CLAIMS

1. A nucleic acid construct comprising a methyl CpG binding protein 2 (MeCP2) promoter operably linked to a nucleotide sequence encoding a progranulin (PGRN) protein, .

2. The nucleic acid construct of claim 1, wherein the MeCP2 promoter is an engineered MeCP2 promoter comprising a minimal promoter sequence and at least one intron.

3. A nucleic acid construct comprising an engineered methyl CpG binding protein 2 (MeCP2) promoter operably linked to a nucleotide sequence encoding a protein of interest (POI), wherein the engineered MeCP2 promoter comprises a minimal promoter sequence and at least one intron.

4. The nucleic acid construct of claim 3, wherein the POI is a progranulin (PGRN) protein.

25. The nucleic acid construct of any one of claim s 1-2 4, wherein: (a) the at least one intron is 3′ to the minimal promoter sequence; or (b) the at least one intron is 5′ to minimal promoter sequence.

36. The nucleic acid construct of any one of claims 1-2 5, wherein the at least one intron is synthetic.

74. The nucleic acid construct of claim 63, wherein the at least one synthetic intron comprises one or more nucleotide sequences of an *MECP2* gene, optionally wherein the at least one synthetic intron comprises one or more intronic sequences of an *MECP2* gene and/or one or more non-expressing exonic sequences of an *MECP2* gene, preferably or wherein the *MECP2* gene is a murine or a human *MECP2* gene, more preferably wherein the MECP2 gene is a murine *MECP2* gene.

85. The nucleic acid construct of claim 63 or 74, wherein the at least one synthetic intron comprises two intronic sequences of a murine *MECP2* gene and two non-expressing exonic sequences of a murine *MECP2* gene.

69. The nucleic acid construct of any one of claims ~~6~~3-5~~8~~, wherein the at least one synthetic intron comprises:

(a) a non-expressing exonic sequence comprising the nucleotide sequence of SEQ ID NO: 4 or a nucleotide sequence having at least 90 % identity to SEQ ID NO: 4;

(b) an intronic sequence comprising the nucleotide sequence of SEQ ID NO: 5 or a nucleotide sequence having at least 90 % identity to the nucleotide sequence of SEQ ID NO: 5;

(c) an intronic sequence comprising the nucleotide sequence of SEQ ID NO: 6 or a nucleotide sequence having at least 90 % identity to the nucleotide sequence of SEQ ID NO: 6; and/or

(d) a non-expressing exonic sequence comprising the nucleotide sequence of SEQ ID NO: 7 or a nucleotide sequence having at least 90 % identity to the nucleotide sequence of SEQ ID NO: 7.

7~~10~~. The nucleic acid construct of any one of claims 3~~6~~-6~~9~~, wherein, in the 5′ to 3′ direction, the at least one synthetic intron comprises:

(a) a non-expressing exonic sequence comprising the nucleotide sequence of SEQ ID NO: 4 or a nucleotide sequence having at least 90 % identity to the nucleotide sequence of SEQ ID NO: 4;

(b) an intronic sequence comprising the nucleotide sequence of SEQ ID NO: 5 or a nucleotide sequence having at least 90 % identity to the nucleotide sequence of SEQ ID NO: 5;

(c) an intronic sequence comprising the nucleotide sequence of SEQ ID NO: 6 or a nucleotide sequence having at least 90 % identity to the nucleotide sequence of SEQ ID NO: 6; and

(d) a non-expressing exonic sequence comprising the nucleotide sequence of SEQ ID NO: 7 or a nucleotide sequence having at least 90 % identity to the nucleotide sequence of SEQ ID NO: 7.

8~~11~~. The nucleic acid construct of any one of claims 3~~6~~-7~~10~~, wherein the at least one synthetic intron comprises the nucleotide sequence of SEQ ID NO: 2 or a nucleotide sequence having at least 90 % identity to the nucleotide sequence of the nucleotide sequence of SEQ ID NO: 2.

~~12~~9. The nucleic acid construct of any one of claims 1~~2~~-2~~5~~, wherein the at least one intron is a natural intron.

