



(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 25/28 (2006.01)
 A61K 31/4164 (2006.01) A61P 25/16 (2006.01)
 A61K 31/455 (2006.01) C12N 15/113 (2010.01)

(21) International Application Number:

PCT/IB2021/050976

(22) International Filing Date:

06 February 2021 (06.02.2021)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/971,775 07 February 2020 (07.02.2020) US
 62/989,489 13 March 2020 (13.03.2020) US
 63/047,151 01 July 2020 (01.07.2020) US

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(81) Designated States (unless otherwise indicated, for every
 kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,
 CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO,
 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.

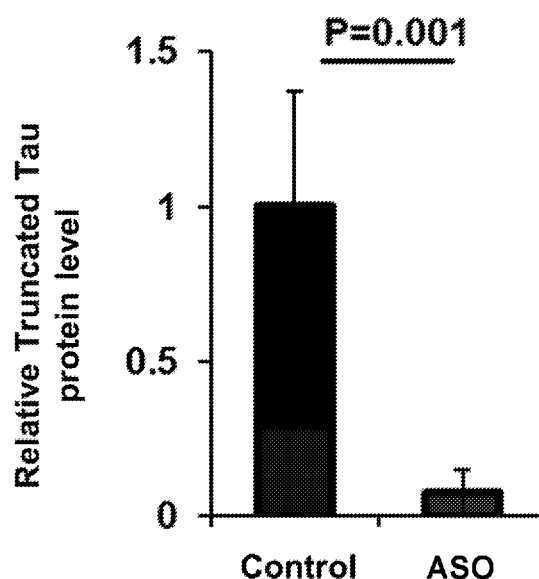
(84) Designated States (unless otherwise indicated, for every
 kind of regional protection available): ARIPO (BW, GH,
 GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,
 UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,
 TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
 EE, ES, FI, FR, GB, GR, HR,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

(54) Title: USE OF MIRNA-485 INHIBITORS FOR TREATING TAUOPATHY

FIG. 1



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

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*

USE OF MIRNA-485 INHIBITORS FOR TREATING TAUOPATHY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This PCT application claims the priority benefit of U.S. Provisional Application Nos. 62/971,775, filed February 7, 2020; 62/989,489, filed March 13, 2020; and 63/047,151, 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_022PC03_Seqlisting_ST25.txt; Size: 263,989 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 tauopathy.

BACKGROUND OF THE DISCLOSURE

[0004] Tau protein is a microtubule-associated protein (MAP) that interacts with tubulin to stabilize, and promote assembly into, microtubules. Microtubules are critical structural components of the cellular cytoskeleton and are involved in various cellular processes, including mitosis, cytokinesis, and vesicular transport. Tau protein is present in multiple cell and tissue types, but is particularly abundant in neurons compared to non-neuronal cells.

[0005] Due to Tau's role in stabilizing microtubules, alteration of Tau expression levels and/or function can disrupt critical cellular processes, which is thought to contribute to various neurodegenerative disorders such as tauopathies.

[0006] However, despite it has been studied for approximately 30 years since tau is known as the major component of fibrillary tangles, concrete evidence that detail tauopathy in molecular and cellular levels is still limited, and most of the pathological data are obtained from studies using postmortem brain. Therefore, how tau protein and its dynamic changes

affect the pathogenesis of various neurodegenerative diseases is still a mystery. Many outstanding questions are being stressed, including which posttranslational modifications are critical for it to gain toxicity, does other neurodegenerative diseases involved proteins interact with tau protein, which brain regions or cell types are most susceptible to the toxicity of tau and how the aggregates cause cellular dysfunction, and which forms of tau during the tangle formation process are toxic.

[0007] Furthermore, traditionally, it is believed that hyperphosphorylation of tau induces it to detach from microtubule and increases its toxicity, but recent findings suggest some phosphorylations are protective instead. Ittner A. et al., Science 2016;354(6314):904-908; Povellato G. et al., Biology Open. 2014;3(1):1-11. Therefore, there is still a need to develop an effective therapeutics for treating tauopathies.

BRIEF SUMMARY OF THE DISCLOSURE

[0008] Provided herein is a method of treating a tauopathy in a subject in need thereof comprising administering to the subject a compound that inhibits miR-485 (miRNA inhibitor).

[0009] 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 a tauopathy associated with a decreased level of a SIRT1 protein and/or a SIRT1 gene.

[0010] In some aspects, the miRNA inhibitor induces autophagy and/or treats or prevents inflammation.

[0011] 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 a tauopathy associated with a decreased level of a CD36 protein and/or a CD36 gene.

[0012] In some aspects, the miRNA inhibitor increases a level of a PGC-1 α protein and/or a PGC-1 α gene in the subject. In some aspects, the subject has a tauopathy associated with a decreased level of a PGC-1 α protein and/or a PGC-1 α gene.

[0013] 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.

[0014] Also provided herein is a method of treating a tauopathy 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 tauopathy 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 tauopathy associated with an abnormal level of a PGC-1 α protein and/or a PGC-1 α 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-1 α protein and/or PGC-1 α gene.

[0015] 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.

[0016] In some aspects, the miRNA inhibitor increases transcription of an SIRT1, PGC-1 α , and/or CD36 gene and/or expression of a SIRT1, PGC-1 α , and/or CD36 protein.

[0017] 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.

[0018] 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).

[0019] 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); 5'-TGTATG-3' (SEQ ID NO: 90), 5'-GTGTATG-3' (SEQ ID NO: 91), 5'-CGTGTATG-3' (SEQ ID NO: 92), 5'-CCGTGTATG-3' (SEQ ID NO: 93), 5'-GCCGTGTATG-3' (SEQ ID NO: 94), 5'-AGCCGTGTATG-3' (SEQ ID NO: 95), 5'-GAGCCGTGTATG-3' (SEQ ID NO: 96), 5'-AGAGCCGTGTATG-3' (SEQ ID NO: 97), 5'-GAGAGCCGTGTATG-3' (SEQ ID NO: 98), 5'-GGAGAGCCGTGTATG-3' (SEQ ID NO: 99), 5'-AGGAGAGCCGTGTATG-3' (SEQ ID NO: 100), 5'-GAGGAGAGCCGTGTATG-3' (SEQ ID NO: 101), 5'-AGAGGAGAGCCGTGTATG-3' (SEQ ID NO: 102), 5'-GAGAGGAGAGCCGTGTATG-3' (SEQ ID NO: 103); 5'-TGTAT-3' (SEQ ID NO: 104), 5'-GTGTAT-3' (SEQ ID NO: 105), 5'-CGTGTAT-3' (SEQ ID NO: 106), 5'-CCGTGTAT-3' (SEQ ID NO: 107), 5'-GCCGTGTAT-3' (SEQ ID NO: 108), 5'-AGCCGTGTAT-3' (SEQ ID NO: 109), 5'-GAGCCGTGTAT-3' (SEQ ID NO: 110), 5'-AGAGCCGTGTAT-3' (SEQ ID NO: 111), 5'-GAGAGCCGTGTAT-3' (SEQ ID NO: 112), 5'-GGAGAGCCGTGTAT-3' (SEQ ID NO: 113), 5'-AGGAGAGCCGTGTAT-3' (SEQ ID NO: 114), 5'-GAGGAGAGCCGTGTAT-3' (SEQ ID NO: 115), 5'-AGAGGAGAGCCGTGTAT-3' (SEQ ID NO: 116), 5'-GAGAGGAGAGCCGTGTAT-3' (SEQ ID NO: 117); 5'-TGTATGA-3' (SEQ ID NO: 118), 5'-GTGTATGA-3' (SEQ ID NO: 119), 5'-CGTGTATGA-3' (SEQ ID NO: 120), 5'-CCGTGTATGA-3' (SEQ ID NO: 121), 5'-GCCGTGTATGA-3' (SEQ ID NO: 122), 5'-AGCCGTGTATGA-3' (SEQ ID NO: 123), 5'-GAGCCGTGTATGA-3' (SEQ ID NO: 124), 5'-AGAGCCGTGTATGA-3' (SEQ ID NO: 125), 5'-GAGAGCCGTGTATGA-3' (SEQ ID NO: 126), 5'-GGAGAGCCGTGTATGA-3' (SEQ ID NO: 127), 5'-AGGAGAGCCGTGTATGA-3' (SEQ ID NO: 128), 5'-GAGGAGAGCCGTGTATGA-3' (SEQ ID NO: 129), 5'-AGAGGAGAGCCGTGTATGA-3' (SEQ ID NO: 130), 5'-GAGAGGAGAGCCGTGTATGA-3' (SEQ ID NO: 131); 5'-TGTATGAC-3' (SEQ ID NO: 132), 5'-GTGTATGAC-3' (SEQ ID NO: 133), 5'-CGTGTATGAC-3' (SEQ ID NO: 134), 5'-CCGTGTATGAC-3' (SEQ ID NO: 135), 5'-GCCGTGTATGAC-3' (SEQ ID NO: 136), 5'-AGCCGTGTATGAC-3' (SEQ ID NO: 137), 5'-GAGCCGTGTATGAC-3' (SEQ ID NO: 138), 5'-AGAGCCGTGTATGAC-3' (SEQ ID NO: 139), 5'-GAGAGCCGTGTATGAC-3' (SEQ ID NO: 140), 5'-GGAGAGCCGTGTATGAC-3' (SEQ ID NO: 141), 5'-AGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 142), 5'-GAGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 143), 5'-AGAGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 144), 5'-GAGAGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 145); 5'-TGTATG-3' (SEQ ID NO: 146), 5'-GTGTATG-3' (SEQ ID NO: 147), 5'-CGTGTATG-3' (SEQ ID NO: 148), 5'-CCGTGTATG-3' (SEQ ID NO: 149), 5'-GCCGTGTATG-3' (SEQ ID NO: 150), 5'-AGCCGTGTATG-3' (SEQ ID NO: 151), 5'-GAGCCGTGTATG-3' (SEQ ID NO: 152), 5'-AGAGCCGTGTATG-3' (SEQ ID NO: 153), 5'-GAGAGCCGTGTATG-3' (SEQ ID NO: 154), 5'-GGAGAGCCGTGTATG-3' (SEQ ID NO: 155), 5'-AGGAGAGCCGTGTATG-3' (SEQ ID NO: 156), 5'-GAGGAGAGCCGTGTATG-3' (SEQ ID NO: 157), 5'-AGAGGAGAGCCGTGTATG-3' (SEQ ID NO: 158), 5'-GAGAGGAGAGCCGTGTATG-3' (SEQ ID NO: 159); 5'-TGTAT-3' (SEQ ID NO: 160), 5'-GTGTAT-3' (SEQ ID NO: 161), 5'-CGTGTAT-3' (SEQ ID NO: 162), 5'-CCGTGTAT-3' (SEQ ID NO: 163), 5'-GCCGTGTAT-3' (SEQ ID NO: 164), 5'-AGCCGTGTAT-3' (SEQ ID NO: 165), 5'-GAGCCGTGTAT-3' (SEQ ID NO: 166), 5'-AGAGCCGTGTAT-3' (SEQ ID NO: 167), 5'-GAGAGCCGTGTAT-3' (SEQ ID NO: 168), 5'-GGAGAGCCGTGTAT-3' (SEQ ID NO: 169), 5'-AGGAGAGCCGTGTAT-3' (SEQ ID NO: 170), 5'-GAGGAGAGCCGTGTAT-3' (SEQ ID NO: 171), 5'-AGAGGAGAGCCGTGTAT-3' (SEQ ID NO: 172), 5'-GAGAGGAGAGCCGTGTAT-3' (SEQ ID NO: 173); 5'-TGTATGA-3' (SEQ ID NO: 174), 5'-GTGTATGA-3' (SEQ ID NO: 175), 5'-CGTGTATGA-3' (SEQ ID NO: 176), 5'-CCGTGTATGA-3' (SEQ ID NO: 177), 5'-GCCGTGTATGA-3' (SEQ ID NO: 178), 5'-AGCCGTGTATGA-3' (SEQ ID NO: 179), 5'-GAGCCGTGTATGA-3' (SEQ ID NO: 180), 5'-AGAGCCGTGTATGA-3' (SEQ ID NO: 181), 5'-GAGAGCCGTGTATGA-3' (SEQ ID NO: 182), 5'-GGAGAGCCGTGTATGA-3' (SEQ ID NO: 183), 5'-AGGAGAGCCGTGTATGA-3' (SEQ ID NO: 184), 5'-GAGGAGAGCCGTGTATGA-3' (SEQ ID NO: 185), 5'-AGAGGAGAGCCGTGTATGA-3' (SEQ ID NO: 186), 5'-GAGAGGAGAGCCGTGTATGA-3' (SEQ ID NO: 187); 5'-TGTATGAC-3' (SEQ ID NO: 188), 5'-GTGTATGAC-3' (SEQ ID NO: 189), 5'-CGTGTATGAC-3' (SEQ ID NO: 190), 5'-CCGTGTATGAC-3' (SEQ ID NO: 191), 5'-GCCGTGTATGAC-3' (SEQ ID NO: 192), 5'-AGCCGTGTATGAC-3' (SEQ ID NO: 193), 5'-GAGCCGTGTATGAC-3' (SEQ ID NO: 194), 5'-AGAGCCGTGTATGAC-3' (SEQ ID NO: 195), 5'-GAGAGCCGTGTATGAC-3' (SEQ ID NO: 196), 5'-GGAGAGCCGTGTATGAC-3' (SEQ ID NO: 197), 5'-AGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 198), 5'-GAGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 199), 5'-AGAGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 200), 5'-GAGAGGAGAGCCGTGTATGAC-3' (SEQ ID NO: 201); 5'-TGTATG-3' (SEQ ID NO: 202), 5'-GTGTATG-3' (SEQ ID NO: 203), 5'-CGTGTATG-3' (SEQ ID NO: 204), 5'-CCGTGTATG-3' (SEQ ID NO: 205), 5'-GCCGTGTATG-3' (SEQ ID NO: 206), 5'-AGCCGTGTATG-3' (SEQ ID NO: 207), 5'-GAGCCGTGTATG-3' (SEQ ID NO: 208), 5'-AGAGCCGTGTATG-3' (SEQ ID NO: 209), 5'-GAGAGCCGTGTATG-3' (SEQ ID NO: 210), 5'-GGAGAGCCGTGTATG-3' (SEQ ID NO: 211), 5'-AGGAGAGCCGTGTATG-3' (SEQ ID NO: 212), 5'-GAGGAGAGCCGTGTATG-3' (SEQ ID NO: 213), 5'-AGAGGAGAGCCGTGTATG-3' (SEQ ID NO: 214), 5'-GAGAGGAGAGCCGTGTATG-3' (SEQ ID NO: 215); 5'-TGTAT-3' (SEQ ID NO: 216), 5'-GTGTAT-3' (SEQ ID NO: 217), 5'-CGTGTAT-3' (SEQ ID NO: 218), 5'-CCGTGTAT-3' (SEQ ID NO: 219), 5'-GCCGTGTAT-3' (SEQ ID NO: 220), 5'-AGCCGTGTAT-3' (SEQ ID NO: 221), 5'-GAGCCGTGTAT-3' (SEQ ID NO: 222), 5'-AGAGCCGTGTAT-3' (SEQ ID NO: 223), 5'-GAGAGCCGTGTAT-3' (SEQ ID NO: 224), 5'-GGAGAGCCGTGTAT-3' (SEQ ID NO: 225), 5'-AGGAGAGCCGTGTAT-3' (SEQ ID NO: 226), 5'-GAGGAGAGCCGTGTAT-3' (SEQ ID NO: 227), 5'-AGAGGAGAGCCGTGTAT-3' (SEQ ID NO: 228), 5'-GAGAGGAGAGCCGTGTAT-3' (SEQ ID NO: 229); 5'-TGTATGA-3' (SEQ ID NO: 230), 5'-GTGTATGA-3' (SEQ ID NO: 231), 5'-CGTGTATGA-3' (SEQ ID NO: 232), 5'-CCGTGTATGA-3' (SEQ ID NO: 233), 5'-GCCGTGTATGA-3' (SEQ ID NO: 234), 5'-AGCCGTGTATGA-3' (SEQ ID NO: 235), 5'-GAGCCGTGTATGA-3' (SEQ ID NO: 236), 5'-AGAGCCGTGTATGA-3' (SEQ ID NO: 237), 5'-GAGAGCCGTGTATGA-3' (SEQ ID NO: 238), 5'-GGAGAGCCGTGTATGA-3' (SEQ ID NO: 239), 5'-AGGAGAGCCGTGT

