MATERIALS AND METHODS FOR TRANGENE EXPRESSION IN NEURAL CELLS

FIELD OF THE INVENTION

[0001] The disclosure is related materials and methods for delivering transgenes to neural cells and methods of treating neurological disorders.

INCORPORATION BY REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

[0002] The application is submitted with a sequence listing in electronic format. The sequence listing is provided as a file entitled "59851P2_SeqListing.xml," created April 29, 2024, which is 182,094 bytes in size. The information in the sequence listing is incorporated herein by reference in its entirety.

CROSS REFERENCE TO RELATED APPLICATIONS

[0003] This application claims the benefit of priority of U.S. Patent Application No. 63/575,574, filed April 5, 2024; U.S. Patent Application No. 63/641,650, filed May 2, 2024; and U.S. Patent Application No. 63/751,045, filed January 29, 2025, the contends of each of which are hereby incorporated by reference.

BACKGROUND

[0004] Neurological diseases and disorders have been reported to be a leading cause of disability worldwide. Steinmetz et al., "Global, regional, and national burden of disorders affecting the nervous system, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021," Lancet Neurol 2024 (doi.org/10.1016/S1474-4422(24)00038-3). Epilepsy is a group of neurological disorders characterized by recurrent epileptic seizures. Seizure medications can provide a therapeutic benefit to patients. However, not all subjects fully respond to seizure medications, and patients often become resistant to existing antiepileptic drugs. Indeed, about 30% of patients suffer from refractory epilepsy, which occurs when antiepilepsy medicines are ineffective at controlling seizures. In many instances, the cause of refractory epilepsy is not known and alternatives to seizure medications are limited. Gene therapy holds great promise for the treatment of epilepsy and other neural disorders.

SUMMARY OF THE INVENTION

[0005] The present disclosure provides materials and methods for delivery of a transgene to target cells. The regulatory elements, transgenes, and expression vectors described herein allow for robust expression of transgenes in target cells, such as neural cells, and, in various aspects, allow

for selective expression in target cells of interest. The regulatory elements, transgenes, and expression vectors are useful in, e.g., expressing a transgene in CNS cells that results in an improvement in at least one symptom related to a neurological disease or disorder, including epilepsy disorders, such as refractory epilepsy.

[0006] A nucleic acid comprising a regulatory element comprising a nucleic acid sequence having at least 80% identity to a sequence of SEQ ID NO: 10-13 or 16-19 (e.g., at least 85% identity, at least 90% identity, at least 95% identity, at least 98% identity, or 100% identity to a sequence of SEQ ID NO: 10-13 or 16-19). Optionally, the regulatory element is operably linked to a transgene, such as a transgene encoding a protein associated with a neurological disease or disorder. In various aspects, the transgene comprises the nucleic acid sequence of any one of SEQ ID NOS: 1-4. Also optionally, the nucleic acid may comprise a regulatory element comprising the nucleic acid sequence of SEQ ID NO: 22. In various aspects, the nucleic acid further comprises a nucleic acid sequence encoding a de-targeting element, such as a de-targeting element that reduces expression of the transgene in excitatory neurons, reduces expression of the transgene in liver cells, and/or reduces expression of the transgene in Dorsal Root Ganglion cells. The de-targeting element(s) may comprise a nucleic acid sequence at least 80%, at least 85%, at least 90%, at least 95%, or 100% identical to a sequence of SEQ ID NOS: 23-25, a sequence of SEQ ID NOS: 49-66, and/or a sequence of SEQ ID NOS: 29-48. The disclosure further provides an expression vector comprising the nucleic acid, such as viral vector (e.g., an AAV1, AAV8, AAV9, scAAV1, scAAV8, or scAAV9 vector). The disclosure also provides a composition comprising the nucleic acid described herein and a physiologically acceptable carrier.

[0007] Also provided is a method of delivering a transgene to a subject, the method comprising administering to the subject the expression vector described herein comprising a transgene.

[0008] Further provided is a method of treating a neurological disease or disorder, the method comprising administering to a subject in need thereof the expression vector comprising a transgene encoding a protein associated with a neurological disease or disorder or a transcription factor that increases expression of a gene associated with a neural disease or disorder. Optionally, the neurological disease or disorder is epilepsy (e.g., refractory epilepsy) or epileptic encephalopathy. Optionally, the neurological disease or disorder is Benign familial neonatal epilepsy (BFNE), Early myoclonic encephalopathy (EME), Ohtahara syndrome, Epilepsy of infancy with migrating focal seizures, infantile spasms (West syndrome), Myoclonic epilepsy in infancy (MEI), Benign infantile epilepsy, Benign familial infantile epilepsy, Dravet syndrome, Myoclonic encephalopathy in nonprogressive disorders, Early onset epilepsy, Febrile seizures, Febrile seizures plus (FS+),

Panayiotopoulos syndrome, Epilepsy with myoclonic atonic (previously astatic) seizures, Doose syndrome, Benign epilepsy with centrotemporal spikes (BECTS), frontal lobe epilepsy (e.g., Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)), Late onset childhood occipital epilepsy (Gastaut type), Epilepsy with myoclonic absences, Lennox-Gastaut syndrome, Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS), Landau-Kleffner syndrome (LKS), Childhood absence epilepsy (CAE), Juvenile absence epilepsy (JAE), Juvenile myoclonic epilepsy (JME), Epilepsy with generalized tonic-clonic seizures alone, Progressive myoclonic epilepsies (PME), Autosomal dominant epilepsy with auditory features (ADEAF), Focal epilepsy, Familial focal epilepsy with variable foci, Self-limited familial and non-familial neonatal infantile seizures, Reflex epilepsies, temporal lobe epilepsy (e.g., Mesial Temporal Lobe Epilepsy (MTLE)), Rasmussen syndrome, Gelastic seizures with hypothalamic hamartoma, Hemiconvulsion-hemiplegia-epilepsy, Benign Rolandic epilepsy, Genetic epilepsy with sleep-related hypermotor epilepsy (SHE), Epilepsy eyelid myoclonia (Jeavons syndrome), or Photosensitive epilepsy. In various aspects, the transgene comprises the nucleic acid sequence of any one of SEQ ID NOS: 1-4.

[0009] The disclosure also provides a method for expressing Syntaxin-binding protein 1 (STXBP1) in a GABAergic neuron. The method comprises contacting a GABAergic neuron cell with the expression vector described herein, wherein the expression vector comprises a transgene comprising the nucleic acid sequence of SEQ ID NO: 3 or SEQ ID NO: 4.

[0010] Also provided is a nucleic acid comprising a transgene comprising the nucleic acid sequence of SEQ ID NO: 3 or SEQ ID NO: 4. In various aspects, the transgene is operably linked to a regulatory element comprising any one or more of SEQ ID NOS: 5-21. In various aspects, the nucleic acid further comprises a nucleic acid sequence encoding a de-targeting element, such as a de-targeting element that reduces expression of the transgene in excitatory neurons, reduces expression of the transgene in liver cells, and/or reduces expression of the transgene in Dorsal Root Ganglion cells. The de-targeting element(s) may comprise a nucleic acid sequence at least 80%, at least 85%, at least 90%, at least 95%, or 100% identical to a sequence of SEQ ID NOS: 23-25, a sequence of SEQ ID NOS: 49-66, and/or a sequence of SEQ ID NOS: 29-48. The disclosure further provides an expression vector comprising the nucleic acid, such as viral vector (e.g., an AAV1, AAV8, AAV9, scAAV1, scAAV8, or scAAV9 vector). The disclosure also provides a composition comprising the nucleic acid described herein and a physiologically acceptable carrier.

[0011] Further provided is a method of treating a neurological disease or disorder, the method comprising administering to a subject in need thereof the expression vector comprising the

transgene comprising the nucleic acid sequence of SEQ ID NO: 3 or SEQ ID NO: 4. Optionally, the neurological disease or disorder is epilepsy (e.g., refractory epilepsy) or epileptic encephalopathy. The neurological disease or disorder, in various aspects, is not STXBP1-related or is of unknown etiology. If desired, the method further comprises detecting mutant STXBP1 in a biological sample of the subject.

[0012] The disclosure provides a nucleic acid comprising a transgene and a posttranscriptional regulatory element comprising SEQ ID NO: 22. The posttranscriptional regulatory element comprising SEQ ID NO: 22 may be located in the 3' untranslated region (UTR) of the transgene or may be located proximal to a poly-adenylation signal. The nucleic acid optionally further comprises a regulatory element comprising any one or more of SEQ ID NOs: 5-21. In various aspects, the nucleic acid further comprises a nucleic acid sequence encoding a de-targeting element, such as a de-targeting element that reduces expression of the transgene in excitatory neurons, reduces expression of the transgene in liver cells, and/or reduces expression of the transgene in Dorsal Root Ganglion cells. The de-targeting element(s) may comprise a nucleic acid sequence at least 80%, at least 85%, at least 90%, at least 95%, or 100% identical to a sequence of SEQ ID NOS: 23-25, a sequence of SEQ ID NOS: 49-66, and/or a sequence of SEQ ID NOS: 29-48. In various aspects, the transgene comprises the nucleic acid sequence of any one of SEQ ID NOS: 1-4. The disclosure further provides an expression vector comprising the nucleic acid, such as viral vector (e.g., an AAV1, AAV8, AAV9, scAAV1, scAAV8, or scAAV9 vector). The disclosure also provides a composition comprising the nucleic acid described herein and a physiologically acceptable carrier.

[0013] Also provided is a method of delivering a transgene to a subject, the method comprising administering to the subject the expression vector comprising a nucleic acid comprising a transgene and a posttranscriptional regulatory element comprising SEQ ID NO: 22.

[0014] Further provided is a method of treating a neurological disease or disorder, the method comprising administering to a subject in need thereof the expression vector comprising a transgene encoding a protein associated with a neurological disease or disorder or a transcription factor that increases expression of a gene associated with a neural disease or disorder and also comprising a posttranscriptional regulatory element comprising SEQ ID NO: 22. Optionally, the neurological disease or disorder is epilepsy (e.g., refractory epilepsy) or epileptic encephalopathy. Optionally, the neurological disease or disorder is Benign familial neonatal epilepsy (BFNE), Early myoclonic encephalopathy (EME), Ohtahara syndrome, Epilepsy of infancy with migrating focal seizures, infantile spasms (West syndrome), Myoclonic epilepsy in infancy (MEI), Benign infantile epilepsy, Benign familial infantile epilepsy, Dravet syndrome, Myoclonic encephalopathy in nonprogressive

disorders, Early onset epilepsy, Febrile seizures, Febrile seizures plus (FS+), Panayiotopoulos syndrome, Epilepsy with myoclonic atonic (previously astatic) seizures, Doose syndrome, Benign epilepsy with centrotemporal spikes (BECTS), frontal lobe epilepsy (e.g., Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)), Late onset childhood occipital epilepsy (Gastaut type), Epilepsy with myoclonic absences, Lennox-Gastaut syndrome, Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS), Landau-Kleffner syndrome (LKS), Childhood absence epilepsy (CAE), Juvenile absence epilepsy (JAE), Juvenile myoclonic epilepsy (JME), Epilepsy with generalized tonic-clonic seizures alone, Progressive myoclonic epilepsies (PME), Autosomal dominant epilepsy with auditory features (ADEAF), Focal epilepsy, Familial focal epilepsy with variable foci, Self-limited familial and non-familial neonatal infantile seizures, Reflex epilepsies, temporal lobe epilepsy (e.g., Mesial Temporal Lobe Epilepsy (MTLE)), Rasmussen syndrome, Gelastic seizures with hypothalamic hamartoma, Hemiconvulsion-hemiplegia-epilepsy, Benign Rolandic epilepsy, Genetic epilepsy with sleep-related hypermotor epilepsy (SHE), Epilepsy eyelid myoclonia (Jeavons syndrome), or Photosensitive epilepsy. In various aspects, the transgene comprises the nucleic acid sequence of any one of SEQ ID NOS: 1-4.

[0015] The disclosure further provides use of the nucleic acid or expression vector described herein in the manufacture of a medicament for the treatment of a neurological disease or disorder, wherein the nucleic acid or expression vector comprises a transgene encoding a protein associated with a neurological disease or disorder or a transcription factor that increases expression of a gene associated with a neural disease or disorder. Also provided is the nucleic acid or expression vector for use in the treatment of a neurological disease or disorder, wherein the nucleic acid or expression vector comprises a transgene encoding a protein associated with a neurological disease or disorder or a transcription factor that increases expression of a gene associated with a neural disease or disorder.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] FIG. 1 illustrates STXBP1 protein expression in HEK293 cells transiently transfected with EF1a-STXBP1 plasmids containing varying UTR Elements.

[0017] FIG. 2 illustrates the percentage of animals with Seizure score 5 in a PTZ assay after treatment with the indicated dose of an AAV9 vector comprising a Syn 1 promoter operably linked to the coding sequence for STXBP1 Iso1-co4, as well as the mutant WPRE element described herein and a polyA (AAV9-Syn1-Iso1-co4-mutwpre-sPA).

[0018] FIG. 3 illustrates seizure incidence in a 6Hz seizure assay after the indicated treatments.

[0019] FIG. 4 illustrates average seizure score of the animals from the assay in FIG. 3.

[0020] FIG. 5 illustrates the percentage of animals showing convulsions in a PTZ assay after the indicated treatments.

[0021] FIG. 6 illustrates total seizure time for the animals in the assay of FIG. 5.

[0022] FIG. 7 illustrates the highest Racine score for each of the animals in the assay of FIG. 5.

[0023] FIG. 8 illustrates the latency to convulsion for the animals in the assay of FIG. 5.

[0024] FIG. 9 illustrates representative images of IHC of pan-neuronal marker NeuN+ and eGFP reporter gene in post-necropsy brain sections from WT mice at four weeks after ICV-administration of AAV9-vectorized promoter candidate sequences.

[0025] FIG. 10 illustrates the percentage of excitatory neurons expressing GFP after transfection with the indicated constructs.

[0026] FIG. 11 illustrates the percentage of inhibitory neurons expressing GFP after transfection with the indicated constructs.

[0027] FIG. 12A is a bar graph illustrating percentage of DRG neurons expressing GFP after transfection with constructs comprising (DT-A) or not comprising (Control) de-targeting elements.

[0028] FIG. 12B is a bar graph illustrating percentage of central brain cells expressing GFP after transfection with constructs comprising (DT-A) or not comprising (Control) de-targeting elements.

[0029] FIG. 13 illustrates a schematic of an experimental plan described in the Examples.

[0030] FIG. 14 illustrates results of an open field assay performed at 8 weeks in the experiment outlined in FIG. 13. *Stxbp1*$^{+/-}$ (HET) vehicle dosed control mice showed a hyperactivity phenotype by travelling more distance as compared to *Stxbp1*$^{+/+}$ (WT) vehicle dosed control mice. HET mice dosed with AAV9-EF1a-STXBP1 at 1E11 vg/animal showed a significant decrease in hyperactivity when compared to HET control. WT mice dosed with AAV9-EF1a-STXBP1 at 1E11 vg/animal showed no difference in activity when compared to WT control.

[0031] FIG. 15 illustrates results of a nesting assay performed at 9 weeks in the experiment outlined in FIG. 13. *Stxbp1*$^{+/-}$ (HET) vehicle dosed control mice showed a lower score for nest quality as compared to *Stxbp1*$^{+/+}$ (WT) vehicle dosed control mice. HET mice dosed with AAV9-EF1a-STXBP1 at 1E11 vg/animal showed a significant increase in nesting score when compared to HET control. WT mice dosed with AAV9-EF1a-STXBP1 at 1E11 vg/animal showed no difference

when compared to WT control.

[0032] FIG. 16 illustrates results of a fear conditioning assay performed at 10 weeks in the experiment outlined in FIG. 13. *Stxbp1*$^{+/-}$ (HET) vehicle dosed control mice showed a deficit in cue based associative memory noted by percentage of freezing as compared to *Stxbp1*$^{+/+}$ (WT) vehicle dosed control mice. HET mice dosed with AAV9-EF1a-STXBP1 at 1E11 vg/animal showed a significant increase in freezing behavior when presented with cue (tone) as compared to HET control. WT mice dosed with AAV9-EF1a-STXBP1 at 1E11 vg/animal showed no difference when compared to WT control.

[0033] FIG. 17 illustrates results of a hindlimb clasping assay performed at 10.5 weeks in the experiment outlined in FIG. 13. HET vehicle dosed control mice showed a higher hindlimb clasping score as compared to *Stxbp1*$^{+/+}$ (WT) vehicle dosed control mice. HET mice dosed with AAV9-EF1a-STXBP1 at 1E11 vg/animal showed a significant decrease in hindlimb clasping score when compared to HET control. WT mice dosed with AAV9-EF1a-STXBP1 at 1E11 vg/animal showed no difference when compared to WT control.

