorporated herein by reference in its entirety.

BACKGROUND OF INVENTION

[0004] Myotonic dystrophy (DM) is a dominantly inherited genetic disease that is characterized by myotonia, muscle loss or degeneration, diminished muscle function, insulin resistance, cardiac arrhythmia, smooth muscle dysfunction, and neurological abnormalities. DM is the most common form of adult-onset muscular dystrophy, with a worldwide incidence of

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about 1 in 8000 people worldwide. Two types of the disease, myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2), have been described. DM1, the more common form of the disease, results from a repeat expansion of a CTG trinucleotide repeat in the 3' non-coding region of DMPK on chromosome 19; DM2 results from a repeat expansion of a CCTG tetranucleotide repeat in the first intron of ZNF9 on chromosome 3. In DM1 patients, the repeat expansion of a CTG trinucleotide repeat, which may comprise greater than ~50 to ~3,000+ total repeats, leads to generation of toxic RNA repeats capable of forming hairpin structures that bind essential intracellular proteins, e.g. muscleblind-like proteins, with high affinity resulting in protein sequestration and the loss-of-function phenotypes that are characteristic of the disease. Apart from supportive care and treatments to address the symptoms of the disease, no effective therapeutic for DM1 is currently available.

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. In some embodiments, complexes provided herein are particularly useful for delivering molecular payloads that inhibit the expression or activity of a DMPK allele comprising an expanded disease-associated-repeat, *e.g.*, in a subject having or suspected of having myotonic dystrophy. 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 inhibit mutant DMPK expression 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.

[0006] Aspects of the disclosure related to complexes comprising a muscle-targeting agent covalently linked to a molecular payload configured for inhibiting expression or activity of a DMPK allele comprising a disease-associated-repeat. In some embodiments, the muscle-targeting agent specifically binds to an internalizing cell surface receptor on muscle cells. In some embodiments, the muscle-targeting agent is a muscle-targeting antibody. In some embodiments, the muscle-targeting antibody specifically binds to an extracellular epitope of a

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transferrin receptor. In some embodiments, the extracellular epitope of the transferrin receptor comprises an epitope of the apical domain of the transferrin receptor.

[0007] In some embodiments, the muscle-targeting antibody specifically binds to an epitope of a sequence in the range of C89 to F760 of SEQ ID NO: 1-3. In some embodiments, the equilibrium dissociation constant (K_d) of binding of the muscle-targeting antibody to the transferrin receptor is in a range from 10^{-11} M to 10^{-6} M. In some embodiments, the muscle-targeting antibody competes for specific binding to an epitope of a transferrin receptor with an antibody listed in Table 1. In some embodiments, the muscle-targeting antibody competes for specific binding to an epitope of a transferrin receptor with an K_d of less than or equal to 10^{-6} M. In some embodiments, the K_d is in a range of 10^{-11} M to 10^{-6} M.

[0008] In some embodiments, the muscle-targeting antibody does not specifically bind to the transferrin binding site of the transferrin receptor and/or wherein the muscle-targeting antibody does not inhibit binding of transferrin to the transferrin receptor. In some embodiments, the muscle-targeting antibody is cross-reactive with extracellular epitopes of two or more of a human, non-human primate and rodent transferrin receptor.

[0009] In some embodiments, the complex is configured to promote transferrin receptor mediated internalization of the molecular payload into a muscle cell. In some embodiments, the muscle-targeting antibody is a chimeric antibody, optionally wherein the chimeric antibody is a humanized monoclonal antibody.

[00010] In some embodiments, the muscle-targeting antibody is in the form of a ScFv, Fab fragment, Fab' fragment, $F(ab')_2$ fragment, or Fv fragment. In some embodiments, the molecular payload is an oligonucleotide.

[00011] In some embodiments, the oligonucleotide comprises at least 15 consecutive nucleotides of a sequence comprising any one of SEQ ID NO: 45-280. In some embodiments, the oligonucleotide comprises a sequence comprising any one of SEQ ID NO: 45-280. In some embodiments, the oligonucleotide comprises a sequence comprising any one of SEQ ID NO: 56, 59, 69, 71, 77, 79, 85, 87, 92, 93, 98, 100, 109, 112, 115, 119, 145, or 161.

[00012] In some embodiments, the oligonucleotide comprises a region of complementarity to any one of SEQ ID NO: 281-516. In some embodiments, the oligonucleotide comprises a region of complementarity to at least 15 consecutive nucleotides of

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any one of SEQ ID NO: 281-516. In some embodiments, the oligonucleotide comprises a region of complementarity to the DMPK allele comprising the disease-associated-repeat expansion.

[00013] In some embodiments, the molecular payload is a polypeptide. In some embodiments, the polypeptide is a muscleblind-like (MBNL) polypeptide.

[00014] In some embodiments, the oligonucleotide comprises an antisense strand that hybridizes, in a cell, with a wild-type DMPK mRNA transcript encoded by the allele, wherein the DMPK mRNA transcript comprises repeating units of a CUG trinucleotide sequence. In some embodiments, the oligonucleotide comprises an antisense strand that hybridizes, in a cell, with a mutant DMPK mRNA transcript encoded by the allele, wherein the DMPK mRNA transcript comprises repeating units of a CUG trinucleotide sequence. In some embodiments, the disease-associated-repeat is 38 to 200 repeating units in length. In some embodiments, the disease-associated-repeat is associated with late onset myotonic dystrophy. In some embodiments, the disease-associated-repeat is 100 to 10,000 repeat units in length. In some embodiments, the disease-associated-repeat is associated with congenital myotonic dystrophy.

[00015] In some embodiments, the oligonucleotide comprises at least one modified internucleotide linkage. In some embodiments, the at least one modified internucleotide linkage is a phosphorothioate linkage. In some embodiments, the oligonucleotide comprises phosphorothioate linkages in the Rp stereochemical conformation and/or in the Sp stereochemical conformation. In some embodiments, the oligonucleotide comprises phosphorothioate linkages that are all in the Rp stereochemical conformation or that are all in the Sp stereochemical conformation.

[00016] In some embodiments, the oligonucleotide comprises one or more modified nucleotides. In some embodiments, the one or more modified nucleotides are 2'-modified nucleotides.

[00017] In some embodiments, the oligonucleotide is a gapmer oligonucleotide that directs RNase H-mediated cleavage of a DMPK mRNA transcript in a cell. In some embodiments, the gapmer oligonucleotide comprises a central portion of 5 to 15 deoxyribonucleotides flanked by wings of 2 to 8 modified nucleotides. In some embodiments, the modified nucleotides of the wings are 2'-modified nucleotides.

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[00018] In some embodiments, the oligonucleotide is a mixmer oligonucleotide. In some embodiments, the mixmer oligonucleotide inhibits binding of muscleblind-like protein 1, muscleblind-like protein 2, or muscleblind-like protein 3 to the DMPK mRNA transcript. In some embodiments, the mixmer oligonucleotide comprises two or more different 2' modified nucleotides.

[00019] In some embodiments, the oligonucleotide is an RNAi oligonucleotide that promotes RNAi-mediated cleavage of the DMPK mRNA transcript. In some embodiments, the RNAi oligonucleotide is a double-stranded oligonucleotide of 19 to 25 nucleotides in length.

[00020] In some embodiments, the RNAi oligonucleotide comprises at least one 2' modified nucleotide. In some embodiments, each 2' modified nucleotide is selected from the group consisting of: 2'-O-methyl, 2'-fluoro (2'-F), 2'-O-methoxyethyl (2'-MOE), and 2', 4'-bridged nucleotides. In some embodiments, the one or more modified nucleotides are bridged nucleotides. In some embodiments, at least one 2' modified nucleotide is a 2',4'-bridged nucleotide selected from: 2',4'-constrained 2'-O-ethyl (cEt) and locked nucleic acid (LNA) nucleotides.

[00021] In some embodiments, the oligonucleotide comprises a guide sequence for a genome editing nuclease.

[00022] In some embodiments, the oligonucleotide is phosphorodiamidite morpholino oligomer.

[00023] In some embodiments, the muscle-targeting agent is covalently linked to the molecular payload via a cleavable linker. In some embodiments, the cleavable linker is selected from: a protease-sensitive linker, pH-sensitive linker, and glutathione-sensitive linker. In some embodiments, the cleavable linker is a protease-sensitive linker. In some embodiments, the protease-sensitive linker comprises a sequence cleavable by a lysosomal protease and/or an endosomal protease. In some embodiments, the protease-sensitive linker comprises a valine-citrulline dipeptide sequence. In some embodiments, the linker is pH-sensitive linker that is cleaved at a pH in a range of 4 to 6.

[00024] In some embodiments, the muscle-targeting agent is covalently linked to the molecular payload via a non-cleavable linker. In some embodiments, the non-cleavable linker is an alkane linker. In some embodiments, the muscle-targeting antibody comprises a non-natural

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amino acid to which the oligonucleotide is covalently linked. In some embodiments, the muscle-targeting antibody is covalently linked to the oligonucleotide via conjugation to a lysine residue or a cysteine residue of the antibody.

[00025] In some embodiments, the muscle-targeting antibody is conjugated to the cysteine via a maleimide-containing linker, optionally wherein the maleimide-containing linker comprises a maleimidocaproyl or maleimidomethyl cyclohexane-1-carboxylate group.

[00026] In some embodiments, the muscle-targeting antibody is a glycosylated antibody that comprises at least one sugar moiety to which the oligonucleotide is covalently linked. In some embodiments, the sugar moiety is a branched mannose. In some embodiments, the muscle-targeting antibody is a glycosylated antibody that comprises one to four sugar moieties each of which is covalently linked to a separate oligonucleotide.

[00027] In some embodiments, the muscle-targeting antibody is a fully-glycosylated antibody. In some embodiments, the muscle-targeting antibody is a partially-glycosylated antibody. In some embodiments, the partially-glycosylated antibody is produced via chemical or enzymatic means. In some embodiments, the partially-glycosylated antibody is produced in a cell, cell that is deficient for an enzyme in the N- or O- glycosylation pathway.

[00028] According to some aspects of the disclosure, methods are provided for delivering a molecular payload to a cell expressing transferrin receptor. In some embodiments, the methods comprise contacting the cell with the complex provided herein.

[00029] According to some aspects of the disclosure, methods are provided for inhibiting activity of DMPK in a cell. In some embodiments, the methods comprise contacting the cell with the complex provided herein in an amount effective for promoting internalization of the molecular payload to the cell. In some embodiments, the cell is *in vitro*. In some embodiments, the cell is in a subject. In some embodiments, the subject is a human.

[00030] According to some aspects of the disclosure, methods are provided for treating a subject having an expansion of a disease-associated-repeat of a DMPK allele that is associated with myotonic dystrophy. In some embodiments, the methods comprise administering to the subject an effective amount of the complex provided herein. In some embodiments, the disease-associated-repeat comprises repeating units of a trinucleotide sequence. In some embodiments, the trinucleotide sequence is a CTG trinucleotide sequence. In some embodiments, the disease-

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associated-repeat is 38 to 200 repeating units in length. In some embodiments, the disease-associated-repeat is associated with late onset myotonic dystrophy. In some embodiments, the disease-associated-repeat is 100 to 10,000 repeating units in length. In some embodiments, the disease-associated-repeat is associated with congenital myotonic dystrophy.

BRIEF DESCRIPTION OF THE DRAWINGS

[00031] **FIG. 1** depicts a non-limiting schematic showing the effect of transfecting Hepa 1-6 cells with an antisense oligonucleotide that targets DMPK (DTX-P-060) on expression levels of DMPK relative to a vehicle transfection;

[00032] **FIG. 2A** depicts a non-limiting schematic showing an HIL-HPLC trace obtained during purification of a muscle targeting complex comprising an anti-transferrin receptor antibody covalently linked to a DMPK antisense oligonucleotide.

[00033] **FIG. 2B** depicts a non-limiting image of an SDS-PAGE analysis of a muscle targeting complex.

[00034] **FIG. 3** depicts a non-limiting schematic showing the ability of a muscle targeting complex (DTX-C-008) comprising DTX-P-060 to reduce expression levels of DMPK.

[00035] **FIGs. 4A-4E** depict non-limiting schematics showing the ability of a muscle targeting complex (DTX-C-008) comprising DTX-P-060 to reduce expression levels of DMPK in mouse muscle tissues *in vivo*, relative to a vehicle experiment. (N=3 C57Bl/6 WT mice)

[00036] **FIGs. 5A-5B** depict non-limiting schematics showing the tissue selectivity of a muscle targeting complex (DTX-C-008) comprising DTX-P-060. The muscle targeting complex (DTX-C-008) comprising DTX-P-060 does not reduce expression levels of DMPK in mouse brain or spleen tissues *in vivo*, relative to a vehicle experiment. (N=3 C57Bl/6 WT mice)

[00037] **FIGs. 6A-6F** depict non-limiting schematics showing the ability of a muscle targeting complex (DTX-C-008) comprising DTX-P-060 to reduce expression levels of DMPK in mouse muscle tissues *in vivo*, relative to a vehicle experiment. (N=5 C57Bl/6 WT mice)

[00038] **FIGs. 7A-7L** depict non-limiting schematics showing the ability of a muscle targeting complex (DTX-C-012) comprising DTX-P-060 to reduce expression levels of DMPK in cynomolgus monkey muscle tissues *in vivo*, relative to a vehicle experiment and compared to a naked DMPK ASO (DTX-P-060). (N=3 male cynomolgus monkeys)

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[00039] **FIGs. 8A-8B** depict non-limiting schematics showing the ability of a muscle targeting complex (DTX-C-012) comprising DTX-P-060 to reduce expression levels of DMPK in cynomolgus monkey smooth muscle tissues *in vivo*, relative to a vehicle experiment and compared to a naked DMPK ASO (DTX-P-060). (N=3 male cynomolgus monkeys)

[00040] **FIGs. 9A-9D** depict non-limiting schematics showing the tissue selectivity of a muscle targeting complex (DTX-C-012) comprising DTX-P-060. The muscle targeting complex comprising DMPK-ASO does not reduce expression levels of DMPK in cynomolgus monkey liver, kidney, brain, or spleen tissues *in vivo*, relative to a vehicle experiment. (N=3 male cynomolgus monkeys)

[00041] **FIG. 10** shows normalized DMPK mRNA tissue expression levels across several tissue types in cynomolgus monkeys. (N=3 male cynomolgus monkeys)

[00042] **FIGs. 11A-11B** depict non-limiting schematics showing the ability of a muscle targeting complex (DTX-C-008) comprising DTX-P-060 to reduce expression levels of DMPK in mouse muscle tissues *in vivo* for up to 28 days after dosing with DTX-C-008, relative to a vehicle experiment and compared to a naked DMPK ASO (DTX-P-060).

[00043] **FIG. 12** shows that a single dose of a muscle targeting complex (DTX-C-012) comprising DTX-P-060 is safe and tolerated in cynomolgus monkeys. (N=3 male cynomolgus monkeys)

DETAILED DESCRIPTION OF INVENTION

[00044] 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. 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 inhibit the expression or activity of target genes in muscle cells, *e.g.*, in a subject having or suspected of having a rare muscle disease. For example, in some embodiments, complexes are provided for targeting a DMPK allele that comprises an expanded disease-associated-repeat to treat subjects having DM1. In some embodiments, complexes provided herein may comprise oligonucleotides that inhibit expression of a DMPK allele comprising an expanded disease-associated-repeat. As another example, complexes may comprise oligonucleotides that interfere with the binding of a disease-

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associated DMPK mRNA to a muscleblind-like protein (*e.g.*, MBNL1, 2, and/or 3), thereby reducing a toxic effect of a disease-associated DMPK allele. In some embodiments, synthetic nucleic acid payloads (*e.g.*, DNA or RNA payloads) may be used that express one or more proteins that reduce a toxic effect of a disease-associated DMPK allele. In some embodiments, complexes may comprise molecular payloads of synthetic cDNAs and/or synthetic mRNAs, *e.g.*, that express one or more muscleblind-like-proteins (*e.g.*, MBNL1, 2, and/or 3) or fragments thereof. In some embodiments, complexes may comprise molecular payloads such as guide molecules (*e.g.*, guide RNAs) that are capable of targeting nucleic acid programmable nucleases (*e.g.*, Cas9) to a sequence at or near a disease-associated repeat sequence of DMPK. In some embodiments, such nucleic programmable nucleases could be used to cleave part or all of a disease-associated repeat sequence from a DMPK gene.

[00045] Further aspects of the disclosure, including a description of defined terms, are provided below.

I. Definitions

[00046] 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 pharmacologically useful (*e.g.*, to treat a condition in the subject).

[00047] 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).

[00048] 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 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

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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 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 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 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 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

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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).

[00049] **CDR:** As used herein, the term "CDR" refers to the complementarity determining region within antibody variable sequences. 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. Subportions 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

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defined according to any of these systems, although preferred embodiments use Kabat or Chothia defined CDRs.

[00050] 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 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.

[00051] 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.

[00052] Complementary: As used herein, the term "complementary" refers to the capacity for precise pairing between two nucleotides or two sets of nucleotides. In particular, complementary is a term that characterizes an extent of hydrogen bond pairing that brings about binding between two nucleotides or two sets of nucleotides. 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.

[00053] 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.

[00054] 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.

[00055] 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 transferring 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.

[00056] Disease-associated-repeat: As used herein, the term “disease-associated-repeat” refers to a repeated nucleotide sequence at a genomic location for which the number of units of the repeated nucleotide sequence is correlated with and/or directly or indirectly contributes to, or causes, genetic disease. Each repeating unit of a disease associated repeat may be 2, 3, 4, 5 or more nucleotides in length. For example, in some embodiments, a disease associated repeat is a dinucleotide repeat. In some embodiments, a disease associated repeat is a trinucleotide repeat. In some embodiments, a disease associated repeat is a tetranucleotide repeat. In some embodiments, a disease associated repeat is a pentanucleotide repeat. In some embodiments,

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embodiments, the disease-associated-repeat comprises CAG repeats, CTG repeats, CUG repeats, CGG repeats, CCTG repeats, or a nucleotide complement of any thereof. In some embodiments, a disease-associated-repeat is in a non-coding portion of a gene. However, in some embodiments, a disease-associated-repeat is in a coding region of a gene. In some embodiments, a disease-associated-repeat is expanded from a normal state to a length that directly or indirectly contributes to, or causes, genetic disease. In some embodiments, a disease-associated-repeat is in RNA (e.g., an RNA transcript). In some embodiments, a disease-associated-repeat is in DNA (e.g., a chromosome, a plasmid). In some embodiments, a disease-associated-repeat is expanded in a chromosome of a germline cell. In some embodiments, a disease-associated-repeat is expanded in a chromosome of a somatic cell. In some embodiments, a disease-associated-repeat is expanded to a number of repeating units that is associated with congenital onset of disease. In some embodiments, a disease-associated-repeat is expanded to a number of repeating units that is associated with childhood onset of disease. In some embodiments, a disease-associated-repeat is expanded to a number of repeating units that is associated with adult onset of disease.

[00057] DMPK: As used herein, the term “DMPK” refers to a gene that encodes myotonin-protein kinase (also known as myotonic dystrophy protein kinase or dystrophia myotonica protein kinase), a serine/threonine protein kinase. Substrates for this enzyme may include myogenin, the beta-subunit of the L-type calcium channels, and phospholemman. In some embodiments, DMPK may be a human (Gene ID: 1760), non-human primate (e.g., Gene ID: 456139, Gene ID: 715328), or rodent gene (e.g., Gene ID: 13400). In humans, a CTG repeat expansion in the 3' non-coding, untranslated region of DMPK is associated with myotonic dystrophy type I (DM1). In addition, multiple human transcript variants (e.g., as annotated under GenBank RefSeq Accession Numbers: NM_001081563.2, NM_004409.4, NM_001081560.2, NM_001081562.2, NM_001288764.1, NM_001288765.1, and NM_001288766.1) have been characterized that encode different protein isoforms.

[00058] DMPK allele: As used herein, the term “DMPK allele” refers to any one of alternative forms (e.g., wild-type or mutant forms) of a DMPK gene. In some embodiments, a DMPK allele may encode for wild-type myotonin-protein kinase that retains its normal and typical functions. In some embodiments, a DMPK allele may comprise one or more disease-associated-repeat expansions. In some embodiments, normal subjects have two DMPK alleles comprising in the range of 5 to 37 repeat units. In some embodiments, the number of CTG

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repeat units in subjects having DM1 is in the range of ~50 to ~3,000+ with higher numbers of repeats leading to an increased severity of disease. In some embodiments, mildly affected DM1 subjects have at least one DMPK allele having in the range of 50 to 150 repeat units. In some embodiments, subjects with classic DM1 have at least one DMPK allele having in the range of 100 to 1,000 or more repeat units. In some embodiments, subjects having DM1 with congenital onset may have at least one DMPK allele comprising more than 2,000 repeat units.

[00059] 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.

[00060] 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.

[00061] 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 VL sequence has been altered to be more "human-like", *i.e.*, more similar to human germline variable sequences. One type of

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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 nonhuman CDR sequences. In one embodiment, humanized anti-transferrin receptor antibodies and antigen binding portions are provided. Such antibodies may be generated by obtaining murine anti-transferrin receptor 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.

[00062] 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 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.

[00063] 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 chemicals.

[00064] 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,

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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.

[00065] 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.

[00066] 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.

[00067] 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

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receptor present on muscle cells. In some embodiments, the muscle-targeting antibody is an antibody that specifically binds to a transferrin receptor.

[00068] Myotonic dystrophy (DM): As used herein, the term “Myotonic dystrophy (DM)” refers to a genetic disease caused by mutations in the DMPK gene or CNBP (ZNF9) gene that is characterized by muscle loss, muscle weakening, and muscle function. Two types of the disease, myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2), have been described. DM1 is associated with an expansion of a CTG trinucleotide repeat in the 3' non-coding region of DMPK. DM2 is associated with an expansion of a CCTG tetranucleotide repeat in the first intron of ZNF9. In both DM1 and DM2, the nucleotide expansions lead to toxic RNA repeats capable of forming hairpin structures that bind critical intracellular proteins, e.g., muscleblind-like proteins, with high affinity. Myotonic dystrophy, the genetic basis for the disease, and related symptoms are described in the art (see, e.g. Thornton, C.A., “Myotonic Dystrophy” *Neurol Clin.* (2014), 32(3): 705–719.; and Konieczny et al. “Myotonic dystrophy: candidate small molecule therapeutics” *Drug Discovery Today* (2017), 22:11.) In some embodiments, subjects are born with a variation of DM1 called congenital myotonic dystrophy. Symptoms of congenital myotonic dystrophy are present from birth and include weakness of all muscles, breathing problems, clubfeet, developmental delays and intellectual disabilities. DM1 is associated with Online Mendelian Inheritance in Man (OMIM) Entry # 160900. DM2 is associated with OMIM Entry # 602668.

[00069] 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, phosphorodiamidite 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 nucleotides (e.g. 2'-O-methyl sugar modifications, purine or pyrimidine modifications). In some embodiments, an oligonucleotide may comprise one or more modified internucleotide linkage. In some embodiments, an oligonucleotide may comprise one or more phosphorothioate linkages, which may be in the Rp or Sp stereochemical conformation.

[00070] 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

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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.

[00071] 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.

[00072] 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

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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.

[00073] 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 disease-associated-repeat expansion, e.g., in a DMPK allele.

[00074] 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).

II. Complexes

[00075] 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 a 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.

[00076] A complex may be used to modulate the activity or function of at least one gene, protein, and/or nucleic acid. In some embodiments, the molecular payload present with a complex is responsible for the modulation of a gene, protein, and/or 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 nucleic acid in a cell. In some embodiments, a molecular payload is an oligonucleotide that targets a disease-associated repeat in muscle cells.

[00077] 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 a disease-associated repeat, e.g. DMPK allele.

A. Muscle-Targeting Agents

[00078] 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. 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). 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.

[00079] 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 a cardiac muscle cell.

[00080] 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

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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-transferrin receptor antibodies can be taken up by muscle cells via binding to transferrin receptor, which may then be endocytosed, *e.g.*, via clathrin-mediated endocytosis.

[00081] 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.

[00082] 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

[00083] 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 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

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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 Antibodies

[00084] 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 as an anti-transferrin receptor 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.

[00085] It should be appreciated that anti-transferrin receptor antibodies may be produced, synthesized, and/or 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-transferrin 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

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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.).

[00086] Any appropriate anti-transferrin receptor antibodies may be used in the complexes disclosed herein. Examples of anti-transferrin receptor antibodies, including associated references and binding epitopes are listed in Table 1. In some embodiments, the anti-transferrin receptor antibody comprises the complementarity determining regions (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) of any of the anti-transferrin receptor antibodies provided herein, e.g., anti-transferrin receptor antibodies listed in Table 1.

[00087] Table 1 – List of anti-transferrin receptor 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 TfR (residues 305-366 of human TfR sequence XM_052730.3, available in GenBank)
(From JCR) Clone M11 Clone M23 Clone M27 Clone B84	<ul style="list-style-type: none"> 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 TfR) and protease-like domain (residues 461-473)
(From Genentech) 7A4, 8A2,	<ul style="list-style-type: none"> WO 2016/081643, filed 5/26/2016, entitled “ANTI-TRANSFERRIN RECEPTOR ANTIBODIES AND METHODS OF USE” 	Apical domain and non-apical regions

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15D2, 10D11, 7B10, 15G11, 16G5, 13C3, 16G4, 16F6, 7G7, 4C2, 1B12, and 13D4	<ul style="list-style-type: none"> US Patent No. 9,708,406, filed 5/20/2014, "Anti-transferrin receptor antibodies and methods of use" 	
(From Armagen) 8D3	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Commercially available anti-transferrin receptor antibodies. 	Novus Biologicals 8100 Southpark Way, A-8 Littleton CO 80120
(From INSERM) BA120g	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> US Patent No. 7,572,895, filed 6/7/2004, entitled "TRANSFERRIN 	"LUCA31 epitope"

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	RECEPTOR ANTIBODIES"	
(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	
R17 217.1.3, 5E9C11, OKT9 (BE0023 clone)	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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. 	

[00088] In some embodiments, the muscle-targeting agent is an anti-transferrin receptor antibody. In some embodiment, an anti-transferrin receptor antibody specifically binds to a transferrin protein having an amino acid sequence as disclosed herein. In some embodiments, an anti-transferrin receptor antibody may specifically bind to any extracellular epitope of a transferrin receptor or an epitope that becomes exposed to an antibody, including the apical domain, the transferrin binding domain, and the protease-like domain. In some embodiments, an anti-transferrin receptor antibody binds to an amino acid segment of a human or non-human primate transferrin receptor, as provided in SEQ ID Nos. 1-3 in the range of amino acids C89 to F760. In some embodiments, an anti-transferrin receptor antibody specifically binds with binding affinity 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. Anti-transferrin receptor antibodies used herein may be capable of competing for binding with other anti-transferrin receptor antibodies, e.g. OKT9, 8D3, that bind to transferrin receptor with 10^{-3} M, 10^{-4} M, 10^{-5} M, 10^{-6} M, 10^{-7} M, or less.

[00089] 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:

MMDQARSASFNLFGGEPLSYTRFSLARQVDGDN SHVEMKLAVDEEENADNNT
KANVTKPKRCSGSICYGTIAVIVFFLIGFMIGYLG YCKGVEPKTECERLAGTESPVREEPG
EDFPAARRLYWDDLKRKLSEKLDSTDFGTIKLLNENS YVPREAGSQKDENLALYVEN
QREFKLSKVWRDQHFKIQVKDSAQNSVIIVDKNGRLVYLVENPGGYVAYSKAATVT

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GKLVHANFGTKKDFEDLYTPVNGSIVIVRAGKITFAEKVANAESLNAIGVLIYMDQTKF
 PIVNAELSFFGHAHLGTGDPYTPGFPSFNHTQFPPSRSSGLPNIPVQTISRAAA EKLFGNM
 EGDCPSDWKTDSTCRMVTSESKNVKLTVSNVLKEIKILNIFGVIKGFVEPDHYVVVGAQ
 RDAWGPGAAGKSGVGTALLLKL AQMFSDMVLKDGFQPSRSIIFASWSAGDFGSGV GATE
 WLEGYLSSLHLKAFTYINLDKAVLGTSNFKVSASPLLYTLIEKTMQNVKHPVTGQFLYQ
 DSNWASKVEKLTLDNAAFPFLAYSGIPAVSFCFCEDTDYPYLGTTMDTYKELIERIPELN
 KVARAAAEVAGQFVIKLT HDVELNLDYERYNSQLLSFVRDLNQYRADIKEMGLSLQW
 LYSARGDFFRATSRLTTDFGNAEKTDRFVMKKLNDRVMRVEYHFLSPYVSPKESPRH
 VFWGSGSHTLPALLENLKL RKQNNGAFNETLFRNQLALATWTIQGAANALSGDVWDI
 DNEF (SEQ ID NO: 1).

[00090] 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:

MMDQARSASFNLFGGEPLSYTRFSLARQVDGDN SHVEMKLGVD EEENTDNNTKPNGT
 KPKRCGGNICYGTIAVIIFFLIGFMIGYLG YCKGVEPKTECERLAGTESPAREEPEEDFPA
 APRLYWDDLKRKLSEKLDTTDFTSTIKLLNENLYVPREAGSQKDENLALYIENQFRE FK
 LSKVWRDQH FVKIQVKDSAQNSVIIVDKNGGLVYLVENPGGYVAYS KAATVTGKLVH
 ANFGTKKDFEDLDSPVNGSIVIVRAGKITFAEKVANAESLNAIGVLIYMDQTKFP IVKAD
 LSFFGHAHLGTGDPYTPGFPSFNHTQFPPSQSSGLPNIPVQTISRAAA EKLFGNMEGDCPS
 DWKTDSTCKMVTSENKSVKLT VSNVLKETKILNIFGVIKGFVEPDHYVVVGAQRDAW
 GPGAAKSSVGTALLLKL AQMFSDMVLKDGFQPSRSIIFASWSAGDFGSGV GATEWLEGY
 LSSLHLKAFTYINLDKAVLGTSNFKVSASPLLYTLIEKTMQDV KHPVTGRSLYQDSNWA
 SKVEKLTLDNAAFPFLAYSGIPAVSFCFCEDTDYPYLGTTMDTYKELVERIPELNKVAR
 AA AEVAGQFVIKLT HDTELNLDYERYNSQLLLFLRDLNQYRADVKEMGLSLQWL YSA
 RGDFFRATSRLTTDFRNAEK RDKFVMKKLNDRVMRVEYYFLSPYVSPKESPRH VFWG
 SGSHTLSALLESLKLRRQNNSAFNETLFRNQLALATWTIQGAANALSGDVWDIDNEF(S
 EQ ID NO: 2)

[00091] 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:

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MMDQARSAFSNLFGGEPLSYTRFSLARQVDGDN SHVEMKLGVD E EENTDNNTKANGT
 KPKRCGGNICYGTIAVIIFFLIGFMIGYLG YCKGVEPKTECERLAGTESPAREEPEEDFPA
 APRLYWDDLKRKLSEKLDTTDFTSTIKLLNENLYVPREAGSQKDENLALYIENQFREFK
 LSKVWRDQHFVKIQVKDSAQNSVIIVDKNGGLVYLVENPGGYVAYS KAATVTGKLVH
 ANFGTKKDFEDLDSPVNGSIVIVRAGKITFAEKVANAESLNAIGVLIYMDQTKFPIVKAD
 LSFFGHAHLGTGDPYTPGFPSFNHTQFPSSQSSGLPNIPVQTISRAAA EKLFGNMEGDCPS
 DWKTDSTCKMVTSENKSVKLTVSNVLKETKILNIFGVIKGFVEPDHYVVVGAQRDAW
 GPGAACKSSVGTALLLKL AQMFSDMVLDGFGQPSRSIIFASWSAGDFGSGATEWLEGY
 LSSLHLKAFTYINLDKAVLGTSNFKVSASPLLYTLIEKTMQDVKHPVTGRSLYQDSNWA
 SKVEKLTLDNAAFPFLAYSGIPAVSFCFCEDTDYPYLGTTMDTYKELVERIPELNKVAR
 AA AEVAGQFVIKLT HDTELNDYERYNSQLLLFLRDLNQYRADVKEMGLSLQWLYSA
 RGDFFRATSRLTTDFRNAEKRDKFVMKKLNDRVMRVEYYFLSPYVSPKESPFRHVFWG
 SGSHTLSALLESLKLRRQNNSAFNETLFRNQLALATWTIQGAANALSGDVWDIDNEF
 (SEQ ID NO: 3).

[00092] An example mouse transferrin receptor amino acid sequence, corresponding to NCBI sequence NP_001344227.1 (transferrin receptor protein 1, mus musculus) is as follows:
 MMDQARSAFSNLFGGEPLSYTRFSLARQVDGDN SHVEMKLAAD E EENADNNMKASV
 RPKKRFNGRLCFAAIALVIFFLIGFMSGYLG YCKRVEQKEECVKLAETEETDKSETMETE
 DVPTSSRLYWADLKTLLSEKLSNIEFADTIKQLSQNTYTPREAGSQKDESLAYYIENQFH
 EFKFSKVWRDEHYVKIQVKSSIGQNMVTIVQSNGNLDPVESPEGYVAFSKPTEVSGKLV
 HANFGTKKDFEELSYSVNGSLVIVRAGEITFAEKVANAQSFNAIGVLIYMDKNKFPVVE
 ADLALFGHAHLGTGDPYTPGFPSFNHTQFPSSQSSGLPNIPVQTISRAAA EKLFGKMEGS
 CPARWNIDSSCKLELSQNQNVKLIVKNVLKERRILNIFGVIKGYEEPDRYVVVGAQRDA
 LGAGVAAKSSVGTGLLLKL AQVFSDMISKDGFRPSRSIIFASWTAGDFGAVGATEWLEG
 YLSSLHLKAFTYINLDKVVLGTSNFKVSASPLLYTLMGKIMQDVKHPVDGKSLYRDSN
 WISKVEKLSFDNAAYPFLAYSGIPAVSFCFCEDADYPYLGTRLDTYEALTQKVPQLNQM
 VRTAAEVAGQLIJKLT HDVELNDYEMYNSKLLSFMKDLNQFKTDIRDMGLSLQWLYS
 ARGDYFRATSRLTTDFHNAEKTNR FVMREINDRIMKVEYHFLSPYVSPRESPFRHIFWG
 SGSHTLSALVENLKL RQKNITAFNETLFRNQLALATWTIQGVANALSGDIWNIDNEF
 (SEQ ID NO: 4)

In some embodiments, an anti-transferrin receptor antibody binds to an amino acid segment of the receptor as follows:

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FVKIQVKDSAQNSVIIVDKNGRLVYLVENPGGYVAYSKAATVTGKLVHANFGTKKDFE
DLYTPVNGSIVIVRAGKITFAEKVANAESLNAIGVLIYMDQTKFPIVNAELSSFFGHAHLG
TGDPYTPGFPSFNHTQFPPSRSSGLPNIPVQTISRAAAELFGNMEGDCPSDWKTDSTCR
MVTSESKNVKLTVSNVLKE (SEQ ID NO: 5) and does not inhibit the binding interactions
between transferrin receptors and transferrin and/or human hemochromatosis protein (also
known as HFE).

[00093] Appropriate methodologies may be used to obtain and/or 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.).

[00094] In some embodiments, an antibody is modified, e.g., modified via glycosylation, phosphorylation, sumoylation, and/or 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 phosphoglycosylation. In some embodiments, the one or more sugar or

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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*”.

[00095] Some aspects of the disclosure provide proteins that bind to transferrin receptor (e.g., an extracellular portion of the transferrin receptor). In some embodiments, transferrin receptor antibodies provided herein bind specifically to transferrin receptor (e.g., human transferrin receptor). 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. In some embodiments, transferrin receptor antibodies provided herein bind specifically to transferrin receptor from human, non-human primates, mouse, rat, *etc.* In some embodiments, transferrin receptor antibodies provided herein bind to human transferrin receptor. In some embodiments, transferrin receptor antibodies provided herein specifically bind to human transferrin receptor. In some embodiments, transferrin receptor antibodies provided herein bind to an apical domain of human transferrin receptor. In some embodiments, transferrin receptor antibodies provided herein specifically bind to an apical domain of human transferrin receptor.

[00096] In some embodiments, transferrin receptor 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-transferrin receptor antibodies selected from Table 1. In some embodiments, transferrin receptor antibodies include the CDR-H1, CDR-H2, and CDR-H3 as provided for any one of the anti-transferrin receptor antibodies selected from Table 1. In

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some embodiments, anti-transferrin receptor antibodies include the CDR-L1, CDR-L2, and CDR-L3 as provided for any one of the anti-transferrin receptor antibodies selected from Table 1. In some embodiments, anti-transferrin antibodies include the CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 as provided for any one of the anti-transferrin receptor antibodies selected from Table 1. The disclosure also includes any nucleic acid sequence that encodes a molecule comprising a CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, or CDR-L3 as provided for any one of the anti-transferrin receptor antibodies selected from Table 1. In some embodiments, antibody heavy and light chain CDR3 domains may play a particularly important role in the binding specificity/affinity of an antibody for an antigen. Accordingly, anti-transferrin receptor antibodies of the disclosure may include at least the heavy and/or light chain CDR3s of any one of the anti-transferrin receptor antibodies selected from Table 1.

[00097] In some examples, any of the anti- transferrin receptor antibodies of the disclosure have one or more CDR (*e.g.*, CDR-H or CDR-L) sequences substantially similar to any of the CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and/or CDR-L3 sequences from one of the anti-transferrin receptor antibodies selected from Table 1. In some embodiments, the position of one or more CDRs along the VH (*e.g.*, CDR-H1, CDR-H2, or CDR-H3) and/or VL (*e.g.*, CDR-L1, CDR-L2, or CDR-L3) region of an antibody described herein can vary by one, two, three, four, five, or six amino acid positions so long as immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% of the binding of the original antibody from which it is derived). For example, in some embodiments, the position defining a CDR of any antibody described herein can vary by shifting the N-terminal and/or C-terminal boundary of the CDR by one, two, three, four, five, or six amino acids, relative to the CDR position of any one of the antibodies described herein, so long as immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% of the binding of the original antibody from which it is derived). In another embodiment, the length of one or more CDRs along the VH (*e.g.*, CDR-H1, CDR-H2, or CDR-H3) and/or VL (*e.g.*, CDR-L1, CDR-L2, or CDR-L3) region of an antibody described herein can vary (*e.g.*, be shorter or longer) by one, two, three, four, five, or more amino acids, so long as immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at

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least 70%, at least 80%, at least 90%, at least 95% of the binding of the original antibody from which it is derived).

[00098] Accordingly, in some embodiments, a CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, and/or CDR-H3 described herein may be one, two, three, four, five or more amino acids shorter than one or more of the CDRs described herein (*e.g.*, CDRs from any of the anti-transferrin receptor antibodies selected from Table 1) so long as immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). In some embodiments, a CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, and/or CDR-H3 described herein may be one, two, three, four, five or more amino acids longer than one or more of the CDRs described herein (*e.g.*, CDRs from any of the anti-transferrin receptor antibodies selected from Table 1) so long as immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). In some embodiments, the amino portion of a CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, and/or CDR-H3 described herein can be extended by one, two, three, four, five or more amino acids compared to one or more of the CDRs described herein (*e.g.*, CDRs from any of the anti-transferrin receptor antibodies selected from Table 1) so long as immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). In some embodiments, the carboxy portion of a CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, and/or CDR-H3 described herein can be extended by one, two, three, four, five or more amino acids compared to one or more of the CDRs described herein (*e.g.*, CDRs from any of the anti-transferrin receptor antibodies selected from Table 1) so long as immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). In some embodiments, the amino portion of a CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, and/or CDR-H3 described herein can be shortened by one, two, three, four, five or more amino acids compared to one or more of the CDRs described herein (*e.g.*, CDRs from any of the anti-

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transferrin receptor antibodies selected from Table 1) so long as immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). In some embodiments, the carboxy portion of a CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, and/or CDR-H3 described herein can be shortened by one, two, three, four, five or more amino acids compared to one or more of the CDRs described herein (*e.g.*, CDRs from any of the anti-transferrin receptor antibodies selected from Table 1) so long as immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). Any method can be used to ascertain whether immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained, for example, using binding assays and conditions described in the art.

