

What is claimed:

1. An isolated polynucleotide set forth in SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, or SEQ ID NO:39; or having at least 95% sequence identity to SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, or SEQ ID NO:39, and encoding the same polypeptide encoded by each of the foregoing, wherein the polynucleotide is not naturally occurring.
2. The isolated polynucleotide of claim 1, having the nucleotide sequence set forth in SEQ ID NO:37.
3. The isolated polynucleotide of claim 1, having the nucleotide sequence set forth in SEQ ID NO:39.
4. A nucleic acid expression cassette comprising:
 - (I) a polynucleotide encoding presenilin 1, wherein the polynucleotide comprises any one of:
 - (a) a polynucleotide set forth in SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, or SEQ ID NO:39; or
 - (b) a polynucleotide having at least 95% identity to SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, or SEQ ID NO:39; and
 - (II) one or more regulatory elements operably linked to the polynucleotide encoding presenilin 1.
- 5.——The nucleic acid expression cassette of claim 4, wherein one of the regulatory elements is a Kozak translation initiation signal, and optionally:-
- ~~6.5. The nucleic acid expression cassette of claim 5, wherein the Kozak translation initiation signal comprises a polynucleotide set forth in SEQ ID NO:5.~~
- 7.——The nucleic acid expression cassette of any one of claims 4-~~65~~, wherein one of the regulatory elements is a chromatin insulator sequence, and optionally:-
- ~~8.6. The nucleic acid expression cassette of claim 7, wherein the chromatin insulator sequence comprises a polynucleotide set forth in SEQ ID NO:4.~~
- 9.——The nucleic acid expression cassette of any one of claims 4-~~86~~, wherein one of the regulatory elements is a neuron-specific promoter, and optionally:-
- ~~10.7. The nucleic acid expression cassette of claim 9, wherein the neuron-specific promoter comprises (i) a polynucleotide set forth in SEQ ID NO:2; (ii) a polynucleotide set forth in SEQ~~

ID NO:3; (iii) a functional fragment of SEQ ID NO:2 or SEQ ID NO:3; or (iv) a polynucleotide with at least 95% identity to (i), (ii), or (iii).

11.—The nucleic acid expression cassette of any one of claims 4-~~10~~7, wherein one or more of the regulatory elements is independently selected from a mRNA stability element, and optionally.

12.—~~The nucleic acid expression cassette of claim 11~~, wherein the mRNA stability element comprises (i) a polynucleotide set forth in SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11; (ii) a polynucleotide with at least 95% sequence identity to SEQ ID NO:9, SEQ ID NO:10, or SEQ ID NO:11, and optionally.

~~**13.8.** The nucleic acid expression cassette of claim 11~~, wherein the mRNA stability element is located 3' of an open reading frame of the polynucleotide encoding presenilin 1 or 5' of a polyadenylation signal.

14.9. The nucleic acid expression cassette of claim ~~13~~8 comprising a first and a second mRNA stability element, wherein the first mRNA stability element is located 3' of an open reading frame of the polynucleotide encoding presenilin 1; and the second mRNA stability element is located 5' of a polyadenylation signal.

15.—The nucleic acid expression cassette of any one of claims 4-~~14~~9, wherein the polynucleotide encoding presenilin 1 is the polynucleotide set forth in SEQ ID NO:37, or.

~~**16.10.** The nucleic acid expression cassette of any one of claims 4-14~~, wherein the polynucleotide encoding presenilin 1 is the polynucleotide set forth in SEQ ID NO:39.

~~**17.11.** A vector comprising the nucleic acid expression cassette of any one of claims 4-16~~10.

18.—The vector of claim ~~17~~11, wherein the vector is a viral vector, optionally an.

19.—~~The vector of claim 18~~12, wherein the ~~viral vector is an~~ adeno-associated virus (AAV) vector, a retroviral vector, a lentiviral vector, or an adenoviral vector, optionally an.

~~**20.12.** The vector of claim 19~~13, wherein the AAV vector that is AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAVDJ, AAVrh10, AAV11, AAV12, AAV2/1, AAV2/5, AAV2/6, AAV2/7, AAV2/8, AAV2/9, AAV2/rh10, AAV2/11, or AAV2/12.

