

or preferential expression of the transgene in a target tissue or cell type (e.g., parvalbumin (PV) neurons) as compared to one or more non-target cell types (e.g., non-PV cells). In some cases, the REs are non-naturally occurring sequences. In some cases, the REs are human-derived regulatory elements. In some cases, the REs comprise a sequence from a non-human species, such as a monkey, or a dog, or a rabbit, or a mouse. In some cases, the compositions described herein are delivered into a cell in vivo, ex vivo, or in vitro using a viral vector and/or virus particles, such as adeno-associated virus (AAV) or lentivirus. In some cases, the compositions described herein are delivered into a cell as gene therapy. Also contemplated herein are methods and compositions for treating a neurological condition or disorder associated with a genetic defect in the CNS. In some cases, the relevant cell type or tissue affected by the genetic defect is a PV cell. In some instances, the neurological condition or disease is Dravet syndrome, Alzheimer's disease, epilepsy, and/or seizures. In some cases, the neurological condition or disease is a psychiatric disorder (e.g., schizophrenia, obsessive compulsive disorder, addiction, depression, anxiety, psychosis); an autism spectrum disorder (e.g., Fragile X syndrome, Rett syndrome); epilepsy (e.g., chronic traumatic encephalopathy, generalized epilepsy with febrile seizures plus (GEFS+), epileptic encephalopathy, temporal lobe epilepsy, focal epilepsy, tuberous sclerosis); or neurodegeneration (e.g., Alzheimer's disease, Parkinson's disease). In some cases, the neurological condition or disease is any seizure and/or epilepsy related condition or disease wherein PV neurons are implicated.

**[0006]** In one example, the present disclosure contemplates a nucleic acid cassette comprising one or more regulatory elements operably linked to a transgene that results in selective expression in any target cell type, e.g., PV neurons in the CNS, over one or more non-target cell types, or non-PV cells in the CNS. In some cases, each regulatory element comprises (i) a sequence of SEQ ID NOs: 1-32, (ii) a functional fragment or a combination thereof, or (iii) a sequence with at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to (i) or (ii). In some cases, sequence identity is determined using BLAST. In some cases, at least one of the regulatory elements is human derived. In some cases, at least one of the regulatory elements is derived from a non-human mammal. In some cases, the regulatory elements are non-naturally occurring. In some cases, the regulatory elements result in selective expression of the transgene in PV neurons that is greater than expression of the same transgene when operably linked to a non-selective regulatory element, as measured by a co-localization assay. In some cases, the non-selective regulatory element is a constitutive promoter. In some cases, the non-selective regulatory element is any one of

domain or nuclease domain has been deactivated, e.g., a nuclease-deactivated Cas (dCas), a deactivated transcription activator-like effector nuclease, or a nuclease-deactivated zinc finger protein. In some cases, the transgene comprises a DNA binding domain linked to a transcriptional modulating domain (e.g., a transcriptional activator or repressor domain). In some cases, the gene editing protein is a Cas protein. In some cases, the regulatory elements combined are less than 2.5kb, less than 2kb, less than 1.5 kb, less than 1 kb, or less than 500 bp in size. In some cases, the non-PV cells comprise one or more of non-PV cell types in the CNS. In some cases, the non-PV cells comprise one or more of excitatory neurons, dopaminergic neurons, astrocytes, microglia, and motor neurons. In some cases, the nucleic acid cassette is a linear construct. In some cases, the nucleic acid cassette is a vector. In some cases, the vector is a plasmid. In some cases, the vector is a viral vector. In some cases, the viral vector is an adeno-associated virus (AAV) vector. In some cases, the AAV vector is AAV1, AAV8, AAV9, scAAV1, scAAV8, or scAAV9. In some cases, the viral vector is a lentiviral vector.

**[0007]** In one example, regulatory elements of any of the nucleic acid cassettes disclosed herein contain less than 600bp of contiguous sequence from within 10kb of the transcription start site of GAD2, GAD1, SYN1, NKX2.1, DLX1, DLX5/6, SST, PV, and/or VIP.

**[0008]** In one example, a method of treating a neurological disorder or condition in a subject in need thereof comprises delivering a therapeutically effective amount of any of the nucleic acid cassette disclosed herein. In some cases, the neurological disorder or condition is a psychiatric disorder (e.g., schizophrenia, obsessive compulsive disorder, addiction, depression, anxiety, psychosis); an autism spectrum disorder (e.g., Fragile X syndrome, Rett syndrome); epilepsy (e.g., chronic traumatic encephalopathy, generalized epilepsy with febrile seizures plus (GEFS+), epileptic encephalopathy, temporal lobe epilepsy, focal epilepsy, tuberous sclerosis); or neurodegeneration (e.g., Alzheimer's disease, Parkinson's disease). In some cases, the neurological disorder or condition is Dravet syndrome or Alzheimer's disease. In some cases, the neurological condition or disease is any seizure and/or epilepsy related condition or disease wherein PV neurons are implicated.