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).

[0020] 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).

[0021] 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).

[0022] 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.

[0023] 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.

[0024] 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.

[0025] 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.

[0026] 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;

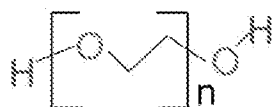
AM is an adjuvant moiety; and,

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.

[0027] 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").

[0028] In some aspects, the water-soluble polymer comprises:



[0029] , (formula I),

[0030] 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.

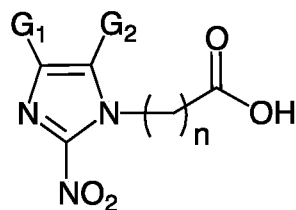
[0031] In some aspects, the water-soluble polymer is linear, branched, or dendritic.

[0032] 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 least 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.

[0033] 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.

[0034] 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.

[0035] In some aspects, the adjuvant moiety comprises:



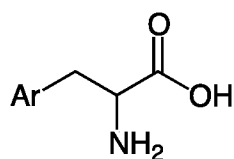
[0036] , (formula II),

[0037] 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.

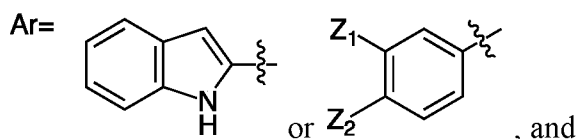
[0038] In some aspects, the adjuvant moiety comprises nitroimidazole. In certain aspects, the adjuvant moiety comprises metronidazole, tinidazole, nimorazole, dimetridazole, pretomanid, ornidazole, megazol, azanidazole, benznidazole, or any combination thereof.

[0039] In some aspects, the adjuvant moiety comprises an amino acid.

[0040] In some aspects, the adjuvant moiety comprises



[0041] (formula III),

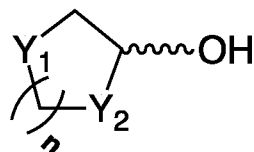


[0042] wherein Ar is

[0043] wherein each of Z1 and Z2 is H or OH.

[0044] 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.

[0045] In some aspects, the vitamin comprises:



[0046] (formula IV),

[0047] wherein each of Y1 and Y2 is C, N, O, or S, and wherein n is 1 or 2.

[0048] 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.

[0049] 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.

- [0050] 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.
- [0051] 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.
- [0052] 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.
- [0053] In some aspects, a tauopathy that can be treated with the present disclosure comprises Frontotemporal dementia (FTD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), corticobasal ganglionic degeneration, dementia pugilistica, Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), Lytico-Bodig disease, tangle-predominant dementia, ganglioglioma, gangliocytoma, meningioangiomas, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, Pick's disease, argyrophilic grain disease, corticobasal degeneration, frontotemporal lobar degeneration, or any combination thereof.
- [0054] In some aspects, the miRNA inhibitor delays tauopathy onset.
- [0055] 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.
- [0056] 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 penicillin.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

- [0057] FIG. 1 provides the truncated tau expression level after exposure to the miR485 inhibitor. The left bar shows the truncated tau expression by control, and the right bar shows the truncated tau expression by the miR485 inhibitor.
- [0058] FIG. 2 provides a schematic representation of the wild-type (WT) or mutant (MT) form in SIRT1 3'-UTR showing the putative miR-485-3p target site. For the MT construct, nucleotides that are underlined represent those that have been mutated from the WT construct.
- [0059] FIGs. 3A and 3B 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.
- [0060] FIGs. 4A and 4B 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.
- [0061] FIGs. 5A and 5B 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.
- [0062] FIGs. 6A and 6B 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).
- [0063] FIGs. 7A, 7B, 7C, 7D, 7E, and 7F show comparison of truncated tau (TauC3) expression in mice treated with either PBS (control) or miR-485 inhibitor. Truncated tau expression in the following brain tissues are shown: (i) hippocampus (FIGs. 7A and 7B), (ii)

frontal cortex (FIGs. 7C and 7D), and (iii) cerebral cortex (FIGs. 7E and 7F). FIGs. 7A, 7C, and 7E show truncated tau expression by Western blot analysis. FIGs. 7B, 7D, and 7F provide quantitative comparison of the results shown in FIGs. 7A, 7C, and 7E, respectively.

[0064] FIG. 8 shows the ability of miR-485 inhibitor to reduce truncated tau expression *in vitro* as measured using Western blot analysis.

[0065] FIG. 9 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.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0066] 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-1 α . 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 tauopathy 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 tauopathy 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-1 α protein and/or PGC-1 α

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-1 α protein and/or PGC-1 α gene in a subject can be useful in treating a tauopathy associated with reduced levels of a SIRT1 protein and/or a PGC-1 α gene.

[0067] 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.

[0068] 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

[0069] 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.

[0070] 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.

[0071] 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).

[0072] 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.

[0073] 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.

[0074] 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.

[0075] 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.

[0076] 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.

[0077] 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.

[0078] 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).

[0079] 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.

[0080] 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.

[0081] 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 elsewhere in the present disclosure.

[0082] 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).

[0083] 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.

[0084] 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.

[0085] 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.

[0086] 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.

[0087] 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.

[0088] 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.

[0089] 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.

[0090] 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.

[0091] 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.

[0092] 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).

- [0093] 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.
- [0094] 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."
- [0095] 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.
- [0096] 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.
- [0097] 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.

[0098] Sequence alignments can be conducted using methods known in the art such as MAFFT, Clustal (ClustalW, Clustal X or Clustal Omega), MUSCLE, etc.

[0099] 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.

[0100] In certain aspects, the percentage identity (%ID) of a first amino acid sequence (or nucleic acid sequence) to a second amino acid sequence (or nucleic acid sequence) is calculated as $\%ID = 100 \times (Y/Z)$, 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.

[0101] 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.

[0102] 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.

[0103] 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.

[0104] 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.

[0105] 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.

[0106] 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).

[0107] 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.

[0108] 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

subunits of the 5' and/or 3' terminus. In some aspects, one, two, or three nucleobases can be removed and still provide on-target binding.

[0109] 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.

[0110] "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.

[0111] 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.

[0112] 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.

[0113] The term "polynucleotide," as used herein, refers to polymers of nucleotides of any length, including ribonucleotides, deoxyribonucleotides, analogs thereof, or mixtures thereof.

[0114] 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.

[0115] 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.

[0116] 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).

[0117] 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.

[0118] Polypeptides include gene products, naturally occurring polypeptides, synthetic polypeptides, homologs, orthologs, paralogs, fragments and other equivalents, variants, and analogs of the foregoing.

[0119] 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.

[0120] 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.

[0121] 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.

[0122] 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.

[0123] As used herein, "prophylactic" refers to a therapeutic or course of action used to prevent the onset of a tauopathy, or to prevent or delay a symptom associated with a tauopathy.

[0124] As used herein, a "prophylaxis" refers to a measure taken to maintain health and prevent the onset of a tauopathy, or to prevent or delay a symptom associated with a tauopathy.

[0125] As used herein, the term "tauopathy" refers to a class of neurodegenerative diseases characterized by the deposition of abnormal tau (tubulin associated unit) protein within the brain (*e.g.*, in neurofibrillary or gliofibrillary tangles). Tauopathies can be further categorized as primary tauopathy or secondary tauopathy. "Primary tauopathy" refers to tauopathies in which tau protein accumulation is the sole or predominant intracerebral protein accumulation. "Secondary tauopathy" refers to tauopathies where tau accumulation is concomitant to intracerebral accumulation of other proteins, *e.g.*, alpha-beta amyloid or prior proteins. In some aspects, a tauopathy that can be treated with the present disclosure is a primary tauopathy. In some aspects, a tauopathy that can be treated with the present disclosure is a secondary tauopathy. In some aspects, a tauopathy that can be treated with the present disclosure comprises both primary and secondary tauopathies.

[0126] Non-limiting examples of primary tauopathy include Progressive Supranuclear Palsy (PSP), Argyrophilic Grain Disease (AGD), Corticobasal Degeneration (CBD), Frontotemporal lobar degeneration with tau aggregation (FTLD-tau; sporadic or caused by MAPT mutations), Frontotemporal dementia with parkinsonism-17 (FTDP-17), Pick's disease (PiD), Tangle-predominant dementia, Guadeloupe-Parkinson Dementia Complex, Guam-Parkinson Dementia Complex (Lytico-Bodig disease), Dementia pugilistica (chronic traumatic encephalopathy), Progressive subcortical gliosis, and combinations thereof. Non-limiting examples of secondary tauopathy include Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), Multiple System Atrophy (MSA), Motor neuron disease (MND) with neurofibrillary tangles, Hallervorden-Spatz disease (HSD), Creutzfeldt-Jakob disease (CJD), Gerstmann-Straussler-Scheinker Disease, Niemann-Pick Disease Type C, Lead encephalopathy, Myotonic dystrophy, Prion protein cerebral amyloid angiopathy, Postencephalitic par-kinsonism, Subacute sclerosing panencephalitis (SSPE), Tuberous sclerosis, Down's syndrome, and combinations thereof.

[0127] 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.

[0128] 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.

[0129] 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.

[0130] 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.

- [0131] 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.
- [0132] 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 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.
- [0133] The terms "treat," "treatment," or "treating," as used herein refers to, *e.g.*, the reduction in severity of a tauopathy; the reduction in the duration of a disease course; the amelioration or elimination of one or more symptoms associated with a tauopathy (*e.g.*, diabetes); the provision of beneficial effects to a subject with a tauopathy, without necessarily curing the tauopathy. The term also includes prophylaxis or prevention of a tauopathy or its symptoms thereof.
- [0134] The term "upstream" refers to a nucleotide sequence that is located 5' to a reference nucleotide sequence.
- [0135] 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.
- [0136] 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

SIRT1 Regulation

[0137] 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.

[0138] 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.”

[0139] 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)	MADEAALALQPGGSPSAAGADREAASSPAGEPLRKRPRRDGPGLERSPGEPGGAAPEREV PAAARGCPGAAAAALWREAEAEAAAAGGEQEAQATAAAGEGDNGPGLQGSPREPPLADNL YDEDDDDGEEEEEEEEAAAAIgyrdNLLFGDEIITNGFHSCEDEEDRASHASSSDWTPrP RIGPYTFVQQHLMIGTDPRTILKDLLPETIPPELDDMTLWQIVINILSEPPKRRKKRDI NTIEDAVKLLQECKKIIVLTGAGVSVSCGIPDFRSRDGIYARLAVDFPDLDPDQAMFDIE YFRKDP RPFFKFAKEIYPGQFQPSLCHKFIALSDKEGKLLRNYTQNIDTLEQVAGIQRII
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(SEQ ID NO: 31)	QCHGSFATASCLICKYKVDCEAVRGDIFNQVPRCPRCPADEPLAIMKPEIVFFGENLPE QFHRAMKYDKDEVDLLIVIGSSLKVRPVALIPSSIPHEVPQILINREPLPHLHFDVELLG DCDVIINELCHRLGGEYAKLCCNPVKLSEITEKPPRTQKELAYLSELPPTPLHVSEDSSS PERTSPDSSVIVTLLDQAAKSNDLLDVSESKGCMEKPKQEVQTSRNVESIAEQMENPDL KNVGSSTGEKNERTSVAGTVRKCPNRVAKQISRRLDGNQYLFPPNRYIFHGAEVYSD SEDDVLSSSSCGSNSDSGTCQSPSLEEPMEDSEIEEFYNGLEDEPDVPERAGGAGFGTD GDDQEAINEAISVKQEVTDNMNYP SNKS
Isoform 2 (UniProt: Q96EB6-2) (SEQ ID NO: 32)	MADEAALALQPGGSPSAAGADREAASSPAGEPLRKRPRRDGPGLERSPGEPGGAAPEREV PAAARGCPGAAAAALWREAEAEAAAAGGEQEAQATAAAGEGDNGPGLQGSPREPPLADNL YDEDDDDGEEEEEEEEAAAAAIGYRDNLFGDEIITNGFHSCEDEEDRASHASSSDWTPRP RIGPYTFVQQHLMIGTDPRTILKDLLPETIPPELDDMTLWQIVINILSEPPKRKKRKDI NTIEDAVKLLQECKKIIVLTGAGVSVSCGIPDFRSRDGIYARLAVDFPDLDPQAMFDIE YFRKDP RPFFKFAKEIYPGQFQPSLCHKFIALSDKEGKLLRNYTQNIDTLEQVAGIQRII QCHGSFATASCLICKYKVDCEAVRGDIFNQVPRCPRCPADEPLAIMKPEIVFFGENLPE QFHRAMKYDKDEVDLLIVIGSSLKVRPVALIPSNQYLFPPNRYIFHGAEVYSDSEDDVL SSSSCGSNSDSGTCQSPSLEEPMEDSEIEEFYNGLEDEPDVPERAGGAGFGTDGDDQEA INEAISVKQEVTDNMNYP SNKS

[0140] 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.”

