

SUMMARY

[0003a] In one aspect, provided herein is an expression cassette comprising a nucleic acid sequence encoding a non-naturally occurring DNA binding protein comprising a DNA binding domain, wherein the DNA binding domain comprises six zinc finger domains comprising the following recognition helices in N-to-C order: SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, and SEQ ID NO:120.

[0003b] In another aspect, provided herein is an expression vector comprising the expression cassette as described herein.

[0003c] In another aspect, provided herein is a viral particle comprising the expression cassette as described herein or the expression vector as described herein.

[0003d] In another aspect, provided herein is a host cell comprising the expression cassette as described herein or the expression vector as described herein.

[0003e] In another aspect, provided herein is a pharmaceutical composition comprising the expression cassette as described herein, the expression vector as described herein, or the viral particle as described herein, and one or more pharmaceutically acceptable excipients.

[0003f] In another aspect, provided herein is a use of the expression cassette as described herein, the expression vector as described herein, the viral particle as described herein, or the pharmaceutical composition as described herein in the manufacture of a medicament for increasing expression of SCN1A in a cell.

[0004] In one example, the application provides an expression cassette, comprising a sequence encoding a non-naturally occurring transcription factor which increases expression of the SCN1A gene in a cell. In certain examples, the transcription factor which increases expression of SCN1A binds to a target site that is capable of increasing SCN1A expression by at least 20% in a transcriptional activation assay. In certain examples, the transcription factor which increases expression of SCN1A is capable of reducing the seizure frequency in a mouse model of Dravet syndrome by at least 20% in a hyperthermic seizure assay. In certain examples, the transcription factor which increases expression of SCN1A binds to a target site that is capable of increasing SCN1A expression by at least 20% in a transcriptional activation assay and the transcription factor is capable of reducing the seizure frequency in a mouse model of Dravet syndrome by at least 20% in a hyperthermic seizure assay.

[0005] In certain examples, the transcription factor which increases expression of SCN1A binds to a genomic location on chromosome 2. In certain examples, the transcription factor which increases expression of SCN1A binds to a genomic location on chromosome 2 that is within 110 kb upstream or downstream of the transcriptional start site of the SCN1A gene. In

certain examples, the transcription factor which increases expression of SCN1A binds to a genomic location on chromosome 2 that is within positions 166179652-165989571 (with reference to GRCh38.p12). In certain examples, the transcription factor which increases expression of SCN1A binds to a genomic location on chromosome 2 that is within positions 166128050-166127958 (with reference to GRCh38.p12). In certain examples, the transcription factor which increases expression of SCN1A binds to a genomic location on chromosome 2 that is within positions 166155414-166140590 (with reference to GRCh38.p12). In certain examples, the transcription factor which increases expression of SCN1A binds to a genomic location on chromosome 2 that is within positions 166179652-1661777272 (with reference to GRCh38.p12). In certain examples, the transcription factor which increases expression of SCN1A binds to a genomic location on chromosome 2 that is within positions 1659990246-165989592 (with reference to GRCh38.p12). In certain examples, the transcription factor which increases expression of SCN1A binds to a genomic region within 200 bp of a genomic location having a sequence of any one of SEQ ID NOs: 35-37, 105-111, 136, 195-211, 224-238, 240-267. In certain examples, the transcription factor which increases expression of SCN1A binds to a genomic region that is at least partially overlapping with a genomic location having a sequence of any one of SEQ ID NOs: 35-37, 105-111, 136, 195-211, 224-238, 240-267. In certain examples, the transcription factor which increases expression of

SCN1A binds to a genomic region having a sequence of any one of SEQ ID NOs: 35-37, 105-111, 136, 195-211, 224-238, 240-267. In certain examples, the transcription factor which increases expression of SCN1A binds to a genomic region having 18-27 nucleotides (e.g., at least 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides).

