



(12) **DEMANDE DE BREVET CANADIEN**
CANADIAN PATENT APPLICATION

(13) **A1**

(86) **Date de dépôt PCT/PCT Filing Date:** 2022/07/01
(87) **Date publication PCT/PCT Publication Date:** 2023/01/12
(85) **Entrée phase nationale/National Entry:** 2024/01/09
(86) **N° demande PCT/PCT Application No.:** US 2022/073362
(87) **N° publication PCT/PCT Publication No.:** 2023/283531
(30) **Priorités/Priorities:** 2021/07/09 (US63/220,039);
2021/07/09 (US63/220,050); 2021/07/09 (US63/220,071);
2021/07/09 (US63/220,085); 2021/07/09 (US63/220,056)

(51) **Cl.Int./Int.Cl.** **C07K 16/40** (2006.01),
A61K 47/68 (2017.01), **A61P 21/00** (2006.01),
C07K 14/435 (2006.01), **C07K 16/18** (2006.01),
C07K 16/28 (2006.01), **C12N 15/113** (2010.01)

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(54) **Titre : COMPLEXES DE CIBLAGE MUSCULAIRE ET LEURS UTILISATIONS POUR LA MODULATION DE GENES ASSOCIES A LA SANTE MUSCULAIRE**

(54) **Title: MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR MODULATION OF GENES ASSOCIATED WITH MUSCLE HEALTH**

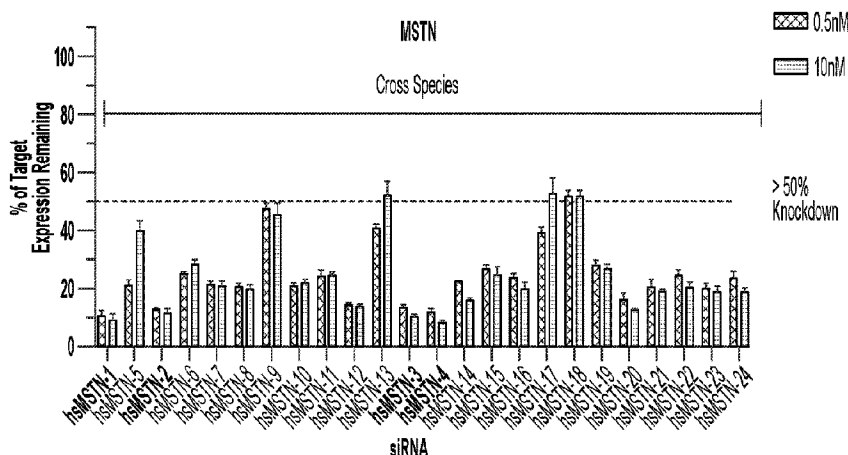


FIG. 5

(57) **Abrégé/Abstract:**

Aspects of the disclosure relate to molecular payloads that modulate the expression or activity of genes involved in muscle growth and maintenance (e.g., MSTN, INHBA, ACVR1B, MLCK1, ACVR1, FBXO32, TRIM63, MEF2D, KLF15, MED1, MED13, and/or PPP1R3A), and complexes comprising a muscle-targeting agent covalently linked to such molecular payloads. In some embodiments, the muscle-targeting agent specifically binds to an internalizing cell surface receptor on a muscle cell (e.g., a cardiac muscle cell, a smooth muscle cell, a skeletal muscle cell). In some embodiments, the molecular payload is an oligonucleotide, such as an antisense oligonucleotide or RNAi oligonucleotide.



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

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

12 January 2023 (12.01.2023)



(10) International Publication Number

WO 2023/283531 A3

(51) International Patent Classification:

A61K 39/395 (2006.01) A61P 21/00 (2006.01)
 A61K 47/68 (2017.01) C07K 14/435 (2006.01)
 C07K 16/28 (2006.01) C07K 16/18 (2006.01)
 C12N 15/113 (2010.01)

(21) International Application Number:

PCT/US2022/073362

(22) International Filing Date:

01 July 2022 (01.07.2022)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/220,039	09 July 2021 (09.07.2021)	US
63/220,050	09 July 2021 (09.07.2021)	US
63/220,071	09 July 2021 (09.07.2021)	US
63/220,085	09 July 2021 (09.07.2021)	US
63/220,056	09 July 2021 (09.07.2021)	US

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(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, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO,

(54) Title: MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR MODULATION OF GENES ASSOCIATED WITH MUSCLE HEALTH

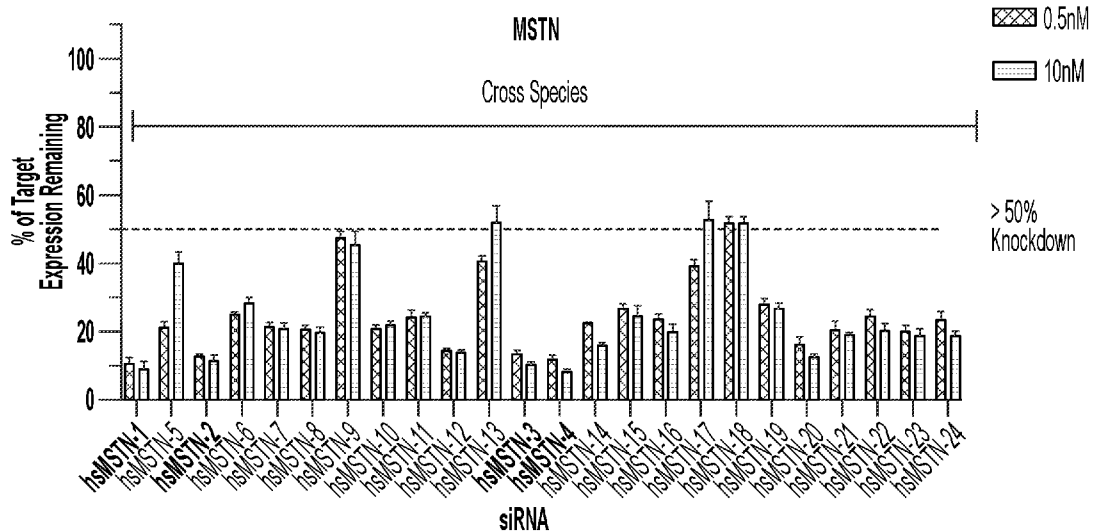


FIG. 5

(57) Abstract: Aspects of the disclosure relate to molecular payloads that modulate the expression or activity of genes involved in muscle growth and maintenance (e.g., MSTN, INHBA, ACVR1B, MLCK1, ACVR1, FBXO32, TRIM63, MEF2D, KLF15, MED1, MED13, and/or PPP1R3A), and complexes comprising a muscle-targeting agent covalently linked to such molecular payloads. In some embodiments, the muscle-targeting agent specifically binds to an internalizing cell surface receptor on a muscle cell (e.g., a cardiac muscle cell, a smooth muscle cell, a skeletal muscle cell). In some embodiments, the molecular payload is an oligonucleotide, such as an antisense oligonucleotide or RNAi oligonucleotide.

[Continued on next page]

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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, ME, MG, MK, MN, 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, GH, GM, KE, LR, LS, MW, MZ, NA, RW, 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, 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))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
- with sequence listing part of description (Rule 5.2(a))

(88) Date of publication of the international search report:

16 March 2023 (16.03.2023)

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR MODULATION OF GENES ASSOCIATED WITH MUSCLE HEALTH

RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 63/220,050, entitled “MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR MODULATION OF GENES ASSOCIATED WITH MUSCLE HEALTH”, filed on July 9, 2021; U.S. Provisional Application No. 63/220,039, entitled “MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR MODULATION OF MLCK1”, filed on July 9, 2021; U.S. Provisional Application No. 63/220,056, entitled “MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR MODULATION OF ACVR1”, filed on July 9, 2021; U.S. Provisional Application No. 63/220,071, entitled “MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR MODULATION OF GENES ASSOCIATED WITH MUSCLE ATROPHY”, filed on July 9, 2021; and U.S. Provisional Application No. 63/220,085, entitled “MUSCLE TARGETING COMPLEXES AND USES THEREOF FOR MODULATION OF GENES ASSOCIATED WITH CARDIAC MUSCLE DISEASE”, filed on July 9, 2021 the contents of each of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present application relates to molecular payloads (e.g., oligonucleotides) that modulate the expression or activity of genes (e.g., MSTN, INHBA, ACVR1B, MLCK1, ACVR1, FBXO32, TRIM63, MEF2D, KLF15, MED1, MED13, or PPP1R3A) associated with muscle health (e.g., muscle growth and maintenance) and targeting complexes for delivering such molecular payloads (e.g., oligonucleotides) to cells (e.g., cardiac, smooth, and/or skeletal muscle 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 (D082470057WO00-SEQ-ZJG.xml; Size: 2,799,490 bytes; and Date of Creation: July 1, 2022) is herein incorporated by reference in its entirety.

BACKGROUND

[0004] The expression and/or activity of several genes, including myostatin (MSTN), inhibin beta A (INHBA), activin receptor type-1B (ACVR1B), myosin light chain kinase (MLCK1), activin A receptor type-1 (ACVR1), atrogin-1 (FBXO32), tripartite motif containing 63 (TRIM63), myocyte-specific enhancer factor 2D (MEF2D), Krüppel-like factor 15 (KLF15), Mediator complex subunit 1 (MED1), Mediator complex subunit 13 (MED13), and protein phosphatase 1 regulatory subunit 3A (PPP1R3A), have been implicated in various aspects of muscle health. Aberrant expression of one or more of these genes, or expression of a mutated form thereof, may be involved in various muscle disorders, including cardiac and skeletal muscle disorders such as cardiac fibrosis, cardiac muscle atrophy, and skeletal muscle atrophy, among others.

SUMMARY

[0005] According to some aspects, the disclosure provides molecular payloads (e.g., oligonucleotides) that modulate the expression or activity of genes (e.g., MSTN, INHBA, ACVR1B, MLCK1, ACVR1, FBXO32, TRIM63, MEF2D, KLF15, MED1, MED13, or PPP1R3A) associated with muscle health (e.g., muscle growth and maintenance) and complexes that target muscle cells (e.g., cardiac and/or skeletal muscle cells) for the purposes of delivering molecular payloads to those cells. In some embodiments, complexes provided herein are designed to target cardiac muscle cells. In some embodiments, complexes provided herein are designed to target skeletal muscle cells. In some embodiments, complexes provided herein are particularly useful for delivering molecular payloads that modulate (e.g., reduce) the expression (e.g., protein and/or RNA level) or activity of genes involved in muscle health, such as muscle growth and maintenance. Such genes include, but are not limited to: MSTN, INHBA, ACVR1B, MLCK1, ACVR1, FBXO32, TRIM63, MEF2D, KLF15, MED1, MED13, and PPP1R3A. In some embodiments, the disclosure provides complexes that target muscle cells for the purposes of delivering molecular payloads that modulate the expression of one or more MSTN, INHBA, ACVR1B, MLCK1, ACVR1, FBXO32, TRIM63, MEF2D, KLF15, MED1, MED13, and PPP1R3A.

[0006] Some aspects of the present disclosure provide complexes comprising an anti-transferrin receptor 1 antibody covalently linked to a molecular payload that modulates the expression or activity of myostatin (MSTN), inhibin beta A (INHBA), activin receptor type-1B (ACVR1B), myosin light chain kinase (MLCK1), activin A receptor type-1 (ACVR1), atrogin-1 (FBXO32), tripartite motif containing 63 (TRIM63), myocyte-specific enhancer factor 2D (MEF2D),

Krüppel-like factor 15 (KLF15), Mediator complex subunit 1 (MED1), Mediator complex subunit 13 (MED13), and/or protein phosphatase 1 regulatory subunit 3A (PPP1R3A) wherein the antibody comprises:

- (i) a heavy chain variable region (VH) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 76; and/or a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 75;
- (ii) a heavy chain variable region (VH) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 71; and/or a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 70;
- (iii) a heavy chain variable region (VH) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 72; and/or a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 70;
- (iv) a heavy chain variable region (VH) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 73; and/or a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 74;
- (v) a heavy chain variable region (VH) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 73; and/or a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 75;
- (vi) a heavy chain variable region (VH) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 76; and/or a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 74;
- (vii) a heavy chain variable region (VH) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 69; and/or a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 70;
- (viii) a heavy chain variable region (VH) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 77; and/or a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 78;
- (ix) a heavy chain variable region (VH) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 79; and/or a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 80; or
- (x) a heavy chain variable region (VH) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 77; and/or a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 80.

[0007] In some embodiments, the antibody comprises:

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

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

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

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

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

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

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

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

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

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

[0008] In some embodiments, the antibody is selected from the group consisting of a full-length IgG, a Fab fragment, a Fab' fragment, a F(ab')₂ fragment, a scFv, and a Fv. In some embodiments, the antibody is a full-length IgG. In some embodiments, the full-length IgG comprises a heavy chain constant region of the isotype IgG1, IgG2, IgG3, or IgG4.

[0009] In some embodiments, the antibody comprises:

(i) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 91; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 90;

(ii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 86; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 85;

(iii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 87; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 85;

(iv) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 88; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 89;

(v) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 88; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 90;

(vi) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 91; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 89;

(vii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 84; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 85;

(viii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 92; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 93;

(ix) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 94; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 95; or

(x) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 92; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 95.

[00010] In some embodiments, the antibody is a Fab fragment.

[00011] In some embodiments, the antibody comprises:

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

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

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

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

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

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

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

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

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

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

[00012] In some embodiments, the antibody comprises:

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

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

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

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

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

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

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

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

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

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

[00013] In some embodiments, the equilibrium dissociation constant (K_D) of binding of the antibody to the transferrin receptor is in a range from 10^{-11} M to 10^{-6} M.

[00014] In some embodiments, the antibody does not specifically bind to the transferrin binding site of the transferrin receptor and/or wherein the antibody does not inhibit binding of transferrin to the transferrin receptor.

[00015] In some embodiments, the antibody is cross-reactive with extracellular epitopes of two or more of a human, non-human primate and rodent transferrin receptor.

[00016] In some embodiments, the anti-TfR1 antibody has undergone pyroglutamate formation resulting from a post-translational modification.

[00017] In some embodiments, the complex is configured to promote transferrin receptor mediated internalization of the molecular payload into a muscle cell.

[00018] In some embodiments, the molecular payload is an oligonucleotide.

[00019] In some embodiments, the molecular payload is an oligonucleotide comprising an antisense strand comprising a region of complementarity to an MSTN target sequence. In some embodiments, the MSTN target sequence is an MSTN mRNA sequence as set forth in SEQ ID NOs: 146-148, or an MSTN target sequence as set forth in any one of SEQ ID NOs: 149-196. In some embodiments, the antisense strand is 18-25 nucleotides in length and/or the region of

complementarity is at least 16 nucleosides in length. In some embodiments, the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 197-220, wherein each of the Us are optionally and independently Ts. In some embodiments, the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 197-220, wherein each of the Us are optionally and independently Ts.

[00020] In some embodiments, wherein the molecular payload is an oligonucleotide comprising an antisense strand comprising a region of complementarity to an INHBA target sequence. In some embodiments, the INHBA target sequence is an INHBA mRNA sequence as set forth in SEQ ID NO: 269 or SEQ ID NO: 270, or an INHBA target sequence as set forth in any one of SEQ ID NOs: 271-318. In some embodiments, the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length. In some embodiments, the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 319-342, wherein each of the Us are optionally and independently Ts. In some embodiments, the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 319-342, wherein each of the Us are optionally and independently Ts.

[00021] In some embodiments, the molecular payload is an oligonucleotide comprising an antisense strand comprising a region of complementarity to an ACVR1B target sequence. In some embodiments, the ACVR1B target sequence is an ACVR1B mRNA sequence as set forth in any one of SEQ ID NOs: 367-370, or an ACVR1B target sequence as set forth in any one of SEQ ID NOs: 221-268. In some embodiments, the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length. In some embodiments, the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 343-366, wherein each of the Us are optionally and independently Ts. In some embodiments, the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 343-366, wherein each of the Us are optionally and independently Ts.

[00022] In some embodiments, the molecular payload is an oligonucleotide comprising an antisense strand comprising a region of complementarity to a MLCK1 target sequence. In some embodiments, the MLCK1 target sequence is a MLCK1 mRNA as set forth in SEQ ID NO: 411. In some embodiments, the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length.

[00023] In some embodiments, the molecular payload is an oligonucleotide comprising an antisense strand comprising a region of complementarity to a ACVR1 target sequence. In some

embodiments, the ACVR1 target sequence is an ACVR1 mRNA sequence as set forth in SEQ ID NO: 429 or SEQ ID NO: 430, or an ACVR1 target sequence as set forth in any one of SEQ ID NOs: 431-478. In some embodiments, the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length. In some embodiments, the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 479-502, wherein each of the Us are optionally and independently Ts. In some embodiments, the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 479-502, wherein each of the Us are optionally and independently Ts.

[00024] In some embodiments, the molecular payload is an oligonucleotide comprising an antisense strand comprising a region of complementarity to a FBXO32 target sequence. In some embodiments, the FBXO32 target sequence is an FBXO32 mRNA sequence as set forth in SEQ ID NO: 505 or SEQ ID NO: 506, or a FBXO32 target sequence as set forth in any one of SEQ ID NOs: 507-554. In some embodiments, the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length. In some embodiments, the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 555-578, wherein each of the Us are optionally and independently Ts. In some embodiments, the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 555-578, wherein each of the Us are optionally and independently Ts.

[00025] In some embodiments, the molecular payload is an oligonucleotide comprising an antisense strand comprising a region of complementarity to TRIM63 target sequence. In some embodiments, the TRIM63 target sequence is a TRIM63 mRNA sequence as set forth in SEQ ID NO: 579 or SEQ ID NO: 580, or a TRIM63 target sequence as set forth in any one of SEQ ID NOs: 581-628. In some embodiments, the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length. In some embodiments, the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 629-652, wherein each of the Us are optionally and independently Ts. In some embodiments, the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 629-652, wherein each of the Us are optionally and independently Ts.

[00026] In some embodiments, the molecular payload is an oligonucleotide comprising an antisense strand comprising a region of complementarity to a MEF2D target sequence. In some embodiments, the MEF2D target sequence is an MEF2D mRNA sequence as set forth in SEQ

ID NO: 664 or SEQ ID NO: 665, or a MEF2D target sequence as set forth in any one of SEQ ID NOs: 668-715. In some embodiments, the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length. In some embodiments, the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 716-223, wherein each of the Us are optionally and independently Ts. In some embodiments, the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 716-223, wherein each of the Us are optionally and independently Ts.

[00027] In some embodiments, the molecular payload is an oligonucleotide comprising an antisense strand comprising a region of complementarity to KLF15 target sequence. In some embodiments, the KLF15 target sequence is a KLF15 mRNA sequence as set forth in SEQ ID NO: 740 or SEQ ID NO: 741, or a KLF15 target sequence as set forth in any one of SEQ ID NOs: 742-789. In some embodiments, the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length. In some embodiments, the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 790-813, wherein each of the Us are optionally and independently Ts. In some embodiments, the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 790-813, wherein each of the Us are optionally and independently Ts.

[00028] In some embodiments, the molecular payload is an oligonucleotide comprising an antisense strand comprising a region of complementarity to a MED1 target sequence. In some embodiments, the MED1 target sequence is a MED1 mRNA sequence as set forth in SEQ ID NO: 814 or SEQ ID NO: 815, or a MED1 target sequence as set forth in any one of SEQ ID NOs: 816-863. In some embodiments, the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length. In some embodiments, the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 864-887, wherein each of the Us are optionally and independently Ts. In some embodiments, the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 864-887, wherein each of the Us are optionally and independently Ts.

[00029] In some embodiments, the molecular payload is an oligonucleotide comprising an antisense strand comprising a region of complementarity to a MED13 target sequence. In some embodiments, the MED13 target sequence is a MED13 mRNA sequence as set forth in SEQ ID NO: 888 or SEQ ID NO: 889, or a MED13 target sequence as set forth in any one of SEQ ID NOs: 890-937. In some embodiments, the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length. In some embodiments, the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth

in any one of SEQ ID NOs: 938-961, wherein each of the Us are optionally and independently Ts. In some embodiments, the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 938-961, wherein each of the Us are optionally and independently Ts.

[00030] In some embodiments, the molecular payload is an oligonucleotide comprising an antisense strand comprising a region of complementarity to PPP1R3A target sequence. In some embodiments, the PPP1R3A target sequence is a PPP1R3A mRNA sequence as set forth in SEQ ID NO: 962 or SEQ ID NO: 963, or a PPP1R3A target sequence as set forth in any one of SEQ ID NOs: 964-1011. In some embodiments, the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length. In some embodiments, the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 1012-1035, wherein each of the Us are optionally and independently Ts. In some embodiments, the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 1012-1035, wherein each of the Us are optionally and independently Ts.

[00031] In some embodiments, the oligonucleotide further comprises a sense strand that hybridizes to the antisense strand to form a double stranded siRNA.

[00032] In some embodiments, the oligonucleotide comprises one or more modified nucleosides. In some embodiments, each nucleoside in the oligonucleotide is a modified nucleoside. In some embodiments, the one or more modified nucleosides are 2' modified nucleotides. In some embodiments, the one or more 2' modified nucleosides are selected from: 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-dimethylaminoethoxyethyl (2'-O-DMAEOE), 2'-O-N-methylacetamido (2'-O-NMA), locked nucleic acid (LNA), ethylene-bridged nucleic acid (ENA), and (S)-constrained ethyl-bridged nucleic acid (cEt). In some embodiments, the 2' modified nucleotide is 2'-O-methyl or 2'-fluoro (2'-F). In some embodiments, the oligonucleotide comprises one or more phosphorothioate internucleoside linkages. In some embodiments, the one or more phosphorothioate internucleoside linkage are present on the antisense strand of the RNAi oligonucleotide. In some embodiments, the two internucleoside linkages at the 3' end of the sense strands are phosphorothioate internucleoside linkages.

[00033] In some embodiments, the oligonucleotide is an siRNA listed in Table 10, Table 13, Table 16, Table 19, Table 22, Table 25, Table 28, Table 31, Table 34, Table 37, or Table 40.

[00034] In some embodiments, the antibody is covalently linked to the molecular payload via: (i) a cleavable linker; or (ii) a non-cleavable linker. In some embodiments, the cleavable linker comprises a valine-citrulline sequence. In some embodiments, the non-cleavable linker is an alkane linker.

[00035] Other aspects of the present disclosure provide methods of reducing MSTN, INHBA, ACVR1B, MLCK1, ACVR1, FBXO32, TRIM63, MEF2D, KLF15, MED1, MED13, and/or PPP1R3A expression in a muscle cell, the method comprising contacting the muscle cell with an effective amount of the complex described herein for promoting internalization of the molecular payload to the muscle cell.

[00036] Other aspects of the present disclosure provide methods of treating muscle atrophy the method comprising administering to a subject in need thereof an effective amount of the complex described herein, wherein the subject has elevated expression or activity of MSTN, INHBA, and/or ACVR1B, and the complex comprises a molecular payload that modulates the expression or activity of MSTN, INHBA, and/or ACVR1B. In some embodiments, the subject is a human. In some embodiments, the administration is intravenous.

[00037] Other aspects of the present disclosure provide methods of treating irritable bowel syndrome (IBS) or irritable bowel disease (IBD) the method comprising administering to a subject in need thereof an effective amount of the complex described herein, wherein the subject has elevated levels of MLCK1 protein and the complex comprises a molecular payload that modulates the expression or activity of MLCK1. In some embodiments, the subject is a human. In some embodiments, the administration is intravenous.

[00038] Other aspects of the present disclosure provide methods of treating a disease associated with an elevated level of ACVR1, the method comprising administering to a subject in need thereof an effective amount of the complex described herein, wherein the subject has elevated levels of ACVR1 protein and the complex comprises a molecular payload that modulates the expression or activity of ACVR1. In some embodiments, the disease associated with an elevated level of ACVR1 is muscle atrophy. In some embodiments, the muscle atrophy is sarcopenia or cachexia. In some embodiments, the subject is a human. In some embodiments, the administration is intravenous.

[00039] Other aspects of the present disclosure provide methods of treating muscle atrophy the method comprising administering to a subject in need thereof an effective amount of the complex described herein, wherein the subject has elevated expression or activity of FBXO32 or TRIM63, and the complex comprises a molecular payload that modulates the

expression or activity of FBXO32 or TRIM63. In some embodiments, the subject is a human. In some embodiments, the administration is intravenous.

[00040] Other aspects of the present disclosure provide methods of treating a heart disease, the method comprising administering to a subject in need thereof an effective amount of the complex described herein, wherein the subject has elevated expression or activity of MEF2D, KLF15, MED1, MED13, and/or PPP1R3A, and the complex comprises a molecular payload that modulates the expression or activity of MEF2D, KLF15, MED1, MED13, and/or PPP1R3A. In some embodiments, the subject is a human. In some embodiments, the administration is intravenous.

[00041] In some embodiments, the complex reduces RNA level of MSTN, INHBA, ACVR1B, MLCK1, ACVR1, FBXO32, TRIM63, MEF2D, KLF15, MED1, MED13, and/or PPP1R3A. In some embodiments, the complex reduces protein level of MSTN, INHBA, ACVR1B, MLCK1, ACVR1, FBXO32, TRIM63, MEF2D, KLF15, MED1, MED13, and/or PPP1R3A.

BRIEF DESCRIPTION OF THE DRAWINGS

[00042] **FIG. 1** depicts a non-limiting schematic showing the effect of transfecting cells with an siRNA.

[00043] **FIG. 2** depicts a non-limiting schematic showing the activity of a muscle targeting complex comprising an siRNA.

[00044] **FIGs. 3A-3B** depict non-limiting schematics showing the activity of a muscle targeting complex comprising an siRNA in mouse muscle tissue (gastrocnemius (FIG. 3A) and heart (FIG. 3B)) *in vivo*, relative to vehicle-treated control experiments. (N=4 C57BL/6 WT mice).

[00045] **FIGs. 4A-4E** depict non-limiting schematics showing the tissue selectivity of a muscle targeting complex (anti-TfR1 antibody-siHPRT) comprising an anti-TfR Fab (RI7 217) conjugated to HPRT-specific siRNA to reduce expression levels of HPRT genes. The data show gene expression in brain (FIG. 4A), liver (FIG. 4B), lung (FIG. 4C), kidney (FIG. 4D), and spleen (FIG. 4E), and demonstrate that muscle targeting complexes do not facilitate gene inhibition in non-muscle tissues.

[00046] **FIG. 5** shows inhibition of MSTN gene expression by 24 siRNAs tested at 0.5 nM and 10 nM doses.

[00047] **FIG. 6** shows dose response curves for inhibition of human MSTN by oligonucleotide candidate sequences over a range of concentrations from 100 nM to 10 fM.

[00048] **FIG. 7** shows inhibition of INHBA gene expression by 24 siRNAs tested at 0.5 nM and 10 nM doses

[00049] **FIG. 8** shows dose response curves for inhibition of human INHBA by oligonucleotide candidate sequences over a range of concentrations from 100 nM to 10 fM.

[00050] **FIG. 9** shows inhibition of ACVR1B gene expression by 24 siRNAs tested at 0.1 nM and 10 nM doses.

[00051] **FIG. 10** shows dose response curves for inhibition of human ACVR1B by oligonucleotide candidate sequences over a range of concentrations from 100 nM to 10 fM.

[00052] **FIG. 11** shows dose response curves for inhibition of murine ACVR1B by oligonucleotide candidate sequences over a range of concentrations from 100 nM to 10 fM.

[00053] **FIG. 12** shows percent knockdown of human ACVR1 expression by oligonucleotide candidate sequences in cell culture at concentrations of 10 nM and 0.5 nM.

[00054] **FIG. 13** shows dose response curves for inhibition of human ACVR1 by different oligonucleotides over a range of concentrations from 100 nM to 10 fM.

[00055] **FIG. 14** depicts the results of a dual-luciferase gene inhibition assay used to identify candidate oligonucleotides capable of inhibiting expression of FBXO32. Candidate oligonucleotides (siRNA molecules) were evaluated at a concentration of 0.1 nM and a concentration of 10 nM in a cross species, human/cyno, or rat/mouse system.

[00056] **FIG. 15** depicts the results of a dual-luciferase gene inhibition assay used to identify candidate oligonucleotides capable of inhibiting expression of TRIM63. Candidate oligonucleotides (siRNA molecules) were evaluated at a concentration of 0.1 nM and a concentration of 10 nM in a cross species, human/cyno, or rat/mouse system.

[00057] **FIGs. 16A-16B** depict a dose response curve for inhibition of human (FIG. 16A) and murine (FIG. 16B) FBXO32 by candidate oligonucleotide sequences over a range of concentrations from 100 nM to 10 fM.

[00058] **FIGs. 17A-17B** depict a dose response curve for inhibition of human (FIG. 17A) and murine (FIG. 17B) TRIM63 by candidate oligonucleotide sequences over a range of concentrations from 100 nM to 10 fM.

[00059] **FIG. 18** shows percent knockdown of human and murine MEF2D expression by oligonucleotide candidate sequences in cell culture at concentrations of 10 nM and 0.1 nM.

[00060] **FIG. 19** shows percent knockdown of human and murine KLF15 expression by oligonucleotide candidate sequences in cell culture at concentrations of 10 nM and 0.1 nM.

[00061] **FIG. 20** shows percent knockdown of human MED1 expression by oligonucleotide candidate sequences in cell culture at concentrations of 10 nM and 0.5 nM.

- [00062] **FIG. 21** shows percent knockdown of human MED13 expression by oligonucleotide candidate sequences in cell culture at concentrations of 10 nM and 0.1 nM.
- [00063] **FIG. 22** shows percent knockdown of human and murine PPP1R3A expression by oligonucleotide candidate sequences in cell culture at concentrations of 10 nM and 0.5 nM.
- [00064] **FIGs. 23A-23B** show dose response curves for inhibition of human MEF2D (FIG. 23A) and murine MEF2D (FIG. 23B) by oligonucleotide candidate sequences over a range of concentrations from 100 nM to 10 fM.
- [00065] **FIGs. 24A-24B** show dose response curves for inhibition of human KLF15 (FIG. 24A) and murine KLF15 (FIG. 24B) by oligonucleotide candidate sequences over a range of concentrations from 100 nM to 10 fM.
- [00066] **FIG. 25** shows dose response curves for inhibition of human MED1 by oligonucleotide candidate sequences over a range of concentrations from 100 nM to 10 fM.
- [00067] **FIG. 26** shows dose response curves for inhibition of human MED13 by oligonucleotide candidate sequences over a range of concentrations from 100 nM to 10 fM.
- [00068] **FIGs. 27A-27B** show dose response curves for inhibition of human PPP1R3A (FIG. 27A) and murine PPP1R3A (FIG. 27B) by oligonucleotide candidate sequences over a range of concentrations from 100 nM to 10 fM.
- [00069] **FIGs. 28A-28H** show that conjugates having an anti-TfR1 Fab conjugated to a DMPK-targeting oligonucleotide (ASO300) reduced mouse DMPK expression in various muscle tissues in a mouse model that expresses human TfR1. The DMPK-targeting oligonucleotide was conjugated to anti-TfR1 Fab 3M12-VH4/VK3. FIG. 28A shows that the conjugate reduced mouse wild-type *Dmpk* in Tibialis Anterior by 79%. FIG. 28B shows that the conjugate reduced mouse wild-type *Dmpk* in gastrocnemius by 76%. FIG. 28C shows that the conjugate reduced mouse wild-type *Dmpk* in the heart by 70%. FIG. 28D shows that the conjugate reduced mouse wild-type *Dmpk* and in diaphragm by 88%. FIGs. 28E-28H show oligonucleotide distributions in Tibialis Anterior (FIG. 28E), gastrocnemius (FIG. 28F), heart (FIG. 28G), and diaphragm (FIG. 28H).

DETAILED DESCRIPTION

- [00070] Some aspects of the present disclosure provide molecular payloads (e.g., oligonucleotides) that modulate the expression or activity of genes (e.g., MSTN, INHBA, or ACD1B) associated with muscle health (e.g., muscle growth and maintenance). Other aspects of the disclosure relate to a recognition that while certain molecular payloads (e.g., oligonucleotides, peptides, small molecules) can have beneficial effects in muscle cells (e.g.,

cardiac muscle cells), it has proven challenging to effectively target such cells. Accordingly, further provided herein are complexes comprising muscle-targeting agents covalently linked to molecular payloads in order to overcome such challenges. In some embodiments, the complexes are particularly useful for delivering molecular payloads that inhibit the expression or activity of target genes in muscle cells, e.g., in a subject having or suspected of having a rare muscle disease. In some embodiments, complexes provided herein are designed to target cardiac muscle cells or cardiac muscle tissues. In some embodiments, complexes provided herein are provided for treating subjects having muscle atrophy (e.g., sarcopenia or cachexia). For example, in some embodiments, complexes are provided for targeting MSTN expression to treat subjects having cardiac muscle wasting, cardiomyopathy, or cardiac cachexia, and/or skeletal muscle atrophy. In some embodiments, complexes are provided for targeting INHBA to treat subjects having muscle atrophy (e.g., cardiac muscle atrophy). In some embodiments, complexes are provided for targeting ACVR1B to treat subjects having cardiac fibrosis or cardiac hypertrophy.

[00071] Myostatin, also referred to as growth differentiation factor 8 (GDF8), is a secreted growth factor that negatively regulates muscle mass. In humans, myostatin is encoded by the MSTN gene. Loss-of-function mutations in the Myostatin gene (MSTN), leading to a hypermuscular phenotype, have been described in cattle, sheep, fish, dogs and humans. Myostatin is expressed in skeletal muscle, with lower levels of expression reported in adipose and cardiac tissues. Inhibition of Myostatin signaling leads to an increase in muscle size.

[00072] Myostatin may inhibit cardiomyocyte proliferation and differentiation by manipulating cell cycle progression, and has been shown to prevent cell cycle G1 to S phase transition by decreasing levels of cyclin-dependent kinase complex 2 (CDK2) and by increasing p21 levels. Physiologically, minimal amounts of cardiac myostatin are secreted from the myocardium into serum, having a limited effect on muscle growth. However, increases in cardiac myostatin can increase its serum concentration, which may cause skeletal muscle atrophy.

[00073] Pathological states that increase cardiac stress and promote heart failure can induce a rise in both cardiac myostatin mRNA and protein levels within the heart. In ischemic or dilated cardiomyopathy, increased levels of myostatin mRNA have been detected within the left ventricle. Furthermore, increases in myostatin levels during chronic heart failure have been shown to cause cardiac cachexia. It has been shown that systemic inhibition of cardiac myostatin maintains overall muscle weight in experimental models with pre-existing heart failure.

[00074] Inhibin beta A (INHBA) is a protein that can exist as an oligomer subunit of activin A and inhibin A. In some instances, INHBA can form a disulfide-linked homodimer (*i.e.*, dimer between two INHBA molecules) to form activin A, which enhances follicle-stimulating hormone (FSH) biosynthesis and secretion, and is involved in several biological processes including cell proliferation and differentiation, immune response and wound repair, and endocrine function. In other instances, INHBA can dimerize with inhibin alpha to form inhibin A, which decreases FSH biosynthesis and secretion.

[00075] Activin A interacts with Activin type 1 receptors (*e.g.*, ACVR1, ACVR1B, and ACVR1C) and Activin type 2 receptors (ACVR2A and ACVR2B). These protein-protein interactions lead to phosphorylation of SMAD2 and SMAD3, which can ultimately result in the changes in gene expression for a large variety of genes.

[00076] Activin A has been shown to negatively regulate muscle mass (*e.g.*, in connection with myostatin) and thus has been implicated in several muscle disorders, including muscle atrophy (*e.g.*, cardiac muscle atrophy), *e.g.*, as described in Lee SJ, et al., “*Regulation of muscle mass by follistatin and activins*”, Mol. Endocrinol. 2010 Oct;24(10):1998-2008; and Lach-Trifilieff et al., Mol Cell Biol. 2014 Feb; 34(4): 606–618. In some instances, muscle atrophy results in life threatening complications. Elevated Activin A level has also been associated with myocardial complications in type 2 diabetes patients (*e.g.*, as described in Lin et al., Acta Cardiol Sin. 2016 Jul; 32(4): 420–427; and Kuo et al., Sci Rep 8, 9957 (2018)). These indications demonstrate that compositions and methods for targeting activin A and its subunit INHBA could provide therapeutic benefit. However, effective treatments that target the function and expression of INHBA (*e.g.*, including dimerization to form activin A) are limited.

[00077] Activin receptor type-1B (ACVR1B), also known as ALK-4, is a transmembrane serine/threonine kinase activin type-1 receptor that interacts with activin receptor type-2 to form an activin receptor complex. The activin receptor complex functions to bind to activin and regulate a diverse array of cellular processes through signal transduction, including neuronal differentiation and survival, wound healing, extracellular matrix production, immunosuppression and carcinogenesis. Within the receptor complex, ACVR1B becomes phosphorylated by activin receptor type-2 proteins following activin binding. Phosphorylated ACVR1B can subsequently phosphorylate several of the SMAD proteins (*e.g.*, SMAD2 and SMAD3) to propagate activin signaling. An interaction between ACVR1B and SMAD7 can alternatively function to inhibit activin signaling.

[00078] It has been established that activin, functioning through its signal transduction pathway through ACVR1B, is a key regulator of cardiac fibrosis (*e.g.*, atrial fibrosis). This regulation is thought to be enhanced by presence of Angiotensin-II. Cardiac fibrosis, a

condition involving excess production of extracellular matrix in the cardiac muscle, is commonly associated with structural remodeling associated with abnormal cardiac function, atrial fibrillation, and/or heart attacks. See, *e.g.*, Wang, Q. et al. “The crucial role of activin A/ALK4 pathway in the pathogenesis of Ang-II-induced atrial fibrosis and vulnerability to atrial fibrillation.” *Basic Res Cardiol.* 2017 Jul;112(4):47, the content of which is incorporated herein by reference. It has further been shown that targeting ACVR1B functions to counteract cardiac fibrosis and dysfunction in subjects having cardiac fibrosis. Additionally, inhibition of ACVR1B has an effect in subjects having cardiac hypertrophy. See, *e.g.*, Chen Y.H. et al., “Haplodeficiency of activin receptor-like kinase 4 alleviates myocardial infarction-induced cardiac fibrosis and preserves cardiac function.” *J Mol Cell Cardiol.* 2017 Apr;105:1-11.; and Wang, Q. et al., “Activin Receptor-Like Kinase 4 Haplodeficiency Mitigates Arrhythmogenic Atrial Remodeling and Vulnerability to Atrial Fibrillation in Cardiac Pathological Hypertrophy.” *J Am Heart Assoc.* 2018 Aug 21;7(16):e008842; the contents of each of which are incorporated herein by reference.

[00079] Some aspects of the present disclosure provide molecular payloads that modulate the expression or activity of MLCK1 (*e.g.*, oligonucleotides targeting MLCK1 RNAs). Other aspects of the disclosure relate to a recognition that while certain molecular payloads (*e.g.*, oligonucleotides, peptides, small molecules) can have beneficial effects in muscle cells, it has proven challenging to effectively target such cells. Accordingly, further provided herein are complexes comprising muscle-targeting agents covalently linked to molecular payloads in order to overcome such challenges. In some embodiments, the complexes are particularly useful for delivering molecular payloads that inhibit the expression or activity of target genes in muscle cells, *e.g.*, in a subject having or suspected of having a rare muscle disease. In some embodiments, complexes provided herein are designed to target smooth muscle cells or smooth muscle tissues. For example, in some embodiments, complexes are provided for targeting a MLCK1 to treat subjects having irritable bowel syndrome (IBS) or inflammatory bowel disease (IBD).

[00080] Myosin light chain kinase (“MLCK1” or “MYLK”), also known as kinase-related protein or telokin, is an enzyme that phosphorylates myosin regulatory light chains in order to facilitate myosin interaction with actin filaments in smooth muscle. MLCK1 is one of four isoforms of myosin light chain kinase and is expressed in smooth muscle. The other isoforms – MLCK2, MLCK3, and MLCK4 – are expressed in skeletal, cardiac, and cancerous cells, respectively.

[00081] It has recently been shown that MLCK1 is a potential therapeutic target for irritable bowel syndrome (See, Graham, W.V. et al. “Intracellular MLCK1 diversion reverses

barrier loss to restore mucosal homeostasis.” *Nature Medicine*, volume 25, 690–700, 2019).

MLCK1 is a critical protein in regulating epithelial barrier dysfunction, which is associated with intestinal diseases (e.g., irritable bowel syndrome). Restoration of the epithelial barrier in smooth muscles tissues (e.g., through inhibition of MLCK1) can limit or reverse these intestinal diseases. Thus, development of novel MLCK1 inhibitors is desired.

[00082] Some aspects of the present disclosure provide molecular payloads that modulate the expression or activity of ACVR1 (e.g., oligonucleotides targeting ACVR1 RNAs). Other aspects of the disclosure relate to a recognition that while certain molecular payloads (e.g., oligonucleotides, peptides, small molecules) can have beneficial effects in muscle cells, it has proven challenging to effectively target such cells. Accordingly, provided herein are complexes comprising muscle-targeting agents covalently linked to molecular payloads in order to overcome such challenges. In some embodiments, the complexes are particularly useful for delivering molecular payloads that inhibit the expression or activity of target genes in muscle cells, e.g., in a subject having or suspected of having a rare muscle disease. In some embodiments, complexes provided herein are designed to target cardiac muscle cells or cardiac muscle tissues. For example, in some embodiments, complexes are provided for targeting an ACVR1 to treat subjects having cardiac disease (e.g., cardiac hypertrophy) or muscle atrophy (e.g., sarcopenia or cachexia).

[00083] Activin A receptor, type 1 (ACVR1), a BMP type I receptor (also known as Activin receptor-like kinase-2 (ALK-2), ACTRIA, ACVRLK2), is a signaling receptor that binds to Activin A. These protein-protein interactions lead to phosphorylation of SMAD2 and SMAD3, which can ultimately result in the changes in gene expression for a large variety of genes.

[00084] ACVR1 has been associated with angiotensin II-induced cardiac hypertrophy and muscle atrophy (e.g., sarcopenia or cachexia). Specifically, deletion of ACVR1 in cardiomyocytes has been shown to reduce cardiac hypertrophy in diseased mice (Shahid, M. et al. “BMP type I receptor ALK2 is required for angiotensin II-induced cardiac hypertrophy” *Am J Physiol Heart Circ Physiol*. 2016 Apr 15;310(8):H984-94). Fibrodysplasia ossificans progressiva (FOP) is caused by heterozygous mutations in ACVR1 (e.g., ACVR1 R206H mutation). These indications demonstrate that compositions and methods for targeting ACVR1 could provide therapeutic benefit. However, effective treatments that target the function and expression of ACVR1 are limited.

[00085] Some aspects of the present disclosure provide molecular payloads (e.g., oligonucleotides) that modulate the expression or activity of genes associated with muscle atrophy (e.g., FBXO32 or TRIM63). Other aspects of the disclosure relate to a recognition that

while certain molecular payloads (*e.g.*, oligonucleotides, peptides, small molecules) can have beneficial effects in muscle cells, it has proven challenging to effectively target such cells. Accordingly, further provided herein are complexes comprising muscle-targeting agents covalently linked to molecular payloads in order to overcome such challenges. In some embodiments, the complexes are particularly useful for delivering molecular payloads that inhibit the expression or activity of target genes in muscle cells, *e.g.*, in a subject having or suspected of having a rare muscle disease. In some embodiments, complexes provided herein are designed to target cardiac muscle cells or cardiac muscle tissues. For example, in some embodiments, complexes are provided for targeting a FBXO32 to treat subjects having muscle atrophy. In some embodiments, complexes are provided for targeting a TRIM63 to treat subjects having muscle atrophy.

[00086] FBXO32, which is also referred to as atrogin-1 and Muscle atrophy F-box gene (MAFbx), is an E3 ubiquitin ligase and a member of the F-box protein family. F-box proteins have been shown to regulate ubiquitin-mediated protein degradation. Although FBXO32 lacks leucine-rich regions and WD40 repeats that are commonly found in F-box proteins, FBXO32 comprises a PDZ domain that is capable of binding other proteins. Serving as an adaptor, FBXO32 bridges proteins to be ubiquitinated with other components of the Skp, Cullin, F-box containing complex (or SCF complex). In humans, FBXO32 protein is encoded by the FBXO32 gene.

[00087] FBXO32 is predominantly expressed in striated muscle and has been implicated in regulating protein synthesis and degradation during muscle atrophy. For example, FBXO32 expression is significantly increased during muscle atrophy. See, *e.g.*, Gomes *et al.*, Proc Natl Acad Sci U S A. 2001 Dec 4;98(25):14440-5. Notably, FBXO32 has been shown to be required for muscle atrophy that is induced by a variety of conditions. For example, in animal models, FBXO32 deficiency prevented muscle atrophy caused by denervation. Small hairpin RNAs (shRNAs) targeting FBXO32 blocked muscle loss induced by fasting in mice. Knockout of FBXO32 also prevented glucocorticoid treatment-induced muscle atrophy. Whereas wild-type mice treated with the synthetic glucocorticoid dexamethasone had decreased wet weight of the triceps surae and tibialis anterior muscles, FBXO32 knockout mice had no muscle sparing. FBXO32 is also a biomarker for cancer cachexia. Furthermore, knockout of FBXO32 prevented myostatin-induced growth inhibition in primary myoblasts. See, *e.g.*, Bodine *et al.*, Science. 2001 Nov 23;294(5547):1704-8; Cong *et al.*, Hum Gene Ther. 2011 Mar;22(3):313-24; Baehr *et al.*, J Physiol. 2011 Oct 1;589(Pt 19):4759-76; and Lokireddy *et al.*, Am J Physiol Cell Physiol 303: C512–C529, 2012; Sukari *et al.*, Semin Cancer Biol. 2016 Feb;36:95-104; Wang *et al.*, Diabetes. 2010 Aug;59(8):1879-89. Further, it has been shown that FBXO32 disrupts Akt-

dependent pathways responsible for physiologic cardiac hypertrophy (see, *e.g.*, Li et al., J Clin Invest. 2007 Nov 1; 117(11): 3211–3223). Overexpression of FBXO32 in cardiac muscle may afford therapeutic values for cardiac hypertrophy.

[00088] TRIM63 is a member of the RING finger protein family and may be referred to as Muscle-specific RING finger protein 1 (MuRF1). Like FBXO32, TRIM63 is a E3 ubiquitin ligase that is predominantly expressed in muscle, including skeletal, cardiac, and smooth muscle, and the iris. For example, TRIM63 may be detected in the M-line and Z-line lattices of myofibrils.

[00089] Several studies have implicated TRIM63 in muscle atrophy. For example, TRIM63 has been shown to be required for skeletal muscle atrophy. Mice that were deficient in TRIM63 did not develop muscle atrophy. See, *e.g.*, Bodine *et al.*, Science. 2001 Nov 23;294(5547):1704-8. Whereas wild-type mice showed significant muscle atrophy when treated with a synthetic glucocorticoid (dexamethasone), TRIM63 null mice showed muscle sparing. Knockout of TRIM63 may maintain protein synthesis in mice, suggesting that TRIM63 is capable of regulating cellular protein levels in a proteasome-independent manner. See, *e.g.*, Bodine *et al.*, J Physiol. 2011 Oct 1;589(Pt 19):4759-76. TRIM63 has been shown to degrade myosin heavy chain protein under dexamethasone-induced atrophy conditions and mice with knockout of TRIM63 show less myosin heavy chain protein degradation than wild-type mice. See, *e.g.*, Clarke *et al.*, Cell Metab. 2007 Nov;6(5):376-85. Similarly, muscles lose myosin-binding protein C (MyBP-C) and myosin light chains 1 and 2 (MyLC1 and MyLC2) from myofibrils when muscle atrophy is induced by denervation or fasting. Loss of MyBP-C, MyLC1, and MyLC2 occur in a TRIM63-dependent manner. See, *e.g.*, Cohen *et al.*, J Cell Biol. 2009 Jun 15;185(6):1083-95. miRNA-based short hairpin RNAs (shRNAs) targeting TRIM63 and genetic knockout of TRIM63 have also been used to determine the role of TRIM63 in acute lung injury-associated skeletal muscle atrophy. TRIM63 deficiency attenuated muscle wasting induced by acute lung injury. See, *e.g.*, Files *et al.*, Am J Respir Crit Care Med. 2012 Apr 15;185(8):825-34.

[00090] Some aspects of the present disclosure relate to a recognition that while certain molecular payloads (*e.g.*, oligonucleotides, peptides, small molecules) can have beneficial effects in muscle cells, it has proven challenging to effectively target such cells. As described herein, the present disclosure provides complexes comprising muscle-targeting agents covalently linked to molecular payloads in order to overcome such challenges. In some embodiments, the complexes are particularly useful for delivering molecular payloads that inhibit the expression or activity of target genes in muscle cells, *e.g.*, in a subject having or suspected of having a rare muscle disease. In some embodiments, complexes provided herein

are designed to target cardiac muscle cells or cardiac muscle tissues. For example, in some embodiments, complexes are provided for targeting a MEF2D, KLF15, MED1, MED13, or PPP1R3A gene to treat subjects having a muscular disease or a heart disease.

[00091] MEF2D is a member of the myocyte-specific enhancer factor 2 (MEF2) family of transcription factors. Alternative splicing MEF2D mRNA results in multiple transcript variants, a ubiquitous isoform and a tissue-specific isoform primarily detected in muscle tissue.

[00092] Krüppel-like factor 15 (KLF15) is a protein that belongs to the Krüppel family of transcription factors and can function as either a repressor or activator of gene transcription. Expression levels of KLF15 are increased by glucocorticoid signaling and blood levels of insulin. In muscle tissues, levels of KLF15 increase in response to exercise and control the ability of muscle tissue to burn fat and generate force. KLF15 specifically interacts with MEF2 and synergistically activates the GLUT4 promoter via an intact KLF15-binding site proximal to the MEF2A site. miR-133 targets KLF15 in cardiac and skeletal muscles to regulate the expression of GLUT4. KLF15 inhibits cardiac hypertrophy by repressing the activity of MEF2 and other cardiac transcription factors (*e.g.*, GATA4 and myocardin). Expression levels of KLF15 are reduced in failing human hearts and in human aortic aneurysm tissues. Accordingly, KLF15 is involved in metabolic control in cardiomyocytes and skeletal muscle tissues and is a therapeutic target for cardiac diseases such as cardiac hypertrophy and cardiac failure (*e.g.*, following a myocardial infarction; see, *e.g.*, Zhao, Y. et al., “Multiple roles of KLF15 in the heart: Underlying mechanisms and therapeutic implications.” J Mol Cell Cardiol. 2019 Apr;129:193-196; the contents of which are incorporated herein by reference in its entirety). KLF15 expression levels also impacts how potassium flows out of heart cells. It has been shown that elevated or reduced levels of KLF15 may result in heart arrhythmias.

[00093] The Mediator (MED) complex is regulator of eukaryotic gene transcription. Recent studies have further demonstrated that several subunits of the MED complex including MED1, MED13, MED14, MED15, MED23, MED25 and CDK8 play important regulatory roles in metabolism (*e.g.*, glucose and lipid metabolism). In part due to their import in metabolism, some of these subunits (*e.g.*, MED1 and MED13) have been linked to cardiovascular diseases (*e.g.*, human congenital heart diseases). However, targeting MED subunits (*e.g.*, MED1 and MED13) with small molecule inhibitors has proven challenging. New methods and compositions for targeting the Mediator complex (*e.g.*, subunits such as MED1 and MED13), *e.g.*, for treating cardiovascular diseases, are needed.

[00094] The glycogen-associated form of protein phosphatase-1 (PP1) derived from skeletal muscle is a heterodimer composed of a 37-kDa catalytic subunit (OMIM entry 176875) and a 124-kDa targeting and regulatory subunit, referred to as protein phosphatase 1 regulatory

subunit 3A (PPP1R3A). PPP1R3A binds to muscle glycogen with high affinity and enhances dephosphorylation of glycogen-bound substrates for PP1 such as glycogen synthase and glycogen phosphorylase kinase. PPP1R3A is a central regulator in heart failure and is implicated in cardiomyocyte metabolic pathways.

[00095] Further aspects of the disclosure, including a description of defined terms, are provided below.

I. Definitions

[00096] **ACVR1:** As used herein, the term “ACVR1”, “ALK2”, or “ALK-2” refers to a gene that encodes activin A receptor type 1, a protein receptor involved in the bone morphogenesis among other functions. In some embodiments, ACVR1 may be a human (Gene ID: 90) (e.g., SEQ ID NO: 429), non-human primate (e.g., Gene ID: 697935 (e.g., SEQ ID NO: 423), Gene ID: 470565 (e.g., SEQ ID NO: 424), Gene ID: 102134051 (e.g., SEQ ID NO: 425)), or rodent gene (e.g., Gene ID: 11477 (e.g., SEQ ID NO: 430), Gene ID: 79558 (e.g., SEQ ID NO: 426)). In humans, several genetic mutations in the gene that lead to alterations in the ACVR1 protein, e.g., L196P, R202I, R206H, Q207E, G328R, G328W, G328E, G356D, R375P, ΔP197-F198, are associated with FOP (e.g., as described in Haupt et al., Bone. 2018 Apr; 109: 232–240). In addition, multiple human transcript variants (e.g., as annotated under GenBank RefSeq Accession Numbers: NM_001105.5 (SEQ ID NO: 429), NM_001111067.4 (SEQ ID NO: 427), NM_001347663.1 (SEQ ID NO: 217), NM_001347664.1 (SEQ ID NO: 218), NM_001347665.1 (SEQ ID NO: 219), NM_001347666.1 (SEQ ID NO: 220), and NM_001347667.2 (SEQ ID NO: 221)) have been characterized that encode different protein isoforms. An exemplary ACVR1 protein, encoded by a human ACVR1 gene, is annotated under NCBI Reference Sequence: NP_001096.1, and has the following amino acid sequence:

MVDGVMILPVLIMIALPSPSMEDEKPKVNPPLYMCVCEGLSCGNEDHCEGQQCFSSLSI
NDGFHVYQKGCQVYEQGKMTCKTPSPGQAVECCQGDWCNRNITAQLPTKGKSFPG
TQNFHLEVGLILSVVFAVCLLACLLGVALRKFKRRNQERLNPRDVEYGTIEGLITTNVG
DSTLADLLDHSCTSGSGSGLPFLVQRTVARQITLLECVGKGRYGEVWRGSWQGENVAV
KIFSSRDEKSWFRETELYNTVMLRHENILGFASDMTSRHSSTQLWLITHYHEMGSLYD
YLQLTTLDTVSCLRIVLSIASGLAHLHIEIFGTQGKPAIAHRDLKSKNILVKKNGQCCCIAD
LGLAVMHSQSTNQLDVGNNPRVGTKRYMAPEVLDETIQVDCFDSYKRVDIWAFLVL
WEVARRMVSNGIVEDYKPPFYDVVPNDPSFEDMRKVVCVDQQRPNIPNRWFSDPTLTS
LAKLMKECWYQNPSARLTALRIKKTTLTKIDNSLDKLTDC (SEQ ID NO: 428)

[00097] **ACVR1B:** As used herein, the term, “ACVR1B” or “ALK-4” refers to a gene that encodes activin A receptor type 1B. ACVR1B is a transmembrane serine/threonine kinase

activin type-1 receptor that interacts with activin receptor type-2 to form an activin receptor complex to enable activin signaling. In some embodiments, ACVR1B may be a human (Gene ID: 91) (e.g., SEQ ID NOs: 367-368), non-human primate (e.g., Gene ID: 696587 (e.g., SEQ ID NO: 384), Gene ID: 101865702 (e.g., SEQ ID NO: 385)), or rodent gene (e.g., Gene ID: 11479 (e.g., SEQ ID NO: 369), Gene ID: 29381 (e.g., SEQ ID NO: 370)). In addition, multiple exemplary human transcripts (e.g., as annotated under GenBank RefSeq Accession Number: NM_004302.5 (SEQ ID NO: 367), NM_020327.3 (SEQ ID NO: 386), NM_020328.4 (SEQ ID NO: 387), XM_017020201.2 (SEQ ID NO: 388), XM_011538966.3 (SEQ ID NO: 389), and XM_011538967.3 (SEQ ID NO: 390)) have been characterized. Exemplary ACVR1B proteins, encoded by a human ACVR1B gene, are annotated under NCBI Reference Sequences: NP_004293.1 (SEQ ID NO: 142), NP_064732.3 (SEQ ID NO: 143), and NP_064733.3 (SEQ ID NO: 144), and have the following amino acid sequences:

NP_004293.1 (SEQ ID NO: 142)

MAESAGASSFFPLVVLLLAGSGGSGPRGVQALLCACTSCSQANYTCETDGACMVSIFNL
DGMEEHVRTCIPKVELVPAGKPFYCLSSDLRNTGCCYTDYCNRIDLRVPSGHLKEPEH
PSMWGPVELVGIIAGPVFLLFLIIIVFLVINYHQRVYHNRQRLDMEDPSCMCLSKDKTL
QDLVYDLSTSGSGSGLPLFVQRTVARTIVLQEIIGKGRFGEVWRGRWRGGDVAVKIFSS
REERSWFREAIEYQTVMLRHENILGFIAADNKDNGTWTQLWLVS DYHEHGS LFDYLN R
YTVTIEGMIKLALSAASGLAHLHMEIVGTQGKPGIAHRDLKSKNILVKKNGMCAIADLG
LAVRHDAVTDITIDIAPNQVRGTRYMAPEVLDETINMKHFDSFKCADIYALGLVYWEI
ARRCNSGGVHEEYQLPYYDLVPSDPSIEEMRKVVCDQKL RPNIPNWWQSYEALRVMG
KMMREC WYANGAARLTALRIKKTLSQLSVQEDVKI

NP_064732.3 (SEQ ID NO: 143)

MVSIFNLDGMEHHVRTCIPKVELVPAGKPFYCLSSDLRNTGCCYTDYCNRIDLRVPSG
HLKEPEHPSMWGPVELVGIIAGPVFLLFLIIIVFLVINYHQRVYHNRQRLDMEDPSCMC
LSKDKTLQDLVYDLSTSGSGSGLPLFVQRTVARTIVLQEIIGKGRFGEVWRGRWRGGDV
AVKIFSSREERSWFREAIEYQTVMLRHENILGFIAADNKDNGTWTQLWLVS DYHEHGS L
FDYLNRYTVTIEGMIKLALSAASGLAHLHMEIVGTQGKPGIAHRDLKSKNILVKKNGM
CAIADLGLAVRHDAVTDITIDIAPNQVRGTRYMAPEVLDETINMKHFDSFKCADIYALG
LVYWEIARRCNSGGVHEEYQLPYYDLVPSDPSIEEMRKVVCDQKL RPNIPNWWQSYEA
LRVMGKMMREC WYANGAARLTALRIKKTLSQLSVQEDVKI

NP_064733.3 (SEQ ID NO: 144)

MAESAGASSFFPLVVLALLAGSGGSGPRGVQALLCACTSCLQANYTCETDGACMVSIFNL
 DGMEHHVRTCIPKVELVPAGKPFYCLSSDLRNTHCCYTDYCNRIDLRVPSGHLKEPEH
 PSMWGPVELVGIIAGPVFLLFLIIIVFLVINYHQRVYHNRQRLDMEDPSCSEMCLSKDKTL
 QDLVYDLSTSGSGSGLPLFVQRTVARTIVLQEIIKGKGRFGEVWRGRWRGGDVAVKIFSS
 REERSWFREAIEYQTVMLRHENILGFIAADNKADCSFLTLPWEVVMVSAAPKLRSLRLQ
 YKGGRGRARFLFPLNNGTWTQLWLVS DYHEHGS LFDYLNRYTVTIEGMIKLALSAASG
 LAHLHMEIVGTQGKPGIAHRDLKSKNILVKKNGMCAIADLGLAVRHDAVTDTIDIAPN
 QRVGTKRYMAPEVLDETINMKHFDSFKCADIYALGLVYWEIARRCNSGGVHEEYQLPY
 YDLVPSDPSIEEMRKVVCDQKL RPNIPNWWQSYEALRVMGKMMREC WYANGAARLT
 ALRIKKTLSQLSVQEDVKI

[00098] Administering: As used herein, the terms “administering” or “administration” means to provide a complex to a subject in a manner that is physiologically and/or pharmacologically useful (*e.g.*, to treat a condition in the subject).

[00099] 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).

[000100] Antibody: As used herein, the term “antibody” refers to a polypeptide that includes at least one immunoglobulin variable domain or at least one antigenic determinant, *e.g.*, paratope that specifically binds to an antigen. In some embodiments, an antibody is a full-length antibody. In some embodiments, an antibody is a chimeric antibody. In some embodiments, an antibody is a humanized antibody. However, in some embodiments, an antibody is a Fab fragment, a F(ab')₂ fragment, a Fv fragment or a scFv fragment. In some embodiments, an antibody is a nanobody derived from a camelid antibody or a nanobody derived from shark antibody. In some embodiments, an antibody is a diabody. In some embodiments, an antibody comprises a framework having a human germline sequence. In another embodiment, an antibody comprises a heavy chain constant domain selected from the group consisting of IgG, IgG1, IgG2, IgG2A, IgG2B, IgG2C, IgG3, IgG4, IgA1, IgA2, IgD, IgM, and IgE constant domains. In some embodiments, an antibody comprises a heavy (H) chain variable region (abbreviated herein as VH), and/or a light (L) chain variable region (abbreviated herein as VL). In some embodiments, an antibody comprises a constant domain, *e.g.*, an Fc region. An

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

[000101] CDR: As used herein, the term "CDR" refers to the complementarity determining region within antibody variable sequences. A typical antibody molecule comprises a heavy chain variable region (VH) and a light chain variable region (VL), which are usually involved in antigen binding. The VH and VL regions can be further subdivided into regions of hypervariability, also known as "complementarity determining regions" ("CDR"), interspersed with regions that are more conserved, which are known as "framework regions" ("FR"). Each VH and VL is typically composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The extent of the framework region and CDRs can be precisely identified using methodology known in the art, for example, by the Kabat definition, the IMGT definition, the Chothia definition, the AbM definition, and/or (e.g., and) the contact definition, all of which are well known in the art. See, e.g., Kabat, E.A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; IMGT®, the international ImMunoGeneTics information system® www.imgt.org, Lefranc, M.-P. et al., Nucleic Acids Res., 27:209-212 (1999); Ruiz, M. et al., Nucleic Acids Res., 28:219-221 (2000); Lefranc, M.-P., Nucleic Acids Res., 29:207-209 (2001); Lefranc, M.-P., Nucleic Acids Res., 31:307-310 (2003); Lefranc, M.-P. et al., In Silico Biol., 5, 0006 (2004) [Epub], 5:45-60 (2005); Lefranc, M.-P. et al., Nucleic Acids Res., 33:D593-597 (2005); Lefranc, M.-P. et al., Nucleic Acids Res., 37:D1006-1012 (2009); Lefranc, M.-P. et al., Nucleic Acids Res., 43:D413-422 (2015); Chothia et al., (1989) Nature 342:877; Chothia, C. et al. (1987) J. Mol. Biol. 196:901-917, Al-lazikani et al (1997) J. Molec. Biol. 273:927-948; and Almagro, J. Mol. Recognit. 17:132-143 (2004). See also 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.

[000102] 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

	IMGT¹	Kabat²	Chothia³
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))

[000103] CDR-grafted antibody: The term "CDR-grafted antibody" refers to antibodies which comprise heavy and light chain variable region sequences from one species but in which the sequences of one or more of the CDR regions of VH and/or VL are replaced with CDR sequences of another species, such as antibodies having murine heavy and light chain variable regions in which one or more of the murine CDRs (*e.g.*, CDR3) has been replaced with human CDR sequences.

[000104] Chimeric antibody: The term "chimeric antibody" refers to antibodies which comprise heavy and light chain variable region sequences from one species and constant region sequences from another species, such as antibodies having murine heavy and light chain variable regions linked to human constant regions.

[000105] Complementary: As used herein, the term "complementary" refers to the capacity for precise pairing between two nucleosides or two sets of nucleosides. In particular, complementary is a term that characterizes an extent of hydrogen bond pairing that brings about binding between two nucleosides or two sets of nucleosides. For example, if a base at one

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

[000106] Conservative amino acid substitution: As used herein, a “conservative amino acid substitution” refers to an amino acid substitution that does not alter the relative charge or size characteristics of the protein in which the amino acid substitution is made. Variants can be prepared according to methods for altering polypeptide sequence known to one of ordinary skill in the art such as are found in references which compile such methods, e.g. Molecular Cloning: A Laboratory Manual, J. Sambrook, et al., eds., Fourth Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 2012, or Current Protocols in Molecular Biology, F.M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. Conservative substitutions of amino acids include substitutions made amongst amino acids within the following groups: (a) M, I, L, V; (b) F, Y, W; (c) K, R, H; (d) A, G; (e) S, T; (f) Q, N; and (g) E, D.

[000107] 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.

[000108] Cross-reactive: As used herein and in the context of a targeting agent (e.g., antibody), the term “cross-reactive,” refers to a property of the agent being capable of specifically binding to more than one antigen of a similar type or class (e.g., antigens of multiple homologs, paralogs, or orthologs) with similar affinity or avidity. For example, in some embodiments, an antibody that is cross-reactive against human and non-human primate antigens of a similar type or class (e.g., a human transferrin receptor and non-human primate transferrin receptor) is capable of binding to the human antigen and non-human primate antigens with a

similar affinity or avidity. In some embodiments, an antibody is cross-reactive against a human antigen and a rodent antigen of a similar type or class. In some embodiments, an antibody is cross-reactive against a rodent antigen and a non-human primate antigen of a similar type or class. In some embodiments, an antibody is cross-reactive against a human antigen, a non-human primate antigen, and a rodent antigen of a similar type or class.

[000109] Disease allele: As used herein, the term “disease allele” refers to any one of alternative forms (*e.g.*, mutant forms) of a gene, such as, but not limited to, a *MLCK1* gene, an *ACVR1* gene, or a *FBXO32* gene, for which the allele is correlated with and/or directly or indirectly contributes to, or causes, disease. A disease allele may comprise gene alterations including, but not limited to, insertions, deletions, missense mutations, nonsense mutations and splice-site mutations relative to a wild-type (non-disease) allele. In some embodiments, a disease allele has a loss-of-function mutation. In some embodiments, a disease allele has a gain-of-function mutation. In some embodiments, a disease allele encodes an activating mutation (*e.g.*, encodes a protein that is constitutively active). In some embodiments, a disease allele is a recessive allele having a recessive phenotype. In some embodiments, a disease allele is a dominant allele having a dominant phenotype. In some embodiments, a disease allele has a loss-of-function mutation in a gene encoding *MLCK1* (*MYLK*). In some embodiments, a loss-of-function mutation is as described in Halim D. et al. “Loss-of-Function Variants in *MYLK* Cause Recessive Megacystis Microcolon Intestinal Hypoperistalsis Syndrome.” *Am J Hum Genet.* 2017 Jul 6;101(1):123-129; Hannuksela M. et al. “A novel variant in *MYLK* causes thoracic aortic dissections: genotypic and phenotypic description.” *BMC Med Genet.* 2016 Sep 1;17(1):61; or Shalata, A. et al. “Fatal thoracic aortic aneurysm and dissection in a large family with a novel *MYLK* gene mutation: delineation of the clinical phenotype.” *Orphanet J Rare Dis.* 2018 Mar 15;13(1):41; the contents of each of which are incorporated herein by reference. In some embodiments, a disease allele has a gain-of-function mutation. In some embodiments, a disease allele encodes an activating mutation (*e.g.*, encodes a protein that is constitutively active). In some embodiments, a disease allele is a recessive allele having a recessive phenotype. In some embodiments, a disease allele is a dominant allele having a dominant phenotype. In some embodiments, a disease allele comprises a duplication (*e.g.*, a 7 base pair duplication (c.3838_3844dupGAAAGCG)), a splice-site variant (*e.g.*, c.3985+5C>A), a deletion (*e.g.*, a 2-bp deletion (c.3272_3273del, p.Ser1091*)), or a missense mutation (*e.g.*, a missense mutation at c.4471G > T (Ala1491Ser)). In some embodiments, a disease allele may comprise one or more deletions or substitutions that lead to alterations in the *ACVR1* protein, *e.g.*, L196P, R202I, R206H, Q207E, G328R, G328W, G328E, G356D, R375P, ΔP197-F198. In some embodiments, a subject may have Fibrodysplasia ossificans progressiva (FOP). In some

embodiments, a subject having FOP may have one or two mutated ACVR1 alleles. In some embodiments, a subject having classic or typical FOP has an ACVR1 allele comprising a mutation that leads to R206H ACVR1 protein. In some embodiments, a subject having atypical FOP has an ACVR1 allele comprising at least one mutation that leads to mutated ACVR1 protein that does not comprise the R206H mutation. In some embodiments, a diseased allele of MEF2D is an isoform of MEF2D lacking the β -exon and is associated with muscle degeneration disorders such as myotonic dystrophy (e.g., as described in Lee et al., The Journal of Biological Chemistry, 285, 33779-33787, 2010, incorporated herein by reference). In some embodiments, a disease allele of MED13 comprises a missense mutation. In some embodiments a disease allele of MED13 encodes a T326I, P327S and/or P327Q mutation. In some embodiments, a disease allele of MED13 comprises an in-frame deletion (e.g., of nucleotides encoding T326). In some embodiments, the disease MED13 allele is as described in Snijders Blok L., et. al, "De novo mutations in MED13, a component of the Mediator complex, are associated with a novel neurodevelopmental disorder" Hum. Genet. 2018, 137:375–388.; the contents of which are incorporated herein by reference.

[000110] FBXO32: As used herein, the term, "FBXO32," refers to a gene that encodes a F-box adaptor protein and is a member of SKP1-cullin-F-box (SCF) ubiquitin protein ligase complex. FBXO32 can bind substrates for ubiquitination by the SCF complex. In some embodiments, FBXO32 may be a human (Gene ID : 114907 (e.g., SEQ ID NO: 505).), non-human primate (e.g., Gene ID: 102141240 (e.g., SEQ ID NO: 653)), or rodent gene (e.g., Gene ID: 67731 (e.g., SEQ ID NO: 506), Gene ID: 171043 (e.g., SEQ ID NO: 654)). In addition, exemplary human transcripts (e.g., as annotated under GenBank RefSeq Accession Number: NM_058229.4 (SEQ ID NO: 505), NM_001242463.2 (SEQ ID NO: 655), and NM_148177.2 (SEQ ID NO: 656)) have been characterized. An exemplary FBXO32 protein, encoded by a human FBXO32 gene, is annotated under NCBI Reference Sequence: NP_478136.1, and has the following amino acid sequence:

MPFLGQDWRSPGQNWVKTADGWKRFLDEKSGSFVSDLSSYCNKEVYNKENLNFNSLNY
DVAACKRRKKDMLNSKTKTQYFHQEKWIYVHKGSTKERHGYCTLGEAFNRLDFSTAIL
DSRRFNYVVRLLLELIAKSQLTSLSGIAQKNFMNILEKVVLKVLEDQQNIRLIRELLQTLTY
TSLCTLVQRVGKSVLVGNINMWVYRMETILHWQQQLNNIQITRPAFKGLTFTDLPLCLQ
LNIMQRLSDGRDLVSLGQAAPDLHVLSEDRLWKKLCQYHFSEKQIRKRLILSDKGQLD
WKKMYFKLVRCYPRKEQYGDTLQLCKHCHILSWKGTDPCTANNPESCSVSLSPQDFI
NLFKF. (SEQ ID NO: 503)

[000111] 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.

[000112] 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.

[000113] Humanized antibody: The term "humanized antibody" refers to antibodies which comprise heavy and light chain variable region sequences from a non-human species (*e.g.*, a mouse) but in which at least a portion of the VH and/or VL sequence has been altered to be more "human-like", *i.e.*, more similar to human germline variable sequences. One type of humanized antibody is a CDR-grafted antibody, in which human CDR sequences are introduced into non-human VH and VL sequences to replace the corresponding non-human CDR sequences. In one embodiment, humanized anti-transferrin receptor 1 antibodies and antigen binding portions are provided. Such antibodies may be generated by obtaining murine anti-transferrin receptor 1 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.

[000114] INHBA: As used herein, the term, "INHBA" or "inhibin, beta A" refers to a gene that encodes inhibin, beta A (INHBA). In some embodiments, an INHBA gene may be a human INHBA gene (Gene ID: 3624 (*e.g.*, SEQ ID NO: 269)), non-human primate INHBA gene (*e.g.*, Gene ID: 102146142 (*e.g.*, SEQ ID NO: 391), Gene ID: 702734 (*e.g.*, SEQ ID NO: 392)), or

rodent INHBA gene (*e.g.*, Gene ID: 16323 (*e.g.*, SEQ ID NO: 270), Gene ID: 29200 (*e.g.*, SEQ ID NO: 393)). In addition, an exemplary human transcript (*e.g.*, as annotated under GenBank RefSeq Accession Number: NM_002192.4 (SEQ ID NO: 269)) has been characterized. An exemplary INHBA protein, encoded by a human INHBA gene, is annotated under NCBI Reference Sequence: NP_002183.1, and has the following amino acid sequence:

MPLLWLRGFLASCWIIVRSSPTPGSEGHSAAPDCPSCALAALPKDVPNSQPEMVEAVK
KHILNMLHLKKRPDVTQVPKAAALLNAIRKLHVGKVGGENGYVEIEDDIGRRAEMNELM
EQTSEIITFAESGTARKTLHFEISKEGSDLSVVERAEVWLFLKVPKANRTRTKVTIRLFQQ
QKHPQGSLDTGEEAAEEVGLKGERSELLSEKVVDARKSTWHVFPVSSSIQRLLDQGKSS
LDVRIACEQCQESGASLVLLGKKKKKEEGEGKKKGGGEGGAGADEEKEQSHRPFLM
LQARQSEDHPRRRRRGLECDGKVNICKKKQFFVSFKDIGWNDWIIAPSGYHANYCEG
ECPSHIAGTSGSSLSFHSTVINHYRMRGHSPFANLKSCCVPTKLRPMSMLYDDGQNIHK
KDIQNMIVEECGCS (SEQ ID NO: 145)

[000115] Internalizing cell surface receptor: As used herein, the term, “internalizing cell surface receptor” refers to a cell surface receptor that is internalized by cells, *e.g.*, upon external stimulation, *e.g.*, ligand binding to the receptor. In some embodiments, an internalizing cell surface receptor is internalized by endocytosis. In some embodiments, an internalizing cell surface receptor is internalized by clathrin-mediated endocytosis. However, in some embodiments, an internalizing cell surface receptor is internalized by a clathrin-independent pathway, such as, for example, phagocytosis, macropinocytosis, caveolae- and raft-mediated uptake or constitutive clathrin-independent endocytosis. In some embodiments, the internalizing cell surface receptor comprises an intracellular domain, a transmembrane domain, and/or an extracellular domain, which may optionally further comprise a ligand-binding domain. In some embodiments, a cell surface receptor becomes internalized by a cell after ligand binding. In some embodiments, a ligand may be a muscle-targeting agent or a muscle-targeting antibody. In some embodiments, an internalizing cell surface receptor is a transferrin receptor.

[000116] Isolated antibody: An “isolated antibody”, as used herein, is intended to refer to an antibody that is substantially free of other antibodies having different antigenic specificities (*e.g.*, an isolated antibody that specifically binds transferrin receptor is substantially free of antibodies that specifically bind antigens other than transferrin receptor). An isolated antibody that specifically binds transferrin receptor complex may, however, have cross-reactivity to other antigens, such as transferrin receptor molecules from other species. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[000117] 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.

[000118] KLF15: As used herein, the term, “KLF15,” refers to a gene that encodes Krüppel-like factor 15 protein, a transcription factor that, in cardiac and skeletal muscle cells, functions to inhibit the activity of MEF2 and other cardiac transcription factors (*e.g.*, GATA4 and myocardin). In some embodiments, KLF15 refers to a human KLF15 (Gene ID: 28999 (*e.g.*, SEQ ID NO: 1045)), a non-human primate KLF15 (*e.g.*, Gene ID: 716386 (*e.g.*, SEQ ID NO: 1046), Gene ID: 470911 (*e.g.*, SEQ ID NO: 1047)), or rodent KLF15 (*e.g.*, Gene ID: 66277 (*e.g.*, SEQ ID NO: 1048), Gene ID: 85497 (*e.g.*, SEQ ID NO: 1049)). In addition, multiple human KLF15 transcript variants (*e.g.*, as annotated under GenBank RefSeq Accession Numbers: NM_014079.4 (SEQ ID NO: 740), XM_011512743.2 (SEQ ID NO: 1050), and XM_005247400.4 (SEQ ID NO: 1051)) have been characterized that encode different protein isoforms. An exemplary KLF15 protein isoform, encoded by a human KLF15 gene, is annotated under NCBI Reference Sequence: NP_054798.1, and has the following amino acid sequence:

MVDHLLPVDENFSSPKCPVGYLGDRLVGRRAYHMLPSPVSEDDSDASSPCSCSSPDSQA
LCSCYGGGLGTESQDSILDFLLSQATLGSGGGSGSSIGASSGPVAVGWPWRAAAPVKGE
HFCLPEFPLGDPDDVPRPFQPTLEEIEEFLEENMEPGVKEVPEGNSKDLDACSQLSAGPH
KSHLHPGSSGRERCSPPPGGASAGGAQGGGPTPDGPIPVLLQIQVPVKQESGTGPAS
PGQAPENVKVAQLLVNIQGQTFALVPQVVPSSNLNLPSKFVRIAPVPIAAKPVGSGPLGP
GPAGLLMGQKFPKNPAAELIKMHKCTFPGCSKMYTKSSHLKAHLRRHTGEKPFCTWP
GCGWRFSSRSDLSRHRRSHSGVKPYQCPVCEKKFARSDHLSKHIKVHRFPRSSRSVRSV
N (SEQ ID NO: 131)

[000119] Mediator (MED) complex subunit: As used herein, the term “Mediator complex subunit” or “subunit of the Mediator complex” refers to an individual component of the Mediator complex. Subunits of the Mediator complex include MED1, MED13, MED14, MED15, MED23, MED25, CDK8, and others. Simple eukaryotes (*e.g.*, *Saccharomyces cerevisiae* (yeast)) commonly have up to 21 MED complex subunits; while mammals typically have between 26 and 31 MED complex subunits.

[000120] MED1: As used herein, the term, “MED1,” generally refers to a gene that encodes Mediator complex subunit 1 (MED1). In some embodiments, MED1 may be a human (Gene ID: 5469 (e.g., SEQ ID NO: 1052)), non-human primate (e.g., Gene ID: 101925389 (e.g., SEQ ID NO: 1053), Gene ID: 697781 (e.g., SEQ ID NO: 1054)), or rodent gene (e.g., Gene ID: 19014 (e.g., SEQ ID NO: 1055), Gene ID: 497991 (e.g., SEQ ID NO: 1056)). In addition, an exemplary human transcript (e.g., as annotated under GenBank RefSeq Accession Number: NM_004774.4 (SEQ ID NO: 814)) has been characterized. An exemplary MED1 protein, encoded by a human MED1 gene, is annotated under NCBI Reference Sequence: NP_004765.2; and has the following amino acid sequence:

MKAQGETEESEKLSKMSSLLERLHAKFNQNRPWSETIKLVRQVMEKRVMSSGGHGHQHLVSCLETQKALKVTSPLPAMTDRLESARQNGLGSHLSASGTECYITSDMFYVEVQLDPAAGQLCDVKVAHHGENPVSCPELVQQLREKNFDEFKHLKGLVNLNLPDGNKLKTKMYLALQSLEQDLSKMAIMYWKATNAGPLDKILHGSVGYLTPRSGGHLMNLYVSPSLLDDKTASPIILHENNVSRSLGMNASVTIEGTSAVYKLPIAPLIMGSHPDNKNWTPSFSSITSANSVDLPACFFLKFPQPIPVSRFAFVQKLQNCTGIPLFETQPTYAPLYELITQFELSKDPDPIPLNHNMRFYAALPGQQHCYFLNKDAPLPDGRSLQGTLVSKITFQHPGRVPLILNLIRHQVAYNTLIGSCVKRTILKEDSPGLLQFEVCPLSESRFSVSFQHPVNDSLVCVMDVQDSTHVSCKLYKGLSDALICTDDFIAKVVQRCMSIPVTMRAIRRAETIQADTPALSIAETVEDMVKKNLPPASSPGYGMTTGNNPMSGTTTPTNTFPGGPITTLFNMSMSIKDRHESVGHGEDFSKVSQNPILTSLLQITGNGGSTIGSSPTPPHHTPPVSSMAGNTKNHPMLMNLLKDNPAQDFSTLYGSSPLERQNSSSGSPRMEICSGSNKTKKKKSSRLPPEKPKHQTEDDFQRELFSMDVDSQNPFDVNMTADTLTPHITPAPSQCSTPPTTYPQVPHPQPSIQRMVRLSSDSIGPDVTDILSDIAEEASKLPSTSDDCPAIGTPLRDSSSSGHSQSTLFDSDFQTNNNENPYTDPADLIADAAGSPSSDSPTNHFFHFDGVDFNPDLLNSQSQSGFGEEYFDESSQSGDNDDFKGFASQALNTLGVPMGLGGDNGETKFKGNNQADTVDFSIISVAGKALAPADLMEHHSQSQGPLTTGDLGKEKTQKRVKKEGNGTSNSTLSGPGLDSKPGKRSRTPSNDGKSKDKPKPKRKKADTEGKSPSHSSSNRPFTPPTSTGGSKSPGSAGRSQTPPGVATPPPIKITIQIPKGTVMVGKPPSSHSQYTSSGSVSSSGSKSHSHSSSSSSASTSGMKSSKSEGSSSSKLSSSMYSSQGSSGSSQSKNSSQSGGKPGSSPITKHGLSSGSSSTKMKPQGKPSLMNPSLSKPNISPSHSRPPGGSDKLASPMKPVPGTPPSSKAKSPISSGSGGSHMSGTSSSSGMKSSSGLGSSGSLSQKTPPSSNSCTASSSSFSSSGSSMSSSQNHGSSKGKSPSRNKKPSLTAVIDKLKHGVVTSGPGGEDPLDGQMGVSTNSSSHPMSSSKHNMSGGEFQGKREKSDKDKSKVSTSGSSVDSSKKTSESKNVGSTGVAKIIISKHDGGSPSIKAKVTLQKPGESSGEGLRPQMASSKNYGSPLISGSTPKHERGSPSHSKSPAYTPQNLDSESESGSSIAEKSYQNSPSSDDGIRPLPEYSTEKHKHKHKEKKKKVKDKDRDRDRDKDRDKKKSHSIKPESWSKSPISSDQSLSMTSNTILSADRP SRLSPDFMIGEEDDDLMDVALIGN (SEQ ID NO: 138)

[000121] MED13: As used herein, the term, “MED13” or “PROSIT240” generally refers to a gene that encodes Mediator complex subunit 13 (MED13). MED13 is one component of a four-subunit kinase module of the Mediator complex that further comprises cyclin C, cyclin-dependent kinase 8 (CDK8), and MED12. In some embodiments, MED13 may be a human (Gene ID : 9969 (e.g., SEQ ID NO: 1057)), non-human primate (e.g., Gene ID: 712277 (e.g., SEQ ID NO: 1058), Gene ID: 102120434 (e.g., SEQ ID NO: 1059)), or rodent gene (e.g., Gene ID: 327987 (e.g., SEQ ID NO: 1060), Gene ID: 303403 (e.g., SEQ ID NO: 1061)). In addition,

an exemplary human transcript of MED13 (e.g., as annotated under GenBank RefSeq Accession Number: NM_005121.3 (SEQ ID NO: 888)) has been characterized. An exemplary MED13 protein, encoded by a human MED13 gene, is annotated under NCBI Reference Sequence: NP_005112.2; and has the following amino acid sequence:

MSASFVPNGASLEDCHCNLFCLADLTGIKWKKYVWQGPTSAPILFPVTEEDPILSSFSRC
LKADVLGVWRRDQRPGRRELWIFWWGEDPSFADLIHHDLSEEEDGVWENGLSYECRT
LLFKAVHNLLERCLMNRFVFRIGKWFVKPYEKDEKPINKSEHLSCSFTFFLHGDSNVCT
SVEINQHQPVYLLSEEHITLAQQSNSPFQVILCPFGLNGTLTGQAFKMSDSATKKLIGEW
KQFYPISSCCLKEMSEEKQEDMDWEDDSLAAVEVLVAGVRMIYPACFVLVPQSDIPTSP
VGSTHCSSSCLGVHQPASTRDPAMSSVTLTPTSPPEEVQTVDPQSVQKWVKFSSVSDG
FNSDSTSHHGKIPRKLANHVVDRVWQECNMNRAQNKRKYSASSGGLCEEATAAKVA
SWDFVEATQRTNCSCLRHKNLKSRNAGQQGQAPSLGQQQQILPKHKTNEKQEKSEKPK
KRPLTPFHHRVSVSDDVGMADASASQRLVISAPDSQVRFNSNIRTNDVAKTPQM HGTEM
ANSPQPPPLSPHPCDVVDEGVTKTPSTPQSQH FYQMPTPDPLVPSKPMEDRIDSLSQSFPF
QYQEAVEPTVYVGTAVNLEEDEANIAWKYYKFPKKKDVEFLPPQLPSDKFKDDPVGPF
GQESVTSVTELMVQCKKPLKVSDEL VQQYQIKNQCLS AIASDAEQEPKIDPYAFVEGDE
EFLFPDKKDRQNSEREAGKKHKVEDGTSSVTLSHEEDAMSLFSPSIKQDAPRPTSHAR
PPSTSLIYDSDLAVSYTDLDNLFNSDEDELTPGSKKSANGSDDKASCKESKTGNLDPLSC
ISTADLHKMYPTPPSLEQHIMGFSPMNMNKEYYGSMDTTPGGTVLEGNSSSIGAQFKIE
VDEGFCSKPSEIKDFS YVYKPENCQILVGCSMFAPLKTLP SQYLPPIKLPEECIYRQSWT
VGKLELLSSGPSMPFIKEGDGSNMDQEYGTAYTPQTHTSFGMPSSAPPSNSGAGILPSP
STPRFPTPRTPTPTPTPRGAGGPASAQGSVKYENS DLYSPASTPSTCRPLNSVEPATVPSI
PEAHSLYVNLILSESVMNLFKDCNFDSCCICVCNMNIKGADVGVYIPDPTQEAQYRCTC
GFSAVMNRKFGNNSGLFLEDELDIIGRNTDCGKEAEKRFEALRATSAEHVNGGLKESEK
LSDDLILLQDQCTNLFSPFGAADQDPFPKSGVISNWVRVEERDCCNDCYLALAHGRQF
MDNMSGGKVDEALVKSSCLHPWSKRNDVSMQCSQDILRMLLSLQPVLDQAIQKKRTV
RPWGVQGGLTWQQFHKMAGRGSYGTDESPEPLPIPTFLLGYDYDYLVLSPFALPYWER
LMLEPYGSQRDIA YVVLCPENEALLNGAKSFFRDLTAIYESCRLGQHRPVSRLTLDGIM
RVGSTASKKLSEKLVAEWFSQAADGNNEAFSKLKYAQVCRYDLGPYLASLPLDSSLL
SQPNLVAPTSQSLITPPQMTNTGNANTPSATLASAASSTMTVTSGVAISTSVATANSTLT
TASTSSSSSSNLNSGVSSNKLPSFPFGSMNSNAAGSMSTQANTVQSGQLGGQQTSA LQ
TAGISGESSSLPTQPHPDVSESTMDRDKVGIPTDGDSHAVTYPPIVYIIDPFTYENTDE
STNSSSVWTLGLLRCFLEMVQTLPPHIKSTVSVQIIPCQYLLQPVKHEDREIYPQHLKSLA
FSAFTQCRRLPTSTNVKTLTGFGPGLAMETALRSPDRPECIRLYAPPFILAPVKDKQTEL
GETFGEAGQKYNVLFVGYCLSHDQRWILASCTDLYGELLETCIINIDVPNRARRKKSSA
RKFGQLKLWEWCLGLVQMSSLPW RVVIGRLGRIGHGELKDWSCLLSRRNLQSLSKRLK
DMCRMCGISAADSPSILSACL VAMEPQGSFVIMPDSVSTGSVFGRSTTLNMQTSQLNTP
QDTSCTHILVFPTSASVQVASATYTTENLDLAFNPNNNDGADGMGIFDLDTGDDLDPDII
NILPASPTGSPVHSPGSHYPHGGDAGKGQSTDRLSTEPHEEVPNILQQPLALGYFVSTA
KAGPLPDWFW SACPQAQYQCPLFLKASLHLHVPSVQSDELLHSKHSPLDSNQTSDVL
RFVLEQYNALSWLTCDPATQDRRSCLPIHFVVLNQLYNFIMNML (SEQ ID NO: 139)

[000122] MEF2D: As used herein, the term, “**MEF2D**,” refers to a gene that encodes myocyte enhancer factor 2D, a member of the myocyte-specific enhancer factor 2 (MEF2) family of transcription factors. MEF2D binds specifically to the MEF2 element, 5'-YTA[AT]4TAR-3', found in numerous muscle-specific, growth factor and stress induced genes. MEF2D mediates cellular functions not only in skeletal and cardiac muscle development, but also in neuronal differentiation and survival. MEF2D also plays diverse roles in the control of

cell growth, survival and apoptosis and in the regulation of neuronal apoptosis. MEF2D has been shown to play important roles in heart development and in heart diseases (e.g., cardiac hypertrophy, cardiomyopathy), and in muscular diseases (e.g., muscle atrophy, myotonic dystrophy). See e.g., Chen et al., *Oncotarget*. 2017 Dec 19; 8(67): 112152–112165, incorporated herein by reference. It has been shown that reducing MEF2D activity in the heart resulted in resistance to cardiac hypertrophy, fetal gene activation, and fibrosis in response to pressure overload and β -chronic adrenergic stimulation in mice, and that overexpression of MEF2D was sufficient to drive the fetal gene program and pathological remodeling of the heart (see, e.g., Kim et al., *J Clin Invest*. 2008 Jan 2; 118(1): 124–132, incorporated herein by reference). Additionally, MEF2D is involved in neuromuscular diseases, such as Parkinson's disease (see, e.g., Yao et al., *The Journal of Biological Chemistry*, 287, 34246-34255, 2012, incorporated herein by reference) and amyotrophic lateral sclerosis (see, e.g., Arosio et al., *Molecular and Cellular Neuroscience*, Volume 74, July 2016, Pages 10-17, incorporated herein by reference). In some embodiments, MEF2D refers to a human (Gene ID: 4209 (e.g., SEQ ID NO: 664)), a non-human primate (e.g., Gene ID: 102143822 (e.g., SEQ ID NO: 1062), or rodent gene (e.g., Gene ID: 17261 (e.g., SEQ ID NO: 666), Gene ID: 81518 (e.g., SEQ ID NO: 1063)). In addition, multiple human MEF2D transcript variants (e.g., as annotated under GenBank RefSeq Accession Numbers: NM_001271629.2 (SEQ ID NO: 665), NM_005920.4 (SEQ ID NO: 664), XM_006711332.3 (SEQ ID NO: 1036), XM_006711334.3 (SEQ ID NO: 1037), XM_006711333.2 (SEQ ID NO: 1038), XM_005245169.4 (SEQ ID NO: 1039), XM_017001315.1 (SEQ ID NO: 1040), XM_006711330.3 (SEQ ID NO: 1041), XM_005245170.3 (SEQ ID NO: 1042), XM_011509569.3 (SEQ ID NO: 1043), and XM_017001314.1 (SEQ ID NO: 1044)) have been characterized that encode different protein isoforms. Exemplary MEF2D protein isoforms, encoded by a human MEF2D gene, are annotated under NCBI Reference Sequence: NP_001258558.1 and NP_005911.1, and has the following amino acid sequence, respectively:

MGRKKKIQIRITDERNRQVTFTKRKFGLMKKAYELSVLCDCEIALIIFNHSNKLRFQYAST
DMDKVLLKYTEYNEPHESRTNADIETLRKKGFNGCDSPEPDGEDSLEQSPILLEDKYRR
ASEELDGLFRRYGSTVPAPNFAMPVTVPVSNQSSLQFSNPSSGLVTPSLVTSSLTDPRLLS
PQQPALQRNSVSPGLPQRPASAGAMLGGDLNSANGACPSVGNGYVSARASPGLLPVA
NGNSLNKVIPAKSPPPPTHSTQLGAPS RKPDLRVITSQAGKGLMHHLNNAQRLGV SQST
HSLTTPVVSVATPSLLSQGLPFSSMPTAYNTDYQLTSAELSSLP AFSSPGGLSLGNVTAW
QQPQQPQQPQQPQQPQQPQQPQQPQQPQQPQQPQQPQQSHLVPVSLSNLIPGSPLPHV
GAALT VTTHPHISIKSEPVSPSRERS PAPP PPAVFPAARPEPGDGLSSPAGGSYETGDRDD
GRGDFGPTLGLLRPAPEPEAE GSAVKRMRLDTWTLK (SEQ ID NO: 140)

MGRKKIQIRITDERNRQVTFTKRKFGLMKKAYELSVLCDCEIALIIFNHSNKLQYAST
DMDKVLLKYTEYNEPHESRTNADIETLRKKGFNGCDSPEPDGEDSLEQSPILLEDKYRR
ASEELDGLFRRYGSTVPAPNFAMPVTVPVSNQSSLOFSNPSGSLVTPSLVTSSLTDPRLLS

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PQQPALQRNSVSPGLPQRPASAGAMLGGDLNSANGACPSPVGNGYVSARASPGLLPVA
NGNSLNKVIPAKSPPPTHTSTQLGAPSRKPDLRVITSQAGKGLMHHLTEDHLDLNNNAQR
LGVSQSTHSLTTPVVSVATPSLLSQGLPFSSMPTAYNTDYQLTSAELSSLPAFSSPGGLSL
GNVTAWQQPQQPQQPQQPQQPQQPQQPQQPQQPQQPQQPQQPQQPQQPQQPQQPQQPQQPQQSHLVPSLSNLIP
GSPLPHVGAAALTVTTHPHISIKSEPVSPSRERSPAPPPPAVFPAARPEPGDGLSSPAGGSYE
TGDRDDGRGDFGPTLGLLRPAPEPEAEGS AVKRMRLDTWTLK (SEQ ID NO: 141)

[000123] Molecular payload: As used herein, the term “molecular payload” refers to a molecule or species that functions to modulate a biological outcome. In some embodiments, a molecular payload is linked to, or otherwise associated with a muscle-targeting agent. In some embodiments, the molecular payload is a small molecule, a protein, a peptide, a nucleic acid, or an oligonucleotide. In some embodiments, the molecular payload functions to modulate the transcription of a DNA sequence, to modulate the expression of a protein, or to modulate the activity of a protein. In some embodiments, the molecular payload is an oligonucleotide that comprises a strand having a region of complementarity to a target gene.

[000124] MLCK1: As used herein, the term, “MLCK1” or “MYLK1” refers to a gene that encodes myosin light chain kinase-1 protein, which is an enzyme that phosphorylates myosin regulatory light chains in order to facilitate myosin interaction with actin filaments in smooth muscle. In some embodiments, MLCK1 may be a human (Gene ID : 4638 (e.g., SEQ ID NO: 412)), non-human primate (*e.g.*, Gene ID: 102130711 (*e.g.*, SEQ ID NO: 413)), or rodent gene (*e.g.*, Gene ID: 107589 (*e.g.*, SEQ ID NO: 414), Gene ID: 288057 (*e.g.*, SEQ ID NO: 415)). In addition, several exemplary human transcripts (*e.g.*, as annotated under GenBank RefSeq Accession Number: NM_001321309.2 (SEQ ID NO: 416), NM_053025.4 (SEQ ID NO: 417), NM_053026.4 (SEQ ID NO: 418), NM_053027.4 (SEQ ID NO: 419), NM_053028.4 (SEQ ID NO: 420), NM_053031.4 (SEQ ID NO: 421), and NM_053032.4 (SEQ ID NO: 422)) has been characterized.

[000125] An exemplary MLCK1 protein, encoded by a human MLCK1 gene, is annotated under NCBI Reference Sequence: NP_444253.3, and has the following amino acid sequence:

MGDVKLVASSHISKTSLSVDPSRVDSMPLTEAPAFILPPRNLCIKEGATAKFEGRVRGYP
EPQVTWHRNGQPITSGGRFLLDCGIRGTFSLVIHAVHEEDRGKYTCEATNGSGARQVTV
ELTVEGSFAKQLGQPVVSKTLGDRFSAPAVETRPSIWGECPPKFATKLGRVVVKEGQM
GRFSCKITGRPQPQVTWLKGNVPLQPSARVSVSEKNGMQVLEIHGVNQDDVGVYTCLV
VNGSGKASMSAELSIQGLDSANRSFVRETKATNSDVRKEVTNVISKESK LDSLEAAKS
KNCSSPQRGGSPWAANSQPQPPRESKLESCKDSPRTAPQTPVLQKTSSSITLQAARVQP
EPRAPGLGVLSPSGEERKRPAAPRPATFPTRQPGLGSQDVVSKAANRRIPMEGQRDSAFP
KFESKPQSQEVKENQTVKFRCEVSGIPKPEVAWFLEGTPVRRQEGSIEVYEDAGSHYLC
LLKARTRDSGTYSCTASNAQGOLSCSWTLOVERLAVMEVAPSFSSVLKDCAVIEGODF

VLQCSVRGTPVPRITWLLNGQPIQYARSTCEAGVAELHIQDALPEDHGTYTCLAENALG
 QVSCSAWVTVHEKKSSRKSEYLLPVAPSKPTAPIFLQGLSDLKVMDSQVTMTVQVSG
 NPPPEVIWLHNGNEIQESEDHFHEQRTQHSLCIQEVFPEDTGTYTCEAWNSAGEVRTQ
 AVLTVQEPHDGTQPWFISKPRSVTASLGQSVLISCAIAGDPFPTVHWRDGGKALCKDTG
 HFEVLQNEVDFTLVLLKKVQPPWHAGQYEILLKNRVGECSCQVSLMLQNSSARALPRGRE
 PASCEDLCGGGVGADGGGSDRYGSLRPGWPARGQGWLEEDGEDVRGVLKRRVETR
 QHTEEAIRQQEVEQLDFRDLLGKKVSTKTLSEDDLKEIPAEQMDFRANLQRQVKPKTVS
 EEERKVHSPQQVDFRSVLAKKGTSKTPVPEKVPKPPKATPDRSVLGGKKKLPAENGSS
 SAETLNAKAVESSKPLSNAQPSGPLKPVGNAKPAETLKPMGNAKPAETLKPMGNAKPD
 ENLKSASKEELKKDVKNDEVNCKRGHAGTTDNEKRSESQGTAPAFKQKLQDVHVAEGK
 KLLLQCQVSSDPPATIIWTLNGKTLKTTKFIILSQEGLCSVSIEKALPEDRGLYKCVAKN
 DAGQAECSCQVTVDAPASENTKAPEMKSRRPKSSLPPVLGTESDATVKKKPAPKTPP
 KAAMPPQIIQFPEDQKVRAGESVELFGKVTGTQPITCTWMKFRKQIQESEHMKVENSEN
 GSKLTILAAARQEHCGCYTLLVENKLGSRQAQVNLTVVDKPDPPAGTPCASDIRSSSLTSL
 WYGSSYDGGSAVQSYSIEIWDSSANKTWKELATCRSTSFNVQDLLPDHEYKFRVRAINV
 YGTSEPSQESELTTVGEKPEEPKDEVEVSDDDEKEPEVDYRTVTINTEQKVSDFYDIEER
 LGSGKFGQVFRLEVEKKTRKVVWAGKFFKAYSACEKENIRQEISIMNCLHHPKLVQCVDA
 FEEKANIVMVLEIVSGGELFERIIDEDFELTERECIKYMRQISEGVEYIHKQGIVHLDLKPE
 NIMCVNKTGTRIKLIDFGLARRLENAGSLKVLFGTPEFVAPEVINYEPIGYATDMWSIGV
 ICYILVSGLSPFMGDNDNETLANVTSATWDFDDEAFDEISDDAKDFISNLLKKDMKNRL
 DCTQCLQHPWLMKDTKNMEAKKLSKDRMKKYMARRKWQKTGNAVRAIGRLSSMA
 MISGLSGRKSSTGSPTSPLNAEKLESEEDVSQAFLEAVAEKPHVKPYFSKTIRDLEVVE
 GSAARFDCKIEGYPDPEVVWFKDDQSIRESRHFQIDYDEDGNCSLIISDVCGDDDAKYT
 CKAVNSLGEATCTAELIVETMEEGEGEGEEEE (SEQ ID NO: 410)

[000126] MSTN: As used herein, the term, “MSTN,” refers to a gene that encodes myostatin a secreted growth factor that negatively regulates muscle mass. In some embodiments, MSTN may be a human (Gene ID: 2660 (e.g., SEQ ID NO: 147)), non-human primate (e.g., Gene ID: 710114 (e.g., SEQ ID NO: 394), Gene ID: 470605 (e.g., SEQ ID NO: 395)), or rodent gene (e.g., Gene ID: 29152 (e.g., SEQ ID NO: 396), Gene ID: 17700 (e.g., SEQ ID NO: 148)). In addition, an exemplary human transcript (e.g., as annotated under GenBank RefSeq Accession Number: NM_005259.3 (SEQ ID NO: 147)) has been characterized. An exemplary myostatin protein, encoded by a human MSTN gene, is annotated under NCBI Reference Sequence: NP_005250.1 and has the following amino acid sequence:

MQKLQLCVYIYLFMLIVAGPVDLNNSEKQKENVEKEGLCNACTWRQNTKSSRIEAIKIQ
 ILSKLRLETAPNISKDVIRQLLPKAPPLRELIDQYDVQRDDSSDGSLEDDDYHATTETIIT

MPTESDFLMQVDGKPKCCFFKFSSKIQYNKVVKAQLWIYLRPVETPTTVFVQILRLIKP
 MKDGTRYTGIRSLKLDMPGTGIWQSIDVKTVLQNWLKQPESNLGIEIKALDENGHD
 AVTFPGPGEDGLNPFLEVKVTDTPKRSRRDFGLDCDEHSTESRCCRYPLTVDFEAFGWD
 WIIAPKRYKANYCSGECEFLQKYPHTLVHQRNPRGSAGPCCTPTKMSPINMLYFNG
 KEQIIYGKIPAMVVDRCGCS (SEQ ID NO: 146)

[000127] Muscle atrophy: As used herein, the term, “muscle atrophy,” refers to a condition characterized by muscle wasting. In some embodiments, muscle atrophy is a highly regulated catabolic process which occurs during periods of disuse and/or in response to systemic inflammation (*e.g.*, cachexia). In some embodiments, muscle atrophy is associated with diminishing muscle mass, reduction in muscle size, and/or reduction in the number of muscle cells in a subject. Conditions, including chronic illnesses (*e.g.*, congestive heart failure, diabetes, cancer, AIDS, and renal disease), severe burns, critical care myopathy, limb denervation, stroke, limb fracture, anorexia, spinal cord injury or other conditions leading to muscle disuse may result in muscle atrophy. In some embodiments, muscle atrophy is caused by cancer cachexia, cardiac cachexia, fasting, diabetes, renal failure, denervation, or glucocorticoid-induced muscle atrophy.