[0141] 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).

[0142] 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. 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.

[0143] 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.

[0144] 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 tauopathy associated with an abnormal (*e.g.*, reduced) level of a SIRT1 protein and/or SIRT1 gene in a subject in need thereof. 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

[0145] 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.

[0146] 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.”

[0147] 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)	MGCDRNCGLIAGAVIGAVLAVFGGILMPVGDLLIQKTIKKQVVLEEGTIAFKNWNVKTGTE VYRQFWIFDVQNPQEVMMNSSNIQVKQRGPTYRVRFLAKENVTQDAEDNTVSFLQPNGA IFEPSLSVGTEADNFTVLNLAVAAASHIYQNQFVQMILNSLINKSKSSMFQVRTLRELLW GYRDPFLSLVPYPVTTTTVGLFYYPYNNADGVYKVFNGKDNISKVAIIDTYKGKRNLSYWE SHCDMINGTDAASFPPFVEKSQVLQFFSSDICRSIYAVFESDVNLKGI PVYRFVLP SKAF ASPVENPDNYCFCTEKIISKNTSYGVLDISKCKEGRPVYISLPHFLYASPDVSEPIDGL NPNEEEHRTYLDIEPITGFTLQFAKRLQVNLLVKPSEKIQVLKLNLRNYIVPILWLNETG TIGDEKANMFRSQVTGKINLLGLIEMILLSVGVMFVAFMISYCACRSKTIK
Isoform 2 (UniProt:P16671-2) (SEQ ID NO: 37)	MGCDRNCGLIAGAVIGAVLAVFGGILMPVGDLLIQKTIKKQVVLEEGTIAFKNWNVKTGTE VYRQFWIFDVQNPQEVMMNSSNIQVKQRGPTYRVRFLAKENVTQDAEDNTVSFLQPNGA IFEPSLSVGTEADNFTVLNLAVAAASHIYQNQFVQMILNSLINKSKSSMFQVRTLRELLW GYRDPFLSLVPYPVTTTTVGLFYYPYNNADGVYKVFNGKDNISKVAIIDTYKGKRNLSYWE SHCDMINGTDAASFPPFVEKSQVLQFFSSDICRETCVHFTSSFSVCKS
Isoform 3 (UniProt:	MGCDRNCGLIAGAVIGAVLAVFGGILMPVGDLLIQKTIKKQVVLEEGTIAFKNWNVKTGTE VYRQFWIFDVQNPQEVMMNSSNIQVKQRGPTYRVRFLAKENVTQDAEDNTVSFLQPNGA IFEPSLSVGTEADNFTVLNLAVAAASHIYQNQFVQMILNSLINKSKSSMFQVRTLRELLW GYRDPFLSLVPYPVTTTTVGLFYYPYNNADGVYKVFNGKDNISKVAIIDTYKGKRSIYAVF

P16671-3) (SEQ ID NO: 38)	ESDVNLKGIPVYRFVLPSKAFASPVENPDNYCFCTEKIISKNCSTSYGVLDISKCKEGRPVYISLPHFLYASPDVSEPIDGLNPNEEEHRTYLDIEPITGFTLQFAKRLQVNLLVKPSEKIQVLKLNLRNYIVPILWLNLTGTIGDEKANMFRSQVTGKINLLGLIEMILLSVGVVMFVAFMISYCACRSKTIK
Isoform 4 (UniProt: P16671-4) (SEQ ID NO: 39)	MGCDRNCGLIAGAVIGAVLAVFGGILMPVGDLLIQKTIKKQVVLEEGTIAFKNWVKGTGEVYRQFWIFDVQNPQEVMMNSSNIQVKQRGPTYRVRFLAKENVTDQDAEDNTVSFLQPNGAIFEPSLSVGTEADNFTVLNLAVAYNNTADGVYKVFNGKDNISKVAIIDTYKGKRNLSYWE SHCDMINGTDAASFPPFVEKSQVLQFFSSDICRSIYAVFESDVNLKGIPVYRFVLPSKAFASPVENPDNYCFCTEKIISKNCSTSYGVLDISKCKEGRPVYISLPHFLYASPDVSEPIDGLNPNEEEHRTYLDIEPITGFTLQFAKRLQVNLLVKPSEKIQVLKLNLRNYIVPILWLNLTGTIGDEKANMFRSQVTGKINLLGLIEMILLSVGVVMFVAFMISYCACRSKTIK

[0148] 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.”

[0149] 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).

[0150] 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.

PGC1 Regulation

[0151] The disclosures provided herein demonstrates that the miR-485 inhibitors of the present disclosure can further regulate the expression of PGC-1 α , *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-1 α protein and/or a PGC-1 α 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-1 α protein and/or PGC-1 α gene in the subject.

[0152] 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).”

[0153] 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 $\rightarrow$ 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 $\rightarrow$ MDETSRLEEDWKKVLQREAGWQ (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 $\rightarrow$ 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 $\rightarrow$

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 → MDETSRLEEDWKKVLQREAGWQ; 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)	MAWDMCNQDSESVWSDIECAALVGEDQPLCPDLPELDLSELVDVNDLDTDSFLGGLKWCSD QSEIISNQYNNEPSNIFEKIDEENEANLLAVLTETLDSLVPDEDEDGLPSFDALTDGDVTTD NEASPSSMPDGTTPPPQEAEEPSLLKKLLAPANTQLSYNECSGLSTQNHANHNHRIRTNP AIVKTENSWSNKAKSICQQQKQRRPCSELLKYLTTNDPPHTKPTENRNRSSRDKCTSKK KSHTQSQSQHLQAKPTTSLPLTPESPNDPKGSPFENKTIERTLSVELSGTAGLTPPTTP PHKANQDNPFRA SPKLKSSCKTVVPPPSKKPRYSESSGTQGNNSTKKGPEQSELYAQLSK SSVLTGGHEERKTKRPSLRFLFGHDYQCQSINSKTEILINISQELQDSRQLENKDVSSDWQ GQICSSTDSDQCYLRETLEASKQVSPCSTRKQLQDQEIARAE LNKHFGHPSQAVFDDEADK TGELRDSDFSNEQFSKLPMFINSGLAMDGFLDDESESDKLSYPWDGTQSYSLFNVSPSC SSFNSPCRDSVSPPKSLFSQRPQRMRSRSPSRHRSRSPYRSRSPGSRSSSRSC YYYESSHYRHRTHRNSPLYVRSRSPYRRPRYDSYEEYQHERLKREBYRREYEKRESE RAKQRRERQQAIEERRVIYVGKIRPDTRTELDRDRFEVFGEIEECTVNLRDDGDSYGF I TYRYTCDAFAALENGYTLRRSNETDFELYFCGRKQFFKSNYADLDSNSDDFDPA STKSKY DSLDFDSLKKEAQRSLRR
Isoform 2 (UniProt: Q9UBK2-2) (SEQ ID NO: 41)	MAWDMCNQDSESVWSDIECAALVGEDQPLCPDLPELDLSELVDVNDLDTDSFLGGLKWCSD QSEIISNQYNNEPSNIFEKIDEENEANLLAVLTETLDSLVPDEDEDGLPSFDALTDGDVTTD NEASPSSMPDGTTPPPQEAEEPSLLKKLLAPANTQLSYNECSGLSTQNHANHNHRIRTNP AIVKTENSWSNKAKSICQQQKQRRPCSELLKYLTTNDPPHTKPTENRNRSSRDKCTSKK KSHTQSQSQHLQAKPTTSLPLTPESP NLF L
Isoform 3 (UniProt: Q9UBK2-3)	MDETSRLEEDWKKVLQREAGWQCAALVGEDQPLCPDLPELDLSELVDVNDLDTDSFLGGL KWCSDQSEIISNQYNNEPSNIFEKIDEENEANLLAVLTETLDSLVPDEDEDGLPSFDALTDG DVTTDNEASPSSMPDGTTPPPQEAEEPSLLKKLLAPANTQLSYNECSGLSTQNHANHNHR

Q9UBK2-3) (SEQ ID NO: 42)	IRTNPAIVKTENSWSNKAKSICQQQKPQRRPCSELLKYLTNDDPPHTKPTENRNSSRDK CTSKKKSHTQSQSQHLQAKPTTSLPLTPESPNDPKGSPFENKTIERTLSVELSGTAGLT PPTTPPHKANQDNPFRA SPKLKSSCKTVVPPPSKKPRYSESSGTQGNNSTKKGPEQSELY AQLSKSSVLTGGHEERKTKRPSLRLFGDHDYQCSINSKTEILINISQELQDSRQLENKDV SSDWQGQICSSTSDQCYLRETLEASKQVSPCSTRKQLQDQEIIRAE LNKHFGHPSQAVFD DEADKTGELRDSDFSNEQFSKLPMFINSGLAMDGLFDDSEDESDKLSYPWDGTQSYSLFN VSPSCSSFNSPCRDSVSPPKSLFSQRPQRMRSRSPYRHRSCSRSPYRHRSPYRHRSPYRHR SSRSCYYYESSHYRHRTHRNSPLYVRSRSPYRHRSPYRHRSPYRHRSPYRHRSPYRHR KRESERAKQERQRQKAIEERRVIYVGKIRPDTRTELDRFEVFGEIEECTVNLRDDGD SYGFITYRYTCDFAALENGTYTLRRSNETDFELYFCGRKQFFKSNYADLDSNSDDFDPAS TKSKYDSLDFDSLLEAKQRLRR
Isoform 4 (UniProt: Q9UBK2-4) (SEQ ID NO: 43)	MDEGYFCAALVGEDQPLCPDLPELDLSELVDNDLDTDSFLGGLKWCSDQSEIISNQYNNE PSNIFEKIDEENEANLLAVLTETLDSLVPDEDGLPSFDALTDGDVTTDNEASPSSMPDGT PPPQEAEEPSLLKKLLAPANTQLSYNECSGLSTQNHANHNHRIRTNPAIVKTENSWSNK AKSICQQQKPQRRPCSELLKYLTNDDPPHTKPTENRNSSRDKCTSKKKSHTQSQSQHLQ AKPTTSLPLTPESPNDPKGSPFENKTIERTLSVELSGTAGLTPTTPPHKANQDNPFRA SPKLKSSCKTVVPPPSKKPRYSESSGTQGNNSTKKGPEQSELYAQLSKSSVLTGGHEERK TKRPSLRLFGDHDYQCSINSKTEILINISQELQDSRQLENKDVSSDWQGQICSSTSDQCY LRETLEASKQVSPCSTRKQLQDQEIIRAE LNKHFGHPSQAVFDDEADKTGELRDSDFSNE QFSKLPMFINSGLAMDGLFDDSEDESDKLSYPWDGTQSYSLFNVSPSCSSFNSPCRDSVS PPKSLFSQRPQRMRSRSPYRHRSCSRSPYRHRSPYRHRSPYRHRSPYRHRSPYRHR HRNSPLYVRSRSPYRHRSPYRHRSPYRHRSPYRHRSPYRHRSPYRHRSPYRHRSPYRHR KRESERAKQERQRQKAIEERRVIYVGKIRPDTRTELDRFEVFGEIEECTVNLRDDGDSYGF ITYRYTCDFAALENGTYTLRRSNETDFELYFCGRKQFFKSNYADLDSNSDDFDPASTKSKYDSL DFDSLLEAKQRLRR
Isoform 5 (UniProt: Q9UBK2-5) (SEQ ID NO: 44)	MDEGYFCAALVGEDQPLCPDLPELDLSELVDNDLDTDSFLGGLKWCSDQSEIISNQYNNE PSNIFEKIDEENEANLLAVLTETLDSLVPDEDGLPSFDALTDGDVTTDNEASPSSMPDGT PPPQEAEEPSLLKKLLAPANTQLSYNECSGLSTQNHANHNHRIRTNPAIVKTENSWSNK AKSICQQQKPQRRPCSELLKYLTNDDPPHTKPTENRNSSRDKCTSKKKSHTQSQSQHLQ AKPTTSLPLTPESPNDPKGSPFENKTIERTLSVELSGTAGVKTNLISK
Isoform 6 (UniProt: Q9UBK2-6) (SEQ ID NO: 45)	MDETSPLREEDWKKVLQREAGWQCAALVGEDQPLCPDLPELDLSELVDNDLDTDSFLGGL KWCSDQSEIISNQYNNEPSNIFEKIDEENEANLLAVLTETLDSLVPDEDGLPSFDALTDG DVTTDNEASPSSMPDGTPPPQEAEEPSLLKKLLAPANTQLSYNECSGLSTQNHANHNHRI RTNPAIVKTENSWSNKAKSICQQQKPQRRPCSELLKYLTNDDPPHTKPTENRNSSRDK CTSKKKSHTQSQSQHLQAKPTTSLPLTPESPNDLFL
Isoform 7 (UniProt: Q9UBK2-7) (SEQ ID NO: 46)	MDEGYFCAALVGEDQPLCPDLPELDLSELVDNDLDTDSFLGGLKWCSDQSEIISNQYNNE PSNIFEKIDEENEANLLAVLTETLDSLVPDEDGLPSFDALTDGDVTTDNEASPSSMPDGT PPPQEAEEPSLVRTLPTV
Isoform 8 (UniProt: Q9UBK2-8)	MAWDMCNQDSESVWSDIECAALVGEDQPLCPDLPELDLSELVDNDLDTDSFLGGLKWCSD QSEIISNQYNNEPSNIFEKIDEENEANLLAVLTETLDSLVPDEDGLPSFDALTDGDVTTD NEASPSSMPDGTPPPQEAEEPSLLKKLLAPANTQLSYNECSGLSTQNHANHNHRIRTNP AIVKTENSWSNKAKSICQQQKPQRRPCSELLKYLTNDDPPHTKPTENRNSSRDKCTSKK KSHTQSQSQHLQAKPTTSLPLTPESPNDPKGSPFENKTIERTLSVELSGTAGVKTNLISK