[0034] FIG. 18 illustrates results of an EEG assay performed in the experiment outlined in FIG. 13. Epileptic activity in the form of spike-wave discharges (SWD) from frontal cortex was determined using electroencephalography (EEG). HET vehicle dosed control mice show a higher number of SWDs score as compared to *Stxbp1*$^{+/+}$ (WT) vehicle dosed control mice within a 3-hour window between 7 and 10 am. HET mice dosed with AAV9-EF1a-STXBP1 at 1E11 vg/animal showed a significant decrease in the SWDs when compared to HET control within the same time window.

[0035] FIG. 19 illustrates results of a PTZ-induced seizure assay performed in the experiment outlined in FIG. 13. In the PTZ-induced seizure assay, seizures were more frequent in vehicle-dosed WT mice compared with vehicle-dosed *Stxbp1*$^{+/-}$ mice, demonstrating a clear phenotypic baseline for increased seizure susceptibility in *Stxbp1*$^{+/-}$ mice. HET mice dosed with AAV9-EF1a-STXBP1 at 1E11 vg/animal showed a significant reduction in seizure susceptibility as compared to HET control. WT mice dosed with AAV9-EF1a-STXBP1 at 1E11 vg/animal showed no difference when compared to WT control. Data are provided as mean values ± standard deviation

[0036] FIG. 20 illustrates the concentration of STXBP1 in hippocampus of the animals in the experiment outlined in FIG. 13.

[0037] FIGs. 21-23 illustrate results from experiments performed in vehicle-dosed WT mice (n=19) and vehicle-dosed *STXBP1*$^{+/-}$ mice (n=15) compared with *STXBP1*$^{+/-}$ mice dosed with AAV9-EF1a-

STXBP1 with DRG-de-targeting (DT-A) regulatory element administered on PND1 at doses of 3E9, 1E10, 3E10, and 6E10 (n=18) vg/animal.

[0038] FIG. 21 illustrates results of a hindlimb clasping assay. There was a significant dose-dependent rescue of *STXBP1*$^{+/-}$ mice at 10.5 weeks after AAV9-EF1a-STXBP1-DT-A at doses of 1E10, E310, and 6E10 vg/animal compared with vehicle-dosed *STXBP1*$^{+/-}$ mice.

[0039] FIG. 22 illustrates results of contextual fear conditioning assays, wherein there was a significant dose-dependent rescue of *STXBP1*$^{+/-}$ mice at 10 weeks after AAV9-EF1a-STXBP1-DT-A at doses of 1E10, 3E10, and 6E10 vg/animal compared with vehicle-dosed *STXBP1*$^{+/-}$ mice.

[0040] FIG. 23 illustrates results of an EEG assay. Compared with vehicle-dosed *STXBP1*$^{+/-}$ mice, EEG also showed a significant dose-dependent rescue in *STXBP1*$^{+/-}$ mice aged between 6 and 12 weeks after AAV9-EF1a-STXBP1-DT-A at doses of 1E10, 3E10, and 6E10 vg/animal. Data are provided as mean values ± standard deviation.

[0041] FIGs. 24A-24B illustrate results of an open field assay (FIG. 24A) and nesting assay (FIG. 24B) performed with vehicle-dosed WT mice, vehicle-dosed *STXBP1*$^{+/-}$ mice, and *STXBP1*$^{+/-}$ mice dosed with of AAV9-EF1a-STXBP1 or AAV9-SEQ ID NO: 11-STXBP1, each at 1E11 vg/animal. Compared with vehicle-dosed *STXBP1*$^{+/-}$ mice, there was significant rescue in *STXBP1*$^{+/-}$ mice dosed with AAV9-EF1a-STXBP1 and AAV9-SEQ ID NO: 11-STXBP1.

[0042] FIG. 24C illustrates the study design utilized for FIGs. 24A, 24B, and 25-27.

[0043] FIG. 25 illustrates results of a hindlimb clasping assay performed in the mice described in FIG. 24.

[0044] FIG. 26 illustrates results of a cued fear conditioning assay performed in the mice described in FIG. 24.

[0045] FIG. 27 illustrates results of a PTZ induced seizure assay performed in the mice described in FIG. 24.

[0046] FIG. 28A illustrates expression of STXBP1 in WT animals treated with AAVs as indicated.

[0047] FIG. 28B illustrates expression of STXBP1 in STXBP1 HET animals treated with AAVs as indicated.

[0048] FIG. 28C illustrates quantification of mean intensity of STXBP1-iso2 IHC in mouse DRG after treatment with vehicle or AAVs as indicated.

[0049] FIG. 28D illustrates the percentage of STXBP1 positive nuclei in mouse brain after treatment with vehicle or AAVs as indicated.

[0050] FIG. 29 illustrates results of a hindlimb clasping assay performed in mice.

[0051] FIG. 30 illustrates results of a cued fear conditioning assay performed in mice.

[0052] FIG. 31 illustrates results of a PTZ induced seizure assay performed in mice.

[0053] FIG. 32A illustrates alanine aminotransferase levels in blood samples from the animals described in Example 6 up to 49 days post-dose.

[0054] FIG. 32B illustrates aspartate aminotransferase levels in blood samples from the animals described in Example 6 up to 49 days post-dose.

[0055] FIG. 32C illustrates glutamate dehydrogenase levels in blood samples from the animals described in Example 6 up to 49 days post-dose.

[0056] FIG. 33 illustrates VCN in the brains of the animals described in Example 6. VCN was assessed using a ddPCR-based method. At 50 ± 3 days post-dose, each vector was widely distributed in cortical and hippocampal regions, with no difference in VCN between AAV9-SEQ ID NO: 13-STXBP1, AAV9-SEQ ID NO: 11-STXBP1, or AAV9-SEQ ID NO: 13-STXBP1-DT-A, and AAV9-EF1a-STXBP1.

[0057] FIG. 34 illustrates transcript expression in the brains of the animals described in Example 6. Transcript expression in the brain was assessed using a ddPCR-based method. Transgene expression was higher with AAV9-SEQ ID NO: 13-STXBP1 than AAV9-SEQ ID NO: 11-STXBP1 and AAV9-EF1a-STXBP1 at a dose of 2E14 vg/animal, and higher with AAV9-SEQ ID NO: 13-STXBP1-DT-A than AAV9-EF1a-STXBP1 at a dose of 2E14 vg/animal. Transgene expression similar with AAV9-SEQ ID NO: 11-STXBP1AAV9-SEQ ID NO: 11-STXBP1 and AAV9-EF1a-STXBP1 2E14 (ns), and with AAV9-EF1a-STXBP1 at a dose of 1E14 and 2E14 vg/animal (ns). Data are provided as mean values ± standard deviation.

[0058] FIG. 35 illustrates VCN in the spinal cords of the animals described in Example 6. At 50 ± 3 days post-dose, each vector was widely distributed in the spinal cord with no difference in VCN between AAV9-SEQ ID NO: 13-STXBP1, AAV9-SEQ ID NO: 11-STXBP1, or AAV9-SEQ ID NO: 13-STXBP1-DT-A, and AAV9-EF1a-STXBP1 in SC:C3, SC:T2, SC:L1, and SC:L2, apart from a higher VCN for AAV9-SEQ ID NO: 13-STXBP1-DT-A versus AAV9-EF1a-STXBP1 in SC:L2.

[0059] FIG. 36 illustrates transgene expression in the spinal cords of the animals described in

Example 6. Transgene expression was significantly lower in SC:C3, SC:T2, SC:L1, and SC:L2 for AAV9-SEQ ID NO: 13-DT-A compared with AAV9-SEQ ID NO: 13-STXBP1, compared with AAV9-SEQ ID NO: 11-STXBP1, and compared with AAV9-EF1a-STXBP1, yet was similar between AAV9-SEQ ID NO: 13-STXBP1, AAV9-SEQ ID NO: 11-STXBP1, and AAV9-EF1a-STXBP1 (each comparison, ns). Data are provided as mean values ± standard deviation.

[0060] FIG. 37 illustrates vector expression in forebrain/midbrain. At 50 ± 3 days post-dose. vector expression was similar in the forebrain/midbrain for AAV9-SEQ ID NO: 13-STXBP1-DT-A compared with AAV9-SEQ ID NO: 13-STXBP1 (ns), AAV9-SEQ ID NO: 11-STXBP1 (ns), and AAV9-EF1a-STXBP1 (ns), and in the DRG, expression was lower for AAV9-SEQ ID NO: 13-STXBP1-DT-A compared with AAV9-SEQ ID NO: 13-STXBP1, AAV9-SEQ ID NO: 11-STXBP1, and AAV9-EF1a-STXBP1.

[0061] FIG. 38 is a chart summarizing data described in Example 6.

[0062] FIG. 39 illustrates neuronal selectivity (%NeuN+eGFP+/%eGFP+) of various promoters.

[0063] FIG. 40 illustrates activity of different promoters in liver.

[0064] FIG. 41 illustrates percentage freezing for animals with the indicated genetics or treatments in a fear conditioning assay. From left to right the bars indicate WT animals treated with vehicle, STXBP1 heterozygous animals treated with vehicle, and STXBP1 heterozygous animals treated with AAV9-SEQ ID NO: 11-STXBP1+DT-A.

[0065] FIG. 42 illustrates hindlimb clasping scores for animals with the indicated genetics or treatments in a fear conditioning assay. From left to right the bars indicate WT animals treated with vehicle, STXBP1 heterozygous animals treated with vehicle, and STXBP1 heterozygous animals treated with AAV9-SEQ ID NO: 11-STXBP1+DT-A.

[0066] FIG. 43 illustrates the number of SWDs for animals with the indicated genetics or treatments in a fear conditioning assay. From left to right the bars indicate WT animals treated with vehicle, STXBP1 heterozygous animals treated with vehicle, and STXBP1 heterozygous animals treated with AAV9-SEQ ID NO: 11-STXBP1+DT-A.

[0067] FIG. 44 illustrates representative IHC images of STXBP1 Iso2 expression in sacral DRG from NHP, from left to right group 1 (vehicle), group 4 (SEQ ID NO: 11) and group 5 (SEQ ID NO: 11 and DRG detargeting).

[0068] FIG. 45 illustrates mean transcripts/VCN for group 4 (SEQ ID NO: 11) and group 5 (SEQ ID

NO: 11 and DRG detargeting) in cortex and hippocampus, DRG, and spinal cord.

[0069] FIG. 46A provides representative IHC images of mouse cortex showing colocalization of SEQ ID NO: 13 driven eGFP expression in cells co-labelled with excitatory neuronal marker CaMKII (top panel) in addition to co-labelling with inhibitory neuronal markers PV, SST, and VIP (bottom panel), performed in a separate assay. Individual excitatory and inhibitory channels are shown for merged images.

[0070] FIG. 46B provides representative IHC images of mouse cortex showing colocalization of SEQ ID NO: 11 driven eGFP expression in cells co-labelled with excitatory neuronal marker CaMKII (top panel) in addition to co-labelling with inhibitory neuronal markers PV, SST, and VIP (bottom panel), performed in a separate assay. Individual excitatory and inhibitory channels are shown for merged images.

[0071] FIG. 47A provides representative EEG traces from the left frontal cortex of WT mice dosed with control and HET mice dosed with either control, AAV9-EF1a-STXBP1 or AAV9-SEQ ID 11-STXBP1. Only HET mice showed a high number of spike wave discharges (SWDs).

[0072] FIG. 47B illustrates quantification of the EEG-SWD from mice as described in FIG. 24C. Vehicle-dosed Stxbp1+/- mice implanted with cortical EEG electrodes had a significantly greater incidence of SWDs (mean 20.5 ± 7.83) compared with Stxbp1+/+ (0 SWD) within a 3-hour observation window. The SWD incidence in Stxbp1+/- mice dosed with AAV9-EF1α-STXBP1 and AAV9-SEQ ID 13-STXBP1 decreased to <5 within the same time window. Data are provided as mean values ± standard error of mean or percent values ± standard error of mean and assessed with ordinary one-way ANOVA or Kruskal Wallis if normality was not satisfied. ns, non-significant ($p > 0.05$); *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$; ****$p \leq 0.0001$.

[0073] FIGs. 48A and 48B illustrate transcript expression in hippocampus (FIG. 48A) and DRG (FIG. 48B) as assessed using a ddPCR method for AAV9-SEQ ID 13-STXBP1 at doses of 1E10, 3E10, and 6E10, and for AAV9-SEQ ID 13-STXBP1-DT-A at a dose of 3E10. Open symbols indicate HET; blue symbols indicate male; red symbols indicate female. Dotted line refers to the limit of detection. Mean levels with range are indicated. P values were calculated using unpaired 1-tailed t test (ns, $p > 0.05$; *$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$).

[0074] FIG. 49 illustrates an alignment of the promoter of SEQ ID NO: 13 against hg38 genome on UCSC genome browser (chromosome 20). Tracks from top to bottom: selected promoter sequence aligned to hg38 genome; Refseq genes from NCBI, thick lines are exons, thin lines are introns;

Vertebrate Multiz Alignment & Conservation (100 Species); DNA accessibility from single-nucleus ATAC-seq in selected cell types of the human brain from CATlas5, darker color indicates increased accessibility; DNase I hypersensitivity of SK-N-SH_RA (blue) and BE2_C (magenta) neuroblastoma cell lines; Density of ChIP-seq peaks in the ReMap 2022 Atlas of regulatory regions; GeneHancer Regulatory Elements and Gene Interactions; ENCODE cCREs including elements with distal enhancer-like signatures (yellow), proximal enhancer-like signatures (orange), and elements with promoter-like signatures (red); ORegAnno transcription factor binding site regulatory elements.

[0075] FIG. 50 illustrates an alignment of the promoter of SEQ ID NO: 11 against hg38 genome on UCSC genome browser (chromosome 20). Tracks from top to bottom: selected promoter sequence aligned to hg38 genome; Refseq genes from NCBI, thick lines are exons, thin lines are introns; Vertebrate Multiz Alignment & Conservation (100 Species); DNA accessibility from single-nucleus ATAC-seq in selected cell types of the human brain from CATlas5, darker color indicates increased accessibility; DNase I hypersensitivity of SK-N-SH_RA (blue) and BE2_C (magenta) neuroblastoma cell lines; Density of ChIP-seq peaks in the ReMap 2022 Atlas of regulatory regions; GeneHancer Regulatory Elements and Gene Interactions; ENCODE cCREs including elements with distal enhancer-like signatures (yellow), proximal enhancer-like signatures (orange), and elements with promoter-like signatures (red); ORegAnno transcription factor binding site regulatory elements.

[0076] FIG. 51 illustrates epileptic activity in the form of spike-wave discharges (SWD) from frontal cortex as determined using EEG. *Stxbp1*$^{+/-}$ (HET) vehicle-dosed control mice (n=11) show a higher number of SWDs score as compared to *Stxbp1*$^{+/+}$ (WT) vehicle-dosed control mice (n=10; $p<0.0001$) within a 3-hour window between 7 and 10 am. HET mice dosed with AAV9-EF1α-STXBP1 containing DRG-detargeting element (DT-A; n=9) or without it (n=7) at 6E10 vg/animal showed a similar decrease in the SWDs when compared to HET control within the same time window ($p<0.0001$). Data are provided as mean values ± standard deviation and assessed with ordinary one-way ANOVA.

[0077] FIG. 52A illustrates STXBP1 protein expression in liver tissue of wildtype and Stxbp1 heterozygous mice treated with vectors expressing an STXBP1 transgene under the control of the indicated promoters.

[0078] FIG. 52B illustrates STXBP1 protein expression in hippocampus tissue of wildtype and Stxbp1 heterozygous mice treated with vectors expressing an STXBP1 transgene under the control of the indicated promoters.

[0079] FIG. 53 illustrates the body weights of *Stxbp1*$^{+/+}$ WT and *Stxbp1*$^{+/-}$ HET mice at necropsy

after dosing with AAV9-EF1a-STXBP1, AAV9-SEQ ID 13-STXBP1 or AAV9-SEQ ID 11-STXBP1 at 1E11 vg/mouse or vehicle at PND1 via bilateral ICV injections.

[0080] FIG. 54A illustrates VCN in hippocampus as assessed using ddPCR methods for AAV9-SEQ ID 13-STXBP1 at doses of 1E10, 3E10, and 6E10 vg/animal, and for AAV9-SEQ ID 13-STXBP1-DT-A at a dose of 3E10 vg/animal. Blue symbols indicate male; red symbols indicate female. Dotted line refers to the limit of detection. Mean levels with range are indicated; P values are calculated using unpaired 1-tailed t test (ns = $P > 0.05$, * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$).

