(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 October 2023 (19.10.2023)

WIPO | PCT

(10) International Publication Number
WO 2023/201324 A1

(51) International Patent Classification:
C07K 16/28 (2006.01) *C12N 15/11* (2006.01)
A61K 39/395 (2006.01) *C12N 15/113* (2010.01)
A61K 47/68 (2017.01) *A61P 21/00* (2006.01)

(21) International Application Number:
PCT/US2023/065764

(22) International Filing Date:
14 April 2023 (14.04.2023)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/331,716 15 April 2022 (15.04.2022) US

(71) Applicant: **DYNE THERAPEUTICS, INC.** [US/US]; 1560 Trapelo Road, Waltham, MA 02451 (US).

(72) Inventors: **WEEDEN, Timothy**; 1560 Trapelo Road, Waltham, MA 02451 (US). **VIEIRA, Benjamin**; 1560 Trapelo Road, Waltham, MA 02451 (US). **NAJIM, John**; 1560 Trapelo Road, Waltham, MA 02451 (US). **ZANOTTI, Stefano**; 1560 Trapelo Road, Waltham, MA 02451 (US). **SUBRAMANIAN, Romesh, R.**; 9 Alan Street, Framingham, MA 01701 (US). **QATANANI, Mohammed, T.**; 1560 Trapelo Road, Waltham, MA 02451 (US). **DESJARDINS, Cody, A.**; 1560 Trapelo Road, Waltham, MA 02451 (US). **TANG, Kim**; 1560 Trapelo Road, Waltham, MA 02451 (US). **QUINN, Brendan**; 1560 Trapelo Road, Waltham, MA 02451 (US).

(74) Agent: **BUSS, Colin, G.** et al.; Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210-2206 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,

(54) Title: MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR TREATING MYOTONIC DYSTROPHY

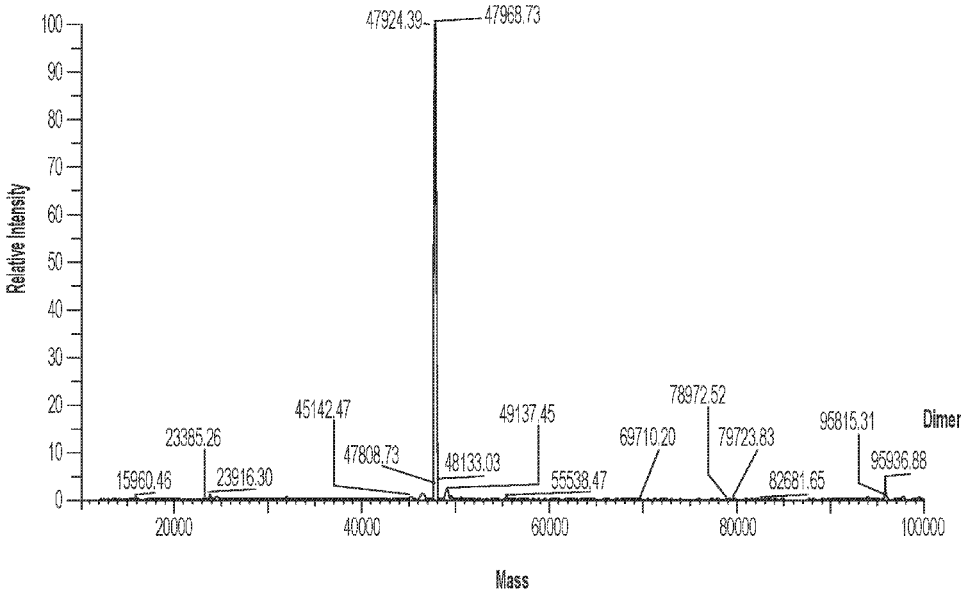


FIG. 1

(57) Abstract: Aspects of the disclosure relate to compositions comprising a plurality of complexes comprising an antibody (e.g., anti-TfR1 antibody) covalently linked to one or more oligonucleotides (e.g. a DMPK targeting oligonucleotide), each oligonucleotide being covalently linked at a linkage site represented by a lysine (K) residue of the antibody. In some embodiments, the antibody comprises a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region, wherein at least 80% (e.g., 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%- 90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of

WO 2023/201324 A1

[Continued on next page]

CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *with sequence listing part of description (Rule 5.2(a))*

the antibodies.

MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR TREATING MYOTONIC DYSTROPHY

RELATED APPLICATION

[0001] This application claims the benefit under 35 U.S.C. § 119(e) of the U.S. Provisional Application No. 63/331,716, entitled "MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR TREATING MYOTONIC DYSTROPHY", filed April 15, 2022; the entire contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present application relates to targeting complexes for delivering an effective amount of oligonucleotide molecular payloads to cells and uses thereof, particularly uses relating to treatment of disease.

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING

[0003] The contents of the electronic sequence listing (D082470075WO00-SEQ-COB.xml; Size: 58,804 bytes; and Date of Creation: March 22, 2023) are herein incorporated by reference in their entirety.

BACKGROUND

[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 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 about 50 to about 3,000 or more 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

[0005] According to some aspects, the present disclosure provides compositions comprising a plurality of complexes. In some embodiments, complexes of compositions provided herein comprise an antibody (e.g., an anti-transferrin receptor 1 (TfR1) antibody) covalently linked to one or more oligonucleotides, each oligonucleotide being covalently linked to the antibody at a linkage site represented by a lysine (K) residue of the antibody. In some embodiments, the antibody comprises a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region. In some embodiments, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies. In some embodiments, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chains of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by a K residue in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of the light chains of the antibodies. In some embodiments, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the antibodies. In some embodiments, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%,

about 13%, about 14%, or about 15%) of the heavy chains of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by the K residue in a sequence motif VNHKPSN (SEQ ID NO: 28) of the heavy chains of the antibodies.

[0006] According to some aspects, the present disclosure provides compositions comprising a plurality of complexes comprising an antibody covalently linked to one or more oligonucleotides, each oligonucleotide being covalently linked at a linkage site represented by a lysine (K) residue of the antibody,

wherein the antibody comprises a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region,

wherein the oligonucleotide comprises a region of complementarity to a DMPK RNA,

and wherein at least 80% of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies.

[0007] According to some aspects, the present disclosure provides compositions comprising a plurality of complexes comprising an antibody covalently linked to one or more oligonucleotides, each oligonucleotide being covalently linked at a linkage site represented by a lysine (K) residue of the antibody,

wherein the antibody comprises a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region,

wherein the oligonucleotide comprises a 5'-X-Y-Z-3' configuration, wherein X and Z are flanking regions comprising one or more modified nucleosides and Y is a gap region comprising one or more 2'-deoxyribonucleosides,

and wherein at least 80% of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies.

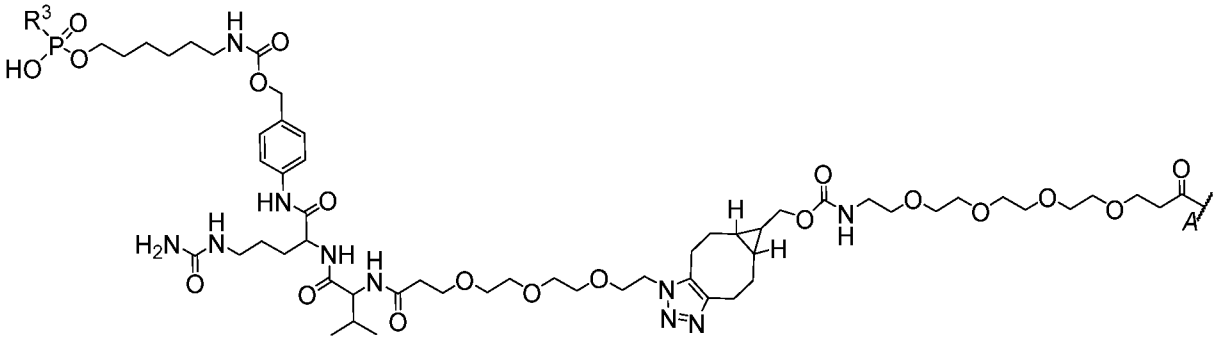
[0008] In some embodiments, about 1%-15% of the heavy chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the antibodies.

[0009] In some embodiments, the antibody is an anti-transferrin receptor (TfR1) antibody comprising: a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14, a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NOs: 6 or 16.

[00010] In some embodiments, the oligonucleotide comprises a 5′-X-Y-Z-3′ configuration wherein X and Z each comprise 4 linked nucleosides and Y comprises 8 linked nucleosides. In some embodiments, the oligonucleotide comprises a 5′-X-Y-Z-3′ configuration of LLEE-D_8-EELL, wherein "L" represents an LNA nucleoside, "E" represents a 2′-MOE modified ribonucleoside, and "D" represents a 2'-deoxyribonucleoside.

[00011] In some embodiments, the oligonucleotide comprises a nucleobase sequence of CAGCGCCCACCAGUCA (SEQ ID NO: 21). In some embodiments, the oligonucleotide comprises the structure +C*+A*oG*oC*dG*dC*dC*dC*dA*dC*dC*dA*oG*oU*+C*+A (SEQ ID NO: 21), wherein +N represents an LNA (2'-4' methylene bridge) ribonucleoside, dN represents a 2'-deoxyribonucleoside, oN represents a 2'-MOE modified ribonucleoside, oC represents a 5-methyl-2'-MOE-cytidine, +C represents a 5-methyl-2'-4'-bicyclic-cytidine (2'-4' methylene bridge), oU represents a 5-methyl-2'-MOE-uridine, and * represents a phosphorothioate internucleoside linkage.

[00012] According to some aspects, the present disclosure provides compositions comprising a plurality of complexes comprising a structure of formula (I): $[R^1]_{n1}$-R^2, wherein each R^1 independently comprises a group of the formula (Ia):



(Ia),

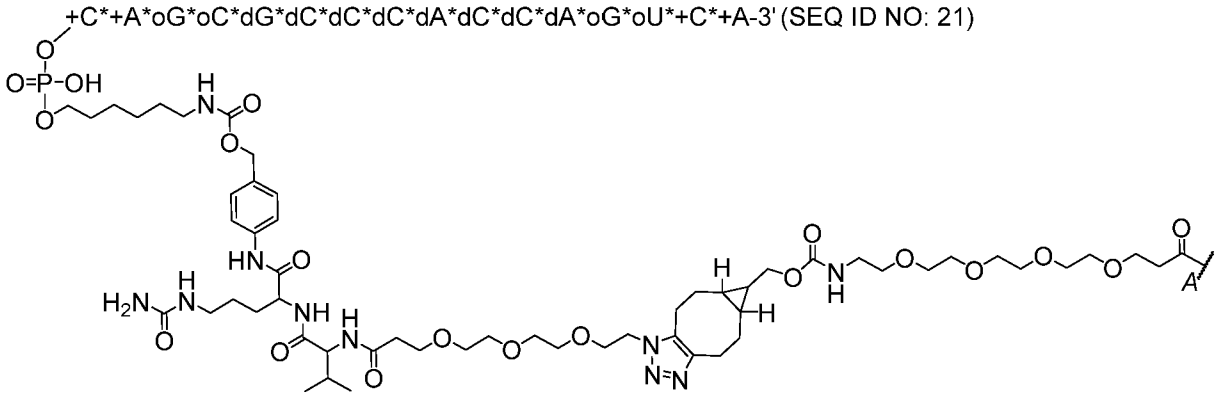
wherein R^2 comprises an anti-transferrin receptor (TfR1) antibody comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region; and wherein the anti-TfR1 antibody comprises: a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14, a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NOs: 6 or 16;

wherein R^3 comprises a structure of +C*+A*oG*oC*dG*dC*dC*dC*dA*dC*dC*dA*oG*oU*+C*+A (SEQ ID NO: 21), wherein +N represents an LNA (2'-4' methylene bridge) ribonucleoside, dN represents a 2'-deoxyribonucleoside, oN represents a 2'-MOE modified ribonucleoside, oC represents a 5-methyl-2'-MOE-cytidine, +C represents a 5-methyl-2'-4'-bicyclic-cytidine (2'-4' methylene bridge), oU represents a 5-methyl-2'-MOE-uridine, and * represents a phosphorothioate internucleoside linkage;

wherein each R^1 is covalently linked at attachment point *A* to R^2 via a linkage site represented by a lysine (K) residue of the anti-TfR1 antibody, and wherein, at least 80% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the anti-TfR1 antibodies; and

wherein in each complex of the plurality of complexes, n1 is independently an integer of one or greater representing the number of instances of R^1.

[00013] According to some aspects, the present disclosure provides compositions comprising a plurality of complexes comprising a structure of formula (I): $[R^1]_{n1}$-R^2, wherein each R^1 independently comprises a group of the formula (Ib):



(Ib),

in which +N represents an LNA (2'-4' methylene bridge) ribonucleoside, dN represents a 2'-deoxyribonucleoside, oN represents a 2'-MOE modified ribonucleoside, oC represents a 5-methyl-2'-MOE-cytidine, +C represents a 5-methyl-2'-4'-bicyclic-cytidine (2'-4' methylene bridge), oU represents a 5-methyl-2'-MOE-uridine, and * represents a phosphorothioate internucleoside linkage, and the oligonucleotide of R^1 comprises a nucleobase sequence of CAGCGCCCACCAGUCA (SEQ ID NO: 21);

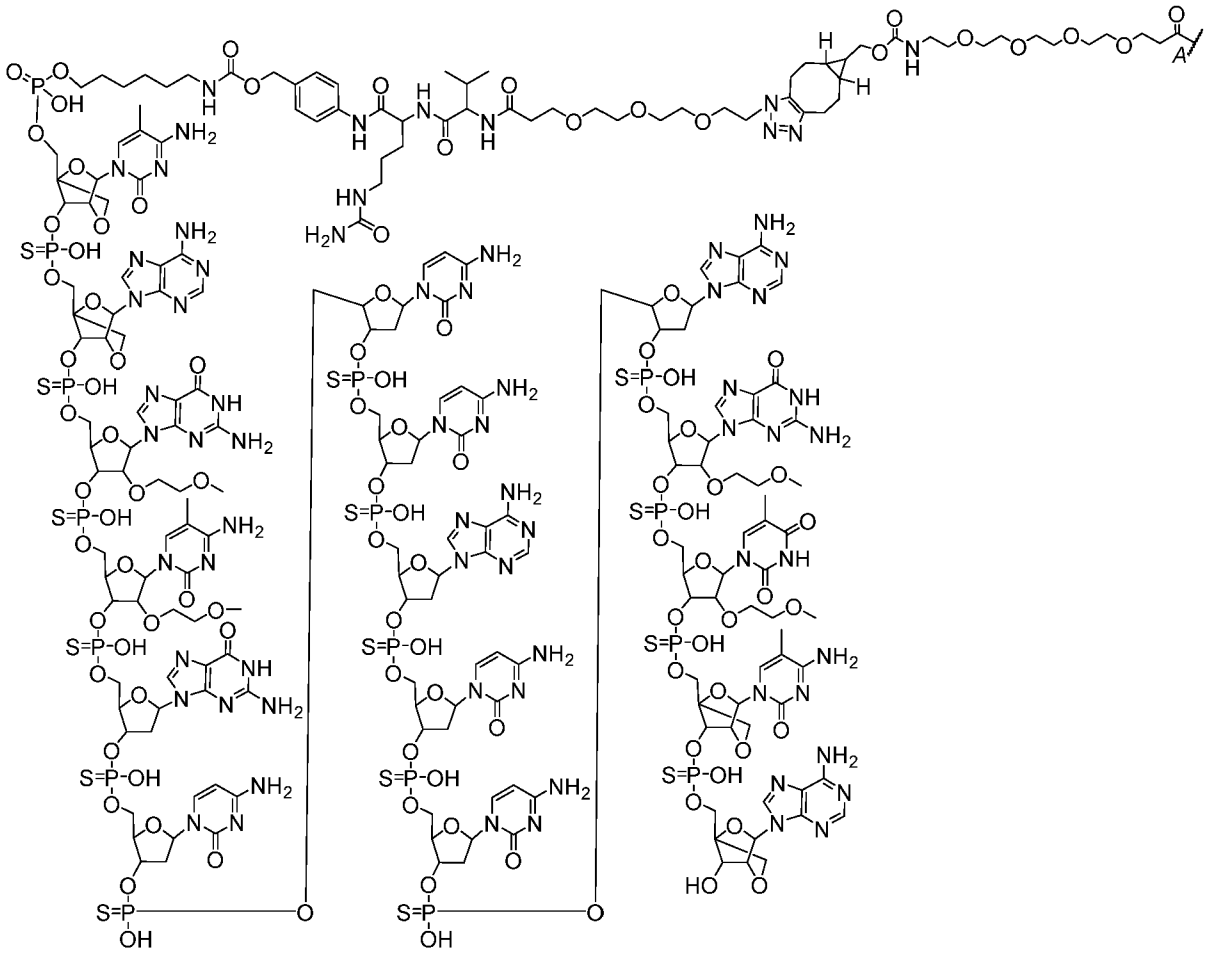
wherein R^2 comprises an anti-transferrin receptor (TfR1) antibody comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region; and wherein the anti-TfR1 antibody comprises: a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14, a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NOs: 6 or 16; and

wherein each R^1 is covalently linked at attachment point *A* to R^2 via a linkage site represented by a lysine (K) residue of the anti-TfR1 antibody, and wherein, at least 80% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the anti-TfR1 antibodies; and

wherein in each complex of the plurality of complexes, n1 is independently an integer of one or greater representing the number of instances of R^1.

[00014] According to some aspects, the present disclosure provides compositions comprising a plurality of complexes comprising a structure of formula (I): $[R^1]_{n1}$-R^2, wherein:

each R^1 comprises a group of the formula (Ic):



(Ic),

wherein R^2 comprises an anti-transferrin receptor (TfR1) antibody comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region; and wherein the anti-TfR1 antibody comprises: a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14, a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NOs: 6 or 16; and

wherein each R^1 is covalently linked at attachment point *A* to R^2 via a linkage site represented by a lysine (K) residue of the anti-TfR1 antibody, and wherein, at least 80% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the anti-TfR1 antibodies; and

wherein in each complex of the plurality of complexes, n1 is independently an integer of one or greater representing the number of instances of R^1.

[00015] In some embodiments 85%-98% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the anti-TfR1 antibodies. In some embodiments, 95%-97% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the anti-TfR1 antibodies.

[00016] In some embodiments, 1%-15% of the heavy chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the anti-TfR1 antibodies. In some embodiments, 4%-8% of the heavy chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the anti-TfR1 antibodies.

[00017] In some embodiments, the antibody is a Fab fragment, a full-length IgG, a Fab' fragment, or a $F(ab')_2$ fragment. In some embodiments, the antibody is a Fab fragment.

[00018] In some embodiments, the VH comprises an amino acid sequence at least 85% identical to SEQ ID NO: 17; and/or the VL comprises an amino acid sequence at least 85% identical to SEQ ID NO: 18. In some embodiments, the antibody comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 17 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO: 18.

[00019] In some embodiments, the heavy chain comprises the amino acid sequence of SEQ ID NO: 19 and the light chain comprises the amino acid sequence of SEQ ID NO: 20.

[00020] In some embodiments, the composition further comprises one or more antibodies that are not covalently linked to an oligonucleotide.

[00021] In some embodiments, the average value of n1 of complexes in the composition is in the range of 0.5 to 5.

[00022] According to some aspects, the present disclosure provides methods of reducing DMPK expression and/or treating myotonic dystrophy in a subject, the method comprising administering to the subject an effective amount of a composition provided herein.

[00023] In some embodiments, the subject has an expansion of a disease-associated-repeat of a DMPK allele that is associated with myotonic dystrophy. In some embodiments, the disease-associated-repeat comprises repeating units of a CTG trinucleotide sequence.

[00024] In some embodiments, the complexes reduce DMPK expression in the subject. In some embodiments, reducing DMPK expression comprises reducing the level of a DMPK mRNA in the muscle cell. In some embodiments, the DMPK mRNA is a mutant DMPK mRNA.

BRIEF DESCRIPTION OF THE DRAWINGS

[00025] **FIG. 1** shows a mass spectrum indicating the intact mass of unlinked anti-TfR1 Fabs having sequences shown in Table 2.

[00026] **FIG. 2** shows a mass spectrum indicating masses of anti-TfR1 antibody-linker complexes of the compositions provided herein, after cleavage of the oligonucleotide via papain digestion. The anti-TfR1 antibody has sequences shown in Table 2.

[00027] **FIGs. 3A-3D** show the amount of DMPK-targeting oligonucleotide (ASO) in the heart (**FIG. 3A**), diaphragm (**FIG. 3B**), gastrocnemius (**FIG. 3C**), or tibialis anterior (**FIG. 3D**), respectively, after administration of conjugates containing an anti-TfR1 Fab covalently linked to the ASO.

[00028] **FIGs. 4A-4D** show the ability of conjugates containing an anti-TfR1 Fab conjugated to a DMPK-targeting oligonucleotide (ASO) to knock down human DMPK RNA in the heart (**FIG. 4A**), diaphragm (**FIG. 4B**), tibialis anterior (**FIG. 4C**) and gastrocnemius (**FIG. 4D**) of mice expressing both human TfR1 and two copies of a mutant human DMPK transgene that harbors expanded CTG repeats.

[00029] **FIGs. 5A-5B** show reduced DMPK foci in nuclei of cardiac muscle fibers in mice expressing both human TfR1 and two copies of a mutant human DMPK transgene that harbors expanded CTG repeats and treated with anti-TfR1 Fab conjugated to DMPK-targeting oligonucleotide (ASO). **FIG. 5A** shows representative images of samples following *in situ*

hybridization staining for DMPK foci and fluorescence staining of myofibers (inset panels). In the microscopy images shown in FIG. 5A, the light rounded shapes show cell nuclei, and the bright puncta within the nuclei show DMPK foci. **FIG. 5B** shows quantification of DMPK foci.

[00030] **FIG. 6** shows the splicing correction activity of conjugates containing an anti-TfR1 Fab covalently linked to a DMPK-targeting oligonucleotide (ASO) in the heart of mice expressing both human TfR1 and two copies of a mutant human DMPK transgene that harbors expanded CTG repeats (hTfR1/DMSXL mice). Composite splicing indices based on splicing of *Ldb3* exon 11, *Mbnl2* exon 6, and *Nfix* exon 7 are shown for control mice treated with vehicle control ("hTfR1 – PBS"), hTfR1/DMSXL mice treated with vehicle control ("hTfR1/DMSXL – PBS"), and hTfR1/DMSXL mice treated with anti-TfR1 Fab-ASO conjugate ("hTfR1/DMSXL – Conjugate").

[00031] **FIG. 7** shows the splicing correction activity of conjugates containing an anti-TfR1 Fab covalently linked to a DMPK-targeting oligonucleotide (ASO) in the diaphragm of mice expressing both human TfR1 and two copies of a mutant human DMPK transgene that harbors expanded CTG repeats (hTfR1/DMSXL mice). Composite splicing indices based on splicing of *Bin1* exon 11, *Insr* exon 11, *Ldb3* exon 11 and *Nfix* exon 7 are shown for control mice treated with vehicle control ("hTfR1 – PBS"), hTfR1/DMSXL mice treated with vehicle control ("hTfR1/DMSXL – PBS"), and hTfR1/DMSXL mice treated with anti-TfR1 Fab-ASO conjugate ("hTfR1/DMSXL – Conjugate").

[00032] **FIG. 8** shows the splicing correction activity of conjugates containing an anti-TfR1 Fab covalently linked to a DMPK-targeting oligonucleotide (ASO) in the tibialis anterior of mice expressing both human TfR1 and two copies of a mutant human DMPK transgene that harbors expanded CTG repeats (hTfR1/DMSXL mice). Composite splicing indices based on splicing of *Bin1* exon 11, *Ldb3* exon 11, *Mbnl2* exon 6, and *Nfix* exon 7 are shown for control mice treated with vehicle control ("hTfR1 – PBS"), hTfR1/DMSXL mice treated with vehicle control ("hTfR1/DMSXL – PBS"), and hTfR1/DMSXL mice treated with anti-TfR1 Fab-ASO conjugate ("hTfR1/DMSXL – Conjugate").

[00033] **FIG. 9** shows the splicing correction activity of conjugates containing an anti-TfR1 Fab covalently linked to a DMPK-targeting oligonucleotide (ASO) in the gastrocnemius of mice expressing both human TfR1 and two copies of a mutant human DMPK transgene that harbors expanded CTG repeats (hTfR1/DMSXL mice). Composite splicing indices based on splicing of *Mbnl2* exon 6, *Nfix* exon 7, and *Ttn* exon 313 are shown for control mice treated with vehicle control ("hTfR1 – PBS"), hTfR1/DMSXL mice treated with vehicle control

("hTfR1/DMSXL – PBS"), and hTfR1/DMSXL mice treated with anti-TfR1 Fab-ASO conjugate ("hTfR1/DMSXL – Conjugate").

[00034] **FIG. 10** shows DMPK knockdown in DM1 patient myotubes and wild-type non-human primate (NHP) myotubes resulting from incubation with conjugates containing an anti-TfR1 Fab covalently linked to a DMPK-targeting oligonucleotide (ASO). Results are shown normalized to expression in DM1 patient myotubes or NHP myotubes treated with vehicle only. Data are shown as mean + standard deviation for n = 4 replicates per condition. Statistics were calculated by one-way ANOVA (*, $P < 0.05$, **, $P < 0.01$).

DETAILED DESCRIPTION

[00035] According to some aspects, the present disclosure provides compositions comprising a plurality of complexes. In some embodiments, complexes of the compositions described herein comprise an antibody (e.g., an anti-transferrin receptor 1 (TfR1)) covalently linked to one or more oligonucleotides, each oligonucleotide being covalently linked at a linkage site represented by a lysine (K) residue of the antibody. In some embodiments, the antibody comprises a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region.

[00036] In some embodiments, light chain constant regions of antibodies of complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of light chain constant regions of the antibodies. For example, in some embodiments, a linkage site is represented by K188 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, a linkage site is represented by K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, linkage sites are represented by K188 (based on Kabat numbering) and K190 (based on Kabat numbering) of light chain constant region(s) of an antibody. In some embodiments, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190

(based on Kabat numbering) of the light chain constant regions of the antibodies. In some embodiments, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the antibodies. In some embodiments, light chain constant regions and heavy chain constant regions of antibodies of complexes in the composition are both independently covalently linked to an oligonucleotide at linkage sites represented by lysine residues in the light chain constant regions (e.g., K188 and/or K190) and in the heavy chain constant regions (e.g., K213) of the antibodies.

[00037] In some embodiments, light chains of antibodies of complexes in the composition are independently covalently linked to an oligonucleotide at linkage sites represented by represented by lysine (K) residues in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of a light chain of an antibody. For example, in some embodiments, a linkage site is represented by the K at position 4 of a sequence motif DYEKHKVYA (SEQ ID NO: 27) of a light chain of an antibody. In some embodiments, a linkage site is represented by the K at position 6 of a sequence motif DYEKHKVYA (SEQ ID NO: 27) of a light chain of an antibody. In some embodiments, linkage sites are represented by the K at position 4 and the K at position 6 of a sequence motif DYEKHKVYA (SEQ ID NO: 27) of the light chains of the antibodies. In some embodiments, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at linkage sites represented by lysine (K) residues in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of the light chains of the antibodies. In some embodiments, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by the lysine (K) residue in motif VNHKPSN (SEQ ID NO: 28) of the heavy chains of the antibodies. In some embodiments, light chains and heavy chains of antibodies of complexes in the composition are

both independently covalently linked to an oligonucleotide at linkage sites represented by lysine residues in the light chains (e.g., the K at position 4 or position 6 in a motif DYEKHKVYA (SEQ ID NO: 27)) and in the heavy chains (e.g., the K in a motif VNHKPSN (SEQ ID NO: 28)) of the antibodies.

[00038] In some aspects, the present disclosure provides methods of reducing expression or activity of DMPK (e.g., reducing the level of a mutant or wild-type DMPK RNA) and/or methods of treating myotonic dystrophy (e.g., DM1) in a subject. In some embodiments, the methods comprise administering to the subject an effective amount of the composition comprising the complexes described herein.

[00039] In some aspects, the present disclosure further provides methods of determining a drug to antibody ratio (DAR) range of complexes in a composition, or methods of analyzing complexes in a composition.

[00040] Further aspects of the disclosure, including a description of defined terms, are provided below.

DEFINITIONS

[00041] **Administering**: As used herein, the terms "administering" or "administration" means to provide a complex to a subject in a manner that is physiologically and/or (e.g., and) pharmacologically useful (*e.g.*, to treat a condition in the subject).

[00042] **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).

[00043] **Antibody:** As used herein, the term "antibody" refers to a polypeptide that includes at least one immunoglobulin variable domain or at least one antigenic determinant, e.g., paratope that specifically binds to an antigen. In some embodiments, an antibody is a full-length antibody. In some embodiments, an antibody is a chimeric antibody. In some embodiments, an antibody is a humanized antibody. However, in some embodiments, an antibody is a Fab fragment, a Fab' fragment, a $F(ab')_2$ fragment, a Fv fragment or a scFv fragment. In some embodiments, an antibody is a nanobody derived from a camelid antibody or a nanobody derived from shark antibody. In some embodiments, an antibody is a diabody.

In some embodiments, an antibody comprises a framework having a human germline sequence. In another embodiment, an antibody comprises a heavy chain constant domain selected from the group consisting of IgG, IgG1, IgG2, IgG2A, IgG2B, IgG2C, IgG3, IgG4, IgA1, IgA2, IgD, IgM, and IgE constant domains. In some embodiments, an antibody comprises a heavy (H) chain variable region (abbreviated herein as VH), and/or (e.g., and) a light (L) chain variable region (abbreviated herein as VL). In some embodiments, an antibody comprises a constant domain, e.g., an Fc region. An immunoglobulin constant domain refers to a heavy or light chain constant domain. Human IgG heavy chain and light chain constant domain amino acid sequences and their functional variations are known. With respect to the heavy chain, in some embodiments, the heavy chain of an antibody described herein can be an alpha (α), delta (Δ), epsilon (ε), gamma (γ) or mu (μ) heavy chain. In some embodiments, the heavy chain of an antibody described herein can comprise a human alpha (α), delta (Δ), epsilon (ε), gamma (γ) or mu (μ) heavy chain. In a particular embodiment, an antibody described herein comprises a human gamma 1 CH1, CH2, and/or (e.g., and) CH3 domain. In some embodiments, the amino acid sequence of the VH domain comprises the amino acid sequence of a human gamma (γ) heavy chain constant region, such as any known in the art. Non-limiting examples of human constant region sequences have been described in the art, e.g., see U.S. Pat. No. 5,693,780 and Kabat E A et al., (1991) supra. In some embodiments, the VH domain comprises an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or at least 99% identical to any of the variable chain constant regions provided herein. In some embodiments, an antibody is modified, e.g., modified via glycosylation, phosphorylation, sumoylation, and/or (e.g., and) methylation. In some embodiments, an antibody is a glycosylated antibody, which is conjugated to one or more sugar or carbohydrate molecules. In some embodiments, the one or more sugar or carbohydrate molecule are conjugated to the antibody via N-glycosylation, O-glycosylation, C-glycosylation, glypiation (GPI anchor attachment), and/or (e.g., and) phosphoglycosylation. In some embodiments, the one or more sugar or carbohydrate molecule are monosaccharides, disaccharides, oligosaccharides, or glycans. In some embodiments, the one or more sugar or carbohydrate molecule is a branched oligosaccharide or a branched glycan. In some embodiments, the one or more sugar or carbohydrate molecule includes a mannose unit, a glucose unit, an N-acetylglucosamine unit, an N-acetylgalactosamine unit, a galactose unit, a fucose unit, or a phospholipid unit. In some embodiments, an antibody is a construct that comprises a polypeptide comprising one or more antigen binding fragments of the disclosure linked to a linker polypeptide or an immunoglobulin constant domain. Linker polypeptides comprise two or more amino acid

residues joined by peptide bonds and are used to link one or more antigen binding portions. Examples of linker polypeptides have been reported (see e.g., Holliger, P., et al. (1993) Proc. Natl. Acad. Sci. USA 90:6444-6448; Poljak, R. J., et al. (1994) Structure 2:1121-1123). Still further, an antibody may be part of a larger immunoadhesion molecule, formed by covalent or noncovalent association of the antibody or antibody portion with one or more other proteins or peptides. Examples of such immunoadhesion molecules include use of the streptavidin core region to make a tetrameric scFv molecule (Kipriyanov, S. M., et al. (1995) Human Antibodies and Hybridomas 6:93-101) and use of a cysteine residue, a marker peptide and a C-terminal polyhistidine tag to make bivalent and biotinylated scFv molecules (Kipriyanov, S. M., et al. (1994) Mol. Immunol. 31:1047-1058).

[00044] **CDR:** As used herein, the term "CDR" refers to the complementarity determining region within antibody variable sequences. A typical antibody molecule comprises a heavy chain variable region (VH) and a light chain variable region (VL), which are usually involved in antigen binding. The VH and VL regions can be further subdivided into regions of hypervariability, also known as “complementarity determining regions” (“CDR”), interspersed with regions that are more conserved, which are known as “framework regions” (“FR”). Each VH and VL is typically composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The extent of the framework region and CDRs can be precisely identified using methodology known in the art, for example, by the Kabat definition, the IMGT definition, the Chothia definition, the AbM definition, and/or (e.g., and) the contact definition, all of which are well known in the art. See, e.g., Kabat, E.A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; IMGT®, the international ImMunoGeneTics information system® http://www.imgt.org, Lefranc, M.-P. et al., Nucleic Acids Res., 27:209-212 (1999); Ruiz, M. et al., Nucleic Acids Res., 28:219-221 (2000); Lefranc, M.-P., Nucleic Acids Res., 29:207-209 (2001); Lefranc, M.-P., Nucleic Acids Res., 31:307-310 (2003); Lefranc, M.-P. et al., In Silico Biol., 5, 0006 (2004) [Epub], 5:45-60 (2005); Lefranc, M.-P. et al., Nucleic Acids Res., 33:D593-597 (2005); Lefranc, M.-P. et al., Nucleic Acids Res., 37:D1006-1012 (2009); Lefranc, M.-P. et al., Nucleic Acids Res., 43:D413-422 (2015); Chothia et al., (1989) Nature 342:877; Chothia, C. et al. (1987) J. Mol. Biol. 196:901-917, Al-lazikani et al (1997) J. Molec. Biol. 273:927-948; and Almagro, J. Mol. Recognit. 17:132-143 (2004). See also hgmp.mrc.ac.uk and bioinf.org.uk/abs. As used herein, a CDR may refer to the CDR defined by any method known in the art. Two antibodies having the same CDR means that the two

antibodies have the same amino acid sequence of that CDR as determined by the same method, for example, the IMGT definition.

[00045] There are three CDRs in each of the variable regions of the heavy chain and the light chain, which are designated CDR1, CDR2 and CDR3, for each of the variable regions. The term "CDR set" as used herein refers to a group of three CDRs that occur in a single variable region capable of binding the antigen. The exact boundaries of these CDRs have been defined differently according to different systems. The system described by Kabat (Kabat *et al.,* Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md. (1987) and (1991)) not only provides an unambiguous residue numbering system applicable to any variable region of an antibody, but also provides precise residue boundaries defining the three CDRs. These CDRs may be referred to as Kabat CDRs. Sub-portions of CDRs may be designated as L1, L2 and L3 or H1, H2 and H3 where the "L" and the "H" designates the light chain and the heavy chains regions, respectively. These regions may be referred to as Chothia CDRs, which have boundaries that overlap with Kabat CDRs. Other boundaries defining CDRs overlapping with the Kabat CDRs have been described by Padlan (FASEB J. 9:133-139 (1995)) and MacCallum (J Mol Biol 262(5):732-45 (1996)). Still other CDR boundary definitions may not strictly follow one of the above systems, but will nonetheless overlap with the Kabat CDRs, although they may be shortened or lengthened in light of prediction or experimental findings that particular residues or groups of residues or even entire CDRs do not significantly impact antigen binding. The methods used herein may utilize CDRs defined according to any of these systems. Examples of CDR definition systems are provided in Table 1.

Table 1. CDR Definitions

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

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

[00046] **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.

[00047] **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.

[00048] **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 (e.g., and) 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, 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. In DM1, the DMPK gene comprises a disease-associated repeat of CTG units.

[00049] **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, Gene ID: 102125829), 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.

[00050] **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 repeat units in subjects having DM1 is in the range of about 50 to about 3,000 or more, 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.

[00051] **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.

[00052] **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.