[00099] In some examples, any of the anti-transferrin receptor antibodies of the disclosure have one or more CDR (*e.g.*, CDR-H or CDR-L) sequences substantially similar to any one of the anti-transferrin receptor antibodies selected from Table 1. For example, the antibodies may include one or more CDR sequence(s) from any of the anti-transferrin receptor antibodies selected from Table 1 containing up to 5, 4, 3, 2, or 1 amino acid residue variations as compared to the corresponding CDR region in any one of the CDRs provided herein (*e.g.*, CDRs from any of the anti-transferrin receptor antibodies selected from Table 1) so long as immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). In some embodiments, any of the amino acid variations in any of the CDRs provided herein may be conservative variations. Conservative variations can be introduced into the CDRs at positions where the residues are not likely to be involved in interacting with a transferrin receptor protein (*e.g.*, a human transferrin receptor protein), for example, as determined based on a crystal structure. Some aspects of the disclosure provide transferrin receptor antibodies that comprise one or more of the heavy chain variable (VH) and/or light chain variable (VL) domains provided herein. In some embodiments, any of the VH domains provided herein include one or more of the CDR-H sequences (*e.g.*, CDR-H1, CDR-H2, and CDR-H3) provided herein, for example,

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any of the CDR-H sequences provided in any one of the anti-transferrin receptor antibodies selected from Table 1. In some embodiments, any of the VL domains provided herein include one or more of the CDR-L sequences (*e.g.*, CDR-L1, CDR-L2, and CDR-L3) provided herein, for example, any of the CDR-L sequences provided in any one of the anti-transferrin receptor antibodies selected from Table 1.

[000100] In some embodiments, anti-transferrin receptor antibodies of the disclosure include any antibody that includes a heavy chain variable domain and/or a light chain variable domain of any anti-transferrin receptor antibody, such as any one of the anti-transferrin receptor antibodies selected from Table 1. In some embodiments, anti-transferrin receptor antibodies of the disclosure include any antibody that includes the heavy chain variable and light chain variable pairs of any anti-transferrin receptor antibody, such as any one of the anti-transferrin receptor antibodies selected from Table 1.

[000101] Aspects of the disclosure provide anti-transferrin receptor antibodies having a heavy chain variable (VH) and/or a light chain variable (VL) domain amino acid sequence homologous to any of those described herein. In some embodiments, the anti-transferrin receptor 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-transferrin receptor antibody, such as any one of the anti-transferrin receptor antibodies selected from Table 1. In some embodiments, the homologous heavy chain variable and/or 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 a light chain variable sequence excluding any of the CDR sequences provided herein. In some embodiments, any of the anti-transferrin receptor 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-transferrin receptor antibody, such as any one of the anti-transferrin receptor antibodies selected from Table 1.

[000102] In some embodiments, an anti-transferrin receptor antibody, which specifically binds to transferrin receptor (*e.g.*, human transferrin receptor), comprises a light chain variable VL domain comprising any of the CDR-L domains (CDR-L1, CDR-L2, and CDR-L3), or CDR-L domain variants provided herein, of any of the anti-transferrin receptor antibodies selected

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from Table 1. In some embodiments, an anti-transferrin receptor antibody, which specifically binds to transferrin receptor (*e.g.*, human transferrin receptor), comprises a light chain variable VL domain comprising the CDR-L1, the CDR-L2, and the CDR-L3 of any anti-transferrin receptor antibody, such as any one of the anti-transferrin receptor antibodies selected from Table 1. In some embodiments, the anti-transferrin receptor antibody comprises a light chain variable (VL) region sequence comprising one, two, three or four of the framework regions of the light chain variable region sequence of any anti-transferrin receptor antibody, such as any one of the anti-transferrin receptor antibodies selected from Table 1. In some embodiments, the anti-transferrin receptor antibody comprises one, two, three or four of the framework regions of a light chain variable region sequence which is at least 75%, 80%, 85%, 90%, 95%, or 100% identical to one, two, three or four of the framework regions of the light chain variable region sequence of any anti-transferrin receptor antibody, such as any one of the anti-transferrin receptor antibodies selected from Table 1. In some embodiments, the light chain variable framework region that is derived from said amino acid sequence consists of said amino acid sequence but for the presence of up to 10 amino acid substitutions, deletions, and/or insertions, preferably up to 10 amino acid substitutions. In some embodiments, the light chain variable framework region that is derived from said amino acid sequence consists of said amino acid sequence with 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid residues being substituted for an amino acid found in an analogous position in a corresponding non-human, primate, or human light chain variable framework region.

[000103] In some embodiments, an anti-transferrin receptor antibody that specifically binds to transferrin receptor comprises the CDR-L1, the CDR-L2, and the CDR-L3 of any anti-transferrin receptor antibody, such as any one of the anti-transferrin receptor antibodies selected from Table 1. In some embodiments, the antibody further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. The primate or human light chain framework region of the antibody selected for use with the light chain CDR sequences described herein, can have, for example, at least 70% (*e.g.*, at least 75%, 80%, 85%, 90%, 95%, 98%, or at least 99%) identity with a light chain framework region of a non-human parent antibody. The primate or human antibody selected can have the same or substantially the same number of amino acids in its light chain complementarity determining regions to that of the light chain complementarity determining regions of any of the antibodies provided herein, *e.g.*, any of the anti-transferrin receptor antibodies selected from Table 1. In some

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embodiments, the primate or human light chain framework region amino acid residues are from a natural primate or human antibody light chain framework region having at least 75% identity, at least 80% identity, at least 85% identity, at least 90% identity, at least 95% identity, at least 98% identity, at least 99% (or more) identity with the light chain framework regions of any anti-transferrin receptor antibody, such as any one of the anti-transferrin receptor antibodies selected from Table 1. In some embodiments, an anti-transferrin receptor antibody further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, an anti-transferrin receptor antibody further comprises one, two, three or all four VL framework regions derived from a human light chain variable lambda subfamily.

[000104] In some embodiments, any of the anti-transferrin receptor antibodies provided herein comprise a light chain variable domain that further comprises a light chain constant region. In some embodiments, the light chain constant region is a kappa, or a lambda light chain constant region. In some embodiments, the kappa or lambda light chain constant region is from a mammal, *e.g.*, from a human, monkey, rat, or mouse. In some embodiments, the light chain constant region is a human kappa light chain constant region. In some embodiments, the light chain constant region is a human lambda light chain constant region. It should be appreciated that any of the light chain constant regions provided herein may be variants of any of the light chain constant regions provided herein. In some embodiments, the light chain constant region comprises an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, 98%, or 99% identical to any of the light chain constant regions of any anti-transferrin receptor antibody, such as any one of the anti-transferrin receptor antibodies selected from Table 1.

[000105] In some embodiments, the anti-transferrin receptor antibody is any anti-transferrin receptor antibody, such as any one of the anti-transferrin receptor antibodies selected from Table 1.

[000106] In some embodiments, an anti-transferrin receptor antibody comprises a VL domain comprising the amino acid sequence of any anti-transferrin receptor antibody, such as any one of the anti-transferrin receptor antibodies selected from Table 1, and wherein the constant regions comprise the amino acid sequences of the constant regions of an IgG, IgE, IgM, IgD, IgA or IgY immunoglobulin molecule, or a human IgG, IgE, IgM, IgD, IgA or IgY immunoglobulin molecule. In some embodiments, an anti-transferrin receptor antibody comprises any of the VL domains, or VL domain variants, and any of the VH domains, or VH

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domain variants, wherein the VL and VH domains, or variants thereof, are from the same antibody clone, and wherein the constant regions comprise 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*.

[000107] In some embodiments, an antibody of the disclosure can bind to a target antigen (e.g., transferrin receptor) with relatively high affinity, *e.g.*, with a K_D less than 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M or lower. For example, anti-transferrin receptor antibodies can bind to a transferrin receptor protein (e.g., human transferrin receptor) with an affinity between 5 pM and 500 nM, *e.g.*, between 50 pM and 100 nM, *e.g.*, between 500 pM and 50 nM. The disclosure also includes antibodies that compete with any of the antibodies described herein for binding to a transferrin receptor protein (e.g., human transferrin receptor) and that have an affinity of 50 nM or lower (e.g., 20 nM or lower, 10 nM or lower, 500 pM or lower, 50 pM or lower, or 5 pM or lower). The affinity and binding kinetics of the anti-transferrin receptor antibody can be tested using any suitable method including but not limited to biosensor technology (e.g., OCTET or BIACORE).

[000108] In some embodiments, an antibody of the disclosure can bind to a target antigen (e.g., transferrin receptor) with relatively high affinity, *e.g.*, with a K_D less than 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M or lower. For example, anti-transferrin receptor antibodies can bind to a transferrin receptor protein (e.g., human transferrin receptor) with an affinity between 5 pM and 500 nM, *e.g.*, between 50 pM and 100 nM, *e.g.*, between 500 pM and 50 nM. The disclosure also includes antibodies that compete with any of the antibodies described herein for binding to a transferrin receptor protein (e.g., human transferrin receptor) and that have an affinity of 50 nM or lower (e.g., 20 nM or lower, 10 nM or lower, 500 pM or lower, 50 pM or lower, or 5 pM or lower). The affinity and binding kinetics of the anti-transferrin receptor antibody can be tested using any suitable method including but not limited to biosensor technology (e.g., OCTET or BIACORE).

[000109] In some embodiments, the muscle-targeting agent is a transferrin receptor antibody (e.g., an antibody and variants thereof as described in International Application Publication WO 2016/081643, incorporated herein by reference).

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[000110] In some embodiments, the heavy chain and light chain CDRs of an example antibody according to different definition systems are provided in Table 1.1. The different definition systems, e.g., the Kabat definition, the Chothia definition, and/or the contact definition have been described. See, e.g., (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, 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 hgmp.mrc.ac.uk and bioinf.org.uk/abs).

Table 1.1 Heavy chain and light chain CDRs of a transferrin receptor antibody

CDRs	Kabat	Chothia	Contact
CDR-H1	SYWMH (SEQ ID NO: 17)	GYTFTSY (SEQ ID NO: 23)	TSYWMH (SEQ ID NO: 25)
CDR-H2	EINPTNGRTNYIEKFKS (SEQ ID NO: 18)	NPTNGR (SEQ ID NO: 24)	WIGEINPTNGRTN (SEQ ID NO: 26)
CDR-H3	GTRAYHY (SEQ ID NO: 19)	GTRAYHY (SEQ ID NO: 19)	ARGTRA (SEQ ID NO: 27)
CDR-L1	RASDNLYSNLA (SEQ ID NO: 20)	RASDNLYSNLA (SEQ ID NO: 20)	YSNLAWY (SEQ ID NO: 28)
CDR-L2	DATNLAD (SEQ ID NO: 21)	DATNLAD (SEQ ID NO: 21)	LLVYDATNLA (SEQ ID NO: 29)
CDR-L3	QHFWGTPLT (SEQ ID NO: 22)	QHFWGTPLT (SEQ ID NO: 22)	QHFWGTPL (SEQ ID NO: 30)

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[000111] The heavy chain variable domain (VH) and light chain variable domain sequences are for also provided:

[000112] VH

QVQLQQPGAELVKPGASVKLSCKASGYTFTSYWMHWVKQRPGQGLEWIGEINPTNGR
TNYIEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYCARGTRAYHYWGQGTSTVTS
S (SEQ ID NO: 33)

[000113] VL

DIQMTQSPASLSVSVGETVTITCRASDNLYSNLAWYQQKQKGKSPQLLVYDATNLADGV
PSRFGSGSGGTQYSLKINSLSQSEDFGTYYCQHFWGTPLTFGAGTKLELK (SEQ ID NO:
34)

[000114] In some embodiments, the transferrin receptor 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 1.1. Alternatively or in addition, the transferrin receptor 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 1.1.

[000115] In some embodiments, the transferrin receptor antibody of the present disclosure comprises a CDR-H1, a CDR-H2, and a CDR-H3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2, or 1 amino acid variation) as compared with the CDR-H1, CDR-H2, and CDR-H3 as shown in Table 1.1. "Collectively" means that the total number of amino acid variations in all of the three heavy chain CDRs is within the defined range. Alternatively or in addition, the transferrin receptor antibody of the present disclosure may comprise a CDR-L1, a CDR-L2, and a CDR-L3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2 or 1 amino acid variation) as compared with the CDR-L1, CDR-L2, and CDR-L3 as shown in Table 1.1.

[000116] In some embodiments, the transferrin receptor antibody of the present disclosure comprises a CDR-H1, a CDR-H2, and a CDR-H3, at least one of 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 counterpart heavy chain CDR as shown in Table 1.1. Alternatively or in addition, the transferrin receptor antibody of the present disclosure may comprise CDR-L1, a CDR-L2, and a CDR-L3, at least one of 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 counterpart light chain CDR as shown in Table 1.1.

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[000117] In some embodiments, the transferrin receptor 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 1.1. In some embodiments, the transferrin receptor antibody of the present disclosure comprises a CDR-L3 containing one amino acid variation as compared with the CDR-L3 as shown in Table 1.1. In some embodiments, the transferrin receptor antibody of the present disclosure comprises a CDR-L3 of QHFAGTPLT (SEQ ID NO: 31 according to the Kabat and Chothia definition system) or QHFAGTPL (SEQ ID NO: 32 according to the Contact definition system). In some embodiments, the transferrin receptor 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 1.1, and comprises a CDR-L3 of QHFAGTPLT (SEQ ID NO: 31 according to the Kabat and Chothia definition system) or QHFAGTPL (SEQ ID NO: 32 according to the Contact definition system).

[000118] In some embodiments, the transferrin receptor 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 1.1. Alternatively or in addition, the transferrin receptor 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 1.1.

[000119] In some embodiments, the transferrin receptor antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 33. Alternatively or in addition, the transferrin receptor antibody of the present disclosure comprises a VL comprising the amino acid sequence of SEQ ID NO: 34.

[000120] In some embodiments, the transferrin receptor antibody of the present disclosure comprises a VH containing no more than 20 amino acid variations (e.g., no more than 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: 33. Alternatively or in addition, the transferrin receptor 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: 34.

[000121] In some embodiments, the transferrin receptor antibody of the present disclosure comprises a VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%,

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95%, or 98%) identical to the VH as set forth in SEQ ID NO: 33. Alternatively or in addition, the transferrin receptor antibody of the present disclosure comprises a VL comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, or 98%) identical to the VL as set forth in SEQ ID NO: 34.

[000122] In some embodiments, the transferrin receptor antibody of the present disclosure is a humanized antibody (e.g., a humanized variant containing one or more CDRs of Table 1.1). In some embodiments, the transferrin receptor 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 shown in Table 1.1, and comprises a humanized heavy chain variable region and/or a humanized light chain variable region.

[000123] Humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity. In some embodiments, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, the humanized antibody may comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences, but are included to further refine and optimize antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region or domain (Fc), typically that of a human immunoglobulin. Antibodies may have Fc regions modified as described in WO 99/58572. Other forms of humanized antibodies have one or more CDRs (one, two, three, four, five, six) which are altered with respect to the original antibody, which are also termed one or more CDRs derived from one or more CDRs from the original antibody. Humanized antibodies may also involve affinity maturation.

[000124] In some embodiments, humanization is achieved by grafting the CDRs (e.g., as shown in Table 1.1) into the IGKV1-NL1*01 and IGHV1-3*01 human variable domains. In some embodiments, the transferrin receptor antibody of the present disclosure is a humanized variant comprising one or more amino acid substitutions at positions 9, 13, 17, 18, 40, 45, and

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70 as compared with the VL as set forth in SEQ ID NO: 34, and/or one or more amino acid substitutions at positions 1, 5, 7, 11, 12, 20, 38, 40, 44, 66, 75, 81, 83, 87, and 108 as compared with the VH as set forth in SEQ ID NO: 33. In some embodiments, the transferrin receptor antibody of the present disclosure is a humanized variant comprising amino acid substitutions at all of positions 9, 13, 17, 18, 40, 45, and 70 as compared with the VL as set forth in SEQ ID NO: 34, and/or amino acid substitutions at all of positions 1, 5, 7, 11, 12, 20, 38, 40, 44, 66, 75, 81, 83, 87, and 108 as compared with the VH as set forth in SEQ ID NO: 33.

[000125] In some embodiments, the transferrin receptor antibody of the present disclosure is a humanized antibody and contains the residues at positions 43 and 48 of the VL as set forth in SEQ ID NO: 34. Alternatively or in addition, the transferrin receptor antibody of the present disclosure is a humanized antibody and contains the residues at positions 48, 67, 69, 71, and 73 of the VH as set forth in SEQ ID NO: 33.

[000126] The VH and VL amino acid sequences of an example humanized antibody that may be used in accordance with the present disclosure are provided:

[000127] Humanized VH

EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMHWVRQAPGQRLEWIGEINPTNGR
TNYIEKFKSRATLTVDKSASTAYMELSSLRSEDVAVYYCARGTRAYHYWGQGTMVTV
SS (SEQ ID NO: 35)

[000128] Humanized VL

DIQMTQSPSSLSASVGDRVTITCRASDNLYSNLAWYQQKPGKSPKLLVYDATNLADGV
PSRFGSGSGTDYSLKINSLSQSEDFGTYYCQHFHWGTPLTFGAGTKLELK (SEQ ID NO:
36)

[000129] In some embodiments, the transferrin receptor antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 35. Alternatively or in addition, the transferrin receptor antibody of the present disclosure comprises a VL comprising the amino acid sequence of SEQ ID NO: 36.

[000130] In some embodiments, the transferrin receptor antibody of the present disclosure comprises a VH containing no more than 20 amino acid variations (e.g., no more than 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: 35. Alternatively or in addition, the transferrin receptor antibody of the present disclosure comprises a VL containing no more than 15 amino acid

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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: 36.

[000131] In some embodiments, the transferrin receptor antibody of the present disclosure comprises a VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, or 98%) identical to the VH as set forth in SEQ ID NO: 35. Alternatively or in addition, the transferrin receptor antibody of the present disclosure comprises a VL comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, or 98%) identical to the VL as set forth in SEQ ID NO: 36.

[000132] In some embodiments, the transferrin receptor antibody of the present disclosure is a humanized variant comprising amino acid substitutions at one or more of positions 43 and 48 as compared with the VL as set forth in SEQ ID NO: 34, and/or amino acid substitutions at one or more of positions 48, 67, 69, 71, and 73 as compared with the VH as set forth in SEQ ID NO: 33. In some embodiments, the transferrin receptor antibody of the present disclosure is a humanized variant comprising a S43A and/or a V48L mutation as compared with the VL as set forth in SEQ ID NO: 34, and/or one or more of A67V, L69I, V71R, and K73T mutations as compared with the VH as set forth in SEQ ID NO: 33.

[000133] In some embodiments, the transferrin receptor antibody of the present disclosure is a humanized variant comprising amino acid substitutions at one or more of positions 9, 13, 17, 18, 40, 43, 48, 45, and 70 as compared with the VL as set forth in SEQ ID NO: 34, and/or amino acid substitutions at one or more of positions 1, 5, 7, 11, 12, 20, 38, 40, 44, 48, 66, 67, 69, 71, 73, 75, 81, 83, 87, and 108 as compared with the VH as set forth in SEQ ID NO: 33.

[000134] In some embodiments, the transferrin receptor antibody of the present disclosure is a chimeric antibody, which can include a heavy constant region and a light constant region from a human antibody. Chimeric antibodies refer to antibodies having a variable region or part of variable region from a first species and a constant region from a second species. Typically, in these chimeric antibodies, the variable region of both light and heavy chains mimics the variable regions of antibodies derived from one species of mammals (e.g., a non-human mammal such as mouse, rabbit, and rat), while the constant portions are homologous to the sequences in antibodies derived from another mammal such as human. In some embodiments, amino acid modifications can be made in the variable region and/or the constant region.

[000135] In some embodiments, the transferrin receptor antibody described herein is a chimeric antibody, which can include a heavy constant region and a light constant region from a

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human antibody. Chimeric antibodies refer to antibodies having a variable region or part of variable region from a first species and a constant region from a second species. Typically, in these chimeric antibodies, the variable region of both light and heavy chains mimics the variable regions of antibodies derived from one species of mammals (*e.g.*, a non-human mammal such as mouse, rabbit, and rat), while the constant portions are homologous to the sequences in antibodies derived from another mammal such as human. In some embodiments, amino acid modifications can be made in the variable region and/or the constant region.

[000136] In some embodiments, the heavy chain of any of the transferrin receptor 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 exemplary human IgG1 constant region is given below:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 37)

[000137] In some embodiments, the light chain of any of the transferrin receptor 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:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP (SEQ ID NO: 38)

[000138] 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.

[000139] Exemplary heavy chain and light chain amino acid sequences of the transferrin receptor antibodies described are provided below:

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[000140] Heavy Chain (VH + human IgG1 constant region)

QVQLQQPGAELVKPGASVKLSCKASGYTFTSYWMHWVKQRPGQGLEWIGEINPTNGR
TNYIEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYCARGTRAYHYWGQGTSTVTS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL
GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL
PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLT
VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 39)

[000141] Light Chain (VL + kappa light chain)

QVQLQQPGAELVKPGASVKLSCKASGYTFTSYWMHWVKQRPGQGLEWIGEINPTNGR
TNYIEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYCARGTRAYHYWGQGTSTVTS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP (SEQ ID
NO: 40)

[000142] Heavy Chain (humanized VH + human IgG1 constant region)

EVQLVQSGAEVKKPGASVKVSCASGYTFTSYWMHWVRQAPGQRLEWIGEINPTNGR
TNYIEKFKSRATLTVDKSASTAYMELSSLRSED TAVYYCARGTRAYHYWGQGTMTVTV
SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL
LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYT
LPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKL
TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 41)

[000143] Light Chain (humanized VL + kappa light chain)

DIQMTQSPSSLSASVGDRVTITCRASDNLYSNLAWYQQKPGKSPKLLVYDATNLADGV
PSRFGSGSGTDYSLKINSLSQSEDFGTYYCQHFHWGTPLTFGAGTKLELKASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP (SEQ ID NO: 42)

[000144] In some embodiments, the transferrin receptor antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, or 98%) identical to SEQ ID NO: 39. Alternatively or in addition, the

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transferrin receptor antibody described herein comprises a light chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, or 98%) identical to SEQ ID NO: 40. In some embodiments, the transferrin receptor antibody described herein comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 39. Alternatively or in addition, the transferrin receptor antibody described herein comprises a light chain comprising the amino acid sequence of SEQ ID NO: 40.

[000145] In some embodiments, the transferrin receptor antibody of the present disclosure comprises a heavy chain containing no more than 20 amino acid variations (e.g., no more than 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 SEQ ID NO: 39. Alternatively or in addition, the transferrin receptor antibody of the present disclosure comprises a light chain 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 light chain as set forth in SEQ ID NO: 40.

[000146] In some embodiments, the transferrin receptor antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, or 98%) identical to SEQ ID NO: 41. Alternatively or in addition, the transferrin receptor antibody described herein comprises a light chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, or 98%) identical to SEQ ID NO: 42. In some embodiments, the transferrin receptor antibody described herein comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 41. Alternatively or in addition, the transferrin receptor antibody described herein comprises a light chain comprising the amino acid sequence of SEQ ID NO: 42.

[000147] In some embodiments, the transferrin receptor antibody of the present disclosure comprises a heavy chain containing no more than 20 amino acid variations (e.g., no more than 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 of a humanized sequence as set forth in SEQ ID NO: 39. Alternatively or in addition, the transferrin receptor antibody of the present disclosure comprises a light chain 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 light chain of a humanized sequence as set forth in SEQ ID NO: 40.

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[000148] In some embodiments, the transferrin receptor antibody is an antigen binding fragment (FAB) of an intact antibody (full-length antibody). Antigen binding fragment of an intact antibody (full-length antibody) can be prepared via routine methods. For example, F(ab')₂ fragments can be produced by pepsin digestion of an antibody molecule, and Fab fragments that can be generated by reducing the disulfide bridges of F(ab')₂ fragments. Exemplary FABs amino acid sequences of the transferrin receptor antibodies described herein are provided below:

[000149] Heavy Chain FAB (VH + a portion of human IgG1 constant region)
 QVQLQQPGAELVKPGASVKLSCKASGYTFTSYWMHWVKQRPGQGLEWIGEINPTNGR
 TNYIEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYCARGTRAYHYWGQGTSVTVS
 SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
 SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP (SEQ ID
 NO: 43)

[000150] Heavy Chain FAB (humanized VH + a portion of human IgG1 constant region)
 EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMHWVRQAPGQRLEWIGEINPTNGR
 TNYIEKFKSRATLTVDKSASTAYMELSSLRSEDTAVYYCARGTRAYHYWGQGTMTVTV
 SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
 QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP (SEQ ID
 NO: 44)

[000151] The transferrin receptor 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 transferrin receptor antibody described herein is a scFv. In some embodiments, the transferrin receptor antibody described herein is a scFv-Fab (e.g., scFv fused to a portion of a constant region). In some embodiments, the transferrin receptor antibody described herein is a scFv fused to a constant region (e.g., human IgG1 constant region as set forth in SEQ ID NO: 39).

b. Other Muscle-Targeting Antibodies

[000152] 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

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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

[000153] 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 CH3 domain (residues 341-447 of human IgG1) and/or 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 antigen-dependent cellular cytotoxicity.

[000154] 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.

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[000155] 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 CH3 domain (residues 341-447 of human IgG1) and/or 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.

[000156] 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*.

[000157] 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 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

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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.

[000158] 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).

[000159] 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 Clq binding and/or 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 to increase the affinity of the antibody for an Fcγ receptor. This approach is described further in International Publication No. WO 00/42072.

[000160] In some embodiments, the heavy and/or light chain variable domain(s) sequence(s) of the antibodies provided herein can be used to generate, for example, CDR-

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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.

[000161] 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.

[000162] 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 C κ or C λ . 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

[000163] 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

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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.

[000164] 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".

[000165] 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

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(SEQ ID NO: 6) 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: 6). 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 DMD. 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: 7) was identified and this muscle-targeting peptide showed improved binding to C2C12 cells relative to the ASSLNIA (SEQ ID NO: 6) peptide.

[000166] 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: 8) appeared most frequently. Accordingly, in some embodiments, the muscle-targeting agent comprises the amino acid sequence TARGEHKEEELI (SEQ ID NO: 8).

[000167] A muscle-targeting agent may be 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 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

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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: 9), CSERSMNFC (SEQ ID NO: 10), CPKTRRVPC (SEQ ID NO: 11), WLSEAGPVVTVRALRGTGSW (SEQ ID NO: 12), ASSLNIA (SEQ ID NO: 6), CMQHSMRVC (SEQ ID NO: 13), and DDTRHWG (SEQ ID NO: 14). 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

[000168] 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.

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iv. Muscle-Targeting Aptamers

[000169] 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 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

[000170] 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.

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[000171] 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.

[000172] 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.

[000173] 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).

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[000174] A muscle-targeting agent may be a 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 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

[000175] Some aspects of the disclosure provide molecular payloads, e.g., for modulating a biological outcome, e.g., the transcription of a DNA 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 muscle-targeting agents 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 DMPK allele comprising a disease-associated-repeat expansion. 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

[000176] Any suitable oligonucleotide may be used as a molecular payload, as described herein. In some embodiments, the oligonucleotide may be designed to cause degradation of an

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mRNA (e.g., the oligonucleotide may be a gapmer, an siRNA, a ribozyme or an aptamer that causes degradation). In some embodiments, the oligonucleotide may be designed to block translation of an mRNA (e.g., the oligonucleotide may be a mixmer, an siRNA or an aptamer that blocks translation). In some embodiments, an oligonucleotide may be designed to caused degradation and block translation of an mRNA. In some embodiments, an oligonucleotide may be a guide nucleic acid (e.g., guide RNA) for directing activity of an enzyme (e.g., a gene editing enzyme). Other examples of oligonucleotides are provided herein. It should be appreciated that, in some embodiments, oligonucleotides in one format (e.g., antisense oligonucleotides) may be suitably adapted to another format (e.g., siRNA oligonucleotides) by incorporating functional sequences (e.g., antisense strand sequences) from one format to the other format.

[000177] Examples of oligonucleotides useful for targeting DMPK are provided in US Patent Application Publication 20100016215A1, published on January 1, 2010, entitled *Compound And Method For Treating Myotonic Dystrophy*; US Patent Application Publication 20130237585A1, published July 19, 2010, *Modulation Of Dystrophia Myotonica-Protein Kinase (DMPK) Expression*; US Patent Application Publication 20150064181A1, published on March 5, 2015, entitled “*Antisense Conjugates For Decreasing Expression Of Dmpk*”; US Patent Application Publication 20150238627A1, published on August 27, 2015, entitled “*Peptide-Linked Morpholino Antisense Oligonucleotides For Treatment Of Myotonic Dystrophy*”; and US Patent Application Publication 20160304877A1, published on October 20, 2016, entitled “*Compounds And Methods For Modulation Of Dystrophia Myotonica-Protein Kinase (Dmpk) Expression*,” the contents of each of which are incorporated herein in their entireties.

[000178] Examples of oligonucleotides for promoting DMPK gene editing include US Patent Application Publication 20170088819A1, published on March 3, 2017, entitled “*Genetic Correction Of Myotonic Dystrophy Type 1*”; and International Patent Application Publication WO18002812A1, published on April 1, 2018, entitled “*Materials And Methods For Treatment Of Myotonic Dystrophy Type 1 (DM1) And Other Related Disorders*,” the contents of each of which are incorporated herein in their entireties.

[000179] In some embodiments, oligonucleotides may have a region of complementarity to a sequence set forth as follows, which is an example human DMPK gene sequence (Gene ID 1760; NM_001081560.2):

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AGGGGGGCTGGACCAAGGGGTGGGGAGAAGGGGAGGAGGCCTCGGCCGGCCGCAG
AGAGAAGTGGCCAGAGAGGGCCAGGGGACAGCCAGGGACAGGCAGACATGCAGCC
AGGGCTCCAGGGCCTGGACAGGGGCTGCCAGGCCCTGTGACAGGAGGACCCCGAG
CCCCCGGCCCGGGAGGGGGCCATGGTGCTGCCTGTCCAACATGTCAGCCGAGGTGC
GGCTGAGGCGGCTCCAGCAGCTGGTGTTGGACCCGGGCTTCCTGGGGCTGGAGCCC
CTGCTCGACCTTCTCCTGGGCGTCCACCAGGAGCTGGGCGCCTCCGAACCTGGCCCAG
GACAAGTACGTGGCCGACTTCTTGCAGTGGGCGGAGCCCATCGTGGTGAGGCTTAA
GGAGGTCCGACTGCAGAGGGACGACTTCGAGATTCTGAAGGTGATCGGACGCGGG
GCGTTCAGCGAGGTAGCGGTAGTGAAGATGAAGCAGACGGGCCAGGTGTATGCCAT
GAAGATCATGAACAAGTGGGACATGCTGAAGAGGGGCGAGGTGTCGTGCTTCCGTG
AGGAGAGGGACGTGTTGGTGAATGGGGACCGGCGGTGGATCACGCAGCTGCACTTC
GCCTTCCAGGATGAGAACTACCTGTACCTGGTCATGGAGTATTACGTGGGCGGGGA
CCTGCTGACACTGCTGAGCAAGTTTGGGGAGCGGATTCCGGCCGAGATGGCGCGCT
TCTACCTGGCGGAGATTGTCATGGCCATAGACTCGGTGCACCGGCTTGGCTACGTGC
ACAGGGACATCAAACCCGACAACATCCTGCTGGACCGCTGTGGCCACATCCGCCTG
GCCGACTTCGGCTCTTGCCCTCAAGCTGCGGGCAGATGGAACGGTGCGGTGCGCTGGT
GGCTGTGGGACCCCCAGACTACCTGTCCCCCGAGATCCTGCAGGCTGTGGGCGGTG
GGCCTGGGACAGGCAGCTACGGGCCCCGAGTGTGACTGGTGGGCGCTGGGTGTATTC
GCCTATGAAATGTTCTATGGGCAGACGCCCTTCTACGCGGATTCCACGGCGGAGAC
CTATGGCAAGATCGTCCACTACAAGGAGCACCTCTCTCTGCCGCTGGTGGACGAAG
GGGTCCCTGAGGAGGCTCGAGACTTCATTACAGCGGTTGCTGTGTCCCCCGGAGACA
CGGCTGGGCCCGGGGTGGAGCAGGCGACTTCCGGACACATCCCTTCTTCTTTGGCCTC
GACTGGGATGGTCTCCGGGACAGCGTGCCCCCTTTACACCGGATTTCTGAAGGTGC
CACCGACACATGCAACTTCGACTTGGTGGAGGACGGGCTCACTGCCATGGAGACAC
TGTCGGACATTTCGGGAAGGTGCGCCGCTAGGGGTCCACCTGCCTTTTGTGGGCTACT
CCTACTCCTGCATGGCCCTCAGGGACAGTGAGGTCCCAGGCCCCACACCCATGGAA
CTGGAGGCCGAGCAGCTGCTTGAGCCACACGTGCAAGCGCCCAGCCTGGAGCCCTC
GGTGTCCCCACAGGATGAAACAGCTGAAGTGGCAGTTCCAGCGGCTGTCCCTGCGG
CAGAGGCTGAGGCCGAGGTGACGCTGCGGGAGCTCCAGGAAGCCCTGGAGGAGGA
GGTGCTACCCGGCAGAGCCTGAGCCGGGAGATGGAGGCCATCCGCACGGACAAC
CAGAACTTCGCCAGTCAACTACGCGAGGCAGAGGCTCGGAACCGGGACCTAGAGG
CACACGTCCGGCAGTTGCAGGAGCGGATGGAGTTGCTGCAGGCAGAGGGAGCCAC

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AGCTGTCACGGGGGTCCCCAGTCCCCGGGCCACGGATCCACCTTCCCATCTAGATG
GCCCCCGGCGGTGGCTGTGGGCCAGTGCCCGCTGGTGGGGCCAGGCCCCATGCAC
CGCCGCCACCTGCTGCTCCCTGCCAGGGTCCCTAGGCCTGGCCTATCGGAGGCGCTT
TCCCTGCTCCTGTTTCGCCGTTGTTCTGTCTCGTGCCGCCGCCCTGGGCTGCATTGGGT
TGGTGGCCACGCCGGCCAACTCACCGCAGTCTGGCGCCGCCAGGAGCCGCCCGC
GCTCCCTGAACCCTAGAACTGTCTTCGACTCCGGGGCCCCGTTGGAAGACTGAGTGC
CCGGGGCACGGCACAGAAGCCGCGCCACCGCCTGCCAGTTCACAACCGCTCCGAG
CGTGGGTCTCCGCCAGCTCCAGTCCTGTGATCCGGGGCCCGCCCCCTAGCGGCCGGG
GAGGGAGGGGCCGGGTCCGCGGCCGGCGAACGGGGCTCGAAGGGTCCTTGTAGCC
GGGAATGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT
GCTGCTGCTGGGGGGATCACAGACCATTTCTTTCTTTCGGCCAGGCTGAGGCCCTGA
CGTGGATGGGCAAACCTGCAGGCCTGGGAAGGCAGCAAGCCGGGCGCTCCGTGTTCC
ATCCTCCACGCACCCCCACCTATCGTTGGTTCGCAAAGTGCAAAGCTTTCTTGTGCA
TGACGCCCTGCTCTGGGGAGCGTCTGGCGCGATCTCTGCCTGCTTACTCGGGAAATT
TGCTTTTGCCAAACCCGCTTTTTTCGGGGATCCCGCGCCCCCCTCCTCACTTGCGCTGC
TCTCGGAGCCCCAGCCGGCTCCGCCCGCTTCGGCGGTTTGGATATTTATTGACCTCG
TCCTCCGACTCGCTGACAGGCTACAGGACCCCCAACAACCCCAATCCACGTTTTGGA
TGCACTGAGACCCCGACATTCCTCGGTATTTATTGTCTGTCCCCACCTAGGACCCCC
ACCCCGACCCTCGCGAATAAAAGGCCCTCCATCTGCCCAAAGCTCTGGA(SEQ ID
NO. 15).

[000180] In some embodiments, oligonucleotides may have a region of complementarity to a sequence set forth as follows, which is an example mouse DMPK gene sequence (Gene ID 13400; NM_001190490.1).