[0006] In certain examples, the transcription factor which increases expression of SCN1A comprises a DNA binding domain. In certain examples, the transcription factor which increases expression of SCN1A comprises a DNA binding domain and a transcription activating domain. In certain examples, the DNA binding domain comprises at least 80% sequence identity to its closest human counterpart. In certain examples, the DNA binding domain comprises at least 90% sequence identity to its closest human counterpart. In certain examples, the DNA binding domain and the transcription activating domain both comprise at least 80% sequence identity to their closest human counterparts. In certain examples, the DNA binding domain and the transcription activating domain both comprise at least 90% sequence identity to their closest human counterparts. In certain examples, the DNA binding domain comprises a guide RNA and a nuclease inactivated Cas protein. In certain examples, the nuclease inactivated Cas protein is a nuclease inactivated Cas9. In certain examples, the DNA binding domain comprises a zinc finger domain. In certain examples, the DNA binding domain comprises six to nine zinc finger domains. In certain examples, the DNA binding domain comprises six zinc fingers. In certain examples, the DNA binding domain comprising six fingers binds to a genomic region having 18 nucleotides. In certain examples, the DNA binding domain comprises nine zinc fingers. In certain examples, the DNA binding domain comprising nine zinc fingers binds to a genomic region having 27 nucleotides. In certain examples, the DNA binding domain comprises a sequence having at least 95% sequence identity to any of SEQ ID NOs: 135, 371, 372 or 376. In certain examples, the DNA binding domain comprises a sequence having any one of SEQ ID NOs: 135, 371, 372 or 376. In certain examples, the DNA binding domain is derived from human EGR1 or human EGR3. In certain examples, the transcription activating domain comprises a VPR, VP64, CITED2 or CITED4 sequence, or a functional fragment thereof. In certain examples, the transcription activating domain comprises a human CITED2 or CITED4 sequence, or a functional fragment thereof.

[0007] In certain examples, the expression cassette encoding a transcription factor which increases expression of SCN1A further comprises a regulatory element that drives expression of the transcription factor at a higher level in PV neurons than in other cell types. In certain examples, the regulatory element comprises a sequence having any one of SEQ ID NOs:

183, 184, 185, or 417. In certain examples, the regulatory element comprises a sequence having SEQ ID NO: 183 or 185.

[0008] In certain examples, the expression cassette encoding a transcription factor which increases expression of SCN1A is a part of a viral vector. In certain examples, the viral vector is an AAV virus. In certain examples, the AAV virus is an AAV9 virus or a scAAV9 virus.

[0009] In another example, the application provides a method of increasing expression of SCN1A in a cell by administering any of expression cassette described herein that encode a transcription factor which increases expression of SCN1A. In certain examples, the cell is a PV neuron. In certain examples, the cell is within a subject. In certain examples, the subject is a mammal. In certain examples, the subject is a human. In certain examples, increasing expression of SCN1A treats a disease, disorder or symptom. In certain examples, the disorder is a central nervous system disorder. In certain examples, the disorder is Dravet Syndrome. In certain examples, the central nervous system disorder is neuronal hyperactivity. In certain examples, treating the central nervous system disorder comprises reducing neuronal hyperactivity. In certain examples, a symptom of the central nervous system disorder is seizures. In certain examples, treating the central nervous system disorder comprises reducing the frequency of seizures. In certain examples, treating the central nervous system disorder comprises reducing the severity of seizures. In certain examples, treating the central nervous system disorder comprises reducing the severity and frequency of seizures.

[0010] In another example, the application provides an expression cassette, comprising a sequence encoding a non-naturally occurring transcription factor which increases expression of the GRN gene in a cell.

[0011] In certain examples, the transcription factor which increases expression of GRN binds to a genomic region having 18-27 nucleotides.

[0012] In certain examples, the transcription factor which increases expression of GRN comprises a DNA binding domain. In certain examples, the transcription factor which increases expression of GRN comprises a DNA binding domain and a transcription activating domain. In certain examples, the DNA binding domain comprises a guide RNA and a nuclease inactivated Cas protein. In certain examples, the nuclease inactivated Cas protein is a nuclease inactivated Cas9. In certain examples, the DNA binding domain comprises a zinc finger domain. In certain examples, the DNA binding domain comprises six to nine zinc finger domains. In certain examples, the DNA binding domain comprises six zinc fingers.

In certain examples, the DNA binding domain comprising six zinc fingers binds to a genomic region having 18 nucleotides. In certain examples, the DNA binding domain comprises nine zinc fingers. In certain examples, the DNA binding domain comprising nine zinc fingers binds to a genomic region having 27 nucleotides. In certain examples, the DNA binding domain comprises a sequence having at least 95% sequence identity to any of SEQ ID NOs: 171 or 412-416. In certain examples, the DNA binding domain comprises a sequence having any one of SEQ ID NOs: 171 or 412-416. In certain examples, the DNA binding domain is derived from human EGR1 or human EGR3. In certain examples, the transcription activating domain comprises a VPR, VP64, CITED2 or CITED4 sequence, or a functional fragment thereof.