[00053] **Humanized antibody:** The term "humanized antibody" refers to antibodies which comprise heavy and light chain variable region sequences from a non-human species (*e.g.,* a mouse) but in which at least a portion of the VH and/or (e.g., and) VL sequence has been altered to be more "human-like", *i.e.,* more similar to human germline variable sequences. One type of humanized antibody is a CDR-grafted antibody, in which human CDR sequences are introduced into non-human VH and VL sequences to replace the corresponding 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.

[00054] **Kabat numbering:** The terms "Kabat numbering", "Kabat definitions and "Kabat labeling" are used interchangeably herein. These terms, which are recognized in the art, refer to a system of numbering amino acid residues which are more variable (i.e. hypervariable) than other amino acid residues in the heavy and light chain variable regions of an antibody, or an antigen binding portion thereof (Kabat et al. (1971) Ann. NY Acad, Sci. 190:382-391 and, Kabat, E. A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). For the heavy chain variable region, the hypervariable region ranges from amino acid positions 31 to 35 for CDR1, amino acid positions 50 to 65 for CDR2, and amino acid positions 95 to 102 for CDR3. For the light chain variable region, the hypervariable region ranges from amino acid positions 24 to 34 for CDR1, amino acid positions 50 to 56 for CDR2, and amino acid positions 89 to 97 for CDR3.

[00055] **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.

[00056] **Oligonucleotide:** As used herein, the term "oligonucleotide" refers to an oligomeric nucleic acid compound of up to 200 nucleotides in length. Examples of

oligonucleotides include, but are not limited to, RNAi oligonucleotides (e.g., siRNAs, shRNAs), microRNAs, gapmers, mixmers, phosphorodiamidate morpholinos, peptide nucleic acids, aptamers, guide nucleic acids (e.g., Cas9 guide RNAs), etc. Oligonucleotides may be single-stranded or double-stranded. In some embodiments, an oligonucleotide may comprise one or more modified nucleosides (e.g., 2′-O-methyl sugar modifications, purine or pyrimidine modifications). In some embodiments, an oligonucleotide may comprise one or more modified internucleoside linkage. In some embodiments, an oligonucleotide may comprise one or more phosphorothioate linkages, which may be in the Rp or Sp stereochemical conformation.

[00057] **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.

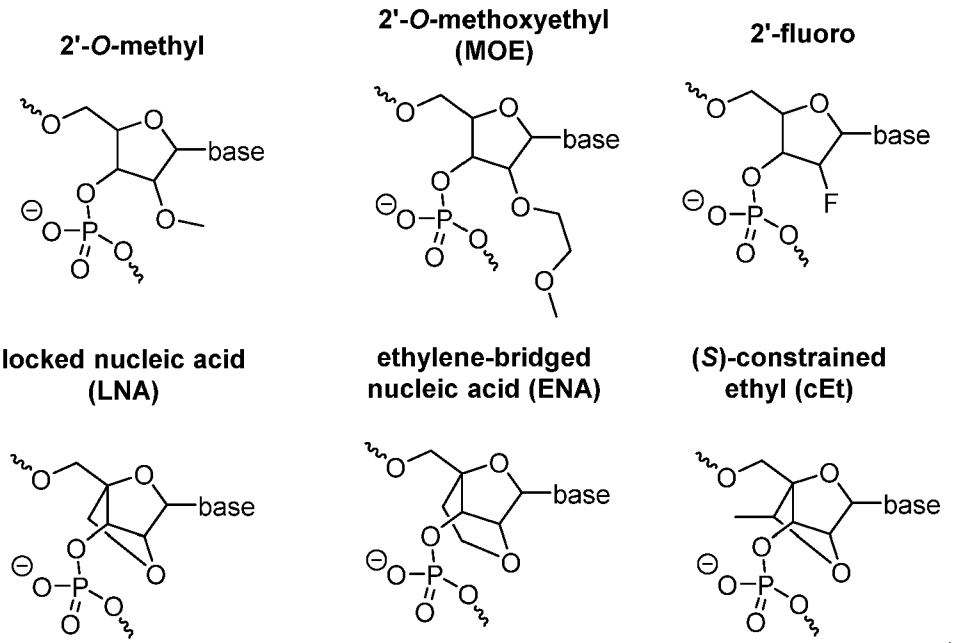
[00058] **Specifically binds:** As used herein, the term "specifically binds" refers to the ability of a molecule to bind to a binding partner with a degree of affinity or avidity that enables the molecule to be used to distinguish the binding partner from an appropriate control in a binding assay or other binding context. With respect to an antibody, the term, "specifically binds", refers to the ability of the antibody to bind to a specific antigen with a degree of affinity or avidity, compared with an appropriate reference antigen or antigens, that enables the antibody to be used to distinguish the specific antigen from others, e.g., to an extent that permits preferential targeting to certain cells, e.g., muscle cells, through binding to the antigen, as described herein. In some embodiments, an antibody specifically binds to a target if the antibody has a K_D for binding the target of at least about 10^{-4} M, 10^{-5} M, 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, 10^{-12} M, 10^{-13} M, or less. In some embodiments, an antibody specifically binds to the transferrin receptor, e.g., an epitope of the apical domain of transferrin receptor.

[00059] **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.

[00060] **Transferrin receptor:** As used herein, the term, "transferrin receptor" (also known as TFRC, CD71, p90, TFR, 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).

[00061] **2'-modified nucleoside**: As used herein, the terms "2'-modified nucleoside" and "2'-modified ribonucleoside" are used interchangeably and refer to a nucleoside having a sugar moiety modified at the 2' position. In some embodiments, the 2'-modified nucleoside is a 2'-4' bicyclic nucleoside, where the 2' and 4' positions of the sugar are bridged (e.g., via a methylene, an ethylene, or a (S)-constrained ethyl bridge). In some embodiments, the 2'-modified nucleoside is a non-bicyclic 2'-modified nucleoside, e.g., where the 2' position of the sugar moiety is substituted. Non-limiting examples of 2'-modified nucleosides include: 2'-deoxy, 2'-fluoro (2'-F), 2'-O-methyl (2'-O-Me), 2'-O-methoxyethyl (2'-MOE), 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), 2'-O-dimethylaminoethyloxyethyl (2'-O-DMAEOE), 2'-O-N-methylacetamido (2'-O-NMA), locked nucleic acid (LNA, methylene-bridged nucleic acid), ethylene-bridged nucleic acid (ENA), and (S)-constrained ethyl-bridged nucleic acid (cEt). In some embodiments, the 2'-modified nucleosides described herein are high-affinity modified nucleotides and oligonucleotides comprising the 2'-modified nucleosides have increased affinity to a target sequences, relative to an unmodified oligonucleotide. Examples of structures of 2'-modified nucleosides are provided below:



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

[00062] **Ranges:** All ranges provided in the present disclosure are inclusive of the end points.

Complexes

[00063] Provided herein are compositions comprising a plurality of complexes. In some embodiments, complexes comprise an antibody covalently linked to one or more oligonucleotides, each oligonucleotide being covalently linked at a linkage site represented by a lysine (K) residue of the antibody. In some embodiments, the antibody comprises a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region. In some embodiments, light chain constant regions of antibodies of complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of light chain constant regions of the antibodies. For example, in some embodiments, a linkage site is represented by K188 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, a linkage site is represented by K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, linkage sites are represented by K188 (based on Kabat numbering) and K190 (based on Kabat numbering) of light chain constant region(s) of an antibody. In some embodiments, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least

85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies. In some embodiments, heavy chain constant regions of antibodies of complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K213 (based on Kabat numbering) of heavy chain constant regions of the antibodies. In some embodiments, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the antibodies.

[00064] In some embodiments, light chain constant regions of antibodies of complexes in the composition are independently covalently linked to an oligonucleotide at linkage sites represented by lysine (K) residues in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of light chains of the antibodies. For example, in some embodiments, antibodies are covalently linked to an oligonucleotide at a linkage site represented by the K at position 4 in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of a light chain. In some embodiments, antibodies are covalently linked to an oligonucleotide at a linkage site represented by the K at position 6 in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of a light chain. In some embodiments, antibodies are covalently linked to an oligonucleotide at a linkage site represented the K at position 4 and at a linkage site represented by the K at position 6 in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of a light chain. In some embodiments, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, or 90%-95%) of light chains of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at linkage sites represented by lysine (K) residues in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of light chains of the antibodies. In some embodiments,

heavy chain constant regions of antibodies of complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by the lysine (K) residue in a sequence a sequence motif VNHKPSN (SEQ ID NO: 28) of heavy chains of the antibodies. In some embodiments, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chains of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by the lysine (K) residue in motif VNHKPSN (SEQ ID NO: 28) of heavy chains of the antibodies.

[00065] Complexes described herein generally comprise a linker that covalently links an antibody (e.g., an anti-TfR1 antibody) described herein to an oligonucleotide (e.g., an oligonucleotide comprising a 5'-X-Y-Z-3' configuration) at a linkage site represented by a lysine (K) residue of the antibody. In some embodiments, in each complex, each oligonucleotide is covalently linked at a linkage site represented by a different lysine (K) residue of the antibody. A linker comprises at least one covalent bond.

[00066] In some embodiments, complexes described herein comprise a structure of formula (I): $[R^1]_{n1}$-R^2, in which each R^1 independently comprises a compound comprising an oligonucleotide (e.g., an oligonucleotide comprising a 5'-X-Y-Z-3' configuration) and R^2 comprises an antibody (e.g., an anti-TfR1 antibody), and wherein in each complex n1 is independently an integer (e.g., one or greater) representing the number of instances of R^1 in each complex. In some embodiments, each R^1 independently comprises a group comprising an oligonucleotide. In some embodiments, each R^1 independently comprises a group that comprises additional elements in addition to an oligonucleotide. In some embodiments, R^2 comprises an antibody (*e.g.*, an anti-TfR1 antibody) comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region. In some embodiments, each R^1 of a complex is independently covalently linked to a different amino acid residue (e.g., lysine) of R^2.

[00067] In some embodiments, each R^1 is covalently linked to R^2 via a linkage site represented by a lysine (K) residue of the antibody. In some embodiments, a linkage site is represented by K188 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, a linkage site is represented by K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, linkage sites are represented by K188 (based on Kabat numbering) and K190 (based on Kabat

numbering) of a light chain constant region of an antibody. In some embodiments, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chain constant regions of the antibodies of the complexes in a composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of light chain constant regions of the antibodies. In some embodiments, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chain constant regions of the antibodies of the complexes in a composition are independently covalently linked to R^1 at a linkage site represented by K213 (based on Kabat numbering) of heavy chain constant regions of the antibodies.

[00068] In some embodiments, each R^1 is covalently linked to R^2 via a linkage site represented by a lysine (K) residue of the antibody. In some embodiments, a linkage site is represented by the K at position 4 of a sequence motif DYEKHKVYA (SEQ ID NO: 27) of a light chain of an antibody. In some embodiments, a linkage site is represented by the K at position 6 of a sequence motif DYEKHKVYA (SEQ ID NO: 27) of a light chain of an antibody. In some embodiments, linkage sites are represented by the K at position 4 and the K at position 6 of a sequence motif DYEKHKVYA (SEQ ID NO: 27) of a light chain of an antibody. In some embodiments, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chains of the antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by a lysine (K) residue in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of the light chains of the antibodies. In some embodiments, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chains of the antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by the lysine (K) residue in a sequence motif VNHKPSN (SEQ ID

NO: 28) of the heavy chains of the antibodies. In some embodiments, R^2 comprises an anti-TfR1 Fab.

[00069] In some embodiments, in each complex n1 is independently an integer (e.g., one or greater). In some embodiments, the antibody comprises a sequence as set forth in Table 2. For example, in some embodiments, the antibody comprises a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14; and/or comprises a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NO: 6 or 16. In some embodiments, the antibody comprises a heavy chain variable region (VH) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 17 and/or comprises a light chain variable region (VL) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 18. In some embodiments, the antibody comprises a VH comprising the amino acid sequence of SEQ ID NO: 17 and/or comprises a VL comprising the amino acid sequence of SEQ ID NO: 18. In some embodiments, the antibody comprises a heavy chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 19 and/or comprises a light chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 20. In some embodiments, the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and/or comprises a light chain comprising the amino acid sequence of SEQ ID NO: 20. In some embodiments, the antibody is a Fab fragment, a full-length IgG, a Fab' fragment, a $F(ab')_2$ fragment, an scFv, or an Fv. In some embodiments, the antibody is a Fab fragment.

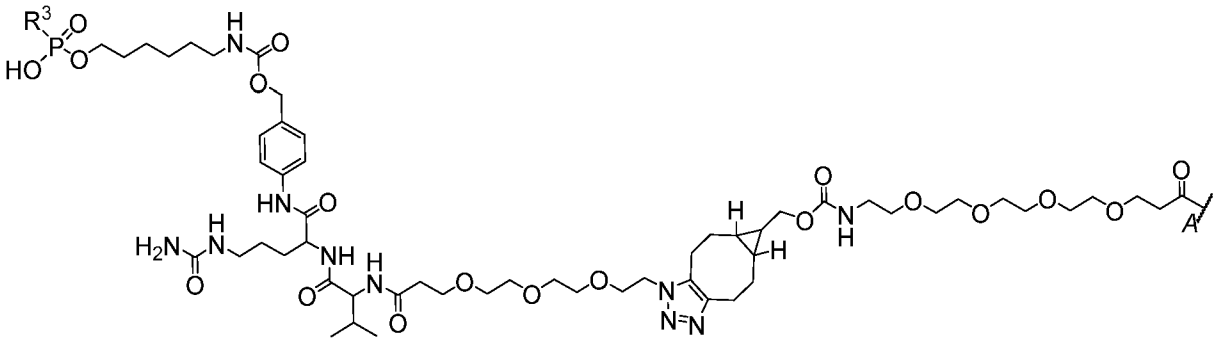
[00070] In some embodiments, the plurality of different complexes comprise a common targeting agent (e.g. an antibody) and a common oligonucleotide (e.g., an oligonucleotide comprising a 5'-X-Y-Z-3' configuration). In such embodiments, different complex types are characterized by having different numbers of oligonucleotides covalently linked to an antibody. For example, in some embodiments, a composition comprises a plurality of complex types in which each complex type comprises a structure of formula (I): $[R^1]_{n1}$-R^2, in which each R^1 independently comprises a compound comprising an oligonucleotide (e.g., an

oligonucleotide comprising a 5'-X-Y-Z-3' configuration) and R^2 comprises an antibody (e.g., anti-TfR1 antibody) comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region. In some embodiments, the value of n1 of each or any complex (e.g., any complex in any of the compositions or methods disclosed herein) is an integer up to the number of amino acid residues in the antibody to which conjugation is desired or targeted (e.g., the number of lysine residues). In some embodiments, in each complex the value of n1 is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, and 27. In some embodiments, in each complex the value of n1 is independently selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 and 26. In some embodiments, in each complex the value of n1 is independently in the range of 1-27, 1-26, 1-10, 1-5, or 1-3. In some embodiments, the average value of n1 of complexes of the composition is in the range of 1 to 5 (e.g., 1-5, 1-4, 1-3, 3--5, or 1-2). In some embodiments, compositions described herein comprise complexes that comprise a structure of formula (I): $[R^1]_{n1}$-R^2, wherein n1 is 0. In some embodiments, the average value of n1 of complexes of the composition is in the range of 0.5 to 5 (e.g., 0.5-5, 1-5, 1-4, 1-3, 3-5, 0.5-4, 0.5-3, 0.5-2, 0.5-1.5, 0.5-1, 0.7-1.5, 1-1.6, 1-1.5, 1-1.4, 1-1.3, 1-1.2, 1.1-1.5, 0.8-2, 0.8-1.5, 0.8-1.3, 0.8-1.2, 0.8-1.1, 0.9-3, 0.9-2, 0.9-1.8, 0.9-1.6, 0.9-1.5, 0.9-1.4, 0.9-1.3, or 0.9-1.2). In some embodiments, in each complex type n1 is independently an integer of one or greater representing the number of instances of R^1 in each complex of the complex type, and in which the different complex types of the composition are characterized by having different n1 values (e.g., n1 values in the range of 1-27, 1-26, 1-25, 1-20, 1-15, 1-10, 1-5, or 1-3).

[00071] In some embodiments, a composition described herein comprises antibody that is not conjugated to an oligonucleotide (e.g., in trace amounts) and antibody conjugated to one or more oligonucleotides. In some embodiments, antibody that is not conjugated to an oligonucleotide may be referred to as a compound comprising a structure of formula (I): $[R^1]_{n1}$-R^2, for which n1 is zero. Accordingly, in some embodiments, a composition for administration to a subject in the methods described herein comprises compounds (e.g., complexes) comprising a structure of formula (I): $[R^1]_{n1}$-R^2, for which each R^1 independently comprises a group comprising an oligonucleotide, R^2 comprises an antibody and n1 is independently an integer of zero or greater that reflects the number of instances of R^1 in each compound (e.g., complex). In some embodiments, the fraction of compounds comprising a structure of formula (I): $[R^1]_{n1}$-R^2, in a composition, for which n1 is zero, compared with all

compounds of that structure in the composition for which n1 is one or greater, is less than 10%, less than 5%, less than 1% less than 0.5%, less than 0.1%, less than 0.05%, or less than 0.01%. As such, in some embodiments, the average value of n1 of complexes in a composition disclosed herein is in the range of 0.5 to 5 (e.g., 0.5-5, 1-5, 1-4, 1-3, 3-5, 0.5-4, 0.5-3, 0.5-2, 0.5-1.5, 0.5-1, 0.7-1.5, 1-1.6, 1-1.5, 1-1.4, 1-1.3, 1-1.2, 1.1-1.5, 0.8-2, 0.8-1.5, 0.8-1.3, 0.8-1.2, 0.8-1.1, 0.9-3, 0.9-2, 0.9-1.8, 0.9-1.6, 0.9-1.5, 0.9-1.4, 0.9-1.3, or 0.9-1.2).

[00072] In some embodiments, complexes described herein comprise a structure of formula (I): $[R^1]_{n1}$-R^2, in which each R^1 independently comprises a group of the formula (Ia):



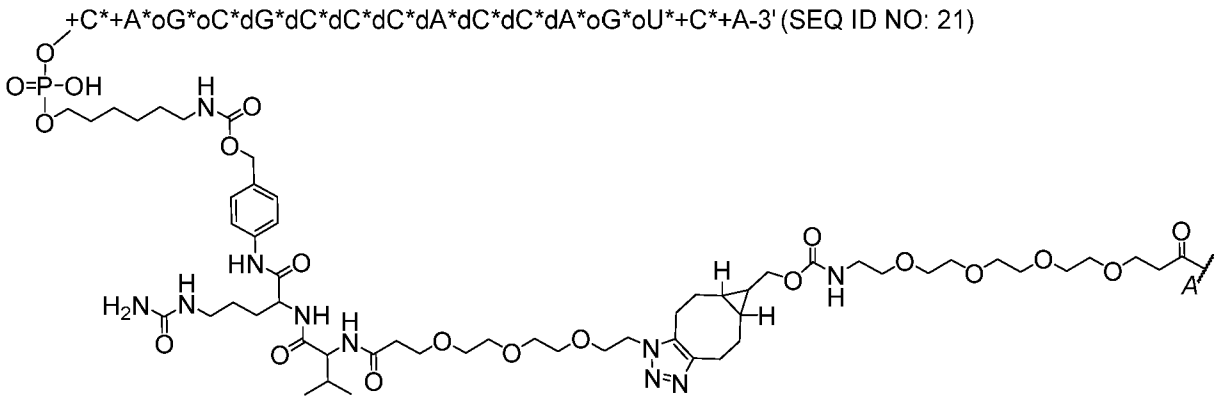
(Ia),

in which R^3 comprises an oligonucleotide, *e.g.*, an oligonucleotide comprising a 5'-X-Y-Z-3' configuration; R^2 comprises an antibody comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region, wherein in each complex n1 is independently an integer (e.g., of one or greater) representing the number of instances of R^1 in each complex, and each R^1 is covalently linked to R^2 at attachment point *A* via a linkage site represented by a lysine (K) residue of the antibody. In some embodiments, a linkage site is represented by K188 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, a linkage site is represented by K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, linkage sites are represented by K188 (based on Kabat numbering) and K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, in a composition comprising a plurality of complexes described herein, at least 80% of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a sequence as set forth in Table 2. For example, in some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain

complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14; and/or comprising a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NO: 6 or 16. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain variable region (VH) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 17 and/or comprising a light chain variable region (VL) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 18. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a VH comprising the amino acid sequence of SEQ ID NO: 17 and/or comprising a VL comprising the amino acid sequence of SEQ ID NO: 18. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 19 and/or comprising a light chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 20. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and/or comprising a light chain comprising the amino acid sequence of SEQ ID NO: 20. In some embodiments, R^2 comprises an antibody that is a Fab fragment, a full-length IgG, a Fab' fragment, a $F(ab')_2$ fragment, an scFv, or an Fv. In some embodiments, R^2 comprises an antibody that is a Fab fragment. In some embodiments, R^3 comprises an oligonucleotide comprising a nucleobase sequence of CAGCGCCCACCAGUCA (SEQ ID NO: 21). In some embodiments, R^3 comprises an oligonucleotide comprising a structure of +C*+A*oG*oC*dG*dC*dC*dC*dA*dC*dC*dA*oG*oU*+C*+A (SEQ ID NO: 21), wherein +N represents an LNA (2'-4' methylene bridge) ribonucleoside, dN represents a 2'-deoxyribonucleoside, oN represents a 2'-MOE modified ribonucleoside, oC represents a 5-methyl-2'-MOE-cytidine, +C represents a 5-methyl-2'-4'-bicyclic-cytidine (2'-4' methylene bridge), oU represents a 5-methyl-2'-MOE-uridine, and * represents a phosphorothioate internucleoside linkage. In some embodiments, R^2 comprises a Fab and each R^1 is covalently linked at attachment point *A* to R^2 via a linkage site represented by a lysine (K) residue of the Fab, and wherein, in a composition comprising a plurality of complexes described herein, at

least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chain constant regions of the Fabs of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies. In some embodiments, in a composition comprising a plurality of complexes described herein, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the antibodies. In some embodiments, compositions described herein comprise complexes that comprise a structure of formula (I): $[R^1]_{n1}$-R^2, wherein n1 is 0. In some embodiments, in each complex n1 is independently an integer (e.g., an integer in the range of 1-27, 1-26, 1-10, 1-5, or 1-3). In some embodiments, in a composition comprising a plurality of complexes described herein, the average value of n1 of complexes of the composition is in the range of 0.5 to 5 (e.g., 0.5-5, 1-5, 1-4, 1-3, 3-5, 0.5-4, 0.5-3, 0.5-2, 0.5-1.5, 0.5-1, 0.7-1.5, 1-1.6, 1-1.5, 1-1.4, 1-1.3, 1-1.2, 1.1-1.5, 0.8-2, 0.8-1.5, 0.8-1.3, 0.8-1.2, 0.8-1.1, 0.9-3, 0.9-2, 0.9-1.8, 0.9-1.6, 0.9-1.5, 0.9-1.4, 0.9-1.3, or 0.9-1.2).

[00073] In some embodiments, complexes described herein comprise a structure of formula (I): $[R^1]_{n1}$- R^2, in which each R^1 comprises a group of the formula (Ib):



(Ib),

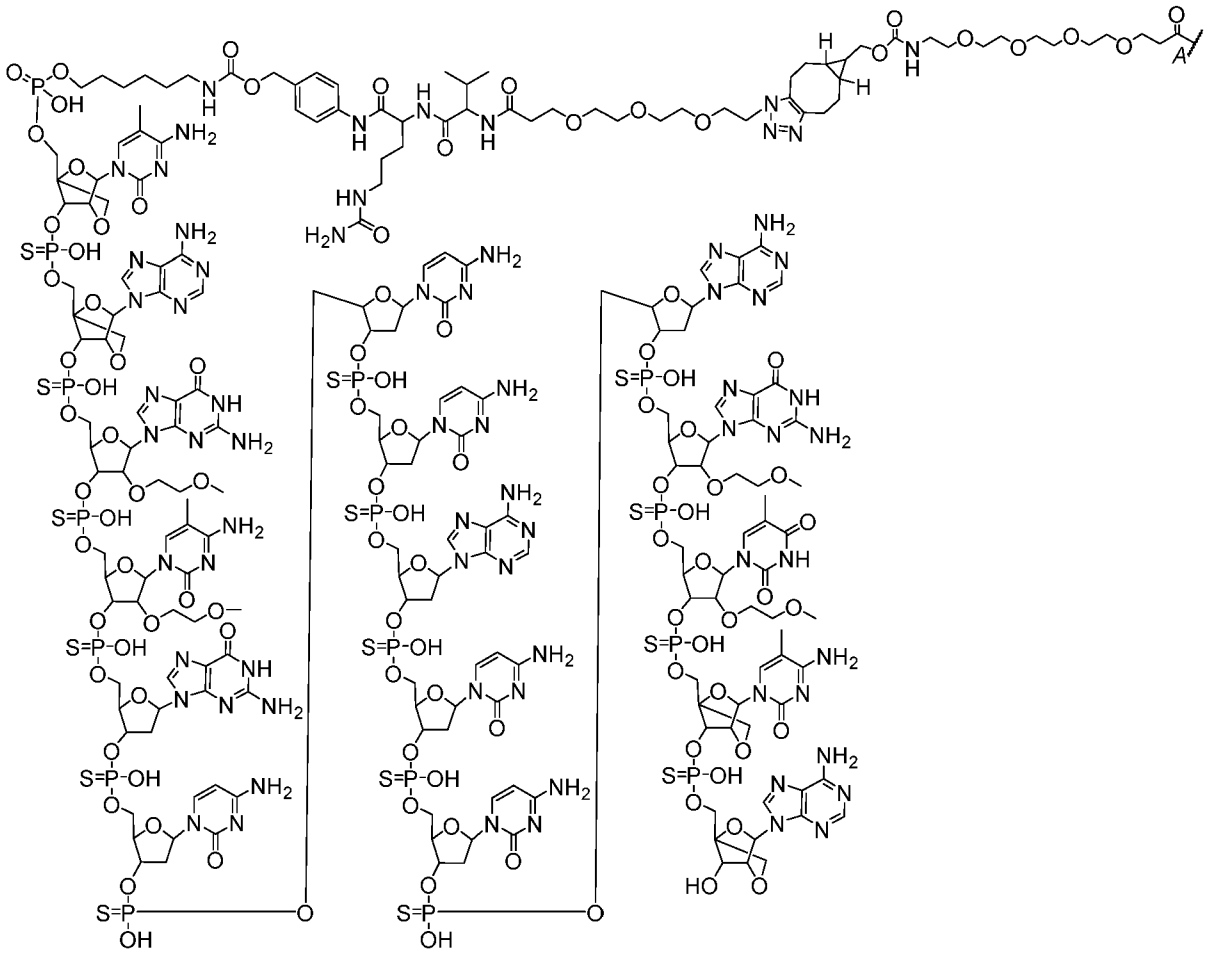
wherein +N represents an LNA (2'-4' methylene bridge) ribonucleoside, dN represents a 2'-deoxyribonucleoside, oN represents a 2'-O-methoxyethyl (MOE) modified ribonucleoside, oC represents a 5-methyl-2'-MOE-cytidine, +C represents a 5-methyl-2'-4'-bicyclic-cytidine (2'-

4' methylene bridge), oU represents a 5-methyl-2'-MOE-uridine, * represents a phosphorothioate internucleoside linkage, and wherein the oligonucleotide comprises a nucleobase sequence of CAGCGCCCACCAGUCA (SEQ ID NO: 21); R^2 comprises an antibody comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region, wherein in each complex n1 is independently an integer (e.g., of one or greater) representing the number of instances of R^1 in each complex, and each R^1 is covalently linked to R^2 at attachment point *A* via a linkage site represented by a lysine (K) residue of the antibody. In some embodiments, a linkage site is represented by K188 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, a linkage site is represented by K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, linkage sites are represented by K188 (based on Kabat numbering) and K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, in a composition comprising a plurality of complexes described herein, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a sequence as set forth in Table 2. For example, in some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14; and/or comprising a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NO: 6 or 16. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain variable region (VH)

comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 17 and/or comprising a light chain variable region (VL) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 18. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a VH comprising the amino acid sequence of SEQ ID NO: 17 and/or comprising a VL comprising the amino acid sequence of SEQ ID NO: 18. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 19 and/or comprising a light chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 20. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and/or comprising a light chain comprising the amino acid sequence of SEQ ID NO: 20. In some embodiments, R^2 comprises an antibody that is a Fab fragment, a full-length IgG, a Fab' fragment, a $F(ab')_2$ fragment, an scFv, or an Fv. In some embodiments, R^2 comprises an antibody that is a Fab fragment. In some embodiments, in each complex n1 is independently an integer (e.g., an integer in the range of 1-27, 1-26, 1-10, 1-5, or 1-3). In some embodiments, R^2 comprises a Fab and each R^1 is covalently linked attachment point *A* to R^2 via a linkage site represented by a lysine (K) residue of the Fab, and wherein, in a composition comprising a plurality of complexes described herein, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, or 90%-95%) of the light chain constant regions of the Fabs of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the Fabs. In some embodiments, in a composition comprising a plurality of complexes described herein, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chain constant regions of the Fabs of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the Fabs. In some embodiments, compositions described herein comprise complexes that comprise a structure of formula (I): $[R^1]_{n1}$-R^2, wherein n1 is 0. In some embodiments, in a composition comprising a plurality of complexes described herein, the average value of n1 of complexes of

the composition is in the range of 0.5 to 5 (e.g., 0.5-5, 1-5, 1-4, 1-3, 3-5, 0.5-4, 0.5-3, 0.5-2, 0.5-1.5, 0.5-1, 0.7-1.5, 1-1.6, 1-1.5, 1-1.4, 1-1.3, 1-1.2, 1.1-1.5, 0.8-2, 0.8-1.5, 0.8-1.3, 0.8-1.2, 0.8-1.1, 0.9-3, 0.9-2, 0.9-1.8, 0.9-1.6, 0.9-1.5, 0.9-1.4, 0.9-1.3, or 0.9-1.2).

[00074] In some embodiments, complexes described herein comprise a structure of formula (I): $[R^1]_{n1}$- R^2, in which each R^1 comprises a group of the formula (Ic):



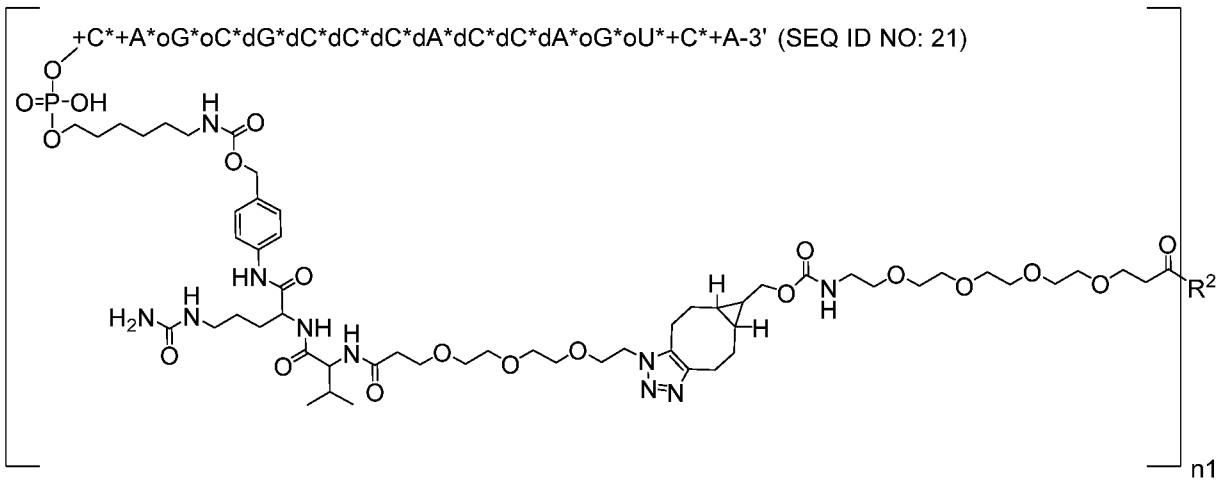
(Ic),

R^2 comprises an antibody comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region, wherein in each complex n1 is independently an integer (e.g., of one or greater) representing the number of instances of R^1 in each complex, wherein each R^1 is covalently linked to R^2 at attachment point *A* via a linkage site represented by a lysine (K) residue of the antibody. In some embodiments, a linkage site is represented by K188 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, a linkage site is represented by K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, linkage sites are represented by K188 (based on Kabat numbering) and K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, in a composition comprising a plurality

of complexes described herein, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a sequence as set forth in Table 2. For example, in some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14; and/or comprising a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NO: 6 or 16. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain variable region (VH) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 17 and/or comprising a light chain variable region (VL) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 18. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a VH comprising the amino acid sequence of SEQ ID NO: 17 and/or comprising a VL comprising the amino acid sequence of SEQ ID NO: 18. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 19 and/or comprising a light chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 20. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and/or comprising a light chain comprising the amino acid sequence of SEQ ID NO: 20. In some embodiments, R^2 comprises an antibody that is a Fab fragment, a full-length IgG, a Fab' fragment, a $F(ab')_2$ fragment, an scFv, or an Fv. In some embodiments, R^2 comprises an antibody that is a Fab fragment. In some embodiments, in each

complex n1 is independently an integer (e.g., an integer in the range of 1-27, 1-26, 1-10, 1-5, or 1-3). In some embodiments, R^2 comprises a Fab and each R^1 is covalently linked at attachment point *A* to R^2 via a linkage site represented by a lysine (K) residue of the Fab, and wherein, in a composition comprising a plurality of complexes described herein, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chain constant regions of the Fabs of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the Fabs. In some embodiments, in a composition comprising a plurality of complexes described herein, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chain constant regions of the Fabs of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the Fabs. In some embodiments, compositions described herein comprise complexes that comprise a structure of formula (I): $[R^1]_{n1}$-R^2, wherein n1 is 0. In some embodiments, in a composition comprising a plurality of complexes described herein, the average value of n1 of complexes of the composition is in the range of 0.5 to 5 (e.g., 0.5-5, 1-5, 1-4, 1-3, 3-5, 0.5-4, 0.5-3, 0.5-2, 0.5-1.5, 0.5-1, 0.7-1.5, 1-1.6, 1-1.5, 1-1.4, 1-1.3, 1-1.2, 1.1-1.5, 0.8-2, 0.8-1.5, 0.8-1.3, 0.8-1.2, 0.8-1.1, 0.9-3, 0.9-2, 0.9-1.8, 0.9-1.6, 0.9-1.5, 0.9-1.4, 0.9-1.3, or 0.9-1.2).