**[0009]** In one example, a method of increasing selective expression of a transgene in PV neurons in CNS comprises contacting a cell with a nucleic acid cassette disclosed herein.

**[0010]** In some examples, the present disclosure contemplates a method of targeting expression of any transgene to PV neurons in the CNS, the method comprising operably linking one or more of PV neuron selective regulatory elements to a transgene. In some cases, each of the regulatory elements comprises (i) a sequence of SEQ ID NOs: 1-32, (ii) a functional fragment

or a combination thereof, or (iii) a sequence with at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to (i) or (ii). In some cases, sequence identity is determined using BLAST. In some cases, the regulatory elements result in selective expression of the transgene in PV neurons that is greater than expression of the same transgene when operably linked to a non-selective regulatory element, as measured by a co-localization assay. In some cases, the immunohistochemical assay comprises an anti-PV antibody (e.g., as described in Example 5 below). In some cases, the non-selective regulatory element is a constitutive promoter. In some cases, the non-selective regulatory element is any one of CAG, EF1 $\alpha$ , SV40, CMV, UBC, PGK, and CBA. In some cases, the regulatory elements result in selective expression of the transgene in PV neurons at a level that is at least 1.5 fold, at least 2 fold, at least 3 fold, at least 4 fold, at least 5 fold, at least 6 fold, at least 7 fold, at least 8 fold, at least 9 fold, at least 10 fold, at least 15 fold, or at least 20 fold as compared to a non-selective regulatory element when operably linked to the transgene, as measured by a co-localization assay. In some cases, the regulatory elements result in selective expression in PV neurons that is at least 2%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% higher than expression in PV neurons when the transgene is operably linked to a non-selective regulatory element. In some cases, the regulatory elements result in selective expression in PV neurons that is about 1.5 times, 2 times, 2.5 times, 3 times, 3.5 times, 4 times, 4.5 times, 5 times, 5.5 times, 6 times, 6.5 times, 7 times, 7.5 times, 8 times, 8.5 times, 9 times, 9.5 times, 10 times, 15 times, 20 times, 25 times, 30 times, 40 times, 50 times, or 100 times higher than expected for natural distribution of PV neurons in CNS. In some cases, the transgene is any one of SCN1A, SNC2A, SNC8A, SCN1B, SCN2B, KV3.1, KV3.3, STXBP1, a DNA binding protein, a gene editing protein, or a functional fragment thereof. In some cases, the regulatory elements and the transgene are in an AAV. In some cases, the AAV is AAV1, AAV8, AAV9, scAAV1, scAAV8, or scAAV9.

**[0011]** In another example, the present disclosure contemplates a method of treating a neurological condition or disorder in a subject in need thereof, the method comprising contacting a cell with a nucleic acid cassette comprising: one or more regulatory elements operably linked to a transgene that result in selective expression of the transgene in PV neurons over one or more non-PV cells in CNS. In some cases, each of the regulatory elements comprises (i) a sequence of SEQ ID NOs: 1-32, (ii) a functional fragment or a

linked to a non-selective regulatory element, as measured by a co-localization assay. In some cases, the non-selective regulatory element is a constitutive promoter. In some cases, the non-selective regulatory element is any one of CAG, EF1 $\alpha$ , SV40, CMV, UBC, PGK, and CBA. In some cases, the regulatory elements result in selective expression in PV neurons at a level that is at least 1.5 fold, at least 2 fold, at least 3 fold, at least 4 fold, at least 5 fold, at least 6 fold, at least 7 fold, at least 8 fold, at least 9 fold, at least 10 fold, at least 15 fold, or at least 20 fold as compared to a non-selective regulatory element when operably linked to the transgene, as measured by a co-localization assay. In some cases, the regulatory elements result in selective expression in PV neurons that is at least 2%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% higher than expression in PV neurons when the transgene is operably linked to a non-selective regulatory element. In some cases, the regulatory elements result in selective expression in PV neurons that is about 1.5 times, 2 times, 2.5 times, 3 times, 3.5 times, 4 times, 4.5 times, 5 times, 5.5 times, 6 times, 6.5 times, 7 times, 7.5 times, 8 times, 8.5 times, 9 times, 9.5 times, 10 times, 15 times, 20 times, 25 times, 30 times, 40 times, 50 times, or 100 times higher than expected for natural distribution of PV neurons in CNS. In some cases, the nucleic acid cassette is in an AAV. In some cases, the AAV is AAV1, AAV8, AAV9, scAAV1, scAAV8, or scAAV9.

