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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 August 2021 (12.08.2021)

WIPO | PCT

(10) International Publication Number
WO 2021/156832 A1

(51) International Patent Classification:

A61K 48/00 (2006.01)	*A61K 47/10* (2006.01)
A61K 31/7088 (2006.01)	*A61K 47/18* (2006.01)
A61K 9/107 (2006.01)	*A61P 25/00* (2006.01)
A61K 31/4164 (2006.01)	*A61P 21/00* (2006.01)
A61K 31/455 (2006.01)	*C12N 15/113* (2010.01)

(21) International Application Number:
PCT/IB2021/050975

(22) International Filing Date:
06 February 2021 (06.02.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

62/971,771	07 February 2020 (07.02.2020)	US
62/989,487	13 March 2020 (13.03.2020)	US
63/047,147	01 July 2020 (01.07.2020)	US

(71) Applicant: **BIORCHESTRA CO., LTD.** [KR/KR]; 2F-216, Venture-dong, KRIBB, 125, Gwahak-ro, Yuseong-gu, Daejeon 34141 (KR).

(72) Inventor: **RYU, Jin-Hyeob**; 922, Gyeryong-ro, Jung-Gu, Daejeon 34964 (KR).

(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, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, 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.

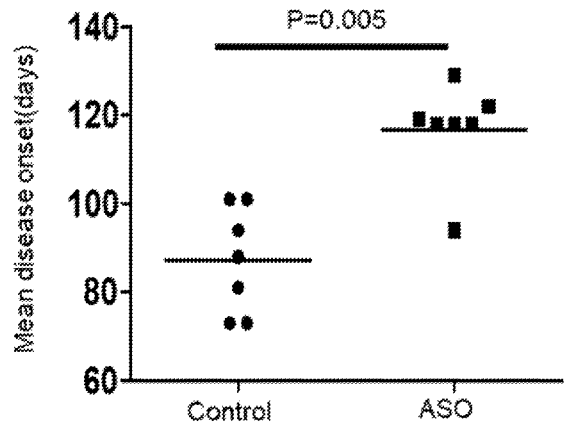
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, 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).

Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report (Art. 21(3))*
— *with sequence listing part of description (Rule 5.2(a))*
— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

(54) Title: USE OF MIRNA-485 INHIBITORS FOR TREATING AMYOTROPHIC LATERAL SCLEROSIS (ALS)

FIG. 3B



(57) Abstract: The present disclosure includes the use of a miRNA inhibitor for treating amyotrophic lateral sclerosis (ALS) associated with a decreased level of SIRT1 protein or SIRT1 gene expression, PGC-1α protein and/or PGC-1α gene expression, CD36 protein and/or CD36 gene expression, NRG1 protein and/or NRG1 gene expression, STMN2 protein and/or STMN2 gene expression, and/or NRXN1 protein and/or NRXN1 gene expression.

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USE OF MIRNA-485 INHIBITORS FOR TREATING AMYOTROPHIC LATERAL SCLEROSIS (ALS)

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This PCT application claims the priority benefit of U.S. Provisional Application Nos. 62/971,771, filed February 7, 2020; 62/989,487, filed March 13, 2020; and 63/047,147, filed July 1, 2020; each of which is incorporated herein by reference in its entirety.

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY VIA EFS-WEB

[0002] The content of the electronically submitted sequence listing in ASCII text file (Name: 4366_021PC03_Seqlisting_ST25.txt; Size: 264,015 bytes; and Date of Creation: February 5, 2021) filed with the application is herein incorporated by reference in its entirety.

FIELD OF THE DISCLOSURE

[0003] The present disclosure provides the use of a miR-485 inhibitor (*e.g.*, polynucleotide encoding a nucleotide molecule comprising at least one miR-485 binding site) for the treatment of amyotrophic lateral sclerosis (ALS).

BACKGROUND OF THE DISCLOSURE

[0004] Sirtulin 1 (also known as NAD-dependent deacetylase sirtuin-1) is an enzyme that in humans is encoded by the SIRT1 gene. It belongs to a family of nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylases and can deacetylate a variety of substrates. Rahman, S., *et al.*, *Cell Communication and Signaling* 9:11 (2011). Accordingly, sirtulin 1 has been described as playing a role in a broad range of physiological functions, including control of gene expression, metabolism, and aging. And, abnormal sirtulin activity has been associated with certain human diseases (*e.g.*, neurodegenerative diseases such as ALS).

[0005] Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND) or Lou Gehrig's disease, is a progressive neurodegenerative disease that affects nerve cells (particularly those that control voluntary muscle movement) in the brain and the spinal cord. Symptoms can include stiff muscles, muscle twitching, gradual weakness due to decrease in

muscle size, and eventual loss of the ability to walk, use their hands, speak, swallow, and breathe. Recent population-based studies have suggested that ALS affects between 4.1 and 8.4 per 100,000 persons worldwide. And, on average, the life expectancy of ALS patients after diagnosis is about 3 to 5 years. The exact cause of ALS is unknown, and there are currently no cures available. The currently available treatments (*e.g.*, mechanical ventilation, feeding tubes, physical and speech therapy) merely address the underlying symptoms. Therefore, new and more effective approaches to treating ALS are highly desirable.

BRIEF SUMMARY OF THE DISCLOSURE

[0006] Provided herein is a method of treating an amyotrophic lateral sclerosis (ALS) in a subject in need thereof comprising administering to the subject a compound that inhibits miR-485 (miRNA inhibitor).

[0007] In some aspects, the miRNA inhibitor increases a level of a SIRT1 protein and/or a SIRT1 gene in the subject. In some aspects, the subject has an ALS associated with a decreased level of a SIRT1 protein and/or a SIRT1 gene.

[0008] In some aspects, the miRNA inhibitor induces autophagy and/or treats or prevents inflammation.

[0009] In some aspects, the miRNA inhibitor increases a level of a CD36 protein and/or a CD36 gene in the subject. In some aspects, the subject has an ALS associated with a decreased level of a CD36 protein and/or a CD36 gene.

[0010] In some aspects, the miRNA inhibitor increases a level of a PGC-1α protein and/or a PGC-1α gene in the subject. In some aspects, the subject has an ALS associated with a decreased level of a PGC-1α protein and/or a PGC-1α gene.

[0011] In some aspects, a miR-485 inhibitor that can be used in the above methods induces neurogenesis. In certain aspects, inducing neurogenesis comprises an increased proliferation, differentiation, migration, and/or survival of neural stem cells and/or progenitor cells. In some aspects, inducing neurogenesis comprises an increased number of neural stem cells and/or progenitor cells. In some aspects, inducing neurogenesis comprises an increased axon, dendrite, and/or synapse development. In some aspects, a miR-485 inhibitor induces phagocytosis.

[0012] Also provided herein is a method of treating a disease or condition associated with an abnormal level of a SIRT1 protein and/or a SIRT1 gene in a subject in need thereof comprising administering to the subject a compound that inhibits miR-485 (miRNA inhibitor),

wherein the miRNA inhibitor increases the level of the SIRT1 protein and/or SIRT1 gene. Also provided herein is a method of treating a disease or condition associated with an abnormal level of a CD36 protein and/or a CD36 gene in a subject in need thereof comprising administering to the subject a compound that inhibits miR-485 (miRNA inhibitor), wherein the miRNA inhibitor increases the level of the CD36 protein and/or CD36 gene. Also provided herein is a method of treating a disease or condition associated with an abnormal level of a PGC-1α protein and/or a PGC-1α gene in a subject in need thereof comprising administering to the subject a compound that inhibits miR-485 (miRNA inhibitor), wherein the miRNA inhibitor increases the level of the PGC-1α protein and/or PGC-1α gene.

[0013] In some aspects, the miRNA inhibitor inhibits miR485-3p. In some aspects, the miR485-3p comprises 5'-GUCAUACACGGCUCUCCUCUCU-3' (SEQ ID NO: 1). In some aspects, the miRNA inhibitor comprises a nucleotide sequence comprising 5'-UGUAUGA-3' (SEQ ID NO: 2) and wherein the miRNA inhibitor comprises about 6 to about 30 nucleotides in length.

[0014] In some aspects, the miRNA inhibitor increases transcription of an SIRT1 gene and/or expression of a SIRT1 protein.

[0015] In some aspects, the miRNA inhibitor comprises at least 1 nucleotide, at least 2 nucleotides, at least 3 nucleotides, at least 4 nucleotides, at least 5 nucleotides, at least 6 nucleotides, at least 7 nucleotides, at least 8 nucleotides, at least 9 nucleotides, at least 10 nucleotides, at least 11 nucleotides, at least 12 nucleotides, at least 13 nucleotides, at least 14 nucleotides, at least 15 nucleotides, at least 16 nucleotides, at least 17 nucleotides, at least 18 nucleotides, at least 19 nucleotides, or at least 20 nucleotides at the 5' of the nucleotide sequence. In some aspects, the miRNA inhibitor comprises at least 1 nucleotide, at least 2 nucleotides, at least 3 nucleotides, at least 4 nucleotides, at least 5 nucleotides, at least 6 nucleotides, at least 7 nucleotides, at least 8 nucleotides, at least 9 nucleotides, at least 10 nucleotides, at least 11 nucleotides, at least 12 nucleotides, at least 13 nucleotides, at least 14 nucleotides, at least 15 nucleotides, at least 16 nucleotides, at least 17 nucleotides, at least 18 nucleotides, at least 19 nucleotides, or at least 20 nucleotides at the 3' of the nucleotide sequence.

[0016] In some aspects, the miRNA inhibitor has a sequence selected from the group consisting of: 5'-UGUAUGA-3' (SEQ ID NO: 2), 5'-GUGUAUGA-3' (SEQ ID NO: 3), 5'-CGUGUAUGA-3' (SEQ ID NO: 4), 5'-CCGUGUAUGA-3' (SEQ ID NO: 5), 5'-

GCCGUGUAUGA-3' (SEQ ID NO: 6), 5'-AGCCGUGUAUGA-3' (SEQ ID NO: 7), 5'-GAGCCGUGUAUGA-3' (SEQ ID NO: 8), 5'-AGAGCCGUGUAUGA-3' (SEQ ID NO: 9), 5'-GAGAGCCGUGUAUGA-3' (SEQ ID NO: 10), 5'-GGAGAGCCGUGUAUGA-3' (SEQ ID NO: 11), 5'-AGGAGAGCCGUGUAUGA-3' (SEQ ID NO: 12), 5'-GAGGAGAGCCGUGUAUGA-3' (SEQ ID NO: 13), 5'-AGAGGAGAGCCGUGUAUGA-3' (SEQ ID NO: 14), 5'-GAGAGGAGAGCCGUGUAUGA-3' (SEQ ID NO: 15); 5'-UGUAUGAC-3' (SEQ ID NO: 16), 5'-GUGUAUGAC-3' (SEQ ID NO: 17), 5'-CGUGUAUGAC-3' (SEQ ID NO: 18), 5'-CCGUGUAUGAC-3' (SEQ ID NO: 19), 5'-GCCGUGUAUGAC-3' (SEQ ID NO: 20), 5'-AGCCGUGUAUGAC-3' (SEQ ID NO: 21), 5'-GAGCCGUGUAUGAC-3' (SEQ ID NO: 22), 5'-AGAGCCGUGUAUGAC-3' (SEQ ID NO: 23), 5'-GAGAGCCGUGUAUGAC-3' (SEQ ID NO: 24), 5'-GGAGAGCCGUGUAUGAC-3' (SEQ ID NO: 25), 5'-AGGAGAGCCGUGUAUGAC-3' (SEQ ID NO: 26), 5'-GAGGAGAGCCGUGUAUGAC-3' (SEQ ID NO: 27), 5'-AGAGGAGAGCCGUGUAUGAC-3' (SEQ ID NO: 28), 5'-GAGAGGAGAGCCGUGUAUGAC-3' (SEQ ID NO: 29), and 5'-AGAGAGGAGAGCCGUGUAUGAC-3' (SEQ ID NO: 30).

[0017] In some aspects, the miRNA inhibitor has a sequence selected from the group consisting of: 5'-TGTATGA-3' (SEQ ID NO: 62), 5'-GTGTATGA-3' (SEQ ID NO: 63), 5'-CGTGTATGA-3' (SEQ ID NO: 64), 5'-CCGTGTATGA-3' (SEQ ID NO: 65), 5'-GCCGTGTATGA-3' (SEQ ID NO: 66), 5'-AGCCGTGTATGA-3' (SEQ ID NO: 67), 5'-GAGCCGTGTATGA-3' (SEQ ID NO: 68), 5'-AGAGCCGTGTATGA-3' (SEQ ID NO: 69), 5'-GAGAGCCGTGTATGA-3' (SEQ ID NO: 70), 5'-GGAGAGCCGTGTATGA-3' (SEQ ID NO: 71), 5'-AGGAGAGCCGTGTATGA-3' (SEQ ID NO: 72), 5'-GAGGAGAGCCGTGTATGA-3' (SEQ ID NO: 73), 5'-AGAGGAGAGCCGTGTATGA-3' (SEQ ID NO: 74), 5'-GAGAGGAGAGCCGTGTATGA-3' (SEQ ID NO: 75); 5'-TGTATGAC-3' (SEQ ID NO: 76), 5'-GTGTATGAC-3' (SEQ ID NO: 77), 5'-CGTGTATGAC-3' (SEQ ID NO: 78), 5'-CCGTGTATGAC-3' (SEQ ID NO: 79), 5'-GCCGTGTATGAC-3' (SEQ ID NO: 80), 5'-AGCCGTGTATGAC-3' (SEQ ID NO: 81), 5'-GAGCCGTGTATGAC-3' (SEQ ID NO: 82), 5'-AGAGCCGTGTATGAC-3' (SEQ ID NO: 83), 5'-GAGAGCCGTGTATGAC-3' (SEQ ID NO: 84), 5'-GGAGAGCCGTGTATGAC-3' (SEQ ID NO: 85), 5'-AGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 86), 5'-GAGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 87), 5'-AGAGGAGAGCCGTGTATGAC-

3' (SEQ ID NO: 88), 5'-GAGAGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 89), and 5'-AGAGAGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 90).

[0018] In some aspects, the sequence of the miRNA inhibitor is at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% sequence identity to 5'- AGAGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 30) or 5'-AGAGAGGAGAGCCGTGTATGAC -3' (SEQ ID NO: 90). In certain aspects, the miRNA inhibitor has a sequence that has at least 90% similarity to 5'- AGAGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 30) or 5'- AGAGAGGAGAGCCGTGTATGAC -3' (SEQ ID NO: 90). In some aspects, the miRNA inhibitor comprises the nucleotide sequence 5'-AGAGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 30) or 5'-AGAGAGGAGAGCCGTGTATGAC -3' (SEQ ID NO: 90) with one substitution or two substitutions. In some aspects, the miRNA inhibitor comprises the nucleotide sequence 5'-AGAGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 30) or 5'-AGAGAGGAGAGCCGTGTATGAC -3' (SEQ ID NO: 90). In some aspects, the miRNA inhibitor comprises the nucleotide sequence 5'- AGAGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 30).

[0019] In some aspects, the miRNA inhibitor comprises at least one modified nucleotide. In certain aspects, the at least one modified nucleotide is a locked nucleic acid (LNA), an unlocked nucleic acid (UNA), an arabino nucleic acid (ABA), a bridged nucleic acid (BNA), and/or a peptide nucleic acid (PNA).

[0020] In some aspects, the miRNA inhibitor comprises a backbone modification. In certain aspects, the backbone modification is a phosphorodiamidate morpholino oligomer (PMO) and/or phosphorothioate (PS) modification.

[0021] In some aspects, the miRNA inhibitor is delivered in a delivery agent. In certain aspects, the delivery agent is a micelle, an exosome, a lipid nanoparticle, an extracellular vesicle, or a synthetic vesicle.

[0022] In some aspects, the miRNA inhibitor is delivered by a viral vector. In certain aspects, the viral vector is an AAV, an adenovirus, a retrovirus, or a lentivirus. In some aspects, the viral vector is an AAV that has a serotype of AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, or any combination thereof.

[0023] In some aspects, the miRNA inhibitor is delivered with a delivery agent. In certain aspects, the delivery agent comprises a lipidoid, a liposome, a lipoplex, a lipid nanoparticle, a polymeric compound, a peptide, a protein, a cell, a nanoparticle mimic, a nanotube, or a conjugate.

[0024] In some aspects, the delivery agent comprises a cationic carrier unit comprising

[WP]-L1-[CC]-L2-[AM] (formula I)

or

[WP]-L1-[AM]-L2-[CC] (formula II)

wherein

WP is a water-soluble biopolymer moiety;

CC is a positively charged carrier moiety;

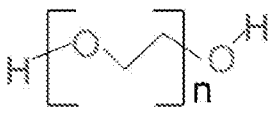
AM is an adjuvant moiety; and,

L1 and L2 are independently optional linkers, and

wherein when mixed with a nucleic acid at an ionic ratio of about 1:1, the cationic carrier unit forms a micelle.

[0025] In some aspects, the miRNA inhibitor interacts with the cationic carrier unit via an ionic bond. In some aspects, the water-soluble polymer comprises poly(alkylene glycols), poly(oxyethylated polyol), poly(olefinic alcohol), poly(vinylpyrrolidone), poly(hydroxyalkylmethacrylamide), poly(hydroxyalkylmethacrylate), poly(saccharides), poly(α-hydroxy acid), poly(vinyl alcohol), polyglycerol, polyphosphazene, polyoxazolines ("POZ") poly(N-acryloylmorpholine), or any combinations thereof. In other aspects, the water-soluble polymer comprises polyethylene glycol ("PEG"), polyglycerol, or poly(propylene glycol) ("PPG").

[0026] In some aspects, the water-soluble polymer comprises:

[0027]  , (formula I),

[0028] In some aspects, n is 1-1000. In certain aspects, the n is at least about 110, at least about 111, at least about 112, at least about 113, at least about 114, at least about 115, at least about 116, at least about 117, at least about 118, at least about 119, at least about 120, at least about 121, at least about 122, at least about 123, at least about 124, at least about 125, at least

about 126, at least about 127, at least about 128, at least about 129, at least about 130, at least about 131, at least about 132, at least about 133, at least about 134, at least about 135, at least about 136, at least about 137, at least about 138, at least about 139, at least about 140, or at least about 141. In further aspects, the n is about 80 to about 90, about 90 to about 100, about 100 to about 110, about 110 to about 120, about 120 to about 130, about 140 to about 150, about 150 to about 160.

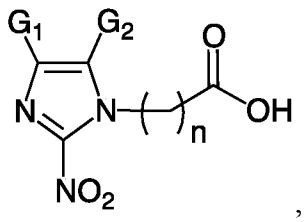
[0029] In some aspects, the water-soluble polymer is linear, branched, or dendritic.

[0030] In some aspects, the cationic carrier moiety comprises one or more basic amino acids. In certain aspects, the cationic carrier moiety comprises at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least 11, at least 12, at least 13, at least 14, at last 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 31, at least 32, at least 33, at least 34, at least 35, at least 36, at least 37, at least 38, at least 39, at least 40, at least 41, at least 42, at least 43, at least 44, at least 45, at least 46, at least 47, at least 48, at least 49, or at least 50 basic amino acids. In certain aspects, the cationic carrier moiety comprises about 30 to about 50 basic amino acids.

[0031] In some aspects, the basic amino acid comprises arginine, lysine, histidine, or any combination thereof. In some aspects, the cationic carrier moiety comprises about 40 lysine monomers.

[0032] In some aspects, the adjuvant moiety is capable of modulating an immune response, an inflammatory response, and/or a tissue microenvironment. In certain aspects, the adjuvant moiety comprises an imidazole derivative, an amino acid, a vitamin, or any combination thereof.

[0033] In some aspects, the adjuvant moiety comprises:

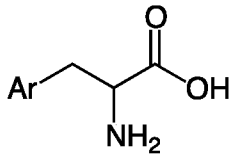
[0034]  , (formula II),

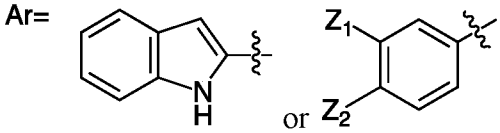
[0035] wherein each of G1 and G2 is H, an aromatic ring, or 1-10 alkyl, or G1 and G2 together form an aromatic ring, and wherein n is 1-10.

[0036] In some aspects, the adjuvant moiety comprises nitroimidazole. In certain aspects, the adjuvant moiety comprises metronidazole, tinidazole, nimorazole, dimetridazole, pretomanid, ornidazole, megazol, azanidazole, benznidazole, or any combination thereof.

[0037] In some aspects, the adjuvant moiety comprises an amino acid.

[0038] In some aspects, the adjuvant moiety comprises

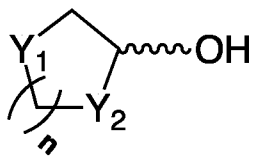
[0039]  (formula III),

[0040] wherein Ar is  , and

[0041] wherein each of Z1 and Z2 is H or OH.

[0042] In some aspects, the adjuvant moiety comprises a vitamin. In certain aspects, the vitamin comprises a cyclic ring or cyclic hetero atom ring and a carboxyl group or hydroxyl group.

[0043] In some aspects, the vitamin comprises:

[0044]  (formula IV),

[0045] wherein each of Y1 and Y2 is C, N, O, or S, and wherein n is 1 or 2.

[0046] In some aspects, the vitamin is selected from the group consisting of vitamin A, vitamin B1, vitamin B2, vitamin B3, vitamin B6, vitamin B7, vitamin B9, vitamin B12, vitamin C, vitamin D2, vitamin D3, vitamin E, vitamin M, vitamin H, and any combination thereof. For example, the vitamin can be vitamin B3.

[0047] In some aspects, the adjuvant moiety comprises at least about two, at least about three, at least about four, at least about five, at least about six, at least about seven, at least about eight, at least about nine, at least about ten, at least about 11, at least about 12, at least about 13, at least about 14, at least about 15, at least about 16, at least about 17, at least about 18, at least about 19, or at least about 20 vitamin B3. In certain aspects, the adjuvant moiety comprises about 10 vitamin B3.

[0048] In some aspects, the delivery agent comprises about a water-soluble biopolymer moiety with about 120 to about 130 PEG units, a cationic carrier moiety comprising a poly-

lysine with about 30 to about 40 lysines, and an adjuvant moiety with about 5 to about 10 vitamin B3.

[0049] In some aspects, the delivery agent is associated with the miRNA inhibitor, thereby forming a micelle. For example, the association can be a covalent bond, a non-covalent bond, or an ionic bond.

[0050] In some aspects, the cationic carrier unit and the miRNA inhibitor in the micelle is mixed in a solution so that the ionic ratio of the positive charges of the cationic carrier unit and the negative charges of the miRNA inhibitor is about 1: 1. In some aspects, the cationic carrier unit is capable of protecting the miRNA inhibitor from enzymatic degradation.

[0051] In some aspects, the ALS that can be treated with the present disclosure comprises sporadic ALS, familial ALS, or both. In some aspects, the miRNA inhibitor delays ALS onset. In some aspects, the miRNA inhibitor improves muscle strength in the subject.

[0052] In some aspects, the delivery agent is a micelle. In some aspects, the micelle comprises (i) about 100 to about 200 PEG units, (ii) about 30 to about 40 lysines, each with an amine group, (iii) about 15 to about 20 lysines, each with a thiol group, and (iv) about 30 to about 40 lysines, each linked to vitamin B3. In some aspects, the micelle comprises (i) about 120 to about 130 PEG units, (ii) about 32 lysines, each with an amine group, (iii) about 16 lysines, each with a thiol group, and (iv) about 32 lysines, each linked to vitamin B3.

[0053] In some aspects, a targeting moiety is further linked to the PEG units. In some aspects, the targeting moiety is a LAT 1 targeting ligand. In some aspects, the targeting moiety is pennyl alanine.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

[0054] FIG. 1 shows an exemplary architecture of a carrier unit of the present disclosure. The example presented includes a cationic carrier moiety, which can interact electrostatically with anionic payloads, *e.g.,* nucleic acids such as antisense oligonucleotides targeting a gene, *e.g.,* miRNA (antimirs). In some aspects, AM can be located between WP and CC. The CC and AM components are portrayed in a linear arrangement for simplicity. However, as described herein, in some aspects, CC and AM can be arranged in a scaffold fashion.

[0055] FIGs. 2A and 2B provide comparison of PGC-1α protein and/or IL-1β protein expression in wild-type (WT) and ALS (SOD1-G93A) mice. FIG. 2A shows the expression of

both PGC-1α and IL-1β proteins in the spinal cord tissue (lumbar region). FIG. 2B shows the expression of PGC-1α protein in skeletal muscle.

[0056] FIGs. 3A, 3B, and 3C provide comparison of disease onset and survival in ALS mice treated with miR-485 inhibitor "(1)" or PBS "(2)." FIG. 3A provides the percentage of mice that do not show disease onset after being treated with miR-485 inhibitor. FIG. 3B provides the average of the days that the disease onset occurred in the mice treated with miR-485 inhibitor. FIG. 3C provides a comparison of the survival curve.

[0057] FIG. 4 provides a comparison of muscle strength of ALS mice treated with miR-485 inhibitor "(1)" or PBS "(2)" as measured by hang wire test. Muscle strength is shown by the amount of time the animals were able to hold onto the hang wire before falling (*i.e.*, latency time to fall).

[0058] FIGs. 5A and 5B show that the administration of a miR-485 inhibitor has no observable effect on body weight of male and female rats, respectively. As shown, male and female rats received one of the following doses of the miR-485 inhibitor: (i) 0 mg/kg (G1), (ii) 3.75 mg/kg (G2), (iii) 7.5 mg/kg (G3), and (iv) 15 mg/kg (G4). Body weight was measured at days 0, 3, 7, and 14 post miR-485 inhibitor administration.

[0059] FIGs. 6A and 6B show that the administration of miR-485 inhibitor has no effect on mortality in male and female rats, respectively. As shown, male and female rats received one of the following doses of the miR-485 inhibitor: (i) 0 mg/kg (G1), (ii) 3.75 mg/kg (G2), (iii) 7.5 mg/kg (G3), and (iv) 15 mg/kg (G4). Mortality of the animals was measured daily from days 0 to 14 days post miR-485 inhibitor administration.

[0060] FIGs. 7A and 7B show that the administration of a miR-485 inhibitor has no lasting clinical adverse effects when administered to male and female rats, respectively. As shown, male and female rats received one of the following doses of the miR-485 inhibitor: (i) 0 mg/kg (G1), (ii) 3.75 mg/kg (G2), (iii) 7.5 mg/kg (G3), and (iv) 15 mg/kg (G4). The adverse effects measured included the following: (i) NOA (no observable abnormalities), (ii) congestion (tail), (iii) edema (face), (iv) edema (forelimb), and (v) edema (hind limb). Adverse effects were measured at 0 hour, 0.5 hour, 1 hour, 2 hours, 4 hours, 6 hours, 1 day, 3 days, 5 days, 8 days, 11 days, and 14 days post miR-485 inhibitor administration.

[0061] FIGs. 8A and 8B show that the administration of a miR-485 inhibitor has no observable pathological abnormalities in male and female rats, respectively. As shown, male

and female rats received one of the following doses of the miR-485 inhibitor: (i) 0 mg/kg (G1), (ii) 3.75 mg/kg (G2), (iii) 7.5 mg/kg (G3), and (iv) 15 mg/kg (G4).

[0062] FIGs. 9A, 9B, 9C, 9D, 9E, 9F, 9G, 9H, and 9I show the therapeutic effects of miR-485 inhibitor after intravenous administration in an ALS mouse model. FIG. 9A provides a schematic of the experimental design. FIG. 9B provides a comparison of disease onset in mice treated with the miR-485 inhibitor compared to the control animals. FIG. 9C provides a comparison of rotarod latency (time it took the animals to fall off the Rotarod-treadmill) for ALS mice treated with PBS ("1") or the miR-485 inhibitor ("2") at different time points (*i.e.*, 107, 114, 119, 121 and 123 days post-birth). FIG. 9D provides a comparison of the latency to when the animals fall from the wired cage for ALS mice treated with PBS ("1") or miR-485 inhibitor ("2") at different time points (*i.e.*, 107, 114, 119, 121 and 123 days post-birth). FIGs. 9E and 9F provide comparison of the number of footslips (FIG. 9E) and the time it took to cross the length of the beam (FIG. 9F) for ALS mouse treated with PBS ("1") or miR-485 inhibitor ("2"). The foot slip data was measured at 110 days post-birth. The beam cross time was measured at five different time points (*i.e.*, 107 114, 119, 121 and 123 days post-birth). FIG. 9G shows the average body weight as a function of time of ALS mice treated with either the miR-485 inhibitor (square) or PBS control (circle). FIG. 9H provides a comparison of body weight loss as a percentage of the peak body weight in the animals from the different treatment groups. FIG. 9I provides a survival curve for ALS animals treated with the miR-485 inhibitor (square) or PBS control (circle).

[0063] FIGs. 10A, 10B, 10C, and 10D show the effect of the miR-485 inhibitor on NSC-34 cells transfected with either the wild-type SOD1 or SOD1 comprising the G93A mutation (SOD1G93A) constructs. FIG. 10A provides Western blot analysis showing the effect of the miR-485 inhibitor on SOD1 aggregation. FIG. 10B provides immunofluorescence analysis of the effect on SOD1 aggregation. The first three columns (from left to right) show the results for NSC-34 cells transfected with the wild-type SOD1 and treated with (i) PBS control (top row), (ii) 50 nM of miR-485 inhibitor (middle row), or (iii) 100 nM of miR-485 inhibitor (bottom row). The last three columns (from left to right) show the results for NSC-34 cells transfected with SOD1G93A construct and treated with (i) PBS control (top row), (ii) 50 nM of miR-485 inhibitor (middle row), or (iii) 100 nM of miR-485 inhibitor (bottom row). The 1st and 4th columns show GFP expression alone. The 2nd and 4th columns show the expression of LC3B alone. The 3rd and 6th columns show an overlay of GFP and LC3B expression. The white

arrows indicate SOD1G93A aggregation in the NSC-34 cells transfected with SOD1G93A and treated with the miR-485 inhibitor. FIG. 10C provides Western blot analysis of the effect of miR-485 inhibitor on SIRT1 and PGC-1α protein expression. FIG. 10D provides Western blot analysis of the effect on cleaved caspase 3 protein expression.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0064] The present disclosure is directed to the use of a miR-485 inhibitor, comprising a nucleotide sequence encoding a nucleotide molecule that comprises at least one miR-485 binding site, wherein the nucleotide molecule does not encode a protein. In some aspects, the miRNA binding site or sites can bind to endogenous miR-485, which inhibits and/or reduces the expression level of an endogenous SIRT1 protein and/or a SIRT1 gene. In some aspects, the binding of endogenous miR-485 to the miRNA binding site or sites can inhibit and/or reduce the expression level of an endogenous CD36 protein and/or a CD36 gene. Similarly, in some aspects, the binding of endogenous miR-485 to the miRNA binding site or sites can inhibit and/or reduce the expression level of an endogenous PGC-1α. In some aspects, the binding of endogenous miR-485 to the miRNA binding site or sites can inhibit and/or reduce the expression level of an endogenous NRG1 protein and/or a NRG1 gene. In some aspects, the binding of endogenous miR-485 to the miRNA binding site or sites can inhibit and/or reduce the expression level of an endogenous STMN2 protein and/or a STMN2 gene. In some aspects, the binding of endogenous miR-485 to the miRNA binding site or sites can inhibit and/or reduce the expression level of an endogenous NRXN1 protein and/or a NRXN1 gene. Accordingly, in some aspects, the present disclosure is directed to a method of increasing a level of a SIRT1 protein and/or SIRT1 gene in a subject in need thereof comprising administering an miR-485 inhibitor to the subject. In further aspects, increasing the level of a SIRT1 protein and/or SIRT1 gene in a subject can be useful in treating a disease or condition associated with reduced levels of a SIRT1 protein and/or a SIRT1 gene. In some aspects, the present disclosure is directed to a method of increasing a level of a CD36 protein and/or CD36 gene in a subject in need thereof comprising administering an miR-485 inhibitor to the subject. In further aspects, increasing the level of a CD36 protein and/or CD36 gene in a subject can be useful in treating a disease or condition associated with reduced levels of a CD36 protein and/or a CD36 gene. In some aspects, the present disclosure is directed to a method of increasing a level of a PGC-1α protein and/or PGC-1α gene in a subject in need thereof comprising

administering an miR-485 inhibitor to the subject. In further aspects, increasing the level of a PGC-1α protein and/or PGC-1α gene in a subject can be useful in treating a disease or condition associated with reduced levels of a PGC-1α protein and/or a PGC-1α gene. In some aspects, the present disclosure is directed to a method of increasing a level of a NRG1 protein and/or NRG1 gene in a subject in need thereof comprising administering an miR-485 inhibitor to the subject. In further aspects, increasing the level of a NRG1 protein and/or NRG1 gene in a subject can be useful in treating a disease or condition associated with reduced levels of a NRG1 protein and/or a NRG1 gene. In some aspects, the present disclosure is directed to a method of increasing a level of a STMN2 protein and/or STMN2 gene in a subject in need thereof comprising administering an miR-485 inhibitor to the subject. In further aspects, increasing the level of a STMN2 protein and/or STMN2 gene in a subject can be useful in treating a disease or condition associated with reduced levels of a STMN2 protein and/or a STMN2 gene. In some aspects, the present disclosure is directed to a method of increasing a level of a NRXN1 protein and/or NRXN1 gene in a subject in need thereof comprising administering an miR-485 inhibitor to the subject. In further aspects, increasing the level of a NRXN1 protein and/or NRXN1 gene in a subject can be useful in treating a disease or condition associated with reduced levels of a NRXN1 protein and/or a NRXN1 gene. As disclosed herein, a disease or condition that can be treated with the present disclosure is amyotrophic lateral sclerosis (ALS).

[0065] Before the present disclosure is described in greater detail, it is to be understood that this disclosure is not limited to the particular compositions or process steps described, as such can, of course, vary. As will be apparent to those of skill in the art upon reading this disclosure, each of the individual aspects described and illustrated herein has discrete components and features which can be readily separated from or combined with the features of any of the other several aspects without departing from the scope or spirit of the present disclosure. Any recited method can be carried out in the order of events recited or in any other order which is logically possible.

[0066] The headings provided herein are not limitations of the various aspects of the disclosure, which can be defined by reference to the specification as a whole. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only, and is not intended to be limiting, since the scope of the present disclosure will be limited only by the appended claims.

I. Terms

[0067] In order that the present disclosure can be more readily understood, certain terms are first defined. As used in this application, except as otherwise expressly provided herein, each of the following terms shall have the meaning set forth below. Additional definitions are set forth throughout the application.

[0068] It is to be noted that the term "a" or "an" entity refers to one or more of that entity; for example, "a nucleotide sequence," is understood to represent one or more nucleotide sequences. As such, the terms "a" (or "an"), "one or more," and "at least one" can be used interchangeably herein. It is further noted that the claims can be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely," "only" and the like in connection with the recitation of claim elements, or use of a negative limitation.

[0069] Furthermore, "and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0070] It is understood that wherever aspects are described herein with the language "comprising," otherwise analogous aspects described in terms of "consisting of" and/or "consisting essentially of" are also provided.

[0071] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary Of Biochemistry And Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

[0072] Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range. Where a range of values is recited, it is to be understood that each intervening integer value, and each fraction thereof, between the recited upper and lower limits of that range is also specifically

disclosed, along with each subrange between such values. The upper and lower limits of any range can independently be included in or excluded from the range, and each range where either, neither or both limits are included is also encompassed within the disclosure. Thus, ranges recited herein are understood to be shorthand for all of the values within the range, inclusive of the recited endpoints. For example, a range of 1 to 10 is understood to include any number, combination of numbers, or sub-range from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

[0073] Where a value is explicitly recited, it is to be understood that values which are about the same quantity or amount as the recited value are also within the scope of the disclosure. Where a combination is disclosed, each subcombination of the elements of that combination is also specifically disclosed and is within the scope of the disclosure. Conversely, where different elements or groups of elements are individually disclosed, combinations thereof are also disclosed. Where any element of a disclosure is disclosed as having a plurality of alternatives, examples of that disclosure in which each alternative is excluded singly or in any combination with the other alternatives are also hereby disclosed; more than one element of a disclosure can have such exclusions, and all combinations of elements having such exclusions are hereby disclosed.

[0074] Nucleotides are referred to by their commonly accepted single-letter codes. Unless otherwise indicated, nucleotide sequences are written left to right in 5' to 3' orientation. Nucleotides are referred to herein by their commonly known one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Accordingly, 'a' represents adenine, 'c' represents cytosine, 'g' represents guanine, 't' represents thymine, and 'u' represents uracil.

[0075] Amino acid sequences are written left to right in amino to carboxy orientation. Amino acids are referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission.

[0076] The term "about" is used herein to mean approximately, roughly, around, or in the regions of. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" can modify a numerical value above and below the stated value by a variance of, *e.g.*, 10 percent, up or down (higher or lower).

[0077] As used herein, the term "adeno-associated virus" (AAV), includes but is not limited to, AAV type 1, AAV type 2, AAV type 3 (including types 3A and 3B), AAV type 4, AAV type 5, AAV type 6, AAV type 7, AAV type 8, AAV type 9, AAV type 10, AAV type 11, AAV type 12, AAV type 13, AAVrh.74, snake AAV, avian AAV, bovine AAV, canine AAV, equine AAV, ovine AAV, goat AAV, shrimp AAV, those AAV serotypes and clades disclosed by Gao et al. (*J. Virol. 78*:6381 (2004)) and Moris et al. (*Virol. 33*:375 (2004)), and any other AAV now known or later discovered. *See, e.g.*, FIELDS et al. VIROLOGY, volume 2, chapter 69 (4th ed., Lippincott-Raven Publishers). In some aspects, an "AAV" includes a derivative of a known AAV. In some aspects, an "AAV" includes a modified or an artificial AAV.

[0078] The terms "administration," "administering," and grammatical variants thereof refer to introducing a composition, such as a miRNA inhibitor of the present disclosure, into a subject via a pharmaceutically acceptable route. The introduction of a composition, such as a micelle comprising a miRNA inhibitor of the present disclosure, into a subject is by any suitable route, including intratumorally, orally, pulmonarily, intranasally, parenterally (intravenously, intra-arterially, intramuscularly, intraperitoneally, or subcutaneously), rectally, intralymphatically, intrathecally, periocularly or topically. Administration includes self-administration and the administration by another. A suitable route of administration allows the composition or the agent to perform its intended function. For example, if a suitable route is intravenous, the composition is administered by introducing the composition or agent into a vein of the subject.

[0079] As used herein, the term "associated with" refers to a close relationship between two or more entities or properties. For instance, when used to describe a disease or condition that can be treated with the present disclosure (*e.g.*, disease or condition associated with an abnormal level of a SIRT1 protein and/or SIRT1 gene), the term "associated with" refers to an increased likelihood that a subject suffers from the disease or condition when the subject exhibits an abnormal expression of the protein and/or gene. In some aspects, the abnormal expression of the protein and/or gene causes the disease or condition. In some aspects, the abnormal expression does not necessarily cause but is correlated with the disease or condition. Non-limiting examples of suitable methods that can be used to determine whether a subject exhibits an abnormal expression of a protein and/or gene associated with a disease or condition are provided elsewherein the present disclosure.

[0080] As used herein, the term "approximately," as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain aspects, the term "approximately" refers to a range of values that fall within 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).

[0081] As used herein, the term "conserved" refers to nucleotides or amino acid residues of a polynucleotide sequence or polypeptide sequence, respectively, that are those that occur unaltered in the same position of two or more sequences being compared. Nucleotides or amino acids that are relatively conserved are those that are conserved amongst more related sequences than nucleotides or amino acids appearing elsewhere in the sequences.

[0082] In some aspects, two or more sequences are said to be "completely conserved" or "identical" if they are 100% identical to one another. In some aspects, two or more sequences are said to be "highly conserved" if they are at least 70% identical, at least 80% identical, at least 90% identical, or at least 95% identical to one another. In some aspects, two or more sequences are said to be "highly conserved" if they are about 70% identical, about 80% identical, about 90% identical, about 95%, about 98%, or about 99% identical to one another. In some aspects, two or more sequences are said to be "conserved" if they are at least 30% identical, at least 40% identical, at least 50% identical, at least 60% identical, at least 70% identical, at least 80% identical, at least 90% identical, or at least 95% identical to one another. In some aspects, two or more sequences are said to be "conserved" if they are about 30% identical, about 40% identical, about 50% identical, about 60% identical, about 70% identical, about 80% identical, about 90% identical, about 95% identical, about 98% identical, or about 99% identical to one another. Conservation of sequence can apply to the entire length of a polynucleotide or polypeptide or can apply to a portion, region or feature thereof.

[0083] The term "derived from," as used herein, refers to a component that is isolated from or made using a specified molecule or organism, or information (*e.g.*, amino acid or nucleic acid sequence) from the specified molecule or organism. For example, a nucleic acid sequence that is derived from a second nucleic acid sequence can include a nucleotide sequence that is identical or substantially similar to the nucleotide sequence of the second nucleic acid sequence. In the case of nucleotides or polypeptides, the derived species can be obtained by, for example, naturally occurring mutagenesis, artificial directed mutagenesis or artificial

random mutagenesis. The mutagenesis used to derive nucleotides or polypeptides can be intentionally directed or intentionally random, or a mixture of each. The mutagenesis of a nucleotide or polypeptide to create a different nucleotide or polypeptide derived from the first can be a random event (*e.g.*, caused by polymerase infidelity) and the identification of the derived nucleotide or polypeptide can be made by appropriate screening methods, *e.g.*, as discussed herein. In some aspects, a nucleotide or amino acid sequence that is derived from a second nucleotide or amino acid sequence has a sequence identity of at least about 50%, at least about 51%, at least about 52%, at least about 53%, at least about 54%, at least about 55%, at least about 56%, at least about 57%, at least about 58%, at least about 59%, at least about 60%, at least about 61%, at least about 62%, at least about 63%, at least about 64%, at least about 65%, at least about 66%, at least about 67%, at least about 68%, at least about 69%, at least about 70%, at least about 71%, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 76%, at least about 77%, at least about 78%, at least about 79%, at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% to the second nucleotide or amino acid sequence, respectively, wherein the first nucleotide or amino acid sequence retains the biological activity of the second nucleotide or amino acid sequence.

[0084] As used herein, a "coding region" or "coding sequence" is a portion of polynucleotide which consists of codons translatable into amino acids. Although a "stop codon" (TAG, TGA, or TAA) is typically not translated into an amino acid, it can be considered to be part of a coding region, but any flanking sequences, for example promoters, ribosome binding sites, transcriptional terminators, introns, and the like, are not part of a coding region. The boundaries of a coding region are typically determined by a start codon at the 5' terminus, encoding the amino terminus of the resultant polypeptide, and a translation stop codon at the 3' terminus, encoding the carboxyl terminus of the resulting polypeptide.

[0085] The terms "complementary" and "complementarity" refer to two or more oligomers (*i.e.,* each comprising a nucleobase sequence), or between an oligomer and a target gene, that are related with one another by Watson-Crick base-pairing rules. For example, the nucleobase sequence "T-G-A (5'→3')," is complementary to the nucleobase sequence "A-C-T (3'→ 5')."

Complementarity can be "partial," in which less than all of the nucleobases of a given nucleobase sequence are matched to the other nucleobase sequence according to base pairing rules. For example, in some aspects, complementarity between a given nucleobase sequence and the other nucleobase sequence can be about 70%, about 75%, about 80%, about 85%, about 90%, or about 95%. Accordingly, in certain aspects, the term "complementary" refers to at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% match or complementarity to a target nucleic acid sequence (*e.g.*, miR-485 nucleic acid sequence). Or, there can be "complete" or "perfect" (100%) complementarity between a given nucleobase sequence and the other nucleobase sequence to continue the example. In some aspects, the degree of complementarity between nucleobase sequences has significant effects on the efficiency and strength of hybridization between the sequences.

[0086] The term "downstream" refers to a nucleotide sequence that is located 3' to a reference nucleotide sequence. In certain aspects, downstream nucleotide sequences relate to sequences that follow the starting point of transcription. For example, the translation initiation codon of a gene is located downstream of the start site of transcription.

[0087] The terms "excipient" and "carrier" are used interchangeably and refer to an inert substance added to a pharmaceutical composition to further facilitate administration of a compound, e.g., a miRNA inhibitor of the present disclosure.

[0088] The term "expression," as used herein, refers to a process by which a polynucleotide produces a gene product, *e.g.*, RNA or a polypeptide. It includes without limitation transcription of the polynucleotide into micro RNA binding site, small hairpin RNA (shRNA), small interfering RNA (siRNA), or any other RNA product. It includes, without limitation, transcription of the polynucleotide into messenger RNA (mRNA), and the translation of mRNA into a polypeptide. Expression produces a "gene product." As used herein, a gene product can be, *e.g.*, a nucleic acid, such as an RNA produced by transcription of a gene. As used herein, a gene product can be either a nucleic acid, RNA or miRNA produced by the transcription of a gene, or a polypeptide which is translated from a transcript. Gene products described herein further include nucleic acids with post transcriptional modifications, *e.g.*, polyadenylation or splicing, or polypeptides with post translational modifications, *e.g.*,

phosphorylation, methylation, glycosylation, the addition of lipids, association with other protein subunits, or proteolytic cleavage.

[0089] As used herein, the term "homology" refers to the overall relatedness between polymeric molecules, *e.g.* between nucleic acid molecules. Generally, the term "homology" implies an evolutionary relationship between two molecules. Thus, two molecules that are homologous will have a common evolutionary ancestor. In the context of the present disclosure, the term homology encompasses both to identity and similarity.

[0090] In some aspects, polymeric molecules are considered to be "homologous" to one another if at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% of the monomers in the molecule are identical (exactly the same monomer) or are similar (conservative substitutions). The term "homologous" necessarily refers to a comparison between at least two sequences (*e.g.*, polynucleotide sequences).

[0091] In the context of the present disclosure, substitutions (even when they are referred to as amino acid substitution) are conducted at the nucleic acid level, *i.e.*, substituting an amino acid residue with an alternative amino acid residue is conducted by substituting the codon encoding the first amino acid with a codon encoding the second amino acid.

[0092] As used herein, the term "identity" refers to the overall monomer conservation between polymeric molecules, *e.g.*, between polynucleotide molecules. The term "identical" without any additional qualifiers, *e.g.*, polynucleotide A is identical to polynucleotide B, implies the polynucleotide sequences are 100% identical (100% sequence identity). Describing two sequences as, *e.g.*, "70% identical," is equivalent to describing them as having, *e.g.*, "70% sequence identity."

[0093] Calculation of the percent identity of two polypeptide or polynucleotide sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second polypeptide or polynucleotide sequences for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In certain aspects, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or 100% of the length of the reference sequence. The

amino acids at corresponding amino acid positions, or bases in the case of polynucleotides, are then compared.

[0094] When a position in the first sequence is occupied by the same amino acid or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm.

[0095] Suitable software programs that can be used to align different sequences (*e.g.*, polynucleotide sequences) are available from various sources. One suitable program to determine percent sequence identity is bl2seq, part of the BLAST suite of program available from the U.S. government's National Center for Biotechnology Information BLAST web site (blast.ncbi.nlm.nih.gov). Bl2seq performs a comparison between two sequences using either the BLASTN or BLASTP algorithm. BLASTN is used to compare nucleic acid sequences, while BLASTP is used to compare amino acid sequences. Other suitable programs are, *e.g.*, Needle, Stretcher, Water, or Matcher, part of the EMBOSS suite of bioinformatics programs and also available from the European Bioinformatics Institute (EBI) at worldwideweb.ebi.ac.uk/Tools/psa.

[0096] Sequence alignments can be conducted using methods known in the art such as MAFFT, Clustal (ClustalW, Clustal X or Clustal Omega), MUSCLE, etc.

[0097] Different regions within a single polynucleotide or polypeptide target sequence that aligns with a polynucleotide or polypeptide reference sequence can each have their own percent sequence identity. It is noted that the percent sequence identity value is rounded to the nearest tenth. For example, 80.11, 80.12, 80.13, and 80.14 are rounded down to 80.1, while 80.15, 80.16, 80.17, 80.18, and 80.19 are rounded up to 80.2. It also is noted that the length value will always be an integer.

[0098] In certain aspects, the percentage identity (%ID) or of a first amino acid sequence (or nucleic acid sequence) to a second amino acid sequence (or nucleic acid sequence) is calculated as %ID = 100 x (Y/Z), where Y is the number of amino acid residues (or nucleobases) scored as identical matches in the alignment of the first and second sequences (as aligned by visual inspection or a particular sequence alignment program) and Z is the total

number of residues in the second sequence. If the length of a first sequence is longer than the second sequence, the percent identity of the first sequence to the second sequence will be higher than the percent identity of the second sequence to the first sequence.

[0099] One skilled in the art will appreciate that the generation of a sequence alignment for the calculation of a percent sequence identity is not limited to binary sequence-sequence comparisons exclusively driven by primary sequence data. It will also be appreciated that sequence alignments can be generated by integrating sequence data with data from heterogeneous sources such as structural data *(e.g.,* crystallographic protein structures), functional data *(e.g.,* location of mutations), or phylogenetic data. A suitable program that integrates heterogeneous data to generate a multiple sequence alignment is T-Coffee, available at worldwideweb.tcoffee.org, and alternatively available, *e.g.,* from the EBI. It will also be appreciated that the final alignment used to calculate percent sequence identity can be curated either automatically or manually.

[0100] As used herein, the terms "isolated," "purified," "extracted," and grammatical variants thereof are used interchangeably and refer to the state of a preparation of desired composition of the present disclosure, e.g., a miRNA inhibitor of the present disclosure, that has undergone one or more processes of purification. In some aspects, isolating or purifying as used herein is the process of removing, partially removing (*e.g.,* a fraction) of a composition of the present disclosure, e.g., a miRNA inhibitor of the present disclosure from a sample containing contaminants.

[0101] In some aspects, an isolated composition has no detectable undesired activity or, alternatively, the level or amount of the undesired activity is at or below an acceptable level or amount. In other aspects, an isolated composition has an amount and/or concentration of desired composition of the present disclosure, at or above an acceptable amount and/or concentration and/or activity. In other aspects, the isolated composition is enriched as compared to the starting material from which the composition is obtained. This enrichment can be by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, at least about 99.9%, at least about 99.99%, at least about 99.999%, at least about 99.9999%, or greater than 99.9999% as compared to the starting material.

[0102] In some aspects, isolated preparations are substantially free of residual biological products. In some aspects, the isolated preparations are 100% free, at least about 99% free, at least about 98% free, at least about 97% free, at least about 96% free, at least about 95% free, at least about 94% free, at least about 93% free, at least about 92% free, at least about 91% free, or at least about 90% free of any contaminating biological matter. Residual biological products can include abiotic materials (including chemicals) or unwanted nucleic acids, proteins, lipids, or metabolites.

[0103] The term "linked" as used herein refers to a first amino acid sequence or polynucleotide sequence covalently or non-covalently joined to a second amino acid sequence or polynucleotide sequence, respectively. The first amino acid or polynucleotide sequence can be directly joined or juxtaposed to the second amino acid or polynucleotide sequence or alternatively an intervening sequence can covalently join the first sequence to the second sequence. The term "linked" means not only a fusion of a first polynucleotide sequence to a second polynucleotide sequence at the 5'-end or the 3'-end, but also includes insertion of the whole first polynucleotide sequence (or the second polynucleotide sequence) into any two nucleotides in the second polynucleotide sequence (or the first polynucleotide sequence, respectively). The first polynucleotide sequence can be linked to a second polynucleotide sequence by a phosphodiester bond or a linker. The linker can be, *e.g.,* a polynucleotide.

[0104] A "miRNA inhibitor," as used herein, refers to a compound that can decrease, alter, and/or modulate miRNA expression, function, and/or activity. The miRNA inhibitor can be a polynucleotide sequence that is at least partially complementary to the target miRNA nucleic acid sequence, such that the miRNA inhibitor hybridizes to the target miRNA sequence. For instance, in some aspects, a miR-485 inhibitor of the present disclosure comprises a nucleotide sequence encoding a nucleotide molecule that is at least partially complementary to the target miR-485 nucleic acid sequence, such that the miR-485 inhibitor hybridizes to the miR-485 sequence. In further aspects, the hybridization of the miR-485 to the miR-485 sequence decreases, alters, and/or modulates the expression, function, and/or activity of miR-485 (*e.g.*, hybridization results in an increase in the expression of SIRT1 protein and/or SIRT1 gene).

[0105] The terms "miRNA," "miR," and "microRNA" are used interchangeably and refer to a microRNA molecule found in eukaryotes that is involved in RNA-based gene regulation. The term will be used to refer to the single-stranded RNA molecule processed from a precursor. In some aspects, the term "antisense oligomers" can also be used to describe the

microRNA molecules of the present disclosure. Names of miRNAs and their sequences related to the present disclosure are provided herein. MicroRNAs recognize and bind to target mRNAs through imperfect base pairing leading to destabilization or translational inhibition of the target mRNA and thereby downregulate target gene expression. Conversely, targeting miRNAs via molecules comprising a miRNA binding site (generally a molecule comprising a sequence complementary to the seed region of the miRNA) can reduce or inhibit the miRNA-induced translational inhibition leading to an upregulation of the target gene.

[0106] The terms "mismatch" or "mismatches" refer to one or more nucleobases (whether contiguous or separate) in an oligomer nucleobase sequence (*e.g.*, miR-485 inhibitor) that are not matched to a target nucleic acid sequence (*e.g.*, miR-485) according to base pairing rules. While perfect complementarity is often desired, in some aspects, one or more (*e.g.*, 6, 5, 4, 3, 2, or 1 mismatches) can occur with respect to the target nucleic acid sequence. Variations at any location within the oligomer are included. In certain aspects, antisense oligomers of the disclosure (*e.g.*, miR-485 inhibitor) include variations in nucleobase sequence near the termini, variations in the interior, and if present are typically within about 6, 5, 4, 3, 2, or 1 subunit of the 5' and/or 3' terminus. In some aspects, one, two, or three nucleobases can be removed and still provide on-target binding.

[0107] As used herein, the terms "modulate," "modify," and grammatical variants thereof, generally refer when applied to a specific concentration, level, expression, function or behavior, to the ability to alter, by increasing or decreasing, *e.g.*, directly or indirectly promoting/stimulating/up-regulating or interfering with/inhibiting/down-regulating the specific concentration, level, expression, function or behavior, such as, *e.g.*, to act as an antagonist or agonist. In some instances, a modulator can increase and/or decrease a certain concentration, level, activity or function relative to a control, or relative to the average level of activity that would generally be expected or relative to a control level of activity. In some aspects, a miRNA inhibitor disclosed herein, *e.g.*, a miR-485 inhibitor, can modulate (e.g., decrease, alter, or abolish) miR-485 expression, function, and/or activity, and thereby, modulate SIRT1 protein or gene expression and/or activity.

[0108] "Nucleic acid," "nucleic acid molecule," "nucleotide sequence," "polynucleotide," and grammatical variants thereof are used interchangeably and refer to the phosphate ester polymeric form of ribonucleosides (adenosine, guanosine, uridine or cytidine; "RNA molecules") or deoxyribonucleosides (deoxyadenosine, deoxyguanosine, deoxythymidine, or

deoxycytidine; "DNA molecules"), or any phosphoester analogs thereof, such as phosphorothioates and thioesters, in either single stranded form, or a double-stranded helix. Single stranded nucleic acid sequences refer to single-stranded DNA (ssDNA) or single-stranded RNA (ssRNA). Double stranded DNA-DNA, DNA-RNA and RNA-RNA helices are possible. The term nucleic acid molecule, and in particular DNA or RNA molecule, refers only to the primary and secondary structure of the molecule, and does not limit it to any particular tertiary forms. Thus, this term includes double-stranded DNA found, *inter alia*, in linear or circular DNA molecules (*e.g.*, restriction fragments), plasmids, supercoiled DNA and chromosomes. In discussing the structure of particular double-stranded DNA molecules, sequences can be described herein according to the normal convention of giving only the sequence in the 5' to 3' direction along the non-transcribed strand of DNA (*i.e.*, the strand having a sequence homologous to the mRNA). A "recombinant DNA molecule" is a DNA molecule that has undergone a molecular biological manipulation. DNA includes, but is not limited to, cDNA, genomic DNA, plasmid DNA, synthetic DNA, and semi-synthetic DNA. A "nucleic acid composition" of the disclosure comprises one or more nucleic acids as described herein.

[0109] The terms "pharmaceutically acceptable carrier," "pharmaceutically acceptable excipient," and grammatical variations thereof, encompass any of the agents approved by a regulatory agency of the U.S. Federal government or listed in the U.S. Pharmacopeia for use in animals, including humans, as well as any carrier or diluent that does not cause the production of undesirable physiological effects to a degree that prohibits administration of the composition to a subject and does not abrogate the biological activity and properties of the administered compound. Included are excipients and carriers that are useful in preparing a pharmaceutical composition and are generally safe, non-toxic, and desirable.

[0110] As used herein, the term "pharmaceutical composition" refers to one or more of the compounds described herein, such as, *e.g.*, a miRNA inhibitor of the present disclosure, mixed or intermingled with, or suspended in one or more other chemical components, such as pharmaceutically acceptable carriers and excipients. One purpose of a pharmaceutical composition is to facilitate administration of preparations comprising a miRNA inhibitor of the present disclosure to a subject.

[0111] The term "polynucleotide," as used herein, refers to polymers of nucleotides of any length, including ribonucleotides, deoxyribonucleotides, analogs thereof, or mixtures thereof.

[0112] In some aspects, the term refers to the primary structure of the molecule. Thus, the term includes triple-, double- and single-stranded deoxyribonucleic acid ("DNA"), as well as triple-, double- and single-stranded ribonucleic acid ("RNA"). It also includes modified, for example by alkylation, and/or by capping, and unmodified forms of the polynucleotide.

[0113] In some aspects, the term "polynucleotide" includes polydeoxyribonucleotides (containing 2-deoxy-D-ribose), polyribonucleotides (containing D-ribose), including tRNA, rRNA, shRNA, siRNA, miRNA and mRNA, whether spliced or unspliced, any other type of polynucleotide which is an N- or C-glycoside of a purine or pyrimidine base, and other polymers containing normucleotidic backbones, for example, polyamide (*e.g.*, peptide nucleic acids "PNAs") and polymorpholino polymers, and other synthetic sequence-specific nucleic acid polymers providing that the polymers contain nucleobases in a configuration which allows for base pairing and base stacking, such as is found in DNA and RNA.

[0114] In some aspects of the present disclosure, a polynucleotide can be, *e.g.*, an oligonucleotide, such as an antisense oligonucleotide. In some aspects, the oligonucleotide is an RNA. In some aspects, the RNA is a synthetic RNA. In some aspects, the synthetic RNA comprises at least one unnatural nucleobase. In some aspects, all nucleobases of a certain class have been replaced with unnatural nucleobases (*e.g.*, all uridines in a polynucleotide disclosed herein can be replaced with an unnatural nucleobase, *e.g.*, 5-methoxyuridine).

[0115] The terms "polypeptide," "peptide," and "protein" are used interchangeably herein to refer to polymers of amino acids of any length, *e.g.*, that are encoded by the SIRT1 gene. The polymer can comprise modified amino acids. The terms also encompass an amino acid polymer that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids such as homocysteine, ornithine, p-acetylphenylalanine, D-amino acids, and creatine), as well as other modifications known in the art. The term "polypeptide," as used herein, refers to proteins, polypeptides, and peptides of any size, structure, or function.

[0116] Polypeptides include gene products, naturally occurring polypeptides, synthetic polypeptides, homologs, orthologs, paralogs, fragments and other equivalents, variants, and analogs of the foregoing.

[0117] A polypeptide can be a single polypeptide or can be a multi-molecular complex such as a dimer, trimer or tetramer. They can also comprise single chain or multichain polypeptides. Most commonly disulfide linkages are found in multichain polypeptides. The term polypeptide can also apply to amino acid polymers in which one or more amino acid residues are an artificial chemical analogue of a corresponding naturally occurring amino acid. In some aspects, a "peptide" can be less than or equal to about 50 amino acids long, *e.g.*, about 5, about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, or about 50 amino acids long.

[0118] The terms "prevent," "preventing," and variants thereof as used herein, refer partially or completely delaying onset of an disease, disorder and/or condition; partially or completely delaying onset of one or more symptoms, features, or clinical manifestations of a particular disease, disorder, and/or condition; partially or completely delaying onset of one or more symptoms, features, or manifestations of a particular disease, disorder, and/or condition; partially or completely delaying progression from a particular disease, disorder and/or condition; and/or decreasing the risk of developing pathology associated with the disease, disorder, and/or condition. In some aspects, preventing an outcome is achieved through prophylactic treatment.

[0119] As used herein, the terms "promoter" and "promoter sequence" are interchangeable and refer to a DNA sequence capable of controlling the expression of a coding sequence or functional RNA. In general, a coding sequence is located 3' to a promoter sequence. Promoters can be derived in their entirety from a native gene, or be composed of different elements derived from different promoters found in nature, or even comprise synthetic DNA segments. It is understood by those skilled in the art that different promoters can direct the expression of a gene in different tissues or cell types, or at different stages of development, or in response to different environmental or physiological conditions. Promoters that cause a gene to be expressed in most cell types at most times are commonly referred to as "constitutive promoters." Promoters that cause a gene to be expressed in a specific cell type are commonly referred to as "cell-specific promoters" or "tissue-specific promoters." Promoters that cause a gene to be expressed at a specific stage of development or cell differentiation are commonly referred to as "developmentally-specific promoters" or "cell differentiation-specific promoters." Promoters that are induced and cause a gene to be expressed following exposure or treatment of the cell with an agent, biological molecule, chemical, ligand, light, or the like

that induces the promoter are commonly referred to as "inducible promoters" or "regulatable promoters." It is further recognized that since in most cases the exact boundaries of regulatory sequences have not been completely defined, DNA fragments of different lengths can have identical promoter activity.

[0120] The promoter sequence is typically bounded at its 3' terminus by the transcription initiation site and extends upstream (5' direction) to include the minimum number of bases or elements necessary to initiate transcription at levels detectable above background. Within the promoter sequence will be found a transcription initiation site (conveniently defined for example, by mapping with nuclease S1), as well as protein binding domains (consensus sequences) responsible for the binding of RNA polymerase. In some aspects, a promoter that can be used with the present disclosure includes a tissue specific promoter.

[0121] As used herein, "prophylactic" refers to a therapeutic or course of action used to prevent the onset of a disease or condition, or to prevent or delay a symptom associated with a disease or condition.

[0122] As used herein, a "prophylaxis" refers to a measure taken to maintain health and prevent the onset of a disease or condition, or to prevent or delay a symptom associated with a disease or condition.

[0123] As used herein, the term "gene regulatory region" or "regulatory region" refers to nucleotide sequences located upstream (5' non-coding sequences), within, or downstream (3' non-coding sequences) of a coding region, and which influence the transcription, RNA processing, stability, or translation of the associated coding region. Regulatory regions can include promoters, translation leader sequences, introns, polyadenylation recognition sequences, RNA processing sites, effector binding sites, or stem-loop structures. If a coding region is intended for expression in a eukaryotic cell, a polyadenylation signal and transcription termination sequence will usually be located 3' to the coding sequence.

[0124] In some aspects, a miR-485 inhibitor disclosed herein (*e.g.*, a polynucleotide encoding a RNA comprising one or more miR-485 binding site) can include a promoter and/or other expression (*e.g.*, transcription) control elements operably associated with one or more coding regions. In an operable association a coding region for a gene product is associated with one or more regulatory regions in such a way as to place expression of the gene product under the influence or control of the regulatory region(s). For example, a coding region and a promoter are "operably associated" if induction of promoter function results in the

transcription of mRNA encoding the gene product encoded by the coding region, and if the nature of the linkage between the promoter and the coding region does not interfere with the ability of the promoter to direct the expression of the gene product or interfere with the ability of the DNA template to be transcribed. Other expression control elements, besides a promoter, for example enhancers, operators, repressors, and transcription termination signals, can also be operably associated with a coding region to direct gene product expression.

[0125] As used herein, the term "similarity" refers to the overall relatedness between polymeric molecules, *e.g.* between polynucleotide molecules (*e.g.* miRNA molecules). Calculation of percent similarity of polymeric molecules to one another can be performed in the same manner as a calculation of percent identity, except that calculation of percent similarity takes into account conservative substitutions as is understood in the art. It is understood that percentage of similarity is contingent on the comparison scale used, *i.e.*, whether the nucleic acids are compared, *e.g.*, according to their evolutionary proximity, charge, volume, flexibility, polarity, hydrophobicity, aromaticity, isoelectric point, antigenicity, or combinations thereof.

[0126] The terms "subject," "patient," "individual," and "host," and variants thereof are used interchangeably herein and refer to any mammalian subject, including without limitation, humans, domestic animals (*e.g.*, dogs, cats and the like), farm animals (*e.g.*, cows, sheep, pigs, horses and the like), and laboratory animals (*e.g.*, monkey, rats, mice, rabbits, guinea pigs and the like) for whom diagnosis, treatment, or therapy is desired, particularly humans. The methods described herein are applicable to both human therapy and veterinary applications.

[0127] As used herein, the phrase "subject in need thereof" includes subjects, such as mammalian subjects, that would benefit from administration of a miRNA inhibitor of the disclosure (*e.g.*, miR-485 inhibitor), *e.g.*, to increase the expression level of SIRT1 protein and/or SIRT1 gene.

[0128] As used herein, the term "therapeutically effective amount" is the amount of reagent or pharmaceutical compound comprising a miRNA inhibitor of the present disclosure that is sufficient to a produce a desired therapeutic effect, pharmacologic and/or physiologic effect on a subject in need thereof. A therapeutically effective amount can be a "prophylactically effective amount" as prophylaxis can be considered therapy.

[0129] The terms "treat," "treatment," or "treating," as used herein refers to, *e.g.*, the reduction in severity of a disease or condition; the reduction in the duration of a disease course;

the amelioration or elimination of one or more symptoms associated with a disease or condition (e.g., diabetes); the provision of beneficial effects to a subject with a disease or condition, without necessarily curing the disease or condition. The term also includes prophylaxis or prevention of a disease or condition or its symptoms thereof.

[0130] The term "upstream" refers to a nucleotide sequence that is located 5' to a reference nucleotide sequence.

[0131] A "vector" refers to any vehicle for the cloning of and/or transfer of a nucleic acid into a host cell. A vector can be a replicon to which another nucleic acid segment can be attached so as to bring about the replication of the attached segment. A "replicon" refers to any genetic element (*e.g.*, plasmid, phage, cosmid, chromosome, virus) that functions as an autonomous unit of replication *in vivo*, *i.e.*, capable of replication under its own control. The term "vector" includes both viral and nonviral vehicles for introducing the nucleic acid into a cell *in vitro*, *ex vivo* or *in vivo*. A large number of vectors are known and used in the art including, for example, plasmids, modified eukaryotic viruses, or modified bacterial viruses. Insertion of a polynucleotide into a suitable vector can be accomplished by ligating the appropriate polynucleotide fragments into a chosen vector that has complementary cohesive termini.

[0132] Vectors can be engineered to encode selectable markers or reporters that provide for the selection or identification of cells that have incorporated the vector. Expression of selectable markers or reporters allows identification and/or selection of host cells that incorporate and express other coding regions contained on the vector. Examples of selectable marker genes known and used in the art include: genes providing resistance to ampicillin, streptomycin, gentamycin, kanamycin, hygromycin, bialaphos herbicide, sulfonamide, and the like; and genes that are used as phenotypic markers, *i.e.*, anthocyanin regulatory genes, isopentanyl transferase gene, and the like. Examples of reporters known and used in the art include: luciferase (Luc), green fluorescent protein (GFP), chloramphenicol acetyltransferase (CAT), β-galactosidase (LacZ), β-glucuronidase (Gus), and the like. Selectable markers can also be considered to be reporters.

II. Methods of Use

[0133] In some aspects, miR-485 inhibitors of the present disclosure can exert therapeutic effects (*e.g.*, in a subject suffering from a neurodegenerative disease, *e.g.*, ALS) by regulating the expression and/or activity of one or more genes. As described herein, in some aspects, miR-

485 inhibitors disclosed herein are capable of regulating the expression and/or activity of a gene selected from *SIRT1, CD36, PGC1, NRXN1, STMN2, NRG1,* or combinations thereof. Not to be bound by any one theory, through such regulation, the miR-485 inhibitors can affect many biological processes, including, but not limited to, protein homeostasis (*e.g.*, SIRT1), those associated with the mitochondria (*e.g.*, PGC1α), neuroinflammation (*e.g.*, CD36 and SIRT1), neurogenesis/synaptogenesis (*e.g.*, SIRT1, PGC1α, STMN2, NRG1, and NRXN1).

SIRT1 Regulation

[0134] In some aspects, the present disclosure provides a method of increasing an expression of a SIRT1 protein and/or a SIRT1 gene in a subject in need thereof, comprising administering to the subject a compound that inhibits miR-485 activity (*i.e.*, miR-485 inhibitor). In certain aspects, inhibiting miR-485 activity increases the expression of a SIRT1 protein and/or SIRT1 gene in the subject.