GAACTGGCCAGAGAGACCCAAGGGATAGTCAGGGACGGGCAGACATGCAGCTAGG
GTTCTGGGGCCTGGACAGGGGCAGCCAGGCCCTGTGACGGGAAGACCCCGAGCTCC
GGCCCGGGGAGGGGCCATGGTGTTCCTGCCAACATGTCAGCCGAAGTGCGGCTG
AGGCAGCTCCAGCAGCTGGTGTCTGGACCCAGGCTTCCTGGGACTGGAGCCCCTGCT
CGACCTTCTCCTGGGCGTCCACCAGGAGCTGGGTGCCTCTCACCTAGCCCAGGACA
AGTATGTGGCCGACTTCTTGCACTGGGTGGAGCCCATTCAGCAAGGCTTAAGGAG
GTCCGACTGCAGAGGGATGATTTTGAAGATTTTGAAGGTGATCGGGCGTGGGGCGTT
CAGCGAGGTAGCGGTGGTGAAGATGAAACAGACGGGCCAAGTGTATGCCATGAAG
ATTATGAATAAGTGGGACATGCTGAAGAGAGGCGAGGTGTCGTGCTTCGGGAAGA

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AAGGGATGTATTAGTGAAAGGGGACCGGCGCTGGATCACACAGCTGCACTTTGCCT
TCCAGGATGAGAACTACCTGTACCTGGTCATGGAATACTACGTGGGCGGGGACCTG
CTAACGCTGCTGAGCAAGTTTGGGGAGCGGATCCCCGCCGAGATGGCTCGCTTCTA
CCTGGCCGAGATTGTCATGGCCATAGACTCCGTGCACCGGCTGGGCTACGTGCACA
GGGACATCAAACCAGATAACATTCTGCTGGACCGATGTGGGCACATTTCGCTGGCA
GACTTCGGCTCCTGCCTCAAAGTGCAGCCTGATGGAATGGTGAGGTCGCTGGTGGCT
GTGGGCACCCCGGACTACCTGTCTCCTGAGATTCTGCAGGCCGTTGGTGGAGGGCCT
GGGGCAGGCAGCTACGGGCCAGAGTGTGACTGGTGGGCACTGGGCGTGTTCGCCTA
TGAGATGTTCTATGGGCAGACCCCTTCTACGCGGACTCCACAGCCGAGACATATG
CCAAGATTGTGCACTACAGGGAACACTTGTCGCTGCCGCTGGCAGACACAGTTGTC
CCCGAGGAAGCTCAGGACCTCATTCGTGGGCTGCTGTGTCCTGCTGAGATAAGGCT
AGGTCGAGGTGGGGCAGACTTCGAGGGTGCCACGGACACATGCAATTTTCGATGTGG
TGGAGGACCGGCTCACTGCCATGGTGAGCGGGGGCGGGGAGACGCTGTCAGACAT
GCAGGAAGACATGCCCCCTGGGGTGCGCCTGCCCTTCGTGGGCTACTCCTACTGCTG
CATGGCCTTCAGAGACAATCAGGTCCCGGACCCACCCCTATGGAAGTAGAGGCC
TGCAGTTGCCTGTGTCAGACTTGCAAGGGCTTGACTTGACAGCCCCAGTGTCCCCAC
CGGATCAAGTGGCTGAAGAGGCTGACCTAGTGGCTGTCCCTGCCCTGTGGCTGAG
GCAGAGACCACGGTAACGCTGCAGCAGCTCCAGGAAGCCCTGGAAGAAGAGGTTC
TCACCCGGCAGAGCCTGAGCCGCGAGCTGGAGGCCATCCGGACCGCCAACCAAGAAC
TTCTCCAGCCAAGTACAGGAGGCCGAGGTCCGAAACCGAGACCTGGAGGCGCATGT
TCGGCAGCTACAGGAACGGATGGAGATGCTGCAGGCCCCAGGAGCCGCAGCCATC
ACGGGGGTCCCCAGTCCCCGGGCCACGGATCCACCTTCCCATCTAGATGGCCCCC
GGCCGTGGCTGTGGGCCAGTGCCCGCTGGTGGGGCCAGGCCCATGCACCGCCGTC
ACCTGCTGCTCCCTGCCAGGATCCCTAGGCCTGGCCTATCCGAGGCGCGTTGCCTGC
TCCTGTTGCGCGCTGCTCTGGCTGCTGCCGCCACACTGGGCTGCACTGGGTTGGTGG
CCTATACCGGCGGTCTCACCCAGTCTGGTGTTCCTCCGGGAGCCACCTTCGCCCCCT
GAACCCTAAGACTCCAAGCCATCTTTCATTTAGGCCTCCTAGGAAGGTCGAGCGAC
CAGGGAGCGACCCAAAGCGTCTCTGTGCCCATCGCGCCCCCCCCCCCCCCCCACCG
CTCCGCTCCACACTTCTGTGAGCCTGGGTCCCCACCCAGCTCCGCTCCTGTGATCCA
GGCCTGCCACCTGGCGGCCGGGGAGGGAGGAACAGGGCTCGTGCCAGCACCCCTG
GTTCCCTGCAGAGCTGGTAGCCACCGCTGCTGCAGCAGCTGGGCATTGCGCCGACCTTG
CTTTACTCAGCCCCGACGTGGATGGGCAAAGTGCCTCAGCTCATCCGATTTCACTTTT

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TCACTCTCCCAGCCATCAGTTACAAGCCATAAGCATGAGCCCCCTATTTCCAGGGAC
 ATCCCATTTCCCATAGTGATGGATCAGCAAGACCTCTGCCAGCACACACGGAGTCTTT
 GGCTTCGGACAGCCTCACTCCTGGGGGTTGCTGCAACTCCTTCCCCGTGTACACGTC
 TGCACTCTAACAACGGAGCCACAGCTGCACTCCCCCCTCCCCCAAAGCAGTGTGGG
 TATTTATTGATCTTGTTATCTGACTCACTGACAGACTCCGGGACCCACGTTTTAGAT
 GCATTGAGACTCGACATTCCTCGGTATTTATTGTCTGTCCCCACCTACGACCTCCACT
 CCCGACCCTTGCGAATAAAATACTTCTGGTCTGCCCTAAA(SEQ ID NO. 16). In some
 embodiments, an oligonucleotide may have a region of complementarity to DMPK gene
 sequences of multiple species, e.g., selected from human, mouse and non-human species.

[000181] In some embodiments, the oligonucleotide may have region of complementarity to a mutant form of DMPK, for example, a mutant form as reported in Botta A. et al. “The CTG repeat expansion size correlates with the splicing defects observed in muscles from myotonic dystrophy type 1 patients.” J Med Genet. 2008 Oct;45(10):639-46.; and Machuca-Tzili L. et al. “Clinical and molecular aspects of the myotonic dystrophies: a review.” Muscle Nerve. 2005 Jul;32(1):1-18.; the contents of each of which are incorporated herein by reference in their entireties.

[000182] In some embodiments, the oligonucleotide may target lncRNA or mRNA, e.g., for degradation. In some embodiments, the oligonucleotide may target, e.g., for degradation, a nucleic acid encoding a protein involved in a mismatch repair pathway, e.g., MSH2, MutLalpha, MutSbeta, MutLalpha. Non-limiting examples of proteins involved in mismatch repair pathways, for which mRNAs encoding such proteins may be targeted by oligonucleotides described herein, are described in Iyer, R.R. et al., “DNA triplet repeat expansion and mismatch repair” Annu Rev Biochem. 2015;84:199-226.; and Schmidt M.H. and Pearson C.E., “Disease-associated repeat instability and mismatch repair” DNA Repair (Amst). 2016 Feb;38:117-26.

[000183] In some embodiments, an oligonucleotide provided herein is an antisense oligonucleotide targeting DMPK. In some embodiments, the oligonucleotide targeting is any one of the antisense oligonucleotides (e.g., a Gapmer) targeting DMPK as described in US Patent Application Publication US20160304877A1, published on October 20, 2016, entitled “Compounds And Methods For Modulation Of Dystrophia Myotonica-Protein Kinase (DMPK) Expression,” incorporated herein by reference). In some embodiments, the DMPK targeting oligonucleotide targets a region of the DMPK gene sequence as set forth in Genbank accession

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No. NM_001081560.2 (SEQ ID NO: 15) or as set forth in Genbank accession No. NG_009784.1.

[000184] In some embodiments, the DMPK targeting oligonucleotide comprises a nucleotide sequence comprising a region complementary to a target region that is at least 10 continuous nucleotides (e.g., at least 10, at least 12, at least 14, at least 16, or more continuous nucleotides) in SEQ ID NO: 15.

[000185] In some embodiments, the DMPK targeting oligonucleotide comprise a gapmer motif. “Gapmer” means a chimeric antisense compound in which an internal region having a plurality of nucleotides that support RNase H cleavage is positioned between external regions having one or more nucleotides, wherein the nucleotides comprising the internal region are chemically distinct from the nucleotide or nucleotides comprising the external regions. The internal region can be referred to as a “gap segment” and the external regions can be referred to as “wing segments.” In some embodiments, the DMPK targeting oligonucleotide comprises one or more modified nucleotides, and/or one or more modified internucleotide linkages. In some embodiments, the internucleotide linkage is a phosphorothioate linkage. In some embodiments, the oligonucleotide comprises a full phosphorothioate backbone. In some embodiments, the oligonucleotide is a DNA gapmer with cET ends (e.g., 3-10-3; cET-DNA-cET). In some embodiments, the DMPK targeting oligonucleotide comprises one or more 6'-(S)-CH₃ biocyclic nucleotides, one or more β-D-2'-deoxyribonucleotides, and/or one or more 5-methylcytosine nucleotides.

a. Oligonucleotide Size/Sequence

[000186] 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, etc.

[000187] In some embodiments, a complementary nucleic acid sequence of an oligonucleotide for purposes of the present disclosure is specifically hybridizable or specific for the target nucleic acid when binding of the sequence to the target molecule (e.g., mRNA) interferes with the normal function of the target (e.g., mRNA) to cause a loss of activity (e.g.,

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inhibiting translation) or expression (e.g., degrading a target mRNA) and there is a sufficient degree of complementarity to avoid non-specific binding of the sequence to non-target sequences under conditions in which avoidance of non-specific binding is desired, e.g., under physiological conditions in the case of in vivo assays or therapeutic treatment, and in the case of in vitro assays, under conditions in which the assays are performed under suitable conditions of stringency. 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 an 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.

[000188] 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, 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.

[000189] In some embodiments, an oligonucleotide comprises at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 consecutive nucleotides of a sequence comprising any one of SEQ ID NO: 45-280. In some embodiments, an oligonucleotide comprises a sequence comprising any one of SEQ ID NO: 45-280. In some embodiments, an oligonucleotide comprises a sequence that shares at least 70%, 75%, 80%, 85%, 90%, 95%, or 97% sequence identity with at least 12 or at least 15 consecutive nucleotides of any one of SEQ ID NO: 45-280.

[000190] In some embodiments, an oligonucleotide comprises a sequence that targets a DMPK sequence comprising any one of SEQ ID NO: 281-516. In some embodiments, an oligonucleotide comprises at least 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides (e.g., consecutive nucleotides) that are complementary to a DMPK sequence comprising any one of

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SEQ ID NO: 281-516. In some embodiments, an oligonucleotide comprises a sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, or 97% complementary with at least 12 or at least 15 consecutive nucleotides of any one of SEQ ID NO: 281-516.

b. Oligonucleotide Modifications:

[000191] The oligonucleotides described herein may be modified, e.g., comprise a modified sugar moiety, a modified internucleoside linkage, a modified nucleotide and/or 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.

[000192] In some embodiments, certain nucleotide 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 modification.

[000193] 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 of the oligonucleotide are modified nucleotides. 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 of the oligonucleotide are modified nucleotides. 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 of the oligonucleotide are modified nucleotides. Optionally, the oligonucleotides may have every

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nucleotide except 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides modified. Oligonucleotide modifications are described further herein.

c. Modified Nucleotides

[000194] In some embodiments, an oligonucleotide include a 2'-modified nucleotide, e.g., a 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-O-methyl, 2'-O-methoxyethyl (2'-O-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).

[000195] In some embodiments, an oligonucleotide can include at least one 2'-O-methyl-modified nucleotide, and in some embodiments, all of the nucleotides include a 2'-O-methyl modification. In some embodiments, an oligonucleotide comprises modified nucleotides 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. In some embodiments, the oligonucleotides are "locked," e.g., comprise modified nucleotides in which the ribose ring is "locked" by a methylene bridge connecting the 2'-O atom and the 4'-C atom. 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.

[000196] Other modifications that may be used in the oligonucleotides disclosed herein include ethylene-bridged nucleic acids (ENAs). ENAs include, but are not limited to, 2'-O,4'-C-ethylene-bridged nucleic acids. 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.

[000197] In some embodiments, the oligonucleotide may comprise a bridged nucleotide, such as a locked nucleic acid (LNA) nucleotide, a constrained ethyl (cEt) nucleotide, or an ethylene bridged nucleic acid (ENA) nucleotide. In some embodiments, the oligonucleotide comprises a modified nucleotide 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

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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.

[000198] In some embodiments, the oligonucleotide comprises at least one nucleotide modified at the 2' position of the sugar, preferably a 2'-O-alkyl, 2'-O-alkyl-O-alkyl or 2'-fluoro-modified nucleotide. In other preferred embodiments, RNA modifications include 2'-fluoro, 2'-amino and 2' O-methyl modifications on the ribose of pyrimidines, abasic residues or an inverted base at the 3' end of the RNA.

[000199] In some embodiments, the oligonucleotide may have at least one modified nucleotide that results in an increase in T_m 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 nucleotide. The oligonucleotide may have a plurality of modified nucleotides that result in a total increase in T_m 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 nucleotide.

[000200] The oligonucleotide may comprise alternating nucleotides of different kinds. For example, an oligonucleotide may comprise alternating deoxyribonucleotides or ribonucleotides and 2'-fluoro-deoxyribonucleotides. An oligonucleotide may comprise alternating deoxyribonucleotides or ribonucleotides and 2'-O-methyl nucleotides. An oligonucleotide may comprise alternating 2'-fluoro nucleotides and 2'-O-methyl nucleotides. An oligonucleotide may comprise alternating bridged nucleotides and 2'-fluoro or 2'-O-methyl nucleotides.

d. Internucleotide Linkages / Backbones

[000201] In some embodiments, oligonucleotide may contain a phosphorothioate or other modified internucleotide linkage. In some embodiments, the oligonucleotide comprises phosphorothioate internucleoside linkages. In some embodiments, the oligonucleotide comprises phosphorothioate internucleoside linkages between at least two nucleotides. In some

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embodiments, the oligonucleotide comprises phosphorothioate internucleoside linkages between all nucleotides. For example, in some embodiments, oligonucleotides comprise modified internucleotide linkages at the first, second, and/or third internucleoside linkage at the 5' or 3' end of the nucleotide sequence.

[000202] 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.

[000203] 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

[000204] 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

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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

[000205] 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)

[000206] 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.

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h. Gapmers

[000207] In some embodiments, the oligonucleotide is a gapmer. A gapmer oligonucleotide generally has the formula 5'-X-Y-Z-3', with X and Z as flanking regions around a gap region Y. In some embodiments, the Y region is a contiguous stretch of nucleotides, e.g., a region of at least 6 DNA nucleotides, which are capable of recruiting an RNase, such as RNase H. In some embodiments, the gapmer binds to the target nucleic acid, at which point an RNase is recruited and can then cleave the target nucleic acid. In some embodiments, the Y region is flanked both 5' and 3' by regions X and Z comprising high-affinity modified nucleotides, e.g., one to six modified nucleotides. Examples of modified nucleotides include, but are not limited to, 2' MOE or 2'OMe or Locked Nucleic Acid bases (LNA). The flanking sequences X and Z may be of one to twenty nucleotides, one to eight nucleotides or one to five nucleotides in length, in some embodiments. The flanking sequences X and Z may be of similar length or of dissimilar lengths. The gap-segment Y may be a nucleotide sequence of five to twenty nucleotides, size to twelve nucleotides or six to ten nucleotides in length, in some embodiments.

[000208] In some embodiments, the gap region of the gapmer oligonucleotides may contain modified nucleotides known to be acceptable for efficient RNase H action in addition to DNA nucleotides, such as C4'-substituted nucleotides, acyclic nucleotides, and arabino-configured nucleotides. In some embodiments, the gap region comprises one or more unmodified internucleosides. In some embodiments, one or both flanking regions each independently comprise one or more phosphorothioate 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 nucleotides. In some embodiments, the gap region and two flanking regions each independently comprise 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 nucleotides.

[000209] A gapmer may be produced using appropriate methods. Representative U.S. patents, U.S. patent publications, and PCT publications that teach the preparation of gapmers include, but are not limited to, U.S. Pat. Nos. 5,013,830; 5,149,797; 5,220,007; 5,256,775; 5,366,878; 5,403,711; 5,491,133; 5,565,350; 5,623,065; 5,652,355; 5,652,356; 5,700,922; 5,898,031; 7,432,250; and 7,683,036; U.S. patent publication Nos. US20090286969,

US20100197762, and US20110112170; and PCT publication Nos. WO2008049085 and WO2009090182, each of which is herein incorporated by reference in its entirety.

i. Mixmers

[000210] 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 nucleotides or comprise two different types of non-naturally occurring nucleotides 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.

[000211] In some embodiments, the mixmer comprises or consists of a repeating pattern of nucleotide analogues and naturally occurring nucleotides, or one type of nucleotide analogue and a second type of nucleotide analogue. However, a mixmer need not comprise a repeating pattern and may instead comprise any arrangement of modified nucleotides and naturally occurring nucleotides or any arrangement of one type of modified nucleotide and a second type of modified nucleotide. The repeating pattern, may, for instance be every second or every third nucleotide is a modified nucleotide, such as LNA, and the remaining nucleotides are naturally occurring nucleotides, such as DNA, or are a 2' substituted nucleotide analogue such as 2'MOE or 2' fluoro analogues, or any other modified nucleotide described herein. It is recognized that the repeating pattern of modified nucleotide, such as LNA units, may be combined with modified nucleotide at fixed positions—e.g. at the 5' or 3' termini.

[000212] 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 nucleotides, such as DNA nucleotides. In some embodiments, the mixmer comprises at least a region consisting of at least two consecutive modified nucleotide, such as at least two consecutive LNAs. In some embodiments, the mixmer comprises at least a region consisting of at least three consecutive modified nucleotide units, such as at least three consecutive LNAs.

[000213] 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 nucleotide

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analogues, such as LNAs. In some embodiments, LNA units may be replaced with other nucleotide analogues, such as those referred to herein.

[000214] Mixmers may be designed to comprise a mixture of affinity enhancing modified nucleotides, such as in non-limiting example LNA nucleotides and 2'-O-methyl nucleotides. 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 nucleotides.

[000215] 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.

j. RNA Interference (RNAi)

[000216] In some embodiments, oligonucleotides provided herein may be in the form of small interfering RNAs (siRNA), also known as short interfering RNA or silencing RNA. SiRNA, is a class of double-stranded RNA molecules, typically about 20-25 base pairs in length that target nucleic acids (e.g., mRNAs) for degradation via the RNA interference (RNAi) pathway in cells. Specificity of siRNA molecules may be determined by the binding of the antisense strand of the molecule to its target RNA. Effective siRNA molecules are generally less than 30 to 35 base pairs in length to prevent the triggering of non-specific RNA interference pathways in the cell via the interferon response, although longer siRNA can also be effective.

[000217] Following selection of an appropriate target RNA sequence, siRNA molecules that comprise a nucleotide sequence complementary to all or a portion of the target sequence, i.e. an antisense sequence, can be designed and prepared using appropriate methods (see, e.g., PCT Publication Number WO 2004/016735; and U.S. Patent Publication Nos. 2004/0077574 and 2008/0081791).

[000218] The siRNA molecule can be double stranded (i.e. a dsRNA molecule comprising an antisense strand and a complementary sense strand) or single-stranded (i.e. a ssRNA molecule comprising just an antisense strand). The siRNA molecules can comprise a duplex, asymmetric duplex, hairpin or asymmetric hairpin secondary structure, having self-complementary sense and antisense strands.

[000219] Double-stranded siRNA may comprise RNA strands that are the same length or different lengths. Double-stranded siRNA molecules can also be assembled from a single

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oligonucleotide in a stem-loop structure, wherein self-complementary sense and antisense regions of the siRNA molecule are linked by means of a nucleic acid based or non-nucleic acid-based linker(s), as well as circular single-stranded RNA having two or more loop structures and a stem comprising self-complementary sense and antisense strands, wherein the circular RNA can be processed either in vivo or in vitro to generate an active siRNA molecule capable of mediating RNAi. Small hairpin RNA (shRNA) molecules thus are also contemplated herein. These molecules comprise a specific antisense sequence in addition to the reverse complement (sense) sequence, typically separated by a spacer or loop sequence. Cleavage of the spacer or loop provides a single-stranded RNA molecule and its reverse complement, such that they may anneal to form a dsRNA molecule (optionally with additional processing steps that may result in addition or removal of one, two, three or more nucleotides from the 3' end and/or the 5' end of either or both strands). A spacer can be of a sufficient length to permit the antisense and sense sequences to anneal and form a double-stranded structure (or stem) prior to cleavage of the spacer (and, optionally, subsequent processing steps that may result in addition or removal of one, two, three, four, or more nucleotides from the 3' end and/or the 5' end of either or both strands). A spacer sequence may be an unrelated nucleotide sequence that is situated between two complementary nucleotide sequence regions which, when annealed into a double-stranded nucleic acid, comprise a shRNA.

[000220] The overall length of the siRNA molecules can vary from about 14 to about 100 nucleotides depending on the type of siRNA molecule being designed. Generally between about 14 and about 50 of these nucleotides are complementary to the RNA target sequence, i.e. constitute the specific antisense sequence of the siRNA molecule. For example, when the siRNA is a double- or single-stranded siRNA, the length can vary from about 14 to about 50 nucleotides, whereas when the siRNA is a shRNA or circular molecule, the length can vary from about 40 nucleotides to about 100 nucleotides.

[000221] An siRNA molecule may comprise a 3' overhang at one end of the molecule, The other end may be blunt-ended or have also an overhang (5' or 3'). When the siRNA molecule comprises an overhang at both ends of the molecule, the length of the overhangs may be the same or different. In one embodiment, the siRNA molecule of the present disclosure comprises 3' overhangs of about 1 to about 3 nucleotides on both ends of the molecule.

k. microRNA (miRNAs)

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[000222] In some embodiments, an oligonucleotide may be a microRNA (miRNA). MicroRNAs (referred to as “miRNAs”) are small non-coding RNAs, belonging to a class of regulatory molecules that control gene expression by binding to complementary sites on a target RNA transcript. Typically, miRNAs are generated from large RNA precursors (termed pri-miRNAs) that are processed in the nucleus into approximately 70 nucleotide pre-miRNAs, which fold into imperfect stem-loop structures. These pre-miRNAs typically undergo an additional processing step within the cytoplasm where mature miRNAs of 18-25 nucleotides in length are excised from one side of the pre-miRNA hairpin by an RNase III enzyme, Dicer.

[000223] As used herein, miRNAs including pri-miRNA, pre-miRNA, mature miRNA or fragments of variants thereof that retain the biological activity of mature miRNA. In one embodiment, the size range of the miRNA can be from 21 nucleotides to 170 nucleotides. In one embodiment the size range of the miRNA is from 70 to 170 nucleotides in length. In another embodiment, mature miRNAs of from 21 to 25 nucleotides in length can be used.

l. Aptamers

[000224] In some embodiments, oligonucleotides provided herein may be in the form of aptamers. Generally, in the context of molecular payloads, aptamer is any nucleic acid that binds specifically to a target, such as a small molecule, protein, nucleic acid in a cell. In some embodiments, the aptamer is a DNA aptamer or an RNA aptamer. In some embodiments, a nucleic acid aptamer is a single-stranded DNA or RNA (ssDNA or ssRNA). It is to be understood that a single-stranded nucleic acid aptamer may form helices and/or loop structures. The nucleic acid that forms the nucleic acid aptamer may comprise naturally occurring nucleotides, modified nucleotides, naturally occurring nucleotides with hydrocarbon linkers (e.g., an alkylene) or a polyether linker (e.g., a PEG linker) inserted between one or more nucleotides, modified nucleotides with hydrocarbon or PEG linkers inserted between one or more nucleotides, or a combination of thereof. Exemplary publications and patents describing aptamers and method of producing aptamers include, e.g., Lorsch and Szostak, 1996; Jayasena, 1999; U.S. Pat. Nos. 5,270,163; 5,567,588; 5,650,275; 5,670,637; 5,683,867; 5,696,249; 5,789,157; 5,843,653; 5,864,026; 5,989,823; 6,569,630; 8,318,438 and PCT application WO 99/31275, each incorporated herein by reference.

m. Ribozymes

[000225] In some embodiments, oligonucleotides provided herein may be in the form of a ribozyme. A ribozyme (ribonucleic acid enzyme) is a molecule, typically an RNA molecule, that

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is capable of performing specific biochemical reactions, similar to the action of protein enzymes. Ribozymes are molecules with catalytic activities including the ability to cleave at specific phosphodiester linkages in RNA molecules to which they have hybridized, such as mRNAs, RNA-containing substrates, lncRNAs, and ribozymes, themselves.

[000226] Ribozymes may assume one of several physical structures, one of which is called a "hammerhead." A hammerhead ribozyme is composed of a catalytic core containing nine conserved bases, a double-stranded stem and loop structure (stem-loop II), and two regions complementary to the target RNA flanking regions the catalytic core. The flanking regions enable the ribozyme to bind to the target RNA specifically by forming double-stranded stems I and III. Cleavage occurs in cis (i.e., cleavage of the same RNA molecule that contains the hammerhead motif) or in trans (cleavage of an RNA substrate other than that containing the ribozyme) next to a specific ribonucleotide triplet by a transesterification reaction from a 3', 5'-phosphate diester to a 2', 3'-cyclic phosphate diester. Without wishing to be bound by theory, it is believed that this catalytic activity requires the presence of specific, highly conserved sequences in the catalytic region of the ribozyme.

[000227] Modifications in ribozyme structure have also included the substitution or replacement of various non-core portions of the molecule with non-nucleotidic molecules. For example, Benseler et al. (J. Am. Chem. Soc. (1993) 115:8483-8484) disclosed hammerhead-like molecules in which two of the base pairs of stem II, and all four of the nucleotides of loop II were replaced with non-nucleoside linkers based on hexaethylene glycol, propanediol, bis(triethylene glycol) phosphate, tris(propanediol)bisphosphate, or bis(propanediol) phosphate. Ma et al. (Biochem. (1993) 32:1751-1758; Nucleic Acids Res. (1993) 21:2585-2589) replaced the six nucleotide loop of the TAR ribozyme hairpin with non-nucleotidic, ethylene glycol-related linkers. Thomson et al. (Nucleic Acids Res. (1993) 21:5600-5603) replaced loop II with linear, non-nucleotidic linkers of 13, 17, and 19 atoms in length.

[000228] Ribozyme oligonucleotides can be prepared using well known methods (see, e.g., PCT Publications WO9118624; WO9413688; WO9201806; and WO 92/07065; and U.S. Patents 5436143 and 5650502) or can be purchased from commercial sources (e.g., US Biochemicals) and, if desired, can incorporate nucleotide analogs to increase the resistance of the oligonucleotide to degradation by nucleases in a cell. The ribozyme may be synthesized in any known manner, e.g., by use of a commercially available synthesizer produced, e.g., by Applied Biosystems, Inc. or Milligen. The ribozyme may also be produced in recombinant

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vectors by conventional means. See, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory (Current edition). The ribozyme RNA sequences may be synthesized conventionally, for example, by using RNA polymerases such as T7 or SP6.

n. Guide Nucleic Acids

[000229] In some embodiments, oligonucleotides are guide nucleic acid, e.g., guide RNA (gRNA) molecules. Generally, a guide RNA is a short synthetic RNA composed of (1) a scaffold sequence that binds to a nucleic acid programmable DNA binding protein (napDNAbp), such as Cas9, and (2) a nucleotide spacer portion that defines the DNA target sequence (e.g., genomic DNA target) to which the gRNA binds in order to bring the nucleic acid programmable DNA binding protein in proximity to the DNA target sequence. In some embodiments, the napDNAbp is a nucleic acid-programmable protein that forms a complex with (e.g., binds or associates with) one or more RNA(s) that targets the nucleic acid-programmable protein to a target DNA sequence (e.g., a target genomic DNA sequence). In some embodiments, a nucleic acid-programmable nuclease, when in a complex with an RNA, may be referred to as a nuclease:RNA complex. Guide RNAs can exist as a complex of two or more RNAs, or as a single RNA molecule.

[000230] Guide RNAs (gRNAs) that exist as a single RNA molecule may be referred to as single-guide RNAs (sgRNAs), though gRNA is also used to refer to guide RNAs that exist as either single molecules or as a complex of two or more molecules. Typically, gRNAs that exist as a single RNA species comprise two domains: (1) a domain that shares homology to a target nucleic acid (i.e., directs binding of a Cas9 complex to the target); and (2) a domain that binds a Cas9 protein. In some embodiments, domain (2) corresponds to a sequence known as a tracrRNA and comprises a stem-loop structure. In some embodiments, domain (2) is identical or homologous to a tracrRNA as provided in Jinek et al., *Science* 337:816-821 (2012), the entire contents of which is incorporated herein by reference.

[000231] In some embodiments, a gRNA comprises two or more of domains (1) and (2), and may be referred to as an extended gRNA. For example, an extended gRNA will bind two or more Cas9 proteins and bind a target nucleic acid at two or more distinct regions, as described herein. The gRNA comprises a nucleotide sequence that complements a target site, which mediates binding of the nuclease:RNA complex to said target site, providing the sequence specificity of the nuclease:RNA complex. In some embodiments, the RNA-programmable nuclease is the (CRISPR-associated system) Cas9 endonuclease, for example, Cas9 (Csn1) from

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Streptococcus pyogenes (see, e.g., “Complete genome sequence of an M1 strain of *Streptococcus pyogenes*.” Ferretti J.J., McShan W.M., Ajdic D.J., Savic D.J., Savic G., Lyon K., Primeaux C., Sezate S., Suvorov A.N., Kenton S., Lai H.S., Lin S.P., Qian Y., Jia H.G., Najar F.Z., Ren Q., Zhu H., Song L., White J., Yuan X., Clifton S.W., Roe B.A., McLaughlin R.E., Proc. Natl. Acad. Sci. U.S.A. 98:4658-4663 (2001); “CRISPR RNA maturation by trans-encoded small RNA and host factor RNase III.” Deltcheva E., Chylinski K., Sharma C.M., Gonzales K., Chao Y., Pirzada Z.A., Eckert M.R., Vogel J., Charpentier E., Nature 471:602-607 (2011); and “A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity.” Jinek M., Chylinski K., Fonfara I., Hauer M., Doudna J.A., Charpentier E. Science 337:816-821 (2012), the entire contents of each of which are incorporated herein by reference.

o. Multimers

[000232] 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/conjugate 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).

[000233] 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.

[000234] 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.

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[000235] 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.

ii. Small Molecules:

[000236] Any suitable small molecule may be used as a molecular payload, as described herein. In some embodiments, the small molecule is as described in US Patent Application Publication 2016052914A1, published on February 25, 2016, entitled “*Compounds And Methods For Myotonic Dystrophy Therapy*”. Further examples of small molecule payloads are provided in Lopez-Morato M, et al., Small Molecules Which Improve Pathogenesis of Myotonic Dystrophy Type 1, (Review) Front. Neurol., 18 May 2018. For example, in some embodiments, the small molecule is an MBNL1 upregulator such as phenylbuthazone, ketoprofen, ISOX, or vorinostat. In some embodiments, the small molecule is an H-Ras pathway inhibitor such as manumycin A. In some embodiments, the small molecule is a protein kinase modulator such as Ro-318220, C16, C51, Metformin, AICAR, lithium chloride, TDZD-8 or Bio. In some embodiments, the small molecule is a plant alkaloid such as harmine. In some embodiments, the small molecule is a transcription inhibitor such as pentamidine, propamidine, heptamidiine or actinomycin D. In some embodiments, the small molecule is an inhibitor of Glycogen synthase kinase 3 beta (GSK3B), for example, as disclosed in Jones K, et al., GSK3 β mediates muscle pathology in myotonic dystrophy. J Clin Invest. 2012 Dec;122(12):4461-72; and Wei C, et al., GSK3 β is a new therapeutic target for myotonic dystrophy type 1. Rare Dis. 2013; 1: e26555; and Palomo V, et al., Subtly Modulating Glycogen Synthase Kinase 3 β : Allosteric Inhibitor Development and Their Potential for the Treatment of Chronic Diseases. J Med Chem. 2017 Jun 22;60(12):4983-5001, the contents of each of which are incorporated herein by reference in their entireties. In some embodiments, the small molecule is a substituted pyrido[2,3-d]pyrimidines

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and pentamidine-like compound, as disclosed in Gonzalez AL, et al., In silico discovery of substituted pyrido[2,3-d]pyrimidines and pentamidine-like compounds with biological activity in myotonic dystrophy models. PLoS One. 2017 Jun 5;12(6):e0178931, the contents of which are incorporated herein by reference in its entirety. In some embodiments, the small molecule is an MBNL1 modulator, for example, as disclosed in: Zhange F, et al., A flow cytometry-based screen identifies MBNL1 modulators that rescue splicing defects in myotonic dystrophy type I. Hum Mol Genet. 2017 Aug 15;26(16):3056-3068, the contents of which are incorporated herein by reference in its entirety.

iii. Peptides

[000237] Any suitable peptide or protein may be used as a molecular payload, as described herein. A peptide or protein payload may correspond to a sequence of a protein that preferentially binds to a nucleic acid, *e.g.* a disease-associated repeat, or a protein, *e.g.* MBNL1, found in muscle cells. In some embodiments, peptides or proteins may be produced, synthesized, and/or derivatized using 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.).

[000238] In some embodiments, the peptide is as described in US Patent Application 2018/0021449, published on 1/25/2018, "Antisense conjugates for decreasing expression of DMPK". In some embodiments, the peptide is as described in Garcia-Lopez et al., "*In vivo* discovery of a peptide that prevents CUG–RNA hairpin formation and reverses RNA toxicity in myotonic dystrophy models", PNAS July 19, 2011. 108 (29) 11866-11871. In some embodiments, the peptide or protein may target, *e.g.*, bind to, a disease-associated repeat, *e.g.* a RNA CUG repeat expansion.

[000239] In some embodiments, the peptide or protein comprises a fragment of an MBNL protein, *e.g.*, MBNL1. In some embodiments, the peptide or protein comprises at least one zinc finger. In some embodiments, the peptide or protein 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. The peptide or protein may comprise naturally-occurring amino acids, *e.g.* cysteine,

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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, the peptide may be linear; in other embodiments, the peptide may be cyclic, e.g. bicyclic.

iv. Nucleic Acid Constructs

[000240] Any suitable gene expression construct may be used as a molecular payload, as described herein. In some embodiments, a gene expression construct may be a vector or a cDNA fragment. In some embodiments, a gene expression construct may be messenger RNA (mRNA). In some embodiments, a mRNA used herein may be a modified mRNA, e.g., as described in US Patent 8,710,200, issued on April 24, 2014, entitled “*Engineered nucleic acids encoding a modified erythropoietin and their expression*”. In some embodiments, a mRNA may comprise a 5' methyl cap. In some embodiments, a mRNA may comprise a polyA tail, optionally of up to 160 nucleotides in length. A gene expression construct may encode a sequence of a protein that preferentially binds to a nucleic acid, e.g. a disease-associated repeat, or a protein, e.g. MBNL1, found in muscle cells. In some embodiments, the gene expression construct may be expressed, e.g., overexpressed, within the nucleus of a muscle cell. In some embodiments, the gene expression construct encodes a MBNL protein, e.g., MBNL1. In some embodiments, the gene expression constructs encodes a protein that comprises at least one zinc finger. In some embodiments, the gene expression construct encodes a protein that binds to a disease-associated repeat. In some embodiments, the gene expression construct encodes a protein that leads to a reduction in the expression of a disease-associated repeat. In some embodiments, the gene expression construct encodes a gene editing enzyme. Additional examples of nucleic acid constructs that may be used as molecular payloads are provided in International Patent Application Publication WO2017152149A1, published on September 19, 2017, entitled, “*Closed-Ended Linear Duplex Dna For Non-Viral Gene Transfer*”; US Patent 8,853,377B2, issued on October 7, 2014, entitled, “*mRNA For Use In Treatment Of Human Genetic Diseases*”; and US Patent US8822663B2, issued on September 2, 2014, *Engineered Nucleic Acids And Methods Of Use Thereof*,” the contents of each of which are incorporated herein by reference in their entirety.

C. Linkers

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[000241] Complexes described herein generally comprise a linker that connects a muscle-targeting agent 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 connects a muscle-targeting agent to a molecular payload. However, in some embodiments, a linker may connect a muscle-targeting agent to a molecular 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 generally stable *in vitro* and *in vivo*, and may be stable in certain cellular environments. Additionally, generally a linker does not negatively impact the functional properties of either the muscle-targeting agent 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.).

[000242] A precursor to a linker typically will contain two different reactive species that allow for attachment to both the muscle-targeting agent 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 is connected to a muscle-targeting agent via conjugation to a lysine residue or a cysteine residue of the muscle-targeting agent. In some embodiments, a linker is connected to a cysteine residue of a muscle-targeting agent 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 connected to a cysteine residue of a muscle-targeting agent or thiol functionalized molecular payload via a 3-arylpropionitrile functional group. In some embodiments, a linker is connected to a muscle-targeting agent and/or a molecular payload via an amide bond, a hydrazide, a triazole, a thioether, or a disulfide bond.

i. Cleavable Linkers

[000243] A cleavable linker may be a protease-sensitive linker, a pH-sensitive linker, or a glutathione-sensitive linker. These linkers are generally cleavable only intracellularly and are preferably stable in extracellular environments, e.g. extracellular to a muscle cell.

[000244] 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

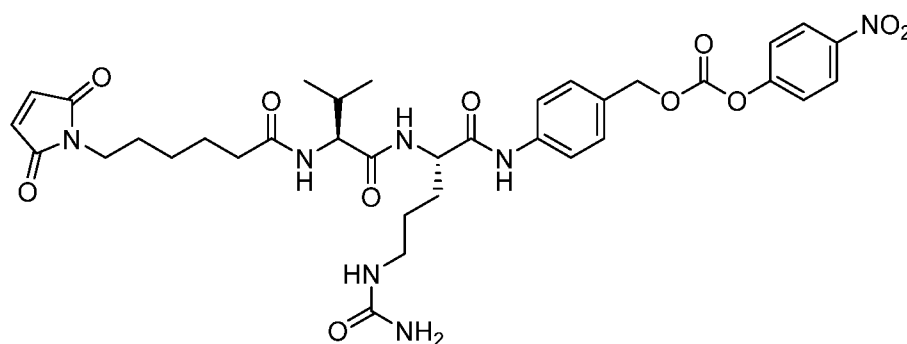
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acids, about 5-10 amino acids, about 10 amino acids, about 5 amino acids, about 3 amino acids, or about 2 amino acids in length. In some embodiments, a peptide sequence may comprise naturally-occurring amino acids, e.g. cysteine, alanine, or non-naturally-occurring 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 dipeptide sequence. In some embodiments, a protease-sensitive linker can be cleaved by a lysosomal protease, e.g. cathepsin B, and/or an endosomal protease.

[000245] 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.

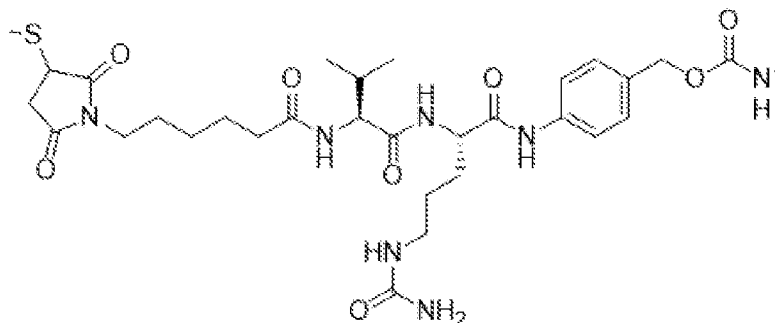
[000246] In some embodiments, a glutathione-sensitive linker comprises a disulfide moiety. In some embodiments, a glutathione-sensitive linker is cleaved by an disulfide exchange reaction with a glutathione species inside a cell. In some embodiments, the disulfide moiety further comprises at least one amino acid, e.g. a cysteine residue.

[000247] In some embodiments, the linker is a Val-cit linker (e.g., as described in US Patent 6,214,345, incorporated herein by reference). In some embodiments, before conjugation, the val-cit linker has a structure of:



[000248] In some embodiments, after conjugation, the val-cit linker has a structure of:

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[000249]

ii. Non-Cleavable Linkers

[000250] 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 will be utilized to covalently link a muscle-targeting agent 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.).

[000251] 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.

iii. Linker conjugation

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[000252] In some embodiments, a linker is connected to a muscle-targeting agent and/or molecular payload via a phosphate, thioether, ether, carbon-carbon, or amide bond. In some embodiments, a linker is connected to an oligonucleotide through a phosphate or phosphorothioate group, e.g. a terminal phosphate of an oligonucleotide backbone. In some embodiments, a linker is connected to an muscle-targeting agent, e.g. an antibody, through a lysine or cysteine residue present on the muscle-targeting agent

[000253] In some embodiments, a linker is connected to a muscle-targeting agent and/or molecular payload by a cycloaddition reaction between an azide and an alkyne to form a triazole, wherein the azide and the alkyne may be located on the muscle-targeting agent, 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 cyclooctane 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 $\beta(1,4)$ -N-Acetylgalactosaminyltransferase*”. In some embodiments, a cycloaddition reaction between an azide and an alkyne to form a triazole, wherein the azide and the alkyne may be located on the muscle-targeting agent, 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 $\beta(1,4)$ -N-Acetylgalactosaminyltransferase*”.

[000254] In some embodiments, a linker further comprises a spacer, e.g., a polyethylene glycol spacer or an acyl/carbomoyl sulfamide spacer, e.g., a HydraSpaceTM spacer. In some embodiments, a spacer is as described in Verkade, J.M.M. et al., “*A Polar Sulfamide Spacer*

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Significantly Enhances the Manufacturability, Stability, and Therapeutic Index of Antibody-Drug Conjugates", *Antibodies*, 2018, 7, 12.