(SEQ ID NO: 47)	
Isoform 9 (UniProt: Q9UBK2-9) (SEQ ID NO: 48)	MPDGTPPPQEAEEPSLLKKLLLAPANTQLSYNECSGLSTQNHANHNHRIRTNPAIVKTEN SWSNKAKSICQQQKPQRRPCSELLKYLTNDPPHTKPTENRNSSRDKCTSKKKSHTQSQ SQHLQAKPTTSLPLTPESPNDPKGSPFENKTIERTLSVELSGTAGLTPPTTPPHKANQD NPFRA SPKLKSSCKTVVPPPSKKPRYSESSGTQGNNSTKKGPESQSELYAQLSKSSVLTGG HEERKTKRPSLRLFGDHDYCSINSKTEILINISQELQDSRQLENKDVSSDWQGGQICSST DSDQCYLRETLEASKQVSPCSTRKQLQDQEIRAE LNKHFGHPSQAVFDDEADKTGELRDS DFSNEQFSKLPFMFINSGLAMDGLFDDSEDES DKLSYPWDGTQSYSLFNVSPSCSSFNSPC RDSVSPPKSLFSQRPQRMRSRSPSRHRSCSRSPYSRSPSRSPGSRSSSRSCYYYESSH YRHRTHRNSPLYVRSRSPYSRRPRYDSYEEYQHERLKREEYRREYEKRESERAKQRE QRQKAI EERRVIYVGKIRPD TTRTELDRFEVFG EIEECTVNLRDDGDSYGFITYRYTCD AFAALENGYTLRRSNETDFELYFCGRKQFFKSNYADLDSNSDDFDPASTKSKYDSLDFDS LLKEAQRSLRR

[0154] 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 .”

[0155] 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).

[0156] 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.

[0157] As will be apparent from the present disclosure, any tauopathy 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 tauopathy 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 tauopathy associated with abnormal (*e.g.*, reduced) level of a PGC1- α protein and/or PGC1- α gene. In some aspects, a tauopathy associated with abnormal (*e.g.*, reduced) level of such proteins and/or genes is not a tauopathy associated with the following: Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), autism spectrum disorder, mental retardation, seizure, stroke, spinal cord injury, or any combination thereof.

[0158] In some aspects, administering a miR-485 inhibitor disclosed herein can improve one or more symptoms of a tauopathy 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 tauopathy 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 tauopathy associated with abnormal (*e.g.*, reduced) levels of PGC1- α protein and/or PGC1- α gene. Non-limiting examples of such symptoms are described below. As described herein, a tauopathy associated with abnormal expression of SIRT1, CD36, and/or PGC1- α is. Accordingly, in some aspects, a miR-485 inhibitor disclosed herein can improve one or more symptoms associated with

tauopathy. 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.

[0159] 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 tauopathy). 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).

[0160] 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 tauopathy 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 tauopathy 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).

- [0161] 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 a tauopathy) compared to a reference (*e.g.*, cognitive symptom in the subject prior to the administering).
- [0162] 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 tauopathy 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).
- [0163] 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 tauopathy) 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 tauopathy) 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).
- [0164] In some aspects, administering a miR-485 inhibitor disclosed herein increases neurogenesis in a subject (*e.g.*, suffering from tauopathy) (*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 tauopathy) 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).

[0165] 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).

[0166] 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).

[0167] 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).

[0168] 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 tauopathy) 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 tauopathy) 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 tauopathy) 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-1 β . In some aspects, an inflammatory mediator produced by glial cells comprises both TNF- α and IL-1 β .

[0169] 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 tauopathy). 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 tauopathy) 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).

[0170] As is known in the art and described herein, tauopathy patients exhibit certain motor and/or non-motor symptoms. For instance, non-limiting examples of motor symptoms associated with tauopathy 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 tauopathy 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.

[0171] 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 tauopathy) 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 tauopathy) 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).

[0172] 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 tauopathy) 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 tauopathy) 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).

[0173] 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 parenterally, intramuscularly, subcutaneously, ophthalmic, intravenously, intraperitoneally, intradermally, intraorbitally, intracerebrally, intracranially, intracerebroventricularly, intraspinally, intraventricular, intrathecally, intracisternally, intracapsularly, intratumorally, or any combination thereof.

[0174] 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.

[0175] 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 does 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

[0176] 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.

[0177] 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.

[0178] 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.

[0179] 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). Sequence alignments for human mature miR-485-3p and miR-485-5p to the corresponding sequences from other exemplary mammalian species are provided in FIG. 2. 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

shown in FIG. 2. 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.

[0180] 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.

[0181] 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.

[0182] 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.

[0183] 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 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.

[0184] 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.

[0185] 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.

[0186] 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.

[0187] 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.

[0188] 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.

[0189] 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).

[0190] 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 5'-AGAGAGGAGAGCCGUGUAUGAC-3' (SEQ ID NO: 30).

[0191] 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); 5'-TGTATGAAG-3' (SEQ ID NO: 90), 5'-GTGTATGAAG-3' (SEQ ID NO: 91), 5'-CGTGTATGAAG-3' (SEQ ID NO: 92), 5'-CCGTGTATGAAG-3' (SEQ ID NO: 93), 5'-GCCGTGTATGAAG-3' (SEQ ID NO: 94), 5'-AGCCGTGTATGAAG-3' (SEQ ID NO: 95), 5'-GAGCCGTGTATGAAG-3' (SEQ ID NO: 96), 5'-AGAGCCGTGTATGAAG-3' (SEQ ID NO: 97), 5'-GAGAGCCGTGTATGAAG-3' (SEQ ID NO: 98), 5'-GGAGAGCCGTGTATGAAG-3' (SEQ ID NO: 99), 5'-AGGAGAGCCGTGTATGAAG-3' (SEQ ID NO: 100), 5'-GAGGAGAGCCGTGTATGAAG-3' (SEQ ID NO: 101), 5'-AGAGGAGAGCCGTGTATGAAG-3' (SEQ ID NO: 102), 5'-GAGAGGAGAGCCGTGTATGAAG-3' (SEQ ID NO: 103); 5'-TGTATGATG-3' (SEQ ID NO: 104), 5'-GTGTATGATG-3' (SEQ ID NO: 105), 5'-CGTGTATGATG-3' (SEQ ID NO: 106), 5'-CCGTGTATGATG-3' (SEQ ID NO: 107), 5'-GCCGTGTATGATG-3' (SEQ ID NO: 108), 5'-AGCCGTGTATGATG-3' (SEQ ID NO: 109), 5'-GAGCCGTGTATGATG-3' (SEQ ID NO: 110), 5'-AGAGCCGTGTATGATG-3' (SEQ ID NO: 111), 5'-GAGAGCCGTGTATGATG-3' (SEQ ID NO: 112), 5'-GGAGAGCCGTGTATGATG-3' (SEQ ID NO: 113), 5'-AGGAGAGCCGTGTATGATG-3' (SEQ ID NO: 114), 5'-GAGGAGAGCCGTGTATGATG-3' (SEQ ID NO: 115), 5'-AGAGGAGAGCCGTGTATGATG-3' (SEQ ID NO: 116), 5'-GAGAGGAGAGCCGTGTATGATG-3' (SEQ ID NO: 117); 5'-TGTATGATGA-3' (SEQ ID NO: 118), 5'-GTGTATGATGA-3' (SEQ ID NO: 119), 5'-CGTGTATGATGA-3' (SEQ ID NO: 120), 5'-CCGTGTATGATGA-3' (SEQ ID NO: 121), 5'-GCCGTGTATGATGA-3' (SEQ ID NO: 122), 5'-AGCCGTGTATGATGA-3' (SEQ ID NO: 123), 5'-GAGCCGTGTATGATGA-3' (SEQ ID NO: 124), 5'-AGAGCCGTGTATGATGA-3' (SEQ ID NO: 125), 5'-GAGAGCCGTGTATGATGA-3' (SEQ ID NO: 126), 5'-GGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 127), 5'-AGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 128), 5'-GAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 129), 5'-AGAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 130), 5'-GAGAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 131); 5'-TGTATGATGA-3' (SEQ ID NO: 132), 5'-GTGTATGATGA-3' (SEQ ID NO: 133), 5'-CGTGTATGATGA-3' (SEQ ID NO: 134), 5'-CCGTGTATGATGA-3' (SEQ ID NO: 135), 5'-GCCGTGTATGATGA-3' (SEQ ID NO: 136), 5'-AGCCGTGTATGATGA-3' (SEQ ID NO: 137), 5'-GAGCCGTGTATGATGA-3' (SEQ ID NO: 138), 5'-AGAGCCGTGTATGATGA-3' (SEQ ID NO: 139), 5'-GAGAGCCGTGTATGATGA-3' (SEQ ID NO: 140), 5'-GGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 141), 5'-AGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 142), 5'-GAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 143), 5'-AGAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 144), 5'-GAGAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 145); 5'-TGTATGATGA-3' (SEQ ID NO: 146), 5'-GTGTATGATGA-3' (SEQ ID NO: 147), 5'-CGTGTATGATGA-3' (SEQ ID NO: 148), 5'-CCGTGTATGATGA-3' (SEQ ID NO: 149), 5'-GCCGTGTATGATGA-3' (SEQ ID NO: 150), 5'-AGCCGTGTATGATGA-3' (SEQ ID NO: 151), 5'-GAGCCGTGTATGATGA-3' (SEQ ID NO: 152), 5'-AGAGCCGTGTATGATGA-3' (SEQ ID NO: 153), 5'-GAGAGCCGTGTATGATGA-3' (SEQ ID NO: 154), 5'-GGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 155), 5'-AGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 156), 5'-GAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 157), 5'-AGAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 158), 5'-GAGAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 159); 5'-TGTATGATGA-3' (SEQ ID NO: 160), 5'-GTGTATGATGA-3' (SEQ ID NO: 161), 5'-CGTGTATGATGA-3' (SEQ ID NO: 162), 5'-CCGTGTATGATGA-3' (SEQ ID NO: 163), 5'-GCCGTGTATGATGA-3' (SEQ ID NO: 164), 5'-AGCCGTGTATGATGA-3' (SEQ ID NO: 165), 5'-GAGCCGTGTATGATGA-3' (SEQ ID NO: 166), 5'-AGAGCCGTGTATGATGA-3' (SEQ ID NO: 167), 5'-GAGAGCCGTGTATGATGA-3' (SEQ ID NO: 168), 5'-GGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 169), 5'-AGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 170), 5'-GAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 171), 5'-AGAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 172), 5'-GAGAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 173); 5'-TGTATGATGA-3' (SEQ ID NO: 174), 5'-GTGTATGATGA-3' (SEQ ID NO: 175), 5'-CGTGTATGATGA-3' (SEQ ID NO: 176), 5'-CCGTGTATGATGA-3' (SEQ ID NO: 177), 5'-GCCGTGTATGATGA-3' (SEQ ID NO: 178), 5'-AGCCGTGTATGATGA-3' (SEQ ID NO: 179), 5'-GAGCCGTGTATGATGA-3' (SEQ ID NO: 180), 5'-AGAGCCGTGTATGATGA-3' (SEQ ID NO: 181), 5'-GAGAGCCGTGTATGATGA-3' (SEQ ID NO: 182), 5'-GGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 183), 5'-AGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 184), 5'-GAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 185), 5'-AGAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 186), 5'-GAGAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 187); 5'-TGTATGATGA-3' (SEQ ID NO: 188), 5'-GTGTATGATGA-3' (SEQ ID NO: 189), 5'-CGTGTATGATGA-3' (SEQ ID NO: 190), 5'-CCGTGTATGATGA-3' (SEQ ID NO: 191), 5'-GCCGTGTATGATGA-3' (SEQ ID NO: 192), 5'-AGCCGTGTATGATGA-3' (SEQ ID NO: 193), 5'-GAGCCGTGTATGATGA-3' (SEQ ID NO: 194), 5'-AGAGCCGTGTATGATGA-3' (SEQ ID NO: 195), 5'-GAGAGCCGTGTATGATGA-3' (SEQ ID NO: 196), 5'-GGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 197), 5'-AGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 198), 5'-GAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 199), 5'-AGAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 200), 5'-GAGAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 201); 5'-TGTATGATGA-3' (SEQ ID NO: 202), 5'-GTGTATGATGA-3' (SEQ ID NO: 203), 5'-CGTGTATGATGA-3' (SEQ ID NO: 204), 5'-CCGTGTATGATGA-3' (SEQ ID NO: 205), 5'-GCCGTGTATGATGA-3' (SEQ ID NO: 206), 5'-AGCCGTGTATGATGA-3' (SEQ ID NO: 207), 5'-GAGCCGTGTATGATGA-3' (SEQ ID NO: 208), 5'-AGAGCCGTGTATGATGA-3' (SEQ ID NO: 209), 5'-GAGAGCCGTGTATGATGA-3' (SEQ ID NO: 210), 5'-GGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 211), 5'-AGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 212), 5'-GAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 213), 5'-AGAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 214), 5'-GAGAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 215); 5'-TGTATGATGA-3' (SEQ ID NO: 216), 5'-GTGTATGATGA-3' (SEQ ID NO: 217), 5'-CGTGTATGATGA-3' (SEQ ID NO: 218), 5'-CCGTGTATGATGA-3' (SEQ ID NO: 219), 5'-GCCGTGTATGATGA-3' (SEQ ID NO: 220), 5'-AGCCGTGTATGATGA-3' (SEQ ID NO: 221), 5'-GAGCCGTGTATGATGA-3' (SEQ ID NO: 222), 5'-AGAGCCGTGTATGATGA-3' (SEQ ID NO: 223), 5'-GAGAGCCGTGTATGATGA-3' (SEQ ID NO: 224), 5'-GGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 225), 5'-AGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 226), 5'-GAGGAGAGCCGTGTATGATGA-3' (SEQ ID NO: 227), 5'-AGAGGAGAGCCGT

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).