[0135] Sirtuin 1 (SIRT1), also known as NAD-dependent deacetylase sirtuin-1, is a protein that in humans is encoded by the *SIRT1* gene. The *SIRT1* gene is located on chromosome 10 in humans (nucleotides 67,884,656 to 67,918,390 of GenBank Accession Number NC_000010.11, plus strand orientation). Synonyms of the *SIRT1* gene, and the encoded protein thereof, are known and include "regulatory protein SIR2 homolog 1," "silent mating-type information regulation 2 homolog 1," "SIR2," "SIR2-Like Protein 1," "SIR2L1," "SIR2alpha," "Sirtuin Type 1," "hSIRT1," or "hSIR2."

[0136] There are at least two known isoforms of human SIRT1 protein, resulting from alternative splicing. SIRT1 isoform 1 (UniProt identifier: Q96EB6-1) consists of 747 amino acids and has been chosen as the canonical sequence (SEQ ID NO: 31). SIRT1 isoform 2 (also known as "delta-exon8) (UniProt identifier: Q96EB6-2) consists of 561 amino acids and differs from the canonical sequence as follows: 454-639: missing (SEQ ID NO: 32). Table 1 below provides the sequences for the two SIRT1 isoforms.

Table 1. SIRT1 Protein Isoforms

Isoform 1 (UniProt: Q96EB6-1) (SEQ ID NO: 31)	MADEAALALQPGGSPSAAGADREAASSPAGEPLRKRPRRDGPGLERSPGEPGGAAPEREV PAAARGCPGAAAAALWREAEAEAAAAGGEQEAQATAAAGEGDNGPGLQGPSREPPLADNL YDEDDDDEGEEEEEAAAAAIGYRDNLLFGDEIITNGFHSCESDEEDRASHASSSDWTPRP RIGPYTFVQQHLMIGTDPRTILKDLLPETIPPPELDDMTLWQIVINILSEPPKRKKRKDI NTIEDAVKLLQECKKIIVLTGAGVSVSCGIPDFRSRDGIYARLAVDFPDLPDPQAMFDIE YFRKDPRPFFKFAKEIYPGQFQPSLCHKFIALSDKEGKLLRNYTQNIDTLEQVAGIQRII QCHGSFATASCLICKYKVDCEAVRGDIFNQVVPRCPRCPADEPLAIMKPEIVFFGENLPE QFHRAMKYDKDEVDLLIVIGSSLKVRPVALIPSSIPHEVPQILINREPLPHLHFDVELLG DCDVIINELCHRLGGEYAKLCCNPVKLSEITEKPPRTQKELAYLSELPPTPLHVSEDSSS PERTSPPDSSVIVTLLDQAAKSNDDLDVSESKGCMEEKPQEVQTSRNVESIAEQMENPDL KNVGSSTGEKNERTSVAGTVRKCWPNRVAKEQISRRLDGNQYLFLPPNRYIFHGAEVYSD

	SEDDVLSSSSCGSNSDSGTCQSPSLEEPMEDESEIEEFYNGLEDEPDVPERAGGAGFGTD GDDQEAINEAISVKQEVTDMNYPSNKS
Isoform 2 (UniProt: Q96EB6-2) (SEQ ID NO: 32)	MADEAALALQPGGSPSAAGADREAASSPAGEPLRKRPRRDGPGLERSPGEPGGAAPEREV PAAARGCPGAAAAALWREAEAEAAAAGGEQEAQATAAAGEGDNGPGLQGPSREPPLADNL YDEDDDDEGEEEEEAAAAAIGYRDNLLFGDEIITNGFHSCESDEEDRASHASSSDWTPRP RIGPYTFVQQHLMIGTDPRTILKDLLPETIPPPELDDMTLWQIVINILSEPPKRKKRKDI NTIEDAVKLLQECKKIIVLTGAGVSVSCGIPDFRSRDGIYARLAVDFPDLPDPQAMFDIE YFRKDPRPFFKFAKEIYPGQFQPSLCHKFIALSDKEGKLLRNYTQNIDTLEQVAGIQRII QCHGSFATASCLICKYKVDCEAVRGDIFNQVVPRCPRCPADEPLAIMKPEIVFFGENLPE QFHRAMKYDKDEVDLLIVIGSSLKVRPVALIPSNQYLFLPPNRYIFHGAEVYSDSEDDVL SSSSCGSNSDSGTCQSPSLEEPMEDESEIEEFYNGLEDEPDVPERAGGAGFGTDGDDQEA INEAISVKQEVTDMNYPSNKS

[0137] As used herein, the term "SIRT1" includes any variants or isoforms of SIRT1 which are naturally expressed by cells. Accordingly, in some aspects, a miR-485 inhibitor disclosed herein can increase the expression of SIRT1 isoform 1. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of SIRT1 isoform 2. In further aspects, a miR-485 inhibitor disclosed herein can increase the expression of both SIRT1 isoform 1 and isoform 2. Unless indicated otherwise, both isoform 1 and isoform 2 are collectively referred to herein as "SIRT1."

[0138] In some aspects, a miR-485 inhibitor of the present disclosure increases the expression of SIRT1 protein and/or SIRT1 gene by at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 150%, at least about 200%, or at least about 300% compared to a reference (*e.g.*, expression of SIRT1 protein and/or SIRT1 gene in a corresponding subject that did not receive an administration of the miR-485 inhibitor).

[0139] Not to be bound by any one theory, in some aspects, a miR-485 inhibitor disclosed herein increases the expression of SIRT1 protein and/or SIRT1 gene by reducing the expression and/or activity of miR-485, e.g., miR-485-3p. In some aspects, a miR-485 inhibitor of the present disclosure can reduce the expression and/or activity of miR-485-3p.

[0140] In some aspects, a miR-485 inhibitor disclosed herein decreases the expression and/or activity of miR-485-3p by at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% compared to a reference (*e.g.*, miR-485-3p expression in a corresponding subject that did not receive an administration of the miR-485 inhibitor). In certain aspects, a miR-485 inhibitor disclosed herein decreases the expression

and/or activity of miR-485-5p by at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% compared to a reference (*e.g.*, miR-485-5p expression in a corresponding subject that did not receive an administration of the miR-485 inhibitor). In further aspects, a miR-485 inhibitor disclosed herein decreases the expression and/or activity of both miR-485-3p and miR-485-5p by at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or about 100% compared to a reference (*e.g.*, miR-485-3p and miR-485-5p expression in a corresponding subject that did not receive an administration of the miR-485 inhibitor). In some aspects, the expression of miR-485-3p and/or miR-485-5p is completely inhibited after the administration of the miR-485 inhibitor.

[0141] As described herein, a miR-485 inhibitor of the present disclosure can increase the expression of SIRT1 protein and/or SIRT1 gene when administered to a subject. Accordingly, in some aspects, the present disclosure provides a method of treating a disease or condition associated with an abnormal (*e.g.*, reduced) level of a SIRT1 protein and/or SIRT1 gene in a subject in need thereof. In some aspects, a disease or condition associated with abnormal (*e.g.*, reduced) level of a SIRT1 protein and/or SIRT1 gene is amyotrophic lateral sclerosis (ALS). In certain aspects, the method comprises administering to the subject a compound that inhibits miR-485 activity (*i.e.*, miR-485 inhibitor), wherein the miR-485 inhibitor increases the level of the SIRT1 protein and/or SIRT1 gene.

CD36 Regulation

[0142] As described herein, Applicant has identified that the human CD36 3'-UTR comprises a target site for miR-485-3p and that the binding of miR-485-3p can decrease CD36 expression (*see, e.g.*, Examples 7 and 8). Accordingly, in some aspects, the present disclosure provides a method of increasing an expression of a CD36 protein and/or a CD36 gene in a subject in need thereof, comprising administering to the subject a compound that inhibits miR-485 activity (*i.e.*, miR-485 inhibitor). In certain aspects, inhibiting miR-485 activity increases the expression of a CD36 protein and/or CD36 gene in the subject.

[0143] Cluster determinant 36 (CD36) is also known as platelet glycoprotein 4, is a protein that in humans is encoded by the *CD36* gene. The *CD36* gene is located on chromosome 7 (nucleotides 80,602,656 to 80,679,277 of GenBank Accession Number NC_000007.14, plus

strand orientation). Synonyms of the *CD36* gene, and the encoded protein thereof, are known and include "platelet glycoprotein IV," "fatty acid translocase," "scavenger receptor class B member 3," "glycoprotein 88," "glycoprotein IIIb," "glycoprotein IV," "thrombospondin receptor," "GPIIIB," "PAS IV," "GP3B," "GPIV," "FAT," "GP4," "BDPLT10," "SCARB3," "CHDS7," "PASIV," or "PAS-4."

[0144] There are at least four known isoform of human CD36 protein, resulting from alternative splicing. CD36 isoform 1 (UniProt identifier: P16671-1) consists of 472 amino acids and has been chosen as the canonical sequence (SEQ ID NO: 36). CD36 isoform 2 (also known as "ex8-del") (UniProt identifier: P16671-2) consists of 288 amino acids and differs from the canonical sequence as follows: 274-288: SIYAVFESDVNLKGI → ETCVHFTSSFSVCKS; and 289-472: missing (SEQ ID NO: 37). CD36 Isoform 3 (also known as "ex6-7-del") (UniProt identifier: P16671-3) consists of 433 amino acids and differs from the canonical sequence as follows: 234-272: missing (SEQ ID NO: 38). CD36 isoform 4 (also known as "ex4-del" (UniProt identifier: P16671-4) consists of 412 amino acids and differs from the canonical sequence as follows: 144-203: missing (SEQ ID NO: 39). Table 2 below provides the sequences for the four CD36 isoforms.

Table 2. CD36 Protein Isoforms

Isoform 1 (UniProt:P16671-1) (SEQ ID NO: 36)	MGCDRNCGLIAGAVIGAVLAVFGGILMPVGDLLIQKTIKKQVVLEEGTIAFKNWVKTGTE VYRQFWIFDVQNPQEVMMNSSNIQVKQRGPYTYRVRFLAKENVTQDAEDNTVSFLQPNGA IFEPSLSVGTEADNFTVLNLAVAAASHIYQNQFVQMILNSLINKSKSSMFQVRTLRELLW GYRDPFLSLVPYPVTTTVGLFYPYNNTADGVYKVFNGKDNISKVAIIDTYKGKRNLSYWE SHCDMINGTDAASFPPFVEKSQVLQFFSSDICRSIYAVFESDVNLKGIPVYRFVLPSKAF ASPVENPDNYCFCTEKIISKNCTSYGVLDISKCKEGRPVYISLPHFLYASPDVSEPIDGL NPNEEEHRTYLDIEPITGFTLQFAKRLQVNLLVKPSEKIQVLKNLKRNYIVPILWLNETG TIGDEKANMFRSQVTGKINLLGLIEMILLSVGVVMFVAFMISYCACRSKTIK
Isoform 2 (UniProt:P16671-2) (SEQ ID NO: 37)	MGCDRNCGLIAGAVIGAVLAVFGGILMPVGDLLIQKTIKKQVVLEEGTIAFKNWVKTGTE VYRQFWIFDVQNPQEVMMNSSNIQVKQRGPYTYRVRFLAKENVTQDAEDNTVSFLQPNGA IFEPSLSVGTEADNFTVLNLAVAAASHIYQNQFVQMILNSLINKSKSSMFQVRTLRELLW GYRDPFLSLVPYPVTTTVGLFYPYNNTADGVYKVFNGKDNISKVAIIDTYKGKRNLSYWE SHCDMINGTDAASFPPFVEKSQVLQFFSSDICRETCVHFTSSFSVCKS
Isoform 3 (UniProt: P16671-3) (SEQ ID NO: 38)	MGCDRNCGLIAGAVIGAVLAVFGGILMPVGDLLIQKTIKKQVVLEEGTIAFKNWVKTGTE VYRQFWIFDVQNPQEVMMNSSNIQVKQRGPYTYRVRFLAKENVTQDAEDNTVSFLQPNGA IFEPSLSVGTEADNFTVLNLAVAAASHIYQNQFVQMILNSLINKSKSSMFQVRTLRELLW GYRDPFLSLVPYPVTTTVGLFYPYNNTADGVYKVFNGKDNISKVAIIDTYKGKRSIYAVF ESDVNLKGIPVYRFVLPSKAFASPVENPDNYCFCTEKIISKNCTSYGVLDISKCKEGRPV YISLPHFLYASPDVSEPIDGLNPNEEEHRTYLDIEPITGFTLQFAKRLQVNLLVKPSEKI QVLKNLKRNYIVPILWLNETGTIGDEKANMFRSQVTGKINLLGLIEMILLSVGVVMFVAF MISYCACRSKTIK
Isoform 4 (UniProt:	MGCDRNCGLIAGAVIGAVLAVFGGILMPVGDLLIQKTIKKQVVLEEGTIAFKNWVKTGTE VYRQFWIFDVQNPQEVMMNSSNIQVKQRGPYTYRVRFLAKENVTQDAEDNTVSFLQPNGA IFEPSLSVGTEADNFTVLNLAVAYNNTADGVYKVFNGKDNISKVAIIDTYKGKRNLSYWE SHCDMINGTDAASFPPFVEKSQVLQFFSSDICRSIYAVFESDVNLKGIPVYRFVLPSKAF ASPVENPDNYCFCTEKIISKNCTSYGVLDISKCKEGRPVYISLPHFLYASPDVSEPIDGL

P16671-4) (SEQ ID NO: 39)	NPNEEEHRTYLDIEPITGFTLQFAKRLQVNLLVKPSEKIQVLKNLKRNYIVPILWLNETG TIGDEKANMFRSQVTGKINLLGLIEMILLSVGVVMFVAFMISYCACRSKTIK

[0145] As used herein, the term "CD36" includes any variants or isoforms of CD36 which are naturally expressed by cells. Accordingly, in some aspects, a miR-485 inhibitor disclosed herein can increase the expression of CD36 isoform 1. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of CD36 isoform 2. In some aspect, a miR-485 inhibitor disclosed herein can increase the expression of CD36 isoform 3. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of CD36 isoform 4. In further aspects, a miR-485 inhibitor disclosed herein can increase the expression of both CD36 isoform 1 and isoform 2, and/or isoform 3 and isoform 4, and/or isoform 1 and isoform 4, and/or isoform 2 and isoform 3. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of all CD36 isoforms. Unless indicated otherwise, isoform 1, isoform 2, isoform 3, and isoform 4 are collectively referred to herein as "CD36."

[0146] In some aspects, a miR-485 inhibitor of the present disclosure increases the expression of CD36 protein and/or CD36 gene by at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 150%, at least about 200%, or at least about 300% compared to a reference (*e.g.*, expression of CD36 protein and/or CD36 gene in a corresponding subject that did not receive an administration of the miR-485 inhibitor).

[0147] Not to be bound by any one theory, in some aspects, a miR-485 inhibitor disclosed herein increases the expression of CD36 protein and/or CD36 gene by reducing the expression and/or activity of miR-485. There are two known mature forms of miR-485: miR-485-3p and miR-485-5p. As disclosed herein, in some aspects, a miR-485 inhibitor of the present disclosure can reduce the expression and/or activity of miR-485-3p. In some aspects, a miR-485 inhibitor can reduce the expression and/or activity of miR-485-5p. In further aspects, a miR-485 inhibitor disclosed herein can reduce the expression and/or activity of both miR-485-3p and miR-485-5p.

[0148] As described herein, a miR-485 inhibitor of the present disclosure can increase the expression of CD36 protein and/or CD36 gene when administered to a subject. Accordingly, in some aspects, the present disclosure provides a method of treating a disease or condition associated with an abnormal (*e.g.*, reduced) level of a CD36 protein and/or CD36 gene in a

subject in need thereof. In some aspects, a disease or condition associated with abnormal (*e.g.*, reduced) level of a CD36 protein and/or CD36 gene is amyotrophic lateral sclerosis (ALS). In certain aspects, the method comprises administering to the subject a compound that inhibits miR-485 activity (*i.e.*, miR-485 inhibitor), wherein the miR-485 inhibitor increases the level of the CD36 protein and/or CD36 gene.

PGC1 Regulation

[0149] The disclosures provided herein demonstrates that the miR-485 inhibitors of the present disclosure can further regulate the expression of PGC-1α, *e.g.*, in a subject suffering from a disease or disorder disclosed herein (*see*, *e.g.*, Example 3). Therefore, in some aspects, the present disclosure provides a method of increasing an expression of a PGC-1α protein and/or a PGC-1α gene in a subject in need thereof, comprising administering to the subject a compound that inhibits miR-485 activity (*i.e.*, miR-485 inhibitor). In certain aspects, inhibiting miR-485 activity increases the expression of a PGC-1α protein and/or PGC-1α gene in the subject.

[0150] Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-α), also known as PPARG Coactivator 1 Alpha or Ligand Effect Modulator-6, is a protein that in humans is encoded by the *PPARGC1A* gene. The *PGC1-α* gene is located on chromosome 4 in humans (nucleotides 23,792,021 to 24,472,905 of GenBank Accession Number NC_000004.12, plus strand orientation). Synonyms of the *PGC1-α* gene, and the encoded protein thereof, are known and include "PPARGC1A," "LEM6," "PGC1," "PGC1A," "PGC-1v," "PPARGC1, "PGC1alpha," or "PGC-1(alpha)."

[0151] There are at least nine known isoforms of human PGC1-α protein, resulting from alternative splicing. PGC1-α isoform 1 (UniProt identifier: Q9UBK2-1) consists of 798 amino acids and has been chosen as the canonical sequence (SEQ ID NO: 40). PGC1-α isoform 2 (also known as "Isoform NT-7a") (UniProt identifier: Q9UBK2-2) consists of 271 amino acids and differs from the canonical sequence as follows: 269-271: DPK → LFL; 272-798: Missing (SEQ ID NO: 41). PGC1-α isoform 3 (also known as "Isoform B5") (UniProt identifier: Q9UBK2-3) consists of 803 amino acids and differs from the canonical sequence as follows: 1-18: MAWDMCNQDSESVWSDIE → MDETSPRLEEDWKKVLQREAGWQ (SEQ ID NO: 42). PGC1-α isoform 4 (also known as "Isoform B4") (UniProt identifier: Q9UBK2-4) consists of 786 amino acids and differs from the canonical sequence as follows: 1-18:

MAWDMCNQDSESVWSDIE → MDEGYF (SEQ ID NO: 43). PGC1-α isoform 5 (also known as "Isoform B4-8a") (UniProt identifier: Q9UBK2-5) consists of 289 amino acids and differs from the canonical sequence as follows: 1-18: MAWDMCNQDSESVWSDIE → MDEGYF; 294-301: LTPPTTPP → VKTNLISK; 302-798: Missing (SEQ ID NO: 44). PGC1-α isoform 6 (also known as "Isoform B5-NT") (UniProt identifier: Q9UBK2-6) consists of 276 amino acids and differs from the canonical sequence as follows: 1-18: MAWDMCNQDSESVWSDIE → MDETSPRLEEDWKKVLQREAGWQ; 269-271: DPK → LFL; 272-798: Missing (SEQ ID NO: 45). PGC1-α isoform 7 (also known as "B4-3ext") (UniProt identifier: Q9UBK2-7) consists of 138 amino acids and differs from the canonical sequence as follows: 1-18: MAWDMCNQDSESVWSDIE → MDEGYF; 144-150: LKKLLLA → VRTLPTV; 151-798: Missing (SEQ ID NO: 46). PGC1-α isoform 8 (also known as "Isoform 8a") (UniProt identifier: Q9UBK2-8) consists of 301 amino acids and differs from the canonical sequence as follows: 294-301: LTPPTTPP → VKTNLISK; 302-798: Missing (SEQ ID NO: 47). PGC1-α isoform 9 (also known as "Isoform 9" or "L-PGG-1alpha") (UniProt identifier: Q9UBK2-9) consists of 671 amino acids and differs from the canonical sequence as follows: 1-127: Missing (SEQ ID NO: 48). Table 3 below provides the sequences for the nine PGC1-α isoforms.

Table 3. PGC1-α Protein Isoforms

Isoform 1 (UniProt: Q9UBK2-1) (SEQ ID NO: 40)	MAWDMCNQDSESVWSDIECAALVGEDQPLCPDLPELDLSELDVNDLDTDSFLGGLKWCSD QSEIISNQYNNEPSNIFEKIDEENEANLLAVLTETLDSLPVDEDGLPSFDALTDGDVTTD NEASPSSMPDGTPPPQEAEEPSLLKKLLLAPANTQLSYNECSGLSTQNHANHNHRIRTNP AIVKTENSWSNKAKSICQQQKPQRRPCSELLKYLTTNDDPPHTKPTENRNSSRDKCTSKK KSHTQSQSQHLQAKPTTLSLPLTPESPNDPKGSPFENKTIERTLSVELSGTAGLTPPTTP PHKANQDNPFRASPKLKSSCKTVVPPPSKKPRYSESSGTQGNNSTKKGPEQSELYAQLSK SSVLTGGHEERKTKRPSLRLFGDHDYCQSINSKTEILINISQELQDSRQLENKDVSSDWQ GQICSSTDSDQCYLRETLEASKQVSPCSTRKQLQDQEIRAELNKHFGHPSQAVFDDEADK TGELRDSDFSNEQFSKLPMFINSGLAMDGLFDDSEDESDKLSYPWDGTQSYSLFNVSPSC SSFNSPCRDSVSPPKSLFSQRPQRMRSRSRSFSRHRSCSRSPYSRSRSRSPGSRSSSRSC YYYESSHYRHRTHRNSPLYVRSRSRSPYSRRPRYDSYEEYQHERLKREEYRREYEKRESE RAKQRERQRQKAIEERRVIYVGKIRPDTTRTELRDRFEVFGEIEECTVNLRDDGDSYGFI TYRYTCDAFAALENGYTLRRSNETDFELYFCGRKQFFKSNYADLDSNSDDFDPASTKSKY DSLDFDSLLKEAQRSLRR
Isoform 2 (UniProt: Q9UBK2-2)	MAWDMCNQDSESVWSDIECAALVGEDQPLCPDLPELDLSELDVNDLDTDSFLGGLKWCSD QSEIISNQYNNEPSNIFEKIDEENEANLLAVLTETLDSLPVDEDGLPSFDALTDGDVTTD NEASPSSMPDGTPPPQEAEEPSLLKKLLLAPANTQLSYNECSGLSTQNHANHNHRIRTNP AIVKTENSWSNKAKSICQQQKPQRRPCSELLKYLTTNDDPPHTKPTENRNSSRDKCTSKK KSHTQSQSQHLQAKPTTLSLPLTPESPNLFL

(SEQ ID NO: 41)	
Isoform 3 (UniProt: Q9UBK2-3) (SEQ ID NO: 42)	MDETSPRLEEDWKKVLQREAGWQCAALVGEDQPLCPDLPELDLSELDVNDLDTDSFLGGL KWCSDQSEIISNQYNNEPSNIFEKIDEENEANLLAVLTETLDSLPVDEDGLPSFDALTDG DVTTDNEASPSSMPDGTPPPQEAEEPSLLKKLLLAPANTQLSYNECSGLSTQNHANHNHR IRTNPAIVKTENSWSNKAKSICQQQKPQRRPCSELLKYLTTNDDPPHTKPTENRNSSRDK CTSKKKSHTQSQSQHLQAKPTTLSLPLTPESPNDPKGSPFENKTIERTLSVELSGTAGLT PPTTPPHKANQDNPFRASPKLKSSCKTVVPPPSKKPRYSESSGTQGNNSTKKGPEQSELY AQLSKSSVLTGGHEERKTKRPSLRLFGDHDYCQSINSKTEILINISQELQDSRQLENKDV SSDWQGQICSSTDSDQCYLRETLEASKQVSPCSTRKQLQDQEIRAELNKHFGHPSQAVFD DEADKTGELRDSDFSNEQFSKLPMFINSGLAMDGLFDDSEDESDKLSYPWDGTQSYSLFN VSPSCSSFNSPCRDSVSPPKSLFSQRPQRMRSRSRSFSRHRSCSRSPYSRSRSRSPGSRS SSRSCYYYESSHYRHRTHRNSPLYVRSRSRSPYSRRPRYDSYEEYQHERLKREEYRREYE KRESERAKQRERQRQKAIEERRVIYVGKIRPDTTRTELRDRFEVFGEIEECTVNLRDDGD SYGFITYRYTCDAFAALENGYTLRRSNETDFELYFCGRKQFFKSNYADLDSNSDDFDPAS TKSKYDSLDFDSLLKEAQRSLRR
Isoform 4 (UniProt: Q9UBK2-4) (SEQ ID NO: 43)	MDEGYFCAALVGEDQPLCPDLPELDLSELDVNDLDTDSFLGGLKWCSDQSEIISNQYNNE PSNIFEKIDEENEANLLAVLTETLDSLPVDEDGLPSFDALTDGDVTTDNEASPSSMPDGT PPPQEAEEPSLLKKLLLAPANTQLSYNECSGLSTQNHANHNHRIRTNPAIVKTENSWSNK AKSICQQQKPQRRPCSELLKYLTTNDDPPHTKPTENRNSSRDKCTSKKKSHTQSQSQHLQ AKPTTLSLPLTPESPNDPKGSPFENKTIERTLSVELSGTAGLTPPTTPPHKANQDNPFRA SPKLKSSCKTVVPPPSKKPRYSESSGTQGNNSTKKGPEQSELYAQLSKSSVLTGGHEERK TKRPSLRLFGDHDYCQSINSKTEILINISQELQDSRQLENKDVSSDWQGQICSSTDSDQC YLRETLEASKQVSPCSTRKQLQDQEIRAELNKHFGHPSQAVFDDEADKTGELRDSDFSNE QFSKLPMFINSGLAMDGLFDDSEDESDKLSYPWDGTQSYSLFNVSPSCSSFNSPCRDSVS PPKSLFSQRPQRMRSRSRSFSRHRSCSRSPYSRSRSRSPGSRSSSRSCYYYESSHYRHRT HRNSPLYVRSRSRSPYSRRPRYDSYEEYQHERLKREEYRREYEKRESERAKQRERQRQKA IEERRVIYVGKIRPDTTRTELRDRFEVFGEIEECTVNLRDDGDSYGFITYRYTCDAFAAL ENGYTLRRSNETDFELYFCGRKQFFKSNYADLDSNSDDFDPASTKSKYDSLDFDSLLKEA QRSLRR
Isoform 5 (UniProt: Q9UBK2-5) (SEQ ID NO: 44)	MDEGYFCAALVGEDQPLCPDLPELDLSELDVNDLDTDSFLGGLKWCSDQSEIISNQYNNE PSNIFEKIDEENEANLLAVLTETLDSLPVDEDGLPSFDALTDGDVTTDNEASPSSMPDGT PPPQEAEEPSLLKKLLLAPANTQLSYNECSGLSTQNHANHNHRIRTNPAIVKTENSWSNK AKSICQQQKPQRRPCSELLKYLTTNDDPPHTKPTENRNSSRDKCTSKKKSHTQSQSQHLQ AKPTTLSLPLTPESPNDPKGSPFENKTIERTLSVELSGTAGVKTNLISK
Isoform 6 (UniProt: Q9UBK2-6) (SEQ ID NO: 45)	MDETSPRLEEDWKKVLQREAGWQCAALVGEDQPLCPDLPELDLSELDVNDLDTDSFLGGL KWCSDQSEIISNQYNNEPSNIFEKIDEENEANLLAVLTETLDSLPVDEDGLPSFDALTDG DVTTDNEASPSSMPDGTPPPQEAEEPSLLKKLLLAPANTQLSYNECSGLSTQNHANHNHR IRTNPAIVKTENSWSNKAKSICQQQKPQRRPCSELLKYLTTNDDPPHTKPTENRNSSRDK CTSKKKSHTQSQSQHLQAKPTTLSLPLTPESPNLFL
Isoform 7 (UniProt: Q9UBK2-7) (SEQ ID NO: 46)	MDEGYFCAALVGEDQPLCPDLPELDLSELDVNDLDTDSFLGGLKWCSDQSEIISNQYNNE PSNIFEKIDEENEANLLAVLTETLDSLPVDEDGLPSFDALTDGDVTTDNEASPSSMPDGT PPPQEAEEPSLVRTLPTV

Isoform 8 (UniProt: Q9UBK2-8) (SEQ ID NO: 47)	MAWDMCNQDSESVWSDIECAALVGEDQPLCPDLPELDLSELDVNDLDTDSFLGGLKWCSD QSEIISNQYNNEPSNIFEKIDEENEANLLAVLTETLDSLPVDEDGLPSFDALTDGDVTTD NEASPSSMPDGTPPPQEAEEPSLLKKLLLAPANTQLSYNECSGLSTQNHANHNHRIRTNP AIVKTENSWSNKAKSICQQQKPQRRPCSELLKYLTTNDDPPHTKPTENRNSSRDKCTSKK KSHTQSQSQHLQAKPTTLSLPLTPESPNDPKGSPFENKTIERTLSVELSGTAGVKTNLIS K
Isoform 9 (UniProt: Q9UBK2-9) (SEQ ID NO: 48)	MPDGTPPPQEAEEPSLLKKLLLAPANTQLSYNECSGLSTQNHANHNHRIRTNPAIVKTEN SWSNKAKSICQQQKPQRRPCSELLKYLTTNDDPPHTKPTENRNSSRDKCTSKKKSHTQSQ SQHLQAKPTTLSLPLTPESPNDPKGSPFENKTIERTLSVELSGTAGLTPPTTPPHKANQD NPFRASPKLKSSCKTVVPPPSKKPRYSESSGTQGNNSTKKGPEQSELYAQLSKSSVLTGG HEERKTKRPSLRLFGDHDYCQSINSKTEILINISQELQDSRQLENKDVSSDWQGQICSST DSDQCYLRETLEASKQVSPCSTRKQLQDQEIRAELNKHFGHPSQAVFDDEADKTGELRDS DFSNEQFSKLPMFINSGLAMDGLFDDSEDESDKLSYPWDGTQSYSLFNVSPSCSSFNSPC RDSVSPPKSLFSQRPQRMRSRSRSFSRHRSCSRSPYSRSRSRSPGSRSSSRSCYYYESSH YRHRTHRNSPLYVRSRSRSPYSRRPRYDSYEEYQHERLKREEYRREYEKRESERAKQRER QRQKAIEERRVIYVGKIRPDTTRTELRDRFEVFGEIEECTVNLRDDGDSYGFITYRYTCD AFAALENGYTLRRSNETDFELYFCGRKQFFKSNYADLDSNSDDFDPASTKSKYDSLDFDS LLKEAQRSLRR

[0152] As used herein, the term "PGC1-α" includes any variants or isoforms of PGC1-α which are naturally expressed by cells. Accordingly, in some aspects, a miR-485 inhibitor disclosed herein can increase the expression of PGC1-α isoform 1. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of PGC1-α isoform 2. Accordingly, in some aspects, a miR-485 inhibitor disclosed herein can increase the expression of PGC1-α isoform 1. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of PGC1-α isoform 2. Accordingly, in some aspects, a miR-485 inhibitor disclosed herein can increase the expression of PGC1-α isoform 3. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of PGC1-α isoform 4. Accordingly, in some aspects, a miR-485 inhibitor disclosed herein can increase the expression of PGC1-α isoform 5. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of PGC1-α isoform 6. Accordingly, in some aspects, a miR-485 inhibitor disclosed herein can increase the expression of PGC1-α isoform 7. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of PGC1-α isoform 8. Accordingly, in some aspects, a miR-485 inhibitor disclosed herein can increase the expression of PGC1-α isoform 9. In further aspects, a miR-485 inhibitor disclosed herein can increase the expression of PGC1-α isoform 1, isoform 2, isoform 3, isoform 4, isoform 5, isoform 6, isoform 7, isoform 8, and isoform 9.. Unless indicated otherwise, both isoform 1 and isoform 2 are collectively referred to herein as "PGC1-α."

[0153] In some aspects, a miR-485 inhibitor of the present disclosure increases the expression of PGC1-α protein and/or PGC1-α gene by at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 150%, at least about 200%, or at least about 300% compared to a reference (*e.g.*, expression of PGC1-α protein and/or PGC1-α gene in a corresponding subject that did not receive an administration of the miR-485 inhibitor).

[0154] Not to be bound by any one theory, in some aspects, a miR-485 inhibitor disclosed herein increases the expression of PGC1-α protein and/or PGC1-α gene by reducing the expression and/or activity of miR-485. There are two known mature forms of miR-485: miR-485-3p and miR-485-5p. In some aspects, a miR-485 inhibitor of the present disclosure can reduce the expression and/or activity of miR-485-3p. In some aspects, a miR-485 inhibitor can reduce the expression and/or activity of miR-485-5p. In further aspects, a miR-485 inhibitor disclosed herein can reduce the expression and/or activity of both miR-485-3p and miR-485-5p.

[0155] As described herein, a miR-485 inhibitor of the present disclosure can increase the expression of PGC1-α protein and/or PGC1-α gene when administered to a subject. Accordingly, in some aspects, the present disclosure provides a method of treating a disease or condition associated with an abnormal (*e.g.*, reduced) level of a PGC1-α protein and/or PGC1-α gene in a subject in need thereof. In some aspects, a disease or condition associated with abnormal (*e.g.*, reduced) level of a PGC1-α protein and/or PGC1-α gene is amyotrophic lateral sclerosis (ALS). In certain aspects, the method comprises administering to the subject a compound that inhibits miR-485 activity (*i.e.*, miR-485 inhibitor), wherein the miR-485 inhibitor increases the level of the PGC1-α protein and/or PGC1-α gene.

NRG1 Regulation

[0156] The disclosures provided herein demonstrates that the miR-485 inhibitors of the present disclosure can further regulate the expression of NRG1, *e.g.*, in a subject suffering from a disease or disorder disclosed herein (*see*, *e.g.*, ALS). Therefore, in some aspects, the present disclosure provides a method of increasing an expression of a NRG1 protein and/or a NRG1 gene in a subject in need thereof, comprising administering to the subject a compound that inhibits miR-485 activity (*i.e.*, miR-485 inhibitor). In certain aspects, inhibiting miR-485 activity increases the expression of a NRG1 protein and/or NRG1 gene in the subject.

[0157] Neuregulin 1 is a cell adhesion molecule that in humans is encoded by the *NRG1* gene. NRG1 is one of four proteins in the neuregulin family that act on the EGFR family of receptors. The *NRG1* gene is located on chromosome 8 in humans (nucleotides 31,639,245 to 32,774,046 of GenBank Accession Number NC_000008.11). Synonyms of the *NRG1* gene, and the encoded protein thereof, are known and include "GGF," "HGL," "HRG," "NDF," "ARIA," "GGF2," "HRG1," "HRGA," "SMDF," "MST131," "MSTP131," and "NRG1-IT2."

[0158] There are at least 11 known isoforms of human NRG1 protein, resulting from alternative splicing. NRG1 isoform 1 (also known as "Alpha") (UniProt identifier: Q02297-1) is 640 amino acids in length and has been chosen as the canonical sequence (SEQ ID NO: 91). NRG1 isoform 2 (also known as "Alpha1A") (UniProt identifier: Q02297-2) is 648 amino acids long and differs from the canonical sequence as follows: 234-234: K → KHLGIEFIE (SEQ ID NO: 92). NRG1 isoform 3 (also known as "Alpha2B") (UniProt identifier: Q02297-3) is 462 amino acids long and differs from the canonical sequence as follows: (i) 424-462: YVSAMTTPAR...SPPVSSMTVS → HNLIAELRRN...SSIPHLGFIL; and (ii) 463-640: Missing (SEQ ID NO: 93). NRG1 isoform 4 (also known as "Alpha3") (UniProt identifier: Q02297-4) consists of 247 amino acids and differs from the canonical sequence as follows: (i) 234-247: KAEELYQKRVLTIT → SAQMSLLVIAAKTT; and (ii) 248-260: Missing (SEQ ID NO: 94). NRG1 isoform 6 (also known as "Beta1" and "Beta1A") (UniProt identifier: Q02297-6) is 645 amino acids in length and differs from the canonical sequence as follows: 213-234: QPGFTGARCTENVPMKVQNQEK → PNEFTGDRCQNYVMASFYKHLGIEFME (SEQ ID NO: 95). NRG1 isoform 7 (also known as "Beta2") (UniProt identifier: Q02297-7) consists of 647 amino acids and differs from the canonical sequence as follows: 213-233: QPGFTGARCTENVPMKVQNQE → PNEFTGDRCQNYVMASFY (SEQ ID NO: 96). NRG1 isoform 8 (also known as "Beta3" and "GGFHFB1") (UniProt identifier: Q02297-8) is made up of 241 amino acids and differs from the canonical sequence as follows: (i) 213-241: QPGFTGARCTENVPMKVQNQEKAEELYQK → PNEFTGDRCQNYVMASFYSTSTPFL SLPE; and (ii) 242-640: Missing (SEQ ID NO: 97). NRG1 isoform 9 (also known as "GGF2" and "GGFHPP2") (UniProt identifier: Q02297-9) is 422 amino acids in length and differs from the canonical sequence as follows: (i) 1-33: MSERKEGRGKGKGKKKERGSGKKPESAAGSQSP → MRWRRAPRRS...EVSRVLCKR C; (2) 134-168: EIITGMPASTEGAYVSSESPIRISVSTEGANTSSS → A; (3) 213-241: QPGFTGARCTENVPMKVQNQEKAEELYQK → PNEFTGDRCQNYVMASFYSTSTPFL

SLPE; and (iv) 242-640: Missing (SEQ ID NO: 98X). NRG1 isoform 10 (also known as "SMDF") (UniProt identifier: Q02297-10) is 296 amino acids long and differs from the canonical sequence as follows: (i) 1-166: Missing; (ii) 167-167: S → MEIYSPDMSE...ETNLQTAPKL; (iii) 213-241: QPGFTGARCTENVPMKVQNQEKAEELYQK → PNEFTGDRCQNYVMASFYSTSTPFL SLPE; and (iv) 242-640: Missing (SEQ ID NO: 99). NRG1 isoform 11 (also known as "Type IV-beta1a") (UniProt identifier: Q02297-11) is 590 amino acids long and differs from the canonical sequence as follows: (i) 1-21: Missing; (ii) 22-33: KKPESAAGSQSP → MGKGRAGRVGTT; (iii) 134-168: EIITGMPASTEGAYVSSESPIRISVSTEGANTSSS → A; and (iv) 213-234: QPGFTGARCTENVPMKVQNQEK → PNEFTGDRCQNYVMASFYKHLGIEFME (SEQ ID NO: 100). NRG1 isoform 12 (UniProt identifier: Q02297-12) consists of 420 amino acids and differs from the canonical sequence as follows: (i) 213-233: QPGFTGARCTENVPMKVQNQE → PNEFTGDRCQNYVMASFY; and (ii) 424-640: Missing (SEQ ID NO: 101).

[0159] Table 4 below provides the amino acid sequences for the NRG1 protein, including known isoforms.

Table 4. NRG1 Protein Sequence

Isoform 1 (UniProt: Q02297-1) (SEQ ID NO: 91)	MSERKEGRGKGKGKKKERGSGKKPESAAGSQSPALPPRLKEMKSQESAAGSKLVLRCETS SEYSSLRFKWFKNGNELNRKNKPQNIKIQKKPGKSELRINKASLADSGEYMCKVISKLGN DSASANITIVESNEIITGMPASTEGAYVSSESPIRISVSTEGANTSSSTSTSTTGTSHLV KCAEKEKTFCVNGGECFMVKDLSNPSRYLCKCQPGFTGARCTENVPMKVQNQEKAEELYQ KRVLTITGICIALLVVGIMCVVAYCKTKKQRKKLHDRLRQSLRSERNNMMNIANGPHHPN PPPENVQLVNQYVSKNVISSEHIVEREAETSFSTSHYTSTAHHSTTVTQTPSHSWSNGHT ESILSESHSVIVMSSVENSRHSSPTGGPRGRLNGTGGPRECNSFLRHARETPDSYRDSPH SERYVSAMTTPARMSPVDFHTPSSPKSPPSEMSPPVSSMTVSMPSMAVSPFMEEERPLLL VTPPRLREKKFDHHPQQFSSFHHNPAHDSNSLPASPLRIVEDEEYETTQEYEPAQEPVKK LANSRRAKRTKPNGHIANRLEVDSNTSSQSSNSESETEDERVGEDTPFLGIQNPLAASLE ATPAFRLADSRTNPAGRFSTQEEIQARLSSVIANQDPIAV
Isoform 2 (UniProt: Q02297-2) (SEQ ID NO: 92)	MSERKEGRGKGKGKKKERGSGKKPESAAGSQSPALPPRLKEMKSQESAAGSKLVLRCETS SEYSSLRFKWFKNGNELNRKNKPQNIKIQKKPGKSELRINKASLADSGEYMCKVISKLGN DSASANITIVESNEIITGMPASTEGAYVSSESPIRISVSTEGANTSSSTSTSTTGTSHLV KCAEKEKTFCVNGGECFMVKDLSNPSRYLCKCQPGFTGARCTENVPMKVQNQEKHLGIEF IEAEELYQKRVLTITGICIALLVVGIMCVVAYCKTKKQRKKLHDRLRQSLRSERNNMMNI ANGPHHPNPPPENVQLVNQYVSKNVISSEHIVEREAETSFSTSHYTSTAHHSTTVTQTPS HSWSNGHTESILSESHSVIVMSSVENSRHSSPTGGPRGRLNGTGGPRECNSFLRHARETP DSYRDSPHSERYVSAMTTPARMSPVDFHTPSSPKSPPSEMSPPVSSMTVSMPSMAVSPFM EEERPLLLVTPPRLREKKFDHHPQQFSSFHHNPAHDSNSLPASPLRIVEDEEYETTQEYE PAQEPVKKLANSRRAKRTKPNGHIANRLEVDSNTSSQSSNSESETEDERVGEDTPFLGIQ NPLAASLEATPAFRLADSRTNPAGRFSTQEEIQARLSSVIANQDPIAV
Isoform 3 (UniProt:	MSERKEGRGKGKGKKKERGSGKKPESAAGSQSPALPPRLKEMKSQESAAGSKLVLRCETS SEYSSLRFKWFKNGNELNRKNKPQNIKIQKKPGKSELRINKASLADSGEYMCKVISKLGN DSASANITIVESNEIITGMPASTEGAYVSSESPIRISVSTEGANTSSSTSTSTTGTSHLV

Q02297-3) (SEQ ID NO: 93)	KCAEKEKTFCVNGGECFMVKDLSNPSRYLCKCQPGFTGARCTENVPMKVQNQEKAEELYQ KRVLTITGICIALLVVGIMCVVAYCKTKKQRKKLHDRLRQSLRSERNNMMNIANGPHHPN PPPENVQLVNQYVSKNVISSEHIVEREAETSFSTSHYTSTAHHSTTVTQTPSHSWSNGHT ESILSESHSVIVMSSVENSRHSSPTGGPRGRLNGTGGPRECNSFLRHARETPDSYRDSPH SERHNLIAELRRNKAHRSKCMQIQLSATHLRSSSIPHLGFIL
Isoform 4 (UniProt: Q02297-4) (SEQ ID NO: 94)	MSERKEGRGKGKGKKKERGSGKKPESAAGSQSPALPPRLKEMKSQESAAGSKLVLRCETS SEYSSLRFKWFKNGNELNRKNKPQNIKIQKKPGKSELRINKASLADSGEYMCKVISKLGN DSASANITIVESNEIITGMPASTEGAYVSSESPIRISVSTEGANTSSSTSTSTTGTSHLV KCAEKEKTFCVNGGECFMVKDLSNPSRYLCKCQPGFTGARCTENVPMKVQNQESAQMSLL VIAAKTT
Isoform 6 (UniProt: Q02297-6) (SEQ ID NO: 95)	MSERKEGRGKGKGKKKERGSGKKPESAAGSQSPALPPRLKEMKSQESAAGSKLVLRCETS SEYSSLRFKWFKNGNELNRKNKPQNIKIQKKPGKSELRINKASLADSGEYMCKVISKLGN DSASANITIVESNEIITGMPASTEGAYVSSESPIRISVSTEGANTSSSTSTSTTGTSHLV KCAEKEKTFCVNGGECFMVKDLSNPSRYLCKCPNEFTGDRCQNYVMASFYKHLGIEFMEA EELYQKRVLTITGICIALLVVGIMCVVAYCKTKKQRKKLHDRLRQSLRSERNNMMNIANG PHHPNPPPENVQLVNQYVSKNVISSEHIVEREAETSFSTSHYTSTAHHSTTVTQTPSHSW SNGHTESILSESHSVIVMSSVENSRHSSPTGGPRGRLNGTGGPRECNSFLRHARETPDSY RDSPHSERYVSAMTTPARMSPVDFHTPSSPKSPPSEMSPPVSSMTVSMPSMAVSPFMEEE RPLLLVTPPRLREKKFDHHPQQFSSFHHNPAHDSNSLPASPLRIVEDEEYETTQEYEPAQ EPVKKLANSRRAKRTKPNGHIANRLEVDSNTSSQSSNSESETEDERVGEDTPFLGIQNPL AASLEATPAFRLADSRTNPAGRFSTQEEIQARLSSVIANQDPIAV
Isoform 7 (UniProt: Q02297-7) (SEQ ID NO: 96)	MSERKEGRGKGKGKKKERGSGKKPESAAGSQSPALPPRLKEMKSQESAAGSKLVLRCETS SEYSSLRFKWFKNGNELNRKNKPQNIKIQKKPGKSELRINKASLADSGEYMCKVISKLGN DSASANITIVESNEIITGMPASTEGAYVSSESPIRISVSTEGANTSSSTSTSTTGTSHLV KCAEKEKTFCVNGGECFMVKDLSNPSRYLCKCPNEFTGDRCQNYVMASFYKAEELYQKRV LTITGICIALLVVGIMCVVAYCKTKKQRKKLHDRLRQSLRSERNNMMNIANGPHHPNPPP ENVQLVNQYVSKNVISSEHIVEREAETSFSTSHYTSTAHHSTTVTQTPSHSWSNGHTESI LSESHSVIVMSSVENSRHSSPTGGPRGRLNGTGGPRECNSFLRHARETPDSYRDSPHSER YVSAMTTPARMSPVDFHTPSSPKSPPSEMSPPVSSMTVSMPSMAVSPFMEEERPLLLVTP PRLREKKFDHHPQQFSSFHHNPAHDSNSLPASPLRIVEDEEYETTQEYEPAQEPVKKLAN SRRAKRTKPNGHIANRLEVDSNTSSQSSNSESETEDERVGEDTPFLGIQNPLAASLEATP AFRLADSRTNPAGRFSTQEEIQARLSSVIANQDPIAV
Isoform 8 (UniProt: Q02297-8) (SEQ ID NO: 97)	MSERKEGRGKGKGKKKERGSGKKPESAAGSQSPALPPRLKEMKSQESAAGSKLVLRCETS SEYSSLRFKWFKNGNELNRKNKPQNIKIQKKPGKSELRINKASLADSGEYMCKVISKLGN DSASANITIVESNEIITGMPASTEGAYVSSESPIRISVSTEGANTSSSTSTSTTGTSHLV KCAEKEKTFCVNGGECFMVKDLSNPSRYLCKCPNEFTGDRCQNYVMASFYSTSTPFLSLP E
Isoform 9 (UniProt: Q02297-9) (SEQ ID NO: 98)	MRWRRAPRRSGRPGPRAQRPGSAARSSPPLPLLPLLLLLGTAALAPGAAAGNEAAPAGAS VCYSSPPSVGSVQELAQRAAVVIEGKVHPQRRQQGALDRKAAAAAGEAGAWGGDREPPAA GPRALGPPAEEPLLAANGTVPSWPTAPVPSAGEPGEEAPYLVKVHQVWAVKAGGLKKDSL LTVRLGTWGHPAFPSCGRLKEDSRYIFFMEPDANSTSRAPAAFRASFPPLETGRNLKKEV SRVLCKRCALPPRLKEMKSQESAAGSKLVLRCETSSEYSSLRFKWFKNGNELNRKNKPQN IKIQKKPGKSELRINKASLADSGEYMCKVISKLGNDSASANITIVESNATSTSTTGTSHL VKCAEKEKTFCVNGGECFMVKDLSNPSRYLCKCPNEFTGDRCQNYVMASFYSTSTPFLSL PE
Isoform 10 (UniProt:	MEIYSPDMSEVAAERSSSPSTQLSADPSLDGLPAAEDMPEPQTEDGRTPGLVGLAVPCCA CLEAERLRGCLNSEKICIVPILACLVSLCLCIAGLKWVFVDKIFEYDSPTHLDPGGLGQD PIISLDATAASAVWVSSEAYTSPVSRAQSESEVQVTVQGDKAVVSFEPSAAPTPKNRIFA

Q02297-10) (SEQ ID NO: 99)	FSFLPSTAPSFPSPTRNPEVRTPKSATQPQTTETNLQTAPKLSTSTSTTGTSHLVKCAEK EKTFCVNGGECFMVKDLSNPSRYLCKCPNEFTGDRCQNYVMASFYSTSTPFLSLPE
Isoform 11 (UniProt: Q02297-11) (SEQ ID NO: 100)	MGKGRAGRVGTTALPPRLKEMKSQESAAGSKLVLRCETSSEYSSLRFKWFKNGNELNRKN KPQNIKIQKKPGKSELRINKASLADSGEYMCKVISKLGNDSASANITIVESNATSTSTTG TSHLVKCAEKEKTFCVNGGECFMVKDLSNPSRYLCKCPNEFTGDRCQNYVMASFYKHLGI EFMEAEELYQKRVLTITGICIALLVVGIMCVVAYCKTKKQRKKLHDRLRQSLRSERNNMM NIANGPHHPNPPPENVQLVNQYVSKNVISSEHIVEREAETSFSTSHYTSTAHHSTTVTQT PSHSWSNGHTESILSESHSVIVMSSVENSRHSSPTGGPRGRLNGTGGPRECNSFLRHARE TPDSYRDSPHSERYVSAMTTPARMSPVDFHTPSSPKSPPSEMSPPVSSMTVSMPSMAVSP FMEEERPLLLVTPPRLREKKFDHHPQQFSSFHHNPAHDSNSLPASPLRIVEDEEYETTQE YEPAQEPVKKLANSRRAKRTKPNGHIANRLEVDSNTSSQSSNSESETEDERVGEDTPFLG IQNPLAASLEATPAFRLADSRTNPAGRFSTQEEIQARLSSVIANQDPIAV
Isoform 12 (UniProt: Q02297-12) (SEQ ID NO: 101)	MSERKEGRGKGKGKKKERGSGKKPESAAGSQSPALPPRLKEMKSQESAAGSKLVLRCETS SEYSSLRFKWFKNGNELNRKNKPQNIKIQKKPGKSELRINKASLADSGEYMCKVISKLGN DSASANITIVESNEIITGMPASTEGAYVSSESPIRISVSTEGANTSSSTSTSTTGTSHLV KCAEKEKTFCVNGGECFMVKDLSNPSRYLCKCPNEFTGDRCQNYVMASFYKAEELYQKRV LTITGICIALLVVGIMCVVAYCKTKKQRKKLHDRLRQSLRSERNNMMNIANGPHHPNPPP ENVQLVNQYVSKNVISSEHIVEREAETSFSTSHYTSTAHHSTTVTQTPSHSWSNGHTESI LSESHSVIVMSSVENSRHSSPTGGPRGRLNGTGGPRECNSFLRHARETPDSYRDSPHSER

[0160] As used herein, the term "NRG1" includes any variants or isoforms of NRG1 which are naturally expressed by cells. Accordingly, in some aspects, a miR-485 inhibitor disclosed herein can increase the expression of NRG1 isoform 1 (*i.e.*, canonical sequence). In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of NRG1 isofrom 2. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of NRG1 isoform 3. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of NRG1 isoform 4. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of NRG1 isoform 6. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of NRG1 isoform 7. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of NRG1 isoform 8. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of NRG1 isoform 9. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of NRG1 isoform 10. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of NRG1 isoform 11. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of NRG1 isoform 12. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of NRG1 isoform 1, NRG1 isoform 2, NRG1 isoform 3, NRG1 isoform 4, NRG1 isoform 6, NRG1 isoform 7, NRG1 isoform 8, NRG1 isoform 9, NRG1 isoform 10, NRG1 isoform 11, and NRG1

isoform 12. Unless indicated otherwise, the above-described isoforms of NRG1 are collectively referred to herein as "NRG1."

[0161] In some aspects, a miR-485 inhibitor of the present disclosure increases the expression of NRG1 protein and/or NRG1 gene by at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 150%, at least about 200%, or at least about 300% compared to a reference (*e.g.*, expression of NRG1 protein and/or NRG1 gene in a corresponding subject that did not receive an administration of the miR-485 inhibitor).

[0162] Not to be bound by any one theory, in some aspects, a miR-485 inhibitor disclosed herein increases the expression of NRG1 protein and/or NRG1 gene by reducing the expression and/or activity of miR-485, *e.g.*, miR-485-3p.

[0163] As described herein, a miR-485 inhibitor of the present disclosure can increase the expression of NRG1 protein and/or NRG1 gene when administered to a subject. Accordingly, in some aspects, the present disclosure provides a method of treating a disease or condition associated with an abnormal (*e.g.*, reduced) level of a NRG1 protein and/or NRG1 gene in a subject in need thereof. In some aspects, a disease or condition associated with abnormal (*e.g.*, reduced) level of a NRG1 protein and/or NRG1 gene is amyotrophic lateral sclerosis (ALS). In certain aspects, the method comprises administering to the subject a compound that inhibits miR-485 activity (*i.e.*, miR-485 inhibitor), wherein the miR-485 inhibitor increases the level of the NRG1 protein and/or NRG1 gene.

STMN2 Regulation

[0164] The disclosures provided herein demonstrates that the miR-485 inhibitors of the present disclosure can further regulate the expression of STMN2, *e.g.*, in a subject suffering from a disease or disorder disclosed herein (*see*, *e.g.*, ALS). Therefore, in some aspects, the present disclosure provides a method of increasing an expression of a STMN2 protein and/or a STMN2 gene in a subject in need thereof, comprising administering to the subject a compound that inhibits miR-485 activity (*i.e.*, miR-485 inhibitor). In certain aspects, inhibiting miR-485 activity increases the expression of a STMN2 protein and/or STMN2 gene in the subject.

[0165] Stathmin-2 is a member of the stathmin family of phosphoproteins and in humans is encoded by the *STMN2* gene. Stathmin proteins function in microtubule dynamics and signal

transduction. The encoded protein plays a regulatory role in neuronal growth and is also thought to be involved in osteogenesis. The *STMN2* gene is located on chromosome 8 in humans (nucleotides 79,611,117 to 79, 666,162 of NC_000008.11). Synonyms of the *STMN2* gene, and the encoded protein thereof, are known and include "SCG10" and "SCGN10."

[0166] There are at least 2 known isoforms of human STMN2 protein, resulting from alternative splicing. STMN2 isoform 1 (UniProt identifier: Q93045-1) is 179 amino acids in length and has been chosen as the canonical sequence (SEQ ID NO: 102). STMN2 isofrom 2 (UniProt identifier: Q93045-2) is 187 amino acids in length and differs from the canonical sequence as follows: 161-179: ERHAAEVRRNKELQVELSG → LVKFISSELKESIESQFLELQREGEKQ (SEQ ID NO: 102).

[0167] Table 5 below provides the amino acid sequences for the STMN2 protein.

Table 5. STMN2 Protein Sequence

Isoform 1 (UniProt: Q93045-1) (SEQ ID NO: 102)	MAKTAMAYKEKMKELSMLSLICSCFYPEPRNINIYTYDDMEVKQINKRASGQAFELILKP PSPISEAPRTLASPKKKDLSLEEIQKKLEAAEERRKSQEAQVLKQLAEKREHEREVLQKA LEENNNFSKMAEEKLILKMEQIKENREANLAAIIERLQEKERHAAEVRRNKELQVELSG
Isoform 2 (UniProt: Q93045-2) (SEQ ID NO: 103)	MAKTAMAYKEKMKELSMLSLICSCFYPEPRNINIYTYDDMEVKQINKRASGQAFELILKP PSPISEAPRTLASPKKKDLSLEEIQKKLEAAEERRKSQEAQVLKQLAEKREHEREVLQKA LEENNNFSKMAEEKLILKMEQIKENREANLAAIIERLQEKLVKFISSELKESIESQFLEL QREGEKQ

[0168] As used herein, the term "STMN2" includes any variants or isoforms of STMN2 which are naturally expressed by cells. Accordingly, in some aspects, a miR-485 inhibitor disclosed herein can increase the expression of STMN2 isoform 1 (*i.e.*, canonical sequence). In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of STMN2 isofrom 2. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of STMN2 isoform 1 and STMN2 isoform 2. Unless indicated otherwise, the above-described isoforms of STMN2 are collectively referred to herein as " STMN2."

[0169] In some aspects, a miR-485 inhibitor of the present disclosure increases the expression of STMN2 protein and/or STMN2 gene by at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 150%, at least about 200%, or at least about 300% compared to a reference (*e.g.*, expression of STMN2 protein and/or STMN2 gene in a corresponding subject that did not receive an administration of the miR-485 inhibitor).

[0170] Not to be bound by any one theory, in some aspects, a miR-485 inhibitor disclosed herein increases the expression of STMN2 protein and/or STMN2 gene by reducing the expression and/or activity of miR-485, *e.g.*, miR-485-3p.

[0171] As described herein, a miR-485 inhibitor of the present disclosure can increase the expression of STMN2 protein and/or STMN2 gene when administered to a subject. Accordingly, in some aspects, the present disclosure provides a method of treating a disease or condition associated with an abnormal (*e.g.*, reduced) level of a STMN2 protein and/or STMN2 gene in a subject in need thereof. In some aspects, a disease or condition associated with abnormal (*e.g.*, reduced) level of a STMN2 protein and/or STMN2 gene is amyotrophic lateral sclerosis (ALS). In certain aspects, the method comprises administering to the subject a compound that inhibits miR-485 activity (*i.e.*, miR-485 inhibitor), wherein the miR-485 inhibitor increases the level of the STMN2 protein and/or STMN2 gene.

NRXN1 Regulation

[0172] The disclosures provided herein demonstrates that the miR-485 inhibitors of the present disclosure can further regulate the expression of NRXN1, *e.g.*, in a subject suffering from a disease or disorder disclosed herein (*see*, *e.g.*, ALS). Therefore, in some aspects, the present disclosure provides a method of increasing an expression of a NRXN1 protein and/or a NRXN1 gene in a subject in need thereof, comprising administering to the subject a compound that inhibits miR-485 activity (*i.e.*, miR-485 inhibitor). In certain aspects, inhibiting miR-485 activity increases the expression of a NRXN1 protein and/or NRXN1 gene in the subject.

[0173] Neurexin 1 is a member of the neurexin family of proteins and in humans is encoded by the *NRXN1* gene. Neurexins are a family of proteins that function in the vertebrate nervous system as cell adhesion molecules and receptors. They are involved in communication through coupling mechanisms of calcium channels and vesicle exocytosis, to ensure that

neurotransmitters are properly released. The *NRXN1* gene is located on chromosome 2 in humans (nucleotides 49,918,503 to 51,032,536 of NC_000002.12). Synonyms of the *NRXN1* gene, and the encoded protein thereof, are known and include "neurexin 1 alpha," "neurexin 1 beta," "PTHSL2," "SCZD17," and "Hs.22998."

[0174] There are two primary isoforms of human NRXN1 protein resulting from alternative promoter usage: NRXN1-alpha and NRXN1-beta.

[0175] For the NRXN1-alpha protein, there are at least four known isoforms resulting from alternative splicing. NRXN1 isoform 1a (UniProt identifier: Q9ULB1-1) is 1,477 amino acids long and has been chosen as the canonical sequence (SEQ ID NO: 104). NRXN1 isoform 2a (UniProt identifier: Q9ULB1-2) consists of 1,496 amino acids and differs from the canonical sequence as follows: (i) 379-386: Missing; (ii) 1239-1239: A → AGNNDNERLAIARQRIPYRLGRVVDEWLLDK; and (iii) 1373-1375: Missing (SEQ ID NO: 105). NRXN1 isoform 3a (UniProt identifier: Q9ULB1-3) is 1,547 amino acids long and differs the from the canonical sequence as follows: (i) 258-258: E → EIKFGLQCVLPVLLHDNDQGKYCCINTAKPLTEK; (ii) 386-386: M → MVNKLHCS; and (iii) 1239-1239: A → AGNNDNERLAIARQRIPYRLGRVVDEWLLDK (SEQ ID NO: 106). NRXN1 isoform 4 (UniProt identifier: Q9ULB1-4) is 139 amino acids in length and differs from the canonical sequence as follows: (i) 1-1335: Missing; (ii) 1336-1344: GKPPTKEPI → MDMRWHCEN; and (iii) 1373-1375: Missing (SEQ ID NO: 107).

[0176] For the NRXN1-beta protein, there at least two known isoforms resulting from alternative splicing. NRXN1 isoform 1b (UniProt identifier: P58400-2) is 472 amino acids in length and has been chosen as the canonical sequence (SEQ ID NO: 108). NRXN1 isoform 3b (UniProt identifier: P58400-1) consists of 442 amino acids and differs from the canonical sequence as follows: 205-234: Missing (SEQ ID NO: 109).

[0177] Tables 6 and 7 below provide the amino acid sequences for the NRXN1 protein.

Table 6. NRXN1-Alpha Protein Sequences

Isoform 1a (UniProt identifier: Q9ULB1-1) (SEQ ID NO: 104)	MGTALLQRGGCFLLCLSLLLLGCWAELGSGLEFPGAEGQWTRFPKWNACCESEMSFQLKT RSARGLVLYFDDEGFCDFLELILTRGGRLQLSFSIFCAEPATLLADTPVNDGAWHSVRIR RQFRNTTLFIDQVEAKWVEVKSKRRDMTVFSGLFVGGLPPELRAAALKLTLASVRREREPF KGWIRDVRVNSSQVLPVDSGEVKLDDEPPNSGGGSPCEAGEEGEGGVCLNGGVCSVVDDQ AVCDCSRTGFRGKDCSQEDNNVEGLAHLMMGDQGKSKGKEEYIATFKGSEYFCYDLSQNP IQSSSDEITLSFKTLQRNGLMLHTGKSADYVNLALKNGAVSLVINLGSGAFEALVEPVNG KFNDNAWHDVKVTRNLRQHSGIGHAMVTISVDGILTTTGYTQEDYTMLGSDDFFYVGGSP STADLPGSPVSNNFMGCLKEVVYKNNDVRLELSRLAKQGDPKMKIHGVVAFKCENVATLD PITFETPESFISLPKWNAKKTGSISFDFRTTEPNGLILFSHGKPRHQKDAKHPQMIKVDF

	FAIEMLDGHLYLLLDMGSGTIKIKALLKKVNDGEWYHVDFQRDGRSGTISVNTLRTPYTA PGESEILDLDDELYLGGLPENKAGLVFPTEVWTALLNYGYVGCIRDLFIDGQSKDIRQMA EVQSTAGVKPSCSKETAKPCLSNPCKNNGMCRDGWNRYVCDCSGTGYLGRSCEREATVLS YDGSMFMKIQLPVVMHTEAEDVSLRFRSQRAYGILMATTSRDSADTLRLELDAGRVKLTV NLDCIRINCNSSKGPETLFAGYNLNDNEWHTVRVVRRGKSLKLTVDDQQAMTGQMAGDHT RLEFHNIETGIITERRYLSSVPSNFIGHLQSLTFNGMAYIDLCKNGDIDYCELNARFGFR NIIADPVTFKTKSSYVALATLQAYTSMHLFFQFKTTSLDGLILYNSGDGNDFIVVELVKG YLHYVFDLGNGANLIKGSSNKPLNDNQWHNVMISRDTSNLHTVKIDTKITTQITAGARNL DLKSDLYIGGVAKETYKSLPKLVHAKEGFQGCLASVDLNGRLPDLISDALFCNGQIERGC EGPSTTCQEDSCSNQGVCLQQWDGFSCDCSMTSFSGPLCNDPGTTYIFSKGGGQITYKWP PNDRPSTRADRLAIGFSTVQKEAVLVRVDSSSGLGDYLELHIHQGKIGVKFNVGTDDIAI EESNAIINDGKYHVVRFTRSGGNATLQVDSWPVIERYPAGRQLTIFNSQATIIIGGKEQG QPFQGQLSGLYYNGLKVLNMAAENDANIAIVGNVRLVGEVPSSMTTESTATAMQSEMSTS IMETTTTLATSTARRGKPPTKEPISQTTDDILVASAECPSDDEDIDPCEPSSGGLANPTR AGGREPYPGSAEVIRESSSTTGMVVGIVAAAALCILILLYAMYKYRNRDEGSYHVDESRN YISNSAQSNGAVVKEKQPSSAKSSNKNKKNKDKEYYV
Isoform 2a (UniProt identifier: Q9ULB1-2) (SEQ ID NO: 105)	MGTALLQRGGCFLLCLSLLLLGCWAELGSGLEFPGAEGQWTRFPKWNACCESEMSFQLKT RSARGLVLYFDDEGFCDFLELILTRGGRLQLSFSIFCAEPATLLADTPVNDGAWHSVRIR RQFRNTTLFIDQVEAKWVEVKSKRRDMTVFSGLFVGGLPPELRAAALKLTLASVRREREPF KGWIRDVRVNSSQVLPVDSGEVKLDDEPPNSGGGSPCEAGEEGEGGVCLNGGVCSVVDDQ AVCDCSRTGFRGKDCSQEDNNVEGLAHLMMGDQGKSKGKEEYIATFKGSEYFCYDLSQNP IQSSSDEITLSFKTLQRNGLMLHTGKSADYVNLALKNGAVSLVINLGSGAFEALVEPVNG KFNDNAWHDVKVTRNLRQVTISVDGILTTTGYTQEDYTMLGSDDFFYVGGSPSTADLPGS PVSNNFMGCLKEVVYKNNDVRLELSRLAKQGDPKMKIHGVVAFKCENVATLDPITFETPE SFISLPKWNAKKTGSISFDFRTTEPNGLILFSHGKPRHQKDAKHPQMIKVDFFAIEMLDG HLYLLLDMGSGTIKIKALLKKVNDGEWYHVDFQRDGRSGTISVNTLRTPYTAPGESEILD LDDELYLGGLPENKAGLVFPTEVWTALLNYGYVGCIRDLFIDGQSKDIRQMAEVQSTAGV KPSCSKETAKPCLSNPCKNNGMCRDGWNRYVCDCSGTGYLGRSCEREATVLSYDGSMFMK IQLPVVMHTEAEDVSLRFRSQRAYGILMATTSRDSADTLRLELDAGRVKLTVNLDCIRIN CNSSKGPETLFAGYNLNDNEWHTVRVVRRGKSLKLTVDDQQAMTGQMAGDHTRLEFHNIE TGIITERRYLSSVPSNFIGHLQSLTFNGMAYIDLCKNGDIDYCELNARFGFRNIIADPVT FKTKSSYVALATLQAYTSMHLFFQFKTTSLDGLILYNSGDGNDFIVVELVKGYLHYVFDL GNGANLIKGSSNKPLNDNQWHNVMISRDTSNLHTVKIDTKITTQITAGARNLDLKSDLYI GGVAKETYKSLPKLVHAKEGFQGCLASVDLNGRLPDLISDALFCNGQIERGCEGPSTTCQ EDSCSNQGVCLQQWDGFSCDCSMTSFSGPLCNDPGTTYIFSKGGGQITYKWPPNDRPSTR ADRLAIGFSTVQKEAVLVRVDSSSGLGDYLELHIHQGKIGVKFNVGTDDIAIEESNAIIN DGKYHVVRFTRSGGNATLQVDSWPVIERYPAGNNDNERLAIARQRIPYRLGRVVDEWLLD KGRQLTIFNSQATIIIGGKEQGQPFQGQLSGLYYNGLKVLNMAAENDANIAIVGNVRLVG EVPSSMTTESTATAMQSEMSTSIMETTTTLATSTARRGKPPTKEPISQTTDDILVASAEC PSDDEDIDPCEPSSANPTRAGGREPYPGSAEVIRESSSTTGMVVGIVAAAALCILILLYA MYKYRNRDEGSYHVDESRNYISNSAQSNGAVVKEKQPSSAKSSNKNKKNKDKEYYV
Isoform 3a (UniProt identifier: Q9ULB1-3) (SEQ ID NO: 106)	MGTALLQRGGCFLLCLSLLLLGCWAELGSGLEFPGAEGQWTRFPKWNACCESEMSFQLKT RSARGLVLYFDDEGFCDFLELILTRGGRLQLSFSIFCAEPATLLADTPVNDGAWHSVRIR RQFRNTTLFIDQVEAKWVEVKSKRRDMTVFSGLFVGGLPPELRAAALKLTLASVRREREPF KGWIRDVRVNSSQVLPVDSGEVKLDDEPPNSGGGSPCEAGEEGEGGVCLNGGVCSVVDDQ AVCDCSRTGFRGKDCSQEIKFGLQCVLPVLLHDNDQGKYCCINTAKPLTEKDNNVEGLAH LMMGDQGKSKGKEEYIATFKGSEYFCYDLSQNPIQSSSDEITLSFKTLQRNGLMLHTGKS ADYVNLALKNGAVSLVINLGSGAFEALVEPVNGKFNDNAWHDVKVTRNLRQHSGIGHAMV NKLHCSVTISVDGILTTTGYTQEDYTMLGSDDFFYVGGSPSTADLPGSPVSNNFMGCLKE VVYKNNDVRLELSRLAKQGDPKMKIHGVVAFKCENVATLDPITFETPESFISLPKWNAKK TGSISFDFRTTEPNGLILFSHGKPRHQKDAKHPQMIKVDFFAIEMLDGHLYLLLDMGSGT IKIKALLKKVNDGEWYHVDFQRDGRSGTISVNTLRTPYTAPGESEILDLDDELYLGGLPE NKAGLVFPTEVWTALLNYGYVGCIRDLFIDGQSKDIRQMAEVQSTAGVKPSCSKETAKPC LSNPCKNNGMCRDGWNRYVCDCSGTGYLGRSCEREATVLSYDGSMFMKIQLPVVMHTEAE DVSLRFRSQRAYGILMATTSRDSADTLRLELDAGRVKLTVNLDCIRINCNSSKGPETLFA GYNLNDNEWHTVRVVRRGKSLKLTVDDQQAMTGQMAGDHTRLEFHNIETGIITERRYLSS VPSNFIGHLQSLTFNGMAYIDLCKNGDIDYCELNARFGFRNIIADPVTFKTKSSYVALAT LQAYTSMHLFFQFKTTSLDGLILYNSGDGNDFIVVELVKGYLHYVFDLGNGANLIKGSSN KPLNDNQWHNVMISRDTSNLHTVKIDTKITTQITAGARNLDLKSDLYIGGVAKETYKSLP

	KLVHAKEGFQGCLASVDLNGRLPDLISDALFCNGQIERGCEGPSTTCQEDSCSNQGVCLQ QWDGFSCDCSMTSFSGPLCNDPGTTYIFSKGGGQITYKWPPNDRPSTRADRLAIGFSTVQ KEAVLVRVDSSSGLGDYLELHIHQGKIGVKFNVGTDDIAIEESNAIINDGKYHVVRFTRS GGNATLQVDSWPVIERYPAGNNDNERLAIARQRIPYRLGRVVDEWLLDKGRQLTIFNSQA TIIIGGKEQGQPFQGQLSGLYYNGLKVLNMAAENDANIAIVGNVRLVGEVPSSMTTESTA TAMQSEMSTSIMETTTTLATSTARRGKPPTKEPISQTTDDILVASAECPSDDEDIDPCEP SSGGLANPTRAGGREPYPGSAEVIRESSSTTGMVVGIVAAAALCILILLYAMYKYRNRDE GSYHVDESRNYISNSAQSNGAVVKEKQPSSAKSSNKNKKNKDKEYYV
Isoform 4a (UniProt identifier: Q9ULB1-4) (SEQ ID NO: 107)	MDMRWHCENSQTTDDILVASAECPSDDEDIDPCEPSSANPTRAGGREPYPGSAEVIRESS STTGMVVGIVAAAALCILILLYAMYKYRNRDEGSYHVDESRNYISNSAQSNGAVVKEKQP SSAKSSNKNKKNKDKEYYV

Table 7. NRXN1-Beta Protein Sequences

Isoform 1b (UniProt identifier: P58400-2) (SEQ ID NO: 108)	MYQRMLRCGAELGSPGGGGGGGGGGGAGGRLALLWIVPLTLSGLLGVAWGASSLGAHHIH HFHGSSKHHSVPIAIYRSPASLRGGHAGTTYIFSKGGGQITYKWPPNDRPSTRADRLAIG FSTVQKEAVLVRVDSSSGLGDYLELHIHQGKIGVKFNVGTDDIAIEESNAIINDGKYHVV RFTRSGGNATLQVDSWPVIERYPAGNNDNERLAIARQRIPYRLGRVVDEWLLDKGRQLTI FNSQATIIIGGKEQGQPFQGQLSGLYYNGLKVLNMAAENDANIAIVGNVRLVGEVPSSMT TESTATAMQSEMSTSIMETTTTLATSTARRGKPPTKEPISQTTDDILVASAECPSDDEDI DPCEPSSGGLANPTRAGGREPYPGSAEVIRESSSTTGMVVGIVAAAALCILILLYAMYKY RNRDEGSYHVDESRNYISNSAQSNGAVVKEKQPSSAKSSNKNKKNKDKEYYV
Isoform 3b (UniProt identifier: P58400-1) (SEQ ID NO: 109)	MYQRMLRCGAELGSPGGGGGGGGGGGAGGRLALLWIVPLTLSGLLGVAWGASSLGAHHIH HFHGSSKHHSVPIAIYRSPASLRGGHAGTTYIFSKGGGQITYKWPPNDRPSTRADRLAIG FSTVQKEAVLVRVDSSSGLGDYLELHIHQGKIGVKFNVGTDDIAIEESNAIINDGKYHVV RFTRSGGNATLQVDSWPVIERYPAGRQLTIFNSQATIIIGGKEQGQPFQGQLSGLYYNGL KVLNMAAENDANIAIVGNVRLVGEVPSSMTTESTATAMQSEMSTSIMETTTTLATSTARR GKPPTKEPISQTTDDILVASAECPSDDEDIDPCEPSSGGLANPTRAGGREPYPGSAEVIR ESSSTTGMVVGIVAAAALCILILLYAMYKYRNRDEGSYHVDESRNYISNSAQSNGAVVKE KQPSSAKSSNKNKKNKDKEYYV

[0178] As used herein, the term "NRXN1" includes any variants or isoforms of NRXN1 which are naturally expressed by cells. Accordingly, in some aspects, a miR-485 inhibitor disclosed herein can increase the expression of NRXN1 isoform 1a. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression NRXN1 isoform 2a. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression NRXN1 isoform 3a. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression NRXN1 isoform 4a. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression NRXN1 isoform 1b. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression NRXN1 isoform 3b. In some aspects, a miR-485 inhibitor disclosed herein can increase the expression of NRXN1 isoform 1a, NRXN1 isoform 2a, NRXN1 isoform 3a, NRXN1 isoform

4a, NRXN1 isoform 1b, and NRXN1 isoform 3b. Unless indicated otherwise, the above-described isoforms of NRXN1 are collectively referred to herein as " NRXN1."

