

CLAIMS

1. A fusion protein comprising a zinc finger protein (ZFP) domain and a transcription repressor domain, wherein the ZFP domain binds to a target region of a human alpha-synuclein gene (*SNCA* gene), wherein the target region is any one of SEQ ID NO. 17-36 and the fusion protein is capable of repressing *SNCA* gene expression.
2. The fusion protein of claim 1, wherein the ZFP domain comprises six zinc fingers and the fusion protein optionally represses expression of the *SNCA* gene by at least 40%, 75%, 90%, 95%, or 99% with no or minimal detectable off-target binding or activity.
3. The fusion protein of claim 1 or claim 2, wherein the transcription repressor domain comprises a KRAB domain amino acid sequence from human KOX1.
4. The fusion protein of any one of the preceding claims, wherein the ZFP domain is linked to the transcription repressor through a peptide linker.
5. A fusion protein comprising a zinc finger protein (ZFP) domain and a transcription repression domain, wherein the ZFP domain binds to a target region in a human alpha-synuclein gene (*SNCA* gene), wherein the ZFP domain comprises a DNA-binding recognition helix sequence shown in the Table below, wherein the sequences identification numbers are shown in the parentheses:

F1	F2	F3	F4	F5	F6
QSGHLAR (37)	QRKDLTQ (61)	RSDHLSR (47)	TRDGLRQ (97)	RSANLAR (110)	DSSDRKK (120)
RSDNLST (38)	RSDNLTR (62)	DRSDLSR (64)	RREHLRA (98)	TSGNLTR (111)	QRSHLSD (121)

F1	F2	F3	F4	F5	F6
ERGTLLAR (39)	MACCRYA (63)	RSADLTR (80)	QSGDLTR (99)	QSGNLAR (85)	RQEHRVA (122)
RSAHLRSR (40)	DRSDLSR (64)	MSCCRSA (81)	RSADLSR (100)	QSGDLTR (99)	QRSNLNI (123)
RSDNLSV (41)	ASWTLTQ (65)	DRSDLSR (64)	DRSNLTR (75)	DRSHLTR (45)	DRSNLTR (75)
LRHHLTR (42)	VAEYRYK (66)	RSDNLSV (41)	RHSHLTS (101)	RSDTLA (112)	RSADLSR (100)
RSDNLST (38)	QSGHLSR (67)	DAHHLHR (82)	RSANLTR (102)	DRSNRTT (113)	HRSSLRR (124)
RSDDLTR (43)	QKFPRDS (68)	RSDHLTQ (83)	DSANLSR (103)	DRSNLSR (44)	DRTSLKW (125)
DRSNLSR (44)	HLCCLGR (69)	RSCCLHL (84)	RNASRTR (104)	QSSDLSR (51)	HRKSLSR (126)
DRSNLSR (44)	DRSHLAR (70)	RSDHLSE (54)	TSSDRTK (105)	DRSHLSR (114)	DRSHLAR (70)
DRSHLTR (45)	DRSHLAR (70)	QSGNLAR (85)	AKWNLDA (106)	QSGDLTR (99)	TQGYLRK (127)
TSGSLSR (46)	QAGHLAK (71)	DRSARTR (86)	QSGHLSR (67)	RSAHLRSR (40)	QSSDLRR (128)
RSDHLRSR (47)	QHAHRNT (72)	RPDTLRD (87)	QNATRTK (107)	RSDALS (115)	DRSALAR (76)
NNRDLIN (48)	TSSNLSR (73)	RSDTLSE (88)	NNRDRTK (108)	QSSDLSR (51)	HRSTRNR (129)
QNAHRKT (49)	DNSTRIK (74)	DRSNLSR (44)	HLCCLGR (69)	DRSNLSR (44)	TSANLSR (130)
QRNHRTT (50)	DRSNLTR (75)	MSCCRSA (81)	RSADLSR (100)	RSAHLRSR (40)	TSANLSR (130)
QSSDLSR (51)	DRSALAR (76)	DRSYRNT (89)	RRSDLKR (109)	RSADLTR (80)	DRSALAR (76)
DSSTRKT (52)	QSATRTK (77)	ERGTLLAR (39)	QSGDLTR (99)	QSSDLSR (51)	AASNRSK (131)
RSDNLSQ (53)	ASNDRKK (78)	YDYGRYT (90)	DRSHLAR (70)	QSGNLAR (85)	DRSALAR (76)
RSDHLSE (54)	QSNHRKT (79)	VYEGLKK (91)	QSGHLSR (67)	RSDVLSE (116)	DRSNRIK (132)
^QNAHRK T (55)	DNSTRIK (74)	DRSNLSR (44)	HLCCLGR (69)	DRSNLSR (44)	TSANLSR (130)
^QNAHRK T (55)	DNSTRIK (74)	^DRSNLS R (92)	HLCCLGR (69)	DRSNLSR (44)	TSANLSR (130)
^QNAHRK T (55)	DNSTRIK (74)	^DRSNLS R (92)	HLCCLGR (69)	^DRSNLS R (92)	TSANLSR (130)
^QRNHRT T (56)	DRSNLTR (75)	MSCCRSA (81)	RSADLSR (100)	RSAHLRSR (40)	TSANLSR (130)
^QRNHRT T (56)	DRSNLTR (75)	^MSCCRS A (93)	RSADLSR (100)	RSAHLRSR (40)	TSANLSR (130)
^QRNHRT T (56)	DRSNLTR (75)	^MSCCRS A (93)	RSADLSR (100)	^RSAHLS R (117)	TSANLSR (130)
^QSSDLS R (57)	DRSALAR (76)	^DRSYRN T (94)	RRSDLKR (109)	^RSADLT R (118)	DRSALAR (76)
^DSSTRK T (58)	QSATRTK (77)	ERGTLLAR (39)	QSGDLTR (99)	QSSDLSR (51)	AASNRSK (131)
^DSSTRK T (58)	QSATRTK (77)	^ERGTLA R (95)	QSGDLTR (99)	QSSDLSR (51)	AASNRSK (131)
^RSDNLS Q (59)	ASNDRKK (78)	YDYGRYT (90)	DRSHLAR (70)	QSGNLAR (85)	DRSALAR (76)
^RSDNLS Q (59)	ASNDRKK (78)	^YDYGRY T (96)	DRSHLAR (70)	QSGNLAR (85)	DRSALAR (76)
^RSDNLS Q (59)	ASNDRKK (78)	^YDYGRY T (96)	DRSHLAR (70)	^QSGNLA R (119)	DRSALAR (76)
^RSDHLS E (60)	QSNHRKT (79)	VYEGLKK (91)	QSGHLSR (67)	RSDVLSE (116)	DRSNRIK (132)