[0013] In certain examples, the expression cassette encoding a transcription factor which increases expression of GRN further comprises a regulatory element that drives expression of the non-naturally occurring transcriptional modulator. In certain examples, the regulatory element is a cell type selective regulatory element.

[0014] In certain examples, the expression cassette encoding a transcription factor that increases expression of GRN is a part of a viral vector. In certain examples, the viral vector is an AAV virus. In certain examples, the AAV virus is an AAV9 virus or a scAAV9 virus.

[0015] In another example, the application provides a method of increasing expression of GRN in a cell by administering any of the expression cassette described herein that encode a transcription factor that increases expression of GRN. In certain examples, increasing expression of GRN treats a disease, disorder or symptom. In certain examples, the cell is within a subject. In certain examples, the subject is a mammal. In certain examples, the subject is a human. In certain examples, the cell is selected from the group consisting of: central nervous system cells, frontal cortex cells, glial cells, microglial cells, and striatum cells. In certain examples, modulating expression of GRN treats a disease or disorder. In certain examples, the disorder is a central nervous system disorder. In certain examples, the disorder is Frontotemporal degeneration (FTD), Parkinson's disease, Alzheimer's disease, or Atherosclerosis. In certain examples, a symptom of the central nervous system disorder is a presence of Lewy bodies, haploinsufficiency of progranulin (GRN), social deficit, lysosomal abnormality, memory loss, loss of motor coordination, or muscular tremors. In certain examples, treating the central nervous system disorder comprises reducing the frequency of muscular tremors and/or reducing the severity of muscular tremors.

[0016] In another example, the application provides an expression cassette encoding a non-naturally occurring DNA binding protein comprising a DNA binding domain comprising three or

more DNA binding domains, wherein the DNA binding protein increases or represses expression of an endogenous gene by a factor of at least 5-fold, and wherein the DNA binding protein has 90% or greater sequence identity to its closest human counterpart. In exemplary examples, the DNA binding domain comprises three or more zinc finger domains.

[0017] In certain examples, the DNA binding protein having 90% or greater sequence identity to its closest human counterpart binds to a target site in the human genome that the human counterpart protein does not naturally bind. In certain examples, the human counterpart is EGR1. In certain examples, the human counterpart is EGR3. In certain examples, the DNA binding protein having 90% or greater sequence identity to its closest human counterpart comprises at least 6 zinc finger domains. In certain examples, the DNA binding protein binding protein having 90% or greater sequence identity to its closest human counterpart comprises 9 zinc finger domains. In certain examples, the DNA binding domain having 90% or greater sequence identity to its closest human counterpart comprises at least one amino acid substitution at position -1, 2, 3 or 6 of recognition helices of one or more zinc finger domains. In certain examples, the DNA binding protein having 90% or greater sequence identity to its closest human counterpart comprises one or more zinc finger domains derived from EGR1 or EGR3.

[0018] In certain examples, the DNA binding protein having 90% or greater sequence identity to its closest human counterpart further comprises a transcription effector domain. In certain examples, the transcription effector domain is derived from CITED2 or CITED4. In certain examples, the transcription effector domain is positioned at C-terminus of the DNA binding domain in the DNA binding protein. In certain examples, the effector domain is positioned at N-terminus of the DNA binding domain in the DNA binding protein. In certain examples, the DNA binding protein having 90% or greater sequence identity to its closest human counterpart comprises an effector domain positioned at N-terminus of the DNA binding domain in the DNA binding protein and an effector domain positioned at C-terminus of the DNA binding domain in the DNA binding protein.

[0019] In certain examples, the DNA binding protein having 90% or greater sequence identity to its closest human counterpart recognizes a target binding site of 18bp or longer. In certain examples, the DNA binding protein having 90% or greater sequence identity to its closest human counterpart recognizes a target binding site of 27bp.

[0020] In certain examples, the expression cassette encoding the DNA binding protein having 90% or greater sequence identity to its closest human counterpart further comprises a cell type selective regulatory element. In certain examples, the expression cassette encoding the

DNA binding protein having 90% or greater sequence identity to its closest human counterpart further comprises a regulatory element that drives expression of the DNA binding protein at a higher level in PV neurons than in other cell types. In certain examples, the regulatory element comprises a sequence having any one of SEQ ID NOs: 183, 184, 185, or 417. In certain examples, the regulatory element comprises a sequence having SEQ ID NO: 183 or 185.