[0179] In some aspects, a miR-485 inhibitor of the present disclosure increases the expression of NRXN1 protein and/or NRXN1 gene by at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 150%, at least about 200%, or at least about 300% compared to a reference (*e.g.*, expression of NRXN1 protein and/or NRXN1 gene in a corresponding subject that did not receive an administration of the miR-485 inhibitor).

[0180] Not to be bound by any one theory, in some aspects, a miR-485 inhibitor disclosed herein increases the expression of NRXN1 protein and/or NRXN1 gene by reducing the expression and/or activity of miR-485, *e.g.*, miR-485-3p.

[0181] As described herein, a miR-485 inhibitor of the present disclosure can increase the expression of NRXN1 protein and/or NRXN1 gene when administered to a subject. Accordingly, in some aspects, the present disclosure provides a method of treating a disease or condition associated with an abnormal (*e.g.*, reduced) level of a NRXN1 protein and/or NRXN1 gene in a subject in need thereof. In some aspects, a disease or condition associated with abnormal (*e.g.*, reduced) level of a NRXN1 protein and/or NRXN1 gene is amyotrophic lateral sclerosis (ALS). In certain aspects, the method comprises administering to the subject a compound that inhibits miR-485 activity (*i.e.*, miR-485 inhibitor), wherein the miR-485 inhibitor increases the level of the NRXN1 protein and/or NRXN1 gene.

[0182] As will be apparent from the present disclosure, any disease or condition associated with abnormal (*e.g.*, reduced) level of a SIRT1 protein and/or SIRT1 gene can be treated with the present disclosure. In some aspects, the present disclosure can be useful in treating any disease or condition associated with abnormal (*e.g.*, reduced) level of a CD36 protein and/or CD36 gene. In some aspects, the present disclosure can also be used to treat a disease or disorder associated with abnormal (*e.g.*, reduced) level of a PGC1-α protein and/or PGC1-α gene. In some aspects, the present disclosure can also be used to treat a disease or disorder associated with abnormal (*e.g.*, reduced) level of a NRG1 protein and/or NRG1 gene. In some aspects, the present disclosure can also be used to treat a disease or disorder associated with abnormal (*e.g.*, reduced) level of a STMN2 protein and/or STMN2 gene. In some aspects, the

present disclosure can also be used to treat a disease or disorder associated with abnormal (*e.g.*, reduced) level of a NRXN1 protein and/or NRXN1 gene.

[0183] In some aspects, a disease or condition associated with abnormal (*e.g.*, reduced) level of such proteins and/or genes is amyotrophic lateral sclerosis (ALS). In some aspects, a disease or condition associated with abnormal (*e.g.*, reduced) level of such proteins and/or genes is not a disease or condition selected from the following: Alzheimer's disease, Parkinson's disease, autism spectrum disorder, mental retardation, seizure, stroke, spinal cord injury, or any combination thereof.

[0184] In some aspects, ALS that can be treated with present disclosure comprises a sporadic ALS, familial ALS, or both. As used herein, the term "sporadic" ALS refers to ALS that is not associated with any family history of ALS occurrence. Approximately about 90% or more of the ALS diagnosis are for sporadic ALS. As used herein, the term "familial" ALS refers to ALS that occurs more than once within a family, suggesting a genetic component to the disease. In some aspects, ALS that can be treated with the present disclosure comprises primary lateral sclerosis (PLS). PLS can affect upper motor neurons in the arms and legs. More than 75% of people with apparent PLS, however, develop lower motor neuron signs within four years of symptom onset, meaning that a definite diagnosis of PLS cannot be made until then. PLS has a better prognosis than classic ALS, as it progresses slower, results in less functional decline, does not affect the ability to breathe, and causes less severe weight loss. In some aspects, ALS comprises progressive muscular astrophy (PMA). PMA can affect lower motor neurons in the arms and legs. While PMA is associated with longer survival on average than classic ALS, it still progresses to other spinal cord regions over time, eventually leading to respiratory failure and death. Upper motor neuron signs can develop late in the course of PMA, in which case the diagnosis might be changed to classic ALS.

[0185] In some aspects, administering a miR-485 inhibitor disclosed herein can improve one or more symptoms of a disease or condition associated with abnormal (*e.g.*, reduced) levels of SIRT1 protein and/or SIRT1 gene. In some aspects, administering a miR-485 inhibitor disclosed herein can improve one or more symptoms of a disease or condition associated with abnormal (*e.g.*, reduced) levels of CD36 protein and/or CD36 gene. In some aspects, administering a miR-485 inhibitor disclosed herein can improve one or more symptoms of a disease or condition associated with abnormal (*e.g.*, reduced) levels of PGC1-α protein and/or PGC1-α gene. In some aspects, administering a miR-485 inhibitor disclosed herein can

improve one or more symptoms of a disease or condition associated with abnormal (*e.g.*, reduced) levels of NRG1 protein and/or NRG1 gene. In some aspects, administering a miR-485 inhibitor disclosed herein can improve one or more symptoms of a disease or condition associated with abnormal (*e.g.*, reduced) levels of STMN2 protein and/or STMN2 gene. In some aspects, administering a miR-485 inhibitor disclosed herein can improve one or more symptoms of a disease or condition associated with abnormal (*e.g.*, reduced) levels of NRXN1 protein and/or NRXN1 gene. Non-limiting examples of such symptoms are described below.

[0186] As described herein, a disease or disorder associated with abnormal expression of SIRT1, CD36, PGC1-α, NRG1, STMN2, and/or NRXN1 is amyotrophic lateral sclerosis (ALS). Accordingly, in some aspects, a miR-485 inhibitor disclosed herein can improve one or more symptoms associated with ALS. Non-limiting examples of symptoms include: difficulty walking or doing normal daily activities; tripping and falling; weakness of the limbs; slurred speech; trouble swallowing; muscle cramps and twitching; inappropriate crying, laughing, or yawning; dementia; cognitive and behavioral changes; and combinations thereof.

[0187] In some aspects, administering a miR-485 inhibitor to a subject can increase the physical strength of one or more limbs of the subject (*e.g.*, suffering from an ALS). For instance, in some aspects, the ability of a subject to hold on to an object (*e.g.*, hang wire or pole) for an extended period of time is increased compared to a reference (*e.g.*, corresponding value in the subject prior to the administering). In some aspects, the period of time that a subject can hold onto an object (*e.g.*, hang wire or pole) is increased by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 100%, at least about 150%, at least about 200%, at least about 250%, or at least about 300% or more compared to a reference (*e.g.*, subjects that did not receive an administration of the miR-485 inhibitor).

[0188] In some aspects, administering a miR-485 inhibitor disclosed herein to a subject can delay disease onset compared to a reference (*e.g.*, disease onset in a corresponding individual that did not receive an administration of the miR-485 inhibitor). In some aspects, disease onset of ALS is delayed by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at

least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 100%, at least about 150%, at least about 200%, at least about 250%, or at least about 300% or more compared to a reference (*e.g.*, subjects that did not receive an administration of the miR-485 inhibitor). In some aspects, disease onset of ALS is delayed by at least about 10 days, at least about 20 days, at least about 30 days, at least about 40 days, at least about 50 days, at least about 60 days, at least about 70 days, at least about 80 days, at least about 90 days, at least about 100 days, at least about 150 days, at least about 200 days, at least about 250 days, at least about 1 year, at least about 2 years, at least about 3 years, at least about 4 years, or at least about 5 years or more compared to a reference (*e.g.*, subjects that did not receive an administration of the miR-485 inhibitor).

[0189] In some aspects, administering a miR-485 inhibitor to a subject can improve one or more cognitive symptom in a subject (*e.g.*, suffering from an ALS) compared to a reference (*e.g.*, cognitive symptom in the subject prior to the administering).

[0190] In some aspects, administering a miR-485 inhibitor of the present disclosure reduces the occurrence or risk of occurrence of one or more symptoms of ALS in a subject (*e.g.*, stumbling, a hard time holding items with your hands, slurred speech, swallowing problems, muscle cramps, worsening posture, a hard time holding your head up, muscle stiffness, or any combination thereof) by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100% compared to a reference (*e.g.*, subjects that did not receive an administration of the miR-485 inhibitor).

[0191] In some aspects, administering a miR-485 inhibitor of the present disclosure increases the phagocytic activity of scavenger cells (*e.g.*, glial cells) (*e.g.*, by increasing the expression of CD36 protein and/or CD36 gene) in a subject (*e.g.*, suffering from an ALS) compared to a reference (*e.g.*, phagocytic activity in the subject prior to the administering). In some aspects, administering a miR-485 inhibitor of the present disclosure increases dendritic spine density of a neuron in a subject (*e.g.*, suffering from an ALS) by at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 150%, at least about 200%, at least about 250%, or at least about 300% or

more compared to a reference (*e.g.*, subjects that did not receive an administration of the miR-485 inhibitor).

[0192] In some aspects, administering a miR-485 inhibitor disclosed herein increases neurogenesis in a subject (*e.g.*, suffering from an ALS) (*e.g.*, by increasing the expression of CD36 protein and/or CD36 gene) compared to a reference (*e.g.*, neurogenesis in the subject prior to the administering). As used herein, the term "neurogenesis" refers to the process by which neurons are created. Neurogenesis encompasses proliferation of neural stem and progenitor cells, differentiation of these cells into new neural cell types, as well as migration and survival of the new cells. The term is intended to cover neurogenesis as it occurs during normal development, predominantly during pre-natal and peri-natal development, as well as neural cells regeneration that occurs following disease, damage or therapeutic intervention. Adult neurogenesis is also termed "nerve" or "neural" regeneration. In some aspects, administering a miR-485 inhibitor of the present disclosure increases neurogenesis in a subject (*e.g.*, suffering from an ALS) by at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 150%, at least about 200%, at least about 250%, or at least about 300% or more compared to a reference (*e.g.*, subjects that did not receive an administration of the miR-485 inhibitor).

[0193] In some aspects, increasing and/or inducing neurogenesis is associated with increased proliferation, differentiation, migration, and/or survival of neural stem cells and/or progenitor cells. Accordingly, in some aspects, administering a miR-485 inhibitor of the present disclosure can increase the proliferation of neural stem cells and/or progenitor cells in the subject. In certain aspects, the proliferation of neural stem cells and/or progenitor cells is increased by at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 150%, at least about 200%, at least about 250%, or at least about 300% or more compared to a reference (*e.g.*, subjects that did not receive an administration of the miR-485 inhibitor). In some aspects, the survival of neural stem cells and/or progenitor cells is increased by at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about

150%, at least about 200%, at least about 250%, or at least about 300% or more compared to a reference (*e.g.*, subjects that did not receive an administration of the miR-485 inhibitor).

[0194] In some aspects, increasing and/or inducing neurogenesis is associated with an increased number of neural stem cells and/or progenitor cells. In certain aspects, the number of neural stem cells and/or progenitor cells is increased by at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 150%, at least about 200%, at least about 250%, or at least about 300% or more compared to a reference (*e.g.*, subjects that did not receive an administration of the miR-485 inhibitor).

[0195] In some aspects, increasing and/or inducing neurogenesis is associated with increased axon, dendrite, and/or synapse development. In certain aspects, axon, dendrite, and/or synapse development is increased by at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 150%, at least about 200%, at least about 250%, or at least about 300% or more compared to a reference (*e.g.*, subjects that did not receive an administration of the miR-485 inhibitor).

[0196] In some aspects, administering a miR-485 inhibitor of the present disclosure decreases neuroinflammation (*e.g.*, by increasing the expression of SIRT1 protein and/or SIRT1 gene) in a subject (*e.g.*, suffering from an ALS) compared to a reference (*e.g.*, neuroinflammation in the subject prior to the administering). In certain aspects, administering a miR-485 inhibitor decreases neuroinflammation in a subject (*e.g.*, suffering from an ALS) by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100% compared to a reference (*e.g.*, subjects that did not receive an administration of the miR-485 inhibitor). In some aspects, decreased neuroinflammation comprises glial cells producing decreased amounts of inflammatory mediators. Accordingly, in certain aspects, administering a miR-485 inhibitor disclosed herein to a subject (*e.g.*, suffering from an ALS) decreases the amount of inflammatory mediators produced by glial cells by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least

about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100% compared to a reference (*e.g.*, subjects that did not receive an administration of the miR-485 inhibitor). In some aspects, an inflammatory mediator produced by glial cells comprises TNF-α. In some aspects, the inflammatory mediator comprises IL-1β. In some aspects, an inflammatory mediator produced by glial cells comprises both TNF-α and IL-1β.

[0197] In some aspects, administering a miR-485 inhibitor disclosed herein increases autophagy (*e.g.*, by increasing the expression of a SIRT1 protein and/or SIRT1 gene) in a subject (*e.g.*, suffering from an ALS). As used herein, the term "autophagy" refers to cellular stress response and a survival pathway that is responsible for the degradation of long-lived proteins, protein aggregates, as well as damaged organelles in order to maintain cellular homeostasis. In some aspects, administering a miR-485 inhibitor disclosed herein to a subject (*e.g.*, suffering from an ALS) increases autophagy by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 100%, at least about 150%, at least about 200%, or at least about 300% or more, compared to a reference (*e.g.*, subjects that did not receive an administration of the miR-485 inhibitor).

[0198] As is known in the art and described herein, ALS patients exhibit certain motor and/or non-motor symptoms. For instance, non-limiting examples of motor symptoms associated with ALS include muscle weakness (*e.g.*, weakness in legs, difficulty grasping a pen or cup, difficulty lifting arms above the head, clumsiness when carrying out fine motor movements with hands or fingers, difficulty breathing), muscle atrophy, fasciculations (*i.e.*, brief, spontaneous, uncontrolled twitching of the muscles), spasticity (*i.e.*, prolonged, uncontrollable contraction of a muscle, leading to tightness and stiffness), dysarthria (*i.e.*, slow, slurred speech, due to an inability to move the mouth and facial muscles), dysphagia (*i.e.*, inability to swallow), and combinations thereof. Non-limiting examples of non-motor symptoms associated with ALS include cognitive impairment, pseudobulbar affect (PBA) (*i.e.*, involuntary and uncontrollable episodes of either laughing or crying that seem inappropriate in the social situation), or both.

[0199] In some aspects, administering a miR-485 inhibitor of the present disclosure improves one or more motor symptoms in a subject (*e.g.*, suffering from an ALS) compared to a reference (*e.g.*, corresponding motor symptoms in the subject prior to the administering). In certain aspects, administering a miR-485 inhibitor of the present disclosure improves one or more motor symptoms in a subject (*e.g.*, suffering from an ALS) by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 100%, at least about 150%, at least about 200%, at least about 250%, or at least about 300% or more compared to a reference (*e.g.*, subjects that did not receive an administration of the miR-485 inhibitor).

[0200] In some aspects, administering a miR-485 inhibitor of the present disclosure improves one or more non-motor symptoms in a subject (*e.g.*, suffering from an ALS) compared to a reference (*e.g.*, corresponding non-motor symptom in the subject prior to the administering). In certain aspects, administering a miR-485 inhibitor disclosed herein improves one or more non-motor symptoms in a subject (*e.g.*, suffering from an ALS) by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 100%, at least about 150%, at least about 200%, at least about 250%, or at least about 300% or more compared to a reference (*e.g.*, subjects that did not receive an administration of the miR-485 inhibitor).

[0201] In some aspects, a miR-485 inhibitor disclosed herein can be administered by any suitable route known in the art. In certain aspects, a miR-485 inhibitor is administered parenthetically, intramuscularly, subcutaneously, ophthalmic, intravenously, intraperitoneally, intradermally, intraorbitally, intracerebrally, intracranially, intracerebroventricularly, intraspinally, intraventricular, intrathecally, intracistemally, intracapsularly, intratumorally, or any combination thereof. In certain aspects, a miR-485 inhibitor is administered intracerebroventricularly (ICV). In certain aspects, a miR-485 inhibitor is administered intravenously.

[0202] In some aspects, a miR-485 inhibitor of the present disclosure can be used in combination with one or more additional therapeutic agents. In some aspects, the additional therapeutic agent and the miR-485 inhibitor are administered concurrently. In certain aspects, the additional therapeutic agent and the miR-485 inhibitor are administered sequentially.

[0203] In some aspects, the administration of a miR-485 inhibitor disclosed herein does not result in any adverse effects. In certain aspects, miR-485 inhibitors of the present disclosure do not adversely affect body weight when administered to a subject. In some aspects, miR-485 inhibitors disclosed herein do not result in increased mortality or cause pathological abnormalities when administered to a subject.

III. miRNA-485 Inhibitors Useful for the Present Disclosure

[0204] Disclosed herein are compounds that can inhibit miR-485 activity (miR-485 inhibitor). In some aspects, a miR-485 inhibitor of the present disclosure comprises a nucleotide sequence encoding a nucleotide molecule that comprises at least one miR-485 binding site, wherein the nucleotide molecule does not encode a protein. As described herein, in some aspects, the miR-485 binding site is at least partially complementary to the target miRNA nucleic acid sequence (*i.e.*, miR-485), such that the miR-485 inhibitor hybridizes to the miR-485 nucleic acid sequence.

[0205] In some aspects, the miR-485 binding site of a miR inhibitor disclosed herein has at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence complementarity to the nucleic acid sequence of a miR-485. In certain aspects, the miR-485 binding site is fully complementary to the nucleic acid sequence of a miR-485.

[0206] The miR-485 hairpin precursor can generate both miR-485-5p and miR-485-3p. In the context of the present disclosure "miR-485" encompasses both miR-485-5p and miR-485-3p unless specified otherwise. The human mature miR-485-3p has the sequence 5'-GUCAUACACGGCUCUCCUCUCU-3' (SEQ ID NO: 1; miRBase Acc. No. MIMAT0002176). A 5' terminal subsequence of miR-485-3p 5'-UCAUACA-3' (SEQ ID NO: 49) is the seed sequence. The human mature miR-485-5p has the sequence 5'-AGAGGCUGGCCGUGAUGAAUUC-3' (SEQ ID NO: 33; miRBase Acc. No.

MIMAT0002175). A 5' terminal subsequence of miR-485-5p 5'-GAGGCUG-3' (SEQ ID NO: 50) is the seed sequence.

[0207] As will be apparent to those in the art, the human mature miR-485-3p has significant sequence similarity to that of other species. For instance, the mouse mature miR-485-3p differs from the human mature miR-485-3p by a single amino acid at each of the 5'- and 3'- ends (*i.e.*, has an extra "A" at the 5'-end and missing "C" at the 3'-end). The mouse mature miR-485-3p has the following sequence: 5'-AGUCAUACACGGCUCUCCUCUC-3' (SEQ ID NO: 34; miRBase Acc. No. MIMAT0003129; underlined portion corresponds to overlap to human mature miR-485-3p). The sequence for the mouse mature miR-485-5p is identical to that of the human: 5'-agaggcuggccgugaugaauuc-3' (SEQ ID NO: 33; miRBase Acc. No. MIMAT0003128). Because of the similarity in sequences, in some aspects, a miR-485 inhibitor of the present disclosure is capable of binding miR-485-3p and/or miR-485-5p from one or more species. In certain aspects, a miR-485 inhibitor disclosed herein is capable of binding to miR-485-3p and/or miR-485-5p from both human and mouse.

[0208] In some aspects, the miR-485 binding site is a single-stranded polynucleotide sequence that is complementary (*e.g.*, fully complementary) to a sequence of a miR-485-3p (or a subsequence thereof). In some aspects, the miR-485-3p subsequence comprises the seed sequence. Accordingly, in certain aspects, the miR-485 binding site has at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence complementarity to the nucleic acid sequence set forth in SEQ ID NO: 49. In certain aspects, the miR-485 binding site is complementary to miR-485-3p except for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 mismatches. In further aspects, the miR-485 binding site is fully complementary to the nucleic acid sequence set forth in SEQ ID NO: 1.

[0209] In some aspects, the miR-485 binding site is a single-stranded polynucleotide sequence that is complementary (*e.g.*, fully complementary) to a sequence of a miR-485-5p (or a subsequence thereof). In some aspects, the miR-485-5p subsequence comprises the seed sequence. In certain aspects, the miR-485 binding site has at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% sequence

complementarity to the nucleic acid sequence set forth in SEQ ID NO: 50. In certain aspects, the miR-485 binding site is complementary to miR-485-5p except for 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 mismatches. In further aspects, the miR-485 binding site is fully complementary to the nucleic acid sequence set forth in SEQ ID NO: 35.

[0210] The seed region of a miRNA forms a tight duplex with the target mRNA. Most miRNAs imperfectly base-pair with the 3' untranslated region (UTR) of target mRNAs, and the 5' proximal "seed" region of miRNAs provides most of the pairing specificity. Without being bound to any theory, it is believed that the first nine miRNA nucleotides (encompassing the seed sequence) provide greater specificity whereas the miRNA ribonucleotides 3' of this region allow for lower sequence specificity and thus tolerate a higher degree of mismatched base pairing, with positions 2-7 being the most important. Accordingly, in specific aspects of the present disclosure, the miR-485 binding site comprises a subsequence that is fully complementary (*i.e.*, 100% complementary) over the entire length of the seed sequence of miR-485.

[0211] miRNA sequences and miRNA binding sequences that can be used in the context of the disclosure include, but are not limited to, all or a portion of those sequences in the sequence listing provided herein, as well as the miRNA precursor sequence, or complement of one or more of these miRNAs. Any aspects of the disclosure involving specific miRNAs or miRNA binding sites by name is contemplated also to cover miRNAs or complementary sequences thereof whose sequences are at least about at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 71%, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 76%, at least about 77%, at least about 78%, at least about 79%, at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to the mature sequence of the specified miRNA sequence or complementary sequence thereof.

[0212] In some aspects, miRNA binding sequences of the present disclosure can include additional nucleotides at the 5′, 3′, or both 5′ and 3′ ends of those sequences in the sequence listing provided herein, as long as the modified sequence is still capable of specifically binding to miR-485. In some aspects, miRNA binding sequences of the present disclosure can differ in

at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleotides with respect to those sequence in the sequence listing provided, as long as the modified sequence is still capable of specifically binding to miR-485.

[0213] It is also specifically contemplated that any methods and compositions discussed herein with respect to miRNA binding molecules or miRNA can be implemented with respect to synthetic miRNAs binding molecules. It is also understood that the disclosures related to RNA sequences in the present disclosure are equally applicable to corresponding DNA sequences.

[0214] In some aspects, a miRNA-485 inhibitor of the present disclosure comprises at least 1 nucleotide, at least 2 nucleotides, at least 3 nucleotides, at least 4 nucleotides, at least 5 nucleotides, at least 6 nucleotides, at least 7 nucleotides, at least 8 nucleotides, at least 9 nucleotides, at least 10 nucleotides, at least 11 nucleotides, at least 12 nucleotides, at least 13 nucleotides, at least 14 nucleotides, at least 15 nucleotides, at least 16 nucleotides, at least 17 nucleotides, at least 18 nucleotides, at least 19 nucleotides, or at least 20 nucleotides at the 5' of the nucleotide sequence. In some aspects, a miRNA-485 inhibitor comprises at least 1 nucleotide, at least 2 nucleotides, at least 3 nucleotides, at least 4 nucleotides, at least 5 nucleotides, at least 6 nucleotides, at least 7 nucleotides, at least 8 nucleotides, at least 9 nucleotides, at least 10 nucleotides, at least 11 nucleotides, at least 12 nucleotides, at least 13 nucleotides, at least 14 nucleotides, at least 15 nucleotides, at least 16 nucleotides, at least 17 nucleotides, at least 18 nucleotides, at least 19 nucleotides, or at least 20 nucleotides at the 3' of the nucleotide sequence.

[0215] In some aspects, a miR-485 inhibitor disclosed herein is about 6 to about 30 nucleotides in length. In certain aspects, a miR-485 inhibitor disclosed herein is 7 nucleotides in length. In further aspects, a miR-485 inhibitor disclosed herein is 8 nucleotides in length. In some aspects, a miR-485 inhibitor is 9 nucleotides in length. In some aspects, a miR-485 inhibitor of the present disclosure is 10 nucleotides in length. In certain aspects, a miR-485 inhibitor is 11 nucleotides in length. In further aspects, a miR-485 inhibitor is 12 nucleotides in length. In some aspects, a miR-485 inhibitor disclosed herein is 13 nucleotides in length. In certain aspects, a miR-485 inhibitor disclosed herein is 14 nucleotides in length. In some aspects, a miR-485 inhibitor disclosed herein is 15 nucleotides in length. In further aspects, a miR-485 inhibitor is 16 nucleotides in length. In certain aspects, a miR-485 inhibitor of the present disclosure is 17 nucleotides in length. In some aspects, a miR-485 inhibitor is 18

nucleotides in length. In some aspects, a miR-485 inhibitor is 19 nucleotides in length. In certain aspects, a miR-485 inhibitor is 20 nucleotides in length. In further aspects, a miR-485 inhibitor of the present disclosure is 21 nucleotides in length. In some aspects, a miR-485 inhibitor is 22 nucleotides in length.

[0216] In some aspects, a miR-485 inhibitor disclosed herein comprises a nucleotide sequence that is at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or about 100% identical to a sequence selected from SEQ ID NOs: 2 to 30. In certain aspects, a miR-485 inhibitor comprises a nucleotide sequence selected from the group consisting of SEQ ID NOs: 2 to 30, wherein the nucleotide sequence can optionally comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 mismatches.

[0217] In some aspects, a miRNA inhibitor comprises 5'-UGUAUGA-3' (SEQ ID NO: 2), 5'-GUGUAUGA-3' (SEQ ID NO: 3), 5'-CGUGUAUGA-3' (SEQ ID NO: 4), 5'-CCGUGUAUGA-3' (SEQ ID NO: 5), 5'-GCCGUGUAUGA-3' (SEQ ID NO: 6), 5'-AGCCGUGUAUGA-3' (SEQ ID NO: 7), 5'-GAGCCGUGUAUGA-3' (SEQ ID NO: 8), 5'-AGAGCCGUGUAUGA-3' (SEQ ID NO: 9), 5'-GAGAGCCGUGUAUGA-3' (SEQ ID NO: 10), 5'-GGAGAGCCGUGUAUGA-3' (SEQ ID NO: 11), 5'-AGGAGAGCCGUGUAUGA-3' (SEQ ID NO: 12), 5'-GAGGAGAGCCGUGUAUGA-3' (SEQ ID NO: 13), 5'-AGAGGAGAGCCGUGUAUGA-3' (SEQ ID NO: 14), or 5'-GAGAGGAGAGCCGUGUAUGA-3' (SEQ ID NO: 15).

[0218] In some aspects, the miRNA inhibitor has 5'-UGUAUGAC-3' (SEQ ID NO: 16), 5'-GUGUAUGAC-3' (SEQ ID NO: 17), 5'-CGUGUAUGAC-3' (SEQ ID NO: 18), 5'-CCGUGUAUGAC-3' (SEQ ID NO: 19), 5'-GCCGUGUAUGAC-3' (SEQ ID NO: 20), 5'-AGCCGUGUAUGAC-3' (SEQ ID NO: 21), 5'-GAGCCGUGUAUGAC-3' (SEQ ID NO: 22), 5'-AGAGCCGUGUAUGAC-3' (SEQ ID NO: 23), 5'-GAGAGCCGUGUAUGAC-3' (SEQ ID NO: 24), 5'-GGAGAGCCGUGUAUGAC-3' (SEQ ID NO: 25), 5'-AGGAGAGCCGUGUAUGAC-3' (SEQ ID NO: 26), 5'-GAGGAGAGCCGUGUAUGAC-3' (SEQ ID NO: 27), 5'-AGAGGAGAGCCGUGUAUGAC-3' (SEQ ID NO: 28), 5'-GAGAGGAGAGCCGUGUAUGAC-3' (SEQ ID NO: 29), or AGAGAGGAGAGCCGUGUAUGAC (SEQ ID NO: 30).

[0219] In some aspects, the miRNA inhibitor has a sequence selected from the group consisting of: 5'-TGTATGA-3' (SEQ ID NO: 62), 5'-GTGTATGA-3' (SEQ ID NO: 63), 5'-CGTGTATGA-3' (SEQ ID NO: 64), 5'-CCGTGTATGA-3' (SEQ ID NO: 65), 5'-GCCGTGTATGA-3' (SEQ ID NO: 66), 5'-AGCCGTGTATGA-3' (SEQ ID NO: 67), 5'-GAGCCGTGTATGA-3' (SEQ ID NO: 68), 5'-AGAGCCGTGTATGA-3' (SEQ ID NO: 69), 5'-GAGAGCCGTGTATGA-3' (SEQ ID NO: 70), 5'-GGAGAGCCGTGTATGA-3' (SEQ ID NO: 71), 5'-AGGAGAGCCGTGTATGA-3' (SEQ ID NO: 72), 5'-GAGGAGAGCCGTGTATGA-3' (SEQ ID NO: 73), 5'-AGAGGAGAGCCGTGTATGA-3' (SEQ ID NO: 74), 5'-GAGAGGAGAGCCGTGTATGA-3' (SEQ ID NO: 75); 5'-TGTATGAC-3' (SEQ ID NO: 76), 5'-GTGTATGAC-3' (SEQ ID NO: 77), 5'-CGTGTATGAC-3' (SEQ ID NO: 78), 5'-CCGTGTATGAC-3' (SEQ ID NO: 79), 5'-GCCGTGTATGAC-3' (SEQ ID NO: 80), 5'-AGCCGTGTATGAC-3' (SEQ ID NO: 81), 5'-GAGCCGTGTATGAC-3' (SEQ ID NO: 82), 5'-AGAGCCGTGTATGAC-3' (SEQ ID NO: 83), 5'-GAGAGCCGTGTATGAC-3' (SEQ ID NO: 84), 5'-GGAGAGCCGTGTATGAC-3' (SEQ ID NO: 85), 5'-AGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 86), 5'-GAGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 87), 5'-AGAGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 88), 5'-GAGAGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 89), and 5'-AGAGAGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 90).

[0220] In some aspects, a miRNA inhibitor disclosed herein (*i.e.*, miR-485 inhibitor) comprises a nucleotide sequence that is at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% identical to 5'-AGAGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 30) or 5'-AGAGAGGAGAGCCGTGTATGAC -3' (SEQ ID NO: 90). In some aspects, the miRNA inhibitor comprises a nucleotide sequence that has at least 90% similarity to 5'-AGAGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 30) or 5'-AGAGAGGAGAGCCGTGTATGAC -3' (SEQ ID NO: 90). In some aspects, the miRNA inhibitor comprises the nucleotide sequence 5'- AGAGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 30) or 5'- AGAGAGGAGAGCCGTGTATGAC -3' (SEQ ID NO: 90) with one substitution or two substitutions. In certain aspects, the miRNA inhibitor comprises the nucleotide sequence 5'- AGAGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 30) or 5'-AGAGAGGAGAGCCGTGTATGAC -3' (SEQ ID NO: 90). In certain aspects, the miRNA

inhibitor comprises the nucleotide sequence 5'- AGAGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 30).

[0221] In some aspects, a miR-485 inhibitor of the present disclosure comprises the sequence disclosed herein, e.g., any one of SEQ ID NOs: 2 to 30, and at least one, at least two, at least three, at least four or at least five additional nucleic acid at the N terminus, at least one, at least two, at least three, at least four, or at least five additional nucleic acid at the C terminus, or both. In some aspects, a miR-485 inhibitor of the present disclosure comprises the sequence disclosed herein, e.g., any one of SEQ ID NOs: 2 to 30, and one additional nucleic acid at the N terminus and/or one additional nucleic acid at the C terminus. In some aspects, a miR-485 inhibitor of the present disclosure comprises the sequence disclosed herein, e.g., any one of SEQ ID NOs: 2 to 30, and one or two additional nucleic acids at the N terminus and/or one or two additional nucleic acids at the C terminus. In some aspects, a miR-485 inhibitor of the present disclosure comprises the sequence disclosed herein, e.g., any one of SEQ ID NOs: 2 to 30, and one to three additional nucleic acids at the N terminus and/or one to three additional nucleic acids at the C terminus. In some aspects, a miR-485 inhibitor comprises 5'-GAGAGGAGAGCCGUGUAUGAC-3' (SEQ ID NO: 29).

[0222] In some aspects, a miR-485 inhibitor of the present disclosure comprises one miR-485 binding site. In further aspects, a miR-485 inhibitor disclosed herein comprises at least two miR-485 binding sites. In certain aspects, a miR-485 inhibitor comprises three miR-485 binding sites. In some aspects, a miR-485 inhibitor comprises four miR-485 binding sites. In some aspects, a miR-485 inhibitor comprises five miR-485 binding sites. In certain aspects, a miR-485 inhibitor comprises six or more miR-485 binding sites. In some aspects, all the miR-485 binding sites are identical. In some aspects, all the miR-485 binding sites are different. In some aspects, at least one of the miR-485 binding sites is different. In some aspects, all the miR-485 binding sites are miR-485-3p binding sites. In other aspects, all the miR-485 binding sites are miR-485-5p binding sites. In further aspects, a miR-485 inhibitor comprises at least one miR-485-3p binding site and at least one miR-485-5p binding site.

III.a. Chemically Modified Polynucleotides

[0223] In some aspects, a miR-485 inhibitor disclosed herein comprises a polynucleotide which includes at least one chemically modified nucleoside and/or nucleotide. When the polynucleotides of the present disclosure are chemically modified the polynucleotides can be referred to as "modified polynucleotides."

[0224] A "nucleoside" refers to a compound containing a sugar molecule (*e.g.,* a pentose or ribose) or a derivative thereof in combination with an organic base (*e.g.,* a purine or pyrimidine) or a derivative thereof (also referred to herein as "nucleobase"). A "nucleotide" refers to a nucleoside including a phosphate group. Modified nucleotides can be synthesized by any useful method, such as, for example, chemically, enzymatically, or recombinantly, to include one or more modified or non-natural nucleosides.

[0225] Polynucleotides can comprise a region or regions of linked nucleosides. Such regions can have variable backbone linkages. The linkages can be standard phosphodiester linkages, in which case the polynucleotides would comprise regions of nucleotides.

[0226] The modified polynucleotides disclosed herein can comprise various distinct modifications. In some aspects, the modified polynucleotides contain one, two, or more (optionally different) nucleoside or nucleotide modifications. In some aspects, a modified polynucleotide can exhibit one or more desirable properties, *e.g.,* improved thermal or chemical stability, reduced immunogenicity, reduced degradation, increased binding to the target microRNA, reduced non-specific binding to other microRNA or other molecules, as compared to an unmodified polynucleotide.

[0227] In some aspects, a polynucleotide of the present disclosure (*e.g.,* a miR-485 inhibitor) is chemically modified. As used herein, in reference to a polynucleotide, the terms "chemical modification" or, as appropriate, "chemically modified" refer to modification with respect to adenosine (A), guanosine (G), uridine (U), thymidine (T) or cytidine (C) ribo- or deoxyribonucleosides in one or more of their position, pattern, percent or population, including, but not limited to, its nucleobase, sugar, backbone, or any combination thereof.

[0228] In some aspects, a polynucleotide of the present disclosure (*e.g.,* a miR-485 inhibitor) can have a uniform chemical modification of all or any of the same nucleoside type or a population of modifications produced by downward titration of the same starting modification in all or any of the same nucleoside type, or a measured percent of a chemical modification of all any of the same nucleoside type but with random incorporation In further aspects, the polynucleotide of the present disclosure (*e.g.,* a miR-485 inhibitor) can have a uniform chemical modification of two, three, or four of the same nucleoside type throughout the entire polynucleotide (such as all uridines and/or all cytidines, etc. are modified in the same way).

[0229] Modified nucleotide base pairing encompasses not only the standard adenine-thymine, adenine-uracil, or guanine-cytosine base pairs, but also base pairs formed between nucleotides and/or modified nucleotides comprising non-standard or modified bases, wherein the arrangement of hydrogen bond donors and hydrogen bond acceptors permits hydrogen bonding between a non-standard base and a standard base or between two complementary non-standard base structures. One example of such non-standard base pairing is the base pairing between the modified nucleobase inosine and adenine, cytosine or uracil. Any combination of base/sugar or linker can be incorporated into polynucleotides of the present disclosure.

[0230] The skilled artisan will appreciate that, except where otherwise noted, polynucleotide sequences set forth in the instant application will recite "T"s in a representative DNA sequence but where the sequence represents RNA, the "T"s would be substituted for "U"s. For example, TD's of the present disclosure can be administered as RNAs, as DNAs, or as hybrid molecules comprising both RNA and DNA units.

[0231] In some aspects, the polynucleotide (*e.g.*, a miR-485 inhibitor) includes a combination of at least two (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 18, 20 or more) modified nucleobases.

[0232] In some aspects, the nucleobases, sugar, backbone linkages, or any combination thereof in a polynucleotide are modified by at least about 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99% or 100%.

(i) Base Modification

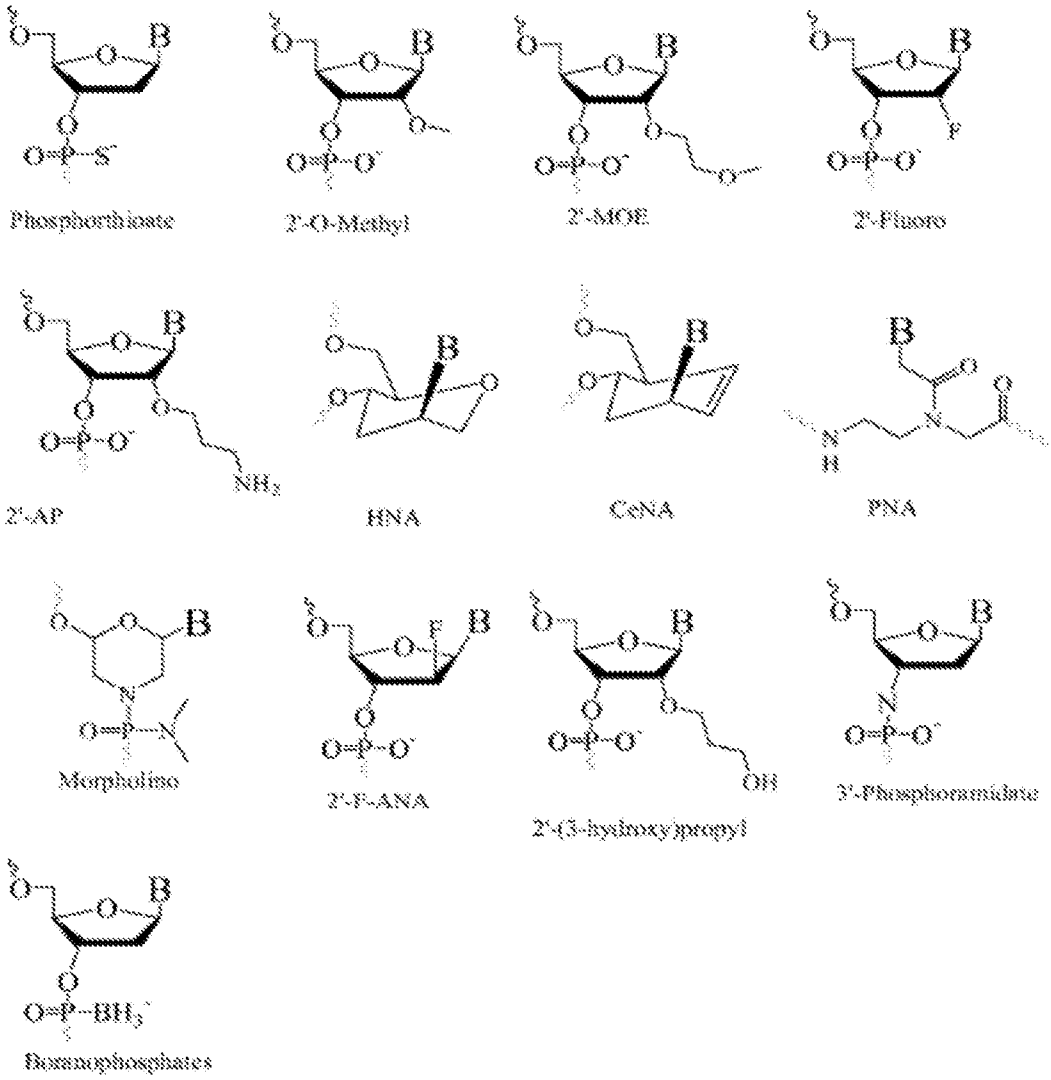
[0233] In certain aspects, the chemical modification is at nucleobases in a polynucleotide of the present disclosure (*e.g.*, a miR-485 inhibitor). In some aspects, the at least one chemically modified nucleoside is a modified uridine (*e.g.*, pseudouridine (ψ), 2-thiouridine (s2U), 1-methyl-pseudouridine (m1ψ), 1-ethyl-pseudouridine (e1ψ), or 5-methoxy-uridine (mo5U)), a modified cytosine (*e.g.*, 5-methyl-cytidine (m5C)) a modified adenosine (e.g, 1-methyl-adenosine (m1A), N6-methyl-adenosine (m6A), or 2-methyl-adenine (m2A)), a modified guanosine (*e.g.*, 7-methyl-guanosine (m7G) or 1-methyl-guanosine (m1G)), or a combination thereof.

[0234] In some aspects, the polynucleotide of the present disclosure (*e.g.*, a miR-485 inhibitor) is uniformly modified (*e.g.*, fully modified, modified throughout the entire sequence) for a particular modification. For example, a polynucleotide can be uniformly modified with the same type of base modification, *e.g.*, 5-methyl-cytidine (m5C), meaning that all cytosine residues in the polynucleotide sequence are replaced with 5-methyl-cytidine (m5C). Similarly, a polynucleotide can be uniformly modified for any type of nucleoside residue present in the sequence by replacement with a modified nucleoside such as any of those set forth above.

[0235] In some aspects, the polynucleotide of the present disclosure (*e.g.*, a miR-485 inhibitor) includes a combination of at least two (*e.g.*, 2, 3, 4 or more) of modified nucleobases. In some aspects, at least about 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99% or 100% of a type of nucleobases in a polynucleotide of the present disclosure (*e.g.*, a miR-485 inhibitor) are modified nucleobases.

(ii) Backbone modifications

[0236] In some aspects, the polynucleotide of the present disclosure (*i.e.*, miR-485 inhibitor) can include any useful linkage between the nucleosides. Such linkages, including backbone modifications, that are useful in the composition of the present disclosure include, but are not limited to the following: 3'-alkylene phosphonates, 3'-amino phosphoramidate, alkene containing backbones, aminoalkylphosphoramidates, aminoalkylphosphotriesters, boranophosphates, $-CH_2-O-N(CH_3)-CH_2-$, $-CH_2-N(CH_3)-N(CH_3)-CH_2-$, $-CH_2-NH-CH_2-$, chiral phosphonates, chiral phosphorothioates, formacetyl and thioformacetyl backbones, methylene (methylimino), methylene formacetyl and thioformacetyl backbones, methyleneimino and methylenehydrazino backbones, morpholino linkages, $-N(CH_3)-CH_2-CH_2-$, oligonucleosides with heteroatom internucleoside linkage, phosphinates, phosphoramidates, phosphorodithioates, phosphorothioate internucleoside linkages, phosphorothioates, phosphotriesters, PNA, siloxane backbones, sulfamate backbones, sulfide sulfoxide and sulfone backbones, sulfonate and sulfonamide backbones, thionoalkylphosphonates, thionoalkylphosphotriesters, and thionophosphoramidates.



[0237] In some aspects, the presence of a backbone linkage disclosed above increase the stability and resistance to degradation of a polynucleotide of the present disclosure (*i.e.*, miR-485 inhibitor).

[0238] In some aspects, at least about 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99% or 100% of the backbone linkages in a polynucleotide of the present disclosure (*i.e.*, miR-485 inhibitor) are modified (*e.g.*, all of them are phosphorothioate).

[0239] In some aspects, a backbone modification that can be included in a polynucleotide of the present disclosure (*i.e.*, miR-485 inhibitor) comprises phosphorodiamidate morpholino oligomer (PMO) and/or phosphorothioate (PS) modification.

(iii) Sugar modifications

[0240] The modified nucleosides and nucleotides which can be incorporated into a polynucleotide of the present disclosure (*i.e.*, miR-485 inhibitor) can be modified on the sugar of the nucleic acid. In some aspects, the sugar modification increases the affinity of the binding of a miR-485 inhibitor to miR-485 nucleic acid sequence. Incorporating affinity-enhancing nucleotide analogues in the miR-485 inhibitor, such as LNA or 2'-substituted sugars, can allow the length and/or the size of the miR-485 inhibitor to be reduced.

[0241] In some aspects, at least about 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99% or 100% of the nucleotides in a polynucleotide of the present disclosure (*i.e.*, miR-485 inhibitor) contain sugar modifications (*e.g.*, LNA).

[0242] In some aspects, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, or 22 nucleotide units in a polynucleotide of the present disclosure are sugar modified (*e.g.*, LNA).

[0243] Generally, RNA includes the sugar group ribose, which is a 5-membered ring having an oxygen. Exemplary, non-limiting modified nucleotides include replacement of the oxygen in ribose (*e.g.*, with S, Se, or alkylene, such as methylene or ethylene); addition of a double bond (*e.g.*, to replace ribose with cyclopentenyl or cyclohexenyl); ring contraction of ribose (*e.g.*, to form a 4-membered ring of cyclobutane or oxetane); ring expansion of ribose (*e.g.*, to form a 6- or 7-membered ring having an additional carbon or heteroatom, such as for anhydrohexitol, altritol, mannitol, cyclohexanyl, cyclohexenyl, and morpholino that also has a phosphoramidate backbone); multicyclic forms (*e.g.*, tricyclo; and "unlocked" forms, such as glycol nucleic acid (GNA) (*e.g.*, R-GNA or S-GNA, where ribose is replaced by glycol units attached to phosphodiester bonds), threose nucleic acid (TNA, where ribose is replace with α-L-threofuranosyl-(3′→2′)) , and peptide nucleic acid (PNA, where 2-amino-ethyl-glycine linkages replace the ribose and phosphodiester backbone). The sugar group can also contain

one or more carbons that possess the opposite stereochemical configuration than that of the corresponding carbon in ribose. Thus, a polynucleotide molecule can include nucleotides containing, *e.g.*, arabinose, as the sugar.

[0244] The 2′ hydroxyl group (OH) of ribose can be modified or replaced with a number of different substituents. Exemplary substitutions at the 2′-position include, but are not limited to, H, halo, optionally substituted C_{1-6} alkyl; optionally substituted C_{1-6} alkoxy; optionally substituted C_{6-10} aryloxy; optionally substituted C_{3-8} cycloalkyl; optionally substituted C_{3-8} cycloalkoxy; optionally substituted C_{6-10} aryloxy; optionally substituted C_{6-10} aryl-C_{1-6} alkoxy, optionally substituted C_{1-12} (heterocyclyl)oxy; a sugar (*e.g.*, ribose, pentose, or any described herein); a polyethyleneglycol (PEG), $-O(CH_2CH_2O)_nCH_2CH_2OR$, where R is H or optionally substituted alkyl, and n is an integer from 0 to 20 (*e.g.*, from 0 to 4, from 0 to 8, from 0 to 10, from 0 to 16, from 1 to 4, from 1 to 8, from 1 to 10, from 1 to 16, from 1 to 20, from 2 to 4, from 2 to 8, from 2 to 10, from 2 to 16, from 2 to 20, from 4 to 8, from 4 to 10, from 4 to 16, and from 4 to 20); "locked" nucleic acids (LNA) in which the 2′-hydroxyl is connected by a C_{1-6} alkylene or C_{1-6} heteroalkylene bridge to the 4'-carbon of the same ribose sugar, where exemplary bridges include methylene, propylene, ether, amino bridges, aminoalkyl, aminoalkoxy, amino, and amino acid.

[0245] In some aspects, nucleotide analogues present in a polynucleotide of the present disclosure (*i.e.*, mir-485 inhibitor) comprise, *e.g.*, 2'-O-alkyl-RNA units, 2'-OMe-RNA units, 2'-O-alkyl-SNA, 2'-amino-DNA units, 2'-fluoro-DNA units, LNA units, arabino nucleic acid (ANA) units, 2'-fluoro-ANA units, HNA units, INA (intercalating nucleic acid) units, 2'MOE units, or any combination thereof. In some aspects, the LNA is, *e.g.*, oxy-LNA (such as beta-D-oxy-LNA, or alpha-L-oxy-LNA), amino-LNA (such as beta-D-amino-LNA or alpha-L-amino-LNA), thio-LNA (such as beta-D-thio0-LNA or alpha-L-thio-LNA), ENA (such a beta-D-ENA or alpha-L-ENA), or any combination thereof. In further aspects, nucleotide analogues that can be included in a polynucleotide of the present disclosure (*i.e.*, miR-485 inhibitor) comprises a locked nucleic acid (LNA), an unlocked nucleic acid (UNA), an arabino nucleic acid (ABA), a bridged nucleic acid (BNA), and/or a peptide nucleic acid (PNA).

[0246] In some aspects, a polynucleotide of the present disclosure (*i.e.*, miR-485 inhibitor) can comprise both modified RNA nucleotide analogues (*e.g.*, LNA) and DNA units. In some aspects, a miR-485 inhibitor is a gapmer. See, *e.g.*, U.S. Pat. Nos. 8,404,649; 8,580,756; 8,163,708; 9,034,837; all of which are herein incorporated by reference in their entireties. In

some aspects, a miR-485 inhibitor is a micromir. See U.S. Pat. Appl. Publ. No. US20180201928, which is herein incorporated by reference in its entirety.

[0247] In some aspects, a polynucleotide of the present disclosure (*i.e.*, miR-485 inhibitor) can include modifications to prevent rapid degradation by endo- and exo-nucleases. Modifications include, but are not limited to, for example, (a) end modifications, e.g., 5' end modifications (phosphorylation, dephosphorylation, conjugation, inverted linkages, etc.), 3' end modifications (conjugation, DNA nucleotides, inverted linkages, etc.), (b) base modifications, e.g., replacement with modified bases, stabilizing bases, destabilizing bases, or bases that base pair with an expanded repertoire of partners, or conjugated bases, (c) sugar modifications (e.g., at the 2' position or 4' position) or replacement of the sugar, as well as (d) internucleoside linkage modifications, including modification or replacement of the phosphodiester linkages.

IV. Vectors and Delivery Systems

[0248] In some aspects, the miR-485 inhibitors of the present disclosure can be administered, *e.g.*, to a subject suffering from a disease or condition associated with abnormal (*e.g.*, reduced) level of a SIRT1 protein and/or SIRT1 gene, using any relevant delivery system known in the art. In certain aspects, the delivery system is a vector. Accordingly, in some aspects, the present disclosure provides a vector comprising a miR-485 inhibitor of the present disclosure.

[0249] In some aspects, the vector is viral vector. In some aspects, the viral vector is an adenoviral vector or an adeno-associated viral vector. In certain aspects, the viral vector is an AAV that has a serotype of AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, or any combination thereof. In some aspects, the adenoviral vector is a third generation adenoviral vector. ADEASY™ is by far the most popular method for creating adenoviral vector constructs. The system consists of two types of plasmids: shuttle (or transfer) vectors and adenoviral vectors. The transgene of interest is cloned into the shuttle vector, verified, and linearized with the restriction enzyme PmeI. This construct is then transformed into ADEASIER-1 cells, which are BJ5183 E. coli cells containing PADEASY™. PADEASY™ is a ~33Kb adenoviral plasmid containing the adenoviral genes necessary for virus production. The shuttle vector and the adenoviral plasmid have matching left and right homology arms which facilitate homologous recombination of the transgene into the adenoviral plasmid. One can also co-transform standard BJ5183 with supercoiled PADEASY™ and the

shuttle vector, but this method results in a higher background of non-recombinant adenoviral plasmids. Recombinant adenoviral plasmids are then verified for size and proper restriction digest patterns to determine that the transgene has been inserted into the adenoviral plasmid, and that other patterns of recombination have not occurred. Once verified, the recombinant plasmid is linearized with PacI to create a linear dsDNA construct flanked by ITRs. 293 or 911 cells are transfected with the linearized construct, and virus can be harvested about 7-10 days later. In addition to this method, other methods for creating adenoviral vector constructs known in the art at the time the present application was filed can be used to practice the methods disclosed herein.

[0250] In some aspects, the viral vector is a retroviral vector, e.g., a lentiviral vector (e.g., a third or fourth generation lentiviral vector). Lentiviral vectors are usually created in a transient transfection system in which a cell line is transfected with three separate plasmid expression systems. These include the transfer vector plasmid (portions of the HIV provirus), the packaging plasmid or construct, and a plasmid with the heterologous envelop gene (*env*) of a different virus. The three plasmid components of the vector are put into a packaging cell which is then inserted into the HIV shell. The virus portions of the vector contain insert sequences so that the virus cannot replicate inside the cell system. Current third generation lentiviral vectors encode only three of the nine HIV-1 proteins (Gag, Pol, Rev), which are expressed from separate plasmids to avoid recombination-mediated generation of a replication-competent virus. In fourth generation lentiviral vectors, the retroviral genome has been further reduced (see, e.g., TAKARA® LENTI-X™ fourth-generation packaging systems).

[0251] Any AAV vector known in the art can be used in the methods disclosed herein. The AAV vector can comprise a known vector or can comprise a variant, fragment, or fusion thereof. In some aspects, the AAV vector is selected from the group consisting of AAV type 1 (AAV1), AAV2, AAV3A, AVV3B, AAV4, AAV5, AAV6, AAV7, AAV8, AVV9, AVV10, AVV11, AVV12, AVV13, AAVrh.74, avian AAV, bovine AAV, canine AAV, equine AAV, goat AVV, primate AAV, non-primate AAV, bovine AAV, shrimp AVV, snake AVV, and any combination thereof.

[0252] In some aspects, the AAV vector is derived from an AAV vector selected from the group consisting of AAV1, AAV2, AAV3A, AVV3B, AAV4, AAV5, AAV6, AAV7, AAV8, AVV9, AVV10, AVV11, AVV12, AVV13, AAVrh.74, avian AAV, bovine AAV, canine

AAV, equine AAV, goat AVV, primate AAV, non-primate AAV, ovine AAV, shrimp AVV, snake AVV, and any combination thereof.

[0253] In some aspects, the AAV vector is a chimeric vector derived from at least two AAV vectors selected from the group consisting of AAV1, AAV2, AAV3A, AVV3B, AAV4, AAV5, AAV6, AAV7, AAV8, AVV9, AVV10, AVV11, AVV12, AVV13, AAVrh.74, avian AAV, bovine AAV, canine AAV, equine AAV, goat AVV, primate AAV, non-primate AAV, ovine AAV, shrimp AVV, snake AVV, and any combination thereof.

[0254] In certain aspects, the AAV vector comprises regions of at least two different AAV vectors known in the art.

[0255] In some aspects, the AAV vector comprises an inverted terminal repeat from a first AAV (*e.g.*, AAV1, AAV2, AAV3A, AVV3B, AAV4, AAV5, AAV6, AAV7, AAV8, AVV9, AVV10, AVV11, AVV12, AVV13, AAVrh.74, avian AAV, bovine AAV, canine AAV, equine AAV, goat AVV, primate AAV, non-primate AAV, ovine AAV, shrimp AVV, snake AVV, or any derivative thereof) and a second inverted terminal repeat from a second AAV (*e.g.*, AAV1, AAV2, AAV3A, AVV3B, AAV4, AAV5, AAV6, AAV7, AAV8, AVV9, AVV10, AVV11, AVV12, AVV13, AAVrh.74, avian AAV, bovine AAV, canine AAV, equine AAV, goat AVV, primate AAV, non-primate AAV, ovine AAV, shrimp AVV, snake AVV, or any derivative thereof).

[0256] In some aspects, the AVV vector comprises a portion of an AAV vector selected from the group consisting of AAV1, AAV2, AAV3A, AVV3B, AAV4, AAV5, AAV6, AAV7, AAV8, AVV9, AVV10, AVV11, AVV12, AVV13, AAVrh.74, avian AAV, bovine AAV, canine AAV, equine AAV, goat AVV, primate AAV, non-primate AAV, ovine AAV, shrimp AVV, snake AVV, and any combination thereof. In some aspects, the AAV vector comprises AAV2.

[0257] In some aspects, the AVV vector comprises a splice acceptor site. In some aspects, the AVV vector comprises a promoter. Any promoter known in the art can be used in the AAV vector of the present disclosure. In some aspects, the promoter is an RNA Pol III promoter. In some aspects, the RNA Pol III promoter is selected from the group consisting of the U6 promoter, the H1 promoter, the 7SK promoter, the 5S promoter, the adenovirus 2 (Ad2) VAI promoter, and any combination thereof. In some aspects, the promoter is a cytomegalovirus immediate-early gene (CMV) promoter, an EF1a promoter, an SV40 promoter, a PGK1 promoter, a Ubc promoter, a human beta actin promoter, a CAG promoter, a TRE promoter,

a UAS promoter, a Ac5 promoter, a polyhedrin promoter, a CaMKIIa promoter, a GAL1 promoter, a GAL10 promoter, a TEF promoter, a GDS promoter, a ADH1 promoter, a CaMV35S promoter, or a Ubi promoter. In a specific aspect, the promoter comprises the U6 promoter.

[0258] In some aspects, the AAV vector comprises a constitutively active promoter (constitutive promoter). In some aspects, the constitutive promoter is selected from the group consisting of hypoxanthine phosphoribosyl transferase (HPRT), adenosine deaminase, pyruvate kinase, beta-actin promoter, cytomegalovirus (CMV), simian virus (*e.g.,* SV40), papilloma virus, adenovirus, human immunodeficiency virus (HIV), Rous sarcoma virus, a retrovirus long terminal repeat (LTR), Murine stem cell virus (MSCV) and the thymidine kinase promoter of herpes simplex virus.

[0259] In some aspects, the promoter is an inducible promoter. In some aspects, the inducible promoter is a tissue specific promoter. In certain aspects, the tissue specific promoter drives transcription of the coding region of the AVV vector in a neuron, a glial cell, or in both a neuron and a glial cell.

[0260] In some aspects, the AVV vector comprises one or more enhancers. In some aspects, the one or more enhancer are present in the AAV alone or together with a promoter disclosed herein. In some aspects, the AAV vector comprises a 3'UTR poly(A) tail sequence. In some aspects, the 3'UTR poly(A) tail sequence is selected from the group consisting of bGH poly(A), actin poly(A), hemoglobin poly(A), and any combination thereof. In some aspects, the 3'UTR poly(A) tail sequence comprises bGH poly(A).

[0261] In some aspects, a miR-485 inhibitor disclosed herein is administered with a delivery agent. Non-limiting examples of delivery agents that can be used include a lipidoid, a liposome, a lipoplex, a lipid nanoparticle, a polymeric compound, a peptide, a protein, a cell, a nanoparticle mimic, a nanotube, a micelle, or a conjugate.

[0262] Thus, in some aspects, the present disclosure also provides a composition comprising a miRNA inhibitor of the present disclosure (*i.e.*, miR-485 inhibitor) and a delivery agent. In some aspects, the delivery agent comprises a cationic carrier unit comprising

[WP]-L1-[CC]-L2-[AM] (formula I)

or

[WP]-L1-[AM]-L2-[CC] (formula II)

wherein

WP is a water-soluble biopolymer moiety;

CC is a positively charged carrier moiety;

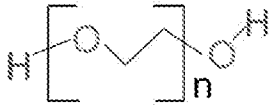
AM is an adjuvant moiety; and,

L1 and L2 are independently optional linkers, and

wherein when mixed with a nucleic acid at an ionic ratio of about 1:1, the cationic carrier unit forms a micelle.

[0263] In some aspects, composition comprising a miRNA inhibitor of the present disclosure (*i.e.*, miR-485 inhibitor) interacts with the cationic carrier unit via an ionic bond.

[0264] In some aspects, the water-soluble polymer comprises poly(alkylene glycols), poly(oxyethylated polyol), poly(olefinic alcohol), poly(vinylpyrrolidone), poly(hydroxyalkylmethacrylamide), poly(hydroxyalkylmethacrylate), poly(saccharides), poly(α-hydroxy acid), poly(vinyl alcohol), polyglycerol, polyphosphazene, polyoxazolines ("POZ") poly(N-acryloylmorpholine), or any combinations thereof. In some aspects, the water-soluble polymer comprises polyethylene glycol ("PEG"), polyglycerol, or poly(propylene glycol) ("PPG"). In some aspects, the water-soluble polymer comprises:



, (formula III),

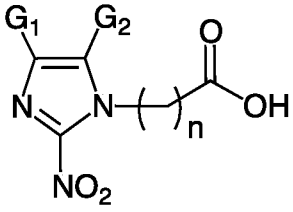
wherein n is 1-1000.

[0265] In some aspects, the n is at least about 110, at least about 111, at least about 112, at least about 113, at least about 114, at least about 115, at least about 116, at least about 117, at least about 118, at least about 119, at least about 120, at least about 121, at least about 122, at least about 123, at least about 124, at least about 125, at least about 126, at least about 127, at least about 128, at least about 129, at least about 130, at least about 131, at least about 132, at least about 133, at least about 134, at least about 135, at least about 136, at least about 137, at least about 138, at least about 139, at least about 140, or at least about 141. In some aspects, the n is about 80 to about 90, about 90 to about 100, about 100 to about 110, about 110 to about 120, about 120 to about 130, about 140 to about 150, about 150 to about 160.

[0266] In some aspects, the water-soluble polymer is linear, branched, or dendritic. In some aspects, the cationic carrier moiety comprises one or more basic amino acids. In some aspects, the cationic carrier moiety comprises at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least 11, at least 12, at least 13, at least 14, at last 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22,

at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 31, at least 32, at least 33, at least 34, at least 35, at least 36, at least 37, at least 38, at least 39, at least 40, at least 41, at least 42, at least 43, at least 44, at least 45, at least 46, at least 47, at least 48, at least 49, or at least 50 basic amino acids. In some aspects, the cationic carrier moiety comprises about 30 to about 50 basic amino acids. In some aspects, the basic amino acid comprises arginine, lysine, histidine, or any combination thereof. In some aspects, the cationic carrier moiety comprises about 40 lysine monomers.

[0267] In some aspects, the adjuvant moiety is capable of modulating an immune response, an inflammatory response, and/or a tissue microenvironment. In some aspects, the adjuvant moiety comprises an imidazole derivative, an amino acid, a vitamin, or any combination thereof. In some aspects, the adjuvant moiety comprises:

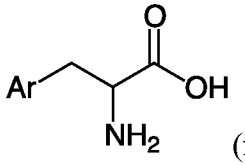


, (formula IV),

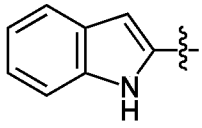
wherein each of G1 and G2 is H, an aromatic ring, or 1-10 alkyl, or G1 and G2 together form an aromatic ring, and wherein n is 1-10.

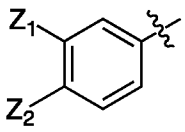
[0268] In some aspects, the adjuvant moiety comprises nitroimidazole. In some aspects, the adjuvant moiety comprises metronidazole, tinidazole, nimorazole, dimetridazole, pretomanid, ornidazole, megazol, azanidazole, benznidazole, or any combination thereof. In some aspects, the adjuvant moiety comprises an amino acid.