[0081] FIG. 54B illustrates VCN in DRG as assessed using ddPCR methods for AAV9- SEQ ID 13-STXBP1 at doses of 1E10, 3E10, and 6E10 vg/animal, and for AAV9- SEQ ID 13-STXBP1-DT-A at a dose of 3E10 vg/animal. Blue symbols indicate male; red symbols indicate female. Dotted line refers to the limit of detection. Mean levels with range are indicated; P values are calculated using unpaired 1-tailed t test (ns = $P > 0.05$, * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$).

[0082] FIG. 54C illustrates VCN in forebrain/midbrain as assessed using ddPCR methods for AAV9- SEQ ID 13-STXBP1 at doses of 1E10, 3E10, and 6E10 vg/animal. Blue symbols indicate male; red symbols indicate female. Dotted line refers to the limit of detection. Mean levels with range are indicated; P values are calculated using unpaired 1-tailed t test (ns = $P > 0.05$, * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$).

[0083] FIG. 55 illustrates transcripts in forebrain/midbrain as assessed using ddPCR methods for AAV9- SEQ ID 13-STXBP1 at doses of 1E10, 3E10, and 6E10 vg/animal. Blue symbols indicate male; red symbols indicate female. Dotted line refers to the limit of detection. Mean levels with range are indicated; P values are calculated using unpaired 1-tailed t test (ns = $P > 0.05$, * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$).

[0084] FIG. 56 provides representative images of STXBP1 IHC in mouse spinal cord and demonstrates exogenous expression from SEQ ID 13-STXBP1 in spinal cord (middle panel, arrowheads), compared with vehicle dosing (left panel), while the SEQ ID 13-STXBP1 +DT-A (right panel) staining was similar to vehicle treatment.

[0085] FIG. 57 illustrates vector distribution, by VCN, in post-necropsy peripheral organs in NHPs. For each organ, the left-most bar corresponds to EF1a-STXBP1, the second bar corresponds to SEQ ID 11-STXBP1, the third bar corresponds to SEQ ID 13-STXBP1, and the right most bar corresponds to SEQ ID 13-STXBP1-DT-A.

[0086] FIG. 58 illustrates RNA expression after treatment with the indicated vectors in post-

necropsy peripheral organs in NHPs. For each organ, the left-most bar corresponds to EF1a-STXBP1, the second bar corresponds to SEQ ID 11-STXBP1, the third bar corresponds to SEQ ID 13-STXBP1, and the right most bar corresponds to SEQ ID 13-STXBP1-DT-A.

[0087] FIG. 59 illustrates VCN in DRG sections as assessed using a ddPCR-based method. At 50 ± 3 days post-dose, each vector was widely distributed in the DRG with no difference in VCN between AAV9-SEQ ID 13-STXBP1 (n=4) or AAV9-SEQ ID 13-STXBP1-DT-A (n=3) across the cervical 3 (C3), thoracic 2 (T2), lumbar 1 (L1), and sacral 3 (S3) regions. Data are provided as mean values ± standard deviation with each symbol corresponding to an individual animal. The left bar corresponds to SEQ ID 13-STXBP1, and the right bar corresponds to SEQ ID 13-STXBP1-DT-A.

[0088] FIG. 60 illustrates aspartate aminotransferase (AST), levels in blood samples from the animals described in Example 6 up to 49 days post-dose.

[0089] FIG. 61 illustrates gamma glutamyltransferase (GGT), levels in blood samples from the animals described in Example 6 up to 49 days post-dose.

[0090] FIG. 62 illustrates body weights of the animals described in Example 6 up to 49 days post-dose.

[0091] FIG. 63 illustrates serum NfL concentrations in juvenile NHPs measured across multiple time points following ICV administration of the indicated treatment. Diamonds correspond to EF1a-STXBP1, squares correspond to SEQ ID 11-STXBP1, triangles correspond to SEQ ID 13-STXBP1, and inverted triangles correspond to SEQ ID 13-STXBP1-DT-A.

[0092] FIG. 64 illustrates Nerve conduction (NC) evaluation at Day 50 post ICV dosing revealed treatment-related peripheral sensory axonopathies in 2/4 animals dosed with AAV9-SEQ ID 13-STXBP1 and 2/3 animals dosed with AAV9-SEQ ID 11-STXBP1. '-' = no change in nerve conduction as compared to baseline for the respective animal; ↓=negligible decrease from baseline for the respective animal in NCV (Nerve Conduction Velocity m/s); ↓↓=minor decrease in NCV as compared to baseline (>10 m/s; yet remaining above LL (LL; lowest value recorded in healthy animals), or slightly below with no assumed functional consequence); ↓↓↓=decrease in NCV as compared to baseline, under LL, potentially clinically relevant consequences; *= sensory nerve action potential amplitude decrease only (within functional range); [1]minimally under LL, considered functionally normal.

DETAILED DESCRIPTION OF THE INVENTION

[0093] The disclosure provides materials and methods for delivery and, in some instances, selective expression of nucleic acids to target cells, including neuronal cells. The regulatory elements, transgenes, expression vectors, and compositions described herein are useful in a variety of contexts, including (but not limited to) gene therapy targeting neural cells for the treatment of neurological disorders, such as epilepsy and/or seizures. The neurological condition or disorder may be associated with a genetic defect in the central nervous system (CNS) or have unknown etiology. The data described herein demonstrate that the expression vectors of the disclosure reduce the symptoms of generalized epilepsy and STXBP1-related disorders in a safe, effective manner, thereby providing a therapeutic benefit to subjects suffering symptoms of epilepsy and other neurological impairments.

[0094] The disclosure provides a method of treating a neurological disease or disorder in a subject. Indeed, the disclosed materials and methods also are useful in, e.g., treating subjects suffering from a variety of neurological disease, including refractory epilepsy syndromes for which conventional antiepileptic drugs are inadequate, ineffective, or contraindicated, including but not limited to Dravet syndrome, Lennox-Gastaut syndrome, Doose syndrome, Rett syndrome, West syndrome, Infantile Spasms, and refractory seizures. Other neurological diseases include, e.g., chronic traumatic encephalopathy, generalized epilepsy with febrile seizures plus (GEFS+), epileptic encephalopathy, temporal lobe epilepsy, focal epilepsy, or tuberous sclerosis. The disclosure further provides a method of treating or reducing the occurrence of seizures in a subject by administering an effective dose of a nucleic acid of the present disclosure to the subject, thereby treating, reducing the occurrence, or ameliorating seizures in the subject.

[0095] Features of regulatory elements, transgenes, and expression vectors are described further below, including reference to nucleic acid and amino acid sequences. In general, "sequence identity" refers to an exact nucleotide-to-nucleotide or amino acid-to-amino acid correspondence of two polynucleotides or polypeptide sequences, respectively. Two or more sequences (polynucleotide or amino acid) can be compared by determining their "percent identity." The percent identity to a reference sequence (e.g., nucleic acid or amino acid sequence) may be calculated as the number of exact matches between two optimally aligned sequences divided by the length of the reference sequence and multiplied by 100. Conservative substitutions are not considered as matches when determining the number of matches for sequence identity. It will be appreciated that where the length of a first sequence (A) is not equal to the length of a second

sequence (B), the percent identity of A:B sequence will be different than the percent identity of B:A sequence. Sequence alignments, such as for the purpose of assessing percent identity, may be performed by any suitable alignment algorithm or program, including but not limited to the Needleman-Wunsch algorithm, the BLAST algorithm, the Smith-Waterman algorithm (see, e.g., the EMBOSS Water aligner), and Clustal Omega alignment program (F. Sievers et al., Mol Sys Biol. 7: 539 (2011)). Optimal alignment may be assessed using any suitable parameters of a chosen algorithm, including default parameters. The BLAST program is based on the alignment method of Karlin and Altschul, Proc. Natl. Acad. Sci. USA 87:2264-2268 (1990) and as discussed in Altschul, et al., J. Mol. Biol. 215:403-410 (1990); Karlin and Altschul, Proc. Natl. Acad. Sci. USA 90:5873-5877 (1993); and Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997).

[0096] A "fragment" of a nucleotide or peptide sequence is a sequence that is smaller than the "full-length" sequence (e.g., a smaller piece of a complete sequence as it is found in nature). A "functional fragment" of a DNA, RNA, or protein sequence refers to a biologically active fragment of the sequence that is shorter than the full-length or reference DNA, RNA, or protein sequence, but which retains at least one biological activity (either functional or structural) that is similar to a biological activity of the full-length or reference DNA, RNA, or protein sequence. For example, a "functional fragment" of a promoter sequence may be a fragment of a promoter sequence found in nature but which retains the ability to drive transcription of a nucleic acid.

[0097] The regulatory elements and transgenes described herein may be described as components of an expression cassette. An "expression cassette" refers to a nucleic molecule comprising one or more regulatory elements operably linked to a nucleic acid (i.e., transgene) to be expressed as an RNA transcript, including mRNA or a non-coding RNA. Any discussion below relating to “a nucleic acid” comprising various regulatory elements and/or transgenes also applies to expression cassettes, and vice versa. A “transgene” is a nucleic acid which is not naturally found the expression cassette or expression vector and is intended to be expressed in a target cell.

[0098] A “target cell” is any cell in which expression of a transgene is desired. For instance, target cells may be neural cells, muscle cells, cardiac cells, skin cells, immune cells, hematopoietic cells, cancer cells, pancreatic cells, or kidney cells. In preferred aspects, the target cells are neural cells, e.g., cerebrum cells, brainstem cells, hippocampus cells, or cerebellum cells. In some aspects, the target cell is a CNS cell, such as an excitatory neuron, an inhibitory neuron, a dopaminergic neuron, a glial cell, an ependymal cell, an oligodendrocyte, an astrocyte, a microglia, a motor neuron, or a vascular cell. In some aspects, the target cell is a GABAergic neuron, a non-GABAergic neuron

(e.g., a cell that does not express one or more of GAD2, GAD1, NKX2.1, DLX1, DLX5, SST and VIP), a non-parvalbumin (PV) neuron (e.g., a GABAergic neuron that does not express parvalbumin, such as non-PV GABAergic neurons that express calretinin (CR), somatostatin (SOM), cholecystokinin (CCK), CR + SOM, CR + neuropeptide Y (NPY), CR + vasointestinal polypeptide (VIP), SOM + NPY, SOM + VIP, VIP + choline acetyltransferase (ChAT), CCK + NPY, CR + SOM + NPY, and CR + SOM + VIP), or another CNS cell (e.g., a CNS cell type that has never expressed any of PV, GAD2, GAD1, NKX2.1, DLX1, DLX5, SST and VIP). In various aspects of the disclosure, the target cell is a GABAergic cell. GABAergic cells are inhibitory neurons which produce gamma-aminobutyric acid. GABAergic cells can be identified by the expression of glutamic acid decarboxylase 2 (GAD2). Other markers of GABAergic cells include GAD1, NKX2.1, DLX1, DLX5, SST, PV, and VIP. Optionally, the neural cell is a PV-expressing GABAergic cell. As described further below, the regulatory element(s) described herein may be employed to selectively drive expression in GABAergic cells (such as GABAergic cells that express PV cells), to a greater degree than another cell type (e.g., another CNS cell type, such as a non-GABAergic neuron (such as non-PV GABAergic neurons)).

[0099] A "non-target cell" is a cell in which expression of RNA or protein product is not desired, or in which only limited expression of RNA or protein product is preferred compared to another cell type. In various aspects, the non-target cell is a liver cell, an excitatory neuron, or a dorsal root ganglion cell.

[00100] Additional features of the materials and methods of the disclosure are described further below.

[00101] REGULATORY ELEMENTS

[00102] The disclosure provides regulatory elements (REs), which are nucleic acid sequences or genetic elements which are capable of influencing (e.g., increasing or decreasing) expression of a transgene (also referenced as "nucleic acid of interest") and/or confer selective expression of a transgene in a particular tissue or cell type of interest. REs can function at the DNA and/or the RNA level by, for example, modulating gene expression at the transcriptional phase, post-transcriptional phase, or at the translational phase of gene expression; by modulating the level of translation (e.g., stability elements that stabilize mRNA for translation), RNA cleavage, RNA splicing, and/or transcriptional termination; by recruiting transcriptional factors to a coding region that increase gene expression; by increasing the rate at which RNA transcripts are produced, increasing the stability of RNA produced, and/or increasing the rate of protein synthesis from RNA transcripts; and/or by

preventing RNA degradation and/or increasing its stability to facilitate protein synthesis.

[00103] The REs are "operably linked" to a transgene in various aspects of the disclosure, meaning that the elements are juxtaposed such that a functional relationship between the elements is formed (e.g., the RE influences expression of the transgene). For instance, a regulatory element, which can comprise promoter and/or enhancer sequences, is operatively linked to a transgene coding region if the regulatory element helps initiate transcription of the coding sequence. There may be intervening residues between the regulatory element and coding region so long as a functional relationship is maintained.

[00104] Regulatory elements may be derived from non-coding DNA sequences. In various aspects, regulatory elements are derived from non-coding DNA are associated with genes, such as upstream sequences, introns, 3' and 5' untranslated regions (UTRs), and/or downstream regions. In other instances, regulatory elements derived from non-coding DNA sequences are not associated with a gene. In some cases, the genomic region from which a regulatory element is derived is distinct from the genomic region from which an operably linked transgene (when present) is derived. In some cases, a RE is derived from a distal genomic region or location with respect to the genomic region or location from which the transgene is derived (such as a naturally occurring or an endogenous version of the transgene). Examples of regulatory elements include, but are not limited to, promoters, enhancers, repressors, silencers, insulator sequences, introns, UTRs, inverted terminal repeat (ITR) sequences, long terminal repeat sequences (LTR), stability elements, posttranslational response elements, and polyadenylation (poly A) sequences, and further include any combination of any of the foregoing, such as enhancer-promoter combinations or repressor-promoter combinations.

[00105] In certain aspects, the RE(s) allow for selective or preferential expression in target cells. In this regard, the RE(s) may drive transcription or translation only (or at least preferentially) in particular target cells, may enhance transcription or translation in particular target cells compared to non-target cells, may reduce transcription or translation in non-target cells compared to target cells, or may inhibit transcription or translation in non-target cells. In certain aspects, the regulatory element allows for selective expression of a transgene in the brain. In certain aspects, the regulatory element allows for selective expression in the frontal cortex, parietal cortex, temporal cortex, hippocampus, medulla, and occipital cortex (i.e., enhanced expression in these areas of the brain compared to expression in other regions of the body). In certain aspects, the regulatory element(s) allows for selective expression of a transgene in neuronal cells, such as unipolar,

bipolar, multipolar, or pseudounipolar neurons. In certain aspects, the neuronal cells are GABAergic neurons. Increasing selectivity of gene expression can improve the efficacy of a gene therapy, decrease the effective dose needed to result in a therapeutic effect, minimize adverse effects or off-target effect, and/or increase patient safety and/or tolerance.

[00106] *Promoters, enhancers*

[00107] In various aspects, the disclosure provides nucleic acids comprising novel promoter sequences, a transgene operably linked to a promoter or fragment thereof which drives the expression of a transgene in a target cell (e.g., an expression cassette), and expression vectors comprising a transgene operably linked to a promoter or fragment thereof optionally in combination with other REs. Promoters are non-coding DNA sequences that interact with transcription factors and RNA polymerase to initiate transcription. Promoter regions are typically upstream of a transgene to drive expression.

[00108] Various types of promoters are known in the art, including constitutive promoters, inducible promoters, tissue specific promoters, and the like. Examples of promoters commonly used to drive transgene expression include viral promoters (e.g., cytomegalovirus promoter) and cellular promoters (e.g., human elongation factor-1α promoter). In preferred aspects of the disclosure, the promoter is a promoter (or functional fragment thereof) that drives transcription in CNS cells.

[00109] In various aspects, the promoter is a constitutive promoter, such as the simian virus 40 (SV40), human cytomegalovirus (CMV) promoter, mouse mammary tumor virus (MMTV), human ubiquitin C (UBC) promoter (e.g., SEQ ID NO: 6), human immunodeficiency virus (HIV) long terminal repeat (LTR) promoter, the human elongation factor-1α (EF1α) promoter (e.g., SEQ ID NO: 5), human phosphoglycerate kinase promoter (PGK) promoter, the MND promoter (a synthetic promoter that contains the U3 region of a modified MoMuLV LTR with myeloproliferative sarcoma virus enhancer), and the CMV early enhancer/chicken beta actin (CAG) promoter. In various aspects, a transgene as described herein is operably linked to a EF1α promoter.