[000128] Muscle-targeting agent: As used herein, the term, “muscle-targeting agent,” refers to a molecule that specifically binds to an antigen expressed on muscle cells (*e.g.*, cardiac muscle cells). The antigen in or on muscle cells may be a membrane protein, for example an integral membrane protein or a peripheral membrane protein. Typically, a muscle-targeting agent specifically binds to an antigen on muscle cells that facilitates internalization of the muscle-targeting agent (and any associated molecular payload) into the muscle cells. In some embodiments, a muscle-targeting agent specifically binds to an internalizing, cell surface receptor on muscles and is capable of being internalized into muscle cells through receptor mediated internalization. In some embodiments, the muscle-targeting agent is a small molecule, a protein, a peptide, a nucleic acid (*e.g.*, an aptamer), or an antibody. In some embodiments, the muscle-targeting agent is linked to a molecular payload.

[000129] Muscle-targeting antibody: As used herein, the term, “muscle-targeting antibody,” refers to a muscle-targeting agent that is an antibody that specifically binds to an antigen found in or on muscle cells (*e.g.*, cardiac muscle cells). In some embodiments, a muscle-targeting antibody specifically binds to an antigen on muscle cells that facilitates internalization of the muscle-targeting antibody (and any associated molecular payment) into the muscle cells. In some embodiments, the muscle-targeting antibody specifically binds to an internalizing, cell surface receptor present on muscle cells. In some embodiments, the muscle-targeting antibody is an antibody that specifically binds to a transferrin receptor.

[000130] Oligonucleotide: As used herein, the term “oligonucleotide” refers to an oligomeric nucleic acid compound of up to 200 nucleotides in length. Examples of oligonucleotides include, but are not limited to, RNAi oligonucleotides (e.g., siRNAs, shRNAs), microRNAs, gapmers, mixmers, phosphorodiamidate morpholinos, peptide nucleic acids, aptamers, guide nucleic acids (e.g., Cas9 guide RNAs), etc. Oligonucleotides may be single-stranded or double-stranded. In some embodiments, an oligonucleotide may comprise one or more modified nucleosides (e.g., 2'-O-methyl sugar modifications, purine or pyrimidine modifications). In some embodiments, an oligonucleotide may comprise one or more modified internucleoside linkages. In some embodiments, an oligonucleotide may comprise one or more phosphorothioate linkages, which may be in the Rp or Sp stereochemical conformation.

[000131] PPP1R3A: As used herein, the term, “PPP1R3A,” refers to a gene that encodes the regulatory subunit of protein phosphatase-1 (PP1). In some embodiments, this regulatory subunit binds to muscle glycogen with high affinity and enhances dephosphorylation of glycogen-bound substrates for PP1 such as glycogen synthase and glycogen phosphorylase kinase. In some embodiments, PPP1R3A may be a human (Gene ID : 5506 (SEQ ID NO: 1064)), non-human primate (e.g., Gene ID: 703562 (e.g., SEQ ID NO: 1065) (*Macaca mulatta*)), or rodent gene (e.g., Gene ID: 140491 (e.g., SEQ ID NO: 963) (*M. musculus*), Gene ID: 500036 (e.g., SEQ ID NO: 1066) (*R. norvegicus*). In addition, an exemplary human transcript (e.g., as annotated under GenBank RefSeq Accession Number: NM_002711.4 (SEQ ID NO: 962)) has been characterized.

[000132] An exemplary PPP1R3A protein, encoded by a human PPP1R3A gene, is annotated under NCBI Reference Sequence: NP_002702.2, and has the following amino acid sequence:

MEPSEVPSQISKDNFLEVPNLSDSLCEDEEVTFQPGFSPQPSRRGSDSSEDIYLDTPSSGTR
RVSFADSFGFNLVSVKEFDCWELPSASTTFDLGTDIFHTEEYVLAPLFDLPSSKEDLMQQ
LQIQKAILESTESLLGSTSIKGIIRVLNVSFELVYVRMSLDDWQTHYDILAEYVPNSCDG
ETDQFSFKIVLPPYQKDGSKEVFCIRYETSVGTFSNNNGTNYTFICQKKEQEPEPVKP
WKEVPNRQIKGCLVKSSKEESSVTSEENNPFENPKNTDTYIPTIICSHEDKEDLEASNRN
VKDVNREHDEHNEKELELMINQHLIRTRSTASRDERNTFSTDPVNFPNKAEGLEKKQIH
GEICTDLFQRLSPSSSAESSVKGDFYCNEKYSSGDDCTHQPSEETTSNMGEIKPSLGDT
SDELVLHTGSKEVLDDNANPAHNGTVQIPCPSSDQLMAGNLNKKHEGGAKNIEVK
DLGCLRRDFHSDTSACLKESTEEGSSKEDYYGNGKDDEEQRIYLGVNEKQRKNFQTLH
DQERKMGNPKISVAGIGASNRDLATLLSEHTAIPTRAITADVSHSPRTNLSWEEAVLTPE
HHHLTSEGSALGGITGQVCSSRTGNVLRNDYLFQVEEKSGGINSQDNQSPQHKQSWN
VLESQGKSRENKTNITEHIKGQTDCEVDWGKRDNTRSLKATTEELFTCQETVCCELSSL
ADHGITEKAEAGTAYIIKTTSESTPESMSAREKAIKLPQETARSDRPIEVKETAFDPHE
GRNDDSHYTLQCRDVGVIYDNDFEKESRLGICNVRVDEMEKEETMSMYNPRKTHDR
EKCGTGNITSVEESSWVITEYQKATSKLDLQLGMLPTDKTVFSENRLRQVQELSKKTD
SDAIVHSAFNSDTNRAPQNSSPFSKHHTAISVTNEQAIAVENAVTTMASQPISTKSENI
NSTREIQGIEKHPYPESKPEEVSRSRGIVTSGSRKERCIGQIFQTEEYSVEKSLGPMILINKP
LENMEEARHENEGLVSSGQSLYTSGEKESDSSASTSLPVEESQAQGNESLFSKYTNSKIP

YFLLFLIFLITVYHYDLMIGLTFYVLSLSWLSWEEGRQKESVKKK (SEQ ID NO: 663)

[000133] Recombinant antibody: The term "recombinant human antibody", as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell (described in more details in this disclosure), antibodies isolated from a recombinant, combinatorial human antibody library (Hoogenboom H. R., (1997) TIB Tech. 15:62-70; Azzazy H., and Highsmith W. E., (2002) Clin. Biochem. 35:425-445; Gavilondo J. V., and Larrick J. W. (2002) BioTechniques 29:128-145; Hoogenboom H., and Chames P. (2000) Immunology Today 21:371-378), antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic for human immunoglobulin genes (see *e.g.*, Taylor, L. D., et al. (1992) Nucl. Acids Res. 20:6287-6295; Kellermann S-A., and Green L. L. (2002) Current Opinion in Biotechnology 13:593-597; Little M. et al (2000) Immunology Today 21:364-370) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire *in vivo*. One embodiment of the disclosure provides fully human antibodies capable of binding human transferrin receptor which can be generated using techniques well known in the art, such as, but not limited to, using human Ig phage libraries such as those disclosed in Jermutus et al., PCT publication No. WO 2005/007699 A2.

[000134] 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.

[000135] 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.

[000136] 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 patient having type 2 diabetes. In some embodiments, the subject is a patient having cancer. In some embodiments, the subject is a human patient who has or is suspected of having heart failure, muscle atrophy (e.g., skeletal and/or cardiac muscle atrophy), muscular dystrophies, cachexia (e.g., cardiac cachexia), muscle hypertrophy, cardiac muscle wasting, and/or cardiomyopathy. In some embodiments, a subject having muscle hypertrophy has at least one mutation in MSTN as in Schuelke, M. et al., “*Myostatin Mutation Associated with Gross Muscle Hypertrophy in a Child*” N Engl J Med 2004; 350:2682-2688, incorporated herein by reference. In some embodiments, the subject is a patient having type 2 diabetes who is suffering from myocardial complications (e.g., heart failure, cardiac muscle atrophy, cachexia, and/or cardiac muscle hypertrophy). In some embodiments, the subject is a cancer patient suffering from cachexia. In some embodiments, the subject is a human patient who has or is suspected of having cardiac fibrosis or cardiac hypertrophy. In some embodiments, the subject is a human patient who has or is suspected of having angiotensin-II-induced cardiac hypertrophy. In some embodiments, the subject has experienced a myocardial infarction (i.e., heart attack). In some embodiments, the subject is a human patient who has or is suspected of having irritable bowel syndrome (IBS). In some embodiments, the subject is a human patient who has or is suspected of having inflammatory bowel disease (IBD). In some embodiments, the subject is a human patient who has familial thoracic aortic aneurysms and dissections (FTAAD). In some embodiments, the

subject is a human patient who has Berdon syndrome (also called “recessive megacystis microcolon intestinal hypoperistalsis syndrome”). In some embodiments, the subject has or is suspected of having cardiac hypertrophy. In some embodiments, the subject has or is suspected of having angiotensin II-induced cardiac hypertrophy. In some embodiments, the subject has muscle atrophy (e.g., cardiac muscle atrophy). In some embodiments, the subject is a human patient who has or is suspected of having typical FOP or atypical FOP. In some embodiments, the subject has at least one ACVR1 allele that comprises one or more deletions or substitutions that lead to alterations in the ACVR1 protein, e.g., L196P, R202I, R206H, Q207E, G328R, G328W, G328E, G356D, R375P, ΔP197-F198.

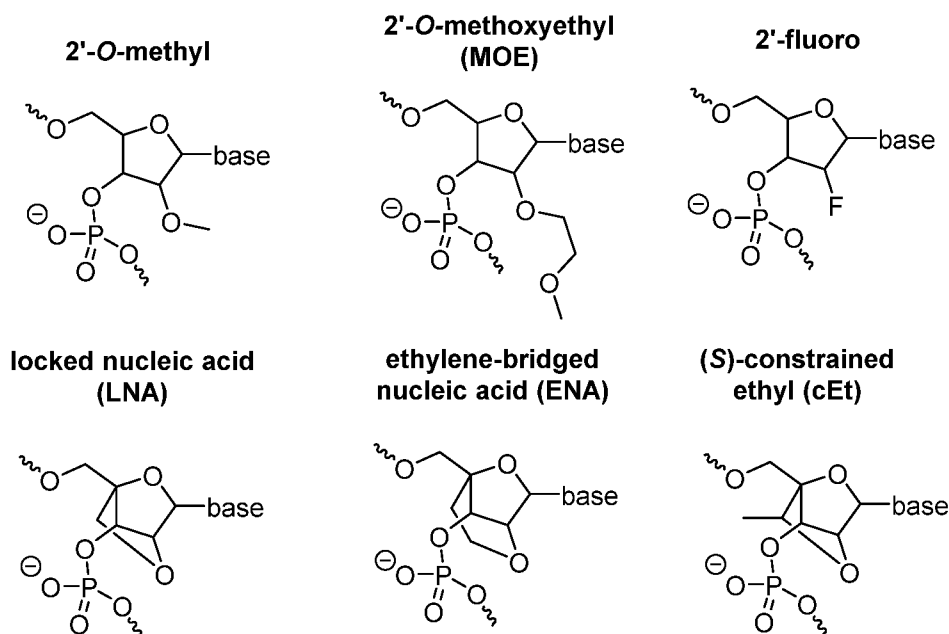
[000137] TRIM63: As used herein, the term, “TRIM63,” refers to a gene that encodes an E3 ubiquitin ligase that is a member of the RING zinc finger protein family. TRIM63 may also be referred to as IRF; SMRZ; MURF1; MURF2; RNF28; or tripartite motif containing 63. In some embodiments, TRIM63 may be a human (Gene ID: 84676 (e.g., SEQ ID NO: 579)), non-human primate (e.g., Gene ID: 102120812 (e.g., SEQ ID NO: 659)), or rodent gene (e.g., Gene ID: 433766 (e.g., SEQ ID NO: 580), Gene ID: 140939 (e.g., SEQ ID NO: 660)). In addition, an exemplary human transcript (e.g., as annotated under GenBank RefSeq Accession Number: NM_032588.3 (SEQ ID NO: 579)) has been characterized.

[000138] An exemplary TRIM63 protein, encoded by a human TRIM63 gene, is annotated under NCBI Reference Sequence: NP_115977.2, and has the following amino acid sequence: MDYKSSLIQDGNPMENLEKQLICPICLEMFTKPVVILPCQHNLCRKCANDIFQAANPYW TSRGSSVSMGGRFRCPTCRHEVIMDRHGVYGLQRNLLVENIIDYKQECSSRPLQKGSHPMCKEHEDEKINIYCLTCEVPTCSMCKVFGIHKACEVAPLQSVFQGGQKTELNNCISMLV AGNDRVQTIITQLEDSRRVTKENSHQVKEELSQKFDTLYAILDEKKSELLQRITQEQUEKKLSFIEALIQYQEQLDKSTKL VETAIQSLDEPGGATFLLTAKQLIKSIVEASKGCQLGKTE QGFENMDFFTL DLEHIADALRAIDFGTDEEEEFIEEEDQEEEEESTEGKEEGHQ. (SEQ ID NO: 504)

[000139] Transferrin receptor: As used herein, the term, “transferrin receptor (also known as 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 (e.g., SEQ ID NO: 397)), non-human primate (e.g., NCBI Gene ID 711568 (e.g., SEQ ID NO: 398) or NCBI Gene ID 102136007 (e.g., SEQ ID NO: 399)), or rodent (e.g., NCBI Gene ID 22042 (e.g., SEQ ID NO: 400)) 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

(SEQ ID NO: 401), NP_003225.2 (SEQ ID NO: 105), NP_001300894.1 (SEQ ID NO: 402), and NP_001300895.1 (SEQ ID NO: 403)).

[000140] 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-dimethylaminoethoxyethyl (2'-O-DMAEOE), 2'-O-N-methylacetamido (2'-O-NMA), locked nucleic acid (LNA, methylene-bridged nucleic acid), ethylene-bridged nucleic acid (ENA), and (S)-constrained ethyl-bridged nucleic acid (cEt). In some embodiments, the 2'-modified nucleosides described herein are high-affinity modified nucleosides and oligonucleotides comprising the 2'-modified nucleosides have increased affinity to a target sequence, relative to an unmodified oligonucleotide. Examples of structures of 2'-modified nucleosides are provided below:



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

II. Complexes

[000141] Provided herein are complexes that comprise a targeting agent, e.g., an antibody, covalently linked to a molecular payload. In some embodiments, a complex comprises a muscle-targeting antibody covalently linked to an oligonucleotide. A complex may comprise an antibody that specifically binds a single antigenic site or that binds to at least two antigenic sites that may exist on the same or different antigens.

[000142] A complex may be used to modulate the activity or function of at least one gene, protein, and/or nucleic acid. In some embodiments, the molecular payload present with a complex is responsible for the modulation of a gene, protein, and/or nucleic acids. A molecular payload may be a small molecule, protein, nucleic acid, oligonucleotide, or any molecular entity capable of modulating the activity or function of a gene, protein, and/or nucleic acid in a cell. In some embodiments, a molecular payload is an oligonucleotide that targets a *MSTN* gene in muscle cells (e.g., cardiac muscle cells). In some embodiments, a molecular payload is an oligonucleotide that targets *INHBA* or activin A in muscle cells (e.g., cardiac muscle cells). In some embodiments, a molecular payload is an oligonucleotide that targets *ACVR1B* in muscle cells (e.g., cardiac muscle cells). In some embodiments, a molecular payload is an oligonucleotide that targets a *MLCK1* gene in muscle cells (e.g., smooth muscle cells). In some embodiments, a molecular payload is an oligonucleotide that targets *ACVR1* in muscle cells (e.g., cardiac muscle cells). In some embodiments, a molecular payload is an oligonucleotide that targets *FBXO32* in muscle cells (e.g., cardiac muscle cells). In some embodiments, a molecular payload is an oligonucleotide that targets *TRIM63* in muscle cells (e.g., cardiac muscle cells). In some embodiments, a molecular payload is an oligonucleotide that targets *MEF2D*, *KLF15*, *MED1*, *MED13*, or *PPP1R3A* in muscle cells (e.g., cardiac muscle cells). In some embodiments, a molecular payload inhibits the function of *MEF2D*, *KLF15*, *MED1*, *MED13*, or *PPP1R3A* in muscle cells. In some embodiments, a molecular payload promotes or enhances the function of *MEF2D*, *KLF15*, *MED1*, *MED13*, or *PPP1R3A* in muscle cells (e.g., increases expression).

[000143] In some embodiments, a complex comprises a muscle-targeting agent, e.g., an anti-transferrin receptor 1 antibody, covalently linked to a molecular payload, e.g., an antisense oligonucleotide that targets *MSTN* gene, an antisense oligonucleotide that targets *INHBA*, or an antisense oligonucleotide that targets *ACVR1B*. In some embodiments, a complex comprises a muscle-targeting agent, e.g., an anti-transferrin receptor 1 antibody, covalently linked to a molecular payload, e.g., an siRNA oligonucleotide that targets *MSTN* gene, an antisense oligonucleotide that targets *INHBA*, or an antisense oligonucleotide that targets *ACVR1B*. In some embodiments, a complex comprises a muscle-targeting agent, e.g., an anti-transferrin receptor 1 antibody, covalently linked to a molecular payload, e.g., an antisense oligonucleotide

or siRNA oligonucleotide that targets MLCK1, ACVR1, FBXO32, TRIM63, MEF2D, KLF15, MED1, MED13, or PPP1R3A.

A. Muscle-Targeting Agents

[000144] Some aspects of the disclosure provide muscle-targeting agents, *e.g.*, for delivering a molecular payload to a muscle cell (*e.g.*, a cardiac muscle cell). In some embodiments, such muscle-targeting agents are capable of binding to a muscle cell, *e.g.*, via specifically binding to an antigen on the muscle cell, and delivering an associated molecular payload to the muscle cell. In some embodiments, muscle-targeting agents are designed to target cardiac muscle cells or cardiac muscle tissues. In some embodiments, the molecular payload is bound (*e.g.*, covalently bound) to the muscle targeting agent and is internalized into the muscle cell upon binding of the muscle targeting agent to an antigen on the muscle cell, *e.g.*, via endocytosis. It should be appreciated that various types of muscle-targeting agents may be used in accordance with the disclosure, and that any muscle targets (*e.g.*, muscle surface proteins) can be targeted by any type of muscle target agents described herein. For example, the muscle-targeting agent may comprise, or consist of, a small molecule, a nucleic acid (*e.g.*, DNA or RNA), a peptide (*e.g.*, an antibody), a lipid (*e.g.*, a microvesicle), or a sugar moiety (*e.g.*, a polysaccharide). Exemplary muscle-targeting agents are described in further detail herein, however, it should be appreciated that the exemplary muscle-targeting agents provided herein are not meant to be limiting.

[000145] Some aspects of the disclosure provide muscle-targeting agents that specifically bind to an antigen on muscle, such as skeletal muscle, smooth muscle, or cardiac muscle. In some embodiments, any of the muscle-targeting agents provided herein bind to (*e.g.*, specifically bind to) an antigen on a cardiac muscle cell, a skeletal muscle cell, and/or a smooth muscle cell. In some embodiments, any of the muscle-targeting agents provided herein bind to (*e.g.*, specifically bind to) an antigen on a cardiac muscle cell.

[000146] By interacting with muscle-specific cell surface recognition elements (*e.g.*, cell membrane proteins), both tissue localization and selective uptake into muscle cells can be achieved. In some embodiments, molecules that are substrates for muscle uptake transporters are useful for delivering a molecular payload into muscle tissue. Binding to muscle surface recognition elements followed by endocytosis can allow even large molecules such as antibodies to enter muscle cells. As another example molecular payloads conjugated to transferrin or anti-transferrin receptor 1 antibodies can be taken up by muscle cells via binding to transferrin receptor, which may then be endocytosed, *e.g.*, via clathrin-mediated endocytosis.

[000147] The use of muscle-targeting agents may be useful for concentrating a molecular payload (*e.g.*, oligonucleotide) in muscle while reducing toxicity associated with effects in other tissues. In some embodiments, the muscle-targeting agent concentrates a bound molecular payload in muscle cells as compared to another cell type within a subject. In some embodiments, the muscle-targeting agent concentrates a bound molecular payload in muscle cells (*e.g.*, cardiac muscle cells) in an amount that is at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, or 100 times greater than an amount in non-muscle cells (*e.g.*, liver, neuronal, blood, or fat cells). In some embodiments, a toxicity of the molecular payload in a subject is reduced by at least 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 90%, or 95% when it is delivered to the subject when bound to the muscle-targeting agent.

[000148] In some embodiments, to achieve muscle selectivity, a muscle recognition element (*e.g.*, a muscle cell antigen) may be required. As one example, a muscle-targeting agent may be a small molecule that is a substrate for a muscle-specific uptake transporter. As another example, a muscle-targeting agent may be an antibody that enters a muscle cell via transporter-mediated endocytosis. As another example, a muscle targeting agent may be a ligand that binds to cell surface receptor on a muscle cell. It should be appreciated that while transporter-based approaches provide a direct path for cellular entry, receptor-based targeting may involve stimulated endocytosis to reach the desired site of action.

i. Muscle-Targeting Antibodies

[000149] In some embodiments, the muscle-targeting agent is an antibody. Generally, the high specificity of antibodies for their target antigen provides the potential for selectively targeting muscle cells (*e.g.*, skeletal, smooth, and/or (*e.g.*, and) cardiac muscle cells). This specificity may also limit off-target toxicity. Examples of antibodies that are capable of targeting a surface antigen of muscle cells have been reported and are within the scope of the disclosure. For example, antibodies that target the surface of muscle cells are described in Arahata K., et al. “Immunostaining of skeletal and cardiac muscle surface membrane with antibody against Duchenne muscular dystrophy peptide” *Nature* 1988; 333: 861-3; Song K.S., et al. “Expression of caveolin-3 in skeletal, cardiac, and smooth muscle cells. Caveolin-3 is a component of the sarcolemma and co-fractionates with dystrophin and dystrophin-associated glycoproteins” *J Biol Chem* 1996; 271: 15160-5; and Weisbart R.H. et al., “Cell type specific targeted intracellular delivery into muscle of a monoclonal antibody that binds myosin IIb” *Mol Immunol.* 2003 Mar, 39(13):78309; the entire contents of each of which are incorporated herein by reference.

a. Anti-transferrin receptor 1 Antibodies

[000150] Some aspects of the disclosure are based on the recognition that agents binding to transferrin receptor, e.g., anti-transferrin-receptor antibodies, are capable of targeting muscle cell. Transferrin receptors are internalizing cell surface receptors that transport transferrin across the cellular membrane and participate in the regulation and homeostasis of intracellular iron levels. Some aspects of the disclosure provide transferrin receptor binding proteins, which are capable of binding to transferrin receptor. Accordingly, aspects of the disclosure provide binding proteins (*e.g.*, antibodies) that bind to transferrin receptor. In some embodiments, binding proteins that bind to transferrin receptor are internalized, along with any bound molecular payload, into a muscle cell. As used herein, an antibody that binds to a transferrin receptor may be referred to interchangeably as an, transferrin receptor antibody, an anti-transferrin receptor 1 antibody, or an anti-TfR1 antibody. Antibodies that bind, e.g., specifically bind, to a transferrin receptor may be internalized into the cell, e.g., through receptor-mediated endocytosis, upon binding to a transferrin receptor.

[000151] It should be appreciated that anti-transferrin receptor 1 antibodies may be produced, synthesized, and/or (e.g., and) derivatized using several known methodologies, e.g., library design using phage display. Exemplary methodologies have been characterized in the art and are incorporated by reference (Díez, P. et al. “High-throughput phage-display screening in array format”, *Enzyme and microbial technology*, 2015, 79, 34-41.; Christoph M. H. and Stanley, J.R. “Antibody Phage Display: Technique and Applications” *J Invest Dermatol.* 2014, 134:2.; Engleman, Edgar (Ed.) “Human Hybridomas and Monoclonal Antibodies.” 1985, Springer.). In other embodiments, an anti-transferrin receptor 1 antibody has been previously characterized or disclosed. Antibodies that specifically bind to transferrin receptor are known in the art (see, e.g., US Patent. No. 4,364,934, filed 12/4/1979, “Monoclonal antibody to a human early thymocyte antigen and methods for preparing same”; US Patent No. 8,409,573, filed 6/14/2006, “Anti-CD71 monoclonal antibodies and uses thereof for treating malignant tumor cells”; US Patent No. 9,708,406, filed 5/20/2014, “Anti-transferrin receptor antibodies and methods of use”; US 9,611,323, filed 12/19/2014, “Low affinity blood brain barrier receptor antibodies and uses therefor”; WO 2015/098989, filed 12/24/2014, “Novel anti-Transferrin receptor antibody that passes through blood-brain barrier”; Schneider C. et al. “Structural features of the cell surface receptor for transferrin that is recognized by the monoclonal antibody OKT9.” *J Biol Chem.* 1982, 257:14, 8516-8522.; Lee et al. “Targeting Rat Anti-Mouse Transferrin Receptor Monoclonal Antibodies through Blood-Brain Barrier in Mouse” 2000, *J Pharmacol. Exp. Ther.*, 292: 1048-1052.).

[000152] Provided herein, in some aspects, are new anti-TfR1 antibodies for use as the muscle targeting agents (e.g., in muscle targeting complexes). In some embodiments, the anti-TfR1 antibody described herein binds to transferrin receptor with high specificity and affinity. In some embodiments, the anti-TfR1 antibody described herein specifically binds to any extracellular epitope of a transferrin receptor or an epitope that becomes exposed to an antibody. In some embodiments, anti-TfR1 antibodies provided herein bind specifically to transferrin receptor from human, non-human primates, mouse, rat, *etc.* In some embodiments, anti-TfR1 antibodies provided herein bind to human transferrin receptor. In some embodiments, the anti-TfR1 antibody described herein binds to an amino acid segment of a human or non-human primate transferrin receptor, as provided in SEQ ID NOs: 105-108. In some embodiments, the anti-TfR1 antibody described herein binds to an amino acid segment corresponding to amino acids 90-96 of a human transferrin receptor as set forth in SEQ ID NO: 105, which is not in the apical domain of the transferrin receptor.

[000153] In some embodiments, the anti-TfR1 antibody described herein (e.g., 3M12 in Table 1 below and its humanized variants) bind an epitope in TfR1, wherein the epitope comprises residues in amino acids 258-291 and/or amino acids 358-381 of SEQ ID NO: 105. In some embodiments, the anti-TfR1 antibodies (e.g., 3M12 in Table 1 below and its humanized variants) described herein bind an epitope comprising residues in amino acids amino acids 258-291 and amino acids 358-381 of SEQ ID NO: 105. In some embodiments, the anti-TfR1 antibodies described herein (e.g., 3M12 in Table 1 below and its humanized variants) bind an epitope comprising one or more of residues K261, S273, Y282, T362, S368, S370, and K371 of human TfR1 as set forth in SEQ ID NO: 105. In some embodiments, the anti-TfR1 antibodies described herein (e.g., 3M12 in Table 1 below and its humanized variants) bind an epitope comprising residues K261, S273, Y282, T362, S368, S370, and K371 of human TfR1 as set forth in SEQ ID NO: 105.

[000154] An example human transferrin receptor amino acid sequence, corresponding to NCBI sequence NP_003225.2 (transferrin receptor protein 1 isoform 1, homo sapiens) is as follows:

MMDQARSAFSNLFSGGEPLSYTRFSLARQVDGDNHSHVEMKLAVDEEENADNNTKANVT
KPKRCSGSICYGTIAVIVFFLIGFMIGYLG YCKGVEPKTECERLAGTESPVREEPGEDFPA
ARRLYWDDLKRKLSEKLDSTDFGTIKLLNENSYPREAGSQKDENLALYVENQFREF
KLSKVWRDQHFVKIQVKDSAQNSVIIVDKNGRLVYLVENPGGYVAYSKAATVTGKLV
HANFGTKKDFEDLYTPVNGSIVIVRAGKITFAEKVANAESLNAIGVLIYMDQTKFPIVNA
ELSFHGHAHLGTGDPYTPGFPSFNHTQFPSPRSSGLPNIPVQTISRAAA EKLFGNMEGDCP
SDWKTDSTCRMVTSSESKNVKLT VSNVLKEIKILNIFGVIKGFVEPDHYVVVGAQRDAW

GPGAAKSGVGTALLLKLQMFSDMVLKDGFPQRSIIFASWSAGDFGSGVATEWLEGY
 LSSLHLKAFTYINLDKAVLGTSNFKVSASPLLYTLIEKTMQNVKHPVTGQFLYQDSNWA
 SKVEKLTLDNAAFPFLAYSGIPAVSFCFCEDTDYPYLGTTMDTYKELIERIPELNKVARA
 AAEVAGQFVIKLTHDVELNLDYERYNSQLLSFVRDLNQYRADIKEMGLSLQWLYSARG
 DFFRATSRLTTDFGNAEKTDRFVMKKLNDRVMRVEYHFLSPYVSPKESPFRRHVFWGSG
 SHTLPALLENLKLRRQNNGAFNETLFRNQLALATWTIQGAANALSGDVWDIDNEF
 (SEQ ID NO: 105).

[000155] An example non-human primate transferrin receptor amino acid sequence, corresponding to NCBI sequence NP_001244232.1(transferrin receptor protein 1, *Macaca mulatta*) is as follows:

MMDQARSASFNLFGGEPLSYTRFSLARQVDGDNSHVEMKLGVDDEEENTDNNTKPNGT
 KPKRCGGNICYGTIAVIIFFLIGFMIGYLG YCKGVEPKTECERLAGTESPAREEPEEDFPA
 APRLYWDDLKRKLSEKLDTTDFTSTIKLLNENLYVPREAGSQKDENLALYIENQFREFK
 LSKVWRDQH FVKIQVKDSAQNSVIIVDKNGGLVYLVENPGGYVAYS KAATVTGKLVH
 ANFGTKKDFEDLDSPVNGSIVIVRAGKITFAEKVANAESLNAIGVLIYMDQTKFPIVKAD
 LSFFGHAHLGTGDPYTPGFPSFNHTQFPSSQSSGLPNIPVQTISRAAA EKLFGNMEGDCPS
 DWKTDSTCKMVTSENKSVKLT VSNVLKETKILNIFGVIKGFVEPDHYVVVGAQRDAW
 GPGAAKSSVGTALLLKLQMFSDMVLKDGFPQRSIIFASWSAGDFGSGVATEWLEGY
 LSSLHLKAFTYINLDKAVLGTSNFKVSASPLLYTLIEKTMQDVKHPVTGRSLYQDSNWA
 SKVEKLTLDNAAFPFLAYSGIPAVSFCFCEDTDYPYLGTTMDTYKELVERIPELNKVAR
 AAAEVAGQFVIKLTHDTELNLDYERYNSQLLLFLRDLNQYRADVKEMGLSLQWLYSA
 RGDFFRATSRLTTDFRNAEKRDKFVMKKLNDRVMRVEYYFLSPYVSPKESPFRRHVFWG
 SGSHTLSALLESLKLRRQNNSAFNETLFRNQLALATWTIQGAANALSGDVWDIDNEF
 (SEQ ID NO: 106)

[000156] An example non-human primate transferrin receptor amino acid sequence, corresponding to NCBI sequence XP_005545315.1 (transferrin receptor protein 1, *Macaca fascicularis*) is as follows:

MMDQARSASFNLFGGEPLSYTRFSLARQVDGDNSHVEMKLGVDDEEENTDNNTKANGT
 KPKRCGGNICYGTIAVIIFFLIGFMIGYLG YCKGVEPKTECERLAGTESPAREEPEEDFPA
 APRLYWDDLKRKLSEKLDTTDFTSTIKLLNENLYVPREAGSQKDENLALYIENQFREFK
 LSKVWRDQH FVKIQVKDSAQNSVIIVDKNGGLVYLVENPGGYVAYS KAATVTGKLVH
 ANFGTKKDFEDLDSPVNGSIVIVRAGKITFAEKVANAESLNAIGVLIYMDQTKFPIVKAD
 LSFFGHAHLGTGDPYTPGFPSFNHTQFPSSQSSGLPNIPVQTISRAAA EKLFGNMEGDCPS
 DWKTDSTCKMVTSENKSVKLT VSNVLKETKILNIFGVIKGFVEPDHYVVVGAQRDAW

GPGAAKSSVGTALLLKLAQMFSDMVLKDGFPQRSIIIFASWSAGDFGSGVATEWLEGY
 LSSLHLKAFTYINLDKAVLGTSNFKVSASPLLYTLIEKTMQDVKHPVTGRSLYQDSNWA
 SKVEKLTLDNAAFPFLAYSGIPAVSFCFCEDTDYPYLGTTMDTYKELVERIPELNKVAR
 AAAEVAGQFVIKLTHDTELNLDYERYNSQLLLFLRDLNQYRADVKEMGLSLQWLISA
 RGDFFRATSRLTTDFRNAEKRDKFVMKKLNDRVMRVEYYFLSPYVSPKESPF RHVFWG
 SGSHTLSALLESLKLRRQNNSAFNETLFRNQLALATWTIQGAANALSGDVWDIDNEF
 (SEQ ID NO: 107).

[000157] An example mouse transferrin receptor amino acid sequence, corresponding to NCBI sequence NP_001344227.1 (transferrin receptor protein 1, mus musculus) is as follows:
 MMDQARSAFSNLFGGEPLSYTRFSLARQVDGDN SHVEMKLAAD EEEENADNNMKASV
 RKPKRFNGRLCFAAIALVIFFLIGFMSGYLG YCKRVEQKEECVKLAETEETDKSETMETE
 DVPTSSRLYWADLKTLLSEKLSNIEFADTIKQLSQNTYTPREAGSQKDESLAYYIENQFH
 EFKFSKVWRDEHYVKIQVKSSIGQNMVTIVQSNGNLDPVESPEGYVAFSKPTEVSGKLV
 HANFGTKKDFEELSYSVNGSLVIVRAGEITFAEKVAN AQSFNAIGVLIYMDKNKFPVVE
 ADLALFGHAHLGTGDPYTPGFPSFNHTQFP PSQSSGLPNIPVQTISRAAA EKLF GKMEGS
 CPARWNIDSSCKLELSQNQNVLKLVKNVLKERRILNIFGVIKGYEEPDRYVVVGAQRDA
 LGAGVAAKSSVGTGLLLKLAQVFSDMISKDGF RPSRSIIIFASWTAGDFGAVGATEWLEG
 YLSSLHLKAFTYINLDKVVLGTSNFKVSASPLLYTLMGKIMQDVKHPVDGKSLYRDSN
 WISKVEKLSFDNAAYPFLAYSGIPAVSFCFCEDADYPYLGTRLDTYEALTQKVPQLNQM
 VRTAAEVAGQLIIKLTHDVELNLDYEMYNSKLLSFMKD LNQFKTDIRDMGLSLQWLIS
 ARGDYFRATSRLTTDFHNAEKTNR FVMREINDRIMKVEYHFLSPYVSPRESPFRHIFWG
 SGSHTLSALVENLKL RQKNITAFNETLFRNQLALATWTIQGVANALSGDIWNIDNEF
 (SEQ ID NO: 108)

[000158] In some embodiments, an anti-transferrin receptor 1 antibody binds to an amino acid segment of the receptor as follows:
 FVKIQVKDSAQNSVIIVDKNGRLVYLVENPGGYVAYS KAATVTGKLVHANFGTKKDFE
 DLYTPVNGSIVIVRAGKITFAEKVAN AESLNAIGVLIYMDQTKFP IVNAEL SFFGHAHLG
 TGDYTPGFPSFNHTQFP PSRSSGLPNIPVQTISRAAA EKLF GNMEGDCPSDWKTDSTCR
 MVTSESKNVKLT VSNVLKE (SEQ ID NO: 109) and does not inhibit the binding interactions between transferrin receptors and transferrin and/or (e.g., and) human hemochromatosis protein (also known as HFE). In some embodiments, the anti-transferrin receptor 1 antibody described herein does not bind an epitope in SEQ ID NO: 109.

[000159] Appropriate methodologies may be used to obtain and/or (e.g., and) produce antibodies, antibody fragments, or antigen-binding agents, e.g., through the use of recombinant DNA protocols. In some embodiments, an antibody may also be produced through the

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

[000160] In some embodiments, an antibody is modified, e.g., modified via glycosylation, phosphorylation, sumoylation, and/or (e.g., and) methylation. In some embodiments, an antibody is a glycosylated antibody, which is conjugated to one or more sugar or carbohydrate molecules. In some embodiments, the one or more sugar or carbohydrate molecule are conjugated to the antibody via N-glycosylation, O-glycosylation, C-glycosylation, glypiation (GPI anchor attachment), and/or (e.g., and) phosphoglycosylation. In some embodiments, the one or more sugar or carbohydrate molecules are monosaccharides, disaccharides, oligosaccharides, or glycans. In some embodiments, the one or more sugar or carbohydrate molecule is a branched oligosaccharide or a branched glycan. In some embodiments, the one or more sugar or carbohydrate molecule includes a mannose unit, a glucose unit, an N-acetylglucosamine unit, an N-acetylgalactosamine unit, a galactose unit, a fucose unit, or a phospholipid unit. In some embodiments, there are about 1-10, about 1-5, about 5-10, about 1-4, about 1-3, or about 2 sugar molecules. In some embodiments, a glycosylated antibody is fully or partially glycosylated. In some embodiments, an antibody is glycosylated by chemical reactions or by enzymatic means. In some embodiments, an antibody is glycosylated in vitro or inside a cell, which may optionally be deficient in an enzyme in the N- or O- glycosylation pathway, e.g., a glycosyltransferase. In some embodiments, an antibody is functionalized with sugar or

carbohydrate molecules as described in International Patent Application Publication WO2014065661, published on May 1, 2014, entitled, “*Modified antibody, antibody-conjugate and process for the preparation thereof*”.

[000161] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VL domain and/or (e.g., and) VH domain of any one of the anti-TfR1 antibodies selected from any one of Tables 2-7, and comprises a constant region comprising the amino acid sequences of the constant regions of an IgG, IgE, IgM, IgD, IgA or IgY immunoglobulin molecule, any class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2), or any subclass (e.g., IgG2a and IgG2b) of immunoglobulin molecule. Non-limiting examples of human constant regions are described in the art, e.g., see Kabat E A et al., (1991) supra.

[000162] In some embodiments, agents binding to transferrin receptor, e.g., anti-TfR1 antibodies, are capable of targeting muscle cell and/or (e.g., and) mediate the transportation of an agent across the blood brain barrier. Transferrin receptors are internalizing cell surface receptors that transport transferrin across the cellular membrane and participate in the regulation and homeostasis of intracellular iron levels. Some aspects of the disclosure provide transferrin receptor binding proteins, which are capable of binding to transferrin receptor. Antibodies that bind, e.g., specifically bind, to a transferrin receptor may be internalized into the cell, e.g., through receptor-mediated endocytosis, upon binding to a transferrin receptor.

[000163] Provided herein, in some aspects, are humanized antibodies that bind to transferrin receptor with high specificity and affinity. In some embodiments, the humanized anti-TfR1 antibody described herein specifically binds to any extracellular epitope of a transferrin receptor or an epitope that becomes exposed to an antibody. In some embodiments, the humanized anti-TfR1 antibodies provided herein bind specifically to transferrin receptor from human, non-human primates, mouse, rat, *etc.* In some embodiments, the humanized anti-TfR1 antibodies provided herein bind to human transferrin receptor. In some embodiments, the humanized anti-TfR1 antibody described herein binds to an amino acid segment of a human or non-human primate transferrin receptor, as provided in SEQ ID NOs: 105-108. In some embodiments, the humanized anti-TfR1 antibody described herein binds to an amino acid segment corresponding to amino acids 90-96 of a human transferrin receptor as set forth in SEQ ID NO: 105, which is not in the apical domain of the transferrin receptor. In some embodiments, the humanized anti-TfR1 antibodies described herein binds to TfR1 but does not bind to TfR2.

[000164] In some embodiments, an anti-TfR1 antibody specifically binds a TfR1 (e.g., a human or non-human primate TfR1) with binding affinity (e.g., as indicated by Kd) of at least about 10^{-4} M, 10^{-5} M, 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, 10^{-12} M, 10^{-13} M, or less.

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

[000165] Non-limiting examples of anti-TfR1 antibodies are provided in Table 2.

Table 2. Examples of Anti-TfR1 Antibodies

Ab	No. system	IMGT	Kabat	Chothia
3-A4	CDR-H1	GFNIKDDY (SEQ ID NO: 1)	DDYMY (SEQ ID NO: 7)	GFNIKDD (SEQ ID NO: 12)
	CDR-H2	IDPENGDT (SEQ ID NO: 2)	WIDPENGDT EYASKFQD (SEQ ID NO: 8)	ENG (SEQ ID NO: 13)
	CDR-H3	TLWLRRGLDY (SEQ ID NO: 3)	WLRRGLDY (SEQ ID NO: 9)	LRRGLD (SEQ ID NO: 14)
	CDR-L1	KSLLSHNGYTY (SEQ ID NO: 4)	RSSKSLLSHNGYTYLF (SEQ ID NO: 10)	SKSLLSHNGYTY (SEQ ID NO: 15)
	CDR-L2	RMS (SEQ ID NO: 5)	RMSNLAS (SEQ ID NO: 11)	RMS (SEQ ID NO: 5)
	CDR-L3	MQHLEYPFT (SEQ ID NO: 6)	MQHLEYPFT (SEQ ID NO: 6)	HLEYPF (SEQ ID NO: 16)
	VH	EVQLQQSGAELVRPGASVKLSCTASGFNIKDDYMYWVKQRPEQGGLWIGWIDPENGDT EYASKFQDKATVTADTSSNTAYLQLSSLTSED TAVYYCTLWLRRGLDYWGQGTSVTVSS (SEQ ID NO: 17)		
	VL	DIVMTQAAPSVPTPGESVSISCRSSKSLLSHNGYTYLFWFLQRPQGSPQLLIYRMSNLASGV PDRFSGSGGTAFTLRISRVEAEDVGVYYCMQHLEYPFTFGGGTKLEIK (SEQ ID NO: 18)		
3-A4 N54T*	CDR-H1	GFNIKDDY (SEQ ID NO: 1)	DDYMY (SEQ ID NO: 7)	GFNIKDD (SEQ ID NO: 12)
	CDR-H2	IDPETGDT (SEQ ID NO: 19)	WIDPETGDTEYASKFQD (SEQ ID NO: 20)	ETG (SEQ ID NO: 21)
	CDR-H3	TLWLRRGLDY (SEQ ID NO: 3)	WLRRGLDY (SEQ ID NO: 9)	LRRGLD (SEQ ID NO: 14)
	CDR-L1	KSLLSHNGYTY (SEQ ID NO: 4)	RSSKSLLSHNGYTYLF (SEQ ID NO: 10)	SKSLLSHNGYTY (SEQ ID NO: 15)
	CDR-L2	RMS (SEQ ID NO: 5)	RMSNLAS (SEQ ID NO: 11)	RMS (SEQ ID NO: 5)
	CDR-L3	MQHLEYPFT (SEQ ID NO: 6)	MQHLEYPFT (SEQ ID NO: 6)	HLEYPF (SEQ ID NO: 16)
	VH	EVQLQQSGAELVRPGASVKLSCTASGFNIKDDYMYWVKQRPEQGGLWIGWIDPETGDTEYASKFQDKATVTADTSSNTAYLQLSSLTSED TAVYYCTLWLRRGLDYWGQGTSVTVS S (SEQ ID NO: 22)		

	VL	DIVMTQAAPSVPVTPGESVSISCRSSKSLLSNGYTYLFWFLQRPQGSPQLLIY RMSNLAGVPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPFTFGGG TKLEIK (SEQ ID NO: 18)		
3-A4 N54S*	CDR-H1	GFNIKDDY (SEQ ID NO: 1)	DDYMY (SEQ ID NO: 7)	GFNIKDD (SEQ ID NO: 12)
	CDR-H2	IDPESGDT (SEQ ID NO: 23)	WIDPESGDTEYASKFQD (SEQ ID NO: 24)	ESG (SEQ ID NO: 25)
	CDR-H3	TLWLRRGLDY (SEQ ID NO: 3)	WLRRGLDY (SEQ ID NO: 9)	LRRGLD (SEQ ID NO: 14)
	CDR-L1	KSLLSNGYTY (SEQ ID NO: 4)	RSSKSLLSNGYTYLF (SEQ ID NO: 10)	SKSLLSNGYTY (SEQ ID NO: 15)
	CDR-L2	RMS (SEQ ID NO: 5)	RMSNLAG (SEQ ID NO: 11)	RMS (SEQ ID NO: 5)
	CDR-L3	MQHLEYPFT (SEQ ID NO: 6)	MQHLEYPFT (SEQ ID NO: 6)	HLEYPF (SEQ ID NO: 16)
	VH	EVQLQQSGAELVRPGASVKLSCTASGFNIKDDYMYWVKQRPEQGGLWIGWI DPESGDTEYASKFQDKATVTADTSSNTAYLQLSSLTSEDNAVYYCTLWLRRL LDYWGGQTSVTVSS (SEQ ID NO: 26)		
	VL	DIVMTQAAPSVPVTPGESVSISCRSSKSLLSNGYTYLFWFLQRPQGSPQLLIY RMSNLAGVPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPFTFGGG TKLEIK (SEQ ID NO: 18)		
3-M12	CDR-H1	GYSITSGYY (SEQ ID NO: 27)	SGYYWN (SEQ ID NO: 33)	GYSITSGY (SEQ ID NO: 38)
	CDR-H2	ITFDGAN (SEQ ID NO: 28)	YITFDGANNYNPSLKN (SEQ ID NO: 34)	FDG (SEQ ID NO: 39)
	CDR-H3	TRSSYDYDVL DY (SEQ ID NO: 29)	SSYDYDVL DY (SEQ ID NO: 35)	SYDYDVL DY (SEQ ID NO: 40)
	CDR-L1	QDISNF (SEQ ID NO: 30)	RASQDISNFLN (SEQ ID NO: 36)	SQDISNF (SEQ ID NO: 41)
	CDR-L2	YTS (SEQ ID NO: 31)	YTSRLHS (SEQ ID NO: 37)	YTS (SEQ ID NO: 31)
	CDR-L3	QQGHTLPYT (SEQ ID NO: 32)	QQGHTLPYT (SEQ ID NO: 32)	GHTLPY (SEQ ID NO: 42)
	VH	DVQLQESGPELVKPSQSLTCSVTGYISITSGYYWNWIRQFPGNKLEWMGYIT FDGANNYNPSLKNRISITRDTSKNQFFLKLTSVTTEDTATYYCTRSSYDYDVL DYWGQGTTLTVSS (SEQ ID NO: 43)		
	VL	DIQMTQTSSLSASLGDRVTISCRASQDISNFLNWYQQRPDGTVKLLIYYTSRL HSGVPSRFSGSGGTDFSLTVSNLEQEDIATYFCQQGHTLPYTFGGGTKLEIK (SEQ ID NO: 44)		
5-H12	CDR-H1	GYSFTDYC (SEQ ID NO: 45)	DYCIN (SEQ ID NO: 51)	GYSFTDY (SEQ ID NO: 56)
	CDR-H2	IYPGSGNT (SEQ ID NO: 46)	WIYPGSGNTRYSERFKG (SEQ ID NO: 52)	GSG (SEQ ID NO: 57)
	CDR-H3	AREDYYPYHGMDY (SEQ ID NO: 47)	EDYYPYHGMDY (SEQ ID NO: 53)	DYYPYHGMD (SEQ ID NO: 58)
	CDR-L1	ESVDGYDNSF (SEQ ID NO: 48)	RASESVDGYDNSFMH (SEQ ID NO: 54)	SESVDGYDNSF (SEQ ID NO: 59)
	CDR-L2	RAS (SEQ ID NO: 49)	RASNLES (SEQ ID NO: 55)	RAS (SEQ ID NO: 49)
	CDR-L3	QQSSED PWT (SEQ ID NO: 50)	QQSSED PWT (SEQ ID NO: 50)	SSEDPW (SEQ ID NO: 60)
	VH	QIQLQQSGPELVVRPGASVKISCKASGYSFTDYCINWVNQRPGQGGLWIGWIYP GSGNTRYSERFKGKATLTVDTSNTAYMQLSSLTSEDSAVYFCAREDYYPYH GMDYWGQGTSTVTVSS (SEQ ID NO: 61)		
	VL	DIVLTQSPTSLAVSLGQRATISCRASESVDGYDNSFMHWYQQKPGQPPKLLIF RASNLESGIPARFSGSGSRDTFTLTINPVEAADVATYYCQQSSED PWTFGGGT KLEIK (SEQ ID NO: 62)		
5-H12 C33Y*	CDR-H1	GYSFTDYY (SEQ ID NO: 63)	DYYIN (SEQ ID NO: 64)	GYSFTDY (SEQ ID NO: 56)
	CDR-H2	IYPGSGNT (SEQ ID NO: 46)	WIYPGSGNTRYSERFKG (SEQ ID NO: 52)	GSG (SEQ ID NO: 57)

	CDR-H3	AREDYYPYHGMDY (SEQ ID NO: 47)	EDYYPYHGMDY (SEQ ID NO: 53)	DYYPYHGMD (SEQ ID NO: 58)
	CDR-L1	ESVDGYDNSF (SEQ ID NO: 48)	RASESVDGYDNSFMH (SEQ ID NO: 54)	SESVDGYDNSF (SEQ ID NO: 59)
	CDR-L2	RAS (SEQ ID NO: 49)	RASNLES (SEQ ID NO: 55)	RAS (SEQ ID NO: 49)
	CDR-L3	QQSSEDPWT (SEQ ID NO: 50)	QQSSEDPWT (SEQ ID NO: 50)	SSEDPW (SEQ ID NO: 60)
	VH	QIQLQQSGPELVPRGASVKISCKASGYSFTDYINWVNQRPGQGLEWIGWIYP GSGNTRYSERFKGKATLTVDTSNTAYMQLSSLTSEDSAVYFCAREDYYPYHGMDYWGQGTSTVTVSS (SEQ ID NO: 65)		
	VL	DIVLTQSPTSLAVSLGQRATISCRASESVDGYDNSFMHWYQQKPGQPPKLLIF RASNLESGIPARFSGSGSRTDFTLTINPVEAADVATYYCQQSSEDPWTFGGGT KLEIK (SEQ ID NO: 62)		
5-H12 C33D*	CDR-H1	GYSFTDYD (SEQ ID NO: 66)	DYDIN (SEQ ID NO: 67)	GYSFTDY (SEQ ID NO: 56)
	CDR-H2	IYPGSGNT (SEQ ID NO: 46)	WIYPGSGNTRYSERFKG (SEQ ID NO: 52)	GSG (SEQ ID NO: 57)
	CDR-H3	AREDYYPYHGMDY (SEQ ID NO: 47)	EDYYPYHGMDY (SEQ ID NO: 53)	DYYPYHGMD (SEQ ID NO: 58)
	CDR-L1	ESVDGYDNSF (SEQ ID NO: 48)	RASESVDGYDNSFMH (SEQ ID NO: 54)	SESVDGYDNSF (SEQ ID NO: 59)
	CDR-L2	RAS (SEQ ID NO: 49)	RASNLES (SEQ ID NO: 55)	RAS (SEQ ID NO: 49)
	CDR-L3	QQSSEDPWT (SEQ ID NO: 50)	QQSSEDPWT (SEQ ID NO: 50)	SSEDPW (SEQ ID NO: 60)
	VH	QIQLQQSGPELVPRGASVKISCKASGYSFTDYDINWVNQRPGQGLEWIGWIYPG SGNTRYSERFKGKATLTVDTSNTAYMQLSSLTSEDSAVYFCAREDYYPYHGMDYWGQGTSTVTVSS (SEQ ID NO: 68)		
	VL	DIVLTQSPTSLAVSLGQRATISCRASESVDGYDNSFMHWYQQKPGQPPKLLIF RASNLESGIPARFSGSGSRTDFTLTINPVEAADVATYYCQQSSEDPWTFGGGT KLEIK (SEQ ID NO: 62)		

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

[000166] In some embodiments, the anti-TfR1 antibody of the present disclosure is a humanized variant of any one of the anti-TfR1 antibodies provided in Table 2. In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a CDR-H1, a CDR-H2, a CDR-H3, a CDR-L1, a CDR-L2, and a CDR-L3 that are the same as the CDR-H1, CDR-H2, and CDR-H3 in any one of the anti-TfR1 antibodies provided in Table 2, and comprises a humanized heavy chain variable region and/or (e.g., and) a humanized light chain variable region.

[000167] Humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementarity determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity. In some embodiments, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, the humanized antibody may comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences, but are included to further refine and optimize antibody performance. In general, the humanized antibody will

comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region or domain (Fc), typically that of a human immunoglobulin. Antibodies may have Fc regions modified as described in WO 99/58572. Other forms of humanized antibodies have one or more CDRs (one, two, three, four, five, six) which are altered with respect to the original antibody, which are also termed one or more CDRs derived from one or more CDRs from the original antibody. Humanized antibodies may also involve affinity maturation.

[000168] Humanized antibodies and methods of making them are known, e.g., as described in Almagro et al., *Front. Biosci.* 13:1619-1633 (2008); Riechmann et al., *Nature* 332:323-329 (1988); Queen et al., *Proc. Nat'l Acad. Sci. USA* 86:10029-10033 (1989); U.S. Pat. Nos. 5,821,337, 7,527,791, 6,982,321, and 7,087,409; Kashmiri et al., *Methods* 36:25-34 (2005); Padlan et al., *Mol. Immunol.* 28:489-498 (1991); Dall'Acqua et al., *Methods* 36:43-60 (2005); Osbourn et al., *Methods* 36:61-68 (2005); and Klimka et al., *Br. J. Cancer*, 83:252-260 (2000), the contents of all of which are incorporated herein by reference. Human framework regions that may be used for humanization are described in e.g., Sims et al. *J. Immunol.* 151:2296 (1993); Carter et al., *Proc. Natl. Acad. Sci. USA*, 89:4285 (1992); Presta et al., *J. Immunol.*, 151:2623 (1993); Almagro et al., *Front. Biosci.* 13:1619-1633 (2008)); Baca et al., *J. Biol. Chem.* 272:10678-10684 (1997); and Rosok et al., *J Biol. Chem.* 271:22611-22618 (1996), the contents of all of which are incorporated herein by reference.

[000169] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising one or more amino acid variations (e.g., in the VH framework region) as compared with any one of the VHs listed in Table 2, and/or (e.g., and) a humanized VL comprising one or more amino acid variations (e.g., in the VL framework region) as compared with any one of the VLs listed in Table 2.

[000170] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized 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 of any of the anti-TfR1 antibodies listed in Table 2 (e.g., any one of SEQ ID NOs: 17, 22, 26, 43, 61, 65, and 68). Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody of the present disclosure comprises a humanized 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 of any one of the anti-TfR1 antibodies listed in Table 2 (e.g., any one of SEQ ID NOs: 18, 44, and 62).

[000171] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized 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 of any of the anti-TfR1 antibodies listed in Table 2 (e.g., any one of SEQ ID NOs: 17, 22, 26, 43, 61, 65, and 68). Alternatively or in addition (e.g., in addition), In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized 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 of any of the anti-TfR1 antibodies listed in Table 2 (e.g., any one of SEQ ID NOs: 18, 44, and 62).

[000172] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising a CDR-H1 having the amino acid sequence of SEQ ID NO: 1 (according to the IMGT definition system), a CDR-H2 having the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 19, or SEQ ID NO: 23 (according to the IMGT definition system), a CDR-H3 having the amino acid sequence of SEQ ID NO: 3 (according to the IMGT definition system), and 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 as set forth in SEQ ID NO: 17, SEQ ID NO: 22, or SEQ ID NO: 26. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody of the present disclosure comprises a humanized VL comprising a CDR-L1 having the amino acid sequence of SEQ ID NO: 4 (according to the IMGT definition system), a CDR-L2 having the amino acid sequence of SEQ ID NO: 5 (according to the IMGT definition system), and a CDR-L3 having the amino acid sequence of SEQ ID NO: 6 (according to the IMGT definition system), and 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 as set forth in SEQ ID NO: 18.

[000173] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising a CDR-H1 having the amino acid sequence of SEQ ID NO: 1 (according to the IMGT definition system), a CDR-H2 having the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 19, or SEQ ID NO: 23 (according to the IMGT definition system), a CDR-H3 having the amino acid sequence of SEQ ID NO: 3 (according to the IMGT definition system), and is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical in the framework regions to the VH as set forth in SEQ ID NO: 17, SEQ ID NO:

22, or SEQ ID NO: 26. Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VL comprising a CDR-L1 having the amino acid sequence of SEQ ID NO: 4 (according to the IMGT definition system), a CDR-L2 having the amino acid sequence of SEQ ID NO: 5 (according to the IMGT definition system), and a CDR-L3 having the amino acid sequence of SEQ ID NO: 6 (according to the IMGT definition system), and is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical in the framework regions to the VL as set forth in any one of SEQ ID NO: 18.

[000174] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising a CDR-H1 having the amino acid sequence of SEQ ID NO: 7 (according to the Kabat definition system), a CDR-H2 having the amino acid sequence of SEQ ID NO: 8, SEQ ID NO: 20, or SEQ ID NO: 24 (according to the Kabat definition system), a CDR-H3 having the amino acid sequence of SEQ ID NO: 9 (according to the Kabat definition system), and 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 as set forth in SEQ ID NO: 17, SEQ ID NO: 22, or SEQ ID NO: 26. Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VL comprising a CDR-L1 having the amino acid sequence of SEQ ID NO: 10 (according to the Kabat definition system), a CDR-L2 having the amino acid sequence of SEQ ID NO: 11 (according to the Kabat definition system), and a CDR-L3 having the amino acid sequence of SEQ ID NO: 6 (according to the Kabat definition system), and 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 as set forth in SEQ ID NO: 18.

[000175] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising a CDR-H1 having the amino acid sequence of SEQ ID NO: 7 (according to the Kabat definition system), a CDR-H2 having the amino acid sequence of SEQ ID NO: 8, SEQ ID NO: 20, or SEQ ID NO: 24 (according to the Kabat definition system), a CDR-H3 having the amino acid sequence of SEQ ID NO: 9 (according to the Kabat definition system), and is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical in the framework regions to the VH as set forth in SEQ ID NO: 17, SEQ ID NO: 22, or SEQ ID NO: 26. Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VL comprising a CDR-L1 having the amino acid sequence of SEQ ID NO: 10 (according to the Kabat definition system), a CDR-L2 having the amino acid sequence of SEQ ID NO: 11 (according to the Kabat definition system),

and a CDR-L3 having the amino acid sequence of SEQ ID NO: 6 (according to the Kabat definition system), and is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical in the framework regions to the VL as set forth in any one of SEQ ID NO: 18.

[000176] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising a CDR-H1 having the amino acid sequence of SEQ ID NO: 12 (according to the Chothia definition system), a CDR-H2 having the amino acid sequence of SEQ ID NO: 13, SEQ ID NO: 21, or SEQ ID NO: 25 (according to the Chothia definition system), a CDR-H3 having the amino acid sequence of SEQ ID NO: 14 (according to the Chothia definition system), and 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 as set forth in SEQ ID NO: 17, SEQ ID NO: 22 or SEQ ID NO: 26. Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VL comprising a CDR-L1 having the amino acid sequence of SEQ ID NO: 15 (according to the Chothia definition system), a CDR-L2 having the amino acid sequence of SEQ ID NO: 5 (according to the Chothia definition system), and a CDR-L3 having the amino acid sequence of SEQ ID NO: 16 (according to the Chothia definition system), and 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 as set forth in SEQ ID NO: 18.

[000177] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising a CDR-H1 having the amino acid sequence of SEQ ID NO: 12 (according to the Chothia definition system), a CDR-H2 having the amino acid sequence of SEQ ID NO: 13, SEQ ID NO: 21, or SEQ ID NO: 25 (according to the Chothia definition system), a CDR-H3 having the amino acid sequence of SEQ ID NO: 14 (according to the Chothia definition system), and is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical in the framework regions to the VH as set forth in SEQ ID NO: SEQ ID NO: 17, SEQ ID NO: 22 or SEQ ID NO: 26. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody of the present disclosure comprises a humanized VL comprising a CDR-L1 having the amino acid sequence of SEQ ID NO: 15 (according to the Chothia definition system), a CDR-L2 having the amino acid sequence of SEQ ID NO: 5 (according to the Chothia definition system), and a CDR-L3 having the amino acid sequence of SEQ ID NO: 16 (according to the Chothia definition system), and is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical in the framework regions to the VL as set forth in any one of SEQ ID NO: 18.

[000178] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising a CDR-H1 having the amino acid sequence of SEQ ID NO: 27 (according to the IMGT definition system), a CDR-H2 having the amino acid sequence of SEQ ID NO: 28 (according to the IMGT definition system), a CDR-H3 having the amino acid sequence of SEQ ID NO: 29 (according to the IMGT definition system), and 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 as set forth in SEQ ID NO: 43. Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VL comprising a CDR-L1 having the amino acid sequence of SEQ ID NO: 30 (according to the IMGT definition system), a CDR-L2 having the amino acid sequence of SEQ ID NO: 31 (according to the IMGT definition system), and a CDR-L3 having the amino acid sequence of SEQ ID NO: 32 (according to the IMGT definition system), and 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 as set forth in SEQ ID NO: 44.

[000179] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising a CDR-H1 having the amino acid sequence of SEQ ID NO: 27 (according to the IMGT definition system), a CDR-H2 having the amino acid sequence of SEQ ID NO: 28 (according to the IMGT definition system), a CDR-H3 having the amino acid sequence of SEQ ID NO: 29 (according to the IMGT definition system), and is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical in the framework regions to the VH as set forth in SEQ ID NO: 43. Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VL comprising a CDR-L1 having the amino acid sequence of SEQ ID NO: 30 (according to the IMGT definition system), a CDR-L2 having the amino acid sequence of SEQ ID NO: 31 (according to the IMGT definition system), and a CDR-L3 having the amino acid sequence of SEQ ID NO: 32 (according to the IMGT definition system), and is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical in the framework regions to the VL as set forth in SEQ ID NO: 44.

[000180] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising a CDR-H1 having the amino acid sequence of SEQ ID NO: 33 (according to the Kabat definition system), a CDR-H2 having the amino acid sequence of SEQ ID NO: 34 (according to the Kabat definition system), a CDR-H3 having the amino acid sequence of SEQ ID NO: 35 (according to the Kabat definition system), and 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 as set forth in SEQ ID NO: 43. Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VL comprising a CDR-L1 having the amino acid sequence of SEQ ID NO: 36 (according to the Kabat definition system), a CDR-L2 having the amino acid sequence of SEQ ID NO: 37 (according to the Kabat definition system), and a CDR-L3 having the amino acid sequence of SEQ ID NO: 32 (according to the Kabat definition system), and 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 as set forth in SEQ ID NO: 44.

[000181] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising a CDR-H1 having the amino acid sequence of SEQ ID NO: 33 (according to the Kabat definition system), a CDR-H2 having the amino acid sequence of SEQ ID NO: 34 (according to the Kabat definition system), a CDR-H3 having the amino acid sequence of SEQ ID NO: 35 (according to the Kabat definition system), and is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical in the framework regions to the VH as set forth in SEQ ID NO: 43. Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VL comprising a CDR-L1 having the amino acid sequence of SEQ ID NO: 36 (according to the Kabat definition system), a CDR-L2 having the amino acid sequence of SEQ ID NO: 37 (according to the Kabat definition system), and a CDR-L3 having the amino acid sequence of SEQ ID NO: 32 (according to the Kabat definition system), and is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical in the framework regions to the VL as set forth in SEQ ID NO: 44.

[000182] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising a CDR-H1 having the amino acid sequence of SEQ ID NO: 38 (according to the Chothia definition system), a CDR-H2 having the amino acid sequence of SEQ ID NO: 39 (according to the Chothia definition system), a CDR-H3 having the amino acid sequence of SEQ ID NO: 40 (according to the Chothia definition system), and 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 as set forth in SEQ ID NO: 43. Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VL comprising a CDR-L1 having the amino acid sequence of SEQ ID NO: 41 (according to the Chothia definition system), a CDR-L2 having the amino acid sequence of SEQ ID NO: 31 (according to the Chothia definition system), and a CDR-L3 having the

amino acid sequence of SEQ ID NO: 42 (according to the Chothia definition system), and 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 as set forth in SEQ ID NO: 44.

[000183] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising a CDR-H1 having the amino acid sequence of SEQ ID NO: 38 (according to the Chothia definition system), a CDR-H2 having the amino acid sequence of SEQ ID NO: 39 (according to the Chothia definition system), a CDR-H3 having the amino acid sequence of SEQ ID NO: 40 (according to the Chothia definition system), and is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical in the framework regions to the VH as set forth in SEQ ID NO: 43. Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VL comprising a CDR-L1 having the amino acid sequence of SEQ ID NO: 41 (according to the Chothia definition system), a CDR-L2 having the amino acid sequence of SEQ ID NO: 31 (according to the Chothia definition system), and a CDR-L3 having the amino acid sequence of SEQ ID NO: 42 (according to the Chothia definition system), and is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical in the framework regions to the VL as set forth in SEQ ID NO: 44.

[000184] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising a CDR-H1 having the amino acid sequence of SEQ ID NO: 45, SEQ ID NO: 63, or SEQ ID NO: 66 (according to the IMGT definition system), a CDR-H2 having the amino acid sequence of SEQ ID NO: 46 (according to the IMGT definition system), a CDR-H3 having the amino acid sequence of SEQ ID NO: 47 (according to the IMGT definition system), and 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 as set forth in SEQ ID NO: 61, SEQ ID NO: 65, or SEQ ID NO: 68. Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VL comprising a CDR-L1 having the amino acid sequence of SEQ ID NO: 48 (according to the IMGT definition system), a CDR-L2 having the amino acid sequence of SEQ ID NO: 49 (according to the IMGT definition system), and a CDR-L3 having the amino acid sequence of SEQ ID NO: 50 (according to the IMGT definition system), and 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 as set forth in SEQ ID NO: 62.

[000185] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising a CDR-H1 having the amino acid sequence of SEQ ID NO: 45, SEQ ID NO: 63, or SEQ ID NO: 66 (according to the IMGT definition system), a CDR-H2 having the amino acid sequence of SEQ ID NO: 46 (according to the IMGT definition system), a CDR-H3 having the amino acid sequence of SEQ ID NO: 47 (according to the IMGT definition system), and is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical in the framework regions to the VH as set forth in SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 68. Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VL comprising a CDR-L1 having the amino acid sequence of SEQ ID NO: 48 (according to the IMGT definition system), a CDR-L2 having the amino acid sequence of SEQ ID NO: 49 (according to the IMGT definition system), and a CDR-L3 having the amino acid sequence of SEQ ID NO: 50 (according to the IMGT definition system), and is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical in the framework regions to the VL as set forth in SEQ ID NO: 62.

[000186] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising a CDR-H1 having the amino acid sequence of SEQ ID NO: 51, SEQ ID NO: 64, or SEQ ID NO: 67 (according to the Kabat definition system), a CDR-H2 having the amino acid sequence of SEQ ID NO: 52 (according to the Kabat definition system), a CDR-H3 having the amino acid sequence of SEQ ID NO: 53 (according to the Kabat definition system), and 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 as set forth in SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 68. Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VL comprising a CDR-L1 having the amino acid sequence of SEQ ID NO: 54 (according to the Kabat definition system), a CDR-L2 having the amino acid sequence of SEQ ID NO: 55 (according to the Kabat definition system), and a CDR-L3 having the amino acid sequence of SEQ ID NO: 50 (according to the Kabat definition system), and 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 as set forth in SEQ ID NO: 62.

[000187] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising a CDR-H1 having the amino acid sequence of SEQ ID NO: 51, SEQ ID NO: 64, or SEQ ID NO: 67 (according to the Kabat definition system), a CDR-H2 having the amino acid sequence of SEQ ID NO: 52 (according to the Kabat

definition system), a CDR-H3 having the amino acid sequence of SEQ ID NO: 53 (according to the Kabat definition system), and is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical in the framework regions to the VH as set forth in SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 68. Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VL comprising a CDR-L1 having the amino acid sequence of SEQ ID NO: 54 (according to the Kabat definition system), a CDR-L2 having the amino acid sequence of SEQ ID NO: 55 (according to the Kabat definition system), and a CDR-L3 having the amino acid sequence of SEQ ID NO: 50 (according to the Kabat definition system), and is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical in the framework regions to the VL as set forth in SEQ ID NO: 62.

[000188] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising a CDR-H1 having the amino acid sequence of SEQ ID NO: 56 (according to the Chothia definition system), a CDR-H2 having the amino acid sequence of SEQ ID NO: 57 (according to the Chothia definition system), a CDR-H3 having the amino acid sequence of SEQ ID NO: 58 (according to the Chothia definition system), and 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 as set forth in SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 68. Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VL comprising a CDR-L1 having the amino acid sequence of SEQ ID NO: 59 (according to the Chothia definition system), a CDR-L2 having the amino acid sequence of SEQ ID NO: 49 (according to the Chothia definition system), and a CDR-L3 having the amino acid sequence of SEQ ID NO: 60 (according to the Chothia definition system), and 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 as set forth in SEQ ID NO: 62.

[000189] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising a CDR-H1 having the amino acid sequence of SEQ ID NO: 56 (according to the Chothia definition system), a CDR-H2 having the amino acid sequence of SEQ ID NO: 57 (according to the Chothia definition system), a CDR-H3 having the amino acid sequence of SEQ ID NO: 58 (according to the Chothia definition system), and is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical in the framework regions to the VH as set forth in SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 68. Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VL comprising a CDR-L1 having the amino acid sequence of SEQ ID

NO: 59 (according to the Chothia definition system), a CDR-L2 having the amino acid sequence of SEQ ID NO: 49 (according to the Chothia definition system), and a CDR-L3 having the amino acid sequence of SEQ ID NO: 60 (according to the Chothia definition system), and is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical in the framework regions to the VL as set forth in SEQ ID NO: 62.

[000190] Examples of amino acid sequences of the humanized anti-TfR1 antibodies described herein are provided in Table 3.

Table 3. Variable Regions of Humanized Anti-TfR1 Antibodies

Antibody	Variable Region Amino Acid Sequence**
3A4 VH3 (N54T*)/Vκ4	V _H : EVQLVQSGSELKKPGASVKVSC ~~T~~ ASGFNIK DDYMYWVRQPPGKGLEWIGWIDP ETGDTEYASKFQDRVT VTADTSTNTAYMELSSLRSEDTAVYYCTL WLRRGLD YWGQGTLVTVSS (SEQ ID NO: 69)
	V _L : DIVMTQSPLSLPVTPGEPASISCRSSK SLLHSNGYTYLFWFQQRPGQSPRLLIYR MSN LASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC MQHLEYPFTFGGGTK VEIK (SEQ ID NO: 70)
3A4 VH3 (N54S*)/Vκ4	V _H : EVQLVQSGSELKKPGASVKVSC ~~T~~ ASGFNIK DDYMYWVRQPPGKGLEWIGWIDP ESGDTEYASKFQDRVT VTADTSTNTAYMELSSLRSEDTAVYYCTL WLRRGLD YWGQGTLVTVSS (SEQ ID NO: 71)
	V _L : DIVMTQSPLSLPVTPGEPASISCRSSK SLLHSNGYTYLFWFQQRPGQSPRLLIYR MSN LASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC MQHLEYPFTFGGGTK VEIK (SEQ ID NO: 70)
3A4 VH3 /Vκ4	V _H : EVQLVQSGSELKKPGASVKVSC ~~T~~ ASGFNIK DDYMYWVRQPPGKGLEWIGWIDP ENG DTEYASKFQDRVTVTADTSTNTAYMELSSLRSEDTAVYYCTL WLRRGLD YWGQGTLVTVSS (SEQ ID NO: 72)
	V _L : DIVMTQSPLSLPVTPGEPASISCRSSK SLLHSNGYTYLFWFQQRPGQSPRLLIYR MSN LASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC MQHLEYPFTFGGGTK VEIK (SEQ ID NO: 70)
3M12 VH3/Vκ2	V _H : QVQLQESGPGLVKPSQTLSTCSVTGYSIT SGYYWNWIRQPPGKGLEWMGYITF DGANNYNPSLKNRVSISR DTSKNQFSLKLSSVTAEDTATYYCTR SSYD YD VLDY WGQGT TVTVSS (SEQ ID NO: 73)
	V _L : DIQMTQSPSSLSASVGDRVTIT CRASQDISN FLNWyQQKPGQPVKLLIY YTSRLH SGVPSRFSGSGSGTDFTLTISLQPEDFATYYC QQGHTLPYTFGQGT TKLEIK (SEQ ID NO: 74)
3M12 VH3/Vκ3	V _H : QVQLQESGPGLVKPSQTLSTCSVTGYSIT SGYYWNWIRQPPGKGLEWMGYITF DGANNYNPSLKNRVSISR DTSKNQFSLKLSSVTAEDTATYYCTR SSYD YD VLDY WGQGT TVTVSS (SEQ ID NO: 73)
	V _L : DIQMTQSPSSLSASVGDRVTIT CRASQDISN FLNWyQQKPGQPVKLLIY YTSRLH SGVPSRFSGSGSGTDFTLTISLQPEDFATYYC QQGHTLPYTFGQGT TKLEIK (SEQ ID NO: 75)
3M12	V _H :

Antibody	Variable Region Amino Acid Sequence**
VH4/Vκ2	QVQLQESGPGGLVKPSQTLSTCTVTGYSIT SGYYWN WIRQPPGKGLEWIGYITFD GANNYNPSLKN RVSISRDTSKNQFSLKLSSVTAEDTATYYCTR SSYDYD VLDYW GGGTTVTVSS (SEQ ID NO: 76)
	VL: DIQMTQSPSSLSASVGDRVITITCRAS QDISN FLNWFYQQKPGQPVKLLIY YTSRLH SGVPSRFGSGSGSGTDFTLTISSLQPEDFATYFC QQGHTLPY TFGQGTKLEIK (SEQ ID NO: 74)
3M12 VH4/Vκ3	VH: QVQLQESGPGGLVKPSQTLSTCTVTGYSIT SGYYWN WIRQPPGKGLEWIGYITFD GANNYNPSLKN RVSISRDTSKNQFSLKLSSVTAEDTATYYCTR SSYDYD VLDYW GGGTTVTVSS (SEQ ID NO: 76)
	VL: DIQMTQSPSSLSASVGDRVITITCRAS QDISN FLNWFYQQKPGQPVKLLIY YTSRLH SGVPSRFGSGSGSGTDFTLTISSLQPEDFATYYC QQGHTLPY TFGQGTKLEIK (SEQ ID NO: 75)
5H12 VH5 (C33Y*)/Vκ3	VH: QVQLVQSGAEVKKPGASVKVSCKASGYSFT DYYIN WVRQAPGQGLEWMGWYIY PGSGNTRYSERFKGR VTITRDTASTAYMELSSLRSEDTAVYYCARE DYYPYH GMDYWGQ GLTVTVSS (SEQ ID NO: 77)
	VL: DIVLTQSPDSLAVSLGERATINCRASE VDGYD NSFMHWYQQKPGQPPKLLIFR ASNLESGVPDR FGSGSGTDFTLTISSLQAEDVAVYYC QQSSEDPWT FGQGTKL EIK (SEQ ID NO: 78)
5H12 VH5 (C33D*)/Vκ4	VH: QVQLVQSGAEVKKPGASVKVSCKASGYSFT DYDIN WVRQAPGQGLEWMGWYIY PGSGNTRYSERFKGR VTITRDTASTAYMELSSLRSEDTAVYYCARE DYYPYH GMDYWGQ GLTVTVSS (SEQ ID NO: 79)
	VL: DIVMTQSPDSLAVSLGERATINCRASE VDGYD NSFMHWYQQKPGQPPKLLIFR ASNLESGVPDR FGSGSGTDFTLTISSLQAEDVAVYYC QQSSEDPWT FGQGTKL EIK (SEQ ID NO: 80)
5H12 VH5 (C33Y*)/Vκ4	VH: QVQLVQSGAEVKKPGASVKVSCKASGYSFT DYYIN WVRQAPGQGLEWMGWYIY PGSGNTRYSERFKGR VTITRDTASTAYMELSSLRSEDTAVYYCARE DYYPYH GMDYWGQ GLTVTVSS (SEQ ID NO: 77)
	VL: DIVMTQSPDSLAVSLGERATINCRASE VDGYD NSFMHWYQQKPGQPPKLLIFR ASNLESGVPDR FGSGSGTDFTLTISSLQAEDVAVYYC QQSSEDPWT FGQGTKL EIK (SEQ ID NO: 80)

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

** CDRs according to the Kabat numbering system are bolded

[000191] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising the CDR-H1, CDR-H2, and CDR-H3 of any one of the anti-TfR1 antibodies provided in Table 2 and comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) amino acid variations in the framework regions as compared with the respective humanized VH provided in Table 3. Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VL comprising the CDR-L1, CDR-L2, and CDR-L3 of any one of the anti-TfR1 antibodies provided in Table 2 and comprises one or more (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) amino acid variations in the framework regions as compared with the respective humanized VL provided in Table 3.

[000192] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 69, and/or (e.g., and) a humanized VL comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 70. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising the amino acid sequence of SEQ ID NO: 69 and a humanized VL comprising the amino acid sequence of SEQ ID NO: 70.

[000193] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 71, and/or (e.g., and) a humanized VL comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 70. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising the amino acid sequence of SEQ ID NO: 71 and a humanized VL comprising the amino acid sequence of SEQ ID NO: 70.

[000194] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 72, and/or (e.g., and) a humanized VL comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 70. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising the amino acid sequence of SEQ ID NO: 72 and a humanized VL comprising the amino acid sequence of SEQ ID NO: 70.

[000195] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 73, and/or (e.g., and) a humanized VL comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 74. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising the amino acid sequence of SEQ ID NO: 73 and a humanized VL comprising the amino acid sequence of SEQ ID NO: 74.

[000196] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 73, and/or (e.g., and) a

humanized VL comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 75. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising the amino acid sequence of SEQ ID NO: 73 and a humanized VL comprising the amino acid sequence of SEQ ID NO: 75.

[000197] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 76, and/or (e.g., and) a humanized VL comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 74. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising the amino acid sequence of SEQ ID NO: 76 and a humanized VL comprising the amino acid sequence of SEQ ID NO: 74.

[000198] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 76, and/or (e.g., and) a humanized VL comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 75. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising the amino acid sequence of SEQ ID NO: 76 and a humanized VL comprising the amino acid sequence of SEQ ID NO: 75.

[000199] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 77, and/or (e.g., and) a humanized VL comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 78. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising the amino acid sequence of SEQ ID NO: 77 and a humanized VL comprising the amino acid sequence of SEQ ID NO: 78.

[000200] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 79, and/or (e.g., and) a humanized VL comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 80. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising the amino acid

sequence of SEQ ID NO: 79 and a humanized VL comprising the amino acid sequence of SEQ ID NO: 80.

[000201] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 77, and/or (e.g., and) a humanized VL comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 80. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a humanized VH comprising the amino acid sequence of SEQ ID NO: 77 and a humanized VL comprising the amino acid sequence of SEQ ID NO: 80.

[000202] In some embodiments, the humanized anti-TfR1 antibody described herein is a full-length IgG, which can include a heavy constant region and a light constant region from a human antibody. In some embodiments, the heavy chain of any of the anti-TfR1 antibodies as described herein may comprise a heavy chain constant region (CH) or a portion thereof (e.g., CH1, CH2, CH3, or a combination thereof). The heavy chain constant region can be of any suitable origin, e.g., human, mouse, rat, or rabbit. In one specific example, the heavy chain constant region is from a human IgG (a gamma heavy chain), e.g., IgG1, IgG2, or IgG4. An example of a human IgG1 constant region is given below:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLTPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 81)

[000203] In some embodiments, the heavy chain of any of the anti-TfR1 antibodies described herein comprises a mutant human IgG1 constant region. For example, the introduction of LALA mutations (a mutant derived from mAb b12 that has been mutated to replace the lower hinge residues Leu234 Leu235 with Ala234 and Ala235) in the CH2 domain of human IgG1 is known to reduce Fcγ receptor binding (Bruhns, P., et al . (2009) and Xu, D. et al. (2000)). The mutant human IgG1 constant region is provided below (mutations bonded and underlined):

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL

PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT
VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 82)

[000204] In some embodiments, the light chain of any of the anti-TfR1 antibodies described herein may further comprise a light chain constant region (CL), which can be any CL known in the art. In some examples, the CL is a kappa light chain. In other examples, the CL is a lambda light chain. In some embodiments, the CL is a kappa light chain, the sequence of which is provided below:

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ
DSKDSTYLSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 83)

[000205] Other antibody heavy and light chain constant regions are well known in the art, e.g., those provided in the IMGT database (www.imgt.org) or at www.vbase2.org/vbstat.php., both of which are incorporated by reference herein.

[000206] In some embodiments, the humanized anti-TfR1 antibody described herein comprises a heavy chain comprising any one of the VH as listed in Table 3 or any variants thereof and a heavy chain constant region that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to SEQ ID NO: 81 or SEQ ID NO: 82. In some embodiments, the humanized anti-TfR1 antibody described herein comprises a heavy chain comprising any one of the VH as listed in Table 3 or any variants thereof and a heavy chain constant region that contains no more than 25 amino acid variations (e.g., no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with SEQ ID NO: 81 or SEQ ID NO: 82. In some embodiments, the humanized anti-TfR1 antibody described herein comprises a heavy chain comprising any one of the VH as listed in Table 3 or any variants thereof and a heavy chain constant region as set forth in SEQ ID NO: 81. In some embodiments, the humanized anti-TfR1 antibody described herein comprises heavy chain comprising any one of the VH as listed in Table 3 or any variants thereof and a heavy chain constant region as set forth in SEQ ID NO: 82.

[000207] In some embodiments, the humanized anti-TfR1 antibody described herein comprises a light chain comprising any one of the VL as listed in Table 3 or any variants thereof and a light chain constant region that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to SEQ ID NO: 83. In some embodiments, the humanized anti-TfR1 antibody described herein comprises a light chain comprising any one of the VL as listed in Table 3 or any variants thereof and a light chain constant region contains no more than 25 amino acid variations (e.g., no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with SEQ ID NO: 83. In some embodiments, the humanized anti-TfR1 antibody described herein comprises a light chain

comprising any one of the VL as listed in Table 3 or any variants thereof and a light chain constant region set forth in SEQ ID NO: 83.

[000208] Examples of IgG heavy chain and light chain amino acid sequences of the anti-TfR1 antibodies described are provided in Table 4 below.

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

Antibody	IgG Heavy Chain/Light Chain Sequences**
3A4 VH3 (N54T*)/Vκ4	Heavy Chain (with wild type human IgG1 constant region) <u>EVQLVQSGSELKPGASVKV</u><u>SCTASGFNIKDDYMYWVR</u><u>OPPGKGLEWIGW</u> <u>IDPETGDTEYASKFQDRVT</u><u>VTADTSTNTAYMELSSLR</u><u>SEDTAVYYCTLWL</u> <u>RRGLDYWGQGLTVTVSS</u><u>ASTKGPSVFPLAPSSKSTSGGTA</u><u>ALGCLVKDYFP</u> <u>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV</u><u>TVPSSSLGTQTYICNVN</u> <u>HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD</u><u>TLMISRT</u> <u>PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL</u> <u>TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL</u> <u>TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSF</u><u>FLYSKL</u> <u>TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK</u> (SEQ ID NO: 84) Light Chain (with kappa light chain constant region) <u>DIVMTQSPLSLPVTPGEPASISCRSSKSL</u><u>LHSNGYTYLFWFQORPGOSPRLLI</u> <u>YRMSNLASGV</u><u>PDRFSGSGSGTDFTLKISRVEAEDVGVYYCMOHLEYPFTE</u> <u>GGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV</u> <u>DNALQSGNSQESVTEQDSKDYSLSSITLSKADYEKHKVYACEVTHQGL</u> <u>SSPVTKSFNRGEC</u> (SEQ ID NO: 85)
3A4 VH3 (N54S*)/Vκ4	Heavy Chain (with wild type human IgG1 constant region) <u>EVQLVQSGSELKPGASVKV</u><u>SCTASGFNIKDDYMYWVR</u><u>OPPGKGLEWIGW</u> <u>IDPESGDTEYASKFQDRVT</u><u>VTADTSTNTAYMELSSLR</u><u>SEDTAVYYCTLWL</u> <u>RRGLDYWGQGLTVTVSS</u><u>ASTKGPSVFPLAPSSKSTSGGTA</u><u>ALGCLVKDYFP</u> <u>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV</u><u>TVPSSSLGTQTYICNVN</u> <u>HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD</u><u>TLMISRT</u> <u>PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL</u> <u>TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL</u> <u>TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSF</u><u>FLYSKL</u> <u>TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK</u> (SEQ ID NO: 86) Light Chain (with kappa light chain constant region) <u>DIVMTQSPLSLPVTPGEPASISCRSSKSL</u><u>LHSNGYTYLFWFQORPGOSPRLLI</u> <u>YRMSNLASGV</u><u>PDRFSGSGSGTDFTLKISRVEAEDVGVYYCMOHLEYPFTE</u> <u>GGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV</u> <u>DNALQSGNSQESVTEQDSKDYSLSSITLSKADYEKHKVYACEVTHQGL</u> <u>SSPVTKSFNRGEC</u> (SEQ ID NO: 85)
3A4 VH3 /Vκ4	Heavy Chain (with wild type human IgG1 constant region) <u>EVQLVQSGSELKPGASVKV</u><u>SCTASGFNIKDDYMYWVR</u><u>OPPGKGLEWIGW</u> <u>IDPENGDT</u><u>EYASKFQDRVT</u><u>VTADTSTNTAYMELSSLR</u><u>SEDTAVYYCTLWL</u> <u>RRGLDYWGQGLTVTVSS</u><u>ASTKGPSVFPLAPSSKSTSGGTA</u><u>ALGCLVKDYFP</u> <u>EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV</u><u>TVPSSSLGTQTYICNVN</u> <u>HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD</u><u>TLMISRT</u> <u>PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL</u> <u>TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL</u> <u>TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSF</u><u>FLYSKL</u> <u>TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK</u> (SEQ ID NO: 87) Light Chain (with kappa light chain constant region) <u>DIVMTQSPLSLPVTPGEPASISCRSSKSL</u><u>LHSNGYTYLFWFQORPGOSPRLLI</u> <u>YRMSNLASGV</u><u>PDRFSGSGSGTDFTLKISRVEAEDVGVYYCMOHLEYPFTE</u> <u>GGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV</u> <u>DNALQSGNSQESVTEQDSKDYSLSSITLSKADYEKHKVYACEVTHQGL</u> <u>SSPVTKSFNRGEC</u> (SEQ ID NO: 85)
3M12	Heavy Chain (with wild type human IgG1 constant region)

Antibody	IgG Heavy Chain/Light Chain Sequences**
VH3/V κ 2	Heavy Chain (with wild type human IgG1 constant region) <u>QVQLQESGPGLVKPSQTLSTCSVTGYSTSGYYWNWIRPPGKGLEWMGY</u> <u>ITFDGANNYNPSLKNRVSISRDTSKNQFSLKLSSVTAEDTATYYCTRSSYDY</u> <u>DVLDYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE</u> PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT EVTCTVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 88) Light Chain (with kappa light chain constant region) <u>DIQMTQSPSSLSASVGDRVITTCRASQDISNFLNWFYQOKPGOPVKLLIYYTS</u> <u>RLHSGVPSRFRSGSGSGTDFTLTISLQPEDFATYFCQOQHTLPYTFGQGTKL</u> <u>EIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQS</u> GNSQESVTEQDSKDYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC (SEQ ID NO: 89)
3M12 VH3/V κ 3	Heavy Chain (with wild type human IgG1 constant region) <u>QVQLQESGPGLVKPSQTLSTCSVTGYSTSGYYWNWIRPPGKGLEWMGY</u> <u>ITFDGANNYNPSLKNRVSISRDTSKNQFSLKLSSVTAEDTATYYCTRSSYDY</u> <u>DVLDYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE</u> PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT EVTCTVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 88) Light Chain (with kappa light chain constant region) <u>DIQMTQSPSSLSASVGDRVITTCRASQDISNFLNWFYQOKPGOPVKLLIYYTS</u> <u>RLHSGVPSRFRSGSGSGTDFTLTISLQPEDFATYFCQOQHTLPYTFGQGTKL</u> <u>EIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQS</u> GNSQESVTEQDSKDYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC (SEQ ID NO: 90)
3M12 VH4/V κ 2	Heavy Chain (with wild type human IgG1 constant region) <u>QVQLQESGPGLVKPSQTLSTCTVTGYSTSGYYWNWIRPPGKGLEWIGYI</u> <u>TFDGANNYNPSLKNRVSISRDTSKNQFSLKLSSVTAEDTATYYCTRSSYDY</u> <u>DVLDYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE</u> PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT EVTCTVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 91) Light Chain (with kappa light chain constant region) <u>DIQMTQSPSSLSASVGDRVITTCRASQDISNFLNWFYQOKPGOPVKLLIYYTS</u> <u>RLHSGVPSRFRSGSGSGTDFTLTISLQPEDFATYFCQOQHTLPYTFGQGTKL</u> <u>EIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQS</u> GNSQESVTEQDSKDYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC (SEQ ID NO: 89)
3M12 VH4/V κ 3	Heavy Chain (with wild type human IgG1 constant region) <u>QVQLQESGPGLVKPSQTLSTCTVTGYSTSGYYWNWIRPPGKGLEWIGYI</u> <u>TFDGANNYNPSLKNRVSISRDTSKNQFSLKLSSVTAEDTATYYCTRSSYDY</u> <u>DVLDYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE</u> PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT EVTCTVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 91) Light Chain (with kappa light chain constant region) <u>DIQMTQSPSSLSASVGDRVITTCRASQDISNFLNWFYQOKPGOPVKLLIYYTS</u> <u>RLHSGVPSRFRSGSGSGTDFTLTISLQPEDFATYFCQOQHTLPYTFGQGTKL</u> <u>EIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQS</u>

Antibody	IgG Heavy Chain/Light Chain Sequences**
5H12 VH5 (C33Y*)/Vκ3	GNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC (SEQ ID NO: 90) Heavy Chain (with wild type human IgG1 constant region) <u>QVQLVQSGAEVKKPGASVKVSCKASGYSTFDY^YINWVRQAPGQGLEWMG</u> <u>WIYPGSGNTRYSERFKGRVTITRDTSASTAYMELSSLRSEDTAVYYCARED</u> <u>YYPYHGMDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK</u> DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 92) Light Chain (with kappa light chain constant region) DIVLTQSPDSLAVSLGERATINCRASESVDGYDNSFMHWYQOKPGOPPKLL IFRASNLESGVPDRFSGSGSRTDFTLTISLQAEDVAVYYCQOQSEDPWTFG QGQTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNFPYPREAKVQWKVD NALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLS SPVTKSFNRGEC (SEQ ID NO: 93)
5H12 VH5 (C33D*)/Vκ4	Heavy Chain (with wild type human IgG1 constant region) <u>QVQLVQSGAEVKKPGASVKVSCKASGYSTFDY^DINWVRQAPGQGLEWMG</u> <u>WIYPGSGNTRYSERFKGRVTITRDTSASTAYMELSSLRSEDTAVYYCARED</u> <u>YYPYHGMDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK</u> DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 94) Light Chain (with kappa light chain constant region) DIVMTQSPDSLAVSLGERATINCRASESVDGYDNSFMHWYQOKPGOPPKL LIFRASNLESGVPDRFSGSGSGTDFTLTISLQAEDVAVYYCQOQSEDPWTF GQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNFPYPREAKVQWKV DNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC (SEQ ID NO: 95)
5H12 VH5 (C33Y*)/Vκ4	Heavy Chain (with wild type human IgG1 constant region) <u>QVQLVQSGAEVKKPGASVKVSCKASGYSTFDY^YINWVRQAPGQGLEWMG</u> <u>WIYPGSGNTRYSERFKGRVTITRDTSASTAYMELSSLRSEDTAVYYCARED</u> <u>YYPYHGMDYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK</u> DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 92) Light Chain (with kappa light chain constant region) DIVMTQSPDSLAVSLGERATINCRASESVDGYDNSFMHWYQOKPGOPPKL LIFRASNLESGVPDRFSGSGSGTDFTLTISLQAEDVAVYYCQOQSEDPWTF GQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNFPYPREAKVQWKV DNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC (SEQ ID NO: 95)

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

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

[000209] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain containing no more than 25 amino acid variations (e.g., no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1

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

[000210] In some embodiments, the humanized anti-TfR1 antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 84, 86, 87, 88, 91, 92, and 94. Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody described herein comprises a light chain comprising an amino acid sequence that is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 85, 89, 90, 93, and 95. In some embodiments, the anti-TfR1 antibody described herein comprises a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs: 84, 86, 87, 88, 91, 92, and 94. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody described herein comprises a light chain comprising the amino acid sequence of any one of SEQ ID NOs: 85, 89, 90, 93, and 95.

[000211] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 84, and/or (e.g., and) a light chain comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 85. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 84 and a light chain comprising the amino acid sequence of SEQ ID NO: 85.

[000212] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 86, and/or (e.g., and) a light chain comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 85. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 86 and a light chain comprising the amino acid sequence of SEQ ID NO: 85.

[000213] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 87, and/or (e.g., and) a light chain comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%,

95%, 98%, or 99%) to SEQ ID NO: 85. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 87 and a light chain comprising the amino acid sequence of SEQ ID NO: 85.

[000214] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 88, and/or (e.g., and) a light chain comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 89. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 88 and a light chain comprising the amino acid sequence of SEQ ID NO: 89.

[000215] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 88, and/or (e.g., and) a light chain comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 90. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 88 and a light chain comprising the amino acid sequence of SEQ ID NO: 90.

[000216] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 91, and/or (e.g., and) a light chain comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 89. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 89.

[000217] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 91, and/or (e.g., and) a light chain comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 90. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 90.

[000218] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 92, and/or (e.g., and) a light chain comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%,

95%, 98%, or 99%) to SEQ ID NO: 93. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 92 and a light chain comprising the amino acid sequence of SEQ ID NO: 93.

[000219] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 94, and/or (e.g., and) a light chain comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 95. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 94 and a light chain comprising the amino acid sequence of SEQ ID NO: 95.

[000220] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 92, and/or (e.g., and) a light chain comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 95. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 92 and a light chain comprising the amino acid sequence of SEQ ID NO: 95.

[000221] In some embodiments, the anti-TfR1 antibody is a Fab fragment, Fab' fragment, or F(ab')₂ fragment of an intact antibody (full-length antibody). Antigen binding fragment of an intact antibody (full-length antibody) can be prepared via routine methods (e.g., recombinantly or by digesting the heavy chain constant region of a full-length IgG using an enzyme such as papain). For example, F(ab')₂ fragments can be produced by pepsin or papain digestion of an antibody molecule, and Fab' fragments that can be generated by reducing the disulfide bridges of F(ab')₂ fragments. In some embodiments, a heavy chain constant region in a Fab fragment of the anti-TfR1 antibody described herein comprises the amino acid sequence of:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 96)

[000222] In some embodiments, the humanized anti-TfR1 antibody described herein comprises a heavy chain comprising any one of the VH as listed in Table 3 or any variants thereof and a heavy chain constant region that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to SEQ ID NO: 96. In some embodiments, the humanized anti-TfR1 antibody described herein comprises a heavy chain comprising any one of the VH as listed in Table 3 or any variants thereof and a heavy chain constant region that contains no more than 25 amino acid variations (e.g., no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12,

11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with SEQ ID NO: 96. In some embodiments, the humanized anti-TfR1 antibody described herein comprises a heavy chain comprising any one of the VH as listed in Table 3 or any variants thereof and a heavy chain constant region as set forth in SEQ ID NO: 96.

[000223] In some embodiments, the humanized anti-TfR1 antibody described herein comprises a light chain comprising any one of the VL as listed in Table 3 or any variants thereof and a light chain constant region that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to SEQ ID NO: 83. In some embodiments, the humanized anti-TfR1 antibody described herein comprises a light chain comprising any one of the VL as listed in Table 3 or any variants thereof and a light chain constant region contains no more than 25 amino acid variations (e.g., no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with SEQ ID NO: 83. In some embodiments, the humanized anti-TfR1 antibody described herein comprises a light chain comprising any one of the VL as listed in Table 3 or any variants thereof and a light chain constant region set forth in SEQ ID NO: 83.

[000224] Examples of Fab heavy chain and light chain amino acid sequences of the anti-TfR1 antibodies described are provided in Table 5 below.

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

Antibody	Fab Heavy Chain/Light Chain Sequences**
3A4 VH3 (N54T*)/VK4	Heavy Chain (with partial human IgG1 constant region) <u>EVQLVQSGSELKPGASVKVSC</u> TASGFNIK DDYMYWVRPPGKGLEWIGW <u>IDPETGDTEYASKFQDRVTVTADTSTNTAYMELSSLR</u> SEDTAVYYCTL WL <u>RRGLDYGQGT</u> LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 97)
	Light Chain (with kappa light chain constant region) DIVMTQSPLSLPVTPGEPASISCR SSKSL LHSNGY TYLFW FQORPGQSPRLLI <u>YRMSNLASGV</u> PDRFSGSGSGTDFTLKISRVEAEDVGVYYC MOHLEYP PTF GGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC (SEQ ID NO: 85)
3A4 VH3 (N54S*)/VK4	Heavy Chain (with partial human IgG1 constant region) <u>EVQLVQSGSELKPGASVKVSC</u> TASGFNIK DDYMYWVRPPGKGLEWIGW <u>IDPESGDTEYASKFQDRVTVTADTSTNTAYMELSSLR</u> SEDTAVYYCTL WL <u>RRGLDYGQGT</u> LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 98)
	Light Chain (with kappa light chain constant region) DIVMTQSPLSLPVTPGEPASISCR SSKSL LHSNGY TYLFW FQORPGQSPRLLI <u>YRMSNLASGV</u> PDRFSGSGSGTDFTLKISRVEAEDVGVYYC MOHLEYP PTF GGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC (SEQ ID NO: 85)
3A4 VH3 /VK4	Heavy Chain (with partial human IgG1 constant region) <u>EVQLVQSGSELKPGASVKVSC</u> TASGFNIK DDYMYWVRPPGKGLEWIGW <u>IDPENGDTEYASKFQDRVTVTADTSTNTAYMELSSLR</u> SEDTAVYYCTL WL

Antibody	Fab Heavy Chain/Light Chain Sequences**
	<u>RRGLDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT</u> (SEQ ID NO: 99) Light Chain (with kappa light chain constant region) <u>DIVMTQSPLSLPVTPGEPASISCRSSKSLHLSNGYTYLFWFOORPGOSPRLLIYRMSNLASGVPDFRSGSGSGTDFTLKISRVEAEDVGVYYCMOHLEYPFTEGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC</u> (SEQ ID NO: 85)
3M12 VH3/Vκ2	Heavy Chain (with partial human IgG1 constant region) <u>QVQLQESGPGLVKPSQTLSTCSVTGYSITSGYYWNWIROPPGKGLEWMGYITFDGANNYNPSLKNRVSISRDTSKNQFSLKLSSVTAEDTATYYCTRSSYDYDVL</u> <u>DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT</u> (SEQ ID NO: 100) Light Chain (with kappa light chain constant region) <u>DIQMTQSPSSLSASVGDRVTITCRASODISNFLNWIYQOKPGQPVKLLIYYTSLRHSGVPSRFSGSGSGTDFTLTISLQPEDFATYFCQOQHTLPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC</u> (SEQ ID NO: 89)
3M12 VH3/Vκ3	Heavy Chain (with partial human IgG1 constant region) <u>QVQLQESGPGLVKPSQTLSTCSVTGYSITSGYYWNWIROPPGKGLEWMGYITFDGANNYNPSLKNRVSISRDTSKNQFSLKLSSVTAEDTATYYCTRSSYDYDVL</u> <u>DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT</u> (SEQ ID NO: 100) Light Chain (with kappa light chain constant region) <u>DIQMTQSPSSLSASVGDRVTITCRASODISNFLNWIYQOKPGQPVKLLIYYTSLRHSGVPSRFSGSGSGTDFTLTISLQPEDFATYFCQOQHTLPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC</u> (SEQ ID NO: 90)
3M12 VH4/Vκ2	Heavy Chain (with partial human IgG1 constant region) <u>QVQLQESGPGLVKPSQTLSTCTVTGYSITSGYYWNWIROPPGKGLEWIGYITFDGANNYNPSLKNRVSISRDTSKNQFSLKLSSVTAEDTATYYCTRSSYDYDVL</u> <u>DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT</u> (SEQ ID NO: 101) Light Chain (with kappa light chain constant region) <u>DIQMTQSPSSLSASVGDRVTITCRASODISNFLNWIYQOKPGQPVKLLIYYTSLRHSGVPSRFSGSGSGTDFTLTISLQPEDFATYFCQOQHTLPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC</u> (SEQ ID NO: 89)
3M12 VH4/Vκ3	Heavy Chain (with partial human IgG1 constant region) <u>QVQLQESGPGLVKPSQTLSTCTVTGYSITSGYYWNWIROPPGKGLEWIGYITFDGANNYNPSLKNRVSISRDTSKNQFSLKLSSVTAEDTATYYCTRSSYDYDVL</u> <u>DYWGQGTITVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHT</u> (SEQ ID NO: 101) Light Chain (with kappa light chain constant region) <u>DIQMTQSPSSLSASVGDRVTITCRASODISNFLNWIYQOKPGQPVKLLIYYTSLRHSGVPSRFSGSGSGTDFTLTISLQPEDFATYFCQOQHTLPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC</u> (SEQ ID NO: 90)
5H12 VH5 (C33Y*)/Vκ3	Heavy Chain (with partial human IgG1 constant region) <u>QVQLVQSGAEVKKPGASVKVSCKASGYSTFDYYINWVRQAPGQGLEWMGWII</u> <u>YPGSGNTRYSERFKGRVTITRDTASTAYMELSSLRSEDTAVYYCAREDA</u>

Antibody	Fab Heavy Chain/Light Chain Sequences**
	YYPYHGMDYWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 102) Light Chain (with kappa light chain constant region) <u>DIVLTQSPD</u> SLAVSLGERATIN CRASESV DGYD NSFMH WYQOKPGQPPKLL LIFRAS NLESG VPDRFSGSGSGTDFTLTISSLOAEDVAVYY COQ SSEDP WTFG QG TKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDYSLSSITLSKADYEKHKVYACEVTHQGLS SPVTKSFNRGEC (SEQ ID NO: 93)
5H12 VH5 (C33D*)/Vκ4	Heavy Chain (with partial human IgG1 constant region) <u>QVQLVQSGAEVKKPGASVKVSCKASGYST</u> FDYDIN WVRQAPGGGLEWMG WIYPGSGNTRYSE RFKGR VTITRDTSASTAYMELSSLRSEDTAVYY CARE D YYPYHGMDYWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 103) Light Chain (with kappa light chain constant region) <u>DIVMTQSPD</u> SLAVSLGERATIN CRASESV DGYD NSFMH WYQOKPGQPPKLL LIFRAS NLESG VPDRFSGSGSGTDFTLTISSLOAEDVAVYY COQ SSEDP WTF GQ GTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDYSLSSITLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC (SEQ ID NO: 95)
5H12 VH5 (C33Y*)/Vκ4	Heavy Chain (with partial human IgG1 constant region) <u>QVQLVQSGAEVKKPGASVKVSCKASGYST</u> FDYYIN WVRQAPGGGLEWMG WIYPGSGNTRYSE RFKGR VTITRDTSASTAYMELSSLRSEDTAVYY CARE D YYPYHGMDYWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHT (SEQ ID NO: 102) Light Chain (with kappa light chain constant region) <u>DIVMTQSPD</u> SLAVSLGERATIN CRASESV DGYD NSFMH WYQOKPGQPPKLL LIFRAS NLESG VPDRFSGSGSGTDFTLTISSLOAEDVAVYY COQ SSEDP WTF GQ GTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKDYSLSSITLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC (SEQ ID NO: 95)

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

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

[000225] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain containing no more than 25 amino acid variations (e.g., no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the heavy chain as set forth in any one of SEQ ID NOs: 97-103. Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody of the present disclosure comprises a light chain containing no more than 25 amino acid variations (e.g., no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the light chain as set forth in any one of SEQ ID NOs: 85, 89, 90, 93, and 95.