6. The fusion protein of any one of the preceding claims, wherein the ZFP domain comprises the DNA-binding recognition helix sequences as shown in a single row of the Table in claim 5.

7. The fusion protein of any one of the preceding claims, wherein the ZFP domain comprises the DNA-binding recognition helix sequences as shown in a single row of the Table in claim 5 ordered from F1 to F6.

8. The fusion protein of claim 6, wherein the ZFP domain comprises the DNA-binding recognition helix ordered from F1 to F6, wherein the sequences are selected from the group consisting of:

QSGHLAR (37), QRKDLTQ (61), RSDHLSR (47), TRDGLRQ (97),
RSANLAR (110), DSSDRKK (120) for F1 to F6, respectively;

RSDNLST (38), RSDNLTR (62), DRSDLSR (64), RREHLRA (98),
TSGNLTR (111), QRSHLSD (121) for F1 to F6, respectively;

ERGTLAR (39), MACCRYA (63), RSADLTR (80), QSGDLTR (99),
QSGNLAR (85), RQEHVA (122) for F1 to F6, respectively;

RSAHLSR (40), DRSDLSR (64), MSCCRSA (81), RSADLSR (100),
QSGDLTR (99), QRSNLNI (123) for F1 to F6, respectively;

RSDNLSV (41), ASWTLTQ (65), DRSDLSR (64), DRSNLTR (75),
DRSHLTR (45), DRSNLTR (75) for F1 to F6, respectively;

LRHHLTR (42), VAEYRYK (66), RSDNLSV (41), RHSHLTS (101),
RSDTLA (112), RSADLSR (100) for F1 to F6, respectively;

RSDNLST (38), QSGHLSR (67), DAHHLHR (82), RSANLTR (102),
DRSNRTT (113), HRSSLRR (124) for F1 to F6, respectively;

RSDDLTR (43), QKFPRDS (68), RSDHLTQ (83), DSANLSR (103),
DRSNLSR (44), DRTSLKW (125) for F1 to F6, respectively;

DRSNLSR (44), HLCCLGR (69), RSCCLHL (84), RNASRTR (104),
QSSDLR (51), HRKSLSR (126) for F1 to F6, respectively;

DRSNLSR (44), DRSHLAR (70), RSDHLSE (54), TSSDRTK (105),
DRSHLSR (114), DRSHLAR (70) for F1 to F6, respectively;

DRSHLTR (45), DRSHLAR (70), QSGNLAR (85), AKWNLDA (106),
QSGDLTR (99), TQGYLRK (127) for F1 to F6, respectively;

TSGSLSR (46), QAGHLAK (71), DRSARTR (86), QSGHLSR (67),
RSAHLSR (40), QSSDLRR (128) for F1 to F6, respectively;

RSDHLSR (47), QHAHRNT (72), RPDTLRD (87), QNATRTK (107),
RSDALSR (115), DRSALAR (76) for F1 to F6, respectively;

NNRDLIN (48), TSSNLSR (73), RSDTLSE (88), NNRDRTK (108),
QSSDLR (51), HRSTRNR (129) for F1 to F6, respectively;

QNAHRKT (49), DNSTRIK (74), DRSNLSR (44), HLCCLGR (69),
DRSNLSR (44), TSANLSR (130) for F1 to F6, respectively;

QRNHRTT (50), DRSNLTR (75), MSCCRSA (81), RSADLSR (100),
RSAHLSR (40), TSANLSR (130) for F1 to F6, respectively;

QSSDLR (51), DRSALAR (76), DRSYRNT (89), RRSDLKR (109),
RSADLTR (80), DRSALAR (76) for F1 to F6, respectively;

DSSTRKT (52), QSATRTK (77), ERGTLAR (39), QSGDLTR (99),
QSSDLR (51), AASNRSK (131) for F1 to F6, respectively;

RSDNLSQ (53), ASNDRKK (78), YDYGRYT (90), DRSHLAR (70),
QSGNLAR (85), DRSALAR (76) for F1 to F6, respectively; and

RSDHLE (54), QSNHRKT (79), VYGLKK (91), QSGHLSR (67), RSDVLE (116), DRSNRIK (132) for F1 to F6, respectively; wherein the SEQ ID NO. of the sequence is indicated in parenthesis.