[00110] In various aspects, the promoter is a tissue-specific or tissue-selective promoter. For instance, in some aspects of the disclosure, the promoter is a CNS selective promoter, meaning that the promoter preferentially drives expression in CNS cells, such as neuronal cells. By "preferentially drives expression" (and similar terminology) is meant that the promoter only promotes expression in a target cell type (e.g., neurons) or mediates a level of expression that is at least two times, at least five times, at least ten times, or at least 25 times greater in a target cell type compared to a non-target cell type. Examples of CNS selective promoters include, e.g., a promoter

selected from the group consisting of Ca2+/calmodulin-dependent kinase subunit a (CaMKII) promoter, aldolase C promoter, beta-tubulin gene promoter, synapsin I promoter (SYN1 or hSYN (e.g., SEQ ID NO: 7)), 67 kDa glutamic acid decarboxylase (GAD67) promoter, GABA(A) receptor delta subunit gene promoter, homeobox Dlx5/6 promoter, glutamate receptor 1 (GluR1) promoter, preprotachykinin 1 (Tael) promoter, Neuron-specific enolase (NSE) promoter, Neurofilament-L promoter, Neuropeptide Y promoter, nestin promoter, dopaminergic receptor 1 (Drdla) promoter, MAP1B promoter, myelin-associated oligodendrocyte basic protein promoter (MOBP), myelin basic protein promoter (MBP), Ta1a-tubulin promoter, decarboxylase promoter, dopamine P-hydroxylase promoter, NCAM promoter, HES-5 promoter, a-intemexin promoter, peripherin promoter, GAP-43 promoter, PaqR4 promoter, STXBP1 promoter, and Synaptosomal-Associated Protein, 25kDa (SNAP25) promoter. In various aspects, a transgene as described herein is operably linked to an STXBP1promoter or a SNAP25 promoter.

[00111] In some aspects, promoter is a GABAergic neuron selective promoter. GABAergic cells are inhibitory neurons which produce gamma-aminobutyric acid. GABAergic neuron selective promoters are regulatory elements that specifically modulate gene expression in a GABAergic neuron. For example, GABAergic neuron-selective promoter enhance expression in a GABAergic neuron relative to one or more other CNS cell types (e.g., excitatory neurons, dopaminergic neurons, astrocytes, microglia, motor neurons, vascular cells, non-GABAergic neurons, or other CNS cells). A PV neuron selective promoter also may be used. PV neuron selective promoters are promoters that specifically modulate gene expression in a PV neuron. For example, PV neuron selective promoters enhance expression in a PV neuron relative to one or more other CNS cell types.

[00112] In some aspects, the transcription regulatory element may comprise one or more sequences set forth SEQ ID NOS: 79-110. In some instances, the transcription regulatory element comprises one or more of SEQ ID NOS: 79-110, (ii) a nucleic acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of SEQ ID NOS: 79-110, (iii) a functional fragment of any sequence of (i) or (ii), or (iv) a combination of any sequence of (i), (ii) and/or (iii). In some cases, sequence identity is measured by BLAST. Transcription regulatory elements selective for expression in GABAergic neurons are further described in International Patent Publication No. WO 2018/187363, which is hereby incorporated by reference in its entirety.

[00113] In various aspects, a transgene may also be operably linked to an enhancer. In general, an

enhancer is a short (50-1500 bp) region of DNA recognized by transcription factors to drive transcription of a gene. Like promoter elements, enhancers are cis-acting. Enhancers are typically located distal from a gene which they influence (e.g., up to 1 Mbp upstream or downstream from the coding region start site). Examples of enhancers include, but are not limited to, SEQ ID NOs: 16-19.

[00114] The disclosure also provides novel promoter and promoter/enhancer elements demonstrated to efficiently drive expression in neuronal cells. In various aspects, the disclosure provides a nucleic acid comprising a regulatory element comprising (i) a nucleic acid sequence of SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and/or SEQ ID NO: 19; (ii) a nucleic acid sequence at least 80% identical (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, 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% identical) to (i); or (iii) a nucleic acid sequence having no more than 15, no more than 10, or no more than 5 mismatched base pairs compared to any one of SEQ ID NOS: 10-13 or 16-19. In various aspects, the regulatory element is a promoter, such as a regulatory element comprising a nucleic acid sequence of SEQ ID NO: 10 or a regulatory element comprising a nucleic acid sequence of SEQ ID NO: 12. In various aspects, the regulatory element is an enhancer, such as a regulatory element comprising a nucleic acid sequence of SEQ ID NO: 16, a regulatory element comprising a nucleic acid sequence of SEQ ID NO: 18, or a regulatory element comprising a nucleic acid sequence of SEQ ID NO: 19. In various aspects, the enhancer is operably linked to a promoter. In this regard, the disclosure provides a nucleic acid comprising (i) regulatory elements comprising SEQ ID NO: 10 and SEQ ID NO: 18 or (ii) regulatory elements comprising SEQ ID NO: 12 and SEQ ID NO: 19. In various aspects, the regulatory element(s) comprises a nucleic acid sequence of SEQ ID NO: 11. In various aspects, the regulatory element(s) comprises a nucleic acid sequence of SEQ ID NO: 13.

[00115] Other promoters and enhancers suitable for use in the context of the disclosure include, but are not limited to, those comprising the nucleic acid sequence of SEQ ID NOS: 5-7 and 14-16.

[00116] *Post-transcriptional regulatory elements*

[00117] REs also include post-transcriptional regulatory elements, such as the woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) or the Hepatitis B posttranscriptional regulatory element. Posttranscriptional regulatory elements are cis-acting RNA elements that promote transport of mRNA from the nucleus to the cytoplasm, thereby enhancing accumulation of

cytoplasmic mRNA and resulting in increased mRNA stability and protein yield. The disclosure provides a nucleic acid comprising posttranscriptional regulatory element comprising the nucleic acid sequence of SEQ ID NO: 22. In various aspects, the disclosure provides a nucleic acid comprising a transgene and a posttranscriptional regulatory element of SEQ ID NO: 22, which is optionally located in a 3' untranslated region (UTR) of the transgene. In various aspects, the posttranscriptional regulatory element of SEQ ID NO: 22 is located proximal to a polyadenylation signal in the nucleic acid.

[00118] *De-targeting elements*

[00119] The nucleic acid of the disclosure also may encode one or more de-targeting elements. "De-targeting" generally refers to decreasing the expression in a non-target cell. In this regard, the nucleic acid may comprise one or more non-coding genetic elements which, when transcribed, impart one or more regions on the resulting mRNA which decrease expression of a transgene in a non-target cell.

[00120] Aspects of the disclosure provide nucleic acid molecules that include one or more de-targeting elements. For example, one or more de-targeting elements that reduce expression of a transgene in excitatory neurons, one more pre de-targeting elements that reduce expression of a transgene in dorsal root ganglion (DRG) neurons, one or more de-targeting elements that reduce expression of a transgene in liver, or combinations thereof, are contemplated. For instance, in some aspects, the nucleic acid comprises a transgene of the disclosure encoding a therapeutic cargo, e.g., a therapeutic protein or a therapeutic RNA, and also includes one or more de-targeting sequences/elements to reduce expression of the transgene in excitatory neurons, DRG cells, and/or liver cells. The presence of one or more de-targeting elements for excitatory neurons in an RNA molecule with a heterologous RNA sequence reduces the activity of the heterologous RNA sequence in excitatory neurons compared to an RNA molecule containing the heterologous RNA sequence without the one or more excitatory neuron de-targeting elements. Similarly, the presence of one or more liver de-targeting elements in an RNA molecule with a heterologous RNA sequence reduces the activity of the heterologous RNA sequence in liver cells, e.g., liver cells of a subject, compared to an RNA molecule containing the heterologous RNA sequence without the one or more liver de-targeting elements. The presence of one or more de-targeting elements for DRG cells in an RNA molecule with a heterologous RNA sequence reduces the activity of the heterologous RNA sequence in DRG cells compared to an RNA molecule containing the heterologous RNA sequence without the one or more DRG cells de-targeting elements. Further, the presence of one or more

excitatory neuron de-targeting elements, one or more DRG cell de-targeting elements, and one or more liver de-targeting elements in an RNA molecule with a heterologous RNA sequence reduces the activity of the heterologous RNA sequence in excitatory neurons, DRG cells, and in liver cells compared to an RNA molecule containing the heterologous RNA sequence without the one or more excitatory neuron de-targeting elements, DRG cell de-targeting elements, and liver de-targeting elements.

[00121] Optionally, the de-targeting sequences described herein does not result in significantly decreased expression of a polypeptide encoded by the mRNA, the mRNA, or the ncRNA in target cells as compared to expression of the polypeptide, mRNA, or ncRNA in target cells from an otherwise equivalent RNA transcript without the de-targeting sequence. In some instances, the de-targeting element may result in expression of a polypeptide encoded by the mRNA, the mRNA, or the ncRNA in target cells at a level that is at least 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% of the expression of the polypeptide, mRNA, or ncRNA in target cells from an otherwise equivalent RNA transcript without the sequence of the de-targeting element. In these aspects, the reduction of expression of the polypeptide in non-target cells is greater than the reduction of expression of the polypeptide, mRNA, or ncRNA in the target cells when compared to otherwise equivalent RNA transcript without the de-targeting element.

[00122] Examples of de-targeting elements include binding sites for microRNA (miRNA or miR) or DNA sequences encoding miRNA binding sites on transcript RNA. miRNAs are small non-coding RNAs (~20 nucleotides) that regulate gene expression post-transcriptionally by hybridizing to complementary recognition sites within an mRNA molecule, leading to inhibition of gene expression by promoting degradation of the mRNA transcript or by repressing translation of the protein encoded by the mRNA. The recognition sites are referenced herein as binding sites, which are regions that hybridize under physiologic conditions (e.g., in a cell of a subject) to a miRNA.

[00123] In any aspect of the disclosure, the de-targeting sequence can be in a 3' untranslated region (UTR), a 5' UTR, or an intron of a mRNA, for example. If the mRNA encoded by the transgene contains more than de-targeting sequence, the multiple sequences may be in different parts or regions of the mRNA. In many aspects, the de-targeting element(s) are in the 3' UTR of the transgene product (e.g., mRNA).

[00124] In various aspects of the disclosure, the nucleic acid encodes at least one miRNA binding site for a miRNA expressed in an excitatory neuron, such as non-GABAergic neurons. In some

aspects, the nucleic acid encodes at least one miR-221 binding site, at least one miR-128 binding site, and/or at least one miR-222 binding site (including any combination of the foregoing). An exemplary miR-221 binding site is encoded by the nucleic acid sequence of SEQ ID NO: 24. An exemplary miR-128 binding site is encoded by the nucleic acid sequence of SEQ ID NO: 23. An exemplary miR-222 binding site is encoded by the nucleic acid sequence of SEQ ID NO: 25. If desired, the nucleic acid may comprise regulatory elements that result in more than one copy of any miR binding site in an RNA transcript. For example, the disclosure provides nucleic acids encoding at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more miR-128 binding sites; at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more miR-221 binding sites; and/or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more miR-222 binding sites. Where multiple binding sites are present, the binding sites may be arranged in any order. For example, for a polynucleotide containing two miR-128 binding sites and two miR-221 binding sites, the binding sites may be arranged in any of the following configurations: miR-128 - miR-128 - miR-221 - miR-221; miR-128 - miR-221 - miR-128 - miR-221; miR-128 - miR221 - miR221 - miR-128; miR-221 -miR128 - miR221 - miR128; miR-221 - miR128 - miR128 - miR221; or miR221 - miR221-miR128 - miR128. In various aspects of the disclosure, the nucleic acid encodes at least one miR-128 binding site and at least one miR-221, such as four miR-128 binding sites and four miR-221 binding sites. In this respect, the nucleic acid may comprise the nucleotide sequence of SEQ ID NO: 26. The four miR-128 binding sites may be followed by the four miR-221 binding sites (i.e., miR-128 - miR-128 - miR-128 - miR-128 - miR-221 - miR-221 -miR-221 - miR-221), although this is not required. In an alternative aspect, the nucleic acid encodes two miR-221 binding sites, two miR-128 binding sites, and two miR-222 binding sites. In this respect, the nucleic acid may comprise the nucleotide sequence of SEQ ID NO: 28. The binding sites may be arranged in the following order, although this is not required: miR-221 - miR-222 -miR-128 - miR-221 - miR-222 - miR-128. An alternative de-targeting element comprises SEQ ID NO: 27.

[00125] In various aspects of the disclosure, the nucleic acid comprises a de-targeting element comprising (i) a nucleic acid sequence of any of SEQ ID NOS: 26-28, (ii) a nucleic acid sequence encoding a transcript which comprises the nucleic acid sequence of any one of SEQ ID NOS: 23-25, (iii) a functional fragment thereof, or (iv) a sequence at least 80% identical (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, 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% identical) to (i)-(iii), or any combination thereof. In various aspects, the nucleic acid comprises a nucleotide sequence that encodes a de-targeting element (present on the transcript) comprising the nucleic acid sequence of any one of

SEQ ID NOS: 23-25 comprising one, two, three, or four nucleotide substitutions present therein. In various aspects, the nucleic acid comprises a nucleotide sequence that encodes a de-targeting element comprising any one of SEQ ID NOS: 23-25 or any combination thereof. In various aspects, the nucleic acid comprises a de-targeting element comprising the nucleic acid sequence of any one of SEQ ID NOS: 26-28 comprising one, two, three, or four nucleotide substitutions present therein. In various aspects, the nucleic acid comprises a de-targeting element comprising any one of SEQ ID NOS: 26-28 or any combination thereof. In various aspects, the nucleic acid comprises a de-targeting element comprising the nucleic acid sequence of SEQ ID NO: 28.

[00126] In instances where a functional fragment of the de-targeting sequence is utilized, the functional fragment may comprise any contiguous stretch of nucleotides in SEQ ID NOS: 23-25 on a transcript or SEQ ID NOS: 26-28 on the coding nucleic acid of at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, or at least 21 nucleotides in length. In various aspects, a functional fragment may comprise one, two, three, or four mismatches as compared to the corresponding contiguous stretch of nucleotides in SEQ ID NOS: 23-25 or SEQ ID NOS: 26-28. A functional fragment may start at any nucleotide in SEQ ID NOS: 23-25 or SEQ ID NOS: 26-28 that allows for its full representation in SEQ ID NOS: 23-25 or SEQ ID NOS: 26-28.

[00127] The nucleic acid molecule may contain any combination of two, three, four or five or more of the sequences described herein. For example, the nucleic acid comprising a sequence of (i) any of SEQ ID NOS: 26-28, (ii) a functional fragment thereof, or (iii) a sequence at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, 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% identical to (i) or (ii), may further comprise a second sequence of (i), (ii), or (iii), a third sequence of (i), (ii), or (iii), a fourth sequence of (i), (ii), or (iii), and/or five or more sequences of (i), (ii), or (iii). In any embodiment, the nucleic acid cassette may comprise two or more copies (e.g., two, three, four, five, or more than five copies) of a sequence of (i), (ii), or (iii).

[00128] In various aspects, the nucleic acid comprising a nucleic acid sequence encoding (i) any of SEQ ID NOS: 23-25, (ii) a functional fragment thereof, or (iii) a sequence at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, 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% identical to (i) or (ii), may further comprise a second sequence of (i), (ii), or (iii), a third sequence of (i), (ii), or (iii), a fourth sequence

of (i), (ii), or (iii), and/or five or more sequences of (i), (ii), or (iii). In any embodiment, the nucleic acid cassette may comprise two or more copies (e.g., two, three, four, five, or more than five copies) of a sequence of (i), (ii), or (iii).

[00129] Reducing expression of the transgene in excitatory neurons relative to target cells means that the reduction in transgene expression driven by the excitatory neuron de-targeting sequences disclosed herein is greater in excitatory neurons than in the target cells. As such, while reduced transgene expression in target cells may be observed in certain embodiments, it is less than that observed in excitatory neurons. In various aspects, an mRNA encoded by the nucleic acid comprising a sequence of (i), (ii), or (iii), may result in decreased expression of a polypeptide encoded by the mRNA in excitatory neurons at a level that is at least 1.5-fold, at least 2-fold, at least 5-fold, or at least 10-fold as compared to expression of the polypeptide in excitatory neurons from an otherwise equivalent mRNA without the sequence of (i), (ii), or (iii). In these aspects of the disclosure, the reduction of polypeptide production in excitatory neurons is greater than the reduction of polypeptide production in the target cells when compared to otherwise equivalent mRNA without the sequence of (i), (ii), or (iii). Similarly, an ncRNA containing a sequence of (i), (ii), or (iii), may have decreased expression in excitatory neurons at a level that is at least 1.5-fold, at least 2-fold, at least 5-fold, or at least 10-fold as compared to expression of the ncRNA without the sequence of (i), (ii), or (iii) in excitatory neurons. In these aspects, the reduction of ncRNA expression in excitatory neurons is greater than the expression reduction of the ncRNA in the target cells when compared to otherwise equivalent ncRNA without the sequence of (i), (ii), or (iii).