[0021] In certain examples, the expression cassette encoding a DNA binding protein having 90% or greater sequence identity to its closest human counterpart is in a viral vector. In certain examples, the viral vector is AAV. In certain examples, the AAV is AAV9 or scAAV9.

[0022] In another example, the application provides a method of treating a disease or condition, the method comprising administering a gene therapy comprising any expression cassette provided herein encoding a DNA binding protein having 90% or greater sequence identity to its closest human counterpart. In certain examples, the DNA binding protein having 90% or greater sequence identity to its closest human counterpart elicits reduced or minimal immune response when expressed in a cell or *in vivo*. In certain examples, the cell is within a subject. In certain examples, the subject is a mammal. In certain examples, the subject is a human. In certain examples, the DNA binding protein having 90% or greater sequence identity to its closest human counterpart increases expression of endogenous SCN1A. In certain examples, the cell is a PV neuron. In certain examples, increasing expression of SCN1A treats a disease, disorder or symptom. In certain examples, the disorder is a central nervous system disorder. In certain examples, the disorder is Dravet Syndrome. In certain examples, the central nervous system disorder is neuronal hyperactivity. In certain examples, treating the central nervous system disorder comprises reducing neuronal hyperactivity. In certain examples, a symptom of the central nervous system disorder is seizures. In certain examples, treating the central nervous system disorder comprises reducing the frequency of seizures. In certain examples, treating the central nervous system disorder comprises reducing the severity of seizures. In certain examples, treating the central nervous system disorder comprises reducing the severity and frequency of seizures. In certain examples, the DNA binding protein having 90% or greater sequence identity to its closest human counterpart increases expression of endogenous GRN. In certain examples, the cell is selected from the group consisting of: central nervous system cells, frontal cortex cells, glial cells, microglial cells, and striatum cells. In certain examples, modulating expression of GRN treats a disease or disorder. In certain examples, the disorder is a central nervous system disorder. In certain examples, the disorder is Frontotemporal degeneration (FTD), Parkinson's disease, Alzheimer's disease, or Atherosclerosis. In certain examples, a symptom of the central

nervous system disorder is a presence of Lewy bodies, haploinsufficiency of progranulin (GRN), social deficit, lysosomal abnormality, memory loss, loss of motor coordination, or muscular tremors. In certain examples, treating the central nervous system disorder comprises reducing the frequency of muscular tremors and/or reducing the severity of muscular tremors.

INCORPORATION BY REFERENCE

[0023] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative cases, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0025] FIG. 1 illustrates the effect of different regulatory elements on expression of luciferase in 293T cells, measured in terms of normalized luciferase activity. For example, combined with a minimal CMV (minCMV) promoter drove expression of luciferase at a level about 1.4 fold higher than the expression driven by the minCMV promoter alone, and about 60 fold higher than the expression driven by a SCP promoter. In the same experiment, SEQ ID NO: 178 linked to a minCMV promoter drove expression of luciferase at a level about 3.5 fold higher than the minCMV promoter alone and about 140 fold higher than a SCP promoter.

[0026] FIG. 2 illustrates the size-normalized activity (calculated by dividing the normalized luciferase activity as shown in **FIG. 1** by the length of the regulatory element in base pairs) of each regulatory element.

[0027] FIG. 3 illustrates selective expression of eGFP under the control of GABAergic-selective regulatory elements (REs), such as REs that are selective for parvalbumin (PV) cells. AAVDJ vectors containing eGFP, under the control of either an EF1 α promoter or a GABAergic/PV-selective RE such as SEQ ID NO: 183, which includes SEQ ID NO: 185, or SEQ ID NO: 184, were injected into a mouse which expressed tdTomato (a red fluorescent protein (RFP)) in GABAergic/PV cells. Top row images show the pattern of eGFP expressed from a construct containing the EF1 α promoter (SEQ ID NO: 186), the GABAergic/PV-selective RE SEQ ID NO: 183, or SEQ ID NO: 184. Lower row images show the GABAergic/PV neurons, which are GAD2-positive. Cells which express both eGFP and tdTomato can be identified either by overlaying the top row image with the lower image, or by identifying fluorescence from the

CLAIMS

WHAT IS CLAIMED IS:

1. An expression cassette comprising a nucleic acid sequence encoding a non-naturally occurring DNA binding protein comprising a DNA binding domain, wherein the DNA binding domain comprises six zinc finger domains comprising the following recognition helices in N-to-C order: SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, and SEQ ID NO:120.
2. The expression cassette of claim 1, wherein the DNA binding domain binds a target site comprising SEQ ID NO: 35.
3. The expression cassette of claim 1 or 2, wherein the DNA binding domain comprises an amino acid sequence having at least 80% sequence identity to SEQ ID NO:131.
4. The expression cassette of any one of claims 1-3, wherein the DNA binding domain comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO:131.
5. The expression cassette of any one of claims 1-4, wherein the DNA binding domain comprises an amino acid sequence having at least 98% sequence identity to SEQ ID NO:131.
6. The expression cassette of any one of claims 1-5, wherein the DNA binding domain comprises SEQ ID NO:131.
7. The expression cassette of any one of claims 1-6, wherein the non-naturally occurring DNA binding protein further comprises a transcription activating domain.
8. The expression cassette of claim 7, wherein the transcription activating domain comprises an amino acid sequence having at least 80% sequence identity to SEQ ID NO:95.

9. The expression cassette of claim 7 or 8, wherein the transcription activating domain comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO:95.
10. The expression cassette of any one of claims 7-9, wherein the transcription activating domain comprises SEQ ID NO:95.
11. The expression cassette of any one of claims 1-10, wherein the expression cassette further comprises a nucleic acid sequence encoding a first nuclear localization sequence (NLS), wherein the first NLS is fused to the N-terminus of the non-naturally occurring transcription factor.
12. The expression cassette of claim 11, wherein the expression cassette further comprises a nucleic acid sequence encoding a second NLS, wherein the second NLS is located between the DNA binding domain and the transcription activating domain.
13. The expression cassette of claim 12, wherein the first NLS is the SV40 large T-antigen NLS and the second NLS is the nucleoplasmin NLS.
14. The expression cassette of claim 13, wherein the DNA binding domain comprises an amino acid sequence having at least 80% sequence identity to SEQ ID NO:131 and the transcription activating domain comprises an amino acid sequence having at least 80% sequence identity SEQ ID NO:95.
15. The expression cassette of claim 13 or 14, wherein the DNA binding domain comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO:131 and the transcription activating domain comprises an amino acid sequence having at least 90% sequence identity SEQ ID NO:95.
16. The expression cassette of any one of claims 13-15, wherein the DNA binding domain comprises SEQ ID NO:131 and the transcription activating domain comprises SEQ ID NO:95.

17. The expression cassette of claim 14, wherein the non-naturally occurring DNA binding protein comprises an amino acid sequence having at least 80% identity to SEQ ID NO:306.
18. The expression cassette of claim 14, wherein the non-naturally occurring DNA binding protein comprises an amino acid sequence having at least 90% identity to SEQ ID NO:306.
19. The expression cassette of claim 14, wherein the non-naturally occurring DNA binding protein comprises an amino acid sequence having at least 95% identity to SEQ ID NO:306.
20. The expression cassette of claim 14, wherein the expression cassette comprises a nucleic acid sequence having at least 80% identity to SEQ ID NO:443.
21. The expression cassette of claim 14, wherein the expression cassette comprises a nucleic acid sequence having at least 90% identity to SEQ ID NO:443.
22. The expression cassette of claim 14, wherein the expression cassette comprises a nucleic acid sequence having at least 95% identity to SEQ ID NO:443.
23. The expression cassette of any one of claims 1-22, wherein the expression cassette further comprises a PV selective regulatory element situated upstream of the sequence encoding the non-naturally occurring DNA binding protein.
24. The expression cassette of claim 23, wherein the PV selective regulatory element comprises SEQ ID NOs: 183 or a functional fragment thereof.
25. The expression cassette of claim 23 or 24, wherein the PV selective regulatory element comprises a sequence having 80% identity to SEQ ID NOs: 183.