[000226] In some embodiments, the humanized anti-TfR1 antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 75% (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) identical to any one of SEQ ID NOs: 97-103. Alternatively or in addition (e.g., in addition), the humanized anti-TfR1 antibody described herein comprises a light chain comprising an amino acid sequence that is at least 75% (e.g.,

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

[000227] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 97, and/or (e.g., and) a light chain comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 85. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 97 and a light chain comprising the amino acid sequence of SEQ ID NO: 85.

[000228] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 98, and/or (e.g., and) a light chain comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 85. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 98 and a light chain comprising the amino acid sequence of SEQ ID NO: 85.

[000229] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 99, and/or (e.g., and) a light chain comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 85. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 99 and a light chain comprising the amino acid sequence of SEQ ID NO: 85.

[000230] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 100, and/or (e.g., and) a light chain comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 89. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 100 and a light chain comprising the amino acid sequence of SEQ ID NO: 89.

[000231] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g.,

80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 100, and/or (e.g., and) a light chain comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 90. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 100 and a light chain comprising the amino acid sequence of SEQ ID NO: 90.

[000232] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 101, and/or (e.g., and) a light chain comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 89. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 101 and a light chain comprising the amino acid sequence of SEQ ID NO: 89.

[000233] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 101, and/or (e.g., and) a light chain comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 90. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 101 and a light chain comprising the amino acid sequence of SEQ ID NO: 90.

[000234] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 102, and/or (e.g., and) a light chain comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 93. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 102 and a light chain comprising the amino acid sequence of SEQ ID NO: 93.

[000235] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 103, and/or (e.g., and) a light chain comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 95. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 103 and a light chain comprising the amino acid sequence of SEQ ID NO: 95.

[000236] In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g.,

80%, 85%, 90%, 95%, 98%, or 99%) identical to SEQ ID NO: 102, and/or (e.g., and) a light chain comprising an amino acid sequence that is at least 80% identical (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) to SEQ ID NO: 95. In some embodiments, the humanized anti-TfR1 antibody of the present disclosure comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 102 and a light chain comprising the amino acid sequence of SEQ ID NO: 95.

[000237] In some embodiments, the humanized anti-TfR1 receptor antibodies described herein can be in any antibody form, including, but not limited to, intact (i.e., full-length) antibodies, antigen-binding fragments thereof (such as Fab, Fab', F(ab')₂, Fv), single chain antibodies, bi-specific antibodies, or nanobodies. In some embodiments, humanized the anti-TfR1 antibody described herein is a scFv. In some embodiments, the humanized anti-TfR1 antibody described herein is a scFv-Fab (e.g., scFv fused to a portion of a constant region). In some embodiments, the anti-TfR1 receptor antibody described herein is a scFv fused to a constant region (e.g., human IgG1 constant region as set forth in SEQ ID NO: 81 or SEQ ID NO: 82, or a portion thereof such as the Fc portion) at either the N-terminus or C-terminus.

[000238] In some embodiments, conservative mutations can be introduced into antibody sequences (e.g., CDRs or framework sequences) at positions where the residues are not likely to be involved in interacting with a target antigen (e.g., transferrin receptor), for example, as determined based on a crystal structure. In some embodiments, one, two or more mutations (e.g., amino acid substitutions) are introduced into the Fc region of an anti-TfR1 antibody described herein (e.g., in a CH₂ domain (residues 231-340 of human IgG1) and/or (e.g., and) CH₃ domain (residues 341-447 of human IgG1) and/or (e.g., and) the hinge region, with numbering according to the Kabat numbering system (e.g., the EU index in Kabat)) to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding and/or (e.g., and) antigen-dependent cellular cytotoxicity.

[000239] In some embodiments, one, two or more mutations (e.g., amino acid substitutions) are introduced into the hinge region of the Fc region (CH₁ domain) such that the number of cysteine residues in the hinge region are altered (e.g., increased or decreased) as described in, e.g., U.S. Pat. No. 5,677,425. The number of cysteine residues in the hinge region of the CH₁ domain can be altered to, e.g., facilitate assembly of the light and heavy chains, or to alter (e.g., increase or decrease) the stability of the antibody or to facilitate linker conjugation.

[000240] In some embodiments, one, two or more mutations (e.g., amino acid substitutions) are introduced into the Fc region of a muscle-targeting antibody described herein (e.g., in a CH₂ domain (residues 231-340 of human IgG1) and/or (e.g., and) CH₃ domain (residues 341-447 of human IgG1) and/or (e.g., and) the hinge region, with numbering according to the Kabat numbering system (e.g., the EU index in Kabat)) to increase or decrease the affinity

of the antibody for an Fc receptor (*e.g.*, an activated Fc receptor) on the surface of an effector cell. Mutations in the Fc region of an antibody that decrease or increase the affinity of an antibody for an Fc receptor and techniques for introducing such mutations into the Fc receptor or fragment thereof are known to one of skill in the art. Examples of mutations in the Fc receptor of an antibody that can be made to alter the affinity of the antibody for an Fc receptor are described in, *e.g.*, Smith P et al., (2012) PNAS 109: 6181-6186, U.S. Pat. No. 6,737,056, and International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631, which are incorporated herein by reference.

[000241] In some embodiments, one, two or more amino acid mutations (*i.e.*, substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to alter (*e.g.*, decrease or increase) half-life of the antibody *in vivo*. See, *e.g.*, International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631; and U.S. Pat. Nos. 5,869,046, 6,121,022, 6,277,375 and 6,165,745 for examples of mutations that will alter (*e.g.*, decrease or increase) the half-life of an antibody *in vivo*.

[000242] In some embodiments, one, two or more amino acid mutations (*i.e.*, substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to decrease the half-life of the anti-TfR1 antibody *in vivo*. In some embodiments, one, two or more amino acid mutations (*i.e.*, substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to increase the half-life of the antibody *in vivo*. In some embodiments, the antibodies can have one or more amino acid mutations (*e.g.*, substitutions) in the second constant (CH2) domain (residues 231-340 of human IgG1) and/or (*e.g.*, and) the third constant (CH3) domain (residues 341-447 of human IgG1), with numbering according to the EU index in Kabat (Kabat E A et al., (1991) *supra*). In some embodiments, the constant region of the IgG1 of an antibody described herein comprises a methionine (M) to tyrosine (Y) substitution in position 252, a serine (S) to threonine (T) substitution in position 254, and a threonine (T) to glutamic acid (E) substitution in position 256, numbered according to the EU index as in Kabat. See U.S. Pat. No. 7,658,921, which is incorporated herein by reference. This type of mutant IgG, referred to as "YTE mutant" has been shown to display fourfold increased half-life as compared to wild-type versions of the same antibody (see Dall'Acqua W F et al., (2006) J Biol Chem 281: 23514-24). In some embodiments, an antibody comprises an IgG constant domain comprising one, two, three or more amino acid substitutions of amino acid residues at positions 251-257, 285-290, 308-314, 385-389, and 428-436, numbered according to the EU index as in Kabat.

[000243] In some embodiments, one, two or more amino acid substitutions are introduced into an IgG constant domain Fc region to alter the effector function(s) of the anti-anti-TfR1 antibody. The effector ligand to which affinity is altered can be, for example, an Fc receptor or the C1 component of complement. This approach is described in further detail in U.S. Pat. Nos. 5,624,821 and 5,648,260. In some embodiments, the deletion or inactivation (through point mutations or other means) of a constant region domain can reduce Fc receptor binding of the circulating antibody thereby increasing tumor localization. See, e.g., U.S. Pat. Nos. 5,585,097 and 8,591,886 for a description of mutations that delete or inactivate the constant domain and thereby increase tumor localization. In some embodiments, one or more amino acid substitutions may be introduced into the Fc region of an antibody described herein to remove potential glycosylation sites on Fc region, which may reduce Fc receptor binding (see, e.g., Shields R L et al., (2001) J Biol Chem 276: 6591-604).

[000244] In some embodiments, one or more amino in the constant region of an anti-TfR1 antibody described herein can be replaced with a different amino acid residue such that the antibody has altered C1q binding and/or (e.g., and) reduced or abolished complement dependent cytotoxicity (CDC). This approach is described in further detail in U.S. Pat. No. 6,194,551 (Idusogie et al). In some embodiments, one or more amino acid residues in the N-terminal region of the CH2 domain of an antibody described herein are altered to thereby alter the ability of the antibody to fix complement. This approach is described further in International Publication No. WO 94/29351. In some embodiments, the Fc region of an antibody described herein is modified to increase the ability of the antibody to mediate antibody dependent cellular cytotoxicity (ADCC) and/or (e.g., and) to increase the affinity of the antibody for an Fcγ receptor. This approach is described further in International Publication No. WO 00/42072.

[000245] In some embodiments, the heavy and/or (e.g., and) light chain variable domain(s) sequence(s) of the antibodies provided herein can be used to generate, for example, CDR-grafted, chimeric, humanized, or composite human antibodies or antigen-binding fragments, as described elsewhere herein. As understood by one of ordinary skill in the art, any variant, CDR-grafted, chimeric, humanized, or composite antibodies derived from any of the antibodies provided herein may be useful in the compositions and methods described herein and will maintain the ability to specifically bind transferrin receptor, such that the variant, CDR-grafted, chimeric, humanized, or composite antibody has at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% or more binding to transferrin receptor relative to the original antibody from which it is derived.

[000246] In some embodiments, the antibodies provided herein comprise mutations that confer desirable properties to the antibodies. For example, to avoid potential complications due

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

[000247] In some embodiments, an antibody is modified, e.g., modified via glycosylation, phosphorylation, sumoylation, and/or (e.g., and) methylation. In some embodiments, an antibody is a glycosylated antibody, which is conjugated to one or more sugar or carbohydrate molecules. In some embodiments, the one or more sugar or carbohydrate molecule are conjugated to the antibody via N-glycosylation, O-glycosylation, C-glycosylation, glypiation (GPI anchor attachment), and/or (e.g., and) phosphoglycosylation. In some embodiments, the one or more sugar or carbohydrate molecules are monosaccharides, disaccharides, oligosaccharides, or glycans. In some embodiments, the one or more sugar or carbohydrate molecule is a branched oligosaccharide or a branched glycan. In some embodiments, the one or more sugar or carbohydrate molecule includes a mannose unit, a glucose unit, an N-acetylglucosamine unit, an N-acetylgalactosamine unit, a galactose unit, a fucose unit, or a phospholipid unit. In some embodiments, there are about 1-10, about 1-5, about 5-10, about 1-4, about 1-3, or about 2 sugar molecules. In some embodiments, a glycosylated antibody is fully or partially glycosylated. In some embodiments, an antibody is glycosylated by chemical reactions or by enzymatic means. In some embodiments, an antibody is glycosylated in vitro or inside a cell, which may optionally be deficient in an enzyme in the N- or O- glycosylation pathway, e.g., a glycosyltransferase. In some embodiments, an antibody is functionalized with sugar or carbohydrate molecules as described in International Patent Application Publication WO2014065661, published on May 1, 2014, entitled, “*Modified antibody, antibody-conjugate and process for the preparation thereof*”.

[000248] In some embodiments, any one of the anti-TfR1 antibodies described herein may comprise a signal peptide in the heavy and/or (e.g., and) light chain sequence (e.g., a N-terminal signal peptide). In some embodiments, the anti-TfR1 antibody described herein comprises any one of the VH and VL sequences, any one of the IgG heavy chain and light chain sequences, or any one of the Fab heavy chain and light chain sequences described herein, and further comprises a signal peptide (e.g., a N-terminal signal peptide). In some embodiments, the signal peptide comprises the amino acid sequence of MGWSCILFLVATATGVHS (SEQ ID NO: 104).

Other known anti-transferrin receptor 1 antibodies

[000249] Any other appropriate anti-transferrin receptor 1 antibodies known in the art may be used as the muscle-targeting agent in the complexes disclosed herein. Examples of known anti-transferrin receptor 1 antibodies, including associated references and binding epitopes, are listed in Table 6. In some embodiments, the anti-transferrin receptor 1 antibody comprises the complementarity determining regions (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) of any of the anti-transferrin receptor 1 antibodies provided herein, e.g., anti-transferrin receptor 1 antibodies listed in Table 6.

Table 6 – List of anti-transferrin receptor 1 antibody clones, including associated references and binding epitope information.

Antibody Clone Name	Reference(s)	Epitope / Notes
OKT9	US Patent. No. 4,364,934, filed 12/4/1979, entitled “MONOCLONAL ANTIBODY TO A HUMAN EARLY THYMOCYTE ANTIGEN AND METHODS FOR PREPARING SAME” Schneider C. et al. “Structural features of the cell surface receptor for transferrin that is recognized by the monoclonal antibody OKT9.” J Biol Chem. 1982, 257:14, 8516-8522.	Apical domain of TfR (residues 305-366 of human TfR sequence XM_052730.3 (SEQ ID NO: 404), available in GenBank)
(From JCR) Clone M11 Clone M23 Clone M27 Clone B84	- WO 2015/098989, filed 12/24/2014, “Novel anti-Transferrin receptor antibody that passes through blood-brain barrier” - US Patent No. 9,994,641, filed 12/24/2014, “Novel anti-Transferrin receptor antibody that passes through blood-brain barrier”	Apical domain (residues 230-244 and 326-347 of TfR) and protease-like domain (residues 461-473)
(From Genentech) 7A4, 8A2, 15D2, 10D11, 7B10, 15G11, 16G5, 13C3, 16G4, 16F6, 7G7, 4C2, 1B12, and 13D4	- WO 2016/081643, filed 5/26/2016, entitled “ANTI-TRANSFERRIN RECEPTOR ANTIBODIES AND METHODS OF USE” - US Patent No. 9,708,406, filed 5/20/2014, “Anti-transferrin receptor antibodies and methods of use”	Apical domain and non-apical regions
(From Armagen)	Lee et al. “Targeting Rat Anti-Mouse Transferrin Receptor Monoclonal	

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

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

[000250] In some embodiments, anti-TfR1 antibodies of the present disclosure include one or more of the CDR-H (*e.g.*, CDR-H1, CDR-H2, and CDR-H3) amino acid sequences from any one of the anti-TfR1 antibodies selected from Table 6. In some embodiments, anti-TfR1 antibodies include the CDR-H1, CDR-H2, and CDR-H3 as provided for any one of the anti-TfR1 antibodies selected from Table 6. In some embodiments, anti-TfR1 antibodies include the CDR-L1, CDR-L2, and CDR-L3 as provided for any one of the anti-TfR1 antibodies selected from Table 6. In some embodiments, anti-TfR1 antibodies include the CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3 as provided for any one of the anti-TfR1 antibodies selected from Table 6. The disclosure also includes any nucleic acid sequence that encodes a molecule comprising a CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, or CDR-L3 as provided for any one of the anti-TfR1 antibodies selected from Table 6. In some embodiments, antibody heavy and light chain CDR3 domains may play a particularly important role in the binding specificity/affinity of an antibody for an antigen. Accordingly, anti-TfR1 antibodies of the disclosure may include at least the heavy and/or (*e.g.*, and) light chain CDR3s of any one of the anti-TfR1 antibodies selected from Table 6.

[000251] In some examples, any of the anti-TfR1 antibodies of the disclosure have one or more CDR (*e.g.*, CDR-H or CDR-L) sequences substantially similar to any of the CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and/or (*e.g.*, and) CDR-L3 sequences from one of the anti-TfR1 antibodies selected from Table 6. In some embodiments, the position of one or more CDRs along the VH (*e.g.*, CDR-H1, CDR-H2, or CDR-H3) and/or (*e.g.*, and) VL (*e.g.*, CDR-L1, CDR-L2, or CDR-L3) region of an antibody described herein can vary by one, two, three, four, five, or six amino acid positions so long as immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% of the binding of the original antibody from which it is derived). For example, in some embodiments, the position defining a CDR of any antibody described herein can vary by shifting the N-terminal and/or (*e.g.*, and) C-terminal boundary of the CDR by one, two, three, four, five, or six amino acids,

relative to the CDR position of any one of the antibodies described herein, so long as immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% of the binding of the original antibody from which it is derived). In another embodiment, the length of one or more CDRs along the VH (*e.g.*, CDR-H1, CDR-H2, or CDR-H3) and/or (*e.g.*, and) VL (*e.g.*, CDR-L1, CDR-L2, or CDR-L3) region of an antibody described herein can vary (*e.g.*, be shorter or longer) by one, two, three, four, five, or more amino acids, so long as immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% of the binding of the original antibody from which it is derived).

[000252] Accordingly, in some embodiments, a CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, and/or (*e.g.*, and) CDR-H3 described herein may be one, two, three, four, five or more amino acids shorter than one or more of the CDRs described herein (*e.g.*, CDRs from any of the anti-transferrin receptor 1 antibodies selected from Table 6) so long as immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). In some embodiments, a CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, and/or (*e.g.*, and) CDR-H3 described herein may be one, two, three, four, five or more amino acids longer than one or more of the CDRs described herein (*e.g.*, CDRs from any of the anti-transferrin receptor 1 antibodies selected from Table 6) so long as immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). In some embodiments, the amino portion of a CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, and/or (*e.g.*, and) CDR-H3 described herein can be extended by one, two, three, four, five or more amino acids compared to one or more of the CDRs described herein (*e.g.*, CDRs from any of the anti-transferrin receptor 1 antibodies selected from Table 6) so long as immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). In some embodiments, the carboxy portion of a CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, and/or (*e.g.*, and) CDR-H3 described herein can be extended by one, two, three, four, five or more amino acids compared to one or more of the CDRs described herein (*e.g.*, CDRs from any of the anti-transferrin receptor 1 antibodies

selected from Table 6) so long as immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). In some embodiments, the amino portion of a CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, and/or (*e.g.*, and) CDR-H3 described herein can be shortened by one, two, three, four, five or more amino acids compared to one or more of the CDRs described herein (*e.g.*, CDRs from any of the anti-transferrin receptor 1 antibodies selected from Table 6) so long as immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). In some embodiments, the carboxy portion of a CDR-L1, CDR-L2, CDR-L3, CDR-H1, CDR-H2, and/or (*e.g.*, and) CDR-H3 described herein can be shortened by one, two, three, four, five or more amino acids compared to one or more of the CDRs described herein (*e.g.*, CDRs from any of the anti-transferrin receptor 1 antibodies selected from Table 6) so long as immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). Any method can be used to ascertain whether immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained, for example, using binding assays and conditions described in the art.

[000253] In some examples, any of the anti-transferrin receptor 1 antibodies of the disclosure have one or more CDR (*e.g.*, CDR-H or CDR-L) sequences substantially similar to any one of the anti-transferrin receptor 1 antibodies selected from Table 6. For example, the antibodies may include one or more CDR sequence(s) from any of the anti-transferrin receptor 1 antibodies selected from Table 6 containing up to 5, 4, 3, 2, or 1 amino acid residue variations as compared to the corresponding CDR region in any one of the CDRs provided herein (*e.g.*, CDRs from any of the anti-transferrin receptor 1 antibodies selected from Table 6) so long as immunospecific binding to transferrin receptor (*e.g.*, human transferrin receptor) is maintained (*e.g.*, substantially maintained, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% relative to the binding of the original antibody from which it is derived). In some embodiments, any of the amino acid variations in any of the CDRs provided herein may be conservative variations. Conservative variations can be introduced into the CDRs at positions where the residues are not likely to be involved in interacting with a transferrin receptor protein (*e.g.*, a human transferrin receptor protein), for example, as determined based on a crystal structure. Some aspects of the disclosure provide transferrin receptor antibodies that

comprise one or more of the heavy chain variable (VH) and/or (e.g., and) light chain variable (VL) domains provided herein. In some embodiments, any of the VH domains provided herein include one or more of the CDR-H sequences (e.g., CDR-H1, CDR-H2, and CDR-H3) provided herein, for example, any of the CDR-H sequences provided in any one of the anti-transferrin receptor 1 antibodies selected from Table 6. In some embodiments, any of the VL domains provided herein include one or more of the CDR-L sequences (e.g., CDR-L1, CDR-L2, and CDR-L3) provided herein, for example, any of the CDR-L sequences provided in any one of the anti-transferrin receptor 1 antibodies selected from Table 6.

[000254] In some embodiments, anti-TfR1 antibodies of the disclosure include any antibody that includes a heavy chain variable domain and/or (e.g., and) a light chain variable domain of any anti-transferrin receptor 1 antibody, such as any one of the anti-TfR1 antibodies selected from Table 6. In some embodiments, anti-TfR1 antibodies of the disclosure include any antibody that includes the heavy chain variable and light chain variable pairs of any anti-transferrin receptor 1 antibody, such as any one of the anti-TfR1 antibodies selected from Table 6.

[000255] Aspects of the disclosure provide anti-TfR1 antibodies having a heavy chain variable (VH) and/or (e.g., and) a light chain variable (VL) domain amino acid sequence homologous to any of those described herein. In some embodiments, the anti-TfR1 antibody comprises a heavy chain variable sequence or a light chain variable sequence that is at least 75% (e.g., 80%, 85%, 90%, 95%, 98%, or 99%) identical to the heavy chain variable sequence and/or any light chain variable sequence of any anti-TfR1 antibody, such as any one of the anti-TfR1 antibodies selected from Table 6. In some embodiments, the homologous heavy chain variable and/or (e.g., and) a light chain variable amino acid sequences do not vary within any of the CDR sequences provided herein. For example, in some embodiments, the degree of sequence variation (e.g., 75%, 80%, 85%, 90%, 95%, 98%, or 99%) may occur within a heavy chain variable and/or (e.g., and) a light chain variable sequence excluding any of the CDR sequences provided herein. In some embodiments, any of the anti-TfR1 antibodies provided herein comprise a heavy chain variable sequence and a light chain variable sequence that comprises a framework sequence that is at least 75%, 80%, 85%, 90%, 95%, 98%, or 99% identical to the framework sequence of any anti-TfR1 antibody, such as any one of the anti-TfR1 antibodies selected from Table 6.

[000256] In some embodiments, an anti-transferrin receptor 1 antibody, which specifically binds to transferrin receptor (e.g., human transferrin receptor), comprises a light chain variable VL domain comprising any of the CDR-L domains (CDR-L1, CDR-L2, and CDR-L3), or CDR-L domain variants provided herein, of any of the anti-transferrin receptor 1 antibodies selected

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

[000257] In some embodiments, an anti-transferrin receptor 1 antibody that specifically binds to transferrin receptor comprises the CDR-L1, the CDR-L2, and the CDR-L3 of any anti-transferrin receptor 1 antibody, such as any one of the anti-transferrin receptor 1 antibodies selected from Table 6. In some embodiments, the antibody further comprises one, two, three or all four VL framework regions derived from the VL of a human or primate antibody. The primate or human light chain framework region of the antibody selected for use with the light chain CDR sequences described herein, can have, for example, at least 70% (*e.g.*, at least 75%, 80%, 85%, 90%, 95%, 98%, or at least 99%) identity with a light chain framework region of a non-human parent antibody. The primate or human antibody selected can have the same or substantially the same number of amino acids in its light chain complementarity determining regions to that of the light chain complementarity determining regions of any of the antibodies provided herein, *e.g.*, any of the anti-transferrin receptor 1 antibodies selected from Table 6. In some embodiments, the primate or human light chain framework region amino acid residues are from a natural primate or human antibody light chain framework region having at least 75% identity, at least 80% identity, at least 85% identity, at least 90% identity, at least 95% identity,

at least 98% identity, at least 99% (or more) identity with the light chain framework regions of any anti-transferrin receptor 1 antibody, such as any one of the anti-transferrin receptor 1 antibodies selected from Table 6. In some embodiments, an anti-transferrin receptor 1 antibody further comprises one, two, three or all four VL framework regions derived from a human light chain variable kappa subfamily. In some embodiments, an anti-transferrin receptor 1 antibody further comprises one, two, three or all four VL framework regions derived from a human light chain variable lambda subfamily.

[000258] In some embodiments, any of the anti-transferrin receptor 1 antibodies provided herein comprise a light chain variable domain that further comprises a light chain constant region. In some embodiments, the light chain constant region is a kappa, or a lambda light chain constant region. In some embodiments, the kappa or lambda light chain constant region is from a mammal, *e.g.*, from a human, monkey, rat, or mouse. In some embodiments, the light chain constant region is a human kappa light chain constant region. In some embodiments, the light chain constant region is a human lambda light chain constant region. It should be appreciated that any of the light chain constant regions provided herein may be variants of any of the light chain constant regions provided herein. In some embodiments, the light chain constant region comprises an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, 98%, or 99% identical to any of the light chain constant regions of any anti-transferrin receptor 1 antibody, such as any one of the anti-transferrin receptor 1 antibodies selected from Table 6.

[000259] In some embodiments, the anti-transferrin receptor 1 antibody is any anti-transferrin receptor 1 antibody, such as any one of the anti-transferrin receptor 1 antibodies selected from Table 6.

[000260] In some embodiments, an anti-transferrin receptor 1 antibody comprises a VL domain comprising the amino acid sequence of any anti-transferrin receptor 1 antibody, such as any one of the anti-transferrin receptor 1 antibodies selected from Table 6, and wherein the constant regions comprise the amino acid sequences of the constant regions of an IgG, IgE, IgM, IgD, IgA or IgY immunoglobulin molecule, or a human IgG, IgE, IgM, IgD, IgA or IgY immunoglobulin molecule. In some embodiments, an anti-transferrin receptor 1 antibody comprises any of the VL domains, or VL domain variants, and any of the VH domains, or VH domain variants, wherein the VL and VH domains, or variants thereof, are from the same antibody clone, and wherein the constant regions comprise the amino acid sequences of the constant regions of an IgG, IgE, IgM, IgD, IgA or IgY immunoglobulin molecule, any class (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2), or any subclass (*e.g.*, IgG2a and IgG2b) of immunoglobulin molecule. Non-limiting examples of human constant regions are described in the art, *e.g.*, see Kabat E A et al., (1991) *supra*.

[000261] In some embodiments, the muscle-targeting agent is a transferrin receptor antibody (e.g., the antibody and variants thereof as described in International Application Publication WO 2016/081643, incorporated herein by reference).

[000262] The heavy chain and light chain CDRs of the antibody according to different definition systems are provided in Table 7. The different definition systems, e.g., the Kabat definition, the Chothia definition, and/or (e.g., and) the contact definition have been described. See, e.g., (e.g., Kabat, E.A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242, Chothia et al., (1989) Nature 342:877; Chothia, C. et al. (1987) J. Mol. Biol. 196:901-917, Al-lazikani et al (1997) J. Molec. Biol. 273:927-948; and Almagro, J. Mol. Recognit. 17:132-143 (2004). See also hgmp.mrc.ac.uk and bioinf.org.uk/abs).

[000263] An example of a transferrin receptor antibody that may be used in accordance with the present disclosure is described in International Application Publication WO 2016/081643, incorporated herein by reference. The CDR amino acid sequences of this antibody are provided in Table 7.

Table 7. Heavy chain and light chain CDRs of a mouse transferrin receptor antibody

Sequence Type	Kabat	Chothia	Contact
CDR-H1	SYWMH (SEQ ID NO: 110)	GYTFTSY (SEQ ID NO: 116)	TSYWMH (SEQ ID NO: 118)
CDR-H2	EINPTNGRTNYIE KFKS (SEQ ID NO: 111)	NPTNGR (SEQ ID NO: 117)	WIGEINPTNGRTN (SEQ ID NO: 119)
CDR-H3	GTRAYHY (SEQ ID NO: 112)	GTRAYHY (SEQ ID NO: 112)	ARGTRA (SEQ ID NO: 120)
CDR-L1	RASDNLYSNLA (SEQ ID NO: 113)	RASDNLYSNLA (SEQ ID NO: 113)	YSNLAWY (SEQ ID NO: 121)
CDR-L2	DATNLAD (SEQ ID NO: 114)	DATNLAD (SEQ ID NO: 114)	LLVYDATNLA (SEQ ID NO: 122)
CDR-L3	QHFWGTPLT (SEQ ID NO: 115)	QHFWGTPLT (SEQ ID NO: 115)	QHFWGTPL (SEQ ID NO: 123)

[000264] The heavy chain variable domain (VH) and light chain variable domain sequences are also provided:

[000265] VH

QVQLQQPGAELVKPGASVKLSCKASGYTFTSYWMHWVKQRPGQGLEWIGEINPTNGR
TNYIEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYCARGTRAYHYWGQGTSTVTS
S (SEQ ID NO: 124)

[000266] VL

DIQMTQSPASLSVSVGETVTITCRASDNLYSNLAWYQQKQKGKSPQLLVYDATNLADGV
PSRFGSGSGGTQYSLKINSLSQSEDFGTYYCQHFHWGTPLTFGAGTKLELK (SEQ ID NO:
125)

[000267] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a CDR-H1, a CDR-H2, and a CDR-H3 that are the same as the CDR-H1, CDR-H2, and CDR-H3 shown in Table 7. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody of the present disclosure comprises a CDR-L1, a CDR-L2, and a CDR-L3 that are the same as the CDR-L1, CDR-L2, and CDR-L3 shown in Table 7.

[000268] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a CDR-H1, a CDR-H2, and a CDR-H3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2, or 1 amino acid variation) as compared with the CDR-H1, CDR-H2, and CDR-H3 as shown in Table 7. “Collectively” means that the total number of amino acid variations in all of the three heavy chain CDRs is within the defined range. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody of the present disclosure may comprise a CDR-L1, a CDR-L2, and a CDR-L3, which collectively contains no more than 5 amino acid variations (e.g., no more than 5, 4, 3, 2 or 1 amino acid variation) as compared with the CDR-L1, CDR-L2, and CDR-L3 as shown in Table 7.

[000269] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a CDR-H1, a CDR-H2, and a CDR-H3, at least one of which contains no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the counterpart heavy chain CDR as shown in Table 7. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody of the present disclosure may comprise CDR-L1, a CDR-L2, and a CDR-L3, at least one of which contains no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the counterpart light chain CDR as shown in Table 7.

[000270] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a CDR-L3, which contains no more than 3 amino acid variations (e.g., no more than 3, 2, or 1 amino acid variation) as compared with the CDR-L3 as shown in Table 7. In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a CDR-L3 containing one amino acid variation as compared with the CDR-L3 as shown in Table 7. In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a CDR-L3 of QHFAGTPLT (SEQ ID NO: 126) (according to the Kabat and Chothia definition system) or QHFAGTPL (SEQ ID NO: 127) (according to the Contact definition system). In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a CDR-H1, a CDR-H2, a CDR-H3, a CDR-L1 and a CDR-L2 that are the same as the CDR-H1, CDR-H2, and CDR-H3

shown in Table 7, and comprises a CDR-L3 of QHFAGTPLT (SEQ ID NO: 126) (according to the Kabat and Chothia definition system) or QHFAGTPL (SEQ ID NO: 127) (according to the Contact definition system).

[000271] In some embodiments, the anti-TfR1 of the present disclosure comprises heavy chain CDRs that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, or 98%) identical to the heavy chain CDRs as shown in Table 7. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody of the present disclosure comprises light chain CDRs that collectively are at least 80% (e.g., 80%, 85%, 90%, 95%, or 98%) identical to the light chain CDRs as shown in Table 7.

[000272] In some embodiments, the anti-TfR1 antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 124. Alternatively or in addition (e.g., in addition), the anti-TfR1 antibody of the present disclosure comprises a VL comprising the amino acid sequence of SEQ ID NO: 125.

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

[000273] In some embodiments, the transferrin receptor antibody of the present disclosure comprises a VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, or 98%) identical to the VH as set forth in SEQ ID NO: 124. Alternatively or in addition (e.g., in addition), the transferrin receptor antibody of the present disclosure comprises a VL comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, or 98%) identical to the VL as set forth in SEQ ID NO: 125.

[000274] In some embodiments, the transferrin receptor antibody of the present disclosure is a humanized antibody (e.g., a humanized variant of an antibody). In some embodiments, the transferrin receptor antibody of the present disclosure comprises a CDR-H1, a CDR-H2, a CDR-H3, a CDR-L1, a CDR-L2, and a CDR-L3 that are the same as the CDR-H1, CDR-H2, and CDR-H3 shown in Table 7, and comprises a humanized heavy chain variable region and/or (e.g., and) a humanized light chain variable region.

[000275] Humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit

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

[000276] In some embodiments, humanization is achieved by grafting the CDRs (e.g., as shown in Table 7) into the IGKV1-NL1*01 and IGHV1-3*01 human variable domains. In some embodiments, the transferrin receptor antibody of the present disclosure is a humanized variant comprising one or more amino acid substitutions at positions 9, 13, 17, 18, 40, 45, and 70 as compared with the VL as set forth in SEQ ID NO: 125, and/or (e.g., and) one or more amino acid substitutions at positions 1, 5, 7, 11, 12, 20, 38, 40, 44, 66, 75, 81, 83, 87, and 108 as compared with the VH as set forth in SEQ ID NO: 124. In some embodiments, the transferrin receptor antibody of the present disclosure is a humanized variant comprising amino acid substitutions at all of positions 9, 13, 17, 18, 40, 45, and 70 as compared with the VL as set forth in SEQ ID NO: 125, and/or (e.g., and) amino acid substitutions at all of positions 1, 5, 7, 11, 12, 20, 38, 40, 44, 66, 75, 81, 83, 87, and 108 as compared with the VH as set forth in SEQ ID NO: 124.

[000277] In some embodiments, the transferrin receptor antibody of the present disclosure is a humanized antibody and contains the residues at positions 43 and 48 of the VL as set forth in SEQ ID NO: 125. Alternatively or in addition (e.g., in addition), the transferrin receptor antibody of the present disclosure is a humanized antibody and contains the residues at positions 48, 67, 69, 71, and 73 of the VH as set forth in SEQ ID NO: 124.

[000278] The VH and VL amino acid sequences of an example humanized antibody that may be used in accordance with the present disclosure are provided:

[000279] Humanized VH

EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMHWVRQAPGQRLEWIGEINPTNGR
TNYIEKFKSRA TLTVDKSASTAYMELSSLRSEDTAVYYCARGTRAYHYWGQGMVTV
SS (SEQ ID NO: 128)

[000280] Humanized VL

DIQMTQSPSSLSASVGDRVTITCRASDNLYSNLAWYQQKPGKSPKLLVYDATNLADGV
PSRFGSGSGTDYTLTISSLQPEDFATYYCQHFHWGTPLTFGQGTKVEIK
(SEQ ID NO: 129)

[000281] In some embodiments, the transferrin receptor antibody of the present disclosure comprises a VH comprising the amino acid sequence of SEQ ID NO: 128. Alternatively or in addition (e.g., in addition), the transferrin receptor antibody of the present disclosure comprises a VL comprising the amino acid sequence of SEQ ID NO: 129.

[000282] In some embodiments, the transferrin receptor antibody of the present disclosure comprises a VH containing no more than 25 amino acid variations (e.g., no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VH as set forth in SEQ ID NO: 128. Alternatively or in addition (e.g., in addition), the transferrin receptor antibody of the present disclosure comprises a VL containing no more than 15 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the VL as set forth in SEQ ID NO: 129.

[000283] In some embodiments, the transferrin receptor antibody of the present disclosure comprises a VH comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, or 98%) identical to the VH as set forth in SEQ ID NO: 128. Alternatively or in addition (e.g., in addition), the transferrin receptor antibody of the present disclosure comprises a VL comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, or 98%) identical to the VL as set forth in SEQ ID NO: 129.

[000284] In some embodiments, the transferrin receptor antibody of the present disclosure is a humanized variant comprising amino acid substitutions at one or more of positions 43 and 48 as compared with the VL as set forth in SEQ ID NO: 125, and/or (e.g., and) amino acid substitutions at one or more of positions 48, 67, 69, 71, and 73 as compared with the VH as set forth in SEQ ID NO: 124. In some embodiments, the transferrin receptor antibody of the present disclosure is a humanized variant comprising a S43A and/or (e.g., and) a V48L mutation as compared with the VL as set forth in SEQ ID NO: 125, and/or (e.g., and) one or more of A67V, L69I, V71R, and K73T mutations as compared with the VH as set forth in SEQ ID NO: 124.

[000285] In some embodiments, the transferrin receptor antibody of the present disclosure is a humanized variant comprising amino acid substitutions at one or more of positions 9, 13, 17, 18, 40, 43, 48, 45, and 70 as compared with the VL as set forth in SEQ ID NO: 125, and/or (e.g., and) amino acid substitutions at one or more of positions 1, 5, 7, 11, 12, 20, 38, 40, 44, 48, 66, 67, 69, 71, 73, 75, 81, 83, 87, and 108 as compared with the VH as set forth in SEQ ID NO: 124.

[000286] In some embodiments, the transferrin receptor antibody of the present disclosure is a chimeric antibody, which can include a heavy constant region and a light constant region from a human antibody. Chimeric antibodies refer to antibodies having a variable region or part of variable region from a first species and a constant region from a second species. Typically, in these chimeric antibodies, the variable region of both light and heavy chains mimics the variable regions of antibodies derived from one species of mammals (e.g., a non-human mammal such as mouse, rabbit, and rat), while the constant portions are homologous to the sequences in antibodies derived from another mammal such as human. In some embodiments, amino acid modifications can be made in the variable region and/or (e.g., and) the constant region.

[000287] In some embodiments, the transferrin receptor antibody described herein is a chimeric antibody, which can include a heavy constant region and a light constant region from a human antibody. Chimeric antibodies refer to antibodies having a variable region or part of variable region from a first species and a constant region from a second species. Typically, in these chimeric antibodies, the variable region of both light and heavy chains mimics the variable regions of antibodies derived from one species of mammals (e.g., a non-human mammal such as mouse, rabbit, and rat), while the constant portions are homologous to the sequences in antibodies derived from another mammal such as human. In some embodiments, amino acid modifications can be made in the variable region and/or (e.g., and) the constant region.

[000288] In some embodiments, the heavy chain of any of the transferrin receptor antibodies as described herein may comprises a heavy chain constant region (CH) or a portion thereof (e.g., CH1, CH2, CH3, or a combination thereof). The heavy chain constant region can of any suitable origin, e.g., human, mouse, rat, or rabbit. In one specific example, the heavy chain constant region is from a human IgG (a gamma heavy chain), e.g., IgG1, IgG2, or IgG4. An example of human IgG1 constant region is given below:

[000289] ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 130)

[000290] In some embodiments, the light chain of any of the transferrin receptor antibodies described herein may further comprise a light chain constant region (CL), which can be any CL known in the art. In some examples, the CL is a kappa light chain. In other examples, the CL is a lambda light chain. In some embodiments, the CL is a kappa light chain, the sequence of which is provided below:

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ
DSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 83)

[000291] Other antibody heavy and light chain constant regions are well known in the art, e.g., those provided in the IMGT database (www.imgt.org) or at www.vbase2.org/vbstat.php, both of which are incorporated by reference herein.

[000292] Examples of heavy chain and light chain amino acid sequences of the transferrin receptor antibodies described are provided below:

[000293] Heavy Chain (VH + human IgG1 constant region)

QVQLQQPGAELVKPGASVKLSCKASGYTFTSYWMHWVKQRPGQGLEWIGEINPTNGR
TNYIEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYCARGTRAYHYWGQGTSTVTS
SASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
SSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELL
GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL
PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT
VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 132)

[000294] Light Chain (VL + kappa light chain)

DIQMTQSPASLSVSVGETVTITCRASDNLYSNLAWYQQKQKGKSPQLLVYDATNLADGV
PSRFSGSGSGTQYSLKINSLSQSEDFGTYYCQHFHWGTPLTFGAGTKLELKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLS
STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 133)

[000295] Heavy Chain (humanized VH + human IgG1 constant region)

EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMHWVRQAPGQRLEWIGEINPTNGR
TNYIEKFKSRATLTVDKSASTAYMELSSLRSEDNAVYYCARGTRAYHYWGQGTMTVTV
SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL
LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYT
LPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL
TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 134)

[000296] Light Chain (humanized VL + kappa light chain)

DIQMTQSPSSLSASVGDRVTITCRASDNLYSNLAWYQQKPGKSPKLLVYDATNLADGV
PSRFSGSGSGTDYTLTISSLQPEDFATYYCQHFHWGTPLTFGQGTKVEIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS
TLTSLKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 135)

[000297] In some embodiments, the transferrin receptor antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, or 98%) identical to SEQ ID NO: 132. Alternatively or in addition (e.g., in addition), the transferrin receptor antibody described herein comprises a light chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, or 98%) identical to SEQ ID NO: 133. In some embodiments, the transferrin receptor antibody described herein comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 132. Alternatively or in addition (e.g., in addition), the transferrin receptor antibody described herein comprises a light chain comprising the amino acid sequence of SEQ ID NO: 133.

[000298] In some embodiments, the transferrin receptor antibody of the present disclosure comprises a heavy chain containing no more than 25 amino acid variations (e.g., no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the heavy chain as set forth in SEQ ID NO: 132. Alternatively or in addition (e.g., in addition), the transferrin receptor antibody of the present disclosure comprises a light chain containing no more than 15 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the light chain as set forth in SEQ ID NO: 133.

[000299] In some embodiments, the transferrin receptor antibody described herein comprises a heavy chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, or 98%) identical to SEQ ID NO: 134. Alternatively or in addition (e.g., in addition), the transferrin receptor antibody described herein comprises a light chain comprising an amino acid sequence that is at least 80% (e.g., 80%, 85%, 90%, 95%, or 98%) identical to SEQ ID NO: 135. In some embodiments, the transferrin receptor antibody described herein comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 134. Alternatively or in addition (e.g., in addition), the transferrin receptor antibody described herein comprises a light chain comprising the amino acid sequence of SEQ ID NO: 135.

[000300] In some embodiments, the transferrin receptor antibody of the present disclosure comprises a heavy chain containing no more than 25 amino acid variations (e.g., no more than 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the heavy chain of humanized antibody as set forth in SEQ ID NO:

134. Alternatively or in addition (e.g., in addition), the transferrin receptor antibody of the present disclosure comprises a light chain containing no more than 15 amino acid variations (e.g., no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid variation) as compared with the light chain of humanized antibody as set forth in SEQ ID NO: 135.

[000301] In some embodiments, the transferrin receptor antibody is an antigen binding fragment (Fab) of an intact antibody (full-length antibody). Antigen binding fragment of an intact antibody (full-length antibody) can be prepared via routine methods. For example, F(ab')₂ fragments can be produced by pepsin digestion of an antibody molecule, and Fab' fragments that can be generated by reducing the disulfide bridges of F(ab')₂ fragments. Examples of Fab amino acid sequences of the transferrin receptor antibodies described herein are provided below:

[000302] Heavy Chain Fab (VH + a portion of human IgG1 constant region)

[000303] QVQLQQPGAELVKPGASVKLSCKASGYTFTSYWMHWVKQRPGQGLEWIGEINPTNGRTNYIEKFKSKATLTVDKSSSTAYMQLSSLTSEDSAVYYCARGTRAYHYWGQGTSVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP (SEQ ID NO: 136)

[000304] Heavy Chain Fab (humanized VH + a portion of human IgG1 constant region)

[000305] EVQLVQSGAEVKKPGASVKVSCASGYTFTSYWMHWVRQAPGQRLEWIGEINPTNGRTNYIEKFKSRATLTVDKSASTAYMELSSLRSEDNAVYYCARGTRAYHYWGQGTMTVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP (SEQ ID NO: 137)

[000306] In some embodiments, the transferrin receptor antibody described herein comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 136.

Alternatively or in addition (e.g., in addition), the transferrin receptor antibody described herein comprises a light chain comprising the amino acid sequence of SEQ ID NO: 133.

[000307] In some embodiments, the transferrin receptor antibody described herein comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 137.

Alternatively or in addition (e.g., in addition), the transferrin receptor antibody described herein comprises a light chain comprising the amino acid sequence of SEQ ID NO: 135.

[000308] The transferrin receptor antibodies described herein can be in any antibody form, including, but not limited to, intact (i.e., full-length) antibodies, antigen-binding fragments thereof (such as Fab, Fab', F(ab')₂, Fv), single chain antibodies, bi-specific antibodies, or nanobodies. In some embodiments, the transferrin receptor antibody described herein is a scFv.

In some embodiments, the transferrin receptor antibody described herein is a scFv-Fab (e.g., scFv fused to a portion of a constant region). In some embodiments, the transferrin receptor antibody described herein is a scFv fused to a constant region (e.g., human IgG1 constant region as set forth in SEQ ID NO: 130).

[000309] In some embodiments, any one of the anti-TfR1 antibodies described herein is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture, optionally in CHO-K1 cell (e.g., CHO-K1 cells derived from European Collection of Animal Cell Culture, Cat. No. 85051005) suspension culture.

[000310] In some embodiments, an antibody provided herein may have one or more post-translational modifications. In some embodiments, N-terminal cyclization, also called pyroglutamate formation (pyro-Glu), may occur in the antibody at N-terminal Glutamate (Glu) and/or Glutamine (Gln) residues during production. As such, it should be appreciated that an antibody specified as having a sequence comprising an N-terminal glutamate or glutamine residue encompasses antibodies that have undergone pyroglutamate formation resulting from a post-translational modification. In some embodiments, pyroglutamate formation occurs in a heavy chain sequence. In some embodiments, pyroglutamate formation occurs in a light chain sequence.

b. Other Muscle-Targeting Antibodies

[000311] In some embodiments, the muscle-targeting antibody is an antibody that specifically binds hemojuvelin, caveolin-3, Duchenne muscular dystrophy peptide, or myosin Iib, or CD63. In some embodiments, the muscle-targeting antibody is an antibody that specifically binds a myogenic precursor protein. Exemplary myogenic precursor proteins include, without limitation, ABCG2, M-Cadherin/Cadherin-15, Caveolin-1, CD34, FoxK1, Integrin alpha 7, Integrin alpha 7 beta 1, MYF-5, MyoD, Myogenin, NCAM-1/CD56, Pax3, Pax7, and Pax9. In some embodiments, the muscle-targeting antibody is an antibody that specifically binds a skeletal muscle protein. Exemplary skeletal muscle proteins include, without limitation, alpha-Sarcoglycan, beta-Sarcoglycan, Calpain Inhibitors, Creatine Kinase MM/CKMM, eIF5A, Enolase 2/Neuron-specific Enolase, epsilon-Sarcoglycan, FABP3/H-FABP, GDF-8/Myostatin, GDF-11/GDF-8, Integrin alpha 7, Integrin alpha 7 beta 1, Integrin beta 1/CD29, MCAM/CD146, MyoD, Myogenin, Myosin Light Chain Kinase Inhibitors, NCAM-1/CD56, and Troponin I. In some embodiments, the muscle-targeting antibody is an antibody that specifically binds a smooth muscle protein. Exemplary smooth muscle proteins include, without limitation, alpha-Smooth Muscle Actin, VE-Cadherin, Caldesmon/CALD1, Calponin 1, Desmin, Histamine H2 R, Motilin R/GPR38, Transgelin/TAGLN, and Vimentin.

However, it should be appreciated that antibodies to additional targets are within the scope of this disclosure and the exemplary lists of targets provided herein are not meant to be limiting.

c. Antibody Features/Alterations

[000312] In some embodiments, conservative mutations can be introduced into antibody sequences (e.g., CDRs or framework sequences) at positions where the residues are not likely to be involved in interacting with a target antigen (e.g., transferrin receptor), for example, as determined based on a crystal structure. In some embodiments, one, two or more mutations (e.g., amino acid substitutions) are introduced into the Fc region of a muscle-targeting antibody described herein (e.g., in a CH2 domain (residues 231-340 of human IgG1) and/or CH3 domain (residues 341-447 of human IgG1) and/or the hinge region, with numbering according to the Kabat numbering system (e.g., the EU index in Kabat)) to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding and/or antigen-dependent cellular cytotoxicity.

[000313] In some embodiments, one, two or more mutations (e.g., amino acid substitutions) are introduced into the hinge region of the Fc region (CH1 domain) such that the number of cysteine residues in the hinge region are altered (e.g., increased or decreased) as described in, e.g., U.S. Pat. No. 5,677,425. The number of cysteine residues in the hinge region of the CH1 domain can be altered to, e.g., facilitate assembly of the light and heavy chains, or to alter (e.g., increase or decrease) the stability of the antibody or to facilitate linker conjugation.

[000314] In some embodiments, one, two or more mutations (e.g., amino acid substitutions) are introduced into the Fc region of a muscle-targeting antibody described herein (e.g., in a CH2 domain (residues 231-340 of human IgG1) and/or CH3 domain (residues 341-447 of human IgG1) and/or the hinge region, with numbering according to the Kabat numbering system (e.g., the EU index in Kabat)) to increase or decrease the affinity of the antibody for an Fc receptor (e.g., an activated Fc receptor) on the surface of an effector cell. Mutations in the Fc region of an antibody that decrease or increase the affinity of an antibody for an Fc receptor and techniques for introducing such mutations into the Fc receptor or fragment thereof are known to one of skill in the art. Examples of mutations in the Fc receptor of an antibody that can be made to alter the affinity of the antibody for an Fc receptor are described in, e.g., Smith P et al., (2012) PNAS 109: 6181-6186, U.S. Pat. No. 6,737,056, and International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631, which are incorporated herein by reference.

[000315] In some embodiments, one, two or more amino acid mutations (*i.e.*, substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to alter (e.g., decrease or increase) half-

life of the antibody *in vivo*. See, e.g., International Publication Nos. WO 02/060919; WO 98/23289; and WO 97/34631; and U.S. Pat. Nos. 5,869,046, 6,121,022, 6,277,375 and 6,165,745 for examples of mutations that will alter (*e.g.*, decrease or increase) the half-life of an antibody *in vivo*.

[000316] In some embodiments, one, two or more amino acid mutations (*i.e.*, substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to decrease the half-life of the anti-transferrin receptor 1 antibody *in vivo*. In some embodiments, one, two or more amino acid mutations (*i.e.*, substitutions, insertions or deletions) are introduced into an IgG constant domain, or FcRn-binding fragment thereof (preferably an Fc or hinge-Fc domain fragment) to increase the half-life of the antibody *in vivo*. In some embodiments, the antibodies can have one or more amino acid mutations (*e.g.*, substitutions) in the second constant (CH2) domain (residues 231-340 of human IgG1) and/or the third constant (CH3) domain (residues 341-447 of human IgG1), with numbering according to the EU index in Kabat (Kabat E A et al., (1991) *supra*). In some embodiments, the constant region of the IgG1 of an antibody described herein comprises a methionine (M) to tyrosine (Y) substitution in position 252, a serine (S) to threonine (T) substitution in position 254, and a threonine (T) to glutamic acid (E) substitution in position 256, numbered according to the EU index as in Kabat. See U.S. Pat. No. 7,658,921, which is incorporated herein by reference. This type of mutant IgG, referred to as "YTE mutant" has been shown to display fourfold increased half-life as compared to wild-type versions of the same antibody (see Dall'Acqua W F et al., (2006) *J Biol Chem* 281: 23514-24). In some embodiments, an antibody comprises an IgG constant domain comprising one, two, three or more amino acid substitutions of amino acid residues at positions 251-257, 285-290, 308-314, 385-389, and 428-436, numbered according to the EU index as in Kabat.

[000317] In some embodiments, one, two or more amino acid substitutions are introduced into an IgG constant domain Fc region to alter the effector function(s) of the anti-transferrin receptor 1 antibody. The effector ligand to which affinity is altered can be, for example, an Fc receptor or the C1 component of complement. This approach is described in further detail in U.S. Pat. Nos. 5,624,821 and 5,648,260. In some embodiments, the deletion or inactivation (through point mutations or other means) of a constant region domain can reduce Fc receptor binding of the circulating antibody thereby increasing tumor localization. See, e.g., U.S. Pat. Nos. 5,585,097 and 8,591,886 for a description of mutations that delete or inactivate the constant domain and thereby increase tumor localization. In some embodiments, one or more amino acid substitutions may be introduced into the Fc region of an antibody described herein to remove

potential glycosylation sites on Fc region, which may reduce Fc receptor binding (see, *e.g.*, Shields R L et al., (2001) J Biol Chem 276: 6591-604).

[000318] In some embodiments, one or more amino in the constant region of a muscle-targeting antibody described herein can be replaced with a different amino acid residue such that the antibody has altered C1q binding and/or reduced or abolished complement dependent cytotoxicity (CDC). This approach is described in further detail in U.S. Pat. No. 6,194,551 (Idusogie et al). In some embodiments, one or more amino acid residues in the N-terminal region of the CH2 domain of an antibody described herein are altered to thereby alter the ability of the antibody to fix complement. This approach is described further in International Publication No. WO 94/29351. In some embodiments, the Fc region of an antibody described herein is modified to increase the ability of the antibody to mediate antibody dependent cellular cytotoxicity (ADCC) and/or to increase the affinity of the antibody for an Fcγ receptor. This approach is described further in International Publication No. WO 00/42072.

[000319] In some embodiments, the heavy and/or light chain variable domain(s) sequence(s) of the antibodies provided herein can be used to generate, for example, CDR-grafted, chimeric, humanized, or composite human antibodies or antigen-binding fragments, as described elsewhere herein. As understood by one of ordinary skill in the art, any variant, CDR-grafted, chimeric, humanized, or composite antibodies derived from any of the antibodies provided herein may be useful in the compositions and methods described herein and will maintain the ability to specifically bind transferrin receptor, such that the variant, CDR-grafted, chimeric, humanized, or composite antibody has at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% or more binding to transferrin receptor relative to the original antibody from which it is derived.

[000320] In some embodiments, the antibodies provided herein comprise mutations that confer desirable properties to the antibodies. For example, to avoid potential complications due to Fab-arm exchange, which is known to occur with native IgG4 mAbs, the antibodies provided herein may comprise a stabilizing ‘Adair’ mutation (Angal S., et al., “A single amino acid substitution abolishes the heterogeneity of chimeric mouse/human (IgG4) antibody,” Mol Immunol 30, 105-108; 1993), where serine 228 (EU numbering; residue 241 Kabat numbering) is converted to proline resulting in an IgG1-like hinge sequence. Accordingly, any of the antibodies may include a stabilizing ‘Adair’ mutation.

[000321] As provided herein, antibodies of this disclosure may optionally comprise constant regions or parts thereof. For example, a VL domain may be attached at its C-terminal end to a light chain constant domain like Cκ or Cλ. Similarly, a VH domain or portion thereof may be attached to all or part of a heavy chain like IgA, IgD, IgE, IgG, and IgM, and any isotype

subclass. Antibodies may include suitable constant regions (see, for example, Kabat et al., Sequences of Proteins of Immunological Interest, No. 91-3242, National Institutes of Health Publications, Bethesda, Md. (1991)). Therefore, antibodies within the scope of this may disclosure include VH and VL domains, or an antigen binding portion thereof, combined with any suitable constant regions.

[000322] In some embodiments, the anti-TfR1 antibody of the present disclosure is a humanized antibody comprising human framework regions with the CDRs of a murine antibody listed in Table 1 or Table 2 (e.g., 3A4, 3M12, or 5H12). In some embodiments, the anti-TfR1 antibody of the present disclosure is an IgG1 kappa that comprises human framework regions with the CDRs of a murine antibody listed in Table 1 or Table 2 (e.g., 3A4, 3M12, or 5H12). In some embodiments, the anti-TfR1 antibody of the present disclosure is a Fab fragment of an IgG1 kappa that comprises human framework regions with the CDRs of a murine antibody listed in Table 1 or Table 2 (e.g., 3A4, 3M12, or 5H12).

[000323] In some embodiments, any one of the anti-TfR1 antibodies described herein is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture, optionally in CHO-K1 cell (e.g., CHO-K1 cells derived from European Collection of Animal Cell Culture, Cat. No. 85051005) suspension culture.

In some embodiments, an antibody provided herein may have one or more post-translational modifications. In some embodiments, N-terminal cyclization, also called pyroglutamate formation (pyro-Glu), may occur in the antibody at N-terminal Glutamate (Glu) and/or Glutamine (Gln) residues during production. In some embodiments, pyroglutamate formation occurs in a heavy chain sequence. In some embodiments, pyroglutamate formation occurs in a light chain sequence.

ii. Muscle-Targeting Peptides

[000324] Some aspects of the disclosure provide muscle-targeting peptides as muscle-targeting agents. Short peptide sequences (e.g., peptide sequences of 5-20 amino acids in length) that bind to specific cell types have been described. For example, cell-targeting peptides have been described in Vines et al., A. "Cell-penetrating and cell-targeting peptides in drug delivery" *Biochim Biophys Acta* 2008, 1786: 126-38; Jarver P., et al., "In vivo biodistribution and efficacy of peptide mediated delivery" *Trends Pharmacol Sci* 2010; 31: 528-35; Samoylova T.I., et al., "Elucidation of muscle-binding peptides by phage display screening" *Muscle Nerve* 1999; 22: 460-6; U.S. Patent No. 6,329,501, issued on December 11, 2001, entitled "METHODS AND COMPOSITIONS FOR TARGETING COMPOUNDS TO MUSCLE"; and Samoylov A.M., et al., "Recognition of cell-specific binding of phage display derived peptides using an acoustic wave sensor." *Biomol Eng* 2002; 18: 269-72; the entire contents of each of which are

incorporated herein by reference. By designing peptides to interact with specific cell surface antigens (e.g., receptors), selectivity for a desired tissue, e.g., muscle, can be achieved. Skeletal muscle-targeting has been investigated and a range of molecular payloads are able to be delivered. These approaches may have high selectivity for muscle tissue without many of the practical disadvantages of a large antibody or viral particle. Accordingly, in some embodiments, the muscle-targeting agent is a muscle-targeting peptide that is from 4 to 50 amino acids in length. In some embodiments, the muscle-targeting peptide is 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 amino acids in length. Muscle-targeting peptides can be generated using any of several methods, such as phage display.

[000325] In some embodiments, a muscle-targeting peptide may bind to an internalizing cell surface receptor that is overexpressed or relatively highly expressed in muscle cells, e.g., a transferrin receptor, compared with certain other cells. In some embodiments, a muscle-targeting peptide may target, e.g., bind to, a transferrin receptor. In some embodiments, a peptide that targets a transferrin receptor may comprise a segment of a naturally occurring ligand, e.g., transferrin. In some embodiments, a peptide that targets a transferrin receptor is as described in US Patent No. 6,743,893, filed 11/30/2000, “RECEPTOR-MEDIATED UPTAKE OF PEPTIDES THAT BIND THE HUMAN TRANSFERRIN RECEPTOR”. In some embodiments, a peptide that targets a transferrin receptor is as described in Kawamoto, M. et al, “A novel transferrin receptor-targeted hybrid peptide disintegrates cancer cell membrane to induce rapid killing of cancer cells.” BMC Cancer. 2011 Aug 18;11:359. In some embodiments, a peptide that targets a transferrin receptor is as described in US Patent No. 8,399,653, filed 5/20/2011, “TRANSFERRIN/TRANSFERRIN RECEPTOR-MEDIATED SIRNA DELIVERY”.

[000326] As discussed above, examples of muscle targeting peptides have been reported. For example, muscle-specific peptides were identified using phage display library presenting surface heptapeptides. As one example a peptide having the amino acid sequence ASSLNIA (SEQ ID NO: 375) bound to C2C12 murine myotubes *in vitro*, and bound to mouse muscle tissue *in vivo*. Accordingly, in some embodiments, the muscle-targeting agent comprises the amino acid sequence ASSLNIA (SEQ ID NO: 375). This peptide displayed improved specificity for binding to heart and skeletal muscle tissue after intravenous injection in mice with reduced binding to liver, kidney, and brain. Additional muscle-specific peptides have been identified using phage display. For example, a 12 amino acid peptide was identified by phage display library for muscle targeting in the context of treatment for DMD. See, Yoshida D., et al., “Targeting of salicylate to skin and muscle following topical injections in rats.” *Int J Pharm*

2002; 231: 177-84; the entire contents of which are hereby incorporated by reference. Here, a 12 amino acid peptide having the sequence SKTFNTHPQSTP (SEQ ID NO: 376) was identified and this muscle-targeting peptide showed improved binding to C2C12 cells relative to the ASSLNIA (SEQ ID NO: 375) peptide.

[000327] An additional method for identifying peptides selective for muscle (*e.g.*, skeletal muscle) over other cell types includes *in vitro* selection, which has been described in Ghosh D., et al., “Selection of muscle-binding peptides from context-specific peptide-presenting phage libraries for adenoviral vector targeting” *J Virol* 2005; 79: 13667-72; the entire contents of which are incorporated herein by reference. By pre-incubating a random 12-mer peptide phage display library with a mixture of non-muscle cell types, non-specific cell binders were selected out. Following rounds of selection the 12 amino acid peptide TARGEHKEEELI (SEQ ID NO: 377) appeared most frequently. Accordingly, in some embodiments, the muscle-targeting agent comprises the amino acid sequence TARGEHKEEELI (SEQ ID NO: 377).

[000328] A muscle-targeting agent may be an amino acid-containing molecule or peptide. A muscle-targeting peptide may correspond to a sequence of a protein that preferentially binds to a protein receptor found in muscle cells. In some embodiments, a muscle-targeting peptide contains a high propensity of hydrophobic amino acids, *e.g.*, valine, such that the peptide preferentially targets muscle cells (*e.g.*, cardiac muscle cells). In some embodiments, a muscle-targeting peptide has not been previously characterized or disclosed. These peptides may be conceived of, produced, synthesized, and/or derivatized using any of several methodologies, *e.g.*, phage displayed peptide libraries, one-bead one-compound peptide libraries, or positional scanning synthetic peptide combinatorial libraries. Exemplary methodologies have been characterized in the art and are incorporated by reference (Gray, B.P. and Brown, K.C. “Combinatorial Peptide Libraries: Mining for Cell-Binding Peptides” *Chem Rev.* 2014, 114:2, 1020–1081.; Samoylova, T.I. and Smith, B.F. “Elucidation of muscle-binding peptides by phage display screening.” *Muscle Nerve*, 1999, 22:4. 460-6.). In some embodiments, a muscle-targeting peptide has been previously disclosed (see, *e.g.*, Writer M.J. et al. “Targeted gene delivery to human airway epithelial cells with synthetic vectors incorporating novel targeting peptides selected by phage display.” *J. Drug Targeting*. 2004;12:185; Cai, D. “BDNF-mediated enhancement of inflammation and injury in the aging heart.” *Physiol Genomics*. 2006, 24:3, 191-7.; Zhang, L. “Molecular profiling of heart endothelial cells.” *Circulation*, 2005, 112:11, 1601-11.; McGuire, M.J. et al. “In vitro selection of a peptide with high selectivity for cardiomyocytes in vivo.” *J Mol Biol*. 2004, 342:1, 171-82.). Exemplary muscle-targeting peptides comprise an amino acid sequence of the following group: CQAQGQLVC (SEQ ID NO: 378), CSERSMNFC (SEQ ID NO: 379), CPKTRRVPC (SEQ ID NO: 380),

WLSEAGPVVTVRALRGTGSW (SEQ ID NO: 381), ASSLNIA (SEQ ID NO: 376), CMQHSMRVC (SEQ ID NO: 382), and DDTRHWG (SEQ ID NO: 383). In some embodiments, a muscle-targeting peptide may comprise about 2-25 amino acids, about 2-20 amino acids, about 2-15 amino acids, about 2-10 amino acids, or about 2-5 amino acids. Muscle-targeting peptides may comprise naturally occurring amino acids, e.g., cysteine, alanine, or non-naturally occurring or modified amino acids. Non-naturally occurring amino acids include β -amino acids, homo-amino acids, proline derivatives, 3-substituted alanine derivatives, linear core amino acids, N-methyl amino acids, and others known in the art. In some embodiments, a muscle-targeting peptide may be linear; in other embodiments, a muscle-targeting peptide may be cyclic, e.g., bicyclic (see, e.g., Silvana, M.G. et al. Mol. Therapy, 2018, 26:1, 132–147.).

iii. Muscle-Targeting Receptor Ligands

[000329] A muscle-targeting agent may be a ligand, e.g., a ligand that binds to a receptor protein. A muscle-targeting ligand may be a protein, e.g., transferrin, which binds to an internalizing cell surface receptor expressed by a muscle cell (e.g., a cardiac muscle cell). Accordingly, in some embodiments, the muscle-targeting agent is transferrin, or a derivative thereof that binds to a transferrin receptor. A muscle-targeting ligand may alternatively be a small molecule, e.g., a lipophilic small molecule that preferentially targets muscle cells relative to other cell types. Exemplary lipophilic small molecules that may target muscle cells include compounds comprising cholesterol, cholesteryl, stearic acid, palmitic acid, oleic acid, oleyl, linolene, linoleic acid, myristic acid, sterols, dihydrotestosterone, testosterone derivatives, glycerine, alkyl chains, trityl groups, and alkoxy acids.

iv. Muscle-Targeting Aptamers

[000330] A muscle-targeting agent may be an aptamer, e.g., an RNA aptamer, which preferentially targets muscle cells relative to other cell types. In some embodiments, a muscle-targeting aptamer has not been previously characterized or disclosed. These aptamers may be conceived of, produced, synthesized, and/or derivatized using any of several methodologies, e.g., Systematic Evolution of Ligands by Exponential Enrichment. Exemplary methodologies have been characterized in the art and are incorporated by reference (Yan, A.C. and Levy, M. “Aptamers and aptamer targeted delivery” RNA biology, 2009, 6:3, 316-20.; Germer, K. et al. “RNA aptamers and their therapeutic and diagnostic applications.” Int. J. Biochem. Mol. Biol. 2013; 4: 27–40.). In some embodiments, a muscle-targeting aptamer has been previously

disclosed (see, e.g., Phillippou, S. et al. “Selection and Identification of Skeletal-Muscle-Targeted RNA Aptamers.” *Mol Ther Nucleic Acids*. 2018, 10:199-214.; Thiel, W.H. et al. “Smooth Muscle Cell-targeted RNA Aptamer Inhibits Neointimal Formation.” *Mol Ther*. 2016, 24:4, 779-87.). Exemplary muscle-targeting aptamers include the A01B RNA aptamer and RNA Apt 14. In some embodiments, an aptamer is a nucleic acid-based aptamer, an oligonucleotide aptamer or a peptide aptamer. In some embodiments, an aptamer may be about 5-15 kDa, about 5-10 kDa, about 10-15 kDa, about 1-5 Da, about 1-3 kDa, or smaller.

v. Other Muscle-Targeting Agents

[000331] One strategy for targeting a muscle cell (e.g., a cardiac muscle cell) is to use a substrate of a muscle transporter protein, such as a transporter protein expressed on the sarcolemma. In some embodiments, the muscle-targeting agent is a substrate of an influx transporter that is specific to muscle tissue. In some embodiments, the influx transporter is specific to skeletal muscle tissue. Two main classes of transporters are expressed on the skeletal muscle sarcolemma, (1) the adenosine triphosphate (ATP) binding cassette (ABC) superfamily, which facilitate efflux from skeletal muscle tissue and (2) the solute carrier (SLC) superfamily, which can facilitate the influx of substrates into skeletal muscle. In some embodiments, the muscle-targeting agent is a substrate that binds to an ABC superfamily or an SLC superfamily of transporters. In some embodiments, the substrate that binds to the ABC or SLC superfamily of transporters is a naturally occurring substrate. In some embodiments, the substrate that binds to the ABC or SLC superfamily of transporters is a non-naturally occurring substrate, for example, a synthetic derivative thereof that binds to the ABC or SLC superfamily of transporters.

[000332] In some embodiments, the muscle-targeting agent is any muscle targeting agents described herein (e.g., antibodies, nucleic acids, small molecules, peptides, aptamers, lipids, sugar moieties) that target SLC superfamily of transporters. In some embodiments, the muscle-targeting agent is a substrate of an SLC superfamily of transporters. SLC transporters are either equilibrative or use proton or sodium ion gradients created across the membrane to drive transport of substrates. Exemplary SLC transporters that have high skeletal muscle expression include, without limitation, the SATT transporter (ASCT1; SLC1A4), GLUT4 transporter (SLC2A4), GLUT7 transporter (GLUT7; SLC2A7), ATRC2 transporter (CAT-2; SLC7A2), LAT3 transporter (KIAA0245; SLC7A6), PHT1 transporter (PTR4; SLC15A4), OATP-J transporter (OATP5A1; SLC21A15), OCT3 transporter (EMT; SLC22A3), OCTN2 transporter (FLJ46769; SLC22A5), ENT transporters (ENT1; SLC29A1 and ENT2; SLC29A2), PAT2 transporter (SLC36A2), and SAT2 transporter (KIAA1382; SLC38A2). These transporters can

facilitate the influx of substrates into skeletal muscle, providing opportunities for muscle targeting.

[000333] In some embodiments, the muscle-targeting agent is a substrate of an equilibrative nucleoside transporter 2 (ENT2) transporter. Relative to other transporters, ENT2 has one of the highest mRNA expressions in skeletal muscle. While human ENT2 (hENT2) is expressed in most body organs such as brain, heart, placenta, thymus, pancreas, prostate, and kidney, it is especially abundant in skeletal muscle. Human ENT2 facilitates the uptake of its substrates depending on their concentration gradient. ENT2 plays a role in maintaining nucleoside homeostasis by transporting a wide range of purine and pyrimidine nucleobases. The hENT2 transporter has a low affinity for all nucleosides (adenosine, guanosine, uridine, thymidine, and cytidine) except for inosine. Accordingly, in some embodiments, the muscle-targeting agent is an ENT2 substrate. Exemplary ENT2 substrates include, without limitation, inosine, 2',3'-dideoxyinosine, and calofarabine. In some embodiments, any of the muscle-targeting agents provided herein are associated with a molecular payload (e.g., oligonucleotide payload). In some embodiments, the muscle-targeting agent is covalently linked to the molecular payload. In some embodiments, the muscle-targeting agent is non-covalently linked to the molecular payload.

[000334] In some embodiments, the muscle-targeting agent is a substrate of an organic cation/carnitine transporter (OCTN2), which is a sodium ion-dependent, high affinity carnitine transporter. In some embodiments, the muscle-targeting agent is carnitine, mildronate, acetylcarnitine, or any derivative thereof that binds to OCTN2. In some embodiments, the carnitine, mildronate, acetylcarnitine, or derivative thereof is covalently linked to the molecular payload (e.g., oligonucleotide payload).

[000335] A muscle-targeting agent may be a protein that is protein that exists in at least one soluble form that targets muscle cells. In some embodiments, a muscle-targeting protein may be hemojuvelin (also known as repulsive guidance molecule C or hemochromatosis type 2 protein), a protein involved in iron overload and homeostasis. In some embodiments, hemojuvelin may be full length or a fragment, or a mutant with at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98% or at least 99% sequence identity to a functional hemojuvelin protein. In some embodiments, a hemojuvelin mutant may be a soluble fragment, may lack a N-terminal signaling, and/or lack a C-terminal anchoring domain. In some embodiments, hemojuvelin may be annotated under GenBank RefSeq Accession Numbers NM_001316767.1 (SEQ ID NO: 405), NM_145277.4 (SEQ ID NO: 406), NM_202004.3 (SEQ ID NO: 407), NM_213652.3 (SEQ ID NO: 408), or NM_213653.3 (SEQ ID NO: 409). It

should be appreciated that a hemojuvelin may be of human, non-human primate, or rodent origin.

B. Molecular Payloads

[000336] Some aspects of the disclosure provide molecular payloads, e.g., for modulating a biological outcome, e.g., the transcription of a DNA sequence, the expression of a protein, or the activity of a protein. In some embodiments, a molecular payload is linked to, or otherwise associated with a muscle-targeting agent. In some embodiments, such molecular payloads are capable of targeting to a muscle cell, e.g., via specifically binding to a nucleic acid or protein in the muscle cell following delivery to the muscle cell by an associated muscle-targeting agent. It should be appreciated that various types of molecular payloads may be used in accordance with the disclosure. For example, the molecular payload may comprise, or consist of, an oligonucleotide (e.g., antisense oligonucleotide), a peptide (e.g., a peptide that binds a nucleic acid or protein associated with disease in a muscle cell), a protein (e.g., a protein that binds a nucleic acid or protein associated with disease in a muscle cell), or a small molecule (e.g., a small molecule that modulates the function of a nucleic acid or protein associated with disease in a muscle cell). In some embodiments, the molecular payload is an oligonucleotide that comprises a strand having a region of complementarity to a MSTN. In some embodiments, the molecular payload is an oligonucleotide that comprises a strand having a region of complementarity to an INHBA gene (e.g., INHBA DNA or INHBA RNA). In some embodiments, the molecular payload is an oligonucleotide that comprises a strand having a region of complementarity to ACVR1B. In some embodiments, the molecular payload is an oligonucleotide that comprises a strand having a region of complementarity to MLCK1. In some embodiments, the molecular payload is an oligonucleotide that comprises a strand having a region of complementarity to wild-type ACVR1. In some embodiments, the molecular payload is an oligonucleotide that comprises a strand having a region of complementarity to a mutant ACVR1 associated with FOP. In some embodiments, the molecular payload is an oligonucleotide that comprises a strand having a region of complementarity to FBXO32 (e.g., complementarity to NM_001242463.2 (SEQ ID NO: 655), NM_058229.4 (SEQ ID NO: 505), NM_148177.2 (SEQ ID NO: 656), XM_005564029.2 (SEQ ID NO: 657), NM_026346.3 (SEQ ID NO: 506), and/or NM_133521.1 (SEQ ID NO: 658)). In some embodiments, the molecular payload is an oligonucleotide that comprises a strand having a region of complementarity to TRIM63. In some embodiments, the molecular payload is an oligonucleotide that comprises a strand having a region of complementarity to a nucleic acid sequence encoding MEF2D, KLF15, MED1, MED13, or PPP1R3A (e.g., mRNA or DNA). In some embodiments, the molecular

payload is an oligonucleotide that comprises a strand having a region of complementarity to the gene encoding MEF2D, KLF15, MED1, MED13, or PPP1R3A. In some embodiments, the molecular payload is an oligonucleotide that comprises a strand having a region of complementarity to a disease allele encoding MEF2D, KLF15, MED1, MED13, or PPP1R3A. In some embodiments, the molecular payload is a DNA decoy, e.g., of a MSTN, INHBA, ACVR1B, MLCK1, ACVR1, FBXO32, TRIM63, MEF2D, KLF15, MED1, MED13, or PPP1R3A nucleic acid. In some embodiments, two or more molecular payloads (e.g., targeting two or more genes) may be linked to a muscle targeting agent. As non-limiting examples, a complex may comprise molecular payloads targeting ACVR1B and MSTN; targeting ACVR1B and INHBA; targeting MSTN and INHBA; or targeting ACVR1B, MSTN and INHBA. Exemplary molecular payloads are described in further detail herein, however, it should be appreciated that the exemplary molecular payloads provided herein are not meant to be limiting.

i. Oligonucleotides

[000337] Any suitable oligonucleotide may be used as a molecular payload, as described herein. In some embodiments, the oligonucleotide may be designed to cause degradation of an mRNA (e.g., the oligonucleotide may be a gapmer, an siRNA, a ribozyme or an aptamer that causes degradation). In some embodiments, the oligonucleotide may be designed to promote or increase expression of a gene (e.g., MEF2D, KLF15, MED1, MED13, or PPP1R3A). In some embodiments, the oligonucleotide may be designed to block translation of an mRNA (e.g., the oligonucleotide may be a mixmer, an siRNA or an aptamer that blocks translation). In some embodiments, an oligonucleotide may be designed to caused degradation and block translation of an mRNA. In some embodiments, an oligonucleotide may be a guide nucleic acid (e.g., guide RNA) for directing activity of an enzyme (e.g., a gene editing enzyme). Other examples of oligonucleotides are provided herein. It should be appreciated that, in some embodiments, oligonucleotides in one format (e.g., antisense oligonucleotides) may be suitably adapted to another format (e.g., siRNA oligonucleotides) by incorporating functional sequences (e.g., antisense strand sequences) from one format to the other format. Oligonucleotides provided herein may be designed to modulate the expression or activity of target genes involved in muscle health, such as muscle growth and maintenance, including MSTN, INHBA and ACVR1B.

[000338] In some embodiments, the oligonucleotide is an antisense oligonucleotide (ASO). In some embodiments, the oligonucleotide is a siRNA. In some embodiments, the oligonucleotide is a short hairpin RNA. In some embodiments, the oligonucleotide is a miRNA-based shRNA. In some embodiments, the oligonucleotide is based on a shRNA based on any one of miR-92b-3p, miR-218, miR-18a, miR-1244, and miR-103, as described in Hu et al.,

Oncotarget. 2017 Nov 3; 8(54): 92079–92089, and in Chen et al., Oncotarget. 2017 Dec 19; 8(67): 112152–112165, incorporated herein by reference. In some embodiments, the oligonucleotide is based on a shRNA based on any one of miR-190a-5p, miR-223-3p, and miR-133.

[000339] In some embodiments, the oligonucleotide is a CRISPR guide RNA targeting MEF2D, KLF15, MED1, MED13, or PPP1R3A. In some embodiments, the oligonucleotide is a CRISPR guide RNA targeting KLF15 or a promoter region associated with KLF15 (e.g., to increase expression of KLF15).

a. MSTN Oligonucleotides

[000340] Examples of oligonucleotides useful for targeting MSTN are provided in Lu-Nguyen, N. et. al. “*Functional muscle recovery following dystrophin and myostatin exon splice modulation in aged mdx mice*” Human Molecular Genetics, Vol. 28, 18, 3091–3100 (2019); Liu, C.M. et. al. “*Myostatin antisense RNA-mediated muscle growth in normal and cancer cachexia mice*” Gene Therapy, Vol. 15, 155–160 (2008); Kang, J.K., “*Antisense-induced myostatin exon skipping leads to muscle hypertrophy in mice following octa-guanidine morpholino oligomer treatment*” Mol Ther. 2011 Jan;19(1):159-64.; Kemaladewi, D.U. et. al. “*Dual exon skipping in myostatin and dystrophin for Duchenne muscular dystrophy*” BMC Med Genomics. 2011 Apr 20;4:36.; Tripathi, A.K. et. al. “*Short hairpin RNA-induced myostatin gene silencing in caprine myoblast cells in vitro*” Appl Biochem Biotechnol. 2013 Jan;169(2):688-94.; Lu-Nguyen, N. et. al., “*Systemic Antisense Therapeutics for Dystrophin and Myostatin Exon Splice Modulation Improve Muscle Pathology of Adult mdx Mice*” Mol. Ther. Nucleic Acids. 2017 Mar 17;6:15-28.; U.S. Patent Application Publication 20050124566A1, published on June 5, 2005, entitled “*RNA interference mediated inhibition of myostatin gene expression using short interfering nucleic acid (siNA)*”; U.S. Patent No. 10,004,814, issued June 26, 2018, entitled “*Systemic delivery of myostatin short interfering nucleic acids (siNA) conjugated to a lipophilic moiety*”; U.S. Patent Application Publication 20110166082A1, published on July 7, 2011, entitled “*Antisense composition and method for treating muscle atrophy*”; U.S. Patent No. 7,887,793, issued February 15, 2011, entitled “*Treatment of Duchenne muscular dystrophy with myoblasts expressing dystrophin and treated to block myostatin signaling*”; and U.S. Patent Application Publication 20180355358A1, published on December 13, 2018, entitled “*Antisense-induced exon exclusion in myostatin*”; the contents of each of which are incorporated herein in their entireties.

[000341] In some embodiments, an oligonucleotide that is useful for targeting MSTN is an oligonucleotide that promotes exon skipping of MSTN RNA sequences. In some embodiments,

an oligonucleotide for targeting MSTN promotes exon skipping of exon 2. Skipping of exon 2 may lead to an improper out-of-phase splicing of exons 1 and 3. In some embodiments, an oligonucleotide for targeting MSTN targets a RNA splice junction, *e.g.*, at intron 1/exon 2 or exon 2/intron 2.

[000342] Examples of oligonucleotides for promoting MSTN gene editing include Crispo, M. et. al. “Efficient Generation of Myostatin Knock-Out Sheep Using CRISPR/Cas9 Technology and Microinjection into Zygotes” PLoS One. 2015 Aug 25;10(8):e0136690; and Zhang, J. et. al. “Comparison of gene editing efficiencies of CRISPR/Cas9 and TALEN for generation of MSTN knock-out cashmere goats” Theriogenology. 2019 Jul 1;132:1-11.

[000343] In some embodiments, oligonucleotides may have a region of complementarity to a human MSTN gene sequence, for example, as provided below (Gene ID: 2660; NCBI Ref. No: NM_005259.3):

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AGATTCAC TGGTGTGGCAAGTTGTCTCTCAGACTGTACATGCATTAAAATTTTGCTTGGCATTAC
CTCAAAAGCAAAAGAAAAGTAAAAGGAAGAAACAAGAAAGAAAAAGATTATATTGATTTTA
AAATCATGCAAAAAC TGAAC TCTGTGTTTATATTTACCTGTTTATGCTGATTGTTGCTGGTCC
AGTGGATCTAAATGAGAACAGTGAGCAAAAAGAAAATGTGGAAAAAGAGGGGCTGTGTAATGCA
TGTACTTGGAGACAAAACACTAAATCTTCAAGAATAGAAGCCATTAAGATACAAATCCTCAGTA
AACTTCGTCTGGAAACAGCTCCTAACATCAGCAAAAGATGTTATAAGACAAC TTTTACCCAAAGC
TCCTCCACTCCGGGAAC TGAATGATCAGTATGATGTCCAGAGGGATGACAGCAGCGATGGCTCT
TTGGAAGATGACGATTATCACGCTACAACGGAAACAATCATTACCATGCCTACAGAGTCTGATT
TTCTAATGCAAGTGGATGGAAAACCCAAATGTTGCTTCTTTAAATTTAGCTCTAAAATACAATA
CAATAAAGTAGTAAAGGCCCAACTATGGATATATTTGAGACCCGTCGAGACTCCTACAACAGTG
TTTGTGCAAATCCTGAGACTCATCAAACCTATGAAAGACGGTACAAGGTATACTGGAATCCGAT
CTCTGAAACTTGACATGAACCCAGGCACTGGTATTTGGCAGAGCATTGATGTGAAGACAGTGT
GCAAAATTGGCTCAAACAACCTGAATCCAACCTTAGGCATTGAAATAAAAGCTTTAGATGAGAAT
GGTCATGATCTTGCTGTAACCTTCCCAGGACCAGGAGAAGATGGGCTGAATCCGTTTTTTAGAGG
TCAAGGTAACAGACACACCAAAAAGATCCAGAAGGGATTTTGGTCTTGACTGTGATGAGCACTC
AACAGAATCACGATGCTGTCGTTACCCTCTAACTGTGGATTTTGAAGCTTTTGGATGGGATTGG
ATTATCGCTCCTAAAAGATATAAGGCCAATTACTGCTCTGGAGAGTGTGAATTTGTATTTTAC
AAAAATATCCTCATACTCATCTGGTACACCAAGCAAACCCAGAGGTTT CAGCAGGCCCTTGCTG
TACTCCCACAAAGATGTCTCCAATTAATATGCTATATTTTAATGGCAAAGAACAATAATATAT
GGGAAAATTCCAGCGATGGTAGTAGACCGCTGTGGGTGCTCATGAGATTTATATTAAGCGTTCA
TAAC TCTCTAAAACATGGAAGGTTTTCCCTCAACAATTTTGAAGCTGTGAAATTAAGTACCAC
AGGCTATAGGCCTAGAGTATGCTACAGTCACTTAAGCATAAGCTACAGTATGTAACTAAAAGG
GGGAATATATGCAATGGTTGGCATTTAACCATCCAAACAAATCATACAAGAAAGTTTTATGATT
TCCAGAGTTTTT GAGCTAGAAGGAGATCAAATTACATTTATGTTCTATATATTACAACATCGG
CGAGGAAATGAAAGCGATTCTCCTTGAGTTCTGATGAATTAAGGAGTATGCTTTAAAGTCTAT
TTCTTTAAAGTTTTGTTTAAATATTTACAGAAAAATCCACATACAGTATTGGTAAAATGCAGGAT
TGTTATATACCATCATTCGAATCATCCTTAAACACTTGAATTTATATTGTATGGTAGTATACTT
GGTAAGATAAAATTCCACAAAAATAGGGATGGTGCAGCATATGCAATTTCCATTCCTATTATAA
TTGACACAGTACATTAACAATCCATGCCAACGGTGCTAATACGATAGGCTGAATGTCTGAGGCT
ACCAGGTTTTATCACATAAAAAACATTCAGTAAAATAGTAAGTTTCTCTTTTCTTCAGGTGCATT
TTCCTACACCTCCAAATGAGGAATGGATTTTCTTTAATGTAAGAAGAAATCATTTTTCTAGAGGT
TGGCTTTTCAATTCTGTAGCATACTTGGAGAACTGCATTATCTTAAAAGGCAGTCAAATGGTGT
TTGTTTTTATCAAAATGTCAAAATAACATACTTGGAGAAGTATGTAATTTTGTCTTTGGAAAAT
TACAACACTGCCTTTGCAACACTGCAGTTTTTATGGTAAAATAATAGAAATGATCGACTCTATC
AATATTGTATAAAAAGACTGAAACAATGCATTTATATAATATGTATACAATATTGTTTTGTAAA
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TAAGTGTCTCCTTTTTTATTTACTTTGGTATATTTTTTACACTAAGGACATTTCAAATTAAGTAC
 TAAGGCACAAAGACATGTCATGCATCACAGAAAAGCAACTACTTATATTTTCAGAGCAAATTAGC
 AGATTAAATAGTGGTCTTAAAACCTCCATATGTTAATGATTAGATGGTTATATTACAATCATT
 ATATTTTTTTTACATGATTAAACATTCACTTATGGATTTCATGATGGCTGTATAAAGTGAATTTGAA
 ATTTCAATGGTTTACTGTCATTGTGTTTAAATCTCAACGTTCCATTATTTTAATACTTGCAAAA
 ACATTACTAAGTATAACCAAAATAATTGACTCTATTATCTGAAATGAAGAATAAACTGATGCTAT
 CTCACAATAAAGTGTACTTTTTATTTTATAATTTGATAATGAATATATTTCTGCATTTATTTAC
 TTCTGTTTTGTAAATTGGGATTTTGTAAATCAAATTTATTGTACTATGACTAAATGAAATTATT
 TCTTACATCTAATTTGTAGAAACAGTATAAGTTATATTAAAGTGTTTTTACATTTTTTTTGAAAG
 ACA

(SEQ ID NO. 147)

[000344] In some embodiments, oligonucleotides may have a region of complementarity to a mouse MSTN gene sequence, for example, as provided below (Gene ID: 17700; NCBI Ref.

No: NM_010834.3):

AGGACTCCCTGGCGTGGCAGGTTGTCTCTCGGACGGTACATGCACTAATATTTCACTTGGCATT
 ACTCAAAAGCAAAAAGAAGAAATAAGAACAAGGGAAAAAAAAGATTGTGCTGATTTTTTAAAT
 GATGCAAAAAGTCAAATGTATGTTTATATTTACCTGTTTCATGCTGATTGCTGCTGGCCAGTG
 GATCTAAATGAGGGCAGTGAGAGAGAAGAAAATGTGGAAAAAGAGGGGCTGTGTAATGCATGTG
 CGTGGAGACAAAACACGAGGTACTCCAGAATAGAAGCCATAAAAATTCAAATCCTCAGTAAGCT
 GCGCCTGGAAACAGCTCCTAACATCAGCAAAGATGCTATAAGACAACCTTCTGCCAAGAGCGCCT
 CCACTCCGGGAAGTGCATCAGTACGACGTCCAGAGGGATGACAGCAGTGATGGCTCTTTGG
 AAGATGACGATTATCACGCTACCACGGAAACAATCATTACCATGCCTACAGAGTCTGACTTTCT
 AATGCAAGCGGATGGCAAGCCCAAATGTTGCTTTTTTAAATTTAGCTCTAAAATACAGTACAAC
 AAAGTAGTAAAAGCCCAACTGTGGATATATCTCAGACCCGTCAAGACTCCTACAACAGTGTTTG
 TGCAAACTCTGAGACTCATCAAACCCATGAAAGACGGTACAAGGTATACTGGAATCCGATCTCT
 GAAACTTGACATGAGCCCAGGCACTGGTATTTGGCAGAGTATTGATGTGAAGACAGTGTTGCAA
 AATTGGCTCAAACAGCCTGAATCCAACCTTAGGCATTGAAATCAAAGCTTTGGATGAGAATGGCC
 ATGATCTTGCTGTAAACCTTCCCAGGACCAGGAGAAGATGGGCTGAATCCCTTTTTAGAAGTCAA
 GGTGACAGACACACCAAGAGGTCCCGGAGAGACTTTGGGCTTGACTGCGATGAGCACTCCACG
 GAATCCCGGTGCTGCCGCTACCCCTCACGGTCGATTTTGAAGCCTTTGGATGGGACTGGATTA
 TCGCACCCAAAAGATATAAGGCCAATTACTGCTCAGGAGAGTGTGAATTTGTGTTTTTACAAAA
 ATATCCGCATACTCATCTTGTGCACCAAGCAAACCCAGAGGCTCAGCAGGCCCTTGCTGCACT
 CCGACAAAAATGTCTCCCATTAATATGCTATATTTTAAATGGCAAAGAACAATAATATATGGGA
 AAATTCCAGCCATGGTAGTAGACCGCTGTGGGTGCTCATGAGCTTTGCATTAGGTTAGAAATTT
 CCAAGTCATGGAAGGTCTTCCCCTCAATTTCGAACTGTGAATTCAAGCACCACAGGCTGTAG
 GCCTTGAGTATGCTCTAGTAACGTAAGCACAAAGCTACAGTGTATGAACTAAAAGAGAGAATAGA
 TGCAATGGTTGGCATTCAACCACCAAAATAAACCATACTATAGGATGTTGTATGATTTCCAGAG
 TTTTTGAAATAGATGGAGATCAAATTACATTTATGTCCATATATGTATATTACAACCTACAATCT
 AGGCAAGGAAGTGAGAGCACATCTTGTGGTCTGCTGAGTTAGGAGGGTATGATTAAAAGGTAAA
 GTCTTATTTCTTAACAGTTTCACTTAATATTTACGGAAGAATCTATATGTAGCCTTTGTAAAGT
 GTAGGATTGTTATCATTTAAAAACATCATGTACACTTATATTTGTATTGTATACTTGGTAAGAT
 AAAATTCCACAAAGTAGGAATGGGGCCTTACATACACATTGCCATTCTTATTATAATTGGACAA
 TCCACCACGGTGCTAATGCAGTGCTGAATGGCTCCTACTGGACCTCTCGATAGAACACTCTACA
 AAGTACGAGTCTCTCTCTCCCTTCCAGGTGCATCTCCACACACACAGCACTAAGTGTTCAATGC
 ATTTTCTTTAAGGAAAGAAGAATCTTTTTTTCTAGAGGTCAACTTTCACTCACTCTAGCACAG
 CGGGAGTGACTGCTGCATCTTAAAAGGCAGCCAAACAGTATTCATTTTTTTAATCTAAATTTCAA
 AATCACTGTCTGCCTTTATCACATGGCAATTTTGTGGTAAAATAATGGAAATGACTGGTTCTAT
 CAATATTGTATAAAAGACTCTGAAACAATTACATTTATATAATATGTATACAATATTGTTTTGT
 AAATAAGTGTCTCCTTTTATATTTACTTTGGTATATTTTTTACACTAATGAAATTTCAAATCATT

AAAGTACAAAGACATGTCATGTATCACAAAAAGGTGACTGCTTCTATTTTCAGAGTGAATTAGC
 AGATTCAATAGTGGTCTTAAAACCTCTGTATGTTAAGATTAGAAGGTTATATTACAATCAATTTA
 TGTATTTTTTTACATTATCAACATTCACTTATGGTTTCATGGTGGCTGTATCTATGAATGTGGCT
 CCCAGTCAAATTTCAATGCCCCACCATTTTAAAAATTACAAGCATTACTAAACATACCAACATG
 TATCTAAAGAAATACAAATATGGTATCTCAATAACAGCTACTTTTTTATTTTATAATTTGACAA
 TGAATACATTTCTTTTATTTACTTTCAGTTTTATAAATTGGAACCTTGTGTTATCAAATGTATTGT
 ACTCATAGCTAAATGAAATTATTTCTTACATAAAAAATGTGTAGAACTATAAATTAAAGTGTTT
 TCACATTTTTTGAAAGGC
 (SEQ ID NO: 148)

[000345] In some embodiments, the oligonucleotide may have region of complementarity to a mutant form of MSTN, for example as reported in as in Schuelke, M. et al., “*Myostatin Mutation Associated with Gross Muscle Hypertrophy in a Child*” N Engl J Med 2004; 350:2682-2688, the contents of which are incorporated herein by reference in its entirety.

[000346] In some embodiments, an oligonucleotide comprises a region of complementarity to an MSTN sequence as set forth in SEQ ID NO: 147 or SEQ ID NO: 148. In some embodiments, the oligonucleotide comprises a region of complementarity that is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to an MSTN sequence as set forth in SEQ ID NO: 147 or SEQ ID NO: 148. In some embodiments, the oligonucleotide comprises a sequence that has at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides that are perfectly complementary to an MSTN sequence as set forth in SEQ ID NO: 147 or SEQ ID NO: 148. In some embodiments, an oligonucleotide may comprise a sequence that targets (*e.g.*, is complementary to) an RNA version (*i.e.*, wherein the T’s are replaced with U’s) of an MSTN sequence as set forth in SEQ ID NO: 147 or SEQ ID NO: 148. In some embodiments, the oligonucleotide comprises a sequence that is complementary (*e.g.*, at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% complementary) to an RNA version of an MSTN sequence as set forth in SEQ ID NO: 147 or SEQ ID NO: 148. In some embodiments, the oligonucleotide comprises a sequence that has at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides that are perfectly complementary to an RNA version of an MSTN sequence as set forth in SEQ ID NO: 147 or SEQ ID NO: 148.

[000347] In some embodiments, an MSTN-targeting oligonucleotide comprises an antisense strand that comprises at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides of a sequence comprising any one of SEQ ID NOs: 197-220. In some embodiments, an MSTN-targeting oligonucleotide comprises an antisense strand that comprises any one of SEQ ID NO: 197-220. In some embodiments, an oligonucleotide comprises an antisense strand that comprises shares at least 70%, 75%, 80%, 85%, 90%, 95%, or 97% sequence identity with at least 12 or at least 15 consecutive nucleotides of any one of SEQ ID NOs: 197-220.

[000348] In some embodiments, an MSTN-targeting oligonucleotide comprises an antisense strand that targets an MSTN sequence comprising any one of SEQ ID NO: 149-196. In some embodiments, an oligonucleotide comprises an antisense strand comprising at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 nucleotides (*e.g.*, consecutive nucleotides) that are complementary to an MSTN sequence comprising any one of SEQ ID NO: 149-196. In some embodiments, an MSTN-targeting oligonucleotide comprises an antisense strand comprising a sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, or 97% complementary with at least 12 or at least 15 consecutive nucleotides of any one of SEQ ID NO: 149-196.

[000349] In some embodiments, an MSTN-targeting oligonucleotide comprises an antisense strand that comprises a region of complementarity to a target sequence as set forth in any one of SEQ ID NOs: 149-196. In some embodiments, the region of complementarity is at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or at least 19 nucleotides in length. In some embodiments, the region of complementarity is 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 nucleotides in length. In some embodiments, the region of complementarity is in the range of 8 to 20, 10 to 20 or 15 to 20 nucleotides in length. In some embodiments, the region of complementarity is fully complementary with all or a portion of its target sequence. In some embodiments, the region of complementarity includes 1, 2, 3 or more mismatches.

[000350] In some embodiments, an MSTN-targeting oligonucleotide further comprises a sense strand that hybridizes to the antisense strand to form a double stranded siRNA. In some embodiments, the MSTN-targeting oligonucleotide comprises an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 197-220. In some embodiments, the MSTN-targeting oligonucleotide further comprises a sense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 173-196.

[000351] In some embodiments, the MSTN-targeting oligonucleotide is a double stranded oligonucleotide (*e.g.*, an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 197-220 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 173-196, wherein the antisense strand and/or (*e.g.*, and) comprises one or more modified nucleosides (*e.g.*, 2'-modified nucleosides). In some embodiment, the one or more modified nucleosides are selected from 2'-O-Me and 2'-F modified nucleosides.

[000352] In some embodiments, the MSTN-targeting oligonucleotide is a double stranded oligonucleotide (*e.g.*, an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 197-220 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 173-196, wherein

each nucleoside in the antisense strand and/or (e.g., and) each nucleoside in the sense strand is a 2'-modified nucleoside selected from 2'-O-Me and 2'-F modified nucleosides.

[000353] In some embodiments, the MSTN-targeting oligonucleotide is a double stranded oligonucleotide (e.g., an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 197-220 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 173-196, wherein each nucleoside in the antisense strand and each nucleoside in the sense strand is a 2'-modified nucleoside selected from 2'-O-Me and 2'-F modified nucleosides, and wherein the antisense strand and/or (e.g., and) the sense strand each comprises one or more phosphorothioate internucleoside linkages. In some embodiments, the sense strand does not comprise any phosphorothioate internucleoside linkages (all the internucleoside linkages in the sense strand are phosphodiester internucleoside linkages), and the antisense strand comprises 1, 2, or 3 phosphorothioate internucleoside linkages. In some embodiments, the antisense strand comprises 2 phosphorothioate internucleoside linkages, optionally wherein the two internucleoside linkages at the 3' end of the antisense strand are phosphorothioate internucleoside linkages and the rest of the internucleoside linkages in the antisense strand are phosphodiester internucleoside linkages,

[000354] In some embodiments, the antisense strand of the MSTN-targeting oligonucleotide comprises a structure of (5' to 3'):
fNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmN*fN*mN, wherein "mN" indicates 2'-O-methyl (2'-O-Me) modified nucleosides; "fN" indicates 2'-fluoro (2'-F) modified nucleosides; "*" indicates a phosphorothioate internucleoside linkage; and the absence of "*" between two nucleosides indicates a phosphodiester internucleoside linkage.

[000355] In some embodiments, the sense strand of the MSTN-targeting oligonucleotide comprises a structure of (5' to 3'):
mNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmN, wherein "mN" indicates 2'-O-methyl (2'-O-Me) modified nucleosides; "fN" indicates 2'-fluoro (2'-F) modified nucleosides; and the absence of "*" between two nucleosides indicates a phosphodiester internucleoside linkage.

[000356] In some embodiments, the antisense strand of the MSTN-targeting oligonucleotide is selected from the modified version of SEQ ID NOs: 197-220 listed in Table 10. In some embodiments, the sense strand of the MSTN-targeting oligonucleotide is selected from the modified version of SEQ ID NOs: 173-196 listed in Table 10. In some embodiments, the MSTN-targeting oligonucleotide is an siRNA selected from the siRNAs listed in Table 10.

Table 8. MSTN Target Sequences

Corresponding nucleotides in NM_005259.3 (SEQ ID NO: 300)	MSTN Target Sequence (5' to 3')	SEQ ID NO:
448-466	TTTGGAAGATGACGATTAT	149
450-468	TGGAAGATGACGATTATCA	150
454-472	AGATGACGATTATCACGCT	151
482-500	ACAATCATTACCATGCCTA	152
630-644	CTACAACAGTGTGTTGTGCA	153
632-650	ACAACAGTGTGTTGTGCAAA	154
671-679	ATGAAAGACGGTACAAGGT	155
697-715	AATCCGATCTCTGAAACTT	156
699-717	TCCGATCTCTGAAACTTGA	157
754-772	TGTGAAGACAGTGTTGCAA	158
760-788	GACAGTGTTGCAAAATTGG	159
762-780	CAGTGTTGCAAAATTGGCT	160
766-784	GTTGCAAAATTGGCTCAAA	161
788-806	CCTGAATCCAACCTTAGGCA	162
789-807	CTGAATCCAACCTTAGGCAT	163
792-810	AATCCAACCTTAGGCATTGA	164
793-811	ATCCAACCTTAGGCATTGAA	165
846-864	CTGTAACCTTCCCAGGACC	166
865-883	AGGAGAAGATGGGCTGAAT	167
1181-1199	ATGCTATATTTTAATGGCA	168
1185-1203	TATATTTTAATGGCAAAGA	169
1201-1219	AGAACAAATAATATATGGG	170
1202-1220	GAACAAATAATATATGGGA	171
1203-1221	AACAAATAATATATGGGAA	172

* The target sequences contain Ts, but binding to RNA and/or DNA is contemplated.

[000357] In some embodiments, an oligonucleotide may comprise or consist of any sequence as provided in Table 9.

Table 9. Oligonucleotide sequences for targeting MSTN

Passenger Strand/Sense Strand (RNA) (5' to 3')	SEQ ID NO:	Guide Strand/Antisense Strand (RNA) (5' to 3')	SEQ ID NO:
UCUUUGGAAGAUGACGAUUAU	173	AUAAUCGUCAUCUCCAAAGAGC	197
UUUGGAAGAUGACGAUUAUCA	174	UGAUAAUCGUCAUCUCCAAAGA	198
GAAGAUGACGAUUAUCACGCU	175	AGCGUGAUAAUCGUCAUCUCCA	199
AAACAAUCAUUAACCAUGCCUA	176	UAGGCAUGGUAAUGAUUGUUUCC	200
UCCUACAACAGUGUUUGUGCA	177	UGCACAAACACUGUUGUAGGAGU	201
CUACAACAGUGUUUGUGCAAA	178	UUUGCACAAACACUGUUGUAGGA	202
CUAUGAAAGACGGUACAAGGU	179	ACCUUGUACCGUCUUAUCAUAGGU	203
GGAAUCCGAUCUCUGAAACUU	180	AAGUUUCAGAGAUCGGAUUCAG	204
AAUCCGAUCUCUGAAACUUGA	181	UCAAGUUUCAGAGAUCGGAUUC	205

GAUGUGAAGACAGUGUUGCAA	182	UUGCAACACUGUCUUCACAUCAA	206
AAGACAGUGUUGCAAAAUUGG	183	CCAAUUUUGCAACACUGUCUUCA	207
GACAGUGUUGCAAAAUUGGCU	184	AGCCAAUUUUGCAACACUGUCUU	208
GUGUUGCAAAAUUGGCUCAAA	185	UUUGAGCCAAUUUUGCAACACUG	209
AACCUGAAUCCAACUUAGGCA	186	UGCCUAAGUUGGAUUCAGGUUGU	210
ACCUGAAUCCAACUUAGGCAU	187	AUGCCUAAGUUGGAUUCAGGUUG	211
UGAAUCCAACUUAGGCAUUGA	188	UCAAUGCCUAAGUUGGAUUCAGG	212
GAAUCCAACUUAGGCAUUGAA	189	UUCAUGCCUAAGUUGGAUUCAG	213
UGCUGUAACCUUCCCAGGACC	190	GGUCCUGGGAAGGUUACAGCAAG	214
CCAGGAGAAGAUGGGCUGAAU	191	AUUCAGCCCAUCUUCUCCUGGUC	215
AUAUGCUAUUUUAAUUGGCA	192	UGCCAUUAAAAUAUAGCAUAUUA	216
GCUAUUUUUAAUUGGCAAAGA	193	UCUUUGCCAUUAAAAUAUAGCAU	217
AAAGAACAAAUAUAUAUUGGG	194	CCCAUAUAUAUUUGUUCUUUGC	218
AAGAACAAAUAUAUAUUGGGA	195	UCCCAUAUAUAUUUGUUCUUUG	219
AGAACAAAUAUAUAUUGGGAA	196	UUCCCAUAUAUAUUUGUUCUUU	220

[000358] In some embodiments, an oligonucleotide is a modified oligonucleotide as provided in Table 10, wherein ‘mN’ represents a 2’-O-methyl modified nucleoside (*e.g.*, mU is 2’-O-methyl modified uridine), ‘fN’ represents a 2’-fluoro modified nucleoside (*e.g.*, fU is 2’-fluoro modified uridine), ‘*’ represents a phosphorothioate internucleoside linkage, and lack of “*” between nucleosides indicate phosphodiester internucleoside linkage.