9. The fusion protein of claim 6, wherein the ZFP domain comprises the F1 to F6 recognition helix regions, and the phosphate contact mutations, if present, of the DNA-binding recognition helix sequences selected from the group consisting of:

QNAHRKT (55), DNSTRIK (74), DRSNLSR (44), HLCCLGR (69), DRSNLSR (44), and TSANLSR (130) for F1 to F6, respectively, and an R-to-Q substitution at the (-5) position of F1;

QNAHRKT (55), DNSTRIK (74), DRSNLSR (44), HLCCLGR (69), DRSNLSR (44), and TSANLSR (130) for F1 to F6, respectively, and an R-to-Q substitution at the (-5) position of F1 and F3;

QNAHRKT (55), DNSTRIK (74), DRSNLSR (44), HLCCLGR (69), DRSNLSR (44), and TSANLSR (130) for F1 to F6, respectively, and an R-to-Q substitution at the (-5) position of F1, F3, and F5;

QRNHRTT (56), DRSNLTR (75), MSCCRSA (81), RSADLSR (100), RSAHLSR (40), and TSANLSR (130) for F1 to F6, respectively, and an R-to-Q substitution at the (-5) position of F1;

QRNHRTT (56), DRSNLTR (75), MSCCRSA (81), RSADLSR (100), RSAHLSR (40), and TSANLSR (130) for F1 to F6, respectively, and an R-to-Q substitution at the (-5) position of F1 and F3;

QRNHRTT (56), DRSNLTR (75), MSCCRSA (81), RSADLSR (100), RSAHLSR (40), and TSANLSR (130) for F1 to F6, respectively, and an R-to-Q substitution at the (-5) position of F1, F3, and F5;

QSSDLSR (57), DRSALAR (76), DRSYRNT (94), RRSDLKR (109), RSADLTR (118), and DRSALAR (76) for F1 to F6, respectively, and an R-to-Q substitution at the (-5) position of F1, F3, and F5;

DSSTRKT (58), QSATRTK (77), ERGTLAR (39), QSGDLTR (99), QSSDLSR (51), and AASNRSK (131) for F1 to F6, respectively, and an R-to-Q substitution at the (-5) position of F1;

DSSTRKT (58), QSATRTK (77), ERGTLAR (39), QSGDLTR (99), QSSDLSR (51), and AASNRSK (131) for F1 to F6, respectively, and an R-to-Q substitution at the (-5) position of F1 and F3;

RSDNLSQ (59), ASNDRKK (78), YDYGRYT (90), DRSHLAR (70), QSGNLAR (85), and DRSALAR (76) for F1 to F6, respectively, and an R-to-Q substitution at the (-5) position of F1;

RSDNLSQ (59), ASNDRKK (78), YDYGRYT (90), DRSHLAR (70), QSGNLAR (85), and DRSALAR (76) for F1 to F6, respectively, and an R-to-Q substitution at the (-5) position of F1 and F3;

RSDNLSQ (59), ASNDRKK (78), YDYGRYT (90), DRSHLAR (70), QSGNLAR (85), and DRSALAR (76) for F1 to F6, respectively, and an R-to-Q substitution at the (-5) position of F1, F3, and F5; and

RSDHLSE (60), QSNHRKT (79), VYEGLKK (91), QSGHLSE (67), RSDVLSE (116), and DRSNRIK (132) for F1 to F6, respectively, and an R-to-Q substitution at the (-5) position of F1.

10. The fusion protein of any one of the preceding claims, wherein the ZFP domain comprises a DNA-binding recognition helix sequence set forth in a single row of the Table below wherein the DNA-binding recognition helix sequences are in

boldface, intramodule and intermodule linkers are underlined and R(-5)Q backbone mutations are indicated by boldface and underline:

SEQ ID NO	Amino Acid Sequences
(133)	MAPKKKRKVGVPAAAMAERPFQCRICMRNFS <u>QSGHLARHIRTHTGE</u> <u>KPFACDICGRKFAQRKDLTQHTKIH</u> <u>THPRAPIKPFQCRICMRNFSRS</u> <u>DHLSRHIRTHTGEKPFACDICGRKFA</u> <u>TRDGLRQHTKIHTGSQKPFQC</u> <u>RICMRNFSRSANLARHIRTHTGEKPFACDICGRKFADSSDRKKHTKI</u> <u>HLRQKDAARGSGGDAKSLTAW</u> <u>SRTLVTFKDVFVDFTREEWKLLDT</u> <u>AQQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREI</u> <u>HQETHPDSETAFEIKSSVRS</u>
(134)	MAPKKKRKVGVPAAAMAERPFQCRICMRNFS <u>RS</u> <u>SDNLSTHIRTHTGEK</u> <u>PFACDICGRKFARSDNLTRHTKIHTGSQKPFQCRICMRNFS</u> <u>DRSDLS</u> <u>RHIRTHTGEKPFACDICGRKFARREHLRAHTKIHTGSQKPFQCRICM</u> <u>RNFSTSGNLTRHIRTHTGEKPFACDICGRKFAQRSHLS</u> <u>DHTKIH</u> <u>LRQ</u> <u>KDAARGSGGDAKSLTAW</u> <u>SRTLVTFKDVFVDFTREEWKLLDTAQQI</u> <u>VYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREI</u> <u>HQET</u> <u>HPDSETAFEIKSSVRS</u>
(135)	MAPKKKRKVGVPAAAMAERPFQCRICMRNFS <u>ER</u> <u>GTLARHIRTHTGE</u> <u>KPFACDICGRKFAMACCRYAHTKIHTGSQKPFQCRICMRNFS</u> <u>RSAD</u> <u>LTRHIRTHTGEKPFACDICGRKFAQSGDLTRHTKIHTHPRAPIKPFQ</u> <u>CRICMRNFSQSGNLARHIRTHTGEKPFACDICGRKFARQEHRVAHT</u> <u>KIHLRQKDAARGSGGDAKSLTAW</u> <u>SRTLVTFKDVFVDFTREEWKLLD</u> <u>TAQQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREI</u> <u>HQETHPDSETAFEIKSSVRS</u>
(136)	MAPKKKRKVGVPAAAMAERPFQCRICMRNFS <u>RS</u> <u>AHLSRHIRTHTGEK</u> <u>PFACDICGRKFADRS</u> <u>DLSRHTKIHTGSQKPFQCRICMRNFS</u> <u>MSCCRS</u> <u>AHIRTHTGEKPFACDICGRKFARSADLSRHTKIHTGSQKPFQCRICM</u> <u>RNFSQSGDLTRHIRTHTGEKPFACDICGRKFAQRSNLNIHTKIH</u> <u>LRQ</u> <u>KDAARGSGGDAKSLTAW</u> <u>SRTLVTFKDVFVDFTREEWKLLDTAQQI</u> <u>VYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREI</u> <u>HQET</u> <u>HPDSETAFEIKSSVRS</u>
(137)	MAPKKKRKVGVPAAAMAERPFQCRICMRNFS <u>QNAHRKTHIRTHTGE</u> <u>KPFACDICGRKFADNSTRIKHTKIHTHPRAPIKPFQCRICMRNFS</u> <u>DR</u> <u>SNLSRHIRTHTGEKPFACDICGRKFAHLCCLGRHTKIHTGSQKPFQC</u> <u>RICMRNFSDRSNLSRHIRTHTGEKPFACDICGRKFATSANLSRHTKIH</u> <u>LRQKDAARGSGGDAKSLTAW</u> <u>SRTLVTFKDVFVDFTREEWKLLDTA</u> <u>QQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREI</u> <u>H</u> <u>QETHPDSETAFEIKSSVRS</u>

SEQ ID NO	Amino Acid Sequences
(138)	MAPKKKRKVGVPAAAMAERPFQCRICMRNFSRS<u>SDNLS</u><u>SVHIRTHTGEK</u> <u>PFACDICGRKFAAS</u><u>WTLT</u><u>QHTKIHTGSQKPFQCRICMRNFS</u><u>DRSDLS</u> RHIRTHTGEKPFACDICGRKFADRSNL<u>TRHTKIHTGSQKPFQCRICM</u> RNFS<u>DRSHL</u><u>TRHIRTHTGEKPFACDICGRKFADRSNL</u><u>TRHTKIHLRQ</u> <u>KDAARGSGGDAKSLTAW</u><u>SRTLVT</u><u>FKDVFVDFTREEWKLLDTAQQI</u> VYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIHQET HPDSETAFEIKSSVRS
(139)	MAPKKKRKVGVPAAAMAERPFQCRICMRNFSQ<u>RNHRT</u><u>THIRTHTGE</u> <u>KPFACDICGRKFADRSNL</u><u>TRHTKIHTGSQKPFQCRICMRNFS</u><u>MSCCR</u> SAHIRTHTGEKPFACDICGRKFARSADLSRHHTKIHTGSQKPFQCRICM RNFS<u>SAHLSR</u><u>HIRTHTGEKPFACDICGRKFATSANLSRHTKIHLRQ</u> <u>KDAARGSGGDAKSLTAW</u><u>SRTLVT</u><u>FKDVFVDFTREEWKLLDTAQQI</u> VYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIHQET HPDSETAFEIKSSVRS
(140)	MAPKKKRKVGVPAAAMAERPFQCRICMRNFSL<u>RHHL</u><u>TRHIRTHTGE</u> <u>KPFACDICGRKFAVAEYRYK</u>HHTKIHTGSQKPFQCRICMRNFSRS<u>DNLS</u> <u>SVHIRTHTGEKPFACDICGRKFARHSHL</u><u>TSHTKIHTGSQKPFQCRICM</u> RNFS<u>SDTLS</u><u>SAHIRTHTGEKPFACDICGRKFARSADLSRHTKIHLRQ</u> <u>KDAARGSGGDAKSLTAW</u><u>SRTLVT</u><u>FKDVFVDFTREEWKLLDTAQQI</u> VYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIHQET HPDSETAFEIKSSVRS
(141)	MAPKKKRKVGVPAAAMAERPFQCRICMRNFSQ<u>SSDLSR</u><u>HIRTHTGEK</u> <u>PFACDICGRKFADRSALARHTKIHTHPRAPIPKPFQCRICMRNFS</u><u>DRS</u> YRNTHIRTHTGEKPFACDICGRKFARRSDLKRHHTKIHTGSQKPFQCR ICMRNFSS<u>SADL</u><u>TRHIRTHTGEKPFACDICGRKFADRSALARHTKI</u> <u>LRQKDAARGSGGDAKSLTAW</u><u>SRTLVT</u><u>FKDVFVDFTREEWKLLDTA</u> QQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIH QETHPDSETAFEIKSSVRS
(142)	MAPKKKRKVGVPAAAMAERPFQCRICMRNFSD<u>SSTRK</u><u>THIRTHTGEK</u> <u>PFACDICGRKFAQSATR</u><u>TKHTKIHTHPRAPIPKPFQCRICMRNFS</u><u>ERG</u> <u>TLARHIRTHTGEKPFACDICGRKFAQSGDL</u><u>TRHTKIHTGSQKPFQCR</u> ICMRNFSQ<u>SSDLSR</u><u>HIRTHTGEKPFACDICGRKFAASNR</u><u>SKHTKIHL</u> <u>RQKDAARGSGGDAKSLTAW</u><u>SRTLVT</u><u>FKDVFVDFTREEWKLLDTAQ</u> QIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIHQE THPDSETAFEIKSSVRS
(143)	MAPKKKRKVGVPAAAMAERPFQCRICMRNFSRS<u>DNLS</u><u>STHIRTHTGEK</u> <u>PFACDICGRKFAQSGHLSRHTKIHTGSQKPFQCRICMRNFS</u><u>DAHHL</u> HRHIRTHTGEKPFACDICGRKFARSANL<u>TRHTKIHTGSQKPFQCRIC</u> MRNFSDR<u>SNRT</u><u>THIRTHTGEKPFACDICGRKFAHRSS</u><u>LRRHTKIHLR</u> <u>QKDAARGSGGDAKSLTAW</u><u>SRTLVT</u><u>FKDVFVDFTREEWKLLDTAQQ</u>