[00130] Reduced expression may also be considered in terms of percentage decrease in excitatory neurons compared to non-excitatory neurons. In this respect, the sequence of (i) any of SEQ ID NOS: 26-28, (ii) a variant, functional fragment, or combination thereof, or (iii) a sequence at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, 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% identical to (i) or (ii), may result in decreased production of a polypeptide encoded by the mRNA, the mRNA itself, or the ncRNA in excitatory neurons at a level 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% lower than expression of the polypeptide, mRNA, or ncRNA in excitatory neurons from an otherwise equivalent RNA transcript without the sequence of (i), (ii), or (iii). In these aspects, the reduction of expression of the polypeptide or RNA transcript in excitatory

neurons is greater than the reduction of expression of the polypeptide in the target cells when compared to otherwise equivalent RNA transcript without the sequence of (i), (ii), or (iii).

[00131] In various aspects, the sequence encoding (i) any of SEQ ID NOS: 23-25, (ii) a variant, functional fragment, or combination thereof, or (iii) a sequence at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, 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% identical to (i) or (ii), may result in decreased production of a polypeptide encoded by the mRNA, the mRNA itself, or the ncRNA in excitatory neurons at a level 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% lower than expression of the polypeptide, mRNA, or ncRNA in excitatory neurons from an otherwise equivalent RNA transcript without the sequence of (i), (ii), or (iii). In these aspects, the reduction of expression of the polypeptide or RNA transcript in excitatory neurons is greater than the reduction of expression of the polypeptide in the target cells when compared to otherwise equivalent RNA transcript without the sequence of (i), (ii), or (iii).

[00132] In various aspects of the disclosure, the nucleic acid encodes at least one miRNA binding site for a miRNA expressed in DRG cells. In various aspects of the disclosure, the nucleic acid encodes a nucleic acid molecule (e.g., mRNA) that comprises one or more binding sites recognized by hsa-mir-196b-5p, hsa-mir-10b-5p, hsa-mir-24-2-5p, hsa-mir-183-3p, hsa-mir-196a-5p, hsa-mir-494-3p, or any combination thereof (each of which are de-targeting elements contemplated by the present disclosure).

[00133] Optionally, the nucleic acid molecule comprises a nucleic acid sequence that encodes one or more binding sites for hsa-mir-196b-5p (e.g., a region comprising the nucleic acid sequence of SEQ ID NO: 29). Optionally, the nucleic acid molecule comprises a nucleic acid sequence that encodes one or more binding sites for hsa-mir-10b-5p (e.g., a region comprising the nucleic acid sequence of SEQ ID NO: 30). Optionally, the nucleic acid molecule comprises a nucleic acid sequence that encodes one or more binding sites for hsa-mir-24-2-5p (e.g., a region comprising the nucleic acid sequence of SEQ ID NO: 31). Optionally, the nucleic acid molecule comprises a nucleic acid sequence that encodes one or more binding sites for hsa-mir-183-3p (e.g., a region comprising the nucleic acid sequence of SEQ ID NO: 32). Optionally, the nucleic acid molecule comprises a nucleic acid sequence that encodes one or more binding sites for hsa-mir-196a-5p (e.g., a region comprising the nucleic acid sequence of SEQ ID NO: 33). Optionally, the nucleic acid

molecule comprises a nucleic acid sequence that encodes one or more binding sites for hsa-mir-494-3p (e.g., a region comprising the nucleic acid sequence of SEQ ID NO: 34).

[00134] In various aspects of the disclosure, the nucleic acid comprises a nucleic acid sequence that encodes a de-targeting element comprising (i) the nucleic acid sequence of any of SEQ ID NOS: 29-48, (ii) a functional fragment thereof, or (iii) a sequence at least 80% identical (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, 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% identical) to (i) or (ii), or any combination thereof. In various aspects, the nucleic acid comprises a nucleic acid sequence that encodes a de-targeting element comprising the nucleic acid sequence of any one of SEQ ID NOS: 29-48 comprising one, two, three, or four nucleotide substitutions present therein. In various aspects, the nucleic acid comprises a nucleic acid sequence that encodes a de-targeting element comprising any one of SEQ ID NOS: 29-48 or any combination thereof. These sequences reduce the expression of the transgene in dorsal root ganglion cells (DRG) relative to target cells (such as neural cells, e.g., neurons) and as such, may be employed in a variety of gene therapy strategies that target cells that are not in the DRG.

[00135] Reducing expression of the transgene in DRG cells relative to target cells means that the reduction in transgene expression driven by the DRG de-targeting sequences disclosed herein is greater in DRG cells than in the target cells. As such, while reduced transgene expression in target cells may be observed in certain embodiments, it is less than that observed in DRG cells. Reduced expression in the DRG can offer a technical advantage by reducing or eliminating DRG toxicity and/or axonopathy in a subject receiving a gene therapy targeted to a non-DRG cell or tissue, e.g., neural cells, e.g., neurons, thereby improving its safety profile. In various aspects, an mRNA containing a sequence of (i), (ii), or (iii), may result in decreased expression of a polypeptide encoded by the mRNA in DRG cells at a level that is at least 1.5-fold, at least 2-fold, at least 5-fold, or at least 10-fold as compared to expression of the polypeptide in DRG cells from an otherwise equivalent mRNA without the sequence of (i), (ii), or (iii). In these aspects of the disclosure, the reduction of polypeptide production in DRG cells is greater than the reduction of polypeptide production in the target cells when compared to otherwise equivalent mRNA without the sequence of (i), (ii), or (iii). Similarly, an ncRNA containing a sequence of (i), (ii), or (iii), may have decreased expression in DRG cells at a level that is at least 1.5-fold, at least 2-fold, at least 5-fold, or at least 10-fold as compared to expression of the ncRNA without the sequence of (i), (ii), or (iii) in DRG cells. In these aspects, the reduction of ncRNA expression in DRG cells is greater than the

expression reduction of the ncRNA in the target cells when compared to otherwise equivalent ncRNA without the sequence of (i), (ii), or (iii).

[00136] Reduced expression may also be considered in terms of percentage decrease in DRG cells compared to non-DRG cells. In this respect, the sequence of (i) any of SEQ ID NOS: 29-48, (ii) a functional fragment, or (iii) a sequence at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, 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% identical to (i) or (ii), may result in decreased production of a polypeptide encoded by the mRNA, the mRNA itself, or the ncRNA in DRG cells at a level 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% lower than expression of the polypeptide, mRNA, or ncRNA in DRG cells from an otherwise equivalent RNA transcript without the sequence of (i), (ii), or (iii). In these aspects, the reduction of expression of the polypeptide or RNA transcript in DRG cells is greater than the reduction of expression of the polypeptide in the target cells when compared to otherwise equivalent RNA transcript without the sequence of (i), (ii), or (iii).

[00137] In instances where a functional fragment of the de-targeting sequence is utilized, the functional fragment may comprise any contiguous stretch of nucleotides in SEQ ID NOS: 29-48 of at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, or at least 21 nucleotides in length. In various aspects, a functional fragment of any of SEQ ID NOS: 29-48 may comprise one, two, three, or four mismatches as compared to the corresponding contiguous stretch of nucleotides in SEQ ID NOS: 29-48. A functional fragment may start at any nucleotide in SEQ ID NOS: 29-48 that allows for its full representation in SEQ ID NOS: 29-48. The nucleic acid may comprise a nucleic acid sequence that encodes any of the functional fragments described herein.

[00138] The nucleic acid molecule may encode a transcript comprising any combination of two, three, four or five or more of the de-targeting sequences described herein. For example, the nucleic acid comprising a nucleic acid sequence that encodes (i) any of SEQ ID NOS: 29-48, (ii) a functional fragment thereof, or (iii) a sequence at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, 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% identical to (i) or (ii), may further comprise a second nucleic acid

sequence that encodes a de-targeting element of (i), (ii), or (iii), a third nucleic acid sequence that encodes a de-targeting element of (i), (ii), or (iii), a fourth nucleic acid sequence that encodes a de-targeting element of (i), (ii), or (iii), and/or five or more nucleic acid sequences that encode de-targeting element of (i), (ii), or (iii). In any embodiment, the nucleic acid cassette may comprise sequences that encode two or more copies (e.g., two, three, four, five, or more than five copies) of a sequence of (i), (ii), or (iii).

[00139] In addition to excitatory neuron (e.g., non-GABAergic neuron) and DRG de-targeting elements, the disclosure further contemplates use of liver de-targeting elements in the nucleic acids (and vectors) described herein. Liver de-targeting elements may be provided in expression cassettes, RNA molecules e.g., RNA transcripts, synthetic RNA molecules, and the like, as described for excitatory neuron and DRG de-targeting elements. Use of liver de-targeting elements to reduce the expression and/or activity of a transgene in liver cells or tissue is contemplated. It will be appreciated that descriptions provided above relating to excitatory neuron and DRG cell de-targeting elements can be applied to the liver de-targeting elements, with the understanding that the tissue/cells being de-targeted by the liver de-targeting elements is live tissue/liver cells and not DRG cells.

[00140] Thus, in certain aspects, the nucleic acid comprises a nucleic acid sequence encoding a de-targeting element comprising (i) the nucleic acid sequence of any SEQ ID NOS: 49-66, (ii) a functional fragment thereof, or (iii) a sequence at least 80% identical (e.g., at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, 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% identical) to (i) or (ii) is provided. In various aspects, the nucleic acid comprises a nucleic acid sequence encoding a de-targeting element comprising the nucleic acid sequence of any one of SEQ ID NOS: 49-66 comprising one, two, three, or four nucleotide substitutions present therein. In various aspects, the nucleic acid comprises a nucleic acid sequence encoding a de-targeting element comprising any one of SEQ ID NOS: 49-66 or any combination thereof. Optionally, the nucleic acid comprises nucleic acid sequences encoding at least two, at least three, or at least four different sequences selected from SEQ ID NOS: 49-66. In these aspects, the sequence decreases expression of the RNA transcript in liver cells.

[00141] Reducing expression of the transgene in liver cells relative to target cells means that the reduction in transgene expression driven by the liver de-targeting sequences disclosed herein is greater in liver cells than in the target cells. As such, while reduced transgene expression in target

cells may be observed in certain embodiments, it is less than that observed in liver cells. In various aspects, an mRNA containing a sequence of (i), (ii), or (iii), may result in decreased expression of a polypeptide encoded by the mRNA in liver cells at a level that is at least 1.5-fold, at least 2-fold, at least 5-fold, or at least 10-fold as compared to expression of the polypeptide in liver cells from an otherwise equivalent mRNA without the sequence of (i), (ii), or (iii). In these aspects of the disclosure, the reduction of polypeptide production in liver cells is greater than the reduction of polypeptide production in the target cells when compared to otherwise equivalent mRNA without the sequence of (i), (ii), or (iii). Similarly, an ncRNA containing a sequence of (i), (ii), or (iii), may have decreased expression in liver cells at a level that is at least 1.5-fold, at least 2-fold, at least 5-fold, or at least 10-fold as compared to expression of the ncRNA without the sequence of (i), (ii), or (iii) in liver cells. In these aspects, the reduction of ncRNA expression in liver cells is greater than the expression reduction of the ncRNA in the target cells when compared to otherwise equivalent ncRNA without the sequence of (i), (ii), or (iii).

[00142] Reduced expression may also be considered in terms of percentage decrease in liver cells compared to non-liver cells. In this respect, the sequence of (i) any of SEQ ID NOS: 49-66, (ii) a functional fragment, or (iii) a sequence at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, 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% identical to (i) or (ii), may result in decreased production of a polypeptide encoded by the mRNA, the mRNA itself, or the ncRNA in liver cells at a level 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% lower than expression of the polypeptide, mRNA, or ncRNA in liver cells from an otherwise equivalent RNA transcript without the sequence of (i), (ii), or (iii). In these aspects, the reduction of expression of the polypeptide or RNA transcript in liver cells is greater than the reduction of expression of the polypeptide in the target cells when compared to otherwise equivalent RNA transcript without the sequence of (i), (ii), or (iii).

[00143] In instances where a functional fragment of the de-targeting sequence is utilized, the functional fragment may comprise any contiguous stretch of nucleotides in SEQ ID NOS: 49-66 of at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20, or at least 21 nucleotides in length. In various aspects, a functional fragment of any of SEQ ID NOS: 49-66 may comprise one, two, three, or four mismatches as compared to the corresponding contiguous stretch of nucleotides in SEQ ID NOS: 49-66. A

functional fragment may start at any nucleotide in SEQ ID NOS: 49-66 that allows for its full representation in SEQ ID NOS: 49-66. The nucleic acid may comprise a nucleic acid sequence that encodes any of the functional fragments described herein.

[00144] The nucleic acid molecule may encode a transcript containing any combination of two, three, four or five or more of the sequences described herein. For example, the nucleic acid comprising a nucleic acid sequence encoding (i) any of SEQ ID NOS: 49-66, (ii) a functional fragment thereof, or (iii) a sequence at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, 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% identical to (i) or (ii), may further comprise a second nucleic acid sequence encoding (i), (ii), or (iii), a third nucleic acid sequence encoding (i), (ii), or (iii), a fourth nucleic acid sequence encoding (i), (ii), or (iii), and/or five or more nucleic acid sequences encoding (i), (ii), or (iii). In any embodiment, the nucleic acid cassette may comprise nucleic acid sequence(s) encoding two or more copies (e.g., two, three, four, five, or more than five copies) of a sequence of (i), (ii), or (iii).

[00145] Additionally, the liver de-targeting elements of SEQ ID NOS: 49-66 (or any of the other de-targeting elements described herein) can be combined with one another or with the liver de-targeting elements set forth in International Patent Application No. PCT/US2023/065801 (International Patent Publication No. 2023/201354), incorporated by reference herein, if desired.

[00146] The liver de-targeting sequences can be employed in any embodiment in which de-targeting in liver is desirable, including embodiments which also comprise use of DRG de-targeting elements and/or excitatory neuron de-targeting elements. Indeed, the DRG, excitatory neuron, and liver de-targeting sequences may be combined with one another (in any combination) or with other de-targeting sequences to produce an expression cassette that more effectively de-targets a single tissue (e.g., excitatory neuron, DRG, or liver) or a combination of tissues (e.g., excitatory neuron and DRG, excitatory neuron and liver, DRG and liver, or all three of excitatory neurons, DRG, and liver). Indeed, a nucleic acid can comprise (i) multiple different DRG de-targeting elements combined with one or more liver de-targeting elements and/or one or more excitatory neuron de-targeting elements, (ii) multiple different liver de-targeting elements combined with one or more DRG de-targeting elements and/or one or more excitatory neuron de-targeting elements, or (iii) multiple different excitatory neuron de-targeting elements combined with one or more DRG de-targeting elements and/or one or more liver de-targeting elements, each element of which may be independently present in one or multiple (e.g., two, three, four or five or more) copies. For instance,

If desired, the nucleic acid may comprise at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more DRG de-targeting elements and/or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more liver de-targeting elements and/or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more excitatory neuron de-targeting elements, which may be the same or different. Where multiple de-targeting elements (e.g., miRNA binding sites) are present, the binding sites may be arranged in any order.

[00147] To illustrate, the nucleic acid may comprise a therapeutic transgene encoding an RNA transcript (e.g., an mRNA), wherein the nucleic acid encodes a first sequence that de-targets expression in DRG cells and a second sequence that de-targets expression in liver cells. The first and second sequences may result in decreased expression of the RNA transcript or a polypeptide encoded by the RNA transcript (e.g., when the RNA transcript is an mRNA) in DRG and liver cells relative to a target tissue, e.g., neural cells such as cerebrum cells, brainstem cells, hippocampus cells, cerebellum cells, or GABAergic cells (e.g., GABAergic cells that are parvalbumin expressing cells). Instead of the first de-targeting element that de-targets DRG cells or the second de-targeting element, or in addition to the first and second de-targeting elements, the nucleic acid may comprise a third sequence encoding a de-targeting element that de-targets expression in excitatory neurons. For example, (a) the first sequence may encode (i) any of SEQ ID NOS: 29-48, (ii) a variant, functional fragment, or combination thereof, or (iii) a sequence at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, 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% identical to (i) or (ii); (b) the second sequence may encode (iv) any of SEQ ID NOS: 49-66, (v) a variant, functional fragment, or combination thereof, or (vi) a sequence at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, 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% identical to (iv) or (v); and/or the third sequence may encode (vii) any of SEQ ID NOS: 23-25, (viii) a variant, functional fragment, or combination thereof, or (ix) a sequence at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, 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% identical to (vii) or (viii).