Table 10. Modified Oligonucleotides for targeting MSTN

siRNA #	Modified Passenger Strand/Sense Strand (RNA) (5' to 3')	SEQ ID NO:	Modified Guide Strand/Antisense Strand (RNA) (5' to 3')	SEQ ID NO:
hsMSTN-1	mUmCfUmUfUmGfGmAfA mGfAmUfGmAfCmGfAmU fUmAfU	173	fAfUmAfAmUfCmGfUmCfAmUfCm UfUmCfCmAfAmAfGmA*fG*mC	197
hsMSTN-5	mUmUfUmGfGmAfAmGfA mUfGmAfCmGfAmUfUmA fUmCfA	174	fUfGmAfUmAfAmUfCmGfUmCfAm UfCmUfUmCfCmAfAmA*fG*mA	198
hsMSTN-2	mGmAfAmGfAmUfGmAfC mGfAmUfUmAfUmCfAmCf GmCfU	175	fAfGmCfGmUfGmAfUmAfAmUfCm GfUmCfAmUfCmUfUmC*fC*mA	199
hsMSTN-6	mAmAfAmCfAmAfUmCfA mUfUmAfCmCfAmUfGmCf CmUfA	176	fUfAmGfGmCfAmUfGmGfUmAfAm UfGmAfUmUfGmUfUmU*fC*mC	200
hsMSTN-7	mUmCfCmUfAmCfAmAfC mAfGmUfGmUfUmUfGmU fGmCfA	177	fUfGmCfAmCfAmAfAmCfAmCfUm GfUmUfGmUfAmGfGmA*fG*mU	201
hsMSTN-8	mCmUfAmCfAmAfCmAfG mUfGmUfUmUfGmUfGmC fAmAfA	178	fUfUmUfGmCfAmCfAmAfAmCfAm CfUmGfUmUfGmUfAmG*fG*mA	202
hsMSTN-9	mCmUfAmUfGmAfAmAfG mAfCmGfGmUfAmCfAmAf GmGfU	179	fAfCmCfUmUfGmUfAmCfCmGfUm CfUmUfUmCfAmUfAmG*fG*mU	203
hsMSTN-10	mGmGfAmAfUmCfCmGfA mUfCmUfCmUfGmAfAmAf CmUfU	180	fAfAmGfUmUfUmCfAmGfAmGfAm UfCmGfGmAfUmUfCmC*fA*mG	204

hsMSTN-11	mAmAfUmCfCmGfAmUfC mUfCmUfGmAfAmAfCmUf UmGfA	181	fUfCmAfAmGfUmUfUmCfAmGfAm GfAmUfCmGfGmAfUmU*fC*mC	205
hsMSTN-12	mGmAfUmGfUmGfAmAfG mAfCmAfGmUfGmUfUmG fCmAfA	182	fUfUmGfCmAfAmCfAmCfUmGfUm CfUmUfCmAfCmAfUmC*fA*mA	206
hsMSTN-13	mAmAfGmAfCmAfGmUfG mUfUmGfCmAfAmAfAmU fUmGfG	183	fCfCmAfAmUfUmUfUmGfCmAfAm CfAmCfUmGfUmCfUmU*fC*mA	207
hsMSTN-3	mGmAfCmAfGmUfGmUfU mGfCmAfAmAfAmUfUmG fGmCfU	184	fAfGmCfCmAfAmUfUmUfUmGfCm AfAmCfAmCfUmGfUmC*fU*mU	208
hsMSTN-4	mGmUfGmUfUmGfCmAfA mAfAmUfUmGfGmCfUmCf AmAfA	185	fUfUmUfGmAfGmCfCmAfAmUfUm UfUmGfCmAfAmCfAmC*fU*mG	209
hsMSTN-14	mAmAfCmCfUmGfAmAfU mCfCmAfAmCfUmUfAmGf GmCfA	186	fUfGmCfCmUfAmAfGmUfUmGfGm AfUmUfCmAfGmGfUmU*fG*mU	210
hsMSTN-15	mAmCfCmUfGmAfAmUfC mCfAmAfCmUfUmAfGmGf CmAfU	187	fAfUmGfCmCfUmAfAmGfUmUfGm GfAmUfUmCfAmGfGmU*fU*mG	211
hsMSTN-16	mUmGfAmAfUmCfCmAfA mCfUmUfAmGfGmCfAmUf UmGfA	188	fUfCmAfAmUfGmCfCmUfAmAfGm UfUmGfGmAfUmUfCmA*fG*mG	212
hsMSTN-17	mGmAfAmUfCmCfAmAfC mUfUmAfGmGfCmAfUmU fGmAfA	189	fUfUmCfAmAfUmGfCmCfUmAfAm GfUmUfGmGfAmUfUmC*fA*mG	213
hsMSTN-18	mUmGfCmUfGmUfAmAfC mCfUmUfCmCfCmAfGmGf AmCfC	190	fGfGmUfCmCfUmGfGmGfAmAfGm GfUmUfAmCfAmGfCmA*fA*mG	214
hsMSTN-19	mCmCfAmGfGmAfGmAfA mGfAmUfGmGfGmCfUmG fAmAfU	191	fAfUmUfCmAfGmCfCmCfAmUfCm UfUmCfUmCfCmUfGmG*fU*mC	215
hsMSTN-20	mAmUfAmUfGmCfUmAfU mAfUmUfUmUfAmAfUmG fGmCfA	192	fUfGmCfCmAfUmUfAmAfAmAfUm AfUmAfGmCfAmUfAmU*fU*mA	216
hsMSTN-21	mGmCfUmAfUmAfUmUfU mUfAmAfUmGfGmCfAmA fAmGfA	193	fUfCmUfUmUfGmCfCmAfUmUfAm AfAmAfUmAfUmAfGmC*fA*mU	217
hsMSTN-22	mAmAfAmGfAmAfCmAfA mAfUmAfAmUfAmUfAmU fGmGfG	194	fCfCmCfAmUfAmUfAmUfUmAfUm UfUmGfUmUfCmUfUmU*fG*mC	218
hsMSTN-23	mAmAfGmAfAmCfAmAfA mUfAmAfUmAfUmAfUmG fGmGfA	195	fUfCmCfCmAfUmAfUmAfUmUfAm UfUmUfGmUfUmCfUmU*fU*mG	219
hsMSTN-24	mAmGfAmAfCmAfAmAfU mAfAmUfAmUfAmUfGmG fGmAfA	196	fUfUmCfCmCfAmUfAmUfAmUfUm AfUmUfUmGfUmUfCmU*fU*mU	220

b. INHBA Oligonucleotides

[000359] Examples of oligonucleotides useful for targeting INHBA are provided in Tada et. al., “Differential expression and cellular localization of activin and inhibin mRNA in the rainbow trout ovary and testis” Gen Comp Endocrinol. 2002 Jan;125(1):142-9.; U.S. Patent 10,260,068, issued on April 16, 2019, and entitled “Prophylactic agent and therapeutic agent for fibrodysplasia ossificans progressiva”; Carlton, AL et. al. “Small molecule inhibition of the CBF β /RUNX interaction decreases ovarian cancer growth and migration through alterations in

genes related to epithelial-to-mesenchymal transition" Gynecol Oncol. 2018 May;149(2):350-360.; and Takabe, K. et al. "Interruption of activin A autocrine regulation by antisense oligodeoxynucleotides accelerates liver tumor cell proliferation" Endocrinology. 1999 Jul;140(7):3125-32.; the contents of each of which are incorporated herein in their entireties.

[000360] In some embodiments, oligonucleotides may have a region of complementarity to a human INHBA sequence, for example, as provided below (Gene ID: 3624; NCBI Ref. No: NM_002192.4):

ACAGTGCCAATACCATGAAGAGGAGCTCAGACAGCTCTTACCACATGATACAAGAGCCGGCTGG
TGGAAGAGTGGGGACCAGAAAGAGAATTTGCTGAAGAGGAGAAGGAAAAAAAAAACACCAAAAA
AAAAAATAAAAAATCCACACACACAAAAAACCTGCGCGTGAGGGGGGAGGAAAAGCAGGGCC
TTTTAAAAAGGCAATCACAACAACCTTTTGCTGCCAGGATGCCCTTGCTTTGGCTGAGAGGATTT
CTGTTGGCAAGTTGCTGGATTATAGTGAGGAGTTCCCCACCCCAGGATCCGAGGGGCACAGCG
CGGCCCCCGACTGTCCGTCTGTGCGCTGGCCGCCCTCCCAAAGGATGTACCCAACCTCTCAGCC
AGAGATGGTGGAGGCCGTCAAGAAGCACATTTTAAACATGCTGCACTTGAAGAAGAGACCCGAT
GTCACCCAGCCGGTACCCAAGGCGGCGCTTCTGAACGCGATCAGAAAGCTTCATGTGGGCAAAG
TCGGGGGAGAACGGGTATGTGGAGATAGAGGATGACATTGGAAGGAGGGCAGAAATGAATGAACT
TATGGAGCAGACCTCGGAGATCATCACGTTTGCCGAGTCAGGAACAGCCAGGAAGACGCTGCAC
TTCGAGATTTCCAAGGAAGGCAGTGACCTGTGAGTGGTGGAGCGTGCAGAAGTCTGGCTCTTCC
TAAAAGTCCCCAAGGCCAACAGGACCAGGACCAAAGTCACCATCCGCCTCTTCCAGCAGCAGAA
GCACCCGCAGGGCAGCTTGGACACAGGGGAAGAGGCCGAGGAAGTGGGCTTAAAGGGGGAGAGG
AGTGAACCTGTTGCTCTCTGAAAAAGTAGTAGACGCTCGGAAGAGCACCTGGCATGTCTTCCCTG
TCTCCAGCAGCATCCAGCGGTTGCTGGACCAGGGCAAGAGCTCCCTGGACGTTTCGGATTGCCTG
TGAGCAGTGCCAGGAGAGTGGCGCCAGCTTGGTTCTCCTGGGCAAGAAGAAGAAGAAGAAGAG
GAGGGGGAAGGGAAAAAGAAGGGCGGAGGTGAAGGTGGGGCAGGAGCAGATGAGGAAAAGGAGC
AGTCGCACAGACCTTTCCTCATGCTGCAGGCCCGGCAGTCTGAAGACCACCTCATCGCCGGCG
TCGGCGGGGCTTGGAGTGTGATGGCAAGGTCAACATCTGCTGTAAGAAACAGTTCTTTGTGAGT
TTCAAGGACATCGGCTGGAATGACTGGATCATTGCTCCCTCTGGCTATCATGCCAACTACTGCG
AGGGTGAGTGCCCGAGCCATATAGCAGGCACGTCCGGGTCTCACTGTCTTCCACTCAACAGT
CATCAACCACTACCGCATGCGGGGCCATAGCCCCCTTGGCCAACCTCAAATCGTGCTGTGTGCCC
ACCAAGCTGAGACCCATGTCCATGTTGTACTATGATGATGGTCAAAACATCATCAAAAAGGACA
TTCAGAACATGATCGTGGAGGAGTGTGGGTGCTCATAGAGTTGCCAGCCCAGGGGGAAAGGGA
GCAAGAGTTGTCCAGAGAAGACAGTGGCAAAATGAAGAAATTTTTAAGGTTTCTGAGTTAACCA
GAAAAATAGAAATTAAAAACAAAACAAAAAACAACAAAAAACAAGTAAATTAAAAAC
AAAACCTGATGAACAGATGAAGGAAGATGTGGAATAATCCTTAGCCAGGGCTCAGAGATGAAG
CAGTGAAAGAGACAGGAATTGGGAGGGAAAGGGAGAATGGTGTACCCTTTATTTCTTCTGAAAT
CACACTGATGACATCAGTTGTTTAAACGGGGTATTGTCTTTCCCCCTTGAGGTTCCCTTGTG
AGCCTTGAATCAACCAATCTAGTCTGCAGTAGTGTGGACTAGAACAACCCAAATAGCATCTAGA
AAGCCATGAGTTTGAAAGGGCCCATCACAGGCACCTTTCCTACCCAATTACCCAGGTCATAAGGT
ATGTCTGTGTGACACTTATCTCTGTGTATATCAGCATACACACACACACACACACACACACA
CACACACAGGCATTTCCACACATTACATATATACACATACTGGTAAAAGAACAATCGTGTGCAG
GTGGTCACACTTCCTTTTTCTGTACCCTTTTGCAACAAAACAAAACAAACAACTTAAAAAAT
TGAGAACAAGTATGGAAAGAATGAAAGATCAAGGAAAAAAGAATACCAAGTTACATTTTCGTTAA
GGTGCTTATGATCTTAGAACTATGCAACCTAATAGGTTTGAACTGTTTACCTGAGAGAGAACA
AAAAGAGAGACTTTTTTGTATTGGAAGTAATCTGATTAAATTTTTATTTTCTTCAAGGAGAGATA
CTTGAAAGGAATATGTTTGTCCATCTGTTGGATCCAAACATTTCTATATTTTGTAAATGTTGTT
GTTGTTTTTTTTTTAATCGTTTACTATTTGCACTACAATGGTGTGTTGACCTGTCTAATCCTTAT
TTAACAAGTATTTTCTTTGGTTGGGGGTGGGGGTGGGGTTAAGAGCTGCACTTAATGTGAGCT
ATAAAAGAACTGCTACAGCACACAAAATAGCTATTTTTTATTATTATAATTATAATTATTATTAT
TATTTTGTACCTTAAAAAATAGACACATACACCAAGACATTTGTGTGAGCCTTTAAACAGTCT

GTCTGTGGTTGGTATCATTACCATCAATGAGTCAGGGGTTGGGATTCAAGGTTGAGTAGTGTG
GATTGTGTTTCAGGCTTAAAAGACCTGAGAAAGTTTGGTTTTTGGACTCCTTTTACATCCATGAAAC
AGGACATTTTCATACTGGATGTACAGTAGTTGTACACTGTTGGATATCAAGTTCAATCAAATTCA
TGGAACATACATGCTTGTATGTGTATATATACATTGCTTGTGCATATGCATATCTGTATGTATAT
ATACATGTATTGTACCATGTCCATACACATTTTAAGCACTTCAGGCTGTCATTTTTTAATGTTT
TTAAAGCAATGAATGTTTGTGTGCAAAACACAGTATTTTTAAGAAGGATAGGCTATAGTTTTTG
CTTTTACTCTGAACTAGGTGGGCGCATTTCAAAAATTCGGATGGGAAAAAGCCTGGAAATTCCA
GTGAATATTTCAGCAAGGCCCTCTTTCATTGTACAGGGATCAAATTTCCCTCCTCTTTTTTGTGCC
CCCTCCCCTTCTACAAGTTATCCCCTGTGGGGAAAACAGGATGATAATCAAACCTCTGGGCTG
ATGTTTTTCCAACCTTAGTGTCTATTGGAATCAATCTTAAATCAGAAGCTTTTTTCAGAAAAATAA
TATTTAGGCCAGAATTAGAGTTGAGTGTATTTTTTAAAAATGATTAAGGCTTGGTTGTGAGAAA
TATTACCTGTACCAGCTGGGAAAAATAATGTCATCACTAACTAAAAGATAATTAATTTGAGAGA
AAGTGTTAAGAGAGGGAGAGTAAGGAAGAGAACAGTTAAGAGGAGGCAGAGGTGAGGGCAGTAG
TAAAAATCTCTAAAATTTTAATTTACAGCCAAAATTCCTTCATGTGTAAATTTGTATTGATTGAG
ATGCAGAAATGAAAAAAAACACCTTTGTTTTATAAATATCAAAGTACATGCTTAAAGCCAAGT
TTTTATCTAGTTTTATTCTAGTACTTAGCTTGCCCTGGAATAGCTAATAAATTATTCATGTATGTG
CTTTTGAAAATCCAGAGCCCTATTTTTTACACACTTGTGTGAAGTTGGCAAACATTTTGAAAAAT
GGAAAAAAGTTTCTAATAATTGGGAACAATTACATTAATTAATATTTTTGTAAAAATATTGAAGCT
TTTAGCCCTATGTCAATTTGTAGATTAAAAATAAATTAATTATAGGAAAGGAAGATAACAGTGAG
AAACCAAACATTACAAAAGGTGGTTTAGCTCTCCTTGAAAAATATACTAAGTTGGTATACTATA
ACACTTGGCTATATGTAGGCAATGTCACTACTGGGCAAATACACTTACTGTGTTCTAGAGGCAG
CCCTTTCTTATGCAGAAAATACAATACGCACTGCATGAGAAGCTTGAGAGTGGATTCTAATCCA
GGTCTGTGACCTTGGATATCATGCATGTGGGAAGGTGGGTGTGGTGAGAAAAGTTTTAAGGCA
AGAGTAGATGGCCATGTTCAACTTTACAAAATTTCTTGAAAACTGGCAGTATTTTGAAGTGA
TCTTCTTTGGTACCGGAACCTGCAGAAACAGTGTGAGAAATTAAGTCCTGGTTCAGTGCAGT
AGCAAAGATGGTCAAGGCCATGGAAAAAGCAGAAATTTACCAAGAAAGCTGATACCCATGTATA
GTTCCCACTCATCTCAAATACATCTGCTATCTTTTTAAGCTAAGTCCTAGACATATCGGGGATA
ACATGGGGGTTGATTAGTGACCACAGTTATCAGAAGCAGAGAAATGTAATTCATATTTTATTT
GAACTTATTCCATATTTTAATTGGATATTGAGTGATTGGGTTATCAAACACCCACAACTTTA
ATTTTGTAAATTTATATGGCTTTGAAATAGAAGTATAAGTTGCTACCATTTTTTGTATAACATT
GAAAGATAGTATTTTACCATCTTTAATCATCTTGGAATAACAAGTCCTGTGAACAACCACTCT
TTCACCTAGCAGCATGAGGCCAAAAGTAAAGGCTTTAAATTATAACATATGGGATTCTTAGTAG
TATGTTTTTTTTCTTGAACTCAGTGGCTCTATCTAACCTTACTATCTCCTCACTCTTTCTCTAA
GACTAACTCTAGGCTCTTAAAAATCTGCCCACACCAATCTTAGAAGCTCTGAAAAGAATTTGT
CTTTAAATATCTTTTAATAGTAACATGTATTTTATGGACCAAATTGACATTTTTCGACTATTTTT
TCCAAAAAAGTCAGGTGAATTTTCAGCACACTGAGTTGGGAATTTCTTATCCCAGAAGACCAACC
AATTTTCATATTTATTTAAGATTGATTCCATACTCCGTTTTCAAGGAGAATCCCTGCAGTCTCCT
TAAAGGTAGAACAATACTTTCTATTTTTTTTTTACCATTGTGGGATTGGACTTTAAGAGGTGA
CTCTAAAAAAACAGAGAACAAATATGTCTCAGTTGTATTAAGCACGGACCCATATTATCATATT
CACTTAAAAAAATGATTTCTGTGCACCTTTTGGCAACTTCTCTTTTCAATGTAGGGAAAAACT
TAGTCACCCTGAAAACCCACAAAATAAATAAACTTGTAGATGTGGGCAGAAGGTTTGGGGGTG
GACATTGTATGTGTTTAAATTAACCCTGTATCACTGAGAAGCTGTTGTATGGGTGAGAGAAAA
TGAATGCTTAGAAGCTGTTACATCTTCAAGAGCAGAAGCAAACCACATGTCTCAGCTATATTA
TTATTTATTTTTTATGCATAAAGTGAATCATTTCTTCTGTATTAATTTCCAAAGGGTTTTACCC
TCTATTTAAATGCTTTGAAAAACAGTGCATTGACAATGGGTTGATATTTTTCTTTAAAAAGAAAA
ATATAATTATGAAAGCCAAGATAATCTGAAGCCTGTTTTATTTTAAACTTTTTATGTTCTGTG
GTTGATGTTGTTTGTGTTGTTTCTATTTTGTGGTTTTTACTTTGTTTTTGTGTTTGTGTT
TGTTTTGTTTTGCATACTACATGCAGTTCTTTAACCAATGTCTGTTTGGCTAATGTAATTAAG
TTGTTAATTTATATGAGTGCATTTCAACTATGTCAATGGTTTCTTAATATTTATGTTGTAGAAG
TACTGGTAATTTTTTTTATTTACAATATGTTTAAAGAGATAACAGTTTGATATGTTTTCATGTGT
TTATAGCAGAAGTTATTTATTTCTATGGCATTCCAGCGGATATTTTGGTGTTTGCGAGGCATGC
AGTCAATATTTTGTACAGTTAGTGGACAGTATTCAGCAACGCCTGATAGCTTCTTTGGCCTTAT
GTAAATAAAAAGACCTGTTTGGGATGTA (SEQ ID NO: 269).

[000361] In some embodiments, oligonucleotides may have a region of complementarity to a mouse INHBA sequence, for example, as provided by Gene ID: 16323; NCBI Ref. No: NM_008380.2:

GGGGTTCGCTAGTGGCTGCTCCTCCAGGCAGCACCGGGCCAGCGTGGAGTTGGAGCTTTGTGAA
GTAGCCAGTAAATCAGAACGCCTCCGCTAGGTGCAGAGCGCGGTGGCAGCGGGCCACTCTGCCA
GTGCGGTAGTCGGTGGGACCGAACTCTACACTCGGGAAGGGGCAGTCTGCGGGTGCGGGGCCTG
AGCTGCCGCTCGCCTCCGTTGGCCAGGAGACCGGCAGCCCCACTGCAGCTGCCAAAAGGGGGG
AAAAATCAAGAGCTGCGCTTTTAAACGAAGTTGCCCTTGCTGGTGTTCAGGGTAAAAATAGAGG
CGGCCGCTTGGACCAGCTTGGCCCCCTGAGTCCAGGCGTCCCGCGAGCCGGGCTGGAGCTGCGCA
TTCGGGAGTGATCCCTGGAACTGCCAGCAGGTGCTGCTCAAGTGCCAATACCATGAAGAGGAA
TTCAGACAGCTCTGACCTCATGAGACAAGAGCCGGCTGACAAAACAGAAGGGACCCGAAAGAGA
ATTTGCTGAAGAGGAGAAGGAAAAAAAAGTCCAAAAAACCTGTGCGTGAGGGGTGGGGAGGA
AAAGCAGGGCCTTTAAAGAAGGCAACCACACGACTTTTGCTGCCAGGATGCCCTTGCTTTGGCT
GAGAGGATTTCTGTTGGCAAGTTGCTGGATTATAGTGAGGAGTTCCCCACCCCAGGATCCGAG
GGGCACGGCTCAGCCCCGGACTGCCCGTCTGTGCGCTGGCCACCCTTCCGAAGGATGGACCTA
ACTCTCAGCCAGAGATGGTAGAGGCTGTCAAGAAGCACATCTTAAACATGCTGCACCTGAAGAA
GAGACCCGATGTCACCCAGCCGGTGCCCAAGGCGGCGCTTCTCAACGCGATCAGAAAGCTTCAT
GTGGGTAAAGTGGGGGAGAACGGGTATGTGGAGATAGAGGACGACATTGGCAGGAGGGCCGAAA
TGAATGAACTCATGGAGCAGACCTCGGAGATCATCACCTTTGCCGAGTCAGGCACAGCCAGGAA
GACACTGCACCTTTGAGATTTCCAAGGAAGGCAGTGACCTGTCAGTAGTGAGCGTGCAGAAGTG
TGGCTCTTCCTGAAAGTCCCCAAGGCTAACAGAACCAGGACCAAAGTCACCATCCGTCTATTTT
AGCAGCAGAAGCACCCACAGGGCAGCTTGGACACGGGGGATGAGGCCGAGGAAATGGGCTTAAA
GGGGGAGAGGAGTGAAGTGTGCTATCAGAGAAAGTAGTTGATGCTCGGAAGAGTACCTGGCAC
ATCTTTCCAGTGTCCAGCAGCATCCAGCGCCTGCTGGACCAGGGAAAGAGTTCCCTGGACGTGC
GGATTGCTTGTGAGCAGTGCCAGGAGAGTGGTGCCAGTCTAGTGCTTCTGGGCAAGAAGAAGAA
GAAAGAGGTGGATGGAGATGGGAAGAAGAAAGATGGGAGTGACGGAGGGCTGGAAGAGGAAAAG
GAACAGTCACATAGACCTTTCTCATGCTGCAGGCTAGGCAGTCCGAAGACCACCCTCATCGCA
GGCGTAGGCGGGGCTTGGAGTGCGACGGCAAGGTCAACATTTGCTGTAAGAAACAGTTCTTTGT
CAGCTTCAAGGACATTGGCTGGAATGACTGGATCATTGCTCCCTCTGGCTATCACGCCAATTAT
TGTGAGGGGGAGTGCCCAAGCCACATAGCAGGCACCTCTGGGTCTCGCTCTCCTTCCACTCAA
CAGTCATTAACCACTACCGCATGAGGGGTCACAGCCCCTTTGCCAACCTTAAGTCATGCTGTGT
GCCCACCAAGCTGAGACCCATGTCCATGCTGTATTACGATGATGGTCAAAACATCATCAAAAAG
GACATTCAAAACATGATTGTGGAGGAGTGTGGCTGCTCCTAGAGTCGCCAGGTCCCAGAGAAAA
TGGATCTAGAGAGTCCAGAGAAGACAGTGGCAAAATGAAGAAAAAATATAAGATTTATGAACT
AAACAAAACAACCAGAAAAATAGAAATAATAATAATAAAAAACCCACAAAAAACAACAAAAAC
AAAAATCAAAAACCTAACTGAAAACAAGACCTAATGAAACAGATGAAGGAAGATGTGGA AAAAT
ATCCTAAGGCAGGGCTCAGAGATGAAGCAGTAAAGGAGACAGGGATTGGGGGGGGGAGGGGGG
AGAAGAGAGAATGGTGTACCTTCATTTCTTCCAAAACCAAACCTGATTGCATCAGTTTTATCCAA
ACTGGGTATTGTCTCTCTCTCTGCTTGTGCGGTTCCCTTGCGAGCCTGGAAGTCTACTTGTCT
ATTCTGCAGTAATGTGGGTTAGCACAAACCAATAATAATGTCTAGAAAGCCATGAGTTTTAAA
GGGCCAGTCCCACCCACTTACCCAGGTTATAAGTATGTCTATGTGACACTATCTCTGTGTATTT
CAACACACACACACACACACACACTCACACACACACACACACACACACACACACACACACAC
GCCCCCCCACACACACACACACTCACACACACACACACACACACACACACACACACACACAC
TCACACACACACACACACACACACACGCCCACACACACAAACACAGAGGTGTTTCCACACACCA
CATGCATACACATACTGGTAAAAGAACAACTTCTGTGCAGGTGGTCACATTTTCTTTTCTGTACC
ACTTTTGCCACCAGACAAAACCAACATAAAACATTGAGAACAAGAGTGGAAAGAATGAAAGACC
AAGGGAAGAAGAATACCAAGTTACATTTTCGTTAAGGTGCTTTTGATCCTAGAACTATGCAACCT
AATAGGTTTGAAACTGTTTACCTGAAAGAGGACAAAAAGAGAGACTTTTTTGTATTGGAAGTAA
CCTGATTAAATTTTTATTTTCTTCAAGGAGAGATACTTGAAAGGAATATGTTTGTCCATCTGTTG
GATTCAAACATTTCTATATTTTGTAAATGTTGTTTTTTTATCGTTTACTATTTGCACTACGAT

GGTGTTTGACCTGTCTAATCCTTATTTAACAAGTATTTTCTTTGGGTGGGGGTGGGGGTGGGGT
TTAAGAGCTGCACTTCATGTGAGCTATAAAAGAACTGCTACAGCACACAAAATAGCTATTTTTTA
TTATTATAATTATAATTATTATTATTATTTTGTACCTTAAAAATAGACACATACACCAAAGACA
TTTGTGTGAGCCTTTAAACAGTCTGTCTGTGGTTGGTATTGTTTACCATCAATGAGTCAGGGGT
ACAGATTTAAGGTTGAGTTAGGTAGATTGTGTTTCAAGGCTTAAAAGACCTGAGAGGTTTGGGTTT
TGACTCTTTTACATCCATGAAACAGGACATTTTCATACTGGATGTACAGTAGTGTACACTGTTGG
ATTATCAAGTTCAAATTCATGAGACTACATGCTTGTATGTGTATATATACATTGCTTGTGCATA
TGCATATCTGTATGTATATATACATGTATTGTACCATGTCCATACACATTTTAAGCACTTCAGG
CTGTCATTTTTAAAAATGTTCTTAAACAATGAATGTTTGTGTGCAAAACACAGTATTTTTTAAGA
AGGATAAGTGATAGATTTTTTTTTTTCTTGCTTTTACTCTGTAGTACGTGGGTACATTTCAAAT
GTTAGGATGGGGAAAGACTGAAAATCCCAGTGAGTATCCAGCCAGGCCCTCTTTAAATGTACAG
GATGAAATCCCCTCTTTTCATATCCCCCTGCTCCCTACAAGTTATCCCCTGTGGGGAAAAATGG
GATGTTACTTTTAAAAACAAAATGGGCTGATTTTTTCAACTTATATTTATTATTATTGGAATCA
ATCTTAAATCAGAAACATTTTTTGGAAAAAATCTTTAGGCTAGAATAATTTTTTGAATAGTGTTA
TTACTACTTAAATAATAAAATAAGCAGGAAAGTATTTAAGACAGTGAGAGTTAAGGGAGAGAGC
ACTCAGGAGCCAGGGAGTTGTACAAATCTCTAATATTCTATTTTTGCAGCCAAAAAAGCTTGTCT
GTATGTTTGTACTTTTTTCAGAGGCCAAACTGAAAAGATTGTCTTACGAATATCAAATACACAC
TTAACCCAAGTTCCTAATTTAACCCAGTGTGGCTTGTCTAAAACAGCTAATCAGTTATTCATT
TACATATTTAAATATAGAGCCTTATTTTTACGGACTTGTTTGAAGTTTGAAAAAGCTTTATAAA
AGTGAAAAAGCTCTAATTGAAAAAATCTATATTCCTCAGTATTTTGTAAAATATTGAAGCTTT
TAGCATTAAGTCAGTCCATAGATTAAAGTCATTGTAGGAAAATGAAATACAAAGGAGAAATTAA
ATCTTAAAAAAGCTGGTTTAACTCTTAAAAAATAAACTAACTCAATATGTATTAAATATACCG
TCAATATACCTTATCACATTAGGCTGTGTGTAGGCCAACTACTTTAGTCTTGTTACTGGGCAAA
CATATTTACTGTGTTCCAGGGGCCCTCCCTGTCTTATGCAGGAAATGCATGTACTGCATAAGAA
ATGAATTATAATTAAGGTCTAATGACCTTGAAGATCTCGCATGCGAGGACAGATGGCATGTTGA
GGACACAGAGGTGAGGTGGATGTCCAGGTTTCAAGCTTTGCCAATTTTTGTGAAAAACCTTTAGCG
CCCTCTGAACTGTTTCTTTAGTATTGGAGCTAATGCCGAGGCCTAGAGAAATAGTGGGCAAGAG
ATCTAACTGTGCCATATCAGAGATGATCTAGACCATGGGAAGAGCAGGATTTATGTAAGTACTA
ATTATAGTTCTCATTATCTGAGATGAATCTGCAATCTTCTTAAAGCCCTTTAAATCTAGATGT
TTTGAGGGTAAGCTTGGGTTTAAATTAGTAGCCATAGTAATTAATCTAGAAAGAAATGAAATTC
CACAGGACAGTGTATTTACTGGAGACCAAGTGACTTGGTTGTACATAAACCTCATCAGAACTC
ATCAAAATTTGTATGGCCTTGCAATAGAATTTAAATTGCTAATATTTTAAACAATATTAGATATTG
TTAACAATTTAGAAAACATGAAGTCTTGTGAACTGGTCTTTCTACATAAGTGCTTAATCCAAAA
TTTGAAAAGCCTTTAATGCTTAAGATCTTAGTTTCTTCATGGTGTGCTTTCCCTAGTGTTAAAG
TGGCTCTGTCTGGTCTCCCCACTTTCTCTAGGATAATTCTTAAATACCTGCCCACACAAGTTCT
AGATGCTCTGAAGAGCATTTGTAGTTAGTATCTCTTTAATACTTGTAAGCTTCATTGACACTTT
TCCTTCCCAAAATAAGTCAAATTTACGACAGCAATGGGGATTTTCTTATCTTAGAAGACCAGC
CAATTCTATGTTTCAATTAAGATTGATTCCACACTCCATTTTCAAGGAGAGGCCTTGTGTTTTCT
TAAAAGGCAGAATAAGTAAAATTTGGGAGCTATGCCAGACTGAACGCAAGACGTGACTTTGTGAT
TCCAGAACAAACATGCCTCAGTTATAGTAACATGCATTCAAATGATTGTGTCACTTGAAAAATA
TGATTTTCTGTGGGCCCTTTTGGCAACTTCTCTTTTGTAGTATCGAGAAAAATGTAATCACCCCAA
AACCCGCATAAGTGTGACTTGTAGATGTGGGCAGGAGGTTGGGGATGGACATTGTATGTGTTT
AAATTAAACCTGTATCACTGAGAAGCTATTGGAGGGGTCAGAGATAATGAATGCATAGATGCT
GTTACATCTTCAAGAGCAAAAGCAAATCACGTGTCTCAGCTATATTATTATTTATTTTATGC
ATAAAGTGAATCATTTCTTCTGTATTAATTTTCAGTGGGGTTTGCCCTCTATTTAAATGCTTTG
AAAAACAGTGCATTGACAATGGTTGATATTTTTCTTTTAAAGAAAAATATAATTATGAAAGCCA
AGATAATCTGAAATCTGTTTTGATCTAAAACCTTTTTATGTTATGTGGTTGATGTTGTTTGTG
TTTTTTATTTTTATTTTGTGAGTTCTTTGCATACTACATGCAATTCTTTAACCAATGTCTGGC
TAATGTAATTAAAGTTGTTAATTTATATGAGTGCATTTCAACTATGTCAATGGTTTCTTAATAT
TTATTTTGTAGAAGTGCTGGTAATTTTTTTATTTACGATATGTTTAAAGAGATAACGGTTGGATA
TGTTTTTCATGTGTTTATAGCAGAAGTTATTTATTTCTATTCCATTCCAGCGGATATTCTGATGT
TTGCGAGGCATGCAGTCAATACTTTGTACAGTTAGTAGGCAGTATTCAGCAATGCCCGATAGCT

TCTTTGGCCTTATGTTAAATAAAAAGACCTGTTTGGGATGTAAAAA
 AAA (SEQ ID NO: 270).

[000362] In some embodiments, an oligonucleotide comprises a region of complementarity to an INHBA sequence as set forth in SEQ ID NO: 269 or SEQ ID NO: 270. In some embodiments, the oligonucleotide comprises a region of complementarity that is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to an INHBA sequence as set forth in SEQ ID NO: 269 or SEQ ID NO: 270. In some embodiments, the oligonucleotide comprises a sequence that has at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides that are perfectly complementary to an INHBA sequence as set forth in SEQ ID NO: 269 or SEQ ID NO: 270. In some embodiments, an oligonucleotide may comprise a sequence that targets (*e.g.*, is complementary to) an RNA version (*i.e.*, wherein the T's are replaced with U's) of an INHBA sequence as set forth in SEQ ID NO: 269 or SEQ ID NO: 270. In some embodiments, the oligonucleotide comprises a sequence that is complementary (*e.g.*, at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% complementary) to an RNA version of an INHBA sequence as set forth in SEQ ID NO: 269 or SEQ ID NO: 270. In some embodiments, the oligonucleotide comprises a sequence that has at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides that are perfectly complementary to an RNA version of an INHBA sequence as set forth in SEQ ID NO: 269 or SEQ ID NO: 270.

[000363] In some embodiments, an INHBA-targeting oligonucleotide comprises an antisense strand that comprises at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides of a sequence comprising any one of SEQ ID NOs: 319-342. In some embodiments, an INHBA -targeting oligonucleotide comprises an antisense strand that comprises any one of SEQ ID NO: 319-342. In some embodiments, an oligonucleotide comprises an antisense strand that comprises shares at least 70%, 75%, 80%, 85%, 90%, 95%, or 97% sequence identity with at least 12 or at least 15 consecutive nucleotides of any one of SEQ ID NOs: 319-342.

[000364] In some embodiments, an INHBA-targeting oligonucleotide comprises an antisense strand that targets an INHBA sequence comprising any one of SEQ ID NO: 271-318. In some embodiments, an oligonucleotide comprises an antisense strand comprising at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 nucleotides (*e.g.*, consecutive nucleotides) that are complementary to an INHBA sequence comprising any one of SEQ ID NO: 271-318. In some embodiments, an INHBA-targeting oligonucleotide comprises an antisense strand comprising a sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, or 97% complementary with at least 12 or at least 15 consecutive nucleotides of any one of SEQ ID NO: 271-318.

[000365] In some embodiments, an INHBA-targeting oligonucleotide comprises an antisense strand that comprises a region of complementarity to a target sequence as set forth in

any one of SEQ ID NOs: 271-318. In some embodiments, the region of complementarity is at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or at least 19 nucleotides in length. In some embodiments, the region of complementarity is 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 nucleotides in length. In some embodiments, the region of complementarity is in the range of 8 to 20, 10 to 20 or 15 to 20 nucleotides in length. In some embodiments, the region of complementarity is fully complementary with all or a portion of its target sequence. In some embodiments, the region of complementarity includes 1, 2, 3 or more mismatches.

[000366] In some embodiments, an INHBA-targeting oligonucleotide further comprises a sense strand that hybridizes to the antisense strand to form a double stranded siRNA. In some embodiments, the INHBA-targeting oligonucleotide comprises an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 319-342. In some embodiments, the INHBA-targeting oligonucleotide further comprises a sense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 295-318.

[000367] In some embodiments, the INHBA-targeting oligonucleotide is a double stranded oligonucleotide (e.g., an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 319-342 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 295-318, wherein the antisense strand and/or (e.g., and) comprises one or more modified nucleosides (e.g., 2'-modified nucleosides). In some embodiment, the one or more modified nucleosides are selected from 2'-O-Me and 2'-F modified nucleosides.

[000368] In some embodiments, the INHBA-targeting oligonucleotide is a double stranded oligonucleotide (e.g., an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 319-342 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 295-318, wherein each nucleoside in the antisense strand and/or (e.g., and) each nucleoside in the sense strand is a 2'-modified nucleoside selected from 2'-O-Me and 2'-F modified nucleosides.

[000369] In some embodiments, the INHBA-targeting oligonucleotide is a double stranded oligonucleotide (e.g., an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 319-342 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 295-318, wherein each nucleoside in the antisense strand and each nucleoside in the sense strand is a 2'-modified nucleoside selected from 2'-O-Me and 2'-F modified nucleosides, and wherein the antisense strand and/or (e.g., and) the sense strand each comprises one or more phosphorothioate internucleoside linkages. In some embodiments, the sense strand does not comprise any

phosphorothioate internucleoside linkages (all the internucleoside linkages in the sense strand are phosphodiester internucleoside linkages), and the antisense strand comprises 1, 2, or 3 phosphorothioate internucleoside linkages. In some embodiments, the antisense strand comprises 2 phosphorothioate internucleoside linkages, optionally wherein the two internucleoside linkages at the 3' end of the antisense strand are phosphorothioate internucleoside linkages and the rest of the internucleoside linkages in the antisense strand are phosphodiester internucleoside linkages,

[000370] In some embodiments, the antisense strand of the INHBA-targeting oligonucleotide comprises a structure of (5' to 3'):

fNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmN*fN*mN, wherein "mN" indicates 2'-O-methyl (2'-O-Me) modified nucleosides; "fN" indicates 2'-fluoro (2'-F) modified nucleosides; "*" indicates a phosphorothioate internucleoside linkage; and the absence of "*" between two nucleosides indicates a phosphodiester internucleoside linkage.

[000371] In some embodiments, the sense strand of the INHBA-targeting oligonucleotide comprises a structure of (5' to 3'):

mNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmN, wherein "mN" indicates 2'-O-methyl (2'-O-Me) modified nucleosides; "fN" indicates 2'-fluoro (2'-F) modified nucleosides; and the absence of "*" between two nucleosides indicates a phosphodiester internucleoside linkage.

[000372] In some embodiments, the antisense strand of the INHBA-targeting oligonucleotide is selected from the modified version of SEQ ID NOs: 319-342 listed in Table 13. In some embodiments, the sense strand of the INHBA-targeting oligonucleotide is selected from the modified version of SEQ ID NOs: 295-318 listed in Table 13. In some embodiments, the INHBA-targeting oligonucleotide is an siRNA selected from the siRNAs listed in Table 13.

Table 11. INHBA Target Sequences

Corresponding nucleotides of Sequence NM_002192.4 (SEQ ID NO: 422)	INHBA Target Sequence (5' to 3')	SEQ ID NO:
227-245	AGGATGCCCTTGCTTTGGC	271
228-246	GGATGCCCTTGCTTTGGCT	272
237-255	TGCTTTGGCTGAGAGGATT	273
246-264	TGAGAGGATTTCTGTTGGC	274
250-268	AGGATTTCTGTTGGCAAGT	275
252-270	GATTTCTGTTGGCAAGTTG	276
260-278	TTGGCAAGTTGCTGGATTA	277
261-279	TGGCAAGTTGCTGGATTAT	278
262-280	GGCAAGTTGCTGGATTATA	279

264-282	CAAGTTGCTGGATTATAGT	280
267-285	GTTGCTGGATTATAGTGAG	281
272-290	TGGATTATAGTGAGGAGTT	282
273-291	GGATTATAGTGAGGAGTTC	283
489-507	TCAGAAAGCTTCATGTGGG	284
521-539	AACGGGTATGTGGAGATAG	285
522-540	ACGGGTATGTGGAGATAGA	286
523-541	CGGGTATGTGGAGATAGAG	287
525-543	GGTATGTGGAGATAGAGGA	288
582-600	AGCAGACCTCGGAGATCAT	289
728-746	ACCAGGACCAAAGTCACCA	290
1191-1209	GCTGTAAGAAACAGTTCCTT	291
1231-1249	CTGGAATGACTGGATCATT	292
1328-1346	TCCTTCCACTCAACAGTCA	293
1407-1425	CCACCAAGCTGAGACCCAT	294

* The target sequences contain Ts, but binding to RNA and/or DNA is contemplated.

[000373] In some embodiments, an oligonucleotide may comprise or consist of any sequence as provided in Table 12.

Table 12. Oligonucleotide sequences for targeting INHBA

Passenger Strand/Sense Strand (RNA) (5' to 3')	SEQ ID NO:	Guide Strand/Antisense Strand (RNA) (5' to 3')	SEQ ID NO:
CCAGGAUGCCCUUGCUUUGGC	295	GCCAAAGCAAGGGCAUCCUGGCA	319
CAGGAUGCCCUUGCUUUGGCU	296	AGCCAAAGCAAGGGCAUCCUGGC	320
CUUGCUUUGGCUGAGAGGAUU	297	AAUCCUCUCAGCCAAAGCAAGGG	321
GCUGAGAGGAUUUCUGUUGGC	298	GCCAAACAGAAAUCCUCUCAGCCA	322
AGAGGAUUUCUGUUGGCAAGU	299	ACUUGCCAAACAGAAAUCCUCUCA	323
AGGAUUUCUGUUGGCAAGUUG	300	CAACUUGCCAACAGAAAUCCUCU	324
UGUUGGCAAGUUGCUGGAUUA	301	UAAUCCAGCAACUUGCCAACAGA	325
GUUGGCAAGUUGCUGGAUUAU	302	AUAAUCCAGCAACUUGCCAACAG	326
UUGGCAAGUUGCUGGAUUAUA	303	UAUAAUCCAGCAACUUGCCAACA	327
GGCAAGUUGCUGGAUUAUAGU	304	ACUAUAAUCCAGCAACUUGCCAA	328
AAGUUGCUGGAUUAUAGUGAG	305	CUCACUAUAAUCCAGCAACUUGC	329
GCUGGAUUAUAGUGAGGAGUU	306	AACUCCUCACUAUAAUCCAGCAA	330
CUGGAUUAUAGUGAGGAGUUC	307	GAACUCCUCACUAUAAUCCAGCA	331
GAUCAGAAAGCUUCAUGUGGG	308	CCCACAUGAAGCUUUCUGAUCGC	332
AGAACGGGUAUGUGGAGAUAG	309	CUAUCUCCACAUACCCGUUCUCC	333
GAACGGGUAUGUGGAGAUAGA	310	UCUAUCUCCACAUACCCGUUCUC	334
AACGGGUAUGUGGAGAUAGAG	311	CUCUAUCUCCACAUACCCGUUCU	335
CGGGUAUGUGGAGAUAGAGGA	312	UCCUCUAUCUCCACAUACCCGUU	336
GGAGCAGACCUCGGAGAUCAU	313	AUGAUCUCCGAGGUCUGCUCCA	337
GGACCAGGACCAAAGUCACCA	314	UGGUGACUUUGGUCCUGGUCCUG	338
CUGCUGUAAGAAACAGUUCUU	315	AAGAACUGUUUCUUACAGCAGAU	339

GGCUGGAAUGACUGGAUCAUU	316	AAUGAUCCAGUCAUCCAGCCGA	340
UGUCCUCCACUCAACAGUCA	317	UGACUGUUGAGUGGAAGGACAGU	341
GCCACCAAGCUGAGACCAU	318	AUGGGUCUCAGCUUGGUGGGCAC	342

[000374] In some embodiments, an oligonucleotide is a modified oligonucleotide as provided in Table 13, wherein ‘mN’ represents a 2’-O-methyl modified nucleoside (*e.g.*, mU is 2’-O-methyl modified uridine), ‘fN’ represents a 2’-fluoro modified nucleoside (*e.g.*, fU is 2’-fluoro modified uridine), ‘*’ represents a phosphorothioate internucleoside linkage, and lack of “*” between nucleosides indicate phosphodiester internucleoside linkage.

Table 13. Modified Oligonucleotides for targeting INHBA

siRNA #	Modified Passenger Strand/Sense Strand (RNA) (5' to 3')	SEQ ID NO:	Modified Guide Strand/Antisense Strand (RNA) (5' to 3')	SEQ ID NO:
hsINHBA-4	mCmCfAmGfGmAfUmGfCmCfCmUfUmGfCmUfUmUfGmGfC	295	fGfCmCfAmAfAmGfCmAfAmGfGmGfCmAfUmCfCmUfGmG*fC*mA	319
hsINHBA-5	mCmAfGmGfAmUfGmCfCmCfUmUfGmCfUmUfUmGfGmCfU	296	fAfGmCfCmAfAmAfGmCfAmAfGmGfGmCfAmUfCmCfUmG*fG*mC	320
hsINHBA-6	mCmUfUmGfCmUfUmUfGmGfCmUfGmAfGmAfGmGfAmUfU	297	fAfAmUfCmCfUmCfUmCfAmGfCmCfAmAfAmGfCmAfAmG*fG*mG	321
hsINHBA-7	mGmCfUmGfAmGfAmGfGmAfUmUfUmCfUmGfUmUfGmGfC	298	fGfCmCfAmAfCmAfGmAfAmAfUmCfCmUfCmUfCmAfGmC*fC*mA	322
hsINHBA-8	mAmGfAmGfGmAfUmUfUmCfUmGfUmUfGmGfCmAfAmGfU	299	fAfCmUfUmGfCmCfAmAfCmAfGmAfAmAfUmCfCmUfCmU*fC*mA	323
hsINHBA-9	mAmGfGmAfUmUfUmCfUmGfUmUfGmGfCmAfAmGfUmUfG	300	fCfAmAfCmUfUmGfCmCfAmAfCmAfGmAfAmAfUmCfCmU*fC*mU	324
hsINHBA-10	mUmGfUmUfGmGfCmAfAmGfUmUfGmCfUmGfGmAfUmUfA	301	fUfAmAfUmCfCmAfGmCfAmAfCmUfUmGfCmCfAmAfCmA*fG*mA	325
hsINHBA-11	mGmUfUmGfGmCfAmAfGmUfUmGfCmUfGmGfAmUfUmAfU	302	fAfUmAfAmUfCmCfAmGfCmAfAmCfUmUfGmCfCmAfAmC*fA*mG	326
hsINHBA-12	mUmUfGmGfCmAfAmGfUmUfGmCfUmGfGmAfUmUfAmUfA	303	fUfAmUfAmAfUmCfCmAfGmCfAmAfCmUfUmGfCmCfAmA*fC*mA	327
hsINHBA-1	mGmGfCmAfAmGfUmUfGmCfUmGfGmAfUmUfAmUfAmGfU	304	fAfCmUfAmUfAmAfUmCfCmAfGmCfAmAfCmUfUmGfCmC*fA*mA	328
hsINHBA-2	mAmAfGmUfUmGfCmUfGmGfAmUfUmAfUmAfGmUfGmAfG	305	fCfUmCfAmCfUmAfUmAfAmUfCmCfAmGfCmAfAmCfUmU*fG*mC	329
hsINHBA-13	mGmCfUmGfGmAfUmUfAmUfAmGfUmGfAmGfGmAfGmUfU	306	fAfAmCfUmCfCmUfCmAfCmUfAmUfAmAfUmCfCmAfGmC*fA*mA	330
hsINHBA-14	mCmUfGmGfAmUfUmAfUmAfGmUfGmAfGmGfAmGfUmUfC	307	fGfAmAfCmUfCmCfUmCfAmCfUmAfUmAfAmUfCmCfAmG*fC*mA	331
hsINHBA-15	mGmAfUmCfAmGfAmAfAmGfCmUfUmCfAmUfGmUfGmGfG	308	fCfCmCfAmCfAmUfGmAfAmGfCmUfUmUfCmUfGmAfUmC*fG*mC	332

hsINHBA-16	mAmGfAmAfCmGfGmGfU mAfUmGfUmGfGmAfGmA fUmAfG	309	fCfUmAfUmCfUmCfCmAfCmAf UmAfCmCfCmGfUmUfCmU*fC *mC	333
hsINHBA-17	mGmAfAmCfGmGfGmUfA mUfGmUfGmGfAmGfAmU fAmGfA	310	fUfCmUfAmUfCmUfCmCfAmCf AmUfAmCfCmCfGmUfUmC*fU *mC	334
hsINHBA-18	mAmAfCmGfGmGfUmAfU mGfUmGfGmAfGmAfUmA fGmAfG	311	fCfUmCfUmAfUmCfUmCfCmAf CmAfUmAfCmCfCmGfUmU*fC *mU	335
hsINHBA-19	mCmGfGmGfUmAfUmGfU mGfGmAfGmAfUmAfGmA fGmGfA	312	fUfCmCfUmCfUmAfUmCfUmCf CmAfCmAfUmAfCmCfCmG*fU *mU	336
hsINHBA-20	mGmGfAmGfCmAfGmAfC mCfUmCfGmGfAmGfAmUf CmAfU	313	fAfUmGfAmUfCmUfCmCfGmAf GmGfUmCfUmGfCmUfCmC*fA *mU	337
hsINHBA-21	mGmGfAmCfCmAfGmGfA mCfCmAfAmAfGmUfCmAf CmCfA	314	fUfGmGfUmGfAmCfUmUfUmGf GmUfCmCfUmGfGmUfCmC*fU *mG	338
hsINHBA-3	mCmUfGmCfUmGfUmAfA mGfAmAfAmCfAmGfUmU fCmUfU	315	fAfAmGfAmAfCmUfGmUfUmUf CmUfUmAfCmAfGmCfAmG*fA *mU	339
hsINHBA-22	mGmGfCmUfGmGfAmAfU mGfAmCfUmGfGmAfUmCf AmUfU	316	fAfAmUfGmAfUmCfCmAfGmUf CmAfUmUfCmCfAmGfCmC*fG *mA	340
hsINHBA-23	mUmGfUmCfCmUfUmCfC mAfCmUfCmAfAmCfAmGf UmCfA	317	fUfGmAfCmUfGmUfUmGfAmGf UmGfGmAfAmGfGmAfCmA*fG *mU	341
hsINHBA-24	mGmCfCmCfAmCfCmAfA mGfCmUfGmAfGmAfCmCf CmAfU	318	fAfUmGfGmGfUmCfUmCfAmGf CmUfUmGfGmUfGmGfGmC*fA *mC	342

c. ACVR1B Oligonucleotides

[000375] In some embodiments, the oligonucleotide is an antisense oligonucleotide (ASO). In some embodiments, the oligonucleotide is a siRNA. In some embodiments, the oligonucleotide is a short hairpin RNA. In some embodiments, the oligonucleotide is a miRNA-based shRNA (e.g., a shRNA based on miR-24, miR-210, miR-199a-5p). In some embodiments, the oligonucleotide is a CRISPR guide RNA targeting ACVR1B. Examples of oligonucleotides useful for targeting ACVR1B are provided in Katoh M., “Cardio-miRNAs and onco-miRNAs: circulating miRNA-based diagnostics for non-cancerous and cancerous diseases.” Front Cell Dev Biol. 2014 Oct 16;2:61.; Mizuno, Y. et al. “miR-210 promotes osteoblastic differentiation through inhibition of AcvR1b.” FEBS Lett. 2009 Jul 7;583(13):2263-8.; Lin, H.S. et al., “miR-199a-5p inhibits monocyte/macrophage differentiation by targeting the activin A type 1B receptor gene and finally reducing C/EBP α expression.” J Leukoc Biol. 2014 Dec;96(6):1023-35.; International Patent Application Publication WO 2016/161477, entitled “A method of treating neoplasias”, filed on March 23, 2016; and U.S. Patent Application Publication US 2014/0088174, entitled “Compounds and methods for altering activin receptor-like kinase signaling”, published on Mar. 27, 2014; the contents of each of which are incorporated herein in their entireties.

[000376] In some embodiments, oligonucleotides may have a region of complementarity to a human ACVR1B sequence, for example, as provided below (Gene ID: 91; NCBI Ref. No: NM_004302.5):

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GGGCGCTGCTGGGCTGCGGCGGCGGCGGCGGCGGCGGTGGTTACTATGGCGGAGTCGGCCGGAG
CCTCCTCCTTCTTCCCCCTTGTTGTCCTCCTGCTCGCCGGCAGCGGCGGGTCCGGGCCCCGGGG
GGTCCAGGCTCTGCTGTGTGCGTGCACCAGCTGCCTCCAGGCCAACTACACGTGTGAGACAGAT
GGGGCCTGCATGGTTTCCATTTTCAATCTGGATGGGATGGAGCACCATGTGCGCACCTGCATCC
CCAAAGTGGAGCTGGTCCCTGCCGGGAAGCCCTTCTACTGCCTGAGCTCGGAGGACCTGCGCAA
CACCCACTGCTGCTACACTGACTACTGCAACAGGATCGACTTGAGGGGTGCCCAGTGGTCACCTC
AAGGAGCCTGAGCACCCGTCCATGTGGGGCCCCGGTGGAGCTGGTAGGCATCATCGCCGGCCCCG
TGTTCCTCCTGTTTCTCATCATCATCATTGTTTTCTTGTTCATTAATACTATCATCAGCGTGTCTA
TCACAACCGCCAGAGACTGGACATGGAAGATCCCTCATGTGAGATGTGTCTCTCCAAAGACAAG
ACGCTCCAGGATCTTGTCTACGATCTCTCCACCTCAGGGTCTGGCTCAGGGTTACCCCTCTTTG
TCCAGCGCACAGTGGCCCCGAACCATCGTTTTACAAGAGATTATTGGCAAGGGTCGGTTTGGGGA
AGTATGGCGGGGCCGCTGGAGGGGTGGTGTGCTGTGAAATATTCTCTTCTCGTGAAGAA
CGGTCTTGGTTCAGGGAAGCAGAGATATACCAGACGGTCATGCTGCGCCATGAAAACATCCTTG
GATTTATTGCTGCTGACAATAAAGATAATGGCACCTGGACACAGCTGTGGCTTGTCTTGACTA
TCATGAGCACGGGTCCCTGTTTGATTATCTGAACCGGTACACAGTGACAATTGAGGGGATGATT
AAGCTGGCCTTGTCTGCTGCTAGTGGGCTGGCACACCTGCACATGGAGATCGTGGGCACCCAAG
GGAAGCCTGGAATTGCTCATCGAGACTTAAAGTCAAAGAACATTCTGGTGAAGAAAAATGGCAT
GTGTGCCATAGCAGACCTGGGCCTGGCTGTCCGTCATGATGCAGTCACTGACACCATTGACATT
GCCCCGAATCAGAGGGTGGGGACCAAACGATACATGGCCCCTGAAGTACTTGATGAAACCATTA
ATATGAAACACTTTGACTCCTTTAAATGTGCTGATATTTATGCCCTCGGGCTTGTATATTGGGA
GATTGCTCGAAGATGCAATTCTGGAGGAGTCCATGAAGAATATCAGCTGCCATATTACGACTTA
GTGCCCTCTGACCCTTCCATTGAGGAAATGCGAAAGGTTGTATGTGATCAGAAGCTGCGTCCCA
ACATCCCCAACTGGTGGCAGAGTTATGAGGCACTGCGGGTGTGAGGGAAGATGATGCGAGAGTG
TTGGTATGCCAACGGCGCAGCCCGCCTGACGGCCCTGCGCATCAAGAAGACCCTCTCCCAGCTC
AGCGTGCAGGAAGACGTGAAGATCTAACTGCTCCCTCTCTCCACACGGAGCTCCTGGCAGCGAG
AACTACGCACAGCTGCCGCGTTGAGCGTACGATGGAGGCCTACCTCTCGTTTTCTGCCCAGCCCT
CTGTGGCCAGGAGCCCTGGCCCGCAAGAGGGACAGAGCCCGGGAGAGACTCGCTCACTCCCATG
TTGGGTTTGAGACAGACACCTTTTCTATTTACCTCCTAATGGCATGGAGACTCTGAGAGCGAAT
TGTGTGGAGAACTCAGTGCCACACCTCGAACTGGTTGTAGTGGGAAGTCCCGCGAAACCCGGTG
CATCTGGCACGTGGCCAGGAGCCATGACAGGGGCGCTTGGGAGGGGGCCGGAGGAACCGAGGTGT
TGCCAGTGCTAAGCTGCCCTGAGGGTTTCTTTCGGGGACCAGCCACAGCACACCAAGGTGGCC
CGGAAGAACCAGAAGTGCAGCCCTCTCACAGGCAGCTCTGAGCCGCGCTTTCCCCTCTCTCCT
GGGATGGACGCTGCCGGGAGACTGCCAGTGGAGACGGAATCTGCCGCTTTGTCTGTCCAGCCGT
GTGTGCATGTGCCGAGGTGCGTCCCCCGTTGTGCCTGGTTTCGTGCCATGCCCTTACACGTGCGT
GTGAGTGTGTGTGTGTGTCTGTAGGTGCGCACTTACCTGCTTGAGCTTTCTGTGCATGTGCAGG
TCGGGGGTGTGGTTCGTATGCTGTCCGTGCTTGTGGTGCCTCTTTTCACTAGTGAGCAGCATC
TAGTTTCCCTGGTGGCCTTCCCTGGAGGTCTCTCCCTCCCCCAGAGCCCTCATGCCACAGTGG
TACTCTGTGTCTGGCAGGCTACTCTGCCCACCCCAGCATCAGCACAGCTCTCCTCCTCCATCTC
AGACTGTGGAACCAAAGCTGGCCCAGTTGTCCATGACAAAAGAGGCTTTTGGGCCAAAATGTGA
GGGTGGTGGGTGGGATGGGCAGGGAAGGAATCCTGGTGGAAAGTCTTGGGTGTTAGTGTGAGCCA
TGGGAAATGAGCCAGCCCAAGGGCATCATCCTCAGCAGCATCGAGGAAGGGCCGAGGAATGTGA
AGCCAGATCTCGGGACTCAGATTGGAATGTTACATCTGTCTTTCATCTCCAGATCCTGGAAC
AGCAGTGTATATTTTTGGTGGTGGTGGGTTTGGGGTGGGGAAGGGAAGGGCGGGCAAGGAGTGG
GGAGGGAGTCTGGGGTGGGAGGGAGGCATCTGCATGGGTCTTCTTTTACTGGACTGTCTGATCA
GGGTGGAGGGAAGGTGAGAGGTTTGCATCCACTTCAGGAGCCCTACTGAAGGGAACAGCCTGAG
CCGAACATGTTATTTAACCTGAGTATAGTATTTAACGAAGCCTAGAAGCACGGCTGTGGGTGGT
GATTTGGTCAGCATATCTTAGGTATATAATAACTTTGAAGCCATAACTTTTAACTGGAGTGGTT
TGATTTCTTTTTTTAATTTTATTGGGAGGGTTTGGATTTTAACTTTTTTTAATGTTGTAAATA

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TTAAGTTTTTGTAAAAGGAAAACCATCTCTGTGATTACCTCTCAATCTATTTGTTTTTAAAGAA
 ATCCCTAAAAAATTATCCAATTGAACGCACATAGCTCAATCACACTGGAAATGTTTGTC
 CTTGCACCTGAGCCTGTTCCCACTCAGCAGTGAGAGTTCTCTTTGCCCTGAGGCTCAGTCTCT
 CTCGTATTTTGTCCCCACCCCAATTCTTGAGTGTTTTTGTCTCTAGGGCCCTTTCTTGCACT
 GTCCAGCTGGTTGTACCTCTCCAGGCATTTATTCAACAAATGTGGGTGAAGTGCCTGCTGGGT
 GCCAGGTGCTGGGAATACATCTGTGGACAAGACATGCTTGGGTCTACTCCTGGAGCACTGTAA
 AAAGAGCTGATTCAAGTAAGTAGATGCCTGTTTTGAGACCAGAAGGTTTCATAATTGGTTCTAC
 GACCCTTTTGAGCCTAGAATTATTGTTCTTATATAAGATCACTGAAGAAAGAGGAACCCCAACA
 ACCCCCTCCACAAAGAGACCAGGGGCGGGTGATGAGACCTGGGGTTTAGAACCCAGGTGAGAC
 CTAAATCACTGCATTCTGAGCCCCCTTCTGTCCCCAGGGGAGGTGTATTGTGTATGTA
 GCCTTAGAGCATCTCTGCCTCCAACCCAGCAGTTCTCTGCCAAAGCTTGTGGAGGAGGGAGAGC
 CCTGTCCCTGCCCTCAGGCTCCCCAGTGCTCCTGGCCCTTCTATTTATTTGACTGATTATTGCT
 TCTTTCCTTGCAATTAAAGGAGATCTTCCCCTAACCTTTGGGCCAATTTACTGGCCACTAATTC
 GTTTAAATACCATTGTGTCAATTGGGGGACCGTCTTTACCCCTGCTGACCTCCCACCTATCCGC
 CCTGCAGCAGAACCTTGGCGGTTTATAGGTAATGATGGAACCTTAGACTCCTCTTCCCAGAGTCA
 CAAGTAGCCTCTGGGATCTGCCAACACACGTCCACTCCCAAGCCACTAGCCCACTCCCCAGTTG
 GCCCTTCTGCCCTTACCCACACACAGTCCAACCTCTTCCACCTCTGGGGAAGATGGAGCAGGTC
 TTTGGGAAGCTCCCACACCCACCTCTGCCACTCTTAACACTAAGTGAGAGTTGGGGAGAACTG
 AAGCCGTGTTTTTGGCCCCCGAGGCTAACCTGATCCATAGTGCTACCTGCACCTCTGGATTCT
 TGGATTACAGACCAAGTCCAAGCCCGTTCTTACGTGCCATAAAGGCCCCCGAACGGCATTCT
 CGGTACTTCTGTTTGTGTGTGTACATTTTATTAGAAAGGACTGTAAATAGCCACTTAGACACT
 TTACCTCTTCAGTATGCAAATGTAAATAAATTGTAATATAGGAAATCTTTTGTTTTAAATATAAG
 AATGAGCCTGTCCAATTTCTGCTGTACATTATTAAGTTTTTATTACAGA (SEQ ID NO: 367).

[000377] In some embodiments, oligonucleotides may have a region of complementarity to a human ACVR1B sequence, for example, as provided below (Gene ID: 91; NCBI Ref. No: NM_020328.4):

GGGCGCTGCTGGGCTGCGGCGGCGGCGGCGGCGGCGGTGTTACTATGGCGGAGTCGGCCGGAG
 CCTCCTCCTTCTTCCCCCTTGTGTCTCCTGCTCGCCGGCAGCGGCGGGTCCGGGCCCGGGG
 GGTCCAGGCTCTGCTGTGTGCGTGACACAGCTGCCTCCAGGCCAACTACACGTGTGAGACAGAT
 GGGGCTGCAATGGTTTCCATTTTCAATCTGGATGGGATGGAGCACCATGTGCGCACCTGCATCC
 CCAAAGTGGAGCTGGTCCCTGCCGGGAAGCCCTTCTACTGCCTGAGCTCGGAGGACCTGCGCAA
 CACCCACTGCTGCTACACTGACTACTGCAACAGGATCGACTTGAGGGTGCCAGTGGTCACCTC
 AAGGAGCCTGAGCACCCGTCCATGTGGGGCCCGGTGGAGCTGGTAGGCATCATCGCCGGCCCGG
 TGTTCTCCTGTTCCTCATCATCATCATTTGTTTTCTTGTTCATTAATCATCAGCGTGTCTA
 TCACAACCGCCAGAGACTGGACATGGAAGATCCCTCATGTGAGATGTGTCTCTCAAAGACAAG
 ACGCTCCAGGATCTTGTCTACGATCTCTCCACCTCAGGGTCTGGCTCAGGGTTACCCCTCTTTG
 TCCAGCGCACAGTGGCCCGAACCATCGTTTTACAAGAGATTATTGGCAAGGGTCGGTTTGGGGA
 AGTATGGCGGGGCCGCTGGAGGGGTGGTGATGTGGCTGTGAAAATATTCTCTCTCGTGAAGAA
 CGGTCTTGGTTCAGGGAAGCAGAGATATAACCAGACGGTCATGCTGCGCCATGAAAACATCCTTG
 GATTTATTGCTGCTGACAATAAAGCAGACTGCTCATTCCCTCACATTGCCATGGGAAGTTGTAAT
 GGTCTCTGCTGCCCCCAAGCTGAGGAGCCTTAGACTCCAATACAAGGGAGGAAGGGGAAGAGCA
 AGATTTTTTATTCCCACTGAATAATGGCACCTGGACACAGCTGTGGCTTGTCTGACTATCATG
 AGCACGGGTCCCTGTTTGATTATCTGAACCGGTACACAGTGACAATTGAGGGGATGATTAAGCT
 GGCCTTGTCTGCTGCTAGTGGGCTGGCACACCTGCACATGGAGATCGTGGGCACCCAAGGGAAG
 CCTGGAATTGCTCATCGAGACTTAAAGTCAAAGAACATTCTGGTGAAGAAAAATGGCATGTGTG
 CCATAGCAGACCTGGGCCTGGCTGTCCGTCATGATGCAGTCACTGACACCATTGACATTGCCCC
 GAATCAGAGGGTGGGGACCAAACGATACATGGCCCTGAAGTACTTGATGAAACCATTAATATG
 AAACACTTTGACTCCTTTAAATGTGCTGATATTTATGCCCTCGGGCTTGTATATTGGGAGATTG
 CTCGAAGATGCAATTCTGGAGGAGTCCATGAAGAATATCAGCTGCCATATTACGACTTAGTGCC
 CTCTGACCCTTCCATTGAGGAAATGCGAAAGGTTGTATGTGATCAGAAGCTGCGTCCCAACATC

CCCAACTGGTGGCAGAGTTATGAGGCACTGCGGGTGATGGGGAAGATGATGCGAGAGTGTTGGT
ATGCCAACGGCGCAGCCCGCCTGACGGCCCTGCGCATCAAGAAGACCCTCTCCCAGCTCAGCGT
GCAGGAAGACGTGAAGATCTAACTGCTCCCTCTCTCCACACGGAGCTCCTGGCAGCGAGAACTA
CGCACAGCTGCCGCGTTGAGCGTACGATGGAGGCCTACCTCTCGTTTTCTGCCCAGCCCTCTGTG
GCCAGGAGCCCTGGCCCGCAAGAGGGACAGAGCCCGGGAGAGACTCGCTCACTCCCATGTTGGG
TTTGAGACAGACACCTTTTCTATTTACCTCCTAATGGCATGGAGACTCTGAGAGCGAATTGTGT
GGAGAACTCAGTGCCACACCTCGAACTGGTTGTAGTGGGAAGTCCCGCGAAACCCGGTGATCT
GGCACGTGGCCAGGAGCCATGACAGGGGCGCTTGGGAGGGGGCCGGAGGAACCGAGGTGTTGCCA
GTGCTAAGCTGCCCTGAGGGTTTCCTTCGGGGACCAGCCACAGCACACCAAGGTGGCCCGGAA
GAACCAGAAGTGACAGCCCTCTCACAGGCAGCTCTGAGCCGCGCTTTCCCCTCCTCCCTGGGAT
GGACGCTGCCGGGAGACTGCCAGTGGAGACGGAATCTGCCGCTTTGTCTGTCCAGCCGTGTGTG
CATGTGCCGAGGTGCGTCCCCCGTTGTGCCTGGTTTCGTGCCATGCCCTTACACGTGCGTGTGAG
TGTGTGTGTGTGTCTGTAGGTGCGCACTTACCTGCTTGAGCTTTCTGTGCATGTGCAGGTCGGG
GGTGTGGTCGTATGCTGTCCGTGCTTGTGGTGCCTCTTTTCAGTAGTGAGCAGCATCTAGTT
TCCCTGGTGCCCTTCCCTGGAGGTCTCTCCCTCCCCCAGAGCCCTCATGCCACAGTGGTACTC
TGTGTCTGGCAGGCTACTCTGCCCACCCCAGCATCAGCACAGCTCTCCTCCTCCATCTCAGACT
GTGGAACCAAAGCTGGCCCAAGTTGTCCATGACAAAAGAGGCTTTTGGGCCAAAATGTGAGGGTG
GTGGGTGGGATGGGCAGGGAAGGAATCCTGGTGGAAAGTCTTGGGTGTTAGTGTGAGCCATGGGA
AATGAGCCAGCCCAAGGGCATCATCCTCAGCAGCATCGAGGAAGGGCCGAGGAATGTGAAGCCA
GATCTCGGGACTCAGATTGGAATGTTACATCTGTCTTTTCATCTCCAGATCCTGGAAACAGCAG
TGTATATTTTTGGTGGTGGTGGGTTTGGGGTGGGGAAGGGAAGGGCGGGCAAGGAGTGGGGAGG
GAGTCTGGGGTGGGAGGGAGGCATCTGCATGGGTCTTCTTTTACTGGACTGTCTGATCAGGGTG
GAGGGAAGGTGAGAGGTTTGCATCCACTTCAGGAGCCCTACTGAAGGGAACAGCCTGAGCCGAA
CATGTTATTTAACCCTGAGTATAGTATTTAACGAAGCCTAGAAGCACGGCTGTGGGTGGTGATTT
GGTCAGCATATCTTAGGTATATAATAACTTTGAAGCCATAACTTTTAACTGGAGTGGTTTGATT
TCTTTTTTTTAAATTTTATTGGGAGGGTTTGGATTTTTAACTTTTTTTTAAATGTTGTAAATATTAAG
TTTTTTGTAAAGGAAAACCATCTCTGTGATTACCTCTCAATCTATTTGTTTTTAAAGAAATCCC
TAAAAAAAAAAATTATCCAATTGAACGCACATAGCTCAATCACACTGGAAATGTTTGTCTTGC
ACCTGAGCCTGTTCCCACTCAGCAGTGAGAGTTCTCTTTGCCCTGAGGCTCAGTCTCTCTCGT
ATTTTGTCCCCACCCCCAATTCTTGGAGTGGTTTTTGTCTTAGGGCCCTTTCTTGCAGTGTCCA
GCTGGTTGTACCCTCTCCAGGCATTTATTCAACAAATGTGGGTGAAGTGCCTGCTGGGTGCCAG
GTGCTGGGAATACATCTGTGGACAAGACATGCTTGGGTCTACTCCTGGAGCACTGTAAAAAGA
GCTGATTCAAGTAAGTAGATGCCTGTTTTTGAGACCAGAAGGTTTTCATAATTGGTTCTACGACCC
TTTTGAGCCTAGAATTATTGTTCTTATATAAGATCACTGAAGAAAGAGGAACCCCCACAACCCC
CTCCACAAAGAGACCAGGGGCGGGTGATGAGACCTGGGGTTTAGAACCCCAGGTGAGACCTCAA
ATCACTGCATTCAATTCTGAGCCCCCTTCTGTCCCCAGGGGAGGTGTATTGTGTATGTAGCCTT
AGAGCATCTCTGCCTCCAACCCAGCAGTTCTCTGCCAAAGCTTGTGGAGGAGGGAGAGCCCTGT
CCCTGCCCTCAGGCTCCCCAGTGCTCCTGGCCCTTCTATTTATTTGACTGATTATTGCTTCTTT
CCTTGCATTAAAGGAGATCTTCCCCTAACCTTTGGGCCAATTTACTGGCCACTAATTTTCGTTTA
AATACCATTGTGTCAATTGGGGGGACCGTCTTTACCCCTGCTGACCTCCCACCTATCCGCCCTGC
AGCAGAACCTTGGCGGTTTATAGGTAAATGATGGAACCTTAGACTCCTCTTCCCAGAGTCACAAGT
AGCCTCTGGGATCTGCCAACACACGTCCACTCCCAAGCCACTAGCCCACTCCCCAGTTGGCCCT
TCTGCCCTTACCCACACACAGTCCAACCTCTTCCACCTCTGGGGAAGATGGAGCAGGTCTTTGG
GAAGCTCCCACACCCACCTCTGCCACTCTTAACACTAAGTGAGAGTTGGGGAGAACTGAAGCC
GTGTTTTTGGCCCCCGAGGCTAACCCCTGATCCATAGTGCTACCTGCACCTCTGGATTCTGGAT
TCACAGACCAAGTCCAAGCCCGTTCTTACGTGCGCATAAAGGCCCCCGAACGGCATTCTCGGTGA
CTTCTGTTTTGTTTTTGTACATTTTATTAGAAAGGACTGTAAAATAGCCACTTAGACACTTTACC
TCTTCAGTATGCAAATGTAAATAAATTGTAATATAGGAAATCTTTTGTTTTAAATATAAGAATGA
GCCTGTCCAATTTCTGCTGTACATTATTAAGTTTATTTCACAGA (SEQ ID NO: 368).

[000378] In some embodiments, oligonucleotides may have a region of complementarity to a mouse ACVR1 sequence, for example, as provided below (Gene ID: 11479; NCBI Ref. No: NM_007395.4)

GAGGGAGGGAGGGAGAGAGGGCGCCGGGGGCGCGCGCGCGCTGGGCGCTGCTGGGCTGCGGCG
GCGGTTACTATGGCGGAGTCGGCCGGAGCCTCCTCCTTCTTCCCCCTTGTTGTCCTCCTGCTCG
CCGGCAGCGGCGGGTCCGGGCCCCGGGGGATCCAGGCTCTGCTGTGTGCGTGCACCAGCTGCCT
ACAGACCAACTACACCTGTGAGACAGATGGGGCTTGCATGGTCTCCATCTTTAACCTGGATGGC
GTGGAGCACCATGTACGTACCTGCATCCCCAAGGTGGAGCTGGTTCCCTGCTGGAAAGCCCTTCT
ACTGCCTGAGTTTCAAGAGGATCTGCGCAACACACACTGCTGCTATATTGACTTCTGCAACAAGAT
TGACCTCAGGGTCCCCAGCGGACACCTCAAGGAGCCTGCGCACCCCTCCATGTGGGGCCCTGTG
GAGCTGGTTCGGCATCATCGCCGGCCCCGTCTTCTCCTCTTCCCTTATCATTATCATCGTCTTCC
TGGTCATCAACTATCACCAGCGTGTCTACCATAACCGCCAGAGGTTGGACATGGAGGACCCCTC
TTGCGAGATGTGTCTCTCCAAAGACAAGACGCTCCAGGATCTCGTCTACGACCTCTCCACGTCA
GGGTCTGGCTCAGGGTTACCCCTTTTTTGTCCAGCGCACAGTGGCCCGAACCATTGTTTTACAAG
AGATTATCGGCAAGGGCCGGTTCGGGGAAGTATGGCGTGGTTCGCTGGAGGGGTGGTGACGTGGC
TGTGAAAATCTTCTCTTCTCGTGAAGAACGGTCTTGGTTCCGTGAAGCAGAGATCTACCAGACC
GTCATGCTGCGCCATGAAAACATCCTTGGCTTTATTGCTGCTGACAATAAAGATAATGGCACCT
GGACCCAGCTGTGGCTTGTCTCTGACTATCACGAGCATGGCTCACTGTTTGATTATCTGAACCG
CTACACAGTGACCATTGAGGGAATGATTAAGCTAGCCTTGTCTGCAGCCAGTGGTTTGGCACAC
CTGCATATGGAGATTGTGGGCACTCAAGGGAAGCCGGGAATTGCTCATCGAGACTTGAAGTCAA
AGAACATCCTGGTGAAAAAAATGGCATGTGTGCCATTGCAGACCTGGGCCTGGCTGTCCGTCA
TGATGCGGTCACTGACACCATAGACATTGCTCCAAATCAGAGGGTGGGGACCAAACGATACATG
GCTCCTGAAGTCCTTGACGAGACAATCAACATGAAGCACTTTGACTCCTTCAAATGTGCCGACA
TCTATGCCCTCGGGCTTGTCTACTGGGAGATTGCACGAAGATGCAATTCTGGAGGAGTCCATGA
AGACTATCAACTGCCGTATTACGACTTAGTGCCCTCCGACCCTTCCATTGAGGAGATGCGAAAG
GTTGTATGTGACCAGAAGCTACGGCCCAATGTCCCCAACTGGTGGCAGAGTTATGAGGCCTTGC
GAGTGATGGGAAAGATGATGCGGGAGTGCTGGTACGCCAATGGTGTCTGCCCGTCTGACAGCTCT
GCGCATCAAGAAGACTCTGTCCCAGCTAAGCGTGCAGGAAGATGTGAAGATTTAAGCTGTTTCT
CTGCCTACACAAAGAACCTGGGCAGTGAGGATGACTGCAGCCACCGTGCAAGCGTCGTGGAGGC
CTACCTCTTGTTTTCTGCCCCGCCCTCTGGCCAGAGCCCTGGCCTGCAAGAGGGACAGAGCCTGG
GAGACGCGCACTCCCGTTGGGTTTGAGACAGACACTTTTTATATTTACCTCCTGATGGCATGGA
GACTCTGAGCAAATCATGTAGACAACTCAATGCCACAACCTCAAACCTGCTTGACGTGGGAAGTAC
AGAGAGCCCAGTGCATCTGGCGTGTGTCAGGAGCGGTGAAGGGTGTGGGCTCGCCCAGGAGC
GGCCCCCATACTTGTGGTCCACTGGGCTGCAGGTTTTTCTCCAGGGACCAGTCAACTGGCATC
AAGATATTGAGAGGAACCGGAAGTTTCTCCTCCTTCCCGTAGGCAGTCTTGAGCCACACCAT
CCCTTCTCATGGACATCCGGAGGGACTGCCCTAGAGACACAACCTGCTGCCTGTCTGTCCAGC
CAAGTGCGCATGTGCCGAGGTGTGTCCACATTGTGCCTGGTCTGTGCCACGCCCGTGTGTGTG
TGTGTGTGTGTGAGTGAGTGTGTGTGTGTACACTTAACCTGCTTGAGCTTTCTGTGCATGTGTA
GGCCAGGGTGTGGTGGCCATACTGTCTCTGAGTGCTGCTGCTTCTCAGTGAGCAGCATGTAGTT
AACCTGGTGCCCTCCTAGGTGTCTCCTGTCCCCAGACCCCATCAGTCAGGGAGGTTCTGTCTTC
TCAGCAGGCTGCTTGCCACCCTGTGTACAGGCCCTCCTCTTCCATTTTACAGACCAGAACCAAA
GCTGGCCCACTTGTCCATGGTAGGAGAAGCTTTTGGGTCAAATGAGGGGGACTTGATGAGCAG
AGAGAGAATGTAGGTGGAAGTCTTGGGTGCTGTGTTTACGCATCAGCCATGGGAAATGAGCCAG
CCCAAGGGCATCTTCTTGGACAGCTGTGAGGAAGGGCCGAGGAATCCGAAGCCAGAGCTTGGGA
CTCAGATTGGAATGTAACATCTGTTTATGTCCCACCCAGATTCTGCAAACCTGCAGTGTATATT
TTTGGTGGTGGGTTTGGGGTGGGAAGGGATGGGTTGCAGGGCGTGGGGAGGGAGGCTGGGGTGG
GAGGGAGGCATCTGCATGGGCTTCTTGTACTGGATTCTCTGATCAGGGTAGAGAAGAGGCAAGG
CTTGCACTCCACTTCAGGGTCCCTACTGAGGAGAGTGAGCGGTCCGAGCTGAATATGGTGTTTAA
CCTAAGTTTAGTATTTAATGAATTCTAGAAGCCTGGCTGTGGGTGGTGATTTGGTCAGCATATC
TTAGGTATATAATAACTTTGAAGCCATAACTTTTTAACTGGAGTGTTTATTTTAATTCAGTTT
ATTTTATTTTATTTTGGGGGGAGGGTCAGGATTTTAACTTTAATATTGTAAAGTTTGTAAAAG

GAGAACCATCTCTGTGACAATTACCTCTTAGTCTGTTTGTGTTTTTAAAGAAATCCCTAAAACAAA
CAAAACACAAAAATTCTCCAGACTCAAACGCACATAGTTCAGTCACTGGAAACGCTTGTCTTTG
CACCTGAGCCTGATCCCGCTGAGCAGTGAGGGCTGCTTTTCCCATGGGGGCTTGCTGTCTCGT
ACTCCCTGCACCCTCGGCCCATCCCGTGAGCACCTCGGCCCTCTGCACATTGCCCGGCTGGTT
GGACCCTTTCCAGATACTTGCTCAGCAAATGTGGGCTGCGAGCCTGCTGAGCGCTGGCCCGGGA
GGATCTCCTCAGGGTGGGGCAGGCTTGGGCGCTGCTCTGCTCCTCTACCACTGGAGGGAATGGA
ATCATGCGATGGGCGAGCACCTGCTGTGGAGACCAGAAGTGCTCATGGCTGGTCCTGAGAGCCT
TGATGAGCTAGGATCACTGTTCTTAAAGACCACTGAAACTGGAAGGGGGACCTGTATCCCTTG
GGAAGAGAAGCCCCTGGCAAGCAGTGGGTCCTGGAGACTGGGTTCAATTGTGAGCCTTTCCTGCC
AGGGGAGGCATGAGTCTTTGCAGGGAACTGTCTCCTCCAGCTTCTCCTGCCTTGGTCTCCCCA
TATTCTTAGCCTTTCTATTTATTTCTGGTGTATAACTTTCCTTGCTTTAAAGGGATCTTCCTT
TAATTCCTTGGGCCAATTTACTGGCCATTGAACAGTGTCCCTTGAGTCCCAACTGTGTCTCTGG
GGAACCTCCTTACCCACCCCTGCTGACCTCCCACTTCCCACCCTGCAGCTGAGTATCCGTGATT
ACAGGCGATTGAACTGTAGAGTCTCTGCTGTACCTGCCAGCAGCAGCCTCACAGTGAC
CCCCACGCCACTGGACAACCTCCAGGAGACCTGTGCGCTCCGTGCAGCTCAGCTCAGCCGCCCTC
TCAGGAAGCCTGGAGCAGGTCTGGGGGACCCCCCCCCCATCACTCTTTACATTAAGCTGAGAGT
TGGGAGAAGCTGTGCTTTGGCTCCCTGAGGCCACCCTGATCCACGGGGCACCCGCACCTCTGCG
TTCTGGATTACAGACCAAGTCTAAAGCCCGTTTCGTTCTGAGTTGCCGTCAAGGCCCTGAAC
GGTACTCTCGGTACTTCTGTTTGTGTTTTTGTACAATTTATTAGAAAGGACTGTAAAATAGCCAC
TTAGACACTTTACCTCTCCAGTATGCAAATGTAAATATATTGTAATATAGGAAATTTTTGTTTT
AATATAAGAATGAGCCTGTCCAGTTTCTGCTGTACATTATTAAAGTTTTATTACAGAACTAAA
AAAAAAAAAAAAAAAAAAAAA (SEQ ID NO: 369).

[000379] In some embodiments, oligonucleotides may have a region of complementarity to a rat ACVR1 sequence, for example, as provided below (Gene ID: 29381; NCBI Ref. No: NM_199230.1)

GGCGGCGGTTACTATGGCGGAGTCGGCCGGAGCCTCCTCCTTCTTCCCCCTTGTTGTCTCCTG
CTCGCCGGCAGTGGCGGGTCCGGGCCCCGGGGGATCCAGGCTCTGCTGTGTGCATGCACCAGCT
GCCTACAGACCAACTACACCTGCGAAACAGATGGGGCCTGCATGGTCTCCATCTTTAACCTGGA
TGGCATGGAGCACCACGTACGCACCTGCATCCCCAAGGTGGAGCTTGTGCCTGCTGGGAAGCCC
TTCTACTGCCTGAGTTTACAGAGACCTGCGCAACACGCACTGCTGCTATATTGACTTCTGCAACA
AGATTGACCTGAGGGTGGCCAGTGGACACCTCAAGGAGCCTGAGCACCCCTCCATGTGGGGCCC
TGTGGAGCTGGTCGGCATCATTGCCGGTCTGTCTTCTCCTCCTTCTCCTCATCATCATCATCGTC
TTCCTGGTCACTCAACTATCATCAGCGTGTCTACCACAACCGCCAAAGACTGGACATGGAGGACC
CCTCATGTGAGATGTGTCTCTCCAAAGACAAGACGCTCCAGGATCTCGTCTACGATCTCTCCAC
TTCAGGATCGGGCTCAGGGTTACCCCTTTTTGTCCAGCGCACAGTGGCCCGAACCATTGTTTTA
CAAGAGATTATCGGCAAGGGCCGGTTTGGGGAAGTATGGCGTGGCCGCTGGAGGGGTGGTGATG
TGGCTGTGAAAATCTTCTCTTCCCGTGAAGAGCGGTCTGTGGTTCCGGGAGGCAGAGATCTACCA
GACTGTCTATGCTGCGCCATGAAAACATCCTTGGGTTTATTGCTGCTGACAATAAAGACAATGGC
ACCTGGACCCAGCTGTGGCTTGTCTCTGACTATCACGAGCACGGCTCACTGTTTCGATTATCTGA
ACCGCTACACAGTGACCATTGAGGGGATGATTAAACTGGCCCTGTCTGCAGCCAGTGGTTTTGGC
ACACCTGCATATGGAGATTGTGGGCACTCAGGGGAAGCCTGGAATTGCTCATCGAGACTTGAAG
TCAAAGAACATTCTGGTGAAGAAGAATGGCATGTGTGCCATTGCAGACCTGGGCCTAGCTGTCC
GTCACGATGCTGTCACTGACACCATAGACATTGCTCCAAATCAGAGGGTGGGAACCAAACGATA
CATGGCTCCTGAAGTACTTGACGAGACCATCAACATGAAGCACTTTGACTCCTTCAAGTGTGCC
GATATCTACGCCCTCGGGCTTGTCTATTGGGAGATTGCTCGGAGGTGCAATTCTGGAGGAGTCC
ATGAAGAGTATCAACTGCCATATTATGATTTAGTGCCCTCTGACCCTTCCATTGAGGAAATGCG
AAAGGTCGTCTGTGACCAGAAGCTACGGCCCAATGTCCCCAACTGGTGGCAGAGTTATGAGGCC
TTGCGAGTGATGGGGAAGATGATGCGGGAGTGCTGGTACGCCAATGGTGCTGCCCGCCTGACAG
CGCTGCGCATCAAGAAGACTTTGTCCCAGCTAAGCGTGCAGGAAGACGTGAAGATTTAAGCTGT
TCCTCTGCCTACGCAAAGAACCTGGGCAGTGAGGATGCCTGCAGCCACCGTGCAAGCGTGGAGG

CCTACCTCTTGTCTTCTGCCCAGCCCTCTGGCCAGAGCCCTGGTCTGCAAGAGGGACAGAGCCTG
 GGAGACGCACACTCCCTACTGGGTTTGAGACAGACACTTTTTATATTTACCTCCTGATGGCATG
 GAGACTCTGAGAGCAAATCATGTAGATGACTCGATGCCACAACCTCGCACTGCGTGCGTGGGAA
 GGACAGAAAGCCCAGTGCATCTGGCATGTTGCCAGGAGTGGTGTATGGGTGCTGGGCTCGCCTGG
 GAGCAGCCCCCATAACCGTGTGTCCACTGGACTGCAGGTTTCCTCCAGGGACCAGTCAACTGGC
 AGATACTGAGAGGAACCGGAAGTGTCCCTCCCTTTTACCTGTGGGCAGTCCCTGAGCCACGCCATC
 CCCTTCTCATCTGGAGGACCGCCCCCTAGAGACACAACCTGCTGCCTGTCTGTCCAGCCAAGTGC
 GCATGTGCCGAGGTGTGTCTCACATTGTGCCTGGTCCGTGCCTCGCCCGTGTGTGTGTGTGTGT
 GTGTGTGTATGTGTGTGTGTAGGTGTGTGTGAGTGTGTGTGTAGTGTAGGTGTGTGAGAGTGT
 GTGTGTAGGTGTGTGAGTGTGGGTGTGTGAGAGTGTGTGTAGGTGTATGTGAGTGTGTAAGTGT
 GTGTAGGTGTGTGAGTGTGTAGGTGTGTGAGTGTG (SEQ ID NO: 370)

[000380] In some embodiments, the oligonucleotide may have a region of complementarity to a mutant form of ACVR1B, for example as reported in Su, G.H. et al. *Proc Natl Acad Sci U S A*. 2001 Mar 13; 98(6): 3254–3257., the contents of which are incorporated herein by reference in their entirety.

[000381] In some embodiments, an oligonucleotide comprises a region of complementarity to an ACVR1B sequence as set forth in SEQ ID NO: 367, SEQ ID NO: 368, SEQ ID NO: 369, or SEQ ID NO: 370. In some embodiments, the oligonucleotide comprises a region of complementarity that is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to an ACVR1B sequence as set forth in SEQ ID NO: 367, SEQ ID NO: 368, SEQ ID NO: 369, or SEQ ID NO: 370. In some embodiments, the oligonucleotide comprises a sequence that has at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides that are perfectly complementary to an ACVR1B sequence as set forth in SEQ ID NO: 367, SEQ ID NO: 368, SEQ ID NO: 369, or SEQ ID NO: 370. In some embodiments, an oligonucleotide may comprise a sequence that targets (*e.g.*, is complementary to) an RNA version (*i.e.*, wherein the T's are replaced with U's) of an ACVR1B sequence as set forth in SEQ ID NO: 367, SEQ ID NO: 368, SEQ ID NO: 369, or SEQ ID NO: 370. In some embodiments, the oligonucleotide comprises a sequence that is complementary (*e.g.*, at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% complementary) to an RNA version of an ACVR1B sequence as set forth in SEQ ID NO: 367, SEQ ID NO: 368, SEQ ID NO: 369, or SEQ ID NO: 370. In some embodiments, the oligonucleotide comprises a sequence that has at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides that are perfectly complementary to an RNA version of an ACVR1B sequence as set forth in SEQ ID NO: 367, SEQ ID NO: 368, SEQ ID NO: 369, or SEQ ID NO: 370.

[000382] In some embodiments, an ACVR1B-targeting oligonucleotide comprises an antisense strand that comprises at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides of a sequence comprising any one of SEQ ID NOs: 343-366. In some embodiments, an ACVR1B-targeting oligonucleotide comprises an antisense strand that comprises any one of

SEQ ID NO: 343-366. In some embodiments, an oligonucleotide comprises an antisense strand that comprises shares at least 70%, 75%, 80%, 85%, 90%, 95%, or 97% sequence identity with at least 12 or at least 15 consecutive nucleotides of any one of SEQ ID NOs: 343-366.

[000383] In some embodiments, an ACVR1B-targeting oligonucleotide comprises an antisense strand that targets an ACVR1B sequence comprising any one of SEQ ID NO: . In some embodiments, an oligonucleotide comprises an antisense strand comprising at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 nucleotides (*e.g.*, consecutive nucleotides) that are complementary to an ACVR1B sequence comprising any one of SEQ ID NO: 221-268. In some embodiments, an ACVR1B-targeting oligonucleotide comprises an antisense strand comprising a sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, or 97% complementary with at least 12 or at least 15 consecutive nucleotides of any one of SEQ ID NO: 221-268.

[000384] In some embodiments, an ACVR1B-targeting oligonucleotide comprises an antisense strand that comprises a region of complementarity to a target sequence as set forth in any one of SEQ ID NOs: 221-268. In some embodiments, the region of complementarity is at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or at least 19 nucleotides in length. In some embodiments, the region of complementarity is 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 nucleotides in length. In some embodiments, the region of complementarity is in the range of 8 to 20, 10 to 20 or 15 to 20 nucleotides in length. In some embodiments, the region of complementarity is fully complementary with all or a portion of its target sequence. In some embodiments, the region of complementarity includes 1, 2, 3 or more mismatches.

[000385] In some embodiments, an ACVR1B-targeting oligonucleotide further comprises a sense strand that hybridizes to the antisense strand to form a double stranded siRNA. In some embodiments, the ACVR1B-targeting oligonucleotide comprises an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 343-366. In some embodiments, the ACVR1B-targeting oligonucleotide further comprises a sense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 245-268 .

[000386] In some embodiments, the ACVR1B-targeting oligonucleotide is a double stranded oligonucleotide (*e.g.*, an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 343-366 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 245-268 , wherein the antisense strand and/or (*e.g.*, and) comprises one or more modified nucleosides (*e.g.*, 2'-modified nucleosides). In some embodiment, the one or more modified nucleosides are selected from 2'-O-Me and 2'-F modified nucleosides.

[000387] In some embodiments, the ACVR1B-targeting oligonucleotide is a double stranded oligonucleotide (e.g., an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 343-366 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 245-268, wherein each nucleoside in the antisense strand and/or (e.g., and) each nucleoside in the sense strand is a 2'-modified nucleoside selected from 2'-O-Me and 2'-F modified nucleosides.

[000388] In some embodiments, the ACVR1B-targeting oligonucleotide is a double stranded oligonucleotide (e.g., an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 343-366 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 245-268, wherein each nucleoside in the antisense strand and each nucleoside in the sense strand is a 2'-modified nucleoside selected from 2'-O-Me and 2'-F modified nucleosides, and wherein the antisense strand and/or (e.g., and) the sense strand each comprises one or more phosphorothioate internucleoside linkages. In some embodiments, the sense strand does not comprise any phosphorothioate internucleoside linkages (all the internucleoside linkages in the sense strand are phosphodiester internucleoside linkages), and the antisense strand comprises 1, 2, or 3 phosphorothioate internucleoside linkages. In some embodiments, the antisense strand comprises 2 phosphorothioate internucleoside linkages, optionally wherein the two internucleoside linkages at the 3' end of the antisense strand are phosphorothioate internucleoside linkages and the rest of the internucleoside linkages in the antisense strand are phosphodiester internucleoside linkages.

[000389] In some embodiments, the antisense strand of the ACVR1B-targeting oligonucleotide comprises a structure of (5' to 3'):

fNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmN*fN*mN, wherein “mN” indicates 2'-O-methyl (2'-O-Me) modified nucleosides; “fN” indicates 2'-fluoro (2'-F) modified nucleosides; “*” indicates a phosphorothioate internucleoside linkage; and the absence of “*” between two nucleosides indicates a phosphodiester internucleoside linkage.

[000390] In some embodiments, the sense strand of the ACVR1B-targeting oligonucleotide comprises a structure of (5' to 3'):

mNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfN, wherein “mN” indicates 2'-O-methyl (2'-O-Me) modified nucleosides; “fN” indicates 2'-fluoro (2'-F) modified nucleosides; and the absence of “*” between two nucleosides indicates a phosphodiester internucleoside linkage.

[000391] In some embodiments, the antisense strand of the ACVR1B-targeting oligonucleotide is selected from the modified version of SEQ ID NOs: 343-366 listed in Table

16. In some embodiments, the sense strand of the ACVR1B-targeting oligonucleotide is selected from the modified version of SEQ ID NOs: 245-268 listed in Table 16. In some embodiments, the ACVR1B-targeting oligonucleotide is an siRNA selected from the siRNAs listed in Table 16.

Table 14. ACVR1B Target Sequences

Reference sequence	Corresponding nucleotides of Reference Sequence	ACVR1B Target Sequence (5' to 3')	SEQ ID NO:
NM_004302.5 (SEQ ID NO: 367)	572-591	ACAAGACGCTCCAGGATCT	221
NM_004302.5 (SEQ ID NO: 367)	1034-1053	GAATTGCTCATCGAGACTT	222
NM_004302.5 (SEQ ID NO: 367)	1418-1437	ACTGGTGGCAGAGTTATGA	223
NM_004302.5 (SEQ ID NO: 367)	1294-1313	TGCAATTCTGGAGGAGTCC	224
NM_004302.5 (SEQ ID NO: 367)	565-584	TCCAAAGACAAGACGCTCC	225
NM_004302.5 (SEQ ID NO: 367)	2970-2989	ATAATAACTTTGAAGCCAT	226
NM_004302.5 (SEQ ID NO: 367)	2984-3003	GCCATAACTTTTAACTGGA	227
NM_004302.5 (SEQ ID NO: 367)	4463-4482	CTTTTGTTTTAATATAAGA	228
NM_004302.5 (SEQ ID NO: 367)	582-601	CCAGGATCTTGTCTACGAT	229
NM_004302.5 (SEQ ID NO: 367)	905-924	ACGGGTCCCTGTTTGATTA	230
NM_004302.5 (SEQ ID NO: 367)	212-231	TTTTCAATCTGGATGGGAT	231
NM_004302.5 (SEQ ID NO: 367)	4435-4454	AATGTAAATAAATTGTAAT	232
NM_004302.5 (SEQ ID NO: 367)	473-491	TCATTGTTTTCCTTGTCAT	233
NM_004302.5 (SEQ ID NO: 367)	1535-1554	TCAGCGTGCAGGAAGACGT	234
NM_004302.5 (SEQ ID NO: 367)	1784-1803	AGAGCGAATTGTGTGGAGA	235
NM_199230.1 (SEQ ID NO: 370)	1401-1420	ATGAGGCCTTGCGAGTGAT	236
NM_199230.1 (SEQ ID NO: 370)	964-983	CCTGCATATGGAGATTGTG	237
NM_199230.1 (SEQ ID NO: 370)	2046-2065	TGCGCATGTGCCGAGGTGT	238
NM_199230.1 (SEQ ID NO: 370)	1104-1123	CTGACACCATAGACATTGC	239
NM_199230.1 (SEQ ID NO: 370)	293-312	CACTGCTGCTATATTGACT	240
NM_199230.1 (SEQ ID NO: 370)	174-193	TCTCCATCTTTAACCTGGA	241
NM_199230.1 (SEQ ID NO: 370)	1654-1673	GACAGAGCCTGGGAGACGC	242

NM_199230.1 (SEQ ID NO: 370)	970-989	TATGGAGATTGTGGGCACT	243
NM_199230.1 (SEQ ID NO: 370)	642-661	AAGAGATTATCGGCAAGGG	244

* The target sequences contain Ts, but binding to RNA and/or DNA is contemplated.

[000392] In some embodiments, an oligonucleotide may comprise or consist of any sequence as provided in Table 15.

Table 15. Oligonucleotide sequences for targeting ACVR1B

Passenger Strand/Sense Strand (RNA) (5' to 3')	SEQ ID NO:	Guide Strand/Antisense Strand (RNA) (5' to 3')	SEQ ID NO:
AGACAAGACGCUCCAGGAUCU	245	AGAUCUGGAGCGUCUUGUCUUU	343
UGGAAUUGCUCUACGAGACUU	246	AAGUCUCGAUGAGCAAUCCAGG	344
CAACUGGUGGCAGAGUUAUGA	247	UCAUAACUCUGCCACCAGUUGGG	345
GAUGCAAUUCUGGAGGAGUCC	248	GGACUCCUCCAGAAUUGCAUCUU	346
UCUCCAAAGACAAGACGCUCC	249	GGAGCGUCUUGUCUUUGGAGAGA	347
AUAUAAUAAUUAAGCCAU	250	AUGGCUUCAAAGUUAUUAUAC	348
AAGCCAUAAUUAACUGGA	251	UCCAGUAAAAGUUAUGGCUUCA	349
AUCUUUUGUUUAAUUAAGA	252	UCUUAUUAUAAAACAAAGAUUU	350
CUCAGGAUCUUGUCUACGAU	253	AUCGUAGACAAGAUCUGGAGCG	351
GCACGGGUCCUGUUUGAUUA	254	UAAUCAACAGGGACCCGUGCUC	352
CAUUUCAAUCUGGAUGGGAU	255	AUCCAUCCAGAUUGAAAUGGA	353
CAAUGUAAAUAUUGUAAU	256	AUUACAUUUUAUUACAUUUGCA	354
CAUCAUUGUUUCCUUGUCAU	257	AUGACAAGGAAAACAAUGAUGAU	355
GCUCAGCGUGCAGGAAGACGU	258	ACGUCUCCUGCACGCUGAGCUG	356
UGAGAGCGAAUUGUGUGGAGA	259	UCUCCACACAAUUCGCUCUCAGA	357
UUAUGAGGCCUUGCGAGUGAU	260	AUCACUCGCAAGGCCUCAUAACU	358
CACCUGCAUAUGGAGAUUGUG	261	CACAAUCUCCAUAUGCAGGUGUG	359
AGUGCGCAUGUGCCGAGGUGU	262	ACACCUCGGCACAUGCGCACUUG	360
CACUGACACCAUAGACAUUGC	263	GCAAUGUCUAUGGUGUCAGUGAC	361
CACACUGCGCUAUUUGACU	264	AGUCAAUUAGCAGCAGUGUGUG	362
GGUCUCCAUCUUUAAACUGGA	265	UCCAGGUUAAAGAUGGAGACCAU	363
GGGACAGAGCCUGGGAGACGC	266	GCGUCUCCAGGCUCUGUCCCUC	364
CAUAUGGAGAUUGUGGGCACU	267	AGUGCCCACAAUCUCCAUAUGCA	365
ACAAGAGAUUAUCGGCAAGGG	268	CCCUUGCCGAUAAUCUCUUGUAA	366

[000393] In some embodiments, an oligonucleotide is a modified oligonucleotide as provided in Table 16, wherein ‘mN’ represents a 2’-O-methyl modified nucleoside (e.g., mU is 2’-O-methyl modified uridine), ‘fN’ represents a 2’-fluoro modified nucleoside (e.g., fU is 2’-fluoro modified uridine), ‘*’ represents a phosphorothioate internucleoside linkage, and lack of “*” between nucleosides indicate phosphodiester internucleoside linkage.