**[0012]** In one example, the present disclosure provides a method of treating Dravet syndrome, comprising contacting a cell with an AAV comprising a transgene, wherein the transgene is any one of (i) SCN1A, SNC2A, SNC8A, SCN1B, SCN2B, or a DNA binding protein, (ii) a functional fragment thereof, or (iii) a sequence having at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to (i) or (ii). In some cases, sequence identity is measured using BLAST. In some cases, the DNA binding protein modulates an endogenous gene. In some cases, the DNA binding protein is a transcriptional modulator. In some cases, the transgene is a DNA binding protein that comprises a DNA binding domain of a DNA binding protein or a DNA cleaving protein (e.g., a nuclease, a restriction enzyme, a recombinase, etc.) wherein the DNA cleaving domain or nuclease domain has been deactivated, e.g., a nuclease-deactivated Cas (dCas), a deactivated transcription activator-like effector nuclease, or a nuclease-deactivated zinc finger protein. In some cases, the DNA binding domain is linked to a transcriptional modulating domain (e.g., a transcriptional activator or repressor domain). In some cases, the transgene comprises a gene editing protein,

e.g., a Cas protein, Cas9. In some cases, the endogenous gene is SCN1A, SNC2A, SNC8A, SCN1B, or SCN2B. In some cases, the AAV further comprises one or more PV neuron selective regulatory elements or one or more regulatory elements disclosed herein operably linked to the transgene. In some cases, each of the regulatory elements independently comprises (i) a sequence of SEQ ID NOs: 1-32, (ii) a functional fragment or a combination thereof, or (iii) a sequence with at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to (i) or (ii).

**[0013]** In another example, the present disclosure provides a method of treating Alzheimer's disease, comprising contacting a cell with an AAV comprising a transgene, wherein the transgene is any one of (i) SCN1A, SNC2A, SNC8A, SCN1B, SCN2B, KV3.1, KV3.3, STXBP1, or a DNA binding protein; (ii) a functional fragment thereof; or (iii) a sequence having at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to (i) or (ii). In some cases, sequence identity is measured using BLAST. In some cases, the DNA binding protein modulates an endogenous gene. In some cases, the endogenous gene is SCN1A, SNC2A, SNC8A, SCN1B, SCN2B, KV3.1, KV3.3, or STXBP1. In some cases, the transgene is a DNA binding protein comprising a transcriptional modulator. In some cases, the transgene is a DNA binding protein that comprises a DNA binding domain of a DNA binding protein or a DNA cleaving protein (e.g., a nuclease, a restriction enzyme, a recombinase, etc.) wherein the DNA cleaving domain or nuclease domain has been deactivated, e.g., a nuclease-deactivated Cas (dCas), a deactivated transcription activator-like effector nuclease, or a nuclease-deactivated zinc finger protein. In some cases, the DNA binding domain is linked to a transcriptional modulating domain (e.g., a transcriptional activator or repressor domain). In some cases, the transgene comprises a gene editing protein, e.g., a Cas protein, Cas9. In some cases, the AAV further comprises one or more PV neuron selective regulatory elements or one or more regulatory elements disclosed herein operably linked to the transgene. In some cases, each of the regulatory elements independently comprises each of the regulatory elements independently comprises (i) a sequence of SEQ ID NOs: 1-32, (ii) a functional fragment or a combination thereof, or (iii) a sequence with at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to (i) or (ii).

**[0013a]** In one aspect, the present disclosure provides a nucleic acid cassette comprising a regulatory element comprising SEQ ID NO: 1, SEQ ID NO: 8 or SEQ ID NO: 30 operably linked to a heterologous transgene.

**[0013b]** In one aspect, the present disclosure provides a nucleic acid cassette comprising a regulatory element comprising a sequence with at least 95% sequence identity to SEQ ID NO: 1 or SEQ ID NO: 8 operably linked to a heterologous transgene that results in selective expression in parvalbumin (PV) neurons in the CNS over one or more non-PV cells in the CNS.