SEQ ID NO	Amino Acid Sequences
	IVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIHQET HPDSETAFEIKSSVRS
(144)	MAPKKKRKVGVPAAAMAERPFQCRICMRNFS RSDDL TRHIRTHTGEK PFACDICGRKFA QKFPRDS HTKIHTGSQKPFQCRICMRNFS RS DHLT QH IRTHTGEKPFACDICGRKF ADSANLS RHTKIHTGSQKPFQCRICM RNFS DRSNLS RHIRTHTGEKPFACDICGRKF ADRTSLK WHTKIHLRQ KDA ARGSGGDAKSLTAW SRLTVTFKDVFDFTREEWKLLDTAQQI VYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIHQET HPDSETAFEIKSSVRS
(145)	MAPKKKRKVGVPAAAMAERPFQCRICMRNFS RS DNLS QHIRTHTGEK PFACDICGRKFA ASNDRKK HTKIHTGSQKPFQCRICMRNFS YDYGR Y THIRTHTGEKPFACDICGRKF ADRS HLARHTKIHTHPRAPIPKPFQC RICMRNFS QSGN LARHIRTHTGEKPFACDICGRKF ADRS ALARHTKI HLRQ KDA ARGSGGDAKSLTAW SRLTVTFKDVFDFTREEWKLLDT AQQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREI HQETHPDSETAFEIKSSVRS
(146)	MAPKKKRKVGVPAAAMAERPFQCRICMRNFS DRSNLS RHIRTHTGEK PFACDICGRKFA HLCC LGRHTKIHTHPRAPIPKPFQCRICMRNFS RS C CLHL HIRTHTGEKPFACDICGRKF ARNAS RTHTKIHTGSQKPFQCR ICMRNFS QSSDL SRHIRTHTGEKPFACDICGRKF HRKS LSRHTKIHL RQKDA ARGSGGDAKSLTAW SRLTVTFKDVFDFTREEWKLLDTAQ QIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIHQE THPDSETAFEIKSSVRS
(147)	MAPKKKRKVGVPAAAMAERPFQCRICMRNFS DRSNLS RHIRTHTGEK PFACDICGRKF ADRS HLARHTKIHTHPRAPIPKPFQCRICMRNFS RS D HLSE HIRTHTGEKPFACDICGRKF ATSSDRT KHTKIHTGSQKPFQCR ICMRNFS DRSHLS RHIRTHTGEKPFACDICGRKF ADRS HLARHTKIHL RQKDA ARGSGGDAKSLTAW SRLTVTFKDVFDFTREEWKLLDTAQ QIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIHQE THPDSETAFEIKSSVRS
(148)	MAPKKKRKVGVPAAAMAERPFQCRICMRNFS DRSHL TRHIRTHTGE KPFACDICGRKF ADRS HLARHTKIHTHPRAPIPKPFQCRICMRNFS QS GN LARHIRTHTGEKPFACDICGRKFA AKWN LDAHTKIHTGSQKPFQ CRICMRNFS QSGDL TRHIRTHTGEKPFACDICGRKF ATQGYLR KHT KIHLRQ KDA ARGSGGDAKSLTAW SRLTVTFKDVFDFTREEWKLLD TAQQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREI HQETHPDSETAFEIKSSVRS
(149)	MAPKKKRKVGVPAAAMAERPFQCRICMRNFS TSGSL SRHIRTHTGEK PFACDICGRKFA QAGHLA KHTKIHTGSQKPFQCRICMRNFS DRSAR