[000255] In some embodiments, a linker is connected to a muscle-targeting agent and/or molecular payload by the Diels-Alder reaction between a dienophile and a diene/hetero-diene, wherein the dienophile and the diene/hetero-diene may be located on the muscle-targeting agent, molecular payload, or the linker. In some embodiments a linker is connected to a muscle-targeting agent and/or molecular payload by other pericyclic reactions, e.g. ene reaction. In some embodiments, a linker is connected to a muscle-targeting agent and/or molecular payload by an amide, thioamide, or sulfonamide bond reaction. In some embodiments, a linker is connected to a muscle-targeting agent and/or molecular payload by a condensation reaction to form an oxime, hydrazone, or semicarbazide group existing between the linker and the muscle-targeting agent and/or molecular payload.

[000256] In some embodiments, a linker is connected to a muscle-targeting agent and/or molecular payload by a conjugate addition reactions between a nucleophile, e.g. an amine or a hydroxyl group, and an electrophile, e.g. a carboxylic acid or an aldehyde. In some embodiments, a nucleophile may exist on a linker and an electrophile may exist on a muscle-targeting agent or molecular payload prior to a reaction between a linker and a muscle-targeting agent or molecular payload. In some embodiments, an electrophile may exist on a linker and a nucleophile may exist on a muscle-targeting agent or molecular payload prior to a reaction between a linker and a muscle-targeting agent or molecular payload. In some embodiments, an electrophile may be an azide, 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, or a thiol group.

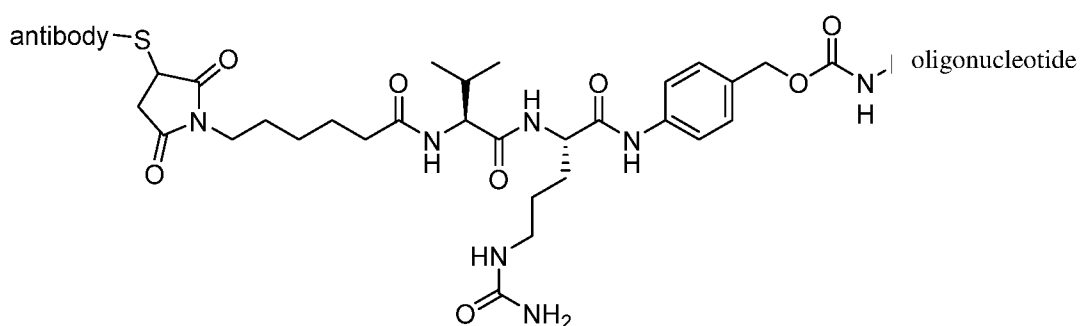
D. Examples of Antibody-Molecular Payload Complexes

[000257] Other aspects of the present disclosure provide complexes comprising any one the muscle targeting agent (e.g., a transferrin receptor antibodies) described herein covalently linked to any of the molecular payloads (e.g., an oligonucleotide) described herein. In some

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embodiments, the muscle targeting agent (e.g., a transferrin receptor antibody) is covalently linked to a molecular payload (e.g., an oligonucleotide) via a linker. Any of the linkers described herein may be used. In some embodiments, the linker is linked to the 5' end, the 3' end, or internally of the oligonucleotide. In some embodiments, the linker is linked to the antibody via a thiol-reactive linkage (e.g., via a cysteine in the antibody).

[000258] An exemplary structure of a complex comprising a transferrin receptor antibody covalently linked to an oligonucleotide via a Val-cit linker is provided below:



wherein the linker is linked to the 5' end, the 3' end, or internally of the oligonucleotide, and wherein the linker is linked to the antibody via a thiol-reactive linkage (e.g., via a cysteine in the antibody).

[000259] It should be appreciated that antibodies can be linked to oligonucleotides with different stoichiometries, a property that may be referred to as a drug to antibody ratios (DAR) with the “drug” being the oligonucleotide. In some embodiments, one oligonucleotide is linked to an antibody (DAR = 1). In some embodiments, two oligonucleotides are linked to an antibody (DAR = 2). In some embodiments, three oligonucleotides are linked to an antibody (DAR = 3). In some embodiments, four oligonucleotides 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. DAR may be increased by conjugating oligonucleotides to different sites on an antibody and/or by conjugating multimers to one or more sites on antibody. For example, a DAR of 2 may be achieved by conjugating a single oligonucleotide to two different sites on an antibody or by conjugating a dimer oligonucleotide to a single site of an antibody.

[000260] In some embodiments, the complex described herein comprises a transferrin receptor antibody (e.g., an antibody or any variant thereof as described herein) covalently linked to an oligonucleotide targeting DMPK (e.g., an oligonucleotide having a region of

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complementarity to a DMPK gene sequence as set forth in SEQ ID NO: 15 or SEQ ID NO: 16). In some embodiments, the complex described herein comprises a transferrin receptor antibody (e.g., an antibody or any variant thereof as described herein) covalently linked to an oligonucleotide targeting DMPK (e.g., an oligonucleotide having a region of complementarity to a DMPK gene sequence as set forth in SEQ ID NO: 15 or SEQ ID NO: 16) via a linker (e.g., a Val-cit linker). In some embodiments, the linker (e.g., a Val-cit linker) is linked to the 5' end, the 3' end, or internally of the nucleotide targeting DMPK (e.g., an oligonucleotide having a region of complementarity to a DMPK gene sequence as set forth in SEQ ID NO: 15 or SEQ ID NO: 16). In some embodiments, the linker (e.g., a Val-cit linker) is linked to the antibody (e.g., an antibody or any variant thereof as described herein) via a thiol-reactive linkage (e.g., via a cysteine in the antibody).

[000261] In some embodiments, the complex described herein comprises a transferrin receptor antibody covalently linked to a DMPK targeting oligonucleotide, wherein the transferrin receptor antibody 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 1.1; and 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 1.1.

[000262] In some embodiments, the complex described herein comprises a transferrin receptor antibody covalently linked to a DMPK targeting oligonucleotide, wherein the transferrin receptor antibody comprises a VH having the amino acid sequence of SEQ ID NO: 33 and a VL having the amino acid sequence of SEQ ID NO: 34. In some embodiments, the complex described herein comprises a transferrin receptor antibody covalently linked to a DMPK targeting oligonucleotide, wherein the transferrin receptor antibody comprises a VH having the amino acid sequence of SEQ ID NO: 35 and a VL having the amino acid sequence of SEQ ID NO: 36.

[000263] In some embodiments, the complex described herein comprises a transferrin receptor antibody covalently linked to a DMPK targeting oligonucleotide, wherein the transferrin receptor antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 39 and a light chain having the amino acid sequence of SEQ ID NO: 40. In some embodiments, the complex described herein comprises a transferrin receptor antibody covalently linked to a DMPK targeting oligonucleotide, wherein the transferrin receptor antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 41 and a light chain having the amino acid sequence of SEQ ID NO: 42.

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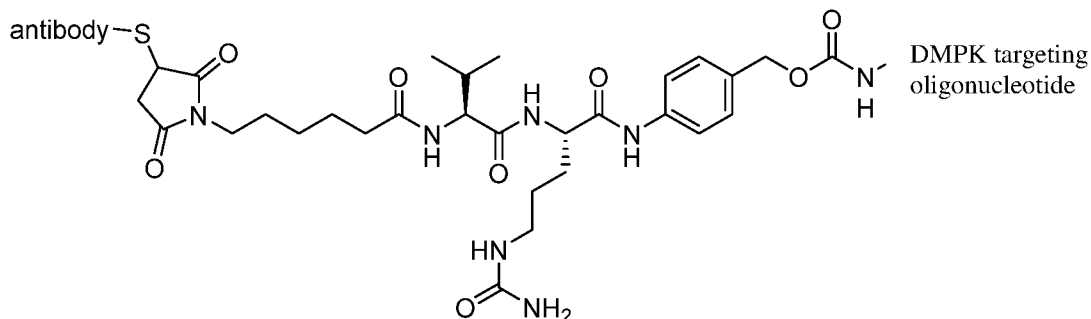
[000264] In some embodiments, the complex described herein comprises a transferrin receptor antibody covalently linked to a DMPK targeting oligonucleotide via a linker (e.g., a Val-cit linker), wherein the transferrin receptor antibody comprises a CDR-H1, a CDR-H2, and a CDR-H3 that are the same as the CDR-H1, CDR-H2, and CDR-H3 shown in Table 1.1; and 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 1.1.

[000265] In some embodiments, the complex described herein comprises a transferrin receptor antibody covalently linked to a DMPK targeting oligonucleotide via a linker (e.g., a Val-cit linker), wherein the transferrin receptor antibody comprises a VH having the amino acid sequence of SEQ ID NO: 33 and a VL having the amino acid sequence of SEQ ID NO: 34. In some embodiments, the complex described herein comprises a transferrin receptor antibody covalently linked to a DMPK targeting oligonucleotide via a linker (e.g., a Val-cit linker), wherein the transferrin receptor antibody comprises a VH having the amino acid sequence of SEQ ID NO: 35 and a VL having the amino acid sequence of SEQ ID NO: 36.

[000266] In some embodiments, the complex described herein comprises a transferrin receptor antibody covalently linked to a DMPK targeting oligonucleotide via a linker (e.g., a Val-cit linker), wherein the transferrin receptor antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 39 and a light chain having the amino acid sequence of SEQ ID NO: 40. In some embodiments, the complex described herein comprises a transferrin receptor antibody covalently linked to a DMPK targeting oligonucleotide via a linker (e.g., a Val-cit linker), wherein the transferrin receptor antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 41 and a light chain having the amino acid sequence of SEQ ID NO: 42.

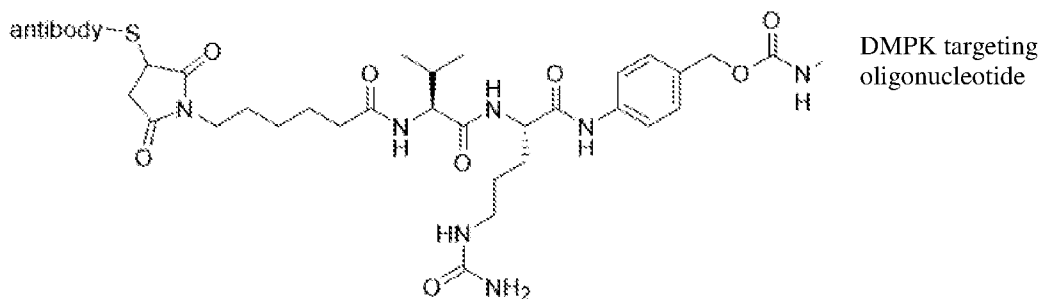
[000267] In some embodiments, the complex described herein comprises a transferrin receptor antibody covalently linked to a DMPK targeting oligonucleotide via a Val-cit linker, wherein the transferrin receptor antibody comprises a CDR-H1, a CDR-H2, and a CDR-H3 that are the same as the CDR-H1, CDR-H2, and CDR-H3 shown in Table 1.1; and 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 1.1, and wherein the complex comprises the structure of:

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wherein the linker Val-cit linker is linked to the 5' end, the 3' end, or internally of the DMPK targeting oligonucleotide, and wherein the Val-cit linker is linked to the antibody (e.g., an antibody or any variant thereof as described herein) via a thiol-reactive linkage (e.g., via a cysteine in the antibody).

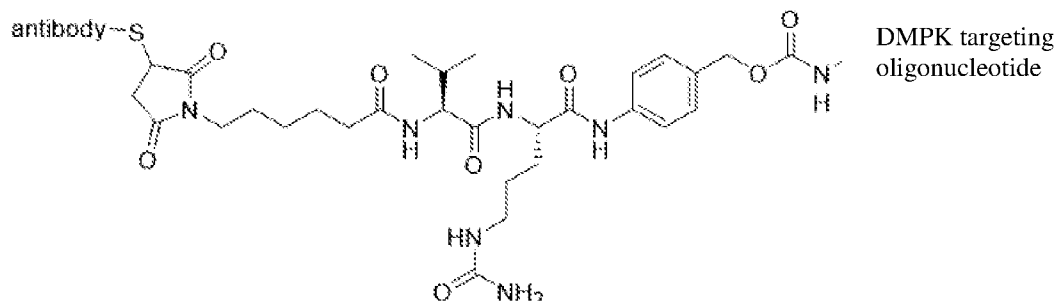
[000268] In some embodiments, the complex described herein comprises a transferrin receptor antibody covalently linked to a DMPK targeting oligonucleotide via a Val-cit linker, wherein the transferrin receptor antibody comprises a VH having the amino acid sequence of SEQ ID NO: 33 and a VL having the amino acid sequence of SEQ ID NO: 34, and wherein the complex comprises the structure of:



wherein the linker Val-cit linker is linked to the 5' end, the 3' end, or internally of DMPK targeting oligonucleotide, and wherein the Val-cit linker is linked to the antibody (e.g., an antibody or any variant thereof as described herein) via a thiol-reactive linkage (e.g., via a cysteine in the antibody).

[000269] In some embodiments, the complex described herein comprises a transferrin receptor antibody covalently linked to a DMPK targeting oligonucleotide via a Val-cit linker, wherein the transferrin receptor antibody comprises a VH having the amino acid sequence of SEQ ID NO: 35 and a VL having the amino acid sequence of SEQ ID NO: 36, and wherein the complex comprises the structure of:

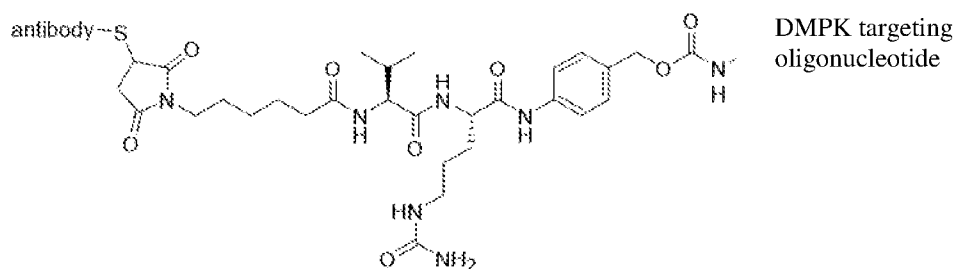
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wherein the linker Val-cit linker is linked to the 5' end, the 3' end, or internally of the DMPK targeting oligonucleotide, and wherein the Val-cit linker is linked to the antibody (e.g., an antibody or any variant thereof as described herein) via a thiol-reactive linkage (e.g., via a cysteine in the antibody).

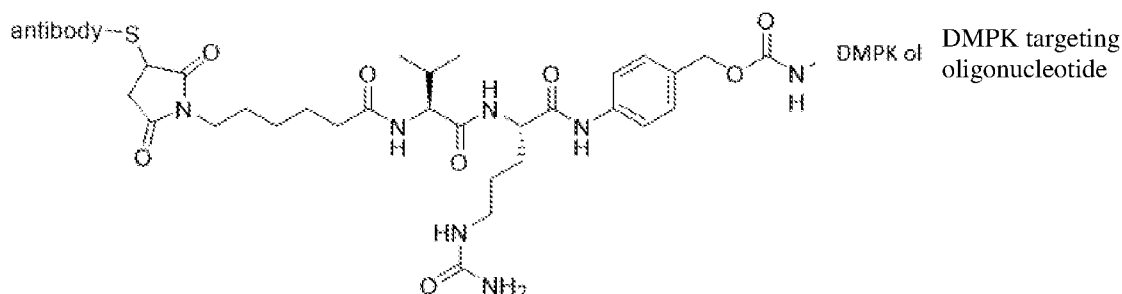
[000270] In some embodiments, the complex described herein comprises a transferrin receptor antibody covalently linked to a DMPK targeting oligonucleotide via a Val-cit linker, wherein the transferrin receptor antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 39 and a light chain having the amino acid sequence of SEQ ID NO: 40, and wherein the complex comprises the structure of:



wherein the linker Val-cit linker is linked to the 5' end, the 3' end, or internally of DMPK targeting oligonucleotide, and wherein the Val-cit linker is linked to the antibody (e.g., an antibody or any variant thereof as described herein) via a thiol-reactive linkage (e.g., via a cysteine in the antibody).

[000271] In some embodiments, the complex described herein comprises a transferrin receptor antibody covalently linked to a DMPK targeting oligonucleotide via a Val-cit linker, wherein the transferrin receptor antibody comprises a heavy chain having the amino acid sequence of SEQ ID NO: 41 and a light chain having the amino acid sequence of SEQ ID NO: 42, and wherein the complex comprises the structure of:

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wherein the linker Val-cit linker is linked to the 5' end, the 3' end, or internally of DMPK targeting oligonucleotide, and wherein the Val-cit linker is linked to the antibody (e.g., an antibody or any variant thereof as described herein) via a thiol-reactive linkage (e.g., via a cysteine in the antibody).

III. Formulations

[000272] 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 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.

[000273] 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).

[000274] 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 therapeutic enhancement of the active ingredient. In some embodiments, an excipient is a buffering agent (e.g., sodium

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citrate, sodium phosphate, a tris base, or sodium hydroxide) or a vehicle (*e.g.*, a buffered solution, petrolatum, dimethyl sulfoxide, or mineral oil).

[000275] 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 pyrrolidone), or a collapse temperature modifier (*e.g.*, dextran, ficoll, or gelatin).

[000276] 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.

[000277] 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 a complexes in a required amount in a selected solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization.

[000278] In some embodiments, a composition may contain at least about 0.1% of the a 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

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[000279] Complexes comprising a muscle-targeting agent covalently to a molecular payload as described herein are effective in treating myotonic dystrophy. In some embodiments, complexes are effective in treating myotonic dystrophy type 1 (DM1). In some embodiments, DM1 is associated with an expansion of a CTG trinucleotide repeat in the 3' non-coding region of DMPK. In some embodiments, the nucleotide expansions lead to toxic RNA repeats capable of forming hairpin structures that bind critical intracellular proteins, e.g., muscleblind-like proteins, with high affinity.

[000280] 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 myotonic dystrophy. In some embodiments, a subject has a DMPK allele, which may optionally contain a disease-associated repeat. In some embodiments, a subject may have a DMPK allele with an expanded disease-associated-repeat that comprises about 2-10 repeat units, about 2-50 repeat units, about 2-100 repeat units, about 50-1,000 repeat units, about 50-500 repeat units, about 50-250 repeat units, about 50-100 repeat units, about 500-10,000 repeat units, about 500-5,000 repeat units, about 500-2,500 repeat units, about 500-1,000 repeat units, or about 1,000-10,000 repeat units. In some embodiments, a subject is suffering from symptoms of DM1, e.g. muscle atrophy or muscle loss. In some embodiments, a subject is not suffering from symptoms of DM1. In some embodiments, subjects have congenital myotonic dystrophy.

[000281] An aspect of the disclosure includes a 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 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, intravenous 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.

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[000282] Compositions for intravenous administration may contain various carriers such as vegetable oils, dimethylactamide, dimethylformamide, 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.

[000283] In some embodiments, a pharmaceutical composition that comprises a complex comprising a muscle-targeting agent covalently 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.

[000284] In some embodiments, a pharmaceutical composition that comprises a complex comprising a muscle-targeting agent covalently 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.

[000285] 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.

[000286] Generally, for administration of any of the complexes described herein, an initial candidate dosage may be about 1 to 100 mg/kg, or more, depending on the factors described above, e.g. safety or efficacy. In some embodiments, a treatment will be administered once. In

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some embodiments, a treatment will be administered daily, biweekly, weekly, bimonthly, monthly, or at any time interval that provide maximum efficacy while minimizing safety risks to the subject. Generally, the efficacy and the treatment and safety risks may be monitored throughout the course of treatment

[000287] 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 DM1, 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.

[000288] In some embodiments, a pharmaceutical composition that comprises a complex comprising a muscle-targeting agent covalently to a molecular payload described herein is administered to a subject at an effective concentration sufficient to inhibit 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.

[000289] In some embodiments, a single dose or administration of a pharmaceutical composition that comprises a complex comprising a muscle-targeting agent covalently to a molecular payload described herein to a subject is sufficient to inhibit activity or expression of a target gene for at least 1-5, 1-10, 5-15, 10-20, 15-30, 20-40, 25-50, or more days. In some embodiments, a single dose or administration of a pharmaceutical composition that comprises a complex comprising a muscle-targeting agent covalently to a molecular payload described herein to a subject is sufficient to inhibit activity or expression of a target gene for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 weeks. In some embodiments, a single dose or administration of a pharmaceutical composition that comprises a complex comprising a muscle-targeting agent covalently to a molecular payload described herein to a subject is sufficient to inhibit activity or expression of a target gene for at least 1, 2, 3, 4, 5, or 6 months.

[000290] In some embodiments, a pharmaceutical composition may comprises more than one complex comprising a muscle-targeting agent covalently to a molecular payload. In some embodiments, a pharmaceutical composition may further comprise any other suitable therapeutic agent for treatment of a subject, e.g. a human subject having DM1. In some embodiments, the other therapeutic agents may enhance or supplement the effectiveness of the complexes

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described herein. In some embodiments, the other therapeutic agents may function to treat a different symptom or disease than the complexes described herein.

EXAMPLES

Example 1: Targeting DMPK with transfected antisense oligonucleotides

[000291] A gapmer antisense oligonucleotide that targets both wild-type and mutant alleles of DMPK (DTX-P-060) was tested *in vitro* for its ability to reduce expression levels of DMPK in an immortalized cell line. Briefly, Hepa 1-6 cells were transfected with the DTX-P-060 (100 nM) formulated with lipofectamine 2000. DMPK expression levels were evaluated 72 hours following transfection. A control experiment was also performed in which vehicle (phosphate-buffered saline) was delivered to Hepa 1-6 cells in culture and the cells were maintained for 72 hours. As shown in FIG. 1, it was found that the DTX-P-060 reduced DMPK expression levels by ~90% compared with controls.

Example 2: Targeting DMPK with a muscle-targeting complex

[000292] A muscle-targeting complex was generated comprising the DMPK ASO used in Example 1 (DTX-P-060) covalently linked, via a cathepsin cleavable linker, to DTX-A-002 (RI7 217 (Fab)), an anti-transferrin receptor antibody.

[000293] Briefly, a maleimidocaproyl-L-valine-L-citrulline-p-aminobenzyl alcohol p-nitrophenyl carbonate (MC-Val-Cit-PABC-PNP) linker molecule was coupled to NH₂-C₆-DTX-P-060 using an amide coupling reaction. Excess linker and organic solvents were removed by gel permeation chromatography. The purified Val-Cit-linker-DTX-P-060 was then coupled to a thiol-reactive anti-transferrin receptor antibody (DTX-A-002).

[000294] The product of the antibody coupling reaction was then subjected to hydrophobic interaction chromatography (HIC-HPLC). FIG. 2A shows a resulting HIC-HPLC chromatogram, in which fractions B7-C2 of the chromatogram (denoted by vertical lines) contained antibody-oligonucleotide complexes (referred to as DTX-C-008) comprising one or two DMPK ASO molecules covalently attached to DTX-A-002, as determined by SDS-PAGE. These HIC-HPLC fractions were combined and densitometry confirmed that this sample of DTX-C-008 complexes had an average ASO to antibody ratio of 1.48. SDS-PAGE analysis demonstrated that 86.4% of this sample of DTX-C-008 complexes comprised DTX-A-002 linked to either one or two DMPK ASO molecules (FIG. 2B).

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[000295] Using the same methods as described above, a control complex was generated comprising the DMPK ASO used in Example 1 (DTX-P-060) covalently linked via a Val-Cit linker to an IgG2a (Fab) antibody (DTX-C-007).

[000296] The purified DTX-C-008 was then tested for cellular internalization and inhibition of DMPK. Hepa 1-6 cells, which have relatively high expression levels of transferrin receptor, were incubated in the presence of vehicle control, DTX-C-008 (100 nM), or DTX-C-007 (100 nM) for 72 hours. After the 72 hour incubation, the cells were isolated and assayed for expression levels of DMPK (FIG. 3). Cells treated with the DTX-C-008 demonstrated a reduction in DMPK expression by ~65% relative to the cells treated with the vehicle control. Meanwhile, cells treated with the DTX-C-007 had DMPK expression levels comparable to the vehicle control (no reduction in DMPK expression). These data indicate that the anti-transferrin receptor antibody of the DTX-C-008 enabled cellular internalization of the complex, thereby allowing the DMPK ASO to inhibit expression of DMPK.

Example 3: Targeting DMPK in mouse muscle tissues with a muscle-targeting complex

[000297] The muscle-targeting complex described in Example 2, DTX-C-008, was tested for inhibition of DMPK in mouse tissues. C57BL/6 wild-type mice were intravenously injected with a single dose of a vehicle control, DTX-P-060 (3 mg/kg of RNA), DTX-C-008 (3 mg/kg of RNA, corresponding to 20 mg/kg antibody conjugate), or DTX-C-007 (3 mg/kg of RNA, corresponding to 20 mg/kg antibody conjugate). DTX-P-060, the DMPK ASO as described in Example 1, was used as a control. Each experimental condition was replicated in three individual C57BL/6 wild-type mice. Following a seven-day period after injection, the mice were euthanized and segmented into isolated tissue types. Individual tissue samples were subsequently assayed for expression levels of DMPK (FIGs. 4A-4E and 5A-5B).

[000298] Mice treated with the DTX-C-008 complex demonstrated a reduction in DMPK expression in a variety of skeletal, cardiac, and smooth muscle tissues. For example, as shown in FIGs 4A-4E, DMPK expression levels were significantly reduced in gastrocnemius (50% reduction), heart (30% reduction), esophagus (45% reduction), tibialis anterior (47% reduction), and soleus (31% reduction) tissues, relative to the mice treated with the vehicle control. Meanwhile, mice treated with the DTX-C-007 complex had DMPK expression levels comparable to the vehicle control (no reduction in DMPK expression) for all assayed muscle tissue types.

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[000299] Mice treated with the DTX-C-008 complex demonstrated no change in DMPK expression in non-muscle tissues such as spleen and brain tissues (FIGs. 5A and 5B).

[000300] These data indicate that the anti-transferrin receptor antibody of the DTX-C-008 enabled cellular internalization of the complex into muscle-specific tissues in an *in vivo* mouse model, thereby allowing the DMPK ASO to inhibit expression of DMPK. These data further demonstrate that the DTX-C-008 complex is capable of specifically targeting muscle tissues.

Example 4: Targeting DMPK in mouse muscle tissues with a muscle-targeting complex

[000301] The muscle-targeting complex described in Example 2, DTX-C-008, was tested for dose-dependent inhibition of DMPK in mouse tissues. C57BL/6 wild-type mice were intravenously injected with a single dose of a vehicle control (phosphate-buffered saline, PBS), DTX-P-060 (10 mg/kg of RNA), DTX-C-008 (3 mg/kg or 10 mg/kg of RNA, wherein 3 mg/kg corresponds to 20 mg/kg antibody conjugate), or DTX-C-007 (3 mg/kg or 10 mg/kg of RNA, wherein 3 mg/kg corresponds to 20 mg/kg antibody conjugate). DTX-P-060, the DMPK ASO as described in Example 1, was used as a control. Each experimental condition was replicated in five individual C57BL/6 wild-type mice. Following a seven-day period after injection, the mice were euthanized and segmented into isolated tissue types. Individual tissue samples were subsequently assayed for expression levels of DMPK (FIGs. 6A-6F).

[000302] Mice treated with the DTX-C-008 complex demonstrated a reduction in DMPK expression in a variety of skeletal muscle tissues. As shown in FIGs 6A-6F, DMPK expression levels were significantly reduced in tibialis anterior (58% and 75% reduction for 3 mg/kg and 10 mg/kg DTX-C-008, respectively), soleus (55% and 66% reduction for 3 mg/kg and 10 mg/kg DTX-C-008, respectively), extensor digitorum longus (EDL) (52% and 72% reduction for 3 mg/kg and 10 mg/kg DTX-C-008, respectively), gastrocnemius (55% and 77% reduction for 3 mg/kg and 10 mg/kg DTX-C-008, respectively), heart (19% and 35% reduction for 3 mg/kg and 10 mg/kg DTX-C-008, respectively), and diaphragm (53% and 70% reduction for 3 mg/kg and 10 mg/kg DTX-C-008, respectively) tissues, relative to the mice treated with the vehicle control. Notably, all assayed muscle tissue types experienced dose-dependent inhibition of DMPK, with greater reduction in DMPK levels at 10 mg/kg antibody conjugate relative to 3 mg/kg antibody conjugate.

[000303] Meanwhile, mice treated with the control DTX-C-007 complex had DMPK expression levels comparable to the vehicle control (no reduction in DMPK expression) for all

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assayed muscle tissue types. These data indicate that the anti-transferrin receptor antibody of the DTX-C-008 enabled cellular internalization of the complex into muscle-specific tissues in an *in vivo* mouse model, thereby allowing the DMPK ASO to inhibit expression of DMPK. These data further demonstrate that the DTX-C-008 complex is capable of specifically targeting muscle tissues for dose-dependent inhibition of DMPK.

Example 5: Targeting DMPK in cynomolgus monkey muscle tissues with a muscle-targeting complex

[000304] A muscle-targeting complex comprising DTX-P-060 (DTX-C-012), was generated and purified using methods described in Example 2. DTX-C-012 is a complex comprising a human anti-transferrin antibody covalently linked, via a cathepsin cleavable Val-Cit linker, to DTX-P-060, an antisense oligonucleotide that targets DMPK. Following HIC-HPLC purification, densitometry confirmed that DTX-C-012 had an average ASO to antibody ratio of 1.32, and SDS-PAGE revealed a purity of 92.3%.

[000305] DTX-C-012 was tested for dose-dependent inhibition of DMPK in male cynomolgus monkey tissues. Male cynomolgus monkeys (19-31 months; 2-3 kg) were intravenously injected with a single dose of a saline control, DTX-P-060 (naked DMPK ASO) (10 mg/kg of RNA), or DTX-C-012 (10 mg/kg of RNA) on Day 0. Each experimental condition was replicated in three individual male cynomolgus monkeys. On Day 7 after injection, tissue biopsies (including muscle tissues) were collected. DMPK mRNA expression levels, ASO detection assays, serum clinical chemistries, tissue histology, clinical observations, and body weights were analyzed. The monkeys were euthanized on Day 14.

[000306] Significant knockdown (KD) of DMPK mRNA expression using DTX-C-012 was observed in soleus, deep flexor, and masseter muscles relative to saline control, with 39% KD, 62% KD, and 41% KD, respectively (FIGs. 7A-7C). Robust knockdown of DMPK mRNA expression DTX-C-012 was further observed in gastrocnemius (62% KD; FIG. 7D), EDL (29% KD; FIG. 7E), tibialis anterior muscle (23% KD; FIG. 7F), diaphragm (54% KD; FIG. 7G), tongue (43% KD; FIG. 7H), heart muscle (36% KD; FIG. 7I), quadriceps (58% KD; FIG. 7J), bicep (51% KD; FIG. 7K), and deltoid muscles (47% KD; FIG. 7L). Knockdown of DMPK mRNA expression DTX-C-012 in smooth muscle was also observed in the intestine, with 63% KD at jejunum-duodenum ends (FIG. 8A) and 70% KD in ileum (FIG. 8B). Notably, naked DMPK ASO (*i.e.*, not linked to a muscle-targeting agent), DTX-P-060, had minimal effects on

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DMPK expression levels relative to the vehicle control (*i.e.*, little or no reduction in DMPK expression) for all assayed muscle tissue types. Monkeys treated with the DTX-C-012 complex demonstrated no change in DMPK expression in non-muscle tissues, such as liver, kidney, brain, and spleen tissues (FIGs. 9A-9D). Additional tissues were examined, as depicted in FIG. 10, which shows normalized DMPK mRNA tissue expression levels across several tissue types in cynomolgus monkeys. (N=3 male cynomolgus monkeys)

[000307] Prior to euthanization, all monkeys were tested for reticulocyte levels, platelet levels, hemoglobin expression, alanine aminotransferase (ALT) expression, aspartate aminotransferase (AST) expression, and blood urea nitrogen (BUN) levels on days 2, 7, and 14 after dosing. As shown in FIG. 12, monkeys dosed with antibody-oligonucleotide complex had normal reticulocyte levels, platelet levels, hemoglobin expression, alanine aminotransferase (ALT) expression, aspartate aminotransferase (AST) expression, and blood urea nitrogen (BUN) levels throughout the length of the experiment. These data show that a single dose of a complex comprising DTX-P-060 is safe and tolerated in cynomolgus monkeys.

[000308] These data demonstrate that the anti-transferrin receptor antibody of the DTX-C-012 complex enabled cellular internalization of the complex into muscle-specific tissues in an *in vivo* cynomolgus monkey model, thereby allowing the DMPK ASO (DTX-P-060) to inhibit expression of DMPK. These data further demonstrate that the DTX-C-012 complex is capable of specifically targeting muscle tissues for dose-dependent inhibition of DMPK without substantially impacting non-muscle tissues. This is direct contrast with the limited ability of DTX-P-060, a naked DMPK ASO (not linked to a muscle-targeting agent), to inhibit expression of DMPK in muscle tissues of an *in vivo* cynomolgus monkey model.

Example 6: Targeting DMPK in mouse muscle tissues with a muscle-targeting complex

[000309] The muscle-targeting complex described in Example 2, DTX-C-008, was tested for time-dependent inhibition of DMPK in mouse tissues. C57BL/6 wild-type mice were intravenously injected with a single dose of a vehicle control (saline), DTX-P-060 (10 mg/kg of RNA), or DTX-C-008 (10 mg/kg of RNA) and euthanized after a prescribed period of time, as described in Table 2. Following euthanization, the mice were segmented into isolated tissue types and tissue samples were subsequently assayed for expression levels of DMPK (FIGs. 11A-11B).

Table 2. Experimental conditions

Group	Dosage	Days after injection before euthanization	Number of mice
1	Vehicle (saline)	3 days	3
2	Vehicle (saline)	7 days	3
3	Vehicle (saline)	14 days	3
4	Vehicle (saline)	28 days	3
5	DTX-P-060	3 days	3
6	DTX-P-060	7 days	3
7	DTX-P-060	14 days	3
8	DTX-P-060	28 days	3
9	DTX-C-008	3 days	3
10	DTX-C-008	7 days	3
11	DTX-C-008	14 days	3
12	DTX-C-008	28 days	3

[000310] Mice treated with the DTX-C-008 complex demonstrated approximately 50% reduction in DMPK expression in gastrocnemius (FIG. 11A) and tibialis anterior (FIG. 11B) muscles for all of Groups 9-12 (3-28 days between injection and euthanization), relative to vehicle. Mice treated with the DTX-P-060 naked oligonucleotide did not demonstrate significant reduction in DMPK expression.

[000311] These data indicate that the DTX-C-008 complex was capable of providing persistent reduction in DMPK expression for up to 28 days following dosage of mice with said DTX-C-008 complex.

Example 7: Evaluation of antisense oligonucleotides that target DMPK in immortalized myoblasts

[000312] Two hundred and thirty-six oligonucleotides for targeting DMPK were generated using *in silico* analysis. Each individual oligonucleotide was evaluated for their ability to target DMPK *in cellulo* at two doses – 0.5 nM (low dose) and 50 nM (high dose).

[000313] Briefly, DM1 C15 immortalized myoblasts were cultured in T-75 flasks until near confluency (~80% confluent). Myoblasts were then disrupted with trypsin and seeded into 96-well microplates at a density of 50,000 cells/well. Cells were allowed to recover overnight before the growth media was washed out and replaced with a no-serum media to induce differentiation into myotubes. Differentiation proceeded for seven days prior to treatment with DMPK-targeting oligonucleotides.

[000314] On day seven following induction of differentiation, DM1 C15 myotubes were transfected with an individual oligonucleotide using 0.3 μ L of Lipofectamine MessengerMax

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per well. All oligonucleotides were tested at both 0.5 nM and 50 nM final concentrations in biological triplicates. After treatment with oligonucleotides, cells were incubated for 72 hours prior to being harvested for total RNA. cDNA was synthesized from the total RNA extracts and qPCR was performed to determine expression levels of DMPK in technical quadruplicate. All qPCR data were analyzed using a traditional $\Delta\Delta CT$ method and were normalized to a plate-based negative control that comprised cells treated with vehicle control (0.3 μ L/well Lipofectamine MessengerMax without any oligonucleotide). Results from these experiments are shown in Table 3. 'Normalized DMPK Remaining' for each antisense oligonucleotide in Table 3 refers to the expression level of DMPK in cell treated with said antisense oligonucleotide relative to the negative control that comprised cells treated with vehicle control (wherein the expression level of the negative control has been normalized to equal 1.00)

[000315] The majority of tested DMPK-targeting antisense oligonucleotides demonstrated a reduction in DMPK expression in differentiated myotubes at both the low and high dose concentrations (0.5 nM and 50 nM, respectively). These data demonstrate that the antisense oligonucleotides shown in Table 3 are capable of targeting DMPK *in cellulo*, suggesting that muscle-targeting complexes comprising these antisense oligonucleotides would be capable of targeting DMPK in muscle tissues *in vivo*.