[00075] In some embodiments, complexes described herein comprise a structure of the formula (Id):



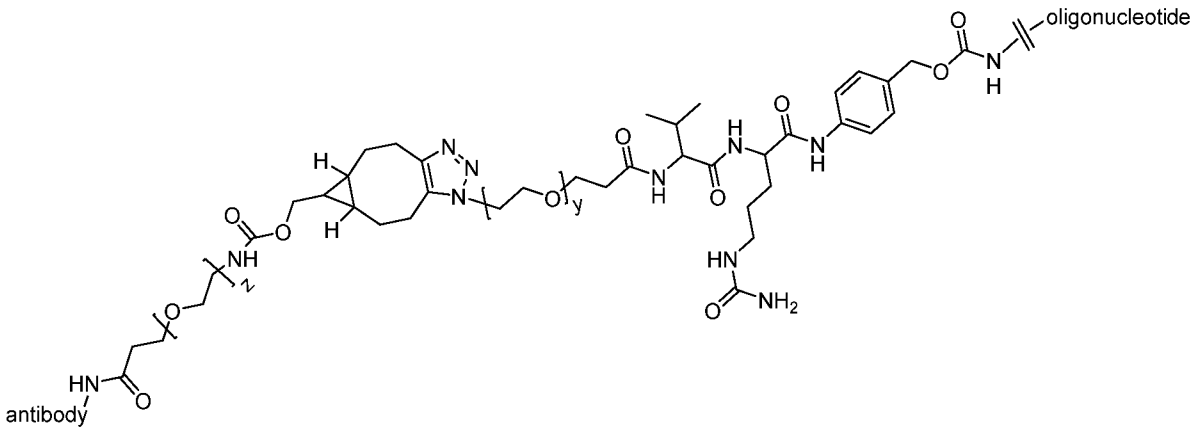
(Id),

wherein +N represents an LNA (2'-4' methylene bridge) ribonucleoside, dN represents a 2'-deoxyribonucleoside, oN represents a 2'-O-methoxyethyl (MOE) modified ribonucleoside, oC represents a 5-methyl-2'-MOE-cytidine, +C represents a 5-methyl-2'-4'-bicyclic-cytidine (2'-4' methylene bridge), oU represents a 5-methyl-2'-MOE-uridine, * represents a phosphorothioate internucleoside linkage, and wherein the oligonucleotide comprises a nucleobase sequence of CAGCGCCCACCAGUCA (SEQ ID NO: 21); wherein R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a CDR-H1, a CDR-H2, a CDR-H3, a CDR-L1, a CDR-L2, and a CDR-L3 selected from Table 2, optionally wherein the anti-TfR1 antibody (e.g., a Fab) comprises a VH comprising the amino acid sequence of SEQ ID NO: 17 and a VL comprising the amino acid sequence of SEQ ID NO: 18, further optionally wherein the anti-TfR1 antibody (e.g, a Fab) comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and a light chain comprising the amino acid sequence of SEQ ID NO: 20; and wherein in each complex n1 is independently an integer (e.g., of one or greater) representing the number of instances of the group enclosed by square brackets, wherein each instance of the group enclosed by square brackets is covalently linked to a linkage site represented by a lysine (K) residue of the antibody (e.g., the Fab). In some embodiments, a linkage site is represented by K188 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, a linkage site is represented by K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, linkage sites are represented by K188 (based on Kabat numbering) and K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, in a composition comprising a plurality of complexes described herein, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chain constant regions of the antibodies (e.g., the Fabs) of the complexes in the composition are independently covalently linked to the group enclosed by square brackets in formula (Id) at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies. In some embodiments, R^2 comprises an antibody (e.g., a Fab) comprising a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2)

comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14; and/or comprising a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NO: 6 or 16. In some embodiments, R^2 comprises an antibody (e.g., a Fab) comprising a heavy chain variable region (VH) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 17 and/or comprising a light chain variable region (VL) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 18. In some embodiments, R^2 comprises an antibody (e.g., a Fab) comprising a VH comprising the amino acid sequence of SEQ ID NO: 17 and/or comprising a VL comprising the amino acid sequence of SEQ ID NO: 18. In some embodiments, R^2 comprises an antibody (e.g., a Fab) comprising a heavy chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 19 and/or comprising a light chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 20. In some embodiments, R^2 comprises an antibody (e.g., a Fab) comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and/or comprising a light chain comprising the amino acid sequence of SEQ ID NO: 20. In some embodiments, in each complex n1 is independently an integer (e.g., an integer in the range of 1-27, 1-26, 1-10, 1-5, or 1-3). In some embodiments, R^2 comprises an antibody (e.g., a Fab) that is covalently linked via a linkage site represented by a lysine (K) residue of the antibody (e.g., the Fab), and wherein, in a composition comprising a plurality of complexes described herein, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, or 90%-95%) of the light chain constant regions of the antibodies (e.g., the Fabs) of the complexes in the composition are independently covalently linked to the group enclosed by square brackets in formula (Id) at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies. In some embodiments, in a composition comprising a plurality of complexes described herein, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about

15%) of the heavy chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to the group enclosed by square brackets in formula (Id) at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the antibodies. In some embodiments, compositions described herein comprise complexes in which the value of n1 is 0. In some embodiments, in a composition comprising a plurality of complexes described herein, the average value of n1 of complexes of the composition is in the range of 0.5 to 5 (e.g., 0.5-5, 1-5, 1-4, 1-3, 3-5, 0.5-4, 0.5-3, 0.5-2, 0.5-1.5, 0.5-1, 0.7-1.5, 1-1.6, 1-1.5, 1-1.4, 1-1.3, 1-1.2, 1.1-1.5, 0.8-2, 0.8-1.5, 0.8-1.3, 0.8-1.2, 0.8-1.1, 0.9-3, 0.9-2, 0.9-1.8, 0.9-1.6, 0.9-1.5, 0.9-1.4, 0.9-1.3, or 0.9-1.2).

[00076] In some embodiments, complexes described herein comprise a structure of formula (A):



(A), wherein y is 0-15 (e.g., 3) and z is 0-15 (e.g., 4). In some embodiments, the antibody is an anti-TfR1 antibody (e.g., the anti-TfR1 antibody provided in Table 2) comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region of each antibody. In some embodiments, the oligonucleotide comprises a 5'-X-Y-Z-3' configuration and comprises the nucleotide sequence of SEQ ID NO: 21. In some embodiments, the amide shown adjacent to the anti-TfR1 antibody in the structure results from a reaction with an amine of the anti-TfR1 antibody, such as a lysine epsilon amine. In some embodiments, a complex described herein comprises an anti-TfR1 Fab covalently linked to the 5' end of an oligonucleotide via a linkage site represented by a lysine (K) residue of the antibody. In some embodiments, a linkage site is represented by K188 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, a linkage site is represented by K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, linkage sites are represented by K188 (based on Kabat numbering) and K190 (based on Kabat numbering) of a light chain constant region of an

antibody. In some embodiments, in a composition comprising a plurality of complexes described herein, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies. In some embodiments, in a composition comprising a plurality of complexes described herein, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the antibodies. In some embodiments, the anti-TfR1 antibody comprises a sequence as set forth in Table 2. For example, in some embodiments, the anti-TfR1 antibody comprises a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14; and/or comprises a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NO: 6 or 16. In some embodiments, the antibody comprises a heavy chain variable region (VH) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 17 and/or comprises a light chain variable region (VL) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 18. In some embodiments, the anti-TfR1 antibody comprises a VH comprising the amino acid sequence of SEQ ID NO: 17 and/or comprises a VL comprising the amino acid sequence of SEQ ID NO: 18. In some embodiments, the anti-TfR1 antibody comprises a heavy chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 19 and/or comprises a light chain comprising an amino acid sequence at least 85% (e.g., at least 95%)

identical to SEQ ID NO: 20. In some embodiments, the anti-TfR1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and/or comprises a light chain comprising the amino acid sequence of SEQ ID NO: 20. In some embodiments, the antibody is a Fab fragment, a full-length IgG, a Fab' fragment, a $F(ab')_2$ fragment, an scFv, or an Fv.

[00077] In some embodiments, such as embodiments in which complexes described herein comprise a structure of formula (A) or comprise a structure comprising a group of the formula (Ia), (Ib), (Ic), or (Id), a linkage site is optionally represented by the K at position 4 of a sequence motif DYEKHKVYA (SEQ ID NO: 27) of a light chain of an antibody of a complex described herein. In some embodiments, a linkage site is optionally represented by the K at position 6 of a sequence motif DYEKHKVYA (SEQ ID NO: 27) of a light chain of an antibody of a complex described herein. In some embodiments, linkage sites are optionally represented by the K at position 4 and/or the K at position 6 of a sequence motif DYEKHKVYA (SEQ ID NO: 27) of a light chain of an antibody of a complex described herein. In some embodiments, in a composition comprising a plurality of complexes described herein, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of light chains of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at linkage sites represented by K residues at positions 4 and/or 6 of a sequence motif DYEKHKVYA (SEQ ID NO: 27) of the light chains of the antibodies. In some embodiments, a linkage site is optionally represented by the K in a sequence motif VNHKPSN (SEQ ID NO: 28) of a heavy chain of an antibody of a complex described herein. In some embodiments, in a composition comprising a plurality of complexes described herein, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chains of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by the K residue in a sequence motif VNHKPSN (SEQ ID NO: 28) of the heavy chains of the antibodies. In some embodiments, in a composition comprising a plurality of complexes described herein, the average value of n1 of complexes of the composition is in the range of 0.5 to 5 (e.g., 0.5-5, 1-5, 1-4, 1-3, 3-5, 0.5-4, 0.5-3, 0.5-2, 0.5-1.5, 0.5-1, 0.7-1.5, 1-1.6, 1-1.5, 1-1.4, 1-1.3, 1-1.2, 1.1-1.5, 0.8-2, 0.8-1.5, 0.8-1.3, 0.8-1.2, 0.8-1.1, 0.9-3, 0.9-2, 0.9-1.8, 0.9-1.6, 0.9-1.5, 0.9-1.4, 0.9-1.3, or 0.9-1.2).

Linkage sites

[00078] Provided herein are compositions comprising a plurality of complexes, wherein each complex comprises an antibody covalently linked to one or more oligonucleotides. In some embodiments, the antibody comprises a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region. In some embodiments, each oligonucleotide is covalently linked at a linkage site represented by a lysine (K) residue of the antibody. In some embodiments, in each complex of the composition, each oligonucleotide is covalently linked at a linkage site represented by a different lysine (K) residue of the antibody.

[00079] In some embodiments, light chain constant regions of antibodies of complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of a light chain constant region of an antibody. For example, in some embodiments, a linkage site is represented by K188 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, a linkage site is represented by K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, linkage sites are represented by K188 (based on Kabat numbering) and K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, at least 80% (e.g., at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, or at least 99%) of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies. In some embodiments, about 80%-98%, 80%-95%, 80%-90%, 80%-85%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95-97%, or 95%-98% of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies. In some embodiments, about 85%-95% (e.g., 85%-95%, 85%-90%, or 90%-95%) of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site

represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies. In some embodiments, 90%-95% (e.g. about 90%, about 91%, about 92%, about 93%, about 94%, or about 95%) of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies. It is to be understood that, complexes comprising light chain constant regions of antibodies covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of a light chain constant region include: complexes comprising antibodies that are covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) of the light chain constant regions of the antibodies; complexes comprising antibodies that are covalently linked to an oligonucleotide at a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies; and/or complexes comprising antibodies that are covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and at a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies.

[00080] In some embodiments, heavy chain constant regions of antibodies of complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K213 (based on Kabat numbering) of a heavy chain constant region of each antibody. For example, in some embodiments, the linkage site is represented by K213 (based on Kabat numbering) of a heavy chain constant region of each antibody. In some embodiments, at least 1% (e.g. at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%) of the heavy chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the antibodies. In some embodiments, 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the antibodies.

[00081] In some embodiments, lysine (K) residue numbers referred to herein are based on Kabat numbering (Kabat et al. (1971) Ann. NY Acad, Sci. 190:382-391 and Kabat et al., Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md. (1987) and (1991)). The variable regions and constant regions of the heavy and light chains of the antibodies provided herein are numbered separately. Kabat numbering of the light chain variable regions and heavy chain variable regions of the antibodies are described in the art, e.g., in Kabat et al. (1971) Ann. NY Acad, Sci. 190:382-391 and Kabat et al., Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md. (1987) and (1991). Kabat numbering of the light chain constant regions and heavy chain constant regions of the antibodies provided herein can be found at imgt.org/IMGTScientificChart/Numbering/Hu_IGHGnber.html and imgt.org/IMGTScientificChart/Numbering/Hu_IGKCnber.html (also see Edelman, G.M. et al., Proc. Natl. Acad. USA, 63, 78-85 (1969). PMID: 5257969; Hieter, P.A. et al., Cell, 22, 197-207 (1980). PMID: 6775818; Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md. 647, 662, 680, 689 (1991)).

[00082] In some embodiments, light chains of antibodies of complexes in the composition are independently covalently linked to an oligonucleotide at linkage sites represented by represented by lysine (K) residues in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of light chains of the antibodies. For example, in some embodiments, a linkage site is represented by the K at position 4 of a sequence motif DYEKHKVYA (SEQ ID NO: 27) of a light chain of an antibody. In some embodiments, a linkage site is represented by the K at position 6 of a sequence motif DYEKHKVYA (SEQ ID NO: 27) of a light chain of an antibody. In some embodiments, linkage sites are represented by the K at position 4 and the K at position 6 of a sequence motif DYEKHKVYA (SEQ ID NO: 27) of a light chain of an antibody. In some embodiments, at least 80% (e.g., at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, or at least 99%) of the light chains of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at linkage sites represented by lysine (K) residues in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of the light chains of the antibodies. In some embodiments, 80%-98%, 80%-95%, 80%-90%, 80%-85%, 85%-98%, 85%-95, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or 95%-98% of the light chains of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at linkage sites represented by lysine (K) residues in a

sequence motif DYEKHKVYA (SEQ ID NO: 27) of the light chains of the antibodies. In some embodiments, 85%-95% (e.g., 85%-95%, 85%-90%, or 90%-95%) of the light chains of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at linkage sites represented by lysine (K) residues in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of the light chains of the antibodies. In some embodiments, 90%-95% (e.g., about 90%, about 91%, about 92%, about 93%, about 94%, or about 95%) of the light chains of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at linkage sites represented by lysine (K) residues in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of the light chains of the antibodies. It is to be understood that, complexes comprising light chains of antibodies covalently linked to an oligonucleotide at a linkage site represented by lysine (K) residues in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of the light chains of the antibodies include: complexes comprising antibodies that are covalently linked to an oligonucleotide at a linkage site represented by the K at position 4 in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of the light chains of the antibodies; complexes comprising antibodies that are covalently linked to an oligonucleotide at a linkage site represented by the K at position 6 in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of the light chains of the antibodies; and/or complexes comprising antibodies that are covalently linked to an oligonucleotide at a linkage site represented the K at position 4 and at a linkage site represented by the K at position 6 in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of the light chains.

[00083] In some embodiments, heavy chains of antibodies of complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by the lysine (K) residue in a sequence a sequence motif VNHKPSN (SEQ ID NO: 28) of a heavy chain of an antibody. In some embodiments, about 1%-15% (e.g. about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chains of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by the lysine (K) residue in a sequence motif VNHKPSN (SEQ ID NO: 28) of the heavy chains of the antibodies. In some embodiments, 1%-10% (e.g., 1%-8%, 1%-5%, 1%-10%, 1%-4%, 2%-8%, 2%-5%, 3%-10%, 4%-10%, 5%-10%, 3%-5%, 4%-8%, 4%-7%, 4%-6%, or 5%-8%) of the heavy chains of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by the lysine (K) residue in a sequence motif VNHKPSN (SEQ ID NO: 28) of the heavy chains of the antibodies.

Antibodies

[00084] In some embodiments, complexes described herein comprise an antibody that binds human transferrin receptor 1 (TfR1). An example human TfR1 amino acid sequence, corresponding to NCBI sequence NP_003225.2 (transferrin receptor protein 1 isoform 1, homo sapiens) is as follows:

MMDQARSAFSNLFGGEPLSYTRFSLARQVDGDNSHVEMKLAVDEEENADNNTKANV
TKPKRCSGSICYGTIAVIVFFLIGFMIGYLGYCKGVEPKTECERLAGTESPVREEPGEDF
PAARRLYWDDLKRKLSEKLDSTDFTGTIKLLNENSYVPREAGSQKDENLALYVENQF
REFKLSKVWRDQHFVKIQVKDSAQNSVIIVDKNGRLVYLVENPGGYVAYSKAATVTG
KLVHANFGTKKDFEDLYTPVNGSIVIVRAGKITFAEKVANAESLNAIGVLIYMDQTKF
PIVNAELSFFGHAHLGTGDPYTPGFPSFNHTQFPPSRSSGLPNIPVQTISRAAAEKLFGN
MEGDCPSDWKTDSTCRMVTSESKNVKLTVSNVLKEIKILNIFGVIKGFVEPDHYVVVG
AQRDAWGPGAAKSGVGTALLLKLAQMFSDMVLKDGFQPSRSIIFASWSAGDFGSVG
ATEWLEGYLSSLHLKAFTYINLDKAVLGTSNFKVSASPLLYTLIEKTMQNVKHPVTGQ
FLYQDSNWASKVEKLTLDNAAFPFLAYSGIPAVSFCFCEDTDYPYLGTTMDTYKELIE
RIPELNKVARAAAEVAGQFVIKLTHDVELNLDYERYNSQLLSFVRDLNQYRADIKEM
GLSLQWLYSARGDFFRATSRLTTDFGNAEKTDRFVMKKLNDRVMRVEYHFLSPYVSP
KESPFRHVFWGSGSHTLPALLENLKLRKQNNGAFNETLFRNQLALATWTIQGAANAL
SGDVWDIDNEF (SEQ ID NO: 23).

[00085] Table 2 provides examples of sequences of an anti-TfR1 antibody useful in the complexes provided herein.

Table 2. Examples of anti-TfR1 antibody sequences

Feature	IMGT	Kabat	Chothia
CDR-H1	GYSITSGYY (SEQ ID NO: 1)	SGYYWN (SEQ ID NO: 7)	GYSITSGY (SEQ ID NO: 12)
CDR-H2	ITFDGAN (SEQ ID NO: 2)	YITFDGANNYNPSLKN (SEQ ID NO: 8)	FDG (SEQ ID NO: 13)
CDR-H3	TRSSYDYDVLDY (SEQ ID NO: 3)	SSYDYDVLDY (SEQ ID NO: 9)	SYDYDVLD (SEQ ID NO: 14)
CDR-L1	QDISNF (SEQ ID NO: 4)	RASQDISNFLN (SEQ ID NO: 10)	SQDISNF (SEQ ID NO: 15)
CDR-L2	YTS (SEQ ID NO: 5)	YTSRLHS (SEQ ID NO: 11)	YTS (SEQ ID NO: 5)
CDR-L3	QQGHTLPYT (SEQ ID NO: 6)	QQGHTLPYT (SEQ ID NO: 6)	GHTLPY (SEQ ID NO: 16)

VH	QVQLQESGPGLVKPSQTLSLTCTVTGYSITSGYYWNWIRQPPGKGLEWI GYITFDGANNYNPSLKNRVSISRDTSKNQFSLKLSSVTAEDTATYYCTR SSYDYDVLDYWGQGTTVTVSS (SEQ ID NO: 17)
VL	DIQMTQSPSSLSASVGDRVTITCRASQDISNFLNWYQQKPGQPVKLLIY YTSRLHSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGHTLPYTFG QGTKLEIK (SEQ ID NO: 18)
Fab HC	QVQLQESGPGLVKPSQTLSLTCTVTGYSITSGYYWNWIRQPPGKGLEWI GYITFDGANNYNPSLKNRVSISRDTSKNQFSLKLSSVTAEDTATYYCTR SSYDYDVLDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 19)
Fab LC	DIQMTQSPSSLSASVGDRVTITCRASQDISNFLNWYQQKPGQPVKLLIY YTSRLHSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGHTLPYTFG QGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV THQGLSSPVTKSFNRGEC (SEQ ID NO: 20)

[00086] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain complementarity determining region 1 (CDR-H1) of SEQ ID NO: 1 (according to the IMGT definition system), a heavy chain complementarity determining region 2 (CDR-H2) of SEQ ID NO: 2 (according to the IMGT definition system), a heavy chain complementarity determining region 3 (CDR-H3) of SEQ ID NO: 3 (according to the IMGT definition system), a light chain complementarity determining region 1 (CDR-L1) of SEQ ID NO: 4 (according to the IMGT definition system), a light chain complementarity determining region 2 (CDR-L2) of SEQ ID NO: 5 (according to the IMGT definition system), and a light chain complementarity determining region 3 (CDR-L3) of SEQ ID NO: 6 (according to the IMGT definition system).

[00087] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain complementarity determining region 1 (CDR-H1) of SEQ ID NO: 7 (according to the Kabat definition system), a heavy chain complementarity determining region 2 (CDR-H2) of SEQ ID NO: 8 (according to the Kabat definition system), a heavy chain complementarity determining region 3 (CDR-H3) of SEQ ID NO: 9 (according to the Kabat definition system), a light chain complementarity determining region 1 (CDR-L1) of SEQ ID NO: 10 (according to the Kabat definition system), a light chain complementarity determining region 2 (CDR-L2) of SEQ ID NO: 11 (according to the Kabat definition system), and a light chain complementarity determining region 3 (CDR-L3) of SEQ ID NO: 6 (according to the Kabat definition system).

[00088] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain complementarity determining region 1 (CDR-H1) of SEQ ID NO: 12

(according to the Chothia definition system), a heavy chain complementarity determining region 2 (CDR-H2) of SEQ ID NO: 13 (according to the Chothia definition system), a heavy chain complementarity determining region 3 (CDR-H3) of SEQ ID NO: 14 (according to the Chothia definition system), a light chain complementarity determining region 1 (CDR-L1) of SEQ ID NO: 15 (according to the Chothia definition system), a light chain complementarity determining region 2 (CDR-L2) of SEQ ID NO: 5 (according to the Chothia definition system), and a light chain complementarity determining region 3 (CDR-L3) of SEQ ID NO: 16 (according to the Chothia definition system).

[00089] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain variable region (VH) containing no more than 25 amino acid variations (*e.g.*, no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) in the framework regions as compared with the VH comprising the amino acid sequence of SEQ ID NO: 17. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody of the present disclosure comprises a light chain variable region (VL) containing no more than 25 amino acid variations (e.g., no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) in the framework regions as compared with the VL comprising the amino acid sequence of SEQ ID NO: 18.

[00090] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VH comprising an amino acid sequence that is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical in the framework regions to the VH comprising the amino acid sequence of SEQ ID NO: 17. Alternatively or in addition (e.g., in addition), in some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VL comprising an amino acid sequence that is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical in the framework regions to the VL comprising the amino acid sequence of SEQ ID NO: 18.

[00091] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 17. Alternatively or in addition (e.g., in addition), in some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VL comprising the amino acid sequence of SEQ ID NO: 18.

[00092] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical to the amino acid sequence of SEQ ID NO: 19. Alternatively or in addition (*e.g.*, in addition), the anti-TfR1 antibody of the present disclosure

comprises a light chain comprising an amino acid sequence least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical to the amino acid sequence of SEQ ID NO: 20. In some embodiments, the anti-TfR1 antibody of the present disclosure is a Fab that comprises a heavy chain comprising an amino acid sequence least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical to the amino acid sequence of SEQ ID NO: 19. Alternatively or in addition (*e.g.*, in addition), the anti-TfR1 antibody of the present disclosure is a Fab that comprises a light chain comprising an amino acid sequence least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical to the amino acid sequence of SEQ ID NO: 20.

[00093] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 19. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody of the present disclosure comprises a light chain comprising the amino acid sequence of SEQ ID NO: 20. In some embodiments, the anti-TfR1 antibody of the present disclosure is a Fab that comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 19. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody of the present disclosure is a Fab that comprises a light chain comprising the amino acid sequence of SEQ ID NO: 20.

[00094] In some embodiments, the anti-TfR1 antibody provided herein may have one or more post-translational modifications. In some embodiments, N-terminal cyclization, also called pyroglutamate formation (pyro-Glu), may occur in the antibody at N-terminal Glutamate (Glu) and/or Glutamine (Gln) residues during production. As such, it should be appreciated that an antibody specified as having a sequence comprising an N-terminal glutamate or glutamine residue encompasses antibodies that have undergone pyroglutamate formation resulting from a post-translational modification. In some embodiments, pyroglutamate formation occurs in a heavy chain sequence. In some embodiments, pyroglutamate formation occurs in a light chain sequence.

Oligonucleotides

[00095] In some embodiments, an oligonucleotide of the complexes described herein is a single stranded oligonucleotide. In some embodiments, the oligonucleotide is useful for targeting DMPK (e.g., for reducing expression or activity of a DMPK RNA, such as the level of a mutant or wild-type DMPK RNA). In some embodiments, an oligonucleotide that is useful for targeting DMPK RNAs. (e.g., for reducing expression or activity of a DMPK RNA, such as the level of a mutant or wild-type DMPK RNA). In some embodiments, the oligonucleotide comprises a region of complementarity to a DMPK RNA. In some

embodiments, the oligonucleotide is useful for reducing levels of toxic DMPK having disease-associated repeat expansions, e.g., in a subject having or suspected of having myotonic dystrophy. In some embodiments, the oligonucleotide is designed to direct RNAse H mediated degradation of the target DMPK RNA residing in the nucleus of cells, e.g., muscle cells (e.g., myotubes) or cells of the nervous system (e.g., central nervous system (CNS) cells). In some embodiments, the oligonucleotide is designed to have desirable bioavailability and/or serum-stability properties. In some embodiments, the oligonucleotide is designed to have desirable binding affinity properties. In some embodiments, the oligonucleotide is designed to have desirable toxicity profiles. In some embodiments, the oligonucleotide is designed to have low-complement activation and/or cytokine induction properties.

[00096] In some embodiments, DMPK-targeting oligonucleotides described herein are designed to caused RNase H mediated degradation of DMPK mRNA. 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.

[00097] 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.

[00098] In some embodiments, oligonucleotides may comprise 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):

AGGGGGGCTGGACCAAGGGGTGGGGAGAAGGGGAGGAGGCCTCGGCCGGCCGCA
GAGAGAAGTGGCCAGAGAGGCCCAGGGGACAGCCAGGGACAGGCAGACATGCAG
CCAGGGCTCCAGGGCCTGGACAGGGGCTGCCAGGCCCTGTGACAGGAGGACCCCG
AGCCCCCGGCCCGGGGAGGGGCCATGGTGCTGCCTGTCCAACATGTCAGCCGAGG

TGCGGCTGAGGCGGCTCCAGCAGCTGGTGTTGGACCCGGGCTTCCTGGGGCTGGA
GCCCCTGCTCGACCTTCTCCTGGGCGTCCACCAGGAGCTGGGCGCCTCCGAACTGG
CCCAGGACAAGTACGTGGCCGACTTCTTGCAGTGGGCGGAGCCCATCGTGGTGAG
GCTTAAGGAGGTCCGACTGCAGAGGGACGACTTCGAGATTCTGAAGGTGATCGGA
CGCGGGGCGTTCAGCGAGGTAGCGGTAGTGAAGATGAAGCAGACGGGCCAGGTG
TATGCCATGAAGATCATGAACAAGTGGGACATGCTGAAGAGGGGCGAGGTGTCGT
GCTTCCGTGAGGAGAGGGACGTGTTGGTGAATGGGGACCGGCGGTGGATCACGCA
GCTGCACTTCGCCTTCCAGGATGAGAACTACCTGTACCTGGTCATGGAGTATTACG
TGGGCGGGGACCTGCTGACACTGCTGAGCAAGTTTGGGGAGCGGATTCCGGCCGA
GATGGCGCGCTTCTACCTGGCGGAGATTGTCATGGCCATAGACTCGGTGCACCGG
CTTGGCTACGTGCACAGGGACATCAAACCCGACAACATCCTGCTGGACCGCTGTG
GCCACATCCGCCTGGCCGACTTCGGCTCTTGCCTCAAGCTGCGGGCAGATGGAAC
GGTGCGGTCGCTGGTGGCTGTGGGCACCCCAGACTACCTGTCCCCCGAGATCCTGC
AGGCTGTGGGCGGTGGGCCTGGGACAGGCAGCTACGGGCCCGAGTGTGACTGGTG
GGCGCTGGGTGTATTCGCCTATGAAATGTTCTATGGGCAGACGCCCTTCTACGCGG
ATTCCACGGCGGAGACCTATGGCAAGATCGTCCACTACAAGGAGCACCTCTCTCT
GCCGCTGGTGGACGAAGGGGTCCCTGAGGAGGCTCGAGACTTCATTCAGCGGTTG
CTGTGTCCCCCGGAGACACGGCTGGGCCGGGGTGGAGCAGGCGACTTCCGGACAC
ATCCCTTCTTCTTTGGCCTCGACTGGGATGGTCTCCGGGACAGCGTGCCCCCCTTTA
CACCGGATTTCGAAGGTGCCACCGACACATGCAACTTCGACTTGGTGGAGGACGG
GCTCACTGCCATGGAGACACTGTCGGACATTCGGGAAGGTGCGCCGCTAGGGGTC
CACCTGCCTTTTGTGGGCTACTCCTACTCCTGCATGGCCCTCAGGGACAGTGAGGT
CCCAGGCCCCACACCCATGGAACTGGAGGCCGAGCAGCTGCTTGAGCCACACGTG
CAAGCGCCCAGCCTGGAGCCCTCGGTGTCCCCACAGGATGAAACAGCTGAAGTGG
CAGTTCCAGCGGCTGTCCCTGCGGCAGAGGCTGAGGCCGAGGTGACGCTGCGGGA
GCTCCAGGAAGCCCTGGAGGAGGAGGTGCTCACCCGGCAGAGCCTGAGCCGGGA
GATGGAGGCCATCCGCACGGACAACCAGAACTTCGCCAGTCAACTACGCGAGGCA
GAGGCTCGGAACCGGGACCTAGAGGCACACGTCCGGCAGTTGCAGGAGCGGATG
GAGTTGCTGCAGGCAGAGGGAGCCACAGCTGTCACGGGGGTCCCCAGTCCCCGGG
CCACGGATCCACCTTCCCATCTAGATGGCCCCCCGGCCGTGGCTGTGGGCCAGTGC
CCGCTGGTGGGGCCAGGCCCCATGCACCGCCGCCACCTGCTGCTCCCTGCCAGGGT
CCCTAGGCCTGGCCTATCGGAGGCGCTTTCCCTGCTCCTGTTCGCCGTTGTTCTGTC
TCGTGCCGCCGCCCTGGGCTGCATTGGGTTGGTGGCCCACGCCGGCCAACTCACCG
CAGTCTGGCGCCGCCCAGGAGCCGCCCGCGCTCCCTGAACCCTAGAACTGTCTTCG

ACTCCGGGGCCCCGTTGGAAGACTGAGTGCCCGGGGCACGGCACAGAAGCCGCGC
CCACCGCCTGCCAGTTCACAACCGCTCCGAGCGTGGGTCTCCGCCCAGCTCCAGTC
CTGTGATCCGGGCCCGCCCCCTAGCGGCCGGGGAGGGAGGGGCCGGGTCCGCGGC
CGGCGAACGGGGCTCGAAGGGTCCTTGTAGCCGGGAATGCTGCTGCTGCTGCTGC
TGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGGGGGGATCACAG
ACCATTTCTTTCTTTCGGCCAGGCTGAGGCCCTGACGTGGATGGGCAAACTGCAGG
CCTGGGAAGGCAGCAAGCCGGGCCGTCCGTGTTCCATCCTCCACGCACCCCCACCT
ATCGTTGGTTCGCAAAGTGCAAAGCTTTCTTGTGCATGACGCCCTGCTCTGGGGAG
CGTCTGGCGCGATCTCTGCCTGCTTACTCGGGAAATTTGCTTTTGCCAAACCCGCTT
TTTCGGGGATCCCGCGCCCCCCTCCTCACTTGCGCTGCTCTCGGAGCCCCAGCCGG
CTCCGCCCGCTTCGGCGGTTTGGATATTTATTGACCTCGTCCTCCGACTCGCTGACA
GGCTACAGGACCCCCAACAACCCCCAATCCACGTTTTGGATGCACTGAGACCCCGA
CATTCCTCGGTATTTATTGTCTGTCCCCACCTAGGACCCCCACCCCCGACCCTCGCG
AATAAAAGGCCCTCCATCTGCCCAAAGCTCTGGA(SEQ ID NO: 24).

[00099] In some embodiments, oligonucleotides may comprise 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).

GAACTGGCCAGAGAGACCCAAGGGATAGTCAGGGACGGGCAGACATGCAGCTAG
GGTTCTGGGGCCTGGACAGGGGCAGCCAGGCCCTGTGACGGGAAGACCCCGAGCT
CCGGCCCGGGGAGGGGCCATGGTGTTGCCTGCCCAACATGTCAGCCGAAGTGCGG
CTGAGGCAGCTCCAGCAGCTGGTGCTGGACCCAGGCTTCCTGGGACTGGAGCCCC
TGCTCGACCTTCTCCTGGGCGTCCACCAGGAGCTGGGTGCCTCTCACCTAGCCCAG
GACAAGTATGTGGCCGACTTCTTGCAGTGGGTGGAGCCCATTGCAGCAAGGCTTA
AGGAGGTCCGACTGCAGAGGGATGATTTTGAGATTTTGAAGGTGATCGGGCGTGG
GGCGTTCAGCGAGGTAGCGGTGGTGAAGATGAAACAGACGGGCCAAGTGTATGCC
ATGAAGATTATGAATAAGTGGGACATGCTGAAGAGAGGCGAGGTGTCGTGCTTCC
GGGAAGAAAGGGATGTATTAGTGAAAGGGGACCGGCGCTGGATCACACAGCTGC
ACTTTGCCTTCCAGGATGAGAACTACCTGTACCTGGTCATGGAATACTACGTGGGC
GGGGACCTGCTAACGCTGCTGAGCAAGTTTGGGGAGCGGATCCCCGCCGAGATGG
CTCGCTTCTACCTGGCCGAGATTGTCATGGCCATAGACTCCGTGCACCGGCTGGGC
TACGTGCACAGGGACATCAAACCAGATAACATTCTGCTGGACCGATGTGGGCACA
TTCGCCTGGCAGACTTCGGCTCCTGCCTCAAACTGCAGCCTGATGGAATGGTGAGG
TCGCTGGTGGCTGTGGGCACCCCGGACTACCTGTCTCCTGAGATTCTGCAGGCCGT
TGGTGGAGGGCCTGGGGCAGGCAGCTACGGGCCAGAGTGTGACTGGTGGGCACTG

GGCGTGTTCGCCTATGAGATGTTCTATGGGCAGACCCCCTTCTACGCGGACTCCAC
AGCCGAGACATATGCCAAGATTGTGCACTACAGGGAACACTTGTCGCTGCCGCTG
GCAGACACAGTTGTCCCCGAGGAAGCTCAGGACCTCATTCGTGGGCTGCTGTGTCC
TGCTGAGATAAGGCTAGGTCGAGGTGGGGCAGACTTCGAGGGTGCCACGGACACA
TGCAATTTCGATGTGGTGGAGGACCGGCTCACTGCCATGGTGAGCGGGGGCGGGG
AGACGCTGTCAGACATGCAGGAAGACATGCCCCTTGGGGTGCGCCTGCCCTTCGT
GGGCTACTCCTACTGCTGCATGGCCTTCAGAGACAATCAGGTCCCGGACCCCACCC
CTATGGAACTAGAGGCCCTGCAGTTGCCTGTGTCAGACTTGCAAGGGCTTGACTTG
CAGCCCCCAGTGTCCCCACCGGATCAAGTGGCTGAAGAGGCTGACCTAGTGGCTG
TCCCTGCCCCTGTGGCTGAGGCAGAGACCACGGTAACGCTGCAGCAGCTCCAGGA
AGCCCTGGAAGAAGAGGTTCTCACCCGGCAGAGCCTGAGCCGCGAGCTGGAGGCC
ATCCGGACCGCCAACCAGAACTTCTCCAGCCAACTACAGGAGGCCGAGGTCCGAA
ACCGAGACCTGGAGGCGCATGTTCGGCAGCTACAGGAACGGATGGAGATGCTGCA
GGCCCCAGGAGCCGCAGCCATCACGGGGGTCCCCAGTCCCCGGGCCACGGATCCA
CCTTCCCATCTAGATGGCCCCCCGGCCGTGGCTGTGGGCCAGTGCCCGCTGGTGGG
GCCAGGCCCCATGCACCGCCGTCACCTGCTGCTCCCTGCCAGGATCCCTAGGCCTG
GCCTATCCGAGGCGCGTTGCCTGCTCCTGTTCGCCGCTGCTCTGGCTGCTGCCGCC
ACACTGGGCTGCACTGGGTTGGTGGCCTATACCGGCGGTCTCACCCCAGTCTGGTG
TTTCCCGGGAGCCACCTTCGCCCCCTGAACCCTAAGACTCCAAGCCATCTTTCATT
TAGGCCTCCTAGGAAGGTCGAGCGACCAGGGAGCGACCCAAAGCGTCTCTGTGCC
CATCGCGCCCCCCCCCCCCCCCCACCGCTCCGCTCCACACTTCTGTGAGCCTGGGT
CCCCACCCAGCTCCGCTCCTGTGATCCAGGCCTGCCACCTGGCGGCCGGGGAGGG
AGGAACAGGGCTCGTGCCCAGCACCCCTGGTTCCTGCAGAGCTGGTAGCCACCGC
TGCTGCAGCAGCTGGGCATTCGCCGACCTTGCTTTACTCAGCCCCGACGTGGATGG
GCAAACTGCTCAGCTCATCCGATTTCACTTTTTCACTCTCCCAGCCATCAGTTACAA
GCCATAAGCATGAGCCCCCTATTTCCAGGGACATCCCATTCCCATAGTGATGGATC
AGCAAGACCTCTGCCAGCACACACGGAGTCTTTGGCTTCGGACAGCCTCACTCCTG
GGGGTTGCTGCAACTCCTTCCCCGTGTACACGTCTGCACTCTAACAACGGAGCCAC
AGCTGCACTCCCCCCTCCCCCAAAGCAGTGTGGGTATTTATTGATCTTGTTATCTG
ACTCACTGACAGACTCCGGGACCCACGTTTTAGATGCATTGAGACTCGACATTCCT
CGGTATTTATTGTCTGTCCCCACCTACGACCTCCACTCCCGACCCTTGCGAATAAA
ATACTTCTGGTCTGCCCTAAA (SEQ ID NO: 25). In some embodiments, an oligonucleotide may comprise a region of complementarity to DMPK gene sequences of

multiple species, e.g., selected from human, mouse and non-human species (e.g., cynomolgus monkey).