Table 16. Modified Oligonucleotides for targeting ACVR1B

siRNA #	Modified Passenger Strand/Sense Strand (RNA) (5' to 3')	SEQ ID NO:	Modified Guide Strand/Antisense Strand (RNA) (5' to 3')	SEQ ID NO:
hsACVR1B-3	mAmGfAmCfAmAfGmAfCmGfCmUfCmCfAmGfGmAfUmCfU	245	fAfGmAfUmCfCmUfGmGfAmGfCmGfUmCfUmUfGmUfCmU*fU*mU	343
hsACVR1B-4	mUmGfGmAfAmUfUmGfCmUfCmAfUmCfGmAfGmAfCmUfU	246	fAfAmGfUmCfUmCfGmAfUmGfAmGfCmAfAmUfUmCfCmA*fG*mG	344
hsACVR1B-5	mCmAfAmCfUmGfGmUfGmGfCmAfGmAfGmUfUmAfUmGfA	247	fUfCmAfUmAfAmCfUmCfUmGfCmCfAmCfCmAfGmUfUmG*fG*mG	345
hsACVR1B-6	mGmAfUmGfCmAfAmUfUmCfUmGfGmAfGmGfAmGfUmCfC	248	fGfGmAfCmUfCmCfUmCfCmAfGmAfAmUfUmGfCmAfUmC*fU*mU	346
hsACVR1B-7	mUmCfUmCfCmAfAmAfGmAfCmAfAmGfAmCfGmCfUmCfC	249	fGfGmAfGmCfGmUfCmUfUmGfUmCfUmUfUmGfGmAfGmA*fG*mA	347
hsACVR1B-8	mAmUfAmUfAmAfUmAfAmCfUmUfUmGfAmAfGmCfCmAfU	250	fAfUmGfGmCfUmUfCmAfAmAfGmUfUmAfUmUfAmUfAmU*fA*mC	348
hsACVR1B-9	mAmAfGmCfCmAfUmAfAmCfUmUfUmUfAmAfCmUfGmGfA	251	fUfCmCfAmGfUmUfAmAfAmAfGmUfUmAfUmGfGmCfUmU*fC*mA	349
hsACVR1B-10	mAmUfCmUfUmUfUmGfUmUfUmUfAmAfUmAfUmAfAmGfA	252	fUfCmUfUmAfUmAfUmUfAmAfAmAfCmAfAmAfAmGfAmU*fU*mU	350
hsACVR1B-1	mCmUfCmCfAmGfGmAfUmCfUmUfGmUfCmUfAmCfGmAfU	253	fAfUmCfGmUfAmGfAmCfAmAfGmAfUmCfCmUfGmGfAmG*fC*mG	351
hsACVR1B-11	mGmCfAmCfGmGfGmUfCmCfCmUfGmUfUmUfGmAfUmUfA	254	fUfAmAfUmCfAmAfAmCfAmGfGmGfAmCfCmCfGmUfGmC*fU*mC	352
hsACVR1B-12	mCmAfUmUfUmUfCmAfAmUfCmUfGmGfAmUfGmGfGmAfU	255	fAfUmCfCmCfAmUfCmCfAmGfAmUfUmGfAmAfAmAfUmG*fG*mA	353
hsACVR1B-13	mCmAfAmAfUmGfUmAfAmAfUmAfAmAfUmUfGmUfAmAfU	256	fAfUmUfAmCfAmAfUmUfUmAfUmUfUmAfCmAfUmUfUmG*fC*mA	354
hsACVR1B-2	mCmAfUmCfAmUfUmGfUmUfUmUfCmCfUmUfGmUfCmAfU	257	fAfUmGfAmCfAmAfGmGfAmAfAmAfCmAfAmUfGmAfUmG*fA*mU	355
hsACVR1B-14	mGmCfUmCfAmGfCmGfUmGfCmAfGmGfAmAfGmAfCmGfU	258	fAfCmGfUmCfUmUfCmCfUmGfCmAfCmGfCmUfGmAfGmC*fU*mG	356
hsACVR1B-15	mUmGfAmGfAmGfCmGfAmAfUmUfGmUfGmUfGmGfAmGfA	259	fUfCmUfCmCfAmCfAmCfAmAfUmUfCmGfCmUfCmUfCmA*fG*mA	357
mmACVR1B-4	mUmUfAmUfGmAfGmGfCmCfUmUfGmCfGmAfGmUfGmAfU	260	fAfUmCfAmCfUmCfGmCfAmAfGmGfCmCfUmCfAmUfAmA*fC*mU	358
mmACVR1B-5	mCmAfCmCfUmGfCmAfUmAfUmGfGmAfGmAfUmUfGmUfG	261	fCfAmCfAmAfUmCfUmCfCmAfUmAfUmGfCmAfGmGfUmG*fU*mG	359

mmACVR1B-6	mAmGfUmGfCmGfCmAfUmGfUmGfCmCfGmAfGmGfUmGfU	262	fAfCmAfCmCfUmCfGmGfCmAfCmAfUmGfCmGfCmAfCmU*fU*mG	360
mmACVR1B-7	mCmAfCmUfGmAfCmAfCmCfAmUfAmGfAmCfAmUfUmGfC	263	fGfCmAfAmUfGmUfCmUfAmUfGmGfUmGfUmCfAmGfUmG*fA*mC	361
mmACVR1B-1	mCmAfCmAfCmUfGmCfUmGfCmUfAmUfAmUfUmGfAmCfU	264	fAfGmUfCmAfAmUfAmUfAmGfCmAfGmCfAmGfUmGfUmG*fU*mG	362
mmACVR1B-2	mGmGfUmCfUmCfCmAfUmCfUmUfUmAfAmCfCmUfGmGfA	265	fUfCmCfAmGfGmUfUmAfAmAfGmAfUmGfGmAfGmAfCmC*fA*mU	363
mmACVR1B-8	mGmGfGmAfCmAfGmAfGmCfCmUfGmGfGmAfGmAfCmGfC	266	fGfCmGfUmCfUmCfCmCfAmGfGmCfUmCfUmGfUmCfCmC*fU*mC	364
mmACVR1B-9	mCmAfUmAfUmGfGmAfGmAfUmUfGmUfGmGfGmCfAmCfU	267	fAfGmUfGmCfCmCfAmCfAmAfUmCfUmCfCmAfUmAfUmG*fC*mA	365
mmACVR1B-3	mAmCfAmAfGmAfGmAfUmUfAmUfCmGfGmCfAmAfGmGfG	268	fCfCmCfUmUfGmCfCmGfAmUfAmAfUmCfUmCfUmUfGmU*fA*mA	366

d. MLCK1 Oligonucleotides

[000394] In some embodiments, the oligonucleotide is an antisense oligonucleotide (ASO). In some embodiments, the oligonucleotide is a siRNA. In some embodiments, the oligonucleotide is a short hairpin RNA. In some embodiments, the oligonucleotide is a miRNA-based shRNA (*e.g.*, based on miR-155 or miR-200c). In some embodiments, the oligonucleotide is a CRISPR guide RNA targeting MLCK1. In some embodiments, the oligonucleotide inhibits the expression or function of MLCK1.

[000395] Examples of oligonucleotides useful for targeting MLCK1 are provided in Weber M. et al. “MiRNA-155 targets myosin light chain kinase and modulates actin cytoskeleton organization in endothelial cells.” *Am J Physiol Heart Circ Physiol.* 2014 Apr 15;306(8):H1192-203.; Thatcher S.E. et al. “Myosin light chain kinase/actin interaction in phorbol dibutyrate-stimulated smooth muscle cells.” *J Pharmacol Sci.* 2011;116(1):116-27.; Kohama K. and Nakamura A. “Targeting of myosin light chain kinase in vascular smooth muscle cells, and its implication for drug discovery.” *Nihon Yakurigaku Zasshi.* 2001 Oct;118(4):269-76.; and U.S. Patent Application Publication 2010/0093830, entitled Modulation of MLCK-L expression and uses thereof,” published on April 15, 2010; the contents of each of which are incorporated herein in their entireties.

[000396] In some embodiments, oligonucleotides may have a region of complementarity to a human MLCK1 sequence, for example, as provided below (Gene ID: 4638; NCBI Ref. No: NM_053025.4):

GGGCTCCCCGCGCCCGCCGGTTCGGCAGCAGGGCGCTGAGCGAGCTCGGAGCCCGCGCTGTGCGC
CTGCGGCCGGGGCGCCCGAGCGCCGGTGCCCCGGCTCCCGGGCCGCCTTCGCCGCGCGGG

AAGGATTCTTCAAAATTAACAGAAACCAATTTCGGGCCAGCTGAAGAGAAAAAATAAAGGTGGCT
CCCGGCTGCCTCTGCTGCAGTTCAGAGCAACTTCAGGAGCTTCCCAGCCGAGAGCTTCAGGACG
CCTTTCTGTCCCCTGGCCCAGTTGCCACAACAAACAACAGAGAAGACGGTGACCATGGGGGA
TGTGAAGCTGGTTGCCTCGTCACACATTTCCAAAACCTCCCTCAGTGTGGATCCCTCAAGAGTT
GACTCCATGCCCCCTGACAGAGGGCCCCTGCTTTTCATTTTGCCCCCTCGGAACCTCTGCATCAAAG
AAGGAGCCACCGCCAAGTTCGAAGGGCGGGTCCGGGGTTACCCAGAGCCCCAGGTGACATGGCA
CAGAAACGGGCAACCCATCACCAGCGGGGGCCGCTTCCTGCTGGATTGCGGCATCCGGGGGACT
TTCAGCCTTGTGATTTCATGCTGTCCATGAGGAGGACAGGGGAAAGTATACCTGTGAAGCCACCA
ATGGCAGTGGTGCTCGCCAGGTGACAGTGGAGTTGACAGTAGAAGGAAGTTTTGCGAAGCAGCT
TGGTACGCCTGTTGTTTCCAAAACCTTAGGGGATAGATTTTCAGCTCCAGCAGTGGAGACCCGT
CCTAGCATCTGGGGGGAGTGCCCAACAAAGTTTGCTACCAAGCTGGGCCGAGTTGTGGTCAAAG
AAGGACAGATGGGACGATTCTCCTGCAAGATCACTGGCCGGCCCCAACCGCAGGTACCTGGCT
CAAGGGAAATGTTCCACTGCAGCCGAGTGCCCGTGTGTCTGTGTCTGAGAAGAACGGCATGCAG
GTTCTGGAAATCCATGGAGTCAACCAAGATGACGTGGGAGTGTACACGTGCCTGGTGGTGAACG
GGTCGGGGAAGGCCTCGATGTCAGCTGAACTTTCCATCCAAGGTTTGAGACAGTGCCAATAGGTC
ATTTGTGAGAGAAACAAAAGCCACCAATTCAGATGTCAGGAAAGAGGTGACCAATGTAATCTCA
AAGGAGTCGAAGCTGGACAGTCTGGAGGCTGCAGCCAAAAGCAAGAACTGCTCCAGCCCCCAGA
GAGGTGGCTCCCCACCCTGGGCTGCAAACAGCCAGCCTCAGCCCCCAAGGGAGTCCAAGCTGGA
GTCATGCAAGGACTCGCCCAGAACGGCCCCGCAGACCCCGGTCTTCAGAAGACTTCCAGCTCC
ATCACCTGTCAGGCCGCAAGAGTTTCAGCCGGAACCAAGAGCACCAGGCCTGGGGGTCTATCAC
CTTCTGGAGAAGAGAGGAAGAGGGCCAGCTCCTCCCCGTCCAGCCACCTTCCCCACCAGGCAGCC
TGGCCTGGGGAGCCAAGATGTTGTGAGCAAGGCTGCTAACAGGAGAATCCCCATGGAGGGCCAG
AGGGATTTCAGCATTCCCCAAATTTGAGAGCAAGCCCCAAAGCCAGGAGGTCAAGGAAAATCAAA
CTGTCAAGTTCAGATGTGAAGTTTCCGGGATTCCAAAGCCTGAAGTGGCCTGGTTCTTGAAGG
CACCCCGCTGAGGAGACAGGAAGGCAGCATTGAGGTTTATGAAGATGCTGGCTCCCATACCTC
TGCCTGCTGAAAGCCCCGACCAGGGACAGTGGGACATACAGCTGCACTGCTTCCAACGCCCAAG
GCCAGCTGTCTGTAGCTGGACCCTCCAAGTGGAAAGGCTTGCCGTGATGGAGGTGGCCCCCTC
CTTCTCCAGTGCTCTGAAGGACTGCGCTGTTATTGAGGGCCAGGATTTTGTGCTGCAGTGCTCC
GTACGGGGGACCCAGTGCCCCGGATCACTTGGCTGCTGAATGGGCAGCCCATCCAGTACGCTC
GCTCCACCTGCGAGGCCGGCGTGGCTGAGCTCCACATCCAGGATGCCCTGCCGGAGGACCATGG
CACCTACACCTGCCTAGCTGAGAATGCCTTGGGGCAGGTGTCCTGCAGCGCCTGGGTACCCGTC
CATGAAAAGAAGAGTAGCAGGAAGAGTGAGTACCTTCTGCCTGTGGCTCCCAGCAAGCCCACTG
CACCCATCTTCTGTCAGGGCCTCTCTGATCTCAAAGTCATGGATGGAAGCCAGGTCACTATGAC
TGTCCAAGTGTGAGGGAATCCACCCCCTGAAGTCATCTGGCTGCACAATGGGAATGAGATCCAA
GAGTCAGAGGACTTCCACTTTGAACAGAGAGGAACTCAGCACAGCCTTTGTATCCAGGAAGTGT
TCCCGGAGGACACGGGCACGTACACCTGCGAGGCCTGGAACAGCGCTGGAGAGGTCCGCACCCA
GGCCGTGCTCACGGTACAAGAGCCTCACGATGGCACCCAGCCCTGGTTCATCAGTAAGCCTCGC
TCAGTGACAGCCTCCCTGGGCCAGAGTGTCTCATCTCCTGCGCCATAGCTGGTGACCCCTTTC
CTACCGTGCCTGGCTCAGAGATGGCAAAGCCCTCTGCAAAGACACTGGCCACTTCGAGGTGCT
TCAGAATGAGGACGTGTTTACCCTGGTTCTAAAGAAGGTGCAGCCCTGGCATGCCGGCCAGTAT
GAGATCCTGCTCAAGAACC GGTTGGCGAATGCAGTTGCCAGGTGTCACTGATGCTACAGAACA
GCTCTGCCAGAGCCCTTCCACGGGGGAGGGAGCCTGCCAGCTGCGAGGACCTCTGTGGTGGAGG
AGTTGGTGCTGATGGTGGTGGTAGTGACCGCTATGGGTCCCTGAGGCCTGGCTGGCCAGCAAGA
GGGCAGGGTTGGCTAGAGGAGGAAGACGGCGAGGACGTGCGAGGGGTGCTGAAGAGGCGCGTGG
AGACGAGGCAGCACACTGAGGAGGCGATCCGCCAGCAGGAGGTGGAGCAGCTGGACTTCCGAGA
CCTCCTGGGGAAGAAGGTGAGTACAAAGACCCTATCGGAAGACGACCTGAAGGAGATCCCAGCC
GAGCAGATGGATTTCCGTGCCAACCTGCAGCGGCAAGTGAAGCCAAAGACTGTGTCTGAGGAAG
AGAGGAAGGTGCACAGCCCCCAGCAGGTGATTTTCGCTCTGTCTGGCCAAGAAGGGGACTTC
CAAGACCCCCGTGCCTGAGAAGGTGCCACCGCCAAAACCTGCCACCCCGGATTTTCGCTCAGTG
CTGGGTGGCAAGAAGAAATTACCAGCAGAGAATGGCAGCAGCAGTGCCGAGACCCTGAATGCCA
AGGCAGTGGAGAGTTCCAAGCCCCTGAGCAATGCACAGCCTTCAGGGCCCTTGAAACCCGTGGG
CAACGCCAAGCCTGCTGAGACCCTGAAGCCAATGGGCAACGCCAAGCCTGCCGAGACCCTGAAG
CCCATGGGCAATGCCAAGCCTGATGAGAACCTGAAATCCGCTAGCAAAGAAGAACTCAAGAAAG

ACGTTAAGAATGATGTGAACTGCAAGAGAGGCCATGCAGGGACCACAGATAATGAAAAGAGATC
AGAGAGCCAGGGGACAGCCCCAGCCTTCAAGCAGAAGCTGCAAGATGTTTCATGTGGCAGAGGGC
AAGAAGCTGCTGCTCCAGTGCCAGGTGTCTTCTGACCCCCCAGCCACCATCATCTGGACGCTGA
ACGGAAAGACCCTCAAGACCACCAAGTTTCATCATCCTCTCCCAGGAAGGCTCACTCTGCTCCGT
CTCCATCGAGAAGGCACTGCCTGAGGACAGAGGCTTATACAAGTGTGTAGCCAAGAATGACGCT
GGCCAGGCGGAGTGCTCCTGCCAAGTCACCGTGGATGATGCTCCAGCCAGTGAGAACACCAAGG
CCCCAGAGATGAAATCCCGGAGGCCCAAGAGCTCTCTTCCCTCCCGTGCTAGGAACTGAGAGTGA
TGCGACTGTGAAAAAGAAACCTGCCCCCAAGACACCTCCGAAGGCAGCAATGCCCCCTCAGATC
ATCCAGTTCCCTGAGGACCAGAAGGTACGCGCAGGAGAGTCAGTGAGAGCTGTTTGGCAAAGTGA
CAGGCACTCAGCCCATCACCTGTACCTGGATGAAGTTCCGAAAGCAGATCCAGGAAAGCGAGCA
CATGAAGGTGGAGAACAGCGAGAATGGCAGCAAGCTCACCATCCTGGCCGCGCGCCAGGAGCAC
TGCGGCTGCTACACACTGCTGGTGGAGAACAAGCTGGGCAGCAGGCAGGCCAGGTCAACCTCA
CTGTCGTGGATAAGCCAGACCCCCAGCTGGCACACCTTGTGCCTCTGACATTCCGAGCTCCTC
ACTGACCCTGTCTTGGTATGGCTCCTCATATGATGGGGGCAGTGCTGTACAGTCCTACAGCATC
GAGATCTGGGACTCAGCCAACAAGACGTGGAAGGAACTAGCCACATGCCGCAGCACCTCTTTCA
ACGTCCAGGACCTGCTGCCTGACCACGAATATAAGTTCCGTGTACGTGCAATCAACGTGTATGG
AACCAGTGAGCCAAGCCAGGAGTCTGAACTCACAACGGTAGGAGAGAAACCTGAAGAGCCGAAG
GATGAAGTGGAGGTGTCAGATGATGATGAGAAGGAGCCCGAGGTTGATTACCGGACAGTGACAA
TCAATACTGAACAAAAAGTATCTGACTTCTACGACATTGAGGAGAGATTAGGATCTGGGAAATT
TGGACAGGTCTTTTCTGACTTGTAGAAAAGAAAACCTCGAAAAGTCTGGGCAGGGAAGTTCTTCAAG
GCATATTTCAGCAAAAAGAGAAAGAGAATATCCGGCAGGAGATTAGCATCATGAACTGCCTCCACC
ACCCTAAGCTGGTCCAGTGTGTGGATGCCTTTGAAGAAAAGGCCAACATCGTCATGGTCCTGGA
GATCGTGTGTCAGGAGGGGAGCTGTTTGAGCGCATCATTGACGAGGACTTTGAGCTGACGGAGCGT
GAGTGCATCAAGTACATGCGGCAGATCTCGGAGGGAGTGGAGTACATCCACAAGCAGGGCATCG
TGCACCTGGACCTCAAGCCGGAGAACATCATGTGTGTCAACAAGACGGGCACCAGGATCAAGCT
CATCGACTTTTGGTCTGGCCAGGAGGCTGGAGAATGCGGGGTCTCTGAAGGTCCTCTTTGGCACC
CCAGAATTTGTGGCTCCTGAAGTGATCAACTATGAGCCCATCGGCTACGCCACAGACATGTGGA
GCATCGGGGTCATCTGCTACATCCTAGTCAGTGGCCTTTCCCCCTTCATGGGAGACAACGATAA
CGAAACCTTGGCCAACGTTACCTCAGCCACCTGGGACTTCGACGACGAGGCATTTCGATGAGATC
TCCGACGATGCCAAGGATTTTCATCAGCAATCTGCTGAAGAAAGATATGAAAAACCGCCTGGACT
GCACGCAGTGCCTTCAGCATCCATGGCTAATGAAAGATACCAAGAACATGGAGGCCAAGAACT
CTCCAAGGACCGGATGAAGAAGTACATGGCAAGAAGGAAATGGCAGAAAACGGGCAATGCTGTG
AGAGCCATTGGAAGACTGTCTCTATGGCAATGATCTCAGGGCTCAGTGGCAGGAAATCCTCAA
CAGGGTCACCAACCAGCCCGCTCAATGCAGAAAAAACTAGAATCTGAAGAAGATGTGTCCCAAGC
TTTCCTTGAGGCTGTTGCTGAGGAAAAGCCTCATGTAAAACCCTATTTCTCTAAGACCATTTCG
GATTTAGAAGTTGTGGAGGGAAGTGCTGCTAGATTTGACTGCAAGATTGAAGGATACCCAGACC
CCGAGGTTGTCTGGTTCAAAGATGACCAGTCAATCAGGGAGTCCCGCCACTTCCAGATAGACTA
CGATGAGGACGGGAACTGCTCTTTAATTATTAGTGATGTTTGCGGGGATGACGATGCCAAGTAC
ACCTGCAAGGCTGTCAACAGTCTTGAGAGAAGCCACCTGCACAGCAGAGCTCATTGTGAAACGA
TGGAGGAAGGTGAAGGGGAAGGGGAAGAGGAAGAAGAGTGAAACAAAGCCAGAGAAAAGCAGTT
TCTAAGTCATATTAAAAGGACTATTTCTCTAAAACCTCAAAAAAAAAAAAAAAAAAACTCAAGATAGT
AAAAGCACCTAGTGTGATAGATTATCGGTTAGGTCATTTGTGGGTTGATTCTTCAGAAACAGCA
GTTGATACCTAGCAGCGTTATTGATGGGCATTAATCTATGTTAGTTGGCACCTTAAGATACTAG
TGCAGCTAGATTTTATTTAGGGAAATCACCAGTAACTTGACTGACCAATTGATTTTLAGAGAGAA
AGTAACCAAACCAATATTTATCTGGGCAAAGTCATAAATCTCCACTTGAATGCGCTCATGAA
AAATAAGGCCAAAACAAGAGTTCTGGGCCACAGCTCAGCCCAGAGGGTTCTGGGGATGGGAGG
CCTCTCTCTCCCCACCCCTGACTCTAGAGAACTGGGTTTTCTCCAGTACTCCAGCAATTTCAT
TTCTGAAAGCAGTTGAGCCACTTTATTCCAAAGTACACTGCAGATGTTCAAACCTCTCCATTTCT
CTTTCCCCTTCCACCTGCCAGTTTTGCTGACTCTCAACTTGTGATGAGTGTAAAGCATTAAAGGAC
ATTATGCTTCTTCGATTCTGAAGACAGGTCCCTGCTCATGGATGACTCTGGCTTCCTTAGGAAA
ATATTTTTCTTCCAAAATCAGTAGGAAATCTAACTTATCCCCTCTTTGCAGATGTCTAGCAGC
TTCAGACATTTGGTTAAGAACCCATGGGAAAAAAAAAAATCCTTGCTAATGTGGTTTTCTTTGTA
AACCAGGATTCTTATTTGTGCTGTTATAGAATATCAGCTCTGAACGTGTGGTAAAGATTTTTGT

GTTTGAATATAGGAGAAATCAGTTTGCTGAAAAGTTAGTCTTAATTATCTATTGGCCACGATGA
AACAGATTTCAACTGATAAAGAGCTGGAGAAGCTCCATGTACTTTGGAATCTCCTCCAAGATAGC
CAGAGTTTAAATACATCTTCATTCTCAACACTCTCCAAAGAACTTGACCTACCTTATGGGTTC
TATTTTTCTTCTTAAATGTGCATCAATCATGCCTTGCCCCAACCTTTAAATATATTCTTAGAC
CTGGTAAATGCACTCAGACTTGCGTCTTTAGGAATTTTTAACTTTCTTTCACTACATTGGCACT
TAAATTTTTCTTTATAAAGCTTTTTGAAGGTCATAAACAAAGACCATAATTGATGATAGACCT
AATACATTTCTCTGTGTGTGTGTGAACATTCCAAATACTTTTTTTTTCTTTTCCACTGTTTG
TAAGGTGCAACAATTTAATATTTTTAAGGGACTTTTTAAGAGTTCCTTAAGAACCAATTTAAAA
TTACTTCAGTGCAATCCTACACAGTATCAACATTAGAATTTTGATATTAGTCTTATGTTATCTT
CCATTCTATTTTTATCTGCTTTTTGCTGCTAGTTTCAAAGTCCAGTATTTTTCTTTTGCTTT
TAAAATAGTTACAATATTTTTCATGATAGCCACAGTATTGCCACAGTTTATTATAATAAAGGGT
TTTTATTTGATTTAGCGCATTCAAAGCTTTTTTCTATCACTTTTGTGTTTCAAGTATAACCTTT
GTGTGCGTGTATGTTGTGTGTGTGCATGTGTGGCGTATATGTGTGTTACAGGTTAATGCCTTCT
TGGAATTGTGTTAATGTTCTCTTGGTTTTATTATGCCATCAGAATGGTAAATGAGAACACTACAA
CTGTAGTCAGCTCACAATTTTTAAATAAAGGATACCACAGTGCATGCTGTTTGTTCATCTTTG
CAGACTTCTCTTTCTTTCCATGCTACCAGTTGTAAAGGACACAGCTATATCCTGGAAATGAAAA
ACAAACACTGTGGTGCCTAGATGTGAAGAACTGGCTTATGTGGTTGTGTTTTGCTATGGAACAG
AATGATTTAGGAAGTTCTTGTTTATATAGGTAGCCGAATTTACACATTTAGTTCAAAATTTCTC
TTGAGCATCAGCTTAGTACTATATCAATCATTCTAGAAGGATATCTTATAGAGCAGGTGTCCCC
AACCCCCGGTAAGTAGCCTGTTAGGAACCAGGTCACACATAAGGAGGTTAGCAGTGGGCAAGTG
AGCAAAGCATCATCTATATTTACAGCCGATCCCCATTGCTCGCATTACCGCCTGAGCTCTGCCT
CCTGTCAGATCAGCGGCAGCATCAGGTTCTCTCAGGAACGAACTCTATTGTGAAGTGTCTCATGT
GAGGGATCTAGGTTTCACGCTCCTTATGAGAATCTAACACCTGATGATCTGTCACTGTCTCCCA
TCACCCCTAGATGGGACAGTCTAGTTGCAGGAAAACAAGCTCAGGGCTTCCACTGATTCTACAT
TATGATGAGTTGTATACTTATTTTTATATTATAATAAAATATATTATTACAATGTAATAATA
GAAATAAAATGCACAATACATGTAATGTGCTTGAATAATCCCAAAACCACCCCTCTCCTGGTC
CATGGAAAACTGTCTTCCATGAAAGTGGTCCCTGGTGCCAAAAAGGTTAGGGACCACTGTTAC
AGAGTATCAGGTCCTCAAGATGCTAAAATCTATATGACATTTTTAACATGTGACATTATCATCA
TCATCATCATCATCACTGATGATACTATTTACCAGGGCATGGTTTGAATTGGTGACTTTGG
TGCAGTTCATTATTGGCAGCCAAATGCTTTATCCATACCTTCATATTGAAGAATTTGTTATCAG
GAACTACCAGTCCTGCTTTACAGGAAGTCTGTTATCAGATATCAGATGGCAAGTTCCCCATGT
CTTCAGATGTTCAAACAATATTGTGGATGGTCTAGAAAGAGTTTAAGACATGCTGTTAAATGTA
GGGCTAGATAAATTCTCTGATTCTTTGATGTAGTCTGGAAAGAAACAATCCATTGTCCAGTTAAT
AAATATTTAGTGTTTTTCAATTTTTAAGACACTCACAATCCACAAATGTCCCTAACAAATTTATTAT
TTTTAAAGAAAATGACTTTTTTATTCTTGCTAGTGAAAAATGTACAATTTATATGCTGCACTGA
GAAAAATAACAGATATACTTTCTTCCATTCAATTTTCATCCCAAACATATAAAAAATAATCCATT
GATTGTTCTTGCATTGCATATCTTATTAAGATATTTCTTACATGCAACTAATAAGACATGC
TGAAGTGTGTCAGCTCTAAATTTATGTAAAGATTTTTTATTTTTGTTAAATGTTTGAAATTTG
CTTTTTGCTCCACACCTCACCTGTTTTTGATAAATCTGTGCTAATAAGTACATAGGAGGTAATA
AATAATTGAGTTGTGAGAAACCAATTCTCCATTTTTCAAGAAAACACAAGTAGCACTACTCTC
TTTATCCCTTGGGACTCCTTCTGTAAATTTGAAAGGGGGGCTAATGTTGGTGGCAGTTGTTGC
TAAGGATCTCTGCACAGAGTTAGGGCTTCACTCTCGGCTTCTGTTAGATGGGGCCATGTGAC
TAGTCCTAGTCAGTGAGCTGTGACCAGAAGTGATGTATGTACCCTCGGGACCAGAGCATTTATG
TGCTGGTACAAGCCTCTCCATAATGACGGGCAACACATGAGATGGTGGCTGCTGCAGCCATCTG
GGTCTCTAGCCAACCCAAAATGGGGACATAACACAAGCAAGAAATAAACATTTGTTCTTATAAA
TCACCAAGATTTTGGGGTTCTCAGTGGCTGCAACATAACCTAGACTATCCTGATACAGGCTTAT
CACCATGTTCTGGATGTGTGGTGACCAGGATGGTAGCCACTACTCACAAGTGGCTATTTAAATT
TAAGTTACTTTAAAAAATAAAAAAATTCAGTTCCTCAGTTGTATGAGTTACATTTCAAAT
GCTCGACAGTCACATGTACATCACTTTTCAAATTATGTGAAATTAAACTGAAAAGCTTGTGTG
AAAGTCTAGAGAGTATGGTCTATAGTTTCATCAATTGTATTGGATAATATAGTCTCGATACTCA
A

(SEQ ID NO: 411)

[000397] In some embodiments, the oligonucleotide may have region of complementarity to a mutant form of MLCK1, for example as reported in Halim D. et al. “Loss-of-Function Variants in MYLK Cause Recessive Megacystis Microcolon Intestinal Hypoperistalsis Syndrome.” Am J Hum Genet. 2017 Jul 6;101(1):123-129; Hannuksela M. et al. “A novel variant in MYLK causes thoracic aortic dissections: genotypic and phenotypic description.” BMC Med Genet. 2016 Sep 1;17(1):61; or Shalata, A. et al. “Fatal thoracic aortic aneurysm and dissection in a large family with a novel MYLK gene mutation: delineation of the clinical phenotype.” Orphanet J Rare Dis. 2018 Mar 15;13(1):41; the contents of each of which are incorporated herein by reference in their entireties.

[000398] In some embodiments, the oligonucleotide comprises a region of complementarity to an MCLK1 mRNA sequence as set forth in SEQ ID NO: 411. In some embodiments, the region of complementarity is at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 19 or at least 20 nucleotides in length. In some embodiments, the region of complementarity is 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides in length. In some embodiments, the region of complementarity is in the range of 8 to 20, 10 to 20 or 15 to 20 nucleotides in length. In some embodiments, the region of complementarity is fully complementarity with all or a portion of its target sequence. In some embodiments, the region of complementarity includes 1, 2, 3 or more mismatches. In some embodiments, the oligonucleotide comprises a region of complementarity that is complementary (e.g., at least 85% at least 90%, at least 95%, or 100%) to an MLCK1 mRNA target sequence as set forth in SEQ ID NO: 411.

e. ACVR1 Oligonucleotides

[000399] Examples of oligonucleotides useful for targeting ACVR1 are provided in Star, G.P. et al., “*ALK2 and BMPR2 knockdown and endothelin-1 production by pulmonary microvascular endothelial cells*”, Microvasc Res. 2013 Jan;85:46-53.; Karbiener M. et al., “*MicroRNA-30c promotes human adipocyte differentiation and co-represses PAI-1 and ALK2*”, RNA Biol. 2011 Sep-Oct;8(5):850-60.; US Patent Application 2018/0087110, published March 29, 2018, “*Compositions and methods for xi chromosome reactivation*”; US Patent Application 2009/0253132, published 10/8/2009, “*Mutated ACVR1 for diagnosis and treatment of fibrodysplasia ossificans progressiva (FOP)*”; WO 2015/152183, published 10/8/2015, “*Prophylactic agent and therapeutic agent for fibrodysplasia ossificans progressiva*”; Lowery, J.W. et al, “*Allele-specific RNA Interference in FOP -Silencing the FOP gene*”, GENE THERAPY, vol. 19, 2012, pages 701 – 702; Takahashi, M. et al. “*Disease-causing allele-specific silencing against the ALK2 mutants, R206H and G356D, in fibrodysplasia ossificans*

progressiva” Gene Therapy (2012) 19, 781–785; Shi, S. et al. “*Antisense-Oligonucleotide Mediated Exon Skipping in Activin-Receptor-Like Kinase 2: Inhibiting the Receptor That Is Overactive in Fibrodysplasia Ossificans Progressiva*” Plos One, July 2013, Vol 8:7, e69096.; US Patent Application 2017/0159056, published 6/8/2017, “*Antisense oligonucleotides and methods of use thereof*”; US Patent No. 8,859,752, issued 10/4/2014, “*SIRNA-based therapy of Fibrodysplasia Ossificans Progressiva (FOP)*”; WO 2004/094636, published 11/4/2004, entitled “*Effective sirna knock-down constructs*”; and Maruyama, R. and T. Yokota, “*Morpholino-Mediated Exon Skipping Targeting Human ACVR1/ALK2 for Fibrodysplasia Ossificans Progressiva*” Methods Mol Biol. 2018;1828:497-502.; the contents of each of which are incorporated herein in their entireties.

[000400] In some embodiments, oligonucleotides may have a region of complementarity to a human ACVR1 sequence, for example, as provided below (Gene ID: 90; NCBI Ref. No: NM_001105.5):

```
CCTTTCCCCTGGAGATTTGAACGCTGCTTGCATGGGAGAAAAGCTACTTAGAGAAGAAAAC
GTTCCACTTAGTAACAGAAGAAAAGTCTTGGTTAAAAAGTTGTCATGAATTTGGCTTTTGG
GAGAGGCAGCAAGCCTGGAGCATTGGTAAGCGTCACACTGCCAAAGTGAGAGCTGCTGGAG
AACTCATAATCCCAGGAACGCCTCTTCTACTCTCCGAGTACCCAGTGACCAGAGTGAGAGA
AGCTCTGAACGAGGGGCACGCGGCTTGAAGGACTGTGGGCAGATGTGACCAAGAGCCTGCAT
TAAGTTGTACAATGGTAGATGGAGTGATGATTCTTCCTGTGCTTATCATGATTGCTCTCCCCT
CCCCTAGTATGGAAGATGAGAAGCCCAAGGTCAACCCCAAACTCTACATGTGTGTGTGTGA
AGGTCTCTCCTGCGGTAATGAGGACCACTGTGAAGGCCAGCAGTGCTTTTCCTCACTGAGCA
TCAACGATGGCTTCCACGTCTACCAGAAAGGCTGCTTCCAGGTTTATGAGCAGGGAAAGAT
GACCTGTAAGACCCCGCCGTCCCCTGGCCAAGCCGTGGAGTGCTGCCAAGGGGACTGGTGT
AACAGGAACATCACGGCCCAGCTGCCCCTAAAGGAAAATCCTTCCCTGGAACACAGAATT
TCCACTTGGAGGTTGGCCTCATTATTCTCTCTGTAGTGTTTCGCAGTATGTCTTTTAGCCTGCC
TGCTGGGAGTTGCTCTCCGAAAATTTAAAAGGCGCAACCAAGAACGCCTCAATCCCCGAGA
CGTGGAGTATGGCACTATCGAAGGGCTCATCACCACCAATGTTGGAGACAGCACTTTAGCA
GATTTATTGGATCATTTCGTGTACATCAGGAAGTGGCTCTGGTCTTCCTTTTCTGGTACAAAGA
ACAGTGGCTCGCCAGATTACACTGTTGGAGTGTGTGCGGAAAGGCAGGTATGGTGAGGTGT
GGAGGGGCAGCTGGCAAGGGGAGAATGTTGCCGTGAAGATCTTCTCCTCCCGTGATGAGAA
GTCATGGTTTCAGGGAAACGGAATTGTACAACACTGTGATGCTGAGGCATGAAAATATCTTA
GGTTTCATTGCTTCAGACATGACATCAAGACACTCCAGTACCCAGCTGTGGTTAATTACACA
TTATCATGAAATGGGATCGTTGTACGACTATCTTCAGCTTACTACTCTGGATACAGTTAGCT
GCCTTCGAATAGTGCTGTCCATAGCTAGTGGTCTTGCACATTTGCACATAGAGATATTTGGG
ACCCAAGGGAAACCAGCCATTGCCCATCGAGATTTAAAGAGCAAAAATATTCTGGTTAAGA
AGAATGGACAGTGTTGCATAGCAGATTTGGGCCTGGCAGTCATGCATTCCCAGAGCACCAA
TCAGCTTGATGTGGGGAACAATCCCCGTGTGGGCACCAAGCGCTACATGGCCCCCGAAGTT
CTAGATGAAACCATCCAGGTGGATTGTTTCGATTCTTATAAAAGGGTCGATATTTGGGCCTT
TGGACTTGTTTTGTGGGAAGTGGCCAGGCGGATGGTGAGCAATGGTATAGTGGAGGATTAC
AAGCCACCGTTCTACGATGTGGTTCCCAATGACCCAAGTTTTGAAGATATGAGGAAGGTAGT
CTGTGTGGATCAACAAAGGCCAAACATAACCAACAGATGGTTCTCAGACCCGACATTAACC
TCTCTGGCCAAGCTAATGAAAGAATGCTGGTATCAAAAATCCATCCGCAAGACTCACAGCAC
TGCGTATCAAAAAGACTTTGACCAAAAATTGATAATTCCTCGACAAATTGAAAACCTGACTGT
TGACATTTTCATAGTGTCAAGAAGGAAGATTTGACGTTGTTGTCATTGTCCAGCTGGGACCT
AATGCTGGCCTGACTGGTTGTCAGAATGGAATCCATCTGTCTCCCTCCCCAAATGGCTGCTT
TGACAAGGCAGACGTCGTACCCAGCCATGTGTTGGGGAGACATCAAAACCACCCTAACCTC
GCTCGATGACTGTGAACTGGGCATTTACGAACTGTTACACTGCAGAGACTAATGTTGGAC
AGACACTGTTGCAAAGGTAGGGACTGGAGGAACACAGAGAAATCCTAAAAGAGATCTGGG
CATTAAAGTCAGTGGCTTTGCATAGCTTTCACAAGTCTCCTAGACACTCCCCACGGGAAACTC
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AAGGAGGTGGTGAATTTTTAATCAGCAATATTGCCTGTGCTTCTCTTCTTTATTGCACTAGGA
 ATTCTTTGCATTCCTTACTTGCACTGTTACTCTTAATTTTAAAGACCCAACTTGCCAAAATGT
 TGGCTGCGTACTCCACTGGTCTGTCTTTGGATAATAGGAATTCAATTTGGCAAAACAAAATG
 TAATGTCAGACTTTGCTGCATTTTACACATGTGCTGATGTTTACAATGATGCCGAACATTAG
 GAATTGTTTATACACAACCTTTGCAAATTATTTATTACTTGTGCACTTAGTAGTTTTTACAAAA
 CTGCTTTGTGCATATGTTAAAGCTTATTTTTATGTGGTCTTATGATTTTTATTACAGAAATGTTT
 TTAACACTATACTCTAAAAATGGACATTTTCTTTTATTATCAGTTAAAATCACATTTTAAAGTGC
 TTCACATTTGTATGTGTGTAGACTGTAACTTTTTTTTTCAGTTCATATGCAGAACGTATTTAGCC
 ATTACCCACGTGACACCACCGAATATATTACTGATTTAGAAAGCAAAGATTTTCAGTAGAATTT
 TAGTCCTGAACGCTACGGGGAAAATGCATTTTCTTCAGAATTATCCATTACGTGCATTTAAA
 CTCTGCCAGAAAAAAATAACTATTTTGTTTTAATCTACTTTTTGTATTTAGTAGTTATTTGTA
 TAAATTAATAAACTGTTTTCAAGTCAAA (SEQ ID NO: 429).

[000401] In some embodiments, oligonucleotides may have a region of complementarity to a sequence set forth as follows, which is an example mouse ACVR1 gene sequence (Gene ID 11477; NM_001110204.1)

CCGCCTCCCCGGGTTCAGCACCCGACCGCCGCTGGACCAGAGGAACAAAGGAGCTGCCCC
 GTGTCACCCAGCCCTTCAGTGGAAGTCTGGAAGGAACAGAGGTGATATTGCAGTGATG
 AGCAGAGAGAAGCCGGCCTCTGGTGCTCTTGAGCTGGTCTGCCCATAGGGAGCCTGCTGGG
 AGAAGGTACAGCTTCCGGAAGACTCCTCCCGGAGCGCCTCTCCCATCCTCCTCTCCCTTGGA
 GCAGTCAGTACCTCTCTGCTGGAGGATCTGGGCTGGGTGTGCCGGGAGCTGGCTTTAACTGT
 AGCCCTGTCAGGCTTTCCCCGGACCTCGCGGAAGAGCGTCACCAGCCCCACGGCTTTCCAA
 CACATCACCTCTTTTCATGCCGTTTGGCACAGATCGAATCTACAGGGATGAATGGATCCAGG
 GTCTGGTTTTTAAGTTCTATGGTAGTCGTCCAAGGAGCCATTGGTATTCATCTAACGCAAACG
 ATCAAGTTACATTCTGAAAGTAACATCCCACCAGAAACCCTCCAGCAGCAGTCACGTCTGTG
 TAAAGCCAAGCCCTGGCATGCGCACTGCCAGGTCAGAGTGTGGTGGTACACGTGTTTAAACA
 GGTCAATTTGTCAACTGAAGGAAAGACCCCGGCTTGACTTACCTGTTATACAATGGTCGATGG
 AGTAATGATCCTTCCTGTGCTAATGATGATGGCTTTCCTTCCCCGAGTGTGGAAGATGAGA
 AGCCCAAGGTCAACCAGAACTTTACATGTGTGTGTGTGAGGGCCTCTCCTGCGGGAACGA
 GGACCACTGTGAAGGCCAGCAGTGTTTTTCTTCTCTGAGCATCAACGATGGCTTCCACGTCT
 ACCAGAAGGGCTGCTTTCAGGTTTATGAGCAGGGGAAGATGACGTGTAAGACCCCGCCGTC
 ACCTGGCCAGGCTGTGGAGTGCTGCCAAGGGGACTGGTGTAAACAGGAACATCACGGCCCAG
 CTGCCCCTAAAGGGAAGTCCTTCCCCGGAACACAGAATTTCCACCTGGAAGTTGGCCTTAT
 CATCCTCTCGGTGGTGTGTTGTCAGTATGTCCTTTAGCTTGCATCCTTGGAGTTGCTCTCAGGAA
 GTTTAAGAGACGCAATCAAGAGCGCCTGAACCCAGAGACGTGGAGTATGGTACCATTGAA
 GGGCTCATCACCACCAATGTGGGAGACAGCACTCTAGCGGAACCTAGATCACTCGTGTA
 CATCAGGAAGTGGCTCCGGTCTTCCCTTCCCTGGTACAGAGAACGGTGGCTCGCCAGATAACC
 CTGTTGGAGTGTGTCGGAAGGGCCGGTATGGAGAAGTATGGAGGGGACAGCTGGCAAGGC
 GAAAATGTCGCTGTGAAGATCTTCTCCTCCCGAGACGAGAAGTCATGGTTCAGGGAGACGG
 AATTGTACAACACTGTGATGTTGAGGCATGAAAATATCTTAGGTTTCATCGCTTCAGACATG
 ACCTCCAGACACTCCAGTACCCAGCTGTGGCTCATCACACATTACCATGAAATGGGATCGTT
 GTATGACTACCTTCAGCTCACTACTCTGGATACGGTTAGCTGCCTTCGGATTGTACTGTCCAT
 AGCCAGCGGCCTTGCCCATTTGCACATAGAGATATTTGGGACCCAAGGGAAGTCCGCCATT
 GCCCATCGAGATCTGAAGAGCAAAAACATCCTGGTGAAGAAGAATGGACAGTGTGCATAG
 CAGATTTGGGCCTGGCAGTCATGCATTCCCAGAGCACAAACCAGCTTGATGTGGGAAACAA
 CCCCCGTGTGGGGACCAAGCGCTACATGGCTCCGGAAGTGCTCGATGAAACCATCCAAGTG
 GATTGCTTTGATTCTTATAAGAGGGTCGATATTTGGGCCTTTGGCCTTGTTCTGTGGGAAGTG
 GCCAGGCGAATGGTGAGCAATGGTATAGTGGAAGATTACAAGCCACCATTCTATGATGTGG
 TTCCAATGACCCAAGTTTTGAAGATATGAGGAAAGTTGTCTGTGTGGATCAACAGAGGCC
 AAACATACCTAACAGATGGTTCTCAGACCCGACATTAACCTTCTCTGGCGAAGCTGATGAAA
 GAGTGCTGGTATCAGAACCCATCCGCAAGACTCACAGCTCTACGTATCAAAAAGACTTTGA
 CCAAAATCGATAATTCCCTAGACAAATTAATAAACTGACTGTTGACCTTGTCACCGGTGTCAA
 GAAGGAGAGTCAATGCTGTCCTTGTCCAGCTGGGACCTAATGCTGGCCTGACTGGTTGTGAG
 AACAGAATCCATCTGACCCCTTCCCGAAGTGGCTGCTTTGACGGAAGCAGATGTCTCTTCC
 CAGCCATGTTCCAGGGGGAGACACCAAAACCACCCTAACCTCGCTCAAAAACCTGTGACTCG

AGCCCTCGATGAACTGTTACACACCACAAAGACTTAACGGTGGGCAGGTCTGGTGGCAAGGG
 GGAGGGAAGTGGAGGAACCCGGAAAGATCCTGCAGGCGATCTGGGCATTAAGACAGTGGC
 TCTCTGCGTATCTTTCGCGGGTCTCCTAGACACTCCCCACGGGAAGCTCAAGGAGGCGGTGA
 ATTCGTAATCAGCAATATCGGCTGCATCTACTCTTCGTTGCACTAGGAATTCTGTGCATTCTC
 TACTTGCACTGTGGCCCTTAATCTTAAAGACCCAACTTGCCAAAACATTGGCTGCGTACTCC
 ACTGGCCTGTCTCTGGATAATAGGAATTCAATCTGGCAACACAAAAATGTACCGTTGGACTC
 TGCTGCATTTTACACACGTGCTGATGTTTACAAGGATGCGAACATTAGGAATTGTTTAGACA
 CAACTTTGCAAATTATTTATTACTGGTGCCTTAGCGGTTTGTGTTGAAACCGCCTCGTGCATA
 TGTTAAAGCTTATTTTTATGTGGTCTTATGATTTTATTACCGAAATGTTTTTAACACCCAACT
 CTGAAACGGACATTTTCTTTTATTATCAGTTAAATTCACATTTAAGTGCTTCACATTTTTTTT
 TAAATGTGTGTAGACTGTAACCTTCTTTTCAGTTCGTATGCAGAACATATTTAGCCATTACC
 CATGCAACACCACCCGATATATTACTGATTTAGAAGCAAAGATTTTCAGTAGAATTTTAGTCC
 CAAACGCTGTGGGGGGAAATGCATCTTCTTCGGAATTATCCATTACGTGCATTTAACTCTG
 CCAGAAAAAAAATAACTATTTTGTGTTTAATCTACTTTTGTATTAGTAGTTATTTGTATAA
 ATTAAATAAACTGTTTTCAAGTCAAAAAAAAAAAAAAAAAA (SEQ ID NO: 430)

[000402] In some embodiments, an oligonucleotide comprises a region of complementarity to an ACVR1 sequence as set forth in SEQ ID NO: 429 or SEQ ID NO: 430. In some embodiments, the oligonucleotide comprises a region of complementarity that is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to an ACVR1 sequence as set forth in SEQ ID NO: 429 or SEQ ID NO: 430. In some embodiments, the oligonucleotide comprises a sequence that has at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides that are perfectly complementary to an ACVR1 sequence as set forth in SEQ ID NO: 429 or SEQ ID NO: 430. In some embodiments, an oligonucleotide may comprise a sequence that targets (*e.g.*, is complementary to) an RNA version (*i.e.*, wherein the T's are replaced with U's) of an ACVR1 sequence as set forth in SEQ ID NO: 429 or SEQ ID NO: 430. In some embodiments, the oligonucleotide comprises a sequence that is complementary (*e.g.*, at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% complementary) to an RNA version of an ACVR1 sequence as set forth in SEQ ID NO: 429 or SEQ ID NO: 430. In some embodiments, the oligonucleotide comprises a sequence that has at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides that are perfectly complementary to an RNA version of an ACVR1 sequence as set forth in SEQ ID NO: 429 or SEQ ID NO: 430.

[000403] In some embodiments, an ACVR1-targeting oligonucleotide comprises an antisense strand that comprises at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides of a sequence comprising any one of SEQ ID NOs: 479-502. In some embodiments, an ACVR1-targeting oligonucleotide comprises an antisense strand that comprises any one of SEQ ID NOs: 479-502. In some embodiments, an ACVR1-targeting oligonucleotide comprises an antisense strand that comprises shares at least 70%, 75%, 80%, 85%, 90%, 95%, or 97% sequence identity with at least 12 or at least 15 consecutive nucleotides of any one of SEQ ID NOs: 479-502.

[000404] In some embodiments, an ACVR1-targeting oligonucleotide comprises an antisense strand that targets an ACVR1 sequence comprising any one of SEQ ID NOs: 431-478. In some embodiments, an oligonucleotide comprises an antisense strand comprising at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 nucleotides (*e.g.*, consecutive nucleotides) that are complementary to an ACVR1 sequence comprising any one of SEQ ID NOs: 431-478. In some embodiments, an ACVR1-targeting oligonucleotide comprises an antisense strand comprising a sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, or 97% complementary with at least 12 or at least 15 consecutive nucleotides of any one of SEQ ID NOs: 431-478.

[000405] In some embodiments, an ACVR1-targeting oligonucleotide comprises an antisense strand comprises a region of complementarity to a target sequence as set forth in any one of SEQ ID NOs: 431-478. In some embodiments, the region of complementarity is at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or at least 19 nucleotides in length. In some embodiments, the region of complementarity is 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 nucleotides in length. In some embodiments, the region of complementarity is in the range of 8 to 20, 10 to 20 or 15 to 20 nucleotides in length. In some embodiments, the region of complementarity is fully complementary with all or a portion of its target sequence. In some embodiments, the region of complementarity includes 1, 2, 3 or more mismatches.

[000406] In some embodiments, an ACVR1-targeting oligonucleotide further comprises a sense strand that hybridizes to the antisense strand to form a double stranded siRNA. In some embodiments, the ACVR1-targeting oligonucleotide comprises an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 479-502. In some embodiments, the ACVR1-targeting oligonucleotide further comprises a sense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 455-478.

[000407] In some embodiments, the ACVR1-targeting oligonucleotide is a double stranded oligonucleotide (*e.g.*, an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 479-502 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 455-478, wherein the antisense strand and/or (*e.g.*, and) comprises one or more modified nucleosides (*e.g.*, 2'-modified nucleosides). In some embodiment, the one or more modified nucleosides are selected from 2'-O-Me and 2'-F modified nucleosides.

[000408] In some embodiments, the ACVR1-targeting oligonucleotide is a double stranded oligonucleotide (*e.g.*, an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 479-502 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 455-478, wherein the

each nucleoside in the antisense strand and/or (e.g., and) each nucleoside in the sense strand is a 2'-modified nucleoside selected from 2'-O-Me and 2'-F modified nucleosides.

[000409] In some embodiments, the ACVR1-targeting oligonucleotide is a double stranded oligonucleotide (e.g., an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 479-502 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 455-478, wherein the each nucleoside in the antisense strand and each nucleoside in the sense strand is a 2'-modified nucleoside selected from 2'-O-Me and 2'-F modified nucleosides, and wherein the antisense strand and/or (e.g., and) the sense strand each comprises one or more phosphorothioate internucleoside linkages. In some embodiments, the sense strand does not comprise any phosphorothioate internucleoside linkages (all the internucleoside linkages in the sense strand are phosphodiester internucleoside linkages), and the antisense strand comprises 1, 2, or 3 phosphorothioate internucleoside linkages. In some embodiments, the antisense strand comprises 2 phosphorothioate internucleoside linkages, optionally wherein the two internucleoside linkages at the 3' end of the antisense strand are phosphorothioate internucleoside linkages and the rest of the internucleoside linkages in the antisense strand are phosphodiester internucleoside linkages,

[000410] In some embodiments, the antisense strand of the ACVR1-targeting oligonucleotide comprises a structure of (5' to 3'):

fNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmN*fN*mN, wherein “mN” indicates 2'-O-methyl (2'-O-Me) modified nucleosides; “fN” indicates 2'-fluoro (2'-F) modified nucleosides; “*” indicates phosphorothioate internucleoside linkage; and the absence of “*” between two nucleosides indicate phosphodiester internucleoside linkage.

[000411] In some embodiments, the sense strand of the ACVR1-targeting oligonucleotide comprises a structure of (5' to 3'):

mNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfN, wherein “mN” indicates 2'-O-methyl (2'-O-Me) modified nucleosides; “fN” indicates 2'-fluoro (2'-F) modified nucleosides; and the absence of “*” between two nucleosides indicate phosphodiester internucleoside linkage.

[000412] In some embodiments, the antisense strand of the ACVR1-targeting oligonucleotide is selected from the modified version of SEQ ID NOs: 479-502 listed in Table 19. In some embodiments, the sense strand of the ACVR1-targeting oligonucleotide is selected from the modified version of SEQ ID NOs: 455-478 listed in Table 19. In some embodiments, the ACVR1-targeting oligonucleotide is a siRNA selected from the siRNAs listed in Table 19.

Table 17. ACVR1 Target Sequences

Corresponding nucleotides of Sequence NM_001105.5 (SEQ ID NO: 429)	ACVR1 Target Sequence	SEQ ID NO:
877-895	TCGTGTACATCAGGAAGTG	431
878-896	CGTGTACATCAGGAAGTGG	432
1380-1398	TTTGGGCCTGGCAGTCATG	433
1573-1591	GTGAGCAATGGTATAGTGG	434
1486-1704	TGAGCAATGGTATAGTGGA	435
1574-1592	CCCAAGTTTTGAAGATATG	436
1633-1651	CCAAGTTTTGAAGATATGA	437
1693-1711	AACAGATGGTTCTCAGACC	438
1696-1714	AGATGGTTCTCAGACCCGA	439
1904-1922	ACCTAATGCTGGCCTGACT	440
2484-2502	TTGCAAATTATTTATTACT	441
2617-2635	TTTTCTTTTATTATCAGTT	442
2667-2685	TGTGTGTAGACTGTAACTT	443
2742-2760	ATATTACTGATTTAGAAGC	444
2752-2770	TTTAGAAGCAAAGATTTCA	445
2757-2775	AAGCAAAGATTTTCAGTAGA	446
2758-2776	AGCAAAGATTTTCAGTAGAA	447
2759-2777	GCAAAGATTTTCAGTAGAAT	448
2760-2778	CAAAGATTTTCAGTAGAATT	449
2834-2852	CATTTAAACTCTGCCAGAA	450
2859-2877	AACTATTTTGTTTTAATCT	451
2882-2900	TTTGTATTTAGTAGTTATT	452
2912-2930	AATAAACTGTTTTCAAGTC	453
2913-2931	ATAAACTGTTTTCAAGTCA	454

* The target sequences contain Ts, but binding to RNA and/or DNA is contemplated.

[000413] In some embodiments, an oligonucleotide may comprise or consist of any sequence as provided in Table 18.

Table 18. Oligonucleotide sequences for targeting ACVR1

Passenger strand (RNA)/Sense strand	SEQ ID NO:	Guide strand (RNA)/Antisense strand	SEQ ID NO:
AUUCGUGUACAUCAGGAAGUG	455	CACUUCCUGAUGUACACGAAUGA	479
UUCGUGUACAUCAGGAAGUGG	456	CCACUUCCUGAUGUACACGAAUG	480
GAUUUGGGCCUGGCAGUCAUG	457	CAUGACUGCCAGGCCCAAUCUG	481
UGGUGAGCAAUGGUAUAGUGG	458	CCACUAUACCAUUGCUCACCAUC	482
GGUGAGCAAUGGUAUAGUGGA	459	UCCACUAUACCAUUGCUCACCAU	483

GACCCAAGUUUUGAAGAU AUG	460	CAUAUCUUCAAAACUUGGGUCAU	484
ACCCAAGUUUUGAAGAU AUGA	461	UCAUAUCUUCAAAACUUGGGUCA	485
CCAACAGAUGGUUCUCAGACC	462	GGUCUGAGAACCAUCUGUUGGGU	486
ACAGAUGGUUCUCAGACCCGA	463	UCGGGUCUGAGAACCAUCUGUUG	487
GGACCUAAUGCUGGCCUGACU	464	AGUCAGGCCAGCAUUAAGGUCCCA	488
CUUUGCAAAUUAUUUAUUACU	465	AGUAAUAAAUAAUUUGCAAAGUU	489
CAUUUUCUUUUUAUUUAUCAGUU	466	AACUGAUAAUAAAAGAAAAUGUC	490
UAUGUGUGUAGACUGUAACUU	467	AAGUUACAGUCUACACACAUACA	491
AUAUAUUACUGAUUUAGAAGC	468	GCUUCUAAAUCAGUAAUUAUUAUC	492
GAUUUAGAAGCAAAGAUUUCA	469	UGAAAUCUUUGCUUCUAAAUCAG	493
AGAAGCAAAGAUUUCAGUAGA	470	UCUACUGAAAUCUUUGCUUCUAA	494
GAAGCAAAGAUUUCAGUAGAA	471	UUCUACUGAAAUCUUUGCUUCUA	495
AAGCAAAGAUUUCAGUAGAAU	472	AUUCUACUGAAAUCUUUGCUUCU	496
AGCAAAGAUUUCAGUAGAAUU	473	AAUUCUACUGAAAUCUUUGCUUC	497
UGCAUUUAAACUCUGCCAGAA	474	UUCUGGCAGAGUUUAAAUGCACG	498
AUAACUAAUUUGUUUUAUUCU	475	AGAUUAAAACAAAAUAGUUAUUU	499
UUUUUGUAUUUAGUAGUUAUU	476	AAUAACUACUAAAUACAAAAGU	500
UAAAUAAACUGUUUUAAGUC	477	GACUUGAAAACAGUUUAUUUAAU	501
AAAUAAACUGUUUUAAGUCA	478	UGACUUGAAAACAGUUUAUUUAA	502

[000414] In some embodiments, an oligonucleotide is a modified oligonucleotide as provided in Table 19, wherein ‘mN’ represents a 2’-O-methyl modified nucleoside (e.g., mU is 2’-O-methyl modified uridine), ‘fN’ represents a 2’-fluoro modified nucleoside (e.g., fU is 2’-fluoro modified uridine), ‘*’ represents a phosphorothioate internucleoside linkage, and lack of “*” between nucleosides indicate phosphodiester internucleoside linkage.

Table 19. Modified Oligonucleotides for targeting ACVR1

siRNA #	Modified Passenger strand/Sense strand	SEQ ID NO:	Modified Guide strand/Antisense strand	SEQ ID NO:
hsACVR1-24	mAmUfUmCfGmUfGmUfAmCf AmUfCmAfGmGfAmAfGmUfG	455	fCfAmCfUmUfCmCfUmGfAm UfGmUfAmCfAmCfGmAfAm U*fG*mA	479
hsACVR1-14	mUmUfCmGfUmGfUmAfCmAf UmCfAmGfGmAfAmGfUmGfG	456	fCfCmAfCmUfUmCfCmUfGm AfUmGfUmAfCmAfCmGfAm A*fU*mG	480
hsACVR1-22	mGmAfUmUfUmGfGmGfCmCf UmGfGmCfAmGfUmCfAmUfG	457	fCfAmUfGmAfCmUfGmCfCm AfGmGfCmCfCmAfAmAfUmC *fU*mG	481
hsACVR1-23	mUmGfGmUfGmAfGmCfAmAf UmGfGmUfAmUfAmGfUmGfG	458	fCfCmAfCmUfAmUfAmCfCm AfUmUfGmCfUmCfAmCfCmA *fU*mC	482
hsACVR1-18	mGmGfUmGfAmGfCmAfAmUf GmGfUmAfUmAfGmUfGmGfA	459	fUfCmCfAmCfUmAfUmAfCm CfAmUfUmGfCmUfCmAfCmC *fA*mU	483
hsACVR1-13	mGmAfCmCfCmAfAmGfUmUf UmUfGmAfAmGfAmUfAmUfG	460	fCfAmUfAmUfCmUfUmCfAm AfAmAfCmUfUmGfGmGfUm C*fA*mU	484

hsACVR1-7	mAmCfCmCfAmAfGmUfUmUf UmGfAmAfGmAfUmAfUmGfA	461	fUfCmAfUmAfUmCfUmUfCm AfAmAfAmCfUmUfGmGfGm U*fC*mA	485
hsACVR1-20	mCmCfAmAfCmAfGmAfUmGf GmUfUmCfUmCfAmGfAmCfC	462	fGfGmUfCmUfGmAfGmAfAm CfCmAfUmCfUmGfUmUfGm G*fG*mU	486
hsACVR1-11	mAmCfAmGfAmUfGmGfUmUf CmUfCmAfGmAfCmCfCmGfA	463	fUfCmGfGmGfUmCfUmGfAm GfAmAfCmCfAmUfCmUfGm U*fU*mG	487
hsACVR1-16	mGmGfAmCfCmUfAmAfUmGf CmUfGmGfCmCfUmGfAmCfU	464	fAfGmUfCmAfGmGfCmCfAm GfCmAfUmUfAmGfGmUfCm C*fC*mA	488
hsACVR1-6	mCmUfUmUfGmCfAmAfAmUf UmAfUmUfUmAfUmUfAmCfU	465	fAfGmUfAmAfUmAfAmAfUm AfAmUfUmUfGmCfAmAfAm G*fU*mU	489
hsACVR1-8	mCmAfUmUfUmUfCmUfUmUf UmAfUmUfAmUfCmAfGmUfU	466	fAfAmCfUmGfAmUfAmAfUm AfAmAfAmGfAmAfAmAfUm G*fU*mC	490
hsACVR1-15	mUmAfUmGfUmGfUmGfUmAf GmAfCmUfGmUfAmAfCmUfU	467	fAfAmGfUmUfAmCfAmGfUm CfUmAfCmAfCmAfCmAfUmA *fC*mA	491
hsACVR1-21	mAmUfAmUfAmUfUmAfCmUf GmAfUmUfUmAfGmAfAmGfC	468	fGfCmUfUmCfUmAfAmAfUm CfAmGfUmAfAmUfAmUfAm U*fU*mC	492
hsACVR1-5	mGmAfUmUfUmAfGmAfAmGf CmAfAmAfGmAfUmUfUmCfA	469	fUfGmAfAmAfUmCfUmUfUm GfCmUfUmCfUmAfAmAfUm C*fA*mG	493
hsACVR1-10	mAmGfAmAfGmCfAmAfAmGf AmUfUmUfCmAfGmUfAmGfA	470	fUfCmUfAmCfUmGfAmAfAm UfCmUfUmUfGmCfUmUfCm U*fA*mA	494
hsACVR1-4	mGmAfAmGfCmAfAmAfGmAf UmUfUmCfAmGfUmAfGmAfA	471	fUfUmCfUmAfCmUfGmAfAm AfUmCfUmUfUmGfCmUfUm C*fU*mA	495
hsACVR1-3	mAmAfGmCfAmAfAmGfAmUf UmUfCmAfGmUfAmGfAmAfU	472	fAfUmUfCmUfAmCfUmGfAm AfAmUfCmUfUmUfGmCfUm U*fC*mU	496
hsACVR1-1	mAmGfCmAfAmAfGmAfUmUf UmCfAmGfUmAfGmAfAmUfU	473	fAfAmUfUmCfUmAfCmUfGm AfAmAfUmCfUmUfUmGfCm U*fU*mC	497
hsACVR1-17	mUmGfCmAfUmUfUmAfAmAf CmUfCmUfGmCfCmAfGmAfA	474	fUfUmCfUmGfGmCfAmGfAm GfUmUfUmAfAmAfUmGfCm A*fC*mG	498
hsACVR1-12	mAmUfAmAfCmUfAmUfUmUf UmGfUmUfUmUfAmAfUmCfU	475	fAfGmAfUmUfAmAfAmAfCm AfAmAfAmUfAmGfUmUfAm U*fU*mU	499
hsACVR1-2	mUmUfUmUfUmGfUmAfUmUf UmAfGmUfAmGfUmUfAmUfU	476	fAfAmUfAmAfCmUfAmCfUm AfAmAfUmAfCmAfAmAfAm A*fG*mU	500
hsACVR1-19	mUmAfAmAfUmAfAmAfCmUf GmUfUmUfUmCfAmAfGmUfC	477	fGfAmCfUmUfGmAfAmAfAm CfAmGfUmUfUmAfUmUfUm A*fA*mU	501
hsACVR1-9	mAmAfAmUfAmAfAmCfUmGf UmUfUmUfCmAfAmGfUmCfA	478	fUfGmAfCmUfUmGfAmAfAm AfCmAfGmUfUmUfAmUfUm U*fA*mA	502

f. FBXO32 Oligonucleotides

[000415] Examples of oligonucleotides useful for targeting FBXO32 are provided in Cong *et al.*, Hum Gene Ther. 2011 Mar;22(3):313-24; Castellero *et al.*, Metabolism. 2013; Oct;62(10):1495-502; Wada *et al.*, Nature Precedings 2008; Lagirand-Cantaloube *et al.*, PLoS

One. 2009;4(3):e4973; US8097596, entitled, “COMPOSITIONS AND METHODS FOR THE TREATMENT OF MUSCLE WASTING,” ISSUED ON January 17, 2012; WO2019139351, entitled, “PHARMACEUTICAL COMPOSITION FOR PREVENTING OR TREATING MUSCULAR DISEASE OR CACHEXIA COMPRISING, AS ACTIVE INGREDIENT, MIRNA LOCATED IN DLK1 -DIO3 CLUSTER OR VARIANT THEREOF,” which was published on July 18, 2019; WO2008156561, entitled, “METHODS AND COMPOSITIONS FOR THE TREATMENT AND DIAGNOSIS OF STATIN-INDUCED MYOPATHY,” which was published on December 24, 2008; and WO2019113393, entitled, “COMPOSITIONS AND METHODS OF TREATING MUSCLE ATROPHY AND MYOTONIC DYSTROPHY,” which was published on June 13, 2019, the contents of each of which are incorporated herein in their entireties. In some embodiments, the oligonucleotide is a CRISPR guide RNA targeting FBXO32.

[000416] In some embodiments, oligonucleotides may have a region of complementarity to a human FBXO32 sequence, for example, as provided below (Gene ID: 114907; NCBI Ref. No: NM_058229.4):

```
AGCACTCCCGGAGCCTGCAACGCTTGAGATCCTCTCCGCGCCCCGCCACCCCGCAGG
GTGCCCCGCGCCGTTCCCGCCGCCCGCCGCCCCCGTCGCGGGCCCCCTGCACCCCGA
GCATCCGCCCCGGGTGGCACGTCCCCGAGCCCACCAGGCCGGCCCCGTCTCCCCAT
CCGTCTAGTCCGCTCGCGGTGCCATGCCATTCCCTCGGGCAGGACTGGCGGTCCCCCG
GGCAGAACTGGGTGAAGACGGCCGACGGCTGGAAGCGCTTCCTGGATGAGAAGAG
CGGCAGTTTCGTGAGCGACCTCAGCAGTTACTGCAACAAGGAGGTATACAATAAGG
AGAATCTTTTCAACAGCCTGAACTATGATGTTGCAGCCAAGAAGAGAAAGAAGGAC
ATGCTGAATAGCAAAACCAAACTCAGTATTTCCACCAAGAAAAATGGATCTATGT
TCACAAAGGAAGTACTAAAGAGCGCCATGGATATTGCACCCTGGGGGAAGCTTTCA
ACAGACTGGACTTCTCAACTGCCATTCTGGATTCCAGAAGATTTAACTACGTGGTCC
GGCTGTTGGAGCTGATAGCAAAGTCACAGCTCACATCCCTGAGTGGCATCGCCCAA
AAGAACTTCATGAATATTTTGGAAAAAGTGGTACTGAAAGTCCTTGAAGACCAGCA
AAACATTAGACTAATAAGGGAAGTACTCCAGACCCTCTACACATCCTTATGTACACT
GGTCCAAAGAGTCGGCAAGTCTGTGCTGGTTCGGGAACATTAACATGTGGGTGTATC
GGATGGAGACGATTCTCCACTGGCAGCAGCAGCTGAACAACATTCAGATCACCAGG
CCTGCCTTCAAAGGCCTCACCTTCACTGACCTGCCTTTGTGCCTACAACTGAACATC
ATGCAGAGGCTGAGCGACGGGCGGGACCTGGTCAGCCTGGGCCAGGCTGCCCCCGA
CCTGCACGTGCTCAGCGAAGACCGGCTGCTGTGGAAGAACTCTGCCAGTACCACT
TCTCCGAGCGGCAGATCCGCAAACGATTAATTCTGTCAGACAAAGGGCAGCTGGAT
TGGAAGAAGATGTATTTCAAACCTTGTCGGATGTTACCCAAGGAAAGAGCAGTATGG
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AGATACCCTTCAGCTCTGCAAACACTGTCACATCCTTTCCTGGAAGGGCACTGACCA
TCCGTGCACTGCCAATAACCCAGAGAGCTGCTCCGTTTCACTTTCACCCCAGGACTT
TATCAACTTGTTCAAGTTCTGAATCCCAGCACATGACAACACTTCAGAAGGGTCCCC
CTGCTGACTGGAGAGCTGGGAATATGGCATTGTTGGACACTTCATTTGTAAATAGTGTA
CATTTTAAACATTGGCTCGAACTTCAGAGATAAGTCATGGAGAGGACATTGGAGG
GGAGAAATGCAGTTGCTGACTGGGAATTTAAGAATGTGAACTTCTCACTAGAATTG
GTATGGAAAAGCAAAATACTGTAAATAAACTTTTTTTCTAACAATTTGCCAGCAAG
ACTATAAGGGCAATAATTCTATTTTCAGCGGTGAAAATGGAGTCCTCTTAATGGTCAC
AGAACTCTCTTATAGTTCCCTAGGAAGAAAAAGGCAAACTCAAATACAAAATAG
GACGCTTTGTTTACAATGTGAAAATTTGTTTAGAAAAGAAAAAATGAAGAAGGAAA
ACTATATAGGAGAAATTCCTGGGCTTTGGGGTTTGATCTGGTGTGTTTGTGAGAAG
GCGAAGGAAGCGCCACCCATCCTAAACCTGCATGGGCACAGAGCCTTACCCTACAG
AGATACCACACAATGGTCTACCTCTAAAAGCGTAGAGTGCCCTCTCTGACAACGCA
TGTGATCCAGTAGGCAGTGTCTGTTTTCTCGTAAGTGTTTTCATCACTATAAAAAG
TGATTTAAATGGAAAGGGATATTGGAGGCAATCCTCTGGTTTCACACTTCCTTTTC
AGGCAAACAGGGCCCTCCTTAGAGTTATCTGTTACCAGAACAAACCCAAAAGCACA
TGTTCCTTTTTTCTGTCATGTTGTAGCTCATTTGGGGGAAAAGAAGGCCAACTTAA
AACAGTCCCAGGGGAGGATTGCTTGAGCCCAGGAGTCTGAGGTTTGCAGTGAGCTA
TGATTGTGCCACTGCACTCCAGCCTGTCTCCAAAACAAAACAAAACAAAAG
CCGTCCCAGAGGAAGTCCTGCTGCAGAAAAGATGATAGAATTGGTCACCCAATCAA
TAGCTGTGAAGACTTCCTTATTCCTGCTGAACTTCCTTCCTTGGATATCTTCATGGAT
AAGCCTGTGTCTGTGGACAGAGTGGGGCCCAAGTGCTGAGGCTCGAAAGACAGGTT
TTACAATCAGCCAATTAAACATCTTACCAGTTGCTGTACCCCTTGCCAAGGGGATGA
GCTGAGGAGCTTCTTTTCTTTAGGTCCAACATCAAATGAGTCCATCTGAGCTAGGG
CTTTTTGCAAAGGTGATTAAAAATCAAGGCTGGAGTTCCAGCCAAATAGGGAGGAG
AGGTACCACAAGTTCATCTTAACTTGCTTCCGGGCTGGGTAGTTAAAACAGGAAG
ATCCCAAGGGGATCTTACGAGGCAAATATCAGCAGGTAAGTGTGGAAGAAAGGAA
ATCTCAGGACCTAATGAGTTCGTTGTAAAATATTCCTGGGAATAGATGGGGGATCT
ACTCCAGTTTTTTTACTTTTTACAGAATATTGTTGCTTTCCTACAACAATGTACATAT
ATTTGCAGTTGTATATGCTTTTTTTTTTTTCCAAATAAACTTGTCACCCTGCATGCCCT
TGGCAAATAAGTGAAGCAGAAATAGGAACACAGTCCACATTCAAGTTGAGGAACA
GTGTATCTTTAAGAGCTGAGCTTTGGGTGACCTGGAAAGGGGGAAAGATGGCTAAG
CATGGAGAGAAACGAGGCAAGAGACAAGCTATGATACAACACCGCTTCAGCCCCCT
GCCCTCAATAGCACACAACCCACATATCAGCTTTCTGAAGAGAAGGAACCTACTGT
TTAGTGCTCCTCACTTTGCAATGTTTGTGCTACGCCAGAATTTCTCCAGTTTTTTTCA

TTATCATCCCCCTGAGAAAAAAATTACATTGAATTTAAATTTTCCCTAATAAGAGAA
ATTAAATATGAAAGAATAGGATTTTGTGGGTAAAGATTGAGCTTTGGAAGGTCACG
AACCATTATTCTATCTAAGGTGTGTGTTTTGTTTTGTTTTTTTTTTGTTTTTTTTTGCA
ATCCCTCTCCCCCTGAACCAATTTACATTGGGAATGCAGGACCTAGACTGCTGAAT
AAAAAGCTACTTCTTCTATAATTGTCAGGTTCTCTCCAATTTCTCAGCTTCCTCAAAG
ACATGGGGTGGAGTTGGGTGTGCCATCACTGAGAGAGCTCTGGAACCTTTGACTCTT
AGTGACATTTTTAGATTTAGGGGTTCATGGCCTTCCACATGTTGCCACCAACTGGTG
ATCTCTGCCCCTTCATGCTGATCAAGAAAGTAGAACTCCTCGTCGCCTTCAGGTTT
GCAGTCGCAGAAACATTGCCTGCTGTGGACTGTCAGCACAAAACCTGGGACACTGGT
GTCATTTAGACTGTCAGCAGTGCACATGATTGTACGATAGACTCCAGGCAACCATGT
GCATCTGTGCAAGATGACCTCTGCCCCAAGAGAAGGGTTACGGTCTAATTAAATGT
TTACCAAGATGGTACCAGTGGGCTCTCCCCGTGTCCTTTGGTGTTATTGGAGCTGGT
GTATGACAGACTCAAGGAAATTTTTTAAGGAAAATGAAGAAGAAATCAACCTTTAT
GGTTCTCTTTCATTGGAAGAGGAGAATAAGGAAAGAAATGGCAGGTAGAGAGGGA
GGGGGAAAGGAATAGAAATGGCATGTCTTTGATGCTGTGGCTTGTGTGGGGACAAT
GGGAAGAGCACAGCAGGCACAACATATCTGTGTTAGTGCCACGTGGTATCTGTAA
GTATGGCCAGAGCCTCACATATAAGTGAAGAGAGTTAAGACAATTCTTGCTCTTTG
ACAATAATAGTCTATAGAATTTCTATTGGCAAACCATCCCAGACAACCTGACCTAT
CAAACAAAAGCAAATAATCCCTGTCTCAGAACTGCTGGTCTAAAAGCTAGAAGGGG
CATGATAATGGAAATTGCTAGAAAAGAGAGAATGCTCTACTCTCTTTCCTGTGCCTA
CCTACCCCCATCCTAAACCCTGTAAACAGAAATTTCAAATAGATGTCAAATATGA
AGTAATTCAGACTTCCAAAGAAGGAAAGAGTTCTGCCAGGGCAGTATGAGCAAAT
CCACAGGGATGTTAAGATTTGGTCCAACCTCAAAGGTTTATGGGCAGTGAGCCTAGA
GTCTCTTGAGAGTAAACCCTTGCATTTGGGACAAGGAGAATATGTGAAGTTCAGGA
GTGCTCACACTAGAGCAAGATCCAGAAAAAAAATCCAATGGCATTTTAAACTA
GATTGCATTATCACTCAATGCTGTTACTTTGAGCAGACAAATCAGTTGAATGGGAGG
GCAAATGGCAGAAATGAACAAAAGCTATTAGGTGAAAGCATCCCCAATGTATCAGT
TGTGAGATGATTTTTGTTTAATGATGATCAGGTTTACATTGAAGTGGCTTGGAAGAC
GTATTTCAGAGGGACTGGGTTTGTACTGCAAACTCTGAACACTAGAGCAGGTTCT
ACTAGCACTTGGGCAGTAAGGTAGCGGGTGTGTATTATGCTATTGCCATAGTTCTCG
TCTTTGTGGATTACATACCCTTTCCCATGAGGAGCTTGCTACTAACAGCCTCCTGTT
TCTGTTGTTTTTATATGGGAGAAGAGAAAGAGCTTGGAATTTCAATTGTCTAAACAA
TTGGTATGATTTACAAGAAGGCAAACCATTCAGGAGATGTTCAACAGTGTATCATTC
TTAGCATTCAATACAATGTTTATTATAAAATATACACCTGAGTTTATGTTTTTCTGCC
AGGCTGAAGGGCAATAATGTCTTGCTATGCAAACTCTATTTTATGTGTGAATTTT

TTTAACTGTAATTTTATGTGTGAATTTTTTTTAACTAAACTCTATCATCATTTTCTATGT
TGACATCTTTTTTTTTTTTTTAAATCTGTTTCCAACCTCTGAGTCTGTGAACTATCTCTTC
TGACTGGATGCTGGCCTAAAATCCTATTAGTGCTTAAACAGACCTCAAAACACTCTG
AACCTGTAGGCCAATACAGAGATGTTGTTCTTTGATATATCTTGGGTCCTTGATGGC
TTCAACAAACAAGGTCATAATTTGTTTAAATTCAGTGTTTTCTGTAGATACCTTCTTC
TCAGTTTCATTAAGAAGAGTAACCATCTTTGGTTTTCCAAAGAATGGAACTCCTAC
CCTAGACTTTAGACTTAGAGCGTCTGCCTTTCACGATGAGTAAGAGATCCAGAATGT
TTAGGGGATGTGCGTCAGCCACCTGGTACAGTGCCAAAGCTGAATGCGAACTTGA
GGCCTCCTGAGGCCTGACCTTCTATGCCCCCAGCCCTCCACCCCAAGCACCTTTTGG
TGTGGCTGGAAACACATGACATTGGATGTGATTTTTCTCAAGCCCTTCACTGTGGAA
GGCATGGGAGACTGCCCAGCATTGGGCATGTGGCTGTTAACGTTTCCATTTCAAGTC
CCTGATTCTTACTGGAGAAGTTAAGGAGCCACTTAATGTTTTTCACAGACCTCTGATT
CTGTTGTGAATGTGGCATTCCAGTGAGTACAACCTGCTTGCTATAAAGAAAGCAGC
ATATTTTGACAATTTTATTTCTTCCTTGGGTACTTACATTTTTATTACAAAAATGGCC
GTTATAAAAAAAGACAGAAGGGCTGGGCAGTGGCTTGCTCCCTAGAAACTGAGATT
CCGAAGCAGGTGTTTCCTCTCCCCTAGACTCAGAGGTACATTTAATCCATCTTCTCC
ATTTCTCCTTCAGGACCAGCTATGAGATTCAGTGCATTTCTAGCCCAGCGGATGTT
CATTCTCCACTAAACTTCATCTTTTACTAAGCAAAGGGGGATTATTCCATGAGGCAG
CCAGGAGCAAGGGGGCCATGATATTCATGACTTTGTCTGCTGGGCATTTTTCAAAGTG
TCCTTGAATTCCTCAGCAAACAAAGCTTTCTGGAGAATCTCTCAAACTTAGGCCC
TGCTCCATTTGGCCAAAAATGATGGCTGCTCCAAACTCTGAACTTCTTAAACTCC
ATCTGCTACATTATTTCTGGAGTTTAAACATGACTTTTTCTGTCTTTGAGTATAGATG
TGTTTGTTTAATTAACGAAGCACAAAGTCTGTTAAGCAGAAGGCTCCAAGCTGTATTC
TATACTTGGGAATCCTTGGTGCCATCTTTATTCTACCAAGTGCCAATCACCATGGCT
AAAGTGGGCGTATATTACAGCCTGTGTCCTAAGCTTAGAAGCTTTAATGTACTTTTT
TAAATGAAAAGTATTAGAGGGGGTTGAACATTGTAACATAAAGTTAGACC
AATTACATGCAGAGATGTTTATTTAATATTGTGTGAGCTGAGTCCTTCTGTATAAAT
TATTTGCACACTTTTCTTGCATGATGAACTGATTTTTTATAGTTGTTTGTACCAGACG
GTGGCATATTTTTGTAAAAAACTTTTGACACTGAATTGCAATAAATGTTTTTCCAAC
AACA (SEQ ID NO: 505).

[000417] In some embodiments, oligonucleotides may have a region of complementarity to a mouse FBXO32 sequence, for example, as provided below (Gene ID: 67731; NCBI Ref. No: NM_026346.3)

GACGGGGCAGCGGCCCGGGATAAATACTGCGCTCGGGCAGCCGCTCAGCATTCCCA
GAGTCAGGAGGCGACCTTCCCCAACGCCTGCGCCCCTGTGAGTGCAAGGATCCCCG

CGCCCACCCAGGATCCGCAGCCCTCCACACTAGTTGACCCACTCTTGTCCCGGTTCGC
CGCCTGCGTCGTTCCCCAGCATCTTCCCAACGCGCCGCATACCCTGGGCAAGCCAGG
CCGGTTCCTGGCTGTCAATCCGTCCCGTCCGTTCGGTCGCGTCCGCGCTCTGTACCAT
GCCGTTCCCTGGGCAAGGACTGGCGGTCCCCGGGCCAGAGCTGGGTGAAGACGGCGG
ACGGCTGGAAGCGCTTCTTGGATGAGAAAAGCGGCAGCTTCGTGAGCGACCTCAGC
AGTTACTGCAACAAGGAGGTATACAGTAAGGAGAATCTGTTCAGCAGCCTGAACTA
CGACGTCGCAGCCAAGAAGAGAAAAGAAAGACATTCAGAACAGCAAAACCAAACT
CAGTACTTCCATCAAGAAAAGTGGATCTATGTTCACAAAGGAAGTACGAAGGAGCG
CCATGGATACTGTACTTTGGGGGAAGCTTTCAACAGACTGGACTTCTCGACTGCCAT
CCTGGATTCCAGAAGATTCAACTACGTAGTAAGGCTGTTGGAGCTGATAGCAAAGT
CACAGCTCACATCCCTGAGTGGCATCGCCCCAAAAGAACTTCATGAACATTTTGGAA
AAAGTGGTACTGAAAGTTCTTGAAGACCAGCAAAACATAAGACTTATACGGGAACT
TCTCCAGACTCTCTACACATCCTTATGCACACTGGTGCAGAGAGTCGGCAAGTCTGT
GCTGGTGGGCAACATTAACATGTGGGTGTATCGGATGGAGACCATTCTACACTGGC
AGCAGCAGCTGAATAGCATCCAGATCAGCAGGCCTGCCTTCAAAGGCCTCACGATC
ACCGACCTGCCTGTGTGCTTACAACTGAACATCATGCAGAGGCTGAGTGACGGGCG
GGACCTGGTCAGCCTGGGCCAGGCAGCCCCAGACCTGCATGTGCTCAGTGAGGACC
GGCTACTGTGGAAGAGACTCTGCCAGTACCACTTCTCAGAGAGGCAGATTCGCAAG
CGTTTGATCTTGTCTGACAAAGGGCAGCTGGATTGGAAGAAGATGTATTTTAAGCTT
GTACGATGTTACCCAAGAAGAGAGCAGTATGGGGTCACCCTGCAGCTTTGCAAACA
CTGCCACATTCTCTCCTGGAAGGGCACTGACCATCCGTGCACGGCCAACAACCCAG
AGAGCTGCTCCGTCTCACTTTCCCCTCAAGACTTTATCAATTTGTTCAAGTTCTGAAT
AATCCCAGCACACGACAACACTTCAGAAGGCTTCTAATTGGATGGCTGGGAGTCGG
GACACTTCATTTGTAAATAGTGTACATTTTAAGCATTGGCTTGAACTGCGGGGGAT
ACGTCATTGAGGAGACGTTGGCGGGGAAGAGATGCAGTTGCCGATGGAAATTTACA
AATGTGAATTCCACATGAGAACTGGTACAGAAAAGCAGAAATACTGTAAATAGACT
TTTTATTTTCCCTAACGATTTGCAAGCAAGACTATAAAGGCAAGAACTCTATGTCAG
CCATGGAAACGGAGTCCTCTTGAGTTCCTAGGAAGAAAAAAGGCAAAAAGCTCAAA
AACAAGATGGAACACTCTGTTTACAATGTGAAAATGTTGTTAAGACAAAAATAAGG
AAGAAGGAAGATGAACGCTGTCATTGAGAAACCCTTGGGCTTTGGGTTTGGATTCTG
GGGTTTGTTCAGCAGGCCAAGAAGTATATCCACCTGAAATCTGCACGGGCTTAA
GTCCTTATCCTATGAAGATGCCACACAATGGTCTACCTCTAAAAGCATAGCGTGTTT
TCTGGCAACATACTTTATCTGGGAGGCAATGTCTGTGTTTCATGTAAGTTCTATACT
CTGTGAAGTGATCTAAGATGGGAAGGCTGTTAGGAAAAAAAAAAAAAAGCCCTCTCT
TGGTTCTGACTTCCTGTCCCCCAGTCCCTCTCAGTCCCTGCACCTCTTCTCCTTTCA

TGTTGTCACTCCTGTAGGGAACCGGGAGGCCAGCTAAAGAACAGCAGAAGTCATGA
AGAGAGAATTAGGCACCTGTGCATGCTCAGAACTTTCCATTTAACTCTTCCTTCTTC
TAGCCTGACTTCTAGGCTTGTCCGGGCTTCCTTGAGTGTCTTCATGGATAAGTGGAT
GTCTGGGACCTTAGGAGAGCCCAAGAACTGAGGCTTGAGAGACACAGTTTCTCACA
CTAGCCAGTTAAACATTCTGCCAGCTGCTGTTTCCCCTCGGCAGGCCAATGAGCTGA
GGCACTGTCTGTTCTGTAGGCCCAGCATCCAACCTCAAGTCACCCTGAACCGGGACTT
TTTCAACAAGCATGATTTCAAAGAAAGCCTGATAGATGTGTTTCGTCTTAACTTGTTT
CAGGACTGAGTTAGAGCAAAGATAAAGAGTCCCGGGGGTTCTTGTGAGACAGAGA
CATGAACACTGTGGAAGAAAGGAGAAGGAGATCTCAGGGCTTAAGGAGTTAATTCC
TGGGGTGGGGGAAATGTTTTTATATTTTACTTTTTTACAGATTGTTGCTTTTCTACAAT
GTACATATATTTGCAATTGTATTTGCTGTTTTTTTTTTTAAATCTCCAAATAAAATTGC
CACTATGCATGCTCTTGCCAAACAAGCAGAAATAGGAATTTGTTCCATGTAAATGTT
AAGGTGTGGTGTGACCTGAAGCATTGATGCGTGGGGTAGTCCTAGGAGGAGAGGAA
AGATGGCTGAGCGTGAACAAGAACAAGGCCGGGGCAGTGAACACTTCTTCCTTCAG
TCGTAGAGCACCCTCGGGTTGGTACTGTACAGGCGGATGGAGTCTGTGGGGCTCCC
TGATTTGCAGGGTCTTACATCTGTGCTTACACCAGAAGTTCTCCATGTTTTCTTTATC
AGCACCATCTCCTGGTGGCCAAATTAAGTTGAATTTAAAGGTTTCGTAATGAGAAAA
GGGATGTGTAAAAGAACAAGATTTCTTTTACATGGAAAAGTTAAAAGTCTAAAGCT
GAACCTTGAGATTACAAACATTGTAACAGAGAAGAGTTTCCTGTTTGCTTTGGGAT
TTTTGAAATCTTCTCCCCAGAAACAATTTTACATTAAGAATGTAGGGCCTTGGGGCT
GGAGAGGTGGCTCAGCAGTTAAGAGCACTGACTGCTCTTCTGAAGGTCCTGAGTTC
AATTCCTAGCAACCACATGGTGGCTCATAACCATCCATAATGAGATCTGATGGCCTC
TTCTGGTGAGTCTGAAGACAGCTACAGTGTACTTACATATAATAAATAAATAAATA
AATAAATAAATAAATAAATAAATAAATAAATAAATCTATCTTTAAAAGAAAAAGAA
TGTAGGACCTAGGTGGAAGGAAGGAAGGAAGGAAGGAAGGAAGCAAGGAAGGAA
GGAAAGCAGGCAGGCCTGCCGCCACAGTGATTCTGAGTGACAGTGTTGAGGTTAGG
GGATCGTGGCCTTTCACATGTCCTCAGCCTGCTCTGTGGTGCTTTTCAGAGATGGGA
ACTTGTAGGGACCTTGGGGTTTACAGGTCCGTCAACTTTGCCAGCTTTGAACTGCCA
GCGCAAACTAGTTAGCCAGTCTTACAGATAGGCAGCAGTACCCAAAGTCATATAG
CATCCATACACCCCAGGCAACAATGTAAAATGGCCCTTACCCCAAGCAGCAAGGGC
ACAGCTTCTTGAAATATTTAGTAGGTGCTTGCAGGTTCTCCATGACCCTTGGTGTCA
TTGGATATGGTATGTGACACAACCGAAGAATCGTTTGACGGATGAAGAAGAGGAAA
GGAGCATGTATTGGTCGCTGTCACTGGCTGGTAGAAAACAGGAAGGATGTGGAAGG
TGGAGAGGGAGTGGGAGAGGTGTAGAAATGATGTATCTTTGATGCTGTTTAGGGTG
GGAGCAACAGAGAGAGGAGGGCAAGCAAGATACCCATATTAGGTCATGGCCAGAG

CCTCATATTCAAGTACTGGGAGTTAAAAAGAAAAGCTCTTAGGACATTAATAGTCT
ATAGAATTCTTGGCAAACCCATGCAGGACTCCCAGACTTAAAACACAAAACCTAAG
AATTCCTGACCCAGAACTGCTAGTACAAAAGCAAGAGGGGTGTGGCTATAGAAGTT
GCTGAGAGAATTGGGACTGTGTATCTCTCTACTGGACCTGACTCCCCTCCTTTGCAT
GTTGAAATGCAGAACTAGAGTTATACCCACTTTGAAGTGATTTCAGAATCCAGAGAA
GGAAAAGAGTTCTGTCCAAGCAAACCAAGGGAGATGGTCACTGGTGACTTTACTTT
GGAGCAATCAGCTGAGAGTCTCTGAATGAGAACCATCGTGTGTGTGTGTGTGTGTG
TGTGTGTGTGTGTGTGTGTGATACAACTGAAGTTTAGGAATGCTCCTTTTATAGCCAGA
ATCAGTAAAAGAAAATCTCACTGTCAGCTGTCAGCTAGACCATGTCGCTACTACCATT
GCTTCAAGTGGGTATCTCAGTTGAACGGGAGGGGAAAAGGTGACAGACAGAAAGGA
ACAGACATTACACAGTGGGCTCTCCAGCCCACCAGCTGAGAGGGGGCTTTCTGGTTA
GTGATGATCAACTTCAGGTGGCACTGGTTTAGAGGAGACATTTTAAAGGGACAAAG
TTTCCACCACAAAAGCTTTCAACGGAAGAGCCGATCTAATTGTGACCATGAAGCCA
GCTGATGGGTGACCACACAAACCCTTCCCCGGGAGGCATTTGCTGTTGACACAGGC
TCCTTATTTCTGCCGCTTCATACGGGAGAAAAAAAAGAGTGGGACTTTGATTTGTC
TAAGCAGTTGGTATGATTCACAGAGAGATAAATCATCACAGGAGATGGTTAGCAGT
GTATGGTTCTCGGCTTCAACGCATTGTTTATTATAAAACATGCACCTGGGTTTATATT
TTTCTGCCTGGTTATAAAGCAATAACATCTTGCTATGCAAACACTAAATTCATGTG
TGAATTTTCAACTGTGATTTTATGTGTGCATTTTTTAAACTAACTCTATCATTTTTTC
TATGTTGACATCTGTTGTTGGTTTGGTTTTGTTTTGTTTTTAATCTGTTTCCAACATC
TGAGTCTGTGAACCATCTCTCCTGACTGGATGCTGGCTTGAAACCTGTTAGTGCTTA
AACAGACTCAGAAACAACCCTGGACCTCTGGGGCAAACGCAGGGGTGTTACTCTTT
GATATATCATGGGCCCTCTGTGGCTTCAACAAACAAAGTCATAATTCCTCTAAATTC
TGTGTTTTCTGTAAATATTTTCTTCTCAGCTCTGCTAAAATGGGGGTGGGGGGG
GGGGGGGAGAGAGAGAACTCCTATCCCAGACTTTAGACCAAAGGGGTGTTAG
AGAGTATGGACTCTGGCATTCTGCATTTGAAGATGAGGAAGCCTTTCAGAAATTGG
GGGTACAGAGGCTTTCTCTGTGCTTCCTGGGAGGTCAGCAAGAGGGTTGAACAGAA
ACCTGAAGCTTCCTGATGCCAGAGCTCTTGAGCCCACCTCTCCCCAGCACCTTGTG
GACGTGTGTAAATTCATGACACCCACTGTAATGCCTCCCAAGATCTTCACTGTGGGA
GGCATGGGAGGTGATCCCATGATGGGCTCCTGCCACAAAATCTTCCAAACCTTTTAA
GTCTGATTCCTGCTGGAGAAGTTAGAGTCCCTCTTTCATTTTCATACCCTCTTACTCT
GCTGTGAGTGCCACATTCAGCTGAGCACCACTGCTTCCTAAGACGTAACCAGTGTG
CTGGGGAGATGGCTCAGTTGATAAAGTGCCTGCAGTGTAAGTGTGAGGACCTGAAT
TCAGGTTCCAGCATCTGTGTAAGAGCCAGGCAGGAACCTTAAGTGCAAGGCGGGGCA
GGGGTGGGGATAGGTTTATTGACCAACCAGTCTTAAGAATGAAGTGGTACCCAGGC

TCATTGAGAGATCCTGTCTCAAAAAATAAAAAATGGACAGAGATCTAGGGATGCACC
 CAACATCTGCCGCAACCTCCCAAGTCATATGCGTGTGCACAGAAATCCCCAGATCTT
 TCTTCTCCCCTGAAATGCAAAGGTACATTTAAACTATCCATCCTCTTTCTTGCCCGTC
 TTTTGGCAGTGAGCCCTGCCATAACATAAGATCCAGTGAGGAGCAGTTCAGCCAGG
 TTGGACAGTGATCCATTCTGTTCATCCTTGTTTGTAAATAAGCAGAATTTATCCTGTAA
 GGCAAGGGGTGGTGATAGCCATAATTTTTGTCTGGCTGGGCTTTTTTCAAAGTGTCTT
 TGAATTCAGCAAGCAAACCTTCTTTGAGAAAGCTCTCTAAACTTAGTCTCTCTCCAT
 TTGGCTGGAAATAATGGATGGCCACATCCAAACTCCAAATTTCTGGATGTGTTCATAT
 GCCTCAGCACTACAGAATCTGACTCTCTCTTTGAGTATAGACATGCGTGTAACTAT
 GCACAGGGCTGTTTAAACAGATGGCTCCAATCCCTGCTCCATACTTGGGAGCCTTTGG
 TTCCATCTTTATACCAAATGCCAATCACACTGGCTACAGAGAGTGTATTATAGTCTG
 TGTCTAAGCTTAGAAGCTTTAAATGTATGTTTTAAAGAAAAAATACTAGAGTGGGTT
 GAACACTTTAACTAACTTGGAAGGTTGGACAGATTATGTGCAAAGATGATTGTTT
 GTTTAATAATGAATAATCTGAATCCTGTATAACTTATTTGCACACCTTTCTTGCATGA
 TGAAGTACATTTTTATAGTTGTTTGTATAAGACAGTGGCATATTTTTGTAAACATTT
 TTTTGACACTGAACTTCAATAAATGTTTTTCTACAACACA (SEQ ID NO: 506).

[000418] In some embodiments, an oligonucleotide comprises a region of complementarity to a FBXO32 sequence as set forth in SEQ ID NO: 505 or SEQ ID NO: 506. In some embodiments, the oligonucleotide comprises a region of complementarity that is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to a FBXO32 sequence as set forth in SEQ ID NO: 505 or SEQ ID NO: 506. In some embodiments, the oligonucleotide comprises a sequence that has at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides that are perfectly complementary to a FBXO32 sequence as set forth in SEQ ID NO: 505 or SEQ ID NO: 506. In some embodiments, an oligonucleotide may comprise a sequence that targets (*e.g.*, is complementary to) an RNA version (*i.e.*, wherein the T's are replaced with U's) of a FBXO32 sequence as set forth in SEQ ID NO: 505 or SEQ ID NO: 506. In some embodiments, the oligonucleotide comprises a sequence that is complementary (*e.g.*, at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% complementary) to an RNA version of a FBXO32 sequence as set forth in SEQ ID NO: 505 or SEQ ID NO: 506. In some embodiments, the oligonucleotide comprises a sequence that has at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides that are perfectly complementary to an RNA version of a FBXO32 sequence as set forth in SEQ ID NO: 505 or SEQ ID NO: 506.

[000419] In some embodiments, a FBXO32-targeting oligonucleotide comprises an antisense strand that comprises at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides of a sequence comprising any one of SEQ ID NOs: 555-578. In some embodiments,

a FBXO32-targeting oligonucleotide comprises an antisense strand that comprises any one of SEQ ID NO: 555-578. In some embodiments, an oligonucleotide comprises an antisense strand that comprises shares at least 70%, 75%, 80%, 85%, 90%, 95%, or 97% sequence identity with at least 12 or at least 15 consecutive nucleotides of any one of SEQ ID NOs: 555-578.

[000420] In some embodiments, a FBXO32-targeting oligonucleotide comprises an antisense strand that targets a FBXO32 sequence comprising any one of SEQ ID NO: 507-554. In some embodiments, an oligonucleotide comprises an antisense strand comprising at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 nucleotides (*e.g.*, consecutive nucleotides) that are complementary to a FBXO32 sequence comprising any one of SEQ ID NO: 507-554. In some embodiments, a FBXO32-targeting oligonucleotide comprises an antisense strand comprising a sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, or 97% complementary with at least 12 or at least 15 consecutive nucleotides of any one of SEQ ID NO: 507-554.

[000421] In some embodiments, a FBXO32-targeting oligonucleotide comprises an antisense strand comprises a region of complementarity to a target sequence as set forth in any one of SEQ ID NOs: 507-554. In some embodiments, the region of complementarity is at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or at least 19 nucleotides in length. In some embodiments, the region of complementarity is 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 nucleotides in length. In some embodiments, the region of complementarity is in the range of 8 to 20, 10 to 20 or 15 to 20 nucleotides in length. In some embodiments, the region of complementarity is fully complementary with all or a portion of its target sequence. In some embodiments, the region of complementarity includes 1, 2, 3 or more mismatches.

[000422] In some embodiments, a FBXO32-targeting oligonucleotide further comprises a sense strand that hybridizes to the antisense strand to form a double stranded siRNA. In some embodiments, the FBXO32-targeting oligonucleotide comprises an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 555-578. In some embodiments, the FBXO32 targeting oligonucleotide further comprises a sense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 531-554.

[000423] In some embodiments, the FBXO32-targeting oligonucleotide is a double stranded oligonucleotide (*e.g.*, an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 555-578 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 531-554, wherein the antisense strand and/or (*e.g.*, and) comprises one or more modified nucleosides (*e.g.*, 2'-modified nucleosides). In some embodiment, the one or more modified nucleosides are selected from 2'-O-Me and 2'-F modified nucleosides.

[000424] In some embodiments, the FBXO32-targeting oligonucleotide is a double stranded oligonucleotide (e.g., an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 555-578 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 531-554, wherein the each nucleoside in the antisense strand and/or (e.g., and) each nucleoside in the sense strand is a 2'-modified nucleoside selected from 2'-O-Me and 2'-F modified nucleosides.

[000425] In some embodiments, the FBXO32-targeting oligonucleotide is a double stranded oligonucleotide (e.g., an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 555-578 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 531-554, wherein the each nucleoside in the antisense strand and each nucleoside in the sense strand is a 2'-modified nucleoside selected from 2'-O-Me and 2'-F modified nucleosides, and wherein the antisense strand and/or (e.g., and) the sense strand each comprises one or more phosphorothioate internucleoside linkages. In some embodiments, the sense strand does not comprise any phosphorothioate internucleoside linkages (all the internucleoside linkages in the sense strand are phosphodiester internucleoside linkages), and the antisense strand comprises 1, 2, or 3 phosphorothioate internucleoside linkages. In some embodiments, the antisense strand comprises 2 phosphorothioate internucleoside linkages, optionally wherein the two internucleoside linkages at the 3' end of the antisense strand are phosphorothioate internucleoside linkages and the rest of the internucleoside linkages in the antisense strand are phosphodiester internucleoside linkages.

[000426] In some embodiments, the antisense strand of the FBXO32-targeting oligonucleotide comprises a structure of (5' to 3'):

fNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmN*fN*mN, wherein “mN” indicates 2'-O-methyl (2'-O-Me) modified nucleosides; “fN” indicates 2'-fluoro (2'-F) modified nucleosides; “*” indicates phosphorothioate internucleoside linkage; and the absence of “*” between two nucleosides indicate phosphodiester internucleoside linkage.