[0192] 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'-AGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 28) or 5'-AGAGGAGAGCCGTGTATGAC -3' (SEQ ID NO: 88). In some aspects, the miRNA inhibitor comprises a nucleotide sequence that has at least 90% similarity to 5'-AGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 28) or 5'-AGAGGAGAGCCGTGTATGAC -3' (SEQ ID NO: 88). In some aspects, the miRNA inhibitor comprises the nucleotide sequence 5'-AGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 28) or 5'-AGAGGAGAGCCGTGTATGAC -3' (SEQ ID NO: 88) with one substitution or two substitutions. In certain aspects, the miRNA inhibitor comprises the nucleotide sequence 5'-AGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 28) or 5'-AGAGGAGAGCCGTGTATGAC -3' (SEQ ID NO: 88). In certain aspects, the miRNA inhibitor comprises the nucleotide sequence 5'-AGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 28).

[0193] 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).

[0194] 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

[0195] 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."

[0196] 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.

[0197] 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.

[0198] 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.

[0199] 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.

[0200] 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).

[0201] 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.

[0202] 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.

[0203] 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.

[0204] 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

[0205] 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 (m1 ψ), 1-ethyl-pseudouridine (e1 ψ), 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.

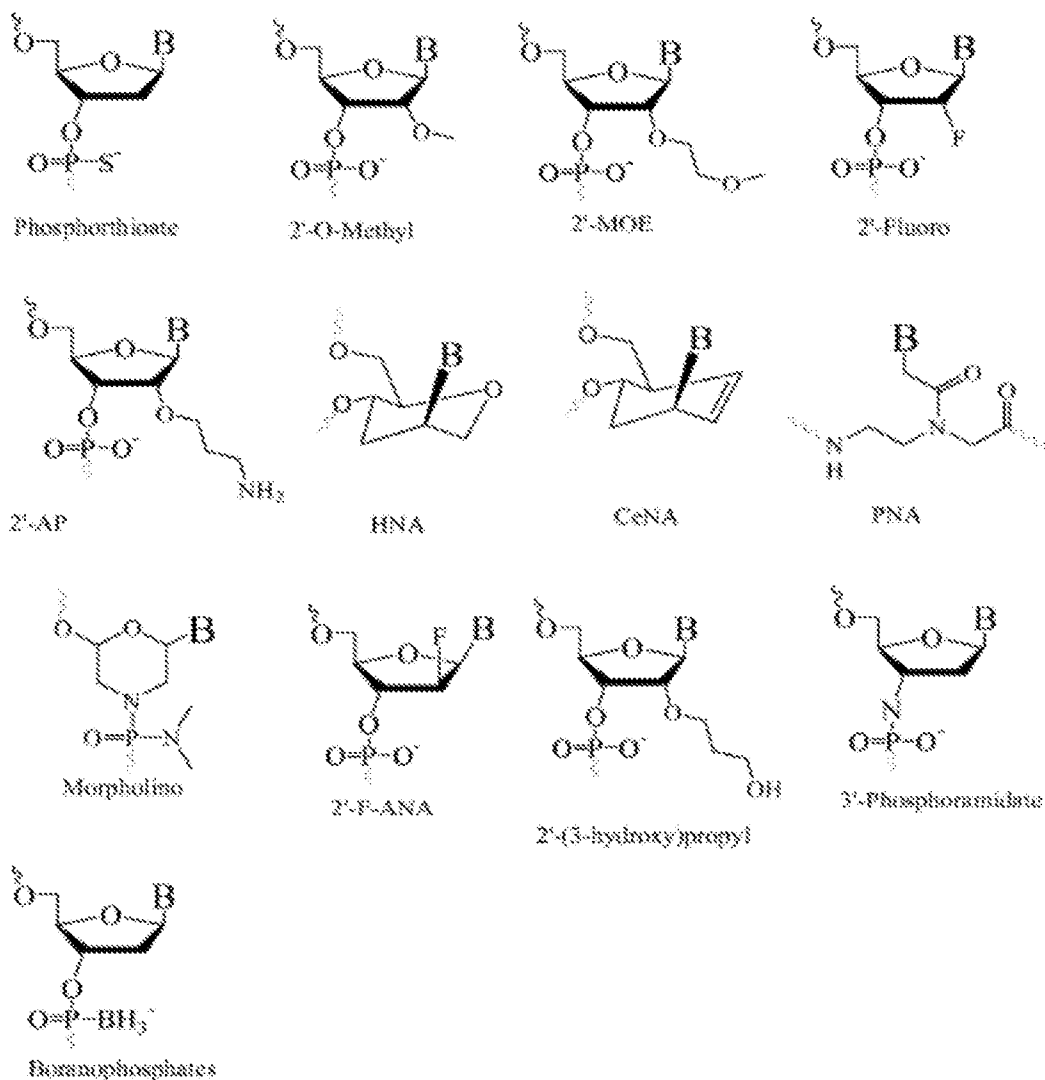
[0206] In some aspects, the polynucleotide of the present disclosure (*e.g.*, a miR-485 inhibitor) is uniformly modified (*e.g.*, fully modified, modified throughout the entire sequence) for a particular modification. For example, a polynucleotide can be uniformly modified with the same type of base 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.

[0207] 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

[0208] 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, $-\text{CH}_2-\text{O}-\text{N}(\text{CH}_3)-\text{CH}_2-$, $-\text{CH}_2-\text{N}(\text{CH}_3)-\text{N}(\text{CH}_3)-\text{CH}_2-$, $-\text{CH}_2-\text{NH}-\text{CH}_2-$, chiral phosphonates, chiral phosphorothioates, formacetyl and thioformacetyl backbones, methylene (methylimino), methylene formacetyl and thioformacetyl backbones, methyleneimino and methylenehydrazino backbones, morpholino linkages, $-\text{N}(\text{CH}_3)-\text{CH}_2-\text{CH}_2-$, 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.



[0209] 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).

[0210] 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).

[0211] 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

[0212] 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.

[0213] 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).

[0214] 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).

[0215] 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 replaced 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.

[0216] 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 C₁₋₆ alkyl; optionally substituted C₁₋₆ alkoxy; optionally substituted C₆₋₁₀ aryloxy; optionally substituted C₃₋₈ cycloalkyl; optionally substituted C₃₋₈ cycloalkoxy; optionally substituted C₆₋₁₀ aryloxy; optionally substituted C₆₋₁₀ aryl-C₁₋₆ alkoxy, optionally substituted C₁₋₁₂ (heterocycl)oxy; a sugar (*e.g.*, ribose, pentose, or any described herein); a polyethyleneglycol (PEG), -O(CH₂CH₂O)_nCH₂CH₂OR, 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 C₁₋₆ alkylene or C₁₋₆ 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.

[0217] 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-thio-LNA or alpha-L-thio-LNA), ENA (such as 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).

[0218] 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.

[0219] 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

[0220] In some aspects, the miR-485 inhibitors of the present disclosure can be administered, *e.g.*, to a subject suffering from a tauopathy 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.

[0221] 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.

[0222] 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).

[0223] 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.

[0224] 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.

[0225] 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.

[0226] In certain aspects, the AAV vector comprises regions of at least two different AAV vectors known in the art.

[0227] 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).

[0228] 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.

[0229] 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.

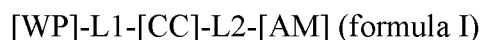
[0230] In some aspects, the AAV vector comprises a constitutively active promoter (constitutive promoter). In some aspects, the constitutive promoter is selected from the group consisting of hypoxanthine phosphoribosyl transferase (HPRT), adenosine deaminase, pyruvate kinase, beta-actin promoter, cytomegalovirus (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.

[0231] 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 AAV vector in a neuron, a glial cell, or in both a neuron and a glial cell.

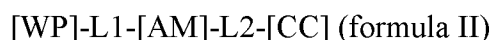
[0232] In some aspects, the AAV vector comprises one or more enhancers. In some aspects, the one or more enhancer are present in the AAV alone or together with a promoter disclosed herein. In some aspects, the AAV vector comprises a 3'UTR poly(A) tail sequence. In some aspects, the 3'UTR poly(A) tail 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).

[0233] 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.

[0234] 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



or



wherein

WP is a water-soluble biopolymer moiety;

CC is a positively charged carrier moiety;

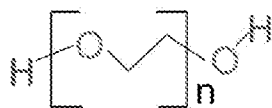
AM is an adjuvant moiety; and,

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.

[0235] 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.

[0236] 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),

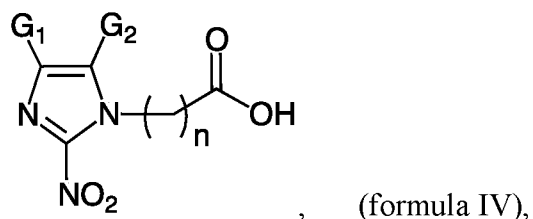
wherein n is 1-1000.

[0237] 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.

[0238] 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 least 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.

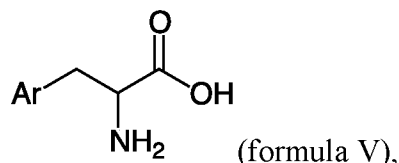
[0239] In some aspects, the adjuvant moiety is capable of modulating an immune response, an inflammatory response, and/or a tissue microenvironment. In some aspects, the adjuvant moiety comprises an imidazole derivative, an amino acid, a vitamin, or any combination thereof. In some aspects, the adjuvant moiety comprises:



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.

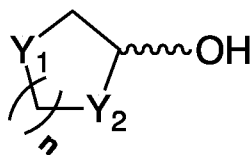
[0240] In some aspects, the adjuvant moiety comprises nitroimidazole. In some aspects, the adjuvant moiety comprises metronidazole, tinidazole, nimorazole, dimetridazole, pretomanid, ornidazole, megazol, azanidazole, benznidazole, or any combination thereof. In some aspects, the adjuvant moiety comprises an amino acid.

[0241] In some aspects, the adjuvant moiety comprises



wherein Ar is or , and
wherein each of Z1 and Z2 is H or OH.

[0242] 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.

[0243] 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.

[0244] 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.

[0245] 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.

[0246] 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 soluble polymer. In some aspects, the thiol groups in the composition form disulfide bonds.

[0247] 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.

[0248] 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.

[0249] 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.

[0250] 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

[0251] 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.

[0252] 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

[0253] 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.

[0254] The following examples are offered by way of illustration and not by way of limitation.

Examples

Example 1: Preparation of miR-485 Inhibitor

[0255] **(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. 9) of a cationic carrier unit to direct micelles of the present disclosure to the LAT1 transporter in the BBB.

[0256] A mixture of N-(tert-butoxycarbonyl)-L-tyrosine methyl ester (Boc-Tyr-OMe) (0.5g, 1.69 mmol) and K₂CO₃ (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.

[0257] **(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. 9).

[0258] 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.

[0259] 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.

[0260] **(b) Synthesis of azido-poly(ethylene glycol)-*b*-poly(L-lysine) (N₃-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. 9).

[0261] Azido-poly(ethylene glycol)-*b*-poly(L-lysine) was synthesized by ring opening polymerization of Lys(TFA)-NCA with azido- PEG (N₃-PEG). In brief, N₃-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 N₃-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.

[0262] N₃-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 N₃-PEG-PLL was obtained after lyophilization.

[0263] **(c) Synthesis of (methoxy or) azido-poly(ethylene glycol)-b-poly(L-lysine/nicotinamide/mercaptopropanamide) (N₃-PEG-PLL(Nic/SH)):** In this step, the tissue-specific adjuvant moieties (AM, see FIG. 9) 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. 9.

[0264] Azido-poly(ethylene glycol)-b-poly(L-lysine/nicotinamide/mercaptopropanamide) (N₃-PEG-PLL(Nic/SH)) was synthesized by chemical modification of N₃-PEG-PLL and nicotinic acid in the presence of EDC/NHS. N₃-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 NH₂ of N₃-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.

[0265] The reaction mixture was added into the N₃-PEG-PLL solution. The reaction mixture was maintained at 37 °C for 16 hours with stirring. After 16 hours, 3,3'-dithiodipropionic 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'-dithiodipropionic acid solution. The mixture solution was stirred for 4 hours at 37 °C after adding crude N₃-PEG-PLL(Nic) solution.

[0266] 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.

[0267] For removing the DTT, the mixture was dialyzed sequentially methanol, 50 % methanol in deionized water, deionized water.

[0268] **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).

[0269] To target brain endothelial tissue in blood vessels, as a LAT1 targeting amino acid, phenyl alanine was introduced by click reaction between N₃-PEG-PLL(Nic/SH) and alkyne modified tyrosine in the presence of copper catalyst. In brief, N₃-PEG-PLL(Nic/SH) (130 mg, 6.5 μ mol) 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 in deionized water and added to the N₃-PEG-PLL(Nic/SH) solution. Then, sodium ascorbate (3.2 mg, 2.5 equiv.) was 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.

[0270] (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.

[0271] 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 μ M) 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.

[0272] 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.

[0273] Micelles (10 μ M 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: Truncated Tau Expression

[0274] It is known that truncated tau proteins can cause severe neurotoxicity. Ozcelik S., et al., Molecular Psychiatry, 21, 1798 (2016). In order to test the effect of the miR-485

inhibitors disclosed herein, 10-month old 5XFAD mice were used. Briefly, the mice received two administrations (once per week) of the miR-485 inhibitor (AGAGAGGAGAGCCGUGUAUGAC (SEQ ID NO: 30)) or a control oligonucleotide (CTTCCCTGAAGGTTCTCCTT (SEQ ID NO: 61)) via intracerebroventricular (ICV) injection. Then, the animals were sacrificed at day 8 post-final miR-485 inhibitor administration and the expression level of truncated tau protein was measured in the mice. FIG. 1 shows that the miR-485 inhibitor can significantly (e.g., nearly ten fold) reduce the truncated tau protein expression. The reduced truncated Tau expression was observed in various regions of the brain – *i.e.*, hippocampus (*see* FIGs. 7A and 7B), frontal cortex (*see* FIGs. 7C and 7D), and cerebral cortex (*see* FIGs. 7E and 7F). At least *in vitro*, the effect on truncated tau appeared to be dose dependent (*see* FIG. 8). These data suggest that the miR-485 inhibitor can treat tauopathy and the neurotoxicity caused by truncated tau proteins.