~~**21.13.** The vector of claim 19~~13 or 20~~14~~12, wherein the vector comprises:

a. a promoter selected from a CAG promoter, a presenilin-1 promoter, a ubiquitin C promoter, a CBA promoter, a synapsin-1 promoter, a PGK promoter, and an EF1 α promoter, operatively linked to:

b. a presenilin-1 coding sequence selected from SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, or SEQ ID NO:39, or a

polynucleotide having at least 95% identity to any of the foregoing PSEN-1 coding sequences and encoding a wild-type PSEN-1 amino acids sequence; and

e.——a polyadenylation sequence selected from a human growth hormone polyadenylation sequence and a rabbit β -globin polyadenylation sequence, wherein the -

22.c. ~~The vector of claim 21~~ optionally and additionally comprising ~~comprises~~ an intron selected from a human beta globin intron (either wild-type or synthetic) or a minute virus of mice intron, wherein the intron is located in between the promoter and the PSEN-1 coding sequence.

23.14. ~~The vector of claim 22~~ 1613, wherein the vector comprises:

a. nucleotides 1-141 of SEQ ID NO:41 or a sequence having at least 95% identity thereto, nucleotides 237-1200 of SEQ ID NO:41 or a sequence having at least 95% identity thereto, nucleotides 1221-1786 of SEQ ID NO:41 or a sequence having at least 95% identity thereto, nucleotides 1899-3299 of SEQ ID NO:41 or a sequence having at least 95% identity thereto, nucleotides 3330-3806 of SEQ ID NO:41 or a sequence having at least 95% identity thereto and nucleotides 4553-4693 of SEQ ID NO:41 or a sequence having at least 95% identity thereto;

b. Nucleotides 1-141 of SEQ ID NO:42 or a sequence having at least 95% identity thereto, nucleotides 237-1323 of SEQ ID NO:42 or a sequence having at least 95% identity thereto, nucleotides 1344-1909 of SEQ ID NO:42 or a sequence having at least 95% identity thereto, nucleotides 1983-3416 of SEQ ID NO:42 or a sequence having at least 95% identity thereto, nucleotides 3447-3923 of SEQ ID NO:42 or a sequence having at least 95% identity thereto, and nucleotides 4554-4694 of SEQ ID NO:42 or a sequence having at least 95% identity thereto;

c. Nucleotides 1-141 of SEQ ID NO:43 or a sequence having at least 95% identity thereto, nucleotides 237-890 of SEQ ID NO:43 or a sequence having at least 95% identity thereto, nucleotides 911-1476 of SEQ ID NO:43 or a sequence having at least 95% identity thereto, nucleotides 1550-2983 of SEQ ID NO:43 or a sequence having at least 95% identity thereto, nucleotides 3014-3490 of SEQ ID NO:43 or a sequence having at least 95% identity thereto, and nucleotides 4553-4694 of SEQ ID NO:43 or a sequence having at least 95% identity thereto ~~of SEQ ID NO:43~~;

d. Nucleotides 1-141 of SEQ ID NO:44 or a sequence having at least 95% identity thereto, nucleotides 237-1415 of SEQ ID NO:44 or a sequence having at least 95% identity thereto, nucleotides 1436-2001 of SEQ ID NO:44 or a sequence having at least 95% identity

thereto, nucleotides 2075-3508 of SEQ ID NO:44 or a sequence having at least 95% identity thereto, nucleotides 3539-4015 of SEQ ID NO:44 or a sequence having at least 95% identity thereto, and nucleotides 4500-4640 of SEQ ID NO:44 ~~or a sequence having at least 95% identity thereto, and nucleotides 4500-4640 of SEQ ID NO:44 or a sequence having at least 95% identity thereto;~~

e. Nucleotides 1-141 of SEQ ID NO:45 or a sequence having at least 95% identity thereto, nucleotides 237-664 of SEQ ID NO:45 or a sequence having at least 95% identity thereto, nucleotides 684-1249 of SEQ ID NO:45 or a sequence having at least 95% identity thereto, nucleotides 1323-2756 of SEQ ID NO:45 or a sequence having at least 95% identity thereto, 2787-3263 of SEQ ID NO:45 or a sequence having at least 95% identity thereto, and nucleotides 4533-4673 of SEQ ID NO:45 or a sequence having at least 95% identity thereto;