[00148] The nucleic acid of the disclosure may comprise multiple de-targeting elements that reduce expression of the transgene in two more tissues (e.g., two, three, four, or five non-target tissues). The nucleic acid of the disclosure may comprise a single de-targeting element that reduces expression of the transgene in two more tissues. An exemplary de-targeting element comprises a

nucleic acid sequence at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, 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% identical to SEQ ID NO: 67 (e.g., 100% identical to SEQ ID NO: 67). In various aspects, the nucleic acid comprises a de-targeting element comprising the nucleic acid sequence of SEQ ID NO: 67 comprising one, two, three, or four nucleotide substitutions present therein.

[00149] In any of the aspects of the disclosure described above involving use of de-targeting elements, the nucleic acid optionally comprises a tissue selective or tissue specific promoter operably linked to a transgene. For instance, the promoter may be a CNS selective promoter operably linked to a therapeutic transgene, such as a therapeutic transgene that encodes a therapeutic expression product for a neurological disease or disorder, such as a neurological disease or disorder associated with seizures and/or *STXBP1* mutation.

[00150] *Polyadenylation sequence*

[00151] In certain embodiments, the nucleic acid further comprises a polyA signal sequence. Suitable polyA signal sequences include, for example, an artificial polyA that is about 75 bp in length (PA75) (see e.g., International Patent Publication No. WO 2018/126116), the bovine growth hormone polyA, SV40 early polyA signal, SV40 late polyA signal, rabbit beta globin polyA, HSV thymidine kinase polyA, protamine gene polyA, adenovirus 5 E1b polyA, growth hormone polyA, or a PBGD polyA. In exemplary embodiments, the polyA sequence is an hGH polyA or a synthetic polyA. See also International Patent Publication No. WO 2019/109051, incorporated herein by reference.

[00152] TRANSGENE

[00153] The nucleic acid molecules provided herein, in various aspects, comprise a transgene operably linked to a regulatory element. Any transgene of interest can be designed and used in the context of the disclosure. In some aspects, the transgene comprises a modified nucleotide sequence (e.g., alternative codons) as compared to a reference nucleotide sequence.

[00154] Optionally, the transgene is a therapeutic transgene. In this regard, the transgene optionally encodes a therapeutic protein, e.g., a protein that reduces the risk of developing a disease or disorder and/or ameliorates one or more symptoms of a disease or disorder (e.g., a neurological disease or disorder), although transgenes which encode an RNA transcript, e.g., an mRNA or a functional RNA, such as an antisense RNA, also are contemplated. The transgene may encode a wildtype version of a protein. In these instances, the transgene may be administered to a subject expressing a mutant version of a protein, or may be administered to a subject to increase

expression levels of the wildtype version of the protein in the subject. Alternatively, the transgene may encode a mutant form of a protein. In these instances, the mutant protein may be associated with increased activity compared to a wildtype version of the protein. The transgene may encode a specific isoform of a protein.

[00155] The transgene may encode a gene product which provides a therapeutic benefit in subjects suffering from a disease or disorder, such as cancer, atherosclerosis, sickle-cell anemia, hemophilia, infection, metabolic disorders, or neurological disorders. In various embodiments, the transgene may encode an intracellular protein (e.g., a cytoplasmic protein, a nuclear protein, an organellar protein such as a mitochondrial protein or lysosomal protein), a membrane protein, or an extracellular protein (i.e., a protein released into the milieu, such as an antibody or a hormone). Examples of potential therapeutic proteins include, but are not limited to, enzymes, structural proteins, signaling proteins, regulatory proteins, immune regulatory proteins, transport proteins, sensory proteins, motor proteins, and storage proteins.

[00156] In various aspects of the disclosure, the transgene encodes a therapeutic protein associated with a neurological disease or disorder, e.g., a protein whose aberrant function (e.g., resulting from a genetic mutation or abnormality) is associated with a neurological disease or disorder. Neurological diseases or disorders include any disorder related to a component of the neural system, e.g., brain, spinal cord, or other nerves. The disease or disorder may be associated with biochemical, electrical, and/or structural abnormalities within the neural system, including abnormalities in neuronal cells, blood vessels of the neural system, and the like. Neurological diseases and disorders include those associated with one or more genetic mutations, as well as those with unknown etiologies. Neurological diseases and disorders include, but are not limited to, conditions associated with epileptic seizures, neurodegenerative disorders, and/or neurodevelopmental disorders. Examples of neurological diseases or disorders include, e.g., Alpers-Huttenlocher Syndrome, Angelman Syndrome, CDKL5 Deficiency Disorder, Dravet Syndrome, Rett Syndrome, Parkinson's Disease and Parkinson's LIDS (side effect of Parkinson's medication), Alzheimer's disease, Creatine Transporter Deficiency, FOXG1 Syndrome, Fragile X Syndrome, Phelan-McDermid Syndrome, Childhood Absence Epilepsy, Childhood Epilepsy Centrotemporal Spikes (Benign Rolandic Epilepsy), Dravet Syndrome, Early Myoclonic Encephalopathy (EME), Epilepsy Eyelid Myoclonia Jeavons Syndrome, Epilepsy of Infancy with Migrating Focal Seizures, Epilepsy Myoclonic Absences, Epileptic Encephalopathy Continuous Spike and Wave During Sleep CSWS, Infantile Spasms (West Syndrome), Juvenile Myoclonic Epilepsy, Landau-Kleffner Syndrome, Lennox-Gastaut Syndrome (LGS), Myoclonic Epilepsy in

Infancy, Ohtahara Syndrome, Panayiotopoulos Syndrome, Progressive Myoclonic Epilepsies, Reflex Epilepsies, Self-Limited Familial and Non-Familial Neonatal Infantile Seizures, Self-Limited Late Onset Occipital Epilepsy Gastaut Syndrome, Epilepsy Generalized Tonic Clonic Seizures Alone, Genetic Epilepsy with Febrile Seizures Plus, Juvenile Absence Epilepsy, Myoclonic Atonic Epilepsy Doose Syndrome, Sleep- related Hypermotor Epilepsy (SHE), febrile seizures, focal epilepsy, West Syndrome, Early Onset Epilepsy, Benign Familial Infantile Epilepsy, and Attention Deficit-Hyperactivity Disorder.

[00157] In some preferred aspects of the disclosure, the transgene encodes STXBP1 or a functional fragment thereof.

[00158] Another example of a transgene contemplated by the disclosure is a transgene that encodes a transcription factor, which may be a transcription activator or a transcription repressor. A transcription factor comprises a DNA binding domain and a transcription modulation domain. A DNA binding domain binds a transcription factor binding site in target DNA. A transcription modulation domain (TMD) contains binding sites for other proteins that promote or repress transcription of a target nucleic acid sequence. The TMD may contact transcriptional machinery (e.g., RNA polymerase) either directly or through other proteins (known as coactivators or comodulators). The transcription factor may be wildtype (i.e., unmodified) or may be a non-naturally occurring transcription factor, such as a transcription factor engineered such that, e.g., a DNA binding domain is operably linked to a transcription modulation domain to which the DNA binding domain is not naturally linked (e.g., derived from a different transcription factor or from a different species). In various aspects, the transgene encodes a transcription factor that modulates expression (e.g., enhances expression) of SCN1A. Transcription factors are further described in International Patent Publication No. WO 2020/0243651, incorporated by reference in its entirety.

[00159] In preferred aspects of the disclosure, the transgene encodes an isoform of STXBP1 (also referred to as Munc18-1, N-Sec1, p67, rbSec1, Sect, Unc-18-1, and Unc18a). In this regard, the transgene optionally comprises the nucleic acid sequence of SEQ ID NO: 3 or the nucleotide sequence of SEQ ID NO: 4. In alternative aspects, the transgene optionally comprises the nucleic acid sequence of SEQ ID NO: 1 or the nucleotide sequence of SEQ ID NO: 2. SEQ ID NOS: 1-4 encode different isoforms of STXBP1. In various aspects of the disclosure, the nucleic acid sequence encoding an isoform of STXBP1 is operably linked to a neural cell specific promoter, such as the neural cell promoters described above. In various aspects of the disclosure, the nucleotide sequence encoding STXBP1 is operably linked to the EF1a promoter. In this regard, the transgene comprising the nucleotide sequence of SEQ ID NO: 3 or SEQ ID NO: 4 is optionally

operably linked to a regulatory sequence comprising SEQ ID NO: 5.

[00160] In some aspects, the transgene of the present disclosure encodes a therapeutic payload, e.g., a therapeutic protein, such as STXBP1 (e.g., encoded by SEQ ID NO: 3 or 4), and is present in a nucleic acid that also encodes one or more de-targeting elements (e.g., excitatory neuron, DRG, and/or liver de-targeting sequences/elements) to reduce expression of the transgene in non-target cells (e.g., excitatory neurons, DRG cells, and/or liver cells), such as de-targeting elements comprising one or more of SEQ ID NOS: 23-25 (e.g., encoded by one or more of SEQ ID NOS: 26-28), SEQ ID NOS: 29-48, and/or SEQ ID NOS: 49-66. Further, the transgene may be operably linked to a promoter active in neural cells, such as a neural cell specific promoter comprising any one of SEQ ID NOS: 10-13. In various aspects, the nucleic acid also comprises a post-translational regulatory element comprising SEQ ID NO: 22.

[00161] VECTORS

[00162] Expression vectors (also referred to herein as "vectors") are nucleic acid-based constructs which can be used to mediate delivery of a polynucleotide to a cell. An expression vector may be an integrating or non-integrating vector, referring to the ability of the expression vector to integrate an expression cassette or transgene into the genome of the host cell. Examples of vectors include non-viral vectors (e.g., plasmids) and viral vectors. A vector generally comprises genetic elements, e.g., regulatory elements, operatively linked to a nucleic acid that encodes an RNA or protein of interest to facilitate expression of the nucleic acid in a target cell. The combination of regulatory elements and the coding nucleic acid of interest to which they are operably linked for expression is referred to as an expression cassette.

[00163] In various aspects, the vector is a non-viral vector. Examples of non-viral vectors include, but are not limited to, linear oligonucleotides and circular plasmids; artificial chromosomes such as human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), and bacterial artificial chromosomes (BACs or PACs)); episomal vectors; transposons (e.g., PiggyBac); and cosmids.

[00164] Methods and compositions for non-viral delivery of nucleic acids are known in the art, including physical and chemical methods. Physical methods generally refer to methods of delivery employing a physical force to counteract the cell membrane barrier in facilitating intracellular delivery of genetic material. Examples of physical methods include the use of a needle, ballistic DNA, electroporation, sonoporation, photoporation, magnetofection, and hydroporation. Chemical methods generally refer to methods in which chemical carriers facilitate entry of a nucleic acid to a cell. Chemical methods may employ, e.g., inorganic particles, lipid-based carriers, polymer-based

carriers and peptide-based carriers.

[00165] In some aspects, a non-viral expression vector is administered to a target cell using an inorganic particle. Inorganic particles include, e.g., nanoparticles, such as nanoparticles that are engineered for various sizes, shapes, and/or porosity to escape from the reticuloendothelial system or to protect an entrapped molecule from degradation. Inorganic nanoparticles for use in delivery a nucleic acid to a target cell may be prepared from metals (e.g., iron, gold, and silver), inorganic salts, or ceramics (e.g., phosphate or carbonate salts of calcium, magnesium, or silicon). The surface of nanoparticles can be coated to facilitate DNA binding or targeted gene delivery. Magnetic nanoparticles (e.g., supermagnetic iron oxide), fullerenes (e.g., soluble carbon molecules), carbon nanotubes (e.g., cylindrical fullerenes), quantum dots, and supramolecular systems also are contemplated.

[00166] Optionally, a vector is delivered to a target cell using a lipid-based delivery system, such as a lipid delivery vehicle comprising cationic lipid (e.g., a cationic liposome). A representative lipid delivery vehicle is a lipid nanoparticle (LNP), which optionally comprises cationic lipids. Cationic lipids include, but are not limited to, cationic lipids, e.g. DOTMA, DMRIE, di-C14-amidine, DOTIM, SAINT, DC-Chol, BGTC, CTAP, DOPC, DODAP, DOPE; Dioleyl phosphatidylethanol-amine, DOSPA, DODAB, DOIC, DMEPC, DOGS, DIMRI, DOTAP, DC-6-14, CLIP1, CLIP6, CLIP9, and oligofectamine. Lipid nanoparticles may comprise, e.g., at least one ionizable cationic lipid, at least neutral lipid (i.e., a non-cationic lipid), at last one sterol, and/or at least one polymer conjugated lipid (e.g., PEG lipid), along with the nucleic acid of interest. In various aspects, the LNP comprises (9Z,12Z)-3-((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl octadeca-9,12-dienoate, also called 3-((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl (9Z,12Z)-octadeca-9,12-dienoate), or another ionizable lipid. LNPs and components thereof are further described in, e.g., International Patent Publication Nos. WO 2017/173054, WO 2015/095340, WO 2014/136086, WO 2012/170930, and WO 2010/053572 and U.S. Patent No. 11,918,643, hereby incorporated by reference in their entireties.

[00167] Optionally, an expression vector is delivered to a target cell using a peptide based delivery vehicle. Peptide based delivery vehicles can have advantages of protecting the genetic material to be delivered, targeting specific cell receptors, disrupting endosomal membranes and delivering genetic material into a nucleus. In some aspects, an expression vector is delivered to a target cell using a polymer based delivery vehicle. Polymer based delivery vehicles may comprise natural proteins, peptides and/or polysaccharides or synthetic polymers. An example of a polymer based

delivery vehicle is a vehicle comprising polyethylenimine (PEI). PEI can condense DNA into positively charged particles which bind to anionic cell surface residues and are brought into the cell via endocytosis. Additional components for polymer based vehicles include, but are not limited to, poly-L-lysine (PLL), poly (DL-lactic acid) (PLA), poly (DL-lactide-co-glycoside) (PLGA), polyornithine, polyarginine, histones, protamines, dendrimers, chitosans, synthetic amino derivatives of dextran, and cationic acrylic polymers.

[00168] In alternative aspects, the vector is a viral vector. Suitable viral vector delivery systems may be based on DNA viruses or RNA viruses. Examples of viral vectors include, but are not limited to, retroviruses (e.g., A-type, B-type, C-type, and D-type viruses), adenoviruses, parvoviruses (e.g., adeno-associated viruses (AAV)), coronaviruses, negative strand RNA viruses (such as orthomyxovirus (e.g., influenza virus)), rhabdoviruses (e.g., rabies and vesicular stomatitis virus), paramyxoviruses (e.g., measles and Sendai virus), positive strand RNA viruses (such as picomavirus and alphavirus), herpesvirus (e.g., Herpes Simplex virus types 1 and 2, Epstein-Barr virus, and cytomegalovirus), and poxvirus (e.g., vaccinia, fowlpox, and canarypox).

[00169] In various aspects, the disclosure provides a retroviral vector comprising the vector components described herein. Retroviruses refer to viruses of the family Retroviridae. Examples of retroviruses include oncoretroviruses, such as murine leukemia virus (MLV), and lentiviruses, such as human immunodeficiency virus 1 (HIV-1). Retroviral genomes are single-stranded (ss) RNAs and comprise various genes that may be provided in cis or trans. For example, a retroviral genome may contain cis-acting sequences such as two long terminal repeats (LTR), with elements for gene expression, reverse transcription, and integration into the host chromosomes. Other components include the packaging signal (psi), for the specific RNA packaging into newly formed virions and the polypurine tract (PPT), the site of the initiation of the positive strand DNA synthesis during reverse transcription. In addition, in some embodiments, the retroviral genome may comprise gag, pol and env genes. The gag gene encodes the structural proteins, the pol gene encodes the enzymes that accompany the ssRNA and carry out reverse transcription of the viral RNA to DNA, and the env gene encodes the viral envelope. Generally, the gag, pol and env are provided in trans for viral replication and packaging.

[00170] The retroviral vector may be a lentiviral vector. At least five serogroups or serotypes of lentiviruses are recognized in the art. Viruses of the different serotypes may differentially infect certain cell types and/or hosts. Lentiviruses include, e.g., primate retroviruses and non-primate retroviruses. Primate retroviruses include HIV and simian immunodeficiency virus (SIV). Non-primate retroviruses include feline immunodeficiency virus (FIV), bovine immunodeficiency virus

(BIV), caprine arthritis-encephalitis virus (CAEV), equine infectious anemia virus (EIAV), and visnavirus.