[0269] In some aspects, the adjuvant moiety comprises



(formula V),

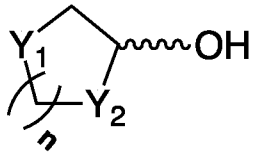
wherein Ar is Ar= 

or 

, and

wherein each of Z1 and Z2 is H or OH.

[0270] In some aspects, the adjuvant moiety comprises a vitamin. In some aspects, the vitamin comprises a cyclic ring or cyclic hetero atom ring and a carboxyl group or hydroxyl group. In some aspects, the vitamin comprises:



(formula VI),

wherein each of Y1 and Y2 is C, N, O, or S, and wherein n is 1 or 2.

[0271] In some aspects, the vitamin is selected from the group consisting of vitamin A, vitamin B1, vitamin B2, vitamin B3, vitamin B6, vitamin B7, vitamin B9, vitamin B12, vitamin C, vitamin D2, vitamin D3, vitamin E, vitamin M, vitamin H, and any combination thereof. In some aspects, the vitamin is vitamin B3.

[0272] In some aspects, the adjuvant moiety comprises at least about two, at least about three, at least about four, at least about five, at least about six, at least about seven, at least about eight, at least about nine, at least about ten, at least about 11, at least about 12, at least about 13, at least about 14, at least about 15, at least about 16, at least about 17, at least about 18, at least about 19, or at least about 20 vitamin B3. In some aspects, the adjuvant moiety comprises about 10 vitamin B3.

[0273] In some aspects, the composition comprises a water-soluble biopolymer moiety with about 120 to about 130 PEG units, a cationic carrier moiety comprising a poly-lysine with about 30 to about 40 lysines, and an adjuvant moiety with about 5 to about 10 vitamin B3.

[0274] In some aspects, the composition comprises (i) a water-soluble biopolymer moiety with about 100 to about 200 PEG units, (ii) about 30 to about 40 lysines with an amine group (e.g., about 32 lysines), (iii) about 15 to 20 lysines, each having a thiol group (e.g., about 16 lysines, each with a thiol group), and (iv) about 30 to 40 lysines fused to vitamin B3 (e.g., about 32 lysines, each fused to vitamin B3). In some aspects, the composition further comprises a targeting moiety, e.g., a LAT1 targeting ligand, e.g., phenyl alanine, linked to the water soluable polymer. In some aspects, the thiol groups in the composition form disulfide bonds.

[0275] In some aspects, the composition comprises (1) a micelle comprising (i) about 100 to about 200 PEG units, (ii) about 30 to about 40 lysines with an amine group (e.g., about 32 lysines), (iii) about 15 to 20 lysines, each having a thiol group (e.g., about 16 lysines, each with a thiol group), and (iv) about 30 to 40 lysines fused to vitamin B3 (e.g., about 32 lysines, each

fused to vitamin B3), and (2) a miR485 inhibitor (e.g., SEQ ID NO: 30), wherein the miR485 inhibitor is encapsulated within the micelle. In some aspects, the composition further comprises a targeting moiety, e.g., a LAT1 targeting ligand, e.g., phenyl alanine, linked to the PEG units. In some aspects, the thiol groups in the micelle form disulfide bonds.

[0276] The present disclosure also provides a micelle comprising a miRNA inhibitor of the present disclosure (*i.e.*, miR-485 inhibitor, e.g., SEQ ID NO: 30) wherein the miRNA inhibitor and the delivery agent are associated with each other.

[0277] In some aspects, the association is a covalent bond, a non-covalent bond, or an ionic bond. In some aspects, the positive charge of the cationic carrier moiety of the cationic carrier unit is sufficient to form a micelle when mixed with the miR-485 inhibitor disclosed herein in a solution, wherein the overall ionic ratio of the positive charges of the cationic carrier moiety of the cationic carrier unit and the negative charges of the miR-485 inhibitor (or vector comprising the inhibitor) in the solution is about 1: 1.

[0278] In some aspects, the cationic carrier unit is capable of protecting the miRNA inhibitor of the present disclosure (*i.e.*, miR-485 inhibitor) from enzymatic degradation. See PCT Publication No. WO2020/261227, published December 30, 2020, which is herein incorporated by reference in its entirety.

V. Pharmaceutical compositions

[0279] In some aspects, the present disclosure also provides pharmaceutical compositions comprising a miR-485 inhibitor disclosed herein (*e.g.*, a polynucleotide or a vector comprising the miR-485 inhibitor) that are suitable for administration to a subject. The pharmaceutical compositions generally comprise a miR-485 inhibitor described herein (*e.g.*, a polynucleotide or a vector) and a pharmaceutically-acceptable excipient or carrier in a form suitable for administration to a subject. Pharmaceutically acceptable excipients or carriers are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition.

[0280] Accordingly, there is a wide variety of suitable formulations of pharmaceutical compositions comprising a miR-485 inhibitor of the present disclosure. (See, *e.g.*, Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa. 18th ed. (1990)). The pharmaceutical compositions are generally formulated sterile and in full compliance with all Good Manufacturing Practice (GMP) regulations of the U.S. Food and Drug Administration.

VI. Kits

[0281] The present disclosure also provides kits or products of manufacture, comprising a miRNA inhibitor of the present disclosure (e.g., a polynucleotide, vector, or pharmaceutical composition disclosed herein) and optionally instructions for use, e.g., instructions for use according to the methods disclosed herein. In some aspects, the kit or product of manufacture comprises a miR-485 inhibitor (*e.g.*, vector, *e.g.*, an AAV vector, a polynucleotide, or a pharmaceutical composition of the present disclosure) in one or more containers. In some aspects, the kit or product of manufacture comprises miR-485 inhibitor (*e.g.*, a vector, *e.g.*, an AAV vector, a polynucleotide, or a pharmaceutical composition of the present disclosure) and a brochure. One skilled in the art will readily recognize that miR-485 inhibitors disclosed herein (*e.g.*, vectors, polynucleotides, and pharmaceutical compositions of the present disclosure, or combinations thereof) can be readily incorporated into one of the established kit formats which are well known in the art.

[0282] The following examples are offered by way of illustration and not by way of limitation.

Examples

Example 1: Preparation of miR-485 Inhibitor

[0283] **(a) Synthesis of alkyne modified tyrosine:** An alkyne modified tyrosine was generated as an intermediate for the synthesis of a tissue specific targeting moiety (TM, see FIG. 1) of a cationic carrier unit to direct micelles of the present disclosure to the LAT1 transporter in the BBB.

[0284] A mixture of N-(tert-butoxycarbonyl)-L-tyrosine methyl ester (Boc-Tyr-OMe) (0.5g, 1.69 mmol) and K_2CO_3 (1.5 equiv., 2.54 mmol) in acetonitrile (4.0 ml) was added drop by drop to propargyl bromide (1.2 equiv., 2.03 mmol). The reaction mixture was heated at 60 °C overnight. After the reaction, the reaction mixture was extracted using water:ethyl acetate (EA). Then, the organic layer was washed using a brine solution. The crude material was purified by flash column (EA in hexane 10%). Next, the resulting product was dissolved in 1,4-dioxane (1.0 ml) and 6.0 M HCl (1.0 ml). The reaction mixture was heated at 100 °C overnight. Next, the dioxane was removed and extracted by EA. Aqueous NaOH (0.5 M) solution was added to the mixture until the pH value become 7. The reactant was concentrated by evaporator and centrifuged at 12,000 rpm at 0°C. The precipitate was washed with deionized water and lyophilized.

[0285] **(b) Synthesis of poly(ethylene glycol)-*b*-poly(L-lysine) (PEG-PLL):** This synthesis step generated the water-soluble biopolymer (WP) and cationic carrier (CC) of a cationic carrier unit of the present disclosure (see FIG. 1).

[0286] Poly(ethylene glycol)-*b*-poly(L-lysine) was synthesized by ring opening polymerization of Lys(TFA)-NCA with monomethoxy PEG (MeO-PEG) as a macroinitiator. In brief, MeO-PEG (600 mg, 0.12 mmol) and Lys(TFA)-NCA (2574 mg, 9.6 mmol) were separately dissolved in DMF containing 1M thiourea and DMF(or NMP). Lys(TFA)-NCA solution was dropped into the MeO-PEG solution by micro syringe and the reaction mixture was stirred at 37 °C for 4 days. The reaction bottles were purged with argon and vacuum. All reactions were conducted in argon atmosphere. After the reaction, the mixture was precipitated into an excess amount of diethyl ether. The precipitate was re-dissolved in methanol and precipitated again into cold diethyl ether. Then it was filtered and white powder was obtained after drying in vacuo. For the deprotection of TFA group in PEG-PLL(TFA), the next step was followed.

[0287] MeO-PEG-PLL(TFA) (500 mg) was dissolved in methanol (60 mL) and 1N NaOH (6 mL) was dropped into the polymer solution with stirring. The mixture was maintained for 1 day with stirring at 37°C. The reaction mixture was dialyzed against 10 mM HEPES for 4 times and distilled water. White powder of PEG-PLL was obtained after lyophilization.

[0288] **(b) Synthesis of azido-poly(ethylene glycol)-*b*-poly(L-lysine) (N_3-PEG-PLL):** This synthesis step generated the water-soluble biopolymer (WP) and cationic carrier (CC) of a cationic carrier unit of the present disclosure (see FIG. 1).

[0289] Azido-poly(ethylene glycol)-*b*-poly(L-lysine) was synthesized by ring opening polymerization of Lys(TFA)-NCA with azido- PEG (N_3-PEG). In brief, N_3-PEG (300 mg, 0.06 mmol) and Lys(TFA)-NCA (1287 mg, 4.8 mmol) were separately dissolved in DMF containing 1M thiourea and DMF(or NMP). Lys(TFA)-NCA solution was dropped into the N_3-PEG solution by micro syringe and the reaction mixture was stirred at 37 °C for 4 days. The reaction bottles were purged with argon and vacuum. All reactions were conducted in argon atmosphere. After the reaction, the mixture was precipitated into an excess amount of diethyl ether. The precipitate was re-dissolved in methanol and precipitated again into cold diethyl ether. Then it was filtered and white powder was obtained after drying in vacuo. For the deprotection of TFA group in PEG-PLL(TFA), the next step was followed.

[0290] N_3-PEG-PLL (500 mg) was dissolved in methanol (60 mL) and 1N NaOH (6 mL) was dropped into the polymer solution with stirring. The mixture was maintained for 1 day with stirring at 37°C. The reaction mixture was dialyzed against 10 mM HEPES for 4 times and distilled water. White powder of N_3-PEG-PLL was obtained after lyophilization.

[0291] **(c) Synthesis of (methoxy or) azido-poly(ethylene glycol)-b-poly(L-lysine/nicotinamide/mercaptopropanamide) (N_3-PEG-PLL(Nic/SH)):** In this step, the tissue-specific adjuvant moieties (AM, see FIG. 1) were attached to the WP-CC component of a cationic carrier unit of the present disclosure. The tissue-specific adjuvant moiety (AM) used in the cationic carrier unit was nicotinamide (vitamin B3). This step would yield the WP-CC-AM components of the cationic carrier unit depicted in FIG. 1.

[0292] Azido-poly(ethylene glycol)-b-poly(L-lysine/nicotinamide/mercaptopropanamide) (N_3-PEG-PLL(Nic/SH)) was synthesized by chemical modification of N_3-PEG-PLL and nicotinic acid in the presence of EDC/NHS. N_3-PEG-PLL (372 mg, 25.8 μmol) and nicotinic acid (556.7 mg, 1.02 equiv. to NH2 of PEG-PLL) were separately dissolved in mixture of deionized water and methanol (1:1). EDC•HCl (556.7 mg, 1.5 equiv. to NH_2 of N_3-PEG-PLL) was added into nicotinic acid solution and NHS (334.2 mg, 1.5 equiv. to NH2 of PEG-PLL) stepwise added into the mixture.

[0293] The reaction mixture was added into the N_3-PEG-PLL solution. The reaction mixture was maintained at 37 °C for 16 hours with stirring. After 16 hours, 3,3'-dithiodiproponic acid (36.8 mg, 0.1 equiv.) was dissolved in methanol, EDC•HCl (40.3 mg, 0.15 equiv.), and NHS (24.2 mg, 0.15 equiv.) were dissolved each in deionized water. Then, NHS and EDC•HCl were added sequentially into 3,3'-dithiodiproponic acid solution. The mixture solution was stirred for 4 hours at 37 °C after adding crude N_3-PEG-PLL(Nic) solution.

[0294] For purification, the mixture was dialyzed against methanol for 2 hours, added DL-dithiothreitol (DTT, 40.6 mg, 0.15 equiv.), then activated for 30 min.

[0295] For removing the DTT, the mixture was dialyzed sequentially methanol, 50 % methanol in deionized water, deionized water.

[0296] **d) Synthesis of Phenyl alanine-poly(ethylene glycol)-b-poly(L-lysine/nicotinamide/mercaptopropanamide) (Phe-PEG-PLL(Nic/SH)):** In this step, the tissue-specific targeting moiety (TM) was attached to the WP-CC-AM component synthesized in the previous step. The TM component (phenyl alanine) was generated by reaction of the intermediate generated in step (a) with the product of step (c).

[0297] To target brain endothelial tissue in blood vessels, as a LAT1 targeting amino acid, phenyl alanine was introduced by click reaction between N_3-PEG-PLL(Nic/SH) and alkyne modified tyrosine in the presence of copper catalyst In brief, N_3-PEG-PLL(Nic/SH) (130 mg, 6.5 μmol) and alkyne modified phenyl alanine (5.7 mg, 4.0 equiv.) were dissolved in deionized water (or 50 mM sodium phosphate buffer). Then, CuSO4•H2O (0.4 mg, 25 mol%) and Tris(3-hydroxypropyltriazolylmethyl)amine (THPTA, 3.4 mg, 1.2 equiv.) were dissolved deionized water and added N_3-PEG-PLL(Nic/SH) solution. Then, sodium ascorbate (3.2 mg, 2.5 equiv.) were added into the mixture solution. The reaction mixture was maintained with stirring for 16 hours at room temperature. After the reaction, the mixture was transferred into dialysis membranes (MWCO = 7,000) and dialyzed against deionized water for 1 day. The final product was obtained after lyophilization.

[0298] (e) **Polyion Complex (PIC) micelle preparation** - Once the cationic carrier units of the present disclosure were generated as described above, micelles were produced. The micelles described in the present example comprised cationic carrier units combined with an antisense oligonucleotide payload.

[0299] Nano sized PIC micelles were prepared by mixing MeO- or Phe-PEG-PLL(Nic) and miRNA. PEG-PLL(Nic) was dissolved in HEPES buffer (10 mM) at 0.5 mg/mL concentration. Then a miRNA solution (22.5 μM) in RNAse free water was mixed with the polymer solution at 2:1 (v/v) ratio of miRNA inhibitor (SEQ ID NOs: 2-30) (*e.g.*, AGAGAGGAGAGCCGUGUAUGAC; SEQ ID NO: 30) to polymer.

[0300] The mixing ratio of polymer to anti-miRNA was determined by optimizing micelle forming conditions, *i.e.*, ratio between amine in polymer (carrier of the present disclosure) to phosphate in anti-miRNA (payload). The mixture of polymer (carrier) and anti-miRNA (payload) was vigorously mixed for 90 seconds by multi-vortex at 3000 rpm, and kept at room temperature for 30 min to stabilize the micelles.

[0301] Micelles (10 μM of Anti-miRNA concentration) were stored at 4 °C prior to use. MeO- or Phe- micelles were prepared using the same method, and different amounts of Phe-containing micelles (25% ~75%) were also prepared by mixing both polymers during micelle preparation.

Example 2: Analysis of IL-1β and PGC-1α expression in ALS

[0302] To begin assessing whether the miR-485 inhibitors disclosed herein can treat ALS, an established ALS animal model (*i.e.*, SOD1-ALS mice) was used. To generate the ALS mice,

female SOD1G93A mutant transgenic mice background B6/SJL were purchased from the Jackson Laboratory and bred with WT B6/SJL. The genotype of SOD1G93A mutant mice was confirmed by PCR analysis of tail DNA following standard PCR conditions provided by The Jackson Laboratory. Mice of mixed genotypes were housed four to five per cage with a 12-hour light/12-hour dark cycle and food and water ad libitum. All animal procedures were performed according to the Konyang University guidelines for care and use of laboratory animals.

[0303] Briefly, tissue samples from the spinal cord (lumbar region) and skeletal muscle from ALS mice and wild-type animals were isolated. Then, western blot was used to measure IL-1β and PGC-1α expression. As shown in FIGs. 2A and 2B, in the spinal cord, there was a marked increase in IL-1β expression, a known inflammatory mediator. In the skeletal muscle, compared to the wild-type animals, the ALS mice expressed lower levels of PGC-1α expression.

[0304] These results suggest that ALS is associated with certain differences in gene expression, which could be targeted using miR-485 inhibitors of the present disclosure.

Example 3: Analysis of miR-485 Inhibitor on Disease Onset

[0305] To begin assessing the above hypothesis, ALS mice were treated with two administrations of a miR-485 inhibitor (total dose = 3 μg/mouse) via ICV injection. Control ALS mice received two administrations of PBS , an antisense oligonucleotide which had previously been tested to slow the progression of ALS, via ICV injection. Then, the onset of ALS was assessed. Mice were assessed for six times in about two weeks. Mice without any symptom were scored as 0. Mice with trembling hind limbs was scored as 1. Mice showing rigidly paralyzed hind limbs when the mice were suspended by tail were scored as 2. Mice showing falling or difficulty in walking were scored as 3. Mice that drag the hind limbs and could not stand were scored as 4. Mice that could not correct the position when the mice were left lying on the back were scored 5. If the score of the assessment in mice was less than 4, the mice were considered as exhibiting disease onset.

[0306] As shown in FIGs. 3A and 3B, animals treated with the miR-485 inhibitor disclosed herein had significantly later disease onset compared to the control animals that were treated with PBS. The average disease onset in the control animals was about 90 days. In the miR-485 treated animals, disease onset was delayed about nearly a month (*i.e.*, about 120 days).

Additionally, the animals treated with the miR-485 inhibitor also exhibited increased survival compared to the control animals (*see* FIG. 3C).

Example 4: Analysis of miR-485 Inhibitor on Muscle Strength

[0307] To determine whether the miR-485 inhibitors can also improve other symptoms associated with ALS, a hang wire test was performed on the mice from Example 3 to measure muscle strength. As shown in FIG. 4, animals treated with the miR-485 inhibitor exhibited much increased latency to fall time compared to animals treated with PBS at all times measured.

[0308] Collectively, the above results demonstrate that the miR-485 inhibitors can have therapeutic effects in ALS subjects by not only delaying disease onset but can also improve one or more symptoms associated with ALS (*e.g.*, muscle weakness). Moreover, the above data shows that compared to other drugs in the art, the miR-485 inhibitor disclosed herein exerts much greater therapeutic effects at significantly lower doses.

Example 5: Analysis of the Therapeutic Effects of miR-485 Inhibitor after Intravenous Administration

[0309] To further assess the therapeutic effects of the miR-485 inhibitors, ALS mice (*see* Example 2) received intravenous administration of either PBS or a miR-485 inhibitor (2.5 mg/kg per dose) starting at about two months (*i.e.*, day 66) post-birth. *See* FIG. 9A. Each of the mice received four total doses at a dosing interval of 1x/week (on days 66, 73, 80, and 87 post-birth). Then, at about 100-125 days post-birth, body weight and motor function was assessed using rotarod, hang wire, and balance beam tests as described further below. Some of the animals were also sacrificed and the expression of various proteins (*e.g.*, ChAT1, Iba1, PGC1, SIRT1, GFAP, TNF, and IL-1) was assessed in lumbar spinal cord using western blot and/or immunohistochemistry.

[0310] Disease onset was assessed by using a neurological score test. Neurological Score test was evaluated as follow: 4 normal (no sign of motor dysfunction); 3 hind limbs tremors were present when the mice were suspended by tail; 2 gait abnormalities; 1 dragging at least one hind limb; 0 inability to right itself in 30 sec when animal was placed on the supine position. When a neurological score 3 or less occurred continuously for 2 weeks, it was evaluated as a disease onset.

[0311] *Rotarod*: Mice were trained on the rotarod apparatus (3cm rod diameter) at a fixed speed of 10 rpm for 600 s once daily for 3 consecutive days. Performance on the rod was evaluated at a constant acceleration rate of 4-40 rpm in 300 s. Two consecutive trials were performed at 60 min intervals.

[0312] *Hang wire test*: For the wire hang test of motor coordination, mice were tested on 2 mm thick and 55 cm long taut metal wires. The custom-built were hang apparatus consisted of a black polystyrene box that was 60 cm long into which mice could fall. The latency of the mice to fall from the wire after being suspended was recorded measuring the longest suspension time in 3 trials per mouse.

[0313] *Balance beam test*: Mice were on a 0.5cm wide, 1m long balance beam apparatus. The balance beam consisted of a transparent Plexiglas structure that was 50 cm high with a dark resting box at the end of the runway. Mice were trained on the beam for three times in the morning, allowing for a resting inter-trial period of a least 15 min. Mice were left in the dark resting box for at least 10 s before being placed back in their home cage. Mice were then re-tested in the afternoon, at least 2 h after the training session. During test session, mice performance was recorded. The test consisted of three trials with a resting inter-trial period of at least 10 min. The number of total paw slips was calculated manually for the last of the three tests.

[0314] As shown in FIG. 9B, compared to the control animals, ALS mice treated with the miR-485 inhibitor had delayed disease onset (by approximately 21 days). Additionally, compared to the control animals, the ALS mice treated with the miR-485 inhibitor also exhibited reduced loss in body weight (*see* FIGs. 9G and 9H) and increased survival (*see* FIG. 9I). And, as shown in FIGs. 9C-9F, ALS mice treated with the miR-485 inhibitor also exhibited improved motor function. For instance, after miR-485 inhibitor administration, the ALS mice exhibited increased latency to fall time (in both the rotarod and hang wire tests – *see* FIGs. 9C and 9D), decreased number of footslips (beam balance test – *see* FIG. 9E), and reduced beam cross time (beam balance test – *see* FIG. 9F).

[0315] The above results further demonstrate the efficacy of the miR-485 inhibitors of the present disclosure in treating ALS, *e.g.*, resulting in improved motor function, reduced loss in body weight, delayed disease onset, and increased survival.

Example 6: Analysis of the safety profile of miR-485 inhibitors

[0316] To assess whether the *in vivo* administration of miR-485 inhibitors could result in any adverse effects, a single dose toxicity test was performed. Briefly, the miR-485 inhibitor was administered to male and female rats at one of the following doses: (i) 0 mg/kg (G1), (ii) 3.75 mg/kg (G2), (iii) 7.5 mg/kg (G3), and (iv) 15 mg/kg (G4). Then, any abnormalities in body weight, mortality, clinical signs, and pathology were observed in the animals at various time points post-transfer.

[0317] As shown in FIGs. 5A and 5B, the administration of the miR-485 inhibitor (at all doses tested) did not appear to have any abnormal effects on body weight in both the male and female rats. Similarly, no mortality and pathological abnormalities were observed in any of the treated animals (*see* FIGs. 6A, 6B, 8A, and 8B). As for possible clinically relevant side effects (*e.g.*, NOA, congestion (tail), and edema (face, forelimb, or hind limb)), any such effects were gone by 1 day post-administration in all the treated animals (*see* FIGs. 7A and 7B).

[0318] The above results demonstrate that the miR-485 inhibitors disclosed herein not only have therapeutic effects in treating ALS, but are also safe when administered *in vivo*.

Example 7: Analysis of the effect of miR-485 inhibitors on SOD1 activity

[0319] SOD1 (also known as copper-zinc superoxide dismutate enzyme) plays an important role in keeping cells (*e.g.*, neurons) safe from oxidative stress. Mutations in SOD1 (*e.g.*, G93A) have been implicated in ALS. Accordingly, to better understand the potential mechanisms by which the miR-485 inhibitors disclosed herein treat ALS, NSC-34 cells (hybrid cell line produced by fusion of motor neuron enriched, embryonic mouse spinal cord cells with mouse neuroblastoma) were transfected with GFP-tagged wild-type SOD1 (SOD1WT) and SOD1 comprising the G93A mutation (SOD1G93A) constructs. Then, the transfected cells were treated with varying concentrations (0, 50, 100, or 300 nM) of the miR-485 inhibitor. Various SOD1-related activity (SOD1 aggregation, SIRT1 and PGC-1α expression, and apoptosis) was assessed in the transfected cells using both Western blot and immunofluorescence. To assess by Western blot, at 48 hours post transfection, total cell extracts were prepared in 2% SDS in Tris buffer (pH 7.5). Then, insolubility in non-denaturing detergents of SOD1 species was assessed. To assess by immunofluorescence, prior to the transfection, the NSC-34 cells were seeded on coverslips and grown overnight. Then, 48 hours after transfection, the cells were washed in PBS, fixed with methanol for 10 min at room temperature, and permeabilized with 0.1% Triton X-100 in PBS for 10 min at room temperature in a moisture chamber. Antibodies and concentrations employed were: mouse GFP (Santacruz),

1:100; rabbit anti-LC3B (Cell Signaling Technology). Images were obtained using a confocal microscope (Leica 524 DMi8).

[0320] As shown in FIG. 10A, miR-485 inhibitor treatment in the transfected NSC-34 cells resulted in concentration dependent reduction in mutant SOD1 aggregation, as assessed by Western blot. This effect of the miR-485 inhibitors to reduce mutant SOD1 aggregation was also confirmed by immunofluorescence (*see* FIG. 10B). As shown, there was significantly reduced number of inclusions formed by SOD1G93A aggregation. Moreover, in the miR-485 inhibitor treated cells, SOD1G93A was frequently co-localized with expression of LC3B (*see* white arrows in FIG. 10B), which is a subunit of the MAP1A and MAP1B microtubule-binding proteins and plays a central role in autophagosome membrane structure. The colocalization of LC3B with SOD1G93A indicated that a portion of the cytoplasmic SOD1 can be degraded through the autophagy-endolysosomal system. Additionally, both SIRT1 and PGC-1α protein expression increased in SOD1G93A transfected NSC-34 cells treated with the miR-485 inhibitor (*see* FIG. 10C). Treatment with the miR-485 inhibitor did not appear to have any significant effect on SIRT1 and PGC-1α protein expression in NSC-34 cells transfected with the wild-type SOD1. Lastly, the miR-485 inhibitor treatment also reduced SOD1G93A-induced apoptosis, as evidenced by the reduced expression of cleaved caspase-3 in NSC-34 cells transfected with SOD1G93A construct and treated with the miR-485 inhibitor.

[0321] Not to be bound by any one theory, the results provided above collectively demonstrate that the miR-485 inhibitors provided herein can treat ALS by repressing SOD1G93A induced neuronal damage.

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[0322] It is to be appreciated that the Detailed Description section, and not the Summary and Abstract sections, is intended to be used to interpret the claims. The Summary and Abstract sections can set forth one or more but not all exemplary aspects of the present disclosure as contemplated by the inventor(s), and thus, are not intended to limit the present disclosure and the appended claims in any way.

[0323] The present disclosure has been described above with the aid of functional building blocks illustrating the implementation of specified functions and relationships thereof. The boundaries of these functional building blocks have been arbitrarily defined herein for the

convenience of the description. Alternate boundaries can be defined so long as the specified functions and relationships thereof are appropriately performed.

[0324] The foregoing description of the specific aspects will so fully reveal the general nature of the disclosure that others can, by applying knowledge within the skill of the art, readily modify and/or adapt for various applications such specific aspects, without undue experimentation, without departing from the general concept of the present disclosure. Therefore, such adaptations and modifications are intended to be within the meaning and range of equivalents of the disclosed aspects, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance.

[0325] The breadth and scope of the present disclosure should not be limited by any of the above-described exemplary aspects, but should be defined only in accordance with the following claims and their equivalents.

[0326] The contents of all cited references (including literature references, patents, patent applications, and websites) that can be cited throughout this application are hereby expressly incorporated by reference in their entirety for any purpose, as are the references cited therein.

WHAT IS CLAIMED IS:

1. A method of treating an amyotrophic lateral sclerosis (ALS) in a subject in need thereof comprising administering to the subject a compound that inhibits miR-485 (miRNA inhibitor).

2. The method of claim 1, wherein the miRNA inhibitor increases a level of a SIRT1 protein and/or a SIRT1 gene in the subject.

3. The method of claim 1 or 2, wherein the subject has an ALS associated with a decreased level of a SIRT1 protein and/or a SIRT1 gene.

4. The method of claim 1 or 2, wherein the miRNA inhibitor induces autophagy and/or treats or prevents inflammation.

5. The method of any one of claims 1 to 4, wherein the miRNA inhibitor increases a level of a CD36 protein and/or a CD36 gene in the subject.

6. The method of any one of claims 1 to 5, wherein the subject has an ALS associated with a decreased level of a CD36 protein and/or a CD36 gene.

7. The method of any one of claims 1 to 6, wherein the miRNA inhibitor increases a level of a PGC-1α protein and/or a PGC-1α gene in the subject.

8. The method of any one of claims 1 to 7, wherein the subject has an ALS associated with a decreased level of a PGC-1α protein and/or a PGC-1α gene.

9. The method of any one of claims 1 to 8, wherein the miRNA inhibitor increases a level of a NRG1 protein and/or a NRG1 gene in the subject.

10. The method of any one of claims 1 to 9, wherein the subject has an ALS associated with a decreased level of a NRG1 protein and/or a NRG1 gene.

11. The method of any one of claims 1 to 8, wherein the miRNA inhibitor increases a level of a STMN2 protein and/or a STMN2 gene in the subject.

12. The method of any one of claims 1 to 9, wherein the subject has an ALS associated with a decreased level of a STMN2 protein and/or a STMN2 gene.

13. The method of any one of claims 1 to 10, wherein the miRNA inhibitor increases a level of a NRXN1 protein and/or a NRXN1 gene in the subject.

14. The method of any one of claims 1 to 9, wherein the subject has an ALS associated with a decreased level of a NRXN1 protein and/or a NRXN1 gene.

15. The method of any one of claims 1 to 14, wherein the miRNA inhibitor induces neurogenesis.

16. The method of claim 15, wherein inducing neurogenesis comprises an increased proliferation, differentiation, migration, and/or survival of neural stem cells and/or progenitor cells.

17. The method of claim 15 or 16, wherein inducing neurogenesis comprises an increased number of neural stem cells and/or progenitor cells.

18. The method of any one of claims 15 to 17, wherein inducing neurogenesis comprises an increased axon, dendrite, and/or synapse development.

19. The method of any one of claims 1 to 18, wherein the miRNA inhibitor induces phagocytosis.

20. A method of treating an amyotrophic lateral sclerosis (ALS) associated with an abnormal level of a SIRT1 protein and/or a SIRT1 gene in a subject in need thereof comprising administering to the subject a compound that inhibits miR-485 (miRNA inhibitor), wherein the miRNA inhibitor increases the level of the SIRT1 protein and/or SIRT1 gene.

21. A method of treating an amyotrophic lateral sclerosis (ALS) associated with an abnormal level of a CD36 protein and/or a CD36 gene in a subject in need thereof comprising administering to the subject a compound that inhibits miR-485 (miRNA inhibitor), wherein the miRNA inhibitor increases the level of the CD36 protein and/or CD36 gene.

22. A method of treating an amyotrophic lateral sclerosis (ALS) associated with an abnormal level of a PGC-1α protein and/or a PGC-1α gene in a subject in need thereof comprising administering to the subject a compound that inhibits miR-485 (miRNA inhibitor), wherein the miRNA inhibitor increases the level of the PGC-1α protein and/or PGC-1α gene.

23. A method of treating an amyotrophic lateral sclerosis (ALS) associated with an abnormal level of a NRG1 protein and/or a NRG1 gene in a subject in need thereof comprising administering to the subject a compound that inhibits miR-485 (miRNA inhibitor), wherein the miRNA inhibitor increases the level of the NRG1 protein and/or NRG1 gene.

24. A method of treating an amyotrophic lateral sclerosis (ALS) associated with an abnormal level of a STMN2 protein and/or a STMN2 gene in a subject in need thereof comprising administering to the subject a compound that inhibits miR-485 (miRNA inhibitor), wherein the miRNA inhibitor increases the level of the STMN2 protein and/or STMN2 gene.

25. A method of treating an amyotrophic lateral sclerosis (ALS) associated with an abnormal level of a NRXN1 protein and/or a NRXN1 gene in a subject in need thereof comprising administering to the subject a compound that inhibits miR-485 (miRNA inhibitor), wherein the miRNA inhibitor increases the level of the NRXN1 protein and/or NRXN1 gene.

26. The method of any one of claims 1 to 25, wherein the miRNA inhibitor inhibits miR485-3p.

27. The method of claim 26, wherein the miR485-3p comprises 5'-gucauacacggcucuccucucu-3' (SEQ ID NO: 1).

28. The method of any one of claims 1 to 26, wherein the miRNA inhibitor comprises a nucleotide sequence comprising 5'- UGUAUGA-3' (SEQ ID NO: 2) and wherein the miRNA inhibitor comprises about 6 to about 30 nucleotides in length.

29. The method of any one of claims 1 to 28, wherein the miRNA inhibitor increases transcription of an SIRT1, PGC-1α, CD36, NRG1, STMN2, and/or NRXN1 gene and/or expression of a SIRT1, PGC-1α, CD36, NRG1, STMN2, and/or NRXN1 protein.

30. The method of any one of claims 1 to 29, wherein the miRNA inhibitor comprises at least 1 nucleotide, at least 2 nucleotides, at least 3 nucleotides, at least 4 nucleotides, at least 5 nucleotides, at least 6 nucleotides, at least 7 nucleotides, at least 8 nucleotides, at least 9 nucleotides, at least 10 nucleotides, at least 11 nucleotides, at least 12 nucleotides, at least 13 nucleotides, at least 14 nucleotides, at least 15 nucleotides, at least 16 nucleotides, at least 17 nucleotides, at least 18 nucleotides, at least 19 nucleotides, or at least 20 nucleotides at the 5' of the nucleotide sequence.

31. The method of any one of claims 1 to 30, wherein the miRNA inhibitor comprises at least 1 nucleotide, at least 2 nucleotides, at least 3 nucleotides, at least 4 nucleotides, at least 5 nucleotides, at least 6 nucleotides, at least 7 nucleotides, at least 8 nucleotides, at least 9 nucleotides, at least 10 nucleotides, at least 11 nucleotides, at least 12 nucleotides, at least 13 nucleotides, at least 14 nucleotides, at least 15 nucleotides, at least 16 nucleotides, at least 17 nucleotides, at least 18 nucleotides, at least 19 nucleotides, or at least 20 nucleotides at the 3' of the nucleotide sequence.

32. The method of any one of claims 1 to 26 and 29 to 31, wherein the miRNA inhibitor has a sequence selected from the group consisting of: 5'-UGUAUGA-3' (SEQ ID NO: 2), 5'-GUGUAUGA-3' (SEQ ID NO: 3), 5'-CGUGUAUGA-3' (SEQ ID NO: 4), 5'-CCGUGUAUGA-3' (SEQ ID NO: 5), 5'-GCCGUGUAUGA-3' (SEQ ID NO: 6), 5'-AGCCGUGUAUGA-3' (SEQ ID NO: 7), 5'-GAGCCGUGUAUGA-3' (SEQ ID NO: 8), 5'-AGAGCCGUGUAUGA-3' (SEQ ID NO: 9), 5'-GAGAGCCGUGUAUGA-3' (SEQ ID NO: 10), 5'-GGAGAGCCGUGUAUGA-3' (SEQ ID NO: 11), 5'-AGGAGAGCCGUGUAUGA-3' (SEQ ID NO: 12), 5'-GAGGAGAGCCGUGUAUGA-3' (SEQ ID NO: 13), 5'-AGAGGAGAGCCGUGUAUGA-3' (SEQ ID NO: 14), 5'-GAGAGGAGAGCCGUGUAUGA-3' (SEQ ID NO: 15); 5'-UGUAUGAC-3' (SEQ ID NO: 16), 5'-GUGUAUGAC-3' (SEQ ID NO: 17), 5'-CGUGUAUGAC-3' (SEQ ID NO:

18), 5'-CCGUGUAUGAC-3' (SEQ ID NO: 19), 5'-GCCGUGUAUGAC-3' (SEQ ID NO: 20), 5'-AGCCGUGUAUGAC-3' (SEQ ID NO: 21), 5'-GAGCCGUGUAUGAC-3' (SEQ ID NO: 22), 5'-AGAGCCGUGUAUGAC-3' (SEQ ID NO: 23), 5'-GAGAGCCGUGUAUGAC-3' (SEQ ID NO: 24), 5'-GGAGAGCCGUGUAUGAC-3' (SEQ ID NO: 25), 5'-AGGAGAGCCGUGUAUGAC-3' (SEQ ID NO: 26), 5'-GAGGAGAGCCGUGUAUGAC-3' (SEQ ID NO: 27), 5'-AGAGGAGAGCCGUGUAUGAC-3' (SEQ ID NO: 28), 5'-GAGAGGAGAGCCGUGUAUGAC-3' (SEQ ID NO: 29), and 5'-AGAGAGGAGAGCCGUGUAUGAC-3' (SEQ ID NO: 30).

33. The method of any one of claims 1 to 26 and 29 to 31, wherein the miRNA inhibitor has a sequence selected from the group consisting of: 5'-TGTATGA-3' (SEQ ID NO: 62), 5'-GTGTATGA-3' (SEQ ID NO: 63), 5'-CGTGTATGA-3' (SEQ ID NO: 64), 5'-CCGTGTATGA-3' (SEQ ID NO: 65), 5'-GCCGTGTATGA-3' (SEQ ID NO: 66), 5'-AGCCGTGTATGA-3' (SEQ ID NO: 67), 5'-GAGCCGTGTATGA-3' (SEQ ID NO: 68), 5'-AGAGCCGTGTATGA-3' (SEQ ID NO: 69), 5'-GAGAGCCGTGTATGA-3' (SEQ ID NO: 70), 5'-GGAGAGCCGTGTATGA-3' (SEQ ID NO: 71), 5'-AGGAGAGCCGTGTATGA-3' (SEQ ID NO: 72), 5'-GAGGAGAGCCGTGTATGA-3' (SEQ ID NO: 73), 5'-AGAGGAGAGCCGTGTATGA-3' (SEQ ID NO: 74), 5'-GAGAGGAGAGCCGTGTATGA-3' (SEQ ID NO: 75); 5'-TGTATGAC-3' (SEQ ID NO: 76), 5'-GTGTATGAC-3' (SEQ ID NO: 77), 5'-CGTGTATGAC-3' (SEQ ID NO: 78), 5'-CCGTGTATGAC-3' (SEQ ID NO: 79), 5'-GCCGTGTATGAC-3' (SEQ ID NO: 80), 5'-AGCCGTGTATGAC-3' (SEQ ID NO: 81), 5'-GAGCCGTGTATGAC-3' (SEQ ID NO: 82), 5'-AGAGCCGTGTATGAC-3' (SEQ ID NO: 83), 5'-GAGAGCCGTGTATGAC-3' (SEQ ID NO: 84), 5'-GGAGAGCCGTGTATGAC-3' (SEQ ID NO: 85), 5'-AGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 86), 5'-GAGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 87), 5'-AGAGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 88), 5'-GAGAGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 89), and 5'-AGAGAGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 90).

34. The method of any one of claims 1 to 31, wherein the sequence of the miRNA inhibitor is at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% sequence identity to 5'- AGAGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 30) or 5'-AGAGAGGAGAGCCGTGTATGAC -3' (SEQ ID NO: 90).

35. The method of claim 34, wherein the miRNA inhibitor has a sequence that has at least 90% similarity to 5'- AGAGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 30) or 5'- AGAGAGGAGAGCCGTGTATGAC -3' (SEQ ID NO: 90).

36. The method of any one of claims 1 to 34, wherein the miRNA inhibitor comprises the nucleotide sequence 5'- AGAGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 30) or 5'- AGAGAGGAGAGCCGTGTATGAC -3' (SEQ ID NO: 90) with one substitution or two substitutions.

37. The method of any one of claims 1 to 34, wherein the miRNA inhibitor comprises the nucleotide sequence 5'- AGAGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 30) or 5'- AGAGAGGAGAGCCGTGTATGAC -3' (SEQ ID NO: 90).

38. The method of claim 37, wherein the miRNA inhibitor comprises the nucleotide sequence 5'- AGAGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 30).

39. The method of any one of claims 1 to 38, wherein the miRNA inhibitor comprises at least one modified nucleotide.

40. The method of claim 39, wherein the at least one modified nucleotide is a locked nucleic acid (LNA), an unlocked nucleic acid (UNA), an arabino nucleic acid (ABA), a bridged nucleic acid (BNA), and/or a peptide nucleic acid (PNA).

41. The method of any one of claims 1 to 40, wherein the miRNA inhibitor comprises a backbone modification.

42. The method of claim 41, wherein the backbone modification is a phosphorodiamidate morpholino oligomer (PMO) and/or phosphorothioate (PS) modification.

43. The method of any one of claims 1 to 42, wherein the miRNA inhibitor is delivered in a delivery agent.

44. The method of claim 43, wherein the delivery agent is a micelle, an exosome, a lipid nanoparticle, an extracellular vesicle, or a synthetic vesicle.

45. The method of any one of claims 1 to 44, wherein the miRNA inhibitor is delivered by a viral vector.

46. The method of claim 45, wherein the viral vector is an AAV, an adenovirus, a retrovirus, or a lentivirus.

47. The method of claim 46, wherein the viral vector is an AAV that has a serotype of AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, or any combination thereof.

48. The method of any one claims 1 to 47, wherein the miRNA inhibitor is delivered with a delivery agent.

49. The method of claim 48, wherein the delivery agent comprises a lipidoid, a liposome, a lipoplex, a lipid nanoparticle, a polymeric compound, a peptide, a protein, a cell, a nanoparticle mimic, a nanotube, or a conjugate.

50. The method of claim 48 or 49, wherein the delivery agent comprises a cationic carrier unit comprising

[WP]-L1-[CC]-L2-[AM] (formula I)

or

[WP]-L1-[AM]-L2-[CC] (formula II)

wherein

WP is a water-soluble biopolymer moiety;

CC is a positively charged carrier moiety;

AM is an adjuvant moiety; and,

L1 and L2 are independently optional linkers, and

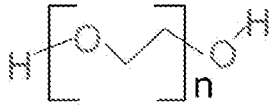
wherein when mixed with a nucleic acid at an ionic ratio of about 1:1, the cationic carrier unit forms a micelle.

51. The method of claim 50, wherein the miRNA inhibitor interacts with the cationic carrier unit via an ionic bond.

52. The method of claims 50 or 51, wherein the water-soluble polymer comprises poly(alkylene glycols), poly(oxyethylated polyol), poly(olefinic alcohol), poly(vinylpyrrolidone), poly(hydroxyalkylmethacrylamide), poly(hydroxyalkylmethacrylate), poly(saccharides), poly(α-hydroxy acid), poly(vinyl alcohol), polyglycerol, polyphosphazene, polyoxazolines ("POZ") poly(N-acryloylmorpholine), or any combinations thereof.

53. The method of claims 50 to 52, wherein the water-soluble polymer comprises polyethylene glycol ("PEG"), polyglycerol, or poly(propylene glycol) ("PPG").

54. The method of any one of claims 50 to 53, wherein the water-soluble polymer comprises:



, (formula I),

wherein n is 1-1000.

55. The method of claim 54, wherein the n is at least about 110, at least about 111, at least about 112, at least about 113, at least about 114, at least about 115, at least about 116, at least about 117, at least about 118, at least about 119, at least about 120, at least about 121, at least about 122, at least about 123, at least about 124, at least about 125, at least about 126, at least about 127, at least about 128, at least about 129, at least about 130, at least about 131, at least about 132, at least about 133, at least about 134, at least about 135, at least about 136, at least about 137, at least about 138, at least about 139, at least about 140, or at least about 141.

56. The method of claim 54, wherein the n is about 80 to about 90, about 90 to about 100, about 100 to about 110, about 110 to about 120, about 120 to about 130, about 140 to about 150, about 150 to about 160.

57. The method of any one of claims 50 to 56, wherein the water-soluble polymer is linear, branched, or dendritic.

58. The method of any one of claims 50 to 57, wherein the cationic carrier moiety comprises one or more basic amino acids.

59. The method of claim 58, wherein the cationic carrier moiety comprises at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least 11, at least 12, at least 13, at least 14, at last 15, at least 16, at least 17, at least 18, at least 19, at least 20, at least 21, at least 22, at least 23, at least 24, at least 25, at least 26, at least 27, at least 28, at least 29, at least 30, at least 31, at least 32, at least 33, at least 34, at least 35, at least 36, at least 37, at least 38, at least 39, at least 40, at least 41, at least 42, at least 43, at least 44, at least 45, at least 46, at least 47, at least 48, at least 49, or at least 50 basic amino acids.

60. The method of claim 59, wherein the cationic carrier moiety comprises about 30 to about 50 basic amino acids.

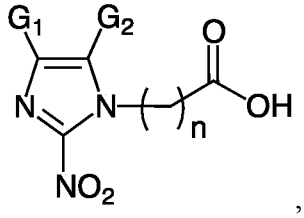
61. The method of claim 59 or 60, wherein the basic amino acid comprises arginine, lysine, histidine, or any combination thereof.

62. The method of any one of claims 50 to 61, wherein the cationic carrier moiety comprises about 40 lysine monomers.

63. The method of any one of claims 50 to 62, wherein the adjuvant moiety is capable of modulating an immune response, an inflammatory response, and/or a tissue microenvironment.

64. The method of any one of claims 50 to 63, wherein the adjuvant moiety comprises an imidazole derivative, an amino acid, a vitamin, or any combination thereof.

65. The method of claim 64, wherein the adjuvant moiety comprises:



, (formula II),

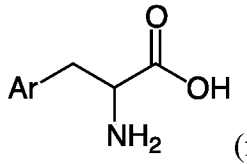
wherein each of G1 and G2 is H, an aromatic ring, or 1-10 alkyl, or G1 and G2 together form an aromatic ring, and wherein n is 1-10.

66. The method of claim 64, wherein the adjuvant moiety comprises nitroimidazole.

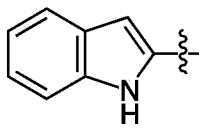
67. The method of claim 64, wherein the adjuvant moiety comprises metronidazole, tinidazole, nimorazole, dimetridazole, pretomanid, ornidazole, megazol, azanidazole, benznidazole, or any combination thereof.

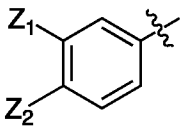
68. The method of any one of claims 50 to 64, wherein the adjuvant moiety comprises an amino acid.

69. The method of claim 68, wherein the adjuvant moiety comprises



(formula III),

wherein Ar is Ar= 

or 

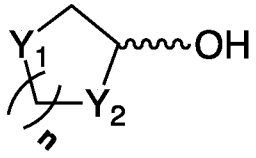
, and

wherein each of Z1 and Z2 is H or OH.

70. The method of any one of claims 50 to 63, wherein the adjuvant moiety comprises a vitamin.

71. The method of claim 70, wherein the vitamin comprises a cyclic ring or cyclic hetero atom ring and a carboxyl group or hydroxyl group.

72. The method of claim 70 or 71, wherein the vitamin comprises:



(formula IV),

wherein each of Y1 and Y2 is C, N, O, or S, and wherein n is 1 or 2.

73. The method of any one of claims 70 to 72, wherein the vitamin is selected from the group consisting of vitamin A, vitamin B1, vitamin B2, vitamin B3, vitamin B6, vitamin B7, vitamin B9, vitamin B12, vitamin C, vitamin D2, vitamin D3, vitamin E, vitamin M, vitamin H, and any combination thereof.

74. The method of any one of claims 70 to 73, wherein the vitamin is vitamin B3.

75. The method of any one of claims 70 to 74, wherein the adjuvant moiety comprises at least about two, at least about three, at least about four, at least about five, at least about six, at least about seven, at least about eight, at least about nine, at least about ten, at least about 11, at least about 12, at least about 13, at least about 14, at least about 15, at least about 16, at least about 17, at least about 18, at least about 19, or at least about 20 vitamin B3.

76. The method of claim 63, wherein the adjuvant moiety comprises about 10 vitamin B3.

77. The method of any one of claims 70 to 76, wherein the delivery agent comprises about a water-soluble biopolymer moiety with about 120 to about 130 PEG units, a cationic carrier moiety comprising a poly-lysine with about 30 to about 40 lysines, and an adjuvant moiety with about 5 to about 10 vitamin B3.

78. The method of any one of claims 70 to 77, wherein the delivery agent is associated with the miRNA inhibitor, thereby forming a micelle.

79. The method of claim 78, wherein the association is a covalent bond, a non-covalent bond, or an ionic bond.

80. The method of claim 78 or 79, wherein the cationic carrier unit and the miRNA inhibitor in the micelle is mixed in a solution so that the ionic ratio of the positive charges of the cationic carrier unit and the negative charges of the miRNA inhibitor is about 1: 1.

81. The method of any one of claims 78 to 80, wherein the cationic carrier unit is capable of protecting the miRNA inhibitor from enzymatic degradation.

82. The method of any one of claims 1 to 81, wherein the ALS comprises sporadic ALS, familial ALS, or both.

83. The method of any one of claims 1 to 82, wherein the miRNA inhibitor delays ALS onset.

84. The method of any one of claims 1 to 83, wherein the miRNA inhibitor improves muscle strength in the subject.

85. The method of claim 48, wherein the delivery agent is a micelle.

86. The method of claim 85, wherein the micelle comprises (i) about 100 to about 200 PEG units, (ii) about 30 to about 40 lysines, each with an amine group, (iii) about 15 to about 20 lysines, each with a thiol group, and (iv) about 30 to about 40 lysines, each linked to vitamin B3.

87. The method of claim 85, wherein the micelle comprises (i) about 120 to about 130 PEG units, (ii) about 32 lysines, each with an amine group, (iii) about 16 lysines, each with a thiol group, and (iv) about 32 lysines, each linked to vitamin B3.

88. The method of claim 86 or 87, wherein a targeting moiety is further linked to the PEG units.

89. The method of claim 88, wherein the targeting moiety is a LAT 1 targeting ligand.

90. The method of claim 89, wherein the targeting moiety is pennyl alanine.

FIG. 1

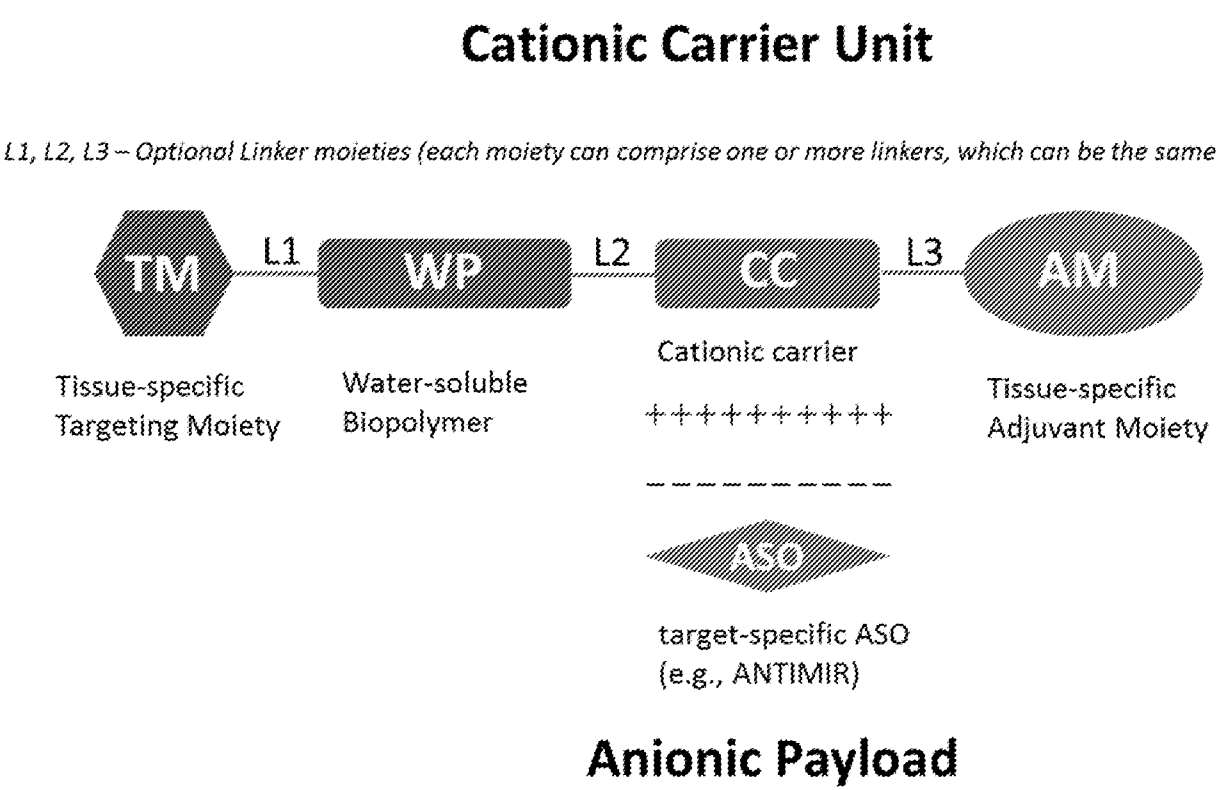

Cationic Carrier Unit
L1, L2, L3 – Optional Linker moieties (each moiety can comprise one or more linkers, which can be the same of different)
TM
L1
WP
L2
CC
L3
AM
Cationic carrier
Tissue-specific
Targeting Moiety
Water-soluble
Biopolymer
Tissue-specific
Adjuvant Moiety
ASO
target-specific ASO
(e.g., ANTIMIR)
Anionic Payload

FIG. 2B

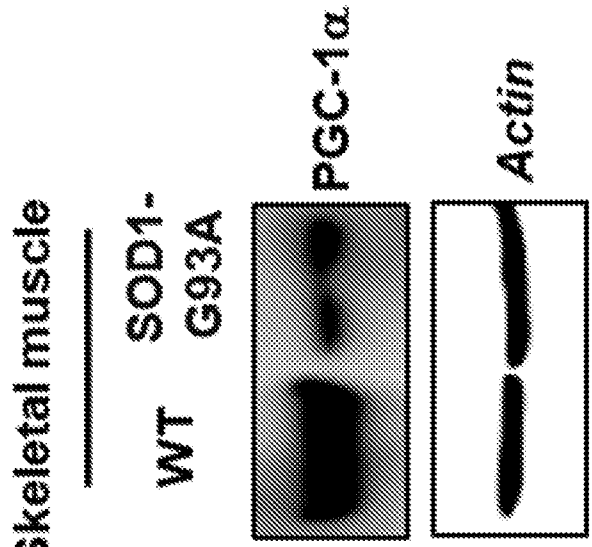
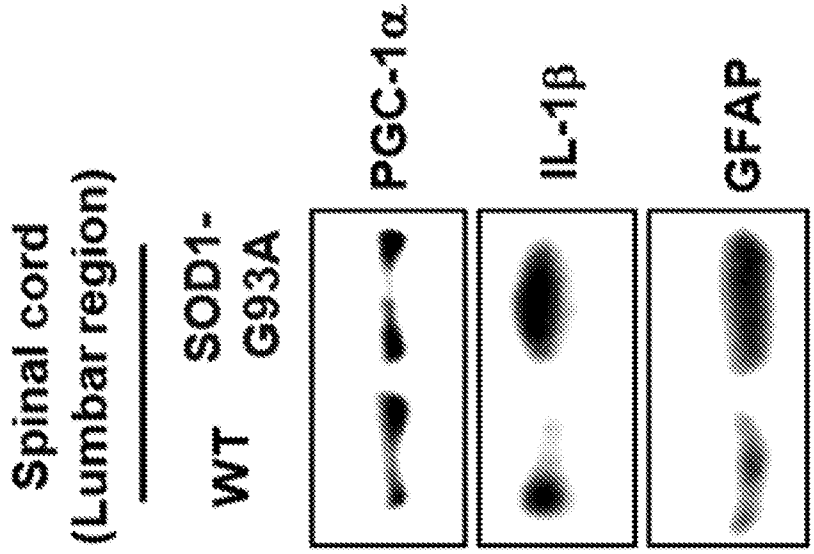

Skeletal muscle
WT
SOD1-G93A
PGC-1α
Actin

FIG. 2A


Spinal cord (Lumbar region)
WT
SOD1-G93A
PGC-1α
IL-1β
GFAP

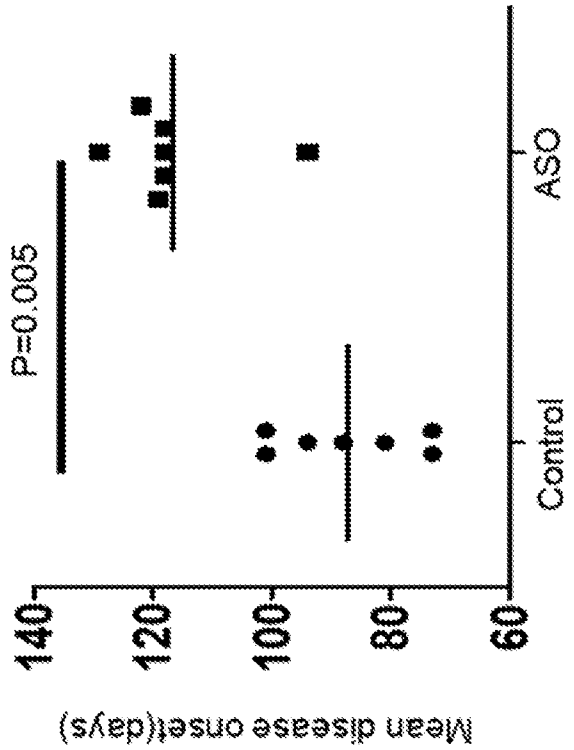

P=0.005
Control
ASO
140
120
100
80
60
Mean disease onset(days)

FIG. 3B

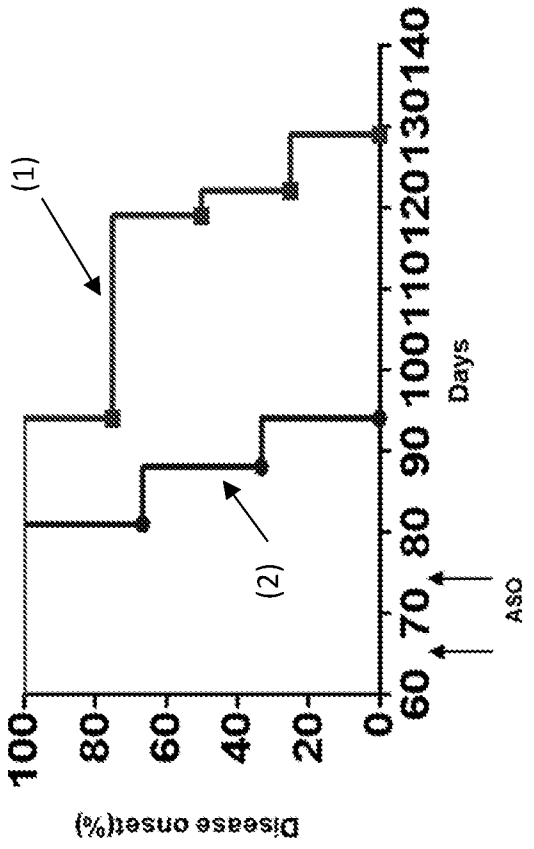

(1)
(2)
ASO
Days
Disease onset(%)
100
80
60
40
20
0
60
70
80
90
100
110
120
130
140

FIG. 3A

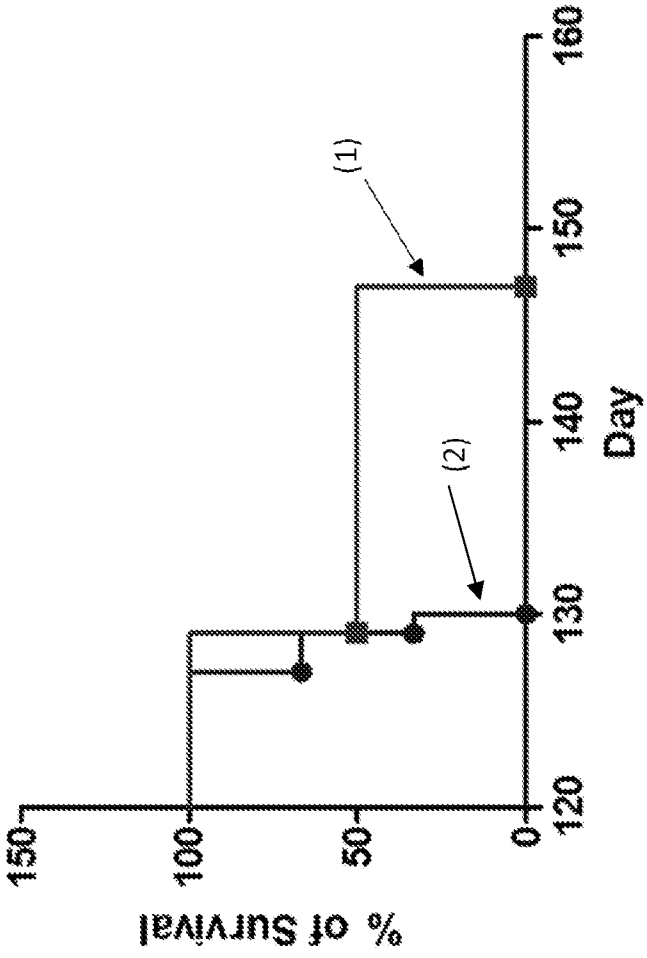


FIG. 3C

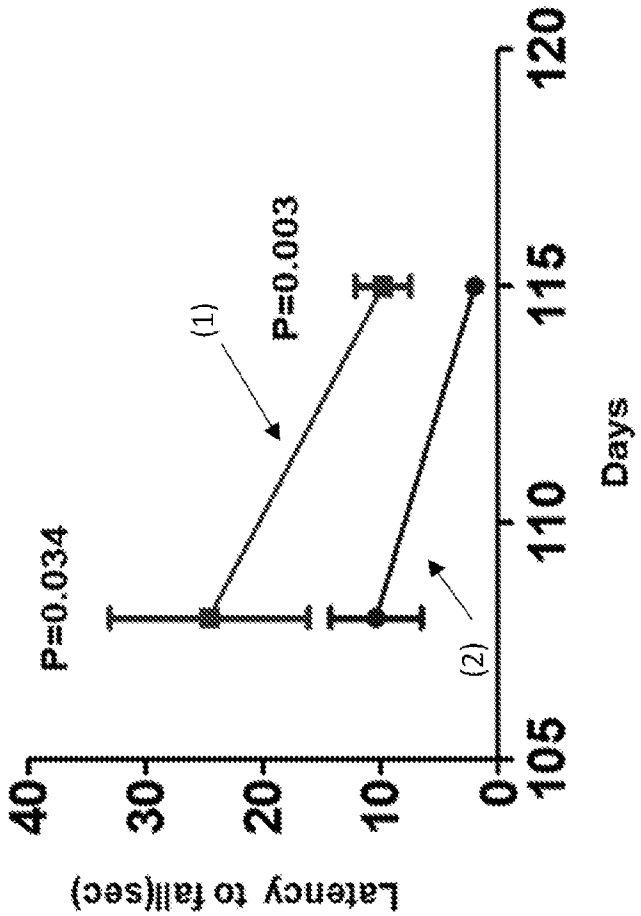

Latency to fall(sec)
40
30
20
10
0
105
110
115
120
Days
P=0.034
P=0.003
(1)
(2)

FIG. 4

FIG. 5A

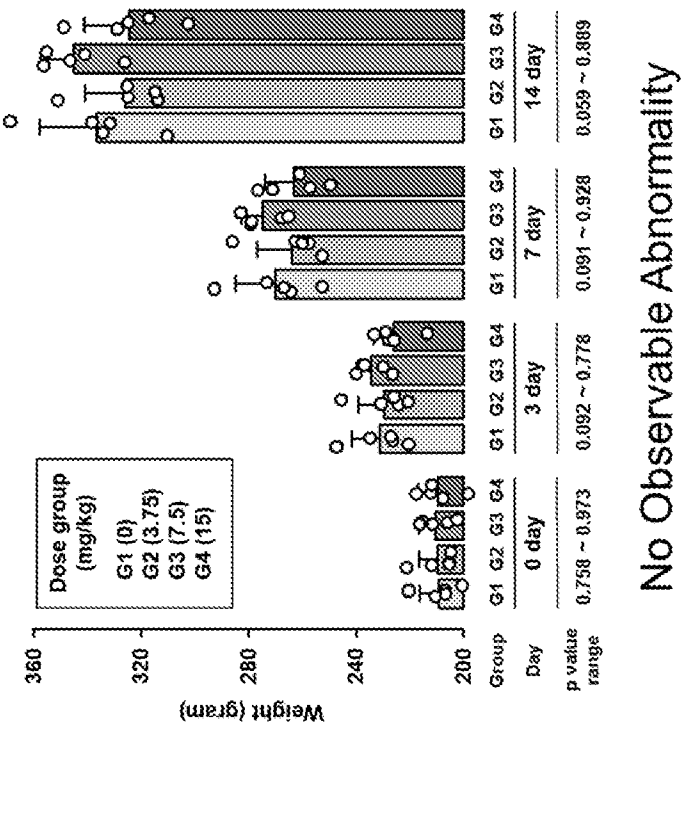

Male
Dose group (mg/kg)
G1 (0)
G2 (3.75)
G3 (7.5)
G4 (15)
Weight (gram)
360
320
280
240
200
Group
Day
p value range
G1 G2 G3 G4
0 day
3 day
7 day
14 day
0.758 ~ 0.973
0.092 ~ 0.778
0.091 ~ 0.928
0.059 ~ 0.889
No Observable Abnormality

FIG. 5B

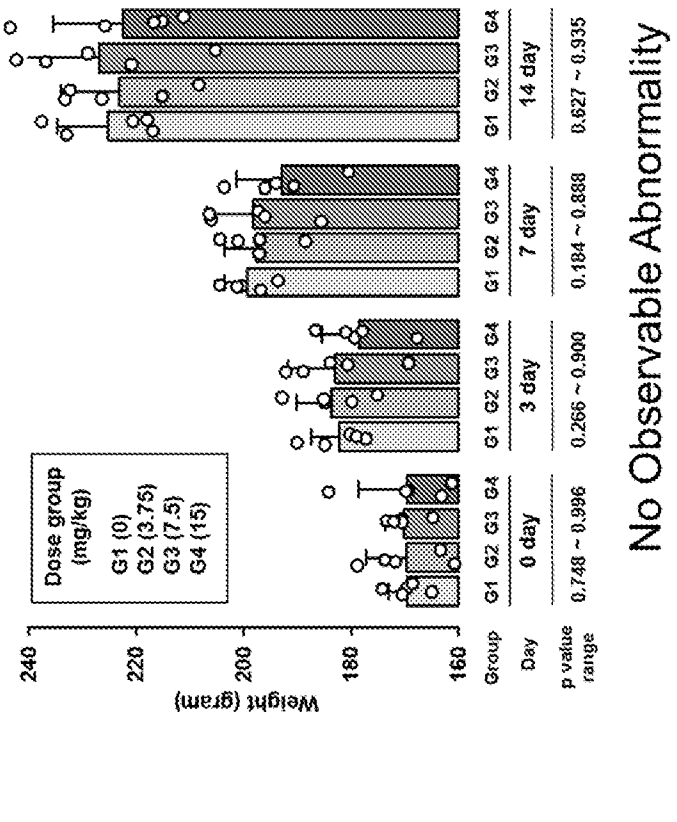

Female
Dose group (mg/kg)
G1 (0)
G2 (3.75)
G3 (7.5)
G4 (15)
Weight (gram)
240
220
200
180
160
Group
Day
p value range
G1 G2 G3 G4
0 day
3 day
7 day
14 day
0.748 ~ 0.996
0.266 ~ 0.900
0.184 ~ 0.888
0.627 ~ 0.935
No Observable Abnormality

FIG. 6A

Sex	Group / Dose (mg/kg)	No. of animals	Days after dosing															Mortality
			0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Male	G1 0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
	G2 3.75	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
	G3 7.5	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
	G4 15	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5

FIG. 6B

Sex	Group / Dose (mg/kg)	No. of animals	Days after dosing															Mortality
			0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Female	G1 0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
	G2 3.75	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
	G3 7.5	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5
	G4 15	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/5