f. Nucleotides 1-141 of SEQ ID NO:46 or a sequence having at least 95% identity thereto, nucleotides 237-684 of SEQ ID NO:46 or a sequence having at least 95% identity thereto, nucleotides 705-1270 of SEQ ID NO:46 or a sequence having at least 95% identity thereto, nucleotides 1344-2777 of SEQ ID NO:46 or a sequence having at least 95% identity thereto, nucleotides 2808-3284 of SEQ ID NO:46 or a sequence having at least 95% identity thereto, and nucleotides 4554-4695 of SEQ ID NO:46 or a sequence having at least 95% identity thereto; or

g. Nucleotides 1-105 of SEQ ID NO:47 or a sequence having at least 95% identity thereto, nucleotides 113-766 of SEQ ID NO:47 or a sequence having at least 95% identity thereto, nucleotides 776-867 of SEQ ID NO:47 or a sequence having at least 95% identity thereto, nucleotides 881-2311 of SEQ ID NO:47 or a sequence having at least 95% identity thereto, nucleotides 2319-2367 of SEQ ID NO:47 or a sequence having at least 95% identity thereto, and nucleotides 2386-2526 of SEQ ID NO:47 or a sequence having at least 95% identity thereto.

24-15. The vector of claim ~~23-17~~14, wherein the vector comprises a nucleotide sequence of any one of SEQ ID NOs:41-47 or a nucleotide sequence having 95% identity to any one of SEQ ID NOs:41-47.

25-16. The nucleic acid expression cassette of any one of claims ~~4-16~~10, wherein the regulatory elements operably linked to the polynucleotide encoding presenilin 1 comprise:

- (i) a Kozak translation initiation signal;
- (ii) a neuron-specific promoter;
- (iii) a chromatin insulator sequence;
- (iv) a mRNA stability element located 3' of an open reading frame of the polynucleotide encoding presenilin 1; and

(v)——a mRNA stability element located 5' of a polyadenylation signal, -

~~26.(v) The nucleic acid expression cassette of claim 25, wherein:~~

the Kozak translation initiation signal comprises a polynucleotide set forth in SEQ ID NO:5;

the chromatin insulator sequence comprises a polynucleotide set forth in SEQ ID NO:4;

the mRNA stability element located 3' of the open reading frame of the polynucleotide encoding presenilin 1 comprises a polynucleotide set forth in SEQ ID NO:9, or SEQ ID NO:10;

the at least one mRNA stability element located 5' of a polyadenylation signal comprises a polynucleotide set forth in SEQ ID NO:11; and

the neuron-specific promoter comprises a polynucleotide set forth in SEQ ID NO:2 or SEQ ID NO:3.

~~27.17.~~ The nucleic acid expression cassette of any one of claims 4-1065, wherein the promoter operably linked to the polynucleotide encoding presenilin 1 is a ubiquitous promoter.

~~28.—Use of the vector of any one of claims 17-2411-15 in the manufacture of a medicament A method of for treating a neurodegenerative disease, disorder, or condition, optionally wherein comprising administering to a subject in need thereof the vector of any one of claims 17-24.~~

~~29.18.~~ The method use of claim 28, wherein the neurodegenerative disease, disorder, or condition is Alzheimer's disease, Familial Alzheimer's Disease (FAD), presenilin 1 (PSEN-1) mediated FAD, frontotemporal dementia, frontotemporal lobar degeneration, Pick's disease, Lewy body dementia, memory loss, cognitive impairment, or mild cognitive impairment.

~~30.19. Use of the vector of any one of claims 17-24claim 18, in the manufacture of a medicament A method of for treating wherein the neurodegenerative disease, disorder, or condition is Familial Alzheimer's Disease (FAD) or presenilin 1 (PSEN-1) mediated FAD comprising administering to a subject in need thereof the vector of any one of claims 17-24.~~

~~31.20.~~ A method of producing presenilin 1 protein comprising:

transforming a host cell with a vector comprising an optimized polynucleotide set forth in SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, or SEQ ID NO:39; or by a vector comprising a polynucleotide having at least 95% identity to SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, or SEQ ID NO:39, and encoding the same polypeptide encoded by each of the foregoing; and

culturing the cell under conditions and for a time that allow expression of the presenilin 1 protein, wherein the expression of the presenilin 1 protein encoded by the optimized

polynucleotide in the host cell is greater than a level of expression of presenilin 1 protein encoded by a wild-type polynucleotide in a host cell, thereby producing presenilin 1 protein.