## CLAIMS

### WHAT IS CLAIMED IS:

1. A nucleic acid cassette comprising a regulatory element comprising SEQ ID NO: 1, SEQ ID NO: 8 or SEQ ID NO: 30 operably linked to a heterologous transgene.
2. The nucleic acid cassette of claim 1, wherein the transgene comprises a nucleic acid sequence encoding a DNA binding protein.
3. The nucleic acid cassette of claim 2, wherein the DNA binding protein is a transcriptional modulator of an endogenous gene.
4. The nucleic acid cassette of claim 2, wherein the DNA binding protein comprises a zinc finger.
5. The nucleic acid cassette of claim 2, wherein the DNA binding protein is a nuclease-deactivated zinc finger protein.
6. The nucleic acid cassette of claim 2, wherein the DNA binding protein is linked to a transcriptional activator domain.
7. The nucleic acid cassette of claim 2, wherein the DNA binding protein is linked to a transcriptional repressor domain.
8. The nucleic acid cassette of claim 2, wherein the DNA binding protein is a transcriptional activator that modulates an endogenous SCN1A gene.
9. The nucleic acid cassette of claim 1, wherein the nucleic acid cassette is an adeno-associated virus (AAV) vector.
10. The nucleic acid cassette of claim 9, wherein the AAV vector is AAV9 or scAAV9.
11. The nucleic acid cassette of claim 8, wherein the nucleic acid cassette is an adeno-associated virus (AAV) vector.
12. The nucleic acid cassette of claim 11, wherein the AAV vector is AAV9 or scAAV9.
13. The nucleic acid cassette of claim 1, wherein the regulatory element comprises SEQ ID NO: 31 or SEQ ID NO: 32.
14. The nucleic acid cassette of claim 13, wherein the heterologous transgene comprises a nucleic acid sequence encoding a DNA binding protein.
15. The nucleic acid cassette of claim 14, wherein the DNA binding protein is a transcriptional activator that modulates an endogenous SCN1A gene.
16. The nucleic acid cassette of claim 13, wherein the nucleic acid cassette is an adeno-associated virus (AAV) vector.
17. The nucleic acid cassette of claim 16, wherein the AAV vector is AAV9 or scAAV9.

18. The nucleic acid cassette of claim 15, wherein the nucleic acid cassette is an adeno-associated virus (AAV) vector.
19. The nucleic acid cassette of claim 18, wherein the AAV vector is AAV9.
20. The nucleic acid cassette of claim 18, wherein the AAV vector is scAAV9.
21. A nucleic acid cassette comprising a regulatory element comprising a sequence with at least 95% sequence identity to SEQ ID NO: 1 or SEQ ID NO: 8 operably linked to a heterologous transgene that results in selective expression in parvalbumin (PV) neurons in the CNS over one or more non-PV cells in the CNS.
22. The nucleic acid cassette of claim 21, wherein the heterologous transgene comprises a nucleic acid sequence encoding a DNA binding protein.
23. The nucleic acid cassette of claim 22, wherein the DNA binding protein is a transcriptional modulator of an endogenous gene.
24. The nucleic acid cassette of claim 22, wherein the DNA binding protein comprises a zinc finger.
25. The nucleic acid cassette of claim 22, wherein the DNA binding protein is linked to a transcriptional activator domain.
26. The nucleic acid cassette of claim 22, wherein the DNA binding protein is a transcriptional activator that modulates an endogenous SCN1A gene.
27. The nucleic acid cassette of claim 21, wherein the nucleic acid cassette is an adeno-associated virus (AAV) vector.
28. The nucleic acid cassette of claim 27, wherein the AAV vector is AAV9 or scAAV9.
29. The nucleic acid cassette of claim 21, wherein the regulatory element comprises a sequence with at least 95% sequence identity to SEQ ID NO: 31 or SEQ ID NO: 32.
30. The nucleic acid cassette of claim 29, wherein the heterologous transgene comprises a nucleic acid sequence encoding a DNA binding protein.
31. The nucleic acid cassette of claim 30, wherein the DNA binding protein is a transcriptional activator that modulates an endogenous SCN1A gene.
32. The nucleic acid cassette of claim 29, wherein the nucleic acid cassette is an adeno-associated virus (AAV) vector.
33. The nucleic acid cassette of claim 32, wherein the AAV vector is AAV9 or scAAV9.
34. The nucleic acid cassette of claim 31, wherein the nucleic acid cassette is an adeno-associated virus (AAV) vector.
35. The nucleic acid cassette of claim 34, wherein the AAV vector is AAV9 or scAAV9.