[000427] In some embodiments, the sense strand of the FBXO32-targeting oligonucleotide comprises a structure of (5' to 3'):

mNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfN, wherein “mN” indicates 2'-O-methyl (2'-O-Me) modified nucleosides; “fN” indicates 2'-fluoro (2'-F) modified nucleosides; and the absence of “*” between two nucleosides indicate phosphodiester internucleoside linkage.

[000428] In some embodiments, the antisense strand of the FBXO32-targeting oligonucleotide is selected from the modified version of SEQ ID NOs: 555-578 listed in Table

22. In some embodiments, the sense strand of the FBXO32-targeting oligonucleotide is selected from the modified version of SEQ ID NOs: 531-554 listed in Table 22. In some embodiments, the FBXO32-targeting oligonucleotide is a siRNA selected from the siRNAs listed in Table 22.

Table 20. FBXO32 Target Sequences

Reference Sequence	Corresponding nucleotides of the Reference Sequence	FBXO32 Target Sequence (5' to 3')	SEQ ID NO:
NM_058229.4 (SEQ ID NO: 297)	1063-1081	CTGGATTGGAAGAAGATGT	507
NM_058229.4 (SEQ ID NO: 297)	1055-1073	AAGGGCAGCTGGATTGGAA	508
NM_058229.4 (SEQ ID NO: 297)	1064-1082	TGGATTGGAAGAAGATGTA	509
NM_058229.4 (SEQ ID NO: 297)	1056-1074	AGGGCAGCTGGATTGGAAG	510
NM_058229.4 (SEQ ID NO: 297)	1052-1070	ACAAAGGGCAGCTGGATTG	511
NM_058229.4 (SEQ ID NO: 297)	5127-5145	TCATCATTTTCTATGTTGA	512
NM_058229.4 (SEQ ID NO: 297)	2295-2313	TGGATATCTTCATGGATAA	513
NM_058229.4 (SEQ ID NO: 297)	5217-5235	CTAAAATCCTATTAGTGCT	514
NM_058229.4 (SEQ ID NO: 297)	842-860	GGCCTGCCTTCAAAGGCCT	515
NM_058229.4 (SEQ ID NO: 297)	1516-1534	GCAAGACTATAAGGGCAAT	516
NM_058229.4 (SEQ ID NO: 297)	1022-1040	GGCAGATCCGCAAACGATT	517
NM_058229.4 (SEQ ID NO: 297)	1448-1466	ACTTCTCACTAGAATTGGT	518
NM_058229.4 (SEQ ID NO: 297)	2756-2774	TACATATATTTGCAGTTGT	519
NM_058229.4 (SEQ ID NO: 297)	5299-5317	CTTGGGTCCTTGATGGCTT	520
NM_058229.4 (SEQ ID NO: 297)	4887-4905	CTTGGAATTTCAATTGTCT	521
NM_026346.3 (SEQ ID NO: 298)	742-760	TGAAAGTTCTTGAAGACCA	522
NM_026346.3	966-984	CCTGTGTGCTTACAACCTGA	523

(SEQ ID NO: 298)			
NM_026346.3 (SEQ ID NO: 298)	655-673	TGTTGGAGCTGATAGCAAA	524
NM_026346.3 (SEQ ID NO: 298)	621-639	CTGGATTCCAGAAGATTCA	525
NM_026346.3 (SEQ ID NO: 298)	628-646	CCAGAAGATTCAACTACGT	526
NM_026346.3 (SEQ ID NO: 298)	697-715	GCATCGCCCCAAAAGAACTT	527
NM_026346.3 (SEQ ID NO: 298)	620-638	CCTGGATTCCAGAAGATTC	528
NM_026346.3 (SEQ ID NO: 298)	740-758	ACTGAAAGTTCTTGAAGAC	529
NM_026346.3 (SEQ ID NO: 298)	1080-1098	AAGAGACTCTGCCAGTACC	530

* The target sequences contain Ts, but binding to RNA and/or DNA is contemplated.

[000429] In some embodiments, an oligonucleotide may comprise or consist of any sequence as provided in Table 21.

Table 21. Oligonucleotide sequences for targeting FBXO32

Passenger Strand/Sense Strand (RNA) (5' to 3')	SEQ ID NO:	Guide Strand/Antisense Strand (RNA) (5' to 3')	SEQ ID NO:
AGCUGGAUUGGAAGAAGAUGU	531	ACAUCUUCUCCAAUCCAGCUGC	555
CAAAGGGCAGCUGGAUUGGAA	532	UUCCAAUCCAGCUGCCCUUUGUC	556
GCUGGAUUGGAAGAAGAUGUA	533	UACAUCUUCUCCAAUCCAGCUG	557
AAAGGGCAGCUGGAUUGGAAG	534	CUUCCAAUCCAGCUGCCCUUUGU	558
AGACAAAGGGCAGCUGGAUUG	535	CAAUCCAGCUGCCCUUUGUCUGA	559
UAUCAUCAUUUUCUAUGUUGA	536	UCAACAUAGAAAAUGAUGAUAGA	560
CUUGGAUAUCUUCAUGGAUAA	537	UUAUCCAUGAAGAUAUCCAAGGA	561
GCCUAAAAUCCUAUUAGUGCU	538	AGCACUAAUAGGAUUUUAGGCCA	562
CAGGCCUGCCUCAAAGGCCU	539	AGGCCUUUGAAGGCAGGCCUGGU	563
CAGCAAGACUAUAAGGGCAAU	540	AUUGCCCUUAUAGUCUUGCUGGC	564
GCGGCAGAUCCGCAAACGAUU	541	AAUCGUUUGCGGAUCUGCCGCUC	565
GAACUUCUCACUAGAAUUGGU	542	ACCAAUUCUAGUGAGAAGUUCAC	566
UGUACAUAUAUUUGCAGUUGU	543	ACAACUGCAAAUAUAUGUACAUI	567
AUCUUGGGUCCUUGAUGGCUU	544	AAGCCAUCAAGGACCCAAGAUAU	568
AGCUUGGAAUUCAAUUGUCU	545	AGACAAUUGAAAUCCAAGCUCU	569
ACUGAAAGUUCUUGAAGACCA	546	UGGUCUUCAAGAACUUUCAGUAC	570
UGCCUGUGUGCUUACAACUGA	547	UCAGUUGUAAGCACACAGGCAGG	571

GCUGUUGGAGCUGAUAGCAAA	548	UUUGCUAUCAGCUCCAACAGCCU	572
UCCUGGAUCCAGAAGAUUCA	549	UGAAUCUUCUGGAAUCCAGGAUG	573
UUCGAGAAGAUUCAACUACGU	550	ACGUAGUUGAAUCUUCUGGAAUC	574
UGGCAUCGCCCAAAGAACUU	551	AAGUUCUUUUGGGCGAUGCCACU	575
AUCCUGGAUCCAGAAGAUUC	552	GAAUCUUCUGGAAUCCAGGAUGG	576
GUACUGAAAGUUCUUGAAGAC	553	GUCUUCAAGAACUUUCAGUACCA	577
GGAAGAGACUCUGCCAGUACC	554	GGUACUGGCAGAGUCUCUUCCAC	578

[000430] In some embodiments, an oligonucleotide is a modified oligonucleotide as provided in Table 22, wherein ‘mN’ represents a 2’-O-methyl modified nucleoside (e.g., mU is 2’-O-methyl modified uridine), ‘fN’ represents a 2’-fluoro modified nucleoside (e.g., fU is 2’-fluoro modified uridine), ‘*’ represents a phosphorothioate internucleoside linkage, and lack of “*” between nucleosides indicate phosphodiester internucleoside linkage.

Table 22. Modified Oligonucleotides for targeting FBXO32

siRNA #	Modified Passenger Strand/Sense Strand (RNA) (5' to 3')	SEQ ID NO:	Modified Guide Strand/Antisense Strand (RNA) (5' to 3')	SEQ ID NO:
hsFBXO32-1	mAmGfCmUfGmGfAmUfUmGfGmAfAmGfAmAfGmAfUmGfU	531	fAfCmAfUmCfUmUfCmUfUmCfCmAfAmUfCmCfAmGfCmU*fG*mC	555
hsFBXO32-2	mCmAfAmAfGmGfGmCfAmGfCmUfGmGfAmUfUmGfGmAfA	532	fUfUmCfCmAfAmUfCmCfAmGfCmUfGmCfCmCfUmUfUmG*fU*mC	556
hsFBXO32-3	mGmCfUmGfGmAfUmUfGmGfAmAfGmAfAmGfAmUfGmUfA	533	fUfAmCfAmUfCmUfUmCfUmUfCmCfAmAfUmCfCmAfGmC*fU*mG	557
hsFBXO32-4	mAmAfAmGfGmGfCmAfGmCfUmGfGmAfUmUfGmGfAmAfG	534	fCfUmUfCmCfAmAfUmCfCmAfGmCfUmGfCmCfCmUfUmU*fG*mU	558
hsFBXO32-5	mAmGfAmCfAmAfAmGfGmGfCmAfGmCfUmGfGmAfUmUfG	535	fCfAmAfUmCfCmAfGmCfUmGfCmCfCmUfUmUfGmUfCmU*fG*mA	559
hsFBXO32-6	mUmAfUmCfAmUfCmAfUmUfUmUfCmUfAmUfGmUfUmGfA	536	fUfCmAfAmCfAmUfAmGfAmAfAmAfUmGfAmUfGmAfUmA*fG*mA	560
hsFBXO32-7	mCmUfUmGfGmAfUmAfUmCfUmUfCmAfUmGfGmAfUmAfA	537	fUfUmAfUmCfCmAfUmGfAmAfGmAfUmAfUmCfCmAfAmG*fG*mA	561
hsFBXO32-8	mGmCfCmUfAmAfAmAfUmCfCmUfAmUfUmAfGmUfGmCfU	538	fAfGmCfAmCfUmAfAmUfAmGfGmAfUmUfUmUfAmGfGmC*fC*mA	562
hsFBXO32-9	mCmAfGmGfCmCfUmGfCmCfUmUfCmAfAmAfGmGfCmCfU	539	fAfGmGfCmCfUmUfUmGfAmAfGmGfCmAfGmGfCmCfUmG*fG*mU	563
hsFBXO32-10	mCmAfGmCfAmAfGmAfCmUfAmUfAmAfGmGfGmCfAmAfU	540	fAfUmUfGmCfCmCfUmUfAmUfAmGfUmCfUmUfGmCfUmG*fG*mC	564
hsFBXO32-11	mGmCfGmGfCmAfGmAfUmCfCmGfCmAfAmAfCmGfAmUfU	541	fAfAmUfCmGfUmUfUmGfCmGfGmAfUmCfUmGfCmCfGmC*fU*mC	565

hsFBXO32-12	mGmAfAmCfUmUfCmUfCmA fCmUfAmGfAmAfUmUfGmGf U	542	fAfCmCfAmAfUmUfCmUfAmG fUmGfAmGfAmAfGmUfUmC*f A*mC	566
hsFBXO32-13	mUmGfUmAfCmAfUmAfUmA fUmUfUmGfCmAfGmUfUmGf U	543	fAfCmAfAmCfUmGfCmAfAmA fUmAfUmAfUmGfUmAfCmA*f U*mU	567
hsFBXO32-14	mAmUfCmUfUmGfGmGfUmC fCmUfUmGfAmUfGmGfCmUf U	544	fAfAmGfCmCfAmUfCmAfAmG fGmAfCmCfCmAfAmGfAmU*f A*mU	568
hsFBXO32-15	mAmGfCmUfUmGfGmAfAmU fUmUfCmAfAmUfUmGfUmCf U	545	fAfGmAfCmAfAmUfUmGfAm AfAmUfUmCfCmAfAmGfCmU *fC*mU	569
mmFBXO32-1	mAmCfUmGfAmAfAmGfUmU fCmUfUmGfAmAfGmAfCmCf A	546	fUfGmGfUmCfUmUfCmAfAmG fAmAfCmUfUmUfCmAfGmU*f A*mC	570
mmFBXO32-2	mUmGfCmCfUmGfUmGfUmG fCmUfUmAfCmAfAmCfUmGf A	547	fUfCmAfGmUfUmGfUmAfAm GfCmAfCmAfCmAfGmGfCmA *fG*mG	571
mmFBXO32-3	mGmCfUmGfUmUfGmGfAmG fCmUfGmAfUmAfGmCfAmAf A	548	fUfUmUfGmCfUmAfUmCfAmG fCmUfCmCfAmAfCmAfGmC*f C*mU	572
mmFBXO32-4	mUmCfCmUfGmGfAmUfUmC fCmAfGmAfAmGfAmUfUmCf A	549	fUfGmAfAmUfCmUfUmCfUmG fGmAfAmUfCmCfAmGfGmA*f U*mG	573
mmFBXO32-5	mUmUfCmCfAmGfAmAfGmA fUmUfCmAfAmCfUmAfCmGf U	550	fAfCmGfUmAfGmUfUmGfAm AfUmCfUmUfCmUfGmGfAmA *fU*mC	574
mmFBXO32-6	mUmGfGmCfAmUfCmGfCmC fCmAfAmAfAmGfAmAfCmUf U	551	fAfAmGfUmUfCmUfUmUfUm GfGmGfCmGfAmUfGmCfCmA *fC*mU	575
mmFBXO32-7	mAmUfCmCfUmGfGmAfUmU fCmCfAmGfAmAfGmAfUmUf C	552	fGfAmAfUmCfUmUfCmUfGmG fAmAfUmCfCmAfGmGfAmU*f G*mG	576
mmFBXO32-8	mGmUfAmCfUmGfAmAfAmG fUmUfCmUfUmGfAmAfGmAf C	553	fGfUmCfUmUfCmAfAmGfAmA fCmUfUmUfCmAfGmUfAmC*f C*mA	577
mmFBXO32-9	mGmGfAmAfGmAfGmAfCmU fCmUfGmCfCmAfGmUfAmCf C	554	fGfGmUfAmCfUmGfGmCfAmG fAmGfUmCfUmCfUmUfCmC*f A*mC	578

g. TRIM63 Oligonucleotides

[000431] Examples of oligonucleotides useful for targeting TRIM63 are provided in Rodriguez *et al.*, Mol Cell Endocrinol. 2015 Sep 15;413:36-48; Castellero *et al.*, Metabolism. 2013 Oct;62(10):1495-502; Clarke *et al.*, Cell Metab. 2007 Nov;6(5):376-85; Wada *et al.*, J Biol Chem. 2011 Nov 4;286(44):38456-65; and Files *et al.*, Am J Respir Crit Care Med. 2012 Apr 15;185(8):825-34, the contents of each of which are incorporated herein in their entireties. In some embodiments, the oligonucleotide is a CRISPR guide RNA targeting TRIM63. In some embodiments, the oligonucleotide is miR-23a, which has been shown to suppress TRIM63 expression.

[000432] In some embodiments, oligonucleotides may have a region of complementarity to a human TRIM63 sequence, for example, as provided below (Gene ID: 84676; NCBI Ref. No: NM_032588.3):

AGACAGAATTCGGGCACCAGGAGAAGGAAGCCAACAGGATCCGACCCGGTGTTTT
GTGACAAAGGCAAGACCCCCAGGTCTACTTAGAGCAAAGTTAGTAGAGGAGGCAG
CTAGGCGTGGCTCTCATTCTTCCCACAGAATGGATTATAAGTCGAGCCTGATCCAG
GATGGGAATCCCATGGAGAACTTGGAGAAGCAGCTGATCTGCCCTATCTGCCTGGA
GATGTTTACCAAGCCAGTGGTCATCTTGCCGTGCCAGCACAACTGTGCCGGAAGT
GTGCCAATGACATCTTCCAGGCTGCAAATCCCTACTGGACCAGCCGGGGCAGCTCA
GTGTCCATGTCTGGAGGCCGTTTCCGCTGCCCCACCTGCCGCCACGAGGTGATCATG
GATCGTCACGGAGTGTACGGCCTGCAGAGGAACCTGCTGGTGGAGAACATCATCGA
CATCTACAAACAGGAGTGCTCCAGTCGGCCGCTGCAGAAGGGCAGTCACCCCATGT
GCAAGGAGCACGAAGATGAGAAAATCAACATCTACTGTCTCACGTGTGAGGTGCCC
ACCTGCTCCATGTGCAAGGTGTTTGGGATCCACAAGGCCTGCGAGGTGGCCCCATT
GCAGAGTGTCTTCCAGGGACAAAAGACTGAACTGAATAACTGTATCTCCATGCTGG
TGGCGGGGAATGACCGTGTGCAGACCATCATCACTCAGCTGGAGGATTCCCGTCGA
GTGACCAAGGAGAACAGTCACCAGGTAAAGGAAGAGCTGAGCCAGAAGTTTGACA
CGTTGTATGCCATCCTGGATGAGAAGAAAAGTGAGTTGCTGCAGCGGATCACGCAG
GAGCAGGAGAAAAAGCTTAGCTTCATCGAGGCCCTCATCCAGCAGTACCAGGAGCA
GCTGGACAAGTCCACAAAGCTGGTGGAACTGCCATCCAGTCCCTGGACGAGCCTG
GGGGAGCCACCTTCCTCTTGACTGCCAAGCAACTCATCAAAGCATTGTGGAAGCT
TCCAAGGGCTGCCAGCTGGGGAAAGACAGAGCAGGGCTTTGAGAACATGGACTTCTT
TACTTTGGATTTAGAGCACATAGCAGACGCCCTGAGAGCCATTGACTTTGGGACAG
ATGAGGAAGAGGAAGAATTCATTGAAGAAGAAGATCAGGAAGAGGAAGAGTCCAC
AGAAGGGAAGGAAGAAGGACACCAGTAAGGAGCTGGATGAATGAGAGGCCCCCAG
ATGCAGAGAGACTGGAGAGGGTGGGGAGGGGCCAGCGGCCTTGGTGACAGGCCC
AGGGTGGGAGGGGTGCGGGCCCCCTGGAGGGGCAATGGGGAGGTGATGTCTTCTCTC
TGCTCAGAGAGCAGGGACTAGGGTAGGACCCTCACCGCTGCGTCCAGCAGACACTG
AACCAGAATTGGAAACGTGCTTGAAACAATCACACAGGACACTTTTCTACATTGGT
GCAAAATGGAATATTTTGTACATTTTAAAATGTGATTTTGTATATACTTGTATATG
TATGCCAATTTGGTGCTTTTTGTAAAGGAACTTTTGTATAATAATGCCTGGTCGTTG
GGTGACCTGCGATTGTCAGAAAGAGGGGAAGGAAGCCAGGTTGATACAGCTGCCC
ACTTCCTTTCCTGAGCAGGAGGATGGGGTAGCACTCACAGGGACGATGTGCTGTAT
TTCAGTGCCTATCCCAGACATACGGGGTGGTAACTGAGTTTGTGTTATATGTTGTTT
TAATAAATGCACAATGCTCTCTTCCTGTTCTTCAA (SEQ ID NO: 579).

[000433] In some embodiments, oligonucleotides may have a region of complementarity to a mouse TRIM63 sequence, for example, as provided below (Gene ID: 433766; NCBI Ref. No: NM_001039048.2)

AGAAGTCGGGGGTCAGGGGACGAAGACAAAGAGGATCCGAGTGGGTTTGGAGACA
AAGACTTGGTGTGACGCAGGTGGGCGAGACAGTCGCATTTCAAAGCAATATGGATT
ATAAATCTAGCCTGATTCCTGATGGAAACGCTATGGAGAACCTGGAGAAGCAGCTG
ATCTGCCCCATCTGCCTGGAGATGTTTACCAAGCCTGTGGTTCATCCTGCCCTGCCAA
CACAACCTCTGCCGGAAGTGTGCCAACGACATCTTCCAGGCTGCGAATCCCTACTG
GACCAACCGCGGTGGCTCAGTGTCCATGTCTGGAGGTCGTTTCCGTTGCCCCCTCGTG
CCGCCATGAAGTGATCATGGACCGGCACGGGGTGTACGGCCTGCAGAGGAACCTGC
TGGTGGAAAACATCATTGACATCTACAAGCAGGAGTGCTCCAGTCGGCCCCTGCAG
AAAGGCAGCCACCCGATGTGCAAGGAACACGAAGACGAGAAAATCAACATCTACT
GTCTCACGTGTGAGGTGCCTACTTGCTCCTTGTGCAAGGTGTTTGGGGCTCACCAGG
CCTGTGAGGTTGCCCCCTTGTCAAAGCATCTTCCAAGGACAGAAGACTGAGCTGAGT
AACTGCATCTCCATGCTGGTGGCGGGCAACGACCGAGTGCAGACGATCATCTCTCA
GCTGGAGGACTCCTGCAGAGTGACCAAGGAGAATAGCCACCAGGTGAAGGAGGAG
CTGAGTCAGAAGTTTGACACCCTCTACGCCATCCTGGACGAGAAGAAGAGCGAGCT
GCTGCAGCGGATCACGCAGGAGCAGGAGGAGAAGCTGGGCTTCATCGAGGCTCTG
ATCCTCCAGTACAGGGAGCAGCTGGAAAAGTCCACCAAACCTTGTGGAGACCGCCAT
CCAGTCCCTGGATGAGCCCGGAGGGGCTACCTTCCTCTCAAGTGCCAAGCAGCTCA
TCAAGAGCATTGTAGAAGCCTCCAAGGGCTGCCAGCTGGGGAAGACAGAGCAAGG
CTTTGAGAACATGGACTACTTTACTCTGGACTTAGAACACATAGCAGAGGCCTTGA
GGGCCATTGACTTTGGGACAGATGAGGAGGAGGAGGAGGAGGAGTTTACAGAAGA
GGAGGCTGATGAGGAAGAGGGCGTGACCACAGAGGGTAAAGAAGAACACCAATGA
AGAAGGAGATGAGTGAGACACGCTCTGGACGCAGAGACGGGGGAGGTGGGGGCAG
GCCCATCTCGGGAGGGGGTTAGGGCTCCTTGGGGGGTACAATAGGGAAGTGTGTCT
TCTCTCTGCTCAGAGAGCAGGGACTAGCATAGGGCTCCCCACCACTGTGTCCAGCA
GCTGCTGAAACACAATTGGAAATGTATCCAAAACGTCACAGGACACTTTTCTACGTT
GGTGCGAAATGAAATATTTTGTATGTTTTTAAATGTGATTTTTGTATATACTTGTAT
ATGTATGCCAATTTGGTGCTTTTTGTACGAGAACTTTTGTATGATCACGCCTGGTCAT
TGTGTGACTGGCGATTGTCACAAAGTGGGAAGGAAGCCAAGACAATAGAGATGCCT
ACTTCCTTTTCTTGGTGGGAGGGGCTGGGTCTCACTCGGTGGCCTAGAGAGGGGCAAT
GTACTGTACAGTGCCCATCCCCAAACATGGGGATAGGACTGAATTTGTGTTATATGT
TGTTTTGCACAAGGGGCTGGGCCTTGGGGCACACACCCTTTGATCCCAGCACTCTGG
AGGCAGAGGCAGTTGGATCTCTATGAGTTCAAGGCCAGCCTGGTCTACATGGAGAG
TTACAGGCCAGCCAGAGCTACATAGAGAGACTCTGCCTCAAAAATAAAAATGAAAA
AGAATAAAAAATAAACTCACAATGCTCTTTTCCTG (SEQ ID NO: 580).

[000434] In some embodiments, an oligonucleotide comprises a region of complementarity to a TRIM63 sequence as set forth in SEQ ID NO: 579 or SEQ ID NO: 580. In some embodiments, the oligonucleotide comprises a region of complementarity that is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to a TRIM63 sequence as set forth in SEQ ID NO: 579 or SEQ ID NO: 580. In some embodiments, the oligonucleotide comprises a sequence that has at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides that are perfectly complementary to a TRIM63 sequence as set forth in SEQ ID NO: 579 or SEQ ID NO: 580. In some embodiments, an oligonucleotide may comprise a sequence that targets (*e.g.*, is complementary to) an RNA version (*i.e.*, wherein the T's are replaced with U's) of a TRIM63 sequence as set forth in SEQ ID NO: 579 or SEQ ID NO: 580. In some embodiments, the oligonucleotide comprises a sequence that is complementary (*e.g.*, at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% complementary) to an RNA version of a TRIM63 sequence as set forth in SEQ ID NO: 579 or SEQ ID NO: 580. In some embodiments, the oligonucleotide comprises a sequence that has at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides that are perfectly complementary to an RNA version of a TRIM63 sequence as set forth in SEQ ID NO: 579 or SEQ ID NO: 580.

[000435] In some embodiments, a TRIM63-targeting oligonucleotide comprises an antisense strand that comprises at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides of a sequence comprising any one of SEQ ID NOs: 629-652. In some embodiments, a TRIM63 -targeting oligonucleotide comprises an antisense strand that comprises any one of SEQ ID NO: 629-652. In some embodiments, an oligonucleotide comprises an antisense strand that comprises shares at least 70%, 75%, 80%, 85%, 90%, 95%, or 97% sequence identity with at least 12 or at least 15 consecutive nucleotides of any one of SEQ ID NOs: 629-652.

[000436] In some embodiments, a TRIM63-targeting oligonucleotide comprises an antisense strand that targets a TRIM63 sequence comprising any one of SEQ ID NO: 581-628. In some embodiments, an oligonucleotide comprises an antisense strand comprising at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 nucleotides (*e.g.*, consecutive nucleotides) that are complementary to a TRIM63 sequence comprising any one of SEQ ID NO: 581-628. In some embodiments, a TRIM63-targeting oligonucleotide comprises an antisense strand comprising a sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, or 97% complementary with at least 12 or at least 15 consecutive nucleotides of any one of SEQ ID NO: 581-628.

[000437] In some embodiments, a TRIM63-targeting oligonucleotide comprises an antisense strand comprises a region of complementarity to a target sequence as set forth in any one of SEQ ID NOs: 581-628. In some embodiments, the region of complementarity is at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at

least 17, or at least 19 nucleotides in length. In some embodiments, the region of complementarity is 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 nucleotides in length. In some embodiments, the region of complementarity is in the range of 8 to 20, 10 to 20 or 15 to 20 nucleotides in length. In some embodiments, the region of complementarity is fully complementary with all or a portion of its target sequence. In some embodiments, the region of complementarity includes 1, 2, 3 or more mismatches.

[000438] In some embodiments, a TRIM63-targeting oligonucleotide further comprises a sense strand that hybridizes to the antisense strand to form a double stranded siRNA. In some embodiments, the TRIM63-targeting oligonucleotide comprises an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 629-652. In some embodiments, the TRIM63 targeting oligonucleotide further comprises a sense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 605-628.

[000439] In some embodiments, the TRIM63-targeting oligonucleotide is a double stranded oligonucleotide (e.g., an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 629-652 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 605-628, wherein the antisense strand and/or (e.g., and) comprises one or more modified nucleosides (e.g., 2'-modified nucleosides). In some embodiment, the one or more modified nucleosides are selected from 2'-O-Me and 2'-F modified nucleosides.

[000440] In some embodiments, the TRIM63-targeting oligonucleotide is a double stranded oligonucleotide (e.g., an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 629-652 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 605-628, wherein the each nucleoside in the antisense strand and/or (e.g., and) each nucleoside in the sense strand is a 2'-modified nucleoside selected from 2'-O-Me and 2'-F modified nucleosides.

[000441] In some embodiments, the TRIM63-targeting oligonucleotide is a double stranded oligonucleotide (e.g., an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 629-652 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 605-628, wherein the each nucleoside in the antisense strand and each nucleoside in the sense strand is a 2'-modified nucleoside selected from 2'-O-Me and 2'-F modified nucleosides, and wherein the antisense strand and/or (e.g., and) the sense strand each comprises one or more phosphorothioate internucleoside linkages. In some embodiments, the sense strand does not comprise any phosphorothioate internucleoside linkages (all the internucleoside linkages in the sense strand are phosphodiester internucleoside linkages), and the antisense strand comprises 1, 2, or 3

phosphorothioate internucleoside linkages. In some embodiments, the antisense strand comprises 2 phosphorothioate internucleoside linkages, optionally wherein the two internucleoside linkages at the 3' end of the antisense strand are phosphorothioate internucleoside linkages and the rest of the internucleoside linkages in the antisense strand are phosphodiester internucleoside linkages,

[000442] In some embodiments, the antisense strand of the TRIM63-targeting oligonucleotide comprises a structure of (5' to 3'):

fNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmN*fN*mN, wherein "mN" indicates 2'-O-methyl (2'-O-Me) modified nucleosides; "fN" indicates 2'-fluoro (2'-F) modified nucleosides; "*" indicates phosphorothioate internucleoside linkage; and the absence of "*" between two nucleosides indicate phosphodiester internucleoside linkage.

[000443] In some embodiments, the sense strand of the TRIM63-targeting oligonucleotide comprises a structure of (5' to 3'):

mNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmN, wherein "mN" indicates 2'-O-methyl (2'-O-Me) modified nucleosides; "fN" indicates 2'-fluoro (2'-F) modified nucleosides; and the absence of "*" between two nucleosides indicate phosphodiester internucleoside linkage.

[000444] In some embodiments, the antisense strand of the TRIM63-targeting oligonucleotide is selected from the modified version of SEQ ID NOs: 629-652 listed in Table 25. In some embodiments, the sense strand of the TRIM63-targeting oligonucleotide is selected from the modified version of SEQ ID NOs: 605-628 listed in Table 25. In some embodiments, the TRIM63-targeting oligonucleotide is a siRNA selected from the siRNAs listed in Table 25.

Table 23. TRIM63 Target Sequences

Reference Sequence	Corresponding nucleotides of the Reference Sequence	TRIM63 Target Sequence (5' to 3')	SEQ ID NO:
NM_032588.3 (SEQ ID NO: 661)	1507-1525	TATGTATGCCAATTGGTG	581
NM_032588.3 (SEQ ID NO: 661)	531-549	AACATCTACTGTCTCACGT	582
NM_032588.3 (SEQ ID NO: 661)	1505-1523	TATATGTATGCCAATTGG	583
NM_032588.3 (SEQ ID NO: 661)	1715-1733	AGTTTGTGTTATATGTTGT	584
NM_032588.3 (SEQ ID NO: 661)	1534-1552	AAAGGAACTTTTGTATAAT	585
NM_032588.3	1737-1755	AATAAATGCACAATGCTCT	586

(SEQ ID NO: 661)			
NM_032588.3 (SEQ ID NO: 661)	138-156	AGAATGGATTATAAGTCGA	587
NM_032588.3 (SEQ ID NO: 661)	157-175	GCCTGATCCAGGATGGGAA	588
NM_032588.3 (SEQ ID NO: 661)	87-105	GAGCAAAGTTAGTAGAGGA	589
NM_032588.3 (SEQ ID NO: 661)	574-592	GCAAGGTGTTTGGGATCCA	590
NM_032588.3 (SEQ ID NO: 661)	748-766	ACCAGGTAAAGGAAGAGCT	591
NM_032588.3 (SEQ ID NO: 661)	1386-1404	AGCAGACACTGAACCAGAA	592
NM_032588.3 (SEQ ID NO: 661)	565-583	GCTCCATGTGCAAGGTGTT	593
NM_001039048.2 (SEQ ID NO: 662)	1667-1685	AATTGTGTATATGTTGT	594
NM_001039048.2 (SEQ ID NO: 662)	1662-1680	GACTGAATTTGTGTTATAT	595
NM_001039048.2 (SEQ ID NO: 662)	522-540	CCTACTGCTCCTTGTGCA	596
NM_001039048.2 (SEQ ID NO: 662)	469-487	GCAAGGAACACGAAGACGA	597
NM_001039048.2 (SEQ ID NO: 662)	1009-1027	TTGAGAACATGGACTACTT	598
NM_001039048.2 (SEQ ID NO: 662)	1660-1678	AGGACTGAATTTGTGTTAT	599
NM_001039048.2 (SEQ ID NO: 662)	526-544	CTTGCTCCTTGTGCAAGGT	600
NM_001039048.2 (SEQ ID NO: 662)	237-255	CGGAAGTGTGCCAACGACA	601
NM_001039048.2 (SEQ ID NO: 662)	493-511	TCAACATCTACTGTCTCAC	602
NM_001039048.2 (SEQ ID NO: 662)	952-970	TCAAGAGCATTGTAGAAGC	603
NM_001039048.2 (SEQ ID NO: 662)	1447-1465	ACTTGTATATGTATGCCAA	604

* The target sequences contain Ts, but binding to RNA and/or DNA is contemplated.

[000445] In some embodiments, an oligonucleotide may comprise or consist of any sequence as provided in Table 24.

Table 24. Oligonucleotide sequences for targeting TRIM63

Passenger Strand/Sense Strand (RNA) (5' to 3')	SEQ ID NO:	Guide Strand/Antisense Strand (RNA) (5' to 3')	SEQ ID NO:
UAUAUGUAUGCCAAUUUGGUG	605	CACCAAAUUGGCAUACAUAUACA	629
UCAACAUCUACUGUCUCACGU	606	ACGUGAGACAGUAGAUGUUGAU U	630
UGUAUAUGUAUGCCAAUUUGG	607	CCAAAUUGGCAUACAUAUACAAG	631
UGAGUUUGUGUUAUAUGUUGU	608	ACAACAUUAACACAAACUCAGU	632
GUAAAGGAACUUUUGUAUAAU	609	AUUAUACAAAAGUCCUUUACAA	633
UUAUAUAAUGCACAAUGCUCU	610	AGAGCAUUGUGCAUUUAUUA A	634
ACAGAAUGGAUUUAUAGUCGA	611	UCGACUUAUAAUCCAUCUGUGG	635
GAGCCUGAUCCAGGAUGGGAA	612	UUCCCAUCCUGGAUCAGGCUCGA	636
UAGAGCAAAGUUAGUAGAGGA	613	UCCUCUACUAAACUUUGCUCUAAG	637
GUGCAAGGUGUUUGGGAUCCA	614	UGGAUCCCAAACACCUUGCACAU	638
UCACCAGGUAAGGAAGAGCU	615	AGCUCUCCUUUACCUGGUGACU	639
CCAGCAGACACUGAACAGAA	616	UUCUGGUUCAGUGUCUGCUGGAC	640
CUGCUGCAUGUGCAAGGUGUU	617	AACACCUUGCACAUGGAGCAGGU	641
UGAAUUUGUGUUAUAUGUUGU	618	ACAACAUUAACACAAAUUCAGU	642
AGGACUGAAUUUGUGUUAU	619	AUAUAACACAAAUUCAGUCCU	643
UGCCUACUUGCUCUUGUGCA	620	UGCACAAGGAGCAAGUAGGCACC	644
GUGCAAGGAACACGAAGACGA	621	UCGUCUUCGUGUCCUUGCACAU	645
CUUUGAGAACAUGGACUACUU	622	AAGUAGUCCAUGUUCUAAAGCC	646
AUAGGACUGAAUUUGUGUUAU	623	AUAACACAAAUUCAGUCCUAUCC	647
UACUUGCUCUUGUGCAAGGU	624	ACCUUGCACAAGGAGCAAGUAGG	648
GCCGGAAGUGUGCCAACGACA	625	UGUCGUUGGCACACUCCGGCAG	649
AAUCAACAUCUACUGUCUCAC	626	GUGAGACAGUAGAUGUUGAUUU U	650
CAUCAAGAGCAUUGUAGAAGC	627	GCUUCUACAAUGCUCUUGAUGAG	651
AUACUUGUAUAUGUAUGCCAA	628	UUGGCAUACAUAUACAAGUAU	652

[000446] In some embodiments, an oligonucleotide is a modified oligonucleotide as provided in Table 25, wherein ‘mN’ represents a 2’-O-methyl modified nucleoside (e.g., mU is 2’-O-methyl modified uridine), ‘fN’ represents a 2’-fluoro modified nucleoside (e.g., fU is 2’-fluoro modified uridine), ‘*’ represents a phosphorothioate internucleoside linkage, and lack of “*” between nucleosides indicate phosphodiester internucleoside linkage.

Table 25. Modified Oligonucleotides for targeting TRIM63

siRNA #	Modified Passenger Strand/Sense Strand (RNA)	SEQ ID NO:	Modified Guide Strand/Antisense Strand (RNA)	SEQ ID NO:
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hsTRIM63-1	mUmAfUmAfUmGfUmAfU mGfCmCfAmAfUmUfUmGf GmUfG	605	fCfAmCfCmAfAmAfUmUfGmGf CmAfUmAfCmAfUmAfUmA*fC *mA	629
hsTRIM63-2	mUmCfAmAfCmAfUmCfUm AfCmUfGmUfCmUfCmAfC mGfU	606	fAfCmGfUmGfAmGfAmCfAmGf UmAfGmAfUmGfUmUfGmA*fU *mU	630
hsTRIM63-3	mUmGfUmAfUmAfUmGfU mAfUmGfCmCfAmAfUmUf UmGfG	607	fCfCmAfAmAfUmUfGmGfCmAf UmAfCmAfUmAfUmAfCmA*fA *mG	631
hsTRIM63-4	mUmGfAmGfUmUfUmGfU mGfUmUfAmUfAmUfGmUf UmGfU	608	fAfCmAfAmCfAmUfAmUfAmAf CmAfCmAfAmAfCmUfCmA*fG *mU	632
hsTRIM63-5	mGmUfAmAfAmGfGmAfA mCfUmUfUmUfGmUfAmUf AmAfU	609	fAfUmUfAmUfAmCfAmAfAmAf GmUfUmCfCmUfUmUfAmC*fA *mA	633
hsTRIM63-6	mUmUfAmAfUmAfAmAfU mGfCmAfCmAfAmUfGmCf UmCfU	610	fAfGmAfGmCfAmUfUmGfUmGf CmAfUmUfUmAfUmUfAmA*fA *mA	634
hsTRIM63-7	mAmCfAmGfAmAfUmGfG mAfUmUfAmUfAmAfGmUf CmGfA	611	fUfCmGfAmCfUmUfAmUfAmAf UmCfCmAfUmUfCmUfGmU*fG *mG	635
hsTRIM63-8	mGmAfGmCfCmUfGmAfUm CfCmAfGmGfAmUfGmGfG mAfA	612	fUfUmCfCmCfAmUfCmCfUmGf GmAfUmCfAmGfGmCfUmC*fG *mA	636
hsTRIM63-9	mUmAfGmAfGmCfAmAfA mGfUmUfAmGfUmAfGmAf GmGfA	613	fUfCmCfUmCfUmAfCmUfAmAf CmUfUmUfGmCfUmCfUmA*fA *mG	637
hsTRIM63-10	mGmUfGmCfAmAfGmGfU mGfUmUfUmGfGmGfAmUf CmCfA	614	fUfGmGfAmUfCmCfCmAfAmAf CmAfCmCfUmUfGmCfAmC*fA *mU	638
hsTRIM63-11	mUmCfAmCfCmAfGmGfUm AfAmAfGmGfAmAfGmAfG mCfU	615	fAfGmCfUmCfUmUfCmCfUmUf UmAfCmCfUmGfGmUfGmA*fC *mU	639
hsTRIM63-12	mCmCfAmGfCmAfGmAfCm AfCmUfGmAfAmCfCmAfG mAfA	616	fUfUmCfUmGfGmUfUmCfAmGf UmGfUmCfUmGfCmUfGmG*fA *mC	640
hsTRIM63-13	mCmUfGmCfUmCfCmAfUm GfUmGfCmAfAmGfGmUfG mUfU	617	fAfAmCfAmCfCmUfUmGfCmAf CmAfUmGfGmAfGmCfAmG*fG *mU	641
mmTRIM63-1	mUmGfAmAfUmUfUmGfU mGfUmUfAmUfAmUfGmUf UmGfU	618	fAfCmAfAmCfAmUfAmUfAmAf CmAfCmAfAmAfUmUfCmA*fG *mU	642
mmTRIM63-2	mAmGfGmAfCmUfGmAfA mUfUmUfGmUfGmUfUmAf UmAfU	619	fAfUmAfUmAfAmCfAmCfAmAf AmUfUmCfAmGfUmCfCmU*fA *mU	643
mmTRIM63-3	mUmGfCmCfUmAfCmUfUm GfCmUfCmCfUmUfGmUfG mCfA	620	fUfGmCfAmCfAmAfGmGfAmGf CmAfAmGfUmAfGmGfCmA*fC *mC	644
mmTRIM63-4	mGmUfGmCfAmAfGmGfA mAfCmAfCmGfAmAfGmAf CmGfA	621	fUfCmGfUmCfUmUfCmGfUmGf UmUfCmCfUmUfGmCfAmC*fA *mU	645
mmTRIM63-5	mCmUfUmUfGmAfGmAfA mCfAmUfGmGfAmCfUmAf CmUfU	622	fAfAmGfUmAfGmUfCmCfAmUf GmUfUmCfUmCfAmAfAmG*fC *mC	646
mmTRIM63-6	mAmUfAmGfGmAfCmUfG mAfAmUfUmUfGmUfGmUf UmAfU	623	fAfUmAfAmCfAmCfAmAfAmUf UmCfAmGfUmCfCmUfAmU*fC *mC	647
mmTRIM63-7	mUmAfCmUfUmGfCmUfCm CfUmUfGmUfGmCfAmAfG mGfU	624	fAfCmCfUmUfGmCfAmCfAmAf GmGfAmGfCmAfAmGfUmA*fG *mG	648

mmTRIM63-8	mGmCfCmGfGmAfAmGfUmGfUmGfCmCfAmAfCmGfAmCfA	625	fUfGmUfCmGfUmUfGmGfCmAfCmAfCmUfUmCfCmGfGmC*fAmG	649
mmTRIM63-9	mAmAfUmCfAmAfCmAfUmCfUmAfCmUfGmUfCmUfCmAfC	626	fGfUmGfAmGfAmCfAmGfUmAfGmAfUmGfUmUfGmAfUmU*fUmU	650
mmTRIM63-10	mCmAfUmCfAmAfGmAfGmCfAmUfUmGfUmAfGmAfAmGfC	627	fGfCmUfUmCfUmAfCmAfAmUfGmCfUmCfUmUfGmAfUmG*fAmG	651
mmTRIM63-11	mAmUfAmCfUmUfGmUfAmUfAmUfGmUfCmAfA	628	fUfUmGfGmCfAmUfAmCfAmUfAmUfAmCfAmAfGmUfAmU*fAmU	652

h. MEF2D Oligonucleotides

[000447] Examples of oligonucleotides useful for targeting MEF2D are provided in Li et al., Am J Cancer Res. 2019; 9(5): 887–905; Hu et al., Oncotarget. 2017 Nov 3; 8(54): 92079–92089; Martis et al., BMC Cancer volume 18, Article number: 1217 (2018); Estrella et al., The Journal of Biological Chemistry, 290, 24367-24380, 2015; Ma et al., Cancer Res; 74(5) March 1, 2014; and Sacilotto et al., Genes & Dev. October 15, 2016 vol. 30 no. 20 2297-2309, the contents of each of which are incorporated herein in their entirety.

[000448] In some embodiments, oligonucleotides may have a region of complementarity to a human MEF2D sequence, for example, as provided below (Gene ID: 4209; NCBI Ref. No: NM_005920.4):

GAGTTACCTTTGGAGCCCCGAAAGGAGGAAGGAAGCAAAATATCAACAACAGCCGAGGCGGCTCAGGCGCTCGGCCCGGTTCCCCGCTTGCCCTGCCGCCCGCCTGCTGGCCCCCGCGCCCACGACGGGGGCCA GGCCTCACGGCGCCGCCAGGGCCCCGCGCGGACGCCGGCCTCATTTATTATTCTCCCCGCCGGAGCT GCGGCTTCCCGGTGTTGAAGATCCCCCGGACCAGGGGCGAGGGCTACCCGCTCTTTGCCGTGACAACA CCGTTCCCCCAGCCGGGCTGGAGGCTGTGCAGAAGGTATCCTGTCAGACCATGAAGTGAAGCACTGTTCC CAGACCGTTTCATGAGCACAGTGTAAGGTGTGCCGAGACCCACCCAGCGAGCCCCCTCCCCCTCCGTA GCACTGAGGACCCCCGAGAAGATGGGGAGGAAAAAGATTTCAGATCCAGCGAATCACCGACGAGCG GAACCGACAGGTGACTTTTACCAAGCGGAAGTTTGGCCTGATGAAGAAGGCGTATGAGCTGAGCGTG CTATGTGACTGCGAGATCGCACTCATCATCTTCAACCACTCCAACAAGCTGTTCCAGTACGCCAGCAC CGACATGGACAAGGTGCTGCTCAAGTACACGGAGTACAATGAGCCACACGAGAGCCGCACCAACGCC GACATCATCGAGACCCTGAGGAAGAAGGGCTTCAACGGCTGCGACAGCCCCGAGCCCGACGGGGAG GACTCGCTGGAACAGAGCCCCCTGCTGGAGGACAAGTACCGACGCGCCAGCGAGGAGCTCGACGGGC TCTTCCGGCGCTATGGGTCAACTGTCCCGGCCCCCACTTTGCCATGCCTGTACGGTGGCCGTGTCCA ATCAGAGCTCACTGCACTTTCAGCAATCCCAGCGGCTCCCTGGTCAACCCCTTCCCTGGTGACATCATCC CTCACGGACCCGCGGCTCCTGTCCCCCAGCAGCCAGCAGCACTACAGAGGAACAGTGTGTCTCCTGGCCT GCCCCAGCGGCCAGCTAGTGCGGGGGCCATGCTGGGGGGTGACCTGAACAGTGCTAACGGAGCCTGC CCCAGCCCTGTTGGGAATGGCTACGTACGTGCTCGGGCTTCCCCTGGCCTCCTCCCTGTGGCCAATGG CAACAGCCTAAACAAGGTATCCCTGCCAAGTCTCCACCCCCACCTACCCACAGCACCCAGCTTGGAG CCCCCAGCCGCAAGCCCGACCTGCGAGTCATCACTTCCCAGGCAGGAAAGGGGTTAATGCATCACTTG ACTGAGGACCATTTAGATCTGAACAATGCCAGCGCCTTGGGGTCTCCAGTCTACTCATTCGCTCAC CACCCAGTGTTTCTGTGGCAACGCCGAGTTTACTCAGCCAGGGCCTCCCCCTTCTCTTCCATGCCAC TGCCTACAACACAGATTACCAGTTGACCAGTGCAGAGCTCTCCTCCTTACCAGCCTTTAGTTACCTGG GGGGCTGTCGCTAGGCAATGTCACTGCCTGGCAACAGCCACAGCAGCCCCAGCAGCCGCAGCAGCCA CAGCCTCCACAGCAGCAGCCACCGCAGCCACAGCAGCCACAGCCACAGCAGCCTCAGCAGCCGCAAC AGCCACCTCAGCAACAGTCCACCTGGTCCCTGTATCTCTCAGCAACCTCATCCCGGGCAGCCCCCTG CCCCAGTGGGTGCTGCCCTCACAGTACCCACCCACCCACATCAGCATCAAGTCAGAACCAGGTGTC CCAAGCCGTGAGCGCAGCCCTGCGCCTCCCCCTCCAGCTGTGTTCCAGCTGCCCCGCCCTGAGCCTG GCGATGGTCTCAGCAGCCAGCCGGGGGATCCTATGAGACGGGAGACCGGGATGACGGACGGGGGG ACTTCGGGGCCCACTGGGCTGTGCGCCAGCCCCAGAGCCTGAGGCTGAGGGCTCAGCTGTGAA GAGGATGCGGCTTGATACCTGGACATTAAAGTGACGATTCCCACTCCCCCTCCTCTCAGCCTCCCTGAT

GAAGAGTTGACAATCTCACCGCCCGCCCTTCCCTGCCCCGGGCTCCTCCCGCTCGACCCCCACTTCCTT
TCTTGTGCTTCGTGTCTCTGTTGACGGTTACATTTGTGTATAATTATTATATTATTATTATTATTATA
TTTTTTTTTAATTTGGATTCTCGCTTTGGAGAGGGGGATGCTCTCATCCCCTCTTTCTGTACCCCCACCA
TTTTCACTGGCTGGGGGGCTCTCTTTTTTCGCGGGAAGGGGGGACACTTTGCACGTTGTACACATATGCT
GCAGGAAGGGGGTGGGGGGCCCAATAAGGCCCTTTGGGAAAGGACAGGTGCCGAGCCCTGCATGTGG
AGCCCTCCCACCCACCCCAAGTAGAGGGAAATAACCAAAAACTACCAAAACAAGAAACCCACA
CTCTAGACTGAAACCCCAAGTGGGCTTGATGGGTGGGTTTGTGTTTCAAGGGGAAAGTGAGGCAGA
GGTCTGAAAAGGGTCTCTGTTTTGTGTTTCATGTAGCCATAGGCACATGGAGCAGAATACTTAAGCC
TGGCCCCCAAATGCCCTGCACACACACGTGCCACACCTGCGCTGATTCTTGTGTGTGTGCACCCCC
AAGGTGTGTGGGTGCTGGCTGAGCTTTGGGCCGGGAAGGCAGCCTGGGAATCTGAGGCTGGAGACAG
GGGTTTGAGGTGGGGGCCTCTCTGGAAGCACATTTGGAGGAAAGACAAGAGAGCCATGAGGAGAG
GGCTGAGGAGGGCAGAAGGGCTAGGCAGGGGGCAAATTGAGCCCCCTCCCTCCCCAGTTTTTCTCTAA
GATATACAGTGC AATAGTCCCCACCCCTCAGTTGACGCCAGCCCTGTAAAGCTGGCCACAGTGTGCA
GGGAGAATGGGGAGAGGGTCTTCAGTGAGGTGGCTGGGGCGAGAGTCGGCCTGGACTTCCCTGGGGT
GCTCCAGGCCAGAGCTCTTTCATTGGGGCGAGTGTGGTGAGGGGACGTCCTTGGTCTTGCACGCACAC
TACCTGGGGGAGTCAACACTGGGATGGTCTGTGGGGTGGGAGGGCCTACGGATGGGTCCGTAGAGGT
CCCACCTCCCTCATTCCTCCTTGGCCCCCTCTCCCTAGCTTCTCCTGTTAGCTCCTTCTGCTCCTGACCCC
ACCTCCTTGCTCTTGGCGCCCCCTATTGTCTCTGGCTACCTCCTTGTCCCACCACCTCCAGGCTGCATCCC
ACCTTCCCTCTTGGCTACTGTAATTGTAAATAGCGACCTTTGGAAAACGTTAGCGGTGTAACAGTCCA
GGAAACTGTTTTTTTTTTGTTGTGTGTGATTGATATGAAATGAGATTCTATTTTTGTCAAAGTATATTGT
AATAATAATGACTCAAACGGCCCGTACTGTACAGACGAGATTCTTCTGCTGTTGTTCTTGCTCCCCTCC
CCTCCTCTGAGTCCGCCCCCTCCCTGCTGCCTCCTCAGTGGGGCAGTGGGCAAGGGGGCCAGGGGCAGC
CGAAGCACGGGGTCCCTGAGACCTCAGGCAGGATTGGAGATCAAACCAGAGGGGGCAGGCCCCCAGC
CTGCTCTCTAGGATCACCCCCCGCCCTAAGGGGCCTGGCCTGGGGTGACGTGGCCAGGCAGACTGTCT
GCCCCACTCCTTCACACAAGCCAGCTCCTCTGCCCAAGGGGTGCGGCGCCCCCTTGGGGTTTCCTCC
CAGTTGGAGAGTAGAGTTAAGACAAGGCCCAGTTTTGTGTTAGCCGACCGTCTTTGCCACCTCTATG
ACCCAGCCTCTTGCAGTATTTCCCATCTTGATGCAGGGAAGGAACCAGAAGCAGAGGGGCCTCTACG
CAGGTACACACGTGTACCTGAGTGTGTTTCATGAGGGCATCTGGTGTTTATGTGTCTGAGTGTAGCTTTG
TATTTATGTGTGTGTGTGTGTGTATGTCTGATTGCACGGGTGTACTTTTGTATTTATGTGTGTGTGGT
TGCACGGGTGTGCCTCTGTGTGTCTCTGACCCTGGCTGGGTGTGTGTGCAAATCTGTGTGACTGGAGCT
CTAGGGGCATCTCTGTGTCTGAGTGTGCCTGGTGTGTGTTTACAAAGGGAGAGTTGGCTGCTCCAGCT
CCACAGCCCTGGGACCCCAACTCCTGTCTTCCCTGCTCCTTTCCCTGTGTTACCCCTCAGCTCTGACAC
ATTGAACTGCAGTTGGGGGGATTGGCAGTTAGCCCTCTGTGCTTCTCCCTGCAGCCCTACCTCTGCCAA
GGTCTCTCCCTCCAGGGACCTCTGCTTCCACCCACATATGTCCACTTAGTCACCCACACTTGACACAGT
TCCTGGAGTACCCTCTTCCCCCAACCCAGACCTGCTTTCAGAGCAAAACTCAAGTCCCTCTTCTCCG
TGAGCTTCTCCCTCAGCTGAGCAGTGATCACTTACTCACTCTTAACCCCAATCCGCTGACTGGGTGG
GGACAGCACGTCCAGCCTTCCACCTCTCCTGCAGGCTTCTAGACGGAGTTTCAAAAACCTGATGAGCC
TCGATCCAGGGCTTGAAAGAAGCCAGGGTGTAACTTGTTCATGCATGCGTCCCCAGAGCCTCGCCCA
GTGCCTGGCACATAGTAGGCACTCAATAAATGCTGAATGGGTGAATAGTTGAATGATAGGTGCTCAAT
AAATGAATGAATGGCCTTCCCTTCTCAGGCTATTTCCACCATTAGTCTGCCACCTTTCTAGGCTGGGC
TTGGCCACCATTAACACGGGGTGGGGGTGAGGGCCCTGCAATTCACGGTGAATATTACCAAGTTT
TGCCCTCTGCCTCATAAAGGCAAACCTGGCTTTTGATTACCATGTGTGGATGTTTCAGTGTCTTTCTT
CTCTGTCCCTGGGGATGGGGTGGTCTGTGAATATGTGACATTTCTGCAGTTCAGTATCCGAAGGTTTCT
CTTGGGGGTAGGGGCTCCTGGGCGGCCAGATGAATGGGTCCCTGGGAACCCAGACCTCAGATGAGGA
CTTAATGTCTTCTTCTCTCAAGCCAAATTCGCCTCCACCCACTCCCTCTGAAGAAGTGGGCATTTGCC
AAAGTAACCACTGGAGTCATCTAATGGCCCTCCCCCTCCCCAGGTTTCCCAACAGCTTTCAGGGACAGT
GGGCAAGAGGACACCCCCCCCCACACCTCAGTGGAACACACCATTTCTCCCCCTCAACAGCACACT
CAGTGCAGCAAGACTGACCCCTGACCCCTCCAGCCCTCCCTACCTTGGACAGGAAGGAAGTAATGC
ACCTTCTCTTGCTGATTATTTATTTGTTTGGAGAGACAGAAATGTAAAAGTGTATCTAGAAATATCTAT
ATCTCTATATATTTTAACTGACTCTTTGGAATCCCCTGGGGTGGGGTGAGGGGTAAAGTTTAGGCTTTC
GCGGAGGGGAGGAGACATGGAGCCTGGGAACCTCTTGTCTCCCTCTGCTGCCTCTCCCCACCCCTT
AAAGCAGTTGGTAGAAGGAATGGTATTTGTATGGGGGGAGGGAGGCTGGAATGGAGAATCTGGATTCT
TCTCCTCTTCCCCATTCTCCAGAGGGAGGGAGGTGGTGAGGAAGAGGAAGGGAGGGGCAGGATGGGC
CATGGAGGTGCCCCACCCCAACACCTGACAATCACCCACACTCCTGGGGCTCTTCTGGGTCTGGGG
CAGGGCGAGTCCAAGTGTGAGGCTGTTGATTTGTTTTCAATATTTCTTTTCGTGCTGTATGGTGATGCT
TTCTTAGTATTCTACACAATAAGAAAAGACAAAAGTCCTCGAGATTCTTATGAGTTTTGTTTGAAAACCT
TTTCACTATATTTGTTGTAAAGAGGTTTACTATTAAAAGAAAAAGAATACACGTTTCTGATA (SEQ ID
NO: 664).

[000449] In some embodiments, oligonucleotides may have a region of complementarity to a human MEF2D sequence, for example, as provided below (Gene ID: 4209; NCBI Ref. No: NM_001271629.2):

ATACCGTGTGCTCCCCTTGGCAAGTCGGTTCTGTCCCTTAAGCTGAGACTGCAGGGCCTGCCCCCAT
TTGAGTTCTTAGGGTGCCTGGGGCCTGAGACCACCCCTGCCCTAGGCCAGCTTTCCTGGACTGCCTG
CCCCACAAACCAACAGCCCCGCCCCAGGTCCCCAGTCGAAGGTATCCTGCAGACCATGAAGTGAAGC
ACTGTTCCAGACCGTTCATGAGCACAGTGTAAGGTGTGCCGAGACCCACCACCCAGCGAGCCCCCTCC
CCTCCGTAGCACTGAGGACCCCCGGAGAAGATGGGGAGGAAAAAGATTTCAGATCCAGCGAATCACCG
ACGAGCGGAACCGACAGGTGACTTTCACCAAGCGGAAGTTTGGCCTGATGAAGAAGGCGTATGAGCT
GAGCGTGCTATGTGACTGCGAGATCGCACTCATCATCTTCAACCACTCCAACAAGCTGTTCCAGTACG
CCAGCACCGACATGGACAAGGTGCTGCTCAAGTACACGGAGTACAATGAGCCACACGAGAGCCGCAC
CAACGCCGACATCATCGAGACCCTGAGGAAGAAGGGCTTCAACGGCTGCGACAGCCCCGAGCCCGAC
GGGGAGGACTCGCTGGAACAGAGCCCCCTGCTGGAGGACAAGTACCGACGCGCCAGCGAGGAGCTC
GACGGGCTCTTCCGGCGCTATGGGTCAACTGTCCCGGCCCCCAACTTTGCCATGCCTGTACGGTGCC
CGTGTCCAATCAGAGCTCACTGCAGTTCAGCAATCCAGCGGCTCCCTGGTCACCCCTTCCCTGGTGA
CATCATCCCTCACGGACCCGCGGCTCCTGTCCCCCAGCAGCCAGCACTACAGAGGAACAGTGTGTCT
CCTGGCCTGCCCCAGCGGCCAGCTAGTGCGGGGGCCATGCTGGGGGGTGACCTGAACAGTGTCTAACG
GAGCCTGCCCCAGCCCTGTTGGGAATGGCTACGTGCTCGGGCTTCCCTGGCCTCCTCCCTGTG
GCCAATGGCAACAGCCTAAACAAGGTATCCCTGCCAAGTCTCCACCCCACTACCCACAGCACCCA
GCTTGGAGCCCCCAGCCGCAAGCCGACCTGCGAGTCATCACTTCCAGGCAGGAAAGGGGTTAATG
CATCACTTGAACAATGCCAGCGCCTTGGGGTCTCCAGTCTACTCATTGCTCACCACCCAGTGGTT
TCTGTGGCAACGCCGAGTTTACTCAGCCAGGGCCTCCCCTTCTCTTCCATGCCCAGTGCCTACAACACA
GATTACCAGTTGACCAGTGCAGAGCTCTCCTCCTTACCAGCCTTTAGTTACCTGGGGGGCTGTCGCTA
GGCAATGTCACTGCCTGGCAACAGCCACAGCAGCCCCAGCAGCCGAGCAGCCACAGCCTCCACAGC
AGCAGCCACCGCAGCCACAGCAGCCACAGCCACAGCAGCCTCAGCAGCCGCAACAGCCACCTCAGCA
ACAGTCCCACCTGGTCCCTGTATCTCTCAGCAACCTCATCCCGGGCAGCCCCCTGCCCCACGTGGGTG
CTGCCCTCACAGTCAACACCCACCCCAACATCAGCATCAAGTCAGAACCGGTGTCCCCAAGCCGTGAG
CGCAGCCCTGCGCCTCCCCCTCCAGCTGTGTTCCAGCTGCCCGCCCTGAGCCTGGCGATGGTCTCAG
CAGCCCAGCCGGGGGATCCTATGAGACGGGAGACCGGGATGACGGACGGGGGGACTTCGGGGCCAC
ACTGGGCCTGCTGCGCCCAGCCCCAGAGCCTGAGGCTGAGGGCTCAGCTGTGAAGAGGATGCGGCTT
GATACCTGGACATTAAAGTGACGATTCCCACTCCCTCCTCTCAGCCTCCCTGATGAAGAGTTGACAA
TCTACCGCCCGCCCTTCCCTGCCCGGGCTCCTCCCGCTCGACCCCCACTTCCTTTCTTGTGCTTCGTG
TCCTGTTGACGGTTACATTTGTGTATAATTATTATATTATTATTATTATTATTATTTTTTTTAAATTTGG
ATTCTCGCTTTGGAGAGGGGGATGCTCTCATCCCCTCTTTCTGTACCCCCACCATTTTCACTGGCTGG
GGGGCTCTCTTTTTCGCGGGAAGGGGGGACACTTTGCACGTTGTACACATATGCTGCAGGAAGGGGGT
GGGGGGCCCAATAAGGCCTTTGGGAAAGGACAGGTGCCGAGCCCTGCATGTGGAGCCCTCCACCCCC
ACCCCCAGATAGAGGGAAATAACCAAAAACTACCAAAACAACAGAAACCCACACTCTAGACTGAAA
CCCCAAAGTGGGCTTGATGGGTGGGTTTGTGTTTCAAGGGGAAAGTGAGGCAGAGGTTCTGAAAAGG
GTCTCTGTTTTTGTGTTTCATGTAGCCATAGGCACATGGAGCAGAATACTTAAGCCTGGCCCCCAAATG
CCCCTGCACACACAGTGCCACACCTGCGCTGATTCTTGTGTGTGCTGCACCCCCAAGGTGTGTGGGT
GCTGGCTGAGCTTTGGGCCGGGAAGGCAGCCTGGGAATCTGAGGCTGGAGACAGGGGTTTGAGGTGG
GGCCCTCTCTGGAAGCACAATTTGAGGGGAAAGACAAGAGAGCCATGAGGAGAGGGCTGAGGAGGGC
AGAAGGGCTAGGCAGGGGGCAAATTGAGCCCCCTCCCTCCCCAGTTTCTCTAAGATATACAGTGCA
ATAGCTCCCCACCCCTCAGTTGACGCCAGCCCTGTAAAGCTGGCCACAGTGTGCAGGGAGAATGGGG
AGAGGGTCTTCAGTGAGGTGGCTGGGGCGAGAGTCGGCCTGGACTTCCCTGGGGTGCTCCAGGCCAG
AGCTCTTTCATTGGGGCGAGTGTGGTGAGGGGACGTCCTTGGTCTTGACGCACACTACCTGGGGGAG
TCAACACTGGGATGGTCTGTGGGGTGGGAGGGCCTACGGATGGGTCCGTAGAGGTCCCACCTCCCTCA
TTCTCTCTTGGCCCCCTCTCCCTAGCTTCTCCTGTAGCTCCTTCTGCTCCTGACCCCACTCCTTGTCTT
GGCGCCCCATTGTCTCTGGCTACCTCCTTGTCCCACCACTCCAGGCTGCATCCCACCTTCCCTCTTG
GCTACTGTAATTGTAAATAGCGACCTTTGGAAAACGTTAGCGGTGTAACAGTCCAGGAACTGTTTTT
TTTTGTTGTTGTTGATTGATATGAAATGAGATTCTATTTTTGTCAAAGTATATTGTAATAATAATGAC
TCAAACGGCCCGTACTGTACAGACGAGATTCTTCTGCTGTTGTTCTTGCTCCCCTCCCCTCCTCTGAGT
CCGCCCCCTCCCTGCTGCCTCCTCAGTGGGGCAGTGGGCAAGGGGCCAGGGGCAGCCGAAGCACGGG
GTCCTGAGACCTCAGGCAGGATTGGAGATCAAACCAGAGGGGGCAGGCCCCCAGCCTGCTCTTAGG
ATCACCCCCCGCCCTAAGGGGCCTGGCCTGGGGTGACGTGGCCAGGCAGACTGTCTGCCCCACTCCTT
CACACAAGCCCAGCTCCTCTGCCCAAGGGGTGCGGCGCCCCCTTGGGGTTTCCCTCCCAGTTGGAGAGT
AGAGTTAAGACAAGGCCAGTTTTGTGTTAGCCGACCGTCTTTGCCACCTCTATGACCCAGCCTCTTG
CAGTATTCCCATACTTGATGCAGGGAAGGAACCAGAAGCAGAGGGGCCTCTACGCAGGTACACACGT
GTACCTGAGTGTGTTTCATGAGGGCATCTGGTGTATTATGTGTCTGAGTGTAGCTTTGATTTATGTGTGT
GTGTGTGTGTATGTCTGATTGCACGGGTGTACTTTTGTATTTATGTGTGTGTGTGGTTGCACGGGTGTG

CCTCTGTGTGTCTCTGACCTGGCTGGGTGTGTGTGCAATCTGTGTGACTGGAGCTCTAGGGGCATCT
 CTGTGTCTGAGTGTGCCTGGTGTGTGTTTACAAAGGGAGAGTTGGCTGCTCCAGCTCCACAGCCCTGG
 GACCCCAACTCCTGTCTTCCCTGCTCCTTTCCTGTGTTCACCTCAGCTCTGACACATTGAACCTGCAG
 TTGGGGGGATTGGCAGTTAGCCCTCTGTGCTTCTCCCTGCAGCCCTACCTCTGCCAAGGTCTCTCCCTC
 CAGGGACCTCTGCTTCCACCCACATATGTCCACTTAGTCACCACACTTGACACAGTTCTTGAGTAC
 CCTCTTCCCCCAACCCAGACCTGCTTTCAGAGCAAACTCAAGTCCCTCTTCTCCGTGAAGCTTCTC
 CCTCAGCTGAGCAGTGATCACTTACTCACTCTTAACCCCAATCCGCTGACTGGGTGGGGACAGCACGT
 CCAGCCTTCCACCTCTCCTGCAGGCTTCTAGACGGAGTTTCAAAAAGTATGATGAGCCTCGATCCAGGG
 CTTGAAAGAAGCCAGGGTGTAACTTTGTTTCATGCATGCGTCCCCAGAGCCTCGCCAGTGCCTGGCAC
 ATAGTAGGCACTCAATAAATGCTGAATGGGTGAATAGTTGAATGATAGGTGCTCAATAAATGAATGA
 ATGGCCTTCCCTTCTCAGGCTATTCCACCATTAGTCTGCCACCTTTCTAGGCTGGGCTTGGCCACCA
 TTAAACACGGGTGGGGTGAGGGCCCCGCAATACCGTGCAATATTACAGTCTTTCGCCCTGCTC
 CTCATAAAGGCAAAACCTGGCTTTTGATTACCATGTGCGATGTTTCAGTGTCTTTCTTCTGTCTCCT
 GGGGATGGGGTGGTCTGTGAATATGTGACATTTCTGCAGTTCAGTATCCGAAGGTTTCTCTTGGGGT
 AGGGGCTCCTGGGCGGCCAGATGAATGGGTCCCTGGGAACCCAGACCTCAGATGAGGACTTAATGTC
 TTCTTCTCTCAAGCCAAATTCGCCTCCACCCACTCCCTCTGAAGAAGTGGGCATTTGCCAAAGTAACC
 ACTGGAGTCATCTAATGGCCCTCCCCCTCCCCAGGTTTCCACAGCTTTCAGGGACAGTGGGCAAGAG
 GACACCCCCCCCCACACCTCAGTGGAAACACACCATTTCTCCCCCTCAACAGCACACTCAGTGCAGC
 AAGACTGACCCCTGACCCCTCCCAGCCCTCCCTACCTTGGACAGGAAGGAAGTAATGCACCTTCTCT
 TGCTGATTATTTATTTGTTTGGAGAGACAGAAATGTAAAAGTGTATCTAGAAATATCTATATCTCTATA
 TATTTTAACTGACTCTTTGGAATCCCTGGGGTGGGGTGAGGGGTAAAGTTTAGGCTTTCGCGGAGGG
 GAGGAGACATGGAGCCTGGGAACCTTGTCTCCCTCTGCTGCCTCTCCCCACCCCTTAAAGCAGTT
 GGTAGAAGGAATGGTATTTGTATGGGGGGAGGGAGGCTGGAATGGAGAATCTGGATTCTCTCTCTCTC
 CCCATTCTCCAGAGGGAGGGAGGTGGTGAGGAAGAGGAAGGGAGGGGCAGGATGGGCCATGGAGGT
 GCCCCACCCCAACCTGACAATCACCCACACTCCTGGGGCTCTTCTGGGTCTGGGGCAGGGCGAG
 TCCAAGTGTGAGGCTGTTGATTTGTTTCAATATTTCTTTTCGTGCTGTATGGTGATGCTTTCTTAGTAT
 TCTACACAATAAGAAAAGACAAAGTCCTCGAGATTCTTATGAGTTTGTGTTGAAAAGTCTTTCACTAT
 ATTTGTTGTAAAGAGGTTTACTATTAAAAGAAAAAGAATACACGTTTCTGATA (SEQ ID NO: 665)

[000450] In some embodiments, oligonucleotides may have a region of complementarity to a mouse MEF2D sequence, for example, as provided below (Gene ID: 17261; NCBI Ref. No: NM_001310587.1)

TGCGCGGTGCCTACGTCGGCCTCGAGTCTGGGGCTGGAGGAGTTGCCTTTGGAGCCCGAAAGGAGGA
 AGGAAGCAAAATATCAACAACCGTCGAGGCGGCTTGGGCGCTCGGCTGCGTGCCTGCCGCCCCGCCG
 CGCCGCCCCCGCGCGCACAGGGGGTCCCGGCCCTGTGGCGCCGCCAGGCCGCGTGGACGCGGCGC
 CTTGCTGTTTCCCGTCGGAGCTGCGGCTTTCGCGTAACCGAGGATTTCGGCGGACCGGGCCGAGGCTCC
 GGGCGCCGTGACACCCCGTCCCCCCCCACGGGCTGGAGGCTGTGCATAGGTGTTCTGCAGACCATGAAC
 TGATCACTAGTCCCCAGACATTCATGAGCACAGTGTGAGGCTCCTGATCACCACCCAGCAGCCCCCTTC
 CTCTCTGGCACTAAGGACCCCGGAGAAGATGGGGAGGAAAAAGATTTCAGATCCAGCGAATCACTGA
 TGAACGGAACCGCCAGGTGACCTTACCAAGCGGAAGTTTGGACTGATGAAGAAGGCCTACGAGCTG
 AGTGTGCTGTGCGACTGCGGAGATCGCGCTCATCATCTTCAACCACTCCAACAAGCTGTTCCAGTATGC
 CAGCACCGACATGGACAAGGTGCTGCTCAAGTACACCGAGTACAACGAGCCACACGAGAGCCGCACC
 AATGCTGACATCATCGAGACCTGAGGAAGAAGGGTTTCAACGGCTGTGACAGCCCAGAGCCGGATG
 GGGAGGACTCACTGGAGCAGAGCCCCCTGCTGGAGGACAAGTACCGGCGGGCCAGTGAGGAGCTGG
 ATGGGCTCTTCAGGCGCTATGGGTTCATCTGTTCCGGCCCCCACTTTGCCATGCCTGTACAGTGCCCC
 TGTTCAATCAGAGCTCCATGCAGTTCAGCAATCCAAGTAGCTCTCTGGTCACTCCTTCCCTGGTGACAT
 CATCCCTTACGGACCCACGGCTCCTGTCCCCCAGCAGCCAGCACTACAGAGAAACAGTGTCTTCCA
 GGCTTGCCCCAGCGGCTGCTAGTGCAGGAGCCATGCTGGGTGGAGACCTCAACAGTGCTAATGGAG
 CCTGCCCCAGCCCCGTGGGAATGGCTATGTCAAGTCCCCGCAATCTCCGCCCCACCCACCAACACCCAGCTT
 GGAGCCCCAGCCGCAAGCTGATCTCGGGTCACTCACTTCCCAGGGAGGCAAAAGGTTAATGCATC
 ATTTGACTGAGGACCATTTAGATCTGAACAATGCCAGCGCCTTGGGGTCTCCCAAGTCTACCCACTCG
 CTCACCACCCAGTGGTTTCCGTGGCAACACCAAGTTTACTCAGCCAGGGCTCCCTTCTCCTCCATG
 CCCACTGCCTACAACACAGATTACCAGCTGCCAGTGCAGAGCTATCCTCCTTACCAGCCTTCAGTTC
 ACCTGCAGGGCTGGCACTAGGCAATGTCACCGCTGGCAGCAGCCCCAGCCGCCCCAGCAGCCACAA
 CCGCCACAACCGCCACAGTCACAGCCACAGCCACCACAGCCACAGCCACAGCAGCCACCTCAGCAAC
 AGCCCCACTTGGTCCCCGTTTCTCTCAGCAACCTCATCCCTGGCAGCCCCCTTGCCTCAGTGGGTGCTG
 CTCTCAGTCACTACCCACCCCAACATCAGCATCAAGTCAGAACCAGTGTCCCCAAGTCGTGAACGC
 AGCCCTGCACCTCCTCCACAGCTGTGTTCCAGCTGCCCGCCCTGAGCCTGGCGAAGGTCTCAGCAG
 CCCAGCTGGAGGATCCTATGAGACCGGGGACCGGGATGATGGACGGGGGGACTTTGGGCCCCACACTA

GGCCTGCTGCGCCCAGCCCCAGAGCCTGAGGCTGAGGGCTCAGCTGTGAAGAGGATGCGGCTGGATA
 CTGGACATTAAAGTGATGGTTCCCACTCCCTCCTTTCAGCCTCCCTGATGAAGAGTTGACAATCTCAC
 CGCCACCCCCCTCCTTATCCTGGGGCTCCTCCCGCTCGACCCCACTTCCTTTCTTCTGCTCCATGTCCTGT
 TGATGGTTACATTTGTGTATAATTATATTATTATTGTTATTATTATTATATTTTTAAATTCGAA
 TTCTCGCTTTAGAGAGAGGGGATGCTCTTGCCCCCTTCTTGCCCCCACCATTTCCTGATGGGGACTCT
 CTTTATTGCGGAAAGGGGGGACACTTTGCACGTTGTACACATATGCTGCAGGAAGGAGGGAGGCGG
 TAGGCCTTGAGAAAGGACAGGTGCCGAGCCCTGCATGTGGAGCCCTCCCATCCCATCCAGATAGAC
 GTAAAGAACCAAAAACTACCCAACAACAAAACCCAGATAGTGGACTGAAACCCAAAGCTGGCTTGAC
 GATGGGCTTGTGTCTCAGGGGATAGGAGGAGGCAGTTTCTGCTTCTGGGCTGTTACGGCTAATACCC
 ATCCTGGTCCCTCCAGCTTCTGCATACGTATCACACTCTCTGATCCTGTGTGTTACACCCCAAGATCT
 GGGTGATAGAAAGGCTGCCTAGGAATCTGAGGCCAGGGAAGGGGCTTGAGGTTGGAATCTCTAGAGA
 TAACATGGAGAGAGACAGCTGTAGAAAGAGGGCTGTATGAGGACAGAAGGACTGGGTGTGGTGAATT
 GGGACCTACCCCAAGCTTTTCTTTGAGATGTACAGTGCAATAGCTCCCCGTCCTTTAGCCTACCCCA
 ATCCTAAAGAAAGCTGGCCATGTACTGGGAGATTTGGGAGAGGACCTTCATTGAAGTGGCTCCAGGA
 TGGGCCAGAGTCGTCTTTGGTTCCCTGGGGCACTGAGAGCAGGAGGCTTGTACGGGGCAGGGTGAG
 GAGGGCACCTCTTGCTTTGTGCACCTGTGTCCAGAAGAGTACTTACTGGGCACATGGAGGCTCCTGT
 AGATGAGGCCCCGGGCCCTTCCCCAGGCCTCTGAGCTCCTGCCCCTGACCCACCTCCCAGCTCTCTGCG
 TGCTCCTTGTCTCGCTACCTCCTGTCCCTCCACCTCCAGGCCACATCCCAAACCTGCCCTCTTGCTACT
 GTAATTGTAAATAGAGACCTTTCAAATGTTAGTGGTGTAAACCGTCCAGGAAACTGTTGTGTTTGTGTT
 GTTGTATTGATATGAAATGAGATTCTATTTTTGTCAAAGTATATTGTAATAATAATGACTCAAATGGCC
 CGTACTGTACAGATGAGATTCTTCTGCTGTGTTCTTGCCCTTCTCTCCAGACTAATGCTTTGTTGCCTCC
 TCAGTGGGGCTGCAGCAAGCACCAGGGGCAGTGGAAGAAGCATTGGGTCCTTGGACCTCTTGCTGGA
 TCTGAGGTCAGACTGGAGGGAATAGTTTGCCCCCTCCCCAGCCTGCTGTCACCACCCCTGCCCTTCCTC
 TGCTTCCCCACCTGGGGAAAGGGGATGGGAGACAGCACACACTCCCTTGGAGTTCCTCCCAGCTGGA
 GGGTAGAGTTAGACAAGGCTCAGTGTGTAGTACGATGGTCTTTGCCACCTGTGACCCAGCCTTTTG
 TAGTATTTTGACACTTGATGCAGGGAAGGAGCCAGAAGCAGAGGGGTGTGAGCATGCTCGTGAGGC
 GTATCTGGGTTACCCCTGTATTTATGTGTTTGTGTGCAGCTGTGCGGATGTACCTTTGAGTGACTCAAG
 CTCCAAGGGCCTCTGTGTGAGCTGGGTGTGTTTACAAGGGATCAGCGCCTTCCAACCTCTGTGGCTTCA
 CCCCCTCCCCGGGCTGCTCTCAGTCCCAAAACATTTTACTAAAGTCATGGGGGACGGGTGCTAGTTGG
 CCTTCTGTTTCTCCCCACAGCCTACCTCCACCAGGGCTTCACATTTGGAGCTCTGCCTCCATATGGCT
 GTCCACTAGCCCCACCCAGGCATGGTTCATCCCTGGAGTTCTGACTTGTTTATGGAGCCAACTCAAGTT
 CTCTTGCCCGGAGCTTTGCCTTTTGTAAAGGCAGGGACCCTCCCTTAACCAGAGTTTACCCAGTAGCT
 GACCAAGCATGGGGTGCTACCCACATGCCTCACCTTCCCACTCCTCCTCACAAGTCCTGGAGGGAGTT
 TTAAGACTTGCTTATGGCCTTGAAAGAAGCCAGGGTTGTAGCCCTGTGCTCCCCCTGAAGTAGCTGGC
 ACATTGTAGGCCCTCAGTAAATGCTGAATGGGTGGATGACAGGTGCTCAATAAATGTGGATTACGGC
 CTCATCTCAGGCCCCTCCTTCAAGGCTGAGCTTGGCCACCATTACAGTTGTGGGTGAAGCCCTATAG
 TTCACAGTGTGCTACTCAACAGTTTGCCATCTGCTTCCCGAAAGCAAACCTGGCTTGTGATTGCCATGT
 ACGGATGCGTGCATGCACTGTGTGTGTGTGTGCGTGTGCGTGTCTGTGTCTGCACACACACGTA
 TGAGTTCTTGTGTGTCTCTGTCCCTGACTGAAGGGGCAGTCTGTGAATGAGTATGTGACATTTCTGCAG
 TTTAGTATCCCCAGGTTTCTCCTGGGGCTATGCAGGGGCTTCTGGCTGGCCAGGTAAATGGATCCCTG
 GGAACCTAGACCTCAAATGGGGACTTATTTTCTTCTCTCACAAGCCAAATTTGCCTACTCTCCACTCC
 CTATACAGAACTGGGTATTTGCCAAAGTAGCCTCTGGCGTCATCCAGTGCCCTTCCCACCCAGGTTCC
 CCTCTGCTTTCAGGGATAGTGGGACCGAGGGCCACCCCAACATGCCTCAGTTTAGCACATTTCTCTCA
 TCCCCAGCAGTGCATCCACCCACCCCTCCCCAACTCCAACAGGAAGGAAGAAAGAAATGCACCTTCTCT
 TGCTCGTTATTTATTTGTTTGGAGAGACAGAAATGATGGAAAAGTATCTAAATCTATCTCTCTCTAT
 TTTTACCTAACTCTCTGGAACCCCTGTGGGGGAATGTAGGCTCTCCTAAGAGGCTGGGAGCTCCTTGT
 CTACCCTGTCTGCCTCTACATAAGCAGAAGGGGTGGGATGTAATGGGGCAGGAGGGCTGAGATTCCC
 AAGGAGAATCTGAATTCTCTACCCCAATTCAAGTCCCAAGAGGGAAGAGGGAGGGATGGGCCA
 GCCAAGAGCTGACCCGTCCCCAACTTGACAATCACCCACACTCCTGGCTCCTGGGTCTGGGTGAGTC
 CAAGTGTGTGGCTGTTGGTTTGTTTTCATTATTTCTTTCCGTGCTGTACGGTGATGCTTTCTAGTATTCT
 GCACATTAAGAAAAGTCTCGAGATTCTTACGAGTTTGGTTTGAAGAACTCTTTCACTATATTTGTTGTA
 AAGAGGTTTACTATTAAGAAAGAAAAAACAATGTTTCTGATACCTCAAAAAAAAAAAAAAAAAA
 AA (SEQ ID NO: 666).

[000451] In some embodiments, oligonucleotides may have a region of complementarity to a mouse MEF2D sequence, for example, as provided below (Gene ID: 17261; NCBI Ref. No: NM_133665.4)

TGCGCGGTGCCTACGTCGGCCTCGAGTCTGGGGCTGGAGGAGTTGCCTTTGGAGCCCGAAAGGAGGA
 AGGAAGCAAAATATCAACAACCGTCGAGGCGGCTTGGGCGCTCGGCTGCGTGCCTGCCGCCCCGCCG
 CGCCGCCCCCGCGCGCACCAGGGGGTCCCGGCCCTGTGGCGCCGCCAGGCCGCGTGACGCGGCGC

CTGACTGAAGGGGCAGTCTGTGAATGAGTATGTGACATTTCTGCAGTTTAGTATCCCCAGGTTTCTCCT
 GGGGCTATGCAGGGGCTTCTGGCTGGCCAGGTAAATGGATCCCTGGGAACCTAGACCTCAAATGGGG
 ACTTATTTTCTTCTCTCACAAGCCAAATTTGCCTACTCTCCACTCCCTATACAGAACTGGGTATTTGC
 CAAAGTAGCCTCTGGCGTCATCCAGTGCCTTCCCACCCAGGTTCCCCTCTGCTTTCAGGGATAGTGG
 GACCGAGGGGCCACCCCCACATGCCTCAGTTTAGCACATTTCTCCATCCCCAGCAGTGCATCCACCCA
 CCTCCCCAACTCCAACAGGAAGGAAGAAAGAAATGCACCTTCTCTTGCTCGTTATTTATTTGTTTGG
 AGAGACAGAAATGATGGAAAAGTATCTAAATCTATCTCTCTCTATTTTTACCTAACTCTCTGGAACC
 CCTGTGGGGGAATGTAGGCTCTCCTAAGAGGCTGGGAGCTCCTTGTTCTACCCTGTCTGCCTCTACATA
 AGCAGAAGGGGTGGGATGTAATGGGGCAGGAGGGCTGAGATTCCCAAGGAGAATCTGAATTCTCTAC
 CCCCATTCAAGTCCCAGAAAGAGGGGAAGAAGGGAGGGATGGGCCAGCCAAGAGCTGACCCGTCCCC
 AAACCTTGACAATCACCCACACTCCTGGCTCCTGGGTCTGGGTGAGTCCAAGTGTGTGGCTGTTGGTTT
 GTTTTCATTATTTCTTTCCGTGCTGTACGGTGATGCTTTCTAGTATTCTGCACATTAAGAAAAGTCCCTCG
 AGATTCTTACGAGTTTGGTTTGAAAACCTTTTCACTATATTTGTTGTAAAGAGGTTTACTATTAAAGA
 AAAAAAAAAAACATGTTTCTGATACCTCAAAAAAAAAAAAAAAAAA (SEQ ID NO: 667)

[000452] In some embodiments, the oligonucleotide may have region of complementarity to an isoform of MEF2D, for example as reported in Martin et al., Mol Cell Biol., Mar. 1994, p. 1647-1656, the contents of which are incorporated herein by reference in its entirety.

[000453] In some embodiments, an oligonucleotide comprises a region of complementarity to a MEF2D sequence as set forth in any one of SEQ ID NOs: 664-667. In some embodiments, the oligonucleotide comprises a region of complementarity that is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to a MEF2D sequence as set forth in any one of SEQ ID NOs: 664-667. In some embodiments, the oligonucleotide comprises a sequence that has at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides that are perfectly complementary to a MEF2D sequence as set forth in any one of SEQ ID NOs: 664-667. In some embodiments, an oligonucleotide may comprise a sequence that targets (*e.g.*, is complementary to) an RNA version (*i.e.*, wherein the T's are replaced with U's) of a MEF2D sequence as set forth in any one of SEQ ID NOs: 664-667. In some embodiments, the oligonucleotide comprises a sequence that is complementary (*e.g.*, at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% complementary) to an RNA version of a MEF2D sequence as set forth in any one of SEQ ID NOs: 664-667. In some embodiments, the oligonucleotide comprises a sequence that has at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides that are perfectly complementary to an RNA version of a MEF2D sequence as set forth in any one of SEQ ID NOs: 664-667.

[000454] In some embodiments, a MEF2D-targeting oligonucleotide comprises an antisense strand that comprises at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides of a sequence comprising any one of SEQ ID NOs: 716-223. In some embodiments, a MEF2D-targeting oligonucleotide comprises an antisense strand that comprises any one of SEQ ID NOs: 716-223. In some embodiments, a MEF2D-targeting oligonucleotide comprises an antisense strand that comprises shares at least 70%, 75%, 80%, 85%, 90%, 95%, or 97%

sequence identity with at least 12 or at least 15 consecutive nucleotides of any one SEQ ID NOs: 716-223.

[000455] In some embodiments, a MEF2D-targeting oligonucleotide comprises an antisense strand that targets a MEF2D sequence comprising any one of SEQ ID NOs: 668-715. In some embodiments, an oligonucleotide comprises an antisense strand comprising at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 nucleotides (*e.g.*, consecutive nucleotides) that are complementary to a MEF2D sequence comprising any one of SEQ ID NOs: 668-715. In some embodiments, a MEF2D-targeting oligonucleotide comprises an antisense strand comprising a sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, or 97% complementary with at least 12 or at least 15 consecutive nucleotides of any one of SEQ ID NOs: 668-715.

[000456] In some embodiments, a MEF2D-targeting oligonucleotide comprises an antisense strand comprises a region of complementarity to a target sequence as set forth in any one of SEQ ID NOs: 668-715. In some embodiments, the region of complementarity is at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or at least 19 nucleotides in length. In some embodiments, the region of complementarity is 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 nucleotides in length. In some embodiments, the region of complementarity is in the range of 8 to 20, 10 to 20 or 15 to 20 nucleotides in length. In some embodiments, the region of complementarity is fully complementary with all or a portion of its target sequence. In some embodiments, the region of complementarity includes 1, 2, 3 or more mismatches.

[000457] In some embodiments, a MEF2D-targeting oligonucleotide further comprises a sense strand that hybridizes to the antisense strand to form a double stranded siRNA. In some embodiments, the MEF2D-targeting oligonucleotide comprises an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 716-223. In some embodiments, the MEF2D-targeting oligonucleotide further comprises a sense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 692-715.

[000458] In some embodiments, the MEF2D-targeting oligonucleotide is a double stranded oligonucleotide (*e.g.*, an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 716-223 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 692-715, wherein the antisense strand and/or (*e.g.*, and) comprises one or more modified nucleosides (*e.g.*, 2'-modified nucleosides). In some embodiment, the one or more modified nucleosides are selected from 2'-O-Me and 2'-F modified nucleosides.

[000459] In some embodiments, the MEF2D-targeting oligonucleotide is a double stranded oligonucleotide (*e.g.*, an siRNA) comprising an antisense strand that comprises the nucleotide

from the modified version of SEQ ID NOs: 692-715 listed in Table 28. In some embodiments, the MEF2D-targeting oligonucleotide is a siRNA selected from the siRNAs listed in Table 28.

Table 26. MEF2D Target Sequences

Reference sequence	Corresponding nucleotides of the Reference Sequence	MEF2D Target Sequence (5' to 3')	SEQ ID NO:
NM_005920.4 (SEQ ID NO: 664)	445-463	TTCAGATCCAGCGAATCAC	668
NM_005920.4 (SEQ ID NO: 664)	616-634	ACAAGGTGCTGCTCAAGTA	669
NM_005920.4 (SEQ ID NO: 664)	1423-1441	CCTACAACACAGATTACCA	670
NM_005920.4 (SEQ ID NO: 664)	2027-2045	ATGAAGAGTTGACAATCTC	671
NM_005920.4 (SEQ ID NO: 664)	2280-2298	ACACTTTGCACGTTGTACA	672
NM_005920.4 (SEQ ID NO: 664)	2289-2307	ACGTTGTACACATATGCTG	673
NM_005920.4 (SEQ ID NO: 664)	2355-2373	GCCGAGCCCTGCATGTGGA	674
NM_005920.4 (SEQ ID NO: 664)	3385-3403	ATATTGTAATAATAATGAC	675
NM_005920.4 (SEQ ID NO: 664)	3387-3406	ATTGTAATAATAATGACTC	676
NM_005920.4 (SEQ ID NO: 664)	3349-3367	TATTGATATGAAATGAGAT	677
NM_005920.4 (SEQ ID NO: 664)	3376-3394	TGTCAAAGTATATTGTAAT	678
NM_005920.4 (SEQ ID NO: 664)	3375-3393	TTGTCAAAGTATATTGTAA	679
NM_005920.4 (SEQ ID NO: 664)	3341-3359	TGTTGTTGTATTGATATGA	680
NM_005920.4 (SEQ ID NO: 664)	1147-1165	GCAACAGCCTAAACAAGGT	681
NM_005920.4 (SEQ ID NO: 664)	1428-1446	AACACAGATTACCAGTTGA	682
NM_005920.4 (SEQ ID NO: 664)	2461-2479	TGGGCTTGATGGGTGGGTT	683
NM_005920.4 (SEQ ID NO: 664)	2840-2858	CTAAGATATACAGTGCAAT	684

NM_005920.4 (SEQ ID NO: 664)	2844-2862	GATATACAGTGCAATAGCT	685
NM_005920.4 (SEQ ID NO: 664)	2924-2942	AGAGGGTCTTCAGTGAGGT	686
NM_005920.4 (SEQ ID NO: 664)	613-625	CCGACATGGACAAGGTGCT	687
NM_133665.4 (SEQ ID NO: 667)	894-912	ATGCAGTTCAGCAATCCAA	688
NM_133665.4 (SEQ ID NO: 667)	902-920	CAGCAATCCAAGTAGCTCT	689
NM_001310587.1 (SEQ ID NO: 666)	1377-1395	GCAACACCAAGTTTACTCA	690
NM_001310587.1 (SEQ ID NO: 666)	1955-1973	GCTGGATACTTGGACATTA	691

* The target sequences contain Ts, but binding to RNA and/or DNA is contemplated.

[000464] In some embodiments, an oligonucleotide may comprise or consist of any sequence as provided in Table 27.

Table 27. Oligonucleotide sequences for targeting MEF2D

Passenger Strand/Sense Strand (RNA) (5' to 3')	SEQ ID NO:	Guide Strand/Antisense Strand (RNA) (5' to 3')	SEQ ID NO:
GAUUCAGAUCCAGCGAAUCAC	692	GUGAUUCGCUGGAUCUGAAUCUU	716
GGACAAGGUGCUGCUCUAGUA	693	UACUUGAGCAGCACCUUGUCCAU	717
UGCCUACAACACAGAUUACCA	694	UGGUAAUCUGUGUUGUAGGCAGU	718
UGAUGAAGAGUUGACAAUCUC	695	GAGAUUGUCAACUCUUCUACAGG	719
GGACACUUUGCACGUUGUACA	696	UGUACAACGUGCAAAGUGUCCCC	720
GCACGUUGUACACAUUAGCUG	697	CAGCAUAUGUGUACAACGUGCAA	721
GUGCCGAGCCCUGCAUGUGGA	698	UCCACAUGCAGGGCUCGGCACCU	722
GUAUAUUGUAAUAAUAAUGAC	699	GUCAUUAUUAAUACAUAUACUU	723
AUAUUGUAAUAAUAAUGACUC	700	GAGUCAUUAUUAAUACAUAUAC	724
UGUAUUGAUUAUGAAUAGAGAU	701	AUCUCAUUUCAUAUCAAUACAAC	725
UUUGUCAAAAGUAUAUUGUAAU	702	AUUACAUAUACUUUGACAAAAA	726
UUUUGUCAAAAGUAUAUUGUAA	703	UUACAUAUACUUUGACAAAAAU	727
GUUGUUGUUGUAUUGAUUGA	704	UCAUAUCAUAACAACAACAACA	728
UGGCAACAGCCUAAACAAGGU	705	ACCUUGUUUAGGCUGUUGCCAUA	729
ACAACACAGAUUACCAGUUGA	706	UCAACUGGUAAUCUGUGUUGUAG	730
AGUGGGCUUGAUGGGUGGGUU	707	AACCCACCCAUAAGCCCACUUU	731
CUCUAAGAUUAUACAGUGCAAU	708	AUUGCACUGUAUAUCUUAGAGAA	732
AAGAUUAUACAGUGCAAUAGCU	709	AGCUAUUGCACUGUAUAUCUUAG	733

GGAGAGGGUCUUCAGUGAGGU	710	ACCUCACUGAAGACCCUCUCCCC	734
CACCGACAUGGACAAGGUGCU	711	AGCACCUUGUCCAUGUCGGUGCU	735
CCAUGCAGUUCAGCAAUCCAA	712	UUGGAUUGCUGAACUGCAUGGAG	736
UUCAGCAAUCCAAGUAGCUCU	713	AGAGCUACUUGGAUUGCUGAACU	737
UGGCAACACCAAGUUUACUCA	714	UGAGUAAACUUGGUGUUGCCACG	738
CGGCUGGAUACUUGGACAUUA	715	UAAUGUCCAAGUAUCCAGCCGCA	739

[000465] In some embodiments, an oligonucleotide is a modified oligonucleotide as provided in Table 28, wherein ‘mN’ represents a 2’-O-methyl modified nucleoside (e.g., mU is 2’-O-methyl modified uridine), ‘fN’ represents a 2’-fluoro modified nucleoside (e.g., fU is 2’-fluoro modified uridine), ‘*’ represents a phosphorothioate internucleoside linkage, and lack of “*” between nucleosides indicate phosphodiester internucleoside linkage.

Table 28. Modified Oligonucleotides for targeting MEF2D

siRNA #	Modified Passenger Strand/Sense Strand (RNA) (5' to 3')	SEQ ID NO:	Modified Guide Strand/Antisense Strand (RNA) (5' to 3')	SEQ ID NO:
hsMEF2D-1	mGmAfUmUfCmAfGmAfUmCfCmAfGmCfGmAfAmUfCmAfC	692	fGfUmGfAmUfUmCfGmCfUmGfGmAfUmCfUmGfAmAfUmC*fU*mU	716
hsMEF2D-2	mGmGfAmCfAmAfGmGfUmGfCmUfGmCfUmCfAmAfGmUfA	693	fUfAmCfUmUfGmAfGmCfAmGfCmAfCmCfUmUfGmUfCmC*fA*mU	717
hsMEF2D-3	mUmGfCmCfUmAfCmAfAmCfAmCfAmGfAmUfUmAfCmCfA	694	fUfGmGfUmAfAmUfCmUfGmUfGmUfUmGfUmAfGmGfCmA*fG*mU	718
hsMEF2D-4	mUmGfAmUfGmAfAmGfAmGfUmUfGmAfCmAfAmUfCmUfC	695	fGfAmGfAmUfUmGfUmCfAmAfCmUfCmUfUmCfAmUfCmA*fG*mG	719
hsMEF2D-5	mGmGfAmCfAmCfUmUfUmGfCmAfCmGfUmUfGmUfAmCfA	696	fUfGmUfAmCfAmAfCmGfUmGfCmAfAmAfGmUfGmUfCmC*fC*mC	720
hsMEF2D-6	mGmCfAmCfGmUfUmGfUmAfCmAfCmAfUmAfUmGfCmUfG	697	fCfAmGfCmAfUmAfUmGfUmGfUmAfCmAfAmCfGmUfGmC*fA*mA	721
hsMEF2D-7	mGmUfGmCfCmGfAmGfCmCfCmUfGmCfAmUfGmUfGmGfA	698	fUfCmCfAmCfAmUfGmCfAmGfGmGfCmUfCmGfGmCfAmC*fC*mU	722
hsMEF2D-8	mGmUfAmUfAmUfUmGfUmAfAmUfAmAfUmAfAmUfGmAfC	699	fGfUmCfAmUfUmAfUmUfAmUfUmAfCmAfAmUfAmUfAmC*fU*mU	723
hsMEF2D-9	mAmUfAmUfUmGfUmAfAmUfAmAfUmAfAmUfGmAfCmUfC	700	fGfAmGfUmCfAmUfUmAfUmUfAmUfUmAfCmAfAmUfAmUfAmU*fA*mC	724
hsMEF2D-10	mUmGfUmAfUmUfGmAfUmAfUmGfAmAfAmUfGmAfGmAfU	701	fAfUmCfUmCfAmUfUmUfCmAfUmAfUmCfAmAfUmAfCmA*fA*mC	725
hsMEF2D-11	mUmUfUmGfUmCfAmAfAmGfUmAfUmAfUmUfGmUfAmAfU	702	fAfUmUfAmCfAmAfUmAfUmAfCmUfUmUfGmAfCmAfAmA*fA*mA	726
hsMEF2D-12	mUmUfUmUfGmUfCmAfAmAfGmUfAmUfAmUfUmGfUmAfA	703	fUfUmAfCmAfAmUfAmUfAmCfUmUfUmGfAmCfAmAfAmA*fA*mU	727

hsMEF2D-13	mGmUfUmGfUmUfGmUfU mGfUmAfUmUfGmAfUmAf UmGfA	704	fUfCmAfUmAfUmCfAm AfUmAfCmAfAmCfAm AfCmAfAmC*fA*mA	728
hsMEF2D-14	mUmGfGmCfAmAfCmAfGm CfCmUfAmAfAmCfAmAfG mGfU	705	fAfCmCfUmUfGmUfUm UfAmGfGmCfUmGfUm UfGmCfCmA*fU*mU	729
hsMEF2D-15	mAmCfAmAfCmAfCmAfGm AfUmUfAmCfCmAfGmUfU mGfA	706	fUfCmAfAmCfUmGfGm UfAmAfUmCfUmGfUm GfUmUfGmU*fA*mG	730
hsMEF2D-16	mAmGfUmGfGmGfCmUfU mGfAmUfGmGfGmUfGmGf GmUfU	707	fAfAmCfCmCfAmCfCm CfAmUfCmAfAmGfCm CfCmAfCmU*fU*mU	731
hsMEF2D-17	mCmUfCmUfAmAfGmAfUm AfUmAfCmAfGmUfGmCfA mAfU	708	fAfUmUfGmCfAmCfUm GfUmAfUmAfUmCfUm UfAmGfAmG*fA*mA	732
hsMEF2D-18	mAmAfGmAfUmAfUmAfC mAfGmUfGmCfAmAfUmAf GmCfU	709	fAfGmCfUmAfUmUfGm CfAmCfUmGfUmAfUm AfUmCfUmU*fA*mG	733
hsMEF2D-19	mGmGfAmGfAmGfGmGfU mCfUmUfCmAfGmUfGmAf GmGfU	710	fAfCmCfUmCfAmCfUm GfAmAfGmAfCmCfCm UfCmUfCmC*fC*mC	734
mmMEF2D-1	mCmAfCmCfGmAfCmAfUm GfGmAfCmAfAmGfGmUfG mCfU	711	fAfGmCfAmCfCmUfUm GfUmCfCmAfUmGfUm CfGmGfUmG*fC*mU	735
mmMEF2D-2	mCmCfAmUfGmCfAmGfUm UfCmAfGmCfAmAfUmCfC mAfA	712	fUfUmGfGmAfUmUfGm CfUmGfAmAfCmUfGm CfAmUfGmG*fA*mG	736
mmMEF2D-3	mUmUfCmAfGmCfAmAfUm CfCmAfAmGfUmAfGmCfU mCfU	713	fAfGmAfGmCfUmAfCm UfUmGfGmAfUmUfGm CfUmGfAmA*fC*mU	737
mmMEF2D-4	mUmGfGmCfAmAfCmAfCm CfAmAfGmUfUmUfAmCfU mCfA	714	fUfGmAfGmUfAmAfAm CfUmUfGmGfUmGfUm UfGmCfCmA*fC*mG	738
mmMEF2D-5	mCmGfGmCfUmGfGmAfUm AfCmUfUmGfGmAfCmAfU mUfA	715	fUfAmAfUmGfUmCfCm AfAmGfUmAfUmCfCm AfGmCfCmG*fC*mA	739

i. KLF15 Oligonucleotides

[000466] Examples of oligonucleotides useful for targeting KLF15 are provided in Schoger, E. et al. “CRISPR-Mediated Activation of Endogenous Gene Expression in the Postnatal Heart.” *Circ Res.* 2019 Nov 15.; Jiang J. et al. “miR-190a-5p participates in the regulation of hypoxia-induced pulmonary hypertension by targeting KLF15 and can serve as a biomarker of diagnosis and prognosis in chronic obstructive pulmonary disease complicated with pulmonary hypertension.” *Int J Chron Obstruct Pulmon Dis.* 2018 Nov 20;13:3777-3790.; Mamet, J. et al., “Intrathecal administration of AXX2 DNA-decoy produces a long-term pain treatment in rat models of chronic pain by inhibiting the KLF6, KLF9 and KLF15 transcription factors.” *Mol Pain.* 2017 Jan-Dec;13:1744806917727917.; Tang, Q. et al. “Absence of miR-223-3p ameliorates hypoxia-induced injury through repressing cardiomyocyte apoptosis and oxidative stress by targeting KLF15.” *Eur J Pharmacol.* 2018 Dec 15;841:67-74.; and Horie, T. et al., “MicroRNA-133 regulates the expression of GLUT4 by targeting KLF15 and is involved

in metabolic control in cardiac myocytes.” Biochem Biophys Res Commun. 2009 Nov 13;389(2):315-20.; the contents of each of which are incorporated herein in their entireties.