Table 3. Ability of DMPK-targeting antisense oligonucleotides to reduce expression of DMPK *in cellulo*

Antisense Oligonucleotide Sequence	SEQ ID NO:	DMPK Target Sequence	SEQ ID NO:	0.5 nM		50 nM	
				Normalized DMPK Remaining	Percent DMPK Reduction	Normalized DMPK Remaining	Percent DMPK Reduction
GGACGGCCCGGC UUGCUGCC	45	GGCAGCAAGCCG GGCCGTCC	281	0.42	58.25	0.31	69.30
GGGCCCCGGAUCA CAGGACUG	46	CAGTCCTGTGATC CGGGCCC	282	0.42	57.97	0.38	61.96
CAAACUUGCUCU CAAGUGUC	47	GACACTGCTGAG CAAGTTTG	283	0.69	31.45	0.46	53.93
AAACUUGCUCAG CAGUGUCA	48	TGACACTGCTGA GCAAGTTT	284	0.69	30.85	0.49	50.69
CGGAUGGCCUCC AUCUCCCG	49	CGGGAGATGGAG GCCATCCG	285	0.71	28.92	0.44	55.57
CUCGGCCGGAU CCGCUCC	50	GGGAGCGGATTC CGGCCGAG	286	0.71	28.64	0.35	64.75
UCUCGGCCGGAU UCCGCUCC	51	GGAGCGGATTCC GGCCGAGA	287	0.72	27.88	0.33	67.46
UGCUCAGCAGUG UCAGCAGG	52	CCTGCTGACACTG CTGAGCA	288	0.73	27.08	0.34	65.78
UUGUCGGGUUUG	53	AGGGACATCAAA	289	0.66	34.16	0.44	55.56

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AUGUCCCU		CCCGACAA					
GUUGCGGGUUUG AUGUCC	54	GGGACATCAAAC CCGACAAC	290	0.67	33.31	0.39	61.07
UCCGCCAGGUAG AAGCGCGC	55	GCGCGCTTCTACC TGGCGGA	291	0.72	27.99	0.20	80.06
CAUGGCAUACAC CUGGCCCG	56	CGGGCCAGGTGT ATGCCATG	292	0.68	31.63	0.26	74.03
AACUUGCUCAGC AGUGUCAG	57	CTGACACTGCTG AGCAAGTT	293	0.80	19.81	0.47	52.64
CAGCUGCGUGAU CCACCGCC	58	GGCGGTGGATCA CGCAGCTG	294	0.81	19.03	0.32	68.34
CGAAUGUCCGAC AGUGUCUC	59	GAGACACTGTCTG GACATTCG	295	0.60	40.21	0.36	64.42
GAAGUCGGCCAG GCGGAUGU	60	ACATCCGCCTGG CCGACTTC	296	0.82	18.36	0.56	44.04
UGUCGGGUUUGA UGUCCUG	61	CAGGGACATCAA ACCCGACA	297	0.70	30.09	0.32	68.14
GGAUGGCCUCCA UCUCCCG	62	CCGGGAGATGGA GGCCATCC	298	0.75	24.93	0.39	60.77
AGGAUGUUGUCG GGUUUGAU	63	ATCAAACCCGAC AACATCCT	299	0.76	24.19	0.61	39.48
GUCGGGUUUGAU GUCCUGU	64	ACAGGGACATCA AACCCGAC	300	0.71	28.89	0.36	64.15
AAUACUCCAUGA CCAGGUAC	65	GTACCTGGTCATG GAGTATT	301	0.71	28.86	0.48	52.07
CUUGUUAUGAU CUUCAUGG	66	CCATGAAGATCA TGAACAAG	302	0.84	16.06	0.51	49.47
UCAGUGCAUCCA AAACGUGG	67	CCACGTTTTGGAT GCACTGA	303	0.84	15.76	0.58	42.06
CUGUCCCGGAGA CCAUCCCA	68	TGGGATGGTCTCC GGGACAG	304	0.64	35.85	0.49	50.78
GGGCCUGGGACC UCACUGUC	69	GACAGTGAGGTC CCAGGCCC	305	0.63	37.19	0.23	76.81
CCCACGUAAUAC UCCAUGAC	70	GTCATGGAGTATT ACGTGGG	306	0.72	28.21	0.54	45.94
CUCUGCCGCAGG GACAGCCG	71	CGGCTGTCCCTGC GGCAGAG	307	0.63	37.09	0.06	93.59
CUGUGCACGUAG CCAAGCCG	72	CGGCTTGGCTAC GTGCACAG	308	0.74	25.67	0.30	70.10
UGCCCAUCCACG UCAGGGCC	73	GGCCCTGACGTG GATGGGCA	309	0.86	13.63	0.67	33.09
AGCGCCUCCGAU AGGCCAGG	74	CCTGGCCTATCGG AGGCGCT	310	0.79	21.19	0.38	61.91
UGUGCACGUAGC CAAGCCCG	75	CCGGCTTGGCTAC GTGCACA	311	0.75	24.74	0.25	75.09
GACCAGGUACAG GAGUUCU	76	AGAACTACCTGT ACCTGGTC	312	0.57	42.85	0.29	70.95
CCAUCUCGGCCG GAAUCCGC	77	GCGGATTCCGGC CGAGATGG	313	0.79	20.50	0.40	59.76
CAUCUCGGCCGG AAUCCGCU	78	AGCGGATTCCGG CCGAGATG	314	0.80	20.21	0.41	59.40
UUGCCAUAAGGUC UCCGCCGU	79	ACGGCGGAGACC TATGGCAA	315	0.64	36.30	0.40	60.12
ACAGCGGUCCAG CAGGAUGU	80	ACATCCTGCTGG ACCGCTGT	316	0.80	19.94	0.45	55.14

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AAAGCGCCUCCG AUAGGCCA	81	TGGCCTATCGGA GGCGCTTT	317	0.80	19.89	0.38	62.04
GCCAAAGAAGAA GGGAUGUG	82	CACATCCCTTCTT CTTTGGC	318	0.75	24.87	0.44	56.19
CACGUAAUACUC CAUGACCA	83	TGGTCATGGAGT ATTACGTG	319	0.76	24.40	0.54	46.50
AUCUCGGCCGGA AUCCGCUC	84	GAGCGGATTCCG GCCGAGAT	320	0.88	11.61	0.34	65.98
GCUUCAUCUUA CUACCGCU	85	AGCGGTAGTGAA GATGAAGC	321	0.69	31.44	0.48	51.78
GCCAUCUCGGCC GGAAUCCG	86	CGGATTCCGGCC GAGATGGC	322	0.81	18.56	0.14	86.39
CAGGGACAGCCG CUGGAACU	87	AGTTCCAGCGGC TGTCCTG	323	0.68	32.09	0.41	58.84
AUGACAAUCUCC GCCAGGUA	88	TACCTGGCGGAG ATTGTCAT	324	0.58	42.38	0.40	60.47
GGCCAUGACAAU CUCCGCCA	89	TGGCGGAGATTG TCATGGCC	325	0.58	42.38	0.25	75.00
AUACUCCAUGAC CAGGUACA	90	TGTACCTGGTCAT GGAGTAT	326	0.77	23.07	0.43	56.84
GCCUCUGCCUCG CGUAGUUG	91	CAACTACGCGAG GCAGAGGC	327	0.65	35.38	0.19	81.18
GAAUGUCCGACA GUGUCUCC	92	GGAGACACTGTC GGACATTC	328	0.70	30.09	0.37	63.41
CGUUCCAUCUGC CCGCAGCU	93	AGCTGCGGGCAG ATGGAACG	329	0.66	33.74	0.31	68.72
CCUUGUAGUGGA CGAUCUUG	94	CAAGATCGTCCA CTACAAGG	330	0.83	17.20	0.34	65.91
AUCUCCGCCAGG UAGAAGCG	95	CGCTTCTACCTGG CGGAGAT	331	0.58	42.37	0.35	65.50
CUCAGGCUCUGC CGGGUGAG	96	CTCACCCGGCAG AGCCTGAG	332	0.70	30.13	0.37	63.07
UGCUUCAUCUUC ACUACCGC	97	GCGGTAGTGAAG ATGAAGCA	333	0.71	28.82	0.40	60.24
GCAGGAUGUUGU CGGGUUUG	98	CAAACCCGACAA CATCCTGC	334	0.56	44.39	0.22	78.03
GGCCUCAGCCUC UGCCGCAG	99	CTGCGGCAGAGG CTGAGGCC	335	0.80	20.12	0.29	71.28
UGUUGUCGGGUU UGAUGUCC	100	GGACATCAAACC CGACAACA	336	0.79	21.00	0.58	42.19
CCACGUAAUACU CCAUGACC	101	GGTCATGGAGTA TTACGTGG	337	0.79	20.84	0.50	50.06
CCGUUCCAUCUG CCCGCAGC	102	GCTGCGGGCAGA TGGAACGG	338	0.68	31.74	0.23	77.46
UUCCCGAGUAAG CAGGCAGA	103	TCTGCCTGCTTAC TCGGGAA	339	0.69	31.49	0.50	49.81
UGAUCUUAUGG CAUACACC	104	GGTGTATGCCAT GAAGATCA	340	0.72	27.70	0.10	89.68
AGGGACAGCCGC UGGAACCTG	105	CAGTTCCAGCGG CTGTCCCT	341	0.71	28.72	0.55	45.34
GGGUUUGAUGUC CCUGUGCA	106	TGCACAGGGACA TCAAACCC	342	0.60	40.12	0.37	62.61
UGACAAUCUCCG CCAGGUAG	107	CTACCTGGCGGA GATTGTCA	343	0.61	38.86	0.33	66.56
CACAGCGGUCCA GCAGGAUG	108	CATCCTGCTGGAC CGCTGTG	344	0.93	6.62	0.40	59.58

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GCGUAGAAGGGC GUCUGCCC	109	GGGCAGACGCCC TTCTACGC	345	0.60	39.53	0.22	77.91
CUCAGCCUCUGC CGCAGGGA	110	TCCCTGCGGCAG AGGCTGAG	346	0.82	17.86	0.20	79.58
GUCUCAGUGCAU CCAAAACG	111	CGTTTTGGATGCA CTGAGAC	347	0.81	18.85	0.54	46.13
GGACGAUCUUGC CAUAGGUC	112	GACCTATGGCAA GATCGTCC	348	0.70	29.82	0.51	48.97
UCAGCAGUGUCA GCAGGUCC	113	GGACCTGCTGAC ACTGCTGA	349	0.67	33.46	0.39	61.11
GCUCCUGGGCGG CGCCAGAC	114	GTCTGGCGCCGC CCAGGAGC	350	0.91	8.52	0.21	78.79
AGCAGGAUGUUG UCGGGUUU	115	AAACCCGACAAC ATCCTGCT	351	0.59	41.05	0.26	74.02
AUCCGCUCCUGC AACUGCCG	116	CGGCAGTTGCAG GAGCGGAT	352	0.87	12.80	0.60	40.06
AGGAGCAGGGAA AGCGCCUC	117	GAGGCGCTTTCCC TGCTCCT	353	0.67	33.24	0.38	62.37
ACACCUGGCCCCG UCUGCUUC	118	GAAGCAGACGGG CCAGGTGT	354	0.67	33.00	0.45	55.40
CCCAGCGCCAC CAGUCACA	119	TGTGACTGGTGG GCGCTGGG	355	0.62	37.93	0.32	67.82
GCUCCCUCUGCC UGCAGCAA	120	TTGCTGCAGGCA GAGGGAGC	356	0.74	26.41	0.30	70.15
GCUCAGGCUCUG CCGGGUGA	121	TCACCCGGCAGA GCCTGAGC	357	0.74	25.69	0.39	60.71
UUGAUGUCCUG UGCACGUA	122	TACGTGCACAGG GACATCAA	358	0.74	25.67	0.45	55.13
GCCUCAGCCUCU GCCGCAGG	123	CCTGCGGCAGAG GCTGAGGC	359	0.84	16.37	0.54	46.42
GGUAGUUCUCAU CCUGGAAG	124	CTTCCAGGATGA GAACTACC	360	0.75	25.48	0.44	56.15
CAGCGCCACCA GUCACACU	125	AGTGTGACTGGT GGGCGCTG	361	0.63	37.28	0.35	64.93
CCCAAACUUGCU CAGCAGUG	126	CACTGCTGAGCA AGTTTGGG	362	0.63	37.02	0.38	61.78
CUUGCCAUAGGU CUCCGCCG	127	CGGCGGAGACCT ATGGCAAG	363	0.73	27.04	0.29	71.05
UACACCUGGCC GUCUGCUU	128	AAGCAGACGGGC CAGGTGTA	364	0.69	31.10	0.43	57.43
CCAGCGCCACC AGUCACAC	129	GTGTGACTGGTG GGCGCTGG	365	0.64	36.17	0.29	70.96
GGCCUCAGCCUG GCCGAAAG	130	CTTTCGGCCAGGC TGAGGCC	366	0.86	14.49	0.35	64.80
AAUCUCCGCCAG GUAGAAGC	131	GCTTCTACCTGGC GGAGATT	367	0.64	35.85	0.35	65.27
AUGGCAUACACC UGGCCCCGU	132	ACGGGCCAGGTG TATGCCAT	368	0.86	14.31	0.50	49.63
CCAUGACAAUCU CCGCCAGG	133	CCTGGCGGAGAT TGTCATGG	369	0.65	34.53	0.24	76.46
UCCCCAAACUUG CUCAGCAG	134	CTGCTGAGCAAG TTTGGGGA	370	0.94	5.73	0.55	44.67
GAUGUUGUCGGG UUUGAUGU	135	ACATCAAACCCG ACAACATC	371	0.90	10.06	0.58	42.42
GUUUGCCCAUCC ACGUCAGG	136	CCTGACGTGGAT GGGCAAAC	372	0.66	34.36	0.46	54.49

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CGGACGGCCCGG CUUGCUGC	137	GCAGCAAGCCGG GCCGTCCG	373	0.95	5.42	0.70	30.41
CUCCGCCAGGUA GAAGCGCG	138	CGCGCTTCTACCT GGCGGAG	374	0.70	30.22	0.22	78.14
GUACAGGUAGUU CUCAUCCU	139	AGGATGAGAACT ACCTGTAC	375	0.68	31.52	0.34	65.57
AGGGCGUCUGCC CAUAGAAC	140	GTTCTATGGGCA GACGCCCT	376	0.87	13.23	0.41	58.98
UGGCCACAGCGG UCCAGCAG	141	CTGCTGGACCGCT GTGGCCA	377	0.70	29.59	0.31	69.44
CGUAGUUGACUG GCGAAGUU	142	AACTTCGCCAGTC AACTACG	378	0.75	25.26	0.38	61.52
UCUGCCGCAGGG ACAGCCGC	143	GCGGCTGTCCCTG CGGCAGA	379	0.77	22.97	0.18	82.10
AAGCGCCUCCGA UAGGCCAG	144	CTGGCCTATCGG AGGCGCTT	380	0.91	8.91	0.56	43.93
GACAGAAACAACG GCGAACAG	145	CTGTTTCGCCGTTG TTCTGTC	381	0.79	21.41	0.30	70.49
GCUCAGCAGUGU CAGCAGGU	146	ACCTGCTGACACT GCTGAGC	382	0.71	29.18	0.27	73.46
AUGAUCUUAUG GCAUACAC	147	GTGTATGCCATG AAGATCAT	383	0.87	12.76	0.60	39.97
UUUGCCCAUCCA CGUCAGGG	148	CCCTGACGTGGA TGGGCAAA	384	0.67	32.79	0.41	59.36
ACUUGCUCAGCA GUGUCAGC	149	GCTGACACTGCT GAGCAAGT	385	0.72	27.84	0.39	60.71
UGAUGUCCUGU GCAUGUAG	150	CTACGTGCACAG GGACATCA	386	0.79	20.58	0.41	59.00
AAAUACCGAGGA AUGUCGGG	151	CCCGACATTCTC GGTATT	387	0.89	11.25	0.49	50.91
GGCGAAUACACC GAGCGCCC	152	GGGCGCTGGGTG TATTCGCC	388	0.80	19.77	0.31	68.72
AGACAAUAAUA CCGAGGAA	153	TTCTTCGGTATTT ATTGTCT	389	0.71	29.37	0.52	48.20
CCCGUCUGCUUC AUCUUCAC	154	GTGAAGATGAAG CAGACGGG	390	0.80	20.31	0.56	43.97
CUGCCUGCAGCA ACUCCAUC	155	GATGGAGTTGCT GCAGGCAG	391	0.77	23.10	0.53	46.69
CCUCAGCCUCUG CCGCAGGG	156	CCCTGCGGCAGA GGCTGAGG	392	0.89	10.87	0.45	55.22
GUGUCCGGAAGU CGCCUGCU	157	AGCAGGCGACTT CCGGACAC	393	0.77	22.99	0.26	73.65
UGCACGUGUGGC UCAAGCAG	158	CTGCTTGAGCCAC ACGTGCA	394	0.89	10.81	0.36	64.18
GACAAUAAAUAC CGAGGAU	159	ATTCCTCGGTATT TATTGTC	395	0.71	28.97	0.52	47.51
GCCAUGACAAUC UCCGCCAG	160	CTGGCGGAGATT GTCATGGC	396	0.69	30.96	0.19	81.00
GCUGUCCCGGAG ACCAUCCC	161	GGGATGGTCTCC GGGACAGC	397	0.77	22.57	0.34	66.27
CAUGACCAGGUA CAGGUAGU	162	ACTACCTGTACCT GGTCATG	398	0.81	19.39	0.41	59.09
AGCGCCCACCAG UCACACUC	163	GAGTGTGACTGG TGGGCGCT	399	0.70	30.36	0.36	63.67
UCUCAGUGCAUC CAAACGU	164	ACGTTTTGGATGC ACTGAGA	400	0.89	10.88	0.49	51.34

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UUUGGGCAGAUG GAGGGCCU	165	AGGCCCTCCATCT GCCCAA	401	0.65	35.14	0.30	70.00
GAUGUCCUGUG CACGUAGC	166	GCTACGTGCACA GGGACATC	402	0.81	18.99	0.38	62.46
CAGCAGUGUCAG CAGGUCCC	167	GGGACCTGCTGA CACTGCTG	403	0.74	25.67	0.48	51.97
CAUGACAAUCUC CGCCAGGU	168	ACCTGGCGGAGA TTGTCATG	404	0.71	29.45	0.29	70.52
ACUUGUUCAUGA UCUUCAUG	169	CATGAAGATCAT GAACAAGT	405	0.75	25.47	0.47	52.89
GUGGAAUCCGCG UAGAAGGG	170	CCCTTCTACGCGG ATTCCAC	406	0.69	30.55	0.51	49.34
UGGCAUGACAA UCUCCGCC	171	GGCGGAGATTGT CATGGCCA	407	0.70	30.46	0.27	72.55
GGGACAGACAAU AAAUACCG	172	CGGTATTTATTGT CTGTCCC	408	0.73	27.19	0.49	50.50
CCGCUCCCCAAA CUUGCUC	173	TGAGCAAGTTTG GGGAGCGG	409	1.00	0.28	0.43	56.82
CGGCUCAGGCUC UGCCGGGU	174	ACCCGGCAGAGC CTGAGCCG	410	0.82	17.97	0.31	69.03
GGCUCCUGGGCG GCGCCAGA	175	TCTGGCGCCGCC AGGAGCC	411	1.00	0.05	0.04	96.23
UUUCCCGAGUAA GCAGGCAG	176	CTGCCTGCTTACT CGGGA	412	0.79	20.69	0.55	44.89
GGAUGUUGUCGG GUUUGAUG	177	CATCAAACCCGA CAACATCC	413	0.96	4.26	0.59	40.81
CAGGUAGUUCUC AUCCUGGA	178	TCCAGGATGAGA ACTACCTG	414	0.74	25.92	0.23	76.71
UGCCCAUAGAAC AUUCAUA	179	TATGAAATGTTCT ATGGGCA	415	0.92	7.67	0.65	34.56
UAGUUCUCAUCC UGGAAGGC	180	GCCTTCCAGGAT GAGAACTA	416	0.83	16.83	0.56	43.88
AUGUCCUGUGC ACGUAGCC	181	GGCTACGTGCAC AGGGACAT	417	0.83	16.78	0.51	49.29
CGGGCCCGGAUC ACAGGACU	182	AGTCCTGTGATCC GGGCCCCG	418	0.83	17.45	0.33	67.11
UGGACGAUCUUG CCAUAGGU	183	ACCTATGGCAAG ATCGTCCA	419	0.81	19.20	0.57	42.52
GUUGGCCGGCGU GGGCCACC	184	GGTGGCCACGC CGGCCAAC	420	1.02	-1.82	0.56	43.57
CUCAGUGCAUCC AAAACGUG	185	CACGTTTTGGATG CACTGAG	421	0.92	7.65	0.46	54.26
UCGAAGUUGCAU GUGUCGGU	186	ACCGACACATGC AACTTCGA	422	0.77	22.96	0.42	58.15
UGGAACACGGAC GGCCCGGC	187	GCCGGGCCGTCC GTGTTCCA	423	1.02	-1.90	0.39	60.96
CCGAGAGCAGCG CAAGUGAG	188	CTCACTTGCCTG CTCTCGG	424	0.84	16.13	0.59	40.93
UCCUGCAACUGC CGGACGUG	189	CACGTCCGGCAG TTGCAGGA	425	0.84	16.06	0.55	44.61
UCACCAACACGU CCCUCUCC	190	GGAGAGGGACGT GTTGGTGA	426	0.53	47.12	0.16	84.09
UGCCUGCAGCAA CUCCAUC	191	GGATGGAGTTGC TGCAGGCA	427	0.86	13.99	0.50	49.75
UUGGCCGCGUG GGCCACCA	192	TGGTGGCCACG CCGGCCAA	428	1.03	-3.19	0.56	44.37

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GAGCCUCUGCCU CGCGUAGU	193	ACTACGCGAGGC AGAGGCTC	429	0.81	18.77	0.22	77.78
AAGGGCGUCUGC CCAAGAGAA	194	TTCTATGGGCAG ACGCCCTT	430	0.87	13.15	0.65	34.56
ACAGACAAUAAA UACCGAGG	195	CCTCGGTATTAT TGTCTGT	431	1.04	-3.95	0.26	74.02
GGACAGACAAUA AAUACCGA	196	TCGGTATTTATT TCTGTCC	432	0.77	22.57	0.47	52.51
ACGUGUGCCUCU AGGUCCCG	197	CGGGACCTAGAG GCACACGT	433	0.84	16.47	0.22	77.73
GGCACGAGACAG AACACCGG	198	CCGTTGTTCTGTC TCGTGCC	434	0.84	16.10	0.32	68.01
UGACCAGGUACA GGUAGUUC	199	GAACCTACCTGTA CCTGGTCA	435	0.78	22.00	0.36	63.73
CUCUGCCGGGUG AGCACCUC	200	GAGGTGCTCACC CGGCAGAG	436	0.75	25.25	0.26	74.36
GACAAUCUCCGC CAGGUAGA	201	TCTACCTGGCGG AGATTGTC	437	0.76	23.70	0.50	49.82
UCUCCGCCAGGU AGAAGCGC	202	GCGCTTCTACCTG GCGGAGA	438	0.80	19.59	0.33	66.52
CUCUGCCUCGCG UAGUUGAC	203	GTCAACTACGCG AGGCAGAG	439	0.83	16.61	0.09	91.21
CUUUGGGCAGAU GGAGGGCC	204	GGCCCTCCATCTG CCCAAAG	440	0.72	28.06	0.33	67.50
ACAGGUAGUUCU CAUCCUGG	205	CCAGGATGAGAA CTACCTGT	441	0.79	20.51	0.15	85.36
CCAAACUUGCTC AGCAGUGU	206	ACACTGCTGAGC AAGTTGG	442	0.76	23.64	0.42	57.70
UCGGGUUUGAUG UCCUGUG	207	CACAGGGACATC AAACCCGA	443	0.78	22.49	0.43	57.16
GGCUUGCUGCCU UCCAGGC	208	GCCTGGGAAGGC AGCAAGCC	444	1.06	-6.32	0.52	48.15
UACAGGUAGUUC UCAUCCUG	209	CAGGATGAGAAC TACCTGTA	445	0.80	19.83	0.27	72.51
UUGCCCAUCCAC GUCAGGGC	210	GCCCTGACGTGG ATGGGCAA	446	0.78	22.23	0.33	67.15
AGGUACAGGUAG UUCUCAUC	211	GATGAGAACTAC CTGTACCT	447	0.81	18.68	0.41	58.92
GACAGACAAUAA AUACCGAG	212	CTCGGTATTTATT GTCTGTC	448	0.82	18.26	0.62	38.07
UAGAACAUUUCA UAGGCGAA	213	TTCGCCTATGAAA TGTTCTA	449	0.80	20.23	0.56	43.67
AGGGCCUUUUUAU UCGCGAGG	214	CCTCGCGAATAA AAGGCCCT	450	0.86	13.63	0.34	66.43
GCCUCGCGUAGU UGACUGGC	215	GCCAGTCAACTA CGCGAGGC	451	0.87	12.98	0.09	91.10
CCAGCAGGAUGU UGUCGGGU	216	ACCCGACAACAT CCTGCTGG	452	0.60	40.29	0.10	89.59
GUAGUUGACUGG CGAAGUUC	217	GAACCTCGCCAG TCAACTAC	453	0.93	7.50	0.55	45.33
UGCAGGAUGGCCU CCAUCUCC	218	GGAGATGGAGGC CATCCGCA	454	0.60	40.15	0.16	84.43
ACAAUCUCCGCC AGGUAGAA	219	TTCTACCTGGCGG AGATTGT	455	0.81	19.09	0.50	49.75
GCGAAUACACCC AGCGCCCA	220	TGGGCGCTGGGT GTATTCGC	456	0.93	6.94	0.30	69.72

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GUAGUUCUCAUC CUGGAAGG	221	CCTTCCAGGATG AGAACTAC	457	0.93	7.43	0.45	55.09
GGCUCAGGCUCU GCCGGGUG	222	CACCCGGCAGAG CCTGAGCC	458	0.93	7.38	0.34	65.82
CCAUCACCAAC ACGUCCCU	223	AGGGACGTGTTG GTGAATGG	459	0.61	39.26	0.13	86.83
ACCAGGUACAGG UAGUUCUC	224	GAGAACTACCTG TACCTGGT	460	0.84	16.09	0.23	76.96
CTGCAGUUUGCC CAUCCACG	225	CGTGGATGGGCA AACTGCAG	461	1.11	-10.69	0.40	60.08
UUGUUCAUGAUC UUCAUGGC	226	GCCATGAAGATC ATGAACAA	462	0.86	14.13	0.55	45.23
UUGAUGUCCUG UGCACGU	227	ACGTGCACAGGG ACATCAAA	463	0.93	6.92	0.57	43.07
GCGGUCCAGCAG GAUGUUGU	228	ACAACATCCTGCT GGACCGC	464	0.61	38.84	0.16	83.64
GUCUAUGGCCAU GACAAUCU	229	AGATTGTCATGG CCATAGAC	465	1.11	-11.00	0.27	73.11
GGAGCAGGGAAA GCGCCUCC	230	GGAGGCGCTTTC CCTGCTCC	466	0.79	21.46	0.12	88.35
UGCCUCGCGUAG UUGACUGG	231	CCAGTCAACTAC GCGAGGCA	467	0.89	11.03	0.12	88.02
GCGGAUGGCCUC CAUCUCCC	232	GGGAGATGGAGG CCATCCGC	468	0.79	21.25	0.28	71.77
UUUCAUAGGCGA AUACACCC	233	GGGTGTATTCGCC TATGAAA	469	0.94	5.56	0.47	53.28
GCCUGUCAGCGA GUCGGAGG	234	CCTCCGACTCGCT GACAGGC	470	0.89	10.81	0.24	75.67
CCACUUCAGCUG UUUCAUCC	235	GGATGAAACAGC TGAAGTGG	471	0.78	22.40	0.36	64.20
CAUCCGCUCCUG CAACUGCC	236	GGCAGTTGCAGG AGCGGATG	472	0.79	21.04	0.23	76.81
UCUAGGGUUCAG GGAGCGCG	237	CGCGCTCCCTGA ACCCTAGA	473	0.78	21.81	0.17	83.22
CACCAACACGUC CCUCUCCU	238	AGGAGAGGGACG TGTTGGTG	474	0.62	37.51	0.18	81.57
CAGGAGCAGGGA AAGCGCCU	239	AGGCGCTTTCCT GCTCCTG	475	0.88	12.48	0.48	51.82
CAAUCUCCGCCA GGUAGAAG	240	CTTCTACCTGGCG GAGATTG	476	0.84	15.95	0.51	49.25
AUGUUGUCGGGU UUGAUGUC	241	GACATCAAACCC GACAACAT	477	0.83	16.93	0.47	52.83
CCAUCCGCUCCU GCAACUGC	242	GCAGTTGCAGGA GCGGATGG	478	0.80	19.53	0.28	71.62
GCGUCACCUCGG CCUCAGCC	243	GGCTGAGGCCGA GGTGACGC	479	0.80	20.02	0.19	81.27
GAGGGCCUUUUA UUCGCGAG	244	CTCGCGAATAAA AGGCCCTC	480	0.92	8.23	0.38	62.21
AGCGGCAGAGAG AGGUGCUC	245	GAGCACCTCTCTC TGCCGCT	481	0.80	19.75	0.09	90.71
CAUCCAAAACGU GGAUUGGG	246	CCCAATCCACGTT TTGGATG	482	0.81	19.12	0.22	77.98
UUGGGCAGAUGG AGGGCCUU	247	AAGGCCCTCCAT CTGCCCAA	483	0.81	19.08	0.22	78.39
CCUCUGCCUCGC GUAGUUGA	248	TCAACTACGCGA GGCAGAGG	484	0.93	7.39	0.15	85.33

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ACAGAACAAACGG CGAACAGG	249	CCTGTTCGCCGTT GTTCTGT	485	0.98	2.07	0.44	55.96
CAGGAUGUUGUC GGGUUUGA	250	TCAAACCCGACA ACATCCTG	486	0.83	17.17	0.21	79.31
CGGCCUCAGCCU CUGCCGCA	251	TGCGGCAGAGGC TGAGGCCG	487	0.93	6.71	0.40	60.06
CAGCAGGAUGUU GUCGGGUU	252	AACCCGACAACA TCCTGCTG	488	0.66	34.18	0.15	84.54
GCAGAGAGAGGU GCUCCUUG	253	CAAGGAGCACCT CTCTCTGC	489	0.83	17.29	0.14	85.95
UCCAGUCCAUG GGUGUGGG	254	CCCACACCCATG GAACTGGA	490	0.84	15.66	0.22	78.48
CCUCAGCCUGGC CGAAAGAA	255	TTCTTTCGGCCAG GCTGAGG	491	0.83	16.83	0.36	63.99
GGGCCUUUUAUU CGCGAGGG	256	CCCTCGCGAATA AAAGGCCC	492	0.95	5.11	0.49	50.65
GUCGGCCAGGCG GAUGUGGC	257	GCCACATCCGCCT GGCCGAC	493	0.85	15.35	0.25	74.59
GCUUGCUGCCUU CCCAGGCC	258	GGCCTGGGAAGG CAGCAAGC	494	0.99	1.14	0.19	81.01
GGUCCAGCAGGA UGUUGUCG	259	CGACAACATCCT GCTGGACC	495	0.68	31.78	0.20	79.93
CGGAGACCAUCC CAGUCGAG	260	CTCGACTGGGAT GGTCTCCG	496	0.86	14.08	0.20	79.93
UCUGCCUCGCGU AGUGACU	261	AGTCAACTACGC GAGGCAGA	497	0.96	3.53	0.13	86.86
AGGUAGUUCUCA UCCUGGAA	262	TTCCAGGATGAG AACTACCT	498	0.93	7.36	0.37	62.62
UCCUUGUAGUGG ACGAUCUU	263	AAGATCGTCCAC TACAAGGA	499	0.87	12.96	0.15	84.87
GCAUCCAAAACG UGGAUUGG	264	CCAATCCACGTTT TGGATGC	500	0.97	2.54	0.27	72.69
GUCCAGCAGGAU GUGUCGG	265	CCGACAACATCC TGCTGGAC	501	0.70	30.00	0.17	82.64
AGCUCCCGCAGC GUCACCUC	266	GAGGTGACGCTG CGGGAGCT	502	0.86	13.72	0.20	80.40
CGAGAGCAGCGC AAGUGAGG	267	CCTCACTTGCGCT GCTCTCG	503	1.02	-2.19	0.63	37.11
CAGGGAAAGCGC CUCCGAUA	268	TATCGGAGGCGC TTTCCCTG	504	0.89	11.10	0.08	91.59
AUUUCAUAGGCG AAUACACC	269	GGTGTATTTCGCCT ATGAAAT	505	1.05	-4.54	0.56	44.15
UCGGCCAGGCGG AUGUGGCC	270	GGCCACATCCGC CTGGCCGA	506	0.73	26.53	0.17	83.04
AAGGGAUGUGUC CGGAAGUC	271	GACTTCCGGACA CATCCCTT	507	0.90	10.37	0.26	73.52
CUUGUAGUGGAC GAUCUUGC	272	GCAAGATCGTCC ACTACAAG	508	0.76	24.09	0.11	89.16
AGUCGGCCAGGC GGAUGUGG	273	CCACATCCGCCTG GCCGACT	509	0.94	6.15	0.33	67.44
GCCUCAGCCUGG CCGAAAGA	274	TCTTTCGGCCAGG CTGAGGC	510	1.05	-4.82	0.37	63.11
AGCGUCACCUCG GCCUCAGC	275	GCTGAGGCCGAG GTGACGCT	511	0.78	22.10	0.35	64.70
CAGCGGCAGAGA GAGGUGCT	276	AGCACCTCTCTCT GCCGCTG	512	0.96	4.49	0.14	86.00

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CCAGCGGCAGAG AGAGGUGC	277	GCACCTCTCTCTG CCGCTGG	513	0.97	3.23	0.15	84.55
UUGUAGUGGACG AUCUUGCC	278	GGCAAGATCGTC CACTACAA	514	0.83	17.22	0.19	81.05
AGGGAAAGCGCC UCCGAUAG	279	CTATCGGAGGCG CTTCCCT	515	1.01	-1.12	0.25	75.50
GGGAAAGCGCCU CCGAUAGG	280	CCTATCGGAGGC GCTTCCC	516	0.90	10.02	0.23	76.79

Example 8: Selected antisense oligonucleotides provided dose-dependent reduction in DMPK expression in immortalized myoblasts

[000316] Eighteen oligonucleotides from Example 7 were selected to be evaluated for their ability to reduce DMPK expression in a dose-responsive manner. DM1 C15 myoblasts were prepared as in Example 7 to yield differentiated myotubes in 96-well microplates. After seven days of differentiation, cells were transfected with individual oligonucleotides using Lipofectamine MessengerMax. Each oligonucleotide was tested in triplicate at concentrations of 0.046 nM, 0.137 nM, 0.412 nM, 1.235 nM, 3.704 nM, 11.11 nM, 33.33 nM, and 100 nM by 3-fold serial dilutions using 0.3 μ L of Lipofectamine MessengerMax per well.

[000317] Following addition of oligonucleotide, cells were incubated for 72 hours prior to harvesting for total RNA. cDNA was synthesized from the total RNA extracts and qPCR was performed to determine expression levels of DMPK using a commercially available Taqman probeset in technical quadruplicate. All qPCR data were analyzed using a traditional $\Delta\Delta$ CT method and were normalized to a plate-based negative control that comprised of cells treated with vehicle control (0.3 μ L/well Lipofectamine MessengerMax without any oligonucleotide). Data for each oligonucleotide to was fit to sigmoidal curve in order to determine an effective concentration of each oligonucleotide that provided a half-maximal response (EC-50). Results from these experiments are shown in Table 4.

[000318] Each of the eighteen antisense oligonucleotides selected for dose-dependent experimentation were capable of dose-dependently reducing DMPK in differentiated myotubes. Further, each of the tested antisense oligonucleotides reduced DMPK with EC-50 values below 25 nM. For example, antisense oligonucleotides comprising SEQ ID NOs: 161, 112, 119, 87, and 109 resulted in EC-50 values of 3.27 nM, 3.59 nM, 5.45 nM, 6.04 nM, and 24.59 nM, respectively. These data demonstrate that the antisense oligonucleotides shown in Table 4 are capable of dose-dependent reduction of DMPK *in cellulo*, suggesting that muscle-targeting

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complexes comprising these antisense oligonucleotides would be capable of targeting DMPK in muscle tissues *in vivo*.

Table 4. Ability of DMPK-targeting antisense oligonucleotides to reduce expression of DMPK in dose-dependent manner *in cellulo*

Antisense Oligonucleotide Sequence	SEQ ID NO:	DMPK Target Sequence	SEQ ID NO:	Results	
				EC-50 (nM)	Percent DMPK reduction at 100 nM
GCAGGAUGUUGUCGGGU UUG	98	CAAACCCGACAA CATCTGC	334	0.1679	89.77
AGCAGGAUGUUGUCGGG UUU	115	AAACCCGACAAC ATCTGCT	351	0.2266	85.81
GCGUAGAAGGGCGUCUG CCC	109	GGGCAGACGCCC TTCTACGC	345	24.59	95.13
CCCAGCGCCCACCAGUCA CA	119	TGTGACTGGTGG GCGCTGGG	355	5.454	63.69
CCAUCUCGGCCGGAUUC CGC	77	GCGGATTCCGGC CGAGATGG	313	0.44	95.42
CGUCCAUCUGCCCGCA GCU	93	AGCTGCGGGCAG ATGGAACG	329	0.19	89.97
CAGGGACAGCCGCUUGA ACU	87	AGTTCCAGCGGC TGTCCCTG	323	6.04	90.59
CAUGGCAUACACCUGGC CCG	56	CGGGCCAGGTGT ATGCCATG	292	0.42	75.28
GCUUCAUCUUCACUACC GCU	85	AGCGGTAGTGAA GATGAAGC	321	0.03	64.06
GAAUGUCCGACAGUGUC UCC	92	GGAGACACTGTC GGACATTC	328	0.07	97.23
GGACGAUCUUGCCAUAU GUC	112	GACCTATGGCAA GATCGTCC	348	3.59	92.18
GCUGUCCCGGAGACCAU CCC	161	GGGATGGTCTCC GGGACAGC	397	3.27	93.07
GACAGAACAACGGCGAA CAG	145	CTGTTCGCCGTTG TTCTGTC	381	0.08	94.32
UGUUGUCGGGUUGAUG UCC	100	GGACATCAAACC CGACAACA	336	0.21	93.95
CGAAUGUCCGACAGUGU	59	GAGACACTGTCTG	295	0.18	95.93

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CUC		GACATTCG			
GGGCCUGGGACCUCACU GUC	69	GACAGTGAGGTC CCAGGCCC	305	0.07	90.58
CUCUGCCGCAGGGACAG CCG	71	CGGCTGTCCCTGC GGCAGAG	307	0.42	93.66
UUGCCAUAGGUCUCCGC CGU	79	ACGGCGGAGACC TATGGCAA	315	0.37	93.70

EQUIVALENTS AND TERMINOLOGY

[000319] 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.

[000320] 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.

[000321] 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 (e.g., an RNA counterpart of a DNA nucleotide or a DNA counterpart of an RNA nucleotide) and/or one or more modified nucleotides and/or one or more modified internucleotide linkages and/or one or more other modification compared with the

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specified sequence while retaining essentially same or similar complementary properties as the specified sequence.

[000322] 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.

[000323] 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.

[000324] 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.

[000325] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

[000326] The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A complex comprising an anti-transferrin receptor antibody covalently linked to an oligonucleotide that targets DMPK,
 wherein the oligonucleotide is 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 nucleotides in length and comprises a region of complementarity to a DMPK sequence as set forth in SEQ ID NO: 15, wherein the region of complementarity is at least 12 nucleotides in length; and
 wherein the anti-transferrin receptor antibody binds in the range of C89 to F760 of human transferrin receptor protein 1 (TfR1) having an amino acid sequence as set forth in SEQ ID NO: 1.
2. The complex of claim 1, wherein the anti-transferrin receptor antibody:
 - (a) is in the form of a ScFv, Fab fragment, Fab' fragment, F(ab')₂ fragment, or Fv fragment;
 - (b) binds human TfR1 with a K_D of 10^{-11} M to 10^{-6} M; and/or
 - (c) comprises a humanized antibody.
3. The complex of claim 1 or claim 2, wherein the anti-transferrin receptor antibody is in the form of a Fab fragment.
4. The complex of any one of claims 1-3, wherein the oligonucleotide targets a non-repeat region of DMPK RNA.
5. The complex of any one of claims 1-4, wherein the oligonucleotide comprises one or more modified nucleosides.
6. The complex of any one of claims 1-5, wherein the oligonucleotide is a gapmer oligonucleotide that directs RNase H-mediated cleavage of a DMPK mRNA transcript in a cell.
7. The complex of claim 6, wherein the oligonucleotide comprises a central portion of 5 to 15 deoxyribonucleosides flanked by wings of 2 to 8 modified nucleosides.

8. The complex of claim 5 or claim 7, wherein the modified nucleosides are 2'-modified nucleosides selected from the group consisting of: 2'-O-methyl, 2'-fluoro, 2'-O-methoxyethyl, and 2', 4'-bridged nucleosides.
9. The complex of any one of claims 1-8, wherein the oligonucleotide comprises one or more modified internucleoside linkages.
10. The complex of any one of claims 1-9, wherein the oligonucleotide comprises one or more phosphorothioate linkages.
11. The complex of any one of claims 1-10, wherein the oligonucleotide comprises a region of complementarity to at least 15 consecutive nucleotides of any one of SEQ ID NOs: 281-516.
12. The complex of any one of claims 1-11, wherein the oligonucleotide comprises at least 15 consecutive nucleotides of any one of SEQ ID NOs: 45-280, wherein the oligonucleotide optionally has one or more RNA counterparts of DNA nucleotides and/or DNA counterparts of RNA nucleotides of any one of SEQ ID NOs: 45-280.
13. The complex of any one of claims 1-10, wherein the oligonucleotide comprises a region of complementarity to at least 12 consecutive nucleotides of SEQ ID NO: 355.
14. The complex of any one of claims 1-10, wherein the oligonucleotide comprises a region of complementarity to at least 12 consecutive nucleotides of SEQ ID NO: 361.
15. The complex of any one of claims 1-10, wherein the oligonucleotide comprises a region of complementarity to at least 12 consecutive nucleotides of SEQ ID NO: 365.
16. The complex of any one of claims 1-10, wherein the oligonucleotide comprises a region of complementarity to at least 12 consecutive nucleotides of SEQ ID NO: 399.