[000100] In some embodiments, the oligonucleotide may comprise a 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.

[000101] In some embodiments, an oligonucleotide provided herein is an antisense oligonucleotide targeting DMPK. In some embodiments, the oligonucleotide targeting DMPK is any one of the antisense oligonucleotides 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 No. NM_001081560.2 (SEQ ID NO: 24) or as set forth in Genbank accession No. NG_009784.1 (SEQ ID NO: 26).

[000102] In some embodiments, a DMPK targeting oligonucleotide provided herein comprises a nucleotide sequence comprising a region complementary to a target region that is at least 8 continuous nucleotides (e.g., at least 8, at least 9, at least 10, at least 12, at least 14, at least 16, at least 18, at least 20 or more continuous nucleotides) of SEQ ID NO: 24.

[000103] In some embodiments, a DMPK targeting oligonucleotide provided herein is 10-35 (e.g., 10-35, 10-30, 10-25, 10-20, 10-15, 15-35, 15-30, 15-25, 15-20, 20-35, 20-30, 13-18, 14-17, 15-18, 20-30, 15-17, 27-30, 25-35, or 30-35) nucleotides in length. In some embodiments, a DMPK targeting oligonucleotide provided herein is 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides in length, optionally 15-30, or 16 nucleotides in length. In some embodiments, a DMPK targeting oligonucleotide provided herein is 16 nucleotides in length.

[000104] In some embodiments, a DMPK targeting oligonucleotide provided herein comprises a region of complementarity of at least 8 (*e.g.*, at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more) consecutive nucleotides to a DMPK RNA.

[000105] In some embodiments, a DMPK targeting oligonucleotide provided herein comprises a region of complementarity of at least 8 (*e.g.*, at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more) consecutive nucleotides to a DMPK sequence as set forth in SEQ ID NO: 24 or 25.

[000106] In some embodiments, a DMPK targeting oligonucleotide provided herein comprises a region of complementarity of at least 8 (*e.g.*, at least 8, 9, 10, 11, 12, 13, 14, 15, or 16) consecutive nucleotides to a target sequence as set forth in SEQ ID NO: 22 (TGACTGGTGGGCGCTG). In some embodiments, an oligonucleotide useful for targeting DMPK comprises at least 8 (e.g., at least 8, 9, 10, 11, 12, 13, 14, 15, or 16) consecutive nucleotides of a sequence as set forth in SEQ ID NO: 21 (CAGCGCCCACCAGUCA). In some embodiments, an oligonucleotide useful for targeting DMPK comprises the nucleotide sequence of SEQ ID NO: 21.

[000107] In some embodiments, the DMPK targeting oligonucleotide comprises a 5'-X-Y-Z-3' configuration. An oligonucleotide comprising a 5'-X-Y-Z-3' configuration can refer to a chimeric antisense compound in which a gap region having a plurality of nucleosides that support RNase H cleavage is positioned between flanking regions having one or more nucleosides, wherein the nucleosides comprising the gap region are chemically distinct from the nucleoside or nucleosides comprising the flanking regions. In some embodiments, an oligonucleotide described herein (e.g., a DMPK-targeting oligonucleotide described herein) comprises a 5'-X-Y-Z-3' configuration, with X and Z as flanking regions around a gap region Y. In some embodiments, the gap region Y comprises one or more 2'-deoxyribonucleosides. In some embodiments, each nucleoside in the gap region Y is a 2'-deoxyribonucleoside, and neither the flanking region X nor the flanking region Z contains any 2'-deoxyribonucleosides.

[000108] In some embodiments, the gap region Y comprises a continuous stretch of 6 or more 2'-deoxyribonucleosides, which are capable of recruiting an RNAse, such as RNAse H. In some embodiments, the oligonucleotide 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 flanking regions X and Z each comprise one or more modified nucleosides. In some embodiments, flanking regions X and Z each comprise one or more high-affinity modified nucleosides, e.g., one to six high-affinity modified nucleosides. Examples of high affinity modified nucleosides include, but are not limited to, 2'-modified nucleosides (e.g., 2'-MOE, 2'-O-Me, 2'-F) or 2'-4' bicyclic nucleosides (e.g., LNA, cEt, ENA). In some embodiments, the flanking regions X and Z may be of 1-20 nucleotides, 1-8 nucleotides, or 1-5 nucleotides in length. The flanking regions X and Z may be of similar length or of dissimilar lengths. In some

embodiments, the gap region Y may comprise a nucleotide sequence of 5-20 nucleotides, 5-15 nucleotides, 5-12 nucleotides, or 6-10 nucleotides in length.

[000109] In some embodiments, the gap region Y comprises one or more unmodified internucleoside linkages. In some embodiments, one or both flanking regions X and Z each independently comprise 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 Y and two flanking regions X and Z 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.

[000110] In some embodiments, the gap region Y in the gapmer is 5-20 nucleosides in length. For example, the gap region Y may be 5-20, 5-15, 5-10, 10-20, 10-15, or 15-20 nucleosides in length. In some embodiments, the gap region Y is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleosides in length. In some embodiments, each nucleoside in the gap region Y is a 2'-deoxyribonucleoside. In some embodiments, all nucleosides in the gap region Y are 2'-deoxyribonucleosides. In some embodiments, one or more of the nucleosides in the gap region Y is a modified nucleoside (e.g., a 2' modified nucleoside such as those described herein). In some embodiments, one or more cytosines in the gap region Y are optionally 5-methyl-cytosines. In some embodiments, each cytosine in the gap region Y is a 5-methyl-cytosine.

[000111] In some embodiments, the flanking region X of the oligonucleotide (X in the 5'-X-Y-Z-3′ configuration) and the flanking region Z of the oligonucleotide (Z in the 5'-X-Y-Z-3′ configuration) are independently 1-20 nucleosides long. For example, the flanking region X of the oligonucleotide and the flanking region Z of the oligonucleotide may be independently 1-20, 1-15, 1-10, 1-7, 1-5, 1-3, 1-2, 2-5, 2-7, 3-5, 3-7, 5-20, 5-15, 5-10, 10-20, 10-15, or 15-20 nucleosides long. In some embodiments, the flanking region X of the oligonucleotide and the flanking region Z of the oligonucleotide are independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleosides long. In some embodiments, the flanking region X of the oligonucleotide and the flanking region Z of the oligonucleotide are of the same length. In some embodiments, the flanking region X of the oligonucleotide and the flanking region Z of the oligonucleotide are of different lengths. In some embodiments, the flanking region X of the oligonucleotide is longer than the flanking region Z of the oligonucleotide. In some embodiments, the flanking region X of the oligonucleotide is shorter than the flanking region Z of the oligonucleotide.

[000112] In some embodiments, an oligonucleotide described herein (e.g., a DMPK targeting oligonucleotide) comprises a 5'-X-Y-Z-3′ configuration of 5-10-5, 4-12-4, 3-14-3, 2-16-2, 1-18-1, 3-10-3, 2-10-2, 1-10-1, 2-8-2, 4-6-4, 3-6-3, 2-6-2, 4-7-4, 3-7-3, 2-7-2, 4-8-4, 3-8-3, 2-8-2, 1-8-1, 2-9-2, 1-9-1, 2-10-2, 1-10-1, 1-12-1, 1-16-1, 2-15-1, 1-15-2, 1-14-3, 3-14-1, 2-14-2, 1-13-4, 4-13-1, 2-13-3, 3-13-2, 1-12-5, 5-12-1, 2-12-4, 4-12-2, 3-12-3, 1-11-6, 6-11-1, 2-11-5, 5-11-2, 3-11-4, 4-11-3, 1-17-1, 2-16-1, 1-16-2, 1-15-3, 3-15-1, 2-15-2, 1-14-4, 4-14-1, 2-14-3, 3-14-2, 1-13-5, 5-13-1, 2-13-4, 4-13-2, 3-13-3, 1-12-6, 6-12-1, 2-12-5, 5-12-2, 3-12-4, 4-12-3, 1-11-7, 7-11-1, 2-11-6, 6-11-2, 3-11-5, 5-11-3, 4-11-4, 1-18-1, 1-17-2, 2-17-1, 1-16-3, 1-16-3, 2-16-2, 1-15-4, 4-15-1, 2-15-3, 3-15-2, 1-14-5, 5-14-1, 2-14-4, 4-14-2, 3-14-3, 1-13-6, 6-13-1, 2-13-5, 5-13-2, 3-13-4, 4-13-3, 1-12-7, 7-12-1, 2-12-6, 6-12-2, 3-12-5, 5-12-3, 1-11-8, 8-11-1, 2-11-7, 7-11-2, 3-11-6, 6-11-3, 4-11-5, 5-11-4, 1-18-1, 1-17-2, 2-17-1, 1-16-3, 3-16-1, 2-16-2, 1-15-4, 4-15-1, 2-15-3, 3-15-2, 1-14-5, 2-14-4, 4-14-2, 3-14-3, 1-13-6, 6-13-1, 2-13-5, 5-13-2, 3-13-4, 4-13-3, 1-12-7, 7-12-1, 2-12-6, 6-12-2, 3-12-5, 5-12-3, 1-11-8, 8-11-1, 2-11-7, 7-11-2, 3-11-6, 6-11-3, 4-11-5, 5-11-4, 1-19-1, 1-18-2, 2-18-1, 1-17-3, 3-17-1, 2-17-2, 1-16-4, 4-16-1, 2-16-3, 3-16-2, 1-15-5, 2-15-4, 4-15-2, 3-15-3, 1-14-6, 6-14-1, 2-14-5, 5-14-2, 3-14-4, 4-14-3, 1-13-7, 7-13-1, 2-13-6, 6-13-2, 3-13-5, 5-13-3, 4-13-4, 1-12-8, 8-12-1, 2-12-7, 7-12-2, 3-12-6, 6-12-3, 4-12-5, 5-12-4, 2-11-8, 8-11-2, 3-11-7, 7-11-3, 4-11-6, 6-11-4, 5-11-5, 1-20-1, 1-19-2, 2-19-1, 1-18-3, 3-18-1, 2-18-2, 1-17-4, 4-17-1, 2-17-3, 3-17-2, 1-16-5, 2-16-4, 4-16-2, 3-16-3, 1-15-6, 6-15-1, 2-15-5, 5-15-2, 3-15-4, 4-15-3, 1-14-7, 7-14-1, 2-14-6, 6-14-2, 3-14-5, 5-14-3, 4-14-4, 1-13-8, 8-13-1, 2-13-7, 7-13-2, 3-13-6, 6-13-3, 4-13-5, 5-13-4, 2-12-8, 8-12-2, 3-12-7, 7-12-3, 4-12-6, 6-12-4, 5-12-5, 3-11-8, 8-11-3, 4-11-7, 7-11-4, 5-11-6, 6-11-5, 1-21-1, 1-20-2, 2-20-1, 1-20-3, 3-19-1, 2-19-2, 1-18-4, 4-18-1, 2-18-3, 3-18-2, 1-17-5, 2-17-4, 4-17-2, 3-17-3, 1-16-6, 6-16-1, 2-16-5, 5-16-2, 3-16-4, 4-16-3, 1-15-7, 7-15-1, 2-15-6, 6-15-2, 3-15-5, 5-15-3, 4-15-4, 1-14-8, 8-14-1, 2-14-7, 7-14-2, 3-14-6, 6-14-3, 4-14-5, 5-14-4, 2-13-8, 8-13-2, 3-13-7, 7-13-3, 4-13-6, 6-13-4, 5-13-5, 1-12-10, 10-12-1, 2-12-9, 9-12-2, 3-12-8, 8-12-3, 4-12-7, 7-12-4, 5-12-6, 6-12-5, 4-11-8, 8-11-4, 5-11-7, 7-11-5, 6-11-6, 1-22-1, 1-21-2, 2-21-1, 1-21-3, 3-20-1, 2-20-2, 1-19-4, 4-19-1, 2-19-3, 3-19-2, 1-18-5, 2-18-4, 4-18-2, 3-18-3, 1-17-6, 6-17-1, 2-17-5, 5-17-2, 3-17-4, 4-17-3, 1-16-7, 7-16-1, 2-16-6, 6-16-2, 3-16-5, 5-16-3, 4-16-4, 1-15-8, 8-15-1, 2-15-7, 7-15-2, 3-15-6, 6-15-3, 4-15-5, 5-15-4, 2-14-8, 8-14-2, 3-14-7, 7-14-3, 4-14-6, 6-14-4, 5-14-5, 3-13-8, 8-13-3, 4-13-7, 7-13-4, 5-13-6, 6-13-5, 4-12-8, 8-12-4, 5-12-7, 7-12-5, 6-12-6, 5-11-8, 8-11-5, 6-11-7, or 7-11-6. The numbers indicate the number of nucleosides in X, Y, and Z regions, respectively, in an oligonucleotide comprising the 5'-X-Y-Z-3' configuration.

[000113] In some embodiments, one or more nucleosides in the flanking region X of the oligonucleotide (X in the 5'-X-Y-Z-3′ configuration) or the flanking region Z of the oligonucleotide (Z in the 5'-X-Y-Z-3′ configuration) are modified nucleosides (e.g., high-affinity modified nucleosides). In some embodiments, the modified nucleoside (e.g., high-affinity modified nucleosides) is a 2'-modified nucleoside. In some embodiments, the 2'-modified nucleoside is a 2'-4' bicyclic nucleoside or a non-bicyclic 2'-modified nucleoside. In some embodiments, the high-affinity modified nucleoside is a 2'-4' bicyclic nucleoside (e.g., LNA, cEt, or ENA) or a non-bicyclic 2'-modified nucleoside (e.g., 2'-fluoro (2'-F), 2'-O-methyl (2'-O-Me), 2'-O-methoxyethyl (2'-MOE), 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), 2'-O-dimethylaminoethyloxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA)).

[000114] In some embodiments, an oligonucleotide described herein (e.g., a DMPK targeting oligonucleotide described herein) comprises a 5'-X-Y-Z-3′ configuration, wherein X and Z are independently 2-7 (e.g., 2, 3, 4, 5, 6, or 7) nucleosides in length and Y is 6-10 (e.g., 6, 7, 8, 9, or 10) nucleosides in length, wherein at least one but not all (e.g., 1, 2, 3, 4, 5, or 6) of positions 1, 2, 3, 4, 5, 6, or 7 in X (the 5'-most position is position 1) is a non-bicyclic 2'-modified nucleoside (e.g., 2'-MOE or 2'-O-Me), wherein the rest of the nucleosides in both X and Z are 2'-4' bicyclic nucleosides (e.g., LNA or cEt), and wherein each nucleoside in Y is a 2'deoxyribonucleoside. In some embodiments, an oligonucleotide described herein (e.g., a DMPK targeting oligonucleotide described herein)comprises a 5'-X-Y-Z-3′ configuration, wherein X and Z are independently 2-7 (e.g., 2, 3, 4, 5, 6, or 7) nucleosides in length and Y is 6-10 (e.g., 6, 7, 8, 9, or 10) nucleosides in length, wherein at least one but not all (e.g., 1, 2, 3, 4, 5, or 6) of positions 1, 2, 3, 4, 5, 6, or 7 in Z (the 5'-most position is position 1) is a non-bicyclic 2'-modified nucleoside (e.g., 2'-MOE or 2'-O-Me), wherein the rest of the nucleosides in both X and Z are 2'-4' bicyclic nucleosides (e.g., LNA or cEt), and wherein each nucleoside in Y is a 2'deoxyribonucleoside. In some embodiments, an oligonucleotide described herein (e.g., a DMPK targeting oligonucleotide described herein) comprises a 5'-X-Y-Z-3′ configuration, wherein X and Z are independently 2-7 (e.g., 2, 3, 4, 5, 6, or 7) nucleosides in length and Y is 6-10 (e.g., 6, 7, 8, 9, or 10) nucleosides in length, wherein at least one but not all (e.g., 1, 2, 3, 4, 5, or 6) of positions 1, 2, 3, 4, 5, 6, or 7 in X and at least one of positions but not all (e.g., 1, 2, 3, 4, 5, or 6) of positions 1, 2, 3, 4, 5, 6, or 7 in Z (the 5'-most position is position 1) is a non-bicyclic 2'-modified nucleoside (e.g., 2'-MOE or 2'-O-Me), wherein the rest of the nucleosides in both X and Z are 2'-4' bicyclic nucleosides (e.g., LNA or cEt), and wherein each nucleoside in Y is a 2'deoxyribonucleoside.

[000115] In some embodiments, an oligonucleotide described herein (e.g., a DMPK targeting oligonucleotide) is 10-20 nucleosides (e.g., 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleosides) in length, comprises a region of complementarity to at least 8 consecutive nucleosides (e.g., at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or 16 consecutive nucleosides) of SEQ ID NO: 22 (TGACTGGTGGGCGCTG), and comprises a 5'-X-Y-Z-3' configuration, wherein X comprises 3-5 (e.g., 3, 4, or 5) linked nucleosides, wherein at least one of the nucleosides in X is a 2'-modified nucleoside (e.g., 2'-MOE modified nucleoside, 2'-O-Me modified nucleoside, LNA, cEt, or ENA); Y comprises 6-10 (e.g., 6, 7, 8, 9, or 10) linked 2'-deoxyribonucleosides, wherein each cytosine in Y is optionally and independently a 5-methyl-cytosine; and Z comprises 3-5 (e.g., 3, 4, or 5) linked nucleosides, wherein at least one of the nucleosides in Z is a 2'- modified nucleoside (e.g., 2'-MOE modified nucleoside, 2'-O-Me modified nucleoside, LNA, cEt, or ENA).

[000116] In some embodiments, an oligonucleotide described herein (e.g., a DMPK targeting oligonucleotide described herein) comprises at least 8 consecutive nucleosides (e.g., at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, or 16 consecutive nucleosides consecutive nucleosides) of the nucleotide sequence of SEQ ID NO: 21 (CAGCGCCCACCAGUCA), and comprises a 5'-X-Y-Z-3' configuration, wherein X comprises 3-5 (e.g., 3, 4, or 5) linked nucleosides, wherein at least one of the nucleosides in X is a 2'-modified nucleoside (e.g., 2'-MOE modified nucleoside, 2'-O-Me modified nucleoside, LNA, cEt, or ENA); Y comprises 6-10 (e.g., 6, 7, 8, 9, or 10) linked 2'-deoxyribonucleosides, wherein each cytosine in Y is optionally and independently a 5-methyl-cytosine; and Z comprises 3-5 (e.g., 3, 4, or 5) linked nucleosides, wherein at least one of the nucleosides in Z is a 2'-modified nucleoside (e.g., 2'-MOE modified nucleoside, 2'-O-Me modified nucleoside, LNA, cEt, or ENA). In some embodiments, each thymine base (T) of the nucleotide sequence of the antisense oligonucleotide may independently and optionally be replaced with a uracil base (U), and each U may independently and optionally be replaced with a T.

[000117] In some embodiments, an oligonucleotide described herein (e.g., a DMPK targeting oligonucleotide described herein) comprises the nucleotide sequence of SEQ ID NO: 21 and comprises a 5'-X-Y-Z-3' configuration, wherein X comprises 3-5 (e.g., 3, 4, or 5) linked nucleosides, wherein at least one of the nucleosides in X is a 2'-modified nucleoside (e.g., 2'-MOE modified nucleoside, 2'-O-Me modified nucleoside, LNA, cEt, or ENA); Y comprises 6-10 (e.g., 6, 7, 8, 9, or 10) linked 2'-deoxyribonucleosides, wherein each cytosine in Y is optionally and independently a 5-methyl-cytosine; and Z comprises 3-5 (e.g., 3, 4, or 5) linked nucleosides, wherein at least one of the nucleosides in Z is a 2'- modified nucleoside

(e.g., 2'-MOE modified nucleoside, 2'-O-Me modified nucleoside, LNA, cEt, or ENA). In some embodiments, each thymine base (T) of the nucleotide sequence of the antisense oligonucleotide may independently and optionally be replaced with a uracil base (U), and each U may independently and optionally be replaced with a T.

[000118] In some embodiments, X comprises at least one 2'-4' bicyclic nucleoside (e.g., LNA, cEt, or ENA) and at least one non-bicyclic 2'-modified nucleoside e.g., 2'-MOE modified nucleoside or 2'-O-Me modified nucleoside, and/or (e.g., and) Z comprises at least one 2'-4' bicyclic nucleoside (e.g., LNA, cEt, or ENA) and at least one non-bicyclic 2'-modified nucleoside (e.g., 2'-MOE modified nucleoside or 2'-O-Me modified nucleoside).

[000119] In some embodiments, the 2'-4' bicyclic nucleoside is selected from LNA, cEt, and ENA nucleosides. In some embodiments, the non-bicyclic 2'-modified nucleoside is a 2'-MOE modified nucleoside or a 2'-OMe modified nucleoside.

[000120] In some embodiments, the nucleosides of the oligonucleotides are joined together by phosphorothioate internucleoside linkages, phosphodiester internucleoside linkages or a combination thereof. In some embodiments, the oligonucleotide comprises only phosphorothioate internucleoside linkages joining each nucleoside (i.e., the oligonucleotide comprises a fully phosphorothioate backbone). In some embodiments, the oligonucleotide comprises at least one phosphorothioate internucleoside linkage. In some embodiments, the oligonucleotide comprises a mix of phosphorothioate and phosphodiester internucleoside linkages. In some embodiments, the oligonucleotide comprises only phosphorothioate internucleoside linkages joining each pair of 2'-deoxyribonucleosides and a mix of phosphorothioate and phosphodiester internucleoside linkages joining the remaining nucleosides.

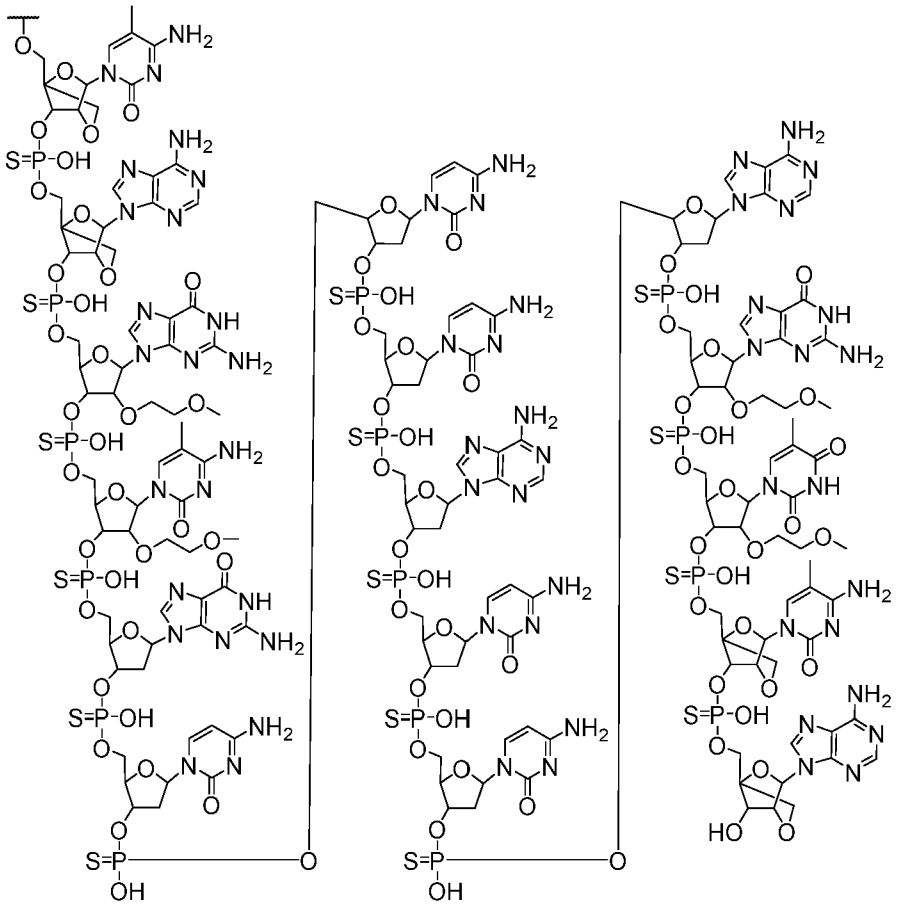
[000121] In some embodiments, the oligonucleotide comprises a 5'-X-Y-Z-3' configuration of LLEE-$(D)_8$-EELL, wherein "E" is a 2'-MOE modified ribonucleoside; "L" is LNA; "D" is a 2'-deoxyribonucleoside; and "10" or "8" is the number of 2'-deoxyribonucleosides in Y, and wherein the oligonucleotide comprises phosphorothioate internucleoside linkages, phosphodiester internucleoside linkages or a combination thereof.

[000122] In some embodiments, each cytidine (e.g., a 2'-modified cytidine) in X and/or Z of the oligonucleotide is optionally and independently a 5-methyl-cytidine, and/or each uridine (e.g., a 2'-modified uridine) in X and/or Z is optionally and independently a 5-methyl-uridine.

[000123] In some embodiments, an oligonucleotide described herein (e.g., a DMPK targeting oligonucleotide described herein) comprises a 5'-X-Y-Z-3' configuration and comprises a nucleobase sequence of CAGCGCCCACCAGUCA (SEQ ID NO: 21). In some

embodiments, an oligonucleotide described herein (e.g., a DMPK targeting oligonucleotide described herein) comprises a structure of +C*+A*oG*oC*dG*dC*dC*dC*dA*dC*dC*dA*oG*oU*+C*+A (SEQ ID NO: 21), wherein +N represents an LNA (2'-4' methylene bridge) ribonucleoside, dN represents a 2'-deoxyribonucleoside, oN represents a 2'-O-methoxyethyl (MOE) modified ribonucleoside, oC represents a 5-methyl-2'-MOE-cytidine, +C represents a 5-methyl-2'-4'-bicyclic-cytidine (2'-4' methylene bridge), oU represents a 5-methyl-2'-MOE-uridine, * represents a phosphorothioate internucleoside linkage.

[000124] In some embodiments, an oligonucleotide described herein (e.g., a DMPK targeting oligonucleotide described herein) comprises a structure of the formula (Ie):



(Ie).

[000125] In some embodiments, an oligonucleotide described herein (e.g., a DMPK targeting oligonucleotide described herein) can be in salt form, e.g., as sodium, potassium, or magnesium salts.

[000126] In some embodiments, the 5' or 3' nucleoside (e.g., terminal nucleoside) of the oligonucleotide is conjugated to an amine group, optionally via a spacer. In some embodiments, the spacer comprises an aliphatic moiety. In some embodiments, the spacer comprises a polyethylene glycol moiety. In some embodiments, a phosphodiester linkage is

present between the spacer and the 5' or 3' nucleoside of the oligonucleotide. In some embodiments, the 5' or 3' nucleoside (e.g., terminal nucleoside) of an oligonucleotide described herein is covalently linked to a spacer that is a substituted or unsubstituted aliphatic, substituted or unsubstituted heteroaliphatic, substituted or unsubstituted carbocyclylene, substituted or unsubstituted heterocyclylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene, -O-, -N(R^A)-, -S-, -C(=O)-, -C(=O)O-, -C(=O)NR^A-, -NR^AC(=O)-, -NR^AC(=O)R^A-, -C(=O)R^A-, -NR^AC(=O)O-, -NR^AC(=O)N(R^A)-, -OC(=O)-, -OC(=O)O-, -OC(=O)N(R^A)-, -$S(O)_2$NR^A-, -N$R^A$$S(O)_2$-, or a combination thereof; each R^A is independently hydrogen or substituted or unsubstituted alkyl. In certain embodiments, the spacer is a substituted or unsubstituted alkylene, substituted or unsubstituted heterocyclylene, substituted or unsubstituted heteroarylene, -O-, -N(R^A)-, or -C(=O)N$(R^A)_2$, or a combination thereof.

[000127] In some embodiments, the 5' or 3' nucleoside of the oligonucleotide is conjugated to a compound of the formula -NH_2-$(CH_2)_n$-, wherein n is an integer from 1 to 12. In some embodiments, n is 6, 7, 8, 9, 10, 11, or 12. In some embodiments, a phosphodiester linkage is present between the compound of the formula NH_2-$(CH_2)_n$- and the 5' or 3' nucleoside of the oligonucleotide. In some embodiments, a compound of the formula NH_2-$(CH_2)_6$- is conjugated to the oligonucleotide via a reaction between 6-amino-1-hexanol (NH_2-$(CH_2)_6$-OH) and the 5' phosphate of the oligonucleotide.

[000128] In some embodiments, the oligonucleotide is conjugated to a targeting agent, e.g., a muscle targeting agent such as an anti-TfR1 antibody, e.g., via an amine group of a lysine of the targeting agent.

[000129] In some embodiments, it should be appreciated that methylation of the nucleobase uracil at the C5 position forms thymine. Thus, in some embodiments, a nucleotide or nucleoside having a C5 methylated uracil (or 5-methyl-uracil) may be equivalently identified as a thymine nucleotide or nucleoside.

[000130] In some embodiments, any one or more of the thymine bases (T's) in any one of the oligonucleotides provided herein may independently and optionally be uracil bases (U's), and/or any one or more of the U's in the oligonucleotides provided herein (e.g., the oligonucleotide as set forth in SEQ ID NO: 21) may independently and optionally be T's.

Compositions

[000131] In some embodiments, compositions described herein comprise complexes (*i.e.*, a plurality of complexes), each of which complex comprises an antibody (e.g., anti-TFR1 antibody) covalently linked to one or more oligonucleotides (e.g., a DMPK-targeting

oligonucleotide described herein) at a linkage site represented by a lysine (K) residue of the antibody, wherein the antibody comprises a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region. In some embodiments, the antibody of such complexes comprises a CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 as set forth in Table 2.

[000132] In some embodiments, light chain constant regions of antibodies of complexes in a composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of a light chain constant region of an antibody. For example, in some embodiments, a linkage site is represented by K188 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, a linkage site is represented by K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, linkage sites are represented by K188 (based on Kabat numbering) and K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, at least 80% (e.g., at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chain constant regions of the antibodies of the complexes in a composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies. In some embodiments, heavy chain constant regions of antibodies of complexes in a composition are independently covalently linked to an oligonucleotide at a linkage site represented by K213 (based on Kabat numbering) of a heavy chain constant region of an antibody. In some embodiments, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chain constant regions of the antibodies of the complexes in a composition are independently covalently linked to an oligonucleotide at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the antibodies. In some embodiments, light chains of antibodies of complexes in a composition are independently covalently linked to an oligonucleotide at linkage sites represented by represented by lysine (K) residues in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of

the light chains of the antibodies. For example, in some embodiments, antibodies are covalently linked to an oligonucleotide at a linkage site represented by the K at position 4 in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of light chains of the antibodies. In some embodiments, antibodies are covalently linked to an oligonucleotide at a linkage site represented by the K at position 6 in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of light chains of the antibodies. In some embodiments, antibodies are covalently linked to an oligonucleotide at a linkage site represented the K at position 4 and at a linkage site represented by the K at position 6 in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of light chains of the antibodies. In some embodiments, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of light chains of the antibodies of the complexes in a composition are independently covalently linked to an oligonucleotide at linkage sites represented by lysine (K) residues in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of the light chains of the antibodies. In some embodiments, heavy chains of antibodies of complexes in a composition are independently covalently linked to an oligonucleotide at a linkage site represented by the lysine (K) residue in a sequence a sequence motif VNHKPSN (SEQ ID NO: 28) of the heavy chains of the antibodies. In some embodiments, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chains of the antibodies of the complexes in a composition are independently covalently linked to an oligonucleotide at a linkage site represented by the lysine (K) residue in motif VNHKPSN (SEQ ID NO: 28) of the heavy chains of the antibodies. In some embodiments, the antibody is an anti-TfR1 Fab.

[000133] In some embodiments, compositions described herein comprise complexes (*i.e.*, a plurality of complexes) wherein each complex comprises a structure of formula (I): $[R^1]_{n1}$-R^2, in which each R^1 independently comprises a compound comprising an oligonucleotide (e.g., a DMPK-targeting oligonucleotide described herein) and is covalently linked to R^2, wherein R^2 comprises an antibody (e.g., anti-TfR1 antibody) comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region. In some embodiments, each R^1 is covalently linked to R^2 via a linkage site represented by a lysine (K) residue of the antibody. In some embodiments, at least 80% (e.g., at least 81%, at least 82%, at

least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies. In some embodiments, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the antibodies. In some embodiments, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chains of the antibodies of the complexes in the composition are independently covalently linked to R^1 at linkage sites represented by lysine (K) residues in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of the light chains of the antibodies. In some embodiments, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chains of the antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by the lysine (K) residue in motif VNHKPSN (SEQ ID NO: 28) of the heavy chains of the antibodies. In some embodiments, in each complex n1 is independently an integer of one or greater representing the number of instances of R^1 in each complex.

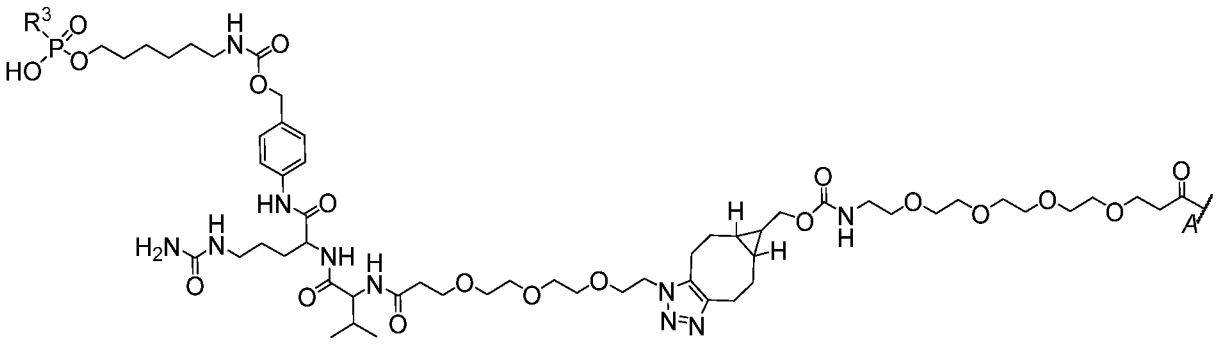
[000134] In some embodiments, the value of n1 of complexes in the composition is independently and optionally an integer from one up to the number of amino acid residues to which conjugation is desired or targeted (e.g., the number of lysine residues) in the antibody (e.g., an antibody comprised within R^2). In some embodiments, the value of n1 of each complex in the composition is independently and optionally selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, and 27. In some embodiments, the value of n1 of each complex in the composition is independently and optionally selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21,

22, 23, 24, 25 and 26. In some embodiments, the value of n1 of each complex in the composition is independently selected and optionally from an integer in the range of 1 to 27, 1 to 26, 1 to 10, 1 to 5, or 1 to 3. In some embodiments, the average value of n1 of complexes of the composition is in the range of 1 to 3, 1 to 5, 1 to 10, 1 to 26, or 1 to 27. In some embodiments, compositions described herein comprise complexes I which the value of n1 is 0. In some embodiments, the average value of n1 of complexes of the composition is in the range of 0.5 to 5 (e.g., 0.5-5, 1-5, 1-4, 1-3, 3-5, 0.5-4, 0.5-3, 0.5-2, 0.5-1.5, 0.5-1, 0.7-1.5, 1-1.6, 1-1.5, 1-1.4, 1-1.3, 1-1.2, 1.1-1.5, 0.8-2, 0.8-1.5, 0.8-1.3, 0.8-1.2, 0.8-1.1, 0.9-3, 0.9-2, 0.9-1.8, 0.9-1.6, 0.9-1.5, 0.9-1.4, 0.9-1.3, or 0.9-1.2).

[000135] In some embodiments, a composition described herein comprises antibody that is not conjugated to an oligonucleotide (e.g., in trace amounts) and antibody conjugated to one or more oligonucleotides. In some embodiments, antibody that is not conjugated to an oligonucleotide may be referred to as a compound comprising a structure of formula (I): $[R^1]_{n1}$-R^2, for which n1 is zero. Accordingly, in some embodiments, a composition for administration to a subject in the methods described herein comprises compounds (e.g., complexes) comprising a structure of formula (I): $[R^1]_{n1}$-R^2, for which each R^1 independently comprises a group comprising an oligonucleotide, R^2 comprises an antibody and n1 is independently an integer of zero or greater that reflects the number of instances of R^1 in each compound (e.g., complex). In some embodiments, the fraction of compounds comprising a structure of formula (I): $[R^1]_{n1}$-R^2, in a composition, for which n1 is zero, compared with all compounds of that structure in the composition for which n1 is one or greater, is less than 10%, less than 5%, less than 1% less than 0.5%, less than 0.1%, less than 0.05%, or less than 0.01%. As such, in some embodiments, the average value of n1 of complexes in a composition disclosed herein is in the range of 0.5 to 5 (e.g., 0.5-5, 1-5, 1-4, 1-3, 3-5, 0.5-4, 0.5-3, 0.5-2, 0.5-1.5, 0.5-1, 0.7-1.5, 1-1.6, 1-1.5, 1-1.4, 1-1.3, 1-1.2, 1.1-1.5, 0.8-2, 0.8-1.5, 0.8-1.3, 0.8-1.2, 0.8-1.1, 0.9-3, 0.9-2, 0.9-1.8, 0.9-1.6, 0.9-1.5, 0.9-1.4, 0.9-1.3, or 0.9-1.2).