FIG. 7A

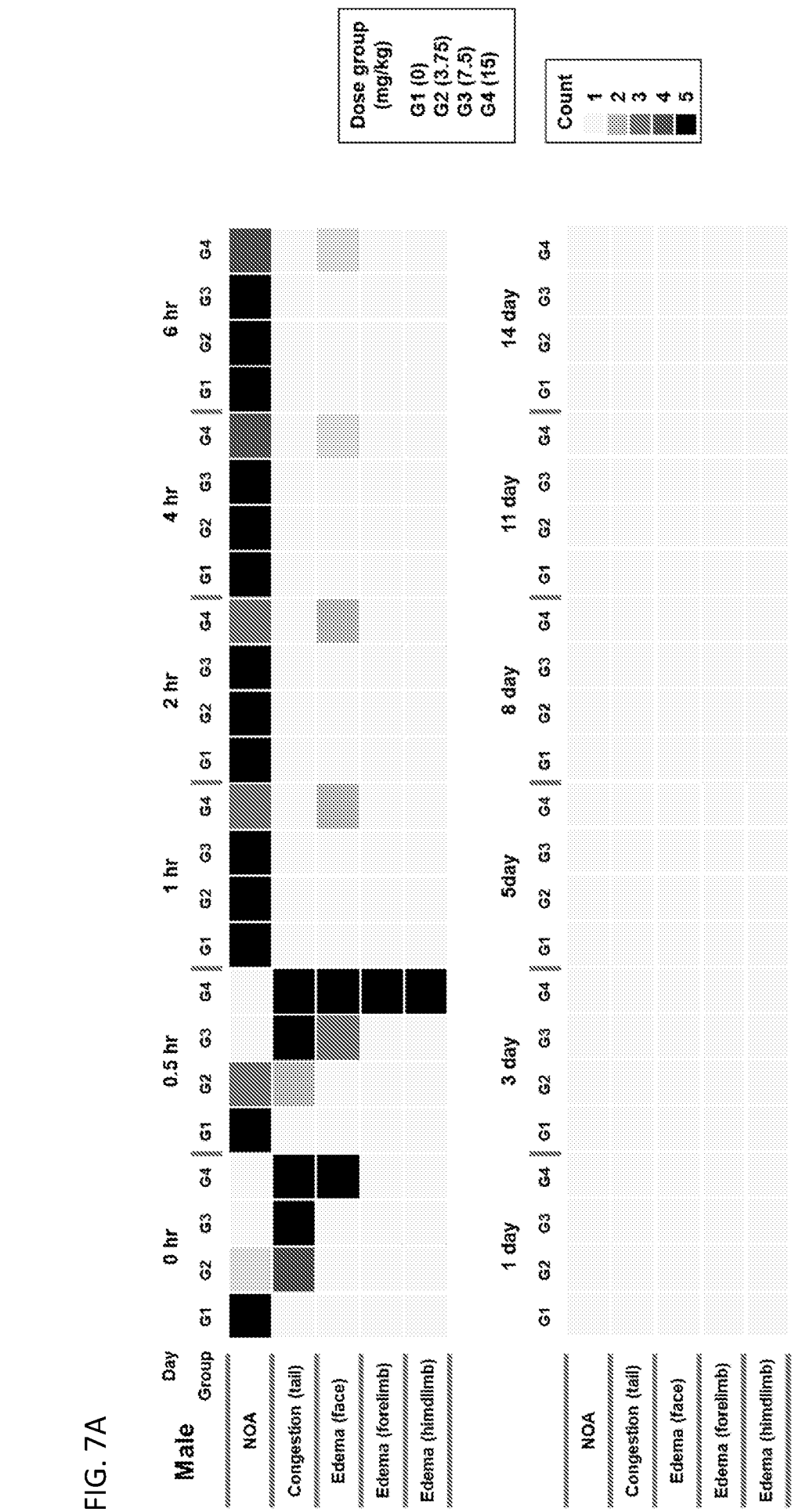

Male
Day
Group
0 hr
0.5 hr
1 hr
2 hr
4 hr
6 hr
1 day
3 day
5day
8 day
11 day
14 day
G1
G2
G3
G4
NOA
Congestion (tail)
Edema (face)
Edema (forelimb)
Edema (himdlimb)
Dose group (mg/kg)
G1 (0)
G2 (3.75)
G3 (7.5)
G4 (15)
Count
1
2
3
4
5

FIG. 7B

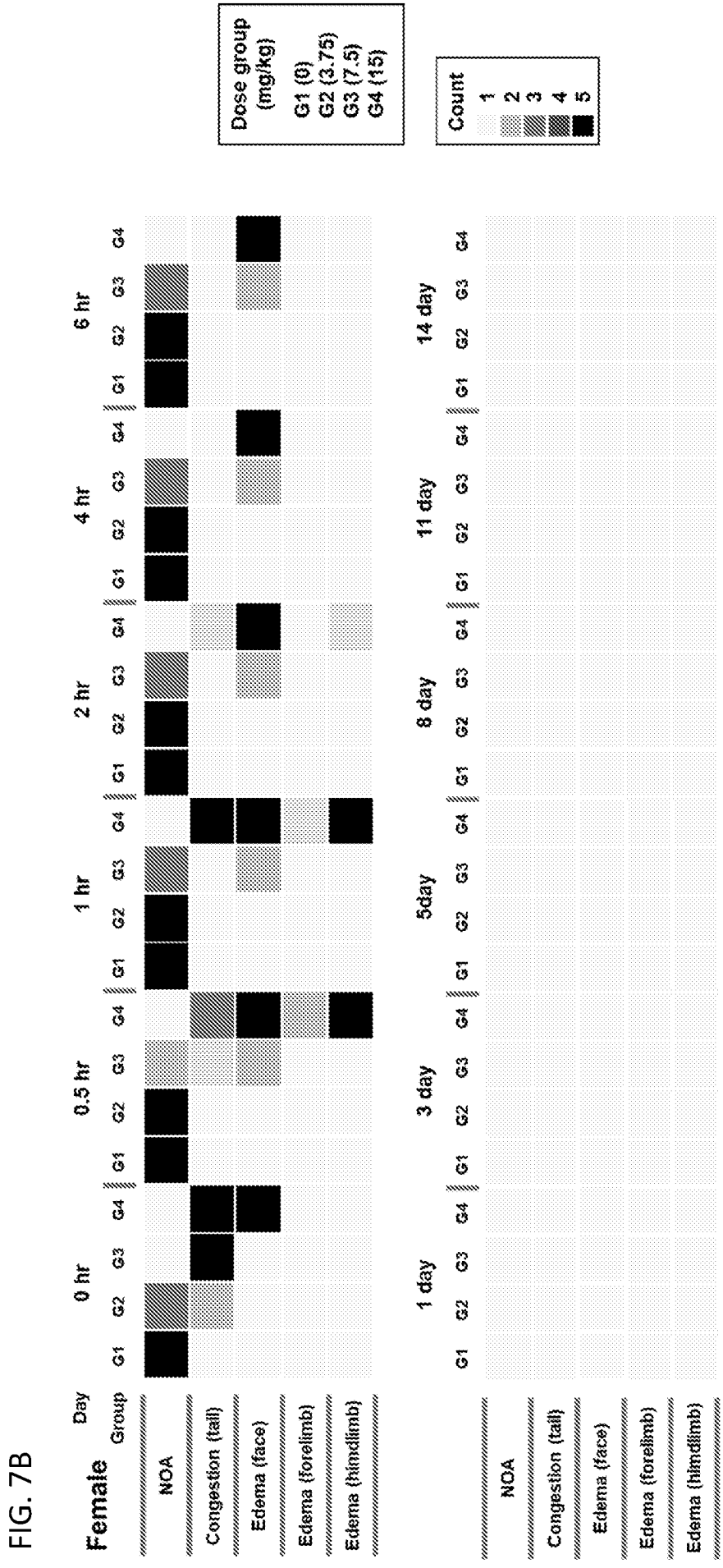

Female
Day
Group
0 hr
0.5 hr
1 hr
2 hr
4 hr
6 hr
1 day
3 day
5day
8 day
11 day
14 day
G1
G2
G3
G4
NOA
Congestion (tail)
Edema (face)
Edema (forelimb)
Edema (hlmdlimb)
Dose group (mg/kg)
G1 (0)
G2 (3.75)
G3 (7.5)
G4 (15)
Count
1
2
3
4
5

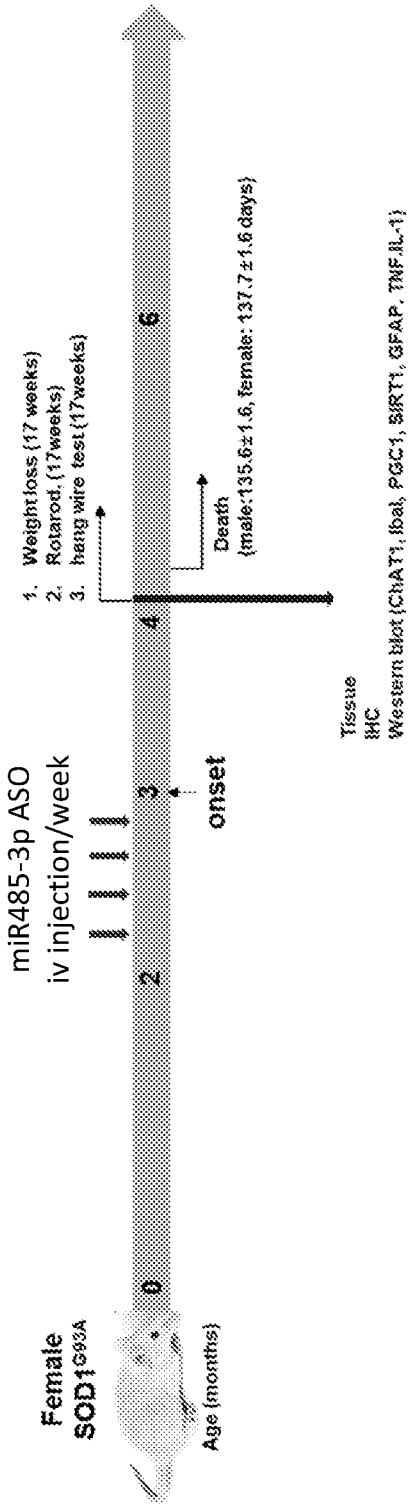
FIG. 8A

Male	Group			
	1	2	3	4
No. of Animals	5	5	5	5
No. of Examined	5	5	5	5
No Finding Noted	5	5	5	5

FIG. 8B

Female	Group			
	1	2	3	4
No. of Animals	5	5	5	5
No. of Examined	5	5	5	5
No Finding Noted	5	5	5	5

FIG. 9A


Female
SOD1G93A
Age (months)
0
2
3
4
6
onset
miR485-3p ASO
iv injection/week
1. Weight loss (17 weeks)
2. Rotarod (17weeks)
3. hang wire test (17weeks)
Death
(male:135.6±1.6, female: 137.7±1.6 days)
Tissue
IHC
Western blot (ChAT1, Iba1, PGC1, SIRT1, GFAP, TNF,IL-1)

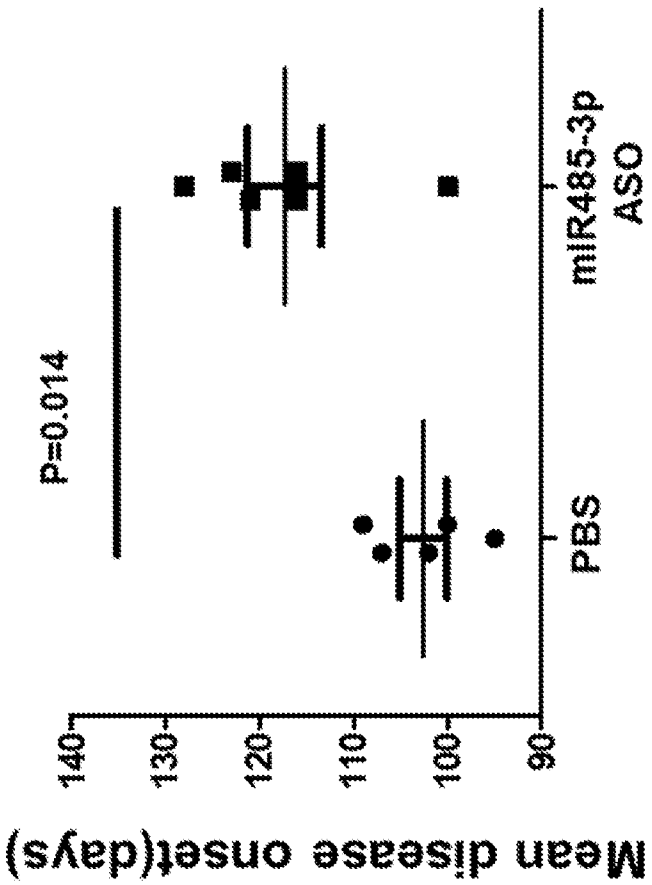

Mean disease onset(days)
140
130
120
110
100
90
P=0.014
PBS
miR485-3p
ASO

FIG. 9B

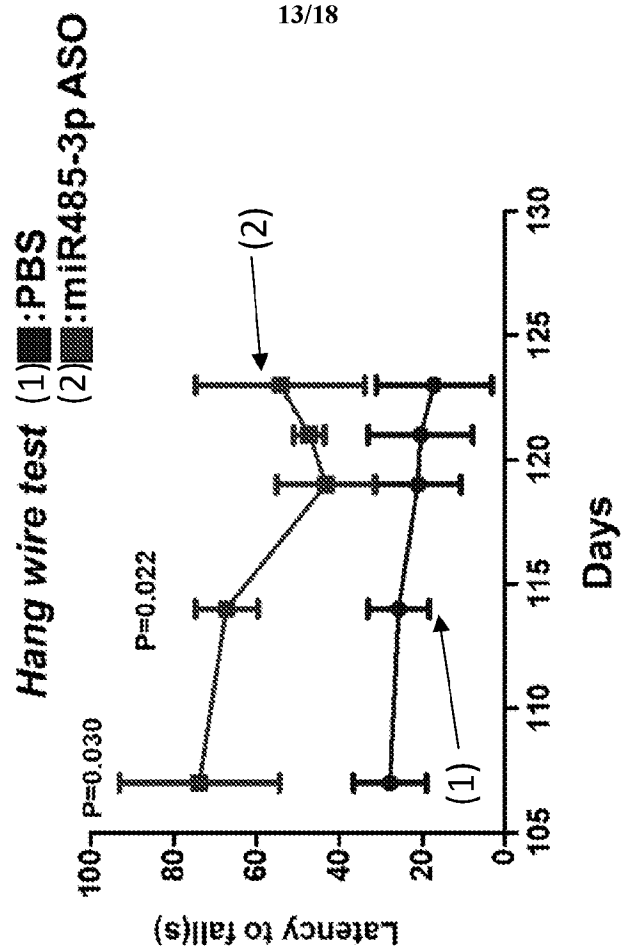

Hang wire test
(1):PBS
(2):miR485-3p ASO
P=0.030
P=0.022
(1)
(2)
Latency to fall(s)
Days
0
20
40
60
80
100
105
110
115
120
125
130

FIG. 9D

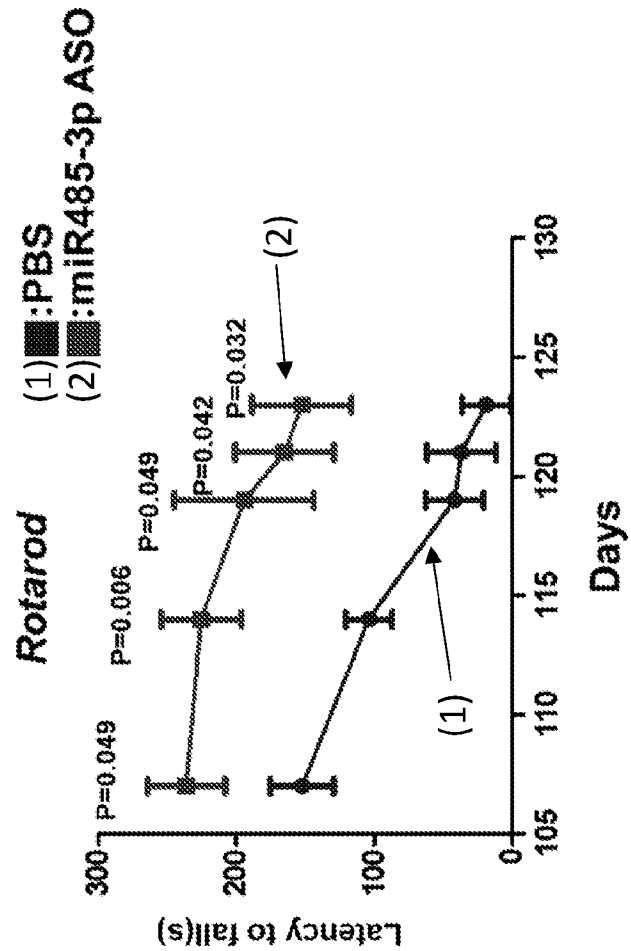

Rotarod
(1):PBS
(2):miR485-3p ASO
P=0.049
P=0.006
P=0.049
P=0.042
P=0.032
(1)
(2)
Latency to fall(s)
Days
0
100
200
300
105
110
115
120
125
130

FIG. 9C

FIG. 9F

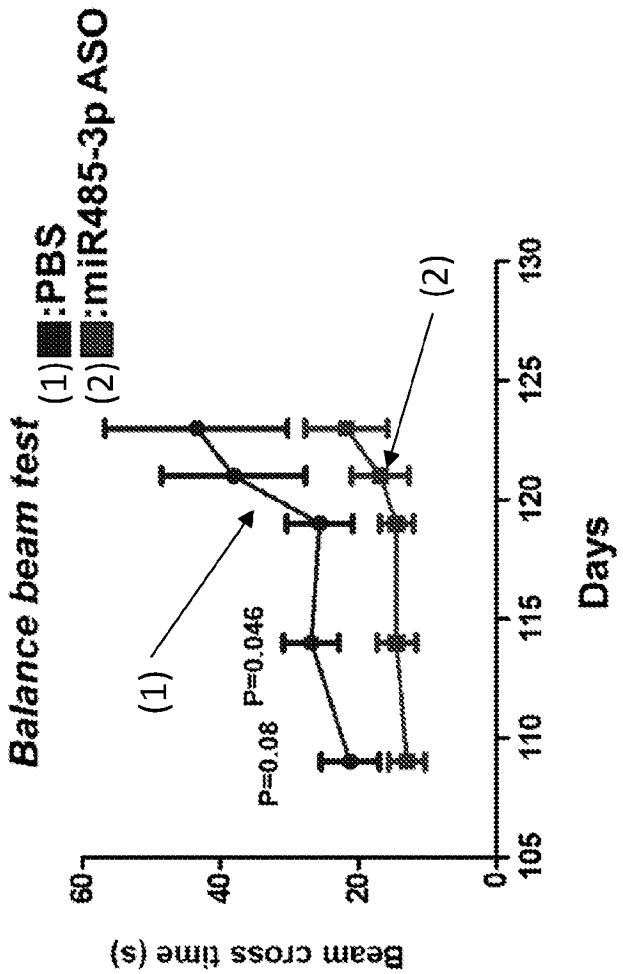
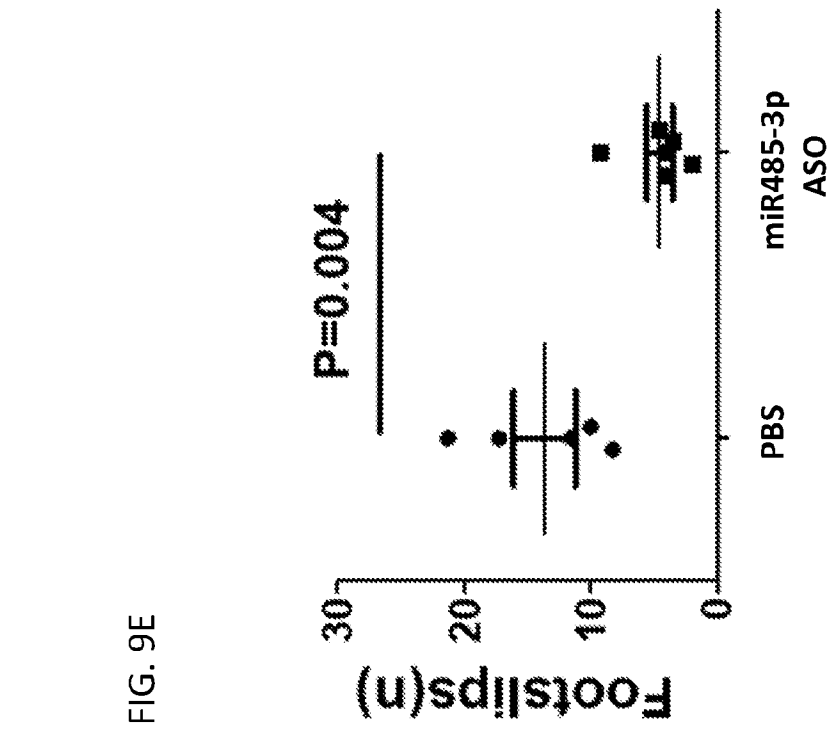

Balance beam test
(1) :PBS
(2) :miR485-3p ASO
(1)
(2)
P=0.08
P=0.046
Beam cross time (s)
Days
0
20
40
60
105
110
115
120
125
130

FIG. 9E


P=0.004
Footslips(n)
0
10
20
30
PBS
miR485-3p ASO

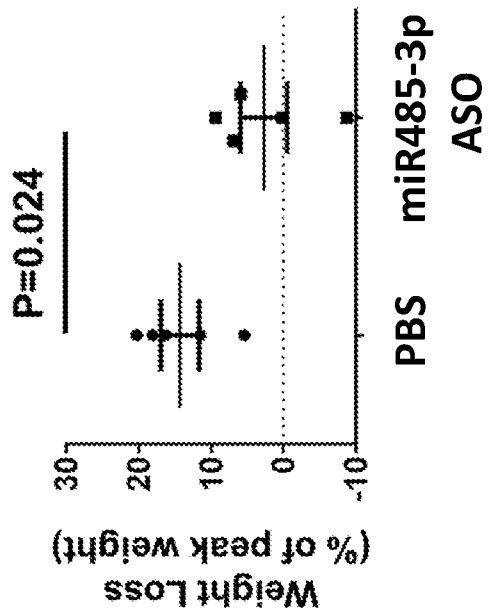


FIG. 9H

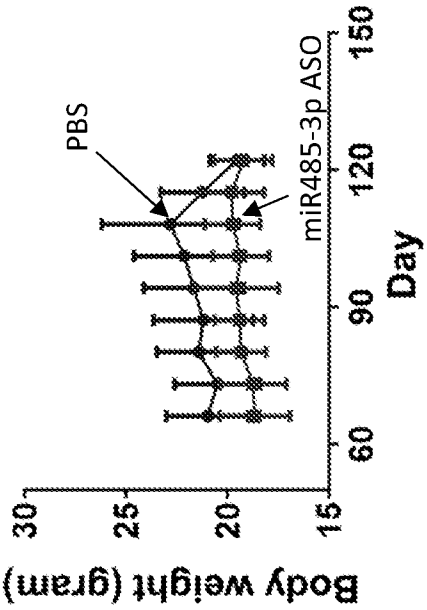


FIG. 9G

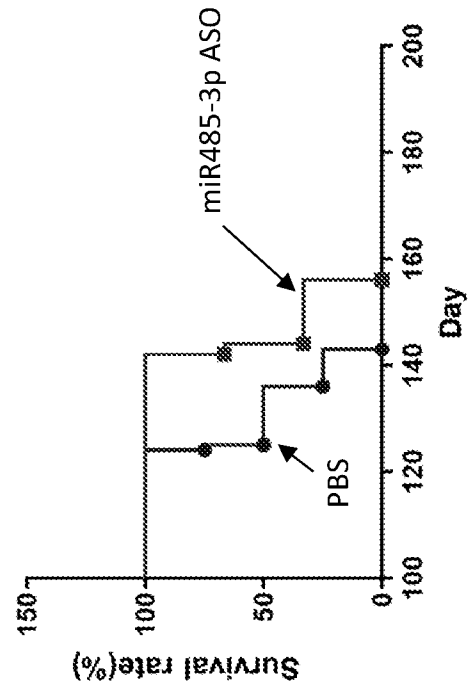
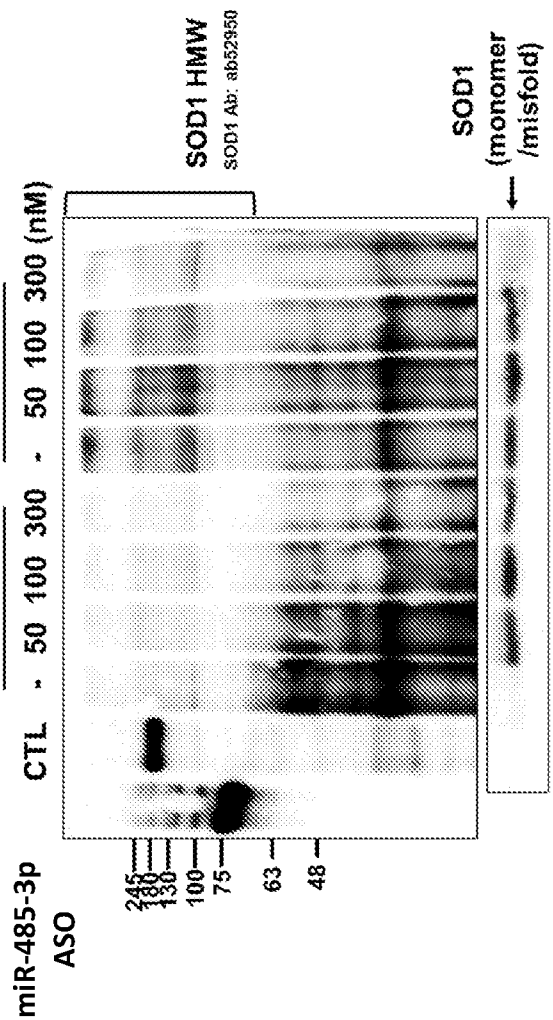


FIG. 9I

FIG. 10A


miR-485-3p ASO
CTL
SOD1WT
SOD1G93A
- 50 100 300 - 50 100 300 (nM)
SOD1 HMW
SOD1 Ab: ab52950
SOD1 (monomer /misfold)
245
180
130
100
75
63
48

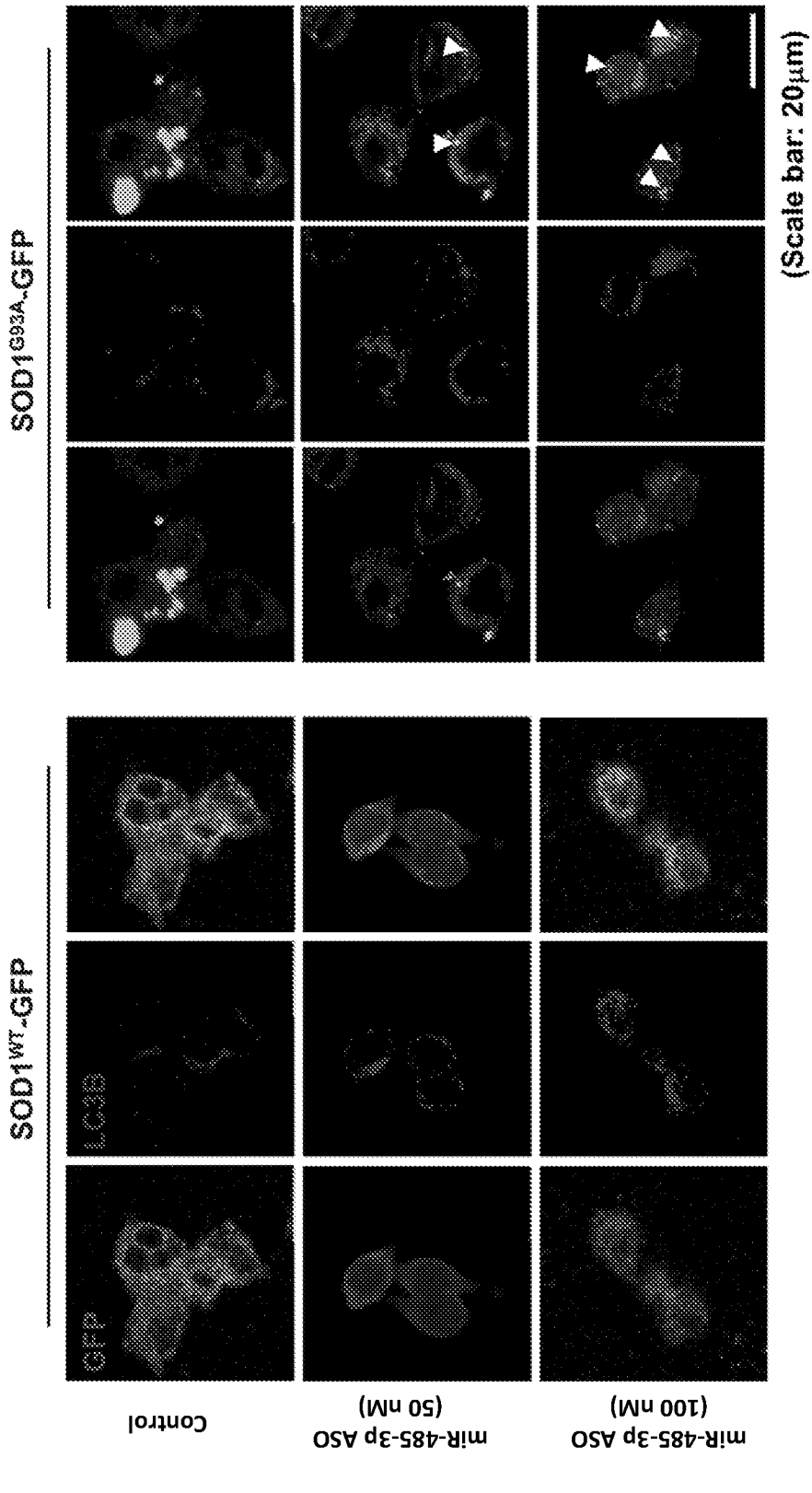

SOD1WT-GFP
SOD1G93A-GFP
GFP
LC3B
Control
miR-485-3p ASO (50 nM)
miR-485-3p ASO (100 nM)
(Scale bar: 20μm)

FIG. 10B

FIG. 10C

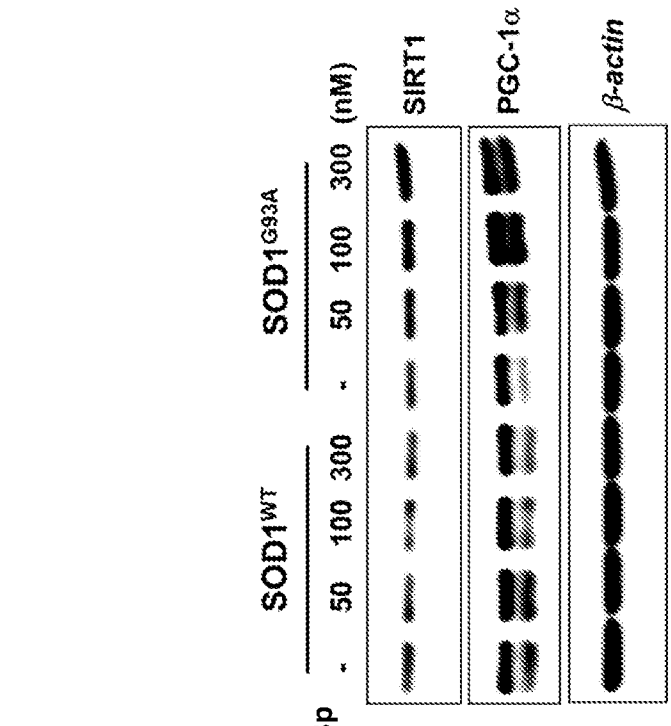
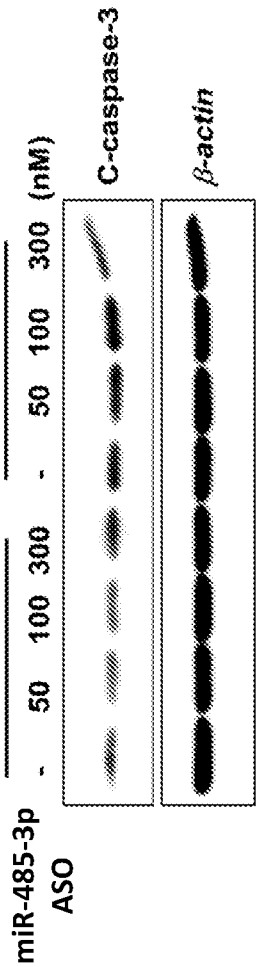


FIG. 10D



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Leu Arg Lys Arg Pro Arg Arg Asp Gly Pro Gly Leu Glu Arg Ser Pro
35 40 45

Gly Glu Pro Gly Gly Ala Ala Pro Glu Arg Glu Val Pro Ala Ala Ala
50 55 60

Arg Gly Cys Pro Gly Ala Ala Ala Ala Ala Leu Trp Arg Glu Ala Glu
65 70 75 80

Ala Glu Ala Ala Ala Ala Gly Gly Glu Gln Glu Ala Gln Ala Thr Ala
85 90 95

Ala Ala Gly Glu Gly Asp Asn Gly Pro Gly Leu Gln Gly Pro Ser Arg
100 105 110

Glu Pro Pro Leu Ala Asp Asn Leu Tyr Asp Glu Asp Asp Asp Asp Glu
115 120 125

Gly Glu Glu Glu Glu Glu Ala Ala Ala Ala Ala Ile Gly Tyr Arg Asp
130 135 140

Asn Leu Leu Phe Gly Asp Glu Ile Ile Thr Asn Gly Phe His Ser Cys
145 150 155 160

Glu Ser Asp Glu Glu Asp Arg Ala Ser His Ala Ser Ser Ser Asp Trp
165 170 175

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Thr Pro Arg Pro Arg Ile Gly Pro Tyr Thr Phe Val Gln Gln His Leu
            180                 185                 190

Met Ile Gly Thr Asp Pro Arg Thr Ile Leu Lys Asp Leu Leu Pro Glu
        195                 200                 205

Thr Ile Pro Pro Pro Glu Leu Asp Asp Met Thr Leu Trp Gln Ile Val
    210                 215                 220

Ile Asn Ile Leu Ser Glu Pro Pro Lys Arg Lys Lys Arg Lys Asp Ile
225                 230                 235                 240

Asn Thr Ile Glu Asp Ala Val Lys Leu Leu Gln Glu Cys Lys Lys Ile
                245                 250                 255

Ile Val Leu Thr Gly Ala Gly Val Ser Val Ser Cys Gly Ile Pro Asp
            260                 265                 270

Phe Arg Ser Arg Asp Gly Ile Tyr Ala Arg Leu Ala Val Asp Phe Pro
        275                 280                 285

Asp Leu Pro Asp Pro Gln Ala Met Phe Asp Ile Glu Tyr Phe Arg Lys
    290                 295                 300

Asp Pro Arg Pro Phe Phe Lys Phe Ala Lys Glu Ile Tyr Pro Gly Gln
305                 310                 315                 320

Phe Gln Pro Ser Leu Cys His Lys Phe Ile Ala Leu Ser Asp Lys Glu
                325                 330                 335

Gly Lys Leu Leu Arg Asn Tyr Thr Gln Asn Ile Asp Thr Leu Glu Gln
            340                 345                 350

Val Ala Gly Ile Gln Arg Ile Ile Gln Cys His Gly Ser Phe Ala Thr
        355                 360                 365

Ala Ser Cys Leu Ile Cys Lys Tyr Lys Val Asp Cys Glu Ala Val Arg
    370                 375                 380

Gly Asp Ile Phe Asn Gln Val Val Pro Arg Cys Pro Arg Cys Pro Ala
```

```
385                 390                 395                 400

Asp Glu Pro Leu Ala Ile Met Lys Pro Glu Ile Val Phe Phe Gly Glu
                405                 410                 415

Asn Leu Pro Glu Gln Phe His Arg Ala Met Lys Tyr Asp Lys Asp Glu
            420                 425                 430

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

Ala Leu Ile Pro Ser Ser Ile Pro His Glu Val Pro Gln Ile Leu Ile
    450                 455                 460

Asn Arg Glu Pro Leu Pro His Leu His Phe Asp Val Glu Leu Leu Gly
465                 470                 475                 480

Asp Cys Asp Val Ile Ile Asn Glu Leu Cys His Arg Leu Gly Gly Glu
                485                 490                 495

Tyr Ala Lys Leu Cys Cys Asn Pro Val Lys Leu Ser Glu Ile Thr Glu
            500                 505                 510

Lys Pro Pro Arg Thr Gln Lys Glu Leu Ala Tyr Leu Ser Glu Leu Pro
        515                 520                 525

Pro Thr Pro Leu His Val Ser Glu Asp Ser Ser Ser Pro Glu Arg Thr
    530                 535                 540

Ser Pro Pro Asp Ser Ser Val Ile Val Thr Leu Leu Asp Gln Ala Ala
545                 550                 555                 560

Lys Ser Asn Asp Asp Leu Asp Val Ser Glu Ser Lys Gly Cys Met Glu
                565                 570                 575

Glu Lys Pro Gln Glu Val Gln Thr Ser Arg Asn Val Glu Ser Ile Ala
            580                 585                 590

Glu Gln Met Glu Asn Pro Asp Leu Lys Asn Val Gly Ser Ser Thr Gly
        595                 600                 605
```

```
Glu Lys Asn Glu Arg Thr Ser Val Ala Gly Thr Val Arg Lys Cys Trp
    610                 615                 620

Pro Asn Arg Val Ala Lys Glu Gln Ile Ser Arg Arg Leu Asp Gly Asn
625                 630                 635                 640

Gln Tyr Leu Phe Leu Pro Pro Asn Arg Tyr Ile Phe His Gly Ala Glu
                645                 650                 655

Val Tyr Ser Asp Ser Glu Asp Asp Val Leu Ser Ser Ser Ser Cys Gly
            660                 665                 670

Ser Asn Ser Asp Ser Gly Thr Cys Gln Ser Pro Ser Leu Glu Glu Pro
        675                 680                 685

Met Glu Asp Glu Ser Glu Ile Glu Glu Phe Tyr Asn Gly Leu Glu Asp
    690                 695                 700

Glu Pro Asp Val Pro Glu Arg Ala Gly Gly Ala Gly Phe Gly Thr Asp
705                 710                 715                 720

Gly Asp Asp Gln Glu Ala Ile Asn Glu Ala Ile Ser Val Lys Gln Glu
                725                 730                 735

Val Thr Asp Met Asn Tyr Pro Ser Asn Lys Ser
            740                 745
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Ala Ala Gly Ala Asp Arg Glu Ala Ala Ser Ser Pro Ala Gly Glu Pro
            20                  25                  30

Leu Arg Lys Arg Pro Arg Arg Asp Gly Pro Gly Leu Glu Arg Ser Pro
        35                  40                  45
```

```
Gly Glu Pro Gly Gly Ala Ala Pro Glu Arg Glu Val Pro Ala Ala Ala
    50                  55                  60

Arg Gly Cys Pro Gly Ala Ala Ala Ala Ala Leu Trp Arg Glu Ala Glu
65                  70                  75                  80

Ala Glu Ala Ala Ala Ala Gly Gly Glu Gln Glu Ala Gln Ala Thr Ala
                85                  90                  95

Ala Ala Gly Glu Gly Asp Asn Gly Pro Gly Leu Gln Gly Pro Ser Arg
            100                 105                 110

Glu Pro Pro Leu Ala Asp Asn Leu Tyr Asp Glu Asp Asp Asp Asp Glu
        115                 120                 125

Gly Glu Glu Glu Glu Glu Ala Ala Ala Ala Ala Ile Gly Tyr Arg Asp
    130                 135                 140

Asn Leu Leu Phe Gly Asp Glu Ile Ile Thr Asn Gly Phe His Ser Cys
145                 150                 155                 160

Glu Ser Asp Glu Glu Asp Arg Ala Ser His Ala Ser Ser Ser Asp Trp
                165                 170                 175

Thr Pro Arg Pro Arg Ile Gly Pro Tyr Thr Phe Val Gln Gln His Leu
            180                 185                 190

Met Ile Gly Thr Asp Pro Arg Thr Ile Leu Lys Asp Leu Leu Pro Glu
        195                 200                 205

Thr Ile Pro Pro Pro Glu Leu Asp Asp Met Thr Leu Trp Gln Ile Val
    210                 215                 220

Ile Asn Ile Leu Ser Glu Pro Pro Lys Arg Lys Lys Arg Lys Asp Ile
225                 230                 235                 240

Asn Thr Ile Glu Asp Ala Val Lys Leu Leu Gln Glu Cys Lys Lys Ile
                245                 250                 255
```

```
Ile Val Leu Thr Gly Ala Gly Val Ser Val Ser Cys Gly Ile Pro Asp
            260                 265                 270

Phe Arg Ser Arg Asp Gly Ile Tyr Ala Arg Leu Ala Val Asp Phe Pro
        275                 280                 285

Asp Leu Pro Asp Pro Gln Ala Met Phe Asp Ile Glu Tyr Phe Arg Lys
    290                 295                 300

Asp Pro Arg Pro Phe Phe Lys Phe Ala Lys Glu Ile Tyr Pro Gly Gln
305                 310                 315                 320

Phe Gln Pro Ser Leu Cys His Lys Phe Ile Ala Leu Ser Asp Lys Glu
                325                 330                 335

Gly Lys Leu Leu Arg Asn Tyr Thr Gln Asn Ile Asp Thr Leu Glu Gln
            340                 345                 350

Val Ala Gly Ile Gln Arg Ile Ile Gln Cys His Gly Ser Phe Ala Thr
        355                 360                 365

Ala Ser Cys Leu Ile Cys Lys Tyr Lys Val Asp Cys Glu Ala Val Arg
    370                 375                 380

Gly Asp Ile Phe Asn Gln Val Val Pro Arg Cys Pro Arg Cys Pro Ala
385                 390                 395                 400

Asp Glu Pro Leu Ala Ile Met Lys Pro Glu Ile Val Phe Phe Gly Glu
                405                 410                 415

Asn Leu Pro Glu Gln Phe His Arg Ala Met Lys Tyr Asp Lys Asp Glu
            420                 425                 430

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

Ala Leu Ile Pro Ser Asn Gln Tyr Leu Phe Leu Pro Pro Asn Arg Tyr
    450                 455                 460

Ile Phe His Gly Ala Glu Val Tyr Ser Asp Ser Glu Asp Asp Val Leu
465                 470                 475                 480
```

Ser Ser Ser Ser Cys Gly Ser Asn Ser Asp Ser Gly Thr Cys Gln Ser
485 490 495

Pro Ser Leu Glu Glu Pro Met Glu Asp Glu Ser Glu Ile Glu Glu Phe
500 505 510

Tyr Asn Gly Leu Glu Asp Glu Pro Asp Val Pro Glu Arg Ala Gly Gly
515 520 525

Ala Gly Phe Gly Thr Asp Gly Asp Asp Gln Glu Ala Ile Asn Glu Ala
530 535 540

Ile Ser Val Lys Gln Glu Val Thr Asp Met Asn Tyr Pro Ser Asn Lys
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Ser

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20 25 30

Leu Ile Gln Lys Thr Ile Lys Lys Gln Val Val Leu Glu Glu Gly Thr
35 40 45

Ile Ala Phe Lys Asn Trp Val Lys Thr Gly Thr Glu Val Tyr Arg Gln
50 55 60

Phe Trp Ile Phe Asp Val Gln Asn Pro Gln Glu Val Met Met Asn Ser
65 70 75 80

Ser Asn Ile Gln Val Lys Gln Arg Gly Pro Tyr Thr Tyr Arg Val Arg
85 90 95

Phe Leu Ala Lys Glu Asn Val Thr Gln Asp Ala Glu Asp Asn Thr Val
100 105 110

Ser Phe Leu Gln Pro Asn Gly Ala Ile Phe Glu Pro Ser Leu Ser Val
115 120 125

Gly Thr Glu Ala Asp Asn Phe Thr Val Leu Asn Leu Ala Val Ala Ala
130 135 140

Ala Ser His Ile Tyr Gln Asn Gln Phe Val Gln Met Ile Leu Asn Ser
145 150 155 160

Leu Ile Asn Lys Ser Lys Ser Ser Met Phe Gln Val Arg Thr Leu Arg
165 170 175

```
Glu Leu Leu Trp Gly Tyr Arg Asp Pro Phe Leu Ser Leu Val Pro Tyr
            180                 185                 190

Pro Val Thr Thr Thr Val Gly Leu Phe Tyr Pro Tyr Asn Asn Thr Ala
        195                 200                 205

Asp Gly Val Tyr Lys Val Phe Asn Gly Lys Asp Asn Ile Ser Lys Val
    210                 215                 220

Ala Ile Ile Asp Thr Tyr Lys Gly Lys Arg Asn Leu Ser Tyr Trp Glu
225                 230                 235                 240

Ser His Cys Asp Met Ile Asn Gly Thr Asp Ala Ala Ser Phe Pro Pro
                245                 250                 255

Phe Val Glu Lys Ser Gln Val Leu Gln Phe Phe Ser Ser Asp Ile Cys
            260                 265                 270

Arg Ser Ile Tyr Ala Val Phe Glu Ser Asp Val Asn Leu Lys Gly Ile
        275                 280                 285

Pro Val Tyr Arg Phe Val Leu Pro Ser Lys Ala Phe Ala Ser Pro Val
    290                 295                 300

Glu Asn Pro Asp Asn Tyr Cys Phe Cys Thr Glu Lys Ile Ile Ser Lys
305                 310                 315                 320

Asn Cys Thr Ser Tyr Gly Val Leu Asp Ile Ser Lys Cys Lys Glu Gly
                325                 330                 335

Arg Pro Val Tyr Ile Ser Leu Pro His Phe Leu Tyr Ala Ser Pro Asp
            340                 345                 350

Val Ser Glu Pro Ile Asp Gly Leu Asn Pro Asn Glu Glu Glu His Arg
        355                 360                 365

Thr Tyr Leu Asp Ile Glu Pro Ile Thr Gly Phe Thr Leu Gln Phe Ala
    370                 375                 380
```

```
Lys Arg Leu Gln Val Asn Leu Leu Val Lys Pro Ser Glu Lys Ile Gln
385                 390                 395                 400


Val Leu Lys Asn Leu Lys Arg Asn Tyr Ile Val Pro Ile Leu Trp Leu
                405                 410                 415


Asn Glu Thr Gly Thr Ile Gly Asp Glu Lys Ala Asn Met Phe Arg Ser
            420                 425                 430


Gln Val Thr Gly Lys Ile Asn Leu Leu Gly Leu Ile Glu Met Ile Leu
        435                 440                 445


Leu Ser Val Gly Val Val Met Phe Val Ala Phe Met Ile Ser Tyr Cys
    450                 455                 460


Ala Cys Arg Ser Lys Thr Ile Lys
465                 470


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1               5                   10                  15


Ala Val Leu Ala Val Phe Gly Gly Ile Leu Met Pro Val Gly Asp Leu
            20                  25                  30


Leu Ile Gln Lys Thr Ile Lys Lys Gln Val Val Leu Glu Glu Gly Thr
        35                  40                  45


Ile Ala Phe Lys Asn Trp Val Lys Thr Gly Thr Glu Val Tyr Arg Gln
    50                  55                  60


Phe Trp Ile Phe Asp Val Gln Asn Pro Gln Glu Val Met Met Asn Ser
65                  70                  75                  80


Ser Asn Ile Gln Val Lys Gln Arg Gly Pro Tyr Thr Tyr Arg Val Arg
                85                  90                  95
```

```
Phe Leu Ala Lys Glu Asn Val Thr Gln Asp Ala Glu Asp Asn Thr Val
            100                 105                 110

Ser Phe Leu Gln Pro Asn Gly Ala Ile Phe Glu Pro Ser Leu Ser Val
        115                 120                 125

Gly Thr Glu Ala Asp Asn Phe Thr Val Leu Asn Leu Ala Val Ala Ala
    130                 135                 140

Ala Ser His Ile Tyr Gln Asn Gln Phe Val Gln Met Ile Leu Asn Ser
145                 150                 155                 160

Leu Ile Asn Lys Ser Lys Ser Ser Met Phe Gln Val Arg Thr Leu Arg
                165                 170                 175

Glu Leu Leu Trp Gly Tyr Arg Asp Pro Phe Leu Ser Leu Val Pro Tyr
            180                 185                 190

Pro Val Thr Thr Thr Val Gly Leu Phe Tyr Pro Tyr Asn Asn Thr Ala
        195                 200                 205

Asp Gly Val Tyr Lys Val Phe Asn Gly Lys Asp Asn Ile Ser Lys Val
    210                 215                 220

Ala Ile Ile Asp Thr Tyr Lys Gly Lys Arg Asn Leu Ser Tyr Trp Glu
225                 230                 235                 240

Ser His Cys Asp Met Ile Asn Gly Thr Asp Ala Ala Ser Phe Pro Pro
                245                 250                 255

Phe Val Glu Lys Ser Gln Val Leu Gln Phe Phe Ser Ser Asp Ile Cys
            260                 265                 270

Arg Glu Thr Cys Val His Phe Thr Ser Ser Phe Ser Val Cys Lys Ser
        275                 280                 285
```

<210> 38
<211> 433
<212> PRT
<213> Homo sapiens

<400> 38

```
Met Gly Cys Asp Arg Asn Cys Gly Leu Ile Ala Gly Ala Val Ile Gly
1               5                  10                  15

Ala Val Leu Ala Val Phe Gly Gly Ile Leu Met Pro Val Gly Asp Leu
            20                  25                  30

Leu Ile Gln Lys Thr Ile Lys Lys Gln Val Val Leu Glu Glu Gly Thr
        35                  40                  45

Ile Ala Phe Lys Asn Trp Val Lys Thr Gly Thr Glu Val Tyr Arg Gln
    50                  55                  60

Phe Trp Ile Phe Asp Val Gln Asn Pro Gln Glu Val Met Met Asn Ser
65                  70                  75                  80

Ser Asn Ile Gln Val Lys Gln Arg Gly Pro Tyr Thr Tyr Arg Val Arg
                85                  90                  95

Phe Leu Ala Lys Glu Asn Val Thr Gln Asp Ala Glu Asp Asn Thr Val
            100                 105                 110

Ser Phe Leu Gln Pro Asn Gly Ala Ile Phe Glu Pro Ser Leu Ser Val
        115                 120                 125

Gly Thr Glu Ala Asp Asn Phe Thr Val Leu Asn Leu Ala Val Ala Ala
    130                 135                 140

Ala Ser His Ile Tyr Gln Asn Gln Phe Val Gln Met Ile Leu Asn Ser
145                 150                 155                 160

Leu Ile Asn Lys Ser Lys Ser Ser Met Phe Gln Val Arg Thr Leu Arg
                165                 170                 175

Glu Leu Leu Trp Gly Tyr Arg Asp Pro Phe Leu Ser Leu Val Pro Tyr
            180                 185                 190

Pro Val Thr Thr Thr Val Gly Leu Phe Tyr Pro Tyr Asn Asn Thr Ala
        195                 200                 205
```

```
Asp Gly Val Tyr Lys Val Phe Asn Gly Lys Asp Asn Ile Ser Lys Val
    210                 215                 220

Ala Ile Ile Asp Thr Tyr Lys Gly Lys Arg Ser Ile Tyr Ala Val Phe
225                 230                 235                 240

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

Pro Ser Lys Ala Phe Ala Ser Pro Val Glu Asn Pro Asp Asn Tyr Cys
            260                 265                 270

Phe Cys Thr Glu Lys Ile Ile Ser Lys Asn Cys Thr Ser Tyr Gly Val
        275                 280                 285

Leu Asp Ile Ser Lys Cys Lys Glu Gly Arg Pro Val Tyr Ile Ser Leu
    290                 295                 300

Pro His Phe Leu Tyr Ala Ser Pro Asp Val Ser Glu Pro Ile Asp Gly
305                 310                 315                 320

Leu Asn Pro Asn Glu Glu Glu His Arg Thr Tyr Leu Asp Ile Glu Pro
                325                 330                 335

Ile Thr Gly Phe Thr Leu Gln Phe Ala Lys Arg Leu Gln Val Asn Leu
            340                 345                 350

Leu Val Lys Pro Ser Glu Lys Ile Gln Val Leu Lys Asn Leu Lys Arg
        355                 360                 365

Asn Tyr Ile Val Pro Ile Leu Trp Leu Asn Glu Thr Gly Thr Ile Gly
    370                 375                 380

Asp Glu Lys Ala Asn Met Phe Arg Ser Gln Val Thr Gly Lys Ile Asn
385                 390                 395                 400

Leu Leu Gly Leu Ile Glu Met Ile Leu Leu Ser Val Gly Val Val Met
                405                 410                 415

Phe Val Ala Phe Met Ile Ser Tyr Cys Ala Cys Arg Ser Lys Thr Ile
            420                 425                 430
```

Lys

<210> 39
<211> 412
<212> PRT
<213> Homo sapiens

<400> 39

```
Met Gly Cys Asp Arg Asn Cys Gly Leu Ile Ala Gly Ala Val Ile Gly
1               5                  10                  15

Ala Val Leu Ala Val Phe Gly Gly Ile Leu Met Pro Val Gly Asp Leu
            20                  25                  30

Leu Ile Gln Lys Thr Ile Lys Lys Gln Val Val Leu Glu Glu Gly Thr
        35                  40                  45

Ile Ala Phe Lys Asn Trp Val Lys Thr Gly Thr Glu Val Tyr Arg Gln
    50                  55                  60

Phe Trp Ile Phe Asp Val Gln Asn Pro Gln Glu Val Met Met Asn Ser
65                  70                  75                  80

Ser Asn Ile Gln Val Lys Gln Arg Gly Pro Tyr Thr Tyr Arg Val Arg
                85                  90                  95

Phe Leu Ala Lys Glu Asn Val Thr Gln Asp Ala Glu Asp Asn Thr Val
            100                 105                 110

Ser Phe Leu Gln Pro Asn Gly Ala Ile Phe Glu Pro Ser Leu Ser Val
        115                 120                 125

Gly Thr Glu Ala Asp Asn Phe Thr Val Leu Asn Leu Ala Val Ala Tyr
    130                 135                 140

Asn Asn Thr Ala Asp Gly Val Tyr Lys Val Phe Asn Gly Lys Asp Asn
145                 150                 155                 160

Ile Ser Lys Val Ala Ile Ile Asp Thr Tyr Lys Gly Lys Arg Asn Leu
```

```
                165                 170                 175

Ser Tyr Trp Glu Ser His Cys Asp Met Ile Asn Gly Thr Asp Ala Ala
            180                 185                 190

Ser Phe Pro Pro Phe Val Glu Lys Ser Gln Val Leu Gln Phe Phe Ser
        195                 200                 205

Ser Asp Ile Cys Arg Ser Ile Tyr Ala Val Phe Glu Ser Asp Val Asn
    210                 215                 220

Leu Lys Gly Ile Pro Val Tyr Arg Phe Val Leu Pro Ser Lys Ala Phe
225                 230                 235                 240

Ala Ser Pro Val Glu Asn Pro Asp Asn Tyr Cys Phe Cys Thr Glu Lys
                245                 250                 255

Ile Ile Ser Lys Asn Cys Thr Ser Tyr Gly Val Leu Asp Ile Ser Lys
            260                 265                 270

Cys Lys Glu Gly Arg Pro Val Tyr Ile Ser Leu Pro His Phe Leu Tyr
        275                 280                 285

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

Glu Glu His Arg Thr Tyr Leu Asp Ile Glu Pro Ile Thr Gly Phe Thr
305                 310                 315                 320

Leu Gln Phe Ala Lys Arg Leu Gln Val Asn Leu Leu Val Lys Pro Ser
                325                 330                 335

Glu Lys Ile Gln Val Leu Lys Asn Leu Lys Arg Asn Tyr Ile Val Pro
            340                 345                 350

Ile Leu Trp Leu Asn Glu Thr Gly Thr Ile Gly Asp Glu Lys Ala Asn
        355                 360                 365

Met Phe Arg Ser Gln Val Thr Gly Lys Ile Asn Leu Leu Gly Leu Ile
    370                 375                 380
```

```
Glu Met Ile Leu Leu Ser Val Gly Val Val Met Phe Val Ala Phe Met
385                 390                 395                 400


Ile Ser Tyr Cys Ala Cys Arg Ser Lys Thr Ile Lys
                405                 410


<210>  40
<211>  798
<212>  PRT
<213>  Homo sapiens

<400>  40

Met Ala Trp Asp Met Cys Asn Gln Asp Ser Glu Ser Val Trp Ser Asp
1               5                   10                  15


Ile Glu Cys Ala Ala Leu Val Gly Glu Asp Gln Pro Leu Cys Pro Asp
            20                  25                  30


Leu Pro Glu Leu Asp Leu Ser Glu Leu Asp Val Asn Asp Leu Asp Thr
        35                  40                  45


Asp Ser Phe Leu Gly Gly Leu Lys Trp Cys Ser Asp Gln Ser Glu Ile
    50                  55                  60


Ile Ser Asn Gln Tyr Asn Asn Glu Pro Ser Asn Ile Phe Glu Lys Ile
65                  70                  75                  80


Asp Glu Glu Asn Glu Ala Asn Leu Leu Ala Val Leu Thr Glu Thr Leu
                85                  90                  95


Asp Ser Leu Pro Val Asp Glu Asp Gly Leu Pro Ser Phe Asp Ala Leu
            100                 105                 110


Thr Asp Gly Asp Val Thr Thr Asp Asn Glu Ala Ser Pro Ser Ser Met
        115                 120                 125


Pro Asp Gly Thr Pro Pro Pro Gln Glu Ala Glu Glu Pro Ser Leu Leu
    130                 135                 140


Lys Lys Leu Leu Leu Ala Pro Ala Asn Thr Gln Leu Ser Tyr Asn Glu
145                 150                 155                 160
```

```
Cys Ser Gly Leu Ser Thr Gln Asn His Ala Asn His Asn His Arg Ile
                165                 170                 175

Arg Thr Asn Pro Ala Ile Val Lys Thr Glu Asn Ser Trp Ser Asn Lys
            180                 185                 190

Ala Lys Ser Ile Cys Gln Gln Gln Lys Pro Gln Arg Arg Pro Cys Ser
        195                 200                 205

Glu Leu Leu Lys Tyr Leu Thr Thr Asn Asp Asp Pro Pro His Thr Lys
    210                 215                 220

Pro Thr Glu Asn Arg Asn Ser Ser Arg Asp Lys Cys Thr Ser Lys Lys
225                 230                 235                 240

Lys Ser His Thr Gln Ser Gln Ser Gln His Leu Gln Ala Lys Pro Thr
                245                 250                 255

Thr Leu Ser Leu Pro Leu Thr Pro Glu Ser Pro Asn Asp Pro Lys Gly
            260                 265                 270

Ser Pro Phe Glu Asn Lys Thr Ile Glu Arg Thr Leu Ser Val Glu Leu
        275                 280                 285

Ser Gly Thr Ala Gly Leu Thr Pro Pro Thr Thr Pro Pro His Lys Ala
    290                 295                 300

Asn Gln Asp Asn Pro Phe Arg Ala Ser Pro Lys Leu Lys Ser Ser Cys
305                 310                 315                 320

Lys Thr Val Val Pro Pro Pro Ser Lys Lys Pro Arg Tyr Ser Glu Ser
                325                 330                 335

Ser Gly Thr Gln Gly Asn Asn Ser Thr Lys Lys Gly Pro Glu Gln Ser
            340                 345                 350

Glu Leu Tyr Ala Gln Leu Ser Lys Ser Ser Val Leu Thr Gly Gly His
        355                 360                 365
```

```
Glu Glu Arg Lys Thr Lys Arg Pro Ser Leu Arg Leu Phe Gly Asp His
    370                 375                 380

Asp Tyr Cys Gln Ser Ile Asn Ser Lys Thr Glu Ile Leu Ile Asn Ile
385                 390                 395                 400

Ser Gln Glu Leu Gln Asp Ser Arg Gln Leu Glu Asn Lys Asp Val Ser
                405                 410                 415

Ser Asp Trp Gln Gly Gln Ile Cys Ser Ser Thr Asp Ser Asp Gln Cys
            420                 425                 430

Tyr Leu Arg Glu Thr Leu Glu Ala Ser Lys Gln Val Ser Pro Cys Ser
        435                 440                 445

Thr Arg Lys Gln Leu Gln Asp Gln Glu Ile Arg Ala Glu Leu Asn Lys
    450                 455                 460

His Phe Gly His Pro Ser Gln Ala Val Phe Asp Asp Glu Ala Asp Lys
465                 470                 475                 480

Thr Gly Glu Leu Arg Asp Ser Asp Phe Ser Asn Glu Gln Phe Ser Lys
                485                 490                 495

Leu Pro Met Phe Ile Asn Ser Gly Leu Ala Met Asp Gly Leu Phe Asp
            500                 505                 510

Asp Ser Glu Asp Glu Ser Asp Lys Leu Ser Tyr Pro Trp Asp Gly Thr
        515                 520                 525

Gln Ser Tyr Ser Leu Phe Asn Val Ser Pro Ser Cys Ser Ser Phe Asn
    530                 535                 540

Ser Pro Cys Arg Asp Ser Val Ser Pro Pro Lys Ser Leu Phe Ser Gln
545                 550                 555                 560

Arg Pro Gln Arg Met Arg Ser Arg Ser Arg Ser Phe Ser Arg His Arg
                565                 570                 575

Ser Cys Ser Arg Ser Pro Tyr Ser Arg Ser Arg Ser Arg Ser Pro Gly
            580                 585                 590
```

```
Ser Arg Ser Ser Ser Arg Ser Cys Tyr Tyr Tyr Glu Ser Ser His Tyr
        595                 600                 605

Arg His Arg Thr His Arg Asn Ser Pro Leu Tyr Val Arg Ser Arg Ser
    610                 615                 620

Arg Ser Pro Tyr Ser Arg Arg Pro Arg Tyr Asp Ser Tyr Glu Glu Tyr
625                 630                 635                 640

Gln His Glu Arg Leu Lys Arg Glu Glu Tyr Arg Arg Glu Tyr Glu Lys
                645                 650                 655

Arg Glu Ser Glu Arg Ala Lys Gln Arg Glu Arg Gln Arg Gln Lys Ala
            660                 665                 670

Ile Glu Glu Arg Arg Val Ile Tyr Val Gly Lys Ile Arg Pro Asp Thr
        675                 680                 685

Thr Arg Thr Glu Leu Arg Asp Arg Phe Glu Val Phe Gly Glu Ile Glu
    690                 695                 700

Glu Cys Thr Val Asn Leu Arg Asp Asp Gly Asp Ser Tyr Gly Phe Ile
705                 710                 715                 720

Thr Tyr Arg Tyr Thr Cys Asp Ala Phe Ala Ala Leu Glu Asn Gly Tyr
                725                 730                 735

Thr Leu Arg Arg Ser Asn Glu Thr Asp Phe Glu Leu Tyr Phe Cys Gly
            740                 745                 750

Arg Lys Gln Phe Phe Lys Ser Asn Tyr Ala Asp Leu Asp Ser Asn Ser
        755                 760                 765

Asp Asp Phe Asp Pro Ala Ser Thr Lys Ser Lys Tyr Asp Ser Leu Asp
    770                 775                 780

Phe Asp Ser Leu Leu Lys Glu Ala Gln Arg Ser Leu Arg Arg
785                 790                 795
```

<210> 41
<211> 271
<212> PRT
<213> Homo sapiens

<400> 41

```
Met Ala Trp Asp Met Cys Asn Gln Asp Ser Glu Ser Val Trp Ser Asp
1               5                  10                  15


Ile Glu Cys Ala Ala Leu Val Gly Glu Asp Gln Pro Leu Cys Pro Asp
            20                  25                  30


Leu Pro Glu Leu Asp Leu Ser Glu Leu Asp Val Asn Asp Leu Asp Thr
        35                  40                  45


Asp Ser Phe Leu Gly Gly Leu Lys Trp Cys Ser Asp Gln Ser Glu Ile
    50                  55                  60


Ile Ser Asn Gln Tyr Asn Asn Glu Pro Ser Asn Ile Phe Glu Lys Ile
65                  70                  75                  80


Asp Glu Glu Asn Glu Ala Asn Leu Leu Ala Val Leu Thr Glu Thr Leu
                85                  90                  95


Asp Ser Leu Pro Val Asp Glu Asp Gly Leu Pro Ser Phe Asp Ala Leu
            100                 105                 110


Thr Asp Gly Asp Val Thr Thr Asp Asn Glu Ala Ser Pro Ser Ser Met
        115                 120                 125


Pro Asp Gly Thr Pro Pro Pro Gln Glu Ala Glu Glu Pro Ser Leu Leu
    130                 135                 140


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


Cys Ser Gly Leu Ser Thr Gln Asn His Ala Asn His Asn His Arg Ile
                165                 170                 175


Arg Thr Asn Pro Ala Ile Val Lys Thr Glu Asn Ser Trp Ser Asn Lys
            180                 185                 190
```

```
Ala Lys Ser Ile Cys Gln Gln Gln Lys Pro Gln Arg Arg Pro Cys Ser
        195                 200                 205

Glu Leu Leu Lys Tyr Leu Thr Thr Asn Asp Asp Pro Pro His Thr Lys
    210                 215                 220

Pro Thr Glu Asn Arg Asn Ser Ser Arg Asp Lys Cys Thr Ser Lys Lys
225                 230                 235                 240

Lys Ser His Thr Gln Ser Gln Ser Gln His Leu Gln Ala Lys Pro Thr
                245                 250                 255

Thr Leu Ser Leu Pro Leu Thr Pro Glu Ser Pro Asn Leu Phe Leu
            260                 265                 270
```

<210> 42
<211> 803
<212> PRT
<213> Homo sapiens

<400> 42

```
Met Asp Glu Thr Ser Pro Arg Leu Glu Glu Asp Trp Lys Lys Val Leu
1               5                   10                  15

Gln Arg Glu Ala Gly Trp Gln Cys Ala Ala Leu Val Gly Glu Asp Gln
            20                  25                  30

Pro Leu Cys Pro Asp Leu Pro Glu Leu Asp Leu Ser Glu Leu Asp Val
        35                  40                  45

Asn Asp Leu Asp Thr Asp Ser Phe Leu Gly Gly Leu Lys Trp Cys Ser
    50                  55                  60

Asp Gln Ser Glu Ile Ile Ser Asn Gln Tyr Asn Asn Glu Pro Ser Asn
65                  70                  75                  80

Ile Phe Glu Lys Ile Asp Glu Glu Asn Glu Ala Asn Leu Leu Ala Val
                85                  90                  95

Leu Thr Glu Thr Leu Asp Ser Leu Pro Val Asp Glu Asp Gly Leu Pro
            100                 105                 110
```

```
Ser Phe Asp Ala Leu Thr Asp Gly Asp Val Thr Thr Asp Asn Glu Ala
        115                 120                 125

Ser Pro Ser Ser Met Pro Asp Gly Thr Pro Pro Pro Gln Glu Ala Glu
    130                 135                 140

Glu Pro Ser Leu Leu Lys Lys Leu Leu Leu Ala Pro Ala Asn Thr Gln
145                 150                 155                 160

Leu Ser Tyr Asn Glu Cys Ser Gly Leu Ser Thr Gln Asn His Ala Asn
                165                 170                 175

His Asn His Arg Ile Arg Thr Asn Pro Ala Ile Val Lys Thr Glu Asn
            180                 185                 190

Ser Trp Ser Asn Lys Ala Lys Ser Ile Cys Gln Gln Gln Lys Pro Gln
        195                 200                 205

Arg Arg Pro Cys Ser Glu Leu Leu Lys Tyr Leu Thr Thr Asn Asp Asp
    210                 215                 220

Pro Pro His Thr Lys Pro Thr Glu Asn Arg Asn Ser Ser Arg Asp Lys
225                 230                 235                 240

Cys Thr Ser Lys Lys Lys Ser His Thr Gln Ser Gln Ser Gln His Leu
                245                 250                 255

Gln Ala Lys Pro Thr Thr Leu Ser Leu Pro Leu Thr Pro Glu Ser Pro
            260                 265                 270

Asn Asp Pro Lys Gly Ser Pro Phe Glu Asn Lys Thr Ile Glu Arg Thr
        275                 280                 285

Leu Ser Val Glu Leu Ser Gly Thr Ala Gly Leu Thr Pro Pro Thr Thr
    290                 295                 300

Pro Pro His Lys Ala Asn Gln Asp Asn Pro Phe Arg Ala Ser Pro Lys
305                 310                 315                 320
```

```
Leu Lys Ser Ser Cys Lys Thr Val Val Pro Pro Pro Ser Lys Lys Pro
                325                 330                 335

Arg Tyr Ser Glu Ser Ser Gly Thr Gln Gly Asn Asn Ser Thr Lys Lys
            340                 345                 350

Gly Pro Glu Gln Ser Glu Leu Tyr Ala Gln Leu Ser Lys Ser Ser Val
        355                 360                 365

Leu Thr Gly Gly His Glu Glu Arg Lys Thr Lys Arg Pro Ser Leu Arg
    370                 375                 380

Leu Phe Gly Asp His Asp Tyr Cys Gln Ser Ile Asn Ser Lys Thr Glu
385                 390                 395                 400

Ile Leu Ile Asn Ile Ser Gln Glu Leu Gln Asp Ser Arg Gln Leu Glu
                405                 410                 415

Asn Lys Asp Val Ser Ser Asp Trp Gln Gly Gln Ile Cys Ser Ser Thr
            420                 425                 430

Asp Ser Asp Gln Cys Tyr Leu Arg Glu Thr Leu Glu Ala Ser Lys Gln
        435                 440                 445

Val Ser Pro Cys Ser Thr Arg Lys Gln Leu Gln Asp Gln Glu Ile Arg
    450                 455                 460

Ala Glu Leu Asn Lys His Phe Gly His Pro Ser Gln Ala Val Phe Asp
465                 470                 475                 480