[00171] Adenovirus (Ad) is a 36 kb double-stranded DNA virus that efficiently transfers DNA in vivo to a variety of different target cell types. Adenoviral vectors are typically made replication-deficient by deleting one or more select genes required for viral replication. The expendable E3 region is also frequently deleted to allow additional room for a larger DNA insert. Adenoviral vectors efficiently transfer DNA to replicating and non-replicating cells and the genetic information remains epi-chromosomal. If desired, the integrative properties of adeno-associated vectors can be conferred to adenovirus by constructing an AAV-Ad chimeric vector comprising AAV ITRs and nucleic acid encoding the rep protein.

[00172] Adenoviral vectors can be derived from any serotype of adenovirus. For instance, an adenovirus can be of subgroup A (e.g., serotypes 12, 18, and 31), subgroup B (e.g., serotypes 3, 7, 11, 14, 16, 21, 34, and 35), subgroup C (e.g., serotypes 1, 2, 5, and 6), subgroup D (e.g., serotypes 8, 9, 10, 13, 15, 17, 19, 20, 22-30, 32, 33, 36-39, and 42-47), subgroup E (serotype 4), subgroup F (serotypes 40 and 41), or any other adenoviral serotype. Preferably, the adenovirus is a subgroup C adenovirus, e.g., serotype 2 or 5. Adenoviral vectors, methods of producing adenoviral vectors, and methods of using adenoviral vectors are disclosed in, for example, U.S. Patent Nos. 5,851,806 and 5,994,106, and International Patent Publication Nos. WO 95/34671 and WO 97/27826, hereby incorporated by reference in their entireties.

[00173] In some aspects, the viral vector provided herein is an adeno-associated virus (AAV). As used herein, "AAV" covers all serotypes, subtypes, and both naturally occurring and recombinant forms, except where required otherwise. AAV is a small, replication-defective, non-enveloped animal virus that infects humans and some other primate species. AAV is not known to cause human disease and induces a mild immune response. AAV vectors infect both dividing and quiescent cells without integrating into the host cell genome. The AAV genome naturally consists of a linear single stranded DNA which is ~4.7kb in length, consisting of two open reading frames (ORF) flanked by an inverted terminal repeat (ITR) sequence that is about 145 bp in length. The ITR comprises a nucleotide sequence at the 5' end (5' ITR) and a nucleotide sequence located at the 3' end (3' ITR) that contain palindromic sequences. The two open reading frames comprise rep and cap genes that are involved in replication and packaging of the virion. In some embodiments, an AAV vector provided herein does not contain the rep or cap genes, which may be provided in trans for producing virions. The genomic sequences of various serotypes of AAV, as well as the

sequences of the native terminal repeats (TRs), rep proteins, and capsid subunits are known in the art.

[00174] The AAV vector of the disclosure may be derived from any serotype of AAV, including AAV1, AAV2, AAV3, AAV3b, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV9.47, AAV9(hul4), AAV10, AAV11, AAV12, AAV13, AAV-DJ, AAV-DJ8, AAV-DJ9, AAVrh8, AAVrhlO, bCap 1, eCap 1, AAV-PHP.B, AAV-PHP.eB, AAV.CAP-B1, AAV.CAP-B2, AAV.CAP-B8, AAV.CAP-B10, AAV.CAP-B18, AAV.CAP-B22, or a chimeric, hybrid, or variant AAV. See, e.g., Goertsen et al., Nat Neurosci 25, 106-115 (2022). Avian AAV, bovine AAV, canine AAV, equine AAV, primate AAV, non-primate AAV, and ovine AAV also are contemplated. In some cases, the AAV may be ligand conjugated. The AAV can also be a self-complementary AAV (scAAV), such as scAAV1, scAAV8, or scAAV9. AAV serotypes differ in their tropism, or the types of cells they infect. Optionally, the vector is an AAV1, AAV8, AAV9, scAAV1, scAAV8, or scAAV9 vector. In some aspects, the AAV is an AAV9 vector or an scAAV9 vector. In certain embodiments, the AAV vector is an AAV9 vector or an scAAV9 vector and comprises a heterologous nucleic acid flanked by ITRs from a AAV serotype other than AAV9. In certain embodiments, the AAV vector is an AAV9 vector or an scAAV9 vector and comprises a heterologous nucleic acid flanked by AAV serotype 2 ITRs (i.e., ITR2).

[00175] If desired, the AAV vector may comprise the genome and capsid from multiple serotypes (e.g., pseudotypes). In this regard, AAV ITRs can be based on the ITRs of any one of AAV1-12 and may be combined with an AAV capsid of a different serotype, selected from any one of AAV1-12, AAV-DJ, AAV-DJ8, or AAV-DJ9 or other modified serotypes. For example, an AAV may comprise the genome of serotype 2 (e.g., ITRs) packaged in the capsid from serotype 5 or serotype 9. Pseudotypes may improve transduction efficiency as well as alter tropism. In particular embodiments, the AAV ITRs and/or capsids are selected based on the cell or tissue to be targeted with the AAV vector. To illustrate, a viral vector having ITRs from a given AAV serotype may be packaged into: a) a viral particle constituted of capsid proteins derived from a different AAV serotype (e.g., AAV2 ITRs and AAV9 capsid proteins, AAV2 ITRs and AAV8 capsid proteins, etc.); b) a mosaic viral particle constituted of a mixture of capsid proteins from different AAV serotypes or mutants (e.g., AAV2 ITRs with AAV1 and AAV9 capsid proteins); c) a chimeric viral particle constituted of capsid proteins that have been truncated by domain swapping between different AAV serotypes or variants (e.g., AAV2 ITRs with AAV8 capsid proteins with AAV9 domains); or d) a targeted viral particle engineered to display selective binding domains, enabling stringent interaction with target cell specific receptors (e.g., AAV5 ITRs with AAV9 capsid proteins genetically modified

by insertion of a peptide ligand, or AAV9 capsid proteins non-genetically modified by coupling of a peptide ligand to the capsid surface).

[00176] Recombinant viral vectors, including "rAAV vectors," refers to viral (e.g., AAV) vectors comprising a polynucleotide sequence not of AAV origin (i.e., a polynucleotide heterologous to AAV), typically a sequence of interest encoding payload for production in the target cell. In general, the heterologous polynucleotide of an rAAV vector is flanked by at least one, and generally by two, AAV ITRs. The term “viral vector” (including AAV vector) encompasses both virus vector particles and virus vector plasmids. An "AAV virus" or "AAV viral particle" or "rAAV vector particle" refers to a viral particle composed of at least one AAV capsid protein and an encapsidated polynucleotide rAAV vector. If the particle comprises a heterologous polynucleotide (i.e., a polynucleotide other than a wild-type AAV genome such as a transgene to be delivered to a mammalian cell), it is typically referred to as an "rAAV vector particle" or simply an "rAAV vector." Thus, production of rAAV particles necessarily includes production of rAAV vectors, as such a vector is contained within an rAAV particle.

[00177] In various aspects, the expression vector is an AAV vector comprising a 5’ ITR and a 3’ ITR, a promoter described herein (e.g., comprising a nucleic acid sequence of any one of SEQ ID NOS: 10-13, such as a nucleic acid sequence of SEQ ID NO: 11 or SEQ ID NO: 13), a transgene as described herein (e.g., a transgene encoding STXBP1, such as a transgene encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 4), a 3’ ITR, and optionally one or more additional regulatory elements described herein, such as the WPRE discussed above (e.g., comprising the nucleic acid sequence of SEQ ID NO: 22) and nucleic acid sequence(s) encoding one or more de-targeting elements discussed above (e.g., one or more de-targeting elements comprising the nucleic acid sequence of SEQ ID NOS: 23-25 (such as those encoded by SEQ ID NOS: 26-28), SEQ ID NOS: 29-46, and/or SEQ ID NOS: 49-66).

[00178] COMPOSITIONS

[00179] The disclosure further provides a composition comprising the nucleic acid or the vector disclosed herein and a physiologically acceptable carrier, i.e., an ingredient in the composition, other than an active ingredient, which is nontoxic to a subject. Pharmaceutical compositions are preferably sterile and stable under conditions of manufacture and storage. Sterile solutions may be accomplished, for example, by filtration through sterile filtration membranes.

[00180] Acceptable carriers and excipients in the pharmaceutical composition are preferably nontoxic to recipients at the dosages and concentrations employed. Acceptable carriers and excipients include, but are not limited to, buffers, such as phosphate buffers (e.g., sodium

phosphate), histidine, citrate buffers (e.g., sodium citrate), HEPES, Tris, glycine, acetate buffers (e.g., sodium acetate), sodium carbonate, lysine, arginine, and mixtures thereof; antioxidants, such as ascorbic acid and methionine; preservatives, such as hexamethonium chloride, octadecyldimethylbenzyl ammonium chloride, resorcinol, and benzalkonium chloride; proteins, such as human serum albumin, gelatin, and immunoglobulins; hydrophilic polymers, such as polyvinylpyrrolidone; amino acids, such as glycine, glutamine, histidine, and lysine; and carbohydrates, such as glucose, mannose, sucrose, dextran, and sorbitol. Physiologically acceptable carriers also include, but are not limited to, sterile water and physiological saline.

[00181] In various aspects, the composition of the disclosure comprises one or more pharmaceutically acceptable salts. Suitable "pharmaceutically acceptable salts" include, but are not limited to, metal salts (e.g., sodium, potassium, and cesium salts) and alkaline earth metal salts (e.g., magnesium salts). Non-limiting examples of pharmaceutically acceptable salts include, without limitation, sodium salts, magnesium salts, and potassium salts (e.g., sodium chloride, magnesium chloride, and potassium chloride; sodium acetate, magnesium acetate, and potassium acetate; sodium citrate, magnesium citrate, and potassium citrate; sodium phosphate, magnesium phosphate, and potassium phosphate; sodium fluoride, magnesium fluoride, and potassium fluoride; sodium bromide, magnesium bromide, and potassium bromide; and sodium iodide, magnesium iodide, and potassium iodide). In various aspects, the composition comprises one or more of sodium chloride, magnesium chloride, and potassium chloride; optionally, the composition comprises sodium chloride, magnesium chloride, and potassium chloride.

[00182] In various aspects, the composition comprises a surfactant. Surfactants improve stability of compositions by, e.g., minimizing surface-induced degradation. Hydrophobic portions of surfactant molecules occupy interfacial positions (e.g., air/liquid), while hydrophilic portions of the molecules remain oriented toward the bulk solvent. Pharmaceutically acceptable non-ionic surfactants include, but are not limited to, Polysorbate 80 (TWEEN™ 80; PS80), Polysorbate 20 (TWEEN™20; PS20), digitonin, TRITON™ X-100, TRITON™ X-144, and poloxamers. Poloxamers, also known as Pluronics®, are amphiphilic block copolymers of poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO). Bodratti et a., J Funct Biomater. 9(1): 11 (2018). The original manufacturer of Pluronics®, BASF, introduced a specific nomenclature wherein the first letter indicates the physical state (Paste (P), Liquid (L), or Flake (F)), and a series of numbers, wherein the first one or two numbers relate to the molecular weight and the last number indicates the weight percent of the PEO block. Commercially available Pluronics® include, e.g., L64, P65, P84, P85, F88, P103, P104, P105, F108, P123, F127. In various aspects, the non-ionic surfactant in the composition is a

poloxamer. In various aspects, the non-ionic surfactant is poloxamer 188.

[00183] Preferably, the composition has a physiologically compatible pH. For example, the pH of the composition is about 6.5 to about 9.0, about 6.5 to about 8.0, about 6.9 to about 7.7, about 7.0 to about 7.5, about 7.2 to about 7.4, about 7.0 to about 7.3, about 7.1 to about 7.4, or about 7.2 to about 7.5. In various embodiments, the pH of the formulation is about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, about 7.5, about 7.6, about 7.7, or about 7.8. In exemplary aspects, the pH of the composition is about 7.2, about 7.3, or about 7.4. In certain embodiments, the pH of the composition is about 7.3.

[00184] In various aspects, the composition does not comprise a saccharide (e.g., monosaccharide, disaccharide, cyclic polysaccharide, sugar alcohol, linear branched dextran, or linear non-branched dextran, such as sucrose, trehalose, glucose, mannitol, or sorbitol). In various aspects, the composition does not comprise amino acids, such as glycine, glutamine, asparagine, arginine, or lysine. In various aspects, the formulation does not comprise calcium, such as calcium chloride.

[00185] Compositions provided herein may be formulated for parenteral administration, subcutaneous administration, intravenous administration, intramuscular administration, intra-arterial administration, intraparenchymal administration, intrathecal administration, intra-cisterna magna administration, intracerebroventricular administration, or intraperitoneal administration. The pharmaceutical composition may also be formulated for, or administered via, nasal, spray, oral, aerosol, rectal, or vaginal administration. Optionally, the composition is formulated for injection or infusion to a human subject. For example, in various aspects, the composition is delivered via a peripheral vein by bolus injection. Alternatively or in addition, the composition is delivered via a peripheral vein by infusion. A composition for gene therapy can be in an acceptable diluent or can comprise a slow release matrix in which the gene delivery vehicle is embedded.

[00186] In various aspects, the composition provided herein is formulated for administration to the CNS or cerebral spinal fluid (CSF), e.g., by intraparenchymal injection, intrathecal injection, intra-cisterna magna injection, or intracerebroventricular injection. The tissue target may be specific, for example the CNS, or it may be a combination of several tissues, for example, the muscle and CNS tissues.

[00187] The composition of the disclosure may be prepared in microcapsules, such as hydroxylmethylcellulose or gelatin-microcapsules and polymethylmethacrylate microcapsules. Other drug delivery systems suitable for formulating the composition described herein include, e.g., liposomes, albumin microspheres, microemulsions, nanoparticles, and nanocapsules.

[00188] In various aspects, a composition provided herein comprises an “effective amount” or a

"therapeutically effective amount" of nucleic acid or expression vector. As used herein, such amounts refer to an amount effective, at dosages and for periods of time necessary to achieve the desired therapeutic result. A therapeutically effective amount may vary depending upon the intended treatment application and/or the subject and disease condition being treated, e.g., the weight and age of the subject, the severity of the disease condition, the manner of administration and the like. The term also applies to a dose that will induce a particular response in a target cell. The specific dose will vary depending on the particular composition chosen, the dosing regimen to be followed, whether it is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

[00189] The disclosure further provides a kit comprising a nucleic acid molecule, vector, or composition described herein in one or more containers. Optionally, the composition is present in a delivery device, a container for storage or shipment or administration, or a container suitable for use in drug substance or drug product manufacturing. The kit may comprise a container (e.g., vial, syringe, or infusion bag) which is a single-use container (i.e., a container that holds one dose formulation plus enough extra to ensure that a full single dose can be administered to a patient from the container, but not so much extra that the container could be used to administer a second dose) or a multiple-use container. The container may be a drug delivery device (e.g., syringe) or container for storage or shipment or administration (e.g., a vial or bag). Containers of the kit can be of any suitable material, e.g., glass, plastic, metal, etc., and of any suitable size, shape, or configuration. The kit may also include instructions or packaging materials that describe how to administer the nucleic acid molecule, vector, or composition contained within the kit to a subject in need thereof.

[00190] Alternatively, the kit may comprise one or more containers comprising the composition and instructions for use in manufacturing or preparing a drug substance or a drug product. For example, the kit may contain one or more containers suitable for use in a filtration system or system for filling parts of a drug delivery system (e.g., vials, syringes, or infusion bags), wherein the container comprises the composition described herein. The kit described herein may include separate containers comprising one or more of the composition components (rAAV vectors, salt, buffer, non-ionic surfactant, etc.).

[00191] METHODS OF TREATMENT

[00192] Provided herein is a method of administering a transgene to a subject, the method comprising administering to the subject the nucleic acid, expression vector, or composition

described herein, wherein the nucleic acid or expression vector comprises the transgene. The nucleic acids and expression vectors may be used to deliver a variety of payloads (e.g., transgenes) to a host cell, including host cells in vivo, such as target cells described herein.

[00193] The disclosure further provides a method of treating a neurological disease or disorder in a subject in need thereof. The method comprises administering to the subject in need thereof the nucleic acid, expression vector, or composition described herein, wherein the nucleic acid or expression vector comprises a transgene encoding a gene product associated with the neurological disease or condition which elicits a therapeutic response in the context of the neurological disease or condition. Neurological diseases and disorders include conditions associated with epileptic seizures, neurodegenerative disorders, and/or neurodevelopmental disorders. Several neurological diseases or disorders are described below.