Example 2: Analysis of the safety profile of miR-485 inhibitors

[0275] 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.

[0276] As shown in FIGs. 3A and 3B, 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. 4A, 4B, 6A, and 6B). 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. 5A and 5B).

[0277] The above results demonstrate that the miR-485 inhibitors disclosed herein not only have therapeutic effects in treating tauopathies, but are also safe when administered *in vivo*.

Example 3: Analysis of the Therapeutic Effects of miR-485 Inhibitor after Intravenous Administration

[0278] To further assess the therapeutic effects of the miR-485 inhibitors disclosed herein on primary tauopathy, 3xTG mice (which have primary tauopathy) will receive an intravenous

administration (*e.g.*, tail vein injection) of either PBS or a miR-485 inhibitor. The miR-485 inhibitor will be administered to the animals at varying doses and/or dosing intervals. The therapeutic effects of the miR-485 inhibitor on the 3xTG mice will be assessed by observing motor function (*e.g.*, Y-maze and passive avoidance tests) and the expression of truncated tau protein in different regions of the brain tissue.

[0279] 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.

[0280] 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.

[0281] 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.

[0282] 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.

[0283] 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 a tauopathy 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 a tauopathy associated with a decreased level of a SIRT1 protein and/or a SIRT1 gene.
4. The method of any one of claims 1 to 3, 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 a tauopathy 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-1 α protein and/or a PGC-1 α gene in the subject.
8. The method of any one of claims 1 to 7, wherein the subject has a tauopathy associated with a decreased level of a PGC-1 α protein and/or a PGC-1 α gene.
9. The method of any one of claims 1 to 8, wherein the miRNA inhibitor induces neurogenesis.
10. The method of claim 9, wherein inducing neurogenesis comprises an increased proliferation, differentiation, migration, and/or survival of neural stem cells and/or progenitor cells.

11. The method of claim 9 or 10, wherein inducing neurogenesis comprises an increased number of neural stem cells and/or progenitor cells.
12. The method of any one of claims 9 to 11, wherein inducing neurogenesis comprises an increased axon, dendrite, and/or synapse development.
13. The method of any one of claims 1 to 12, wherein the miRNA inhibitor induces phagocytosis.
14. A method of treating a tauopathy 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.
15. A method of treating a tauopathy 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.
16. A method of treating a tauopathy associated with an abnormal level of a PGC-1 α protein and/or a PGC-1 α 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-1 α protein and/or PGC-1 α gene.
17. The method of any one of claims 1 to 16, wherein the miRNA inhibitor inhibits miR485-3p.
18. The method of claim 17, wherein the miR485-3p comprises 5'-gucauacacggcucuccucucu-3' (SEQ ID NO: 1).
19. The method of any one of claims 1 to 18, 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.

20. The method of any one of claims 1 to 19, wherein the miRNA inhibitor increases transcription of an SIRT1, PGC-1 α , and/or CD36 gene and/or expression of a SIRT1, PGC-1 α , and/or CD36 protein.
21. The method of any one of claims 1 to 20, 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.
22. The method of any one of claims 1 to 21, 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.
23. The method of any one of claims 1 to 17 and 20 to 22, 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).

24. The method of any one of claims 1 to 17 and 20 to 22, 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).

25. The method of any one of claims 1 to 23, 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).

26. The method of claim 24, 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).

27. The method of any one of claims 1 to 25, 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.
28. The method of any one of claims 1 to 26, wherein the miRNA inhibitor comprises the nucleotide sequence 5'- AGAGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 30) or 5'- AGAGAGGAGAGCCGTGTATGAC -3' (SEQ ID NO: 90).
29. The method of claim 28, wherein the miRNA inhibitor comprises the nucleotide sequence 5'- AGAGAGGAGAGCCGUGUAUGAC -3' (SEQ ID NO: 30).
30. The method of any one of claims 1 to 27, wherein the miRNA inhibitor comprises at least one modified nucleotide.
31. The method of claim 30, 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).
32. The method of any one of claims 1 to 31, wherein the miRNA inhibitor comprises a backbone modification.
33. The method of claim 32, wherein the backbone modification is a phosphorodiamidate morpholino oligomer (PMO) and/or phosphorothioate (PS) modification.
34. The method of any one of claims 1 to 33, wherein the miRNA inhibitor is delivered in a delivery agent.
35. The method of claim 34, wherein the delivery agent is a micelle, an exosome, a lipid nanoparticle, an extracellular vesicle, or a synthetic vesicle.

36. The method of any one of claims 1 to 35, wherein the miRNA inhibitor is delivered by a viral vector.
37. The method of claim 36, wherein the viral vector is an AAV, an adenovirus, a retrovirus, or a lentivirus.
38. The method of claim 37, 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.
39. The method of any one claims 1 to 38, wherein the miRNA inhibitor is delivered with a delivery agent.
40. The method of claim 39, 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.
41. The method of claim 39 or 40, 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

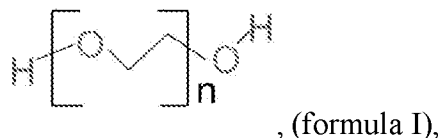
wherein when mixed with a nucleic acid at an ionic ratio of about 1:1, the cationic carrier unit forms a micelle.

42. The method of claim 41, wherein the miRNA inhibitor interacts with the cationic carrier unit via an ionic bond.

43. The method of claims 41 or 42, 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.

44. The method of claims 41 to 43, wherein the water-soluble polymer comprises polyethylene glycol ("PEG"), polyglycerol, or poly(propylene glycol) ("PPG").

45. The method of any one of claims 41 to 44, wherein the water-soluble polymer comprises:



wherein n is 1-1000.

46. The method of claim 45, 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.

47. The method of claim 45, 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.

48. The method of any one of claims 41 to 47, wherein the water-soluble polymer is linear, branched, or dendritic.

49. The method of any one of claims 41 to 48, wherein the cationic carrier moiety comprises one or more basic amino acids.

50. The method of claim 49, 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.

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

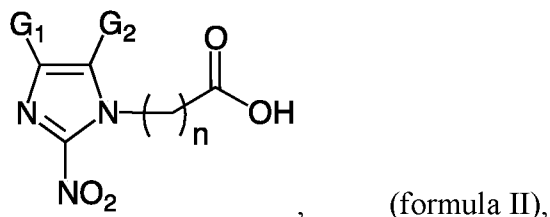
52. The method of claim 50 or 51, wherein the basic amino acid comprises arginine, lysine, histidine, or any combination thereof.

53. The method of any one of claims 41 to 52, wherein the cationic carrier moiety comprises about 40 lysine monomers.

54. The method of any one of claims 41 to 53, wherein the adjuvant moiety is capable of modulating an immune response, an inflammatory response, and/or a tissue microenvironment.

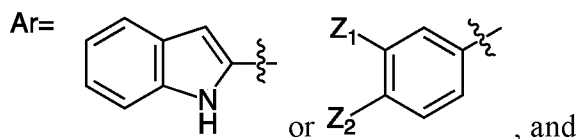
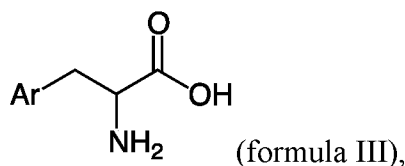
55. The method of any one of claims 41 to 54, wherein the adjuvant moiety comprises an imidazole derivative, an amino acid, a vitamin, or any combination thereof.

56. The composition of claim 55, wherein the adjuvant moiety comprises:



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.

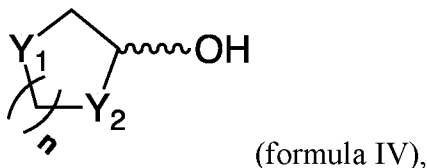
57. The method of claim 55, wherein the adjuvant moiety comprises nitroimidazole.
58. The method of claim 55, wherein the adjuvant moiety comprises metronidazole, tinidazole, nimorazole, dimetridazole, pretomanid, ornidazole, megazol, azanidazole, benznidazole, or any combination thereof.
59. The method of any one of claims 41 to 55, wherein the adjuvant moiety comprises an amino acid.
60. The method of claim 59, wherein the adjuvant moiety comprises



wherein Ar is

wherein each of Z1 and Z2 is H or OH.

61. The method of any one of claims 41 to 54, wherein the adjuvant moiety comprises a vitamin.
62. The method of claim 61, wherein the vitamin comprises a cyclic ring or cyclic hetero atom ring and a carboxyl group or hydroxyl group.
63. The method of claim 61 or 62, wherein the vitamin comprises:



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

64. The method of any one of claims 61 to 63, 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.

65. The method of any one of claims 61 to 64, wherein the vitamin is vitamin B3.

66. The method of any one of claims 61 to 65, 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.

67. The method of claim 66, wherein the adjuvant moiety comprises about 10 vitamin B3.

68. The method of any one of claims 61 to 67, 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.

69. The method of any one of claims 61 to 68, wherein the delivery agent is associated with the miRNA inhibitor, thereby forming a micelle.

70. The method of claim 69, wherein the association is a covalent bond, a non-covalent bond, or an ionic bond.

71. The method of claim 69 or 70, 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.

72. The method of any one of claims 69 to 71, wherein the cationic carrier unit is capable of protecting the miRNA inhibitor from enzymatic degradation.

73. The method of any one of claims 1 to 72, wherein the tauopathy comprises Frontotemporal dementia (FTD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD),

corticobasal ganglionic degeneration, dementia pugilistica, Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), Lytico-Bodig disease, tangle-predominant dementia, ganglioglioma, gangliocytoma, meningioangiomas, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, Pick's disease, argyrophilic grain disease, corticobasal degeneration, frontotemporal lobar degeneration, or any combination thereof.