26. The expression cassette of any one of claims 23-25, wherein the PV selective regulatory element comprises a sequence having 90% identity to SEQ ID NOs: 183.
27. The expression cassette of any one of claims 23-26, wherein the PV selective regulatory element comprises SEQ ID NO: 183.
28. The expression cassette of claim 23, wherein the expression cassette further comprises a polyA sequence positioned downstream of the polynucleotide encoding the non-naturally occurring DNA binding protein.
29. The expression cassette of claim 28, wherein the polyA sequence comprises SEQ ID NO: 327.
30. The expression cassette of claim 28 or 29, wherein the expression cassette further comprises:
a first nucleic acid sequence encoding a first nuclear localization sequence (NLS), wherein the first NLS is fused to the N-terminus of the non-naturally occurring DNA binding protein; and
a second nucleic acid sequence encoding a second NLS, wherein the second NLS is located between the DNA binding domain and the transcription activating domain;
wherein the DNA binding domain comprises an amino acid sequence having at least 80% sequence identity to SEQ ID NO:131 and the transcription activating domain comprises an amino acid sequence having at least 80% sequence identity SEQ ID NO:95.
31. The expression cassette of claim 30, wherein the expression cassette comprises a nucleic acid sequence having at least 80% sequence identity to SEQ ID NO: 354.
32. The expression cassette of claim 30 or 31, wherein the expression cassette comprises a nucleic acid sequence having at least 90% sequence identity to SEQ ID NO: 354.
33. The expression cassette of any one of claims 30-32, wherein the expression cassette comprises a nucleic acid sequence having at least 98% sequence identity to SEQ ID NO: 354.

34. An expression vector comprising the expression cassette of any one of claims 1 to 33.
35. The expression vector of claim 34, wherein the expression vector is a viral vector.
36. The expression vector of claim 35, wherein the viral vector is an adeno-associated virus (AAV) vector.
37. The expression vector of claim 36, wherein the AAV vector is AAV1, AAV2, AAV5, AAV8, AAV9, scAAV1, scAAV2, scAAV5, scAAV8, or scAAV9.
38. The expression vector of claim 36 or 37, wherein the expression cassette further comprises a 5' AAV inverted terminal repeat (ITR) sequence and a 3' AAV ITR sequence.
39. The expression vector of claim 38, wherein the 5' AAV ITR sequence and the 3' AAV ITR sequence are selected from AAV1, AAV2, AAV5, AAV8, AAV9, scAAV1, scAAV2, scAAV5, scAAV8, or scAAV9 ITR sequences.
40. A viral particle comprising the expression cassette of any one of claims 1 to 33 or the expression vector of any one of claims 34 to 39.
41. The viral particle of claim 40, wherein the viral particle comprises capsid proteins of an AAV.
42. The viral particle of claim 41, wherein the AAV is an AA1, AAV2, AAV5, AAV8 or AAV9.
43. A host cell comprising the expression cassette of any one of claims 1 to 33 or the expression vector of any one of claims 34 to 39.

44. A pharmaceutical composition comprising the expression cassette of any one of claims 1 to 33, the expression vector of any one of claims 34 to 39, or the viral particle of any one of claims 40 to 42, and one or more pharmaceutically acceptable excipients.
45. Use of the expression cassette of any one of claims 1 to 33, the expression vector of any one of claims 34 to 39, the viral particle of any one of claims 40 to 42, or the pharmaceutical composition of claim 44 in the manufacture of a medicament for increasing expression of SCN1A in a cell.
46. The use of claim 45, wherein the cell is a PV neuron.
47. The use of claim 46, wherein the PV neuron is within a subject.
48. The use of claim 47, wherein the medicament is for treating a disease, disorder, or symptom in the subject.
49. The use of claim 48, wherein the subject is a mammal.
50. The use of claim 49, wherein the subject is a primate.
51. The use of claim 50, wherein the primate is a non-human primate.
52. The use of claim 51, wherein the non-human primate is an old world monkey, an orangutan, a gorilla, a chimpanzee, a marmoset, a crab-eating macaque, a rhesus macaque or a pig-tailed macaque.
53. The use of claim 50, wherein the primate is a human.
54. The use of claim 48, wherein the disorder is a central nervous system disorder.

55. The use of claim 54, wherein the central nervous system disorder is epilepsy associated with SCN1A haploinsufficiency.
56. The use of claim 55, wherein the central nervous system disorder is Dravet Syndrome.
57. The use of claim 54, wherein a symptom of the central nervous system disorder is neuronal hyperactivity.
58. The use of claim 57, wherein treatment of the central nervous system disorder comprises reduction of neuronal hyperactivity.
59. The use of claim 54, wherein a symptom of the central nervous system disorder is seizures.
60. The use of claim 59, wherein treatment of the central nervous system disorder comprises reduction of the frequency and/or severity of seizures.
61. The expression cassette of any one of claims 1 to 33, the expression vector of any one of claims 34 to 39, the viral particle of any one of claims 40 to 42, or the pharmaceutical composition of claim 44 for use in therapy.