[000136] In some embodiments, compositions described herein comprise complexes that comprise a structure of formula (I): $[R^1]_{n1}$-R^2, wherein each R^1 in a complex of a composition

provided herein independently comprises a group of the formula (Ia):



(Ia),

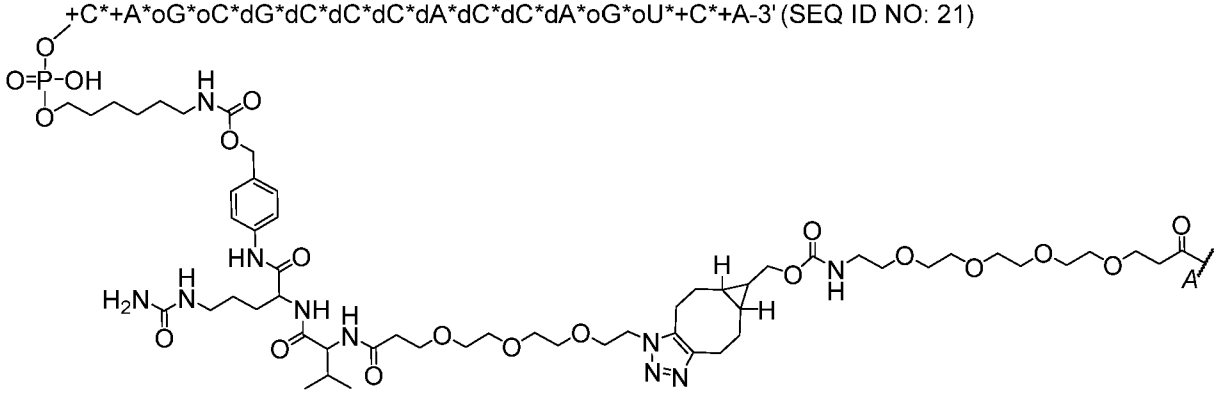
in which R^3 comprises an oligonucleotide, *e.g.*, an oligonucleotide comprising a 5'-X-Y-Z-3' configuration; R^2 comprises an antibody comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region, wherein in each complex n1 is independently an integer (e.g., of one or greater) representing the number of instances of R^1 in each complex, and each R^1 is covalently linked to R^2 at attachment point *A* via a linkage site represented by a lysine (K) residue of the antibody. In some embodiments, light chain constant regions of antibodies of complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of light chain constant regions of the antibodies. For example, in some embodiments, a linkage site is represented by K188 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, a linkage site is represented by K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, linkage sites are represented by K188 (based on Kabat numbering) and K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies. In some embodiments, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chain constant regions of the antibodies of

the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the antibodies. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a sequence as set forth in Table 2. For example, in some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14; and/or comprising a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NO: 6 or 16. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain variable region (VH) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 17 and/or comprising a light chain variable region (VL) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 18. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a VH comprising the amino acid sequence of SEQ ID NO: 17 and/or comprising a VL comprising the amino acid sequence of SEQ ID NO: 18. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 19 and/or comprising a light chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 20. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and/or comprising a light chain comprising the amino acid sequence of SEQ ID NO: 20. In some embodiments, R^2 comprises an antibody (e.g., a Fab) that is a Fab fragment, a full-length IgG, a Fab' fragment, a $F(ab')_2$ fragment, an scFv, or an Fv. In some embodiments, R^2 comprises an antibody that is a Fab fragment. In some embodiments, R^3 comprises an oligonucleotide comprising a nucleobase sequence of CAGCGCCCACCAGUCA (SEQ ID NO: 21). In some embodiments, R^3 comprises an oligonucleotide comprising a structure of +C*+A*oG*oC*dG*dC*dC*dC*dA*dC*dC*dA*oG*oU*+C*+A (SEQ ID NO: 21), wherein +N represents an LNA (2'-4' methylene bridge) ribonucleoside, dN represents a 2'-deoxyribonucleoside, oN represents a 2'-MOE modified ribonucleoside, oC represents a 5-

methyl-2'-MOE-cytidine, +C represents a 5-methyl-2'-4'-bicyclic-cytidine (2'-4' methylene bridge), oU represents a 5-methyl-2'-MOE-uridine, and * represents a phosphorothioate internucleoside linkage. In some embodiments, in each complex n1 is independently an integer (e.g., an integer in the range of 1-27, 1-26, 1-10, 1-5, or 1-3). In some embodiments, compositions described herein comprise complexes that comprise a structure of formula (I): $[R^1]_{n1}$-R^2, wherein n1 is 0. In some embodiments, the average value of n1 of complexes of the composition is in the range of 0.5 to 5 (e.g., 0.5-5, 1-5, 1-4, 1-3, 3-5, 0.5-4, 0.5-3, 0.5-2, 0.5-1.5, 0.5-1, 0.7-1.5, 1-1.6, 1-1.5, 1-1.4, 1-1.3, 1-1.2, 1.1-1.5, 0.8-2, 0.8-1.5, 0.8-1.3, 0.8-1.2, 0.8-1.1, 0.9-3, 0.9-2, 0.9-1.8, 0.9-1.6, 0.9-1.5, 0.9-1.4, 0.9-1.3, or 0.9-1.2)..

[000137] In some embodiments, compositions described herein comprise complexes that comprise a structure of formula (I): $[R^1]_{n1}$-R^2, in which each instance of R^1 in a complex of a composition provided herein comprises a group of the formula (Ib):

+C*+A*oG*oC*dG*dC*dC*dC*dA*dC*dC*dA*oG*oU*+C*+A-3' (SEQ ID NO: 21)



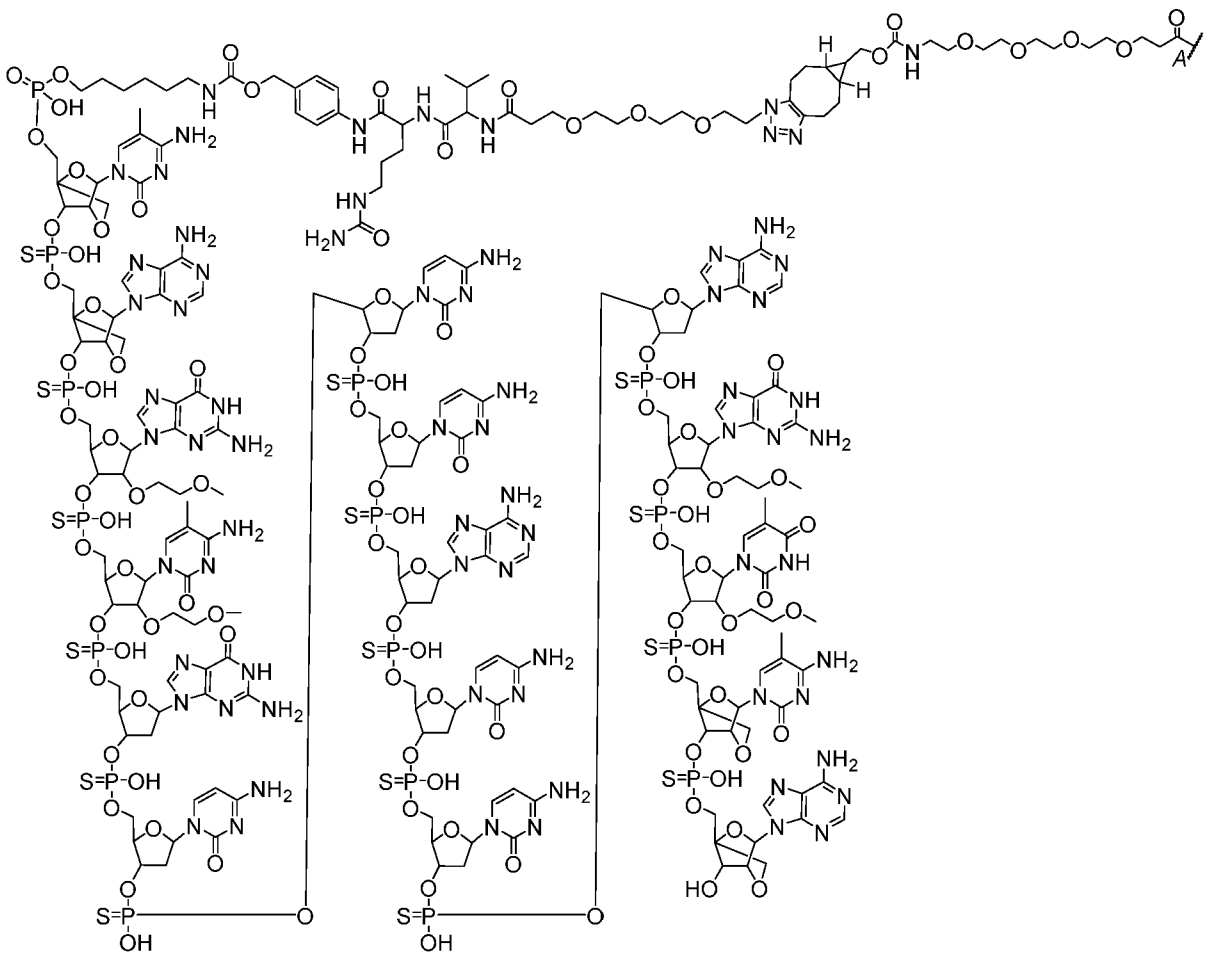
(Ib),

wherein +N represents an LNA (2'-4' methylene bridge) ribonucleoside, dN represents a 2'-deoxyribonucleoside, oN represents a 2'-O-methoxyethyl (MOE) modified ribonucleoside, oC represents a 5-methyl-2'-MOE-cytidine, +C represents a 5-methyl-2'-4'-bicyclic-cytidine (2'-4' methylene bridge), oU represents a 5-methyl-2'-MOE-uridine, * represents a phosphorothioate internucleoside linkage, and wherein the oligonucleotide comprises a nucleobase sequence of CAGCGCCCACCAGUCA (SEQ ID NO: 21); wherein R^2 comprises an antibody comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region, wherein in each complex n1 is independently an integer (e.g., of one or greater) representing the number of instances of R^1 in each complex, and each R^1 is covalently linked to R^2 at attachment point *A* via a linkage site represented by a lysine (K) residue of the antibody. In some embodiments, light chain constant regions of antibodies of complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190

(based on Kabat numbering) of a light chain constant region of an antibody. For example, in some embodiments, a linkage site is represented by K188 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, a linkage site is represented by K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, linkage sites are represented by K188 (based on Kabat numbering) and K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies. In some embodiments, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the antibodies. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a sequence as set forth in Table 2. For example, in some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14; and/or comprising a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NO: 6 or 16. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain variable region (VH) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 17 and/or comprising a light chain variable region (VL) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 18. In some embodiments,

R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a VH comprising the amino acid sequence of SEQ ID NO: 17 and/or comprising a VL comprising the amino acid sequence of SEQ ID NO: 18. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 19 and/or comprising a light chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 20. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and/or comprising a light chain comprising the amino acid sequence of SEQ ID NO: 20. In some embodiments, R^2 comprises an antibody that is a Fab fragment, a full-length IgG, a Fab' fragment, a $F(ab')_2$ fragment, an scFv, or an Fv. In some embodiments, R^2 comprises an antibody that is a Fab fragment. In some embodiments, in each complex n1 is independently an integer (e.g., an integer in the range of 1-27, 1-26, 1-10, 1-5, or 1-3). In some embodiments, compositions described herein further comprise complexes that comprise a structure of formula (I): $[R^1]_{n1}$-R^2, wherein n1 is 0. In some embodiments, the average value of n1 of complexes of the composition is in the range of 0.5 to 5 (e.g., 0.5-5, 1-5, 1-4, 1-3, 3-5, 0.5-4, 0.5-3, 0.5-2, 0.5-1.5, 0.5-1, 0.7-1.5, 1-1.6, 1-1.5, 1-1.4, 1-1.3, 1-1.2, 1.1-1.5, 0.8-2, 0.8-1.5, 0.8-1.3, 0.8-1.2, 0.8-1.1, 0.9-3, 0.9-2, 0.9-1.8, 0.9-1.6, 0.9-1.5, 0.9-1.4, 0.9-1.3, or 0.9-1.2).

[000138] In some embodiments, compositions described herein comprise complexes that comprise a structure of formula (I): $[R^1]_{n1}$-R^2, in which each instance of R^1 in a complex of a composition provided herein comprises a group of the formula (Ic):



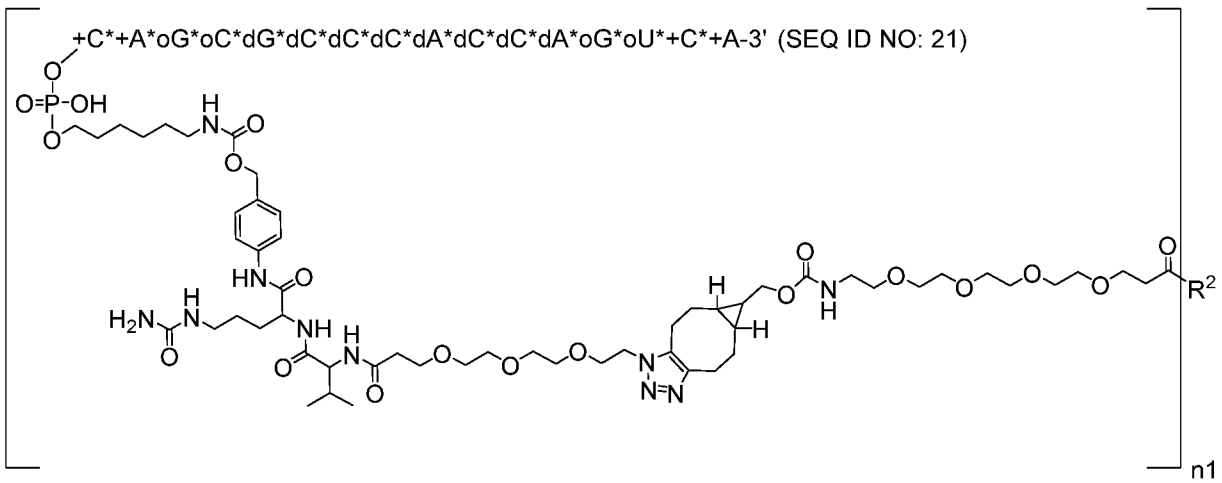
(Ic),

wherein R^2 comprises an antibody comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region, wherein in each complex n1 is independently an integer (e.g., of one or greater) representing the number of instances of R^1 in each complex, wherein each R^1 is covalently linked to R^2 at attachment point *A* via a linkage site represented by a lysine (K) residue of the antibody. In some embodiments, light chain constant regions of antibodies of complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of light chain constant regions of the antibodies. For example, in some embodiments, a linkage site is represented by K188 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, a linkage site is represented by K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, linkage sites are represented by K188 (based on Kabat numbering) and K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least

89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies. In some embodiments, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the antibodies. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a sequence as set forth in Table 2. For example, in some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14; and/or comprising a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NO: 6 or 16. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain variable region (VH) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 17 and/or comprising a light chain variable region (VL) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 18. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a VH comprising the amino acid sequence of SEQ ID NO: 17 and/or comprising a VL comprising the amino acid sequence of SEQ ID NO: 18. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 19 and/or comprising a light chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 20. In some embodiments, R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and/or

comprising a light chain comprising the amino acid sequence of SEQ ID NO: 20. In some embodiments, R^2 comprises an antibody that is a Fab fragment, a full-length IgG, a Fab' fragment, a $F(ab')_2$ fragment, an scFv, or an Fv. In some embodiments, R^2 comprises an antibody that is a Fab fragment. In some embodiments, in each complex n1 is independently an integer (e.g., an integer in the range of 1-27, 1-26, 1-10, 1-5, or 1-3). In some embodiments, compositions described herein further comprise complexes that comprise a structure of formula (I): $[R^1]_{n1}$-R^2, wherein n1 is 0. In some embodiments, the average value of n1 of complexes of the composition is in the range of 0.5 to 5 (e.g., 0.5-5, 1-5, 1-4, 1-3, 3-5, 0.5-4, 0.5-3, 0.5-2, 0.5-1.5, 0.5-1, 0.7-1.5, 1-1.6, 1-1.5, 1-1.4, 1-1.3, 1-1.2, 1.1-1.5, 0.8-2, 0.8-1.5, 0.8-1.3, 0.8-1.2, 0.8-1.1, 0.9-3, 0.9-2, 0.9-1.8, 0.9-1.6, 0.9-1.5, 0.9-1.4, 0.9-1.3, or 0.9-1.2).

[000139] In some embodiments, compositions described herein comprise complexes that comprise a structure of the formula (Id):



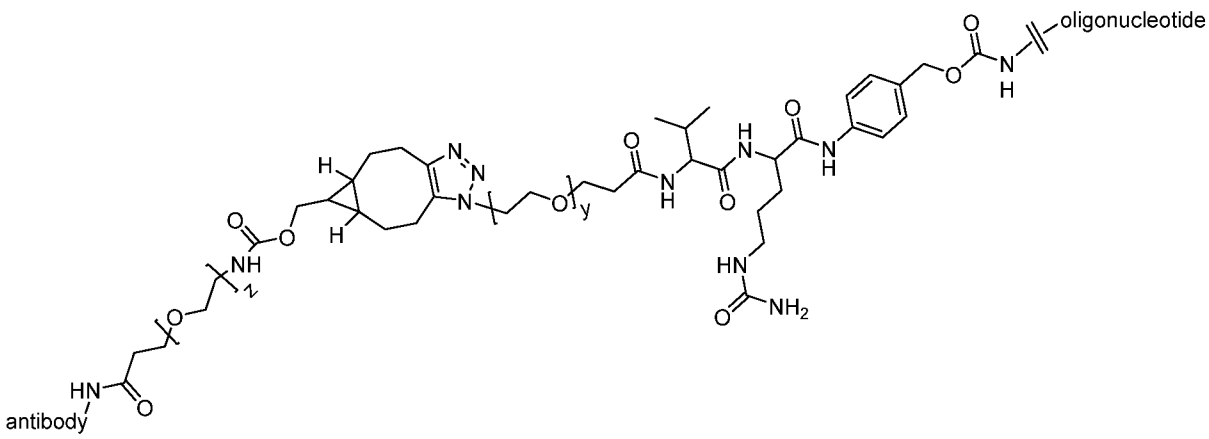
(Id),

wherein +N represents an LNA (2'-4' methylene bridge) ribonucleoside, dN represents a 2'-deoxyribonucleoside, oN represents a 2'-O-methoxyethyl (MOE) modified ribonucleoside, oC represents a 5-methyl-2'-MOE-cytidine, +C represents a 5-methyl-2'-4'-bicyclic-cytidine (2'-4' methylene bridge), oU represents a 5-methyl-2'-MOE-uridine, * represents a phosphorothioate internucleoside linkage, and wherein the oligonucleotide comprises a nucleobase sequence of CAGCGCCCACCAGUCA (SEQ ID NO: 21); wherein R^2 comprises an anti-TfR1 antibody (e.g., a Fab) comprising a CDR-H1, a CDR-H2, a CDR-H3, a CDR-L1, a CDR-L2, and a CDR-L3 selected from Table 2, optionally wherein the anti-TfR1 antibody (e.g., a Fab) comprises a VH comprising the amino acid sequence of SEQ ID NO: 17 and a VL comprising the amino acid sequence of SEQ ID NO: 18, further optionally wherein the anti-TfR1 antibody (e.g., a Fab) comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and a light chain comprising the amino acid sequence of SEQ ID NO: 20; and

wherein in each complex n1 is independently an integer (e.g., of one or greater) representing the number of instances of the group enclosed by square brackets, wherein each instance of the group enclosed by square brackets is covalently linked to a linkage site represented by a lysine (K) residue of the antibody (e.g., the Fab). In some embodiments, light chain constant regions of antibodies of complexes in the composition are independently covalently linked to the group enclosed by square brackets in formula (Id) at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of light chain constant regions of the antibodies. For example, in some embodiments, a linkage site is represented by K188 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, a linkage site is represented by K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, linkage sites are represented by K188 (based on Kabat numbering) and K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chain constant regions of the antibodies (e.g., the Fabs) of the complexes in the composition are independently covalently linked to the group enclosed by square brackets in formula (Id) at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies. In some embodiments, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to the group in square brackets in formula (Id) at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the antibodies. In some embodiments, R^2 comprises an antibody (e.g., a Fab) comprising a sequence as set forth in Table 2. For example, in some embodiments, R^2 comprises an antibody (e.g., a Fab) comprising a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14; and/or comprising a light chain complementarity determining region 1 (CDR-L1)

comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NO: 6 or 16. In some embodiments, R^2 comprises an antibody (e.g., a Fab) comprising a heavy chain variable region (VH) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 17 and/or comprising a light chain variable region (VL) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 18. In some embodiments, R^2 comprises an antibody (e.g., a Fab) comprising a VH comprising the amino acid sequence of SEQ ID NO: 17 and/or comprising a VL comprising the amino acid sequence of SEQ ID NO: 18. In some embodiments, R^2 comprises an antibody (e.g., a Fab) comprising a heavy chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 19 and/or comprising a light chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 20. In some embodiments, R^2 comprises an antibody (e.g., a Fab) comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and/or comprising a light chain comprising the amino acid sequence of SEQ ID NO: 20. In some embodiments, in each complex n1 is independently an integer (e.g., an integer in the range of 1-27, 1-26, 1-10, 1-5, or 1-3). In some embodiments, in each complex n1 is independently an integer of one or greater. In some embodiments, compositions described herein further comprise complexes in which n1 is 0. In some embodiments, the average value of n1 of complexes of the composition is in the range of 0.5 to 5 (e.g., 0.5-5, 1-5, 1-4, 1-3, 3-5, 0.5-4, 0.5-3, 0.5-2, 0.5-1.5, 0.5-1, 0.7-1.5, 1-1.6, 1-1.5, 1-1.4, 1-1.3, 1-1.2, 1.1-1.5, 0.8-2, 0.8-1.5, 0.8-1.3, 0.8-1.2, 0.8-1.1, 0.9-3, 0.9-2, 0.9-1.8, 0.9-1.6, 0.9-1.5, 0.9-1.4, 0.9-1.3, or 0.9-1.2).

[000140] In some embodiments, compositions described herein comprise complexes that comprise a structure of formula (A):



(A), wherein y is 0-15 (e.g., 3) and z is 0-15 (e.g., 4). In some embodiments, the antibody is an

an-TfR1 antibody (e.g., the anti-TfR1 antibody provided in Table 2) comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region. In some embodiments, the oligonucleotide comprises a 5'-X-Y-Z-3' configuration and comprises the nucleobase sequence of SEQ ID NO: 21. In some embodiments, the amide shown adjacent to the antibody in the structure results from a reaction with an amine of the antibody, such as a lysine epsilon amine. In some embodiments, a complex described herein comprises an anti-TfR1 Fab covalently linked to the 5' end of an oligonucleotide via a linkage site represented by a lysine (K) residue of the antibody. In some embodiments, light chain constant regions of antibodies of complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of light chain constant regions of the antibodies. For example, in some embodiments, a linkage site is represented by K188 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, a linkage site is represented by K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, linkage sites are represented by K188 (based on Kabat numbering) and K190 (based on Kabat numbering) of a light chain constant region of an antibody. In some embodiments, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-97%, or more) of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies. In some embodiments, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the antibodies. In some embodiments, the anti-TfR1 antibody comprises a sequence as set forth in Table 2. For example, in some embodiments, the antibody comprises a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain

complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14; and/or comprises a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NO: 6 or 16. In some embodiments, the antibody comprises a heavy chain variable region (VH) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 17 and/or comprises a light chain variable region (VL) comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 18. In some embodiments, the anti-TfR1 antibody comprises a VH comprising the amino acid sequence of SEQ ID NO: 17 and/or comprises a VL comprising the amino acid sequence of SEQ ID NO: 18. In some embodiments, the anti-TfR1 antibody comprises a heavy chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 19 and/or comprises a light chain comprising an amino acid sequence at least 85% (e.g., at least 95%) identical to SEQ ID NO: 20. In some embodiments, the anti-TfR1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and/or comprises a light chain comprising the amino acid sequence of SEQ ID NO: 20. In some embodiments, the antibody is a Fab fragment, a full-length IgG, a Fab' fragment, a $F(ab')_2$ fragment, an scFv, or an Fv.

[000141] In some embodiments, such as embodiments in which compositions comprise complexes comprising a structure of formula (A) or a structure comprising a group of the formula (Ia), (Ib), (Ic), or (Id), a linkage site is optionally represented by the K at position 4 of a sequence motif DYEKHKVYA (SEQ ID NO: 27) of a light chain of an antibody of a complex described herein. In some embodiments, a linkage site is optionally represented by the K at position 6 of a sequence motif DYEKHKVYA (SEQ ID NO: 27) of a light chain of an antibody of a complex described herein. In some embodiments, linkage sites are optionally represented by the K at position 4 and/or the K at position 6 of a sequence motif DYEKHKVYA (SEQ ID NO: 27) of a light chain of an antibody of a complex described herein. In some embodiments, in a composition comprising a plurality of complexes described herein, at least 80% (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85% at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, a least 96%, at least 97%, at least 98%, at least 99%, 80%-98%, 80%-95%, 80%-90%, 85%-98%, 85%-95%, 85%-90%, 90%-98%, 90%-95%, 95%-

97%, or more) of light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at linkage sites represented by K residues in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of the light chains of the antibodies. In some embodiments, a linkage site is optionally represented by the K in a sequence motif VNHKPSN (SEQ ID NO: 28) of a heavy chain of an antibody of a complex described herein. In some embodiments, in a composition comprising a plurality of complexes described herein, about 1%-15% (e.g., about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, or about 15%) of the heavy chains of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by the K residue in a sequence motif VNHKPSN (SEQ ID NO: 28) of the heavy chains of the antibodies. In some embodiments, in a composition comprising a plurality of complexes described herein, the average value of n1 of complexes of the composition is in the range of 0.5 to 5 (e.g., 0.5-5, 1-5, 1-4, 1-3, 3-5, 0.5-4, 0.5-3, 0.5-2, 0.5-1.5, 0.5-1, 0.7-1.5, 1-1.6, 1-1.5, 1-1.4, 1-1.3, 1-1.2, 1.1-1.5, 0.8-2, 0.8-1.5, 0.8-1.3, 0.8-1.2, 0.8-1.1, 0.9-3, 0.9-2, 0.9-1.8, 0.9-1.6, 0.9-1.5, 0.9-1.4, 0.9-1.3, or 0.9-1.2).

[000142] In some embodiments, compositions comprising complexes (*i.e.*, a plurality of complexes) are formulated in a manner suitable for the methods described herein. In some embodiments, compositions comprising muscle-targeting complexes are delivered to a subject using a formulation that minimizes degradation, facilitates delivery and/or (e.g., and) uptake, or provides another beneficial property to the complexes in the formulation. Accordingly, in some embodiments, compositions comprising complexes (*e.g.*, a plurality of complexes comprising an oligonucleotide covalently linked with a Fab) are formulated with one or more pharmaceutically acceptable carriers and/or excipients. In some embodiments, compositions comprising muscle-targeting complexes (*e.g.*, complexes comprising an oligonucleotide covalently linked with a Fab) are formulated with one or more pharmaceutically acceptable carriers and/or excipients in aqueous solutions. In some embodiments, compositions comprising a plurality of the complexes and one or more pharmaceutically acceptable carriers and/or excipients can be lyophilized (e.g., for storage). In some embodiments, the lyophilized composition may be reconstituted (e.g., with water) for administration to a subject. In some embodiments, compositions comprising a plurality of the complexes can be frozen (e.g., for storage). In some embodiments, the frozen composition may be thawed prior to administration to a subject, e.g., to produce an aqueous solution. The compositions (e.g., in aqueous solutions, in frozen compositions, or in lyophilized compositions) can be suitably prepared 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.

[000143] In some embodiments, a 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.

Methods of Use / Treatment

[000144] Complexes comprising an anti-TfR1 antibody (e.g., Fab) covalently linked to a molecular payload (*e.g.*, a DMPK-targeting oligonucleotide) as described herein are effective in treating a subject having a myotonic dystrophy, e.g., DM1. In some embodiments, complexes comprise a molecular payload that is an oligonucleotide, *e.g.*, an oligonucleotide that facilitates reduced expression or activity of DMPK (e.g., reduced level of a mutant or wild-type DMPK RNA).

[000145] 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, such as DM1. In some embodiments, a subject has a DMPK allele, which may optionally contain a disease-associated repeat, e.g., a CTG trinucleotide repeat expansion. 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, muscle loss, excessive daytime sleepiness or cognitive delay. In some embodiments, a subject is not suffering from symptoms of DM1. In some embodiments, subjects have congenital myotonic dystrophy. In some embodiments, a subject is ambulant. In some embodiments, a subject is non-ambulant

[000146] An aspect of the disclosure includes a method involving administering to a subject an effective amount of a complex as described herein. In some embodiments, an effective amount of a pharmaceutical composition that comprises a complex comprising a muscle-targeting agent covalently linked to a molecular payload can be administered to a subject in need of treatment.

[000147] 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, 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 lyophilized form may be reconstituted with an aqueous or liquid solution.

[000148] Compositions for intravenous administration may contain various carriers such as vegetable oils, dimethylactamide, dimethyformamide, ethyl lactate, ethyl carbonate, isopropyl myristate, ethanol, and polyols (glycerol, propylene glycol, liquid polyethylene glycol, and the like). For intravenous injection, water soluble antibodies can be administered by the drip method, whereby a pharmaceutical formulation containing the antibody and a physiologically acceptable excipients is infused. Physiologically acceptable excipients may include, for example, 5% dextrose, 0.9% saline, Ringer's solution or other suitable excipients. Intramuscular preparations, e.g., a sterile formulation of a suitable soluble salt form of the antibody, can be dissolved and administered in a pharmaceutical excipient such as Water-for-Injection, 0.9% saline, or 5% glucose solution.

[000149] In some embodiments, a pharmaceutical composition that comprises a complex comprising a muscle-targeting agent covalently linked to a molecular payload is administered via site-specific or local delivery techniques. Examples of these techniques include implantable depot sources of the complex, local delivery catheters, site specific carriers, direct injection, or direct application.

[000150] In some embodiments, a pharmaceutical composition that comprises a complex comprising a muscle-targeting agent covalently linked to a molecular payload is administered at an effective concentration that confers therapeutic effect on a subject. Effective amounts vary, as recognized by those skilled in the art, depending on the severity of the disease, unique characteristics of the subject being treated, e.g. age, physical conditions, health, or weight, the duration of the treatment, the nature of any concurrent therapies, the route of administration and related factors. These related factors are known to those in the art and may be addressed with no more than routine experimentation. In some embodiments, an effective concentration is the maximum dose that is considered to be safe for the patient. In some embodiments, an effective concentration will be the lowest possible concentration that provides maximum efficacy.

[000151] 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.

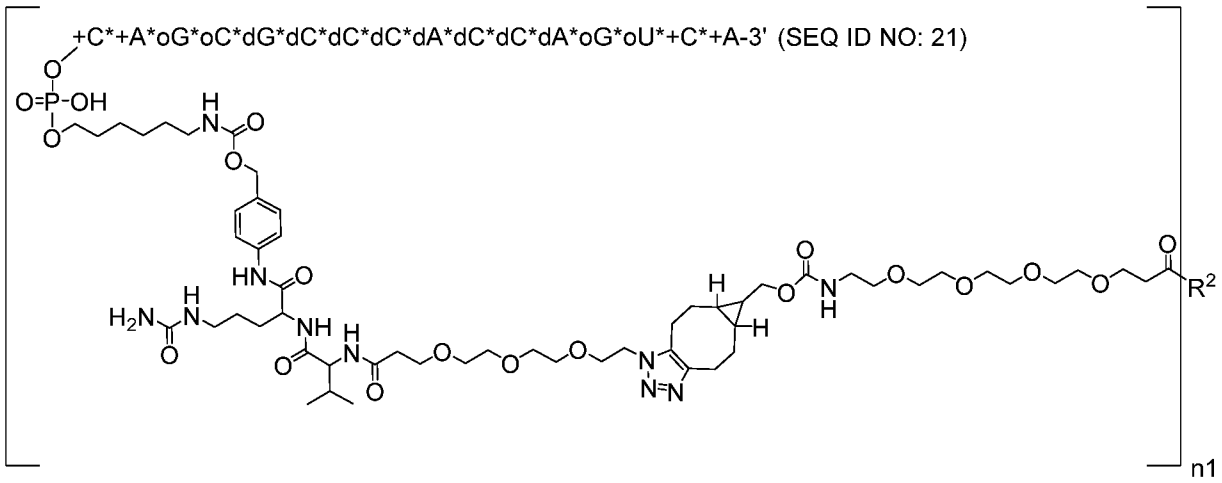
[000152] The efficacy of treatment may be assessed using any suitable methods. In some embodiments, the efficacy of treatment may be assessed by evaluation of observation of symptoms associated with a myotonic dystrophy, e.g. muscle atrophy or muscle weakness, through measures of a subject's self-reported outcomes, e.g. mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, or by quality-of-life indicators, e.g. lifespan.

[000153] In some embodiments, a pharmaceutical composition that comprises a complex comprising a muscle-targeting agent covalently linked to a molecular payload described herein is administered to a subject at an effective concentration sufficient to modulate activity or expression of a target gene by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% or at least 95% relative to a control, e.g. baseline level of gene expression prior to treatment.

EXAMPLES

Example 1. Peptide mapping to determine conjugation sites of oligonucleotides on anti-TfR1 Fab-oligonucleotide conjugates

[000154] Peptide mapping was performed to determine conjugation sites of anti-TfR1 conjugates comprising the anti-TfR1 Fab having the heavy chain and light chain sequences shown in Table 2 covalently linked (through lysine conjugation) via a linker comprising a Valine-Citrulline sequence to an antisense oligonucleotide (ASO) targeting DMPK. The DMPK targeting ASO comprises a 5'-X-Y-Z-3' configuration and comprises the nucleobase sequence of SEQ ID NO: 21. The conjugates comprise a structure of formula (Id):



(Id),

wherein +N represents an LNA (2'-4' methylene bridge) ribonucleoside, dN represents a 2'-deoxyribonucleoside, oN represents a 2'-O-methoxyethyl (MOE) modified ribonucleoside, oC represents a 5-methyl-2'-MOE-cytidine, +C represents a 5-methyl-2'-4'-bicyclic-cytidine (2'-4' methylene bridge), oU represents a 5-methyl-2'-MOE-uridine, * represents a phosphorothioate internucleoside linkage, and wherein the oligonucleotide comprises a nucleobase sequence of CAGCGCCCACCAGUCA (SEQ ID NO: 21), and wherein R^2 is the anti-TfR1 Fab provided in Table 2, and wherein in each conjugate n1 is independently an integer of 1-3.

Papain Digestion

[000155] The oligonucleotides were cleaved from the anti-TfR1 conjugates by digestion with papain. Thermo Scientific Immobilized Papain (P/N: 20341) was activated prior to digestion by adding 0.5 mL of the 50% slurry to 4 mL of freshly prepared Papain Activation Buffer (20 mM Sodium Phosphate, 10 mM EDTA, 20 mM Cysteine, pH 7.0). Papain resin was mixed thoroughly and centrifuged at 3000 rcf for 5 minutes to pull down the resin. The supernatant was discarded and the wash was repeated a second time. After two washes, the papain was resuspended to a 50% slurry by the addition of 250 µL Papain Activation Buffer. Anti-TfR1 conjugates underwent buffer exchange into Papain Digest buffer (20 mM Sodium Phosphate, 10 mM EDTA, pH 7.0) using Thermo Scientific Zeba desalting columns (P/N: 89882). The columns were equilibrated with 0.3 mL buffer 3 times prior to addition of conjugate. 40 µL of conjugate at a concentration of at least 8 mg/mL was added to 100 µL of equilibrated immobilized papain resin. Samples were incubated at 40 °C for 1 hour with shaking at 1400 rpm. After incubation, papain resin was removed by adding each sample to a

filter tube and centrifuging briefly until all liquid sample was filtered through. Another set of Zeba columns were equilibrated with LC-MS grade water, 3x300 µL. 100 µL of papain-digested conjugate was added to each column and spun at 1500 rcf for 3 minutes to buffer exchange. 40 µg of material was diluted to a 50 µL volume with LC-MS water. Complete digestion of the oligonucleotide was observed in all samples.