[000467] In some embodiments, oligonucleotides may have a region of complementarity to a human KLF15 sequence, for example, as provided below (Gene ID: 28999; NCBI Ref. No: NM_014079.4):

AGTGCTCCGCCGACGACACCCGCGGGCCGGCGGGCGATCGAGCCAGCGCAGGACCCGCGGCTCGGCC
 CCCGGCCGCGCCGACGAGAGTCTAGCCGCGCCCGCCAGCCAGCCCGCCGCGCCGACGACCCG
 CGGGGCTTGGCCGCGGTCCGGCGTGCGCCAAGTTCAGCCGCCACCGGCACGGCCAGGCCAGCATGG
 TGGACCACTTACTTCCAGTGGACGAGAACTTCTCGTCGCCAAAATGCCAGTTGGGTATCTGGGTGAT
 AGGCTGGTTGGCCGCGGGCATATCACATGCTGCCCTCACCCGTCTCTGAAGATGACAGCGATGCCTC
 CAGCCCCTGCTCCTGTTCCAGTCCCGACTCTCAAGCCCTCTGCTCCTGCTATGGTGGAGGCCTGGGCAC
 CGAGAGCCAGGACAGCATCTTGGACTTCCTATTGTCCCAGGCCACGCTGGGCAGTGGCGGGGGCAGC
 GGCAGTAGCATTGGGGCCAGCAGTGGCCCCGTGGCCTGGGGGGCCCTGGCGAAGGGCAGCGGCCCTG
 TGAAGGGGGAGCATTTCTGCTTGCCCGAGTTTCCTTTGGGTGATCCTGATGACGTCCACGGCCCTTCC
 AGCCTACCCTGGAGGAGATTGAAGAGTTTCTGGAGGAGAACATGGAGCCTGGAGTCAAGGAGGTCCC
 TGAGGGCAACAGCAAGGACTTGGATGCCTGCAGCCAGCTCTCAGCTGGGCCACACAAGAGCCACCTC
 CATCCTGGGTCCAGCGGGAGAGAGCGCTGTTCCCTCCACCAGGTGGTGCCAGTGCAGGAGGTGCCC
 AGGGCCCAGGTGGGGGGCCCCACGCCTGATGGCCCCATCCAGTGTGCTGCAGATCCAGCCCCTGCCT
 GTGAAGCAGGAATCGGGCACAGGGCCTGCCTCCCCTGGGCAAGCCCCAGAGAATGTCAAGGTTGCC
 AGCTCCTGGTCAACATCCAGGGGCAGACCTTCGCACTCGTGCCCCAGGTGGTACCCTCCTCCAATTG
 AACCTGCCCTCCAAGTTTGTGCGCATTGCCCTGTGCCCATTGCCGCCAAGCCTGTTGGATCGGGACC
 CCTGGGGCCTGGCCCTGCCGGTCTCCTCATGGGGCCAGAAGTTCCCCAAGAACCCAGCCGCAGAACTCA
 TCAAAATGCACAAATGTACTTTCCCTGGGTGCAGCAAGATGTACACAAAAGCAGCCACCTCAAGGC
 CCACCTGCGCCGGCACACGGGTGAGAAGCCCTTCGCCTGCACCTGGCCAGGCTGCGGCTGGAGGTTCT
 CGCGCTCTGACGAGCTGTGCGCGGCACAGGCGCTCGCACTCAGGTGTGAAGCCGTACCAGTGTCTGTG
 TGCAGAGAAGAAGTTTCGCGCGGAGCGACCACTCTCCAAGCACATCAAGGTGCACCGCTTCCCGCGGA
 GCAGCCGCTCCGTGCGCTCCGTGAACTGAAAGCGCCCTGAACCCCAGCCTGTCCGTACCCCGGATCC
 CCACCCCATCCCCATTTTTTTAAGCAATAATTTATTTGCCTCCTCCAGAGGGACATGGCAATGTTACCA
 GCCACCTTCTGAAGCCTGGGAGGTGTGAACCCAGGGCCCCGCCAACCGCTGCCTTTCTCGGGAGTACT
 TAGAGCCTCGAACC CGCTCCCTGGGGGCTGGGCCCCAGGCGCACGGGGCTGGAGGCAGGCCTTCGT
 GCCTTCGTGCCTTCGTGCCTTCCCGCGGTGGCCAGGCCTCTGCTGCAGCCGCTGGTTGCAGGCAGAGT
 TTTGGGGACCTTCCCTTCTCCCACTGGGCTCCCCATCCTGGGCCAAGGCCAGAACTTTAGTGCTAG
 GGGAAGATGAAATGTGCAGTTTTGAAATGTTGGGTTTCCAGAGAGAGTCATGCTGGAGGAGAAGGAA
 GTAGGCCAGAAGTCCAGGGCTGCACTGTGGTGTGAGGGTGGCTTTGTCTAAGATGCCTGCTCAGCATG
 ATCACCAGAGGGTGTGGGCAGGTCCCTGGAGCCGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGCAGGAC
 CGGGCCGCTGGGCCCTCATGTGGGAGAGAGGTGAAAAGCGTCCCCCACTAGGGGGCTGGCAGTGCAT
 GTGCTTGAGTTAAATGTGCAGGGCAGACAGAGCCAGAAGGGCCTGTACCCAGGGGCTCGTCCCCTCC
 TCCGTTTCCAGACAAATCCAGACACCAGCCTTTAGGGTGGCCTTGGGAGGAGAGGGCCAGGCTGT
 CCTGGGTGTGAGAGAACTAGATAGAGCCTCCCAACCCTGATTTAGAAATGCATTCTTATTTGTCTA
 GAAATTAATAAATGAACTAGCTTGTTTTGACAGGTTTATTTACATCCTATGAATGTATGTAAATAAA
 CTGTACATAGGTCCATCCACATAAAATATCTTTTAATAACATATCAACATTTGTGTAAATTTGAAATTT
 AAAAAAATCTATGAAGCTGGTGTACATATGTTACAATTACGTATATTTTCTTTGGTCTTCATAAAAAT
 ATATTTACTTTGCCAATAAAAAGAAAAAGAACTCACA (SEQ ID NO: 740)

[000468] In some embodiments, oligonucleotides may have a region of complementarity to a mouse KLF15 sequence, for example, as provided below (Gene ID: 66277; NCBI Ref. No: NM_023184.4)

GTGAGCGGCCGAGAGCGGGGAGAGCGGGCAGCGCGAGCGCCAGCTCGGCCGACGGGAGTGC GG
 GCTGCGGCCAGGAGCGCTGGACGCGCGGCCGCATACGGAGCCGGGCCGACGCGGAGGCCGCGCC
 AGGCGACGCGGAGTCCAGTCACCACAGGCTCGGCCAGGCCAGCATGGTGGACCACCTGCTTCCAGTG
 GACGAGACCTTCTCGTCACCGAAATGCTCAGTGGGTTACCTAGGGGACAGGCTGGCCAGCCGGCAGC
 CATAACCATGTTGCCCTCGCCCATCTCGGAGGATGACAGCGATGTCTCCAGCCCCTGCTCTTGTGCC
 AGCCCTGACTCGCAAGCCTTCTGTTCTGTACAGTGCGGGTCCAGGCCCTGAGGCCAGGGCAGCAT
 CTTGGATTTCTCCTGTCCCGGGCCACACTGGGCAGTGGTGGTGGCAGTGGAGGTATTGGAGATAGCA
 GTGGCCCTGTGACCTGGGGATCATGGAGGAGAGCCTCTGTGCCTGTGAAGGAGGAACATTTCTGCTTC
 CCTGAATTTCTGTCAGGGGACACTGATGACGTCTCCAGGCCCTCCAGCCTACCCTGGAGGAGATTGA

AGAATTCTTGGGAAGAGAACATGGAGGCTGAGGTCAAGGAGGCCCCAGAGAACGGTAGCAGGGACCT
 GGAGACCTGTAGCCAGCTCTCAGCTGGGTACACCGGAGCCACCTTCATCCAGAGTCTGCTGGGAGA
 GAGCGCTGTACCCACCAGGTGGCAGAGTGGGGTGGTGGCCAAAGTGCAGGTGAGGGGCCAG
 CACATGATGGCCCCGTGCCGGTGCTACTGCAGATCCAGCCTGTTGCTGTGAAGCAGGAGGCAGGTAC
 AGGGCCAGCCTCCCCAGGGCAGGCCCCAGAGAGCGTCAAGGTCGCCCAGCTTCTAGTCAACATCCAG
 GGGCAGACCTTTGCACTCCTGCCTCAAGTGGTACCATCCTCCAACCTTGAACCTGCCCTCAAAGTTTGTG
 CGAATTGCGCCTGTGCCCATTTGCCGCCAAACCTATTGGCTCAGGATCCCTAGGGCCCCGGCCCTGCTGG
 CCTCCTTGTGGGCCAGAAGTTTCCCAAGAACCCAGCAGCAGAACTTCTCAAAATGCACAAATGCACTT
 TCCCAGGCTGCAGCAAGATGTACACCAAGAGCAGCCACCTCAAGGCCACCTGCGTCGGCACACAGG
 CGAGAAGCCCTTTGCCTGCACCTGGCCAGGCTGCGGCTGGAGGTTTTCCCGCTCAGATGAGTTGTCAA
 GGCACCGGCGATCTCACTCGGGTGTGAAGCCGTACCAGTGTCCCGTGTGCGAGAAGAAATTCGCGCG
 GAGTGACCACCTCTCCAAACACATCAAAGTGCATCGCTTCCACGAAGCAGCGCGCAGTACGCGCC
 ATCAACTGAGCGCAGTGGCCGCCCTTCCCTCCCCAGCTCCACGTTTTGTTTTTAAATGCAATAACTTA
 TTGCCTCTTTTTCAGAAGGATGTGACAATATTACCAGCCCCCTCCCCCTTCTGAATCTTAGGAGGTATGA
 CCCAGAGCCACCATGGCTGCCTTTCTGGGGAAGACCTAGAGTCCCTATGGTCCCTGGGGGCTGGTTCC
 CCGGTGGCCAGGTGGCCAGGCAGGCCTGTGCCCTTGTGCCTTTGTGCCTTCTGCCAGCTGGAAGC
 AGTGTGTTGGGGGGCCCTTGCCCTCTTCCCACTGGGCTCCCTACCTGGGCCAAAGTCAACATCATTGCTG
 GGAAGAAGTGTGTTTGGCTGTGTCAAAATAGTAGCTCCCAGAGGAAGCAAGCCATGCTGGGAAAAAG
 GAAGTGGGTCAAAAAAGCGTAGGGCTGCACTGTGATGTGAGGACCGCCATATGCAAGAGGCCTTTGA
 GGGTCCAGGAGGATGGCCACCCTCGCTCTAGGCCGTAATGCATGTGCTTAAATGCAAGACAAATGGA
 GCCATAGCCAGCCGTACCCAGCCTGGCTCACCTCCTCCAGACACCAGACACCAGCCTCCTGGTTGTG
 GTGAGAGGAGAAGGGAACAGGTCTGGTGGATGCCAAGCAACTAGTTAGTGCCTCCCAGTCTGACCTA
 GATTTGCATTCTCATCAGGACTAGAAATTAGTACCAATTGAACTAGCTTGTTTTGACAGGTCTATTTC
 ACATCCTATGAATGTATGTAAATAAACTGTACATAGGTACGCATCTACATAAAATATCTTTTAATAAC
 ACGTTGACATTTGTGTAAATTTGAAATTTAAAAAAATTTCTATAAAGTTGGTGTACATATGTTACAATTA
 TGTATATTTTCTTTGGTCTTCATAAAAAATATATTTACTTTGCCAATAAAAAAGAGGAAAAAAAAAAAA
 GAACTC (SEQ ID NO: 741)

[000469] In some embodiments, an oligonucleotide comprises a region of complementarity to a KLF15 sequence as set forth in SEQ ID NO: 740 or SEQ ID NO: 741. In some embodiments, the oligonucleotide comprises a region of complementarity that is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to a KLF15 sequence as set forth in SEQ ID NO: 740 or SEQ ID NO: 741. In some embodiments, the oligonucleotide comprises a sequence that has at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides that are perfectly complementary to a KLF15 sequence as set forth in SEQ ID NO: 740 or SEQ ID NO: 741. In some embodiments, an oligonucleotide may comprise a sequence that targets (*e.g.*, is complementary to) an RNA version (*i.e.*, wherein the T's are replaced with U's) of a KLF15 sequence as set forth in SEQ ID NO: 740 or SEQ ID NO: 741. In some embodiments, the oligonucleotide comprises a sequence that is complementary (*e.g.*, at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% complementary) to an RNA version of a KLF15 sequence as set forth in SEQ ID NO: 740 or SEQ ID NO: 741. In some embodiments, the oligonucleotide comprises a sequence that has at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides that are perfectly complementary to an RNA version of a KLF15 sequence as set forth in SEQ ID NO: 740 or SEQ ID NO: 741.

[000470] In some embodiments, a KLF15-targeting oligonucleotide comprises an antisense strand that comprises at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides of a sequence comprising any one of SEQ ID NOs: 790-813. In some embodiments, a KLF15-targeting oligonucleotide comprises an antisense strand that comprises any one of SEQ ID NOs:

790-813. In some embodiments, a KLF15-targeting oligonucleotide comprises an antisense strand that comprises shares at least 70%, 75%, 80%, 85%, 90%, 95%, or 97% sequence identity with at least 12 or at least 15 consecutive nucleotides of any one of SEQ ID NOs: 790-813.

[000471] In some embodiments, a KLF15-targeting oligonucleotide comprises an antisense strand that targets a KLF15 sequence comprising any one of SEQ ID NOs: 742-789. In some embodiments, an oligonucleotide comprises an antisense strand comprising at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 nucleotides (*e.g.*, consecutive nucleotides) that are complementary to a KLF15 sequence comprising any one of SEQ ID NOs: 742-789. In some embodiments, a KLF15-targeting oligonucleotide comprises an antisense strand comprising a sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, or 97% complementary with at least 12 or at least 15 consecutive nucleotides of any one of SEQ ID NOs: 742-789.

[000472] In some embodiments, a KLF15-targeting oligonucleotide comprises an antisense strand comprises a region of complementarity to a target sequence as set forth in any one of SEQ ID NOs: 742-789. In some embodiments, the region of complementarity is at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or at least 19 nucleotides in length. In some embodiments, the region of complementarity is 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 nucleotides in length. In some embodiments, the region of complementarity is in the range of 8 to 20, 10 to 20 or 15 to 20 nucleotides in length. In some embodiments, the region of complementarity is fully complementary with all or a portion of its target sequence. In some embodiments, the region of complementarity includes 1, 2, 3 or more mismatches.

[000473] In some embodiments, a KLF15-targeting oligonucleotide further comprises a sense strand that hybridizes to the antisense strand to form a double stranded siRNA. In some embodiments, the KLF15-targeting oligonucleotide comprises an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 790-813. In some embodiments, the KLF15-targeting oligonucleotide further comprises a sense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 766-789.

[000474] In some embodiments, the KLF15-targeting oligonucleotide is a double stranded oligonucleotide (*e.g.*, an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 790-813 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 766-789, wherein the antisense strand and/or (*e.g.*, and) comprises one or more modified nucleosides (*e.g.*, 2'-modified nucleosides). In some embodiment, the one or more modified nucleosides are selected from 2'-O-Me and 2'-F modified nucleosides.

[000475] In some embodiments, the KLF15-targeting oligonucleotide is a double stranded oligonucleotide (e.g., an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 790-813 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 766-789, wherein the each nucleoside in the antisense strand and/or (e.g., and) each nucleoside in the sense strand is a 2'-modified nucleoside selected from 2'-O-Me and 2'-F modified nucleosides.

[000476] In some embodiments, the KLF15-targeting oligonucleotide is a double stranded oligonucleotide (e.g., an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 790-813 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 766-789, wherein the each nucleoside in the antisense strand and each nucleoside in the sense strand is a 2'-modified nucleoside selected from 2'-O-Me and 2'-F modified nucleosides, and wherein the antisense strand and/or (e.g., and) the sense strand each comprises one or more phosphorothioate internucleoside linkages. In some embodiments, the sense strand does not comprise any phosphorothioate internucleoside linkages (all the internucleoside linkages in the sense strand are phosphodiester internucleoside linkages), and the antisense strand comprises 1, 2, or 3 phosphorothioate internucleoside linkages. In some embodiments, the antisense strand comprises 2 phosphorothioate internucleoside linkages, optionally wherein the two internucleoside linkages at the 3' end of the antisense strand are phosphorothioate internucleoside linkages and the rest of the internucleoside linkages in the antisense strand are phosphodiester internucleoside linkages.

[000477] In some embodiments, the antisense strand of the KLF15-targeting oligonucleotide comprises a structure of (5' to 3'):

fNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmN*fN*mN, wherein “mN” indicates 2'-O-methyl (2'-O-Me) modified nucleosides; “fN” indicates 2'-fluoro (2'-F) modified nucleosides; “*” indicates phosphorothioate internucleoside linkage; and the absence of “*” between two nucleosides indicate phosphodiester internucleoside linkage.

[000478] In some embodiments, the sense strand of the KLF15-targeting oligonucleotide comprises a structure of (5' to 3'):

mNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfNmNfN, wherein “mN” indicates 2'-O-methyl (2'-O-Me) modified nucleosides; “fN” indicates 2'-fluoro (2'-F) modified nucleosides; and the absence of “*” between two nucleosides indicate phosphodiester internucleoside linkage.

[000479] In some embodiments, the antisense strand of the KLF15-targeting oligonucleotide is selected from the modified version of SEQ ID NOs: 790-813 listed in Table

31. In some embodiments, the sense strand of the KLF15-targeting oligonucleotide is selected from the modified version of SEQ ID NOs: 766-789 listed in Table 31. In some embodiments, the KLF15-targeting oligonucleotide is a siRNA selected from the siRNAs listed in Table 31.

Table 29. KLF15 Target Sequences

Reference sequence	Corresponding nucleotides of the Reference Sequence	KLF15 Target Sequence (5' to 3')	SEQ ID NO:
NM_014079.4 (SEQ ID NO: 740)	1180-1199	GCAGCAAGATGTACACCAA	742
NM_014079.4 (SEQ ID NO: 740)	2350-2369	AATGTATGTAAATAAACTG	743
NM_014079.4 (SEQ ID NO: 740)	2352-2371	TGTATGTAAATAAACTGTA	744
NM_014079.4 (SEQ ID NO: 740)	2354-2372	TATGTAAATAAACTGTACA	745
NM_014079.4 (SEQ ID NO: 740)	2358-2377	TAAATAAACTGTACATAGG	746
NM_014079.4 (SEQ ID NO: 740)	2476-2495	TATATTTTCTTTGGTCCTT	747
NM_014079.4 (SEQ ID NO: 740)	2503-2522	TATATTTACTTTGCCAATA	748
NM_014079.4 (SEQ ID NO: 740)	240-259	CCAAAATGCCCAGTTGGGT	749
NM_014079.4 (SEQ ID NO: 740)	619-638	TGGAGGAGATTGAAGAGTT	750
NM_014079.4 (SEQ ID NO: 740)	1511-1530	GCAATAATTTATTTGCCTC	751
NM_014079.4 (SEQ ID NO: 740)	2379-2398	CATCCACATAAAATATCTT	752
NM_014079.4 (SEQ ID NO: 740)	688-707	GCAAGGACTTGGATGCCTG	753
NM_014079.4 (SEQ ID NO: 740)	1340-1359	CCAGTGTCTTGTGTGCGAG	754
NM_014079.4 (SEQ ID NO: 740)	1615-1634	CGGGAGTACTTAGAGCCTC	755
NM_014079.4 (SEQ ID NO: 740)	2330-2349	GGTTTATTTACATCCTAT	756
NM_023184.4 (SEQ ID NO: 741)	1532-1551	TCTGAATCTTAGGAGGTAT	757

NM_023184.4 (SEQ ID NO: 741)	2204-2223	CATCTACATAAAATATCTT	758
NM_023184.4 (SEQ ID NO: 741)	1160-1179	AAGATGTACACCAAGAGCA	759
NM_023184.4 (SEQ ID NO: 741)	997-1016	CTCAAAGTTTGTGCGAATT	760
NM_023184.4 (SEQ ID NO: 741)	2118-2137	GAAATTAGTACCAATTGAA	761
NM_023184.4 (SEQ ID NO: 741)	393-412	AGGGCAGCATCTTGGATTT	762
NM_023184.4 (SEQ ID NO: 741)	2231-2250	ACGTTGACATTTGTGTAAA	763
NM_023184.4 (SEQ ID NO: 741)	2120-2139	AATTAGTACCAATTGAACT	764
NM_023184.4 (SEQ ID NO: 741)	263-282	CAGCCATACCACATGTTGC	765

* The target sequences contain Ts, but binding to RNA and/or DNA is contemplated.

[000480] In some embodiments, an oligonucleotide may comprise or consist of any sequence as provided in Table 30.

Table 30. Oligonucleotide sequences for targeting KLF15

Passenger Strand/Sense Strand (RNA) (5' to 3')	SEQ ID NO:	Guide Strand/Antisense Strand (RNA) (5' to 3')	SEQ ID NO:
CUGCAGCAAGAUGUACACCAA	766	UUGGUGUACAUCUUGCUGCAGCC	790
UGAAUGUAUGUAAAUAACUG	767	CAGUUUAUUUACAUACAUAUA	791
AAUGUAUGUAAAUAACUGUA	768	UACAGUUUAUUUACAUACAUA	792
UGUAUGUAAAUAACUGUACA	769	UGUACAGUUUAUUUACAUACAUA	793
UGUAAAUAACUGUACAUAAGG	770	CCUAUGUACAGUUUAUUUACAUA	794
CGUAUAUUUUCUUUGGUCCUU	771	AAGGACCAAAGAAAUAUACGUA	795
AAUAUAUUUACUUUGCCAAUA	772	UAUUGGCAAAGUAAAUAUAUUUU	796
CGCCAAAUGCCAGUUGGGU	773	ACCCAACUGGGCAUUUUGGCGAC	797
CCUGGAGGAGAUUGAAGAGUU	774	AACUCUCAAUCUCCUCCAGGGU	798
AAGCAAUAAUUUAUUUGCCUC	775	GAGGCAAUAAAUAUUGCUUAA	799
UCCAUCCACAUAUUUAUUCUU	776	AAGAUUUUUUAUGUGGAUGGACC	800
CAGCAAGGACUUGGAUGCCUG	777	CAGGCAUCCAAGUCCUUGCUGUU	801
UACCAGUGUCCUGUGUGCGAG	778	CUCGCACACAGGACACUGGUACG	802
CUCGGGAGUACUUAGAGCCUC	779	GAGGCUCUAAGUACUCCCGAGAA	803
CAGGUUUUUUCACAUCCUAU	780	AUAGGAUGUGAAAUAACCUGUC	804
CUUCUGAAUCUUAGGAGGUAU	781	AUACCUCCUAAGAUUCAGAAGGG	805

CGCAUCUACAUA AAAUAUCUU	782	AAGAUUUUUUAUGUAGAUGCGUA	806
GCAAGAUGUACACCAAGAGCA	783	UGCUCUUGGUGUACAUCUUGCUG	807
CCCUCAAAGUUUGUGCGAAUU	784	AAUUCGCACAAACUUUGAGGGCA	808
UAGAAAUUAGUACCAAUUGAA	785	UUCAAUUGGUACUAAUUUCUAGU	809
CCAGGGCAGCAUCUUGGAUUU	786	AAAUCCAAGAUGCUGCCCUGGGC	810
ACACGUUGACAUUUGUGUAAA	787	UUUACACAAAUGUCAACGUGUUA	811
GAAAUUAGUACCAAUUGAACU	788	AGUUCAAUUGGUACUAAUUUCUA	812
GGCAGCCAUACCACAUGUUGC	789	GCAACAUGUGGUAUGGCUGCCGG	813

[000481] In some embodiments, an oligonucleotide is a modified oligonucleotide as provided in Table 31, wherein ‘mN’ represents a 2’-O-methyl modified nucleoside (e.g., mU is 2’-O-methyl modified uridine), ‘fN’ represents a 2’-fluoro modified nucleoside (e.g., fU is 2’-fluoro modified uridine), ‘*’ represents a phosphorothioate internucleoside linkage, and lack of “*” between nucleosides indicate phosphodiester internucleoside linkage.

Table 31. Modified Oligonucleotides for targeting KLF15

siRNA #	Modified Passenger Strand/Sense Strand (RNA) (5' to 3')	SEQ ID NO:	Modified Guide Strand/Antisense Strand (RNA) (5' to 3')	SEQ ID NO:
hsKLF15-1	mCmUfGmCfAmGfCmAfAmGfAmUfGmUfAmCfAmCfCmAfA	766	fUfUmGfGmUfGmUfAmCfAmUfCmUfUmGfCmUfGmCfAmG*fC*mC	790
hsKLF15-2	mUmGfAmAfUmGfUmAfUmGfUmAfAmAfUmAfAmAfCmUfG	767	fCfAmGfUmUfUmAfUmUfUmAfCmAfUmAfCmAfUmUfCmA*fU*mA	791
hsKLF15-3	mAmAfUmGfUmAfUmGfUmAfAmAfUmAfAmAfCmUfGmUfA	768	fUfAmCfAmGfUmUfUmAfUmUfUmAfCmAfUmAfCmAfUmU*fC*mA	792
hsKLF15-4	mUmGfUmAfUmGfUmAfAmAfUmAfAmAfCmUfGmUfAmCfA	769	fUfGmUfAmCfAmGfUmUfUmAfUmUfUmAfCmAfUmAfCmA*fU*mU	793
hsKLF15-5	mUmGfUmAfAmAfUmAfAmAfCmUfGmUfAmCfAmUfAmGfG	770	fCfCmUfAmUfGmUfAmCfAmGfUmUfUmAfUmUfUmAfCmA*fU*mA	794
hsKLF15-6	mCmGfUmAfUmAfUmUfUmUfCmUfUmUfGmGfUmCfCmUfU	771	fAfAmGfGmAfCmCfAmAfAmGfAmAfAmAfUmAfUmAfCmG*fU*mA	795
hsKLF15-7	mAmAfUmAfUmAfUmUfUmAfCmUfUmUfGmCfCmAfAmUfA	772	fUfAmUfUmGfGmCfAmAfAmGfUmAfAmAfUmAfUmAfUmU*fU*mU	796
hsKLF15-8	mCmGfCmCfAmAfAmAfUmGfCmCfCmAfGmUfUmGfGmGfU	773	fAfCmCfCmAfAmCfUmGfGmGfCmAfUmUfUmUfGmGfCmG*fA*mC	797
hsKLF15-9	mCmCfUmGfGmAfGmGfAmGfAmUfUmGfAmAfGmAfGmUfU	774	fAfAmCfUmCfUmUfCmAfAmUfCmUfCmCfUmCfCmAfGmG*fG*mU	798
hsKLF15-10	mAmAfGmCfAmAfUmAfAmUfUmUfAmUfUmUfGmCfCmUfC	775	fGfAmGfGmCfAmAfAmUfAmAfAmUfUmAfUmUfGmCfUmU*fA*mA	799
hsKLF15-11	mUmCfCmAfUmCfCmAfCmAfUmAfAmAfAmUfAmUfCmUfU	776	fAfAmGfAmUfAmUfUmUfUmAfUmGfUmGfGmAfUmGfGmA*fC*mC	800

hsKLF15-12	mCmAfGmCfAmAfGmGfAmCfUmUfGmGfAmUfGmCfCmUfG	777	fCfAmGfGmCfAmUfCmCfAmAfGmUfCmCfUmUfGmCfUmG*fU*mU	801
hsKLF15-13	mUmAfCmCfAmGfUmGfUmCfCmUfGmUfGmUfGmCfGmAfG	778	fCfUmCfGmCfAmCfAmCfAmGfGmAfCmAfCmUfGmGfUmA*fC*mG	802
hsKLF15-14	mCmUfCmGfGmGfAmGfUmAfCmUfUmAfGmAfGmCfCmUfC	779	fGfAmGfGmCfUmCfUmAfAmGfUmAfCmUfCmCfCmGfAmG*fA*mA	803
hsKLF15-15	mCmAfGmGfUmUfUmAfUmUfUmCfAmCfAmUfCmCfUmAfU	780	fAfUmAfGmGfAmUfGmUfGmAfAmAfUmAfAmAfCmCfUmG*fU*mC	804
mmKLF15-1	mCmUfUmCfUmGfAmAfUmCfUmUfAmGfGmAfGmGfUmAfU	781	fAfUmAfCmCfUmCfCmUfAmAfGmAfUmUfCmAfGmAfAmG*fG*mG	805
mmKLF15-2	mCmGfCmAfUmCfUmAfCmAfUmAfAmAfAmUfAmUfCmUfU	782	fAfAmGfAmUfAmUfUmUfUmAfUmGfUmAfGmAfUmGfCmG*fU*mA	806
mmKLF15-3	mGmCfAmAfGmAfUmGfUmAfCmAfCmCfAmAfGmAfGmCfA	783	fUfGmCfUmCfUmUfGmGfUmGfUmAfCmAfUmCfUmUfGmC*fU*mG	807
mmKLF15-3	mCmCfCmUfCmAfAmAfGmUfUmUfGmUfGmCfGmAfAmUfU	784	fAfAmUfUmCfGmCfAmCfAmAfAmCfUmUfUmGfAmGfGmG*fC*mA	808
mmKLF15-5	mUmAfGmAfAmAfUmUfAmGfUmAfCmCfAmAfUmUfGmAfA	785	fUfUmCfAmAfUmUfGmGfUmAfCmUfAmAfUmUfUmCfUmA*fG*mU	809
mmKLF15-6	mCmCfAmGfGmGfCmAfGmCfAmUfCmUfUmGfGmAfUmUfU	786	fAfAmAfUmCfCmAfAmGfAmUfGmCfUmGfCmCfUmUfGmG*fG*mC	810
mmKLF15-7	mAmCfAmCfGmUfUmGfAmCfAmUfUmUfGmUfGmUfAmAfA	787	fUfUmUfAmCfAmCfAmAfAmUfGmUfCmAfAmCfGmUfGmU*fU*mA	811
mmKLF15-8	mGmAfAmAfUmUfAmGfUmAfCmCfAmAfUmUfGmAfAmCfU	788	fAfGmUfUmCfAmAfUmUfGmGfUmAfCmUfAmAfUmUfUmC*fU*mA	812
mmKLF15-9	mGmGfCmAfGmCfCmAfUmAfCmCfAmCfAmUfGmUfUmGfC	789	fGfCmAfAmCfAmUfGmUfGmGfUmAfUmGfGmCfUmGfCmC*fG*mG	813

j. MED1 Oligonucleotides

[000482] Examples of oligonucleotides useful for targeting MED1 are provided in Cai, Q. et. al. “MicroRNA-1291 mediates cell proliferation and tumorigenesis by downregulating MED1 in prostate cancer” *Oncol Lett.* 2019 Mar;17(3):3253-3260.; Zhang, L. et. al. “Silencing MED1 Sensitizes Breast Cancer Cells to Pure Anti-Estrogen Fulvestrant In Vitro and In Vivo” *PLoS One.* 2013, 8(7): e70641.; Mouillet J.F. et. al. “MiR-205 silences MED1 in hypoxic primary human trophoblasts” *FASEB J.* 2010 Jun;24(6):2030-9.; and Ndong, Jde. L. et al. “Down-regulation of the expression of RB18A/MED1, a cofactor of transcription, triggers strong tumorigenic phenotype of human melanoma cells” *Int J Cancer.* 2009, 124 (11):2597-606.; the contents of each of which are incorporated herein in their entireties.

[000483] In some embodiments, oligonucleotides may have a region of complementarity to a human MED1 sequence, for example, as provided below (Gene ID: 5469; NCBI Ref. No: NM_004774.4):

GAAGTTCCGTTGGGGAAGATGGCGGCGGCCTCGAGCACCCCTTCTCTTCTTGCCGCCGGGGACTTCAGATTGATCCTTCCCGGGAAGAGTAGGGACTGCTGGTGCCCTGCGTCCCGGGATCCCGAGCCAACTTGTTTCTCCGTTAGTGGTGGGGAAGGGCTTATCCTTTTGTGGCGGATCTAGCTTCTCCTCGCCTTCAGGATGAAGCTCAGGGGGAAACCGAGGAGTCAGAAAAGCTGAGTAAGATGAGTTCTCTCCTGGAACGGCTCCATGCAAAAATTTAACCAAAATAGACCCTGGAGTGAAACCATTAAAGCTTGTGCGTCAAGTCATGGAGAAGAGGGTTGTGATGAGTTCTGGAGGGCATCAACATTTGGTCAGCTGTTTGGAGACATTGCAGAAGGCTCTCAAAGTAACATCTTTACCAGCAATGACTGATCGTTTGGAGTCCATAGCAAGACAGAATGGACTGGGCTCTCATCTCAGTGCCAGTGGCACTGAATGTTACATCACGTCAGATATGTTCTATGTGGAAGTGCAGTTAGATCCTGCAGGACAGCTTTGTGATGTAAAAGTGGCTCACCATGGGGAGAATCCTGTGAGCTGTCCGGA GCTTGTACAGCAGCTAAGGGAAAAAATTTTGATGAATTTTCTAAGCACCTTAAGGGCCTTGTTAATCTGTATAACCTTCCAGGGGACAACAACTGAAGACTAAAATGTACTTGGCTCTCCAATCCTTAGAACAA GATCTTTCTAAAATGGCAATTATGTACTGGAAAGCAACTAATGCTGGTCCCTTGGATAAGATTCTTCA TGGAAGTGTGGCTATCTCACACCAAGGAGTGGGGGTCATTTAATGAACCTGAAGTACTATGTCTCTC CTTCTGACCTACTGGATGACAAGACTGCATCTCCCATCATTTTGCATGAGAATAATGTTTCTCGATCTT TGGGCATGAATGCATCAGTGACAATTGAAGGAACATCTGCTGTGTACAAACTCCCAATTGCACCATTAA TTATGGGGTCACATCCAGTTGACAATAAATGGACCCCTTCTTCTCCTCAATCACCAGTGCCAAACAG TGTGATCTTCTGCTGCTGTTTCTTCTTGAAATTTCCCCAGCCAATCCCAGTATCTAGAGCATTTGTTTCAG AAAGTGCAGAACTGCACAGGAATTCCATTGTTTGAAACTCAACCAACTTATGCACCCCTGTATGAACT GATCACTCAGTTTGTAGCTATCAAAGGACCCTGACCCCATACCTTTGAATCACAACATGAGATTTTATG CTGCTCTTCTGGTTCAGCAGCACTGCTATTTCTCAACAAGGATGCTCCTCTTCCAGATGGCCGAAGTCTACAGGGAACCCCTTGTTAGCAAAAATCACCTTTCAGCACCCCTGGCCGAGTTCCTCTTATCCTAAATCTGATCAGACACCAAGTGGCCTATAACACCCTCATTGGAAGCTGTGTCAAAAGAACTATTCTGAAAGAAGATTCTCCTGGGCTTCTCCAATTTGAAGTGTGTCTCTCTCAGAGTCTCGTTTCAGCGTATCTTTTCAGCAC CCTGTGAATGACTCCCTGGTGTGTGTGGTAATGGATGTGCAGGACTCAACACATGTGAGCTGTAACTCTACAAAGGGCTGTGCGATGCACTGATCTGCACAGATGACTTCATTGCCAAAGTTGTTCAAAGATGTATGTCCATCCCTGTGACGATGAGGGCTATTCGGAGGAAAGCTGAAACCATTCAAGCCGACACCCCAAGC ACTGTCCCTCATTGCAGAGACAGTTGAAGACATGGTGAAGAAAGAACCTGCCCCGGCTAGCAGCCCA GGGTATGGCATGACCACAGGCAACAACCCAATGAGTGGTACCACTACACCAACCAACACCTTTCCGG GGGGTCCCATTACCACCTTGTTTAATATGAGCATGAGCATCAAAGATCGGCATGAGTCGGTGGGCCAT GGGGAGGACTTCAGCAAGGTGTCTCAGAACCCCAATTCTTACCAGTTTGTGCAAATCACAGGGAACGG GGGGGTCTACCATTGGCTCGAGTCCGACCCCTCCTCATCACACGCCGCCACCTGTCTCTTCGATGGCC GGCAACACCAAGAACCACCCGATGCTCATGAACCTTCTTAAAGATAATCCTGCCCAGGATTTCTCAAC CCTTATGGAAGCAGCCCTTTAGAAAGGCAGAACTCCTCTTCCGGCTCACCCCGCATGGAAATATGCT CGGGGAGCAACAAGACCAAGAAAAAGAGTCATCAAGATTACCACCTGAGAAACCAAGCACCAGACTGAAGATGACTTTCAGAGGGAGCTATTTCAATGGATGTTGACTCACAGAACCCCTATCTTTGATGTC AACATGACAGCTGACACGCTGGATACGCCACACATCACTCCAGCTCCAAGCCAGTGTAGCACTCCCC AACAACTTACCCACAACCAGTACCTCACCCCCAACCCAGTATTCAAAGGATGGTCCGACTATCCAGTT CAGACAGCATTTGGCCAGATGTAAGTGCATCCTTTTCAGACATTGCAGAAGAAGCTTCTAAACTTCCC AGCACTAGTATGATGCCCAGCCATTGGCACCCCTCTTCGAGATTCTTCAAGCTCTGGGCATTCTCAG AGTACCCTGTTTGACTCTGATGTTCTTCAAACTAACTAATGAAAATCCATACACTGATCCAGCTGATCTTATTGCAGATGCTGCTGGAAGCCCCAGTAGTGACTCTCCTACCAATCATTTTTTTCATGATGGAGT AGATTTCAATCCTGATTTATTGAACAGCCAGAGCCAAAGTGGTTTTTGGAGAAGAATATTTTGATGAAA GCAGCCAAAGTGGGGATAATGATGATTTCAAAGGATTTGCATCTCAGGCACTAAATACTTTGGGGGTG CCAATGCTTGGAGGTGATAATGGGGAGACCAAGTTTAAAGGGCAATAACCAAGCCGACACAGTTGATT TCAGTATTATTTAGTAGCCGGCAAAGCTTTAGCTCCTGCAGATCTTATGGAGCATCACAGTGGTAGT CAGGGTCTTTACTGACCACTGGGGACTTAGGGAAAGAAAAGACTCAAAAGAGGGTAAAGGAAGGC AATGGCACCAAGTAATAGTACTCTCTCGGGGCCCGGATTAGACAGCAAACCAAGGGAAGCGCAGTCGGA CCCCTTCTAATGATGGGAAAAGCAAAGATAAGCCTCCAAAGCGGAAGAAGGCAGACACTGAGGGGAA AGTCTCCATCTCATAGTTCTTCTAACAGACCTTTTACCCACCTACCAGTACAGGTGGATCTAAATCGC CAGGCAGTGCAGGAAGATCTCAGACTCCCCAGGTGTTGCCACACCACCCATTCCCAAAATCACTATT CAGATTCTAAGGGAACAGTGTGTTGGGCAAGCCTTCTCTCACAGTCAGTATACCAGCAGTGGTTC TGTGTCTTCTCAGGCAGCAAAAGCCACCATAGCCATTCTTCTCCTCTTCTCATCTGCTTCCACCTC AGGGAAGATGAAAAGCAGTAAATCAGAAGGTTTCATCAAGTTCCAAGTTAAGTAGCAGTATGTATTCT AGCCAGGGGTCTTCTGGATCTAGCCAGTCCAAAAATTCATCCCAGTCTGGGGGGAAGCCAGGCTCCTC TCCCATAACCAAGCATGGACTGAGCAGTGGCTCTAGCAGCACCAAGATGAAACCTCAAGGAAAGCCA TCATCACTTATGAATCCTTCTTTAAGTAAACCAACATATCCCCTTCTCATTTCAAGGCCACCTGGAGGC TCTGACAAGCTTGCTCTCCAATGAAGCCTGTTCCTGGAACCTCCTCCATCCTCTAAAGCCAAGTCCCCT

ATCAGTTCAGGTTCTGGTGGTTCATATGTCTGGAAGTCAAGCTCTGGCATGAAGTCATCTTCA
 GGGTTAGGATCCTCAGGCTCGTTGTCCCAGAAAACCTCCCCATCATCTAATTCCTGTACGGCATCTTCC
 TCCCTCTTTCTCAAGTGGCTCTTCCATGTCATCCTCTCAGAACCAGCATGGGAGTTCTAAAGGAAAA
 TCTCCCAGCAGAAAACAAGAGCCGTCCTTGACAGCTGTCATAGATAAACTGAAGCATGGGGTTGTCA
 CCAGTGGCCCTGGGGGTGAAGACCCACTGGACGGCCAGATGGGGGTGAGCACAAATTCCTCCAGCCA
 TCCTATGTCTCCAAACATAACATGTCAGGAGGAGAGTTTCAGGGCAAGCGTGAGAAAAGTGATAAA
 GACAAATCAAAGGTTTCCACCTCCGGGAGTTCAGTGGATTCTTCTAAGAAGACCTCAGAGTCAAAAA
 ATGTGGGGAGCACAGGTGTGGCAAAAATTATCATCAGTAAGCATGATGGAGGCTCCCTAGCATTAA
 AGCCAAAGTGACTTTGCAGAAACCTGGGGAAAGTAGTGGAGAAGGGCTTAGGCCTCAAATGGCTTCT
 TCTAAAAACTATGGCTCTCCACTCATCAGTGGTTCCACTCCAAAGCATGAGCGTGGCTCTCCAGCCA
 TAGTAAGTCACCAGCATATACCCCCAGAATCTGGACAGTGAAAGTGAGTCAGGCTCCTCCATAGCA
 GAGAAATCTTATCAGAATAGTCCCAGCTCAGACGATGGTATCCGACCACTCCAGAATACAGCACAG
 AGAAACATAAGAAGCACAAAAAGGAAAAAGAAAGTAAAGACAAAGATAGGGACCGAGACCGG
 GACAAAGACCGAGACAAGAAAAAATCTCATAGCATCAAGCCAGAGAGTTGGTCCAAATCACCCATCT
 CTTCAGACCAGTCTTGTCTATGACAAGTAACACAATCTTATCTGCAGACAGACCCTCAAGGCTCAGC
 CCAGACTTTATGATTGGGGAGGAAGATGATGATCTTATGGATGTGGCCCTGATTGGGAATTAGGAACC
 TTATTTCTCAAAGAAACAGGGCCAGAGGAAAAAAACTATTGATAAGTTTATAGGCAAAACCACCAT
 AAGGGGTGAGTCAGACAGGTCTGATTTGGTTAAGAATCCTAAATGGCATGGCTTTGACATCAAGCTGG
 GTGAATTAGAAAGGCATATCCAGACCCTATTAAAGAAACCACAGGGTTTGATTCTGGTTACCAGGAA
 GTCTTCTTTGTTCTGTGCCAGAAAGAAAGTTAAAATACTTGCTTAAGAAAGGGAGGGGGGTGGGAG
 GGGTGTAGGGAGAGGGAAGGGAGGGAAACAGTTTGTGGGAAATATTCATATATATTTTCTTCTCCCT
 TTTTCCATTTTTAGGCCATGTTTTAAACTCATTTTAGTGCATGTATATGAAGGGCTGGGCAGAAAATGA
 AAAAGCAATACATTCCTTGATGCATTTGCATGAAGGTTGTTCAACTTTGTTTGAGGTAGTTGTCCGTTT
 GAGTCATGGGCAAATGAAGGACTTTGGTCATTTTGGACACTTAAGTAATGTTTGGTGTCTGTTTCTTAG
 GAGTGAAGTGGGGAGGGAAGATTATTTAGCTATTTATTTGTAATATTTTAACCCCTTATCTGTTTGT
 TTTATACAGTGTTCGTTCTAAATCTATGAGGTTTAGGGTTCAAAATGATGGAAGGCCGAAGAGCAAG
 GCTTATATGGTGGTAGGGAGCTTATAGCTTGTGCTAATACTGTAGCATCAAGCCCAAGCAAATTAGTC
 AGAGCCCGCCTTTAGAGTTAAATATAATAGAAAAACCAAAATGATATTTTTATTTTAGGAGGGTTAA
 ATAGGGTTCAGAGATCATAGGAATATTAGGAGTTACCTCTCTGTGGAGGTATTGACTTGTAATCTCAT
 TTTCTTTCAAAAAAAAAAAAAAAAAAGCTAAGGTGGCTTGTGGGATGTAAACATGTTTTAGATGCAG
 TAAGGTTTAGTGTAGGACAGCCTTCCTGACCCAGTGGCATGAAAACCATACAGGATTAATAGTTCTC
 TACTTCCACAATGTGCCAAAAGTCTGCATCCCAGCATTTTGTGTTGCAGGAGAACTGATGCCATTCTCA
 AGAGCTGGACTCACTGTTTCTCTTCATCACAAGGAGAAGGAGTCCAAACTTAATCACTCCACTGTAT
 GCTCCCTGAGATAAAACAGTAAAAAATCCGCAGCCATAGTTCACTTAAACAATTTCAAGTCACTTT
 TGAAGTAATGGGGGCTGGAATGCTAGGTGAGCATGAAGATAAAACCCTTGCTACTATGTAGCAACCC
 AATTGGACCTTTTTGGAGAAATAGGTCTGAGTCTGGATTCTGGGGGACATCAATAAGAGCCCTTCACA
 TAAAAATATAGAAATCCAGGAGACTGTTTCGAGTGCAACAGAAGTTCTCAGTATTTGGAGGGTCTCT
 CAAAAATCTGCGGCCTTACTTTGATATTGACACCTGCACTGTGCCATTCTGATTATTCATTTCAGGA
 TCTGTATCAGCGGGATGGGGCATGGTCCCCAGCACAACTCTTCTGGGTAAAAAAGCCAGGT
 GATTCCTTTGTGTGTTATGTGTAAGTGGAGTGACTTCATCATATATGGAAGAAGATTTCTATATTCAG
 CTTTTCTGCAGGTGGAGTCAGCATAGAGTTGGAAAAATCAGCTTTGGCTTTCTTTCTGTCTCATTTCT
 CTCTAGTGTCTCTTTTTATTGTCTCAGCTCTCAACAACCTTGCCACTTTTGTGTCCCAAGGTAATAA
 GATGTAGGAAACAAAACATTGTAAAGTGGAGCAAGAAAAGTTATCAATTAACCACATCAGAGTCAAA
 TGTCTTGGGTGACACTAAGGAGGATATGGGCAGGTGATACCAGAGTGCTTTATCTTGTGATGTTGATA
 CAGTAGCAGCCTCTCAGACATTCAGCCAGGTGGATTCTCATGAGTTTGTACCTAGTTTTGAATCCT
 ATCCCGTTGGTTTCTGCAGGAAAAAATTTATGTGGTTTTTAAATTTGTTCTGAGTGGGGA
 GAATCTTAGGGGGAATGTACTGAATAGTATCATGGGCTCAGCTCCCCCATGCAGGGCCAACAATAC
 CAAAATGAGTAAACTGGGAAGCTTTTCTCTTTCTGTCTTCATCCCAGATCAAAGAATCCCGAGTTA
 GGATCTGGATGAAGGATAAGCCCCTGAATTGTGATGGGCTCACCCCACTGACCCAGCATCTGAA
 CTGTCTTAACAGGGAGCCGGGGCTAAACTGCTTACCCCTGCCTGAGAACCAGGGAGCACTGCATTTCT
 CCACAGGGTGGAGGAGAAGAGGCAGAATAAACCAAGCCTGGGACACCTCCCTCCTGTCTAGGTGTAC
 TCATTCTTCTGTTTCAAAGAAGGCAAGGACATGAAGTCAACTTCTACCTATCTTCTGCTGCTGGTGTCT
 TTATGTATTCTCAGTTTGACCTGATTCTCTTCTGTCTTTTGACTTAACATTAGGGGTTCTTGGTCATAA
 CCTGCTCTGATGTACATAAAGATTTAGGTTCAATATCAATGTGTCTTAAACAGAAGTATTTTAGCG
 GGTGGGGGGTGGGGTGGTGGGGACAAACAACGCAGGATATAATTGCCAAAACAGGCTTGAGGTTGG
 TGACTCTTGAAAGATTTTCTTCTCAGGCCTAGATCAGAAAATTAAGTGCAGCAATATCATGAATTCT
 CAGAAGCCCTTTCAGGGAGCCAGTGAGTCATACAGTATCCACAGTTGAGTCACTTAAAGATGTGAGTA
 TACGAAACATTATTCACAATCCTTGGGCAATCTATTTTTTCTTCTCCCTCCTCCCTGCCCCC
 ATACATTTCTATGTTAGTTTGGAGGGGAGGAGTAACTAACATCTCAGAAAGCTAGATTGG
 GAAACATGCTCAGCTATAAGAACTGAGCTTTAAATTTTGAAGTTTAAATGTACATCAGGAGCAGCTG
 GGGAGGGTCTTTTTTTAAAAAATCTTTCAAATTTGGTTTTCTGTGCATATGGCCGTTTTGTAAATACT

TTGGGGTTTTTCATTTTTTTGAAAGTAGATGAAATCTGTTGTGGGATTTTTTTTCCCGAAACATTACAAA
ATAACCTGTTTATTTACATGCAAATAAACTTCTTTGATAAAAAGTAA (SEQ ID NO: 814)

[000484] In some embodiments, oligonucleotides may have a region of complementarity to a mouse MED1 sequence, for example, as provided below by Gene ID: 19014; NCBI Ref. No:

NM_001080118.1:

GATCTTTGGGAAGTTCCGTTGGGGAAGATGGCGGCGGCCGCGAGCACCCCTTCTTCTTGTGCCGCCGGG
GACTTCAGACTGAGCCTTCCCCGGAAGAGTCGGGGCCGCTGGTGCGCCGCTTCCCCGGAGCCCAGGCT
AACTTGGTTCCCTCTGAGTGGCGGGGAAAGGCTCCCCGGCTCGTGGCGGACCCAAGACCTCCCCGCT
GTCAGGATGAAGGCTCAGGGGGAACCGAGGACTCAGAGAGGCTGAGTAAGATGAGCTCCCTCCTGG
AACGGCTCCATGCAAAATTTAACCAGAACAGACCTTGGAGTGAAACCATTAAGCTTGTGCGTCAAGT
AATGGAGAAGAGGGTTCGTAATGAGTTCTGGAGGGCATCAGCATTTGGTCAGCTGTTTGGAGACATTG
CAGAAGGCTCTCAAAGTAACATCTTTGCCAGCAATGACTGATCGTTTGGAAATCTATAGCCAGACAGAA
TGGACTGGGCTCTCACCTCAGTGCCAGTGGCACTGAGTGTTACATCACGTCAGATATGTTCTATGTGG
AAGTGCAGTTAGATCCTGCAGGACAGCTTTGTGATGTCAAAGTGGCTCACCATGGGGAGAATCCTGTG
AGCTGTCCAGAGCTTGTACAGCAGTTAAGGGAAAAGAATTTTGAGGAATTTTCCAAGCATCTTAAGGG
TCTTGTTAATCTGTATAATCTCCCAGGGGACAACAACTGAAGACTAAAATGTATCTGGCTCTCCAAT
CCTTAGAACAGGACCTTTCTAAAATGGCTATTATGTACTGGAAGGCAACCAACGCCGCTCCCTTGGAT
AAGATTCTTCATGGAAGTGTTGGTTATCTCACCCCGCGGAGTGGGGGTCATTTAATGAATATGAAATA
CTATGCCTCTCCATCTGACCTGCTGGATGATAAGACTGCCTCTCCTATCATTTTGCATGAAAAGAATGT
TCTCGGTCTTTGGGAATGAATGCCTCAGTGACAATTGAAGGAACCTCTGCTATGTACAAACTCCCAA
TTGCCCATTAATTAATGGGGTACACCCAGCTGACAACAAATGGACCCCTTCTTCTCCGCAGTCACTA
GTGCCAACAGTGTTGATCTTCTGCGTGTTTCTTCTTGAATTTCCCCAGCCAATTCAGTATCTAAAG
CATTTGTTTCAGAACTGCAAAATTCACAGGAATCCCGTTGTTTGAGACTCCGCCCACCTACCTGCCC
CTGTATGAACTCATCACTCAGTTTGAGCTGTCAAAGGATCCTGACCCCTTACCTTTGAATCACAACATG
CGATTTTACGCTGCTCTTCCAGGTCAGCAGCACTGCTATTTTCTCAATAAAGATGCTCCTCTTCTGTAT
GGTCAGAGCCTGCAGGGAACACTGGTCAGCAAAATCACCTTCCAGCACCCCTGGCCGAGTCTCTTAT
CTTGAATATGATCAGACACCAAGTGGCCTATAAAGCTCAATTTGGAAGCTGTGTCAAAGAAGAACTATT
TAAAAGAAGATTCTCCTGGGCTCCTCCAGTTTGAAGTGTGTCTCTCTCAGAATCTCGTTCAGTGTAT
CTTTTCAGCACCCCTGTGAATGACTCCCTTGTGTGTGTGGTGTGGATGTGCAAGACTCAACACATGTG
AGCTGTAAACTCTACAAGGGGCTGTGAGATGCACTAATCTGTACAGACGACTTCATTGCCAAAGTTGT
TCAAAGATGTATGTCCATTCTGTGACGATGAGGGCTATTTCGGAGGAAGGCTGAAACCATACAGGCT
GACACCCAGCACTGTCTCTCATTTGCAGAGACAGTTGAAGACATGGTGAAAAAGAACCTGCCCCCGG
CTAGCAGCCCAGGGTATGGCATGACCACAGGCAACAACCCAATGAGTGGTACCACTACACCAACCAA
CACCTTTCCGGGGGGTCCCATTACCACCTTGTTTAATATGAGCATGAGCATCAAAGATCGGCATGAGT
CGGTGGGCCATGGGGAGGACTTCAGCAAGGTGTCTCAGAACCCAATTTCTTACCAGTTTGTGCAAATC
ACAGGGAACGGGGGGTCTACCATTGGCTCGAGTCCGACCCCTCCTCATCACACGCCGCCACCTGTCTC
TTCGATGGCCGGCAACACCAAGAACCACCCGATGCTCATGAACCTTCTTAAAGATAACCCTGCCAGG
ATTTCTCAACCTTTATGGAAGCAGCCCTTAGAAAGGCAGAACTCCTCTTCCGGATCACCCCGGATG
GAAATGTGCTCGGGGAGCAACAAGGCCAAGAAGAAGAAGTCGTCAAGAGTCCCACCTGACAAACCC
AAGCACCAAGACTGAAGACGATTTCCAGAGGGAGCTCTTTTCCATGGATGTGCACTCACAGAACCCTAT
GTTTGACGTCAGCATGACCGCTGACGCGCTGGATACACCTCATATCACCCAGCTCCAAGCCAGTGTA
GCACTCCCCAGCAACGTACCCACAGCCAGTGTCTCACCCCCAGCCCAGTATTCAGAGGATGGTCCGA
CTGTCCAGTTCAGACAGCATTGGCCCAGATGTAACCTGATATTCTTTCAGATATTGCCGAAGAAGCTTC
AAAGCTTCCCAGCACGAGTGATGACTGCCACCAATTGGCACCCCTGTTTCGAGATTCTTCAAGTTCTG
GGCATTCTCAGAGTGCCCTCTTTGATTCTGATGTCTTTCAAATAATAAATGAAAATCCATACACTG
ATCCAGCTGACCTTATTGCAGATGCTGCTGGAAGCCCCAATAGTGATTCTCCTACCAATCATTTTTTCC
CTGATGGAGTAGATTTCAATCCTGATTTGTTGAACAGCCAAAGCCAAAGTGGTTTTGGAGAGGAGTAT
TTTGATGAAAGTAGTCAGAGTGGGGATAATGATGATTTCAAAGGATTTGCATCTCAGGCATTAAATAC
ATTGGGGATGCCAATGCTTGGAGGTGACAATGGGGAGCCAAATTTAAGGGCAGCAGCCAGGCTGAC
ACGGTGGAGTTCAGTATTATCAGTACCGGTTAAGGCTTTGGGTGCTGCAGATCTGATGGAGACCA
CAGTGGGAGTCAGAGTCTTTACTGACCACTGGAGAATTAGGGAAAGAAAAAAGTCAAAAGAGGGTG
AAGGAAGGCAACGGCACAGGTGCTAGCAGTGGATCAGGTCCAGGGTCAGACAGCAAGCCAGGCAAG
CGCAGCCGCACTCCCTCCAATGATGGGAAGAGCAAGGATAAGCCTCCAAAGCGGAAGAAGGCAGAC
ACTGAGGGGAAGTCCCCATCTCACAGTTCTTCTAATAGACCTTTACCCACCTACCAGCACGGGTGG
GTCCAAATCCCCAGGCAGTTCAGGACGATCTCAGACGCCCCAGGTGTTGCCACCCCGCCATTCCCA
AGATTACCATTTCAGATTCCTAAAGGGACAGTGTGGTGGGCAAGCCCTCCTCTCACAGTCAGTACACT
AGCAGTGGTTCTGTGTCTTCTCTGGCAGCAAAAGCCACCATAGTCATTCTTCTCCTCCTCTTCTCTTA
GCTTCTGCTTCCACCTCAGGCAAGGTGAAAAGCAGTAAATCTGAAGGCTCATCAAGTTCCAAGCTCAG
TGGCAGTATGTATGCTAGCCAAGGGTCTTCTGGATCCAGCCAGTCCAAAAATTCATCTCAGACTGGGG

GGAAGCCAGGCTCCTCTCCCATTACCAAACATGGACTGAGCAGTGGGTCCAGCAGTACCAAGATGAA
 ACCTCAAGGCAAGCCATCCTCCCTTATGAACCTTCTATAAGTAAGCCAAACATATCCCCCTCCCATTC
 AAGGCCTCCCGGAGGCTCAGATAAGCTTGCCTCTCCAATGAAGCCTGTTCTTCTGGAACCCCCCATCCT
 CTAAGCCAAAGTCCCCTATCAGTTCAGGTTCCAGTGGTTCTCATGTGTCAGGAAGTAGTTCAAGCTCT
 GGTATGAAGTCATCTTCAGGGTCAGCATCCTCAGGCTCAGTGTCTCAAAAAACCCCTCCAGCATCTAA
 TTCTTGTACACCATCTTCTCTTCGTTTTCTCAAGTGGTTCTTCCATGTCATCCTCTCAGAATCAACAT
 GGCAGTTCCAAAGGGAAATCTCCAGTAGGAATAAGAAGCCTTCCCTTGACAGCTGTCATAGATAAATT
 GAAGCATGGGGTGGTTACCAGTGGGCCTGGGGGTGAGGATCCAATAGACAGTCAGATGGGCGCAAGC
 ACAAATTCTTCTAACCATCCCATGTCCTCCAAACATAACACGTCAGGAGGGGAGTTCAGAGCAAACG
 TGAGAAAAGTGATAAAGACAAATCCAAGGTCTCTGCTTCTGGGGGGTCAGTGGATTCTCTAAGAAG
 ACTTCAGAGTCAAAAAATGTGGGGAGCACGGGGGTGGCAAAAAATCATTATCAGCAAGCACGACGGA
 GGCTCCCCGAGCATCAAAGCCAAAGTGACGCTACAGAAACCTGGAGAAAGTGGTGAGATGGGCTCA
 GGCCACAGATAGCCTCATCAAGAAGTATGGCTCTCCACTTATCAGTGGTTCCACTCCAAAGCAGGAA
 CGGGGTTCTCCAGCCACAGTAAGTCGCCAGCATATACACCACAGAATGTGGACAGTGAAAGTGAGT
 CAGGCTCTCCATAGCAGAGAGATCCTACCAGAACAGTCCCAGCTCAGAGGATGGTATCCGACCACTT
 CCAGAGTACAGCACTGAGAAGCATAAGAAGCACAAAAAGGAAAAGAAGAAAGTCAGAGACAAAGA
 CAGAGACAAGAAGAAGTCTCACAGCATGAAGCCAGAGAACTGGTCGAAATCCCCATTTCTTCAGAT
 CCGACGGCGTCTGTGACAAATAACCCTATCTTATCTGCAGACAGGCCTTCTAGGCTCAGCCCTGACTT
 CATGATTGGGGAGGAAGATGATGATCTCATGGATGTGGCCCTGATTGGCAATTAGCCTAACTTTCTAA
 ACAGACACGTCCAGAGGAGAACTAATGATATATGTAAACCAACCCGAGGGGTGAGTCAGACAGGCC
 CTGTCTAGTGTCTAAGAGCCCTAAAGGGCATGGCCTCTACACCAAGCTGGGTACATTTATAAACATACA
 TCTAGACCCTGCTGCCGAAACCATGTGGTTGGTTGTTTCAGAAACAAGTCATATTTCTTTGCCAGAAAG
 CAATGAATAAATTACTTGCTTAAGGGGAGAGGGGTGGTGGGAGAGGGGTGTAGAGAGGGAGGGGTGG
 GAAATTGTTGTGGGAAATATTCATATATTTTTCTCCCTTTTTCCATTTTCAGGACATGCTTTAAACTCAT
 TTAGTGCATGTATTTGAAGGGCTGGGCAGAAAATGAAAAAGCAATACATTCCTTGATGCATTCGCAT
 GAAGGTTGCTCACCTGTGGGAGATGCCCATTTGGAAGCATGGGCACGGGAAGGACTTTGACAGTTCTG
 GACACTGAAAGCAATGTTTGGTGTCTGTTTCTTAGGAGTGATGGGGGAGGGAAAAATTATTTTAGTTAT
 TTATTTGTAATATTTTAATCCTTGATGTTTGTGTTTATGCAATGTTTGTTCCTAAATCTATGAAGGTTAT
 GGTTCAGAACAGTAGGAGGCAGGTAGCAAGGCTCGCCTGGTGGGGAGCTCGCAGCCTGTGCTGACGC
 TGCAGCACCAGTCCCACAGAGCTAATCACAGCCTGTCTTTGGAGTTGAATAGAAAAACCAAACTATT
 ATCTTTGGAGGTTTTTTCACAGGGTTCAGACACCATAGGAATATTAGGAGTGAGTTACCTCCCTATGCA
 GATAAAAGATTTATCTTCTTTTATTAAAAAGGAAGGGTGGCTTTGGGGGGTATACATTTGTTTTTCAGA
 GTCTATACCCTATCGTATAAAAAATCAGTATAGAATTAATAGTTCTCCTACTTCCACAATGTGCCAAAA
 GTCTACATCCCAGCATTTTGTGTTGCAGGAGAGCTGATGCCATTCTTAAGAGCTGGACTCTTTGTTTCTC
 TTCATCACAAGAAGAAGGAGTTCAGACTTAACACTCTCCACTGTATGCTCCCCGAGATAAACAGTTAA
 AAAAAAAAAGCAGCCATAGTTCACTTAAACAATTCAAGCTCACTTGAGTGATTGATTAGGGCCTGG
 AATGCTAAGTGAGCATGAAGATAACCCCTTGCTACCGTGTAGCACACAGTCGGACCTTTTTGGAGAAAC
 AGGTCTGAGTCTGGATTCTGAGGGACATCAAAGGAAGACCTCATAAATAGAGAAATGCAGGAGACCG
 TTTTGAGTGCAACAGAGTTCTCAGTATTTGGAGGGTCTCTCAAAAGTCCGCGGCCTTACTTTGATTT
 CACCACCTGCACTGTGCCATTCTGATGATTCCGTTTGGGATCTGTATCAGCGGGGTGGGGGTGGGGC
 GTGATCCCCAGCACAACCTCTTCTGGATTACAAAACAAGCAAAAGCCAGGTGATTCATGTTTGTGTGTG
 TTATAAGTGAGTGACTTCATCAGATACGGACGATTTCTACATCCAACACTGCAGGTTGTTGGAGTTA
 GCAT (SEQ ID NO: 815)

[000485] In some embodiments, the oligonucleotide may have region of complementarity to a mutant form of MED1.

[000486] In some embodiments, an oligonucleotide comprises a region of complementarity to a MED1 sequence as set forth in SEQ ID NO: 814 or SEQ ID NO: 815. In some embodiments, the oligonucleotide comprises a region of complementarity that is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% complementary to an a MED1 sequence as set forth in SEQ ID NO: 814 or SEQ ID NO: 815. In some embodiments, the oligonucleotide comprises a sequence that has at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides that are perfectly complementary to a MED1 sequence as set forth in SEQ ID NO: 814 or SEQ ID NO: 815. In some embodiments, an oligonucleotide may comprise a sequence

that targets (*e.g.*, is complementary to) an RNA version (*i.e.*, wherein the T's are replaced with U's) of a MED1 sequence as set forth in SEQ ID NO: 814 or SEQ ID NO: 815. In some embodiments, the oligonucleotide comprises a sequence that is complementary (*e.g.*, at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% complementary) to an RNA version of a MED1 sequence as set forth in SEQ ID NO: 814 or SEQ ID NO: 815. In some embodiments, the oligonucleotide comprises a sequence that has at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides that are perfectly complementary to an RNA version of a MED1 sequence as set forth in SEQ ID NO: 814 or SEQ ID NO: 815.

[000487] In some embodiments, a MED1-targeting oligonucleotide comprises an antisense strand that comprises at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 consecutive nucleotides of a sequence comprising any one of SEQ ID NOs: 864-887. In some embodiments, a MED1-targeting oligonucleotide comprises an antisense strand that comprises any one of SEQ ID NOs: 864-887. In some embodiments, a MED1-targeting oligonucleotide comprises an antisense strand that comprises shares at least 70%, 75%, 80%, 85%, 90%, 95%, or 97% sequence identity with at least 12 or at least 15 consecutive nucleotides of any one of SEQ ID NOs: 864-887.

[000488] In some embodiments, a MED1-targeting oligonucleotide comprises an antisense strand that targets a MED1 sequence comprising any one of SEQ ID NOs: 816-863. In some embodiments, an oligonucleotide comprises an antisense strand comprising at least 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 nucleotides (*e.g.*, consecutive nucleotides) that are complementary to a MED1 sequence comprising any one of SEQ ID NOs: 816-863. In some embodiments, a MED1-targeting oligonucleotide comprises an antisense strand comprising a sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, or 97% complementary with at least 12 or at least 15 consecutive nucleotides of any one of SEQ ID NOs: 816-863.

[000489] In some embodiments, a MED1-targeting oligonucleotide comprises an antisense strand comprises a region of complementarity to a target sequence as set forth in any one of SEQ ID NOs: 816-863. In some embodiments, the region of complementarity is at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, or at least 19 nucleotides in length. In some embodiments, the region of complementarity is 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 nucleotides in length. In some embodiments, the region of complementarity is in the range of 8 to 20, 10 to 20 or 15 to 20 nucleotides in length. In some embodiments, the region of complementarity is fully complementary with all or a portion of its target sequence. In some embodiments, the region of complementarity includes 1, 2, 3 or more mismatches.

[000490] In some embodiments, a MED1-targeting oligonucleotide further comprises a sense strand that hybridizes to the antisense strand to form a double stranded siRNA. In some

embodiments, the MED1-targeting oligonucleotide comprises an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 864-887. In some embodiments, the MED1-targeting oligonucleotide further comprises a sense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 840-863.

[000491] In some embodiments, the MED1-targeting oligonucleotide is a double stranded oligonucleotide (e.g., an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 864-887 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 840-863, wherein the antisense strand and/or (e.g., and) comprises one or more modified nucleosides (e.g., 2'-modified nucleosides). In some embodiment, the one or more modified nucleosides are selected from 2'-O-Me and 2'-F modified nucleosides.

[000492] In some embodiments, the MED1-targeting oligonucleotide is a double stranded oligonucleotide (e.g., an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 864-887 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 840-863, wherein the each nucleoside in the antisense strand and/or (e.g., and) each nucleoside in the sense strand is a 2'-modified nucleoside selected from 2'-O-Me and 2'-F modified nucleosides.

[000493] In some embodiments, the MED1-targeting oligonucleotide is a double stranded oligonucleotide (e.g., an siRNA) comprising an antisense strand that comprises the nucleotide sequence of any one of SEQ ID NOs: 864-887 and a sense strand that hybridizes to the antisense strand and comprises the nucleotide sequence of any one of SEQ ID NOs: 840-863, wherein the each nucleoside in the antisense strand and each nucleoside in the sense strand is a 2'-modified nucleoside selected from 2'-O-Me and 2'-F modified nucleosides, and wherein the antisense strand and/or (e.g., and) the sense strand each comprises one or more phosphorothioate internucleoside linkages. In some embodiments, the sense strand does not comprise any phosphorothioate internucleoside linkages (all the internucleoside linkages in the sense strand are phosphodiester internucleoside linkages), and the antisense strand comprises 1, 2, or 3 phosphorothioate internucleoside linkages. In some embodiments, the antisense strand comprises 2 phosphorothioate internucleoside linkages, optionally wherein the two internucleoside linkages at the 3' end of the antisense strand are phosphorothioate internucleoside linkages and the rest of the internucleoside linkages in the antisense strand are phosphodiester internucleoside linkages,

[000494] In some embodiments, the antisense strand of the MED1-targeting oligonucleotide comprises a structure of (5' to 3'):

[illegible]

[000495] In some embodiments, the sense strand of the MED1-targeting oligonucleotide comprises a structure of (5' to 3'):

[illegible]

[000496] In some embodiments, the antisense strand of the MED1-targeting oligonucleotide is selected from the modified version of SEQ ID NOs: 864-887 listed in Table 34. In some embodiments, the sense strand of the MED1-targeting oligonucleotide is selected from the modified version of SEQ ID NOs: 840-863 listed in Table 34. In some embodiments, the MED1-targeting oligonucleotide is a siRNA selected from the siRNAs listed in Table 34.

Table 32. MED1 Target Sequences

Reference sequence NM_004774.4 (SEQ ID NO: 814)	Corresponding nucleotides of the Reference Sequence	MED1 Target Sequence (5' to 3')	SEQ ID NO:
NM_004774.4	503-521	GTTACATCACGTCAGATAT	816
NM_004774.4	508-526	ATCACGTCAGATATGTTCT	817
NM_004774.4	515-533	CAGATATGTTCTATGTGGA	818
NM_004774.4	1432-1450	ATCAGACACCAAGTGGCCT	819
NM_004774.4	1676-1692	ACTTCATTGCCAAAGTTGT	820
NM_004774.4	1688-1706	AAGTTGTTCAAAGATGTAT	821
NM_004774.4	1693-1711	GTTCAAAGATGTATGTCCA	822
NM_004774.4	1837-1855	CCAGGGTATGGCATGACCA	823
NM_004774.4	1923-1941	CTTGTTTAATATGAGCATG	824
NM_004774.4	2126-2144	ACCCGATGCTCATGAACCT	825
NM_004774.4	2786-2804	GAGTAGATTTCAAATCCTGA	826
NM_004774.4	3454-3472	AGCAGTG GTTCTGTGTCTT	827
NM_004774.4	2005-2023	CCAATTCTTACCAGTTTGT	828
NM_004774.4	1978-1996	GAGGACTTCAGCAAGGTGT	829
NM_004774.4	4601-4619	CAGGCTCCTCCATAGCAGA	830
NM_004774.4	5482-5500	GTGTCTGTTTCTTAGGAGT	831
NM_004774.4	400-418	AAGGCTCTCAAAGTAACAT	832
NM_004774.4	1940-1958	TGAGCATCAAAGATCGGCA	833

NM_004774.4	5363-5381	GCAATACATTCTTGATGC	834
NM_004774.4	6157-6175	AAAACAATTTCAAGCTCAC	835
NM_004774.4	1937-1955	GCATGAGCATCAAAGATCG	836
NM_004774.4	995-1013	TGTACAAACTCCCAATTGC	837
NM_004774.4	4600-4618	TCAGGCTCCTCCATAGCAG	838
NM_004774.4	5483-5501	TGTCTGTTTCTTAGGAGTG	839

* The target sequences contain Ts, but binding to RNA and/or DNA is contemplated.

[000497] In some embodiments, an oligonucleotide may comprise or consist of any sequence as provided in Table 33.

Table 33. Oligonucleotide sequences for targeting MED1

Passenger Strand/Sense Strand (RNA) (5' to 3')	SEQ ID NO:	Guide Strand/Antisense Strand (RNA) (5' to 3')	SEQ ID NO:
AUGUUACAUCACGUCAGAUAU	840	AUAUCUGACGUGAUGUACAUC	864
ACAUCACGUCAGAUUAUGUUCU	841	AGAACAUAUCUGACGUGAUGUAA	865
GUCAGAUUAUGUUCUAUGUGGA	842	UCCACAUAGAACAUAUCUGACGU	866
UGAUCAGACACCAAGUGGCCU	843	AGGCCACUUGGUGUCUGAUCAGA	867
UGACUUCAUUGCCAAAGUUGU	844	ACAACUUUGGCAAUGAAGUCAUC	868
CAAAGUUGUCAAAGAUGUAU	845	AUACAUCUUUGAACAACUUUGGC	869
UUGUUCAAAGAUGUAUGUCCA	846	UGGACAUACAUCUUUGAACAACU	870
GCCCAGGGUAUGGCAUGACCA	847	UGGUCAUGCCAUACCCUGGGCUG	871
ACCUUGUUUAAUAUGAGCAUG	848	CAUGCUCUAUUUAAACAAGGUGG	872
CCACCCGAUGCUCUAUGAACCU	849	AGGUUCAUGAGCAUCGGGUGGUU	873
UGGAGUAGAUUCAAUCCUGA	850	UCAGGAUUGAAAUCUACUCCAUC	874
CCAGCAGUGGUUCUGUGUCUU	851	AAGACACAGAACCACUGCUGGUA	875
ACCCAAUUCUUAACAGUUUGU	852	ACAAACUGGUAAGAAUUGGGUUC	876
GGGAGGACUUCAGCAAGGUGU	853	ACACCUUGCUGAAGUCCUCCCA	877
GUCAGGCUCCUCCAUGCAGA	854	UCUGCUAUGGAGGAGCCUGACUC	878
UGGUGUCUGUUUCUAGGAGU	855	ACUCCUAAGAAACAGACACCAA	879
AGAAGGCUCUCAAGUAACAU	856	AUGUUACUUUGAGAGCCUUCUGC	880
CAUGAGCAUCAAGAUCGGCA	857	UGCCGAUCUUUGAUGCUCUAGCU	881
AAGCAAUACAUCCUUGAUGC	858	GCAUCAAGGAAUGUAUUGCUUUU	882
UUAAAACAAUUUCAAGCUCAC	859	GUGAGCUUGAAAUUGUUUUAAGU	883
GAGCAUGAGCAUCAAGAUCG	860	CGAUCUUUGAUGCUCUAGCUCAU	884
UGUGUACAAACUCCCAAUUGC	861	GCAAUUGGGAGUUUGUACACAGC	885
AGUCAGGCUCCUCCAUGCAG	862	CUGCUAUGGAGGAGCCUGACUCA	886
GGUGUCUGUUUCUAGGAGUG	863	CACUCCUAAGAAACAGACACCAA	887

[000498] In some embodiments, an oligonucleotide is a modified oligonucleotide as provided in Table 34, wherein ‘mN’ represents a 2’-O-methyl modified nucleoside (e.g., mU is 2’-O-methyl modified uridine), ‘fN’ represents a 2’-fluoro modified nucleoside (e.g., fU is 2’-fluoro modified uridine), ‘*’ represents a phosphorothioate internucleoside linkage, and lack of “*” between nucleosides indicate phosphodiester internucleoside linkage.

Table 34. Modified Oligonucleotides for targeting MED1

siRNA #	Modified Passenger Strand/Sense Strand (RNA) (5' to 3')	SEQ ID NO:	Modified Guide Strand/Antisense Strand (RNA) (5' to 3')	SEQ ID NO:
hsMED1-1	mAmUfGmUfUmAfCmAfU mCfAmCfGmUfCmAfGmAf UmAfU	840	fAfUmAfUmCfUmGfAmCfGmUfG mAfUmGfUmAfAmCfAmU*fU*mC	864
hsMED1-2	mAmCfAmUfCmAfCmGfU mCfAmGfAmUfAmUfGmU fUmCfU	841	fAfGmAfAmCfAmUfAmUfCmUfG mAfCmGfUmGfAmUfGmU*fA*mA	865
hsMED1-3	mGmUfCmAfGmAfUmAfU mGfUmUfCmUfAmUfGmU fGmGfA	842	fUfCmCfAmCfAmUfAmGfAmAfC mAfUmAfUmCfUmGfAmC*fG*mU	866
hsMED1-4	mUmGfAmUfCmAfGmAfC mAfCmCfAmAfGmUfGmGf CmCfU	843	fAfGmGfCmCfAmCfUmUfGmGfU mGfUmCfUmGfAmUfCmA*fG*mA	867
hsMED1-5	mUmGfAmCfUmUfCmAfU mUfGmCfCmAfAmAfGmUf UmGfU	844	fAfCmAfAmCfUmUfUmGfGmCfA mAfUmGfAmAfGmUfCmA*fU*mC	868
hsMED1-6	mCmAfAmAfGmUfUmGfU mUfCmAfAmAfGmAfUmG fUmAfU	845	fAfUmAfCmAfUmCfUmUfUmGfA mAfCmAfAmCfUmUfUmG*fG*mC	869
hsMED1-7	mUmUfGmUfUmCfAmAfA mGfAmUfGmUfAmUfGmU fCmCfA	846	fUfGmGfAmCfAmUfAmCfAmUfC mUfUmUfGmAfAmCfAmA*fC*mU	870
hsMED1-8	mGmCfCmCfAmGfGmGfU mAfUmGfGmCfAmUfGmA fCmCfA	847	fUfGmGfUmCfAmUfGmCfCmAfU mAfCmCfCmUfGmGfGmC*fU*mG	871
hsMED1-9	mAmCfCmUfUmGfUmUfU mAfAmUfAmUfGmAfGmC fAmUfG	848	fCfAmUfGmCfUmCfAmUfAmUfU mAfAmAfCmAfAmGfGmU*fG*mG	872
hsMED1-10	mCmCfAmCfCmCfGmAfU mGfCmUfCmAfUmGfAmAf CmCfU	849	fAfGmGfUmUfCmAfUmGfAmGfC mAfUmCfGmGfGmUfGmG*fU*mU	873
hsMED1-11	mUmGfGmAfGmUfAmGfA mUfUmUfCmAfAmUfCmCf UmGfA	850	fUfCmAfGmGfAmUfUmGfAmAfA mUfCmUfAmCfUmCfCmA*fU*mC	874
hsMED1-12	mCmCfAmGfCmAfGmUfG mGfUmUfCmUfGmUfGmU fCmUfU	851	fAfAmGfAmCfAmCfAmGfAmAfC mCfAmCfUmGfCmUfGmG*fU*mA	875
hsMED1-13	mAmCfCmCfAmAfUmUfC mUfUmAfCmCfAmGfUmUf UmGfU	852	fAfCmAfAmAfCmUfGmGfUmAfA mGfAmAfUmUfGmGfGmU*fU*mC	876
hsMED1-14	mGmGfGmAfGmGfAmCfU mUfCmAfGmCfAmAfGmGf UmGfU	853	fAfCmAfCmCfUmUfGmCfUmGfA mAfGmUfCmCfUmCfCmA*fC*mA	877
hsMED1-15	mGmUfCmAfGmGfCmUfC mCfUmCfCmAfUmAfGmCf AmGfA	854	fUfCmUfGmCfUmAfUmGfGmAfG mGfAmGfCmCfUmGfAmC*fU*mC	878

hsMED1-16	mUmGfGmUfGmUfCmUfG mUfUmUfCmUfUmAfGmG fAmGfU	855	fAfCmUfCmCfUmAfAmGfAmAfA mCfAmGfAmCfAmCfCmA*fA*mA	879
hsMED1-17	mAmGfAmAfGmGfCmUfC mUfCmAfAmAfGmUfAmA fCmAfU	856	fAfUmGfUmUfAmCfUmUfUmGfA mGfAmGfCmCfUmUfCmU*fG*mC	880
hsMED1-18	mCmAfUmGfAmGfCmAfU mCfAmAfAmGfAmUfCmGf GmCfA	857	fUfGmCfCmGfAmUfCmUfUmUfG mAfUmGfCmUfCmAfUmG*fC*mU	881
hsMED1-19	mAmAfGmCfAmAfUmAfC mAfUmUfCmCfUmUfGmAf UmGfC	858	fGfCmAfUmCfAmAfGmGfAmAfU mGfUmAfUmUfGmCfUmU*fU*mU	882
hsMED1-20	mUmUfAmAfAmAfCmAfA mUfUmUfCmAfAmGfCmUf CmAfC	859	fGfUmGfAmGfCmUfUmGfAmAfA mUfUmGfUmUfUmUfAmA*fG*m U	883
hsMED1-21	mGmAfGmCfAmUfGmAfG mCfAmUfCmAfAmAfGmAf UmCfG	860	fCfGmAfUmCfUmUfUmGfAmUfG mCfUmCfAmUfGmCfUmC*fA*mU	884
hsMED1-22	mUmGfUmGfUmAfCmAfA mAfCmUfCmCfCmAfAmUf UmGfC	861	fGfCmAfAmUfUmGfGmGfAmGfU mUfUmGfUmAfCmAfCmA*fG*mC	885
hsMED1-23	mAmGfUmCfAmGfGmCfU mCfCmUfCmCfAmUfAmGf CmAfG	862	fCfUmGfCmUfAmUfGmGfAmGfG mAfGmCfCmUfGmAfCmU*fC*mA	886
hsMED1-24	mGmGfUmGfUmCfUmGfU mUfUmCfUmUfAmGfGmA fGmUfG	863	fCfAmCfUmCfCmUfAmAfGmAfA mAfCmAfGmAfCmAfCmC*fA*mA	887

k. MED13 Oligonucleotides

[000499] Examples of oligonucleotides useful for targeting MED13 are provided in Xu, M. et al. “MicroRNA-499-5p regulates skeletal myofiber specification via NFATc1/MEF2C pathway and Thrap1/MEF2C axis” Life Sci. 2018, 215:236-245.; and Grueter, C.E., et al. “A cardiac microRNA governs systemic energy homeostasis by regulation of MED13” Cell. 2012, 149(3):671-83.; the contents of each of which are incorporated herein in their entireties.

[000500] In some embodiments, oligonucleotides may have a region of complementarity to a human MED13 sequence, for example, as provided below by Gene ID: 9969; NCBI Ref. No: NM_005121.3:

CTCTCTCTGGTCGGAGGCGGCGGTAATGGCGGATGGTGGGTTGTGGCGCCGGCGGGCTGCTGTGA
GGGACGATGAGTGCCTCCTTCGTGCCGAACGGGGCCAGCCTGGAAGATTGTCACTGTAACCTCTTCTG
CCTGGCTGACTTGACAGGAATTAAGTGGAATAATATGTATGGCAAGGCCCAACTTCTGCCCCATTC
TGTTTCCTGTGACAGAAGAAGACCCCATTTTGAGCAGTTTGTAGTCGCTGCCTTAAGGCAGATGTACTT
GGTGTGTTGGCGGCGAGATCAAAGACCTGGAAGAAGAGAATTGTGGATATTTGGTGGGGTGAAGACC
CCAGTTTTGCTGACCTTATTCACCATGACTTATCAGAAGAAGAAGATGGAGTGTGGGAGAATGGACTT
TCCTATGAATGCCGTACTCTGCTTTTCAAAGCAGTTTCAATCTATTGGAACGGTGTTTAATGAACAG
GAATTTTGTACGTATTGGCAAGTGGTTTGTAAAGCCTTATGAAAAAGATGAAAAACCTATAAATAAAA
GTGAACACTTGTCTGCTCCTTCACCTTTTCTTGCATGGAGACAGCAATGTTTGTACCAGTGTGGAAA
TTAACCAACATCAACCTGTATACCTTCTCAGTGAAGAGCATATCACCCCTTGCTCAACAGTCTAATAGC
CCATTTCAAGTTATCTTATGCCCATTGGAATAATGGCACTCTCACAGGACAGGCATTCAAGATGTCT
GATTCAGCTACAAAAAATTAATTGGTGAATGGAAACAGTTCTATCCTATCTCATGTTGCTTGAAGGA
GATGTCTGAAGAAAAACAGGAAGATATGGATTGGGAAGATGATTCCTTTAGCTGCAGTAGAAGTTCTT
GTTGCTGGTGTCCGAATGATCTACCCAGCATGCTTTGTTCTAGTCCCTCAGTCAGACATTCTACTCCT
AGCCCTGTGGGATCCACTCACTGTTTCATCTTCTTGGCTTGGGTGTCCACCAAGTGCCTGCTTCCACAAGA
GATCCTGCTATGTCTTCGGTTACGCTTACACCACCTACGTCTCTGAGGAAGTCCAAACAGTTGATCCT
CAGTCTGTCCAGAAGTGGGTCAAATTTCTTCAGTATCTGATGGCTTCAACTCCGATAGTACTAGCCAC

CATGGTGGGAAAATACCCAGAAAATTAGCAAATCATGTGGTGGATAGAGTTTGGCAAGAATGCAATA
TGAACAGAGCACAGAACAAGAGGAAGTATCTGCTTCATCAGGTGGTCTATGCGAAGAAGCGACAGC
TGCTAAAGTGGCATCCTGGGATTTTGTGTAAGCCACACAAAGAACAATTTGCAGTTGTTTGAGGCACA
AAAATCTCAAGTCAAGAAATGCTGGACAACAAGGACAGGCACCATCTTTAGGTCAGCAACAACAAT
ACTTCCTAAGCACAAAGACCAATGAGAAGCAAGAAAAGAGTGAAAAGCCACAGAAACGCCCCCTTGACT
CCTTTTCACCATCGTGTGTCTGTAGTGATGATGTTGGCATGGACGCAGATTCAGCCAGCCAAAGACT
TGTGATCTCTGCTCCAGACAGTCAAGTGAGATTTTCAAATATCCGAACATAATGATGTAGCAAAGACTC
CTCAGATGCATGGCACCGAAATGGCAAATTCACCTCAACCACCCCCACTTAGTCCTCACCCTTGTGAT
GTGGTTGATGAAGGAGTGACTAAAACACCTTCAACTCCTCAGAGTCAACATTTTTATCAAATGCCAAC
ACCAGATCCCTTGGTTCTTCTAAACCAATGGAAGATAGGATAGACAGTTTGTCCCAGTCTTTCCAC
CTCAATATCAGGAAGCTGTAGAACCTACAGTATATGTTGGTACAGCAGTAAACTTGGAAGAAGATGA
AGCCAATATAGCCTGGAAGTATTACAAGTTCCCAAAGAAAAGATGTAGAGTTTTTACCACCTCAAC
TTCCAAGTGATAAATTCAAGGATGATCCAGTTGGACCTTTTGGACAGGAAAGTGTAAACATCAGTTACA
GAGTTAATGGTGCAATGTAAGAAACCTTTAAAAGTTTCTGATGAATTAGTGCAGCAATATCAAATTAA
AAACCAGTGTCTTTCAGCAATAGCATCTGATGCAGAACAAGAACCTAAAATTGATCCATATGCATTTG
TTGAAGGAGATGAGGAATTCCTTTTTCCTGATAAAAAAGATAGACAAAATAGTGAGAGAGAAGCTGG
AAAAAACACAAGGTAGAAGATGGGACATCTAGTGTAACAGTGTTATCATATGAAGAAGATGCTATG
TCATTATTTAGTCCCTCTATCAAGCAAGATGCTCCACGCCCTACTAGTCATGCCCGTCTCCATCAACA
AGTTTGATTTATGACTCAGACCTGGCTGTCTCTTATACTGACCTTGATAATCTCTTCAATTCTGATGAA
GATGAACTAACACCTGGATCTAAAAATCAGCAAATGGATCAGATGATAAAGCCAGCTGCAAGGAAT
CAAAGACAGGAAATCTGGACCCGTTATCTTGCATAAGCACTGCAGATCTTCATAAAATGTATCCTACA
CCACCATCATTTGGAACAACATATTATGGGATTTTCCCCAATGAATATGAATAATAAGAATATGGTAG
TATGGATACAACACCTGGAGGAACTGTTCTAGAAGGAAATAGTTCTAGTATAGGAGCGCAGTTCAAA
ATTGAGGTTGATGAGGGATTCTGTAGCCCCAAACCTTCTGAAATTAAGATTTTTCTTATGTCTATAAG
CCTGAAAATTGTCAAATTCATAGTGGGATGTTCCATGTTGCACCTCTAAAACTCTACCAAGCCAATA
TCTGCCCCCTATCAAATTGCCAGAAGAGTGATTTACCGTCAGAGTTGGACTGTTGGAAAATTGGAAT
TGCTTTCTTCAGGGCCTTCAATGCCATTCATCAAAGAGGGTGATGGAAGTAATATGGATCAAGAATAT
GGCACTGCTTATACACCTCAAACCTCATACTTCTTTTGGGATGCCTCCTAGCAGTGCACCTCCTAGTAAC
AGCGGAGCAGGAATTCCTTCTTCCATCCACCCCTCGGTTTCCAACCTCAAGGACTCCAAGGACTCC
TCGGACTCCTCGTGGAGCTGGTGGACCTGCTAGTGCTCAAGGTTCAAGTCAAATATGAAAATTCAGACT
TGATTCACCAGCTTCTACCCCATCTACATGCAGACCCCTTAATTCTGTTGAACCTGCAACTGTCCCTT
CCATCCCTGAAGCACACAGTCTTTATGTAAACCTCATCCTTTCAGAATCAGTTATGAATTTGTTTAAAG
ACTGTAACCTTTGATAGTTGTTGCATCTGTGTTTGAACATGAACATCAAGGGTGCCGATGTTGGAGTTT
ACATTCAGATCCAACGCAGGAAGCACAATATAGGTGTACCTGTGGCTTCAGTGCTGTCTGAACAGA
AAATTTGGAAACAATTACAGGATTATTTCTTGAAGATGAACCTAGATATCATAGGACGCAATACAGACTG
TGGCAAAGAACAGCAAAAAACGTTTGAAGCTCAGGCTACCTCTGCTGAACATGTTAATGGAGGA
CTAAAGGAATCTGAAAAATTATCTGATGATTTGATATTATTGCTACAAGATCAGTGCACCTAATTTATTT
TCACCCTTTGGAGCAGCAGACCAAGATCCTTTTCCTAAAAGTGGTGTAATTAGCAATTGGGTACGTGT
TGAAGAGCGTGACTGTTGCAATGACTGCTACCTTGCAATTAGAACATGGGCGTCAGTTTCATGGATAACA
TGTCAGGAGGAAAAGTTGATGAAGCACTTGTGAAAAGTTTCATGCTTACACCCCTGGTCCAAAAGAAA
CGATGTGAGTATGCAGTGCTCACAGGATATACTTCGAATGCTCCTCTCTCTTCAGCCAGTTCTTCAGGA
TGCCATTCAAGAAAAAAGAACAGTAAGACCTTGGGGTGTTTCAGGGTCCCTCTCACTTGGCAACAATTTT
ATAAAATGGCTGGCCGAGGCTCTTATGGAACCTGATGAATCCCCAGAACCACTGCCAATCCCCACATTT
TTGTTGGGTTATGATTATGATTATCTGGTGCTTTCTCCATTTGCTCTTCTTATTTGGGAGAGACTTATGC
TGGAACCTATGGATCTCAAAGAGATATAGCCTATGTTGTACTGTGTCCAGAAAATGAAGCCTTGTTA
AATGGAGCAAAAAGCTTTTTAGAGATCTTACTGCAATATATGAGTCTGTGCGATTAGGTCAACATAG
ACCTGTTTCTCGACTGTTAACAGATGGGATCATGAGAGTTGGATCTACTGCATCAAAGAACTATCAG
AAAAGTTGGTAGCAGAATGGTTTTCTCAGGCAGCTGACGGTAACAATGAAGCATTTTCTAAACTCAAG
CTTTATGCACAAGTCTGCAGATATGACCTAGGTCCTTATCTTGCTTCCCTGCCATTGGACAGCTCTCTA
CTTTCCCAGCCAAATTTAGTTGCCCTACAAGTCAGTCTTTGATTACTCCACCTCAGATGACAAATACT
GGAAATGCTAATACTCCATCTGCCACCTTAGCATCTGCAGCGAGCAGCACTATGACAGTGACTTCAGG
TGTTGCCATATCTACTTCAGTTGCCACAGCTAATTCAACTTTGACCACAGCTTCAACTTCATCTTCATC
ATCCTCCAACCTGAATAGTGAGATATCATCAAATAAACTACCTTCGTTTCCACCCCTTGGCAGTATGAA
CAGTAATGCTGCAGGATCCATGTCTACACAAGCAAATACAGTTCAGAGTGGTCAGCTAGGAGGGCAA
CAGACATCAGCTCTACAGACAGCTGGGATTTCTGGAGAATCATCTTCACTTCCCACTCAGCCGCATCC
TGATGTGTCTGAAAGCACGATGGATCGGGATAAAGTGGGAATCCCCACAGATGGTGATTACATGCA
GTCACGTATCCACCTGCAATTGTTGTTTATATAATTGATCTCTTTACATACGAAAATACAGACGAGAG
CACTAACTCTTCTAGTGTGTGGACATTGGGGCTACTTCGATGCTTTCTAGAAATGGTCCAGACTCTTCC
TCTCATATCAGAGTACTGTTTCTGTACAGATTATTCCTTGTCAGTACCTGTGTCAACCTGTGAAGCA
TGAAGATAGAGAAATCTATCCCCAGCATTTAAAATCCCTGGCTTTTTTCGGCTTTTACCCAGTGTCGGA
GGCCACTTCCAACATCAACCAATGTGAAAACATTGACTGGCTTTGGTCCAGGTTTAGCCATGGAACT
GCCCTTAGAAGTCTCTGATAGACCAGAGTGTAATTCGACTTTATGCACCTCCTTTTATTTCTGGCTCCAGTG
AAGGACAAACAGACAGAGCTAGGAGAAACATTTGGAGAAGCTGGACAGAAATATAATGTTCTTTTTG

TGGGATACTGTTTATCACATGATCAAAGGTGGATTCTTGCATCTTGCACAGATCTATATGGAGAACTTT
TAGAAACTTGTATCATTAAACATCGATGTTCCAAATAGGGGCTCGTCGGAAAAAAGTTCTGCTAGAAAA
TTTGGTCTACAGAACTTTGGGAGTGGTGCTTAGGACTTGTACAAATGAGTTCATTGCCATGGAGAGT
TGTAATTGGTCGTCTAGGAAGGATTGGTTCATGGAGAATTGAAAAGATTGGAGCTGTTTGTCTGAGTCGTC
GAAACTTGCAGTCTCTAAGTAAAAGGCTCAAAGACATGTGTAGAATGTGTGGTATATCTGCTGCAGAC
TCCCCTAGCATTTCTCAGTGCTTGTCTTGGTGGCAATGGAGCCGCAAGGCTCTTTTGTATTATGCCAGAT
TCTGTGTCAACTGGTTCTGTATTTTGGAGAAGCACGACTCTAAATATGCAGACATCTCAGCTAAATAC
CCCACAGGATACATCATGTACTCATATACTTGTGTTTCTACTTCTGCTTCTGTGCAAGTAGCTTCAGC
TACTTATAACACTGAAAATTTGGATTTAGCTTTCAATCCCAACAATGATGGAGCAGATGGAATGGGTA
TCTTTGATTTTGTAGACACAGGAGATGATCTTGACCCTGATATCATTAAATATCCTTCTCTGCTTCTCCAA
CTGGTTCTCCTGTACATTCTCCAGGATCTCATTACCCCATGGAGGTGATGCGGGCAAGGGTCAGAGT
ACTGATCGGCTACTATCAACAGAACCTCATGAGGAAGTACCTAATATTCTTCAGCAACCATTTGGCCCT
TGGTTACTTTGTATCAACTGCCAAAGCAGGTCCATTACCTGACTGGTTCTGGTCAGCATGTCTCAAGC
ACAATATCAGTGTCCCTTTTTCTTAAGGCCTCTTTGCACCTCCACGTGCCTTCAGTGCAATCTGACGA
GCTGCTTCACAGTAAACACTCCCACCCACTTGACTCAAATCAGACTTCAGATGTCCTCAGGTTTGT
GGAACAGTACAATGCACCTCTCTGGCTAACCTGTGACCCTGCAACCCAGGACAGACGCTCATGTCTCC
CAATTCATTTTGTGGTGCTGAATCAGTTATATAACTTTATTATGAATATGCTGTGATCTTCATTTGATG
GAACTGTGCAAGAAAAGAACAAGGAAAAATGGATGTTTCGCTGCAGGATTAAGTTACAATTATCTTC
TCAGTGAAGGTCATTTGTGATGGGGTCTAATTTCTTATTACTTCAACAAATATTGTTTTGACTTGGGGG
AGGGGCTATAACCCCTGCTATTTTTCATTGACTCTATTGAACTCTTTAGGATGATGACTGATCATACAAA
ACGTATTATAACATTTTCGTAGCAAAATTAACCTTTTTTTTTTCCAGTCACAGTATTTGTGAAAAGTAA
TGAGCCATAGTACCCAGTCATGTTAAATGAATATTAAGCATGGAGAGGAAACATGAGGAACAATG
AATTTCAACATATGGCTTCAGAACATGAAGATGTTCTTGTATGGATTATAGTATCTAGTATTCAAAAA
TGCCTGCATCTCTCTCTTATTTATTGTAAGTTTTTAATGTATAAATTGCTTATATTTCTTAACCTCTT
TTATAAAAAATTTTCTAGAAAGGTTTATACTGCCTTCTTGCTTTAAAGCAATTGGTCTAAAATATATGTA
ATCGTCTTAATTAAGGTTGCAGTAGGGTTGCTTTTAGAGTATTATTTTTTTGTAAGGGGGTGGGTGG
GACAGTAAATTTGTATTGTCTCGATGTACAGTTTAAACGGGGATAGAGGGGGAATAATGTCCATACCAT
TGTGTGTGGAGGATTTACAGCTAAGCTGTAGTTGCAGAGTACATGTACAGTAATGAAGTTCAGTGTGT
TTATAAATTGAAAAGGTACCAGGTCTTACAGCATTTTATATATCACATCTTTACAGAATAACATGATG
GCAATATACAAGTGGTATTGTTAGGTGGTTTAACTTAGAATAAAATGAGAATCTTTCAGTTATATTTTG
TACTATGGTTTAGGGCTATGACTAATATTTTCAAGGCCATTTCCGGTGAAAGAACTTAGTTTTACAAGA
AAAACCATTTGCTACTGAATGCTTAACTAATTTTAGTGTTTAAATGTTACATGCTTAAATTTTTTTCAG
TTTTAACAGTGGCATATTTAGGCATGGAAATATTATTATGAAATTTATTTTCAGGATCTGCTATAAGGT
TGAAATTTAGCCAGCTCTAGGCATTTTACAAATTTTCAAGCAGTCATTCTTGATTTGTTGACTTT
TTTTTTTAAATTAAGATTGGGAATGTATGTGAGAGTATGCATATGTATGGGTGTGTGTGTGTGCGCG
CAATCAAACTGTGGTGTAATAGATTCTCAGTGAATTTCTGGTATTTCAGACTCTATCCACTAGTGAAA
GAACCATTTTTTAACTTCCCTTGCTTTTTTATTTATTTAATTTTCTTGTTTTGGAGATGTCAGTCCCA
AACACCAGAGTCTGTACTTTTCTATAACACAGCTCAGATTAAAGGTAGGGCATATGCCAAGGAGGTTCT
CACCTCCCTAAAGAAGGGACTTGAATTTTAGGGACTTTAATTCACCCCTCCTTCAATACAACCTTTCCCC
CTTCTTGTTTTGCACATGCCAAGATAACTTGCTTTTATGCAGGCTGTACCCCTTGAAAAATCCTTTCTAC
AGTGCTGCTCACAAAAGAGCCCAAGTTCGCCTCTACCTGCATTGCTGACTTGAATTCACAGTCGCCG
AGTCTACCTAGCTTTCTTGGAAGCAGTCTAGCAAAATTTCTATTTGTACGTTCACTAATTATCTACAAG
GACAAAATCAGTTGTATTTACAAAACCTCTACTTCAGTGTTTGTTTTAGTTTTTTTTTACTGAACTTG
TTTTTGTGAATACTCTGTGCTTAGAATTAATATCACTTTCTTATGAACAACATAACTTCTTCAGATTG
TGTATATGAAAACATTAGCAAGTCTTGTTTTTCTATGAAGCAAACACAATTGGTGACAAAGGTTGTC
AATCATTTCTTCAAAATTATAATGCAGTTCTAATGGTCAGCATATTTTGATATTAATTTAAAGATCAC
CTCTCTGCATTTGTTTTTAAATTATGCTAATACACCACACATTATGTTGGTATGTTTTGTTCTGTACTTT
CTTTAAAAAATACTTGTCTGAGATTGAAAGGAAAATGTGCTTATTTGGAATTTCCATAAA
AAGAGTATCCTTTTTATACACTTAATAGTGACTTTACAAAATAAAAGTTATATTCTCAGTTGTTTTAAAA
TCACTAACCTATGATAACCACACCTCAATTTGAAAGTAGATTAAATTTATTTCCCTGACAGGTTATTTA
ATATGGAGCCATAAGGAGGGAACCCAGTACACAATTATTTTTTATTTGGGAATCAGGGAATAGTTCCC
AAATATACAGGATTTATTGATAAGATTTTTTTTTCTTCCCTTCATATATCCATTCAAACCTCAATGGAAAG
TTATTAAATAACCATTAGAAAAGCTCAGTAGACTTATTTGAGAAATTAAGCCTTGTGCAGGATGATGG
ATTTGACTTACTAATGTACTGTACAGACAAATATGGGTAGTTTTGTTTAAATAGGTAAGCAAAATAT
TATACTTTATAGCAGTGGATTACCAACACCTTGACTTCTTTGTTACAGTGCTAACATCTTTTTTTTTGTG
CAGGTATCCATGATTATTAAGCAGGGTGGAAAGTTCAGTATTTTGTCAATTTAAAAAGATTAGTTATATA
ATGTCGTGCTTCCAGCCAGTGAGAAACATCTAGCCATACCTTTCTTATGCAAGCCATTGAGTTATCAGG
ACTGTGAATTAACACTGTATGAATAAATTTCTGTACACCTTATTGTTTGGCCAGAAGGCCACCAAGTG
TACTTATATGTAATCTTAAATTTTAAAGTAGCTGAATTTTAAATATTTCTAAACTTTTCTTAAACCA
CTAAAATTAAGCTCTTACTACTTAGTCAACTATCCTCAGCTGTATTTCGTACTCAATTGTCAGTATGGCA
CAGATTACTGTATTAATAATTCTCTCTTTCGTCTTCATATTTACCTTCTGAGGTAATTTTTTAACTTAAT
GTGTTACTACAAAGATTTGCAGATCTTTAATCAAGCACTATGTTAATACTGTAATATCAGAATACTAT
GTTGCATTATTTAAATGTTCAATTTGAATAGATTAAAAAGTTTTTAAATGCTATGTCATCATATAATT

TGCTATTCATCCACTATGGCATTGCATATCAATCAGTTAATACACTTAATGTTGCATGAGTGATATTTT
GGTCTGGGTTTCCTCTTAAGATTTTAGTTTGTCTGAATTAAGGAAAAATGTTTTTAATATACATTCTTA
TTTTGTCCCAACCCCTCCAGAAATAAGCTGGAAATCTTAACTTTTTGGGGGGTCTTTTTTGGTGTTTTAA
TGGGCCCAGAACTGTGGTTTAAATTTTTATGTATGTATTTCTTTTTTGTGGAGTATAAATTTAAAAAC
TGGATTTGGGACCTAAAATACTCCTCAGGTGTATGTATTCATGAAGTTTTAAAAACATCTTTAGTTTTCA
AAGTAACTGGATATGTGGACCTTAAAGTTATTGAGTTTAAAGCTACAAATTGTAACGTCATTACTGGA
CATGTCAGCATCAACCCCTCTCAAAATAGCTTGGTCACCTTATGAAGGGGCGTTTTAAAGTTGTTGTTTA
GCAGTGACATTTAATATGGTCCAATTGCTTTTCTTTTTAACGTGACAAAAAGAGAATAAGGAACAAAC
ACTATTGCTGCCGAATGCCATAACACTGAGTTGTACAAATTGTGATTGAGGAAATGAAAAGGTTTATA
CTTTTTAAAAAACAACAAAAACAAAAACAAAACTTCAATGGAATAAATTATTCATGAAGCC
TTCA (SEQ ID NO: 888)

[000501] In some embodiments, oligonucleotides may have a region of complementarity to a mouse MED13 sequence, for example, as provided below by Gene ID:327987; NCBI Ref. No: NM_001080931.2:

CTCTCTGGTTCGGAGGCGGCGGTAATGGCGGATGGTGGGTTGTGGCGCCGGCGGGCTGCTGTGAGG
GACGATGAGTTCTCTTCGTGTGCAACGGGGCCAGCCTGGAAGATTGTCAGTGTAACTCTTCTGCC
TGGCCGACTTGACAGGAATTAAGTGGAAAAGATATGTATGGCAAGGCCCAACTTCCGCCCTATTCTG
TTTCCGGTGACAGAAGAAGACCCCATTTTGAGCAGTTTTAGTCGATGCCTTAAGGCAGATGTACTTGG
TGTTTGGCGGCGAGATCAAAGACCTGGAAGAAGAGAATTGTGGATATTTTGGTGGGGTAAAGATCCC
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DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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NOTE POUR LE TOME / VOLUME NOTE:

CLAIMS

What is claimed is:

1. A complex comprising an anti-transferrin receptor 1 antibody covalently linked to a molecular payload that modulates the expression or activity of myostatin (MSTN), inhibin beta A (INHBA), activin receptor type-1B (ACVR1B), myosin light chain kinase (MLCK1), activin A receptor type-1 (ACVR1), atrogin-1 (FBXO32), tripartite motif containing 63 (TRIM63), myocyte-specific enhancer factor 2D (MEF2D), Krüppel-like factor 15 (KLF15), Mediator complex subunit 1 (MED1), Mediator complex subunit 13 (MED13), and/or protein phosphatase 1 regulatory subunit 3A (PPP1R3A), wherein the antibody comprises:

(i) a heavy chain variable region (VH) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 76; and/or a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 75;

(ii) a heavy chain variable region (VH) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 71; and/or a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 70;

(iii) a heavy chain variable region (VH) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 72; and/or a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 70;

(iv) a heavy chain variable region (VH) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 73; and/or a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 74;

(v) a heavy chain variable region (VH) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 73; and/or a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 75;

(vi) a heavy chain variable region (VH) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 76; and/or a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 74;

(vii) a heavy chain variable region (VH) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 69; and/or a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 70;

(viii) a heavy chain variable region (VH) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 77; and/or a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 78;

(ix) a heavy chain variable region (VH) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 79; and/or a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 80; or

(x) a heavy chain variable region (VH) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 77; and/or a light chain variable region (VL) comprising an amino acid sequence at least 95% identical to SEQ ID NO: 80.