~~13. The nucleic acid construct of claim 12, wherein the at least one natural intron comprises a nucleotide sequence of an *MECP2* gene, preferably a murine or a human *MECP2* gene.~~

~~14. The nucleic acid construct of claim 13, wherein the at least one natural intron comprises a nucleotide sequence of a murine *MECP2* gene.~~

~~15. The nucleic acid construct of claim 14, wherein the at least one natural intron comprises the nucleotide sequence of SEQ ID NO: 9 or a nucleotide sequence having at least 90 % identity to the nucleotide sequence of SEQ ID NO: 9.~~

10~~6~~. The nucleic acid construct of any one of claims ~~2-15~~1-9, wherein the minimal promoter sequence comprises the nucleotide sequence of SEQ ID NO: 1, or a functional variant or fragment thereof having at least 90 % identity to the nucleotide sequence of SEQ ID NO: 1.

11~~7~~. The nucleic acid construct of any one of claims 1-8~~11~~, wherein the engineered MeCP2 promoter comprises the nucleotide sequence of SEQ ID NO: 3 or a functional variant or fragment thereof having at least 90 % identity to the nucleotide sequence of SEQ ID NO: 3.

~~18. The nucleic acid construct of any one of claims 1-5 or 12-15, wherein the engineered MeCP2 promoter comprises the nucleotide sequence of SEQ ID NO: 8 or a functional variant or fragment thereof having at least 90 % identity to the nucleotide sequence of SEQ ID NO: 8.~~

12~~9~~. The nucleic acid sequence of any one of claims 1-11~~8~~, wherein the engineered MeCP2 promoter is at least about 1000 bp, 1500 bp, 2000 bp, 2100 bp, 2150 bp, 2175 bp, 2200 bp, 2210 bp, 2220 bp, 2230 bp, 2240 bp, 2250 bp, 2260 bp, 2280 bp, 2290 bp, 2300 bp,

2310 bp, 2320, or 2330 bp in length, ~~preferably~~ or wherein the MeCP2 promoter is about 2200-2350 bp in length.

13~~20~~. The nucleic acid construct of any one of claims 1~~, 2 or 4~~-12~~9~~, wherein:

(a) the PGRN protein is a human PGRN protein;

(b) the PGRN protein is a wild type protein;

(c) the nucleotide sequence encoding the PGRN protein is a human nucleotide sequence;

(d) the nucleotide sequence encoding the PGRN proteins is a wild type nucleotide sequence;

(e) the nucleotide sequence encoding the PGRN protein is not codon optimised; and/or

(f) the nucleotide sequence encoding the PGRN protein is at least about 1600 bp, 1700 bp, 1750 bp, 1760 bp, 1770 bp, or 1780 bp, ~~preferably~~ or wherein the nucleotide sequence encoding the PGRN protein is about 1780 bp in length.

14~~21~~. The nucleic acid construct of any one of claims 1~~, 2 or 4-20~~-13, wherein:

the nucleotide sequence encoding the PGRN protein comprises the nucleotide sequence of SEQ ID NO: 12 or a functional variant or fragment thereof having at least ~~70~~90 % identity to the nucleotide sequence of SEQ ID NO: 12; and/or

the PGRN protein comprises the amino acid sequence of SEQ ID NO: 13 or a functional variant or fragment thereof having at least 90~~70~~ % identity to the amino acid sequence of SEQ ID NO: 13.

15~~22~~. The nucleic acid construct of any one of claims 1-14~~21~~, which further comprises:

(a) a woodchuck hepatitis virus (WHP) posttranscriptional regulatory element (WPRE) sequence, optionally wherein the WPRE is 3′ to the nucleotide sequence encoding the POI or the PGRN protein and/or the WPRE comprises the nucleotide sequence of SEQ ID NO: 15 or a functional variant or fragment thereof having at least 90 % identity to the nucleotide sequence of SEQ ID NO: 15;

(b) a polyadenylation signal sequence, optionally wherein the polyadenylation signal sequence is 3′ to the nucleotide sequence encoding the POI or the PGRN protein and/or the polyadenylation signal sequence comprises the nucleotide sequence SEQ ID NO:

16 or a functional variant or fragment thereof having at least 90 % identity to the nucleotide sequence of SEQ ID NO: 16; or

(c) (a) and (b) above, optionally wherein, in the 5′ to 3′ direction, the nucleic acid construct comprises the MeCP2 promoter, the nucleotide sequence encoding the POI or the PGRN protein, the WPRE, and the polyadenylation signal sequence.