[000156] A mass spectrum of intact mass of the unlinked anti-TfR1 antibody is shown in FIG. 1. The intact mass of the unlinked antibody is 47968.73 Da as determined by mass spectrometry and is consistent with the theoretical mass of the antibody with a post-translational modification (PTM) that converted the first residue (Q) of the heavy chain to a pyroglutamate, which is 47968.01 Da (the theoretical mass of the antibody without the PTM is 47986.03 Da). A mass spectrum showing masses of anti-TfR1 antibody-linker complexes of the compositions provided herein after cleavage of the oligonucleotides via papain digestion is shown in FIG. 2. Two major peaks were observed, corresponding to a linker to antibody ratio (LAR) of 1 ("LAR1") and a LAR of 2 ("LAR2"), respectively. Next to each peak, the mass of the anti-TfR1 antibody-linker complex is shown, which equals the intact antibody (with a pyroglutamate PTM) mass (47968.01 Da) plus the linker mass (~927.07 Da per linker). The anti-TfR1 antibody-linker complex with an LAR of 1 has a theoretical mass of 48895.08. The anti-TfR1 antibody-linker complex with an LAR of 2 has a theoretical mass of 49822.15. The data shown in FIG. 1 suggest that the anti-TfR1 conjugates of the composition tested primarily comprised conjugates in which the antibody of the conjugate was linked to one DMPK-targeting ASO molecule and conjugates in which the antibody of the conjugate was linked to two DMPK-targeting ASO molecules.

Chymotrypsin Digestion

[000157] The anti-TfR1 linker conjugates, with oligonucleotides cleaved, were digested with immobilized chymotrypsin. 15 µL of Thermo SMART Chymotrypsin resin (Kit P/N: 60109104MBLPH) was added to an Eppendorf tube. 150 µL of Chymotrypsin Smart Digest Buffer was added. 40 µg of the anti-TfR1 linker conjugate in a 50 µL sample prepared after papain digest was added. A heat block was set to 70 °C and 1400 rpm mix, and incubated for 2.5 hours. After incubation, the papain resin was removed by adding each sample to a filter tube and centrifuging briefly until all liquid sample is filtered through. A stock solution of 500 mM tris(2-carboxyethyl)phosphine (TCEP) in water was prepared. The stock solution was added to the digest sample to a final concentration of 20 mM TCEP, and was incubated for 30 mins at room temp to reduce disulfides. Samples were concentrated by speed vac until the total

sample volume was about 100 µL. 25 µL of peptide sample (about 10 ug total peptide) was then injected into the mass spectrometer for peptide mapping analysis. There was 100% sequence coverage in all chymotrypsin digests (data not shown) and papain-cleaved linkers were identified in all conjugate groups. Oligonucleotides were then quantified per heavy and light chains of the antibodies.

[000158] A summary of the percent occupancy of oligonucleotide per linker site is shown below in Table 7. The hot spot linker sites were lysine 188 (K188) and lysine 190 (K190) in the light chain constant regions in the composition based on Kabat numbering. Collectively, about 96% of lysine residues corresponding to K188 and K190 were covalently linked to an oligonucleotide. Some linkage was observed at linker site lysine 213 (K213) based on Kabat numbering in the heavy chain constant regions in the compositions, as 4-8% of lysine residues corresponding to K213 were covalently linked to an oligonucleotide. Small amount of modification on other lysines was observed at extremely low levels (<1%).

Table 7.

Site**	% Occupancy per Linker Site
Heavy Constant K213	~4-8%
Light Constant K188	about 96% (includes complexes in which K188 is linked and in which K190 is linked)*
Light Constant K190	

*hot spot is K188 and/or K190

** based on Kabat numbering

Example 2. *In vivo* tissue distribution of conjugates containing anti-TfR1 Fab conjugated to a DMPK-targeting oligonucleotide in DM1 mouse model

[000159] Conjugates (labeled in this Example as "Anti-TfR1 Fab-ASO conjugate") as described in Example 1, containing an anti-TfR1 Fab covalently linked to a DMPK-targeting oligonucleotide (ASO) were tested in a mouse model that expresses both human TfR1 and a human DMPK mutant that harbors expanded CUG repeats.

[000160] The conjugates were administered intravenously to the mice at day 0 and day 7, each time at a dose equivalent to 9.7 mg/kg of the ASO. The tissue exposure of the ASO was tested by hybridization ELISA (Burki et al., Nucleic Acid Ther. 2015 Oct;25(5):275-84, incorporated herein by reference), and the levels of ASO in the tissue were graphed. FIGs. 3A, 3B, 3C, and 3D show the amount of ASO in the heart, diaphragm, gastrocnemius, or tibialis

anterior, respectively, two weeks after the first injection. These results demonstrate that conjugates comprising an anti-TfR1 antibody (e.g., an anti-TfR1 Fab having the VH and VL sequences provided in Table 2) are capable of delivering an oligonucleotide (e.g., a DMPK-targeting ASO) to various muscle tissues following intravenous administration.

Example 3. Sustained knockdown of toxic human DMPK in hTfR1/DMSXL homozygous mice at 4 weeks after repeat dosing of anti-TfR1 Fab-ASO conjugates

[000161] Conjugates (labeled in this Example as "Anti-TfR1 Fab-ASO conjugate") as described in Example 1, containing an anti-TfR1 Fab covalently linked to a DMPK-targeting oligonucleotide (ASO) were tested in a mouse model that expresses both human TfR1 and two copies of a mutant human DMPK transgene that harbors expanded CUG repeats (hTfR1/DMSXL mice).

[000162] Mice were administered either vehicle control (PBS) or 10 mg/kg ASO-equivalent dose of anti-TfR1 Fab-ASO conjugate at days 0 and 7. Mice were sacrificed at day 28 (four weeks following administration of the first dose of anti-TfR1 Fab-ASO conjugate), and tissues were collected. RNA was extracted and selected tissue samples were fixed, paraffin embedded and sectioned, then subjected to *in situ* hybridization. Reverse transcription-quantitative polymerase chain reaction (RT-qPCR) of the RNA samples was performed to measure human DMPK and mouse Ppib (peptidylprolyl isomerase) as an internal control. DMPK expression is shown in FIGs. 4A-4D as geometric means +/- standard deviation (n = 6-9). Significance was assessed by Student's t-test (**** $P < 0.0001$).

[000163] FIG. 4A shows that anti-TfR1 Fab-ASO conjugate knocked down DMPK expression in heart by 49% relative to PBS-treated mice. FIG. 4B shows that anti-TfR1 Fab-ASO conjugate knocked down DMPK expression in diaphragm by 40% relative to PBS-treated mice. FIG. 4C shows that anti-TfR1 Fab-ASO conjugate knocked down DMPK expression in tibialis anterior by 49% relative to PBS-treated mice. FIG. 4D shows that anti-TfR1 Fab-ASO conjugate knocked down DMPK expression in gastrocnemius by 44% relative to PBS-treated mice.

[000164] FIGs. 5A and 5B show that anti-TfR1 Fab-ASO conjugate reduced DMPK foci within nuclei of myofibers. FIG. 5A shows reduced DMPK foci by *in situ* hybridization, and FIG. 5B shows quantification of DMPK foci in fluorescent microscopy images, demonstrating the conjugate reduced foci area by 49%. Data are presented as mean +/- standard deviation (n = 7). Significance was assessed by t-test (* $P < 0.05$).

[000165] These results demonstrate that administration of anti-TfR1 Fab-ASO conjugate leads to robust, sustained knockdown of human toxic DMPK in cardiac and skeletal muscle.

Example 4. Correction of splicing defects in hTfR1/DMSXL homozygous mice by anti-TfR1 Fab-ASO conjugates

[000166] Conjugates (labeled in this Example as "Anti-TfR1 Fab-ASO conjugate") as described in Example 2, containing an anti-TfR1 Fab covalently linked to a DMPK-targeting oligonucleotide (ASO) were tested in a mouse model ("hTfR1/DMSXL") that expresses both human TfR1 and two copies of a mutant human DMPK transgene that harbors expanded CUG repeats. These mice are known to display splicing defects that are consistent with those observed in patients afflicted with DM1 (Huguet, et al. (2012) *PLOS Genetics* 8(11): e1003043). Mice were administered either vehicle control ("hTfR1/DMSXL – PBS") or 10 mg/kg ASO-equivalent dose of anti-TfR1 Fab-ASO conjugate ("hTfR1/DMSXL – Conjugate") on days 0 and 7. Mice expressing only the human TfR1 but not the mutant human DMPK transgene (hTfR1 mice) and treated with PBS ("hTfR1 – PBS") were used as another control to define the extent of the splicing phenotype in hTfR1/DMSXL mice and assess the magnitude of the effect of the conjugate on splicing. Mice were sacrificed on day 28 (four weeks following administration of the first dose of anti-TfR1 Fab-ASO conjugate), tissues were collected, and RNA was extracted. Reverse transcription-quantitative polymerase chain reaction (RT-qPCR) was performed to measure exon inclusion in a set of RNAs known to be mis-spliced during DM1 progression in humans and mice (Nakamori, et al. (2013) *Ann. Neurol.* 74(6): 862-872; Huguet, et al. (2012) *PLOS Genetics* 8(11): e1003043). Exon inclusion was calculated as normalized percent spliced in (PSI) for each splicing RNA marker, and composite splicing indices were calculated using the normalized PSI values from splicing markers in heart (FIG. 6), diaphragm (FIG. 7), tibialis anterior (FIG. 8), and gastrocnemius (FIG. 9). Composite splicing indices were calculated as previously described (Tanner MK, et al. (2021) *Nucleic Acids Res.* 49:2240-2254), and are shown as mean +/- standard deviation.

[000167] FIG. 6 shows that anti-TfR1 Fab-ASO conjugate corrected splicing in heart tissue of hTfR1/DMSXL mice, as demonstrated by composite splicing index data. The normalized PSI values used to generate the composite splicing index data showed correction of *Mbnl2* exon 6 (E6) and *Nfix* E7 splicing in heart tissue of hTfR1/DMSXL mice by treatment with anti-TfR1 Fab-ASO conjugate, but did not show correction of *Ldb3* E11 splicing. Composite splicing index data shown in FIG. 6 were based on *Ldb3* E11, *Mbnl2* E6, and *Nfix* E7 splicing data; *Bin1* E11, *Dtna* E12, *Insr* E11, and *Mbnl2* E5 were not included because their

normalized PSI values in heart tissue were not changed in hTfR1/DMSXL mice relative to hTfR1 mice under the experimental conditions tested.

[000168] FIG. 7 shows that anti-TfR1 Fab-ASO conjugate corrected splicing in diaphragm tissue of hTfR1/DMSXL mice, as demonstrated by composite splicing index data. The normalized PSI values used to generate the composite splicing index data showed correction of *Bin1* E11, *Insr* E11, *Ldb3* E11 and *Nfix* E7 splicing in diaphragm tissue of hTfR1/DMSXL mice by treatment with anti-TfR1 Fab-ASO conjugate. Composite splicing index data shown in FIG. 7 were based on *Bin1* E11, *Insr* E11, *Ldb3* E11 and *Nfix* E7 splicing data; *Dtna* E12, *Mbnl2* E5, *Mbnl2* E6, and *Ttn* E313 were not included because their normalized PSI values in diaphragm tissue were not changed in hTfR1/DMSXL mice relative to hTfR1 mice under the experimental conditions tested.

[000169] FIG. 8 shows that anti-TfR1 Fab-ASO conjugate corrected splicing in tibialis anterior tissue of hTfR1/DMSXL mice, as demonstrated by composite splicing index data. The normalized PSI values used to generate the composite splicing index data showed correction of *Bin1* E11, *Ldb3* E11, and *Nfix* E7 splicing in tibialis anterior tissue of hTfR1/DMSXL mice by treatment with anti-TfR1 Fab-ASO conjugate, but did not show correction of *Mbnl2* E6 splicing. Composite splicing index data shown in FIG. 8 were based on *Bin1* E11, *Ldb3* E11, *Mbnl2* E6, and *Nfix* E7 splicing data; *Dtna* E12, *Insr* E11, *Mbnl2* E5, and *Ttn* E313 were not included because their normalized PSI values in tibialis anterior tissue were not changed in hTfR1/DMSXL mice relative to hTfR1 mice under the experimental conditions tested.

[000170] FIG. 9 shows that anti-TfR1 Fab-ASO conjugate corrected splicing in gastrocnemius tissue of hTfR1/DMSXL mice, as demonstrated by composite splicing index data. The normalized PSI values used to generate the composite splicing index data showed correction of *Mbnl2* E6, *Nfix* E7, and *Ttn* E313 splicing in gastrocnemius tissue of hTfR1/DMSXL mice by treatment with anti-TfR1 Fab-ASO conjugate. Composite splicing index data shown in FIG. 9 were based on *Mbnl2* E6, *Nfix* E7, and *Ttn* E313 splicing data; *Bin1* E11, *Dtna* E12, *Insr* E11, *Ldb3* E11, and *Mbnl2* E5 were not included because their normalized PSI values in gastrocnemius tissue were not changed in hTfR1/DMSXL mice relative to hTfR1 mice under the experimental conditions tested.

[000171] These results demonstrate that administration of anti-TfR1 Fab-ASO conjugate facilitates correction of DM1 splicing defects in cardiac and skeletal muscle.

Example 5. DMPK knockdown in non-human primate and DM1 patient myotubes

[000172] Conjugates (labeled in this Example as "Anti-TfR1 Fab-ASO conjugate") as described in Example 2, containing an anti-TfR1 Fab covalently linked to a DMPK-targeting oligonucleotide (ASO) were tested in human DM1 patient myotubes (32F cells) and in non-human primate (NHP) myotubes. The DM1 patient myotubes used express both a mutant DMPK mRNA containing 380 CUG repeats and a wild-type DMPK mRNA. The NHP myotubes used express only wild-type DMPK.

[000173] DM1 patient cells or NHP cells were seeded at a density of 50,000 cells per well in 96 well plates in growth medium and were allowed to recover overnight. The following day, the growth medium was changed to a low-serum differentiation medium and the cells were treated with conjugates at a concentration equivalent to 125 nM, 250 nM, or 500 nM ASO. The cells were incubated for ten days, then cDNA was synthesized using the Cells-to-Ct kit with crude cell lysates as the source of total RNA.

[000174] cDNA was used to assess total DMPK knockdown using Taqman PCR. The data was normalized to PPIB expression and the $2^{-\Delta\Delta Ct}$ method was used to determine DMPK knock down compared to a PBS-treated control ("Vehicle"). Data shown in FIG. 10 are presented as mean DMPK expression relative to species-matched vehicle control + standard deviation (n = 4 replicates per condition).

[000175] The results show that the anti-TfR1 Fab-ASO conjugates achieved knockdown of DMPK expression in both normal NHP myotubes and DM1 patient myotubes, with greater knockdown of DMPK expression in DM1 patient cells (expressing both DMPK mRNA containing 380 CUG repeats and wild-type DMPK mRNA) compared to NHP cells (expressing only wild-type DMPK mRNA) when treated at physiologically relevant concentrations (FIG. 10). At an ASO-equivalent concentration of 125 nM, the conjugates achieved approximately 40% DMPK knockdown relative to vehicle-only control in NHP myotubes, and approximately 65% DMPK knockdown in DM1 patient myotubes. At an ASO-equivalent concentration of 250 nM, the conjugates achieved approximately 45% DMPK knockdown relative to vehicle-only control in NHP myotubes, and approximately 80% DMPK knockdown in DM1 patient myotubes. At an ASO-equivalent concentration of 500 nM, the conjugates achieved approximately 60% DMPK knockdown relative to vehicle-only control in NHP myotubes, and approximately 90% DMPK knockdown in DM1 patient myotubes.

[000176] These results indicate that conjugates containing anti-TfR1 Fab covalently linked to a DMPK-targeting oligonucleotide can achieve greater knockdown of DMPK in human myotubes expressing both wild-type DMPK mRNA and mutant DMPK mRNA (with

expanded CUG repeats) relative to cynomolgus monkey myotubes expressing wild-type DMPK.

ADDITIONAL EMBODIMENTS

1. A composition comprising a plurality of complexes comprising an antibody covalently linked to one or more oligonucleotides, each oligonucleotide being covalently linked at a linkage site represented by a lysine (K) residue of the antibody,

wherein the antibody comprises a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region,

wherein the oligonucleotide comprises a region of complementarity to a DMPK RNA,

and wherein at least 80% of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies.

2. A composition comprising a plurality of complexes comprising an antibody covalently linked to one or more oligonucleotides, each oligonucleotide being covalently linked at a linkage site represented by a lysine (K) residue of the antibody,

wherein the antibody comprises a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region,

wherein the oligonucleotide comprises a 5'-X-Y-Z-3' configuration, wherein X and Z are flanking regions comprising one or more modified nucleosides and Y is a gap region comprising one or more 2'-deoxyribonucleosides,

and wherein at least 80% of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies.

3. The composition of embodiment 1 or embodiment 2, wherein about 1%-15% of the heavy chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the antibodies.

4. A composition comprising a plurality of complexes comprising an antibody covalently linked to one or more oligonucleotides, each oligonucleotide being covalently linked at a linkage site represented by a lysine (K) residue of the antibody,

wherein the antibody comprises a heavy chain and a light chain,

wherein the oligonucleotide comprises a region of complementarity to a DMPK RNA,

and wherein at least 80% of light chains of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by a lysine (K) residue in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of the light chains of the antibodies.

5. A composition comprising a plurality of complexes comprising an antibody covalently linked to one or more oligonucleotides, each oligonucleotide being covalently linked at a linkage site represented by a lysine (K) residue of the antibody,

wherein the antibody comprises a heavy chain and a light chain,

wherein the oligonucleotide comprises a 5'-X-Y-Z-3' configuration, wherein X and Z are flanking regions comprising one or more modified nucleosides and Y is a gap region comprising one or more 2'-deoxyribonucleosides,

and wherein at least 80% of light chains of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by a lysine (K) residue in a sequence motif DYEKHKVYA (SEQ ID NO: 27) of the light chains of the antibodies.

6. The composition of embodiment 4 or embodiment 5, wherein about 1%-15% of the heavy chains of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by the lysine (K) residue in a sequence motif VNHKPSN (SEQ ID NO: 28) of the heavy chains of the antibodies.

7. The composition of any one of embodiments 1-6, wherein the antibody is an anti-transferrin receptor (TfR1) antibody comprising: a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14, a light chain complementarity

determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NOs: 6 or 16.

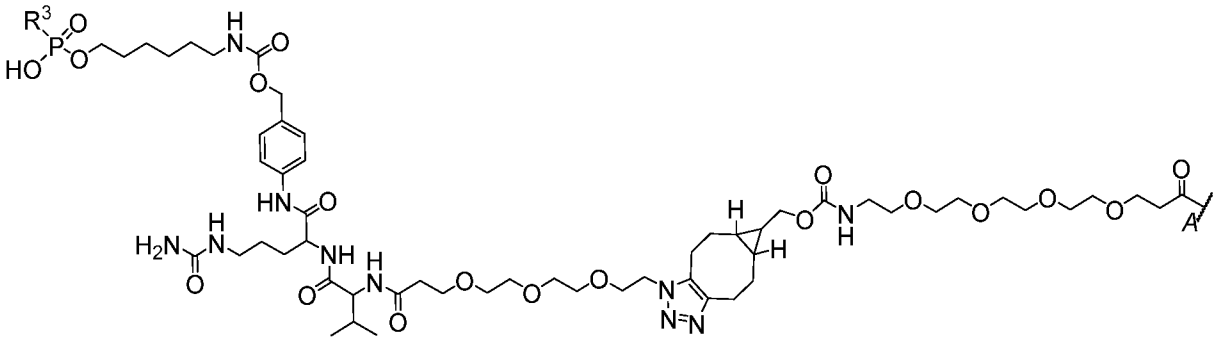
8. The composition of any one of embodiments 1-7, wherein the oligonucleotide comprises a 5′-X-Y-Z-3′ configuration wherein X and Z each comprise 4 linked nucleosides and Y comprises 8 linked nucleosides.

9. The composition of any one of embodiments 1-8, wherein the oligonucleotide comprises a 5′-X-Y-Z-3′ configuration of LLEE-D_8-EELL, wherein "L" represents an LNA nucleoside, "E" represents a 2′-MOE modified ribonucleoside, and "D" represents a 2'-deoxyribonucleoside.

10. The composition of any one of embodiments 1-9, wherein the oligonucleotide comprises a nucleobase sequence of CAGCGCCCACCAGUCA (SEQ ID NO: 21).

11. The composition of any one of embodiments 1-10, wherein the oligonucleotide comprises the structure +C*+A*oG*oC*dG*dC*dC*dC*dA*dC*dC*dA*oG*oU*+C*+A (SEQ ID NO: 21), wherein +N represents an LNA (2'-4' methylene bridge) ribonucleoside, dN represents a 2'-deoxyribonucleoside, oN represents a 2'-MOE modified ribonucleoside, oC represents a 5-methyl-2'-MOE-cytidine, +C represents a 5-methyl-2'-4'-bicyclic-cytidine (2'-4' methylene bridge), oU represents a 5-methyl-2'-MOE-uridine, and * represents a phosphorothioate internucleoside linkage.

12. A composition comprising a plurality of complexes comprising a structure of formula (I): $[R^1]_{n1}$-R^2, wherein
each R^1 independently comprises a group of the formula (Ia):



(Ia),

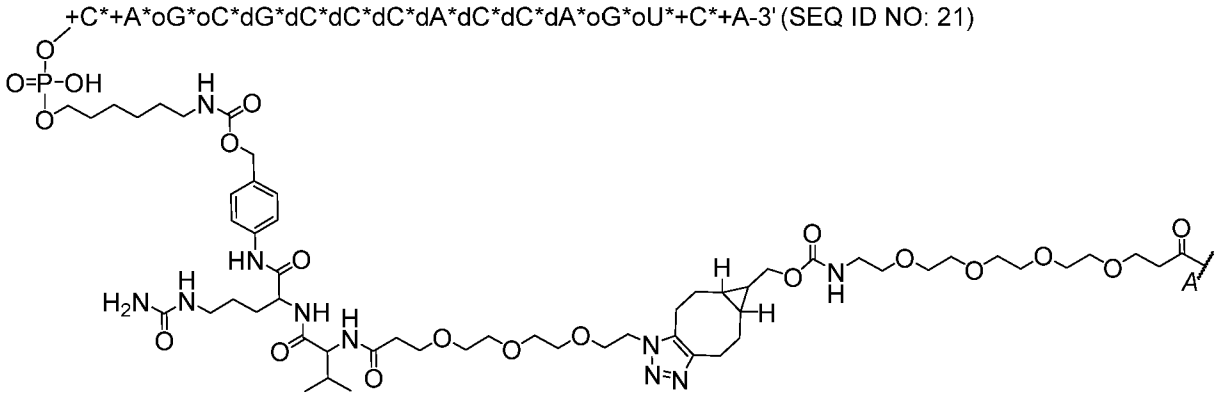
wherein R^2 comprises an anti-transferrin receptor (TfR1) antibody comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region; and wherein the anti-TfR1 antibody comprises: a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14, a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NOs: 6 or 16;

R^3 comprises a structure of
+C*+A*oG*oC*dG*dC*dC*dC*dA*dC*dC*dA*oG*oU*+C*+A (SEQ ID NO: 21), wherein +N represents an LNA (2'-4' methylene bridge) ribonucleoside, dN represents a 2'-deoxyribonucleoside, oN represents a 2'-MOE modified ribonucleoside, oC represents a 5-methyl-2'-MOE-cytidine, +C represents a 5-methyl-2'-4'-bicyclic-cytidine (2'-4' methylene bridge), oU represents a 5-methyl-2'-MOE-uridine, and * represents a phosphorothioate internucleoside linkage;

wherein each R^1 is covalently linked at attachment point *A* to R^2 via a linkage site represented by a lysine (K) residue of the anti-TfR1 antibody, and wherein, at least 80% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the anti-TfR1 antibodies; and

wherein in each complex of the plurality of complexes, n1 is independently an integer of one or greater representing the number of instances of R^1.

13. A composition comprising a plurality of complexes comprising a structure of formula (I): $[R^1]_{n1}$-R^2, wherein
each R^1 independently comprises a group of the formula (Ib):



(Ib),

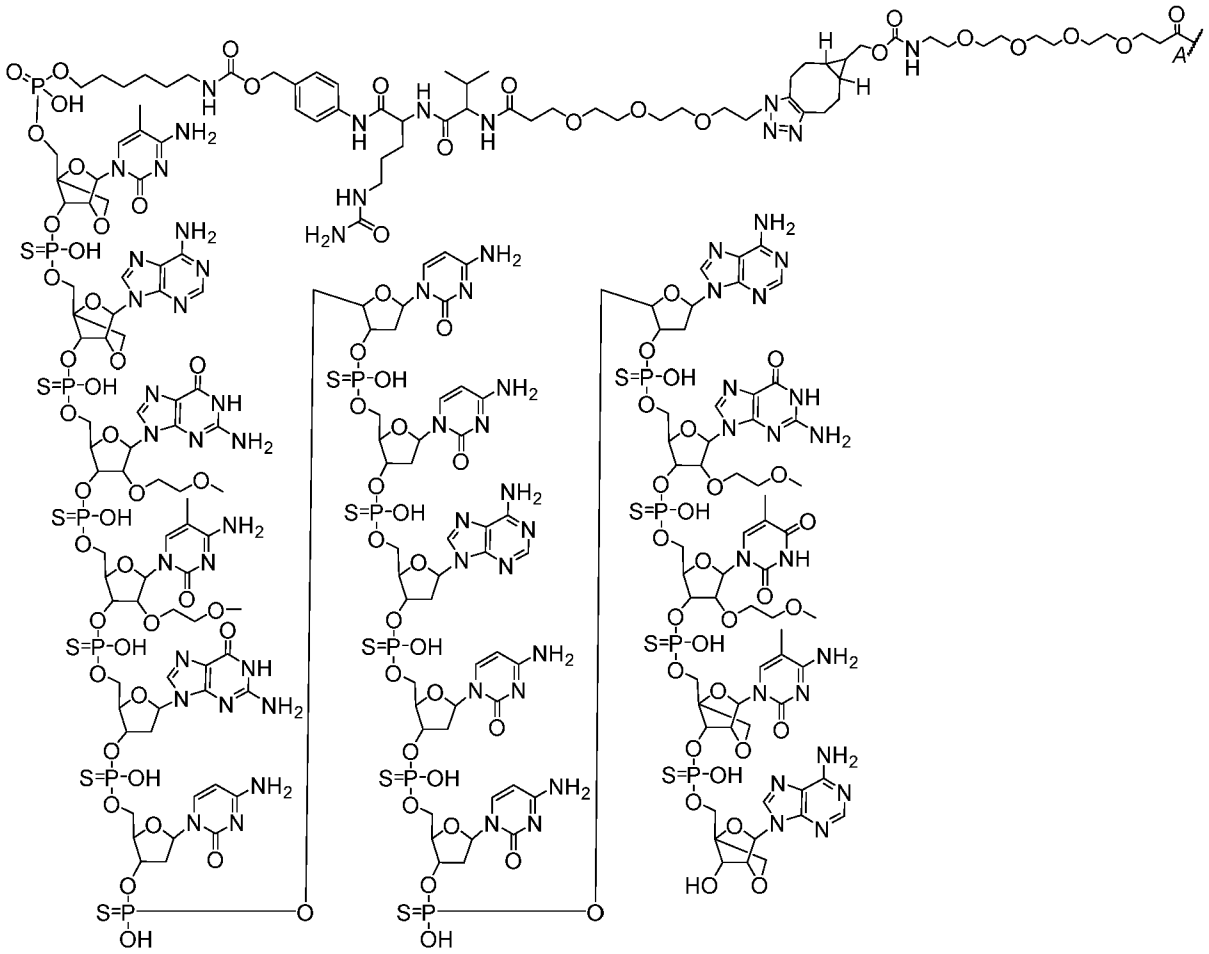
in which +N represents an LNA (2'-4' methylene bridge) ribonucleoside, dN represents a 2'-deoxyribonucleoside, oN represents a 2'-MOE modified ribonucleoside, oC represents a 5-methyl-2'-MOE-cytidine, +C represents a 5-methyl-2'-4'-bicyclic-cytidine (2'-4' methylene bridge), oU represents a 5-methyl-2'-MOE-uridine, and * represents a phosphorothioate internucleoside linkage, and the oligonucleotide of R^1 comprises a nucleobase sequence of CAGCGCCCACCAGUCA (SEQ ID NO: 21);

R^2 comprises an anti-transferrin receptor (TfR1) antibody comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region; and wherein the anti-TfR1 antibody comprises: a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14, a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NOs: 6 or 16; and

wherein each R^1 is covalently linked at attachment point *A* to R^2 via a linkage site represented by a lysine (K) residue of the anti-TfR1 antibody, and wherein, at least 80% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the anti-TfR1 antibodies; and

wherein in each complex of the plurality of complexes, n1 is independently an integer of one or greater representing the number of instances of R^1.

14. A composition comprising a plurality of complexes comprising a structure of formula (I): $[R^1]_{n1}$-R^2, wherein: each R^1 comprises a group of the formula (Ic):



(Ic),

R^2 comprises an anti-transferrin receptor (TfR1) antibody comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region; and wherein the anti-TfR1 antibody comprises: a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14, a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NOs: 6 or 16; and

wherein each R^1 is covalently linked at attachment point *A* to R^2 via a linkage site represented by a lysine (K) residue of the anti-TfR1 antibody, and wherein, at least 80% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the anti-TfR1 antibodies; and

wherein in each complex of the plurality of complexes, n1 is independently an integer of one or greater representing the number of instances of R^1.

15. The composition of any one of embodiments 12-14, wherein 85%-98% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the anti-TfR1 antibodies.

16. The composition of any one of embodiments 12-15, wherein 95%-97% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the anti-TfR1 antibodies.

17. The composition of any one of embodiments 12-16, wherein 1%-15% of the heavy chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the anti-TfR1 antibodies.

18. The composition of any one of embodiments 12-17, wherein 4%-8% of the heavy chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the anti-TfR1 antibodies.

19. The composition of any one of embodiments 1-18, wherein the antibody is a Fab fragment, a full-length IgG, a Fab' fragment, or a $F(ab')_2$ fragment.

20. The composition of any one of embodiments 1-19, wherein the antibody is a Fab fragment.

21. The composition of any one of embodiments 1-20, wherein the VH comprises an amino acid sequence at least 85% identical to SEQ ID NO: 17; and/or wherein the VL comprises an amino acid sequence at least 85% identical to SEQ ID NO: 18.

22. The composition of any one of embodiments 1-21, wherein the antibody comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 17 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO: 18.

23. The composition of any one of embodiments 1-22, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 19 and the light chain comprises the amino acid sequence of SEQ ID NO: 20.

24. The composition of any one of embodiments 1-23, further comprising one or more antibodies that are not covalently linked to an oligonucleotide.

25. The composition of embodiment 24, wherein the average value of n1 of complexes in the composition is in the range of 0.5 to 5.

26. A method of reducing DMPK expression in a subject, the method comprising administering to the subject an effective amount of the composition of any one of embodiments 1-25.

27. A method of treating myotonic dystrophy in a subject, the method comprising administering to the subject an effective amount of the composition of any one of embodiments 1-25.

28. The method of embodiment 26 or embodiment 27, wherein the subject has an expansion of a disease-associated-repeat of a DMPK allele that is associated with myotonic dystrophy.

29. The method of embodiment 28, wherein the disease-associated-repeat comprises repeating units of a CTG trinucleotide sequence.

30. The method of any one of embodiments 26-29, wherein the complexes reduce DMPK expression in the subject.

31. The method of embodiment 30, wherein reducing DMPK expression comprises reducing the level of a DMPK mRNA in the muscle cell, optionally wherein the DMPK mRNA is a mutant DMPK mRNA.

EQUIVALENTS AND TERMINOLOGY

[000177] 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.

[000178] 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.

[000179] 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 (e.g., and) one or more modified nucleotides and/or (e.g., and) one or more modified internucleoside linkages and/or (e.g., and) one or more other

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

[000180] 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. Unless otherwise indicated, ranges of values herein are inclusive of their endpoints (e.g., a range of X to Y is inclusive of the values X and Y). It should be understood that recitations herein of a value from X to Y indicates that the specified value falls in the range of X to Y. 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.

[000181] 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.

[000182] The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

CLAIMS

What is claimed is:

1. A composition comprising a plurality of complexes comprising an antibody covalently linked to one or more oligonucleotides, each oligonucleotide being covalently linked at a linkage site represented by a lysine (K) residue of the antibody,

wherein the antibody comprises a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region,

wherein the oligonucleotide comprises a region of complementarity to a DMPK RNA,

and wherein at least 80% of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies.

2. A composition comprising a plurality of complexes comprising an antibody covalently linked to one or more oligonucleotides, each oligonucleotide being covalently linked at a linkage site represented by a lysine (K) residue of the antibody,

wherein the antibody comprises a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region,

wherein the oligonucleotide comprises a 5'-X-Y-Z-3' configuration, wherein X and Z are flanking regions comprising one or more modified nucleosides and Y is a gap region comprising one or more 2'-deoxyribonucleosides,

and wherein at least 80% of the light chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the antibodies.

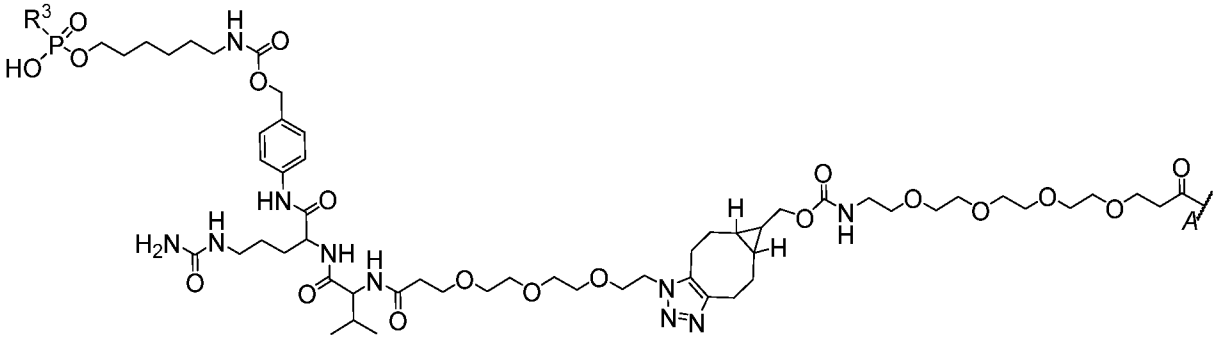
3. The composition of claim 1 or claim 2, wherein about 1%-15% of the heavy chain constant regions of the antibodies of the complexes in the composition are independently covalently linked to an oligonucleotide at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the antibodies.

4. The composition of any one of claims 1-3, wherein the antibody is an anti-transferrin receptor (TfR1) antibody comprising: a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14, a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NOs: 6 or 16.

5. The composition of any one of claims 1-4, wherein the oligonucleotide comprises a 5′-X-Y-Z-3′ configuration wherein X and Z each comprise 4 linked nucleosides and Y comprises 8 linked nucleosides, optionally wherein the oligonucleotide comprises a 5′-X-Y-Z-3′ configuration of LLEE-D_8-EELL, wherein “L” represents an LNA nucleoside, “E” represents a 2′-MOE modified ribonucleoside, and “D” represents a 2’-deoxyribonucleoside.

6. The composition of any one of claims 1-5, wherein the oligonucleotide comprises a nucleobase sequence of CAGCGCCCACCAGUCA (SEQ ID NO: 21), optionally wherein the oligonucleotide comprises the structure +C*+A*oG*oC*dG*dC*dC*dC*dA*dC*dC*dA*oG*oU*+C*+A (SEQ ID NO: 21), wherein +N represents an LNA (2’-4’ methylene bridge) ribonucleoside, dN represents a 2’-deoxyribonucleoside, oN represents a 2’-MOE modified ribonucleoside, oC represents a 5-methyl-2’-MOE-cytidine, +C represents a 5-methyl-2’-4’-bicyclic-cytidine (2’-4’ methylene bridge), oU represents a 5-methyl-2’-MOE-uridine, and * represents a phosphorothioate internucleoside linkage.