74. The method of any one of claims 1 to 73, wherein the miRNA inhibitor delays tauopathy onset.

75. The method of claim 39, wherein the delivery agent is a micelle.

76. The method of claim 75, 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.

77. The method of claim 76, 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.

78. The method of claim 76 or 77, wherein a targeting moiety is further linked to the PEG units.

79. The method of claim 78, wherein the targeting moiety is a LAT 1 targeting ligand.

80. The method of claim 79, wherein the targeting moiety is penntyl alanine.

FIG. 1

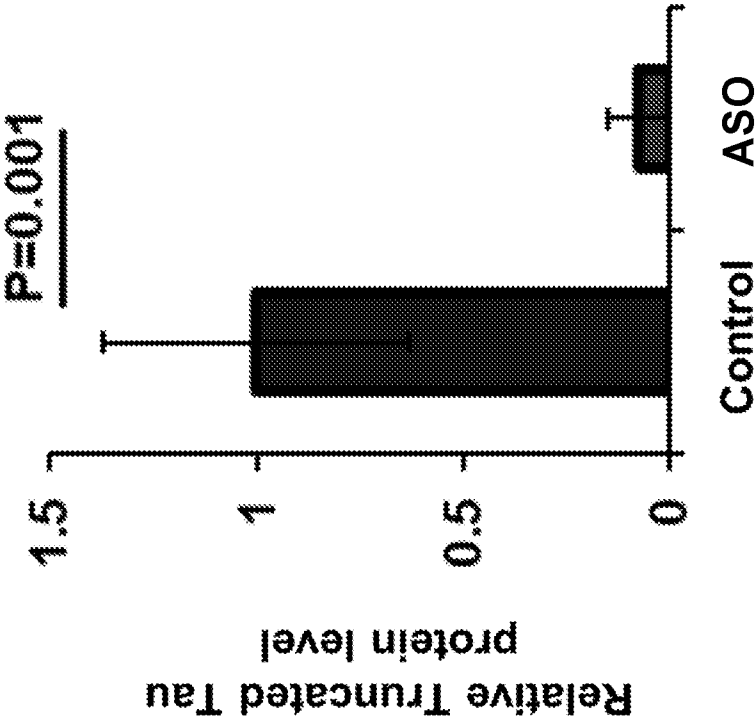


FIG. 2

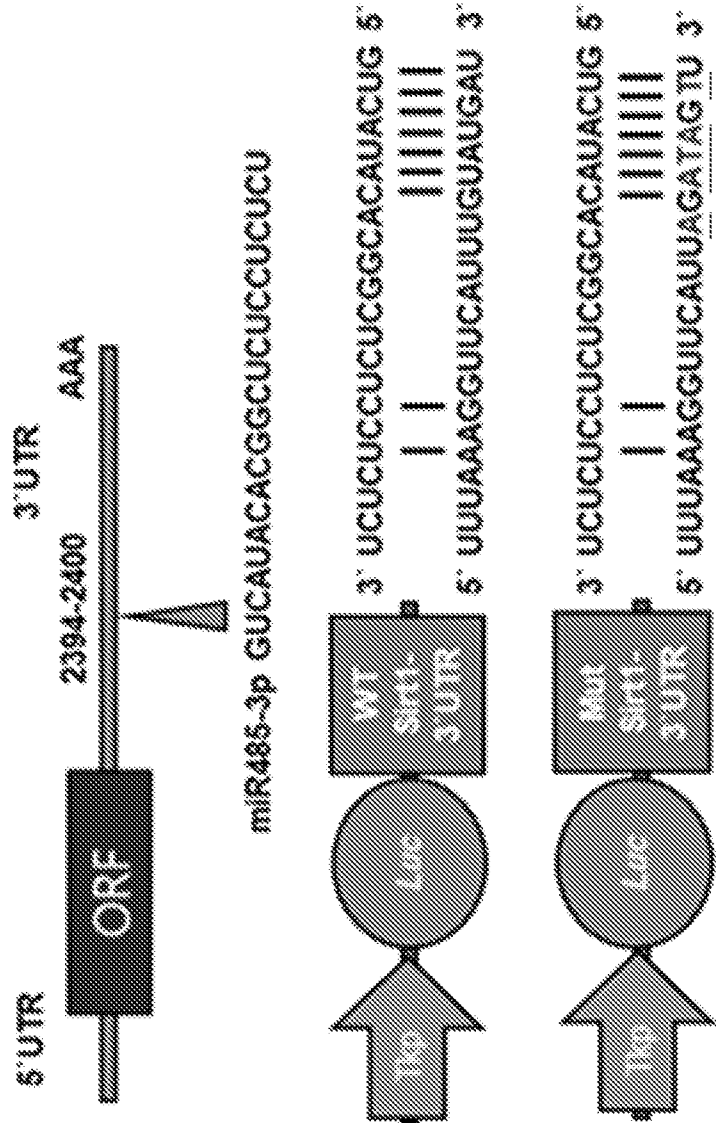
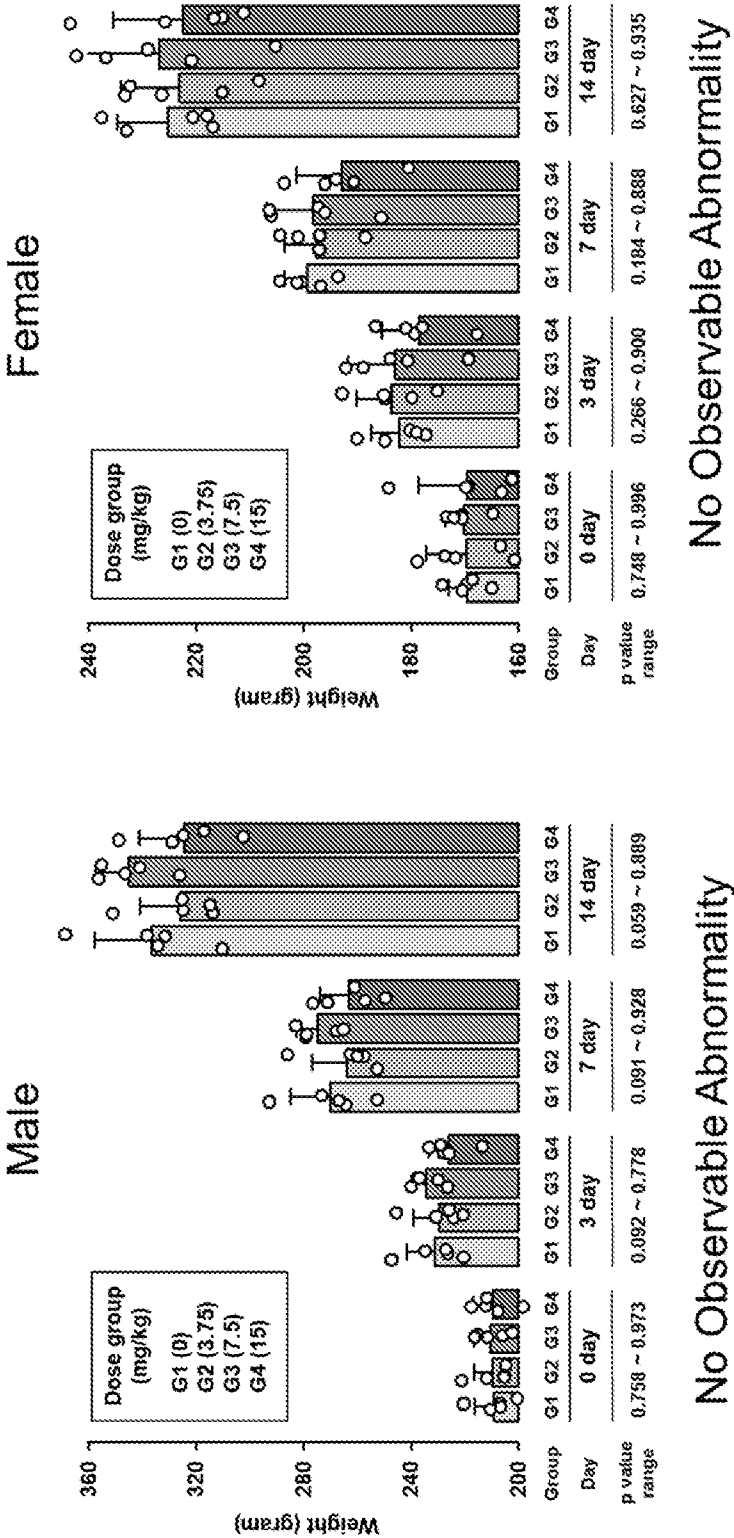


FIG. 3A



[illegible][illegible]