17. The complex of any one of claims 1-10, wherein the oligonucleotide comprises at least 12 consecutive nucleotides of SEQ ID NO: 119, wherein the oligonucleotide optionally has one or more DNA counterparts of RNA nucleotides of SEQ ID NO: 119.
18. The complex of any one of claims 1-10, wherein the oligonucleotide comprises at least 12 consecutive nucleotides of SEQ ID NO: 125, wherein the oligonucleotide optionally has one or more DNA counterparts of RNA nucleotides of SEQ ID NO: 125.
19. The complex of any one of claims 1-10, wherein the oligonucleotide comprises at least 12 consecutive nucleotides of SEQ ID NO: 129, wherein the oligonucleotide optionally has one or more DNA counterparts of RNA nucleotides of SEQ ID NO: 129.
20. The complex of any one of claims 1-10, wherein the oligonucleotide comprises at least 12 consecutive nucleotides of SEQ ID NOs: 163, wherein the oligonucleotide optionally has one or more DNA counterparts of RNA nucleotides of SEQ ID NO: 163.
21. The complex of any one of claims 1-20, wherein the anti-transferrin receptor antibody is covalently linked to the oligonucleotide via a cleavable linker.
22. The complex of claim 21, wherein the cleavable linker comprises a protease-sensitive linker comprising a valine-citrulline sequence.
23. The complex of any one of claims 1-20, wherein the anti-transferrin receptor antibody is covalently linked to the oligonucleotide via a non-cleavable linker.
24. The complex of claim 23, wherein the non-cleavable linker is an alkane linker.
25. The complex of any one of claims 1-24, wherein the anti-transferrin receptor antibody is covalently linked to the oligonucleotide via conjugation to a lysine residue of the anti-transferrin receptor antibody.

26. The complex of any one of claims 1-24, wherein the anti-transferrin receptor antibody is covalently linked to the oligonucleotide via conjugation to a cysteine residue of the anti-transferrin receptor antibody.
27. The complex of any one of claims 1-26, wherein the complex is configured to promote transferrin receptor mediated internalization of the oligonucleotide into a muscle cell.
28. A method of treating a disease or condition in a subject, the method comprising contacting the muscle cell with the complex of any one of claims 1-27, wherein the disease or condition is capable of being improved or prevented by reducing expression level of DMPK in a muscle cell.
29. A method of treating myotonic dystrophy type 1 (DM1) in a subject, the method comprising administering to the subject an effective amount of the complex of any one of claims 1-27.
30. Use of the complex of any one of claims 1-27 in the manufacture of a medicament for treating a disease or condition in a subject, wherein the disease or condition is capable of being improved or prevented by reducing expression level of DMPK in a muscle cell.
31. Use of the complex of any one of claims 1-27 in the manufacture of a medicament for treating myotonic dystrophy type 1 (DM1) in a subject.
32. A complex that comprises an anti-transferrin receptor antibody covalently linked to an oligonucleotide that targets DMPK for use in therapy,
wherein the oligonucleotide is 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 nucleotides in length and comprises a region of complementarity to a DMPK sequence as set forth in SEQ ID NO: 15, wherein the region of complementarity is at least 12 nucleotides in length, wherein the oligonucleotide is an oligonucleotide comprising a central portion of 5 to 15 deoxyribonucleotides flanked by wings of 2 to 8 modified nucleotides, wherein the modified nucleotides are 2'-modified nucleosides; and

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

1.

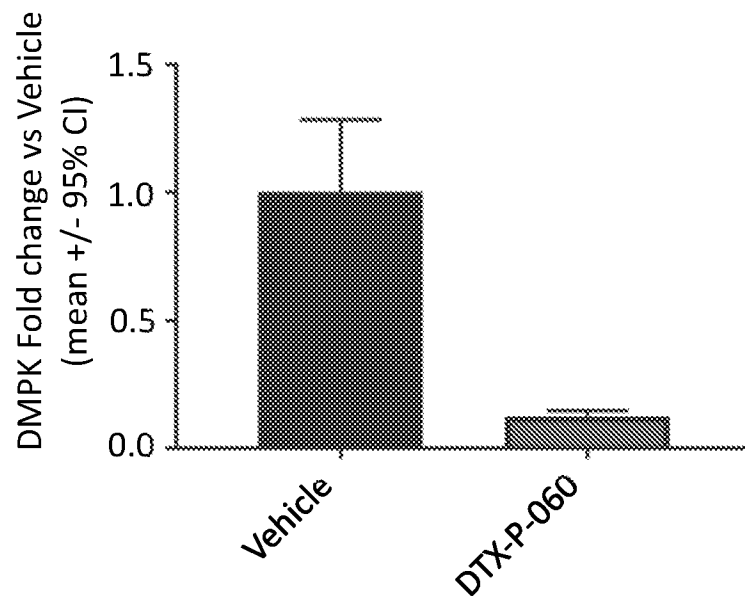


FIG. 1

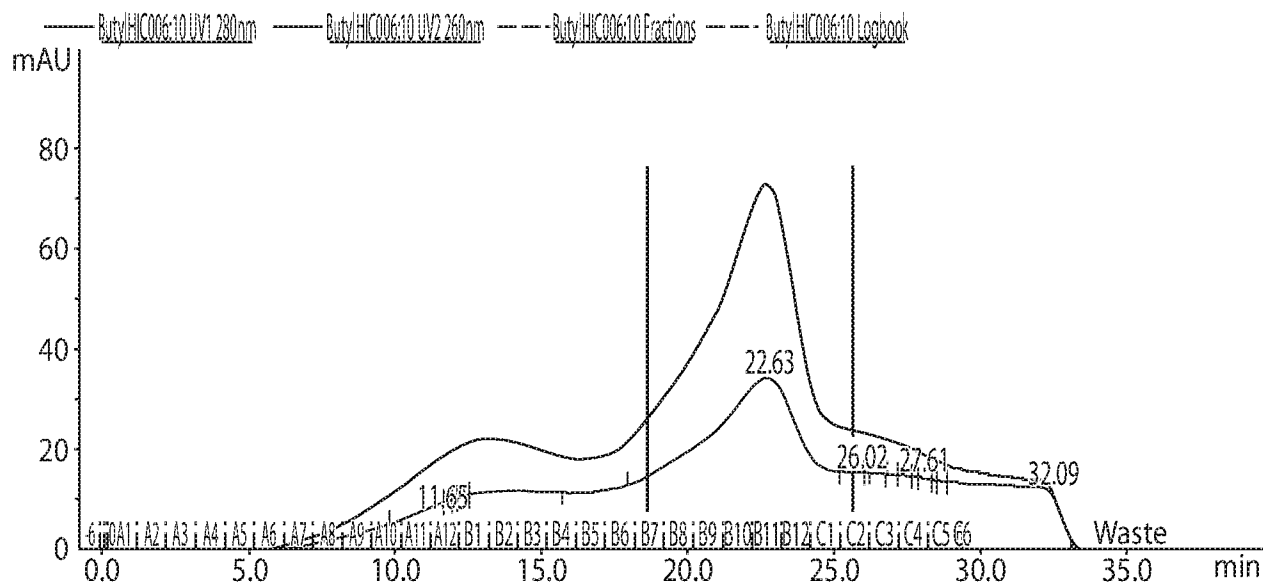
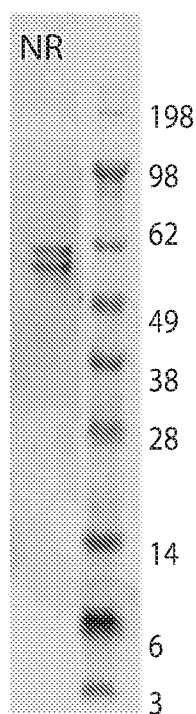