7. A composition comprising a plurality of complexes comprising a structure of formula (I): $[R^1]_{n1}$-R^2, wherein each R^1 independently comprises a group of the formula (Ia):



(Ia),

wherein R^2 comprises an anti-transferrin receptor (TfR1) antibody comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region; and wherein the anti-TfR1 antibody comprises: a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14, a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NOs: 6 or 16;

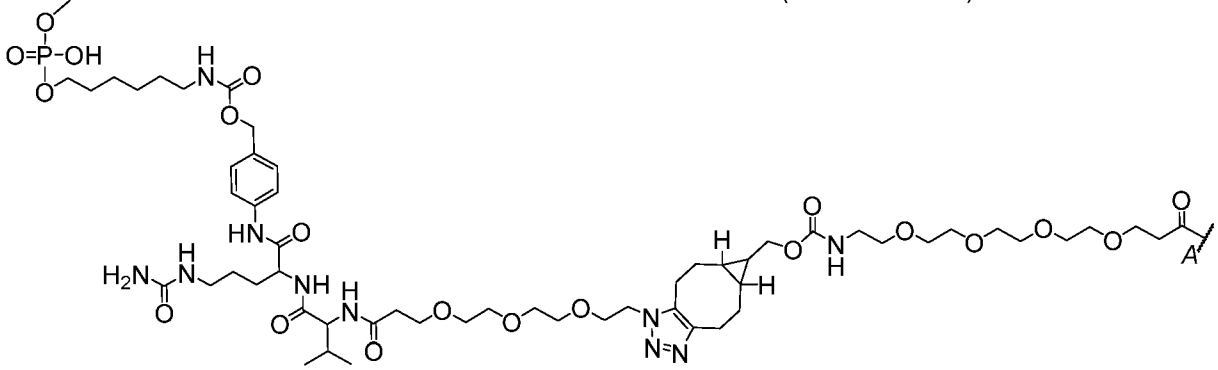
wherein R^3 comprises a structure of +C*+A*oG*oC*dG*dC*dC*dC*dA*dC*dC*dA*oG*oU*+C*+A (SEQ ID NO: 21), wherein +N represents an LNA (2'-4' methylene bridge) ribonucleoside, dN represents a 2'-deoxyribonucleoside, oN represents a 2'-MOE modified ribonucleoside, oC represents a 5-methyl-2'-MOE-cytidine, +C represents a 5-methyl-2'-4'-bicyclic-cytidine (2'-4' methylene bridge), oU represents a 5-methyl-2'-MOE-uridine, and * represents a phosphorothioate internucleoside linkage;

wherein each R^1 is covalently linked at attachment point *A* to R^2 via a linkage site represented by a lysine (K) residue of the anti-TfR1 antibody, and wherein, at least 80% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the anti-TfR1 antibodies; and

wherein in each complex of the plurality of complexes, n1 is independently an integer of one or greater representing the number of instances of R^1.

8. A composition comprising a plurality of complexes comprising a structure of formula (I): $[R^1]_{n1}$-R^2, wherein each R^1 independently comprises a group of the formula (Ib):

+C*+A*oG*oC*dG*dC*dC*dC*dA*dC*dC*dA*oG*oU*+C*+A-3' (SEQ ID NO: 21)



(Ib),

in which +N represents an LNA (2'-4' methylene bridge) ribonucleoside, dN represents a 2'-deoxyribonucleoside, oN represents a 2'-MOE modified ribonucleoside, oC represents a 5-methyl-2'-MOE-cytidine, +C represents a 5-methyl-2'-4'-bicyclic-cytidine (2'-4' methylene bridge), oU represents a 5-methyl-2'-MOE-uridine, and * represents a phosphorothioate internucleoside linkage, and the oligonucleotide of R^1 comprises a nucleobase sequence of CAGCGCCCACCAGUCA (SEQ ID NO: 21);

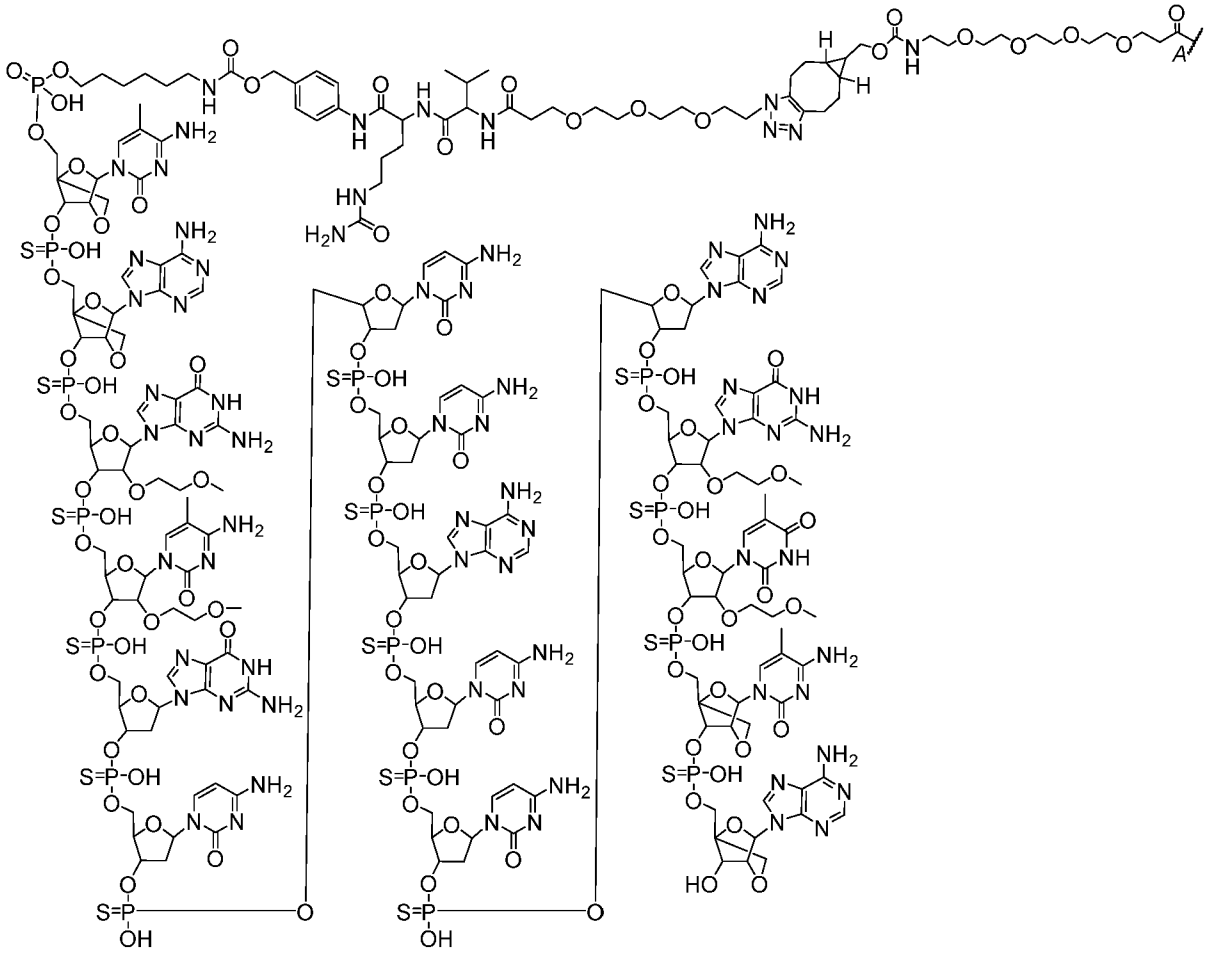
wherein R^2 comprises an anti-transferrin receptor (TfR1) antibody comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region; and wherein the anti-TfR1 antibody comprises: a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14, a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or 15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NOs: 6 or 16; and

wherein each R^1 is covalently linked at attachment point *A* to R^2 via a linkage site represented by a lysine (K) residue of the anti-TfR1 antibody, and wherein, at least 80% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on

Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the anti-TfR1 antibodies; and

wherein in each complex of the plurality of complexes, n1 is independently an integer of one or greater representing the number of instances of R^1.

9. A composition comprising a plurality of complexes comprising a structure of formula (I): $[R^1]_{n1}$-R^2, wherein: each R^1 comprises a group of the formula (Ic):



(Ic),

wherein R^2 comprises an anti-transferrin receptor (TfR1) antibody comprising a heavy chain comprising a heavy chain variable region (VH) and a heavy chain constant region, and a light chain comprising a light chain variable region (VL) and a light chain constant region; and wherein the anti-TfR1 antibody comprises: a heavy chain complementarity determining region 1 (CDR-H1) comprising a sequence as set forth in SEQ ID NOs: 1, 7, or 12, a heavy chain complementarity determining region 2 (CDR-H2) comprising a sequence as set forth in SEQ ID NOs: 2, 8, or 13, a heavy chain complementarity determining region 3 (CDR-H3) comprising a sequence as set forth in SEQ ID NOs: 3, 9, or 14, a light chain complementarity determining region 1 (CDR-L1) comprising a sequence as set forth in SEQ ID NOs: 4, 10, or

15, a light chain complementarity determining region 2 (CDR-L2) comprising a sequence as set forth in SEQ ID NOs: 5 or 11, and a light chain complementarity determining region 3 (CDR-L3) comprising a sequence as set forth in SEQ ID NOs: 6 or 16; and

wherein each R^1 is covalently linked at attachment point *A* to R^2 via a linkage site represented by a lysine (K) residue of the anti-TfR1 antibody, and wherein, at least 80% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the anti-TfR1 antibodies; and

wherein in each complex of the plurality of complexes, n1 is independently an integer of one or greater representing the number of instances of R^1.

10. The composition of any one of claims 7-9, wherein:

(a) 85%-98% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the anti-TfR1 antibodies; or

(b) 95%-97% of the light chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K188 (based on Kabat numbering) and/or a linkage site represented by K190 (based on Kabat numbering) of the light chain constant regions of the anti-TfR1 antibodies.

11. The composition of any one of claims 7-10, wherein:

(a) 1%-15% of the heavy chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the anti-TfR1 antibodies; or

(b) 4%-8% of the heavy chain constant regions of the anti-TfR1 antibodies of the complexes in the composition are independently covalently linked to R^1 at a linkage site represented by K213 (based on Kabat numbering) of the heavy chain constant regions of the anti-TfR1 antibodies.

12. The composition of any one of claims 1-11, wherein the antibody is a Fab fragment, a full-length IgG, a Fab' fragment, or a $F(ab')_2$ fragment.

13. The composition of any one of claims 1-12, wherein the antibody is a Fab fragment.

14. The composition of any one of claims 1-13, wherein the VH comprises an amino acid sequence at least 85% identical to SEQ ID NO: 17; and/or wherein the VL comprises an amino acid sequence at least 85% identical to SEQ ID NO: 18, optionally wherein the antibody comprises a heavy chain variable region (VH) comprising the amino acid sequence of SEQ ID NO: 17 and a light chain variable region (VL) comprising the amino acid sequence of SEQ ID NO: 18.

15. The composition of any one of claims 1-14, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 19 and the light chain comprises the amino acid sequence of SEQ ID NO: 20.

16. The composition of any one of claims 1-15, further comprising one or more antibodies that are not covalently linked to an oligonucleotide.

17. The composition of claim 16, wherein the average value of n1 of complexes in the composition is in the range of 0.5 to 5.

18. A method of reducing DMPK expression and/or treating myotonic dystrophy in a subject, the method comprising administering to the subject an effective amount of the composition of any one of claims 1-17.

19. The method of claim 18, wherein the subject has an expansion of a disease-associated-repeat of a DMPK allele that is associated with myotonic dystrophy, optionally wherein the disease-associated-repeat comprises repeating units of a CTG trinucleotide sequence.

20. The method of claim 18 or claim 19, wherein the complexes reduce DMPK expression in the subject, optionally wherein reducing DMPK expression comprises reducing the level of a DMPK mRNA in the muscle cell, further optionally wherein the DMPK mRNA is a mutant DMPK mRNA.

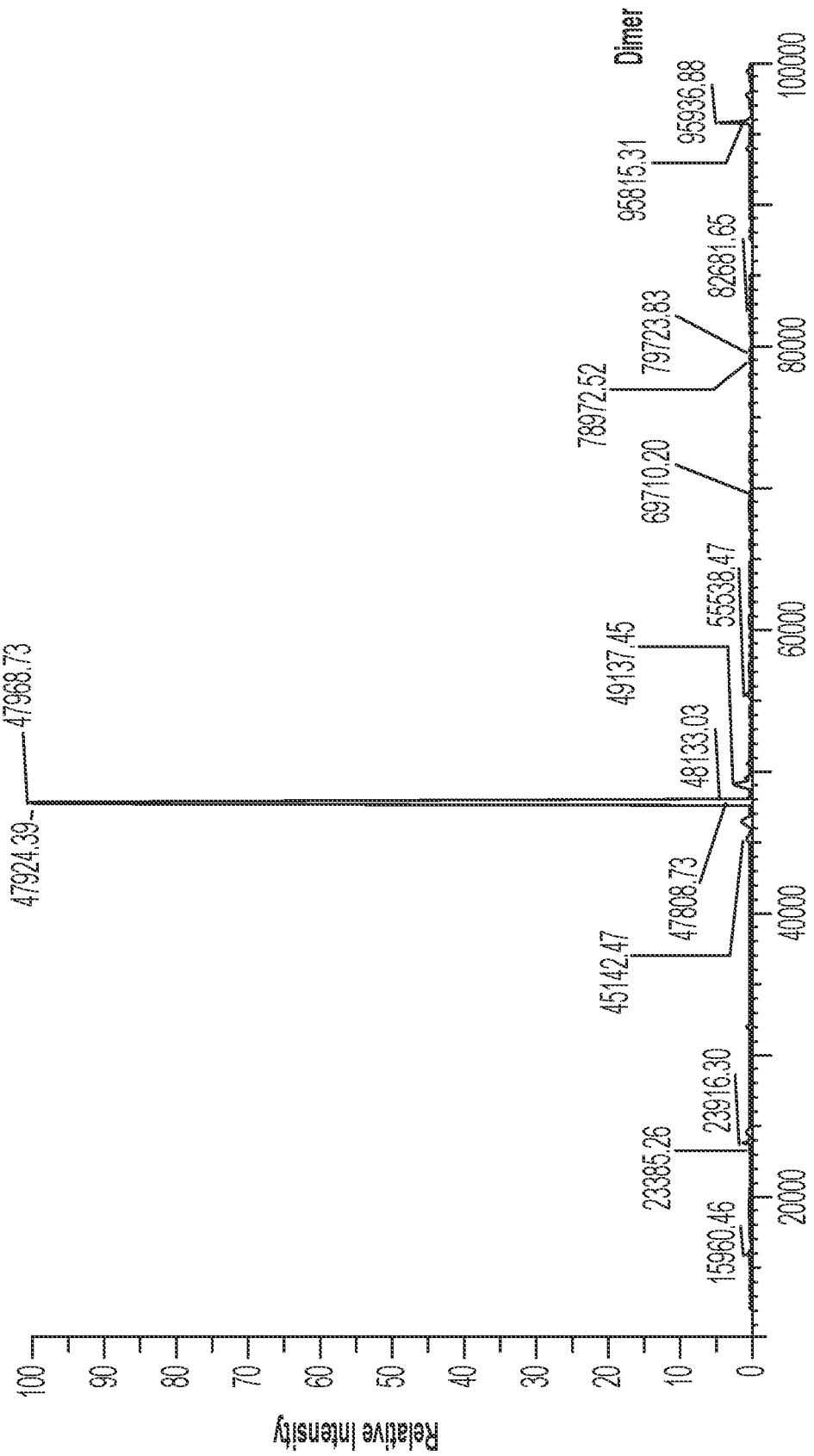

Relative Intensity
100
90
80
70
60
50
40
30
20
10
0
Mass
20000
40000
60000
80000
100000
15960.46
23385.26
23916.30
45142.47
47808.73
47924.39
47968.73
48133.03
49137.45
55538.47
69710.20
78972.52
79723.83
82681.65
95815.31
95936.88
Dimer

FIG. 1

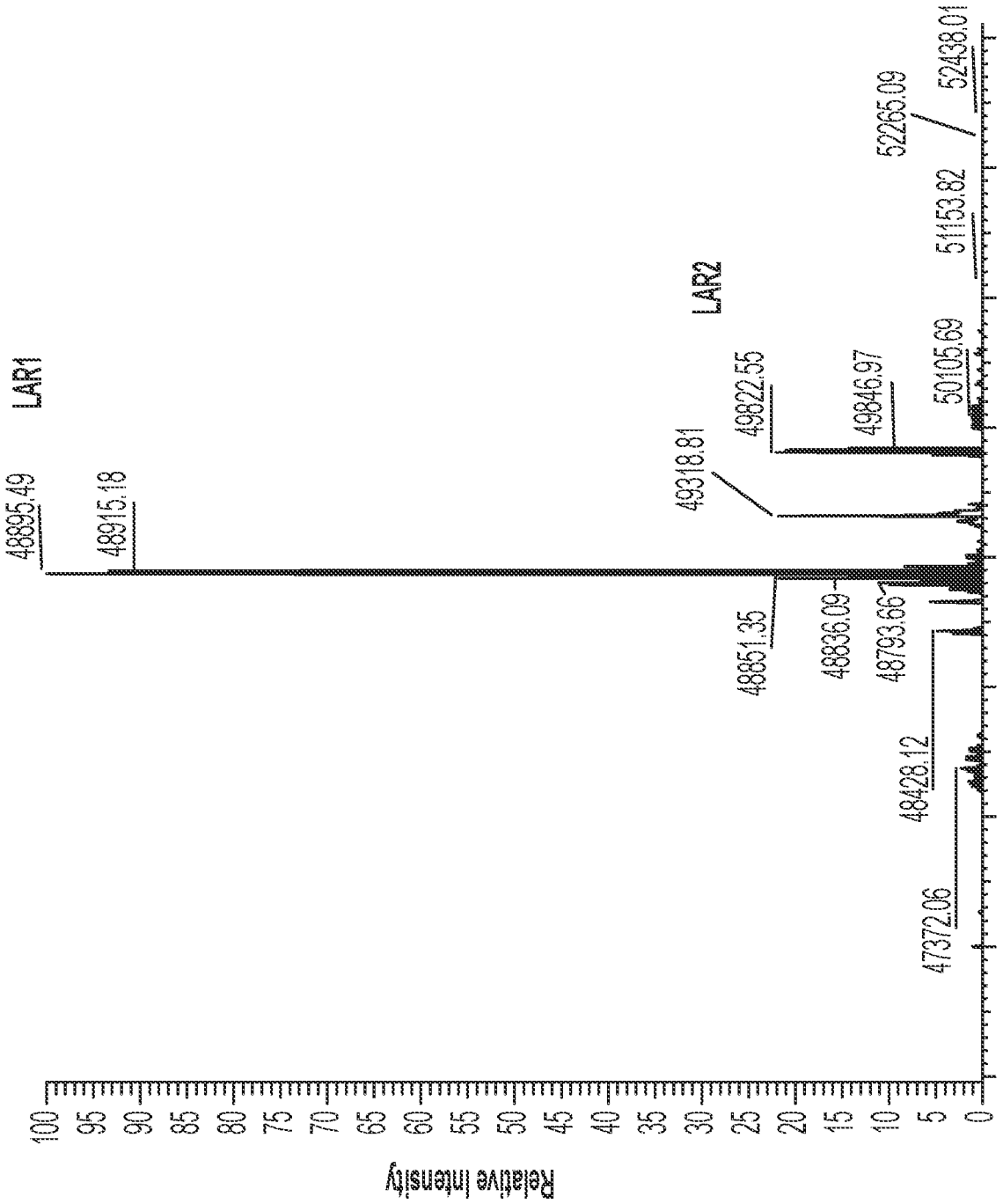

LAR1
LAR2
48895.49
48915.18
49318.81
49822.55
49846.97
50105.69
51153.82
52265.09
52438.01
48851.35
48836.09
48793.66
48428.12
47372.06
Relative Intensity
Mass
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
46000
48000
50000
52000

FIG. 2

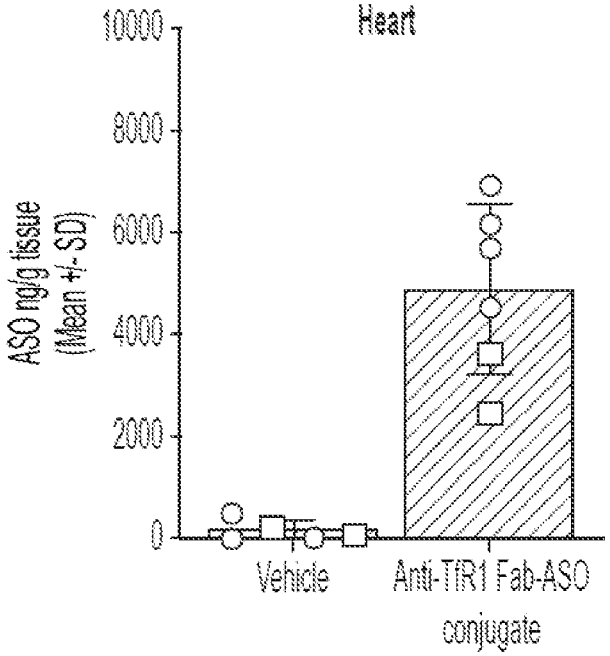


FIG. 3A

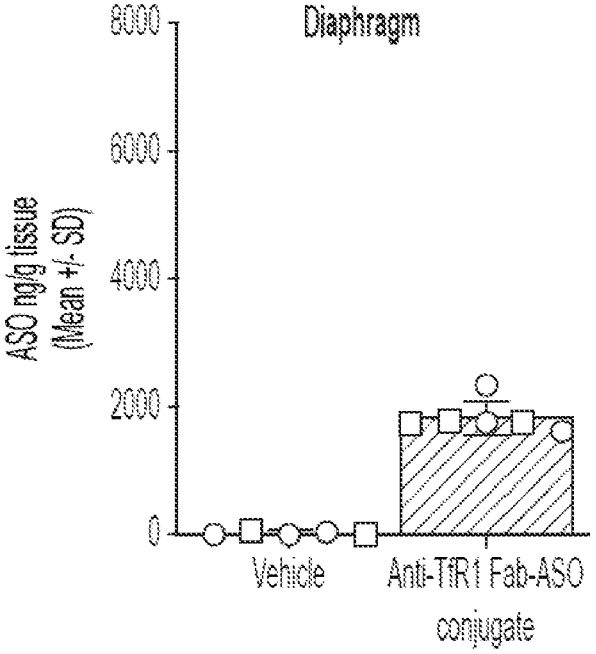


FIG. 3B

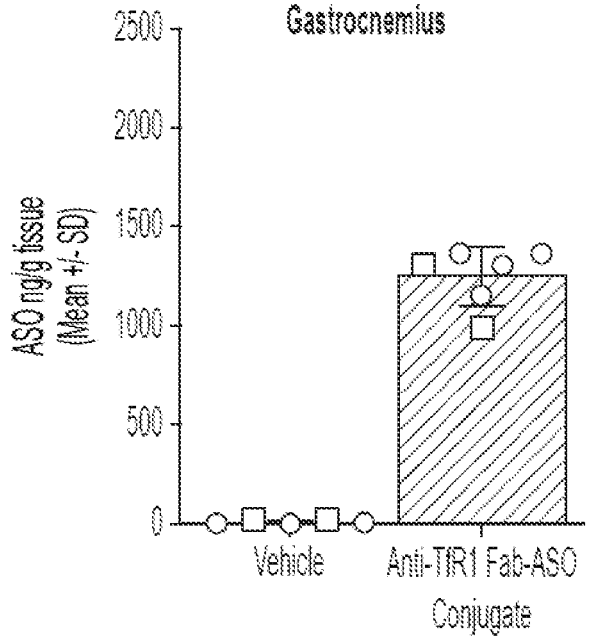


FIG. 3C

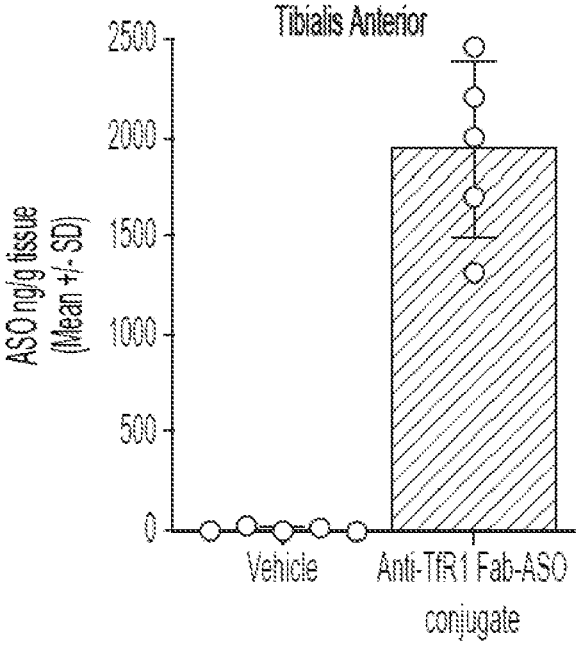


FIG. 3D

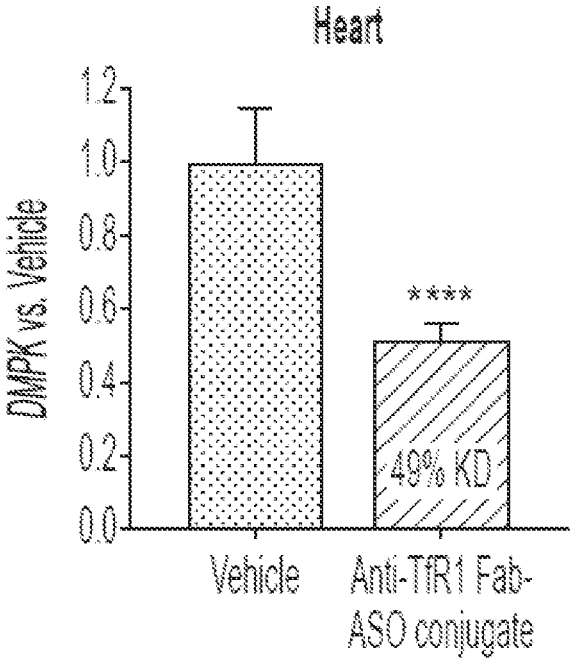


FIG. 4A

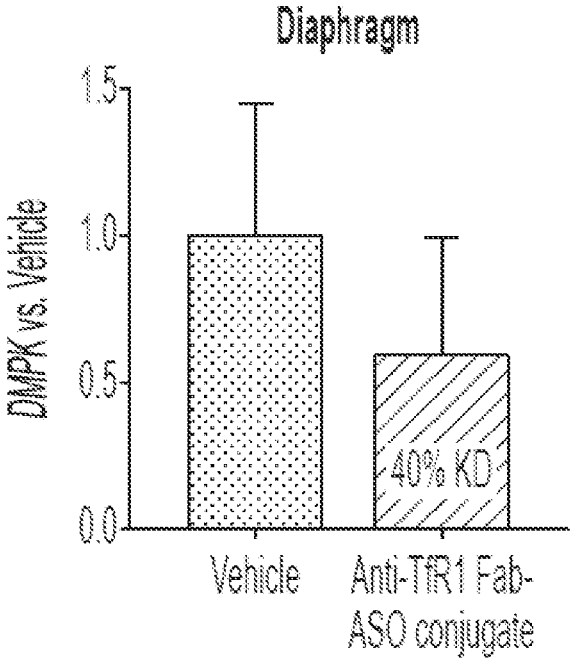


FIG. 4B

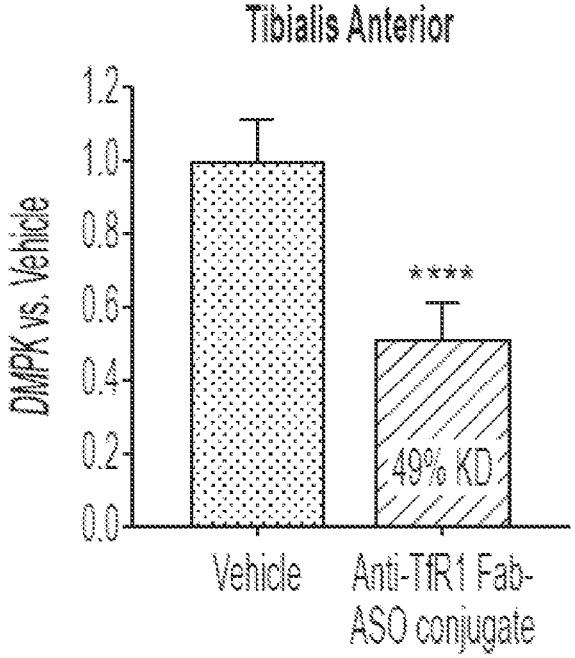


FIG. 4C

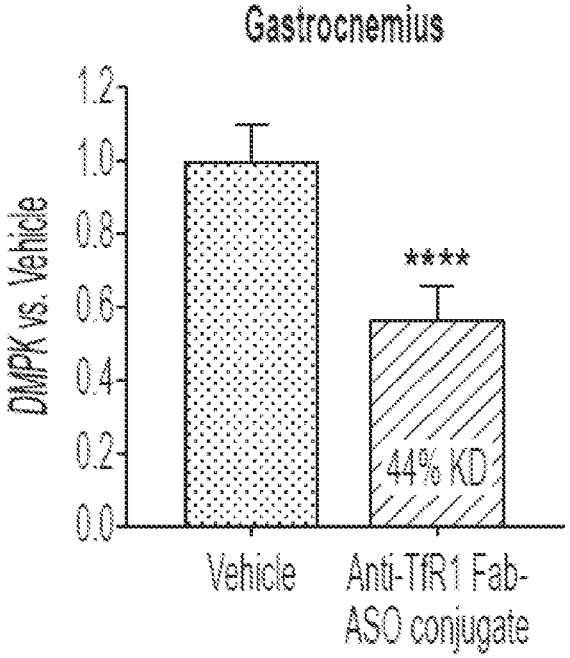


FIG. 4D

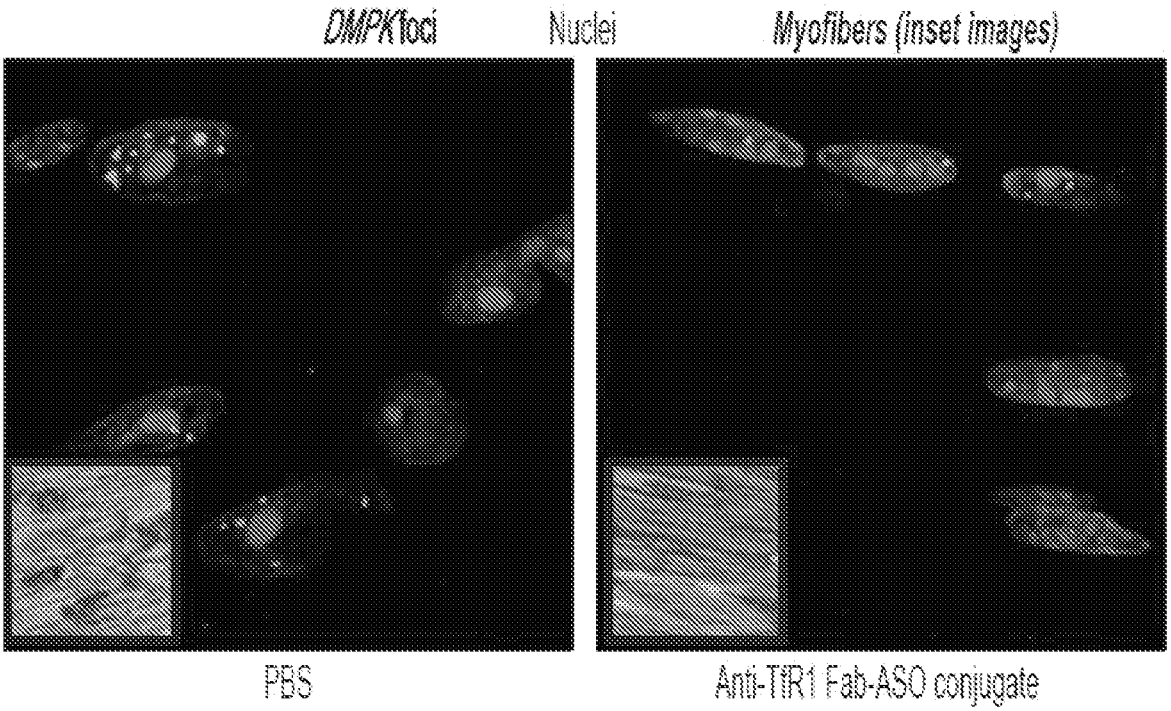

DMPK foci
Nuclei
Myofibers (inset images)
PBS
Anti-TfR1 Fab-ASO conjugate

FIG. 5A

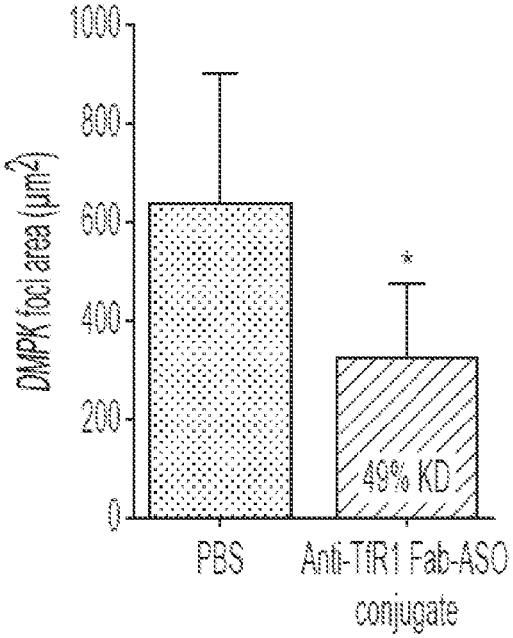

DMPK foci area (μm²)
1000
800
600
400
200
0
*
49% KD
PBS
Anti-TfR1 Fab-ASO conjugate