Asp Glu Ala Asp Lys Thr Gly Glu Leu Arg Asp Ser Asp Phe Ser Asn
                485                 490                 495

Glu Gln Phe Ser Lys Leu Pro Met Phe Ile Asn Ser Gly Leu Ala Met
            500                 505                 510

Asp Gly Leu Phe Asp Asp Ser Glu Asp Glu Ser Asp Lys Leu Ser Tyr
        515                 520                 525

Pro Trp Asp Gly Thr Gln Ser Tyr Ser Leu Phe Asn Val Ser Pro Ser
    530                 535                 540
```

```
Cys Ser Ser Phe Asn Ser Pro Cys Arg Asp Ser Val Ser Pro Pro Lys
545                 550                 555                 560

Ser Leu Phe Ser Gln Arg Pro Gln Arg Met Arg Ser Arg Ser Arg Ser
                565                 570                 575

Phe Ser Arg His Arg Ser Cys Ser Arg Ser Pro Tyr Ser Arg Ser Arg
            580                 585                 590

Ser Arg Ser Pro Gly Ser Arg Ser Ser Ser Arg Ser Cys Tyr Tyr Tyr
        595                 600                 605

Glu Ser Ser His Tyr Arg His Arg Thr His Arg Asn Ser Pro Leu Tyr
    610                 615                 620

Val Arg Ser Arg Ser Arg Ser Pro Tyr Ser Arg Arg Pro Arg Tyr Asp
625                 630                 635                 640

Ser Tyr Glu Glu Tyr Gln His Glu Arg Leu Lys Arg Glu Glu Tyr Arg
                645                 650                 655

Arg Glu Tyr Glu Lys Arg Glu Ser Glu Arg Ala Lys Gln Arg Glu Arg
            660                 665                 670

Gln Arg Gln Lys Ala Ile Glu Glu Arg Arg Val Ile Tyr Val Gly Lys
        675                 680                 685

Ile Arg Pro Asp Thr Thr Arg Thr Glu Leu Arg Asp Arg Phe Glu Val
    690                 695                 700

Phe Gly Glu Ile Glu Glu Cys Thr Val Asn Leu Arg Asp Asp Gly Asp
705                 710                 715                 720

Ser Tyr Gly Phe Ile Thr Tyr Arg Tyr Thr Cys Asp Ala Phe Ala Ala
                725                 730                 735

Leu Glu Asn Gly Tyr Thr Leu Arg Arg Ser Asn Glu Thr Asp Phe Glu
            740                 745                 750
```

```
Leu Tyr Phe Cys Gly Arg Lys Gln Phe Phe Lys Ser Asn Tyr Ala Asp
        755                 760                 765

Leu Asp Ser Asn Ser Asp Asp Phe Asp Pro Ala Ser Thr Lys Ser Lys
    770                 775                 780

Tyr Asp Ser Leu Asp Phe Asp Ser Leu Leu Lys Glu Ala Gln Arg Ser
785                 790                 795                 800

Leu Arg Arg
```

<210> 43
<211> 786
<212> PRT
<213> Homo sapiens

<400> 43

```
Met Asp Glu Gly Tyr Phe Cys Ala Ala Leu Val Gly Glu Asp Gln Pro
1               5                   10                  15

Leu Cys Pro Asp Leu Pro Glu Leu Asp Leu Ser Glu Leu Asp Val Asn
            20                  25                  30

Asp Leu Asp Thr Asp Ser Phe Leu Gly Gly Leu Lys Trp Cys Ser Asp
        35                  40                  45

Gln Ser Glu Ile Ile Ser Asn Gln Tyr Asn Asn Glu Pro Ser Asn Ile
    50                  55                  60

Phe Glu Lys Ile Asp Glu Glu Asn Glu Ala Asn Leu Leu Ala Val Leu
65                  70                  75                  80

Thr Glu Thr Leu Asp Ser Leu Pro Val Asp Glu Asp Gly Leu Pro Ser
                85                  90                  95

Phe Asp Ala Leu Thr Asp Gly Asp Val Thr Thr Asp Asn Glu Ala Ser
            100                 105                 110

Pro Ser Ser Met Pro Asp Gly Thr Pro Pro Pro Gln Glu Ala Glu Glu
        115                 120                 125
```

```
Pro Ser Leu Leu Lys Lys Leu Leu Leu Ala Pro Ala Asn Thr Gln Leu
    130                 135                 140

Ser Tyr Asn Glu Cys Ser Gly Leu Ser Thr Gln Asn His Ala Asn His
145                 150                 155                 160

Asn His Arg Ile Arg Thr Asn Pro Ala Ile Val Lys Thr Glu Asn Ser
                165                 170                 175

Trp Ser Asn Lys Ala Lys Ser Ile Cys Gln Gln Gln Lys Pro Gln Arg
            180                 185                 190

Arg Pro Cys Ser Glu Leu Leu Lys Tyr Leu Thr Thr Asn Asp Asp Pro
        195                 200                 205

Pro His Thr Lys Pro Thr Glu Asn Arg Asn Ser Ser Arg Asp Lys Cys
    210                 215                 220

Thr Ser Lys Lys Lys Ser His Thr Gln Ser Gln Ser Gln His Leu Gln
225                 230                 235                 240

Ala Lys Pro Thr Thr Leu Ser Leu Pro Leu Thr Pro Glu Ser Pro Asn
                245                 250                 255

Asp Pro Lys Gly Ser Pro Phe Glu Asn Lys Thr Ile Glu Arg Thr Leu
            260                 265                 270

Ser Val Glu Leu Ser Gly Thr Ala Gly Leu Thr Pro Pro Thr Thr Pro
        275                 280                 285

Pro His Lys Ala Asn Gln Asp Asn Pro Phe Arg Ala Ser Pro Lys Leu
    290                 295                 300

Lys Ser Ser Cys Lys Thr Val Val Pro Pro Pro Ser Lys Lys Pro Arg
305                 310                 315                 320

Tyr Ser Glu Ser Ser Gly Thr Gln Gly Asn Asn Ser Thr Lys Lys Gly
                325                 330                 335

Pro Glu Gln Ser Glu Leu Tyr Ala Gln Leu Ser Lys Ser Ser Val Leu
```

```
            340                 345                 350

Thr Gly Gly His Glu Glu Arg Lys Thr Lys Arg Pro Ser Leu Arg Leu
        355                 360                 365

Phe Gly Asp His Asp Tyr Cys Gln Ser Ile Asn Ser Lys Thr Glu Ile
    370                 375                 380

Leu Ile Asn Ile Ser Gln Glu Leu Gln Asp Ser Arg Gln Leu Glu Asn
385                 390                 395                 400

Lys Asp Val Ser Ser Asp Trp Gln Gly Gln Ile Cys Ser Ser Thr Asp
                405                 410                 415

Ser Asp Gln Cys Tyr Leu Arg Glu Thr Leu Glu Ala Ser Lys Gln Val
            420                 425                 430

Ser Pro Cys Ser Thr Arg Lys Gln Leu Gln Asp Gln Glu Ile Arg Ala
        435                 440                 445

Glu Leu Asn Lys His Phe Gly His Pro Ser Gln Ala Val Phe Asp Asp
    450                 455                 460

Glu Ala Asp Lys Thr Gly Glu Leu Arg Asp Ser Asp Phe Ser Asn Glu
465                 470                 475                 480

Gln Phe Ser Lys Leu Pro Met Phe Ile Asn Ser Gly Leu Ala Met Asp
                485                 490                 495

Gly Leu Phe Asp Asp Ser Glu Asp Glu Ser Asp Lys Leu Ser Tyr Pro
            500                 505                 510

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

Ser Ser Phe Asn Ser Pro Cys Arg Asp Ser Val Ser Pro Pro Lys Ser
    530                 535                 540

Leu Phe Ser Gln Arg Pro Gln Arg Met Arg Ser Arg Ser Arg Ser Phe
545                 550                 555                 560
```

```
Ser Arg His Arg Ser Cys Ser Arg Ser Pro Tyr Ser Arg Ser Arg Ser
                565                 570                 575

Arg Ser Pro Gly Ser Arg Ser Ser Ser Arg Ser Cys Tyr Tyr Tyr Glu
            580                 585                 590

Ser Ser His Tyr Arg His Arg Thr His Arg Asn Ser Pro Leu Tyr Val
        595                 600                 605

Arg Ser Arg Ser Arg Ser Pro Tyr Ser Arg Arg Pro Arg Tyr Asp Ser
    610                 615                 620

Tyr Glu Glu Tyr Gln His Glu Arg Leu Lys Arg Glu Glu Tyr Arg Arg
625                 630                 635                 640

Glu Tyr Glu Lys Arg Glu Ser Glu Arg Ala Lys Gln Arg Glu Arg Gln
                645                 650                 655

Arg Gln Lys Ala Ile Glu Glu Arg Arg Val Ile Tyr Val Gly Lys Ile
            660                 665                 670

Arg Pro Asp Thr Thr Arg Thr Glu Leu Arg Asp Arg Phe Glu Val Phe
        675                 680                 685

Gly Glu Ile Glu Glu Cys Thr Val Asn Leu Arg Asp Asp Gly Asp Ser
    690                 695                 700

Tyr Gly Phe Ile Thr Tyr Arg Tyr Thr Cys Asp Ala Phe Ala Ala Leu
705                 710                 715                 720

Glu Asn Gly Tyr Thr Leu Arg Arg Ser Asn Glu Thr Asp Phe Glu Leu
                725                 730                 735

Tyr Phe Cys Gly Arg Lys Gln Phe Phe Lys Ser Asn Tyr Ala Asp Leu
            740                 745                 750

Asp Ser Asn Ser Asp Asp Phe Asp Pro Ala Ser Thr Lys Ser Lys Tyr
        755                 760                 765

Asp Ser Leu Asp Phe Asp Ser Leu Leu Lys Glu Ala Gln Arg Ser Leu
```

770 775 780

Arg Arg
785

<210> 44
<211> 289
<212> PRT
<213> Homo sapiens

<400> 44

Met Asp Glu Gly Tyr Phe Cys Ala Ala Leu Val Gly Glu Asp Gln Pro
1 5 10 15

Leu Cys Pro Asp Leu Pro Glu Leu Asp Leu Ser Glu Leu Asp Val Asn
20 25 30

Asp Leu Asp Thr Asp Ser Phe Leu Gly Gly Leu Lys Trp Cys Ser Asp
35 40 45

Gln Ser Glu Ile Ile Ser Asn Gln Tyr Asn Asn Glu Pro Ser Asn Ile
50 55 60

Phe Glu Lys Ile Asp Glu Glu Asn Glu Ala Asn Leu Leu Ala Val Leu
65 70 75 80

Thr Glu Thr Leu Asp Ser Leu Pro Val Asp Glu Asp Gly Leu Pro Ser
85 90 95

Phe Asp Ala Leu Thr Asp Gly Asp Val Thr Thr Asp Asn Glu Ala Ser
100 105 110

Pro Ser Ser Met Pro Asp Gly Thr Pro Pro Pro Gln Glu Ala Glu Glu
115 120 125

Pro Ser Leu Leu Lys Lys Leu Leu Leu Ala Pro Ala Asn Thr Gln Leu
130 135 140

Ser Tyr Asn Glu Cys Ser Gly Leu Ser Thr Gln Asn His Ala Asn His
145 150 155 160

```
Asn His Arg Ile Arg Thr Asn Pro Ala Ile Val Lys Thr Glu Asn Ser
                165                 170                 175

Trp Ser Asn Lys Ala Lys Ser Ile Cys Gln Gln Gln Lys Pro Gln Arg
            180                 185                 190

Arg Pro Cys Ser Glu Leu Leu Lys Tyr Leu Thr Thr Asn Asp Asp Pro
        195                 200                 205

Pro His Thr Lys Pro Thr Glu Asn Arg Asn Ser Ser Arg Asp Lys Cys
    210                 215                 220

Thr Ser Lys Lys Lys Ser His Thr Gln Ser Gln Ser Gln His Leu Gln
225                 230                 235                 240

Ala Lys Pro Thr Thr Leu Ser Leu Pro Leu Thr Pro Glu Ser Pro Asn
                245                 250                 255

Asp Pro Lys Gly Ser Pro Phe Glu Asn Lys Thr Ile Glu Arg Thr Leu
            260                 265                 270

Ser Val Glu Leu Ser Gly Thr Ala Gly Val Lys Thr Asn Leu Ile Ser
        275                 280                 285

Lys
```

<210> 45
<211> 276
<212> PRT
<213> Homo sapiens

<400> 45

```
Met Asp Glu Thr Ser Pro Arg Leu Glu Glu Asp Trp Lys Lys Val Leu
1               5                   10                  15

Gln Arg Glu Ala Gly Trp Gln Cys Ala Ala Leu Val Gly Glu Asp Gln
            20                  25                  30

Pro Leu Cys Pro Asp Leu Pro Glu Leu Asp Leu Ser Glu Leu Asp Val
        35                  40                  45
```

```
Asn Asp Leu Asp Thr Asp Ser Phe Leu Gly Gly Leu Lys Trp Cys Ser
    50                  55                  60

Asp Gln Ser Glu Ile Ile Ser Asn Gln Tyr Asn Asn Glu Pro Ser Asn
65                  70                  75                  80

Ile Phe Glu Lys Ile Asp Glu Glu Asn Glu Ala Asn Leu Leu Ala Val
                85                  90                  95

Leu Thr Glu Thr Leu Asp Ser Leu Pro Val Asp Glu Asp Gly Leu Pro
            100                 105                 110

Ser Phe Asp Ala Leu Thr Asp Gly Asp Val Thr Thr Asp Asn Glu Ala
        115                 120                 125

Ser Pro Ser Ser Met Pro Asp Gly Thr Pro Pro Pro Gln Glu Ala Glu
    130                 135                 140

Glu Pro Ser Leu Leu Lys Lys Leu Leu Leu Ala Pro Ala Asn Thr Gln
145                 150                 155                 160

Leu Ser Tyr Asn Glu Cys Ser Gly Leu Ser Thr Gln Asn His Ala Asn
                165                 170                 175

His Asn His Arg Ile Arg Thr Asn Pro Ala Ile Val Lys Thr Glu Asn
            180                 185                 190

Ser Trp Ser Asn Lys Ala Lys Ser Ile Cys Gln Gln Gln Lys Pro Gln
        195                 200                 205

Arg Arg Pro Cys Ser Glu Leu Leu Lys Tyr Leu Thr Thr Asn Asp Asp
    210                 215                 220

Pro Pro His Thr Lys Pro Thr Glu Asn Arg Asn Ser Ser Arg Asp Lys
225                 230                 235                 240

Cys Thr Ser Lys Lys Lys Ser His Thr Gln Ser Gln Ser Gln His Leu
                245                 250                 255

Gln Ala Lys Pro Thr Thr Leu Ser Leu Pro Leu Thr Pro Glu Ser Pro
```

```
            260                 265                 270


Asn Leu Phe Leu
        275


<210>  46
<211>  138
<212>  PRT
<213>  Homo sapiens

<400>  46

Met Asp Glu Gly Tyr Phe Cys Ala Ala Leu Val Gly Glu Asp Gln Pro
1               5                   10                  15


Leu Cys Pro Asp Leu Pro Glu Leu Asp Leu Ser Glu Leu Asp Val Asn
            20                  25                  30


Asp Leu Asp Thr Asp Ser Phe Leu Gly Gly Leu Lys Trp Cys Ser Asp
        35                  40                  45


Gln Ser Glu Ile Ile Ser Asn Gln Tyr Asn Asn Glu Pro Ser Asn Ile
    50                  55                  60


Phe Glu Lys Ile Asp Glu Glu Asn Glu Ala Asn Leu Leu Ala Val Leu
65                  70                  75                  80


Thr Glu Thr Leu Asp Ser Leu Pro Val Asp Glu Asp Gly Leu Pro Ser
                85                  90                  95


Phe Asp Ala Leu Thr Asp Gly Asp Val Thr Thr Asp Asn Glu Ala Ser
            100                 105                 110


Pro Ser Ser Met Pro Asp Gly Thr Pro Pro Pro Gln Glu Ala Glu Glu
        115                 120                 125


Pro Ser Leu Val Arg Thr Leu Pro Thr Val
    130                 135


<210>  47
<211>  301
<212>  PRT
<213>  Homo sapiens
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<400> 47

```
Met Ala Trp Asp Met Cys Asn Gln Asp Ser Glu Ser Val Trp Ser Asp
1               5                  10                  15

Ile Glu Cys Ala Ala Leu Val Gly Glu Asp Gln Pro Leu Cys Pro Asp
            20                  25                  30

Leu Pro Glu Leu Asp Leu Ser Glu Leu Asp Val Asn Asp Leu Asp Thr
        35                  40                  45

Asp Ser Phe Leu Gly Gly Leu Lys Trp Cys Ser Asp Gln Ser Glu Ile
    50                  55                  60

Ile Ser Asn Gln Tyr Asn Asn Glu Pro Ser Asn Ile Phe Glu Lys Ile
65                  70                  75                  80

Asp Glu Glu Asn Glu Ala Asn Leu Leu Ala Val Leu Thr Glu Thr Leu
                85                  90                  95

Asp Ser Leu Pro Val Asp Glu Asp Gly Leu Pro Ser Phe Asp Ala Leu
            100                 105                 110

Thr Asp Gly Asp Val Thr Thr Asp Asn Glu Ala Ser Pro Ser Ser Met
        115                 120                 125

Pro Asp Gly Thr Pro Pro Pro Gln Glu Ala Glu Glu Pro Ser Leu Leu
    130                 135                 140

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

Cys Ser Gly Leu Ser Thr Gln Asn His Ala Asn His Asn His Arg Ile
                165                 170                 175

Arg Thr Asn Pro Ala Ile Val Lys Thr Glu Asn Ser Trp Ser Asn Lys
            180                 185                 190

Ala Lys Ser Ile Cys Gln Gln Gln Lys Pro Gln Arg Arg Pro Cys Ser
        195                 200                 205
```

```
Glu Leu Leu Lys Tyr Leu Thr Thr Asn Asp Asp Pro Pro His Thr Lys
    210                 215                 220

Pro Thr Glu Asn Arg Asn Ser Ser Arg Asp Lys Cys Thr Ser Lys Lys
225                 230                 235                 240

Lys Ser His Thr Gln Ser Gln Ser Gln His Leu Gln Ala Lys Pro Thr
                245                 250                 255

Thr Leu Ser Leu Pro Leu Thr Pro Glu Ser Pro Asn Asp Pro Lys Gly
            260                 265                 270

Ser Pro Phe Glu Asn Lys Thr Ile Glu Arg Thr Leu Ser Val Glu Leu
        275                 280                 285

Ser Gly Thr Ala Gly Val Lys Thr Asn Leu Ile Ser Lys
    290                 295                 300
```

<210> 48
<211> 671
<212> PRT
<213> Homo sapiens

<400> 48

```
Met Pro Asp Gly Thr Pro Pro Pro Gln Glu Ala Glu Glu Pro Ser Leu
1               5                   10                  15

Leu Lys Lys Leu Leu Leu Ala Pro Ala Asn Thr Gln Leu Ser Tyr Asn
            20                  25                  30

Glu Cys Ser Gly Leu Ser Thr Gln Asn His Ala Asn His Asn His Arg
        35                  40                  45

Ile Arg Thr Asn Pro Ala Ile Val Lys Thr Glu Asn Ser Trp Ser Asn
    50                  55                  60

Lys Ala Lys Ser Ile Cys Gln Gln Gln Lys Pro Gln Arg Arg Pro Cys
65                  70                  75                  80

Ser Glu Leu Leu Lys Tyr Leu Thr Thr Asn Asp Asp Pro Pro His Thr
                85                  90                  95
```

```
Lys Pro Thr Glu Asn Arg Asn Ser Ser Arg Asp Lys Cys Thr Ser Lys
            100                 105                 110

Lys Lys Ser His Thr Gln Ser Gln Ser Gln His Leu Gln Ala Lys Pro
        115                 120                 125

Thr Thr Leu Ser Leu Pro Leu Thr Pro Glu Ser Pro Asn Asp Pro Lys
    130                 135                 140

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

Leu Ser Gly Thr Ala Gly Leu Thr Pro Pro Thr Thr Pro Pro His Lys
                165                 170                 175

Ala Asn Gln Asp Asn Pro Phe Arg Ala Ser Pro Lys Leu Lys Ser Ser
            180                 185                 190

Cys Lys Thr Val Val Pro Pro Pro Ser Lys Lys Pro Arg Tyr Ser Glu
        195                 200                 205

Ser Ser Gly Thr Gln Gly Asn Asn Ser Thr Lys Lys Gly Pro Glu Gln
    210                 215                 220

Ser Glu Leu Tyr Ala Gln Leu Ser Lys Ser Ser Val Leu Thr Gly Gly
225                 230                 235                 240

His Glu Glu Arg Lys Thr Lys Arg Pro Ser Leu Arg Leu Phe Gly Asp
                245                 250                 255

His Asp Tyr Cys Gln Ser Ile Asn Ser Lys Thr Glu Ile Leu Ile Asn
            260                 265                 270

Ile Ser Gln Glu Leu Gln Asp Ser Arg Gln Leu Glu Asn Lys Asp Val
        275                 280                 285

Ser Ser Asp Trp Gln Gly Gln Ile Cys Ser Ser Thr Asp Ser Asp Gln
    290                 295                 300
```

```
Cys Tyr Leu Arg Glu Thr Leu Glu Ala Ser Lys Gln Val Ser Pro Cys
305                 310                 315                 320

Ser Thr Arg Lys Gln Leu Gln Asp Gln Glu Ile Arg Ala Glu Leu Asn
                325                 330                 335

Lys His Phe Gly His Pro Ser Gln Ala Val Phe Asp Asp Glu Ala Asp
            340                 345                 350

Lys Thr Gly Glu Leu Arg Asp Ser Asp Phe Ser Asn Glu Gln Phe Ser
        355                 360                 365

Lys Leu Pro Met Phe Ile Asn Ser Gly Leu Ala Met Asp Gly Leu Phe
    370                 375                 380

Asp Asp Ser Glu Asp Glu Ser Asp Lys Leu Ser Tyr Pro Trp Asp Gly
385                 390                 395                 400

Thr Gln Ser Tyr Ser Leu Phe Asn Val Ser Pro Ser Cys Ser Ser Phe
                405                 410                 415

Asn Ser Pro Cys Arg Asp Ser Val Ser Pro Pro Lys Ser Leu Phe Ser
            420                 425                 430

Gln Arg Pro Gln Arg Met Arg Ser Arg Ser Arg Ser Phe Ser Arg His
        435                 440                 445

Arg Ser Cys Ser Arg Ser Pro Tyr Ser Arg Ser Arg Ser Arg Ser Pro
    450                 455                 460

Gly Ser Arg Ser Ser Ser Arg Ser Cys Tyr Tyr Tyr Glu Ser Ser His
465                 470                 475                 480

Tyr Arg His Arg Thr His Arg Asn Ser Pro Leu Tyr Val Arg Ser Arg
                485                 490                 495

Ser Arg Ser Pro Tyr Ser Arg Arg Pro Arg Tyr Asp Ser Tyr Glu Glu
            500                 505                 510

Tyr Gln His Glu Arg Leu Lys Arg Glu Glu Tyr Arg Arg Glu Tyr Glu
        515                 520                 525
```

Lys Arg Glu Ser Glu Arg Ala Lys Gln Arg Glu Arg Gln Arg Gln Lys
530 535 540

Ala Ile Glu Glu Arg Arg Val Ile Tyr Val Gly Lys Ile Arg Pro Asp
545 550 555 560

Thr Thr Arg Thr Glu Leu Arg Asp Arg Phe Glu Val Phe Gly Glu Ile
565 570 575

Glu Glu Cys Thr Val Asn Leu Arg Asp Asp Gly Asp Ser Tyr Gly Phe
580 585 590

Ile Thr Tyr Arg Tyr Thr Cys Asp Ala Phe Ala Ala Leu Glu Asn Gly
595 600 605

Tyr Thr Leu Arg Arg Ser Asn Glu Thr Asp Phe Glu Leu Tyr Phe Cys
610 615 620

Gly Arg Lys Gln Phe Phe Lys Ser Asn Tyr Ala Asp Leu Asp Ser Asn
625 630 635 640

Ser Asp Asp Phe Asp Pro Ala Ser Thr Lys Ser Lys Tyr Asp Ser Leu
645 650 655

Asp Phe Asp Ser Leu Leu Lys Glu Ala Gln Arg Ser Leu Arg Arg
660 665 670

<210> 49
<211> 7
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<213> Artificial Sequence

<220>
<223> oligonucleotide

<400> 49
ucauaca 7

<210> 50
<211> 7
<212> RNA
<213> Artificial Sequence

<220>
<223> oligonucleotide

<400> 50
gaggcug 7

<210> 51
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide

<400> 51
cgaggtcgac ttcctaga 18

<210> 52
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide

<400> 52
catacacggc tctcctctct aaa 23

<210> 53
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide

<400> 53
tcctgtggca tccatgaaac 20

<210> 54
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide

<400> 54
caatgcctgg gtacatggtg 20

<210> 55
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide

<400> 55
ccaagtggag gagcagct 18

<210> 56
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide

<400> 56
gacaaggtac aacccatcgg 20

<210> 57
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide

<400> 57
ttcgacacat gggataacga gg 22

<210> 58
<211> 21
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide

<400> 58
tttttgctgt gagtcccgga g 21

<210> 59
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide

<400> 59
cagcctagca gcacgtaaat 20

<210> 60
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> oligonucleotide

<400> 60
gaatcgagca ccagttacg 19

<210> 61
<211> 22
<212> DNA
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<220>
<223> oligonucleotide

<400> 61
ccttccctga aggttcctcc tt 22

<210> 62
<211> 7
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 62
tgtatga 7

<210> 63
<211> 8
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 63
gtgtatga 8

<210> 64
<211> 9
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 64
cgtgtatga 9

<210> 65
<211> 10
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 65
ccgtgtatga 10

<210> 66
<211> 11
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 66
gccgtgtatg a 11

<210> 67
<211> 12
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 67
agccgtgtat ga 12

<210> 68
<211> 13
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 68
gagccgtgta tga 13

<210> 69
<211> 14
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 69
agagccgtgt atga 14

<210> 70
<211> 15
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 70
gagagccgtg tatga 15

<210> 71
<211> 16
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 71
ggagagccgt gtatga 16

<210> 72
<211> 17
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 72
aggagagccg tgtatga 17

<210> 73
<211> 18
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 73
gaggagagcc gtgtatga 18

<210> 74
<211> 19
<212> DNA
<213> artificial Sequence

<220>
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<400> 74
agaggagagc cgtgtatga 19

<210> 75
<211> 20
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 75
gagaggagag ccgtgtatga 20

<210> 76
<211> 8
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 76
tgtatgac 8

<210> 77
<211> 9
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 77
gtgtatgac 9

<210> 78
<211> 10
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 78
cgtgtatgac 10

<210> 79
<211> 11
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 79
ccgtgtatga c 11

<210> 80
<211> 12
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 80
gccgtgtatg ac 12

<210> 81
<211> 13
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 81
agccgtgtat gac 13

<210> 82
<211> 14
<212> DNA
<213> artificial Sequence

<220>
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<400> 82
gagccgtgta tgac 14

<210> 83
<211> 15
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 83
agagccgtgt atgac 15

<210> 84
<211> 16
<212> DNA
<213> artificial Sequence

<220>
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<400> 84
gagagccgtg tatgac 16

<210> 85
<211> 17
<212> DNA
<213> artificial Sequence

<220>
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<400> 85
ggagagccgt gtatgac 17

<210> 86
<211> 18
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 86
aggagagccg tgtatgac 18

<210> 87
<211> 19
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 87
gaggagagcc gtgtatgac 19

<210> 88
<211> 20
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 88
agaggagagc cgtgtatgac 20

<210> 89
<211> 21
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 89
gagaggagag ccgtgtatga c 21

<210> 90
<211> 22
<212> DNA
<213> artificial Sequence

<220>
<223> oligonucleotide

<400> 90
agagaggaga gccgtgtatg ac 22

<210> 91
<211> 640
<212> PRT
<213> artificial Sequence

<220>
<223> NRG1 Isoform 1

<400> 91

```
Met Ser Glu Arg Lys Glu Gly Arg Gly Lys Gly Lys Gly Lys Lys Lys
1               5                  10                  15


Glu Arg Gly Ser Gly Lys Lys Pro Glu Ser Ala Ala Gly Ser Gln Ser
            20                  25                  30


Pro Ala Leu Pro Pro Arg Leu Lys Glu Met Lys Ser Gln Glu Ser Ala
        35                  40                  45


Ala Gly Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser Glu Tyr Ser
    50                  55                  60


Ser Leu Arg Phe Lys Trp Phe Lys Asn Gly Asn Glu Leu Asn Arg Lys
65                  70                  75                  80


Asn Lys Pro Gln Asn Ile Lys Ile Gln Lys Lys Pro Gly Lys Ser Glu
                85                  90                  95


Leu Arg Ile Asn Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr Met Cys
            100                 105                 110


Lys Val Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala Asn Ile Thr
        115                 120                 125


Ile Val Glu Ser Asn Glu Ile Ile Thr Gly Met Pro Ala Ser Thr Glu
    130                 135                 140


Gly Ala Tyr Val Ser Ser Glu Ser Pro Ile Arg Ile Ser Val Ser Thr
145                 150                 155                 160


Glu Gly Ala Asn Thr Ser Ser Ser Thr Ser Thr Ser Thr Thr Gly Thr
                165                 170                 175
```

```
Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn
            180                 185                 190

Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr
        195                 200                 205

Leu Cys Lys Cys Gln Pro Gly Phe Thr Gly Ala Arg Cys Thr Glu Asn
    210                 215                 220

Val Pro Met Lys Val Gln Asn Gln Glu Lys Ala Glu Glu Leu Tyr Gln
225                 230                 235                 240

Lys Arg Val Leu Thr Ile Thr Gly Ile Cys Ile Ala Leu Leu Val Val
                245                 250                 255

Gly Ile Met Cys Val Val Ala Tyr Cys Lys Thr Lys Lys Gln Arg Lys
            260                 265                 270

Lys Leu His Asp Arg Leu Arg Gln Ser Leu Arg Ser Glu Arg Asn Asn
        275                 280                 285

Met Met Asn Ile Ala Asn Gly Pro His His Pro Asn Pro Pro Pro Glu
    290                 295                 300

Asn Val Gln Leu Val Asn Gln Tyr Val Ser Lys Asn Val Ile Ser Ser
305                 310                 315                 320

Glu His Ile Val Glu Arg Glu Ala Glu Thr Ser Phe Ser Thr Ser His
                325                 330                 335

Tyr Thr Ser Thr Ala His His Ser Thr Thr Val Thr Gln Thr Pro Ser
            340                 345                 350

His Ser Trp Ser Asn Gly His Thr Glu Ser Ile Leu Ser Glu Ser His
        355                 360                 365

Ser Val Ile Val Met Ser Ser Val Glu Asn Ser Arg His Ser Ser Pro
    370                 375                 380
```

```
Thr Gly Gly Pro Arg Gly Arg Leu Asn Gly Thr Gly Gly Pro Arg Glu
385                 390                 395                 400

Cys Asn Ser Phe Leu Arg His Ala Arg Glu Thr Pro Asp Ser Tyr Arg
                405                 410                 415

Asp Ser Pro His Ser Glu Arg Tyr Val Ser Ala Met Thr Thr Pro Ala
            420                 425                 430

Arg Met Ser Pro Val Asp Phe His Thr Pro Ser Ser Pro Lys Ser Pro
        435                 440                 445

Pro Ser Glu Met Ser Pro Pro Val Ser Ser Met Thr Val Ser Met Pro
    450                 455                 460

Ser Met Ala Val Ser Pro Phe Met Glu Glu Glu Arg Pro Leu Leu Leu
465                 470                 475                 480

Val Thr Pro Pro Arg Leu Arg Glu Lys Lys Phe Asp His His Pro Gln
                485                 490                 495

Gln Phe Ser Ser Phe His His Asn Pro Ala His Asp Ser Asn Ser Leu
            500                 505                 510

Pro Ala Ser Pro Leu Arg Ile Val Glu Asp Glu Glu Tyr Glu Thr Thr
        515                 520                 525

Gln Glu Tyr Glu Pro Ala Gln Glu Pro Val Lys Lys Leu Ala Asn Ser
    530                 535                 540

Arg Arg Ala Lys Arg Thr Lys Pro Asn Gly His Ile Ala Asn Arg Leu
545                 550                 555                 560

Glu Val Asp Ser Asn Thr Ser Ser Gln Ser Ser Asn Ser Glu Ser Glu
                565                 570                 575

Thr Glu Asp Glu Arg Val Gly Glu Asp Thr Pro Phe Leu Gly Ile Gln
            580                 585                 590

Asn Pro Leu Ala Ala Ser Leu Glu Ala Thr Pro Ala Phe Arg Leu Ala
        595                 600                 605
```

Asp Ser Arg Thr Asn Pro Ala Gly Arg Phe Ser Thr Gln Glu Glu Ile
610 615 620

Gln Ala Arg Leu Ser Ser Val Ile Ala Asn Gln Asp Pro Ile Ala Val
625 630 635 640

<210> 92
<211> 648
<212> PRT
<213> artificial Sequence

<220>
<223> NRG1 Isoform 2

<400> 92

Met Ser Glu Arg Lys Glu Gly Arg Gly Lys Gly Lys Gly Lys Lys Lys
1 5 10 15

Glu Arg Gly Ser Gly Lys Lys Pro Glu Ser Ala Ala Gly Ser Gln Ser
20 25 30

Pro Ala Leu Pro Pro Arg Leu Lys Glu Met Lys Ser Gln Glu Ser Ala
35 40 45

Ala Gly Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser Glu Tyr Ser
50 55 60

Ser Leu Arg Phe Lys Trp Phe Lys Asn Gly Asn Glu Leu Asn Arg Lys
65 70 75 80

Asn Lys Pro Gln Asn Ile Lys Ile Gln Lys Lys Pro Gly Lys Ser Glu
85 90 95

Leu Arg Ile Asn Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr Met Cys
100 105 110

Lys Val Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala Asn Ile Thr
115 120 125

Ile Val Glu Ser Asn Glu Ile Ile Thr Gly Met Pro Ala Ser Thr Glu
130 135 140

```
Gly Ala Tyr Val Ser Ser Glu Ser Pro Ile Arg Ile Ser Val Ser Thr
145                 150                 155                 160

Glu Gly Ala Asn Thr Ser Ser Ser Thr Ser Thr Ser Thr Thr Gly Thr
                165                 170                 175

Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn
            180                 185                 190

Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr
        195                 200                 205

Leu Cys Lys Cys Gln Pro Gly Phe Thr Gly Ala Arg Cys Thr Glu Asn
    210                 215                 220

Val Pro Met Lys Val Gln Asn Gln Glu Lys His Leu Gly Ile Glu Phe
225                 230                 235                 240

Ile Glu Ala Glu Glu Leu Tyr Gln Lys Arg Val Leu Thr Ile Thr Gly
                245                 250                 255

Ile Cys Ile Ala Leu Leu Val Val Gly Ile Met Cys Val Val Ala Tyr
            260                 265                 270

Cys Lys Thr Lys Lys Gln Arg Lys Lys Leu His Asp Arg Leu Arg Gln
        275                 280                 285

Ser Leu Arg Ser Glu Arg Asn Asn Met Met Asn Ile Ala Asn Gly Pro
    290                 295                 300

His His Pro Asn Pro Pro Pro Glu Asn Val Gln Leu Val Asn Gln Tyr
305                 310                 315                 320

Val Ser Lys Asn Val Ile Ser Ser Glu His Ile Val Glu Arg Glu Ala
                325                 330                 335

Glu Thr Ser Phe Ser Thr Ser His Tyr Thr Ser Thr Ala His His Ser
            340                 345                 350
```

```
Thr Thr Val Thr Gln Thr Pro Ser His Ser Trp Ser Asn Gly His Thr
        355                 360                 365

Glu Ser Ile Leu Ser Glu Ser His Ser Val Ile Val Met Ser Ser Val
    370                 375                 380

Glu Asn Ser Arg His Ser Ser Pro Thr Gly Gly Pro Arg Gly Arg Leu
385                 390                 395                 400

Asn Gly Thr Gly Gly Pro Arg Glu Cys Asn Ser Phe Leu Arg His Ala
                405                 410                 415

Arg Glu Thr Pro Asp Ser Tyr Arg Asp Ser Pro His Ser Glu Arg Tyr
            420                 425                 430

Val Ser Ala Met Thr Thr Pro Ala Arg Met Ser Pro Val Asp Phe His
        435                 440                 445

Thr Pro Ser Ser Pro Lys Ser Pro Pro Ser Glu Met Ser Pro Pro Val
    450                 455                 460

Ser Ser Met Thr Val Ser Met Pro Ser Met Ala Val Ser Pro Phe Met
465                 470                 475                 480

Glu Glu Glu Arg Pro Leu Leu Leu Val Thr Pro Pro Arg Leu Arg Glu
                485                 490                 495

Lys Lys Phe Asp His His Pro Gln Gln Phe Ser Ser Phe His His Asn
            500                 505                 510

Pro Ala His Asp Ser Asn Ser Leu Pro Ala Ser Pro Leu Arg Ile Val
        515                 520                 525

Glu Asp Glu Glu Tyr Glu Thr Thr Gln Glu Tyr Glu Pro Ala Gln Glu
    530                 535                 540

Pro Val Lys Lys Leu Ala Asn Ser Arg Arg Ala Lys Arg Thr Lys Pro
545                 550                 555                 560

Asn Gly His Ile Ala Asn Arg Leu Glu Val Asp Ser Asn Thr Ser Ser
                565                 570                 575
```

Gln Ser Ser Asn Ser Glu Ser Glu Thr Glu Asp Glu Arg Val Gly Glu
580 585 590

Asp Thr Pro Phe Leu Gly Ile Gln Asn Pro Leu Ala Ala Ser Leu Glu
595 600 605

Ala Thr Pro Ala Phe Arg Leu Ala Asp Ser Arg Thr Asn Pro Ala Gly
610 615 620

Arg Phe Ser Thr Gln Glu Glu Ile Gln Ala Arg Leu Ser Ser Val Ile
625 630 635 640

Ala Asn Gln Asp Pro Ile Ala Val
645

<210> 93
<211> 462
<212> PRT
<213> artificial Sequence

<220>
<223> NRG1 Isoform 3

<400> 93

Met Ser Glu Arg Lys Glu Gly Arg Gly Lys Gly Lys Gly Lys Lys Lys
1 5 10 15

Glu Arg Gly Ser Gly Lys Lys Pro Glu Ser Ala Ala Gly Ser Gln Ser
20 25 30

Pro Ala Leu Pro Pro Arg Leu Lys Glu Met Lys Ser Gln Glu Ser Ala
35 40 45

Ala Gly Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser Glu Tyr Ser
50 55 60

Ser Leu Arg Phe Lys Trp Phe Lys Asn Gly Asn Glu Leu Asn Arg Lys
65 70 75 80

Asn Lys Pro Gln Asn Ile Lys Ile Gln Lys Lys Pro Gly Lys Ser Glu
85 90 95

```
Leu Arg Ile Asn Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr Met Cys
            100                 105                 110

Lys Val Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala Asn Ile Thr
        115                 120                 125

Ile Val Glu Ser Asn Glu Ile Ile Thr Gly Met Pro Ala Ser Thr Glu
    130                 135                 140

Gly Ala Tyr Val Ser Ser Glu Ser Pro Ile Arg Ile Ser Val Ser Thr
145                 150                 155                 160

Glu Gly Ala Asn Thr Ser Ser Ser Thr Ser Thr Ser Thr Thr Gly Thr
                165                 170                 175

Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn
            180                 185                 190

Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr
        195                 200                 205

Leu Cys Lys Cys Gln Pro Gly Phe Thr Gly Ala Arg Cys Thr Glu Asn
    210                 215                 220

Val Pro Met Lys Val Gln Asn Gln Glu Lys Ala Glu Glu Leu Tyr Gln
225                 230                 235                 240

Lys Arg Val Leu Thr Ile Thr Gly Ile Cys Ile Ala Leu Leu Val Val
                245                 250                 255

Gly Ile Met Cys Val Val Ala Tyr Cys Lys Thr Lys Lys Gln Arg Lys
            260                 265                 270

Lys Leu His Asp Arg Leu Arg Gln Ser Leu Arg Ser Glu Arg Asn Asn
        275                 280                 285

Met Met Asn Ile Ala Asn Gly Pro His His Pro Asn Pro Pro Pro Glu
    290                 295                 300
```

Asn Val Gln Leu Val Asn Gln Tyr Val Ser Lys Asn Val Ile Ser Ser
305 310 315 320

Glu His Ile Val Glu Arg Glu Ala Glu Thr Ser Phe Ser Thr Ser His
325 330 335

Tyr Thr Ser Thr Ala His His Ser Thr Thr Val Thr Gln Thr Pro Ser
340 345 350

His Ser Trp Ser Asn Gly His Thr Glu Ser Ile Leu Ser Glu Ser His
355 360 365

Ser Val Ile Val Met Ser Ser Val Glu Asn Ser Arg His Ser Ser Pro
370 375 380

Thr Gly Gly Pro Arg Gly Arg Leu Asn Gly Thr Gly Gly Pro Arg Glu
385 390 395 400

Cys Asn Ser Phe Leu Arg His Ala Arg Glu Thr Pro Asp Ser Tyr Arg
405 410 415

Asp Ser Pro His Ser Glu Arg His Asn Leu Ile Ala Glu Leu Arg Arg
420 425 430

Asn Lys Ala His Arg Ser Lys Cys Met Gln Ile Gln Leu Ser Ala Thr
435 440 445

His Leu Arg Ser Ser Ser Ile Pro His Leu Gly Phe Ile Leu
450 455 460

<210> 94
<211> 247
<212> PRT
<213> artificial Sequence

<220>
<223> NRG1 Isoform 4

<400> 94

Met Ser Glu Arg Lys Glu Gly Arg Gly Lys Gly Lys Gly Lys Lys Lys
1 5 10 15

```
Glu Arg Gly Ser Gly Lys Lys Pro Glu Ser Ala Ala Gly Ser Gln Ser
            20                  25                  30

Pro Ala Leu Pro Pro Arg Leu Lys Glu Met Lys Ser Gln Glu Ser Ala
        35                  40                  45

Ala Gly Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser Glu Tyr Ser
    50                  55                  60

Ser Leu Arg Phe Lys Trp Phe Lys Asn Gly Asn Glu Leu Asn Arg Lys
65                  70                  75                  80

Asn Lys Pro Gln Asn Ile Lys Ile Gln Lys Lys Pro Gly Lys Ser Glu
                85                  90                  95

Leu Arg Ile Asn Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr Met Cys
            100                 105                 110

Lys Val Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala Asn Ile Thr
        115                 120                 125

Ile Val Glu Ser Asn Glu Ile Ile Thr Gly Met Pro Ala Ser Thr Glu
    130                 135                 140

Gly Ala Tyr Val Ser Ser Glu Ser Pro Ile Arg Ile Ser Val Ser Thr
145                 150                 155                 160

Glu Gly Ala Asn Thr Ser Ser Ser Thr Ser Thr Ser Thr Thr Gly Thr
                165                 170                 175

Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn
            180                 185                 190

Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr
        195                 200                 205

Leu Cys Lys Cys Gln Pro Gly Phe Thr Gly Ala Arg Cys Thr Glu Asn
    210                 215                 220

Val Pro Met Lys Val Gln Asn Gln Glu Ser Ala Gln Met Ser Leu Leu
225                 230                 235                 240
```

Val Ile Ala Ala Lys Thr Thr
245

<210> 95
<211> 645
<212> PRT
<213> artificial Sequence

<220>
<223> NRG1 Isoform 6

<400> 95

Met Ser Glu Arg Lys Glu Gly Arg Gly Lys Gly Lys Gly Lys Lys Lys
1 5 10 15

Glu Arg Gly Ser Gly Lys Lys Pro Glu Ser Ala Ala Gly Ser Gln Ser
20 25 30

Pro Ala Leu Pro Pro Arg Leu Lys Glu Met Lys Ser Gln Glu Ser Ala
35 40 45

Ala Gly Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser Glu Tyr Ser
50 55 60

Ser Leu Arg Phe Lys Trp Phe Lys Asn Gly Asn Glu Leu Asn Arg Lys
65 70 75 80

Asn Lys Pro Gln Asn Ile Lys Ile Gln Lys Lys Pro Gly Lys Ser Glu
85 90 95

Leu Arg Ile Asn Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr Met Cys
100 105 110

Lys Val Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala Asn Ile Thr
115 120 125

Ile Val Glu Ser Asn Glu Ile Ile Thr Gly Met Pro Ala Ser Thr Glu
130 135 140

Gly Ala Tyr Val Ser Ser Glu Ser Pro Ile Arg Ile Ser Val Ser Thr
145 150 155 160

```
Glu Gly Ala Asn Thr Ser Ser Ser Thr Ser Thr Ser Thr Thr Gly Thr
                165                 170                 175

Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn
            180                 185                 190

Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr
        195                 200                 205

Leu Cys Lys Cys Pro Asn Glu Phe Thr Gly Asp Arg Cys Gln Asn Tyr
    210                 215                 220

Val Met Ala Ser Phe Tyr Lys His Leu Gly Ile Glu Phe Met Glu Ala
225                 230                 235                 240

Glu Glu Leu Tyr Gln Lys Arg Val Leu Thr Ile Thr Gly Ile Cys Ile
                245                 250                 255

Ala Leu Leu Val Val Gly Ile Met Cys Val Val Ala Tyr Cys Lys Thr
            260                 265                 270

Lys Lys Gln Arg Lys Lys Leu His Asp Arg Leu Arg Gln Ser Leu Arg
        275                 280                 285

Ser Glu Arg Asn Asn Met Met Asn Ile Ala Asn Gly Pro His His Pro
    290                 295                 300

Asn Pro Pro Pro Glu Asn Val Gln Leu Val Asn Gln Tyr Val Ser Lys
305                 310                 315                 320

Asn Val Ile Ser Ser Glu His Ile Val Glu Arg Glu Ala Glu Thr Ser
                325                 330                 335

Phe Ser Thr Ser His Tyr Thr Ser Thr Ala His His Ser Thr Thr Val
            340                 345                 350

Thr Gln Thr Pro Ser His Ser Trp Ser Asn Gly His Thr Glu Ser Ile
        355                 360                 365
```

```
Leu Ser Glu Ser His Ser Val Ile Val Met Ser Ser Val Glu Asn Ser
    370                 375                 380

Arg His Ser Ser Pro Thr Gly Gly Pro Arg Gly Arg Leu Asn Gly Thr
385                 390                 395                 400

Gly Gly Pro Arg Glu Cys Asn Ser Phe Leu Arg His Ala Arg Glu Thr
                405                 410                 415

Pro Asp Ser Tyr Arg Asp Ser Pro His Ser Glu Arg Tyr Val Ser Ala
            420                 425                 430

Met Thr Thr Pro Ala Arg Met Ser Pro Val Asp Phe His Thr Pro Ser
        435                 440                 445

Ser Pro Lys Ser Pro Pro Ser Glu Met Ser Pro Pro Val Ser Ser Met
    450                 455                 460

Thr Val Ser Met Pro Ser Met Ala Val Ser Pro Phe Met Glu Glu Glu
465                 470                 475                 480

Arg Pro Leu Leu Leu Val Thr Pro Pro Arg Leu Arg Glu Lys Lys Phe
                485                 490                 495

Asp His His Pro Gln Gln Phe Ser Ser Phe His His Asn Pro Ala His
            500                 505                 510

Asp Ser Asn Ser Leu Pro Ala Ser Pro Leu Arg Ile Val Glu Asp Glu
        515                 520                 525

Glu Tyr Glu Thr Thr Gln Glu Tyr Glu Pro Ala Gln Glu Pro Val Lys
    530                 535                 540

Lys Leu Ala Asn Ser Arg Arg Ala Lys Arg Thr Lys Pro Asn Gly His
545                 550                 555                 560

Ile Ala Asn Arg Leu Glu Val Asp Ser Asn Thr Ser Ser Gln Ser Ser
                565                 570                 575

Asn Ser Glu Ser Glu Thr Glu Asp Glu Arg Val Gly Glu Asp Thr Pro
            580                 585                 590
```

Phe Leu Gly Ile Gln Asn Pro Leu Ala Ala Ser Leu Glu Ala Thr Pro
595 600 605

Ala Phe Arg Leu Ala Asp Ser Arg Thr Asn Pro Ala Gly Arg Phe Ser
610 615 620

Thr Gln Glu Glu Ile Gln Ala Arg Leu Ser Ser Val Ile Ala Asn Gln
625 630 635 640

Asp Pro Ile Ala Val
645

<210> 96
<211> 637
<212> PRT
<213> artificial Sequence

<220>
<223> NRG1 Isoform 7

<400> 96

Met Ser Glu Arg Lys Glu Gly Arg Gly Lys Gly Lys Gly Lys Lys Lys
1 5 10 15

Glu Arg Gly Ser Gly Lys Lys Pro Glu Ser Ala Ala Gly Ser Gln Ser
20 25 30

Pro Ala Leu Pro Pro Arg Leu Lys Glu Met Lys Ser Gln Glu Ser Ala
35 40 45

Ala Gly Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser Glu Tyr Ser
50 55 60

Ser Leu Arg Phe Lys Trp Phe Lys Asn Gly Asn Glu Leu Asn Arg Lys
65 70 75 80

Asn Lys Pro Gln Asn Ile Lys Ile Gln Lys Lys Pro Gly Lys Ser Glu
85 90 95

Leu Arg Ile Asn Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr Met Cys
100 105 110

```
Lys Val Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala Asn Ile Thr
        115                 120                 125

Ile Val Glu Ser Asn Glu Ile Ile Thr Gly Met Pro Ala Ser Thr Glu
    130                 135                 140

Gly Ala Tyr Val Ser Ser Glu Ser Pro Ile Arg Ile Ser Val Ser Thr
145                 150                 155                 160

Glu Gly Ala Asn Thr Ser Ser Ser Thr Ser Thr Ser Thr Thr Gly Thr
                165                 170                 175

Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn
            180                 185                 190

Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr
        195                 200                 205

Leu Cys Lys Cys Pro Asn Glu Phe Thr Gly Asp Arg Cys Gln Asn Tyr
    210                 215                 220

Val Met Ala Ser Phe Tyr Lys Ala Glu Glu Leu Tyr Gln Lys Arg Val
225                 230                 235                 240

Leu Thr Ile Thr Gly Ile Cys Ile Ala Leu Leu Val Val Gly Ile Met
                245                 250                 255

Cys Val Val Ala Tyr Cys Lys Thr Lys Lys Gln Arg Lys Lys Leu His
            260                 265                 270

Asp Arg Leu Arg Gln Ser Leu Arg Ser Glu Arg Asn Asn Met Met Asn
        275                 280                 285

Ile Ala Asn Gly Pro His His Pro Asn Pro Pro Pro Glu Asn Val Gln
    290                 295                 300

Leu Val Asn Gln Tyr Val Ser Lys Asn Val Ile Ser Ser Glu His Ile
305                 310                 315                 320
```

```
Val Glu Arg Glu Ala Glu Thr Ser Phe Ser Thr Ser His Tyr Thr Ser
                325                 330                 335

Thr Ala His His Ser Thr Thr Val Thr Gln Thr Pro Ser His Ser Trp
            340                 345                 350

Ser Asn Gly His Thr Glu Ser Ile Leu Ser Glu Ser His Ser Val Ile
        355                 360                 365

Val Met Ser Ser Val Glu Asn Ser Arg His Ser Ser Pro Thr Gly Gly
    370                 375                 380

Pro Arg Gly Arg Leu Asn Gly Thr Gly Gly Pro Arg Glu Cys Asn Ser
385                 390                 395                 400

Phe Leu Arg His Ala Arg Glu Thr Pro Asp Ser Tyr Arg Asp Ser Pro
                405                 410                 415

His Ser Glu Arg Tyr Val Ser Ala Met Thr Thr Pro Ala Arg Met Ser
            420                 425                 430

Pro Val Asp Phe His Thr Pro Ser Ser Pro Lys Ser Pro Pro Ser Glu
        435                 440                 445

Met Ser Pro Pro Val Ser Ser Met Thr Val Ser Met Pro Ser Met Ala
    450                 455                 460

Val Ser Pro Phe Met Glu Glu Glu Arg Pro Leu Leu Leu Val Thr Pro
465                 470                 475                 480

Pro Arg Leu Arg Glu Lys Lys Phe Asp His His Pro Gln Gln Phe Ser
                485                 490                 495

Ser Phe His His Asn Pro Ala His Asp Ser Asn Ser Leu Pro Ala Ser
            500                 505                 510

Pro Leu Arg Ile Val Glu Asp Glu Glu Tyr Glu Thr Thr Gln Glu Tyr
        515                 520                 525

Glu Pro Ala Gln Glu Pro Val Lys Lys Leu Ala Asn Ser Arg Arg Ala
    530                 535                 540
```

```
Lys Arg Thr Lys Pro Asn Gly His Ile Ala Asn Arg Leu Glu Val Asp
545                 550                 555                 560


Ser Asn Thr Ser Ser Gln Ser Ser Asn Ser Glu Ser Glu Thr Glu Asp
                565                 570                 575


Glu Arg Val Gly Glu Asp Thr Pro Phe Leu Gly Ile Gln Asn Pro Leu
            580                 585                 590


Ala Ala Ser Leu Glu Ala Thr Pro Ala Phe Arg Leu Ala Asp Ser Arg
        595                 600                 605


Thr Asn Pro Ala Gly Arg Phe Ser Thr Gln Glu Glu Ile Gln Ala Arg
    610                 615                 620


Leu Ser Ser Val Ile Ala Asn Gln Asp Pro Ile Ala Val
625                 630                 635


<210>  97
<211>  241
<212>  PRT
<213>  artificial Sequence

<220>
<223>  NRG1 Isoform 8

<400>  97

Met Ser Glu Arg Lys Glu Gly Arg Gly Lys Gly Lys Gly Lys Lys Lys
1               5                   10                  15


Glu Arg Gly Ser Gly Lys Lys Pro Glu Ser Ala Ala Gly Ser Gln Ser
            20                  25                  30


Pro Ala Leu Pro Pro Arg Leu Lys Glu Met Lys Ser Gln Glu Ser Ala
        35                  40                  45


Ala Gly Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser Glu Tyr Ser
    50                  55                  60


Ser Leu Arg Phe Lys Trp Phe Lys Asn Gly Asn Glu Leu Asn Arg Lys
65                  70                  75                  80
```

```
Asn Lys Pro Gln Asn Ile Lys Ile Gln Lys Lys Pro Gly Lys Ser Glu
                85                  90                  95

Leu Arg Ile Asn Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr Met Cys
            100                 105                 110

Lys Val Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala Asn Ile Thr
        115                 120                 125

Ile Val Glu Ser Asn Glu Ile Ile Thr Gly Met Pro Ala Ser Thr Glu
    130                 135                 140

Gly Ala Tyr Val Ser Ser Glu Ser Pro Ile Arg Ile Ser Val Ser Thr
145                 150                 155                 160

Glu Gly Ala Asn Thr Ser Ser Ser Thr Ser Thr Ser Thr Thr Gly Thr
                165                 170                 175

Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn
            180                 185                 190

Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr
        195                 200                 205

Leu Cys Lys Cys Pro Asn Glu Phe Thr Gly Asp Arg Cys Gln Asn Tyr
    210                 215                 220

Val Met Ala Ser Phe Tyr Ser Thr Ser Thr Pro Phe Leu Ser Leu Pro
225                 230                 235                 240

Glu
```

<210> 98
<211> 422
<212> PRT
<213> artificial Sequence

<220>
<223> NRG1 Isoform 9

<400> 98

```
Met Arg Trp Arg Arg Ala Pro Arg Arg Ser Gly Arg Pro Gly Pro Arg
1               5                  10                  15

Ala Gln Arg Pro Gly Ser Ala Ala Arg Ser Ser Pro Pro Leu Pro Leu
            20                  25                  30

Leu Pro Leu Leu Leu Leu Leu Gly Thr Ala Ala Leu Ala Pro Gly Ala
        35                  40                  45

Ala Ala Gly Asn Glu Ala Ala Pro Ala Gly Ala Ser Val Cys Tyr Ser
    50                  55                  60

Ser Pro Pro Ser Val Gly Ser Val Gln Glu Leu Ala Gln Arg Ala Ala
65                  70                  75                  80

Val Val Ile Glu Gly Lys Val His Pro Gln Arg Arg Gln Gln Gly Ala
                85                  90                  95

Leu Asp Arg Lys Ala Ala Ala Ala Ala Gly Glu Ala Gly Ala Trp Gly
            100                 105                 110

Gly Asp Arg Glu Pro Pro Ala Ala Gly Pro Arg Ala Leu Gly Pro Pro
        115                 120                 125

Ala Glu Glu Pro Leu Leu Ala Ala Asn Gly Thr Val Pro Ser Trp Pro
    130                 135                 140

Thr Ala Pro Val Pro Ser Ala Gly Glu Pro Gly Glu Glu Ala Pro Tyr
145                 150                 155                 160

Leu Val Lys Val His Gln Val Trp Ala Val Lys Ala Gly Gly Leu Lys
                165                 170                 175

Lys Asp Ser Leu Leu Thr Val Arg Leu Gly Thr Trp Gly His Pro Ala
            180                 185                 190

Phe Pro Ser Cys Gly Arg Leu Lys Glu Asp Ser Arg Tyr Ile Phe Phe
        195                 200                 205
```

```
Met Glu Pro Asp Ala Asn Ser Thr Ser Arg Ala Pro Ala Ala Phe Arg
    210                 215                 220

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

Ser Arg Val Leu Cys Lys Arg Cys Ala Leu Pro Pro Arg Leu Lys Glu
                245                 250                 255

Met Lys Ser Gln Glu Ser Ala Ala Gly Ser Lys Leu Val Leu Arg Cys
            260                 265                 270

Glu Thr Ser Ser Glu Tyr Ser Ser Leu Arg Phe Lys Trp Phe Lys Asn
        275                 280                 285

Gly Asn Glu Leu Asn Arg Lys Asn Lys Pro Gln Asn Ile Lys Ile Gln
    290                 295                 300

Lys Lys Pro Gly Lys Ser Glu Leu Arg Ile Asn Lys Ala Ser Leu Ala
305                 310                 315                 320

Asp Ser Gly Glu Tyr Met Cys Lys Val Ile Ser Lys Leu Gly Asn Asp
                325                 330                 335

Ser Ala Ser Ala Asn Ile Thr Ile Val Glu Ser Asn Ala Thr Ser Thr
            340                 345                 350

Ser Thr Thr Gly Thr Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys
        355                 360                 365

Thr Phe Cys Val Asn Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser
    370                 375                 380

Asn Pro Ser Arg Tyr Leu Cys Lys Cys Pro Asn Glu Phe Thr Gly Asp
385                 390                 395                 400

Arg Cys Gln Asn Tyr Val Met Ala Ser Phe Tyr Ser Thr Ser Thr Pro
                405                 410                 415

Phe Leu Ser Leu Pro Glu
            420
```

<210> 99
<211> 296
<212> PRT
<213> artificial Sequence

<220>
<223> NRG1 Isoform 10

<400> 99

Met Glu Ile Tyr Ser Pro Asp Met Ser Glu Val Ala Ala Glu Arg Ser
1 5 10 15

Ser Ser Pro Ser Thr Gln Leu Ser Ala Asp Pro Ser Leu Asp Gly Leu
20 25 30

Pro Ala Ala Glu Asp Met Pro Glu Pro Gln Thr Glu Asp Gly Arg Thr
35 40 45

Pro Gly Leu Val Gly Leu Ala Val Pro Cys Cys Ala Cys Leu Glu Ala
50 55 60

Glu Arg Leu Arg Gly Cys Leu Asn Ser Glu Lys Ile Cys Ile Val Pro
65 70 75 80

Ile Leu Ala Cys Leu Val Ser Leu Cys Leu Cys Ile Ala Gly Leu Lys
85 90 95

Trp Val Phe Val Asp Lys Ile Phe Glu Tyr Asp Ser Pro Thr His Leu
100 105 110

Asp Pro Gly Gly Leu Gly Gln Asp Pro Ile Ile Ser Leu Asp Ala Thr
115 120 125

Ala Ala Ser Ala Val Trp Val Ser Ser Glu Ala Tyr Thr Ser Pro Val
130 135 140

Ser Arg Ala Gln Ser Glu Ser Glu Val Gln Val Thr Val Gln Gly Asp
145 150 155 160

Lys Ala Val Val Ser Phe Glu Pro Ser Ala Ala Pro Thr Pro Lys Asn
165 170 175

```
Arg Ile Phe Ala Phe Ser Phe Leu Pro Ser Thr Ala Pro Ser Phe Pro
            180                 185                 190

Ser Pro Thr Arg Asn Pro Glu Val Arg Thr Pro Lys Ser Ala Thr Gln
        195                 200                 205

Pro Gln Thr Thr Glu Thr Asn Leu Gln Thr Ala Pro Lys Leu Ser Thr
    210                 215                 220

Ser Thr Ser Thr Thr Gly Thr Ser His Leu Val Lys Cys Ala Glu Lys
225                 230                 235                 240

Glu Lys Thr Phe Cys Val Asn Gly Gly Glu Cys Phe Met Val Lys Asp
                245                 250                 255

Leu Ser Asn Pro Ser Arg Tyr Leu Cys Lys Cys Pro Asn Glu Phe Thr
            260                 265                 270

Gly Asp Arg Cys Gln Asn Tyr Val Met Ala Ser Phe Tyr Ser Thr Ser
        275                 280                 285

Thr Pro Phe Leu Ser Leu Pro Glu
    290                 295
```

<210> 100
<211> 590
<212> PRT
<213> artificial Sequence

<220>
<223> NRG1 Isoform 11

<400> 100

```
Met Gly Lys Gly Arg Ala Gly Arg Val Gly Thr Thr Ala Leu Pro Pro
1               5                   10                  15

Arg Leu Lys Glu Met Lys Ser Gln Glu Ser Ala Ala Gly Ser Lys Leu
            20                  25                  30

Val Leu Arg Cys Glu Thr Ser Ser Glu Tyr Ser Ser Leu Arg Phe Lys
        35                  40                  45
```

```
Trp Phe Lys Asn Gly Asn Glu Leu Asn Arg Lys Asn Lys Pro Gln Asn
    50                  55                  60

Ile Lys Ile Gln Lys Lys Pro Gly Lys Ser Glu Leu Arg Ile Asn Lys
65                  70                  75                  80

Ala Ser Leu Ala Asp Ser Gly Glu Tyr Met Cys Lys Val Ile Ser Lys
                85                  90                  95

Leu Gly Asn Asp Ser Ala Ser Ala Asn Ile Thr Ile Val Glu Ser Asn
            100                 105                 110

Ala Thr Ser Thr Ser Thr Thr Gly Thr Ser His Leu Val Lys Cys Ala
        115                 120                 125

Glu Lys Glu Lys Thr Phe Cys Val Asn Gly Gly Glu Cys Phe Met Val
    130                 135                 140

Lys Asp Leu Ser Asn Pro Ser Arg Tyr Leu Cys Lys Cys Pro Asn Glu
145                 150                 155                 160

Phe Thr Gly Asp Arg Cys Gln Asn Tyr Val Met Ala Ser Phe Tyr Lys
                165                 170                 175

His Leu Gly Ile Glu Phe Met Glu Ala Glu Glu Leu Tyr Gln Lys Arg
            180                 185                 190

Val Leu Thr Ile Thr Gly Ile Cys Ile Ala Leu Leu Val Val Gly Ile
        195                 200                 205

Met Cys Val Val Ala Tyr Cys Lys Thr Lys Lys Gln Arg Lys Lys Leu
    210                 215                 220

His Asp Arg Leu Arg Gln Ser Leu Arg Ser Glu Arg Asn Asn Met Met
225                 230                 235                 240

Asn Ile Ala Asn Gly Pro His His Pro Asn Pro Pro Pro Glu Asn Val
                245                 250                 255
```

```
Gln Leu Val Asn Gln Tyr Val Ser Lys Asn Val Ile Ser Ser Glu His
            260                 265                 270

Ile Val Glu Arg Glu Ala Glu Thr Ser Phe Ser Thr Ser His Tyr Thr
        275                 280                 285

Ser Thr Ala His His Ser Thr Thr Val Thr Gln Thr Pro Ser His Ser
    290                 295                 300

Trp Ser Asn Gly His Thr Glu Ser Ile Leu Ser Glu Ser His Ser Val
305                 310                 315                 320

Ile Val Met Ser Ser Val Glu Asn Ser Arg His Ser Ser Pro Thr Gly
                325                 330                 335

Gly Pro Arg Gly Arg Leu Asn Gly Thr Gly Gly Pro Arg Glu Cys Asn
            340                 345                 350

Ser Phe Leu Arg His Ala Arg Glu Thr Pro Asp Ser Tyr Arg Asp Ser
        355                 360                 365

Pro His Ser Glu Arg Tyr Val Ser Ala Met Thr Thr Pro Ala Arg Met
    370                 375                 380

Ser Pro Val Asp Phe His Thr Pro Ser Ser Pro Lys Ser Pro Pro Ser
385                 390                 395                 400

Glu Met Ser Pro Pro Val Ser Ser Met Thr Val Ser Met Pro Ser Met
                405                 410                 415

Ala Val Ser Pro Phe Met Glu Glu Glu Arg Pro Leu Leu Leu Val Thr
            420                 425                 430

Pro Pro Arg Leu Arg Glu Lys Lys Phe Asp His His Pro Gln Gln Phe
        435                 440                 445

Ser Ser Phe His His Asn Pro Ala His Asp Ser Asn Ser Leu Pro Ala
    450                 455                 460

Ser Pro Leu Arg Ile Val Glu Asp Glu Glu Tyr Glu Thr Thr Gln Glu
465                 470                 475                 480
```

Tyr Glu Pro Ala Gln Glu Pro Val Lys Lys Leu Ala Asn Ser Arg Arg
485 490 495

Ala Lys Arg Thr Lys Pro Asn Gly His Ile Ala Asn Arg Leu Glu Val
500 505 510

Asp Ser Asn Thr Ser Ser Gln Ser Ser Asn Ser Glu Ser Glu Thr Glu
515 520 525

Asp Glu Arg Val Gly Glu Asp Thr Pro Phe Leu Gly Ile Gln Asn Pro
530 535 540

Leu Ala Ala Ser Leu Glu Ala Thr Pro Ala Phe Arg Leu Ala Asp Ser
545 550 555 560

Arg Thr Asn Pro Ala Gly Arg Phe Ser Thr Gln Glu Glu Ile Gln Ala
565 570 575

Arg Leu Ser Ser Val Ile Ala Asn Gln Asp Pro Ile Ala Val
580 585 590

<210> 101
<211> 420
<212> PRT
<213> artificial Sequence

<220>
<223> NRG1 Isoform 12

<400> 101

Met Ser Glu Arg Lys Glu Gly Arg Gly Lys Gly Lys Gly Lys Lys Lys
1 5 10 15

Glu Arg Gly Ser Gly Lys Lys Pro Glu Ser Ala Ala Gly Ser Gln Ser
20 25 30

Pro Ala Leu Pro Pro Arg Leu Lys Glu Met Lys Ser Gln Glu Ser Ala
35 40 45

Ala Gly Ser Lys Leu Val Leu Arg Cys Glu Thr Ser Ser Glu Tyr Ser
50 55 60

```
Ser Leu Arg Phe Lys Trp Phe Lys Asn Gly Asn Glu Leu Asn Arg Lys
65                  70                  75                  80

Asn Lys Pro Gln Asn Ile Lys Ile Gln Lys Lys Pro Gly Lys Ser Glu
                85                  90                  95

Leu Arg Ile Asn Lys Ala Ser Leu Ala Asp Ser Gly Glu Tyr Met Cys
            100                 105                 110

Lys Val Ile Ser Lys Leu Gly Asn Asp Ser Ala Ser Ala Asn Ile Thr
        115                 120                 125

Ile Val Glu Ser Asn Glu Ile Ile Thr Gly Met Pro Ala Ser Thr Glu
    130                 135                 140

Gly Ala Tyr Val Ser Ser Glu Ser Pro Ile Arg Ile Ser Val Ser Thr
145                 150                 155                 160

Glu Gly Ala Asn Thr Ser Ser Ser Thr Ser Thr Ser Thr Thr Gly Thr
                165                 170                 175

Ser His Leu Val Lys Cys Ala Glu Lys Glu Lys Thr Phe Cys Val Asn
            180                 185                 190

Gly Gly Glu Cys Phe Met Val Lys Asp Leu Ser Asn Pro Ser Arg Tyr
        195                 200                 205

Leu Cys Lys Cys Pro Asn Glu Phe Thr Gly Asp Arg Cys Gln Asn Tyr
    210                 215                 220

Val Met Ala Ser Phe Tyr Lys Ala Glu Glu Leu Tyr Gln Lys Arg Val
225                 230                 235                 240

Leu Thr Ile Thr Gly Ile Cys Ile Ala Leu Leu Val Val Gly Ile Met
                245                 250                 255

Cys Val Val Ala Tyr Cys Lys Thr Lys Lys Gln Arg Lys Lys Leu His
            260                 265                 270
```

```
Asp Arg Leu Arg Gln Ser Leu Arg Ser Glu Arg Asn Asn Met Met Asn
        275                 280                 285

Ile Ala Asn Gly Pro His His Pro Asn Pro Pro Pro Glu Asn Val Gln
    290                 295                 300

Leu Val Asn Gln Tyr Val Ser Lys Asn Val Ile Ser Ser Glu His Ile
305                 310                 315                 320

Val Glu Arg Glu Ala Glu Thr Ser Phe Ser Thr Ser His Tyr Thr Ser
                325                 330                 335

Thr Ala His His Ser Thr Thr Val Thr Gln Thr Pro Ser His Ser Trp
            340                 345                 350

Ser Asn Gly His Thr Glu Ser Ile Leu Ser Glu Ser His Ser Val Ile
        355                 360                 365

Val Met Ser Ser Val Glu Asn Ser Arg His Ser Ser Pro Thr Gly Gly
    370                 375                 380

Pro Arg Gly Arg Leu Asn Gly Thr Gly Gly Pro Arg Glu Cys Asn Ser
385                 390                 395                 400

Phe Leu Arg His Ala Arg Glu Thr Pro Asp Ser Tyr Arg Asp Ser Pro
                405                 410                 415

His Ser Glu Arg
            420
```