FIG. 2A



NuPage 4-12% 1mm SDS-PAGE
MES running buffer, 150v 50min

FIG. 2B

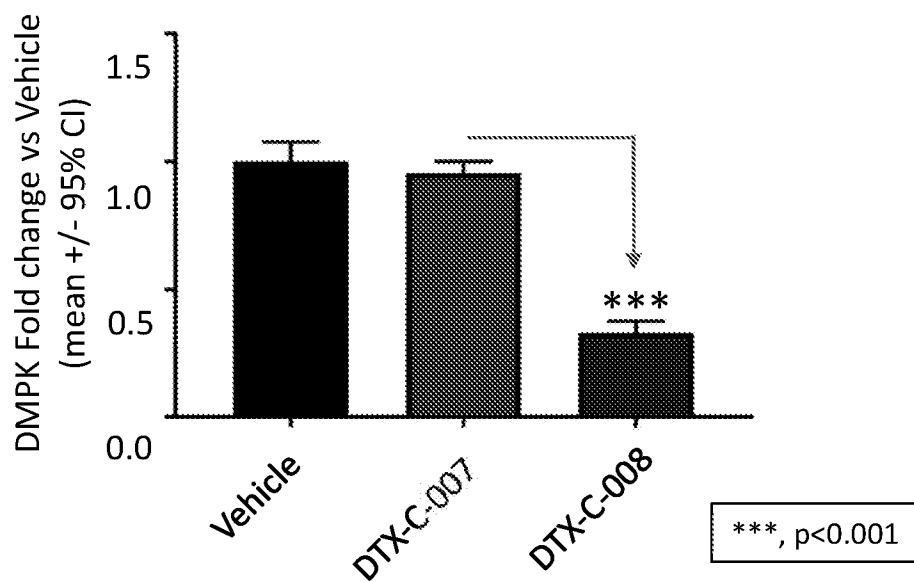


FIG. 3

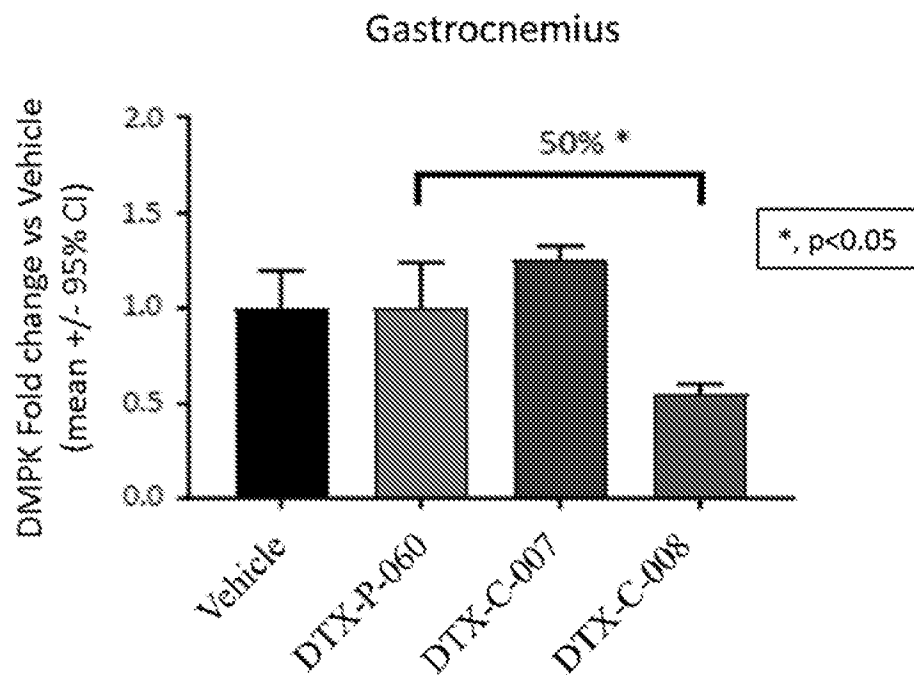


FIG. 4A

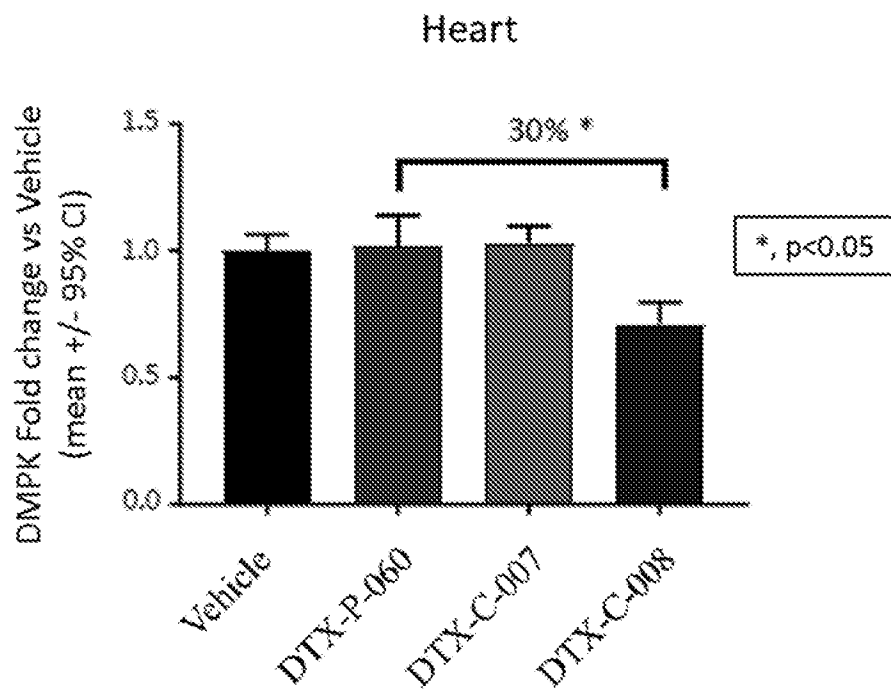


FIG. 4B

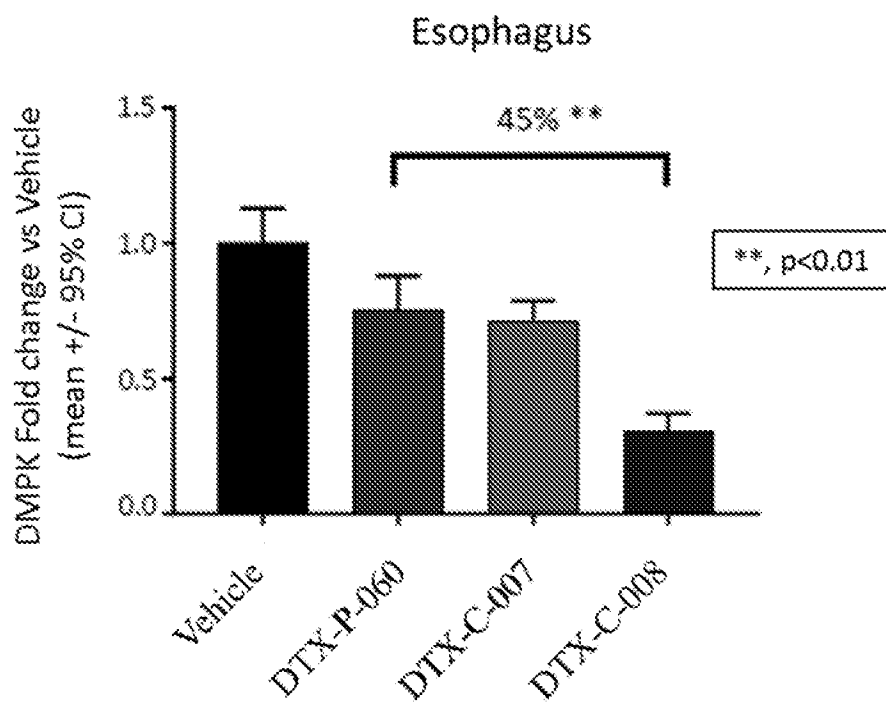


FIG. 4C

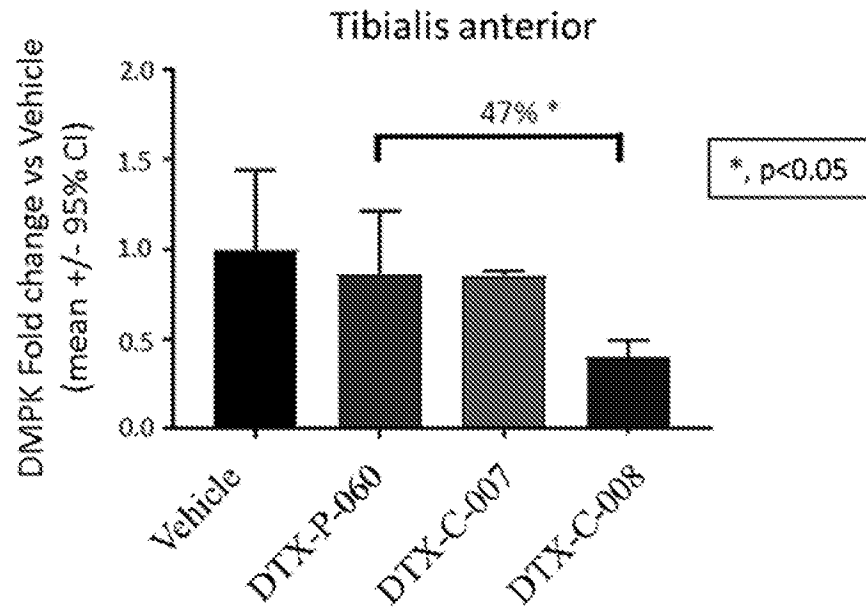


FIG. 4D

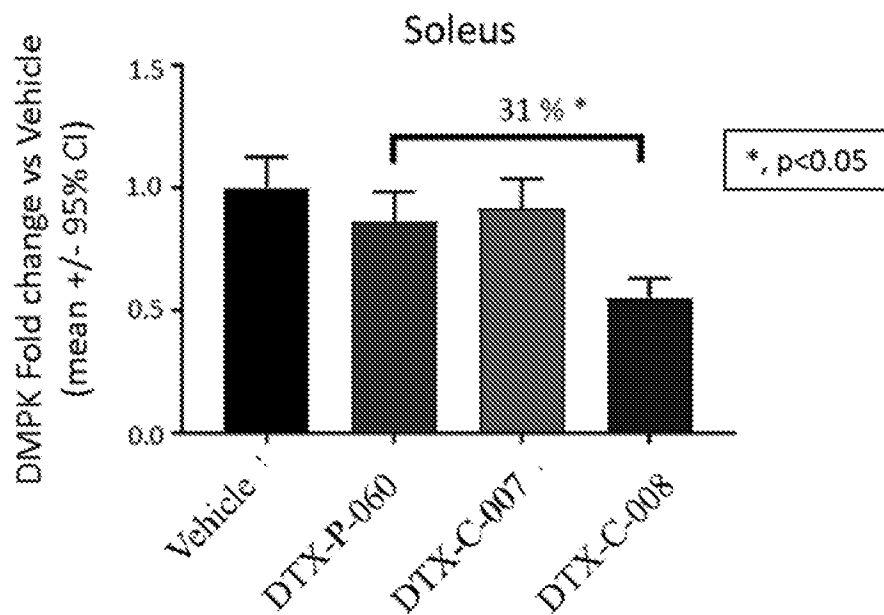


FIG. 4E

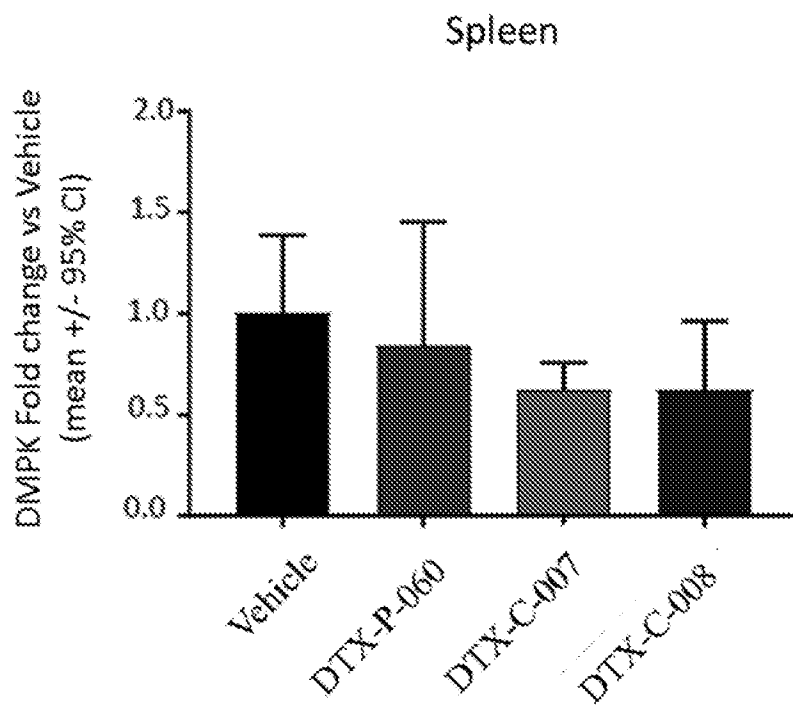


FIG. 5A

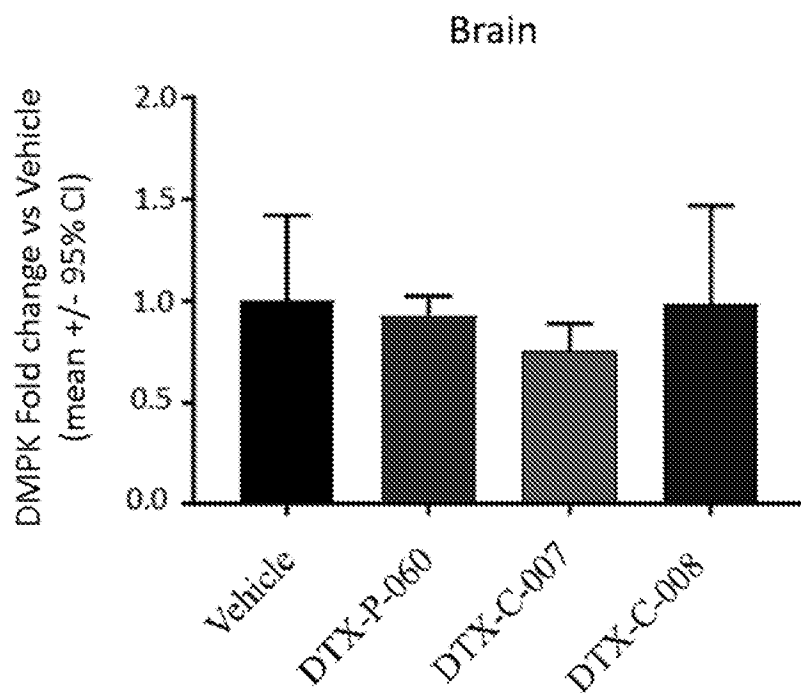


FIG. 5B

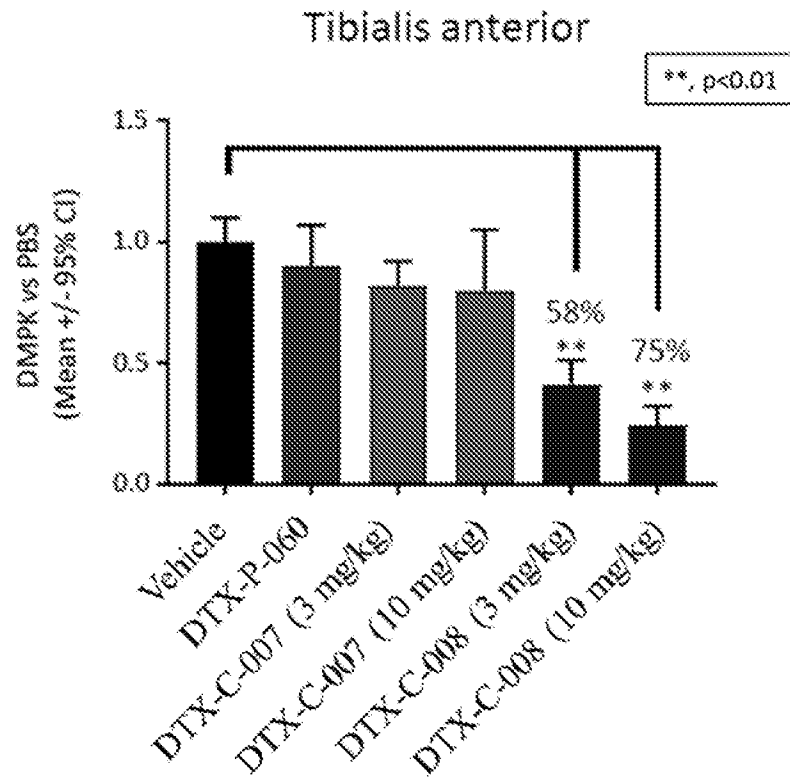


FIG. 6A

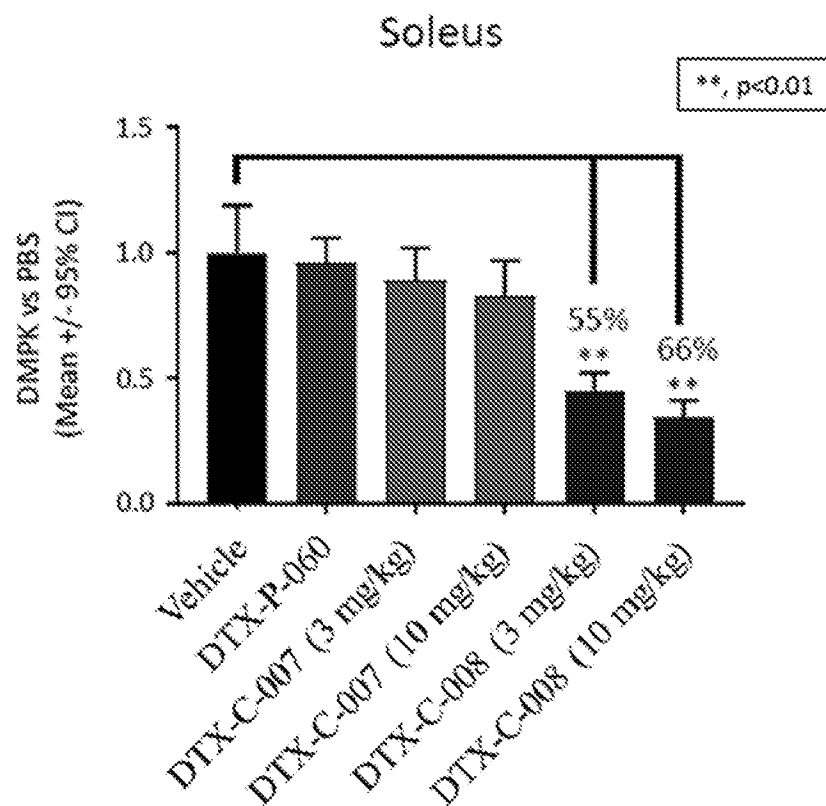


FIG. 6B

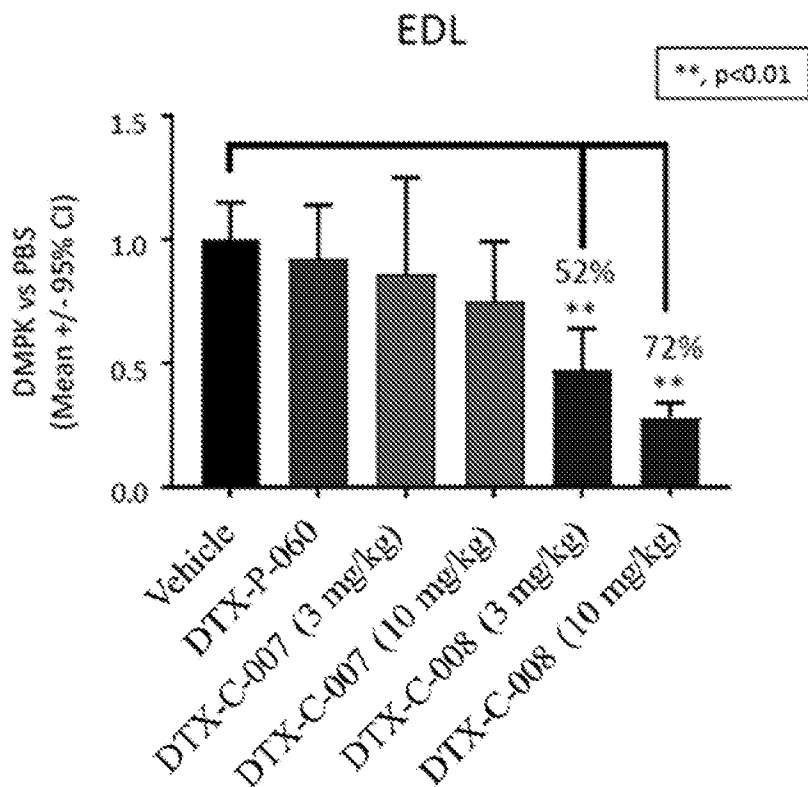


FIG. 6C

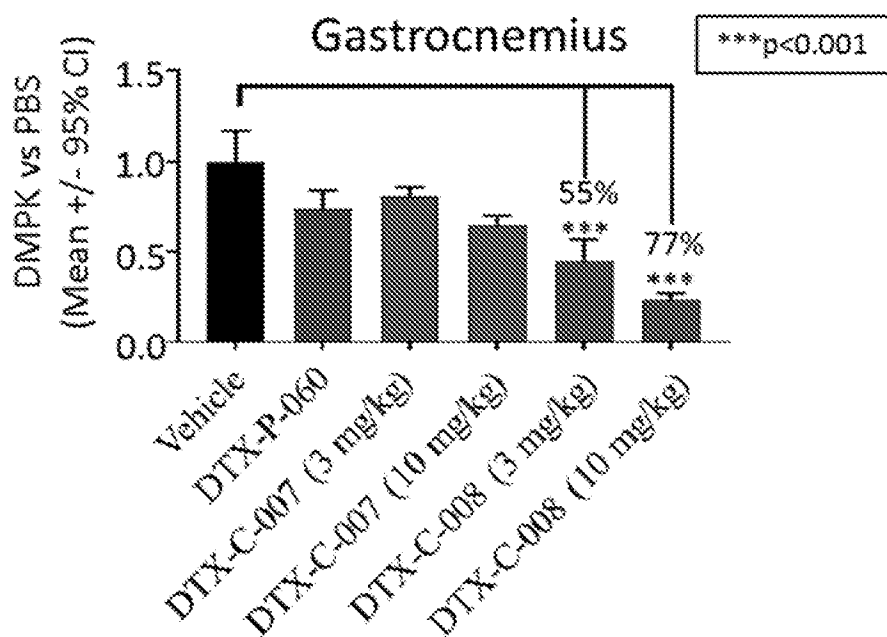


FIG. 6D

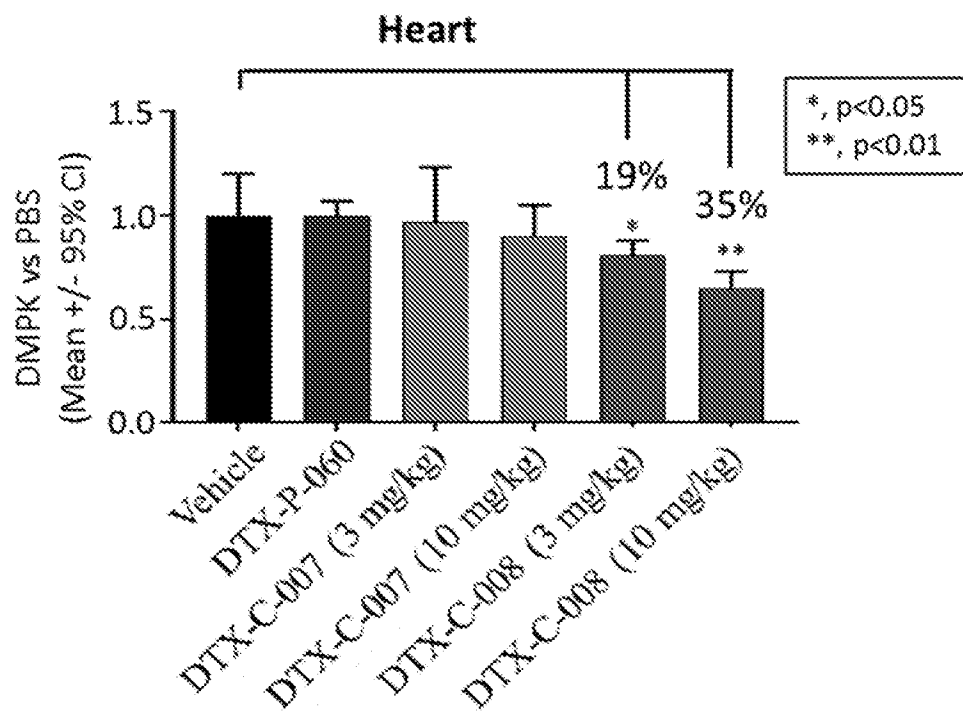


FIG. 6E

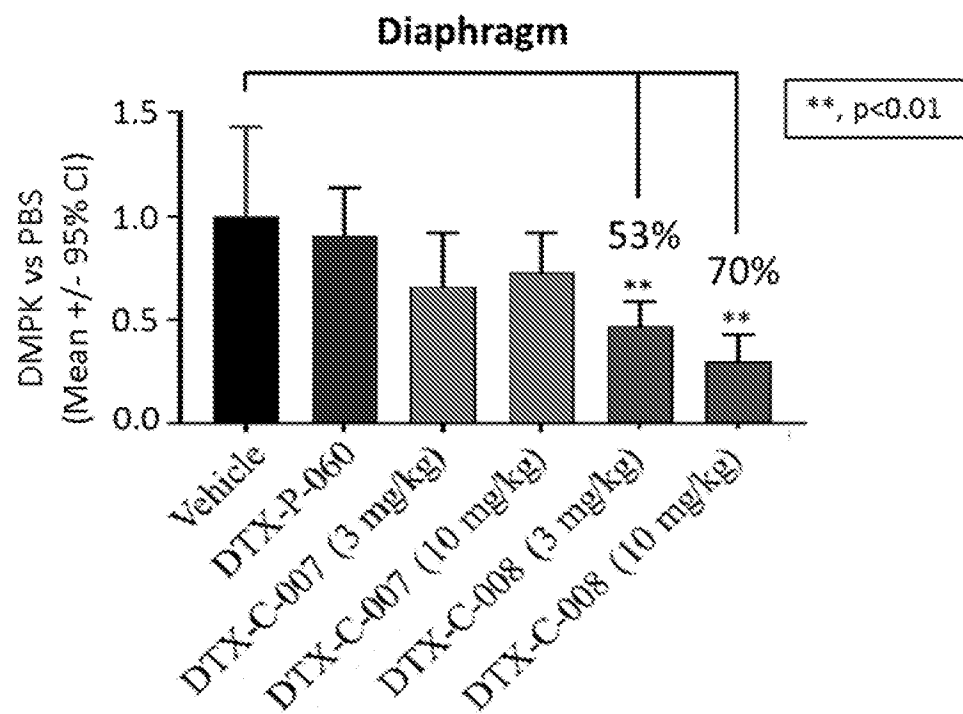


FIG. 6F

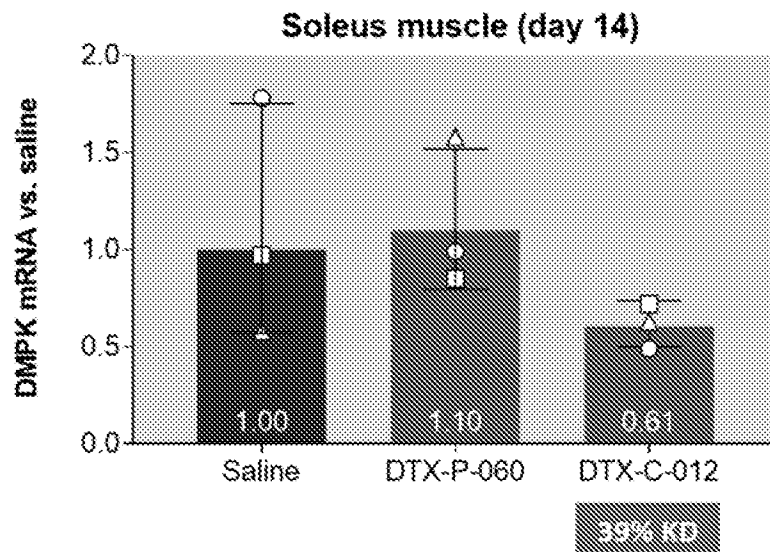


FIG. 7A

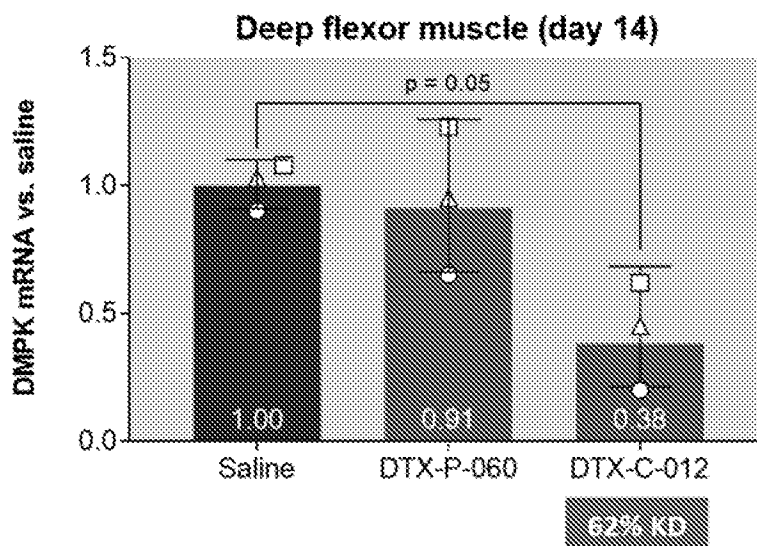


FIG. 7B

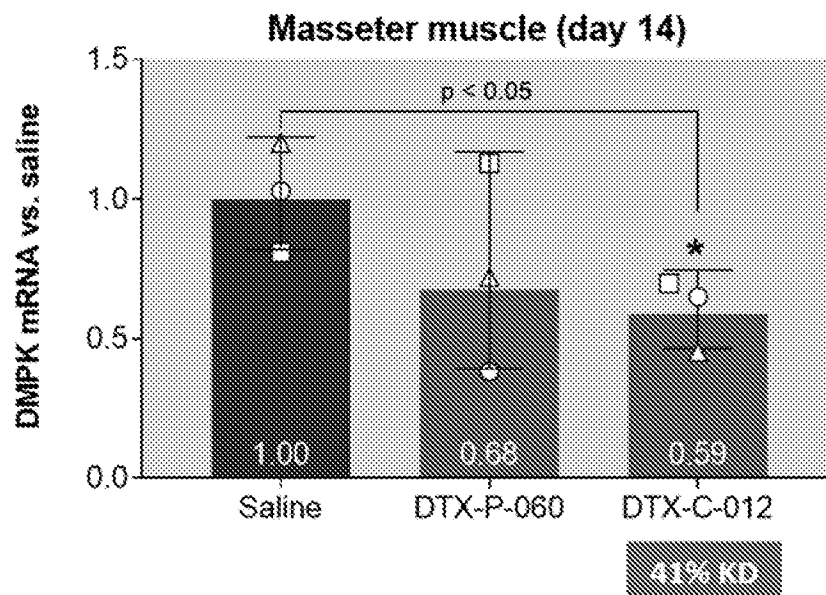


FIG. 7C

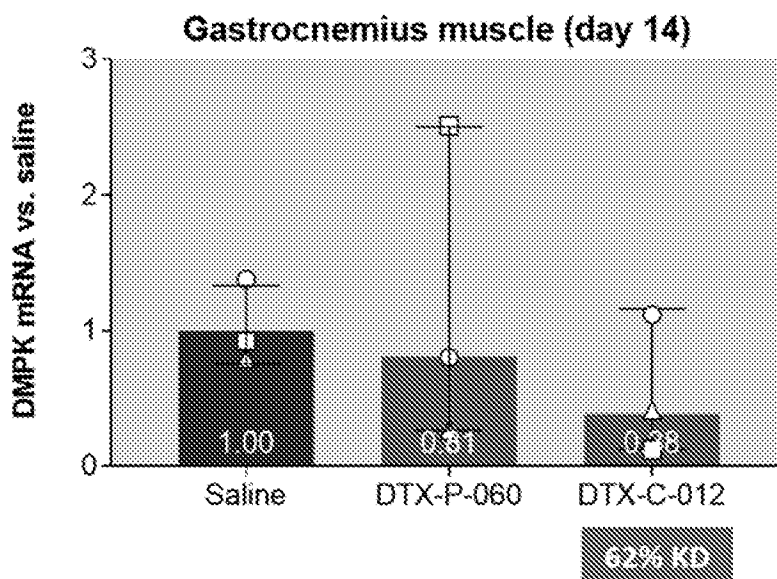


FIG. 7D

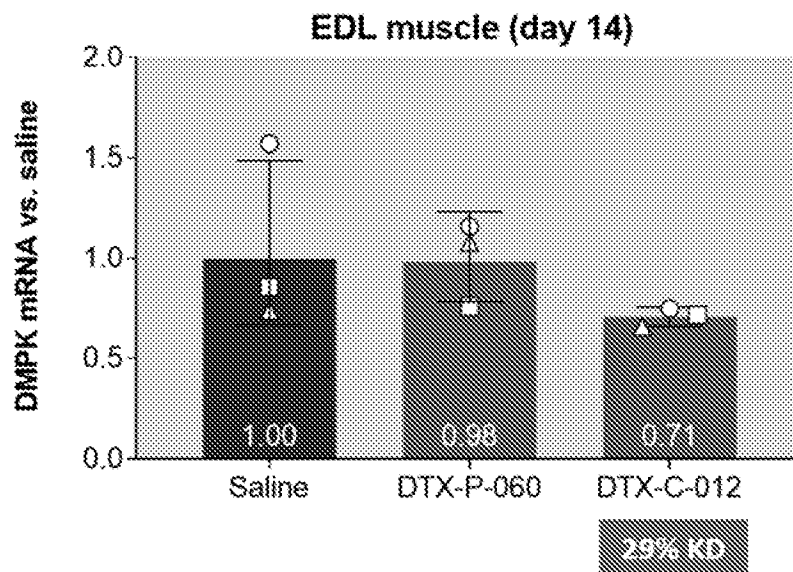


FIG. 7E

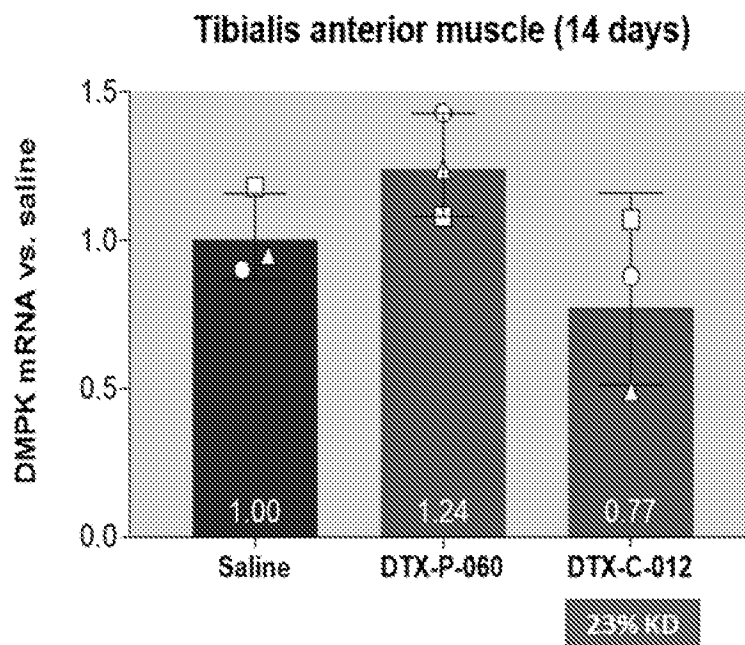


FIG. 7F

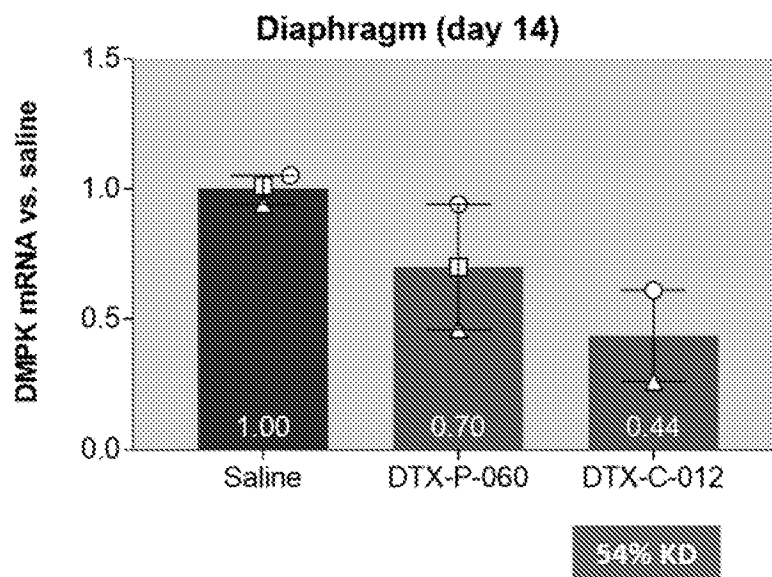


FIG. 7G

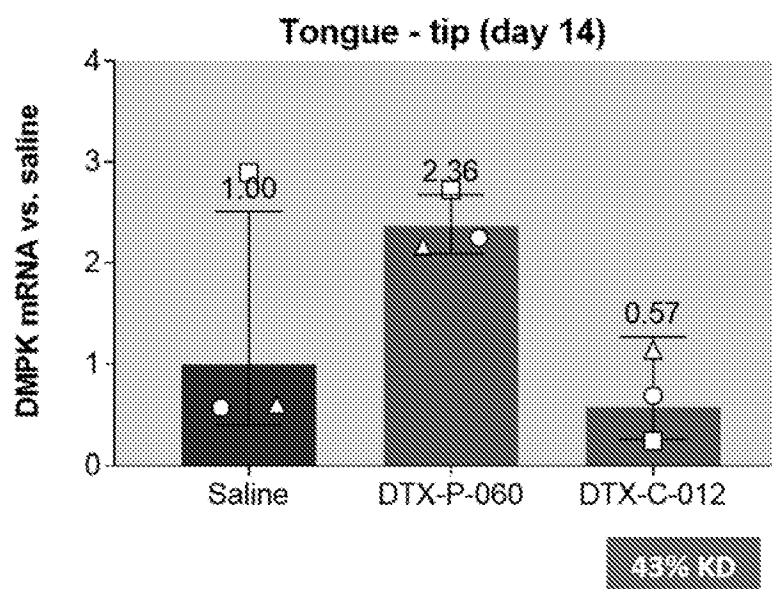


FIG. 7H

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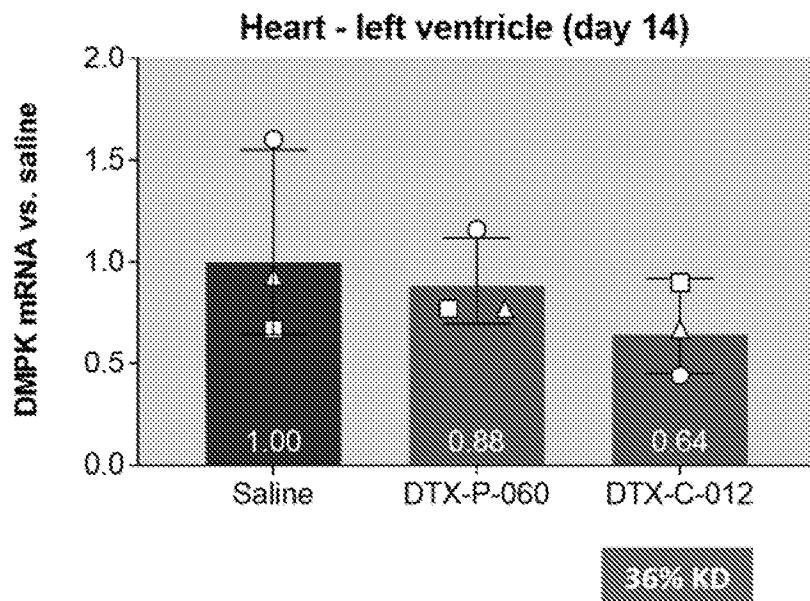


FIG. 7I

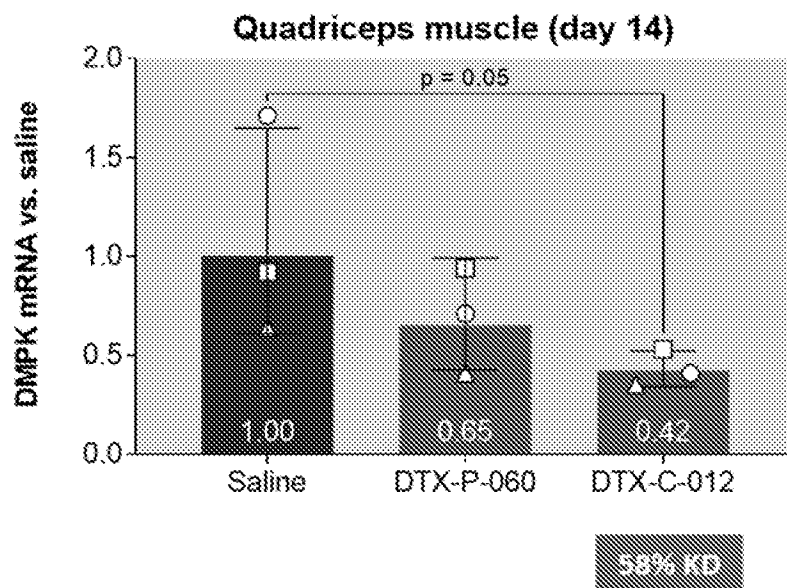


FIG. 7J

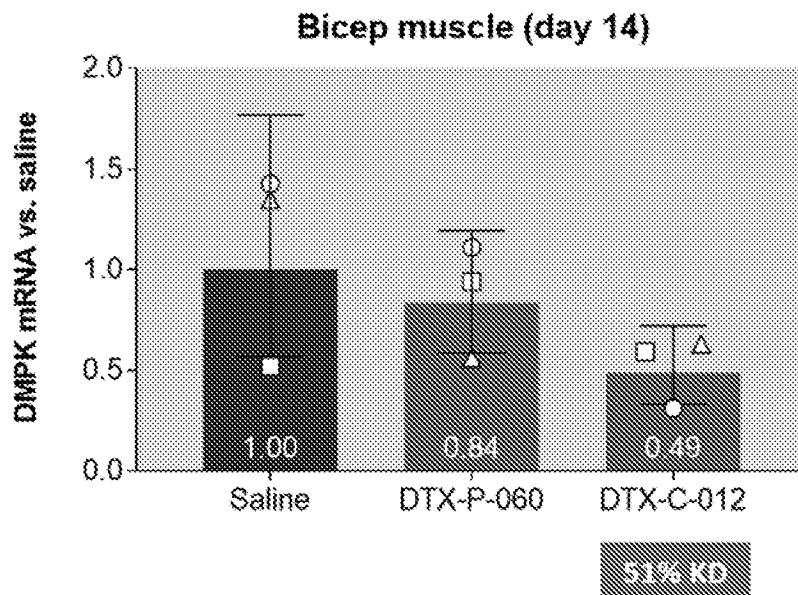


FIG. 7K

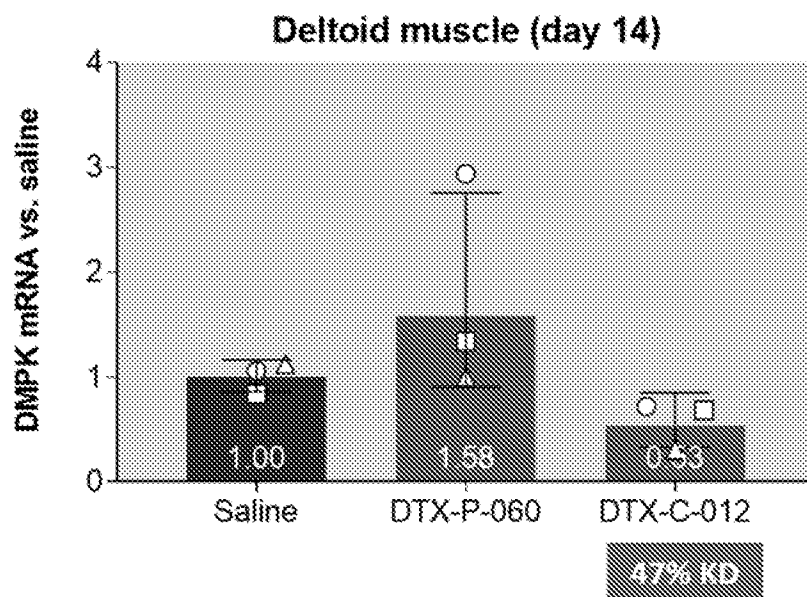


FIG. 7L

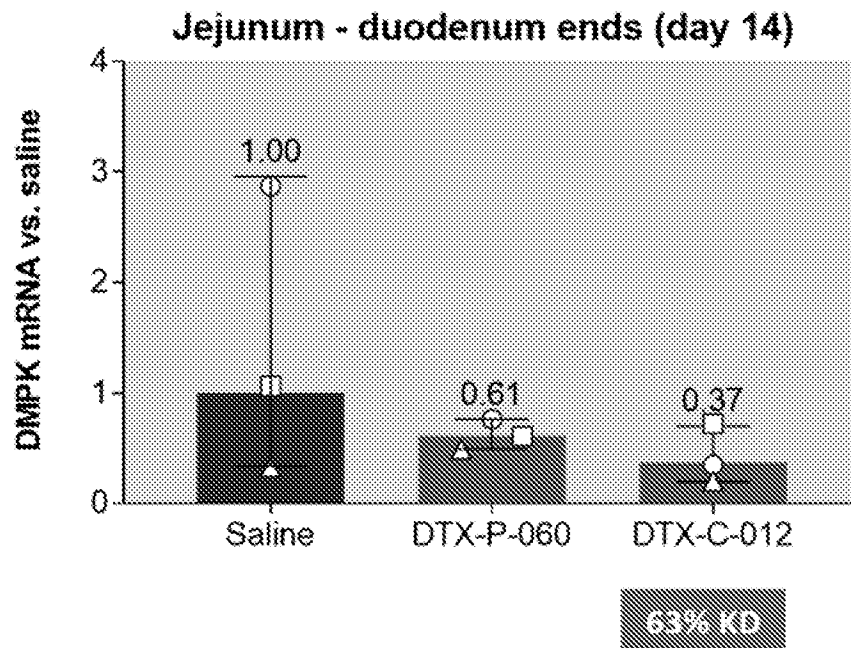


FIG. 8A

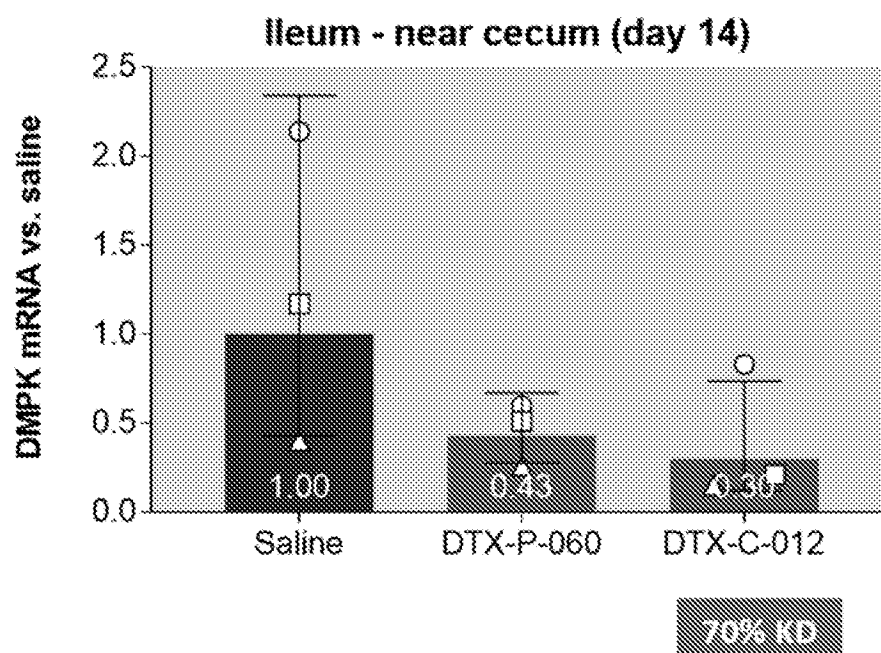


FIG. 8B

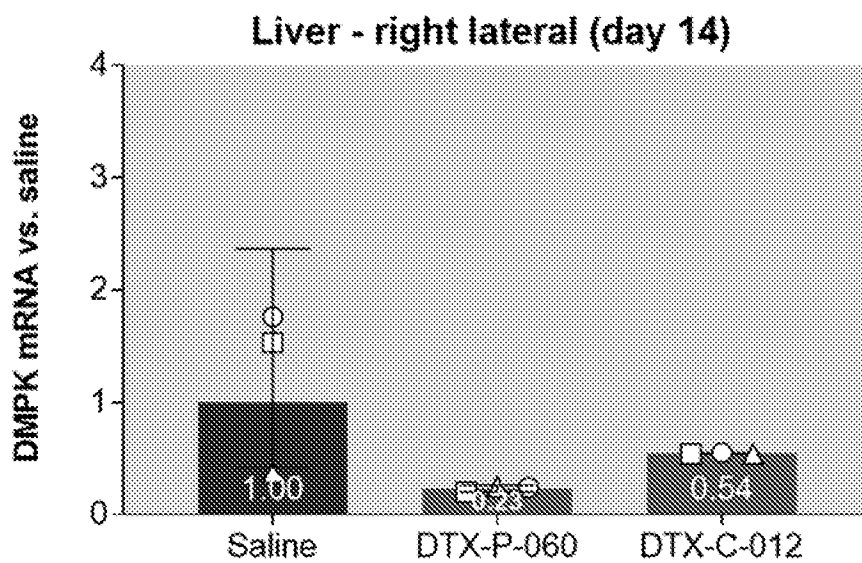


FIG. 9A

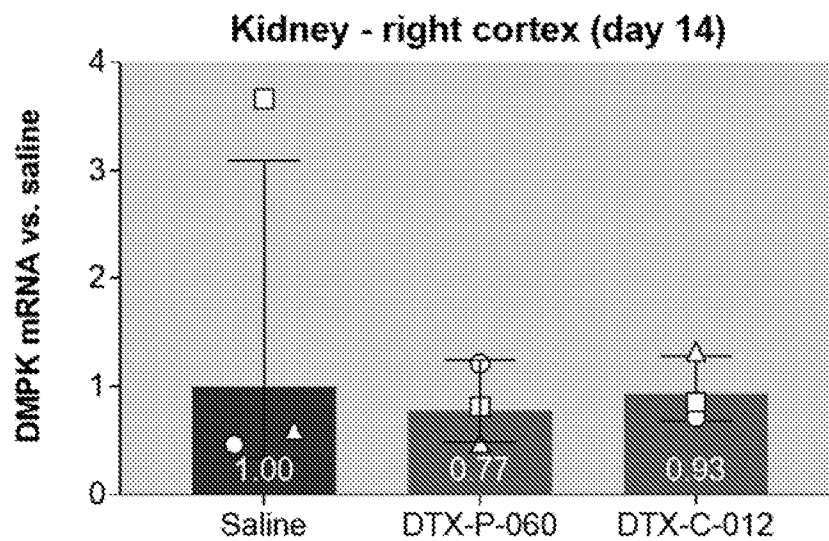


FIG. 9B

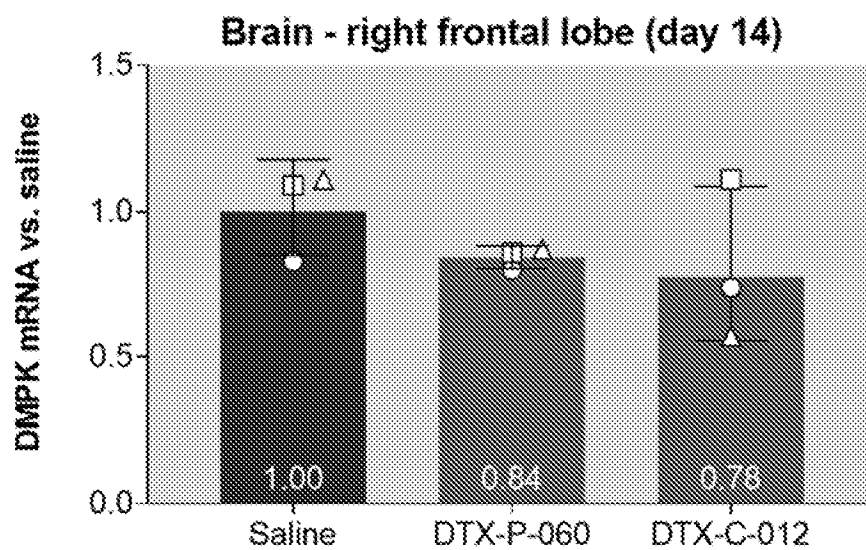


FIG. 9C

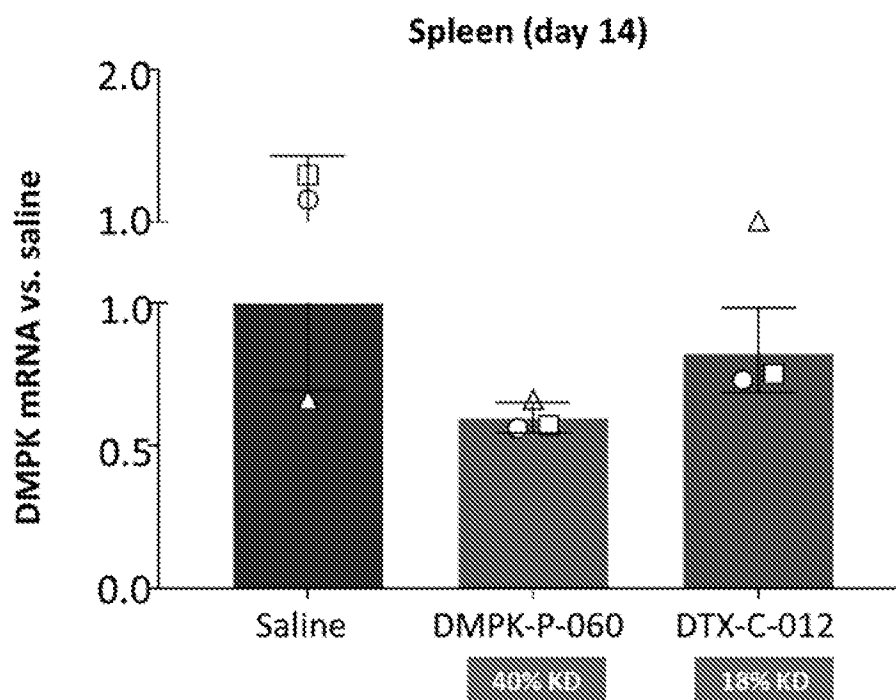


FIG. 9D

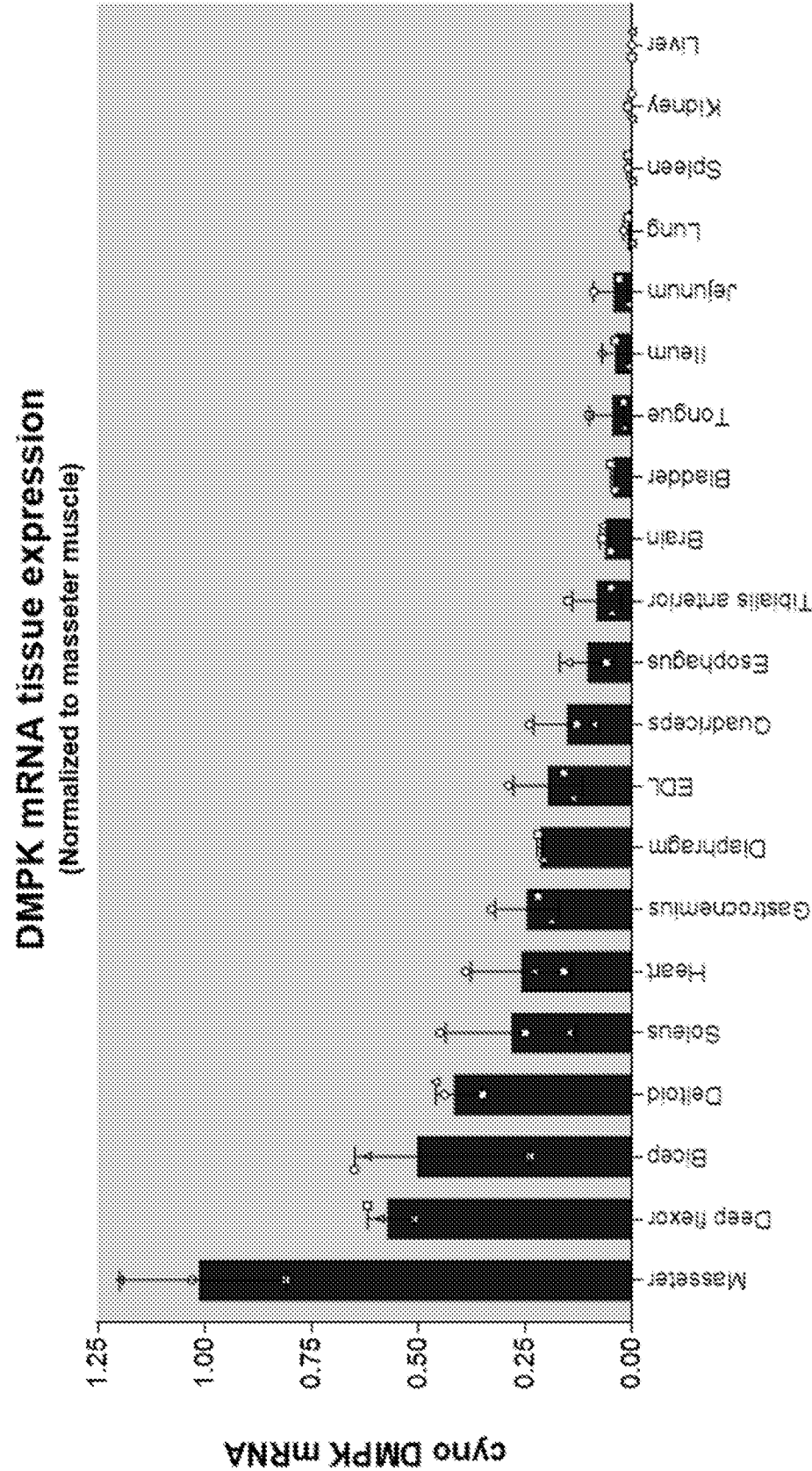


FIG. 10

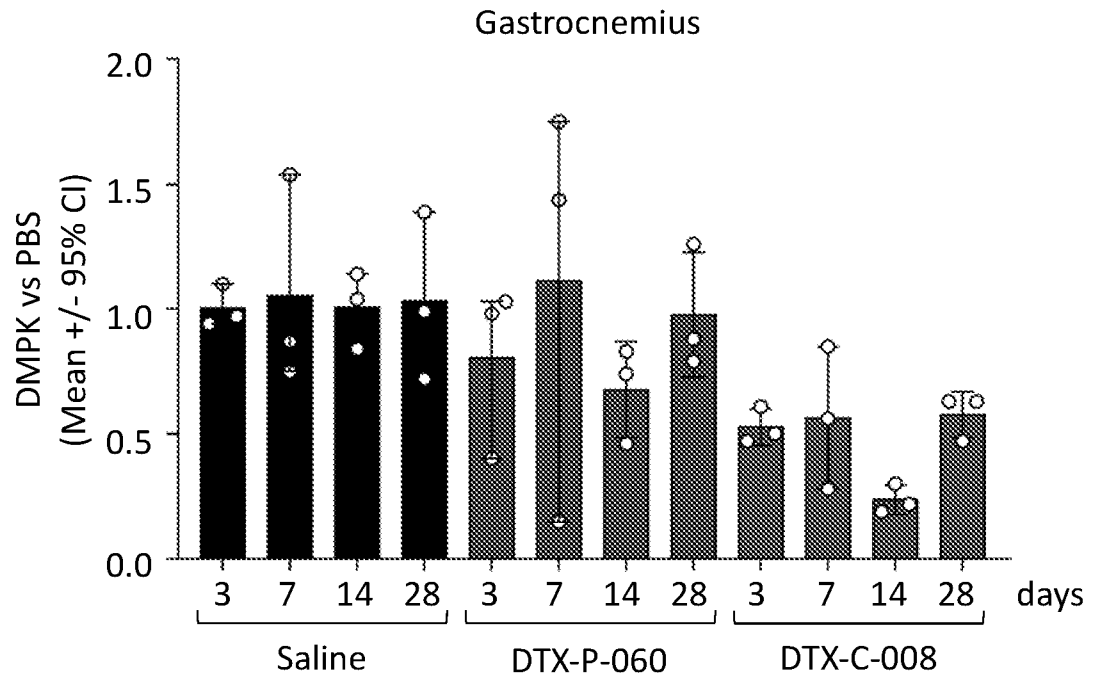


FIG. 11A

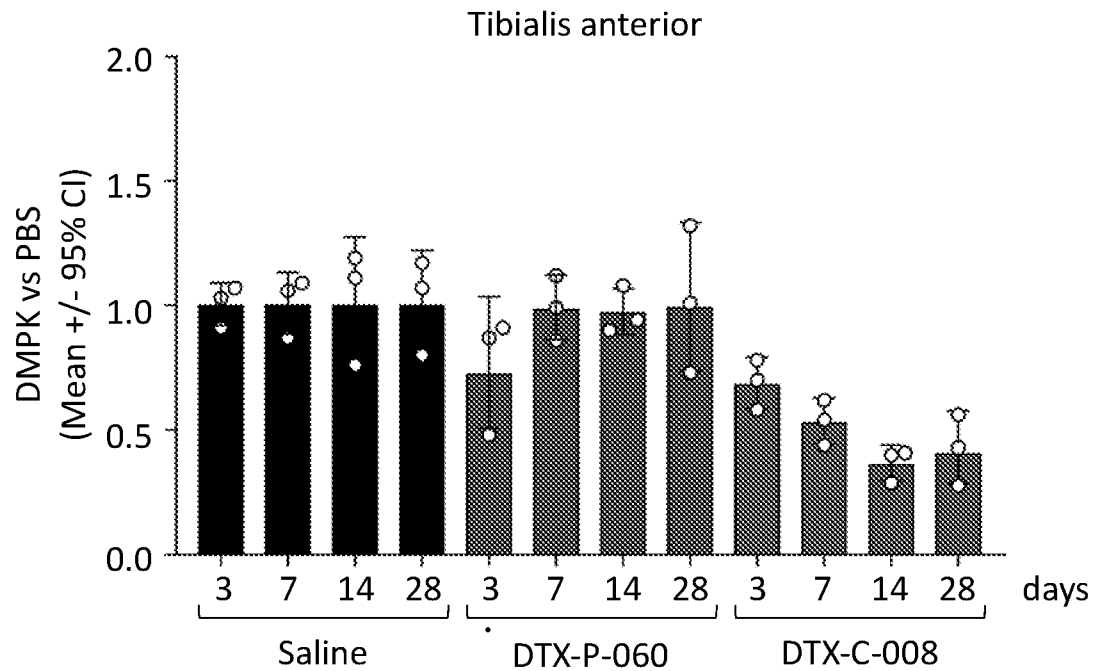


FIG. 11B

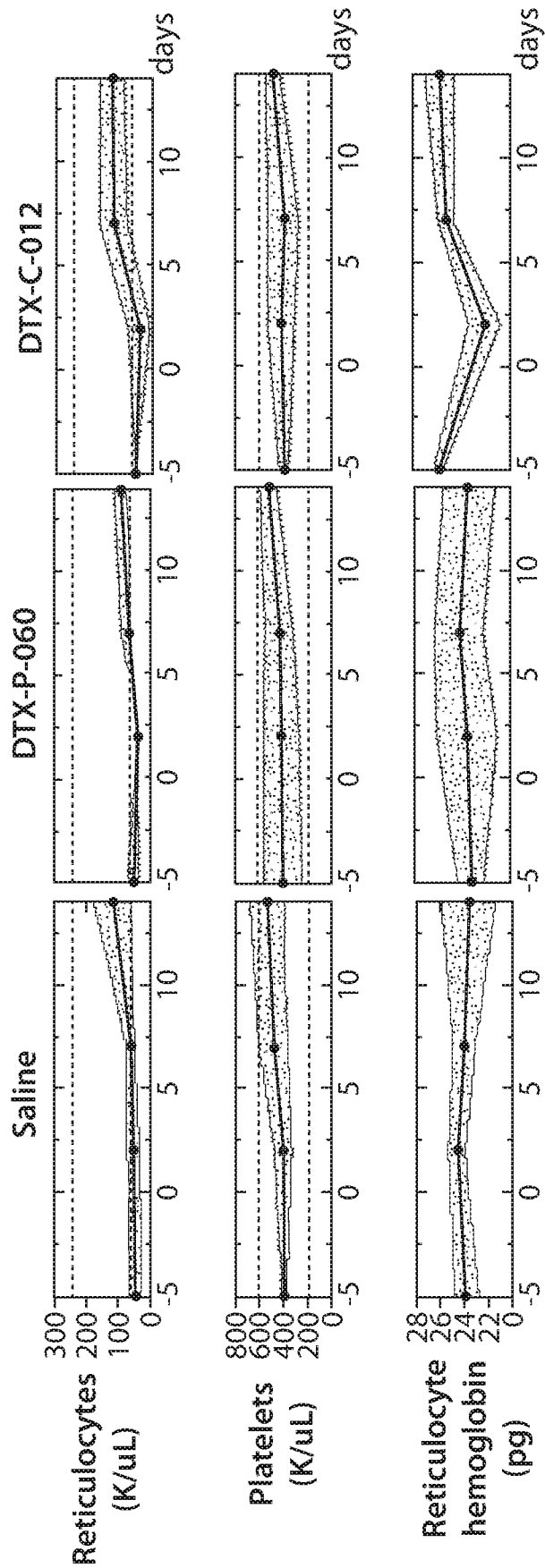


FIG. 12

SEQUENCE LISTING

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<130> D0824.70000W000

<140> Not Yet Assigned

<141> Concurrently Herewith

<150> US 62/859672

<151> 2019-06-10

<150> US 62/858888

<151> 2019-06-07

<150> US 62/855761

<151> 2019-05-31

<150> US 62/779161

<151> 2019-12-13

<150> US 62/713914

<151> 2019-08-02

<160> 516

<170> PatentIn version 3.5

<210> 1

<211> 760

<212> PRT

<213> Homo sapiens

<400> 1

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20 25 30

Asn Ser His Val Glu Met Lys Leu Ala Val Asp Glu Glu Glu Asn Ala
35 40 45

Asp Asn Asn Thr Lys Ala Asn Val Thr Lys Pro Lys Arg Cys Ser Gly
50 55 60

Ser Ile Cys Tyr Gly Thr Ile Ala Val Ile Val Phe Phe Leu Ile Gly
65 70 75 80

Phe Met Ile Gly Tyr Leu Gly Tyr Cys Lys Gly Val Glu Pro Lys Thr
85 90 95

Glu Cys Glu Arg Leu Ala Gly Thr Glu Ser Pro Val Arg Glu Glu Pro
100 105 110

Gly Glu Asp Phe Pro Ala Ala Arg Arg Leu Tyr Trp Asp Asp Leu Lys
115 120 125

Arg Lys Leu Ser Glu Lys Leu Asp Ser Thr Asp Phe Thr Gly Thr Ile
130 135 140

Lys Leu Leu Asn Glu Asn Ser Tyr Val Pro Arg Glu Ala Gly Ser Gln
145 150 155 160

Lys Asp Glu Asn Leu Ala Leu Tyr Val Glu Asn Gln Phe Arg Glu Phe
165 170 175

Lys Leu Ser Lys Val Trp Arg Asp Gln His Phe Val Lys Ile Gln Val
180 185 190

Lys Asp Ser Ala Gln Asn Ser Val Ile Ile Val Asp Lys Asn Gly Arg
195 200 205

Leu Val Tyr Leu Val Glu Asn Pro Gly Gly Tyr Val Ala Tyr Ser Lys
210 215 220

Ala Ala Thr Val Thr Gly Lys Leu Val His Ala Asn Phe Gly Thr Lys
225 230 235 240

Lys Asp Phe Glu Asp Leu Tyr Thr Pro Val Asn Gly Ser Ile Val Ile
245 250 255

Val Arg Ala Gly Lys Ile Thr Phe Ala Glu Lys Val Ala Asn Ala Glu
260 265 270

Ser Leu Asn Ala Ile Gly Val Leu Ile Tyr Met Asp Gln Thr Lys Phe
275 280 285

Pro Ile Val Asn Ala Glu Leu Ser Phe Phe Gly His Ala His Leu Gly
 290 295 300

Thr Gly Asp Pro Tyr Thr Pro Gly Phe Pro Ser Phe Asn His Thr Gln
 305 310 315 320

Phe Pro Pro Ser Arg Ser Ser Gly Leu Pro Asn Ile Pro Val Gln Thr
 325 330 335

Ile Ser Arg Ala Ala Ala Glu Lys Leu Phe Gly Asn Met Glu Gly Asp
 340 345 350

Cys Pro Ser Asp Trp Lys Thr Asp Ser Thr Cys Arg Met Val Thr Ser
 355 360 365

Glu Ser Lys Asn Val Lys Leu Thr Val Ser Asn Val Leu Lys Glu Ile
 370 375 380

Lys Ile Leu Asn Ile Phe Gly Val Ile Lys Gly Phe Val Glu Pro Asp
 385 390 395 400

His Tyr Val Val Val Gly Ala Gln Arg Asp Ala Trp Gly Pro Gly Ala
 405 410 415

Ala Lys Ser Gly Val Gly Thr Ala Leu Leu Leu Lys Leu Ala Gln Met
 420 425 430

Phe Ser Asp Met Val Leu Lys Asp Gly Phe Gln Pro Ser Arg Ser Ile
 435 440 445

Ile Phe Ala Ser Trp Ser Ala Gly Asp Phe Gly Ser Val Gly Ala Thr
 450 455 460

Glu Trp Leu Glu Gly Tyr Leu Ser Ser Leu His Leu Lys Ala Phe Thr
 465 470 475 480

Tyr Ile Asn Leu Asp Lys Ala Val Leu Gly Thr Ser Asn Phe Lys Val
 485 490 495

Ser Ala Ser Pro Leu Leu Tyr Thr Leu Ile Glu Lys Thr Met Gln Asn
500 505 510

Val Lys His Pro Val Thr Gly Gln Phe Leu Tyr Gln Asp Ser Asn Trp
515 520 525

Ala Ser Lys Val Glu Lys Leu Thr Leu Asp Asn Ala Ala Phe Pro Phe
530 535 540

Leu Ala Tyr Ser Gly Ile Pro Ala Val Ser Phe Cys Phe Cys Glu Asp
545 550 555 560

Thr Asp Tyr Pro Tyr Leu Gly Thr Thr Met Asp Thr Tyr Lys Glu Leu
565 570 575

Ile Glu Arg Ile Pro Glu Leu Asn Lys Val Ala Arg Ala Ala Ala Glu
580 585 590

Val Ala Gly Gln Phe Val Ile Lys Leu Thr His Asp Val Glu Leu Asn
595 600 605

Leu Asp Tyr Glu Arg Tyr Asn Ser Gln Leu Leu Ser Phe Val Arg Asp
610 615 620

Leu Asn Gln Tyr Arg Ala Asp Ile Lys Glu Met Gly Leu Ser Leu Gln
625 630 635 640

Trp Leu Tyr Ser Ala Arg Gly Asp Phe Phe Arg Ala Thr Ser Arg Leu
645 650 655

Thr Thr Asp Phe Gly Asn Ala Glu Lys Thr Asp Arg Phe Val Met Lys
660 665 670

Lys Leu Asn Asp Arg Val Met Arg Val Glu Tyr His Phe Leu Ser Pro
675 680 685

Tyr Val Ser Pro Lys Glu Ser Pro Phe Arg His Val Phe Trp Gly Ser
690 695 700

Gly Ser His Thr Leu Pro Ala Leu Leu Glu Asn Leu Lys Leu Arg Lys
705 710 715 720

Gln Asn Asn Gly Ala Phe Asn Glu Thr Leu Phe Arg Asn Gln Leu Ala
725 730 735

Leu Ala Thr Trp Thr Ile Gln Gly Ala Ala Asn Ala Leu Ser Gly Asp
740 745 750

Val Trp Asp Ile Asp Asn Glu Phe
755 760

<210> 2

<211> 760

<212> PRT

<213> Macaca mulatta

<400> 2

Met Met Asp Gln Ala Arg Ser Ala Phe Ser Asn Leu Phe Gly Gly Glu
1 5 10 15

Pro Leu Ser Tyr Thr Arg Phe Ser Leu Ala Arg Gln Val Asp Gly Asp
20 25 30

Asn Ser His Val Glu Met Lys Leu Gly Val Asp Glu Glu Glu Asn Thr
35 40 45

Asp Asn Asn Thr Lys Pro Asn Gly Thr Lys Pro Lys Arg Cys Gly Gly
50 55 60

Asn Ile Cys Tyr Gly Thr Ile Ala Val Ile Ile Phe Phe Leu Ile Gly
65 70 75 80

Phe Met Ile Gly Tyr Leu Gly Tyr Cys Lys Gly Val Glu Pro Lys Thr
85 90 95

Glu Cys Glu Arg Leu Ala Gly Thr Glu Ser Pro Ala Arg Glu Glu Pro
100 105 110

Glu Glu Asp Phe Pro Ala Ala Pro Arg Leu Tyr Trp Asp Asp Leu Lys
115 120 125

Arg Lys Leu Ser Glu Lys Leu Asp Thr Thr Asp Phe Thr Ser Thr Ile

130		135		140											
Lys 145	Leu	Leu	Asn	Glu	Asn	Leu	Tyr	Val	Pro	Arg	Glu	Ala	Gly	Ser	Gln 160
Lys	Asp	Glu	Asn	Leu	Ala	Leu	Tyr	Ile	Glu	Asn	Gln	Phe	Arg	Glu 175	Phe
Lys	Leu	Ser	Lys	Val	Trp	Arg	Asp	Gln	His	Phe	Val	Lys	Ile	Gln	Val 190
Lys	Asp	Ser	Ala	Gln	Asn	Ser	Val	Ile	Ile	Val	Asp	Lys	Asn	Gly	Gly
Leu	Val	Tyr	Leu	Val	Glu	Asn	Pro	Gly	Gly	Tyr	Val	Ala	Tyr	Ser	Lys
Ala	Ala	Thr	Val	Thr	Gly	Lys	Leu	Val	His	Ala	Asn	Phe	Gly	Thr	Lys
Lys	Asp	Phe	Glu	Asp	Leu	Asp	Ser	Pro	Val	Asn	Gly	Ser	Ile	Val	Ile
Val	Arg	Ala	Gly	Lys	Ile	Thr	Phe	Ala	Glu	Lys	Val	Ala	Asn	Ala	Glu
Ser	Leu	Asn	Ala	Ile	Gly	Val	Leu	Ile	Tyr	Met	Asp	Gln	Thr	Lys	Phe
Pro	Ile	Val	Lys	Ala	Asp	Leu	Ser	Phe	Phe	Gly	His	Ala	His	Leu	Gly
Thr	Gly	Asp	Pro	Tyr	Thr	Pro	Gly	Phe	Pro	Ser	Phe	Asn	His	Thr	Gln
Phe	Pro	Pro	Ser	Gln	Ser	Ser	Gly	Leu	Pro	Asn	Ile	Pro	Val	Gln	Thr
Ile	Ser	Arg	Ala	Ala	Ala	Glu	Lys	Leu	Phe	Gly	Asn	Met	Glu	Gly	Asp