SEQ ID NO	Amino Acid Sequences
	<u>TRHIRTHTGEKPFACDICGRKFAQSGHLSRHTKIH</u> <u>THPRAPIPKPFQC</u> <u>RICMRNFSRSAHLSRHIRTHTGEKPFACDICGRKFAQSSDLRRHTKI</u> <u>HLRQKDAARGSGGDAKSLTAWSR</u> <u>TLVTFKDV</u> <u>FVDF</u> <u>TREEWKLLDT</u> <u>AQQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREI</u> <u>HQETHPDSETAFEIKSSVRS</u>
(150)	<u>MAPKKKRKVGVPAAAMAERPFQCRICMRNFSRSDHLSRHIRTHTGEK</u> <u>PFACDICGRKFAQSNHRKTHTKIH</u> <u>TGSQKPFQCRICMRNFSVYEGL</u> <u>KKHIRTHTGEKPFACDICGRKFAQSGHLSRHTKIH</u> <u>THPRAPIPKPFQC</u> <u>RICMRNFSRSDVLSRHIRTHTGEKPFACDICGRKFADRSNRIKHTKIH</u> <u>LRQKDAARGSGGDAKSLTAWSR</u> <u>TLVTFKDV</u> <u>FVDF</u> <u>TREEWKLLDTA</u> <u>QQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIH</u> <u>QETHPDSETAFEIKSSVRS</u>
(151)	<u>MAPKKKRKVGVPAAAMAERPFQCRICMRNFSRSDHLSRHIRTHTGEK</u> <u>PFACDICGRKFAQH</u> <u>AHRNTHTKIH</u> <u>TGSQKPFQCRICMRNFSRPDTL</u> <u>RDHIRTHTGEKPFACDICGRKFAQN</u> <u>ATRTKHTKIH</u> <u>THPRAPIPKPFQ</u> <u>CRICMRNFSRSDALSRHIRTHTGEKPFACDICGRKFADRSALARHTK</u> <u>IHLRQKDAARGSGGDAKSLTAWSR</u> <u>TLVTFKDV</u> <u>FVDF</u> <u>TREEWKLLDT</u> <u>AQQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREI</u> <u>HQETHPDSETAFEIKSSVRS</u>
(152)	<u>MAPKKKRKVGVPAAAMAERPFQCRICMRNFSNNRDLINHIRTHTGEK</u> <u>PFACDICGRKFATSSNLSRHTKIH</u> <u>THPRAPIPKPFQCRICMRNFSRSDT</u> <u>LSEHIRTHTGEKPFACDICGRKFANNRDR</u> <u>TKHTKIH</u> <u>TGSQKPFQCRI</u> <u>CMRNFSQSSDLSRHIRTHTGEKPFACDICGRKFAHRSTRNRHTKIH</u> <u>LRQKDAARGSGGDAKSLTAWSR</u> <u>TLVTFKDV</u> <u>FVDF</u> <u>TREEWKLLDTA</u> <u>QIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIH</u> <u>QETHPDSETAFEIKSSVRS</u>
(153)	<u>MAPKKKRKVGVPAAAMAERPFQCRICM</u> <u>QNF</u> <u>SQNAHRKTHIRTHTGE</u> <u>KPFACDICGRKFADNSTRIKHTKIH</u> <u>THPRAPIPKPFQCRICMRNFSDR</u> <u>SNLSRHIRTHTGEKPFACDICGRKFAHL</u> <u>CCLGRHTKIH</u> <u>TGSQKPFQC</u> <u>RICMRNFSDRSNLSRHIRTHTGEKPFACDICGRKFATSANLSRHTKIH</u> <u>LRQKDAARGSGGDAKSLTAWSR</u> <u>TLVTFKDV</u> <u>FVDF</u> <u>TREEWKLLDTA</u> <u>QQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIH</u> <u>QETHPDSETAFEIKSSVRS</u>
(154)	<u>MAPKKKRKVGVPAAAMAERPFQCRICM</u> <u>QNF</u> <u>SQNAHRKTHIRTHTGE</u> <u>KPFACDICGRKFADNSTRIKHTKIH</u> <u>THPRAPIPKPFQCRICM</u> <u>QNFSDR</u> <u>SNLSRHIRTHTGEKPFACDICGRKFAHL</u> <u>CCLGRHTKIH</u> <u>TGSQKPFQC</u> <u>RICMRNFSDRSNLSRHIRTHTGEKPFACDICGRKFATSANLSRHTKIH</u> <u>LRQKDAARGSGGDAKSLTAWSR</u> <u>TLVTFKDV</u> <u>FVDF</u> <u>TREEWKLLDTA</u> <u>QQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIH</u> <u>QETHPDSETAFEIKSSVRS</u>