<210> 102
<211> 179
<212> PRT
<213> artificial Sequence

<220>
<223> STMN2 Isoform 1

<400> 102

```
Met Ala Lys Thr Ala Met Ala Tyr Lys Glu Lys Met Lys Glu Leu Ser
1               5                   10                  15
```

Met Leu Ser Leu Ile Cys Ser Cys Phe Tyr Pro Glu Pro Arg Asn Ile
            20   25   30

Asn Ile Tyr Thr Tyr Asp Asp Met Glu Val Lys Gln Ile Asn Lys Arg
        35   40   45

Ala Ser Gly Gln Ala Phe Glu Leu Ile Leu Lys Pro Pro Ser Pro Ile
    50   55   60

Ser Glu Ala Pro Arg Thr Leu Ala Ser Pro Lys Lys Lys Asp Leu Ser
65   70   75   80

Leu Glu Glu Ile Gln Lys Lys Leu Glu Ala Ala Glu Glu Arg Arg Lys
                85   90   95

Ser Gln Glu Ala Gln Val Leu Lys Gln Leu Ala Glu Lys Arg Glu His
            100   105   110

Glu Arg Glu Val Leu Gln Lys Ala Leu Glu Glu Asn Asn Asn Phe Ser
        115   120   125

Lys Met Ala Glu Glu Lys Leu Ile Leu Lys Met Glu Gln Ile Lys Glu
    130   135   140

Asn Arg Glu Ala Asn Leu Ala Ala Ile Ile Glu Arg Leu Gln Glu Lys
145   150   155   160

Glu Arg His Ala Ala Glu Val Arg Arg Asn Lys Glu Leu Gln Val Glu
                165   170   175

Leu Ser Gly

<210> 103
<211> 187
<212> PRT
<213> artificial Sequence

<220>
<223> STMN2 Isoform 2

<400> 103

```
Met Ala Lys Thr Ala Met Ala Tyr Lys Glu Lys Met Lys Glu Leu Ser
1               5                   10                  15

Met Leu Ser Leu Ile Cys Ser Cys Phe Tyr Pro Glu Pro Arg Asn Ile
            20                  25                  30

Asn Ile Tyr Thr Tyr Asp Asp Met Glu Val Lys Gln Ile Asn Lys Arg
        35                  40                  45

Ala Ser Gly Gln Ala Phe Glu Leu Ile Leu Lys Pro Pro Ser Pro Ile
    50                  55                  60

Ser Glu Ala Pro Arg Thr Leu Ala Ser Pro Lys Lys Lys Asp Leu Ser
65                  70                  75                  80

Leu Glu Glu Ile Gln Lys Lys Leu Glu Ala Ala Glu Glu Arg Arg Lys
                85                  90                  95

Ser Gln Glu Ala Gln Val Leu Lys Gln Leu Ala Glu Lys Arg Glu His
            100                 105                 110

Glu Arg Glu Val Leu Gln Lys Ala Leu Glu Glu Asn Asn Asn Phe Ser
        115                 120                 125

Lys Met Ala Glu Glu Lys Leu Ile Leu Lys Met Glu Gln Ile Lys Glu
    130                 135                 140

Asn Arg Glu Ala Asn Leu Ala Ala Ile Ile Glu Arg Leu Gln Glu Lys
145                 150                 155                 160

Leu Val Lys Phe Ile Ser Ser Glu Leu Lys Glu Ser Ile Glu Ser Gln
                165                 170                 175

Phe Leu Glu Leu Gln Arg Glu Gly Glu Lys Gln
            180                 185
```

<210> 104
<211> 1477
<212> PRT
<213> artificial Sequence

<220>

<223> NRXN1-Alpha Isoform 1a

<400> 104

```
Met Gly Thr Ala Leu Leu Gln Arg Gly Gly Cys Phe Leu Leu Cys Leu
1               5                  10                  15


Ser Leu Leu Leu Leu Gly Cys Trp Ala Glu Leu Gly Ser Gly Leu Glu
            20                  25                  30


Phe Pro Gly Ala Glu Gly Gln Trp Thr Arg Phe Pro Lys Trp Asn Ala
        35                  40                  45


Cys Cys Glu Ser Glu Met Ser Phe Gln Leu Lys Thr Arg Ser Ala Arg
    50                  55                  60


Gly Leu Val Leu Tyr Phe Asp Asp Glu Gly Phe Cys Asp Phe Leu Glu
65                  70                  75                  80


Leu Ile Leu Thr Arg Gly Gly Arg Leu Gln Leu Ser Phe Ser Ile Phe
                85                  90                  95


Cys Ala Glu Pro Ala Thr Leu Leu Ala Asp Thr Pro Val Asn Asp Gly
            100                 105                 110


Ala Trp His Ser Val Arg Ile Arg Arg Gln Phe Arg Asn Thr Thr Leu
        115                 120                 125


Phe Ile Asp Gln Val Glu Ala Lys Trp Val Glu Val Lys Ser Lys Arg
    130                 135                 140


Arg Asp Met Thr Val Phe Ser Gly Leu Phe Val Gly Gly Leu Pro Pro
145                 150                 155                 160


Glu Leu Arg Ala Ala Ala Leu Lys Leu Thr Leu Ala Ser Val Arg Glu
                165                 170                 175


Arg Glu Pro Phe Lys Gly Trp Ile Arg Asp Val Arg Val Asn Ser Ser
            180                 185                 190


Gln Val Leu Pro Val Asp Ser Gly Glu Val Lys Leu Asp Asp Glu Pro
        195                 200                 205
```

```
Pro Asn Ser Gly Gly Gly Ser Pro Cys Glu Ala Gly Glu Glu Gly Glu
    210                 215                 220

Gly Gly Val Cys Leu Asn Gly Gly Val Cys Ser Val Val Asp Asp Gln
225                 230                 235                 240

Ala Val Cys Asp Cys Ser Arg Thr Gly Phe Arg Gly Lys Asp Cys Ser
                245                 250                 255

Gln Glu Asp Asn Asn Val Glu Gly Leu Ala His Leu Met Met Gly Asp
            260                 265                 270

Gln Gly Lys Ser Lys Gly Lys Glu Glu Tyr Ile Ala Thr Phe Lys Gly
        275                 280                 285

Ser Glu Tyr Phe Cys Tyr Asp Leu Ser Gln Asn Pro Ile Gln Ser Ser
    290                 295                 300

Ser Asp Glu Ile Thr Leu Ser Phe Lys Thr Leu Gln Arg Asn Gly Leu
305                 310                 315                 320

Met Leu His Thr Gly Lys Ser Ala Asp Tyr Val Asn Leu Ala Leu Lys
                325                 330                 335

Asn Gly Ala Val Ser Leu Val Ile Asn Leu Gly Ser Gly Ala Phe Glu
            340                 345                 350

Ala Leu Val Glu Pro Val Asn Gly Lys Phe Asn Asp Asn Ala Trp His
        355                 360                 365

Asp Val Lys Val Thr Arg Asn Leu Arg Gln His Ser Gly Ile Gly His
    370                 375                 380

Ala Met Val Thr Ile Ser Val Asp Gly Ile Leu Thr Thr Thr Gly Tyr
385                 390                 395                 400

Thr Gln Glu Asp Tyr Thr Met Leu Gly Ser Asp Asp Phe Phe Tyr Val
                405                 410                 415
```

```
Gly Gly Ser Pro Ser Thr Ala Asp Leu Pro Gly Ser Pro Val Ser Asn
            420                 425                 430

Asn Phe Met Gly Cys Leu Lys Glu Val Val Tyr Lys Asn Asn Asp Val
        435                 440                 445

Arg Leu Glu Leu Ser Arg Leu Ala Lys Gln Gly Asp Pro Lys Met Lys
    450                 455                 460

Ile His Gly Val Val Ala Phe Lys Cys Glu Asn Val Ala Thr Leu Asp
465                 470                 475                 480

Pro Ile Thr Phe Glu Thr Pro Glu Ser Phe Ile Ser Leu Pro Lys Trp
                485                 490                 495

Asn Ala Lys Lys Thr Gly Ser Ile Ser Phe Asp Phe Arg Thr Thr Glu
            500                 505                 510

Pro Asn Gly Leu Ile Leu Phe Ser His Gly Lys Pro Arg His Gln Lys
        515                 520                 525

Asp Ala Lys His Pro Gln Met Ile Lys Val Asp Phe Phe Ala Ile Glu
    530                 535                 540

Met Leu Asp Gly His Leu Tyr Leu Leu Leu Asp Met Gly Ser Gly Thr
545                 550                 555                 560

Ile Lys Ile Lys Ala Leu Leu Lys Lys Val Asn Asp Gly Glu Trp Tyr
                565                 570                 575

His Val Asp Phe Gln Arg Asp Gly Arg Ser Gly Thr Ile Ser Val Asn
            580                 585                 590

Thr Leu Arg Thr Pro Tyr Thr Ala Pro Gly Glu Ser Glu Ile Leu Asp
        595                 600                 605

Leu Asp Asp Glu Leu Tyr Leu Gly Gly Leu Pro Glu Asn Lys Ala Gly
    610                 615                 620

Leu Val Phe Pro Thr Glu Val Trp Thr Ala Leu Leu Asn Tyr Gly Tyr
625                 630                 635                 640
```

```
Val Gly Cys Ile Arg Asp Leu Phe Ile Asp Gly Gln Ser Lys Asp Ile
                645                 650                 655

Arg Gln Met Ala Glu Val Gln Ser Thr Ala Gly Val Lys Pro Ser Cys
            660                 665                 670

Ser Lys Glu Thr Ala Lys Pro Cys Leu Ser Asn Pro Cys Lys Asn Asn
        675                 680                 685

Gly Met Cys Arg Asp Gly Trp Asn Arg Tyr Val Cys Asp Cys Ser Gly
    690                 695                 700

Thr Gly Tyr Leu Gly Arg Ser Cys Glu Arg Glu Ala Thr Val Leu Ser
705                 710                 715                 720

Tyr Asp Gly Ser Met Phe Met Lys Ile Gln Leu Pro Val Val Met His
                725                 730                 735

Thr Glu Ala Glu Asp Val Ser Leu Arg Phe Arg Ser Gln Arg Ala Tyr
            740                 745                 750

Gly Ile Leu Met Ala Thr Thr Ser Arg Asp Ser Ala Asp Thr Leu Arg
        755                 760                 765

Leu Glu Leu Asp Ala Gly Arg Val Lys Leu Thr Val Asn Leu Asp Cys
    770                 775                 780

Ile Arg Ile Asn Cys Asn Ser Ser Lys Gly Pro Glu Thr Leu Phe Ala
785                 790                 795                 800

Gly Tyr Asn Leu Asn Asp Asn Glu Trp His Thr Val Arg Val Val Arg
                805                 810                 815

Arg Gly Lys Ser Leu Lys Leu Thr Val Asp Asp Gln Gln Ala Met Thr
            820                 825                 830

Gly Gln Met Ala Gly Asp His Thr Arg Leu Glu Phe His Asn Ile Glu
        835                 840                 845
```

```
Thr Gly Ile Ile Thr Glu Arg Arg Tyr Leu Ser Ser Val Pro Ser Asn
    850                 855                 860

Phe Ile Gly His Leu Gln Ser Leu Thr Phe Asn Gly Met Ala Tyr Ile
865                 870                 875                 880

Asp Leu Cys Lys Asn Gly Asp Ile Asp Tyr Cys Glu Leu Asn Ala Arg
                885                 890                 895

Phe Gly Phe Arg Asn Ile Ile Ala Asp Pro Val Thr Phe Lys Thr Lys
            900                 905                 910

Ser Ser Tyr Val Ala Leu Ala Thr Leu Gln Ala Tyr Thr Ser Met His
        915                 920                 925

Leu Phe Phe Gln Phe Lys Thr Thr Ser Leu Asp Gly Leu Ile Leu Tyr
    930                 935                 940

Asn Ser Gly Asp Gly Asn Asp Phe Ile Val Val Glu Leu Val Lys Gly
945                 950                 955                 960

Tyr Leu His Tyr Val Phe Asp Leu Gly Asn Gly Ala Asn Leu Ile Lys
                965                 970                 975

Gly Ser Ser Asn Lys Pro Leu Asn Asp Asn Gln Trp His Asn Val Met
            980                 985                 990

Ile Ser Arg Asp Thr Ser Asn Leu  His Thr Val Lys Ile  Asp Thr Lys
        995                 1000                1005

Ile Thr  Thr Gln Ile Thr Ala  Gly Ala Arg Asn Leu  Asp Leu Lys
    1010                1015                1020

Ser Asp  Leu Tyr Ile Gly Gly  Val Ala Lys Glu Thr  Tyr Lys Ser
    1025                1030                1035

Leu Pro  Lys Leu Val His Ala  Lys Glu Gly Phe Gln  Gly Cys Leu
    1040                1045                1050

Ala Ser  Val Asp Leu Asn Gly  Arg Leu Pro Asp Leu  Ile Ser Asp
    1055                1060                1065
```

```
Ala Leu  Phe Cys Asn Gly Gln  Ile Glu Arg Gly Cys  Glu Gly Pro
    1070                1075                1080

Ser Thr  Thr Cys Gln Glu Asp  Ser Cys Ser Asn Gln  Gly Val Cys
    1085                1090                1095

Leu Gln  Gln Trp Asp Gly Phe  Ser Cys Asp Cys Ser  Met Thr Ser
    1100                1105                1110

Phe Ser  Gly Pro Leu Cys Asn  Asp Pro Gly Thr Thr  Tyr Ile Phe
    1115                1120                1125

Ser Lys  Gly Gly Gly Gln Ile  Thr Tyr Lys Trp Pro  Pro Asn Asp
    1130                1135                1140

Arg Pro  Ser Thr Arg Ala Asp  Arg Leu Ala Ile Gly  Phe Ser Thr
    1145                1150                1155

Val Gln  Lys Glu Ala Val Leu  Val Arg Val Asp Ser  Ser Ser Gly
    1160                1165                1170

Leu Gly  Asp Tyr Leu Glu Leu  His Ile His Gln Gly  Lys Ile Gly
    1175                1180                1185

Val Lys  Phe Asn Val Gly Thr  Asp Asp Ile Ala Ile  Glu Glu Ser
    1190                1195                1200

Asn Ala  Ile Ile Asn Asp Gly  Lys Tyr His Val Val  Arg Phe Thr
    1205                1210                1215

Arg Ser  Gly Gly Asn Ala Thr  Leu Gln Val Asp Ser  Trp Pro Val
    1220                1225                1230

Ile Glu  Arg Tyr Pro Ala Gly  Arg Gln Leu Thr Ile  Phe Asn Ser
    1235                1240                1245

Gln Ala  Thr Ile Ile Ile Gly  Gly Lys Glu Gln Gly  Gln Pro Phe
    1250                1255                1260
```

```
Gln Gly  Gln Leu Ser Gly Leu  Tyr Tyr Asn Gly Leu  Lys Val Leu
    1265                1270                1275

Asn Met  Ala Ala Glu Asn Asp  Ala Asn Ile Ala Ile  Val Gly Asn
    1280                1285                1290

Val Arg  Leu Val Gly Glu Val  Pro Ser Ser Met Thr  Thr Glu Ser
    1295                1300                1305

Thr Ala  Thr Ala Met Gln Ser  Glu Met Ser Thr Ser  Ile Met Glu
    1310                1315                1320

Thr Thr  Thr Thr Leu Ala Thr  Ser Thr Ala Arg Arg  Gly Lys Pro
    1325                1330                1335

Pro Thr  Lys Glu Pro Ile Ser  Gln Thr Thr Asp Asp  Ile Leu Val
    1340                1345                1350

Ala Ser  Ala Glu Cys Pro Ser  Asp Asp Glu Asp Ile  Asp Pro Cys
    1355                1360                1365

Glu Pro  Ser Ser Gly Gly Leu  Ala Asn Pro Thr Arg  Ala Gly Gly
    1370                1375                1380

Arg Glu  Pro Tyr Pro Gly Ser  Ala Glu Val Ile Arg  Glu Ser Ser
    1385                1390                1395

Ser Thr  Thr Gly Met Val Val  Gly Ile Val Ala Ala  Ala Ala Leu
    1400                1405                1410

Cys Ile  Leu Ile Leu Leu Tyr  Ala Met Tyr Lys Tyr  Arg Asn Arg
    1415                1420                1425

Asp Glu  Gly Ser Tyr His Val  Asp Glu Ser Arg Asn  Tyr Ile Ser
    1430                1435                1440

Asn Ser  Ala Gln Ser Asn Gly  Ala Val Val Lys Glu  Lys Gln Pro
    1445                1450                1455

Ser Ser  Ala Lys Ser Ser Asn  Lys Asn Lys Lys Asn  Lys Asp Lys
    1460                1465                1470
```

Glu Tyr Tyr Val
    1475

<210> 105
<211> 1496
<212> PRT
<213> artificial Sequence

<220>
<223> NRXN1-Alpha Isoform 2a

<400> 105

Met Gly Thr Ala Leu Leu Gln Arg Gly Gly Cys Phe Leu Leu Cys Leu
1   5   10   15

Ser Leu Leu Leu Leu Gly Cys Trp Ala Glu Leu Gly Ser Gly Leu Glu
            20   25   30

Phe Pro Gly Ala Glu Gly Gln Trp Thr Arg Phe Pro Lys Trp Asn Ala
        35   40   45

Cys Cys Glu Ser Glu Met Ser Phe Gln Leu Lys Thr Arg Ser Ala Arg
    50   55   60

Gly Leu Val Leu Tyr Phe Asp Asp Glu Gly Phe Cys Asp Phe Leu Glu
65   70   75   80

Leu Ile Leu Thr Arg Gly Gly Arg Leu Gln Leu Ser Phe Ser Ile Phe
                85   90   95

Cys Ala Glu Pro Ala Thr Leu Leu Ala Asp Thr Pro Val Asn Asp Gly
            100   105   110

Ala Trp His Ser Val Arg Ile Arg Arg Gln Phe Arg Asn Thr Thr Leu
        115   120   125

Phe Ile Asp Gln Val Glu Ala Lys Trp Val Glu Val Lys Ser Lys Arg
    130   135   140

Arg Asp Met Thr Val Phe Ser Gly Leu Phe Val Gly Gly Leu Pro Pro
145   150   155   160

```
Glu Leu Arg Ala Ala Ala Leu Lys Leu Thr Leu Ala Ser Val Arg Glu
                165                 170                 175

Arg Glu Pro Phe Lys Gly Trp Ile Arg Asp Val Arg Val Asn Ser Ser
            180                 185                 190

Gln Val Leu Pro Val Asp Ser Gly Glu Val Lys Leu Asp Asp Glu Pro
        195                 200                 205

Pro Asn Ser Gly Gly Gly Ser Pro Cys Glu Ala Gly Glu Glu Gly Glu
    210                 215                 220

Gly Gly Val Cys Leu Asn Gly Gly Val Cys Ser Val Val Asp Asp Gln
225                 230                 235                 240

Ala Val Cys Asp Cys Ser Arg Thr Gly Phe Arg Gly Lys Asp Cys Ser
                245                 250                 255

Gln Glu Asp Asn Asn Val Glu Gly Leu Ala His Leu Met Met Gly Asp
            260                 265                 270

Gln Gly Lys Ser Lys Gly Lys Glu Glu Tyr Ile Ala Thr Phe Lys Gly
        275                 280                 285

Ser Glu Tyr Phe Cys Tyr Asp Leu Ser Gln Asn Pro Ile Gln Ser Ser
    290                 295                 300

Ser Asp Glu Ile Thr Leu Ser Phe Lys Thr Leu Gln Arg Asn Gly Leu
305                 310                 315                 320

Met Leu His Thr Gly Lys Ser Ala Asp Tyr Val Asn Leu Ala Leu Lys
                325                 330                 335

Asn Gly Ala Val Ser Leu Val Ile Asn Leu Gly Ser Gly Ala Phe Glu
            340                 345                 350

Ala Leu Val Glu Pro Val Asn Gly Lys Phe Asn Asp Asn Ala Trp His
        355                 360                 365
```

```
Asp Val Lys Val Thr Arg Asn Leu Arg Gln Val Thr Ile Ser Val Asp
    370                 375                 380

Gly Ile Leu Thr Thr Thr Gly Tyr Thr Gln Glu Asp Tyr Thr Met Leu
385                 390                 395                 400

Gly Ser Asp Asp Phe Phe Tyr Val Gly Gly Ser Pro Ser Thr Ala Asp
                405                 410                 415

Leu Pro Gly Ser Pro Val Ser Asn Asn Phe Met Gly Cys Leu Lys Glu
            420                 425                 430

Val Val Tyr Lys Asn Asn Asp Val Arg Leu Glu Leu Ser Arg Leu Ala
        435                 440                 445

Lys Gln Gly Asp Pro Lys Met Lys Ile His Gly Val Val Ala Phe Lys
    450                 455                 460

Cys Glu Asn Val Ala Thr Leu Asp Pro Ile Thr Phe Glu Thr Pro Glu
465                 470                 475                 480

Ser Phe Ile Ser Leu Pro Lys Trp Asn Ala Lys Lys Thr Gly Ser Ile
                485                 490                 495

Ser Phe Asp Phe Arg Thr Thr Glu Pro Asn Gly Leu Ile Leu Phe Ser
            500                 505                 510

His Gly Lys Pro Arg His Gln Lys Asp Ala Lys His Pro Gln Met Ile
        515                 520                 525

Lys Val Asp Phe Phe Ala Ile Glu Met Leu Asp Gly His Leu Tyr Leu
    530                 535                 540

Leu Leu Asp Met Gly Ser Gly Thr Ile Lys Ile Lys Ala Leu Leu Lys
545                 550                 555                 560

Lys Val Asn Asp Gly Glu Trp Tyr His Val Asp Phe Gln Arg Asp Gly
                565                 570                 575

Arg Ser Gly Thr Ile Ser Val Asn Thr Leu Arg Thr Pro Tyr Thr Ala
            580                 585                 590
```

```
Pro Gly Glu Ser Glu Ile Leu Asp Leu Asp Asp Glu Leu Tyr Leu Gly
        595                 600                 605

Gly Leu Pro Glu Asn Lys Ala Gly Leu Val Phe Pro Thr Glu Val Trp
    610                 615                 620

Thr Ala Leu Leu Asn Tyr Gly Tyr Val Gly Cys Ile Arg Asp Leu Phe
625                 630                 635                 640

Ile Asp Gly Gln Ser Lys Asp Ile Arg Gln Met Ala Glu Val Gln Ser
                645                 650                 655

Thr Ala Gly Val Lys Pro Ser Cys Ser Lys Glu Thr Ala Lys Pro Cys
            660                 665                 670

Leu Ser Asn Pro Cys Lys Asn Asn Gly Met Cys Arg Asp Gly Trp Asn
        675                 680                 685

Arg Tyr Val Cys Asp Cys Ser Gly Thr Gly Tyr Leu Gly Arg Ser Cys
    690                 695                 700

Glu Arg Glu Ala Thr Val Leu Ser Tyr Asp Gly Ser Met Phe Met Lys
705                 710                 715                 720

Ile Gln Leu Pro Val Val Met His Thr Glu Ala Glu Asp Val Ser Leu
                725                 730                 735

Arg Phe Arg Ser Gln Arg Ala Tyr Gly Ile Leu Met Ala Thr Thr Ser
            740                 745                 750

Arg Asp Ser Ala Asp Thr Leu Arg Leu Glu Leu Asp Ala Gly Arg Val
        755                 760                 765

Lys Leu Thr Val Asn Leu Asp Cys Ile Arg Ile Asn Cys Asn Ser Ser
    770                 775                 780

Lys Gly Pro Glu Thr Leu Phe Ala Gly Tyr Asn Leu Asn Asp Asn Glu
785                 790                 795                 800
```

```
Trp His Thr Val Arg Val Val Arg Arg Gly Lys Ser Leu Lys Leu Thr
                805                 810                 815

Val Asp Asp Gln Gln Ala Met Thr Gly Gln Met Ala Gly Asp His Thr
            820                 825                 830

Arg Leu Glu Phe His Asn Ile Glu Thr Gly Ile Ile Thr Glu Arg Arg
        835                 840                 845

Tyr Leu Ser Ser Val Pro Ser Asn Phe Ile Gly His Leu Gln Ser Leu
    850                 855                 860

Thr Phe Asn Gly Met Ala Tyr Ile Asp Leu Cys Lys Asn Gly Asp Ile
865                 870                 875                 880

Asp Tyr Cys Glu Leu Asn Ala Arg Phe Gly Phe Arg Asn Ile Ile Ala
                885                 890                 895

Asp Pro Val Thr Phe Lys Thr Lys Ser Ser Tyr Val Ala Leu Ala Thr
            900                 905                 910

Leu Gln Ala Tyr Thr Ser Met His Leu Phe Phe Gln Phe Lys Thr Thr
        915                 920                 925

Ser Leu Asp Gly Leu Ile Leu Tyr Asn Ser Gly Asp Gly Asn Asp Phe
    930                 935                 940

Ile Val Val Glu Leu Val Lys Gly Tyr Leu His Tyr Val Phe Asp Leu
945                 950                 955                 960

Gly Asn Gly Ala Asn Leu Ile Lys Gly Ser Ser Asn Lys Pro Leu Asn
                965                 970                 975

Asp Asn Gln Trp His Asn Val Met Ile Ser Arg Asp Thr Ser Asn Leu
            980                 985                 990

His Thr Val Lys Ile Asp Thr Lys  Ile Thr Thr Gln Ile  Thr Ala Gly
        995                 1000                1005

Ala Arg  Asn Leu Asp Leu Lys  Ser Asp Leu Tyr Ile  Gly Gly Val
    1010                1015                1020
```

```
Ala Lys  Glu Thr Tyr Lys Ser  Leu Pro Lys Leu Val  His Ala Lys
    1025                1030                1035

Glu Gly  Phe Gln Gly Cys Leu  Ala Ser Val Asp Leu  Asn Gly Arg
    1040                1045                1050

Leu Pro  Asp Leu Ile Ser Asp  Ala Leu Phe Cys Asn  Gly Gln Ile
    1055                1060                1065

Glu Arg  Gly Cys Glu Gly Pro  Ser Thr Thr Cys Gln  Glu Asp Ser
    1070                1075                1080

Cys Ser  Asn Gln Gly Val Cys  Leu Gln Gln Trp Asp  Gly Phe Ser
    1085                1090                1095

Cys Asp  Cys Ser Met Thr Ser  Phe Ser Gly Pro Leu  Cys Asn Asp
    1100                1105                1110

Pro Gly  Thr Thr Tyr Ile Phe  Ser Lys Gly Gly Gly  Gln Ile Thr
    1115                1120                1125

Tyr Lys  Trp Pro Pro Asn Asp  Arg Pro Ser Thr Arg  Ala Asp Arg
    1130                1135                1140

Leu Ala  Ile Gly Phe Ser Thr  Val Gln Lys Glu Ala  Val Leu Val
    1145                1150                1155

Arg Val  Asp Ser Ser Ser Gly  Leu Gly Asp Tyr Leu  Glu Leu His
    1160                1165                1170

Ile His  Gln Gly Lys Ile Gly  Val Lys Phe Asn Val  Gly Thr Asp
    1175                1180                1185

Asp Ile  Ala Ile Glu Glu Ser  Asn Ala Ile Ile Asn  Asp Gly Lys
    1190                1195                1200

Tyr His  Val Val Arg Phe Thr  Arg Ser Gly Gly Asn  Ala Thr Leu
    1205                1210                1215
```

```
Gln Val  Asp Ser Trp Pro Val  Ile Glu Arg Tyr Pro  Ala Gly Asn
    1220                1225                1230

Asn Asp  Asn Glu Arg Leu Ala  Ile Ala Arg Gln Arg  Ile Pro Tyr
    1235                1240                1245

Arg Leu  Gly Arg Val Val Asp  Glu Trp Leu Leu Asp  Lys Gly Arg
    1250                1255                1260

Gln Leu  Thr Ile Phe Asn Ser  Gln Ala Thr Ile Ile  Ile Gly Gly
    1265                1270                1275

Lys Glu  Gln Gly Gln Pro Phe  Gln Gly Gln Leu Ser  Gly Leu Tyr
    1280                1285                1290

Tyr Asn  Gly Leu Lys Val Leu  Asn Met Ala Ala Glu  Asn Asp Ala
    1295                1300                1305

Asn Ile  Ala Ile Val Gly Asn  Val Arg Leu Val Gly  Glu Val Pro
    1310                1315                1320

Ser Ser  Met Thr Thr Glu Ser  Thr Ala Thr Ala Met  Gln Ser Glu
    1325                1330                1335

Met Ser  Thr Ser Ile Met Glu  Thr Thr Thr Thr Leu  Ala Thr Ser
    1340                1345                1350

Thr Ala  Arg Arg Gly Lys Pro  Pro Thr Lys Glu Pro  Ile Ser Gln
    1355                1360                1365

Thr Thr  Asp Asp Ile Leu Val  Ala Ser Ala Glu Cys  Pro Ser Asp
    1370                1375                1380

Asp Glu  Asp Ile Asp Pro Cys  Glu Pro Ser Ser Ala  Asn Pro Thr
    1385                1390                1395

Arg Ala  Gly Gly Arg Glu Pro  Tyr Pro Gly Ser Ala  Glu Val Ile
    1400                1405                1410

Arg Glu  Ser Ser Ser Thr Thr  Gly Met Val Val Gly  Ile Val Ala
    1415                1420                1425
```

Ala Ala Ala Leu Cys Ile Leu Ile Leu Leu Tyr Ala Met Tyr Lys
    1430   1435   1440

Tyr Arg Asn Arg Asp Glu Gly Ser Tyr His Val Asp Glu Ser Arg
    1445   1450   1455

Asn Tyr Ile Ser Asn Ser Ala Gln Ser Asn Gly Ala Val Val Lys
    1460   1465   1470

Glu Lys Gln Pro Ser Ser Ala Lys Ser Ser Asn Lys Asn Lys Lys
    1475   1480   1485

Asn Lys Asp Lys Glu Tyr Tyr Val
    1490   1495

<210> 106
<211> 1547
<212> PRT
<213> artificial Sequence

<220>
<223> NRXN1-Alpha Isoform 3a

<400> 106

Met Gly Thr Ala Leu Leu Gln Arg Gly Gly Cys Phe Leu Leu Cys Leu
1   5   10   15

Ser Leu Leu Leu Leu Gly Cys Trp Ala Glu Leu Gly Ser Gly Leu Glu
            20   25   30

Phe Pro Gly Ala Glu Gly Gln Trp Thr Arg Phe Pro Lys Trp Asn Ala
        35   40   45

Cys Cys Glu Ser Glu Met Ser Phe Gln Leu Lys Thr Arg Ser Ala Arg
    50   55   60

Gly Leu Val Leu Tyr Phe Asp Asp Glu Gly Phe Cys Asp Phe Leu Glu
65   70   75   80

Leu Ile Leu Thr Arg Gly Gly Arg Leu Gln Leu Ser Phe Ser Ile Phe
                85   90   95

```
Cys Ala Glu Pro Ala Thr Leu Leu Ala Asp Thr Pro Val Asn Asp Gly
            100                 105                 110

Ala Trp His Ser Val Arg Ile Arg Arg Gln Phe Arg Asn Thr Thr Leu
        115                 120                 125

Phe Ile Asp Gln Val Glu Ala Lys Trp Val Glu Val Lys Ser Lys Arg
    130                 135                 140

Arg Asp Met Thr Val Phe Ser Gly Leu Phe Val Gly Gly Leu Pro Pro
145                 150                 155                 160

Glu Leu Arg Ala Ala Ala Leu Lys Leu Thr Leu Ala Ser Val Arg Glu
                165                 170                 175

Arg Glu Pro Phe Lys Gly Trp Ile Arg Asp Val Arg Val Asn Ser Ser
            180                 185                 190

Gln Val Leu Pro Val Asp Ser Gly Glu Val Lys Leu Asp Asp Glu Pro
        195                 200                 205

Pro Asn Ser Gly Gly Gly Ser Pro Cys Glu Ala Gly Glu Glu Gly Glu
    210                 215                 220

Gly Gly Val Cys Leu Asn Gly Gly Val Cys Ser Val Val Asp Asp Gln
225                 230                 235                 240

Ala Val Cys Asp Cys Ser Arg Thr Gly Phe Arg Gly Lys Asp Cys Ser
                245                 250                 255

Gln Glu Ile Lys Phe Gly Leu Gln Cys Val Leu Pro Val Leu Leu His
            260                 265                 270

Asp Asn Asp Gln Gly Lys Tyr Cys Cys Ile Asn Thr Ala Lys Pro Leu
        275                 280                 285

Thr Glu Lys Asp Asn Asn Val Glu Gly Leu Ala His Leu Met Met Gly
    290                 295                 300
```

```
Asp Gln Gly Lys Ser Lys Gly Lys Glu Glu Tyr Ile Ala Thr Phe Lys
305                 310                 315                 320

Gly Ser Glu Tyr Phe Cys Tyr Asp Leu Ser Gln Asn Pro Ile Gln Ser
                325                 330                 335

Ser Ser Asp Glu Ile Thr Leu Ser Phe Lys Thr Leu Gln Arg Asn Gly
            340                 345                 350

Leu Met Leu His Thr Gly Lys Ser Ala Asp Tyr Val Asn Leu Ala Leu
        355                 360                 365

Lys Asn Gly Ala Val Ser Leu Val Ile Asn Leu Gly Ser Gly Ala Phe
    370                 375                 380

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

His Asp Val Lys Val Thr Arg Asn Leu Arg Gln His Ser Gly Ile Gly
                405                 410                 415

His Ala Met Val Asn Lys Leu His Cys Ser Val Thr Ile Ser Val Asp
            420                 425                 430

Gly Ile Leu Thr Thr Thr Gly Tyr Thr Gln Glu Asp Tyr Thr Met Leu
        435                 440                 445

Gly Ser Asp Asp Phe Phe Tyr Val Gly Gly Ser Pro Ser Thr Ala Asp
    450                 455                 460

Leu Pro Gly Ser Pro Val Ser Asn Asn Phe Met Gly Cys Leu Lys Glu
465                 470                 475                 480

Val Val Tyr Lys Asn Asn Asp Val Arg Leu Glu Leu Ser Arg Leu Ala
                485                 490                 495

Lys Gln Gly Asp Pro Lys Met Lys Ile His Gly Val Val Ala Phe Lys
            500                 505                 510

Cys Glu Asn Val Ala Thr Leu Asp Pro Ile Thr Phe Glu Thr Pro Glu
        515                 520                 525
```

```
Ser Phe Ile Ser Leu Pro Lys Trp Asn Ala Lys Lys Thr Gly Ser Ile
    530                 535                 540

Ser Phe Asp Phe Arg Thr Thr Glu Pro Asn Gly Leu Ile Leu Phe Ser
545                 550                 555                 560

His Gly Lys Pro Arg His Gln Lys Asp Ala Lys His Pro Gln Met Ile
                565                 570                 575

Lys Val Asp Phe Phe Ala Ile Glu Met Leu Asp Gly His Leu Tyr Leu
            580                 585                 590

Leu Leu Asp Met Gly Ser Gly Thr Ile Lys Ile Lys Ala Leu Leu Lys
        595                 600                 605

Lys Val Asn Asp Gly Glu Trp Tyr His Val Asp Phe Gln Arg Asp Gly
    610                 615                 620

Arg Ser Gly Thr Ile Ser Val Asn Thr Leu Arg Thr Pro Tyr Thr Ala
625                 630                 635                 640

Pro Gly Glu Ser Glu Ile Leu Asp Leu Asp Asp Glu Leu Tyr Leu Gly
                645                 650                 655

Gly Leu Pro Glu Asn Lys Ala Gly Leu Val Phe Pro Thr Glu Val Trp
            660                 665                 670

Thr Ala Leu Leu Asn Tyr Gly Tyr Val Gly Cys Ile Arg Asp Leu Phe
        675                 680                 685

Ile Asp Gly Gln Ser Lys Asp Ile Arg Gln Met Ala Glu Val Gln Ser
    690                 695                 700

Thr Ala Gly Val Lys Pro Ser Cys Ser Lys Glu Thr Ala Lys Pro Cys
705                 710                 715                 720

Leu Ser Asn Pro Cys Lys Asn Asn Gly Met Cys Arg Asp Gly Trp Asn
                725                 730                 735
```

```
Arg Tyr Val Cys Asp Cys Ser Gly Thr Gly Tyr Leu Gly Arg Ser Cys
            740                 745                 750

Glu Arg Glu Ala Thr Val Leu Ser Tyr Asp Gly Ser Met Phe Met Lys
        755                 760                 765

Ile Gln Leu Pro Val Val Met His Thr Glu Ala Glu Asp Val Ser Leu
    770                 775                 780

Arg Phe Arg Ser Gln Arg Ala Tyr Gly Ile Leu Met Ala Thr Thr Ser
785                 790                 795                 800

Arg Asp Ser Ala Asp Thr Leu Arg Leu Glu Leu Asp Ala Gly Arg Val
                805                 810                 815

Lys Leu Thr Val Asn Leu Asp Cys Ile Arg Ile Asn Cys Asn Ser Ser
            820                 825                 830

Lys Gly Pro Glu Thr Leu Phe Ala Gly Tyr Asn Leu Asn Asp Asn Glu
        835                 840                 845

Trp His Thr Val Arg Val Val Arg Arg Gly Lys Ser Leu Lys Leu Thr
    850                 855                 860

Val Asp Asp Gln Gln Ala Met Thr Gly Gln Met Ala Gly Asp His Thr
865                 870                 875                 880

Arg Leu Glu Phe His Asn Ile Glu Thr Gly Ile Ile Thr Glu Arg Arg
                885                 890                 895

Tyr Leu Ser Ser Val Pro Ser Asn Phe Ile Gly His Leu Gln Ser Leu
            900                 905                 910

Thr Phe Asn Gly Met Ala Tyr Ile Asp Leu Cys Lys Asn Gly Asp Ile
        915                 920                 925

Asp Tyr Cys Glu Leu Asn Ala Arg Phe Gly Phe Arg Asn Ile Ile Ala
    930                 935                 940

Asp Pro Val Thr Phe Lys Thr Lys Ser Ser Tyr Val Ala Leu Ala Thr
945                 950                 955                 960
```

```
Leu Gln Ala Tyr Thr Ser Met His Leu Phe Phe Gln Phe Lys Thr Thr
               965                 970                 975

Ser Leu Asp Gly Leu Ile Leu Tyr Asn Ser Gly Asp Gly Asn Asp Phe
           980                 985                 990

Ile Val Val Glu Leu Val Lys Gly  Tyr Leu His Tyr Val  Phe Asp Leu
        995                1000                1005

Gly Asn  Gly Ala Asn Leu Ile  Lys Gly Ser Ser Asn  Lys Pro Leu
    1010                1015                1020

Asn Asp  Asn Gln Trp His Asn  Val Met Ile Ser Arg  Asp Thr Ser
    1025                1030                1035

Asn Leu  His Thr Val Lys Ile  Asp Thr Lys Ile Thr  Thr Gln Ile
    1040                1045                1050

Thr Ala  Gly Ala Arg Asn Leu  Asp Leu Lys Ser Asp  Leu Tyr Ile
    1055                1060                1065

Gly Gly  Val Ala Lys Glu Thr  Tyr Lys Ser Leu Pro  Lys Leu Val
    1070                1075                1080

His Ala  Lys Glu Gly Phe Gln  Gly Cys Leu Ala Ser  Val Asp Leu
    1085                1090                1095

Asn Gly  Arg Leu Pro Asp Leu  Ile Ser Asp Ala Leu  Phe Cys Asn
    1100                1105                1110

Gly Gln  Ile Glu Arg Gly Cys  Glu Gly Pro Ser Thr  Thr Cys Gln
    1115                1120                1125

Glu Asp  Ser Cys Ser Asn Gln  Gly Val Cys Leu Gln  Gln Trp Asp
    1130                1135                1140

Gly Phe  Ser Cys Asp Cys Ser  Met Thr Ser Phe Ser  Gly Pro Leu
    1145                1150                1155
```

```
Cys Asn  Asp Pro Gly Thr Thr  Tyr Ile Phe Ser Lys  Gly Gly Gly
    1160                1165                1170

Gln Ile  Thr Tyr Lys Trp Pro  Pro Asn Asp Arg Pro  Ser Thr Arg
    1175                1180                1185

Ala Asp  Arg Leu Ala Ile Gly  Phe Ser Thr Val Gln  Lys Glu Ala
    1190                1195                1200

Val Leu  Val Arg Val Asp Ser  Ser Ser Gly Leu Gly  Asp Tyr Leu
    1205                1210                1215

Glu Leu  His Ile His Gln Gly  Lys Ile Gly Val Lys  Phe Asn Val
    1220                1225                1230

Gly Thr  Asp Asp Ile Ala Ile  Glu Glu Ser Asn Ala  Ile Ile Asn
    1235                1240                1245

Asp Gly  Lys Tyr His Val Val  Arg Phe Thr Arg Ser  Gly Gly Asn
    1250                1255                1260

Ala Thr  Leu Gln Val Asp Ser  Trp Pro Val Ile Glu  Arg Tyr Pro
    1265                1270                1275

Ala Gly  Asn Asn Asp Asn Glu  Arg Leu Ala Ile Ala  Arg Gln Arg
    1280                1285                1290

Ile Pro  Tyr Arg Leu Gly Arg  Val Val Asp Glu Trp  Leu Leu Asp
    1295                1300                1305

Lys Gly  Arg Gln Leu Thr Ile  Phe Asn Ser Gln Ala  Thr Ile Ile
    1310                1315                1320

Ile Gly  Gly Lys Glu Gln Gly  Gln Pro Phe Gln Gly  Gln Leu Ser
    1325                1330                1335

Gly Leu  Tyr Tyr Asn Gly Leu  Lys Val Leu Asn Met  Ala Ala Glu
    1340                1345                1350

Asn Asp  Ala Asn Ile Ala Ile  Val Gly Asn Val Arg  Leu Val Gly
    1355                1360                1365
```

```
Glu Val  Pro Ser Ser Met Thr  Thr Glu Ser Thr Ala  Thr Ala Met
    1370                1375                1380

Gln Ser  Glu Met Ser Thr Ser  Ile Met Glu Thr Thr  Thr Thr Leu
    1385                1390                1395

Ala Thr  Ser Thr Ala Arg Arg  Gly Lys Pro Pro Thr  Lys Glu Pro
    1400                1405                1410

Ile Ser  Gln Thr Thr Asp Asp  Ile Leu Val Ala Ser  Ala Glu Cys
    1415                1420                1425

Pro Ser  Asp Asp Glu Asp Ile  Asp Pro Cys Glu Pro  Ser Ser Gly
    1430                1435                1440

Gly Leu  Ala Asn Pro Thr Arg  Ala Gly Gly Arg Glu  Pro Tyr Pro
    1445                1450                1455

Gly Ser  Ala Glu Val Ile Arg  Glu Ser Ser Ser Thr  Thr Gly Met
    1460                1465                1470

Val Val  Gly Ile Val Ala Ala  Ala Ala Leu Cys Ile  Leu Ile Leu
    1475                1480                1485

Leu Tyr  Ala Met Tyr Lys Tyr  Arg Asn Arg Asp Glu  Gly Ser Tyr
    1490                1495                1500

His Val  Asp Glu Ser Arg Asn  Tyr Ile Ser Asn Ser  Ala Gln Ser
    1505                1510                1515

Asn Gly  Ala Val Val Lys Glu  Lys Gln Pro Ser Ser  Ala Lys Ser
    1520                1525                1530

Ser Asn  Lys Asn Lys Lys Asn  Lys Asp Lys Glu Tyr  Tyr Val
    1535                1540                1545
```

<210> 107
<211> 139
<212> PRT
<213> artificial Sequence

<220>
<223> NRXN1-Alpha Isoform 4a

<400> 107

Met Asp Met Arg Trp His Cys Glu Asn Ser Gln Thr Thr Asp Asp Ile
1   5   10   15

Leu Val Ala Ser Ala Glu Cys Pro Ser Asp Asp Glu Asp Ile Asp Pro
            20   25   30

Cys Glu Pro Ser Ser Ala Asn Pro Thr Arg Ala Gly Gly Arg Glu Pro
        35   40   45

Tyr Pro Gly Ser Ala Glu Val Ile Arg Glu Ser Ser Ser Thr Thr Gly
    50   55   60

Met Val Val Gly Ile Val Ala Ala Ala Ala Leu Cys Ile Leu Ile Leu
65   70   75   80

Leu Tyr Ala Met Tyr Lys Tyr Arg Asn Arg Asp Glu Gly Ser Tyr His
                85   90   95

Val Asp Glu Ser Arg Asn Tyr Ile Ser Asn Ser Ala Gln Ser Asn Gly
            100   105   110

Ala Val Val Lys Glu Lys Gln Pro Ser Ser Ala Lys Ser Ser Asn Lys
        115   120   125

Asn Lys Lys Asn Lys Asp Lys Glu Tyr Tyr Val
    130   135

<210> 108
<211> 472
<212> PRT
<213> artificial Sequence

<220>
<223> NRXN1-Beta Isoform 1b

<400> 108

Met Tyr Gln Arg Met Leu Arg Cys Gly Ala Glu Leu Gly Ser Pro Gly
1   5   10   15

```
Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Ala Gly Gly Arg Leu Ala
            20                  25                  30

Leu Leu Trp Ile Val Pro Leu Thr Leu Ser Gly Leu Leu Gly Val Ala
        35                  40                  45

Trp Gly Ala Ser Ser Leu Gly Ala His His Ile His His Phe His Gly
    50                  55                  60

Ser Ser Lys His His Ser Val Pro Ile Ala Ile Tyr Arg Ser Pro Ala
65                  70                  75                  80

Ser Leu Arg Gly Gly His Ala Gly Thr Thr Tyr Ile Phe Ser Lys Gly
                85                  90                  95

Gly Gly Gln Ile Thr Tyr Lys Trp Pro Pro Asn Asp Arg Pro Ser Thr
            100                 105                 110

Arg Ala Asp Arg Leu Ala Ile Gly Phe Ser Thr Val Gln Lys Glu Ala
        115                 120                 125

Val Leu Val Arg Val Asp Ser Ser Ser Gly Leu Gly Asp Tyr Leu Glu
    130                 135                 140

Leu His Ile His Gln Gly Lys Ile Gly Val Lys Phe Asn Val Gly Thr
145                 150                 155                 160

Asp Asp Ile Ala Ile Glu Glu Ser Asn Ala Ile Ile Asn Asp Gly Lys
                165                 170                 175

Tyr His Val Val Arg Phe Thr Arg Ser Gly Gly Asn Ala Thr Leu Gln
            180                 185                 190

Val Asp Ser Trp Pro Val Ile Glu Arg Tyr Pro Ala Gly Asn Asn Asp
        195                 200                 205

Asn Glu Arg Leu Ala Ile Ala Arg Gln Arg Ile Pro Tyr Arg Leu Gly
    210                 215                 220
```

```
Arg Val Val Asp Glu Trp Leu Leu Asp Lys Gly Arg Gln Leu Thr Ile
225                 230                 235                 240

Phe Asn Ser Gln Ala Thr Ile Ile Ile Gly Gly Lys Glu Gln Gly Gln
                245                 250                 255

Pro Phe Gln Gly Gln Leu Ser Gly Leu Tyr Tyr Asn Gly Leu Lys Val
            260                 265                 270

Leu Asn Met Ala Ala Glu Asn Asp Ala Asn Ile Ala Ile Val Gly Asn
        275                 280                 285

Val Arg Leu Val Gly Glu Val Pro Ser Ser Met Thr Thr Glu Ser Thr
    290                 295                 300

Ala Thr Ala Met Gln Ser Glu Met Ser Thr Ser Ile Met Glu Thr Thr
305                 310                 315                 320

Thr Thr Leu Ala Thr Ser Thr Ala Arg Arg Gly Lys Pro Pro Thr Lys
                325                 330                 335

Glu Pro Ile Ser Gln Thr Thr Asp Asp Ile Leu Val Ala Ser Ala Glu
            340                 345                 350

Cys Pro Ser Asp Asp Glu Asp Ile Asp Pro Cys Glu Pro Ser Ser Gly
        355                 360                 365

Gly Leu Ala Asn Pro Thr Arg Ala Gly Gly Arg Glu Pro Tyr Pro Gly
    370                 375                 380

Ser Ala Glu Val Ile Arg Glu Ser Ser Ser Thr Thr Gly Met Val Val
385                 390                 395                 400

Gly Ile Val Ala Ala Ala Ala Leu Cys Ile Leu Ile Leu Leu Tyr Ala
                405                 410                 415

Met Tyr Lys Tyr Arg Asn Arg Asp Glu Gly Ser Tyr His Val Asp Glu
            420                 425                 430

Ser Arg Asn Tyr Ile Ser Asn Ser Ala Gln Ser Asn Gly Ala Val Val
        435                 440                 445
```

Lys Glu Lys Gln Pro Ser Ser Ala Lys Ser Ser Asn Lys Asn Lys Lys
450 455 460

Asn Lys Asp Lys Glu Tyr Tyr Val
465 470

<210> 109
<211> 442
<212> PRT
<213> artificial Sequence

<220>
<223> NRXN1-Beta Isoform 3b

<400> 109

Met Tyr Gln Arg Met Leu Arg Cys Gly Ala Glu Leu Gly Ser Pro Gly
1 5 10 15

Gly Gly Gly Gly Gly Gly Gly Gly Gly Gly Ala Gly Gly Arg Leu Ala
20 25 30

Leu Leu Trp Ile Val Pro Leu Thr Leu Ser Gly Leu Leu Gly Val Ala
35 40 45

Trp Gly Ala Ser Ser Leu Gly Ala His His Ile His His Phe His Gly
50 55 60

Ser Ser Lys His His Ser Val Pro Ile Ala Ile Tyr Arg Ser Pro Ala
65 70 75 80

Ser Leu Arg Gly Gly His Ala Gly Thr Thr Tyr Ile Phe Ser Lys Gly
85 90 95

Gly Gly Gln Ile Thr Tyr Lys Trp Pro Pro Asn Asp Arg Pro Ser Thr
100 105 110

Arg Ala Asp Arg Leu Ala Ile Gly Phe Ser Thr Val Gln Lys Glu Ala
115 120 125

Val Leu Val Arg Val Asp Ser Ser Ser Gly Leu Gly Asp Tyr Leu Glu
130 135 140

```
Leu His Ile His Gln Gly Lys Ile Gly Val Lys Phe Asn Val Gly Thr
145                 150                 155                 160

Asp Asp Ile Ala Ile Glu Glu Ser Asn Ala Ile Ile Asn Asp Gly Lys
                165                 170                 175

Tyr His Val Val Arg Phe Thr Arg Ser Gly Gly Asn Ala Thr Leu Gln
            180                 185                 190

Val Asp Ser Trp Pro Val Ile Glu Arg Tyr Pro Ala Gly Arg Gln Leu
        195                 200                 205

Thr Ile Phe Asn Ser Gln Ala Thr Ile Ile Ile Gly Gly Lys Glu Gln
    210                 215                 220

Gly Gln Pro Phe Gln Gly Gln Leu Ser Gly Leu Tyr Tyr Asn Gly Leu
225                 230                 235                 240

Lys Val Leu Asn Met Ala Ala Glu Asn Asp Ala Asn Ile Ala Ile Val
                245                 250                 255

Gly Asn Val Arg Leu Val Gly Glu Val Pro Ser Ser Met Thr Thr Glu
            260                 265                 270

Ser Thr Ala Thr Ala Met Gln Ser Glu Met Ser Thr Ser Ile Met Glu
        275                 280                 285

Thr Thr Thr Thr Leu Ala Thr Ser Thr Ala Arg Arg Gly Lys Pro Pro
    290                 295                 300

Thr Lys Glu Pro Ile Ser Gln Thr Thr Asp Asp Ile Leu Val Ala Ser
305                 310                 315                 320

Ala Glu Cys Pro Ser Asp Asp Glu Asp Ile Asp Pro Cys Glu Pro Ser
                325                 330                 335

Ser Gly Gly Leu Ala Asn Pro Thr Arg Ala Gly Gly Arg Glu Pro Tyr
            340                 345                 350
```

```
Pro Gly Ser Ala Glu Val Ile Arg Glu Ser Ser Ser Thr Thr Gly Met
        355                 360                 365

Val Val Gly Ile Val Ala Ala Ala Ala Leu Cys Ile Leu Ile Leu Leu
    370                 375                 380

Tyr Ala Met Tyr Lys Tyr Arg Asn Arg Asp Glu Gly Ser Tyr His Val
385                 390                 395                 400

Asp Glu Ser Arg Asn Tyr Ile Ser Asn Ser Ala Gln Ser Asn Gly Ala
                405                 410                 415

Val Val Lys Glu Lys Gln Pro Ser Ser Ala Lys Ser Ser Asn Lys Asn
            420                 425                 430

Lys Lys Asn Lys Asp Lys Glu Tyr Tyr Val
        435                 440
```

<210> 110
<211> 2527
<212> PRT
<213> artificial Sequence

<220>
<223> LRKK2 Protein

<400> 110

```
Met Ala Ser Gly Ser Cys Gln Gly Cys Glu Glu Asp Glu Glu Thr Leu
1               5                   10                  15

Lys Lys Leu Ile Val Arg Leu Asn Asn Val Gln Glu Gly Lys Gln Ile
            20                  25                  30

Glu Thr Leu Val Gln Ile Leu Glu Asp Leu Leu Val Phe Thr Tyr Ser
        35                  40                  45

Glu Arg Ala Ser Lys Leu Phe Gln Gly Lys Asn Ile His Val Pro Leu
    50                  55                  60

Leu Ile Val Leu Asp Ser Tyr Met Arg Val Ala Ser Val Gln Gln Val
65                  70                  75                  80
```

```
Gly Trp Ser Leu Leu Cys Lys Leu Ile Glu Val Cys Pro Gly Thr Met
                85                  90                  95

Gln Ser Leu Met Gly Pro Gln Asp Val Gly Asn Asp Trp Glu Val Leu
            100                 105                 110

Gly Val His Gln Leu Ile Leu Lys Met Leu Thr Val His Asn Ala Ser
        115                 120                 125

Val Asn Leu Ser Val Ile Gly Leu Lys Thr Leu Asp Leu Leu Leu Thr
    130                 135                 140

Ser Gly Lys Ile Thr Leu Leu Ile Leu Asp Glu Glu Ser Asp Ile Phe
145                 150                 155                 160

Met Leu Ile Phe Asp Ala Met His Ser Phe Pro Ala Asn Asp Glu Val
                165                 170                 175

Gln Lys Leu Gly Cys Lys Ala Leu His Val Leu Phe Glu Arg Val Ser
            180                 185                 190

Glu Glu Gln Leu Thr Glu Phe Val Glu Asn Lys Asp Tyr Met Ile Leu
        195                 200                 205

Leu Ser Ala Leu Thr Asn Phe Lys Asp Glu Glu Glu Ile Val Leu His
    210                 215                 220

Val Leu His Cys Leu His Ser Leu Ala Ile Pro Cys Asn Asn Val Glu
225                 230                 235                 240

Val Leu Met Ser Gly Asn Val Arg Cys Tyr Asn Ile Val Val Glu Ala
                245                 250                 255

Met Lys Ala Phe Pro Met Ser Glu Arg Ile Gln Glu Val Ser Cys Cys
            260                 265                 270

Leu Leu His Arg Leu Thr Leu Gly Asn Phe Phe Asn Ile Leu Val Leu
        275                 280                 285

Asn Glu Val His Glu Phe Val Val Lys Ala Val Gln Gln Tyr Pro Glu
    290                 295                 300
```

```
Asn Ala Ala Leu Gln Ile Ser Ala Leu Ser Cys Leu Ala Leu Leu Thr
305                 310                 315                 320

Glu Thr Ile Phe Leu Asn Gln Asp Leu Glu Glu Lys Asn Glu Asn Gln
                325                 330                 335

Glu Asn Asp Asp Glu Gly Glu Glu Asp Lys Leu Phe Trp Leu Glu Ala
            340                 345                 350

Cys Tyr Lys Ala Leu Thr Trp His Arg Lys Asn Lys His Val Gln Glu
        355                 360                 365

Ala Ala Cys Trp Ala Leu Asn Asn Leu Leu Met Tyr Gln Asn Ser Leu
    370                 375                 380

His Glu Lys Ile Gly Asp Glu Asp Gly His Phe Pro Ala His Arg Glu
385                 390                 395                 400

Val Met Leu Ser Met Leu Met His Ser Ser Ser Lys Glu Val Phe Gln
                405                 410                 415

Ala Ser Ala Asn Ala Leu Ser Thr Leu Leu Glu Gln Asn Val Asn Phe
            420                 425                 430

Arg Lys Ile Leu Leu Ser Lys Gly Ile His Leu Asn Val Leu Glu Leu
        435                 440                 445

Met Gln Lys His Ile His Ser Pro Glu Val Ala Glu Ser Gly Cys Lys
    450                 455                 460

Met Leu Asn His Leu Phe Glu Gly Ser Asn Thr Ser Leu Asp Ile Met
465                 470                 475                 480

Ala Ala Val Val Pro Lys Ile Leu Thr Val Met Lys Arg His Glu Thr
                485                 490                 495

Ser Leu Pro Val Gln Leu Glu Ala Leu Arg Ala Ile Leu His Phe Ile
            500                 505                 510
```

```
Val Pro Gly Met Pro Glu Glu Ser Arg Glu Asp Thr Glu Phe His His
        515                 520                 525

Lys Leu Asn Met Val Lys Lys Gln Cys Phe Lys Asn Asp Ile His Lys
    530                 535                 540

Leu Val Leu Ala Ala Leu Asn Arg Phe Ile Gly Asn Pro Gly Ile Gln
545                 550                 555                 560

Lys Cys Gly Leu Lys Val Ile Ser Ser Ile Val His Phe Pro Asp Ala
                565                 570                 575

Leu Glu Met Leu Ser Leu Glu Gly Ala Met Asp Ser Val Leu His Thr
            580                 585                 590

Leu Gln Met Tyr Pro Asp Asp Gln Glu Ile Gln Cys Leu Gly Leu Ser
        595                 600                 605

Leu Ile Gly Tyr Leu Ile Thr Lys Lys Asn Val Phe Ile Gly Thr Gly
    610                 615                 620

His Leu Leu Ala Lys Ile Leu Val Ser Ser Leu Tyr Arg Phe Lys Asp
625                 630                 635                 640

Val Ala Glu Ile Gln Thr Lys Gly Phe Gln Thr Ile Leu Ala Ile Leu
                645                 650                 655

Lys Leu Ser Ala Ser Phe Ser Lys Leu Leu Val His His Ser Phe Asp
            660                 665                 670

Leu Val Ile Phe His Gln Met Ser Ser Asn Ile Met Glu Gln Lys Asp
        675                 680                 685

Gln Gln Phe Leu Asn Leu Cys Cys Lys Cys Phe Ala Lys Val Ala Met
    690                 695                 700

Asp Asp Tyr Leu Lys Asn Val Met Leu Glu Arg Ala Cys Asp Gln Asn
705                 710                 715                 720

Asn Ser Ile Met Val Glu Cys Leu Leu Leu Leu Gly Ala Asp Ala Asn
                725                 730                 735
```

```
Gln Ala Lys Glu Gly Ser Ser Leu Ile Cys Gln Val Cys Glu Lys Glu
            740                 745                 750

Ser Ser Pro Lys Leu Val Glu Leu Leu Leu Asn Ser Gly Ser Arg Glu
        755                 760                 765

Gln Asp Val Arg Lys Ala Leu Thr Ile Ser Ile Gly Lys Gly Asp Ser
    770                 775                 780

Gln Ile Ile Ser Leu Leu Leu Arg Arg Leu Ala Leu Asp Val Ala Asn
785                 790                 795                 800

Asn Ser Ile Cys Leu Gly Gly Phe Cys Ile Gly Lys Val Glu Pro Ser
                805                 810                 815

Trp Leu Gly Pro Leu Phe Pro Asp Lys Thr Ser Asn Leu Arg Lys Gln
            820                 825                 830

Thr Asn Ile Ala Ser Thr Leu Ala Arg Met Val Ile Arg Tyr Gln Met
        835                 840                 845

Lys Ser Ala Val Glu Glu Gly Thr Ala Ser Gly Ser Asp Gly Asn Phe
    850                 855                 860

Ser Glu Asp Val Leu Ser Lys Phe Asp Glu Trp Thr Phe Ile Pro Asp
865                 870                 875                 880

Ser Ser Met Asp Ser Val Phe Ala Gln Ser Asp Asp Leu Asp Ser Glu
                885                 890                 895

Gly Ser Glu Gly Ser Phe Leu Val Lys Lys Lys Ser Asn Ser Ile Ser
            900                 905                 910

Val Gly Glu Phe Tyr Arg Asp Ala Val Leu Gln Arg Cys Ser Pro Asn
        915                 920                 925

Leu Gln Arg His Ser Asn Ser Leu Gly Pro Ile Phe Asp His Glu Asp
    930                 935                 940
```

```
Leu Leu Lys Arg Lys Arg Lys Ile Leu Ser Ser Asp Asp Ser Leu Arg
945                 950                 955                 960


Ser Ser Lys Leu Gln Ser His Met Arg His Ser Asp Ser Ile Ser Ser
                965                 970                 975


Leu Ala Ser Glu Arg Glu Tyr Ile Thr Ser Leu Asp Leu Ser Ala Asn
            980                 985                 990


Glu Leu Arg Asp Ile Asp Ala Leu  Ser Gln Lys Cys Cys  Ile Ser Val
        995                 1000                1005


His Leu  Glu His Leu Glu Lys  Leu Glu Leu His Gln  Asn Ala Leu
    1010                1015                1020


Thr Ser  Phe Pro Gln Gln Leu  Cys Glu Thr Leu Lys  Ser Leu Thr
    1025                1030                1035


His Leu  Asp Leu His Ser Asn  Lys Phe Thr Ser Phe  Pro Ser Tyr
    1040                1045                1050


Leu Leu  Lys Met Ser Cys Ile  Ala Asn Leu Asp Val  Ser Arg Asn
    1055                1060                1065


Asp Ile  Gly Pro Ser Val Val  Leu Asp Pro Thr Val  Lys Cys Pro
    1070                1075                1080


Thr Leu  Lys Gln Phe Asn Leu  Ser Tyr Asn Gln Leu  Ser Phe Val
    1085                1090                1095


Pro Glu  Asn Leu Thr Asp Val  Val Glu Lys Leu Glu  Gln Leu Ile
    1100                1105                1110


Leu Glu  Gly Asn Lys Ile Ser  Gly Ile Cys Ser Pro  Leu Arg Leu
    1115                1120                1125


Lys Glu  Leu Lys Ile Leu Asn  Leu Ser Lys Asn His  Ile Ser Ser
    1130                1135                1140


Leu Ser  Glu Asn Phe Leu Glu  Ala Cys Pro Lys Val  Glu Ser Phe
    1145                1150                1155
```

```
Ser Ala  Arg Met Asn Phe Leu  Ala Ala Met Pro Phe  Leu Pro Pro
    1160                1165                1170

Ser Met  Thr Ile Leu Lys Leu  Ser Gln Asn Lys Phe  Ser Cys Ile
    1175                1180                1185

Pro Glu  Ala Ile Leu Asn Leu  Pro His Leu Arg Ser  Leu Asp Met
    1190                1195                1200

Ser Ser  Asn Asp Ile Gln Tyr  Leu Pro Gly Pro Ala  His Trp Lys
    1205                1210                1215

Ser Leu  Asn Leu Arg Glu Leu  Leu Phe Ser His Asn  Gln Ile Ser
    1220                1225                1230

Ile Leu  Asp Leu Ser Glu Lys  Ala Tyr Leu Trp Ser  Arg Val Glu
    1235                1240                1245

Lys Leu  His Leu Ser His Asn  Lys Leu Lys Glu Ile  Pro Pro Glu
    1250                1255                1260

Ile Gly  Cys Leu Glu Asn Leu  Thr Ser Leu Asp Val  Ser Tyr Asn
    1265                1270                1275

Leu Glu  Leu Arg Ser Phe Pro  Asn Glu Met Gly Lys  Leu Ser Lys
    1280                1285                1290

Ile Trp  Asp Leu Pro Leu Asp  Glu Leu His Leu Asn  Phe Asp Phe
    1295                1300                1305

Lys His  Ile Gly Cys Lys Ala  Lys Asp Ile Ile Arg  Phe Leu Gln
    1310                1315                1320

Gln Arg  Leu Lys Lys Ala Val  Pro Tyr Asn Arg Met  Lys Leu Met
    1325                1330                1335

Ile Val  Gly Asn Thr Gly Ser  Gly Lys Thr Thr Leu  Leu Gln Gln
    1340                1345                1350
```

```
Leu Met  Lys Thr Lys Lys Ser  Asp Leu Gly Met Gln  Ser Ala Thr
    1355                1360                1365

Val Gly  Ile Asp Val Lys Asp  Trp Pro Ile Gln Ile  Arg Asp Lys
    1370                1375                1380

Arg Lys  Arg Asp Leu Val Leu  Asn Val Trp Asp Phe  Ala Gly Arg
    1385                1390                1395

Glu Glu  Phe Tyr Ser Thr His  Pro His Phe Met Thr  Gln Arg Ala
    1400                1405                1410

Leu Tyr  Leu Ala Val Tyr Asp  Leu Ser Lys Gly Gln  Ala Glu Val
    1415                1420                1425

Asp Ala  Met Lys Pro Trp Leu  Phe Asn Ile Lys Ala  Arg Ala Ser
    1430                1435                1440

Ser Ser  Pro Val Ile Leu Val  Gly Thr His Leu Asp  Val Ser Asp
    1445                1450                1455

Glu Lys  Gln Arg Lys Ala Cys  Met Ser Lys Ile Thr  Lys Glu Leu
    1460                1465                1470

Leu Asn  Lys Arg Gly Phe Pro  Ala Ile Arg Asp Tyr  His Phe Val
    1475                1480                1485

Asn Ala  Thr Glu Glu Ser Asp  Ala Leu Ala Lys Leu  Arg Lys Thr
    1490                1495                1500

Ile Ile  Asn Glu Ser Leu Asn  Phe Lys Ile Arg Asp  Gln Leu Val
    1505                1510                1515

Val Gly  Gln Leu Ile Pro Asp  Cys Tyr Val Glu Leu  Glu Lys Ile
    1520                1525                1530

Ile Leu  Ser Glu Arg Lys Asn  Val Pro Ile Glu Phe  Pro Val Ile
    1535                1540                1545

Asp Arg  Lys Arg Leu Leu Gln  Leu Val Arg Glu Asn  Gln Leu Gln
    1550                1555                1560
```

```
Leu Asp  Glu Asn Glu Leu Pro  His Ala Val His Phe  Leu Asn Glu
    1565                1570                1575

Ser Gly  Val Leu Leu His Phe  Gln Asp Pro Ala Leu  Gln Leu Ser
    1580                1585                1590

Asp Leu  Tyr Phe Val Glu Pro  Lys Trp Leu Cys Lys  Ile Met Ala
    1595                1600                1605

Gln Ile  Leu Thr Val Lys Val  Glu Gly Cys Pro Lys  His Pro Lys
    1610                1615                1620

Gly Ile  Ile Ser Arg Arg Asp  Val Glu Lys Phe Leu  Ser Lys Lys
    1625                1630                1635

Arg Lys  Phe Pro Lys Asn Tyr  Met Ser Gln Tyr Phe  Lys Leu Leu
    1640                1645                1650

Glu Lys  Phe Gln Ile Ala Leu  Pro Ile Gly Glu Glu  Tyr Leu Leu
    1655                1660                1665

Val Pro  Ser Ser Leu Ser Asp  His Arg Pro Val Ile  Glu Leu Pro
    1670                1675                1680

His Cys  Glu Asn Ser Glu Ile  Ile Ile Arg Leu Tyr  Glu Met Pro
    1685                1690                1695

Tyr Phe  Pro Met Gly Phe Trp  Ser Arg Leu Ile Asn  Arg Leu Leu
    1700                1705                1710

Glu Ile  Ser Pro Tyr Met Leu  Ser Gly Arg Glu Arg  Ala Leu Arg
    1715                1720                1725

Pro Asn  Arg Met Tyr Trp Arg  Gln Gly Ile Tyr Leu  Asn Trp Ser
    1730                1735                1740

Pro Glu  Ala Tyr Cys Leu Val  Gly Ser Glu Val Leu  Asp Asn His
    1745                1750                1755
```

```
Pro Glu  Ser Phe Leu Lys Ile  Thr Val Pro Ser Cys  Arg Lys Gly
    1760                1765                1770

Cys Ile  Leu Leu Gly Gln Val  Val Asp His Ile Asp  Ser Leu Met
    1775                1780                1785

Glu Glu  Trp Phe Pro Gly Leu  Leu Glu Ile Asp Ile  Cys Gly Glu
    1790                1795                1800

Gly Glu  Thr Leu Leu Lys Lys  Trp Ala Leu Tyr Ser  Phe Asn Asp
    1805                1810                1815

Gly Glu  Glu His Gln Lys Ile  Leu Leu Asp Asp Leu  Met Lys Lys
    1820                1825                1830

Ala Glu  Glu Gly Asp Leu Leu  Val Asn Pro Asp Gln  Pro Arg Leu
    1835                1840                1845

Thr Ile  Pro Ile Ser Gln Ile  Ala Pro Asp Leu Ile  Leu Ala Asp
    1850                1855                1860

Leu Pro  Arg Asn Ile Met Leu  Asn Asn Asp Glu Leu  Glu Phe Glu
    1865                1870                1875

Gln Ala  Pro Glu Phe Leu Leu  Gly Asp Gly Ser Phe  Gly Ser Val
    1880                1885                1890

Tyr Arg  Ala Ala Tyr Glu Gly  Glu Glu Val Ala Val  Lys Ile Phe
    1895                1900                1905

Asn Lys  His Thr Ser Leu Arg  Leu Leu Arg Gln Glu  Leu Val Val
    1910                1915                1920

Leu Cys  His Leu His His Pro  Ser Leu Ile Ser Leu  Leu Ala Ala
    1925                1930                1935

Gly Ile  Arg Pro Arg Met Leu  Val Met Glu Leu Ala  Ser Lys Gly
    1940                1945                1950

Ser Leu  Asp Arg Leu Leu Gln  Gln Asp Lys Ala Ser  Leu Thr Arg
    1955                1960                1965
```

```
Thr Leu  Gln His Arg Ile Ala  Leu His Val Ala Asp  Gly Leu Arg
    1970                1975                1980

Tyr Leu  His Ser Ala Met Ile  Ile Tyr Arg Asp Leu  Lys Pro His
    1985                1990                1995

Asn Val  Leu Leu Phe Thr Leu  Tyr Pro Asn Ala Ala  Ile Ile Ala
    2000                2005                2010

Lys Ile  Ala Asp Tyr Gly Ile  Ala Gln Tyr Cys Cys  Arg Met Gly
    2015                2020                2025

Ile Lys  Thr Ser Glu Gly Thr  Pro Gly Phe Arg Ala  Pro Glu Val
    2030                2035                2040

Ala Arg  Gly Asn Val Ile Tyr  Asn Gln Gln Ala Asp  Val Tyr Ser
    2045                2050                2055

Phe Gly  Leu Leu Leu Tyr Asp  Ile Leu Thr Thr Gly  Gly Arg Ile
    2060                2065                2070

Val Glu  Gly Leu Lys Phe Pro  Asn Glu Phe Asp Glu  Leu Glu Ile
    2075                2080                2085

Gln Gly  Lys Leu Pro Asp Pro  Val Lys Glu Tyr Gly  Cys Ala Pro
    2090                2095                2100

Trp Pro  Met Val Glu Lys Leu  Ile Lys Gln Cys Leu  Lys Glu Asn
    2105                2110                2115

Pro Gln  Glu Arg Pro Thr Ser  Ala Gln Val Phe Asp  Ile Leu Asn
    2120                2125                2130

Ser Ala  Glu Leu Val Cys Leu  Thr Arg Arg Ile Leu  Leu Pro Lys
    2135                2140                2145

Asn Val  Ile Val Glu Cys Met  Val Ala Thr His His  Asn Ser Arg
    2150                2155                2160
```

```
Asn Ala  Ser Ile Trp Leu Gly  Cys Gly His Thr Asp  Arg Gly Gln
    2165                 2170                 2175

Leu Ser  Phe Leu Asp Leu Asn  Thr Glu Gly Tyr Thr  Ser Glu Glu
    2180                 2185                 2190

Val Ala  Asp Ser Arg Ile Leu  Cys Leu Ala Leu Val  His Leu Pro
    2195                 2200                 2205

Val Glu  Lys Glu Ser Trp Ile  Val Ser Gly Thr Gln  Ser Gly Thr
    2210                 2215                 2220

Leu Leu  Val Ile Asn Thr Glu  Asp Gly Lys Lys Arg  His Thr Leu
    2225                 2230                 2235

Glu Lys  Met Thr Asp Ser Val  Thr Cys Leu Tyr Cys  Asn Ser Phe
    2240                 2245                 2250

Ser Lys  Gln Ser Lys Gln Lys  Asn Phe Leu Leu Val  Gly Thr Ala
    2255                 2260                 2265

Asp Gly  Lys Leu Ala Ile Phe  Glu Asp Lys Thr Val  Lys Leu Lys
    2270                 2275                 2280

Gly Ala  Ala Pro Leu Lys Ile  Leu Asn Ile Gly Asn  Val Ser Thr
    2285                 2290                 2295

Pro Leu  Met Cys Leu Ser Glu  Ser Thr Asn Ser Thr  Glu Arg Asn
    2300                 2305                 2310

Val Met  Trp Gly Gly Cys Gly  Thr Lys Ile Phe Ser  Phe Ser Asn
    2315                 2320                 2325

Asp Phe  Thr Ile Gln Lys Leu  Ile Glu Thr Arg Thr  Ser Gln Leu
    2330                 2335                 2340

Phe Ser  Tyr Ala Ala Phe Ser  Asp Ser Asn Ile Ile  Thr Val Val
    2345                 2350                 2355

Val Asp  Thr Ala Leu Tyr Ile  Ala Lys Gln Asn Ser  Pro Val Val
    2360                 2365                 2370
```

```
Glu Val  Trp Asp Lys Lys Thr  Glu Lys Leu Cys Gly  Leu Ile Asp
    2375                2380                2385

Cys Val  His Phe Leu Arg Glu  Val Met Val Lys Glu  Asn Lys Glu
    2390                2395                2400

Ser Lys  His Lys Met Ser Tyr  Ser Gly Arg Val Lys  Thr Leu Cys
    2405                2410                2415

Leu Gln  Lys Asn Thr Ala Leu  Trp Ile Gly Thr Gly  Gly Gly His
    2420                2425                2430

Ile Leu  Leu Leu Asp Leu Ser  Thr Arg Arg Leu Ile  Arg Val Ile
    2435                2440                2445

Tyr Asn  Phe Cys Asn Ser Val  Arg Val Met Met Thr  Ala Gln Leu
    2450                2455                2460

Gly Ser  Leu Lys Asn Val Met  Leu Val Leu Gly Tyr  Asn Arg Lys
    2465                2470                2475

Asn Thr  Glu Gly Thr Gln Lys  Gln Lys Glu Ile Gln  Ser Cys Leu
    2480                2485                2490

Thr Val  Trp Asp Ile Asn Leu  Pro His Glu Val Gln  Asn Leu Glu
    2495                2500                2505

Lys His  Ile Glu Val Arg Lys  Glu Leu Ala Glu Lys  Met Arg Arg
    2510                2515                2520

Thr Ser  Val Glu
    2525
```