Cys Pro Ser Asp Trp Lys Thr Asp Ser Thr Cys Lys Met Val Thr Ser
355 360 365

Glu Asn Lys Ser Val Lys Leu Thr Val Ser Asn Val Leu Lys Glu Thr
370 375 380

Lys Ile Leu Asn Ile Phe Gly Val Ile Lys Gly Phe Val Glu Pro Asp
385 390 395 400

His Tyr Val Val Val Gly Ala Gln Arg Asp Ala Trp Gly Pro Gly Ala
405 410 415

Ala Lys Ser Ser Val Gly Thr Ala Leu Leu Leu Lys Leu Ala Gln Met
420 425 430

Phe Ser Asp Met Val Leu Lys Asp Gly Phe Gln Pro Ser Arg Ser Ile
435 440 445

Ile Phe Ala Ser Trp Ser Ala Gly Asp Phe Gly Ser Val Gly Ala Thr
450 455 460

Glu Trp Leu Glu Gly Tyr Leu Ser Ser Leu His Leu Lys Ala Phe Thr
465 470 475 480

Tyr Ile Asn Leu Asp Lys Ala Val Leu Gly Thr Ser Asn Phe Lys Val
485 490 495

Ser Ala Ser Pro Leu Leu Tyr Thr Leu Ile Glu Lys Thr Met Gln Asp
500 505 510

Val Lys His Pro Val Thr Gly Arg Ser Leu Tyr Gln Asp Ser Asn Trp
515 520 525

Ala Ser Lys Val Glu Lys Leu Thr Leu Asp Asn Ala Ala Phe Pro Phe
530 535 540

Leu Ala Tyr Ser Gly Ile Pro Ala Val Ser Phe Cys Phe Cys Glu Asp
545 550 555 560

Thr Asp Tyr Pro Tyr Leu Gly Thr Thr Met Asp Thr Tyr Lys Glu Leu

565

570

575

Val Glu Arg Ile Pro Glu Leu Asn Lys Val Ala Arg Ala Ala Ala Glu
 580 585 590

Val Ala Gly Gln Phe Val Ile Lys Leu Thr His Asp Thr Glu Leu Asn
 595 600 605

Leu Asp Tyr Glu Arg Tyr Asn Ser Gln Leu Leu Leu Phe Leu Arg Asp
 610 615 620

Leu Asn Gln Tyr Arg Ala Asp Val Lys Glu Met Gly Leu Ser Leu Gln
 625 630 635 640

Trp Leu Tyr Ser Ala Arg Gly Asp Phe Phe Arg Ala Thr Ser Arg Leu
 645 650 655

Thr Thr Asp Phe Arg Asn Ala Glu Lys Arg Asp Lys Phe Val Met Lys
 660 665 670

Lys Leu Asn Asp Arg Val Met Arg Val Glu Tyr Tyr Phe Leu Ser Pro
 675 680 685

Tyr Val Ser Pro Lys Glu Ser Pro Phe Arg His Val Phe Trp Gly Ser
 690 695 700

Gly Ser His Thr Leu Ser Ala Leu Leu Glu Ser Leu Lys Leu Arg Arg
 705 710 715 720

Gln Asn Asn Ser Ala Phe Asn Glu Thr Leu Phe Arg Asn Gln Leu Ala
 725 730 735

Leu Ala Thr Trp Thr Ile Gln Gly Ala Ala Asn Ala Leu Ser Gly Asp
 740 745 750

Val Trp Asp Ile Asp Asn Glu Phe
 755 760

<210> 3

<211> 760

<212> PRT

<213> Macaca fascicularis

<400> 3

Met Met Asp Gln Ala Arg Ser Ala Phe Ser Asn Leu Phe Gly Gly Glu
1 5 10 15

Pro Leu Ser Tyr Thr Arg Phe Ser Leu Ala Arg Gln Val Asp Gly Asp
20 25 30

Asn Ser His Val Glu Met Lys Leu Gly Val Asp Glu Glu Glu Asn Thr
35 40 45

Asp Asn Asn Thr Lys Ala Asn Gly Thr Lys Pro Lys Arg Cys Gly Gly
50 55 60

Asn Ile Cys Tyr Gly Thr Ile Ala Val Ile Ile Phe Phe Leu Ile Gly
65 70 75 80

Phe Met Ile Gly Tyr Leu Gly Tyr Cys Lys Gly Val Glu Pro Lys Thr
85 90 95

Glu Cys Glu Arg Leu Ala Gly Thr Glu Ser Pro Ala Arg Glu Glu Pro
100 105 110

Glu Glu Asp Phe Pro Ala Ala Pro Arg Leu Tyr Trp Asp Asp Leu Lys
115 120 125

Arg Lys Leu Ser Glu Lys Leu Asp Thr Thr Asp Phe Thr Ser Thr Ile
130 135 140

Lys Leu Leu Asn Glu Asn Leu Tyr Val Pro Arg Glu Ala Gly Ser Gln
145 150 155 160

Lys Asp Glu Asn Leu Ala Leu Tyr Ile Glu Asn Gln Phe Arg Glu Phe
165 170 175

Lys Leu Ser Lys Val Trp Arg Asp Gln His Phe Val Lys Ile Gln Val
180 185 190

Lys Asp Ser Ala Gln Asn Ser Val Ile Ile Val Asp Lys Asn Gly Gly
195 200 205

Leu Val Tyr Leu Val Glu Asn Pro Gly Gly Tyr Val Ala Tyr Ser Lys
210 215 220

Ala Ala Thr Val Thr Gly Lys Leu Val His Ala Asn Phe Gly Thr Lys
225 230 235 240

Lys Asp Phe Glu Asp Leu Asp Ser Pro Val Asn Gly Ser Ile Val Ile
245 250 255

Val Arg Ala Gly Lys Ile Thr Phe Ala Glu Lys Val Ala Asn Ala Glu
260 265 270

Ser Leu Asn Ala Ile Gly Val Leu Ile Tyr Met Asp Gln Thr Lys Phe
275 280 285

Pro Ile Val Lys Ala Asp Leu Ser Phe Phe Gly His Ala His Leu Gly
290 295 300

Thr Gly Asp Pro Tyr Thr Pro Gly Phe Pro Ser Phe Asn His Thr Gln
305 310 315 320

Phe Pro Pro Ser Gln Ser Ser Gly Leu Pro Asn Ile Pro Val Gln Thr
325 330 335

Ile Ser Arg Ala Ala Ala Glu Lys Leu Phe Gly Asn Met Glu Gly Asp
340 345 350

Cys Pro Ser Asp Trp Lys Thr Asp Ser Thr Cys Lys Met Val Thr Ser
355 360 365

Glu Asn Lys Ser Val Lys Leu Thr Val Ser Asn Val Leu Lys Glu Thr
370 375 380

Lys Ile Leu Asn Ile Phe Gly Val Ile Lys Gly Phe Val Glu Pro Asp
385 390 395 400

His Tyr Val Val Val Gly Ala Gln Arg Asp Ala Trp Gly Pro Gly Ala
405 410 415

Ala Lys Ser Ser Val Gly Thr Ala Leu Leu Leu Lys Leu Ala Gln Met
420 425 430

Phe Ser Asp Met Val Leu Lys Asp Gly Phe Gln Pro Ser Arg Ser Ile
435 440 445

Ile Phe Ala Ser Trp Ser Ala Gly Asp Phe Gly Ser Val Gly Ala Thr
450 455 460

Glu Trp Leu Glu Gly Tyr Leu Ser Ser Leu His Leu Lys Ala Phe Thr
465 470 475 480

Tyr Ile Asn Leu Asp Lys Ala Val Leu Gly Thr Ser Asn Phe Lys Val
485 490 495

Ser Ala Ser Pro Leu Leu Tyr Thr Leu Ile Glu Lys Thr Met Gln Asp
500 505 510

Val Lys His Pro Val Thr Gly Arg Ser Leu Tyr Gln Asp Ser Asn Trp
515 520 525

Ala Ser Lys Val Glu Lys Leu Thr Leu Asp Asn Ala Ala Phe Pro Phe
530 535 540

Leu Ala Tyr Ser Gly Ile Pro Ala Val Ser Phe Cys Phe Cys Glu Asp
545 550 555 560

Thr Asp Tyr Pro Tyr Leu Gly Thr Thr Met Asp Thr Tyr Lys Glu Leu
565 570 575

Val Glu Arg Ile Pro Glu Leu Asn Lys Val Ala Arg Ala Ala Glu
580 585 590

Val Ala Gly Gln Phe Val Ile Lys Leu Thr His Asp Thr Glu Leu Asn
595 600 605

Leu Asp Tyr Glu Arg Tyr Asn Ser Gln Leu Leu Leu Phe Leu Arg Asp
610 615 620

Leu Asn Gln Tyr Arg Ala Asp Val Lys Glu Met Gly Leu Ser Leu Gln
625 630 635 640

Trp Leu Tyr Ser Ala Arg Gly Asp Phe Phe Arg Ala Thr Ser Arg Leu
645 650 655

Thr Thr Asp Phe Arg Asn Ala Glu Lys Arg Asp Lys Phe Val Met Lys
660 665 670

Lys Leu Asn Asp Arg Val Met Arg Val Glu Tyr Tyr Phe Leu Ser Pro
675 680 685

Tyr Val Ser Pro Lys Glu Ser Pro Phe Arg His Val Phe Trp Gly Ser
690 695 700

Gly Ser His Thr Leu Ser Ala Leu Leu Glu Ser Leu Lys Leu Arg Arg
705 710 715 720

Gln Asn Asn Ser Ala Phe Asn Glu Thr Leu Phe Arg Asn Gln Leu Ala
725 730 735

Leu Ala Thr Trp Thr Ile Gln Gly Ala Ala Asn Ala Leu Ser Gly Asp
740 745 750

Val Trp Asp Ile Asp Asn Glu Phe
755 760

<210> 4
<211> 763
<212> PRT
<213> Mus musculus

<400> 4

Met Met Asp Gln Ala Arg Ser Ala Phe Ser Asn Leu Phe Gly Gly Glu
1 5 10 15

Pro Leu Ser Tyr Thr Arg Phe Ser Leu Ala Arg Gln Val Asp Gly Asp
20 25 30

Asn Ser His Val Glu Met Lys Leu Ala Ala Asp Glu Glu Glu Asn Ala
35 40 45

Asp Asn Asn Met Lys Ala Ser Val Arg Lys Pro Lys Arg Phe Asn Gly

50

55

60

Arg Leu Cys Phe Ala Ala Ile Ala Leu Val Ile Phe Phe Leu Ile Gly
 65 70 75 80

Phe Met Ser Gly Tyr Leu Gly Tyr Cys Lys Arg Val Glu Gln Lys Glu
 85 90 95

Glu Cys Val Lys Leu Ala Glu Thr Glu Glu Thr Asp Lys Ser Glu Thr
 100 105 110

Met Glu Thr Glu Asp Val Pro Thr Ser Ser Arg Leu Tyr Trp Ala Asp
 115 120 125

Leu Lys Thr Leu Leu Ser Glu Lys Leu Asn Ser Ile Glu Phe Ala Asp
 130 135 140

Thr Ile Lys Gln Leu Ser Gln Asn Thr Tyr Thr Pro Arg Glu Ala Gly
 145 150 155 160

Ser Gln Lys Asp Glu Ser Leu Ala Tyr Tyr Ile Glu Asn Gln Phe His
 165 170 175

Glu Phe Lys Phe Ser Lys Val Trp Arg Asp Glu His Tyr Val Lys Ile
 180 185 190

Gln Val Lys Ser Ser Ile Gly Gln Asn Met Val Thr Ile Val Gln Ser
 195 200 205

Asn Gly Asn Leu Asp Pro Val Glu Ser Pro Glu Gly Tyr Val Ala Phe
 210 215 220

Ser Lys Pro Thr Glu Val Ser Gly Lys Leu Val His Ala Asn Phe Gly
 225 230 235 240

Thr Lys Lys Asp Phe Glu Glu Leu Ser Tyr Ser Val Asn Gly Ser Leu
 245 250 255

Val Ile Val Arg Ala Gly Glu Ile Thr Phe Ala Glu Lys Val Ala Asn
 260 265 270

Ala Gln Ser Phe Asn Ala Ile Gly Val Leu Ile Tyr Met Asp Lys Asn
275 280 285

Lys Phe Pro Val Val Glu Ala Asp Leu Ala Leu Phe Gly His Ala His
290 295 300

Leu Gly Thr Gly Asp Pro Tyr Thr Pro Gly Phe Pro Ser Phe Asn His
305 310 315 320

Thr Gln Phe Pro Pro Ser Gln Ser Ser Gly Leu Pro Asn Ile Pro Val
325 330 335

Gln Thr Ile Ser Arg Ala Ala Ala Glu Lys Leu Phe Gly Lys Met Glu
340 345 350

Gly Ser Cys Pro Ala Arg Trp Asn Ile Asp Ser Ser Cys Lys Leu Glu
355 360 365

Leu Ser Gln Asn Gln Asn Val Lys Leu Ile Val Lys Asn Val Leu Lys
370 375 380

Glu Arg Arg Ile Leu Asn Ile Phe Gly Val Ile Lys Gly Tyr Glu Glu
385 390 395 400

Pro Asp Arg Tyr Val Val Val Gly Ala Gln Arg Asp Ala Leu Gly Ala
405 410 415

Gly Val Ala Ala Lys Ser Ser Val Gly Thr Gly Leu Leu Leu Lys Leu
420 425 430

Ala Gln Val Phe Ser Asp Met Ile Ser Lys Asp Gly Phe Arg Pro Ser
435 440 445

Arg Ser Ile Ile Phe Ala Ser Trp Thr Ala Gly Asp Phe Gly Ala Val
450 455 460

Gly Ala Thr Glu Trp Leu Glu Gly Tyr Leu Ser Ser Leu His Leu Lys
465 470 475 480

Ala Phe Thr Tyr Ile Asn Leu Asp Lys Val Val Leu Gly Thr Ser Asn

485

490

495

Phe Lys Val Ser Ala Ser Pro Leu Leu Tyr Thr Leu Met Gly Lys Ile
 500 505 510

Met Gln Asp Val Lys His Pro Val Asp Gly Lys Ser Leu Tyr Arg Asp
 515 520 525

Ser Asn Trp Ile Ser Lys Val Glu Lys Leu Ser Phe Asp Asn Ala Ala
 530 535 540

Tyr Pro Phe Leu Ala Tyr Ser Gly Ile Pro Ala Val Ser Phe Cys Phe
 545 550 555 560

Cys Glu Asp Ala Asp Tyr Pro Tyr Leu Gly Thr Arg Leu Asp Thr Tyr
 565 570 575

Glu Ala Leu Thr Gln Lys Val Pro Gln Leu Asn Gln Met Val Arg Thr
 580 585 590

Ala Ala Glu Val Ala Gly Gln Leu Ile Ile Lys Leu Thr His Asp Val
 595 600 605

Glu Leu Asn Leu Asp Tyr Glu Met Tyr Asn Ser Lys Leu Leu Ser Phe
 610 615 620

Met Lys Asp Leu Asn Gln Phe Lys Thr Asp Ile Arg Asp Met Gly Leu
 625 630 635 640

Ser Leu Gln Trp Leu Tyr Ser Ala Arg Gly Asp Tyr Phe Arg Ala Thr
 645 650 655

Ser Arg Leu Thr Thr Asp Phe His Asn Ala Glu Lys Thr Asn Arg Phe
 660 665 670

Val Met Arg Glu Ile Asn Asp Arg Ile Met Lys Val Glu Tyr His Phe
 675 680 685

Leu Ser Pro Tyr Val Ser Pro Arg Glu Ser Pro Phe Arg His Ile Phe
 690 695 700

Trp Gly Ser Gly Ser His Thr Leu Ser Ala Leu Val Glu Asn Leu Lys
705 710 715 720

Leu Arg Gln Lys Asn Ile Thr Ala Phe Asn Glu Thr Leu Phe Arg Asn
725 730 735

Gln Leu Ala Leu Ala Thr Trp Thr Ile Gln Gly Val Ala Asn Ala Leu
740 745 750

Ser Gly Asp Ile Trp Asn Ile Asp Asn Glu Phe
755 760

<210> 5
<211> 197
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 5

Phe Val Lys Ile Gln Val Lys Asp Ser Ala Gln Asn Ser Val Ile Ile
1 5 10 15

Val Asp Lys Asn Gly Arg Leu Val Tyr Leu Val Glu Asn Pro Gly Gly
20 25 30

Tyr Val Ala Tyr Ser Lys Ala Ala Thr Val Thr Gly Lys Leu Val His
35 40 45

Ala Asn Phe Gly Thr Lys Lys Asp Phe Glu Asp Leu Tyr Thr Pro Val
50 55 60

Asn Gly Ser Ile Val Ile Val Arg Ala Gly Lys Ile Thr Phe Ala Glu
65 70 75 80

Lys Val Ala Asn Ala Glu Ser Leu Asn Ala Ile Gly Val Leu Ile Tyr
85 90 95

Met Asp Gln Thr Lys Phe Pro Ile Val Asn Ala Glu Leu Ser Phe Phe
100 105 110

Gly His Ala His Leu Gly Thr Gly Asp Pro Tyr Thr Pro Gly Phe Pro
 115 120 125

Ser Phe Asn His Thr Gln Phe Pro Pro Ser Arg Ser Ser Gly Leu Pro
 130 135 140

Asn Ile Pro Val Gln Thr Ile Ser Arg Ala Ala Ala Glu Lys Leu Phe
 145 150 155 160

Gly Asn Met Glu Gly Asp Cys Pro Ser Asp Trp Lys Thr Asp Ser Thr
 165 170 175

Cys Arg Met Val Thr Ser Glu Ser Lys Asn Val Lys Leu Thr Val Ser
 180 185 190

Asn Val Leu Lys Glu
 195

<210> 6
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 6

Ala Ser Ser Leu Asn Ile Ala
 1 5

<210> 7
 <211> 12
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 7

Ser Lys Thr Phe Asn Thr His Pro Gln Ser Thr Pro
 1 5 10

<210> 8

<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 8

Thr Ala Arg Gly Glu His Lys Glu Glu Glu Leu Ile
1 5 10

<210> 9
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 9

Cys Gln Ala Gln Gly Gln Leu Val Cys
1 5

<210> 10
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 10

Cys Ser Glu Arg Ser Met Asn Phe Cys
1 5

<210> 11
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 11

Cys Pro Lys Thr Arg Arg Val Pro Cys
1 5

<210> 12
 <211> 20
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 12

Trp Leu Ser Glu Ala Gly Pro Val Val Thr Val Arg Ala Leu Arg Gly
 1 5 10 15

Thr Gly Ser Trp
 20

<210> 13
 <211> 9
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 13

Cys Met Gln His Ser Met Arg Val Cys
 1 5

<210> 14
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 14

Asp Asp Thr Arg His Trp Gly
 1 5

<210> 15
 <211> 2859
 <212> DNA
 <213> Homo sapiens

<400> 15
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ggcctggaca ggggctgcca ggccctgtga caggaggacc ccgagccccc ggcccgggga	180
ggggccatgg tgctgcctgt ccaacatgtc agccgagggtg cggctgaggc ggctccagca	240
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ccaccaggag ctgggcgcct ccgaactggc ccaggacaag tacgtggccg acttcttgca	360
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gattctgaag gtgatcggac gcggggcggt cagcgaggta gcggtagtga agatgaagca	480
gacgggccag gtgtatgcca tgaagatcat gaacaagtgg gacatgctga agaggggcga	540
ggtgtcgtgc ttccgtgagg agaggacgt gttggtgaat ggggaccggc ggtggatcac	600
gcagctgcac ttgccttcc aggatgagaa ctacctgtac ctggtcattg agtattacgt	660
gggcggggac ctgctgacac tgctgagcaa gtttggggag cggattccgg ccgagatggc	720
gcgcttctac ctggcggaga ttgtcatggc catagactcg gtgcaccggc ttggctacgt	780
gcacagggac atcaaaccg acaacatcct gctggaccgc tgtggccaca tccgcctggc	840
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gggcaccca gactacctgt ccccgagat cctgcaggct gtgggcggtg ggcctgggac	960
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cgggctcact gccatggaga cactgtcgga cattcgggaa ggtgcgccgc taggggtcca	1380
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gaacttcgcc agtcaactac gcgaggcaga ggctcggaac cgggacctag aggcacacgt	1740
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tgccagggtc ctaggcctg gcctatcgga ggcgctttcc ctgctcctgt tcgccgttgt	1980
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cgcagtctgg cgccgccag gagccgccg cgctccctga accctagaac tgtcttcgac	2100
tccggggccc cgttggaaga ctgagtgcg ggggcacggc acagaagccg cgcccaccgc	2160
ctgccagttc acaaccgctc cgagcgtggg tctccgcca gctccagtcc tgtgatccgg	2220
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aagggtcctt gtagccggga atgctgctgc tgctgctgct gctgctgctg ctgctgctgc	2340
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gaggccctga cgtggatggg caaactgcag gcctgggaag gcagcaagcc gggccgtccg	2460
tgttccatcc tccacgcacc cccacctatc gttggttcgc aaagtgcaaa gctttcttgt	2520
gcatgacgcc ctgctctggg gagcgtctgg cgcgatctct gcctgcttac tcgggaaatt	2580
tgcttttgcc aaaccgctt tttcggggat cccgcgccc cctcctcact tgcgctgctc	2640
tcggagcccc agccggctcc gcccgttcg gcggtttgga tattttattga cctcgtcctc	2700
cgactcgtg acaggctaca ggacccccaa caaccccaat ccacgttttg gatgactga	2760
gaccccgaca ttctctggta tttattgtct gtccccacct aggaccccca ccccgaccc	2820
tcgcaataa aaggccctcc atctgcccga agctctgga	2859

<210> 16
 <211> 2683
 <212> DNA
 <213> Mus musculus

<400> 16	
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aggggcatg gtgttgctg cccaacatgt cagccgaagt gcggctgagg cagctccagc	180

agctggtgct ggacccaggc ttcctgggac tggagcccct gctcgacctt ctcctgggcg	240
tccaccagga gctgggtgcc tctcacctag cccaggacaa gtatgtggcc gacttcttgc	300
agtgggtgga gccattgca gcaaggctta aggaggtccg actgcagagg gatgattttg	360
agattttgaa ggtgatcggg cgtggggcgt tcagcgaggt agcgggtggtg aagatgaaac	420
agacgggcca agtgtatgcc atgaagatta tgaataagtg ggacatgctg aagagaggcg	480
aggtgtcgtg cttccgggaa gaaagggatg tattagtgaag aggggaccgg cgctggatca	540
cacagctgca ctttgccttc caggatgaga actacctgta cctgggtcatg gaatactacg	600
tgggcgggga cctgctaacg ctgctgagca agtttgggga gcggatcccc gccgagatgg	660
ctcgcttcta cctggccgag attgtcatgg ccatagactc cgtgcaccgg ctgggctacg	720
tgcacaggga catcaaacca gataacattc tgctggaccg atgtgggcac attcgcctgg	780
cagacttcgg ctcctgcctc aaactgcagc ctgatggaat ggtgaggtcg ctggtggctg	840
tgggcacccc ggactacctg tctcctgaga ttctgcaggc cgttgggtgga gggcctgggg	900
caggcagcta cgggccagag tgtgactggt gggcactggg cgtgttcgcc tatgagatgt	960
tctatgggca gaccccttc tacgcggact ccacagccga gacatatgcc aagattgtgc	1020
actacaggga acacttgtcg ctgccgctgg cagacacagt tgtccccgag gaagctcagg	1080
acctcattcg tgggctgctg tgtcctgctg agataaggct aggtcgaggt ggggcagact	1140
tcgaggggtgc cacggacaca tgcaatttcg atgtgggtgga ggaccggctc actgccatgg	1200
tgagcggggg cggggagacg ctgtcagaca tgcaggaaga catgcccctt ggggtgcgcc	1260
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tgcagcccc agtgtcccca ccggatcaag tggctgaaga ggctgacctg gtggctgtcc	1440
ctgcccctgt ggctgaggca gagaccacgg taacgctgca gcagctccag gaagccctgg	1500
aagaagaggt tctcaccgg cagagcctga gccgcgagct ggaggccatc cggaccgcca	1560
accagaactt ctccagccaa ctacaggagg ccgaggtccg aaaccgagac ctggaggcgc	1620
atgttcggca gctacaggaa cggatggaga tgctgcaggc cccaggagcc gcagccatca	1680
cgggggtccc cagtccccgg gccacggatc caccttccca tctagatggc cccccggccg	1740
tggctgtggg ccagtggcg ctggtggggc caggccccat gcaccgccgt cacctgctgc	1800

tccctgccag gatccctagg cctggcctat ccgaggcgcg ttgcctgctc ctgttcgccg	1860
ctgctctggc tgctgccgcc aactgggct gactgggtt ggtggcctat accggcggtc	1920
tcacccagct ctggtgtttc ccgggagcca ccttcgcccc ctgaacccta agactccaag	1980
ccatctttca tttaggcctc ctaggaaggt cgagcgacca gggagcgacc caaagcgtct	2040
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ggtccccacc cagctccgct cctgtgatcc aggctgcca cctggcggcc ggggagggag	2160
gaacagggct cgtgccagc acccctgggt cctgcagagc tggtagccac cgctgctgca	2220
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acacacggag tctttggctt cggacagcct cactcctggg ggttgctgca actccttccc	2460
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agtgtgggta tttattgatc ttgttatctg actcactgac agactccggg acccacgttt	2580
tagatgcatt gagactcgac attcctcggt atttattgtc tgtccccacc tacgacctcc	2640
actcccgacc cttgcgaata aaatacttct ggtctgccct aaa	2683

<210> 17
 <211> 5
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 17

Ser	Tyr	Trp	Met	His
1				5

<210> 18
 <211> 17
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 18

Glu	Ile	Asn	Pro	Thr	Asn	Gly	Arg	Thr	Asn	Tyr	Ile	Glu	Lys	Phe	Lys
1				5					10					15	

Ser

<210> 19
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 19

Gly	Thr	Arg	Ala	Tyr	His	Tyr
1				5		

<210> 20
 <211> 11
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 20

Arg	Ala	Ser	Asp	Asn	Leu	Tyr	Ser	Asn	Leu	Ala
1				5					10	

<210> 21
 <211> 7
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 21

Asp	Ala	Thr	Asn	Leu	Ala	Asp
1				5		

<210> 22
 <211> 9
 <212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 22

Gln His Phe Trp Gly Thr Pro Leu Thr
1 5

<210> 23

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 23

Gly Tyr Thr Phe Thr Ser Tyr
1 5

<210> 24

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 24

Asn Pro Thr Asn Gly Arg
1 5

<210> 25

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 25

Thr Ser Tyr Trp Met His
1 5

<210> 26

<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 26

Trp Ile Gly Glu Ile Asn Pro Thr Asn Gly Arg Thr Asn
1 5 10

<210> 27
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 27

Ala Arg Gly Thr Arg Ala
1 5

<210> 28
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 28

Tyr Ser Asn Leu Ala Trp Tyr
1 5

<210> 29
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 29

Leu Leu Val Tyr Asp Ala Thr Asn Leu Ala
1 5 10

<210> 30
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 30

Gln His Phe Trp Gly Thr Pro Leu
1 5

<210> 31
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 31

Gln His Phe Ala Gly Thr Pro Leu Thr
1 5

<210> 32
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 32

Gln His Phe Ala Gly Thr Pro Leu
1 5

<210> 33
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 33

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala

1	5	10	15
Ser Val Lys	Leu Ser Cys Lys	Ala Ser Gly Tyr Thr	Phe Thr Ser Tyr
	20	25	30
Trp Met His	Trp Val Lys Gln	Arg Pro Gly Gln Gly	Leu Glu Trp Ile
	35	40	45
Gly Glu Ile	Asn Pro Thr Asn	Gly Arg Thr Asn	Tyr Ile Glu Lys Phe
	50	55	60
Lys Ser Lys	Ala Thr Leu Thr	Val Asp Lys Ser	Ser Ser Thr Ala Tyr
65	70	75	80
Met Gln Leu	Ser Ser Leu Thr	Ser Glu Asp Ser	Ala Val Tyr Tyr Cys
	85	90	95
Ala Arg Gly	Thr Arg Ala Tyr	His Tyr Trp Gly	Gln Gly Thr Ser Val
	100	105	110
Thr Val Ser	Ser		
	115		

<210> 34
 <211> 107
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Synthetic polypeptide

 <400> 34

Asp Ile Gln	Met Thr Gln	Ser Pro Ala	Ser Leu Ser	Val Ser Val	Gly
1	5	10	15		
Glu Thr Val	Thr Ile Thr	Cys Arg Ala	Ser Asp Asn	Leu Tyr Ser	Asn
	20	25	30		
Leu Ala Trp	Tyr Gln Gln	Lys Gln Gly	Lys Ser Pro	Gln Leu Leu	Val
	35	40	45		
Tyr Asp Ala	Thr Asn Leu	Ala Asp Gly	Val Pro Ser	Arg Phe Ser	Gly

50

55

60

Ser Gly Ser Gly Thr Gln Tyr Ser Leu Lys Ile Asn Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Gly Thr Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 35

<211> 116

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic polypeptide

<400> 35

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn Pro Thr Asn Gly Arg Thr Asn Tyr Ile Glu Lys Phe
50 55 60

Lys Ser Arg Ala Thr Leu Thr Val Asp Lys Ser Ala Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Thr Arg Ala Tyr His Tyr Trp Gly Gln Gly Thr Met Val
100 105 110

Thr Val Ser Ser

115

<210> 36
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 36

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Asp Asn Leu Tyr Ser Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Lys Leu Leu Val
35 40 45

Tyr Asp Ala Thr Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Lys Ile Asn Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Gly Thr Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 37
<211> 330
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 37

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu

225 230 235 240
 Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270
 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285
 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300
 Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320
 Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 325 330

 <210> 38
 <211> 110
 <212> PRT
 <213> Artificial Sequence

 <220>
 <223> Synthetic polypeptide

 <400> 38
 Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15

 Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30

 Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60

 Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr

65		70		75		80									
Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys
			85						90					95	
Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro		
			100					105					110		
<210>	39														
<211>	446														
<212>	PRT														
<213>	Artificial Sequence														
<220>															
<223>	Synthetic polypeptide														
<400>	39														
Gln	Val	Gln	Leu	Gln	Gln	Pro	Gly	Ala	Glu	Leu	Val	Lys	Pro	Gly	Ala
1				5					10					15	
Ser	Val	Lys	Leu	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr
			20					25					30		
Trp	Met	His	Trp	Val	Lys	Gln	Arg	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Ile
		35					40					45			
Gly	Glu	Ile	Asn	Pro	Thr	Asn	Gly	Arg	Thr	Asn	Tyr	Ile	Glu	Lys	Phe
	50					55				60					
Lys	Ser	Lys	Ala	Thr	Leu	Thr	Val	Asp	Lys	Ser	Ser	Ser	Thr	Ala	Tyr
65					70					75				80	
Met	Gln	Leu	Ser	Ser	Leu	Thr	Ser	Glu	Asp	Ser	Ala	Val	Tyr	Tyr	Cys
			85						90				95		
Ala	Arg	Gly	Thr	Arg	Ala	Tyr	His	Tyr	Trp	Gly	Gln	Gly	Thr	Ser	Val
			100					105					110		
Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala
		115					120					125			
Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu

130

135

140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
 145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
 165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
 180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
 195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
 210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
 225 230 235 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
 245 250 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
 260 265 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
 275 280 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
 290 295 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
 305 310 315 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
 325 330 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
 340 345 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
370 375 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385 390 395 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
405 410 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
420 425 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 40
<211> 226
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 40

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn Pro Thr Asn Gly Arg Thr Asn Tyr Ile Glu Lys Phe
50 55 60

Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Thr Arg Ala Tyr His Tyr Trp Gly Gln Gly Thr Ser Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro
225

<210> 41
<211> 446
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 41

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
 35 40 45

Gly Glu Ile Asn Pro Thr Asn Gly Arg Thr Asn Tyr Ile Glu Lys Phe
 50 55 60

Lys Ser Arg Ala Thr Leu Thr Val Asp Lys Ser Ala Ser Thr Ala Tyr
 65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Gly Thr Arg Ala Tyr His Tyr Trp Gly Gln Gly Thr Met Val
 100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
 115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
 130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
 145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
 165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
 180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
 195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
 210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe

225		230		235		240
Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro	245	250	255			
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val	260	265	270			
Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr	275	280	285			
Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val	290	295	300			
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys	305	310	315			320
Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser	325	330	335			
Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro	340	345	350			
Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val	355	360	365			
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly	370	375	380			
Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp	385	390	395			400
Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp	405	410	415			
Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His	420	425	430			
Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys	435	440	445			

<210> 42
 <211> 217
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 42

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Asp Asn Leu Tyr Ser Asn
 20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Lys Leu Leu Val
 35 40 45

Tyr Asp Ala Thr Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Tyr Ser Leu Lys Ile Asn Ser Leu Gln Ser
 65 70 75 80

Glu Asp Phe Gly Thr Tyr Tyr Cys Gln His Phe Trp Gly Thr Pro Leu
 85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Ala Ser Thr Lys Gly
 100 105 110

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
 115 120 125

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
 130 135 140

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
 145 150 155 160

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
 165 170 175

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
180 185 190

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
195 200 205

Ser Cys Asp Lys Thr His Thr Cys Pro
210 215

<210> 43
<211> 226
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide

<400> 43

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn Pro Thr Asn Gly Arg Thr Asn Tyr Ile Glu Lys Phe
50 55 60

Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Thr Arg Ala Tyr His Tyr Trp Gly Gln Gly Thr Ser Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
 130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
 145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
 165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
 180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
 195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
 210 215 220

Cys Pro
 225

<210> 44
 <211> 226
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Synthetic polypeptide

<400> 44

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
 20 25 30

Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Arg Leu Glu Trp Ile
 35 40 45

Gly Glu Ile Asn Pro Thr Asn Gly Arg Thr Asn Tyr Ile Glu Lys Phe
 50 55 60

Lys Ser Arg Ala Thr Leu Thr Val Asp Lys Ser Ala Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Thr Arg Ala Tyr His Tyr Trp Gly Gln Gly Thr Met Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro
225

<210> 45
<211> 20
<212> RNA
<213> Artificial Sequence

<220>
<223> Synthetic Polynucleotide

<400> 45

ggacggcccg gcuugcugcc	20
<210> 46	
<211> 20	
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