SEQ ID NO	Amino Acid Sequences
(155)	MAPKKKRKVGVPAAAMAERPFCRICM <u>Q</u> NFSQNAHRKTHIRTH <u>TGE</u> KPFACDICGRKFADNSTRICKHTKIHTHPRAPIPKPFQCRICM <u>Q</u> NFS <u>DR</u> SNLSRHIRTH <u>TGE</u> KPFACDICGRKFAHLCC <u>LGR</u> HTKIHTGSQKPFQCRICM <u>Q</u> NFS <u>DR</u> SNLSRHIRTH <u>TGE</u> KPFACDICGRKFATSANLSRHHTKI HLRQKDAARGSGGDAKSLTAWSRITLVTFKDVFDFTREEWKLLDTAQQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIHQETHPDSETAFEIKSSVRS
(156)	MAPKKKRKVGVPAAAMAERPFCRICM <u>Q</u> NFSQRNHRTTHIRTH <u>TGE</u> KPFACDICGRKFADRSNLTRHTKIHTGSQKPFQCRICMRNFSMSCCR SAHIRTH <u>TGE</u> KPFACDICGRKFARSADLSRHHTKIHTGSQKPFQCRICMRNFSR <u>SAHLS</u> RHIRTH <u>TGE</u> KPFACDICGRKFATSANLSRHHTKIHLRQK DAARGSGGDAKSLTAWSRITLVTFKDVFDFTREEWKLLDTAQQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIHQETHPDSETAFEIKSSVRS
(157)	MAPKKKRKVGVPAAAMAERPFCRICM <u>Q</u> NFSQRNHRTTHIRTH <u>TGE</u> KPFACDICGRKFADRSNLTRHTKIHTGSQKPFQCRICM <u>Q</u> NFSMSCC RSAHIRTH <u>TGE</u> KPFACDICGRKFARSADLSRHHTKIHTGSQKPFQCRICMRNFSR <u>SAHLS</u> RHIRTH <u>TGE</u> KPFACDICGRKFATSANLSRHHTKIHLRQK DAARGSGGDAKSLTAWSRITLVTFKDVFDFTREEWKLLDTAQQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIHQETHPDSETAFEIKSSVRS
(158)	MAPKKKRKVGVPAAAMAERPFCRICM <u>Q</u> NFSQRNHRTTHIRTH <u>TGE</u> KPFACDICGRKFADRSNLTRHTKIHTGSQKPFQCRICM <u>Q</u> NFSMSCC RSAHIRTH <u>TGE</u> KPFACDICGRKFARSADLSRHHTKIHTGSQKPFQCRICM <u>Q</u> NFSR <u>SAHLS</u> RHIRTH <u>TGE</u> KPFACDICGRKFATSANLSRHHTKIHLRQK DAARGSGGDAKSLTAWSRITLVTFKDVFDFTREEWKLLDTAQQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIHQETHPDSETAFEIKSSVRS
(159)	MAPKKKRKVGVPAAAMAERPFCRICM <u>Q</u> NFSQSSDLRHIRTH <u>TGE</u> KPFACDICGRKFADRSALARHTKIHTHPRAPIPKPFQCRICM <u>Q</u> NFS <u>DR</u> YRNTHIRTH <u>TGE</u> KPFACDICGRKFARRSDLKRHTKIHTGSQKPFQCRICM <u>Q</u> NFSR <u>SA</u> DLTRHIRTH <u>TGE</u> KPFACDICGRKFADRSALARHTKIHLRQK DAARGSGGDAKSLTAWSRITLVTFKDVFDFTREEWKLLDTAQQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIHQETHPDSETAFEIKSSVRS
(160)	MAPKKKRKVGVPAAAMAERPFCRICM <u>Q</u> NFS <u>DS</u> STRKTHIRTH <u>TGE</u> KPFACDICGRKFAQSATRHTKIHTHPRAPIPKPFQCRICMRNFSERG TLARHIRTH <u>TGE</u> KPFACDICGRKFAQSGDLTRHTKIHTGSQKPFQCRICMRNFSQSSDLRHIRTH <u>TGE</u> KPFACDICGRKFAAASNRSKHTKIHL