<210> 111
<211> 873
<212> PRT
<213> artificial Sequence

<220>
<223> VLDLR isoform long

<400> 111

```
Met Gly Thr Ser Ala Leu Trp Ala Leu Trp Leu Leu Leu Ala Leu Cys
1               5                  10                  15

Trp Ala Pro Arg Glu Ser Gly Ala Thr Gly Thr Gly Arg Lys Ala Lys
            20                  25                  30

Cys Glu Pro Ser Gln Phe Gln Cys Thr Asn Gly Arg Cys Ile Thr Leu
        35                  40                  45

Leu Trp Lys Cys Asp Gly Asp Glu Asp Cys Val Asp Gly Ser Asp Glu
    50                  55                  60

Lys Asn Cys Val Lys Lys Thr Cys Ala Glu Ser Asp Phe Val Cys Asn
65                  70                  75                  80

Asn Gly Gln Cys Val Pro Ser Arg Trp Lys Cys Asp Gly Asp Pro Asp
                85                  90                  95

Cys Glu Asp Gly Ser Asp Glu Ser Pro Glu Gln Cys His Met Arg Thr
            100                 105                 110

Cys Arg Ile His Glu Ile Ser Cys Gly Ala His Ser Thr Gln Cys Ile
        115                 120                 125

Pro Val Ser Trp Arg Cys Asp Gly Glu Asn Asp Cys Asp Ser Gly Glu
    130                 135                 140

Asp Glu Glu Asn Cys Gly Asn Ile Thr Cys Ser Pro Asp Glu Phe Thr
145                 150                 155                 160

Cys Ser Ser Gly Arg Cys Ile Ser Arg Asn Phe Val Cys Asn Gly Gln
                165                 170                 175

Asp Asp Cys Ser Asp Gly Ser Asp Glu Leu Asp Cys Ala Pro Pro Thr
            180                 185                 190

Cys Gly Ala His Glu Phe Gln Cys Ser Thr Ser Ser Cys Ile Pro Ile
        195                 200                 205
```

```
Ser Trp Val Cys Asp Asp Asp Ala Asp Cys Ser Asp Gln Ser Asp Glu
    210                 215                 220

Ser Leu Glu Gln Cys Gly Arg Gln Pro Val Ile His Thr Lys Cys Pro
225                 230                 235                 240

Ala Ser Glu Ile Gln Cys Gly Ser Gly Glu Cys Ile His Lys Lys Trp
                245                 250                 255

Arg Cys Asp Gly Asp Pro Asp Cys Lys Asp Gly Ser Asp Glu Val Asn
            260                 265                 270

Cys Pro Ser Arg Thr Cys Arg Pro Asp Gln Phe Glu Cys Glu Asp Gly
        275                 280                 285

Ser Cys Ile His Gly Ser Arg Gln Cys Asn Gly Ile Arg Asp Cys Val
    290                 295                 300

Asp Gly Ser Asp Glu Val Asn Cys Lys Asn Val Asn Gln Cys Leu Gly
305                 310                 315                 320

Pro Gly Lys Phe Lys Cys Arg Ser Gly Glu Cys Ile Asp Ile Ser Lys
                325                 330                 335

Val Cys Asn Gln Glu Gln Asp Cys Arg Asp Trp Ser Asp Glu Pro Leu
            340                 345                 350

Lys Glu Cys His Ile Asn Glu Cys Leu Val Asn Asn Gly Gly Cys Ser
        355                 360                 365

His Ile Cys Lys Asp Leu Val Ile Gly Tyr Glu Cys Asp Cys Ala Ala
    370                 375                 380

Gly Phe Glu Leu Ile Asp Arg Lys Thr Cys Gly Asp Ile Asp Glu Cys
385                 390                 395                 400

Gln Asn Pro Gly Ile Cys Ser Gln Ile Cys Ile Asn Leu Lys Gly Gly
                405                 410                 415

Tyr Lys Cys Glu Cys Ser Arg Gly Tyr Gln Met Asp Leu Ala Thr Gly
            420                 425                 430
```

```
Val Cys Lys Ala Val Gly Lys Glu Pro Ser Leu Ile Phe Thr Asn Arg
        435                 440                 445

Arg Asp Ile Arg Lys Ile Gly Leu Glu Arg Lys Glu Tyr Ile Gln Leu
    450                 455                 460

Val Glu Gln Leu Arg Asn Thr Val Ala Leu Asp Ala Asp Ile Ala Ala
465                 470                 475                 480

Gln Lys Leu Phe Trp Ala Asp Leu Ser Gln Lys Ala Ile Phe Ser Ala
                485                 490                 495

Ser Ile Asp Asp Lys Val Gly Arg His Val Lys Met Ile Asp Asn Val
            500                 505                 510

Tyr Asn Pro Ala Ala Ile Ala Val Asp Trp Val Tyr Lys Thr Ile Tyr
        515                 520                 525

Trp Thr Asp Ala Ala Ser Lys Thr Ile Ser Val Ala Thr Leu Asp Gly
    530                 535                 540

Thr Lys Arg Lys Phe Leu Phe Asn Ser Asp Leu Arg Glu Pro Ala Ser
545                 550                 555                 560

Ile Ala Val Asp Pro Leu Ser Gly Phe Val Tyr Trp Ser Asp Trp Gly
                565                 570                 575

Glu Pro Ala Lys Ile Glu Lys Ala Gly Met Asn Gly Phe Asp Arg Arg
            580                 585                 590

Pro Leu Val Thr Ala Asp Ile Gln Trp Pro Asn Gly Ile Thr Leu Asp
        595                 600                 605

Leu Ile Lys Ser Arg Leu Tyr Trp Leu Asp Ser Lys Leu His Met Leu
    610                 615                 620

Ser Ser Val Asp Leu Asn Gly Gln Asp Arg Arg Ile Val Leu Lys Ser
625                 630                 635                 640
```

```
Leu Glu Phe Leu Ala His Pro Leu Ala Leu Thr Ile Phe Glu Asp Arg
                645                 650                 655

Val Tyr Trp Ile Asp Gly Glu Asn Glu Ala Val Tyr Gly Ala Asn Lys
            660                 665                 670

Phe Thr Gly Ser Glu Leu Ala Thr Leu Val Asn Asn Leu Asn Asp Ala
        675                 680                 685

Gln Asp Ile Ile Val Tyr His Glu Leu Val Gln Pro Ser Gly Lys Asn
    690                 695                 700

Trp Cys Glu Glu Asp Met Glu Asn Gly Gly Cys Glu Tyr Leu Cys Leu
705                 710                 715                 720

Pro Ala Pro Gln Ile Asn Asp His Ser Pro Lys Tyr Thr Cys Ser Cys
                725                 730                 735

Pro Ser Gly Tyr Asn Val Glu Glu Asn Gly Arg Asp Cys Gln Ser Thr
            740                 745                 750

Ala Thr Thr Val Thr Tyr Ser Glu Thr Lys Asp Thr Asn Thr Thr Glu
        755                 760                 765

Ile Ser Ala Thr Ser Gly Leu Val Pro Gly Gly Ile Asn Val Thr Thr
    770                 775                 780

Ala Val Ser Glu Val Ser Val Pro Pro Lys Gly Thr Ser Ala Ala Trp
785                 790                 795                 800

Ala Ile Leu Pro Leu Leu Leu Leu Val Met Ala Ala Val Gly Gly Tyr
                805                 810                 815

Leu Met Trp Arg Asn Trp Gln His Lys Asn Met Lys Ser Met Asn Phe
            820                 825                 830

Asp Asn Pro Val Tyr Leu Lys Thr Thr Glu Glu Asp Leu Ser Ile Asp
        835                 840                 845

Ile Gly Arg His Ser Ala Ser Val Gly His Thr Tyr Pro Ala Ile Ser
    850                 855                 860
```

Val Val Ser Thr Asp Asp Asp Leu Ala
865 870

<210> 112
<211> 845
<212> PRT
<213> artificial Sequence

<220>
<223> VLDLR isoform short

<400> 112

Met Gly Thr Ser Ala Leu Trp Ala Leu Trp Leu Leu Leu Ala Leu Cys
1 5 10 15

Trp Ala Pro Arg Glu Ser Gly Ala Thr Gly Thr Gly Arg Lys Ala Lys
20 25 30

Cys Glu Pro Ser Gln Phe Gln Cys Thr Asn Gly Arg Cys Ile Thr Leu
35 40 45

Leu Trp Lys Cys Asp Gly Asp Glu Asp Cys Val Asp Gly Ser Asp Glu
50 55 60

Lys Asn Cys Val Lys Lys Thr Cys Ala Glu Ser Asp Phe Val Cys Asn
65 70 75 80

Asn Gly Gln Cys Val Pro Ser Arg Trp Lys Cys Asp Gly Asp Pro Asp
85 90 95

Cys Glu Asp Gly Ser Asp Glu Ser Pro Glu Gln Cys His Met Arg Thr
100 105 110

Cys Arg Ile His Glu Ile Ser Cys Gly Ala His Ser Thr Gln Cys Ile
115 120 125

Pro Val Ser Trp Arg Cys Asp Gly Glu Asn Asp Cys Asp Ser Gly Glu
130 135 140

Asp Glu Glu Asn Cys Gly Asn Ile Thr Cys Ser Pro Asp Glu Phe Thr
145 150 155 160

```
Cys Ser Ser Gly Arg Cys Ile Ser Arg Asn Phe Val Cys Asn Gly Gln
                165                 170                 175

Asp Asp Cys Ser Asp Gly Ser Asp Glu Leu Asp Cys Ala Pro Pro Thr
            180                 185                 190

Cys Gly Ala His Glu Phe Gln Cys Ser Thr Ser Ser Cys Ile Pro Ile
        195                 200                 205

Ser Trp Val Cys Asp Asp Asp Ala Asp Cys Ser Asp Gln Ser Asp Glu
    210                 215                 220

Ser Leu Glu Gln Cys Gly Arg Gln Pro Val Ile His Thr Lys Cys Pro
225                 230                 235                 240

Ala Ser Glu Ile Gln Cys Gly Ser Gly Glu Cys Ile His Lys Lys Trp
                245                 250                 255

Arg Cys Asp Gly Asp Pro Asp Cys Lys Asp Gly Ser Asp Glu Val Asn
            260                 265                 270

Cys Pro Ser Arg Thr Cys Arg Pro Asp Gln Phe Glu Cys Glu Asp Gly
        275                 280                 285

Ser Cys Ile His Gly Ser Arg Gln Cys Asn Gly Ile Arg Asp Cys Val
    290                 295                 300

Asp Gly Ser Asp Glu Val Asn Cys Lys Asn Val Asn Gln Cys Leu Gly
305                 310                 315                 320

Pro Gly Lys Phe Lys Cys Arg Ser Gly Glu Cys Ile Asp Ile Ser Lys
                325                 330                 335

Val Cys Asn Gln Glu Gln Asp Cys Arg Asp Trp Ser Asp Glu Pro Leu
            340                 345                 350

Lys Glu Cys His Ile Asn Glu Cys Leu Val Asn Asn Gly Gly Cys Ser
        355                 360                 365
```

```
His Ile Cys Lys Asp Leu Val Ile Gly Tyr Glu Cys Asp Cys Ala Ala
    370                 375                 380

Gly Phe Glu Leu Ile Asp Arg Lys Thr Cys Gly Asp Ile Asp Glu Cys
385                 390                 395                 400

Gln Asn Pro Gly Ile Cys Ser Gln Ile Cys Ile Asn Leu Lys Gly Gly
                405                 410                 415

Tyr Lys Cys Glu Cys Ser Arg Gly Tyr Gln Met Asp Leu Ala Thr Gly
            420                 425                 430

Val Cys Lys Ala Val Gly Lys Glu Pro Ser Leu Ile Phe Thr Asn Arg
        435                 440                 445

Arg Asp Ile Arg Lys Ile Gly Leu Glu Arg Lys Glu Tyr Ile Gln Leu
    450                 455                 460

Val Glu Gln Leu Arg Asn Thr Val Ala Leu Asp Ala Asp Ile Ala Ala
465                 470                 475                 480

Gln Lys Leu Phe Trp Ala Asp Leu Ser Gln Lys Ala Ile Phe Ser Ala
                485                 490                 495

Ser Ile Asp Asp Lys Val Gly Arg His Val Lys Met Ile Asp Asn Val
            500                 505                 510

Tyr Asn Pro Ala Ala Ile Ala Val Asp Trp Val Tyr Lys Thr Ile Tyr
        515                 520                 525

Trp Thr Asp Ala Ala Ser Lys Thr Ile Ser Val Ala Thr Leu Asp Gly
    530                 535                 540

Thr Lys Arg Lys Phe Leu Phe Asn Ser Asp Leu Arg Glu Pro Ala Ser
545                 550                 555                 560

Ile Ala Val Asp Pro Leu Ser Gly Phe Val Tyr Trp Ser Asp Trp Gly
                565                 570                 575

Glu Pro Ala Lys Ile Glu Lys Ala Gly Met Asn Gly Phe Asp Arg Arg
            580                 585                 590
```

```
Pro Leu Val Thr Ala Asp Ile Gln Trp Pro Asn Gly Ile Thr Leu Asp
        595                 600                 605

Leu Ile Lys Ser Arg Leu Tyr Trp Leu Asp Ser Lys Leu His Met Leu
    610                 615                 620

Ser Ser Val Asp Leu Asn Gly Gln Asp Arg Arg Ile Val Leu Lys Ser
625                 630                 635                 640

Leu Glu Phe Leu Ala His Pro Leu Ala Leu Thr Ile Phe Glu Asp Arg
                645                 650                 655

Val Tyr Trp Ile Asp Gly Glu Asn Glu Ala Val Tyr Gly Ala Asn Lys
            660                 665                 670

Phe Thr Gly Ser Glu Leu Ala Thr Leu Val Asn Asn Leu Asn Asp Ala
        675                 680                 685

Gln Asp Ile Ile Val Tyr His Glu Leu Val Gln Pro Ser Gly Lys Asn
    690                 695                 700

Trp Cys Glu Glu Asp Met Glu Asn Gly Gly Cys Glu Tyr Leu Cys Leu
705                 710                 715                 720

Pro Ala Pro Gln Ile Asn Asp His Ser Pro Lys Tyr Thr Cys Ser Cys
                725                 730                 735

Pro Ser Gly Tyr Asn Val Glu Glu Asn Gly Arg Asp Cys Gln Arg Ile
            740                 745                 750

Asn Val Thr Thr Ala Val Ser Glu Val Ser Val Pro Pro Lys Gly Thr
        755                 760                 765

Ser Ala Ala Trp Ala Ile Leu Pro Leu Leu Leu Leu Val Met Ala Ala
    770                 775                 780

Val Gly Gly Tyr Leu Met Trp Arg Asn Trp Gln His Lys Asn Met Lys
785                 790                 795                 800
```

Ser Met Asn Phe Asp Asn Pro Val Tyr Leu Lys Thr Thr Glu Glu Asp
805 810 815

Leu Ser Ile Asp Ile Gly Arg His Ser Ala Ser Val Gly His Thr Tyr
820 825 830

Pro Ala Ile Ser Val Val Ser Thr Asp Asp Asp Leu Ala
835 840 845

<210> 113
<211> 902
<212> PRT
<213> artificial Sequence

<220>
<223> GRIA4 isoform 1

<400> 113

Met Arg Ile Ile Ser Arg Gln Ile Val Leu Leu Phe Ser Gly Phe Trp
1 5 10 15

Gly Leu Ala Met Gly Ala Phe Pro Ser Ser Val Gln Ile Gly Gly Leu
20 25 30

Phe Ile Arg Asn Thr Asp Gln Glu Tyr Thr Ala Phe Arg Leu Ala Ile
35 40 45

Phe Leu His Asn Thr Ser Pro Asn Ala Ser Glu Ala Pro Phe Asn Leu
50 55 60

Val Pro His Val Asp Asn Ile Glu Thr Ala Asn Ser Phe Ala Val Thr
65 70 75 80

Asn Ala Phe Cys Ser Gln Tyr Ser Arg Gly Val Phe Ala Ile Phe Gly
85 90 95

Leu Tyr Asp Lys Arg Ser Val His Thr Leu Thr Ser Phe Cys Ser Ala
100 105 110

Leu His Ile Ser Leu Ile Thr Pro Ser Phe Pro Thr Glu Gly Glu Ser
115 120 125

```
Gln Phe Val Leu Gln Leu Arg Pro Ser Leu Arg Gly Ala Leu Leu Ser
    130                 135                 140

Leu Leu Asp His Tyr Glu Trp Asn Cys Phe Val Phe Leu Tyr Asp Thr
145                 150                 155                 160

Asp Arg Gly Tyr Ser Ile Leu Gln Ala Ile Met Glu Lys Ala Gly Gln
                165                 170                 175

Asn Gly Trp His Val Ser Ala Ile Cys Val Glu Asn Phe Asn Asp Val
            180                 185                 190

Ser Tyr Arg Gln Leu Leu Glu Glu Leu Asp Arg Arg Gln Glu Lys Lys
        195                 200                 205

Phe Val Ile Asp Cys Glu Ile Glu Arg Leu Gln Asn Ile Leu Glu Gln
    210                 215                 220

Ile Val Ser Val Gly Lys His Val Lys Gly Tyr His Tyr Ile Ile Ala
225                 230                 235                 240

Asn Leu Gly Phe Lys Asp Ile Ser Leu Glu Arg Phe Ile His Gly Gly
                245                 250                 255

Ala Asn Val Thr Gly Phe Gln Leu Val Asp Phe Asn Thr Pro Met Val
            260                 265                 270

Ile Lys Leu Met Asp Arg Trp Lys Lys Leu Asp Gln Arg Glu Tyr Pro
        275                 280                 285

Gly Ser Glu Thr Pro Pro Lys Tyr Thr Ser Ala Leu Thr Tyr Asp Gly
    290                 295                 300

Val Leu Val Met Ala Glu Thr Phe Arg Ser Leu Arg Arg Gln Lys Ile
305                 310                 315                 320

Asp Ile Ser Arg Arg Gly Asn Ala Gly Asp Cys Leu Ala Asn Pro Ala
                325                 330                 335

Ala Pro Trp Gly Gln Gly Ile Asp Met Glu Arg Thr Leu Lys Gln Val
            340                 345                 350
```

```
Arg Ile Gln Gly Leu Thr Gly Asn Val Gln Phe Asp His Tyr Gly Arg
        355                 360                 365

Arg Val Asn Tyr Thr Met Asp Val Phe Glu Leu Lys Ser Thr Gly Pro
    370                 375                 380

Arg Lys Val Gly Tyr Trp Asn Asp Met Asp Lys Leu Val Leu Ile Gln
385                 390                 395                 400

Asp Val Pro Thr Leu Gly Asn Asp Thr Ala Ala Ile Glu Asn Arg Thr
                405                 410                 415

Val Val Val Thr Thr Ile Met Glu Ser Pro Tyr Val Met Tyr Lys Lys
            420                 425                 430

Asn His Glu Met Phe Glu Gly Asn Asp Lys Tyr Glu Gly Tyr Cys Val
        435                 440                 445

Asp Leu Ala Ser Glu Ile Ala Lys His Ile Gly Ile Lys Tyr Lys Ile
    450                 455                 460

Ala Ile Val Pro Asp Gly Lys Tyr Gly Ala Arg Asp Ala Asp Thr Lys
465                 470                 475                 480

Ile Trp Asn Gly Met Val Gly Glu Leu Val Tyr Gly Lys Ala Glu Ile
                485                 490                 495

Ala Ile Ala Pro Leu Thr Ile Thr Leu Val Arg Glu Glu Val Ile Asp
            500                 505                 510

Phe Ser Lys Pro Phe Met Ser Leu Gly Ile Ser Ile Met Ile Lys Lys
        515                 520                 525

Pro Gln Lys Ser Lys Pro Gly Val Phe Ser Phe Leu Asp Pro Leu Ala
    530                 535                 540

Tyr Glu Ile Trp Met Cys Ile Val Phe Ala Tyr Ile Gly Val Ser Val
545                 550                 555                 560
```

```
Val Leu Phe Leu Val Ser Arg Phe Ser Pro Tyr Glu Trp His Thr Glu
                565                 570                 575

Glu Pro Glu Asp Gly Lys Glu Gly Pro Ser Asp Gln Pro Pro Asn Glu
            580                 585                 590

Phe Gly Ile Phe Asn Ser Leu Trp Phe Ser Leu Gly Ala Phe Met Gln
        595                 600                 605

Gln Gly Cys Asp Ile Ser Pro Arg Ser Leu Ser Gly Arg Ile Val Gly
    610                 615                 620

Gly Val Trp Trp Phe Phe Thr Leu Ile Ile Ile Ser Ser Tyr Thr Ala
625                 630                 635                 640

Asn Leu Ala Ala Phe Leu Thr Val Glu Arg Met Val Ser Pro Ile Glu
                645                 650                 655

Ser Ala Glu Asp Leu Ala Lys Gln Thr Glu Ile Ala Tyr Gly Thr Leu
            660                 665                 670

Asp Ser Gly Ser Thr Lys Glu Phe Phe Arg Arg Ser Lys Ile Ala Val
        675                 680                 685

Tyr Glu Lys Met Trp Thr Tyr Met Arg Ser Ala Glu Pro Ser Val Phe
    690                 695                 700

Thr Arg Thr Thr Ala Glu Gly Val Ala Arg Val Arg Lys Ser Lys Gly
705                 710                 715                 720

Lys Phe Ala Phe Leu Leu Glu Ser Thr Met Asn Glu Tyr Ile Glu Gln
                725                 730                 735

Arg Lys Pro Cys Asp Thr Met Lys Val Gly Gly Asn Leu Asp Ser Lys
            740                 745                 750

Gly Tyr Gly Val Ala Thr Pro Lys Gly Ser Ser Leu Arg Thr Pro Val
        755                 760                 765

Asn Leu Ala Val Leu Lys Leu Ser Glu Ala Gly Val Leu Asp Lys Leu
    770                 775                 780
```

```
Lys Asn Lys Trp Trp Tyr Asp Lys Gly Glu Cys Gly Pro Lys Asp Ser
785                 790                 795                 800


Gly Ser Lys Asp Lys Thr Ser Ala Leu Ser Leu Ser Asn Val Ala Gly
                805                 810                 815


Val Phe Tyr Ile Leu Val Gly Gly Leu Gly Leu Ala Met Leu Val Ala
            820                 825                 830


Leu Ile Glu Phe Cys Tyr Lys Ser Arg Ala Glu Ala Lys Arg Met Lys
        835                 840                 845


Leu Thr Phe Ser Glu Ala Ile Arg Asn Lys Ala Arg Leu Ser Ile Thr
    850                 855                 860


Gly Ser Val Gly Glu Asn Gly Arg Val Leu Thr Pro Asp Cys Pro Lys
865                 870                 875                 880


Ala Val His Thr Gly Thr Ala Ile Arg Gln Ser Ser Gly Leu Ala Val
                885                 890                 895


Ile Ala Ser Asp Leu Pro
            900


<210>  114
<211>  433
<212>  PRT
<213>  artificial Sequence

<220>
<223>  GRIA4 isoform 2

<400>  114

Met Arg Ile Ile Ser Arg Gln Ile Val Leu Leu Phe Ser Gly Phe Trp
1               5                   10                  15


Gly Leu Ala Met Gly Ala Phe Pro Ser Ser Val Gln Ile Gly Gly Leu
            20                  25                  30


Phe Ile Arg Asn Thr Asp Gln Glu Tyr Thr Ala Phe Arg Leu Ala Ile
        35                  40                  45
```

```
Phe Leu His Asn Thr Ser Pro Asn Ala Ser Glu Ala Pro Phe Asn Leu
    50                  55                  60

Val Pro His Val Asp Asn Ile Glu Thr Ala Asn Ser Phe Ala Val Thr
65                  70                  75                  80

Asn Ala Phe Cys Ser Gln Tyr Ser Arg Gly Val Phe Ala Ile Phe Gly
                85                  90                  95

Leu Tyr Asp Lys Arg Ser Val His Thr Leu Thr Ser Phe Cys Ser Ala
            100                 105                 110

Leu His Ile Ser Leu Ile Thr Pro Ser Phe Pro Thr Glu Gly Glu Ser
        115                 120                 125

Gln Phe Val Leu Gln Leu Arg Pro Ser Leu Arg Gly Ala Leu Leu Ser
    130                 135                 140

Leu Leu Asp His Tyr Glu Trp Asn Cys Phe Val Phe Leu Tyr Asp Thr
145                 150                 155                 160

Asp Arg Gly Tyr Ser Ile Leu Gln Ala Ile Met Glu Lys Ala Gly Gln
                165                 170                 175

Asn Gly Trp His Val Ser Ala Ile Cys Val Glu Asn Phe Asn Asp Val
            180                 185                 190

Ser Tyr Arg Gln Leu Leu Glu Glu Leu Asp Arg Arg Gln Glu Lys Lys
        195                 200                 205

Phe Val Ile Asp Cys Glu Ile Glu Arg Leu Gln Asn Ile Leu Glu Gln
    210                 215                 220

Ile Val Ser Val Gly Lys His Val Lys Gly Tyr His Tyr Ile Ile Ala
225                 230                 235                 240

Asn Leu Gly Phe Lys Asp Ile Ser Leu Glu Arg Phe Ile His Gly Gly
                245                 250                 255
```

```
Ala Asn Val Thr Gly Phe Gln Leu Val Asp Phe Asn Thr Pro Met Val
            260                 265                 270

Ile Lys Leu Met Asp Arg Trp Lys Lys Leu Asp Gln Arg Glu Tyr Pro
        275                 280                 285

Gly Ser Glu Thr Pro Pro Lys Tyr Thr Ser Ala Leu Thr Tyr Asp Gly
    290                 295                 300

Val Leu Val Met Ala Glu Thr Phe Arg Ser Leu Arg Arg Gln Lys Ile
305                 310                 315                 320

Asp Ile Ser Arg Arg Gly Asn Ala Gly Asp Cys Leu Ala Asn Pro Ala
                325                 330                 335

Ala Pro Trp Gly Gln Gly Ile Asp Met Glu Arg Thr Leu Lys Gln Val
            340                 345                 350

Arg Ile Gln Gly Leu Thr Gly Asn Val Gln Phe Asp His Tyr Gly Arg
        355                 360                 365

Arg Val Asn Tyr Thr Met Asp Val Phe Glu Leu Lys Ser Thr Gly Pro
    370                 375                 380

Arg Lys Val Gly Tyr Trp Asn Asp Met Asp Lys Leu Val Leu Ile Gln
385                 390                 395                 400

Asp Val Pro Thr Leu Gly Asn Asp Thr Ala Ala Ile Glu Asn Arg Thr
                405                 410                 415

Val Val Val Thr Thr Ile Met Pro Leu Met Lys Asn Pro Ile Leu Arg
            420                 425                 430

Asn
```

<210> 115
<211> 271
<212> PRT
<213> artificial Sequence

<220>

<223> NXPH1

<400> 115

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Met Gln Ala Ala Cys Trp Tyr Val Leu Phe Leu Leu Gln Pro Thr Val
1               5                  10                  15


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


Leu Lys Ser Gly Ser Ser Lys Ser Thr Leu Lys His Ile Trp Thr Glu
        35                  40                  45


Ser Ser Lys Asp Leu Ser Ile Ser Arg Leu Leu Ser Gln Thr Phe Arg
    50                  55                  60


Gly Lys Glu Asn Asp Thr Asp Leu Asp Leu Arg Tyr Asp Thr Pro Glu
65                  70                  75                  80


Pro Tyr Ser Glu Gln Asp Leu Trp Asp Trp Leu Arg Asn Ser Thr Asp
                85                  90                  95


Leu Gln Glu Pro Arg Pro Arg Ala Lys Arg Arg Pro Ile Val Lys Thr
            100                 105                 110


Gly Lys Phe Lys Lys Met Phe Gly Trp Gly Asp Phe His Ser Asn Ile
        115                 120                 125


Lys Thr Val Lys Leu Asn Leu Leu Ile Thr Gly Lys Ile Val Asp His
    130                 135                 140


Gly Asn Gly Thr Phe Ser Val Tyr Phe Arg His Asn Ser Thr Gly Gln
145                 150                 155                 160


Gly Asn Val Ser Val Ser Leu Val Pro Pro Thr Lys Ile Val Glu Phe
                165                 170                 175


Asp Leu Ala Gln Gln Thr Val Ile Asp Ala Lys Asp Ser Lys Ser Phe
            180                 185                 190


Asn Cys Arg Ile Glu Tyr Glu Lys Val Asp Lys Ala Thr Lys Asn Thr
        195                 200                 205
```

Leu Cys Asn Tyr Asp Pro Ser Lys Thr Cys Tyr Gln Glu Gln Thr Gln
210 215 220

Ser His Val Ser Trp Leu Cys Ser Lys Pro Phe Lys Val Ile Cys Ile
225 230 235 240

Tyr Ile Ser Phe Tyr Ser Thr Asp Tyr Lys Leu Val Gln Lys Val Cys
245 250 255

Pro Asp Tyr Asn Tyr His Ser Asp Thr Pro Tyr Phe Pro Ser Gly
260 265 270

<210> 116
<211> 724
<212> PRT
<213> artificial Sequence

<220>
<223> PSD-95 isoform 1

<400> 116

Met Asp Cys Leu Cys Ile Val Thr Thr Lys Lys Tyr Arg Tyr Gln Asp
1 5 10 15

Glu Asp Thr Pro Pro Leu Glu His Ser Pro Ala His Leu Pro Asn Gln
20 25 30

Ala Asn Ser Pro Pro Val Ile Val Asn Thr Asp Thr Leu Glu Ala Pro
35 40 45

Gly Tyr Glu Leu Gln Val Asn Gly Thr Glu Gly Glu Met Glu Tyr Glu
50 55 60

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

Gly Gly Thr Asp Asn Pro His Ile Gly Asp Asp Pro Ser Ile Phe Ile
85 90 95

Thr Lys Ile Ile Pro Gly Gly Ala Ala Ala Gln Asp Gly Arg Leu Arg
100 105 110

```
Val Asn Asp Ser Ile Leu Phe Val Asn Glu Val Asp Val Arg Glu Val
        115                 120                 125

Thr His Ser Ala Ala Val Glu Ala Leu Lys Glu Ala Gly Ser Ile Val
    130                 135                 140

Arg Leu Tyr Val Met Arg Arg Lys Pro Pro Ala Glu Lys Val Met Glu
145                 150                 155                 160

Ile Lys Leu Ile Lys Gly Pro Lys Gly Leu Gly Phe Ser Ile Ala Gly
                165                 170                 175

Gly Val Gly Asn Gln His Ile Pro Gly Asp Asn Ser Ile Tyr Val Thr
            180                 185                 190

Lys Ile Ile Glu Gly Gly Ala Ala His Lys Asp Gly Arg Leu Gln Ile
        195                 200                 205

Gly Asp Lys Ile Leu Ala Val Asn Ser Val Gly Leu Glu Asp Val Met
    210                 215                 220

His Glu Asp Ala Val Ala Ala Leu Lys Asn Thr Tyr Asp Val Val Tyr
225                 230                 235                 240

Leu Lys Val Ala Lys Pro Ser Asn Ala Tyr Leu Ser Asp Ser Tyr Ala
                245                 250                 255

Pro Pro Asp Ile Thr Thr Ser Tyr Ser Gln His Leu Asp Asn Glu Ile
            260                 265                 270

Ser His Ser Ser Tyr Leu Gly Thr Asp Tyr Pro Thr Ala Met Thr Pro
        275                 280                 285

Thr Ser Pro Arg Arg Tyr Ser Pro Val Ala Lys Asp Leu Leu Gly Glu
    290                 295                 300

Glu Asp Ile Pro Arg Glu Pro Arg Arg Ile Val Ile His Arg Gly Ser
305                 310                 315                 320
```

```
Thr Gly Leu Gly Phe Asn Ile Val Gly Gly Glu Asp Gly Glu Gly Ile
                325                 330                 335

Phe Ile Ser Phe Ile Leu Ala Gly Gly Pro Ala Asp Leu Ser Gly Glu
            340                 345                 350

Leu Arg Lys Gly Asp Gln Ile Leu Ser Val Asn Gly Val Asp Leu Arg
        355                 360                 365

Asn Ala Ser His Glu Gln Ala Ala Ile Ala Leu Lys Asn Ala Gly Gln
    370                 375                 380

Thr Val Thr Ile Ile Ala Gln Tyr Lys Pro Glu Glu Tyr Ser Arg Phe
385                 390                 395                 400

Glu Ala Lys Ile His Asp Leu Arg Glu Gln Leu Met Asn Ser Ser Leu
                405                 410                 415

Gly Ser Gly Thr Ala Ser Leu Arg Ser Asn Pro Lys Arg Gly Phe Tyr
            420                 425                 430

Ile Arg Ala Leu Phe Asp Tyr Asp Lys Thr Lys Asp Cys Gly Phe Leu
        435                 440                 445

Ser Gln Ala Leu Ser Phe Arg Phe Gly Asp Val Leu His Val Ile Asp
    450                 455                 460

Ala Ser Asp Glu Glu Trp Trp Gln Ala Arg Arg Val His Ser Asp Ser
465                 470                 475                 480

Glu Thr Asp Asp Ile Gly Phe Ile Pro Ser Lys Arg Arg Val Glu Arg
                485                 490                 495

Arg Glu Trp Ser Arg Leu Lys Ala Lys Asp Trp Gly Ser Ser Ser Gly
            500                 505                 510

Ser Gln Gly Arg Glu Asp Ser Val Leu Ser Tyr Glu Thr Val Thr Gln
        515                 520                 525

Met Glu Val His Tyr Ala Arg Pro Ile Ile Ile Leu Gly Pro Thr Lys
    530                 535                 540
```

```
Asp Arg Ala Asn Asp Asp Leu Leu Ser Glu Phe Pro Asp Lys Phe Gly
545                 550                 555                 560

Ser Cys Val Pro His Thr Thr Arg Pro Lys Arg Glu Tyr Glu Ile Asp
                565                 570                 575

Gly Arg Asp Tyr His Phe Val Ser Ser Arg Glu Lys Met Glu Lys Asp
            580                 585                 590

Ile Gln Ala His Lys Phe Ile Glu Ala Gly Gln Tyr Asn Ser His Leu
        595                 600                 605

Tyr Gly Thr Ser Val Gln Ser Val Arg Glu Val Ala Glu Gln Gly Lys
    610                 615                 620

His Cys Ile Leu Asp Val Ser Ala Asn Ala Val Arg Arg Leu Gln Ala
625                 630                 635                 640

Ala His Leu His Pro Ile Ala Ile Phe Ile Arg Pro Arg Ser Leu Glu
                645                 650                 655

Asn Val Leu Glu Ile Asn Lys Arg Ile Thr Glu Glu Gln Ala Arg Lys
            660                 665                 670

Ala Phe Asp Arg Ala Thr Lys Leu Glu Gln Glu Phe Thr Glu Cys Phe
        675                 680                 685

Ser Ala Ile Val Glu Gly Asp Ser Phe Glu Glu Ile Tyr His Lys Val
    690                 695                 700

Lys Arg Val Ile Glu Asp Leu Ser Gly Pro Tyr Ile Trp Val Pro Ala
705                 710                 715                 720

Arg Glu Arg Leu
```

<210> 117
<211> 767
<212> PRT
<213> artificial Sequence

<220>
<223> PSD-95 isoform 2

<400> 117

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Met Ser Gln Arg Pro Arg Ala Pro Arg Ser Ala Leu Trp Leu Leu Ala
1               5                   10                  15


Pro Pro Leu Leu Arg Trp Ala Pro Pro Leu Leu Thr Val Leu His Ser
            20                  25                  30


Asp Leu Phe Gln Ala Leu Leu Asp Ile Leu Asp Tyr Tyr Glu Ala Ser
        35                  40                  45


Leu Ser Glu Ser Gln Lys Tyr Arg Tyr Gln Asp Glu Asp Thr Pro Pro
    50                  55                  60


Leu Glu His Ser Pro Ala His Leu Pro Asn Gln Ala Asn Ser Pro Pro
65                  70                  75                  80


Val Ile Val Asn Thr Asp Thr Leu Glu Ala Pro Gly Tyr Glu Leu Gln
                85                  90                  95


Val Asn Gly Thr Glu Gly Glu Met Glu Tyr Glu Glu Ile Thr Leu Glu
            100                 105                 110


Arg Gly Asn Ser Gly Leu Gly Phe Ser Ile Ala Gly Gly Thr Asp Asn
        115                 120                 125


Pro His Ile Gly Asp Asp Pro Ser Ile Phe Ile Thr Lys Ile Ile Pro
    130                 135                 140


Gly Gly Ala Ala Ala Gln Asp Gly Arg Leu Arg Val Asn Asp Ser Ile
145                 150                 155                 160


Leu Phe Val Asn Glu Val Asp Val Arg Glu Val Thr His Ser Ala Ala
                165                 170                 175


Val Glu Ala Leu Lys Glu Ala Gly Ser Ile Val Arg Leu Tyr Val Met
            180                 185                 190
```

```
Arg Arg Lys Pro Pro Ala Glu Lys Val Met Glu Ile Lys Leu Ile Lys
        195                 200                 205

Gly Pro Lys Gly Leu Gly Phe Ser Ile Ala Gly Gly Val Gly Asn Gln
    210                 215                 220

His Ile Pro Gly Asp Asn Ser Ile Tyr Val Thr Lys Ile Ile Glu Gly
225                 230                 235                 240

Gly Ala Ala His Lys Asp Gly Arg Leu Gln Ile Gly Asp Lys Ile Leu
                245                 250                 255

Ala Val Asn Ser Val Gly Leu Glu Asp Val Met His Glu Asp Ala Val
            260                 265                 270

Ala Ala Leu Lys Asn Thr Tyr Asp Val Val Tyr Leu Lys Val Ala Lys
        275                 280                 285

Pro Ser Asn Ala Tyr Leu Ser Asp Ser Tyr Ala Pro Pro Asp Ile Thr
    290                 295                 300

Thr Ser Tyr Ser Gln His Leu Asp Asn Glu Ile Ser His Ser Ser Tyr
305                 310                 315                 320

Leu Gly Thr Asp Tyr Pro Thr Ala Met Thr Pro Thr Ser Pro Arg Arg
                325                 330                 335

Tyr Ser Pro Val Ala Lys Asp Leu Leu Gly Glu Glu Asp Ile Pro Arg
            340                 345                 350

Glu Pro Arg Arg Ile Val Ile His Arg Gly Ser Thr Gly Leu Gly Phe
        355                 360                 365

Asn Ile Val Gly Gly Glu Asp Gly Glu Gly Ile Phe Ile Ser Phe Ile
    370                 375                 380

Leu Ala Gly Gly Pro Ala Asp Leu Ser Gly Glu Leu Arg Lys Gly Asp
385                 390                 395                 400

Gln Ile Leu Ser Val Asn Gly Val Asp Leu Arg Asn Ala Ser His Glu
                405                 410                 415
```

```
Gln Ala Ala Ile Ala Leu Lys Asn Ala Gly Gln Thr Val Thr Ile Ile
            420                 425                 430

Ala Gln Tyr Lys Pro Glu Glu Tyr Ser Arg Phe Glu Ala Lys Ile His
        435                 440                 445

Asp Leu Arg Glu Gln Leu Met Asn Ser Ser Leu Gly Ser Gly Thr Ala
    450                 455                 460

Ser Leu Arg Ser Asn Pro Lys Arg Gly Phe Tyr Ile Arg Ala Leu Phe
465                 470                 475                 480

Asp Tyr Asp Lys Thr Lys Asp Cys Gly Phe Leu Ser Gln Ala Leu Ser
                485                 490                 495

Phe Arg Phe Gly Asp Val Leu His Val Ile Asp Ala Ser Asp Glu Glu
            500                 505                 510

Trp Trp Gln Ala Arg Arg Val His Ser Asp Ser Glu Thr Asp Asp Ile
        515                 520                 525

Gly Phe Ile Pro Ser Lys Arg Arg Val Glu Arg Arg Glu Trp Ser Arg
    530                 535                 540

Leu Lys Ala Lys Asp Trp Gly Ser Ser Ser Gly Ser Gln Gly Arg Glu
545                 550                 555                 560

Asp Ser Val Leu Ser Tyr Glu Thr Val Thr Gln Met Glu Val His Tyr
                565                 570                 575

Ala Arg Pro Ile Ile Ile Leu Gly Pro Thr Lys Asp Arg Ala Asn Asp
            580                 585                 590

Asp Leu Leu Ser Glu Phe Pro Asp Lys Phe Gly Ser Cys Val Pro His
        595                 600                 605

Thr Thr Arg Pro Lys Arg Glu Tyr Glu Ile Asp Gly Arg Asp Tyr His
    610                 615                 620
```

```
Phe Val Ser Ser Arg Glu Lys Met Glu Lys Asp Ile Gln Ala His Lys
625                 630                 635                 640


Phe Ile Glu Ala Gly Gln Tyr Asn Ser His Leu Tyr Gly Thr Ser Val
                645                 650                 655


Gln Ser Val Arg Glu Val Ala Glu Gln Gly Lys His Cys Ile Leu Asp
            660                 665                 670


Val Ser Ala Asn Ala Val Arg Arg Leu Gln Ala Ala His Leu His Pro
        675                 680                 685


Ile Ala Ile Phe Ile Arg Pro Arg Ser Leu Glu Asn Val Leu Glu Ile
    690                 695                 700


Asn Lys Arg Ile Thr Glu Glu Gln Ala Arg Lys Ala Phe Asp Arg Ala
705                 710                 715                 720


Thr Lys Leu Glu Gln Glu Phe Thr Glu Cys Phe Ser Ala Ile Val Glu
                725                 730                 735


Gly Asp Ser Phe Glu Glu Ile Tyr His Lys Val Lys Arg Val Ile Glu
            740                 745                 750


Asp Leu Ser Gly Pro Tyr Ile Trp Val Pro Ala Arg Glu Arg Leu
        755                 760                 765


<210>  118
<211>  720
<212>  PRT
<213>  artificial Sequence

<220>
<223>  PSD-95 isoform 3

<400>  118

Met Asp Cys Leu Cys Ile Val Thr Thr Lys Lys Tyr Arg Tyr Gln Asp
1               5                   10                  15


Glu Asp Thr Pro Pro Leu Glu His Ser Pro Ala His Leu Pro Asn Gln
            20                  25                  30
```

```
Ala Asn Ser Pro Pro Val Ile Val Asn Thr Asp Thr Leu Glu Ala Pro
        35                  40                  45

Gly Tyr Val Asn Gly Thr Glu Gly Glu Met Glu Tyr Glu Glu Ile Thr
    50                  55                  60

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

Asp Asn Pro His Ile Gly Asp Asp Pro Ser Ile Phe Ile Thr Lys Ile
                85                  90                  95

Ile Pro Gly Gly Ala Ala Ala Gln Asp Gly Arg Leu Arg Val Asn Asp
            100                 105                 110

Ser Ile Leu Phe Val Asn Glu Val Asp Val Arg Glu Val Thr His Ser
        115                 120                 125

Ala Ala Val Glu Ala Leu Lys Glu Ala Gly Ser Ile Val Arg Leu Tyr
    130                 135                 140

Val Met Arg Arg Lys Pro Pro Ala Glu Lys Val Met Glu Ile Lys Leu
145                 150                 155                 160

Ile Lys Gly Pro Lys Gly Leu Gly Phe Ser Ile Ala Gly Gly Val Gly
                165                 170                 175

Asn Gln His Ile Pro Gly Asp Asn Ser Ile Tyr Val Thr Lys Ile Ile
            180                 185                 190

Glu Gly Gly Ala Ala His Lys Asp Gly Arg Leu Gln Ile Gly Asp Lys
        195                 200                 205

Ile Leu Ala Val Asn Ser Val Gly Leu Glu Asp Val Met His Glu Asp
    210                 215                 220

Ala Val Ala Ala Leu Lys Asn Thr Tyr Asp Val Val Tyr Leu Lys Val
225                 230                 235                 240

Ala Lys Pro Ser Asn Ala Tyr Leu Ser Asp Ser Tyr Ala Pro Pro Asp
                245                 250                 255
```

```
Ile Thr Thr Ser Tyr Ser Gln His Leu Asp Asn Glu Ile Ser His Ser
            260                 265                 270

Ser Tyr Leu Gly Thr Asp Tyr Pro Thr Ala Met Thr Pro Thr Ser Pro
        275                 280                 285

Arg Arg Tyr Ser Pro Val Ala Lys Asp Leu Leu Gly Glu Glu Asp Ile
    290                 295                 300

Pro Arg Glu Pro Arg Arg Ile Val Ile His Arg Gly Ser Thr Gly Leu
305                 310                 315                 320

Gly Phe Asn Ile Val Gly Gly Glu Asp Gly Glu Gly Ile Phe Ile Ser
                325                 330                 335

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

Gly Asp Gln Ile Leu Ser Val Asn Gly Val Asp Leu Arg Asn Ala Ser
        355                 360                 365

His Glu Gln Ala Ala Ile Ala Leu Lys Asn Ala Gly Gln Thr Val Thr
    370                 375                 380

Ile Ile Ala Gln Tyr Lys Pro Glu Glu Tyr Ser Arg Phe Glu Ala Lys
385                 390                 395                 400

Ile His Asp Leu Arg Glu Gln Leu Met Asn Ser Ser Leu Gly Ser Gly
                405                 410                 415

Thr Ala Ser Leu Arg Ser Asn Pro Lys Arg Gly Phe Tyr Ile Arg Ala
            420                 425                 430

Leu Phe Asp Tyr Asp Lys Thr Lys Asp Cys Gly Phe Leu Ser Gln Ala
        435                 440                 445

Leu Ser Phe Arg Phe Gly Asp Val Leu His Val Ile Asp Ala Ser Asp
    450                 455                 460
```

```
Glu Glu Trp Trp Gln Ala Arg Arg Val His Ser Asp Ser Glu Thr Asp
465                 470                 475                 480

Asp Ile Gly Phe Ile Pro Ser Lys Arg Arg Val Glu Arg Arg Glu Trp
                485                 490                 495

Ser Arg Leu Lys Ala Lys Asp Trp Gly Ser Ser Ser Gly Ser Gln Gly
            500                 505                 510

Arg Glu Asp Ser Val Leu Ser Tyr Glu Thr Val Thr Gln Met Glu Val
        515                 520                 525

His Tyr Ala Arg Pro Ile Ile Ile Leu Gly Pro Thr Lys Asp Arg Ala
    530                 535                 540

Asn Asp Asp Leu Leu Ser Glu Phe Pro Asp Lys Phe Gly Ser Cys Val
545                 550                 555                 560

Pro His Thr Thr Arg Pro Lys Arg Glu Tyr Glu Ile Asp Gly Arg Asp
                565                 570                 575

Tyr His Phe Val Ser Ser Arg Glu Lys Met Glu Lys Asp Ile Gln Ala
            580                 585                 590

His Lys Phe Ile Glu Ala Gly Gln Tyr Asn Ser His Leu Tyr Gly Thr
        595                 600                 605

Ser Val Gln Ser Val Arg Glu Val Ala Glu Gln Gly Lys His Cys Ile
    610                 615                 620

Leu Asp Val Ser Ala Asn Ala Val Arg Arg Leu Gln Ala Ala His Leu
625                 630                 635                 640

His Pro Ile Ala Ile Phe Ile Arg Pro Arg Ser Leu Glu Asn Val Leu
                645                 650                 655

Glu Ile Asn Lys Arg Ile Thr Glu Glu Gln Ala Arg Lys Ala Phe Asp
            660                 665                 670

Arg Ala Thr Lys Leu Glu Gln Glu Phe Thr Glu Cys Phe Ser Ala Ile
        675                 680                 685
```

Val Glu Gly Asp Ser Phe Glu Glu Ile Tyr His Lys Val Lys Arg Val
690 695 700

Ile Glu Asp Leu Ser Gly Pro Tyr Ile Trp Val Pro Ala Arg Glu Arg
705 710 715 720

<210> 119
<211> 313
<212> PRT
<213> artificial Sequence

<220>
<223> Synaptophysin isoform 1

<400> 119

Met Leu Leu Leu Ala Asp Met Asp Val Val Asn Gln Leu Val Ala Gly
1 5 10 15

Gly Gln Phe Arg Val Val Lys Glu Pro Leu Gly Phe Val Lys Val Leu
20 25 30

Gln Trp Val Phe Ala Ile Phe Ala Phe Ala Thr Cys Gly Ser Tyr Ser
35 40 45

Gly Glu Leu Gln Leu Ser Val Asp Cys Ala Asn Lys Thr Glu Ser Asp
50 55 60

Leu Ser Ile Glu Val Glu Phe Glu Tyr Pro Phe Arg Leu His Gln Val
65 70 75 80

Tyr Phe Asp Ala Pro Thr Cys Arg Gly Gly Thr Thr Lys Val Phe Leu
85 90 95

Val Gly Asp Tyr Ser Ser Ser Ala Glu Phe Phe Val Thr Val Ala Val
100 105 110

Phe Ala Phe Leu Tyr Ser Met Gly Ala Leu Ala Thr Tyr Ile Phe Leu
115 120 125

Gln Asn Lys Tyr Arg Glu Asn Asn Lys Gly Pro Met Leu Asp Phe Leu
130 135 140

```
Ala Thr Ala Val Phe Ala Phe Met Trp Leu Val Ser Ser Ser Ala Trp
145                 150                 155                 160


Ala Lys Gly Leu Ser Asp Val Lys Met Ala Thr Asp Pro Glu Asn Ile
                165                 170                 175


Ile Lys Glu Met Pro Val Cys Arg Gln Thr Gly Asn Thr Cys Lys Glu
            180                 185                 190


Leu Arg Asp Pro Val Thr Ser Gly Leu Asn Thr Ser Val Val Phe Gly
        195                 200                 205


Phe Leu Asn Leu Val Leu Trp Val Gly Asn Leu Trp Phe Val Phe Lys
    210                 215                 220


Glu Thr Gly Trp Ala Ala Pro Phe Leu Arg Ala Pro Pro Gly Ala Pro
225                 230                 235                 240


Glu Lys Gln Pro Ala Pro Gly Asp Ala Tyr Gly Asp Ala Gly Tyr Gly
                245                 250                 255


Gln Gly Pro Gly Gly Tyr Gly Pro Gln Asp Ser Tyr Gly Pro Gln Gly
            260                 265                 270


Gly Tyr Gln Pro Asp Tyr Gly Gln Pro Ala Gly Ser Gly Gly Ser Gly
        275                 280                 285


Tyr Gly Pro Gln Gly Asp Tyr Gly Gln Gln Gly Tyr Gly Pro Gln Gly
    290                 295                 300


Ala Pro Thr Ser Phe Ser Asn Gln Met
305                 310


<210>  120
<211>  193
<212>  PRT
<213>  artificial Sequence

<220>
<223>  Synaptophysin isoform 2
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<400> 120

```
Ala Leu Ala Thr Tyr Ile Phe Leu Gln Asn Lys Tyr Arg Glu Asn Asn
1               5                  10                  15

Lys Gly Pro Met Leu Asp Phe Leu Ala Thr Ala Val Phe Ala Phe Met
            20                  25                  30

Trp Leu Val Ser Ser Ser Ala Trp Ala Lys Gly Leu Ser Asp Val Lys
        35                  40                  45

Met Ala Thr Asp Pro Glu Asn Ile Ile Lys Glu Met Pro Val Cys Arg
    50                  55                  60

Gln Thr Gly Asn Thr Cys Lys Glu Leu Arg Asp Pro Val Thr Ser Gly
65                  70                  75                  80

Leu Asn Thr Ser Val Val Phe Gly Phe Leu Asn Leu Val Leu Trp Val
                85                  90                  95

Gly Asn Leu Trp Phe Val Phe Lys Glu Thr Gly Trp Ala Ala Pro Phe
            100                 105                 110

Leu Arg Ala Pro Pro Gly Ala Pro Glu Lys Gln Pro Ala Pro Gly Asp
        115                 120                 125

Ala Tyr Gly Asp Ala Gly Tyr Gly Gln Gly Pro Gly Gly Tyr Gly Pro
    130                 135                 140

Gln Asp Ser Tyr Gly Pro Gln Gly Gly Tyr Gln Pro Asp Tyr Gly Gln
145                 150                 155                 160

Pro Ala Gly Ser Gly Gly Ser Gly Tyr Gly Pro Gln Gly Asp Tyr Gly
                165                 170                 175

Gln Gln Gly Tyr Gly Pro Gln Gly Ala Pro Thr Ser Phe Ser Asn Gln
            180                 185                 190

Met
```

<210> 121
<211> 277
<212> PRT
<213> artificial Sequence

<220>
<223> Caspase-3

<400> 121

Met Glu Asn Thr Glu Asn Ser Val Asp Ser Lys Ser Ile Lys Asn Leu
1 5 10 15

Glu Pro Lys Ile Ile His Gly Ser Glu Ser Met Asp Ser Gly Ile Ser
20 25 30

Leu Asp Asn Ser Tyr Lys Met Asp Tyr Pro Glu Met Gly Leu Cys Ile
35 40 45

Ile Ile Asn Asn Lys Asn Phe His Lys Ser Thr Gly Met Thr Ser Arg
50 55 60

Ser Gly Thr Asp Val Asp Ala Ala Asn Leu Arg Glu Thr Phe Arg Asn
65 70 75 80

Leu Lys Tyr Glu Val Arg Asn Lys Asn Asp Leu Thr Arg Glu Glu Ile
85 90 95

Val Glu Leu Met Arg Asp Val Ser Lys Glu Asp His Ser Lys Arg Ser
100 105 110

Ser Phe Val Cys Val Leu Leu Ser His Gly Glu Glu Gly Ile Ile Phe
115 120 125

Gly Thr Asn Gly Pro Val Asp Leu Lys Lys Ile Thr Asn Phe Phe Arg
130 135 140

Gly Asp Arg Cys Arg Ser Leu Thr Gly Lys Pro Lys Leu Phe Ile Ile
145 150 155 160

Gln Ala Cys Arg Gly Thr Glu Leu Asp Cys Gly Ile Glu Thr Asp Ser
165 170 175

```
Gly Val Asp Asp Asp Met Ala Cys His Lys Ile Pro Val Glu Ala Asp
            180                 185                 190

Phe Leu Tyr Ala Tyr Ser Thr Ala Pro Gly Tyr Tyr Ser Trp Arg Asn
        195                 200                 205

Ser Lys Asp Gly Ser Trp Phe Ile Gln Ser Leu Cys Ala Met Leu Lys
    210                 215                 220

Gln Tyr Ala Asp Lys Leu Glu Phe Met His Ile Leu Thr Arg Val Asn
225                 230                 235                 240

Arg Lys Val Ala Thr Glu Phe Glu Ser Phe Ser Phe Asp Ala Thr Phe
                245                 250                 255

His Ala Lys Lys Gln Ile Pro Cys Ile Val Ser Met Leu Thr Lys Glu
            260                 265                 270

Leu Tyr Phe Tyr His
        275
```

<210> 122
<211> 8873
<212> DNA
<213> artificial Sequence

<220>
<223> pLenti-III-mir-GFP vector

<400> 122

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ttttggattg aagccaatat gataatgagg gggtggagtt tgtgacgtgg cgcggggcgt       60

gggaacgggg cgggtgacgt agtagtgtgg cggaagtgtg atgttgcaag tgtggcggaa      120

cacatgtaag cgacggatgt ggcaaaagtg acgttttgg tgtgcgccgg tgtacacagg      180

aagtgacaat tttcgcgcgg ttttaggcgg atgttgtagt aaatttgggc gtaaccgagt      240

aagatttggc cattttcgcg ggaaaactga ataagaggaa gtgaaatctg aataattttg      300

tgttactcat agcgcgtaat acggcagacc tcagcgctag attattgaag catttatcag      360

ggttattgtc tcatgagcgg atacatattt gaatgtattt agaaaaataa acaaataggg      420

gttccgcgca catttccccg aaaagtgcca cctgacgtta actataacgg tcctaaggta      480

gcgaaaatgt agtcttatgc aatactcttg tagtcttgca acatggtaac gatgagttag      540
```

caacatgcct tacaaggaga gaaaaagcac cgtgcatgcc gattggtgga agtaaggtgg 600

tacgatcgtg ccttattagg aaggcaacag acgggtctga catggattgg acgaaccact 660

gaattgccgc attgcagaga tattgtattt aagtgcctag ctcgatacat aaacgggtct 720

ctctggttag accagatctg agcctgggag ctctctggct aactagggaa cccactgctt 780

aagcctcaat aaagcttgcc ttgagtgctt caagtagtgt gtgcccgtct gttgtgtgac 840

tctggtaact agagatccct cagacccttt tagtcagtgt ggaaaatctc tagcagtggc 900

gcccgaacag ggacttgaaa gcgaaaggga aaccagagga gctctctcga cgcaggactc 960

ggcttgctga agcgcgcacg gcaagaggcg aggggcggcg actggtgagt acgccaaaaa 1020

ttttgactag cggaggctag aaggagagag atgggtgcga gagcgtcagt attaagcggg 1080

ggagaattag atcgcgatgg gaaaaaattc ggttaaggcc aggggaaag aaaaaatata 1140

aattaaaaca tatagtatgg gcaagcaggg agctagaacg attcgcagtt aatcctggcc 1200

tgttagaaac atcagaaggc tgtagacaaa tactgggaca gctacaacca tcccttcaga 1260

caggatcaga agaacttaga tcattatata atacagtagc aaccctctat tgtgtgcatc 1320

aaaggataga gataaaagac accaaggaag ctttagacaa gatagaggaa gagcaaaaca 1380

aaagtaagac caccgcacag caagcccgct gatcttcaga cctggaggag gagatatgag 1440

ggacattgga gaagtgaatt atataaatat aaagtagtaa aaattgaacc attaggagta 1500

gcacccacca aggcaaagag aagagtggtg cagagagaaa aaagagcagt gggaatagga 1560

gctttgttcc ttgggttctt gggagcagca ggaagcacta tgggcgcagc gtcaatgacg 1620

ctgacggtac aggccagaca attattgtct ggtatagtgc agcagcagaa caatttgctg 1680

agggctattg aggcgcaaca gcatctgttg caactcacag tctggggcat caagcagctc 1740

caggcaagaa tcctggctgt ggaaagatac ctaaaggatc aacagctcct ggggatttgg 1800

ggttgctctg gaaaactcat ttgcaccact gctgtgcctt ggaatgctag ttggagtaat 1860

aaatctctgg aacagatttg gaatcacacg acctggatgg agtgggacag agaaattaac 1920

aattacacaa gcttaataca ctccttaatt gaagaatcgc aaaaccagca agaaaagaat 1980

gaacaagaat tattggaatt agataaatgg gcaagtttgt ggaattggtt taacataaca 2040

aattggctgt ggtatataaa attattcata atgatagtag gaggcttggt aggtttaaga 2100

atagtttttg ctgtactttc tatagtgaat agagttaggc agggatattc accattatcg 2160

tttcagaccc acctcccaac cccgagggga cccgacaggc ccgaaggaat agaagaagaa 2220

ggtggagaga gagacagaga cagatccatt cgattagtga acggatctcg acggtatcga 2280

aagcttggga ttcgaattta aaagaaaagg ggggattggg gggtacagtg caggggaaag 2340

aatagtagac ataatagcaa cagacataca aactaaagaa ctacaaaaac aaattacaaa 2400

aattcaaaat tttcgggttt ttcgaaccta gggttccgcg ttacataact tacggtaaat 2460

ggcccgcctg gctgaccgcc caacgacccc cgcccattga cgtcaataat gacgtatgtt 2520

cccatagtaa cgccaatagg gactttccat tgacgtcaat gggtggagta tttacggtaa 2580

actgcccact tggcagtaca tcaagtgtat catatgccaa gtacgccccc tattgacgtc 2640

aatgacggta aatggcccgc ctggcattat gcccagtaca tgaccttatg ggactttcct 2700

acttggcagt acatctacgt ttagtcatcg ctattaccat ggtgatgcgg ttttggcagt 2760

acatcaatgg gcgtggatag cggtttgact cacggggatt tccaagtctc caccccattg 2820

acgtcaatgg gagtttgttt tggcaccaaa atcaacggga ctttccaaaa tgtcgtaaca 2880

actccgcccc attgacgcaa atgggcggta ggcgtgtacg gtgggaggtc tatataagca 2940

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gcaagctgcc cgtgccctgg cccaccctcg tgaccaccct gacctacggc gtgcagtgct 3300

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aggaggacgg caacatcctg gggcacaagc tggagtacaa ctacaacagc cacaacgtct 3540

atatcatggc cgacaagcag aagaacggca tcaaggtgaa cttcaagatc cgccacaaca 3600

tcgaggacgg cagcgtgcag ctcgccgacc actaccagca gaacaccccc atcggcgacg 3660

gccccgtgct gctgcccgac aaccactacc tgagcaccca gtccgccctg agcaaagacc 3720

ccaacgagaa gcgcgatcac atggtcctgc tggagttcgt gaccgccgcc gggatcactc 3780

tcggcatgga cgagctgtac aagtgaggta ccgatatcga attcatagct agccctgcag 3840

gtctagactc gaggtcatac acggctctcc tctctgcggc cgcagtcgag tacccatacg 3900

acgtcccaga ctacgcttga gtttaaacac gcgtggtgtg gaaagtcccc aggctcccca 3960

gcaggcagaa gtatgcaaag catgcatctc aattagtcag caaccaggtg tggaaagtcc 4020

ccaggctccc cagcaggcag aagtatgcaa agcatgcatc tcaattagtc agcaaccata 4080

gtcccgcccc taactccgcc catcccgccc ctaactccgc ccagttccgc ccattctccg 4140

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