FIG. 5B

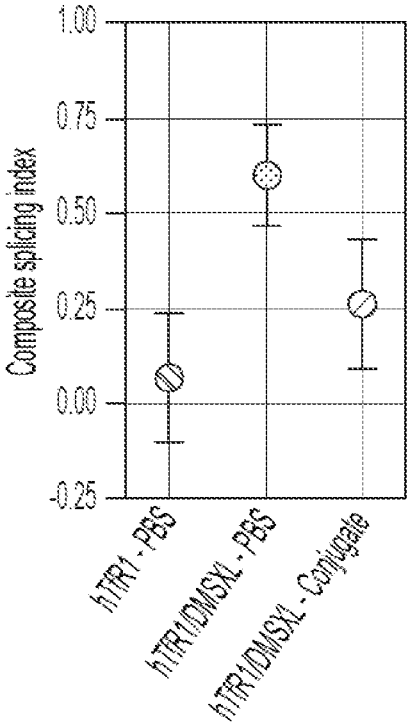


FIG. 6

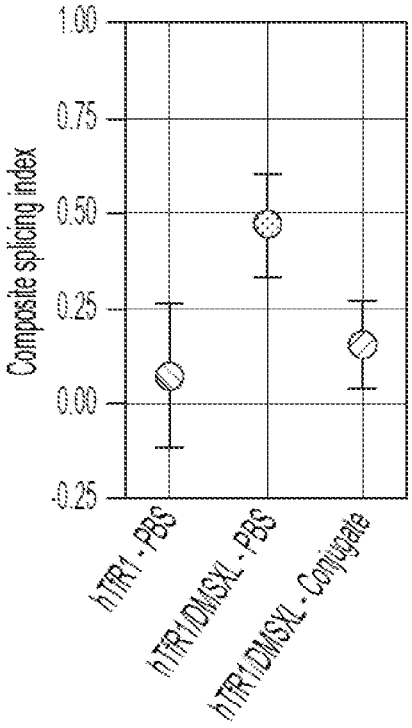


FIG. 7

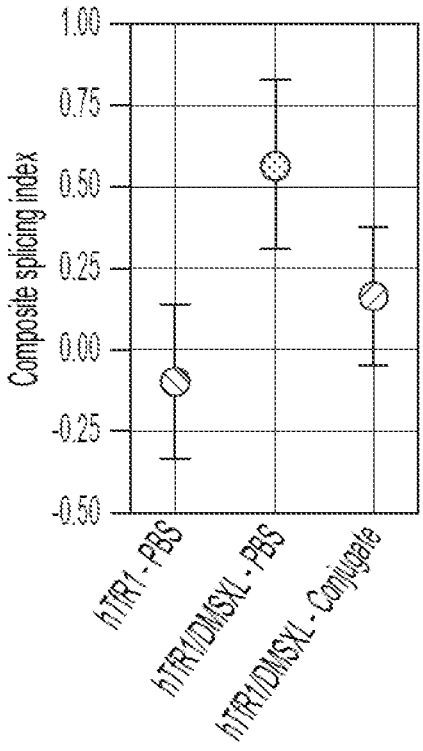


FIG. 8

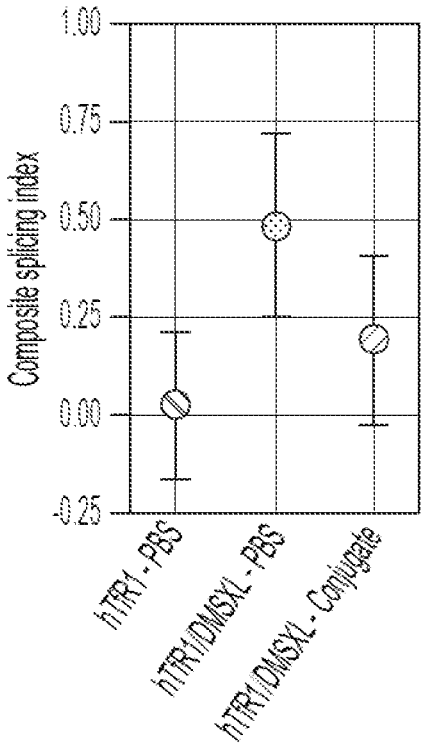


FIG. 9

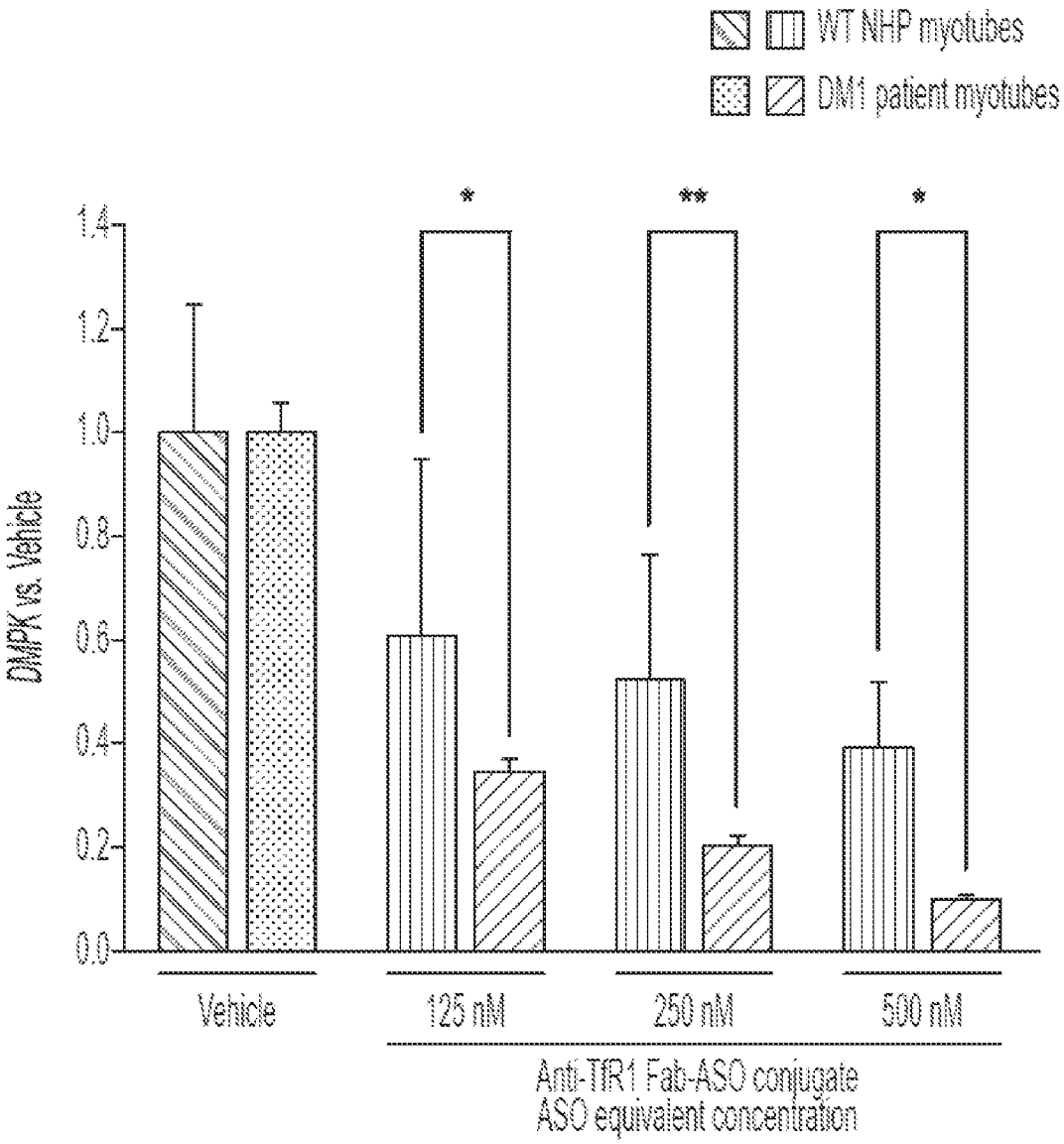

WT NHP myotubes
DM1 patient myotubes
DMPK vs. Vehicle
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
*
**
*
Vehicle
125 nM
250 nM
500 nM
Anti-TfR1 Fab-ASO conjugate
ASO equivalent concentration

FIG. 10

This XML file does not appear to have any style information associated with it. The document tree is shown below.


```
<ST26SequenceListing originalFreeTextLanguageCode="en" dtdVersion="V1_3" fileName="D082470075WO00-SEQ-COB.xml" softwareName="WIPO Sequence"
softwareVersion="2.2.0" productionDate="2023-03-22">
  <ApplicationIdentification>
    <IPOfficeCode>WO</IPOfficeCode>
    <ApplicationNumberText/>
    <FilingDate/>
  </ApplicationIdentification>
  <ApplicantFileReference>D0824.70075WO00</ApplicantFileReference>
  <EarliestPriorityApplicationIdentification>
    <IPOfficeCode>US</IPOfficeCode>
    <ApplicationNumberText>63/331,716</ApplicationNumberText>
    <FilingDate>2022-04-15</FilingDate>
  </EarliestPriorityApplicationIdentification>
  <ApplicantName languageCode="en">Dyne Therapeutics, Inc.</ApplicantName>
  <InventionTitle languageCode="en">MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR TREATING MYOTONIC DYSTROPHY</InventionTitle>
  <SequenceTotalQuantity>28</SequenceTotalQuantity>
  <SequenceData sequenceIDNumber="1">
    <INSDSeq>
      <INSDSeq_length>9</INSDSeq_length>
      <INSDSeq_moltype>AA</INSDSeq_moltype>
      <INSDSeq_division>PAT</INSDSeq_division>
      <INSDSeq_feature-table>
        <INSDFeature>
          <INSDFeature_key>REGION</INSDFeature_key>
          <INSDFeature_location>1..9</INSDFeature_location>
          <INSDFeature_quals>
            <INSDQualifier id="q1">
              <INSDQualifier_name>note</INSDQualifier_name>
              <INSDQualifier_value>Synthetic</INSDQualifier_value>
            </INSDQualifier>
          </INSDFeature_quals>
        </INSDFeature>
        <INSDFeature>
          <INSDFeature_key>source</INSDFeature_key>
          <INSDFeature_location>1..9</INSDFeature_location>
          <INSDFeature_quals>
            <INSDQualifier>
              <INSDQualifier_name>mol_type</INSDQualifier_name>
              <INSDQualifier_value>protein</INSDQualifier_value>
            </INSDQualifier>
            <INSDQualifier id="q2">
              <INSDQualifier_name>organism</INSDQualifier_name>
              <INSDQualifier_value>synthetic construct</INSDQualifier_value>
            </INSDQualifier>
          </INSDFeature_quals>
        </INSDFeature>
      </INSDSeq_feature-table>
      <INSDSeq_sequence>GYSITSGYY</INSDSeq_sequence>
    </INSDSeq>
  </SequenceData>
  <SequenceData sequenceIDNumber="2">
    <INSDSeq>
      <INSDSeq_length>7</INSDSeq_length>
      <INSDSeq_moltype>AA</INSDSeq_moltype>
      <INSDSeq_division>PAT</INSDSeq_division>
      <INSDSeq_feature-table>
        <INSDFeature>
          <INSDFeature_key>REGION</INSDFeature_key>
          <INSDFeature_location>1..7</INSDFeature_location>
          <INSDFeature_quals>
            <INSDQualifier id="q3">
              <INSDQualifier_name>note</INSDQualifier_name>
              <INSDQualifier_value>Synthetic</INSDQualifier_value>
            </INSDQualifier>
          </INSDFeature_quals>
        </INSDFeature>
        <INSDFeature>
          <INSDFeature_key>source</INSDFeature_key>
          <INSDFeature_location>1..7</INSDFeature_location>
          <INSDFeature_quals>
            <INSDQualifier>
              <INSDQualifier_name>mol_type</INSDQualifier_name>
              <INSDQualifier_value>protein</INSDQualifier_value>
            </INSDQualifier>
            <INSDQualifier id="q4">
              <INSDQualifier_name>organism</INSDQualifier_name>
              <INSDQualifier_value>synthetic construct</INSDQualifier_value>
            </INSDQualifier>
          </INSDFeature_quals>
        </INSDFeature>
      </INSDSeq_feature-table>
      <INSDSeq_sequence>ITFDGAN</INSDSeq_sequence>
    </INSDSeq>
  </SequenceData>
  <SequenceData sequenceIDNumber="3">
    <INSDSeq>
      <INSDSeq_length>12</INSDSeq_length>
      <INSDSeq_moltype>AA</INSDSeq_moltype>
      <INSDSeq_division>PAT</INSDSeq_division>
      <INSDSeq_feature-table>
        <INSDFeature>
          <INSDFeature_key>REGION</INSDFeature_key>
          <INSDFeature_location>1..12</INSDFeature_location>
          <INSDFeature_quals>
```

```
          <INSDQualifier id="q5">
            <INSDQualifier_name>note</INSDQualifier_name>
            <INSDQualifier_value>Synthetic</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
      <INSDFeature>
        <INSDFeature_key>source</INSDFeature_key>
        <INSDFeature_location>1..12</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier>
            <INSDQualifier_name>mol_type</INSDQualifier_name>
            <INSDQualifier_value>protein</INSDQualifier_value>
          </INSDQualifier>
          <INSDQualifier id="q6">
            <INSDQualifier_name>organism</INSDQualifier_name>
            <INSDQualifier_value>synthetic construct</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
    </INSDSeq_feature-table>
    <INSDSeq_sequence>TRSSYDYDVLDY</INSDSeq_sequence>
  </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="4">
  <INSDSeq>
    <INSDSeq_length>6</INSDSeq_length>
    <INSDSeq_moltype>AA</INSDSeq_moltype>
    <INSDSeq_division>PAT</INSDSeq_division>
    <INSDSeq_feature-table>
      <INSDFeature>
        <INSDFeature_key>REGION</INSDFeature_key>
        <INSDFeature_location>1..6</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier id="q7">
            <INSDQualifier_name>note</INSDQualifier_name>
            <INSDQualifier_value>Synthetic</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
      <INSDFeature>
        <INSDFeature_key>source</INSDFeature_key>
        <INSDFeature_location>1..6</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier>
            <INSDQualifier_name>mol_type</INSDQualifier_name>
            <INSDQualifier_value>protein</INSDQualifier_value>
          </INSDQualifier>
          <INSDQualifier id="q8">
            <INSDQualifier_name>organism</INSDQualifier_name>
            <INSDQualifier_value>synthetic construct</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
    </INSDSeq_feature-table>
    <INSDSeq_sequence>QDISNF</INSDSeq_sequence>
  </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="5">
  <INSDSeq>
    <INSDSeq_length/>
    <INSDSeq_moltype/>
    <INSDSeq_division/>
    <INSDSeq_sequence>000</INSDSeq_sequence>
  </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="6">
  <INSDSeq>
    <INSDSeq_length>9</INSDSeq_length>
    <INSDSeq_moltype>AA</INSDSeq_moltype>
    <INSDSeq_division>PAT</INSDSeq_division>
    <INSDSeq_feature-table>
      <INSDFeature>
        <INSDFeature_key>REGION</INSDFeature_key>
        <INSDFeature_location>1..9</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier id="q11">
            <INSDQualifier_name>note</INSDQualifier_name>
            <INSDQualifier_value>Synthetic</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
      <INSDFeature>
        <INSDFeature_key>source</INSDFeature_key>
        <INSDFeature_location>1..9</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier>
            <INSDQualifier_name>mol_type</INSDQualifier_name>
            <INSDQualifier_value>protein</INSDQualifier_value>
          </INSDQualifier>
          <INSDQualifier id="q12">
            <INSDQualifier_name>organism</INSDQualifier_name>
            <INSDQualifier_value>synthetic construct</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
    </INSDSeq_feature-table>
    <INSDSeq_sequence>QQGHTLPYT</INSDSeq_sequence>
```

```
  </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="7">
  <INSDSeq>
    <INSDSeq_length>6</INSDSeq_length>
    <INSDSeq_moltype>AA</INSDSeq_moltype>
    <INSDSeq_division>PAT</INSDSeq_division>
    <INSDSeq_feature-table>
      <INSDFeature>
        <INSDFeature_key>REGION</INSDFeature_key>
        <INSDFeature_location>1..6</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier id="q13">
            <INSDQualifier_name>note</INSDQualifier_name>
            <INSDQualifier_value>Synthetic</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
      <INSDFeature>
        <INSDFeature_key>source</INSDFeature_key>
        <INSDFeature_location>1..6</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier>
            <INSDQualifier_name>mol_type</INSDQualifier_name>
            <INSDQualifier_value>protein</INSDQualifier_value>
          </INSDQualifier>
          <INSDQualifier id="q14">
            <INSDQualifier_name>organism</INSDQualifier_name>
            <INSDQualifier_value>synthetic construct</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
    </INSDSeq_feature-table>
    <INSDSeq_sequence>SGYYWN</INSDSeq_sequence>
  </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="8">
  <INSDSeq>
    <INSDSeq_length>16</INSDSeq_length>
    <INSDSeq_moltype>AA</INSDSeq_moltype>
    <INSDSeq_division>PAT</INSDSeq_division>
    <INSDSeq_feature-table>
      <INSDFeature>
        <INSDFeature_key>REGION</INSDFeature_key>
        <INSDFeature_location>1..16</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier id="q15">
            <INSDQualifier_name>note</INSDQualifier_name>
            <INSDQualifier_value>Synthetic</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
      <INSDFeature>
        <INSDFeature_key>source</INSDFeature_key>
        <INSDFeature_location>1..16</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier>
            <INSDQualifier_name>mol_type</INSDQualifier_name>
            <INSDQualifier_value>protein</INSDQualifier_value>
          </INSDQualifier>
          <INSDQualifier id="q16">
            <INSDQualifier_name>organism</INSDQualifier_name>
            <INSDQualifier_value>synthetic construct</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
    </INSDSeq_feature-table>
    <INSDSeq_sequence>YITFDGANNYNPSLKN</INSDSeq_sequence>
  </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="9">
  <INSDSeq>
    <INSDSeq_length>10</INSDSeq_length>
    <INSDSeq_moltype>AA</INSDSeq_moltype>
    <INSDSeq_division>PAT</INSDSeq_division>
    <INSDSeq_feature-table>
      <INSDFeature>
        <INSDFeature_key>REGION</INSDFeature_key>
        <INSDFeature_location>1..10</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier id="q17">
            <INSDQualifier_name>note</INSDQualifier_name>
            <INSDQualifier_value>Synthetic</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
      <INSDFeature>
        <INSDFeature_key>source</INSDFeature_key>
        <INSDFeature_location>1..10</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier>
            <INSDQualifier_name>mol_type</INSDQualifier_name>
            <INSDQualifier_value>protein</INSDQualifier_value>
          </INSDQualifier>
          <INSDQualifier id="q18">
            <INSDQualifier_name>organism</INSDQualifier_name>
            <INSDQualifier_value>synthetic construct</INSDQualifier_value>
          </INSDQualifier>
```

```
      </INSDFeature_quals>
    </INSDFeature>
  </INSDSeq_feature-table>
  <INSDSeq_sequence>SSYDYDVLDY</INSDSeq_sequence>
 </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="10">
 <INSDSeq>
  <INSDSeq_length>11</INSDSeq_length>
  <INSDSeq_moltype>AA</INSDSeq_moltype>
  <INSDSeq_division>PAT</INSDSeq_division>
  <INSDSeq_feature-table>
    <INSDFeature>
      <INSDFeature_key>REGION</INSDFeature_key>
      <INSDFeature_location>1..11</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier id="q19">
          <INSDQualifier_name>note</INSDQualifier_name>
          <INSDQualifier_value>Synthetic</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
    <INSDFeature>
      <INSDFeature_key>source</INSDFeature_key>
      <INSDFeature_location>1..11</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier>
          <INSDQualifier_name>mol_type</INSDQualifier_name>
          <INSDQualifier_value>protein</INSDQualifier_value>
        </INSDQualifier>
        <INSDQualifier id="q20">
          <INSDQualifier_name>organism</INSDQualifier_name>
          <INSDQualifier_value>synthetic construct</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
  </INSDSeq_feature-table>
  <INSDSeq_sequence>RASQDISNFLN</INSDSeq_sequence>
 </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="11">
 <INSDSeq>
  <INSDSeq_length>7</INSDSeq_length>
  <INSDSeq_moltype>AA</INSDSeq_moltype>
  <INSDSeq_division>PAT</INSDSeq_division>
  <INSDSeq_feature-table>
    <INSDFeature>
      <INSDFeature_key>REGION</INSDFeature_key>
      <INSDFeature_location>1..7</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier id="q21">
          <INSDQualifier_name>note</INSDQualifier_name>
          <INSDQualifier_value>Synthetic</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
    <INSDFeature>
      <INSDFeature_key>source</INSDFeature_key>
      <INSDFeature_location>1..7</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier>
          <INSDQualifier_name>mol_type</INSDQualifier_name>
          <INSDQualifier_value>protein</INSDQualifier_value>
        </INSDQualifier>
        <INSDQualifier id="q22">
          <INSDQualifier_name>organism</INSDQualifier_name>
          <INSDQualifier_value>synthetic construct</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
  </INSDSeq_feature-table>
  <INSDSeq_sequence>YTSRLHS</INSDSeq_sequence>
 </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="12">
 <INSDSeq>
  <INSDSeq_length>8</INSDSeq_length>
  <INSDSeq_moltype>AA</INSDSeq_moltype>
  <INSDSeq_division>PAT</INSDSeq_division>
  <INSDSeq_feature-table>
    <INSDFeature>
      <INSDFeature_key>REGION</INSDFeature_key>
      <INSDFeature_location>1..8</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier id="q23">
          <INSDQualifier_name>note</INSDQualifier_name>
          <INSDQualifier_value>Synthetic</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
    <INSDFeature>
      <INSDFeature_key>source</INSDFeature_key>
      <INSDFeature_location>1..8</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier>
          <INSDQualifier_name>mol_type</INSDQualifier_name>
          <INSDQualifier_value>protein</INSDQualifier_value>
        </INSDQualifier>
```

```
        <INSDQualifier id="q24">
          <INSDQualifier_name>organism</INSDQualifier_name>
          <INSDQualifier_value>synthetic construct</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
  </INSDSeq_feature-table>
  <INSDSeq_sequence>GYSITSGY</INSDSeq_sequence>
 </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="13">
 <INSDSeq>
  <INSDSeq_length/>
  <INSDSeq_moltype/>
  <INSDSeq_division/>
  <INSDSeq_sequence>000</INSDSeq_sequence>
 </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="14">
 <INSDSeq>
  <INSDSeq_length>8</INSDSeq_length>
  <INSDSeq_moltype>AA</INSDSeq_moltype>
  <INSDSeq_division>PAT</INSDSeq_division>
  <INSDSeq_feature-table>
    <INSDFeature>
      <INSDFeature_key>REGION</INSDFeature_key>
      <INSDFeature_location>1..8</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier id="q27">
          <INSDQualifier_name>note</INSDQualifier_name>
          <INSDQualifier_value>Synthetic</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
    <INSDFeature>
      <INSDFeature_key>source</INSDFeature_key>
      <INSDFeature_location>1..8</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier>
          <INSDQualifier_name>mol_type</INSDQualifier_name>
          <INSDQualifier_value>protein</INSDQualifier_value>
        </INSDQualifier>
        <INSDQualifier id="q28">
          <INSDQualifier_name>organism</INSDQualifier_name>
          <INSDQualifier_value>synthetic construct</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
  </INSDSeq_feature-table>
  <INSDSeq_sequence>SYDYDVLD</INSDSeq_sequence>
 </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="15">
 <INSDSeq>
  <INSDSeq_length>7</INSDSeq_length>
  <INSDSeq_moltype>AA</INSDSeq_moltype>
  <INSDSeq_division>PAT</INSDSeq_division>
  <INSDSeq_feature-table>
    <INSDFeature>
      <INSDFeature_key>REGION</INSDFeature_key>
      <INSDFeature_location>1..7</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier id="q29">
          <INSDQualifier_name>note</INSDQualifier_name>
          <INSDQualifier_value>Synthetic</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
    <INSDFeature>
      <INSDFeature_key>source</INSDFeature_key>
      <INSDFeature_location>1..7</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier>
          <INSDQualifier_name>mol_type</INSDQualifier_name>
          <INSDQualifier_value>protein</INSDQualifier_value>
        </INSDQualifier>
        <INSDQualifier id="q30">
          <INSDQualifier_name>organism</INSDQualifier_name>
          <INSDQualifier_value>synthetic construct</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
  </INSDSeq_feature-table>
  <INSDSeq_sequence>SQDISNF</INSDSeq_sequence>
 </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="16">
 <INSDSeq>
  <INSDSeq_length>6</INSDSeq_length>
  <INSDSeq_moltype>AA</INSDSeq_moltype>
  <INSDSeq_division>PAT</INSDSeq_division>
  <INSDSeq_feature-table>
    <INSDFeature>
      <INSDFeature_key>REGION</INSDFeature_key>
      <INSDFeature_location>1..6</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier id="q31">
          <INSDQualifier_name>note</INSDQualifier_name>
```

```
          <INSDQualifier_value>Synthetic</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
    <INSDFeature>
      <INSDFeature_key>source</INSDFeature_key>
      <INSDFeature_location>1..6</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier>
          <INSDQualifier_name>mol_type</INSDQualifier_name>
          <INSDQualifier_value>protein</INSDQualifier_value>
        </INSDQualifier>
        <INSDQualifier id="q32">
          <INSDQualifier_name>organism</INSDQualifier_name>
          <INSDQualifier_value>synthetic construct</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
  </INSDSeq_feature-table>
  <INSDSeq_sequence>GHTLPY</INSDSeq_sequence>
 </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="17">
 <INSDSeq>
  <INSDSeq_length>119</INSDSeq_length>
  <INSDSeq_moltype>AA</INSDSeq_moltype>
  <INSDSeq_division>PAT</INSDSeq_division>
  <INSDSeq_feature-table>
    <INSDFeature>
      <INSDFeature_key>REGION</INSDFeature_key>
      <INSDFeature_location>1..119</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier id="q33">
          <INSDQualifier_name>note</INSDQualifier_name>
          <INSDQualifier_value>Synthetic</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
    <INSDFeature>
      <INSDFeature_key>source</INSDFeature_key>
      <INSDFeature_location>1..119</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier>
          <INSDQualifier_name>mol_type</INSDQualifier_name>
          <INSDQualifier_value>protein</INSDQualifier_value>
        </INSDQualifier>
        <INSDQualifier id="q34">
          <INSDQualifier_name>organism</INSDQualifier_name>
          <INSDQualifier_value>synthetic construct</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
  </INSDSeq_feature-table>
  <INSDSeq_sequence>QVQLQESGPGLVKPSQTLSLTCTVTGYSITSGYYWNWIRQPPGKGLEWIGYITFDGANNYNPSLKNRVSISRDTSKNQFSLKLSSVTAEDTATYYCTRSSYDYDVLDYWGQGTTVTVSS</INSDSeq_
 </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="18">
 <INSDSeq>
  <INSDSeq_length>107</INSDSeq_length>
  <INSDSeq_moltype>AA</INSDSeq_moltype>
  <INSDSeq_division>PAT</INSDSeq_division>
  <INSDSeq_feature-table>
    <INSDFeature>
      <INSDFeature_key>REGION</INSDFeature_key>
      <INSDFeature_location>1..107</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier id="q35">
          <INSDQualifier_name>note</INSDQualifier_name>
          <INSDQualifier_value>Synthetic</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
    <INSDFeature>
      <INSDFeature_key>source</INSDFeature_key>
      <INSDFeature_location>1..107</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier>
          <INSDQualifier_name>mol_type</INSDQualifier_name>
          <INSDQualifier_value>protein</INSDQualifier_value>
        </INSDQualifier>
        <INSDQualifier id="q36">
          <INSDQualifier_name>organism</INSDQualifier_name>
          <INSDQualifier_value>synthetic construct</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
  </INSDSeq_feature-table>
  <INSDSeq_sequence>DIQMTQSPSSLSASVGDRVTITCRASQDISNFLNWYQQKPGQPVKLLIYYTSRLHSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGHTLPYTFGQGTKLEIK</INSDSeq_sequence>
 </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="19">
 <INSDSeq>
  <INSDSeq_length>227</INSDSeq_length>
  <INSDSeq_moltype>AA</INSDSeq_moltype>
  <INSDSeq_division>PAT</INSDSeq_division>
  <INSDSeq_feature-table>
    <INSDFeature>
      <INSDFeature_key>REGION</INSDFeature_key>
```

```
      <INSDFeature_location>1..227</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier id="q37">
          <INSDQualifier_name>note</INSDQualifier_name>
          <INSDQualifier_value>Synthetic</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
    <INSDFeature>
      <INSDFeature_key>source</INSDFeature_key>
      <INSDFeature_location>1..227</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier>
          <INSDQualifier_name>mol_type</INSDQualifier_name>
          <INSDQualifier_value>protein</INSDQualifier_value>
        </INSDQualifier>
        <INSDQualifier id="q38">
          <INSDQualifier_name>organism</INSDQualifier_name>
          <INSDQualifier_value>synthetic construct</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
  </INSDSeq_feature-table>
  <INSDSeq_sequence>QVQLQESGPGLVKPSQTLSLTCTVTGYSITSGYYWNWIRQPPGKGLEWIGYITFDGANNYNPSLKNRVSISRDTSKNQFSLKLSSVTAEDTATYYCTRSSYDYDVLDYWGQGTTVTVSSASTKGPSVFP
 </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="20">
 <INSDSeq>
  <INSDSeq_length>214</INSDSeq_length>
  <INSDSeq_moltype>AA</INSDSeq_moltype>
  <INSDSeq_division>PAT</INSDSeq_division>
  <INSDSeq_feature-table>
    <INSDFeature>
      <INSDFeature_key>REGION</INSDFeature_key>
      <INSDFeature_location>1..214</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier id="q39">
          <INSDQualifier_name>note</INSDQualifier_name>
          <INSDQualifier_value>Synthetic</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
    <INSDFeature>
      <INSDFeature_key>source</INSDFeature_key>
      <INSDFeature_location>1..214</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier>
          <INSDQualifier_name>mol_type</INSDQualifier_name>
          <INSDQualifier_value>protein</INSDQualifier_value>
        </INSDQualifier>
        <INSDQualifier id="q40">
          <INSDQualifier_name>organism</INSDQualifier_name>
          <INSDQualifier_value>synthetic construct</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
  </INSDSeq_feature-table>
  <INSDSeq_sequence>DIQMTQSPSSLSASVGDRVTITCRASQDISNFLNWYQQKPGQPVKLLIYYTSRLHSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGHTLPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGT
 </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="21">
 <INSDSeq>
  <INSDSeq_length>16</INSDSeq_length>
  <INSDSeq_moltype>RNA</INSDSeq_moltype>
  <INSDSeq_division>PAT</INSDSeq_division>
  <INSDSeq_feature-table>
    <INSDFeature>
      <INSDFeature_key>misc_feature</INSDFeature_key>
      <INSDFeature_location>1..16</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier id="q41">
          <INSDQualifier_name>note</INSDQualifier_name>
          <INSDQualifier_value>Synthetic</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
    <INSDFeature>
      <INSDFeature_key>source</INSDFeature_key>
      <INSDFeature_location>1..16</INSDFeature_location>
      <INSDFeature_quals>
        <INSDQualifier>
          <INSDQualifier_name>mol_type</INSDQualifier_name>
          <INSDQualifier_value>other RNA</INSDQualifier_value>
        </INSDQualifier>
        <INSDQualifier id="q42">
          <INSDQualifier_name>organism</INSDQualifier_name>
          <INSDQualifier_value>synthetic construct</INSDQualifier_value>
        </INSDQualifier>
      </INSDFeature_quals>
    </INSDFeature>
  </INSDSeq_feature-table>
  <INSDSeq_sequence>cagcgcccaccagtca</INSDSeq_sequence>
 </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="22">
 <INSDSeq>
  <INSDSeq_length>16</INSDSeq_length>
  <INSDSeq_moltype>DNA</INSDSeq_moltype>
```

```
    <INSDSeq_division>PAT</INSDSeq_division>
    <INSDSeq_feature-table>
      <INSDFeature>
        <INSDFeature_key>misc_feature</INSDFeature_key>
        <INSDFeature_location>1..16</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier id="q43">
            <INSDQualifier_name>note</INSDQualifier_name>
            <INSDQualifier_value>Synthetic</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
      <INSDFeature>
        <INSDFeature_key>source</INSDFeature_key>
        <INSDFeature_location>1..16</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier>
            <INSDQualifier_name>mol_type</INSDQualifier_name>
            <INSDQualifier_value>other DNA</INSDQualifier_value>
          </INSDQualifier>
          <INSDQualifier id="q44">
            <INSDQualifier_name>organism</INSDQualifier_name>
            <INSDQualifier_value>synthetic construct</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
    </INSDSeq_feature-table>
    <INSDSeq_sequence>tgactggtgggcgctg</INSDSeq_sequence>
  </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="23">
  <INSDSeq>
    <INSDSeq_length>760</INSDSeq_length>
    <INSDSeq_moltype>AA</INSDSeq_moltype>
    <INSDSeq_division>PAT</INSDSeq_division>
    <INSDSeq_feature-table>
      <INSDFeature>
        <INSDFeature_key>source</INSDFeature_key>
        <INSDFeature_location>1..760</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier>
            <INSDQualifier_name>mol_type</INSDQualifier_name>
            <INSDQualifier_value>protein</INSDQualifier_value>
          </INSDQualifier>
          <INSDQualifier id="q45">
            <INSDQualifier_name>organism</INSDQualifier_name>
            <INSDQualifier_value>Homo sapiens</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
    </INSDSeq_feature-table>
    <INSDSeq_sequence>MMDQARSAFSNLFGGEPLSYTRFSLARQVDGDNSHVEMKLAVDEEENADNNTKANVTKPKRCSGSICYGTIAVIVFFLIGFMIGYLGYCKGVEPKTECERLAGTESPVREEPGEDFPAARRLYWDDLKRI
  </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="24">
  <INSDSeq>
    <INSDSeq_length>2859</INSDSeq_length>
    <INSDSeq_moltype>DNA</INSDSeq_moltype>
    <INSDSeq_division>PAT</INSDSeq_division>
    <INSDSeq_feature-table>
      <INSDFeature>
        <INSDFeature_key>source</INSDFeature_key>
        <INSDFeature_location>1..2859</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier>
            <INSDQualifier_name>mol_type</INSDQualifier_name>
            <INSDQualifier_value>genomic DNA</INSDQualifier_value>
          </INSDQualifier>
          <INSDQualifier id="q53">
            <INSDQualifier_name>organism</INSDQualifier_name>
            <INSDQualifier_value>Homo sapiens</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
    </INSDSeq_feature-table>
    <INSDSeq_sequence>agggggggctggaccaaggggtggggagaaggggaggaggcctcggccggccgcagagagaagtggccagagaggcccaggggacagccagggacaggcagacatgcagccagggctccagggcctggaca
  </INSDSeq>
</SequenceData>
<SequenceData sequenceIDNumber="25">
  <INSDSeq>
    <INSDSeq_length>2683</INSDSeq_length>
    <INSDSeq_moltype>DNA</INSDSeq_moltype>
    <INSDSeq_division>PAT</INSDSeq_division>
    <INSDSeq_feature-table>
      <INSDFeature>
        <INSDFeature_key>source</INSDFeature_key>
        <INSDFeature_location>1..2683</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier>
            <INSDQualifier_name>mol_type</INSDQualifier_name>
            <INSDQualifier_value>genomic DNA</INSDQualifier_value>
          </INSDQualifier>
          <INSDQualifier id="q54">
            <INSDQualifier_name>organism</INSDQualifier_name>
            <INSDQualifier_value>Mus musculus</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
```

```
    </INSDSeq_feature-table>
    <INSDSeq_sequence>gaactggccagagagacccaagggatagtcagggacgggcagacatgcagctagggttctggggcctggacaggggcagccaggccctgtgacgggaagaccccgagctccggcccggggaggggccat
  </INSDSeq>
 </SequenceData>
 <SequenceData sequenceIDNumber="26">
  <INSDSeq>
    <INSDSeq_length>19841</INSDSeq_length>
    <INSDSeq_moltype>DNA</INSDSeq_moltype>
    <INSDSeq_division>PAT</INSDSeq_division>
    <INSDSeq_feature-table>
      <INSDFeature>
        <INSDFeature_key>source</INSDFeature_key>
        <INSDFeature_location>1..19841</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier>
            <INSDQualifier_name>mol_type</INSDQualifier_name>
            <INSDQualifier_value>genomic DNA</INSDQualifier_value>
          </INSDQualifier>
          <INSDQualifier id="q55">
            <INSDQualifier_name>organism</INSDQualifier_name>
            <INSDQualifier_value>Homo sapiens</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
    </INSDSeq_feature-table>
    <INSDSeq_sequence>tttcctacttgaagcctgacgtagtaaagatcgggggagggttagacagatacagtggtccccaaccattttggcaccagggactggtcttatggaagacagtttttccacagactgttgggggatgg
  </INSDSeq>
 </SequenceData>
 <SequenceData sequenceIDNumber="27">
  <INSDSeq>
    <INSDSeq_length>9</INSDSeq_length>
    <INSDSeq_moltype>AA</INSDSeq_moltype>
    <INSDSeq_division>PAT</INSDSeq_division>
    <INSDSeq_feature-table>
      <INSDFeature>
        <INSDFeature_key>REGION</INSDFeature_key>
        <INSDFeature_location>1..9</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier id="q49">
            <INSDQualifier_name>note</INSDQualifier_name>
            <INSDQualifier_value>Synthetic</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
      <INSDFeature>
        <INSDFeature_key>source</INSDFeature_key>
        <INSDFeature_location>1..9</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier>
            <INSDQualifier_name>mol_type</INSDQualifier_name>
            <INSDQualifier_value>protein</INSDQualifier_value>
          </INSDQualifier>
          <INSDQualifier id="q50">
            <INSDQualifier_name>organism</INSDQualifier_name>
            <INSDQualifier_value>synthetic construct</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
    </INSDSeq_feature-table>
    <INSDSeq_sequence>DYEKHKVYA</INSDSeq_sequence>
  </INSDSeq>
 </SequenceData>
 <SequenceData sequenceIDNumber="28">
  <INSDSeq>
    <INSDSeq_length>7</INSDSeq_length>
    <INSDSeq_moltype>AA</INSDSeq_moltype>
    <INSDSeq_division>PAT</INSDSeq_division>
    <INSDSeq_feature-table>
      <INSDFeature>
        <INSDFeature_key>REGION</INSDFeature_key>
        <INSDFeature_location>1..7</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier id="q51">
            <INSDQualifier_name>note</INSDQualifier_name>
            <INSDQualifier_value>Synthetic</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
      <INSDFeature>
        <INSDFeature_key>source</INSDFeature_key>
        <INSDFeature_location>1..7</INSDFeature_location>
        <INSDFeature_quals>
          <INSDQualifier>
            <INSDQualifier_name>mol_type</INSDQualifier_name>
            <INSDQualifier_value>protein</INSDQualifier_value>
          </INSDQualifier>
          <INSDQualifier id="q52">
            <INSDQualifier_name>organism</INSDQualifier_name>
            <INSDQualifier_value>synthetic construct</INSDQualifier_value>
          </INSDQualifier>
        </INSDFeature_quals>
      </INSDFeature>
    </INSDSeq_feature-table>
    <INSDSeq_sequence>VNHKPSN</INSDSeq_sequence>
  </INSDSeq>
 </SequenceData>
</ST26SequenceListing>
```