SEQ ID NO	Amino Acid Sequences
	<u>RQKDAARGSGGDAKSLTAW</u> SRTLVTFKDVFVDFTREEWKLLDTAQ QIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIHQE THPDSETAFEIKSSVRS
(161)	MAPKKRKRKVGVPAAAMAERPFQCRICM <u>QNFSDSSTRKTHIR</u> THTGEK <u>PFACDICGRKFAQSATR</u> TKHTKIHTHPRAPIPKPFQCRICM <u>QNFSE</u> <u>RGT</u> LARHIRTHTGEKPFACDICGRKFA <u>QSGDLTR</u> HTKIHTGSQKPFQC RICMRNFS <u>QSSDLSR</u> HIRTHTGEKPFACDICGRKFAAASNRSKHTKIHT <u>LRQKDAARGSGGDAKSLTAW</u> SRTLVTFKDVFVDFTREEWKLLDTA QQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIH QETHPDSETAFEIKSSVRS
(162)	MAPKKRKRKVGVPAAAMAERPFQCRICM <u>QNFSDNL</u> SQHIRTHTGE <u>KPFACDICGRKFAASNDRK</u> KHTKIHTGSQKPFQCRICMRNFSYDYG <u>RYTHIR</u> THTGEKPFACDICGRKFAD <u>RS</u> HLARHTKIHTHPRAPIPKPFQ CRICMRNFS <u>QSGNLAR</u> HIRTHTGEKPFACDICGRKFAD <u>RS</u> SALARHT KIHL <u>RQKDAARGSGGDAKSLTAW</u> SRTLVTFKDVFVDFTREEWKLLD TAQQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREI HQETHPDSETAFEIKSSVRS
(163)	MAPKKRKRKVGVPAAAMAERPFQCRICM <u>QNFSDNL</u> SQHIRTHTGE <u>KPFACDICGRKFAASNDRK</u> KHTKIHTGSQKPFQCRICM <u>QNFSDYDYG</u> <u>RYTHIR</u> THTGEKPFACDICGRKFAD <u>RS</u> HLARHTKIHTHPRAPIPKPFQ CRICMRNFS <u>QSGNLAR</u> HIRTHTGEKPFACDICGRKFAD <u>RS</u> SALARHT KIHL <u>RQKDAARGSGGDAKSLTAW</u> SRTLVTFKDVFVDFTREEWKLLD TAQQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREI HQETHPDSETAFEIKSSVRS
(164)	MAPKKRKRKVGVPAAAMAERPFQCRICM <u>QNFSDNL</u> SQHIRTHTGE <u>KPFACDICGRKFAASNDRK</u> KHTKIHTGSQKPFQCRICM <u>QNFSDYDYG</u> <u>RYTHIR</u> THTGEKPFACDICGRKFAD <u>RS</u> HLARHTKIHTHPRAPIPKPFQ CRICM <u>QNFSDYDYG</u> <u>QSGNLAR</u> HIRTHTGEKPFACDICGRKFAD <u>RS</u> SALARHT KIHL <u>RQKDAARGSGGDAKSLTAW</u> SRTLVTFKDVFVDFTREEWKLLD TAQQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREI HQETHPDSETAFEIKSSVRS
(165)	MAPKKRKRKVGVPAAAMAERPFQCRICM <u>QNFSDHLS</u> EHIRTHTGEK <u>PFACDICGRKFAQSNHR</u> KTHTKIHTGSQKPFQCRICMRNFSVYEGL <u>KKHIR</u> THTGEKPFACDICGRKFA <u>QSGHLSR</u> HHTKIHTHPRAPIPKPFQC RICMRNFS <u>RS</u> DLSEHIRTHTGEKPFACDICGRKFAD <u>RSNR</u> IKHTKIHT <u>LRQKDAARGSGGDAKSLTAW</u> SRTLVTFKDVFVDFTREEWKLLDTA QQIVYRNVMLENYKNLVSLGYQLTKPDVILRLEKGEEPWLVEREIH QETHPDSETAFEIKSSVRS

11. The fusion protein of any one of claims 5-9, wherein the target region is any one of SEQ ID NO. 17-36 and the fusion protein is capable of repressing SNCA gene expression.
12. A nucleic acid construct comprising a coding sequence for the fusion protein of any one of claims 1-11, wherein the coding sequence is linked operably to a transcription regulatory element.
13. The nucleic acid construct of claim 12, wherein the transcription regulatory element is a mammalian promoter that is constitutively active or inducible in a brain cell, and wherein the promoter is optionally a human synapsin I promoter.
14. A recombinant virus comprising the nucleic acid construct of claim 12 or 13.
15. The recombinant virus of claim 14, wherein the recombinant virus is an adeno-associated viral vector, an adenoviral vector, or a lentiviral vector.
16. A pharmaceutical composition comprising the nucleic acid construct of claim 12 or 13, or the recombinant virus of claim 14 or 15, and a pharmaceutically acceptable carrier.
17. A host cell comprising the nucleic acid construct of claim 12 or 13, or the recombinant virus of claim 14 or 15.
18. The host cell of claim 17, wherein the host cell is a human cell.

19. The host cell of claim 17, wherein the host cell is a brain cell or a pluripotent stem cell, wherein the stem cell is optionally an embryonic stem cell or an inducible pluripotent stem cell (iPSC).

20. Use of a fusion protein of any one of claims 1-11, a nucleic acid construct of claim 12 or 13 or a recombinant virus of claim 14 or 15, in the manufacture of a medicament for inhibiting expression of alpha-synuclein in a human brain cell and thereby inhibiting the expression of alpha-synuclein in the cell, wherein the cell is in the brain of a patient suffering from or at risk of developing Parkinson's disease, Lewy body dementia, Alzheimer's disease, multiple system atrophy, or another synucleinopathy.

21. The use of claim 20, wherein the human brain cell is a neuron, a glial cell, an ependymal cell, or a neuroepithelial cell.

22. The use of any one of claims 20-21, wherein the recombinant virus that expresses the fusion protein is to be introduced to the cell.

23. The use of claim 22, wherein the recombinant virus is an adeno-associated virus (AAV), optionally of serotype 9.

24. Use of a recombinant AAV encoding a fusion protein of any one of claims 1-11 in the manufacture of a medicament for treating a synucleinopathy in a patient,

wherein said recombinant AAV encoding said fusion protein is to be administered to the patient.

25. The use of claim 24, wherein the AAV is to be administered to the patient via intravenous, intrathecal, intracerebroventricular, intra-cisternal magna, intrastriatal, or intranigral injection, or injection into any brain region.

26. The use of claim 24 or 25, wherein the synucleinopathy is Parkinson's disease, Lewy body dementia, Alzheimer's disease, or multiple system atrophy.

27. A fusion protein of any one of claims 1-11, a nucleic acid construct of claim 12 or 13, a recombinant virus of claim 14 or 15, or a pharmaceutical composition of claim 16 for use as a medicament.

28. Use of a fusion protein of any one of claims 1-11, a nucleic acid construct of claim 12 or 13, or a recombinant virus of claim 14 or 15 in the manufacture of a medicament for treating a synucleinopathy in a patient.