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

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

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

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

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

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

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

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

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

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

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

3. The complex of claim 1 or claim 2, wherein the antibody is selected from the group consisting of a full-length IgG, a Fab fragment, a Fab' fragment, a F(ab')₂ fragment, a scFv, and a Fv.
4. The complex of claim 3, wherein the antibody is a full-length IgG, optionally wherein the full-length IgG comprises a heavy chain constant region of the isotype IgG1, IgG2, IgG3, or IgG4.
5. The complex of claim 4, wherein the antibody comprises:
 - (i) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 91; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 90;
 - (ii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 86; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 85;
 - (iii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 87; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 85;
 - (iv) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 88; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 89;
 - (v) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 88; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 90;
 - (vi) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 91; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 89;
 - (vii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 84; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 85;
 - (viii) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 92; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 93;

(ix) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 94; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 95; or

(x) a heavy chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 92; and/or a light chain comprising an amino acid sequence at least 85% identical to SEQ ID NO: 95.

6. The complex of claim 3, wherein the antibody is a Fab.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

9. The complex of any one of claims 1 to 8, wherein the equilibrium dissociation constant (K_D) of binding of the antibody to the transferrin receptor is in a range from 10^{-11} M to 10^{-6} M.

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

11. The complex of any one of claims 1 to 10, wherein the antibody is cross-reactive with extracellular epitopes of two or more of a human, non-human primate and rodent transferrin receptor.

12. The complex of any one of claims 1 to 11, wherein the complex is configured to promote transferrin receptor mediated internalization of the molecular payload into a muscle cell.

13. The complex of any one of claims 1-12, wherein the molecular payload comprises an oligonucleotide comprising an antisense strand comprising a region of complementarity to an MSTN target sequence, optionally wherein the MSTN target sequence is an MSTN mRNA sequence as set forth in SEQ ID NOs: 146-148, or an MSTN target sequence as set forth in any one of SEQ ID NOs: 149-196, further optionally wherein the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length.

14. The complex of claim 13, wherein the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 197-220, wherein each of the Us are optionally and independently Ts, optionally wherein the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 197-220, wherein each of the Us are optionally and independently Ts.

15. The complex of any one of claims 1-12, wherein the molecular payload comprises an oligonucleotide comprising an antisense strand comprising a region of complementarity to an INHBA target sequence, optionally wherein the INHBA target sequence is an INHBA mRNA sequence as set forth in SEQ ID NO: 269 or SEQ ID NO: 270, or an INHBA target sequence as set forth in any one of SEQ ID NOs: 271-318, further optionally wherein the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length.

16. The complex of claim 15, wherein the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 319-342, wherein each of the Us are optionally and independently Ts, optionally wherein the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 319-342, wherein each of the Us are optionally and independently Ts.

17. The complex of any one of claims 1-12, wherein the molecular payload comprises an oligonucleotide comprising an antisense strand comprising a region of complementarity to an ACVR1B target sequence, optionally wherein the ACVR1B target sequence is an ACVR1B mRNA sequence as set forth in any one of SEQ ID NOs: 367-370, or an ACVR1B target sequence as set forth in any one of SEQ ID NOs: 221-268, further optionally wherein the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length.

18. The complex of claim 17, wherein the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 343-366, wherein each of the Us are optionally and independently Ts, optionally wherein the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 343-366, wherein each of the Us are optionally and independently Ts.

19. The complex of any one of claims 1-12, wherein the molecular payload comprises an oligonucleotide comprising an antisense strand comprising a region of complementarity to a MLCK1 target sequence, optionally wherein the MLCK1 target sequence is a MLCK1 mRNA as set forth in SEQ ID NO: 411, further optionally wherein the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length.

20. The complex of any one of claims 1-12, wherein the molecular payload comprises an oligonucleotide comprising an antisense strand comprising a region of complementarity to a ACVR1 target sequence, optionally wherein the ACVR1 target sequence is an ACVR1 mRNA sequence as set forth in SEQ ID NO: 429 or SEQ ID NO: 430, or an ACVR1 target sequence as set forth in any one of SEQ ID NOs: 431-478, further optionally wherein the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length.

21. The complex of claim 20, wherein the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 479-502, wherein each of the Us are optionally and independently Ts, optionally wherein the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 479-502, wherein each of the Us are optionally and independently Ts.

22. The complex of any one of claims 1-12, wherein the molecular payload comprises an oligonucleotide comprising an antisense strand comprising a region of complementarity to a FBXO32 target sequence, optionally wherein the FBXO32 target sequence

is an FBXO32 mRNA sequence as set forth in SEQ ID NO: 505 or SEQ ID NO: 506, or a FBXO32 target sequence as set forth in any one of SEQ ID NOs: 507-554, further optionally wherein the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length.

23. The complex of claim 22, wherein the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 555-578, wherein each of the Us are optionally and independently Ts, optionally wherein the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 555-578, wherein each of the Us are optionally and independently Ts.

24. The complex of any one of claims 1-12, wherein the molecular payload comprises an oligonucleotide comprising an antisense strand comprising a region of complementarity to a TRIM63 target sequence, optionally wherein the TRIM63 target sequence is a TRIM63 mRNA sequence as set forth in SEQ ID NO: 579 or SEQ ID NO: 580, or a TRIM63 target sequence as set forth in any one of SEQ ID NOs: 581-628, further optionally wherein the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length.

25. The complex of claim 24, wherein the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 629-652, wherein each of the Us are optionally and independently Ts, optionally wherein the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 629-652, wherein each of the Us are optionally and independently Ts.

26. The complex of any one of claims 1-12, wherein the molecular payload comprises an oligonucleotide comprising an antisense strand comprising a region of complementarity to a MEF2D target sequence, optionally wherein the MEF2D target sequence is an MEF2D mRNA sequence as set forth in SEQ ID NO: 664 or SEQ ID NO: 665, or a MEF2D target sequence as set forth in any one of SEQ ID NOs: 668-715, further optionally wherein the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length.

27. The complex of claim 26, wherein the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 716-723, wherein each of the Us are optionally and independently Ts, optionally wherein the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 716-723, wherein each of the Us are optionally and independently Ts.

28. The complex of any one of claims 1-12, wherein the molecular payload comprises an oligonucleotide comprising an antisense strand comprising a region of complementarity to a KLF15 target sequence, optionally wherein the KLF15 target sequence is a KLF15 mRNA sequence as set forth in SEQ ID NO: 740 or SEQ ID NO: 741, or a KLF15 target sequence as set forth in any one of SEQ ID NOs: 742-789, further optionally wherein the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length.

29. The complex of claim 28, wherein the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 790-813, wherein each of the Us are optionally and independently Ts, optionally wherein the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 790-813, wherein each of the Us are optionally and independently Ts.

30. The complex of any one of claims 1-12, wherein the molecular payload comprises an oligonucleotide comprising an antisense strand comprising a region of complementarity to a MED1 target sequence, optionally wherein the MED1 target sequence is a MED1 mRNA sequence as set forth in SEQ ID NO: 814 or SEQ ID NO: 815, or a MED1 target sequence as set forth in any one of SEQ ID NOs: 816-863, further optionally wherein the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length.

31. The complex of claim 30, wherein the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 864-887, wherein each of the Us are optionally and independently Ts, optionally wherein the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 864-887, wherein each of the Us are optionally and independently Ts.

32. The complex of any one of claims 1-12, wherein the molecular payload comprises an oligonucleotide comprising an antisense strand comprising a region of complementarity to a MED13 target sequence, optionally wherein the MED13 target sequence is a MED13 mRNA sequence as set forth in SEQ ID NO: 888 or SEQ ID NO: 889, or a MED13 target sequence as set forth in any one of SEQ ID NOs: 890-937, further optionally wherein the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length.

33. The complex of claim 32, wherein the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 938-961,

wherein each of the Us are optionally and independently Ts, optionally wherein the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 938-961, wherein each of the Us are optionally and independently Ts.

34. The complex of any one of claims 1-12, wherein the molecular payload comprises an oligonucleotide comprising an antisense strand comprising a region of complementarity to PPP1R3A target sequence, optionally wherein the PPP1R3A target sequence is a PPP1R3A mRNA sequence as set forth in SEQ ID NO: 962 or SEQ ID NO: 963, or a PPP1R3A target sequence as set forth in any one of SEQ ID NOs: 964-1011, further optionally wherein the antisense strand is 18-25 nucleotides in length and/or the region of complementarity is at least 16 nucleosides in length.

35. The complex of claim 21, wherein the antisense strand comprises at least 16 consecutive nucleotides of a nucleotide sequence set forth in any one of SEQ ID NOs: 1012-1035, wherein each of the Us are optionally and independently Ts, optionally wherein the antisense strand comprises the nucleotide sequence of any one of SEQ ID NOs: 1012-1035, wherein each of the Us are optionally and independently Ts.

36. The complex of any one of claims 13-35, wherein the oligonucleotide further comprises a sense strand that hybridizes to the antisense strand to form a double stranded siRNA.

37. The complex of any one of claims 13-36, wherein the oligonucleotide comprises one or more modified nucleosides, optionally wherein each nucleoside in the oligonucleotide is a modified nucleoside.

38. The complex of claim 37, wherein the one or more modified nucleosides are 2' modified nucleotides, optionally wherein the one or more 2' modified nucleosides are selected from: 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-dimethylaminoethoxyethyl (2'-O-DMAEOE), 2'-O-N-methylacetamido (2'-O-NMA), locked nucleic acid (LNA), ethylene-bridged nucleic acid (ENA), and (S)-constrained ethyl-bridged nucleic acid (cEt), optionally wherein the 2' modified nucleotide is 2'-O-methyl or 2'-fluoro (2'-F).

39. The complex of any one of claims 13-38, wherein the oligonucleotide comprises one or more phosphorothioate internucleoside linkages, optionally wherein the one or more phosphorothioate internucleoside linkage are present on the antisense strand of the RNAi

oligonucleotide, further optionally wherein the two internucleoside linkages at the 3' end of the sense strands are phosphorothioate internucleoside linkages.

40. The complex of any one of claims 13-39, wherein the oligonucleotide is an siRNA listed in Table 10, Table 13, Table 16, Table 19, Table 22, Table 25, Table 28, Table 31, Table 34, Table 37, or Table 40.

41. The complex of any one of claims 1-40, wherein the antibody is covalently linked to the molecular payload via

(i) a cleavable linker, optionally wherein the cleavable linker comprises a valine-citrulline sequence; or

(ii) a non-cleavable linker, optionally wherein the non-cleavable linker is an alkane linker.

42. A method of reducing MSTN, INHBA, ACVR1B, MLCK1, ACVR1, FBXO32, TRIM63, MEF2D, KLF15, MED1, MED13, and/or PPP1R3A expression in a muscle cell, the method comprising contacting the muscle cell with an effective amount of the complex of any one of claims 1-41 for promoting internalization of the molecular payload to the muscle cell.

43. A method of treating muscle atrophy the method comprising administering to a subject in need thereof an effective amount of the complex of any one of claims 1-41, wherein the subject has elevated expression or activity of MSTN, INHBA, and/or ACVR1B, and the complex comprises a molecular payload that modulates the expression or activity of MSTN, INHBA, and/or ACVR1B, optionally wherein the subject is human, and optionally wherein the administration is intravenous.

44. A method of treating irritable bowel syndrome (IBS) or irritable bowel disease (IBD) the method comprising administering to a subject in need thereof an effective amount of the complex of any one of claims 1-41, wherein the subject has elevated levels of MLCK1 protein and the complex comprises a molecular payload that modulates the expression or activity of MLCK1, optionally wherein the subject is human, and optionally wherein the administration is intravenous.

45. A method of treating a subject having a disease associated with elevated level of ACVR1, the method comprising administering to the subject an effective amount of the complex of any one of claims 1-41, wherein the complex comprises a molecular payload that modulates the expression or activity of ACVR1, optionally wherein the disease is muscle atrophy, further optionally wherein the muscle atrophy is sarcopenia or cachexia, further optionally wherein the subject is human, and optionally wherein the administration is intravenous.

46. A method of treating muscle atrophy the method comprising administering to a subject in need thereof an effective amount of the complex of any one of claims 1-41, wherein the subject has elevated expression or activity of FBXO32 or TRIM63, and the complex comprises a molecular payload that modulates the expression or activity of FBXO32 or TRIM63, optionally wherein the subject is human, and optionally wherein the administration is intravenous.

47. A method of treating a heart disease, the method comprising administering to a subject in need thereof an effective amount of the complex of any one of claims 1-41, wherein the subject has elevated expression or activity of MEF2D, KLF15, MED1, MED13, and/or PPP1R3A, and the complex comprises a molecular payload that modulates the expression or activity of MEF2D, KLF15, MED1, MED13, and/or PPP1R3A, optionally wherein the subject is human, and optionally wherein the administration is intravenous.

48. The method of any one of claims 42-47, wherein the complex reduces RNA level of MSTN, INHBA, ACVR1B, MLCK1, ACVR1, FBXO32, TRIM63, MEF2D, KLF15, MED1, MED13, and/or PPP1R3A.

49. The method of any one of claims 42-48, wherein the complex reduces protein level of MSTN, INHBA, ACVR1B, MLCK1, ACVR1, FBXO32, TRIM63, MEF2D, KLF15, MED1, MED13, and/or PPP1R3A.

50. An oligonucleotide comprising an siRNA listed in Tables 9, 10, 12, 13, 15, 16, 18, 19, 21, 22, 24, 25, 27, 28, 30, 31, 33, 34, 36, 37, 39, and 40.

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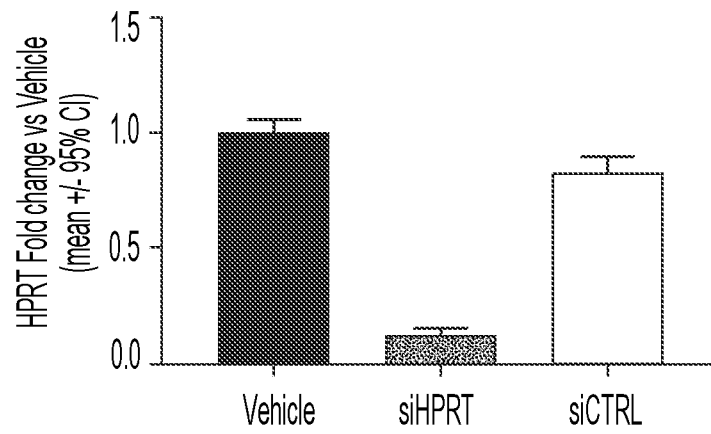


FIG. 1

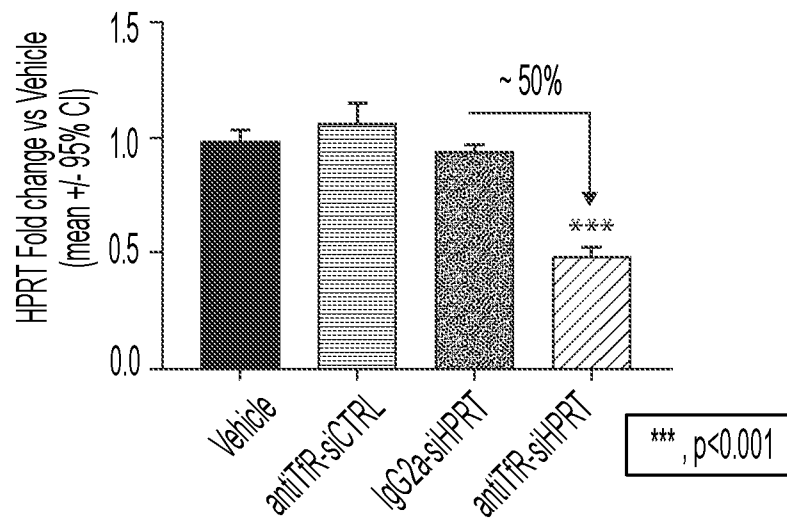


FIG. 2

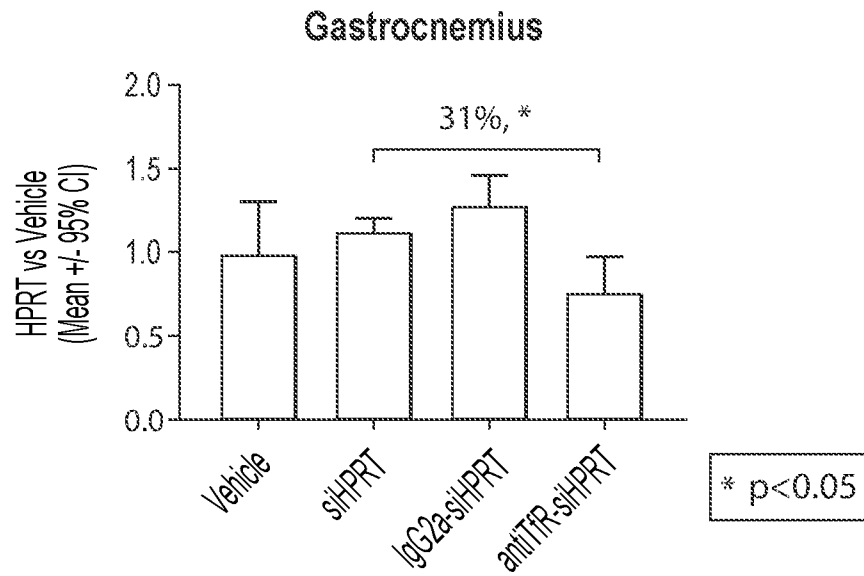


FIG. 3A

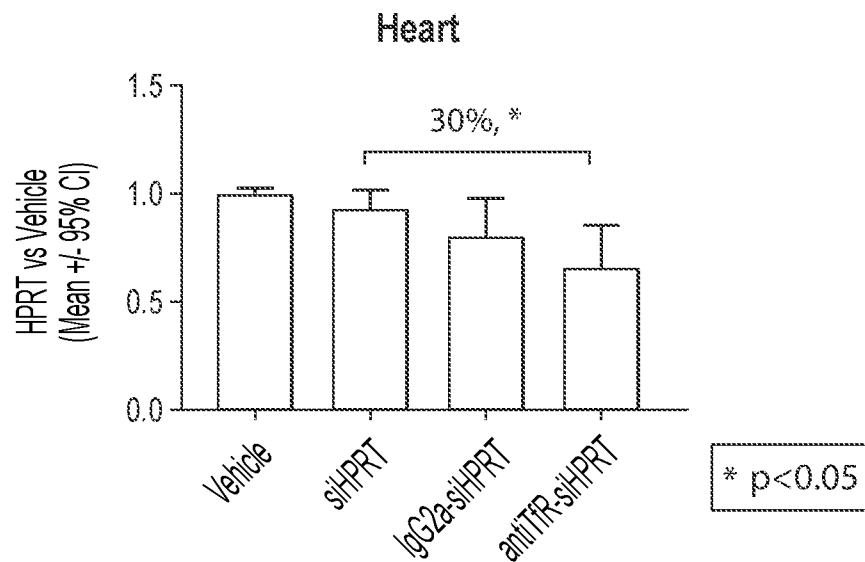


FIG. 3B

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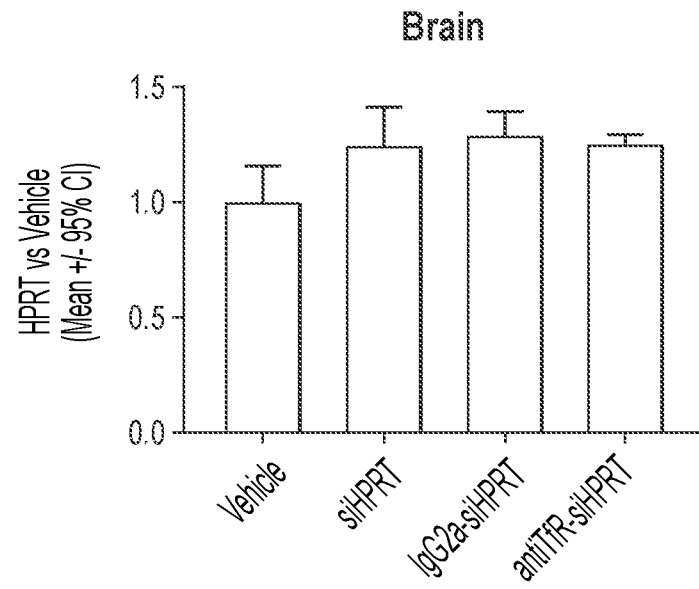


FIG. 4A

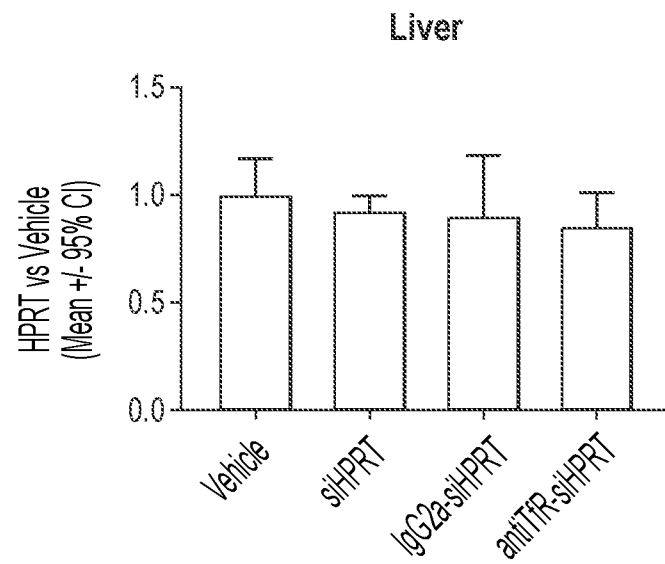


FIG. 4B

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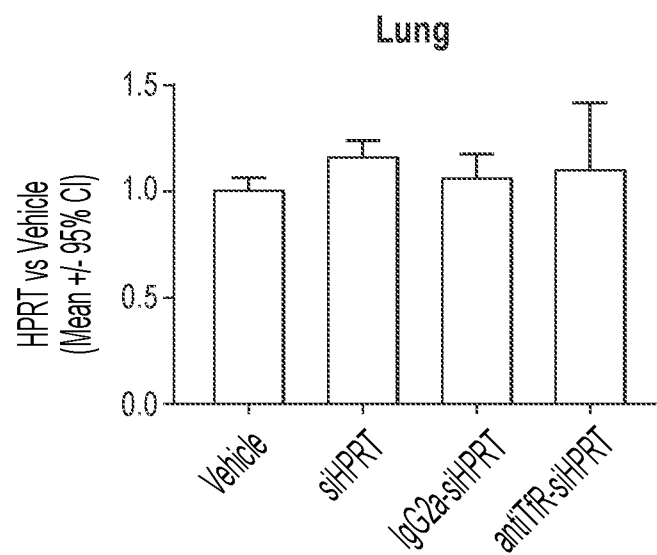


FIG. 4C

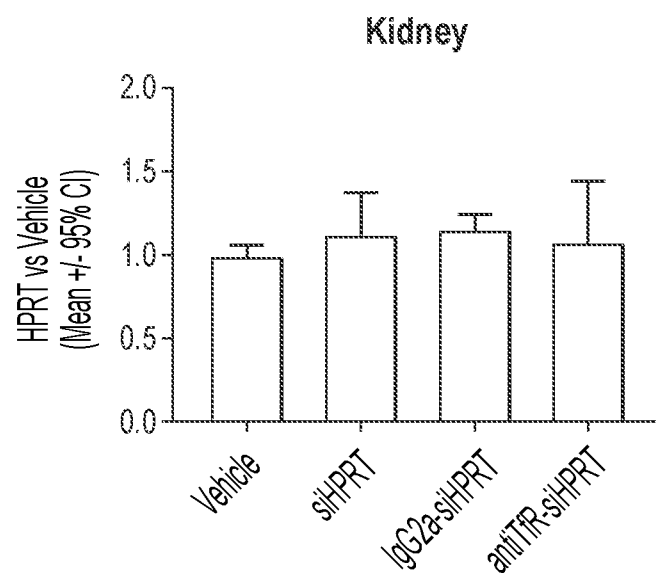


FIG. 4D

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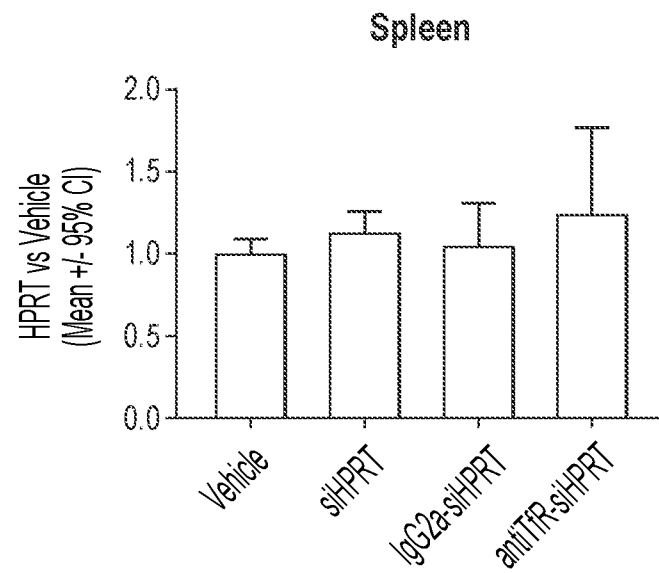


FIG. 4E

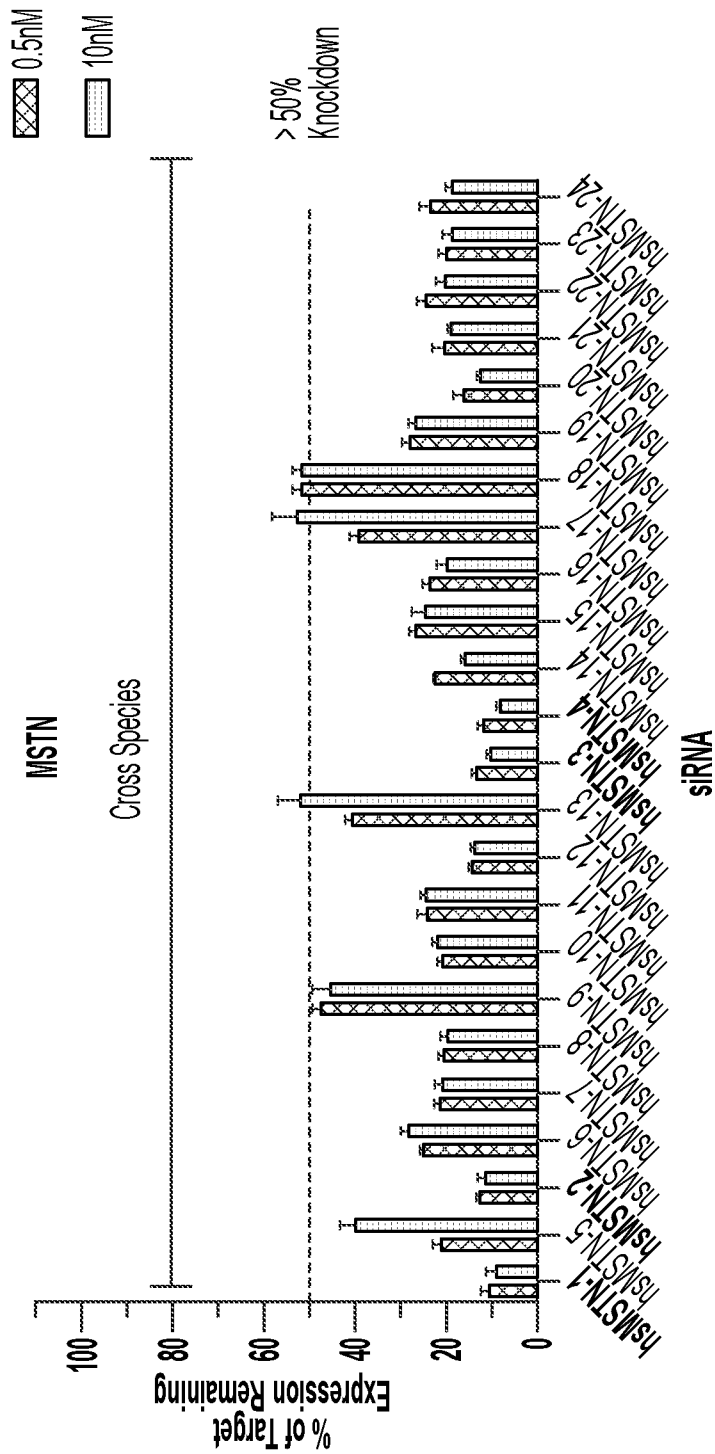


FIG. 5

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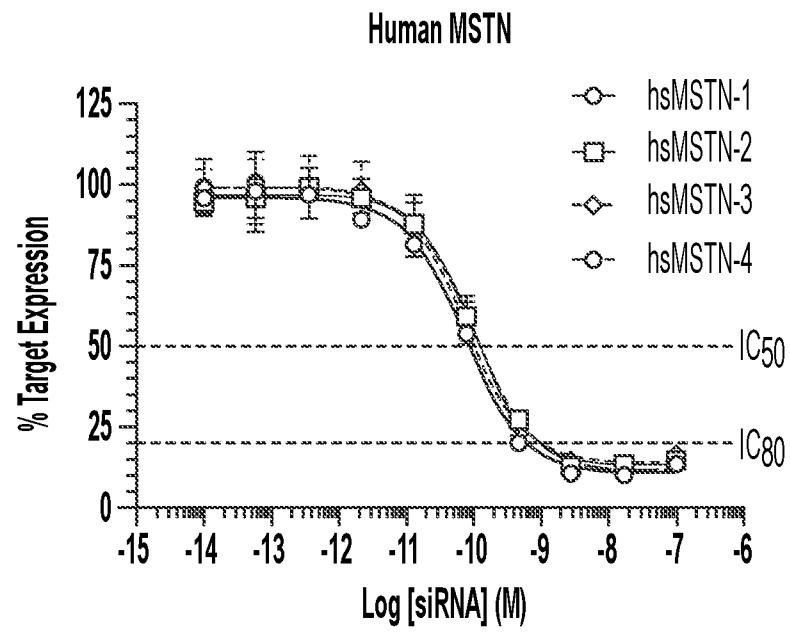


FIG. 6

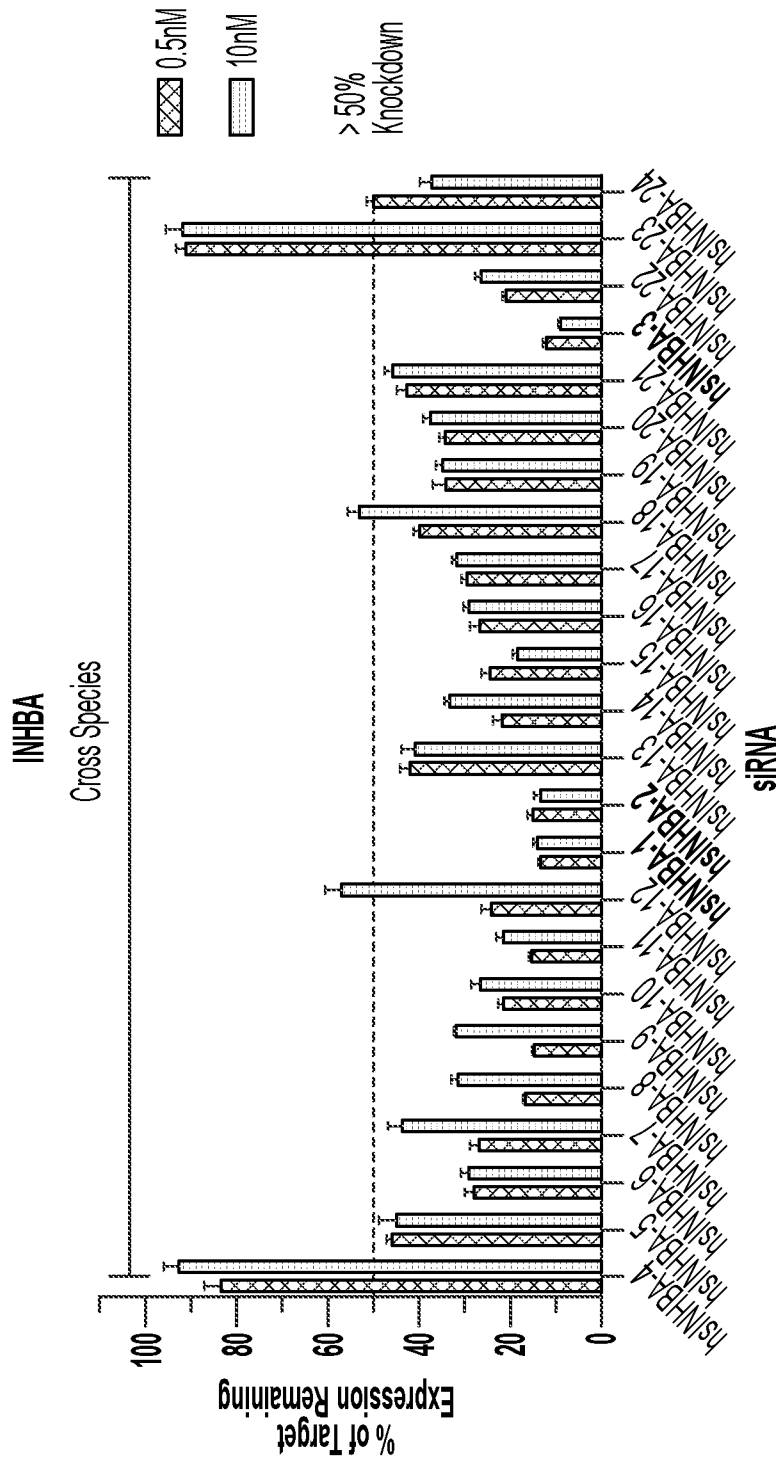
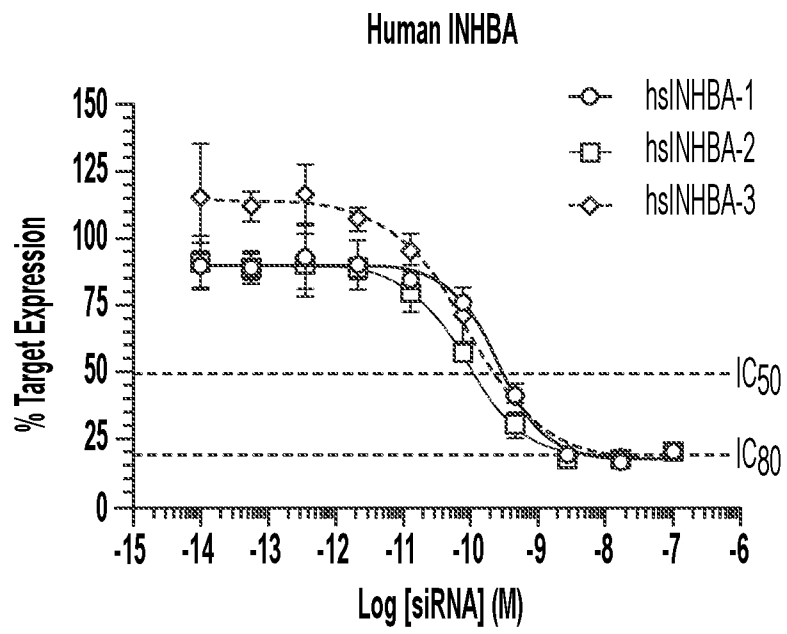


FIG. 7

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**FIG. 8**

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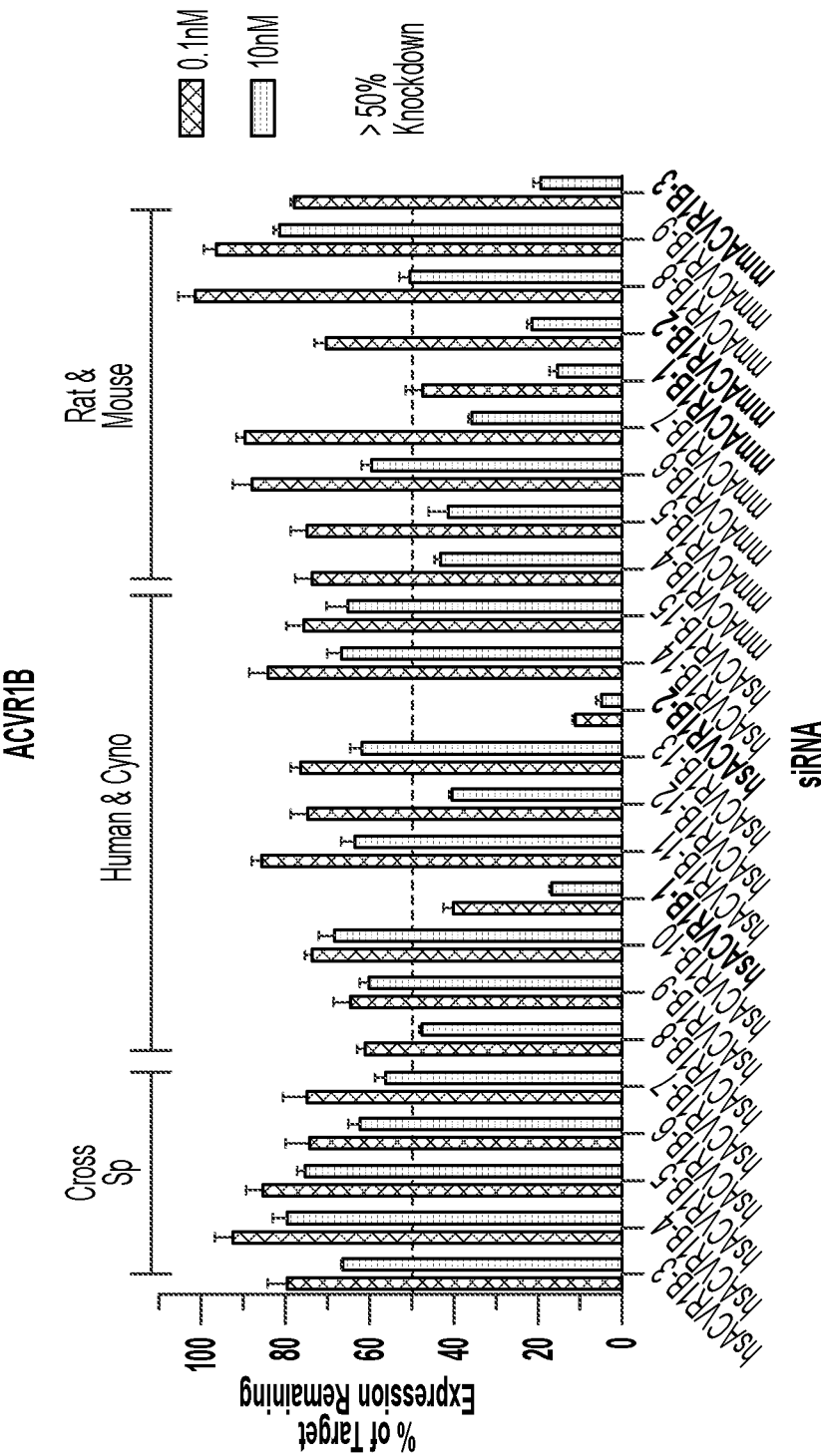


FIG. 9

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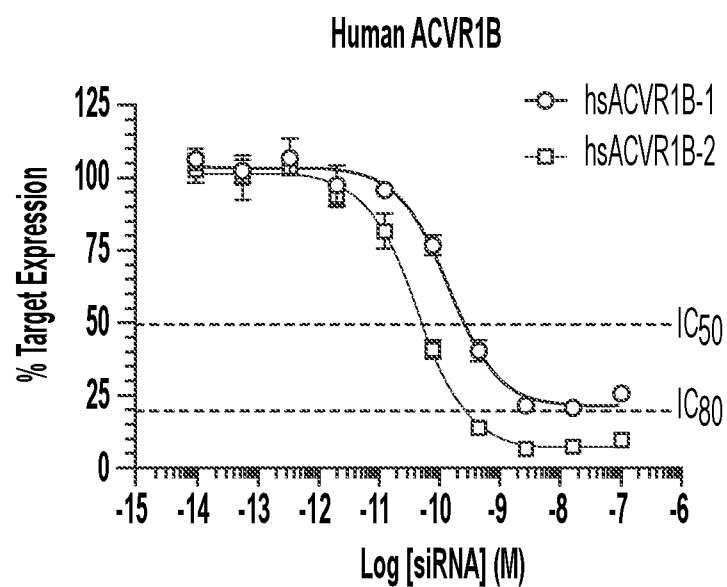


FIG. 10

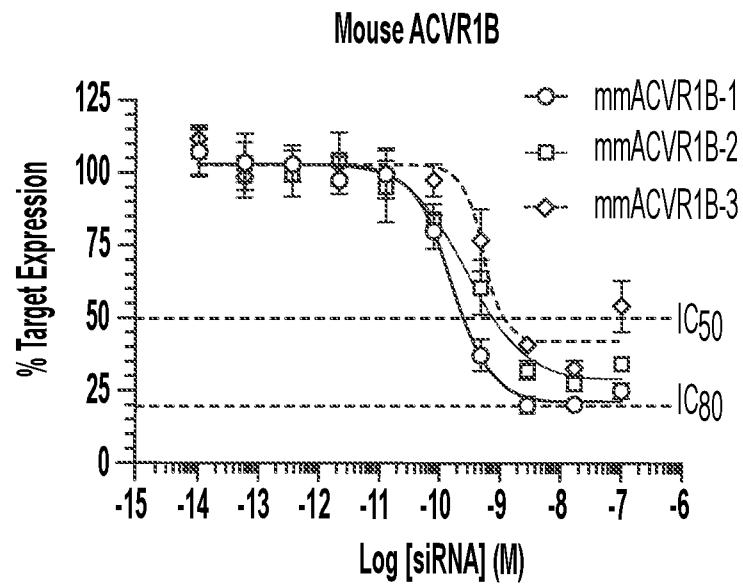


FIG. 11

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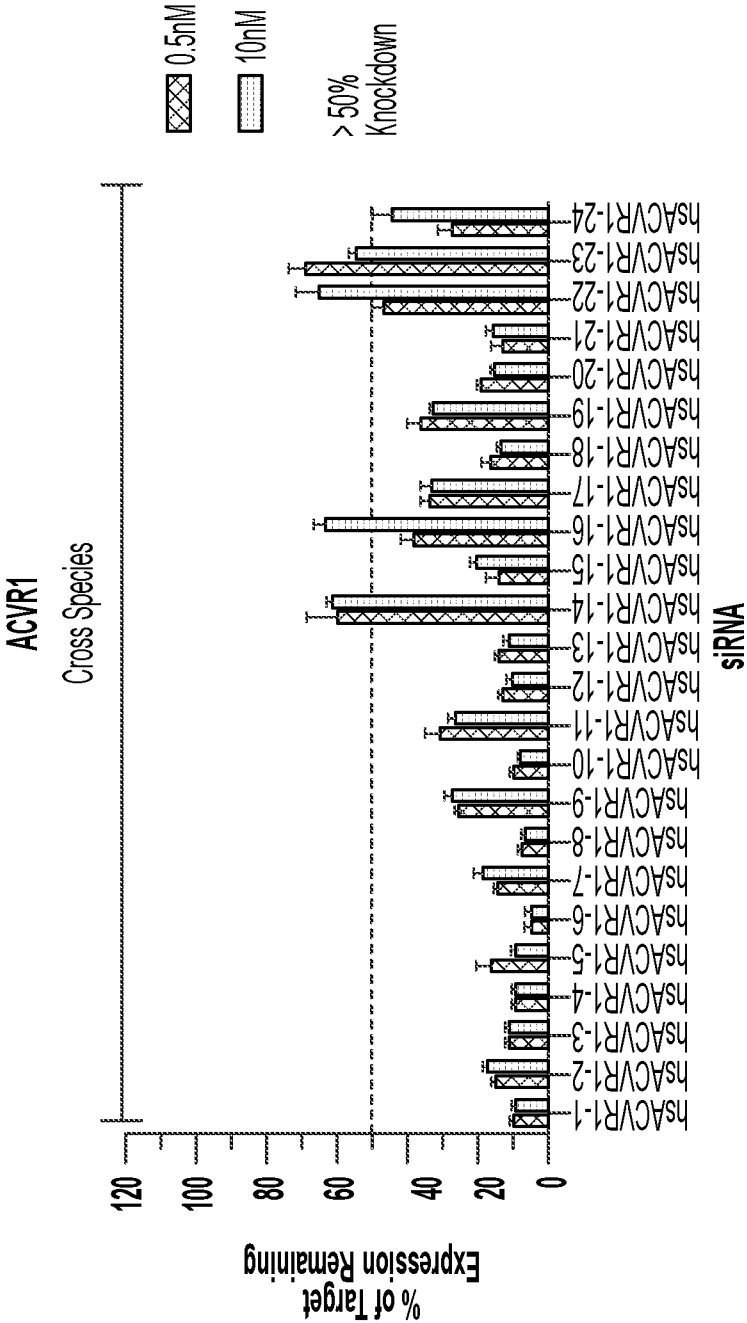


FIG. 12

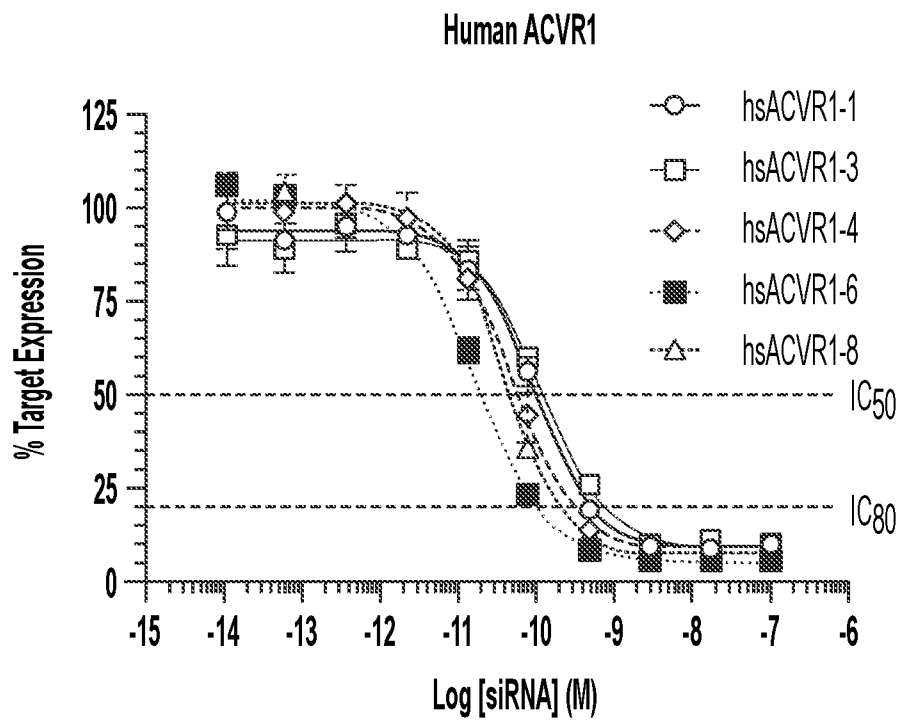


FIG. 13

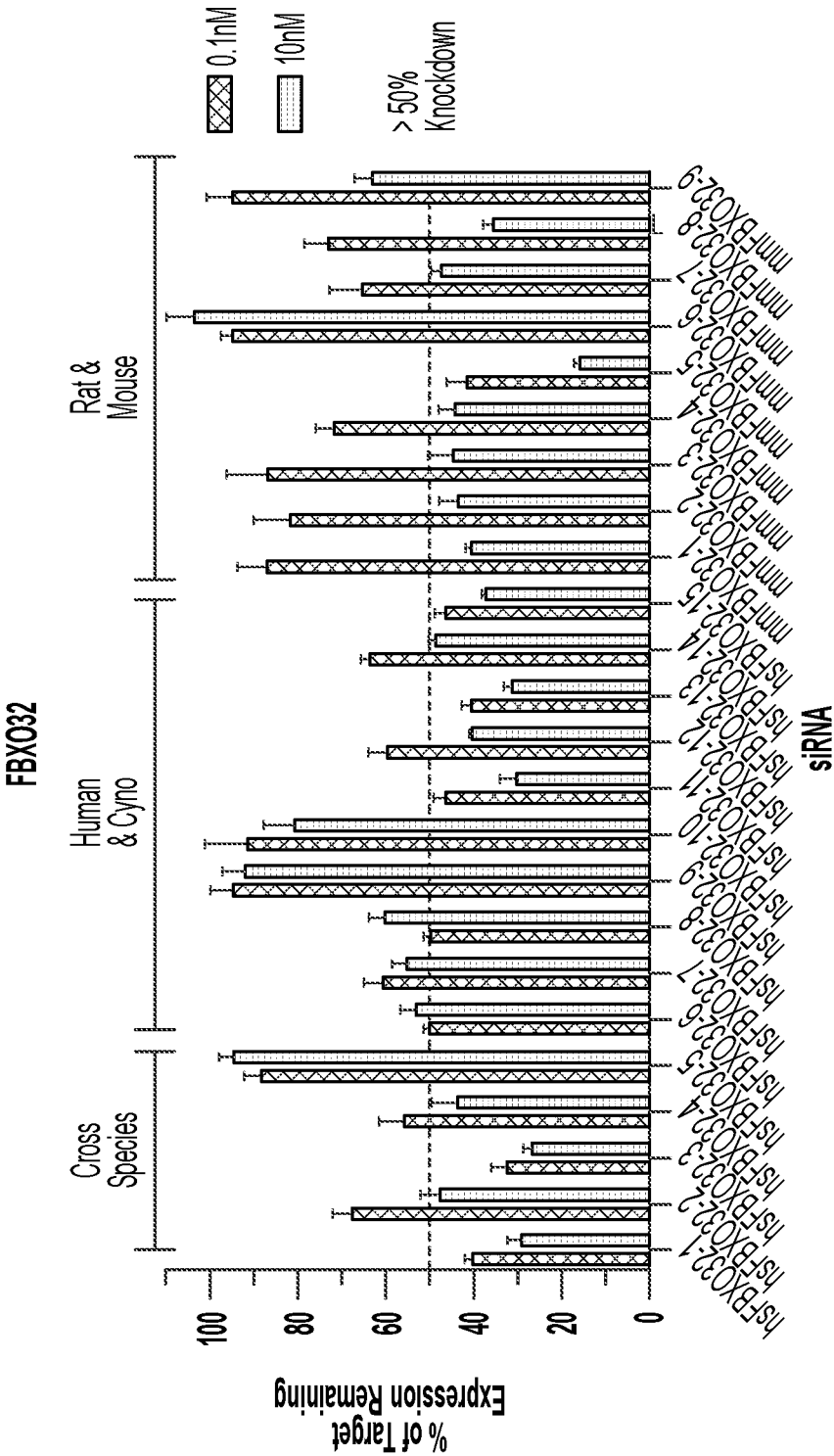


FIG. 14

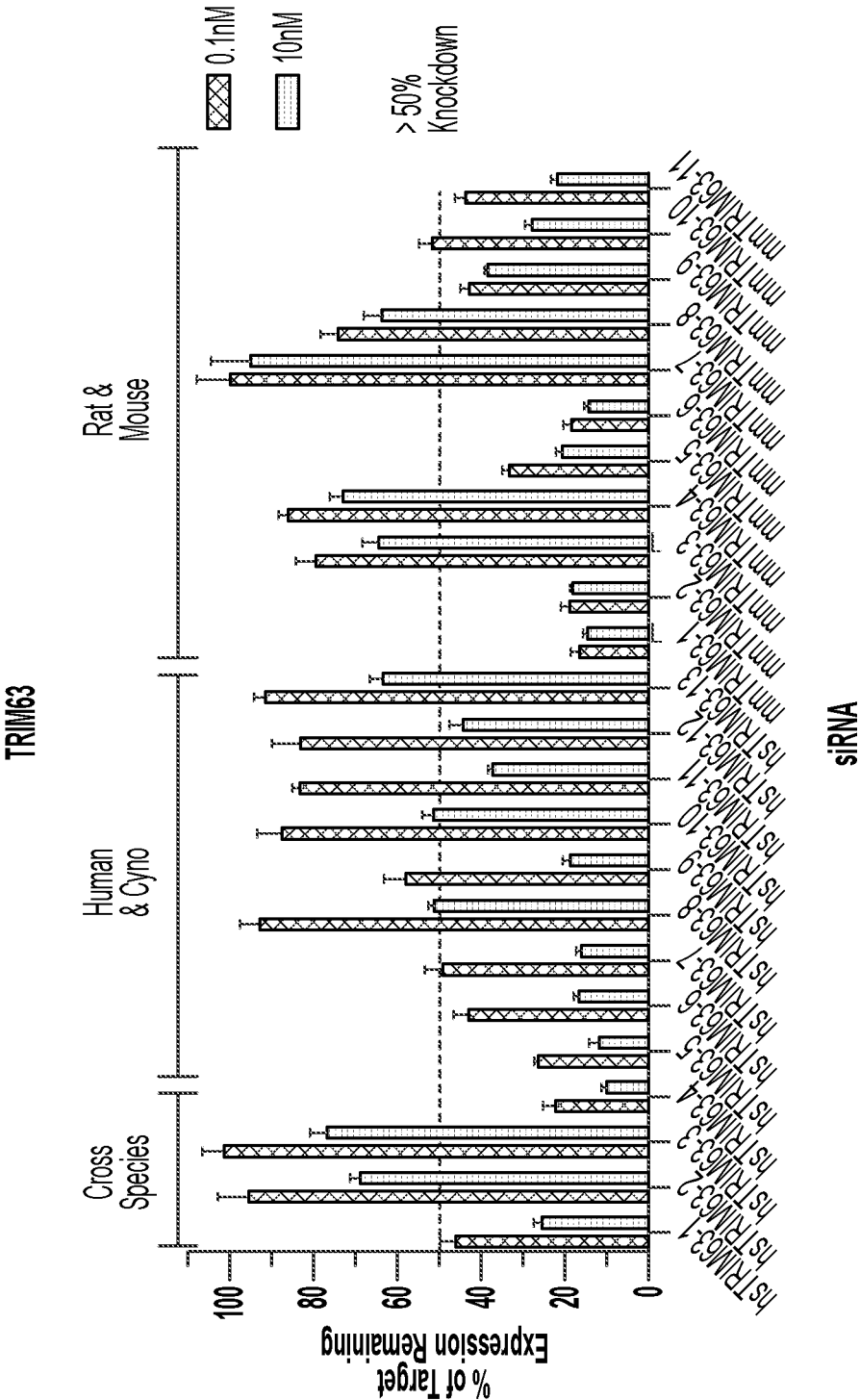


FIG. 15

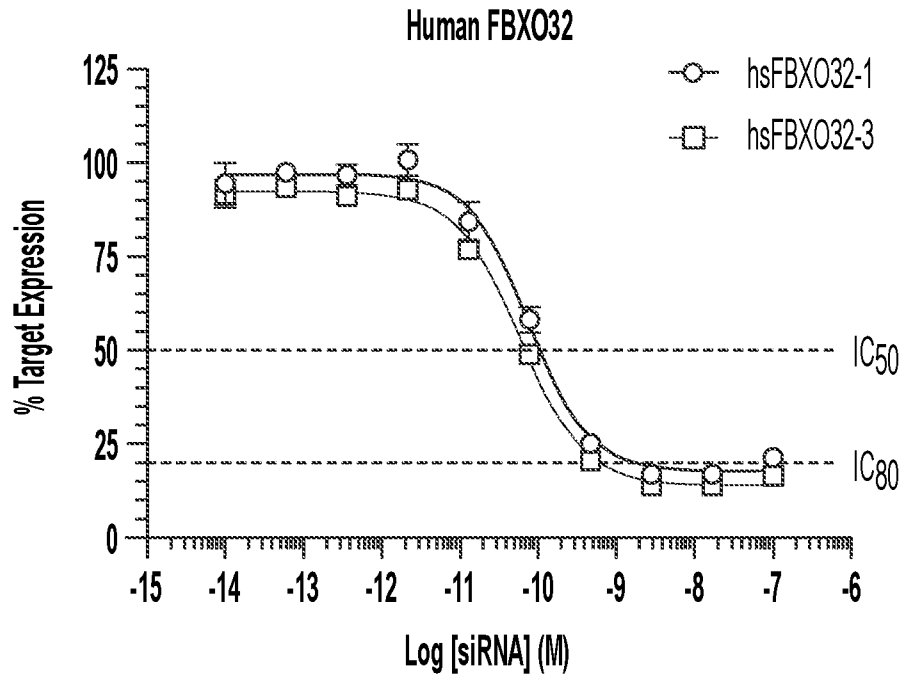


FIG. 16A

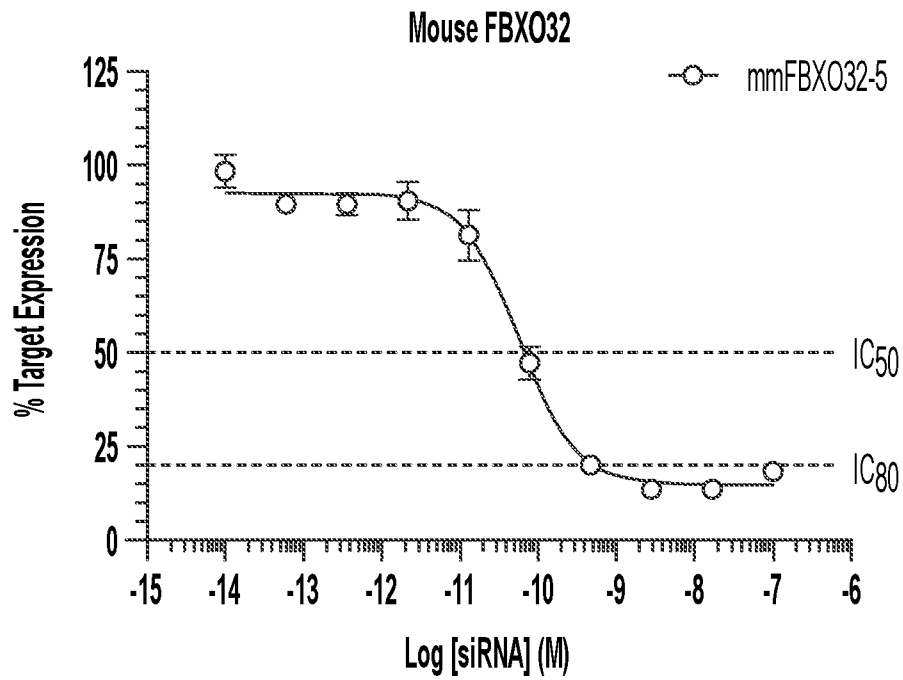


FIG. 16B

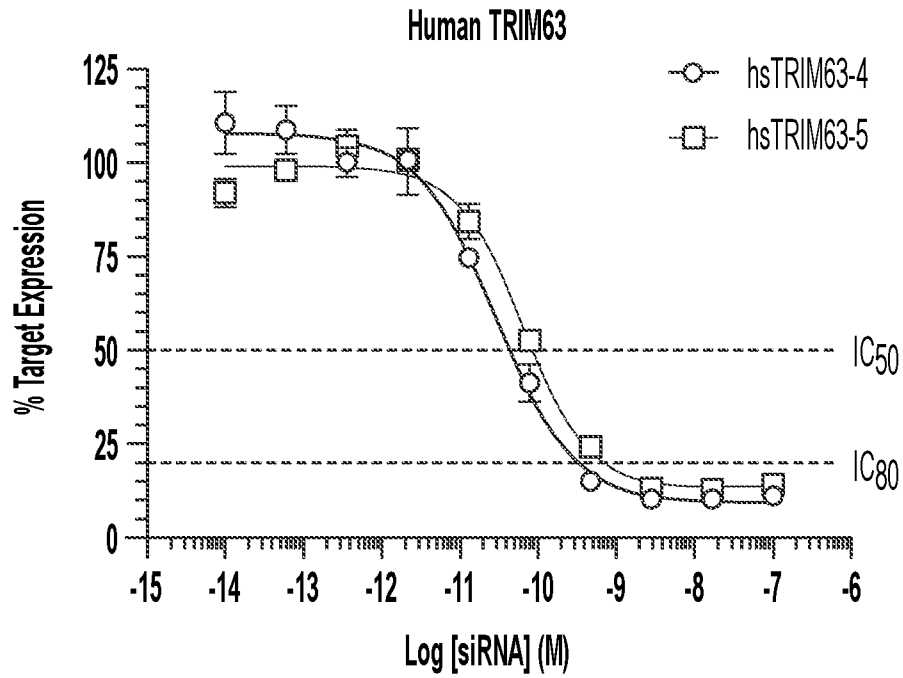


FIG. 17A

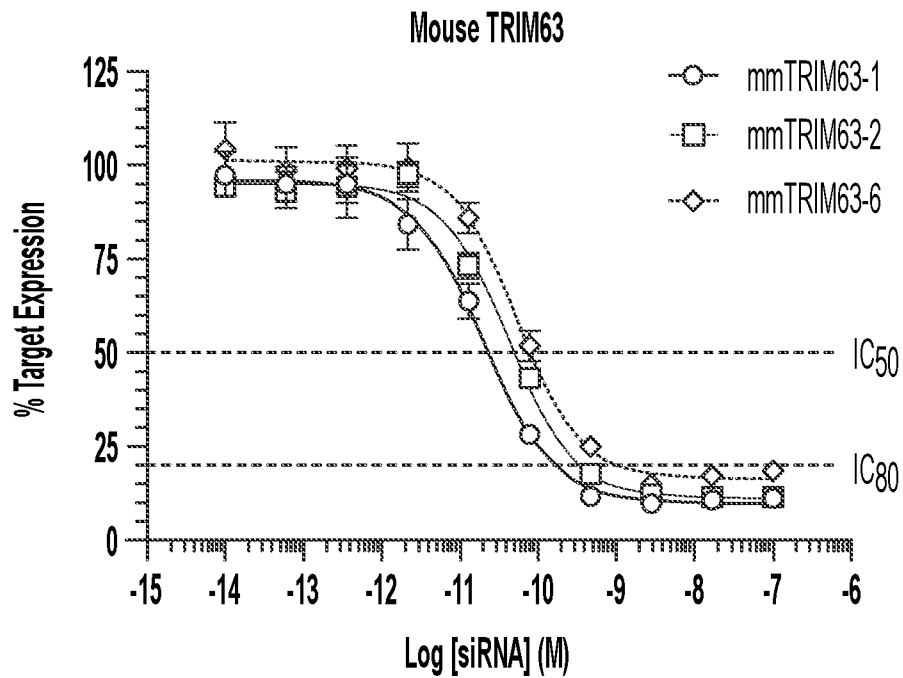
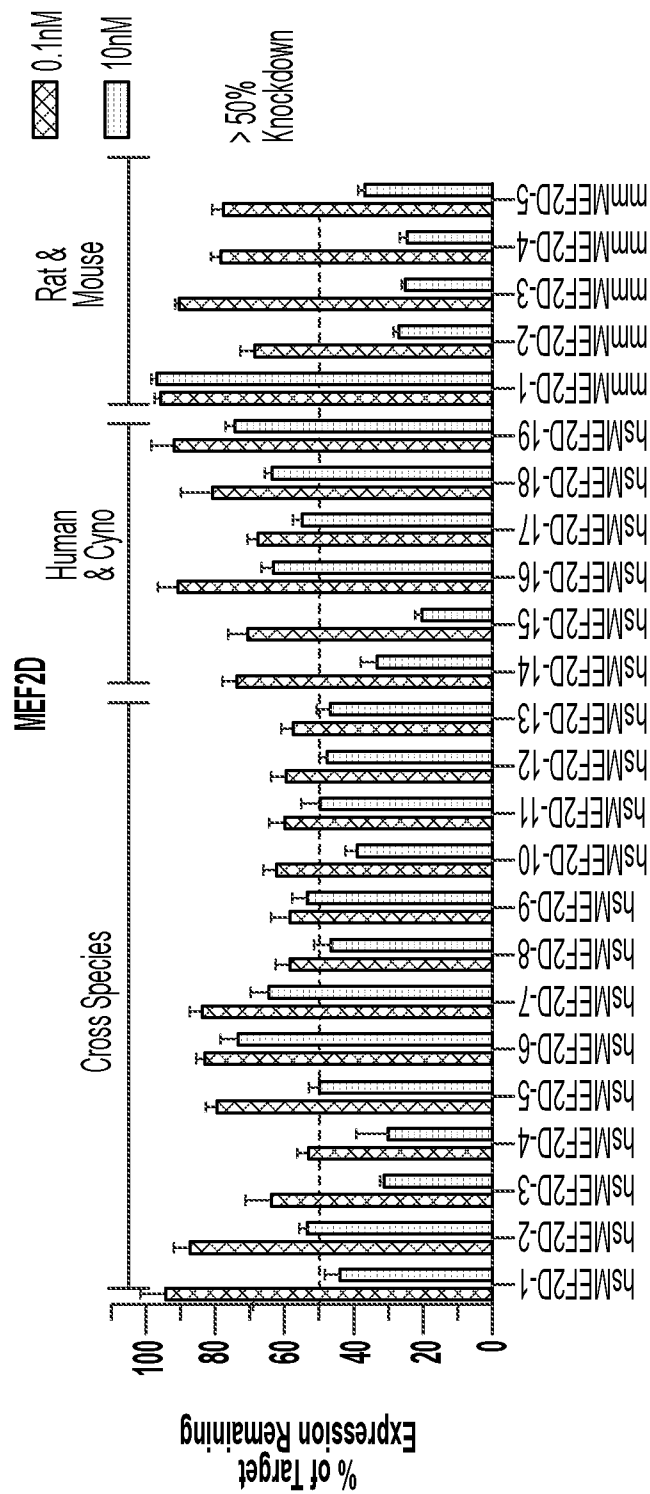


FIG. 17B



siRNA

FIG. 18

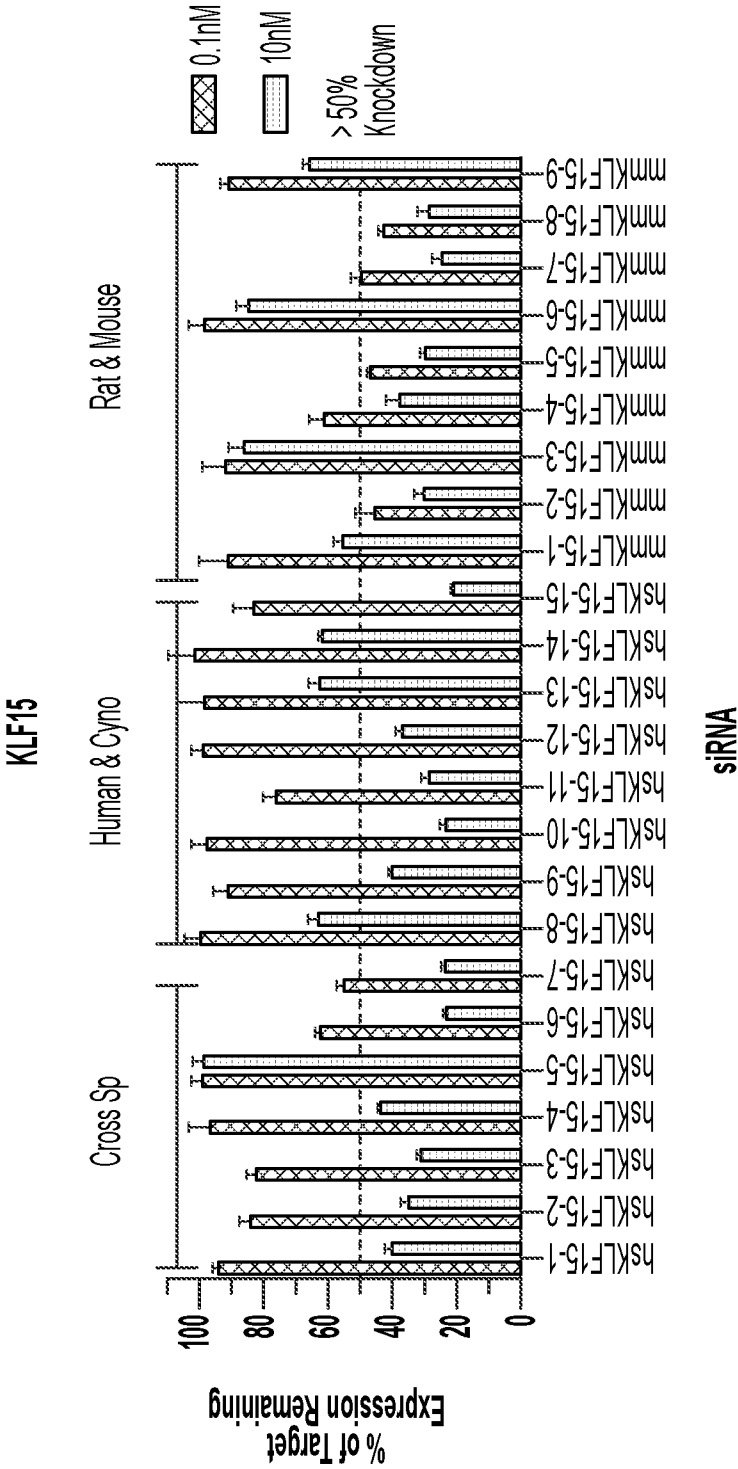
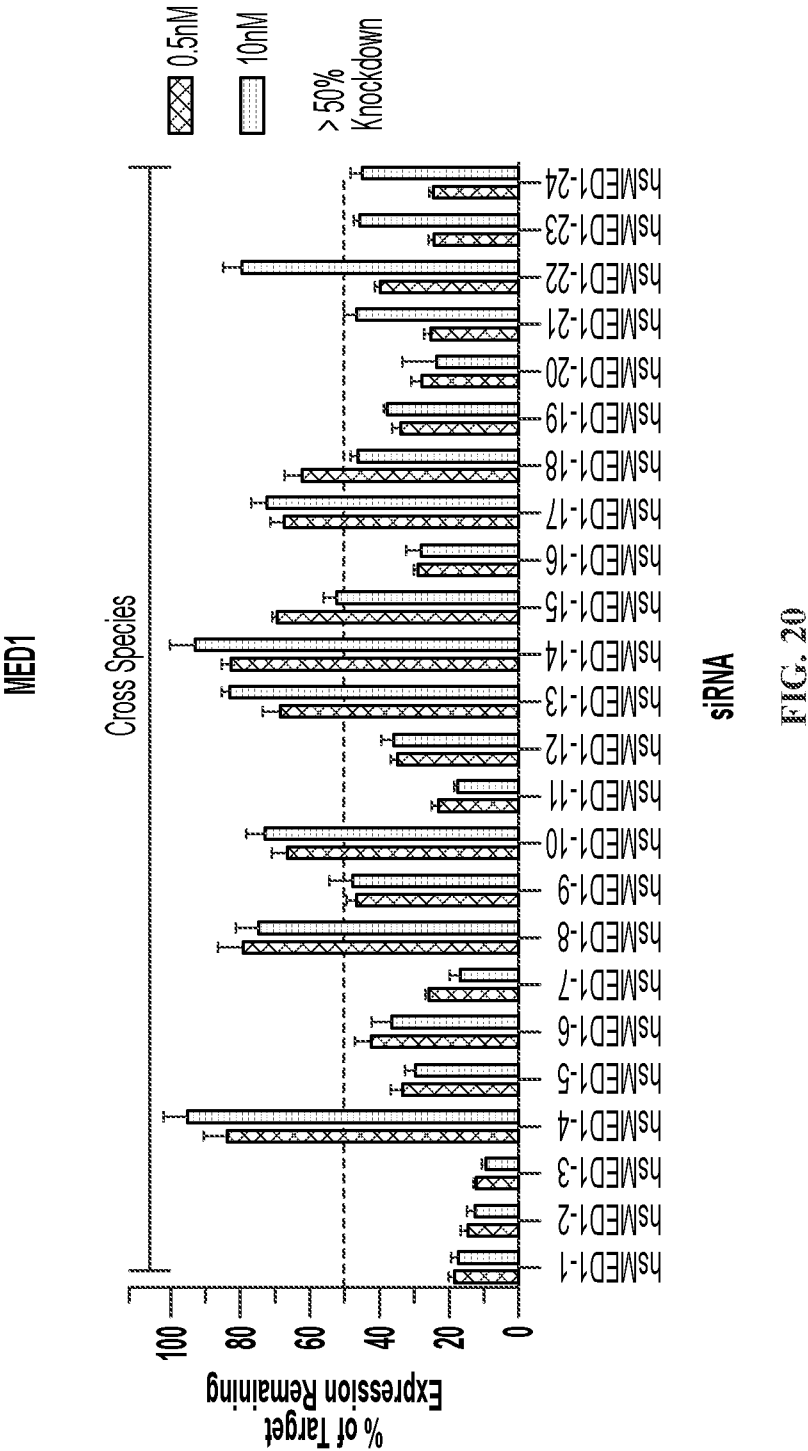


FIG. 19

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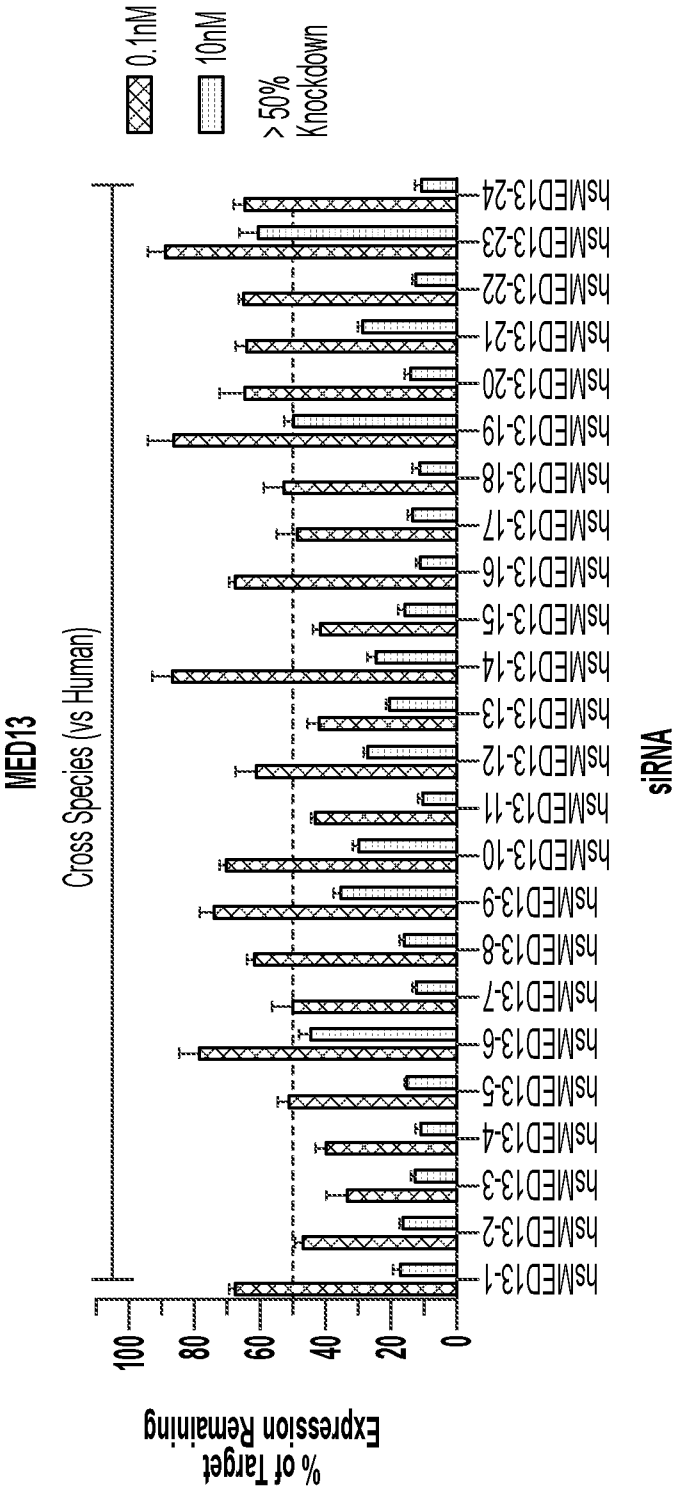


FIG. 21

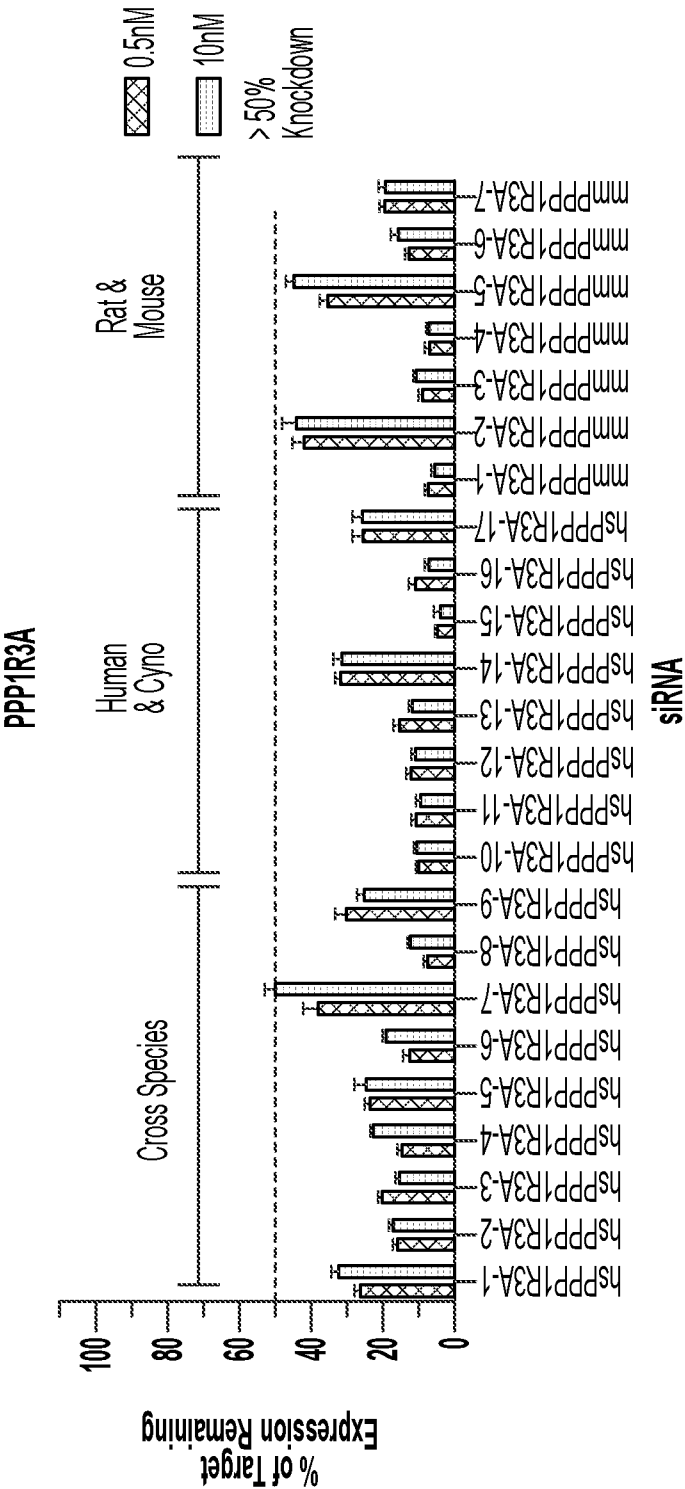


FIG. 22

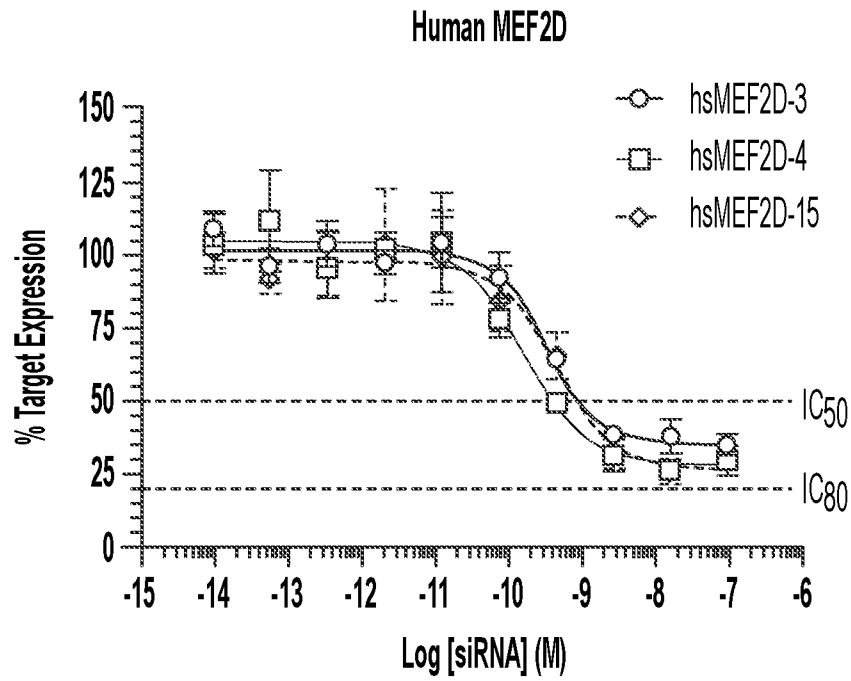


FIG. 23A

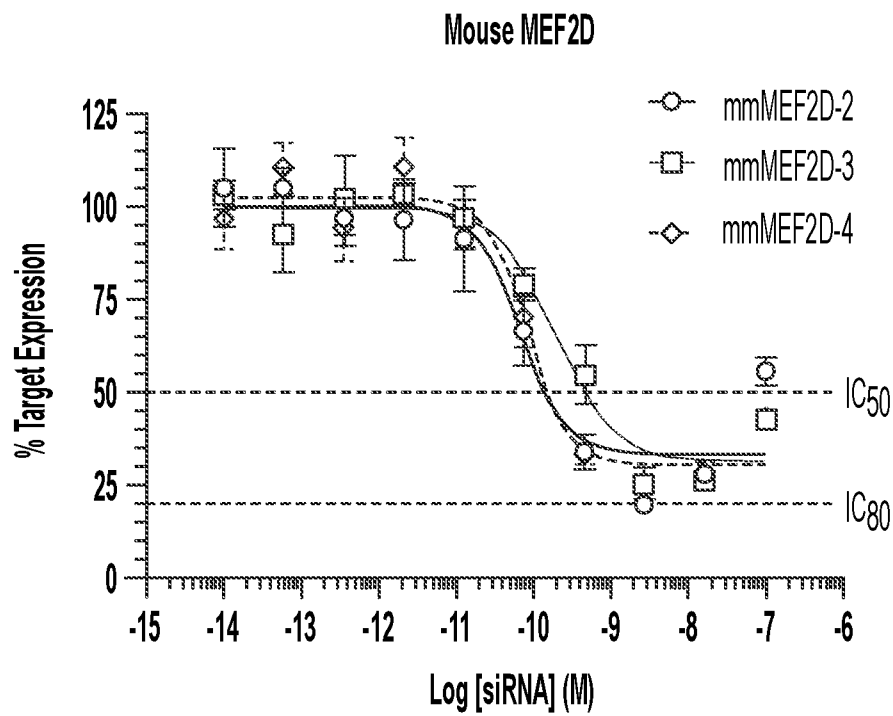


FIG. 23B

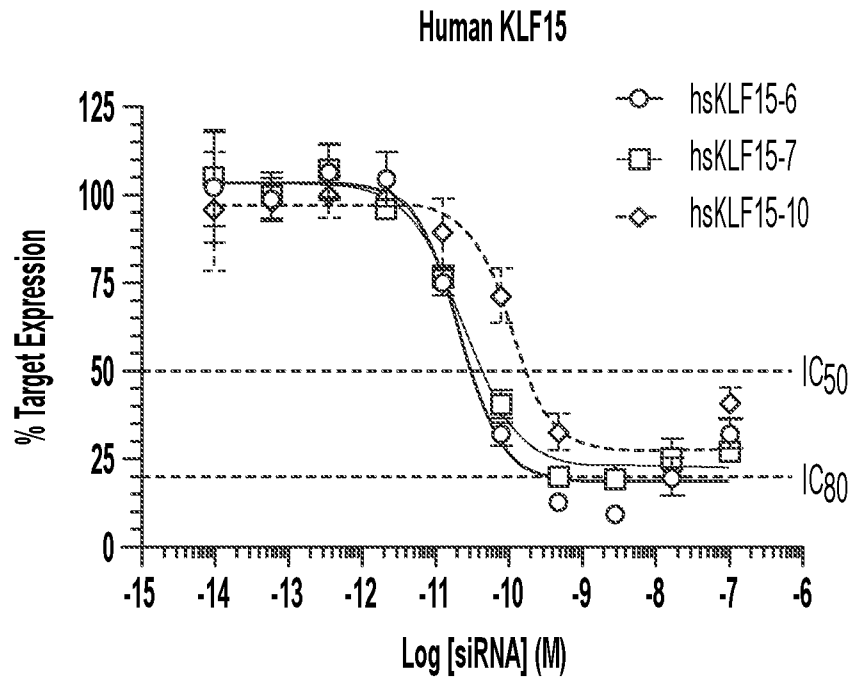


FIG. 24A

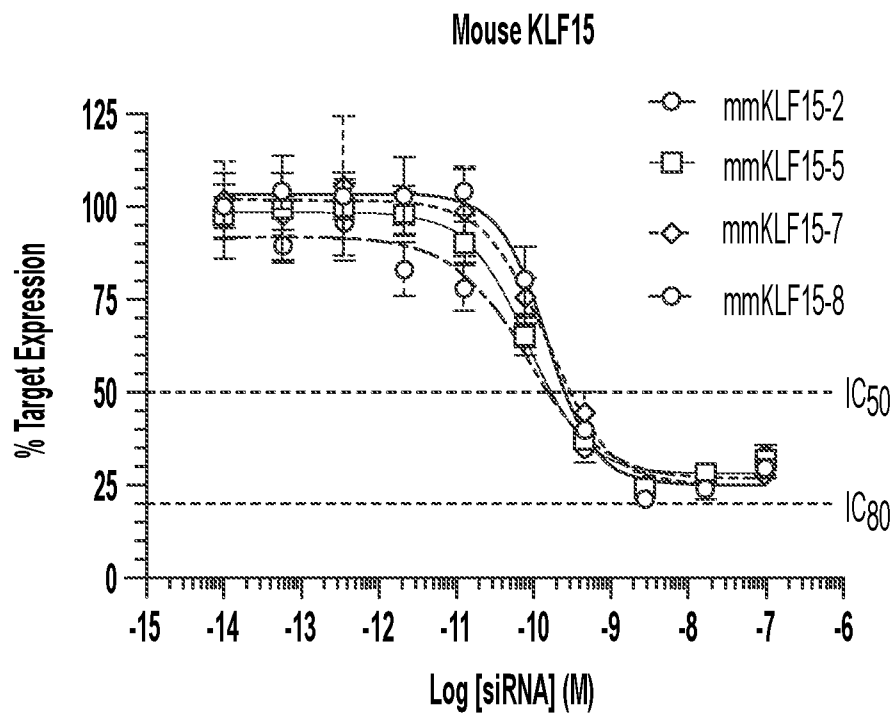


FIG. 24B

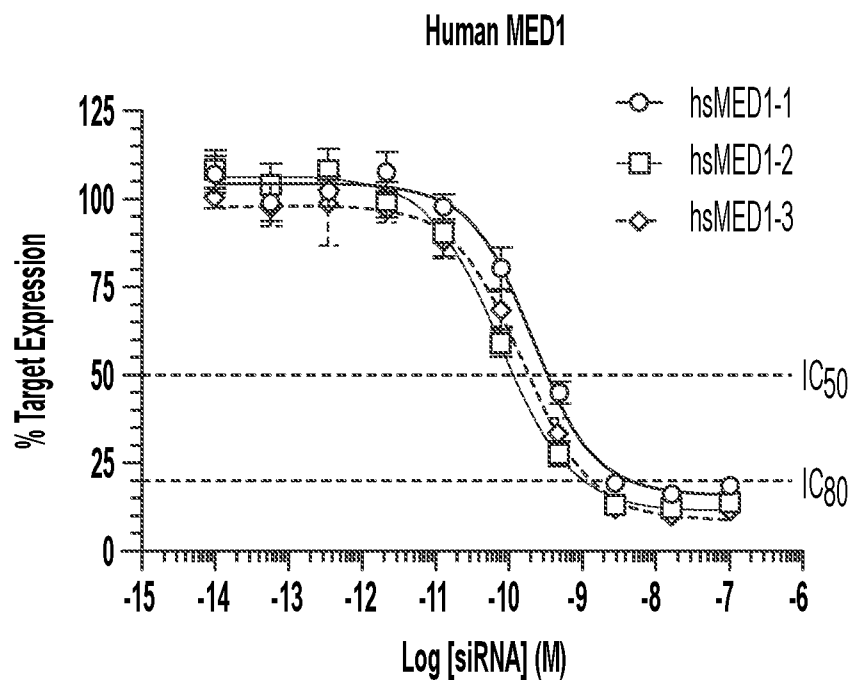


FIG. 25

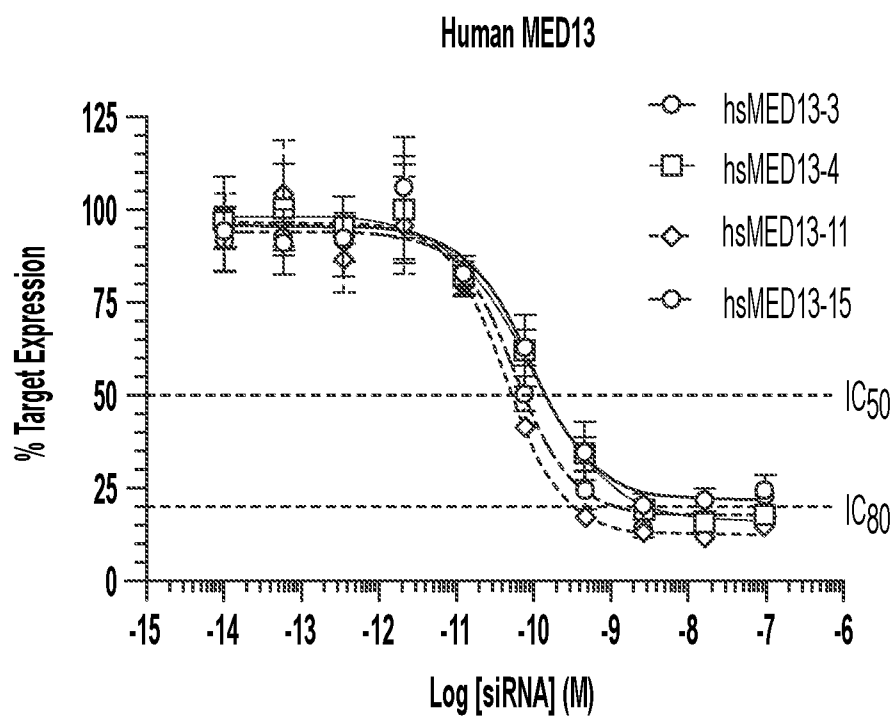


FIG. 26

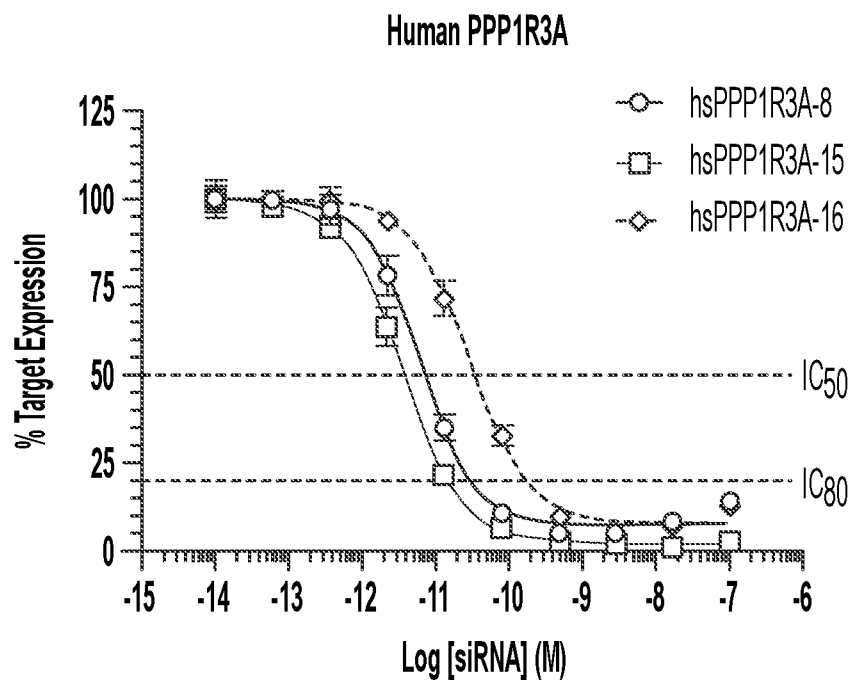


FIG. 27A

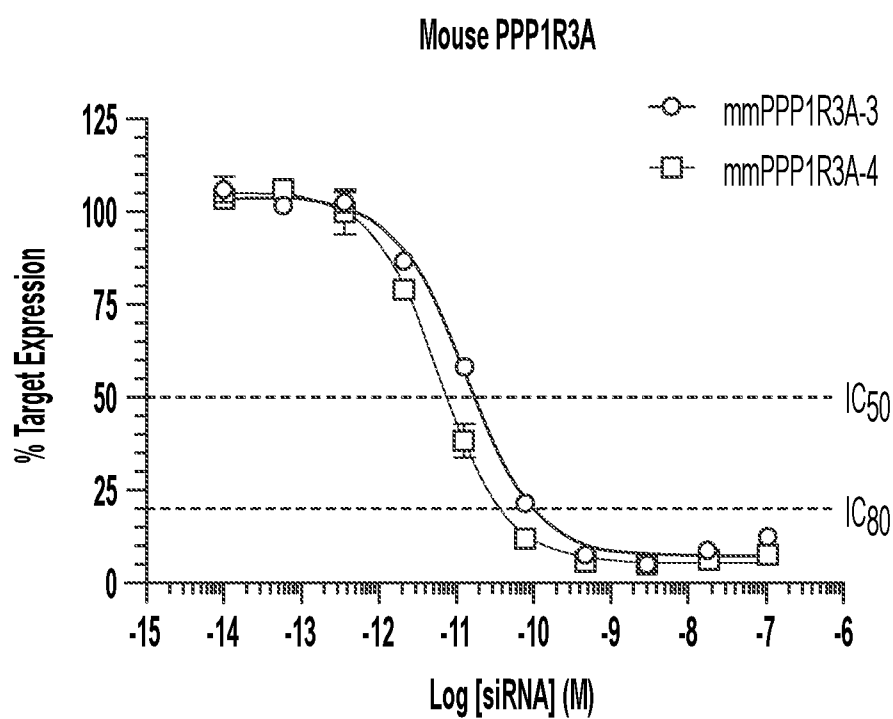


FIG. 27B

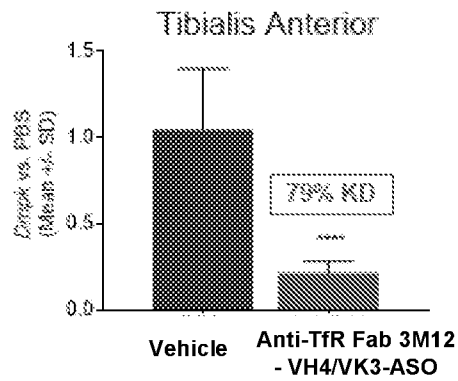


FIG. 28A

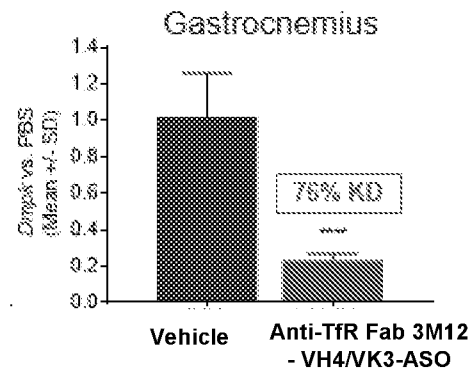


FIG. 28B

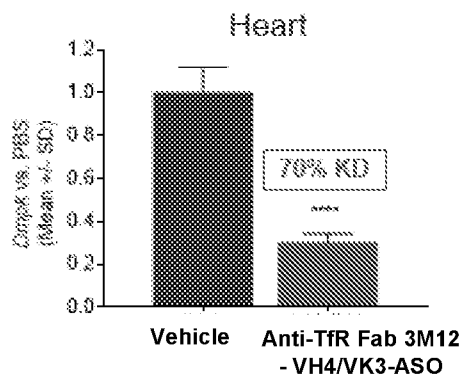


FIG. 28C

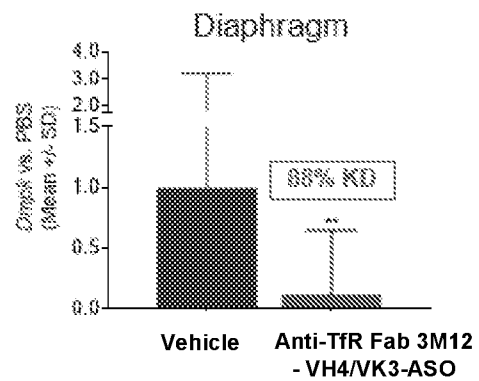


FIG. 28D

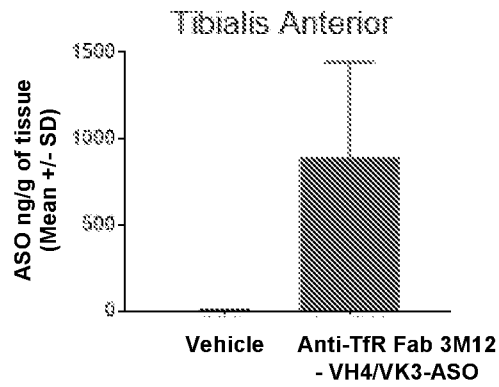


FIG. 28E

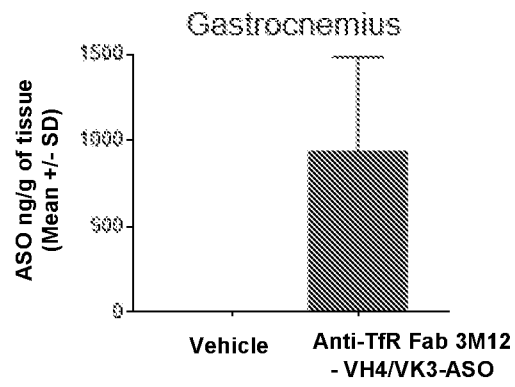


FIG. 28F

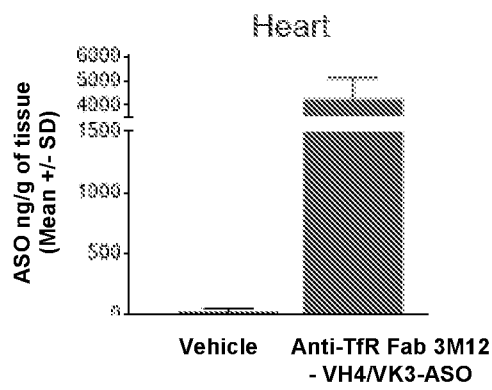


FIG. 28G

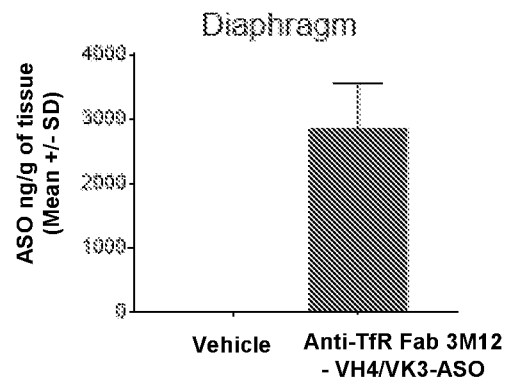


FIG. 28H

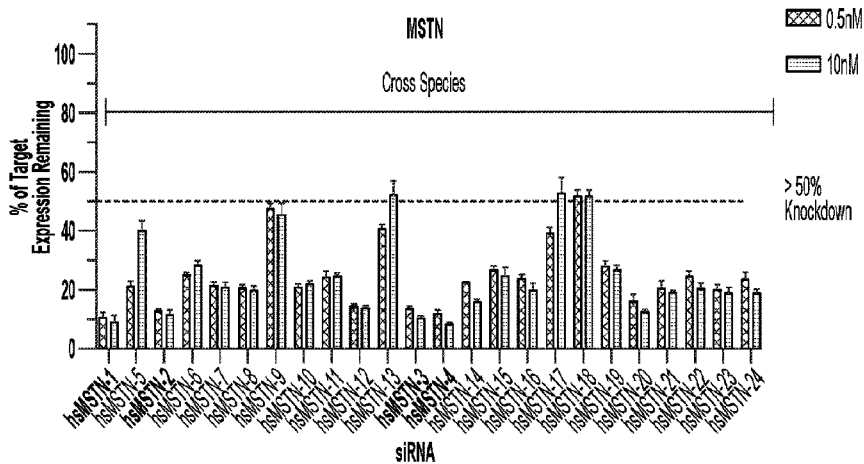


FIG. 5