~~23~~16. The nucleic acid construct of any one of claims 1-15~~22~~, which is 3700 to 4700 bp, 3800 to 4800 bp, 3900 to 4700 bp, 4000 to 4600 bp, 4000 to 4500 bp, 4000 to 4400 bp, 4000 to 4300 bp, or 4000 to 4200 bp in length.

17~~24~~. A vector comprising a nucleic acid construct as defined in any one of claims 1-16~~23~~.

18~~25~~. The vector of claim 17~~24~~, which is a plasmid or a viral vector.

19~~26~~. The vector of claim 17~~24~~ or 18~~25~~, which is a viral vector comprising the nucleotide sequence of:

(a) SEQ ID NO: 11 or a functional variant or fragment thereof having at least ~~7~~90 % identity to the nucleotide sequence of SEQ ID NO: 11;

(b) SEQ ID NO: 10 or a functional variant or fragment thereof having at least ~~7~~90 % identity to the nucleotide sequence of SEQ ID NO: 10.

20~~7~~. The vector of claim any one of claims 17~~24~~-19~~26~~, which is a viral vector selected from: (a) an adeno-associated virus (AAV) vector or which comprises an AAV genome or a derivative thereof, optionally wherein said derivative is a chimeric, shuffled or capsid modified derivative; or (b) a lentiviral vector or which comprises a lentivirus genome or a derivative thereof.

21~~8~~. The viral vector of claim 20~~7~~, which is an AAV vector comprising a genome derived from AAV serotype 2 (AAV2), AAV serotype 3 (AAV3), AAV serotype 4 (AAV4), AAV serotype 5 (AAV5), AAV serotype 6 (AAV6), AAV serotype 7 (AAV7), AAV serotype 8 (AAV8), AAV serotype 9 (AAV9), or AAV serotype rh10 (AAVrh10), ~~preferably~~ or wherein the AAV comprises a genome derived from AAV2, AAV9 or AAVrH10.

229. The AAV vector of claim 218, wherein the AAV vector comprises a genome derived from AAV2, ~~preferably~~ or wherein the AAV is AAV-TT.

230. The AAV vector of claim 218 or 229, wherein the AAV vector comprises a nucleotide sequence which, in the 5′ to 3′ direction, comprises one or more of:

(a) a 5′ ITR;

(b) a 5′ adjacent fragment;

(c) a minimal MeCP2 promoter sequence;

(d) at least one synthetic intron;

(e) a Kozak sequence;

(f) a polynucleotide sequence encoding a PGRN protein;

(g) an SV40 poly(A) sequence;

(h) a 3′ adjacent fragment; and

(i) a 3′ ITR.

2431. The AAV vector of claim 230, wherein:

(a) the 5′ ITR comprises or consists of the nucleotide sequence of SEQ ID NO: 20 or a functional variant or fragment thereof having at least ~~7~~90 % identity to SEQ ID NO: 20;

(b) the 5′ adjacent fragment comprises or consists of the nucleotide sequence of SEQ ID NO: 21 or a functional variant or fragment thereof having at least ~~7~~90 % identity to SEQ ID NO: 21;

(c) the minimal MeCP2 promoter sequence comprises or consists of the nucleotide sequence of SEQ ID NO: 1 or a functional variant or fragment thereof having at least ~~7~~90 % identity to SEQ ID NO: 1;

(d) the at least one synthetic intron comprises or consists of the nucleotide sequence of SEQ ID NO: 2 or a functional variant or fragment thereof having at least ~~7~~90 % identity to SEQ ID NO: 2;

(e) the Kozak sequence comprises or consist of the nucleotide sequence of SEQ ID NO: 24;

(f) the polynucleotide sequence encoding a PGRN protein comprises or consists of the nucleotide sequence of SEQ ID NO: 12 or a functional variant or fragment thereof having at least ~~7~~90 % identity to SEQ ID NO: 12;

(g) the SV40 poly(A) sequence comprises or consists of the nucleotide sequence of SEQ ID NO: 16 or a functional variant or fragment thereof having at least 70 % identity to SEQ ID NO: 16;

(h) the 3′ adjacent fragment comprises or consists of the nucleotide sequence of SEQ ID NO: 22 or a functional variant or fragment thereof having at least ~~7~~90 % identity to SEQ ID NO: 22; and/or

(i) the 3′ ITR comprises or consists of the nucleotide sequence of SEQ ID NO: 23 or a functional variant or fragment thereof having at least ~~7~~90 % identity to SEQ ID NO: 23.