FIG. 5B

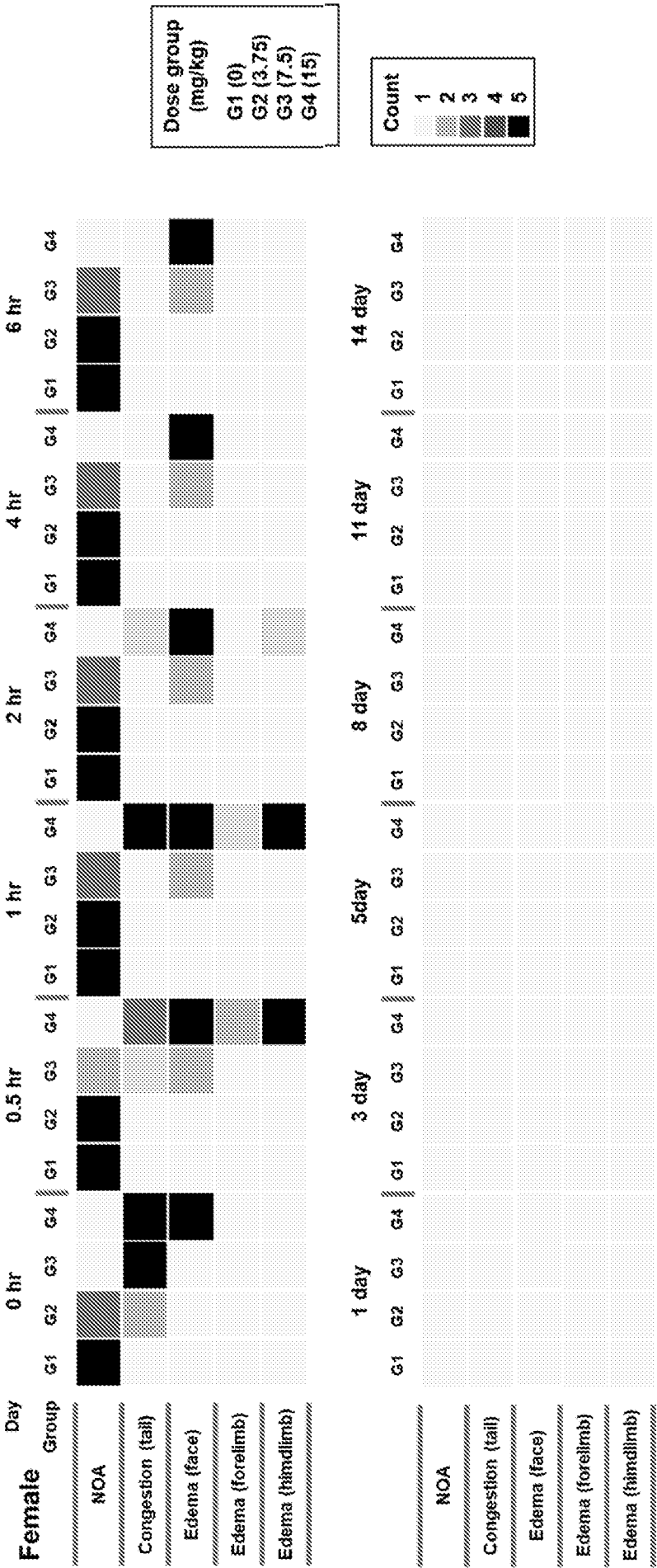


FIG. 6A

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. 6B

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. 7A

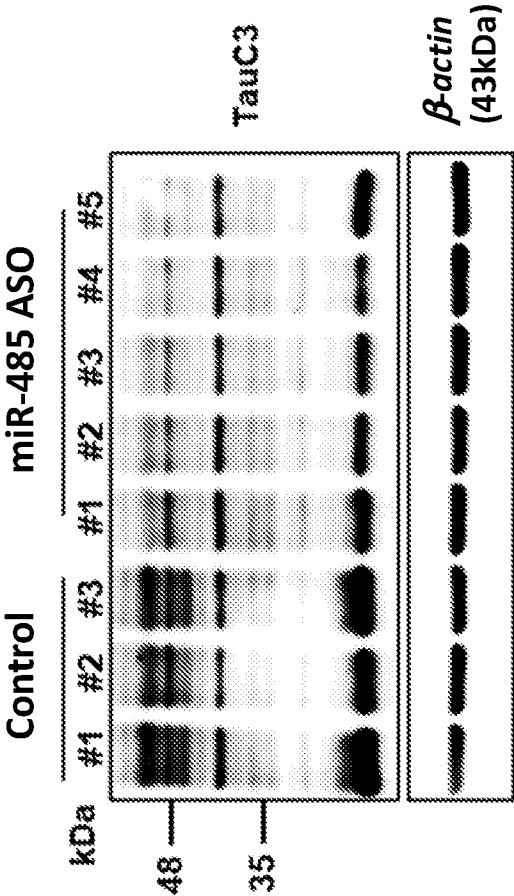


FIG. 7B

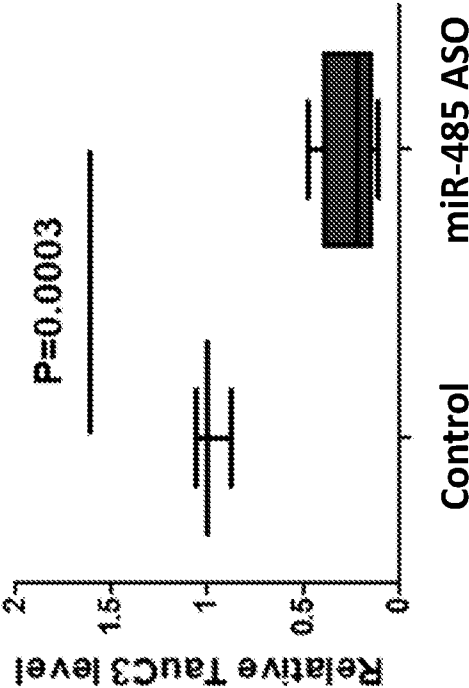


FIG. 7D

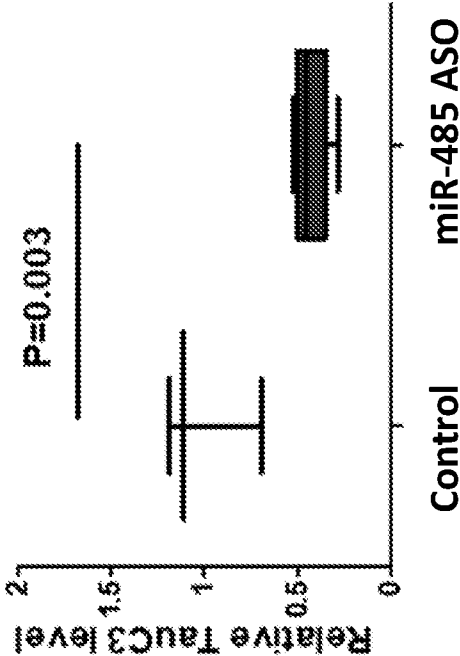


FIG. 7C

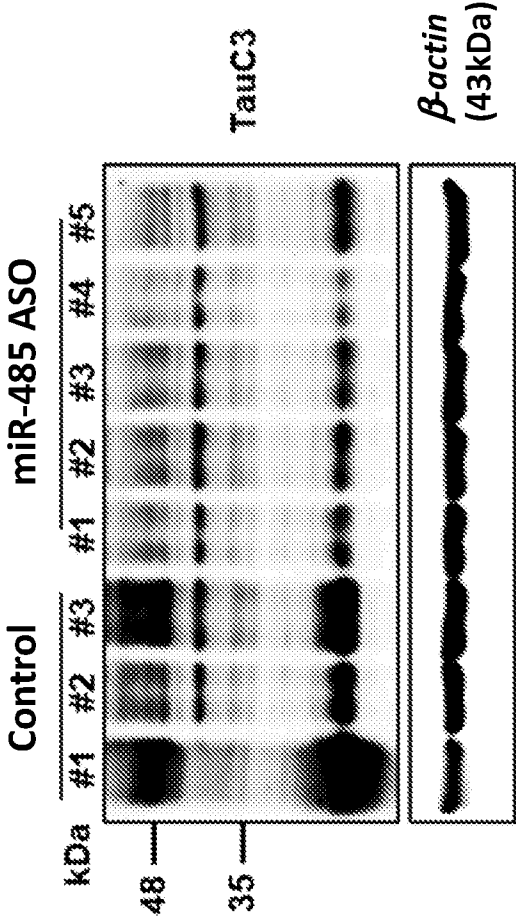


FIG. 7F

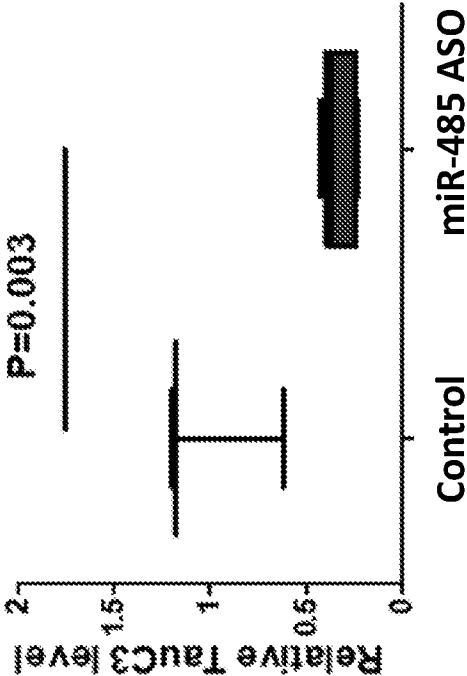


FIG. 7E

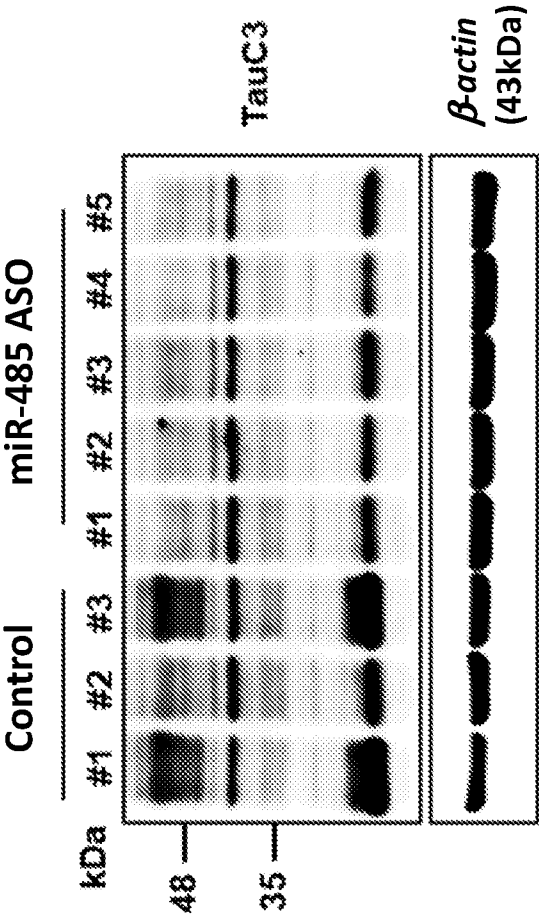


FIG. 8

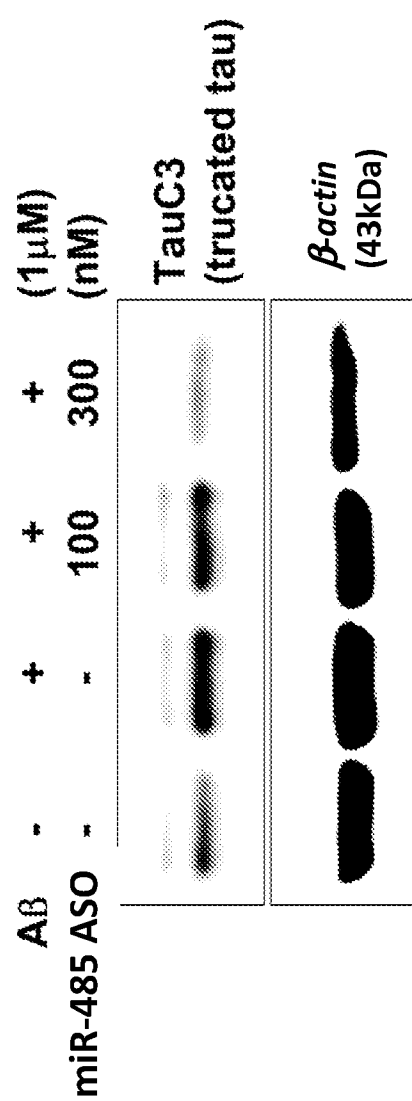
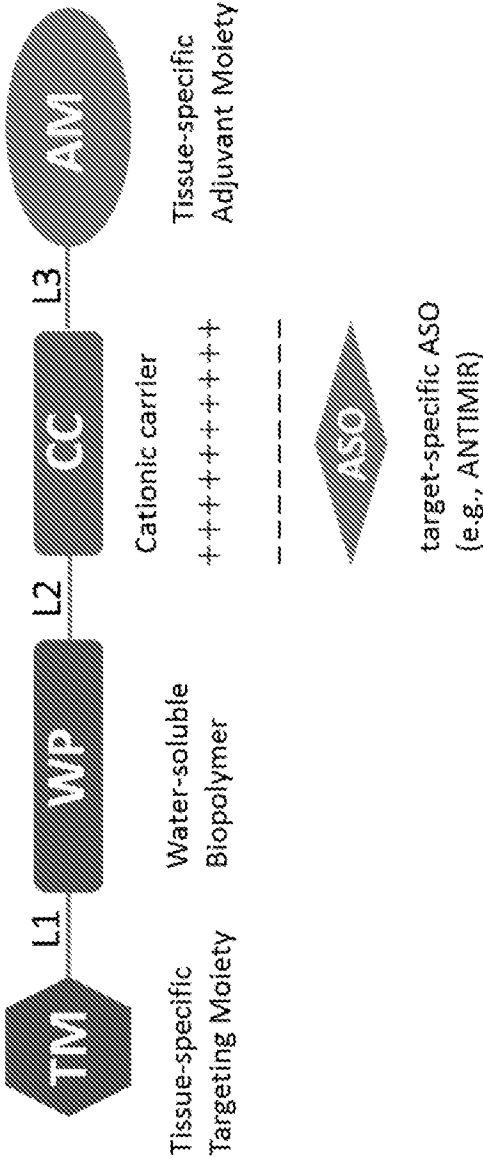


FIG. 9

Cationic Carrier Unit

L1, L2, L3 -- Optional Linker moieties (each moiety can comprise one or more linkers, which can be the same of different)



Anionic Payload

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 Arg Gly Cys Pro Gly Ala Ala Ala Ala Ala Leu Trp Arg Glu Ala Glu
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 580 585 590

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Arg Gly Cys Pro Gly Ala Ala Ala Ala Ala Leu Trp Arg Glu Ala Glu
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Asn Thr Ile	Glu Asp Ala	Val Lys Leu	Leu Gln Glu	Cys Lys Lys	Ile	
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Ile Val Leu	Thr Gly Ala	Gly Val Ser	Val Ser Cys	Gly Ile Pro	Asp	
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Asp Glu Pro	Leu Ala Ile	Met Lys Pro	Glu Ile Val	Phe Phe Gly	Glu	
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Asn Leu Pro	Glu Gln Phe	His Arg Ala	Met Lys Tyr	Asp Lys Asp	Glu	
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Ala Leu Ile Pro Ser Asn Gln Tyr Leu Phe Leu Pro Pro Asn Arg Tyr
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Ala Val Leu Ala Val Phe Gly Gly Ile Leu Met Pro Val Gly Asp Leu
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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

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		
			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		
			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		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		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		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

<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

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<220>
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<400> 49
ucauaca 7

<210> 50
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<220>
<223> oligonucleotide

<400> 50
gaggcug 7

<210> 51
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
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<400> 51
cgaggtcgac ttcctaga 18

<210> 52
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<400> 52
catacacggc ttcctctct aaa 23

<210> 53
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tcctgtggca tccatgaaac	20
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caatgcctgg gtacatggtg	20
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ccaagtggag gagcagct	18
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gacaaggtac aacccatcgg	20
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ttcgacacat gggataacga gg	22
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ttttgctgt gagtcccgga g	21
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	cagcctagca gcacgtaaat	20
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	gaatcgagca ccagttacg	19
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	ccttcctga aggttcctcc tt	22
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	tgtatga	7
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	gtgtatga	8
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	cgtgtatga	9
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ccgtgtatga	10
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gccgtgtatg a	11
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agccgtgtat ga	12
<210> 68	
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<400> 68	
gagccgtgta tga	13
<210> 69	
<211> 14	
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<223> oligonucleotide	
<400> 69	
agagccgtgt atga	14
<210> 70	
<211> 15	
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<400> 70	
gagagccgtg tatga	15

<210> 71
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<220>
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<400> 71
ggagagccgt gtatga

16

<210> 72
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<212> DNA
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<220>
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<400> 72
aggagagccg tgtatga

17

<210> 73
<211> 18
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<220>
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gaggagagcc gtgtatga

18

<210> 74
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<220>
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agaggagagc cgtgtatga

19

<210> 75
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<220>
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<400> 75
gagaggagag ccgtgtatga

20

<210> 76
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<220>
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<210> 82 <211> 14 <212> DNA <213> artificial Sequence	

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	gagccgtgta tgac	14
<210>	83	
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<400>	83	
	agagccgtgt atgac	15
<210>	84	
<211>	16	
<212>	DNA	
<213>	artificial Sequence	
<220>		
<223>	oligonucleotide	
<400>	84	
	gagagccgtg tatgac	16
<210>	85	
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<400>	85	
	ggagagccgt gtatgac	17
<210>	86	
<211>	18	
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<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
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<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
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 225	Gly	Val	Cys	Leu	Asn 230	Gly	Gly	Val	Cys	Ser 235	Val	Val	Asp	Asp	Gln 240
Ala	Val	Cys	Asp	Cys 245	Ser	Arg	Thr	Gly	Phe 250	Arg	Gly	Lys	Asp	Cys 255	Ser
Gln	Glu	Asp	Asn 260	Asn	Val	Glu	Gly	Leu 265	Ala	His	Leu	Met	Met 270	Gly	Asp
Gln	Gly	Lys 275	Ser	Lys	Gly	Lys	Glu 280	Glu	Tyr	Ile	Ala	Thr 285	Phe	Lys	Gly
Ser	Glu 290	Tyr	Phe	Cys	Tyr	Asp 295	Leu	Ser	Gln	Asn	Pro 300	Ile	Gln	Ser	Ser
Ser 305	Asp	Glu	Ile	Thr	Leu 310	Ser	Phe	Lys	Thr	Leu 315	Gln	Arg	Asn	Gly	Leu 320
Met	Leu	His	Thr	Gly 325	Lys	Ser	Ala	Asp	Tyr 330	Val	Asn	Leu	Ala	Leu 335	Lys
Asn	Gly	Ala	Val 340	Ser	Leu	Val	Ile	Asn 345	Leu	Gly	Ser	Gly	Ala 350	Phe	Glu
Ala	Leu	Val 355	Glu	Pro	Val	Asn	Gly 360	Lys	Phe	Asn	Asp	Asn 365	Ala	Trp	His
Asp	Val 370	Lys	Val	Thr	Arg	Asn 375	Leu	Arg	Gln	His	Ser 380	Gly	Ile	Gly	His
Ala 385	Met	Val	Thr	Ile	Ser 390	Val	Asp	Gly	Ile	Leu 395	Thr	Thr	Thr	Gly	Tyr 400
Thr	Gln	Glu	Asp	Tyr 405	Thr	Met	Leu	Gly	Ser 410	Asp	Asp	Phe	Phe	Tyr 415	Val
Gly	Gly	Ser	Pro 420	Ser	Thr	Ala	Asp	Leu 425	Pro	Gly	Ser	Pro	Val 430	Ser	Asn
Asn	Phe	Met 435	Gly	Cys	Leu	Lys	Glu 440	Val	Val	Tyr	Lys	Asn 445	Asn	Asp	Val
Arg	Leu 450	Glu	Leu	Ser	Arg	Leu 455	Ala	Lys	Gln	Gly	Asp 460	Pro	Lys	Met	Lys
Ile 465	His	Gly	Val	Val	Ala 470	Phe	Lys	Cys	Glu	Asn 475	Val	Ala	Thr	Leu	Asp 480
Pro	Ile	Thr	Phe	Glu 485	Thr	Pro	Glu	Ser	Phe 490	Ile	Ser	Leu	Pro	Lys 495	Trp

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

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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
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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				
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Asn Lys Asp Lys Glu Tyr Tyr Val				
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	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
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
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
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			

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 1940						Leu Val Met Glu Leu 1945						Ala Ser Lys Gly 1950					
Ser Leu Asp Arg Leu Leu 1955						Gln Gln Asp Lys Ala 1960						Ser Leu Thr Arg 1965					
Thr Leu Gln His Arg Ile 1970						Ala Leu His Val Ala 1975						Asp Gly Leu Arg 1980					
Tyr Leu His Ser Ala Met 1985						Ile Ile Tyr Arg Asp 1990						Leu Lys Pro His 1995					
Asn Val Leu Leu Phe Thr 2000						Leu Tyr Pro Asn Ala 2005						Ala Ile Ile Ala 2010					
Lys Ile Ala Asp Tyr Gly 2015						Ile Ala Gln Tyr Cys 2020						Cys Arg Met Gly 2025					
Ile Lys Thr Ser Glu Gly 2030						Thr Pro Gly Phe Arg 2035						Ala Pro Glu Val 2040					
Ala Arg Gly Asn Val Ile 2045						Tyr Asn Gln Gln Ala 2050						Asp Val Tyr Ser 2055					
Phe Gly Leu Leu Leu Tyr 2060						Asp Ile Leu Thr Thr 2065						Gly Gly Arg Ile 2070					
Val Glu Gly Leu Lys Phe 2075						Pro Asn Glu Phe Asp 2080						Glu Leu Glu Ile 2085					
Gln Gly Lys Leu Pro Asp 2090						Pro Val Lys Glu Tyr 2095						Gly Cys Ala Pro 2100					
Trp Pro Met Val Glu Lys 2105						Leu Ile Lys Gln Cys 2110						Leu Lys Glu Asn 2115					
Pro Gln Glu Arg Pro Thr 2120						Ser Ala Gln Val Phe 2125						Asp Ile Leu Asn 2130					
Ser Ala Glu Leu Val Cys 2135						Leu Thr Arg Arg Ile 2140						Leu Leu Pro Lys 2145					
Asn Val Ile Val Glu Cys 2150						Met Val Ala Thr His 2155						His Asn Ser Arg 2160					
Asn Ala Ser Ile Trp Leu 2165						Gly Cys Gly His Thr 2170						Asp Arg Gly Gln 2175					
Leu Ser Phe Leu Asp Leu 2180						Asn Thr Glu Gly Tyr 2185						Thr Ser Glu Glu 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 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 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

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

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
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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
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Gly Gln Phe Arg Val Val Lys Glu Pro Leu Gly Phe Val Lys Val Leu
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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

<400> 120

Ala Leu Ala Thr Tyr Ile Phe Leu Gln Asn Lys Tyr Arg Glu Asn Asn
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Lys Gly Pro Met Leu Asp Phe Leu Ala Thr Ala Val Phe Ala Phe Met
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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
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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
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<210> 122
<211> 8873
<212> DNA
<213> artificial Sequence

<220>
<223> pLenti-III-mir-GFP vector

<400> 122
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