2532. The AAV vector of any one of claims 2229-2431, wherein the AAV vector comprises or consists of the nucleotide sequence of:
(a) SEQ ID NO: 17 or a functional variant or fragment thereof having at least ~~7~~90 % identity to the nucleotide sequence of SEQ ID NO: 17.;

~~33. The AAV vector of any one of claims 29-32, wherein the AAV vector comprises or consists of the nucleotide sequence of:~~

(~~a~~b) SEQ ID NO: 18 or a functional variant or fragment thereof having at least 70 % identity to the nucleotide sequence of SEQ ID NO: 18; or

(c~~b~~) SEQ ID NO: 19 or a functional variant or fragment thereof having at least 70 % identity to the nucleotide sequence of SEQ ID NO: 19.

~~34~~26. A host cell which comprises a nucleic acid construct according to any one of claims 1-1623 and/or a vector according to any one of claims 17-2524-33, and/or which produces a viral vector according to any one of claims 19-2526-33, optionally wherein the host cell is a HEK293 cell or a HEK293T cell.

2735. A pharmaceutical composition comprising a nucleic acid construct according to any one of claims 1-2316, a vector according to claim 17 or1824 or 25, and/or a viral vector according to any one of claims 26-3319-25 together with a pharmaceutically acceptable carrier, excipient or diluent.

2836. A nucleic acid construct as defined in any one of claims 1-1623, a vector as defined in claim 1724 or 1825, a viral vector as defined in any one of claims 19-2526-33, and/or a pharmaceutical composition as defined in claim 2735 for use in a method of treating or

preventing a disease characterized by progranulin (PGRN) deficiency in a patient in need thereof.

~~37. A method of treating or preventing a disease characterized by progranulin (PGRN) deficiency in a patient in need thereof, said method comprising administering to the patient a therapeutically effective amount of a nucleic acid construct as defined in any one of claims 1-23, a vector as defined in claim 24 or 25, a viral vector as defined in any one of claims 26-33, and/or a pharmaceutical composition as defined in claim 35.~~

2938. Use of a nucleic acid construct as defined in any one of claims 1-2316, a vector as defined in claim 2417 or 2518, or a viral vector as defined in any one of claims 19-2526-33, ~~and/or a pharmaceutical composition as defined in claim 35~~ for the manufacture of a medicament for the treatment or prevention of a disease characterized by progranulin (PGRN) deficiency in a patient in need thereof.

3039. The nucleic acid construct, vector, viral vector, or pharmaceutical composition for use according to claim 2836, ~~the method of claim 37,~~ or the use of claim 2938, wherein:

the disease characterized by PGRN deficiency is a disease of the central nervous system;

the disease characterized by PGRN deficiency is characterized by a deficiency of PGRN in the neurons and/or the astrocytes of the patient;

the patient has a loss of function mutation in at least one allele of their *GRN* gene; and/or

the patient has a loss of function mutation in both alleles of their *GRN* gene.

3140. The nucleic acid construct, vector, viral vector, or pharmaceutical composition for use according to claim 2836 or 3039, ~~the method of claim 37 or 39,~~ or the use of claim 3829 or 309, wherein the disease characterized by PGRN deficiency is frontotemporal dementia (FTD) or neuronal ceroid lipofuscinosis type 11 (NCL11).

3241. The nucleic acid construct, vector, viral vector, or pharmaceutical composition for use according to claim 28, 30 or 3136, 39 or 40, ~~the method of claim 37, 39 or 40,~~ or the use of claim any one of claims 38-4029-31, wherein said nucleic acid construct, vector, viral vector,

or pharmaceutical composition are administered to the patient by delivery to the brain and/or the cerebrospinal fluid (CSF) of the patient, optionally wherein the delivery is by injection to:

(i) the brain of the patient, ~~preferably~~ wherein the injection to the brain is selected from intracerebral injection, intraparenchymal injection, intraputaminal injection, and combinations thereof; and/or

(ii) the CSF of the patient, ~~preferably~~ wherein the injection to the CSF is selected from intra-cisterna magna injection, intrathecal injection, intracerebroventricular (ICV) injection, and combinations thereof.