[00194] The disclosure provides a method of treating epilepsy in a subject in need thereof. As explained above, epilepsy is a non-infectious disease of the brain characterized by recurrent unprovoked seizures. Seizures generally result from excessive neuronal firing, which lead to bursts of motor, sensory, or mental function disturbance. Epilepsy is a heterogenous disorder both in terms of causes of the disease, which can involve structural abnormalities, infection, metabolic dysregulation, autoimmune aspects, and/or genetic abnormalities, as well as clinical manifestation of the disease.

[00195] A number of genetic abnormalities have been associated with neurological diseases and disorders described herein, including epilepsy. For example, mutations in the following genes (or disruption of expression of the native encoded protein) have been linked to epilepsy: *ALDH7A1, ALG13, ARHGEF9, ARX, BRAT1, CACNA1A, CACNA1D, CACNB4, CDKL5, CHD2, CHRNA2, CHRNA4, CHRNB2, CLCN2, CLN, CLN2, CLN5, DEPDC5, DNM1, DOCK7, FGF13, FLNA, FMRI, FOLR1, FOXG1, GABRA1, GABRB3, GABRD, GABRG2, GBA1, GLI3, GNAO1, GRIN1, GRIN2A, GRIN2B, GRN, HCN1, HCN4, HNRNPU, KCNQ2, KCNQ3, KCNT1, KV3.1, KV3.2, KV3.3, LGI1, MAGI2, MECP2, MEF2C, Myoclonin1/EFHCl, NEDDL4, NDP, NPRL2, NXRN1, PCDH19, PIGASPTAN1, PLCB1, PNKP, POLG1, PPP3CASTXBP1, PRRT2, PTEN, SCA2TCF4, SCN1A, SCN1B, SCN2A, SCN2B, SCN8A, SETBP122q, SHANK3, SIK1Trisomy21, SLC13A5, SLC25A22, SLC2A1, SLC6A1, SLC6A8, SPTAN1, ST3GAL3, STRADA, STXBP1, SYNGAP1, TBC1D24, UBE3A,* and *WWOX*. The subject of the disclosure may have a mutation in any one or more of these genes or otherwise exhibit aberrant activity and/or expression of the associated gene product. In various aspects, the subject exhibits one or more mutations in genes encoding subunits of voltage-gated Na+ channels (SCN1A, SCN1B) and/or the γ-aminobutyric acid type A receptor

(GABRG2, GABRD). In various aspects, the subject exhibits one or more mutations in the *STXBP1* gene. In some cases, a subject may exhibit a loss of function mutation in STXBP1, an STXBP1 hypomorph mutation, a nonsense mutation in STXBP1, or a full or partial deletion of STXBP1.

[00196] Examples of epilepsy disorders include, but are not limited to, Benign familial neonatal epilepsy (BFNE), Early myoclonic encephalopathy (EME), Ohtahara syndrome, Epilepsy of infancy with migrating focal seizures, infantile spasms (West syndrome), Myoclonic epilepsy in infancy (MEI), Benign infantile epilepsy, Benign familial infantile epilepsy, Dravet syndrome, Myoclonic encephalopathy in nonprogressive disorders, Early onset epilepsy, Febrile seizures, Febrile seizures plus (FS+), Panayiotopoulos syndrome, Epilepsy with myoclonic atonic (previously astatic) seizures, Doose syndrome, Benign epilepsy with centrotemporal spikes (BECTS), frontal lobe epilepsy (e.g., Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)), Late onset childhood occipital epilepsy (Gastaut type), Epilepsy with myoclonic absences, Lennox-Gastaut syndrome, Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS), Landau-Kleffner syndrome (LKS), Childhood absence epilepsy (CAE), Juvenile absence epilepsy (JAE), Juvenile myoclonic epilepsy (JME), Epilepsy with generalized tonic-clonic seizures alone, Progressive myoclonic epilepsies (PME), Autosomal dominant epilepsy with auditory features (ADEAF), Focal epilepsy, Familial focal epilepsy with variable foci, Self-limited familial and non-familial neonatal infantile seizures, Reflex epilepsies, temporal lobe epilepsy (e.g., Mesial Temporal Lobe Epilepsy (MTLE)), Rasmussen syndrome, Gelastic seizures with hypothalamic hamartoma, Hemiconvulsion-hemiplegia-epilepsy, Benign Rolandic epilepsy, Genetic epilepsy with sleep-related hypermotor epilepsy (SHE), Epilepsy eyelid myoclonia (Jeavons syndrome), and Photosensitive epilepsy.

[00197] Optionally, the subject is suffering from refractory epilepsy. "Refractory epilepsy" refers to an epilepsy which is resistant to treatment, e.g., disabling seizures continue despite adequate trials of two antiseizure medications, either alone or in combination. Engel, Ann Indian Acad Neurol. 17(Suppl 1): S12–S17 (2014).

[00198] Other neurological diseases or disorder include, but are not limited to, CDKL5 deficiency disorder, Parkinson's disease and Parkinson's Levodopa-induced dyskinesia (LIDS), Alzheimer's disease, creatine transporter deficiency, FOXG1 syndrome, fragile X syndrome, Phelan-McDermid syndrome, and attention deficit-hyperactivity disorder.

[00199] In various aspects, the disclosure provides a method of treating an STXBP1 (syntaxin-1B)-related disorder in a subject in need thereof. The method comprises administering to the subject

the nucleic acid, expression vector, or composition described herein which comprises a transgene encoding STXBP1, such as a protein encoded by the nucleic acid sequence of any one of SEQ ID NOS: 1-4 (e.g., the nucleic acid sequence of SEQ ID NO: 3 or SEQ ID NO: 4). Syntaxin-1B is a presynaptic protein that forms part of the SNARE complex, which mediates calcium-dependent synaptic vesicle release. Smirnova et al., Genomics 36:551–553 (1996). Heterozygous pathogenic variants in the STXBP1 gene lead to a spectrum of early-onset neurodevelopmental and epileptic disorders, which can result in severe developmental delay, treatment-resistant seizures, and sudden unexpected death in epilepsy. Xian et al., Brain 145, 1668-1683 (2022); Hamdan et al., Ann Neurol 65, 748-753 (2009); and Swanson et al., Genomics 48, 373-376 (1998). Common seizure types associated with *STXBP1* mutations include neonatal seizures, infantile spasms, tonic (stiffening) seizures, clonic seizures, focal impaired awareness seizures, and generalized tonic-clonic seizures. Epilepsy syndromes which may stem, at least in part, from *STXBP1* mutations include Ohtahara syndrome, West syndrome, and Lennox-Gastaut syndrome. Not all subjects with *STXBP1* mutations experience seizures, however. STXBP1-related disorders also may be accompanied by developmental delay, autism spectrum disorder, increased or decreased muscle tone, or movement disorders. There are no disease-modifying treatments for STXBP1-related disorders, and current management is principally focused on treating symptoms, for example with anti-seizure medication, and supportive care.

[00200] In various aspects, the disclosure provides a method of treating a neurologic disease or disorder that is not STXBP1-related, or is of unknown etiology, by administering to the subject the nucleic acid, expression vector, or composition described herein which comprises a transgene encoding STXBP1. A neurologic disease or disorder that is not STXBP1-related is one that is not caused or exacerbated by a mutation and/or dysregulation of the STXBP1 gene in the subject. In some of these embodiments, the subject has a mutation and/or dysregulation of a different neuronal gene (e.g., as described elsewhere herein) that causes and/or exacerbates the neurologic disease or condition. In certain embodiments, the transgene encodes an STXBP1 protein, where in some embodiments the STXBP1 protein is encoded by the nucleic acid sequence of any one of SEQ ID NOS: 1-4 (e.g., the nucleic acid sequence of SEQ ID NO: 3 or SEQ ID NO: 4). Examples of epilepsy disorders that may have non-STXBP1-related etiologies and/or unknown etiologies include, but are not limited to, Benign familial neonatal epilepsy (BFNE), Early myoclonic encephalopathy (EME), Ohtahara syndrome, Epilepsy of infancy with migrating focal seizures, infantile spasms (West syndrome), Myoclonic epilepsy in infancy (MEI), Benign infantile epilepsy, Benign familial infantile epilepsy, Dravet syndrome, Myoclonic encephalopathy in nonprogressive

disorders, Early onset epilepsy, Febrile seizures, Febrile seizures plus (FS+), Panayiotopoulos syndrome, Epilepsy with myoclonic atonic (previously astatic) seizures, Doose syndrome, Benign epilepsy with centrotemporal spikes (BECTS), frontal lobe epilepsy (e.g., Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)), Late onset childhood occipital epilepsy (Gastaut type), Epilepsy with myoclonic absences, Lennox-Gastaut syndrome, Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS), Landau-Kleffner syndrome (LKS), Childhood absence epilepsy (CAE), Juvenile absence epilepsy (JAE), Juvenile myoclonic epilepsy (JME), Epilepsy with generalized tonic-clonic seizures alone, Progressive myoclonic epilepsies (PME), Autosomal dominant epilepsy with auditory features (ADEAF), Focal epilepsy, Familial focal epilepsy with variable foci, Self-limited familial and non-familial neonatal infantile seizures, Reflex epilepsies, temporal lobe epilepsy (e.g., Mesial Temporal Lobe Epilepsy (MTLE)), Rasmussen syndrome, Gelastic seizures with hypothalamic hamartoma, Hemiconvulsion-hemiplegia-epilepsy, Benign Rolandic epilepsy, Genetic epilepsy with sleep-related hypermotor epilepsy (SHE), Epilepsy eyelid myoclonia (Jeavons syndrome), and Photosensitive epilepsy.

[00201] The terms "treat," "treatment," "therapy" and the like refer to achieving a desired pharmacologic and/or physiologic effect, including, but not limited to, alleviating, delaying, or slowing progression of the disease or disorder (or symptom(s) thereof); reducing effects or symptoms of a disease or disorder; preventing onset of a disease or disorder (or symptom(s) thereof); preventing reoccurrence, inhibiting, or ameliorating onset of a diseases or disorder; and/or obtaining a beneficial or desired result with respect to a disease, disorder, or medical condition. "Treatment" does not require 100% remission or prevention of a disease or disorder (or symptom(s) thereof), but encompasses any level of treatment of a disease in a mammal, particularly in a human, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease or at risk of acquiring the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; and (c) relieving the disease, i.e., causing regression of the disease or symptom(s) thereof. A therapeutic benefit includes eradication or amelioration of the underlying disorder being treated. A therapeutic benefit also may include the eradication or amelioration of one or more of the symptoms associated with the underlying disorder such that an improvement is observed in the subject, notwithstanding that the subject may still be afflicted with the underlying disorder. In this regard, the treatment can result in a decrease or cessation of symptoms. Indeed, the disclosure provides a method of treating or reducing the occurrence of seizures in a subject by administering an effective dose of a nucleic acid of the present disclosure to the subject, thereby treating, reducing the occurrence, or ameliorating

seizures in the subject.

[00202] The vector of the disclosure may be administered to a subject at risk of developing a particular disease, or to a subject reporting one or more of the physiological symptoms of a disease, even if disease diagnosis has not been determined.

[00203] The nucleic acid or vector described herein may be administered by any one or more routes of administration, including the use of multiple (different) routes of administration over the course of a therapeutic regimen. The vector may be administered systemically, regionally or locally by any means, such as by injection, instillation, or infusion. For instance, in some aspects, the vector is administered via injection. In some aspects, administration is performed through a cannula. Optionally, the vector is administered as a bolus (e.g., as a single injection). In some aspects, the vector is administered continuously (e.g., as an infusion using a pump). The nucleic acid or vector is administered in an amount effective to achieve a desired biological response, as described further herein.

[00204] Examples of routes of administration include, but are not limited to, parenteral administration, subcutaneous administration, intramuscular administration, intraarterial administration, intravenous administration, intraperitoneal administration, intrathecal administration, and intracranial administration (e.g., intracerebroventricular administration or intraparenchymal administration).

[00205] In some aspects, the disclosure provides for methods of administering a composition disclosed herein to a subject (e.g., a primate) via intrathecal administration or intracerebroventricular administration. The intrathecal space, into which the nucleic acid or vector is delivered in the case of intrathecal administration, is a space which is located around the spinal cord and filled with cerebrospinal fluid. This space is surrounded by a double-layer membrane consisting of arachnoid mater and dura mater. The intrathecal space is a space beneath the arachnoid mater, the inner layer of the double-layer membrane, and therefore, intrathecal administration means administration into the subarachnoid space. The space around the brain and the space around the spinal cord are both filled with CSF, and the cerebral ventricles in the brain are also filled with CSF. The cerebral ventricles, the pericerebral space, and the intrathecal space are generally connected to form one continuous space in which the CSF circulates.

[00206] In some aspects, the intrathecal administration comprises an intrathecal cisternal administration. Optionally, delivery is accomplished using an intrathecal infusion device (e.g., a Medtronic device) which can be inserted in the lumbar subarachnoid space and a catheter extended upwards toward the cranium for administration. In some aspects, intrathecal

administration to a human comprises surgically inserting a catheter at about the L4/L5 interspace and administering either (i) a bolus dose (via syringe or Ommaya reservoir), (ii) a short term infusion (via a pump), or (iii) a long term infusion (via an implantable programmable pump system, e.g., Synchromed II, Medtronic, where the pump is placed in a subcutaneous pocket somewhere in the body such as the abdominal region). See, e.g., Hamza M, et al. Neuromodulation 18(7):636-48 (2015).

[00207] In some aspects, the nucleic acid or vector is administered intrathecally via intrathecal lumbar administration, e.g., into the lumbar cistern by means of a lumbar puncture. For instance, a spinal tip can be performed at the bedside with local anesthetic under sterile conditions. The administration procedure may be performed in connection with collection of cerebrospinal fluid (CSF), when the lumbar cistern is accessed.

[00208] In some aspects, the nucleic acid or vector is administered via intracerebroventricular (ICV) administration, which optionally comprises inserting a cannula through a hole in the skull, through the brain tissue, into a CSF-filled ventricle of the brain. A single cannula may be inserted (e.g., into either of the two lateral ventricles) or two cannulas may be inserted (into both lateral ventricles), although the disclosure is not dependent on any particular configuration. In some aspects, the cannula is connected to a syringe or infusion pump for one-time administration, or a controlled device, such as an Ommaya reservoir. The disclosure further provides for administration of any of the vectors disclosed herein to one or more lateral ventricles of a subject.

[00209] In some aspects, the nucleic acid or vector is administered via ICV administration to any one or more ventricles of the brain. In some aspects, the nucleic acid or vector is administered via ICV administration unilaterally into one ventricle, e.g., into the left lateral ventricle or right lateral ventricle. In some aspects, the nucleic acid or vector is administered via ICV administration unilaterally into the left lateral ventricle. In some embodiments, the nucleic acid or vector is administered via ICV administration unilaterally into the right lateral ventricle. In some aspects, the nucleic acid or vector is administered via ICV administration bilaterally, e.g., into the left and right lateral ventricle. In some embodiments, the nucleic acid or vector is administered via ICV administration to one ventricle of the brain, e.g., into only the left ventricle. In some aspects, the nucleic acid or vector is administered via ICV administration to only the left lateral ventricle. In some aspects, the composition is administered via ICV administration to only the right lateral ventricle. In some aspects, the nucleic acid or vector is administered via ICV administration to only the third ventricle. In some aspects, the nucleic acid or vector is administered via ICV administration to only the fourth ventricle. In some aspects, the nucleic acid or vector is

administered via ICV administration to more than one ventricle of the brain, e.g., into the left ventricle, right ventricle, and third ventricle. In some aspects, the nucleic acid or vector is administered via ICV administration simultaneously, e.g., into the left ventricle and right ventricle at the same time point. In some aspects, the nucleic acid or vector is administered via ICV administration sequentially, e.g., into the left ventricle and right ventricle at different time points. In some aspects, each dose of the nucleic acid or vector is administered via ICV administration at least 24 hours apart.

[00210] In some aspects, the nucleic acid or vector disclosed herein is administered via a catheter-based device. Permanent catheter-based devices and temporary catheter-based devices are contemplated. In some aspects, for permanent access, a catheter that is connected to a subcutaneous reservoir (e.g., an Ommaya reservoir) is implanted. An Ommaya reservoir can be accessed repeatedly at the bedside with a sterile puncture through the scalp into the reservoir by using a 25-gauge needle. In some embodiments, a few milliliters of CSF is withdrawn before injecting a therapeutic agent.

[00211] In situations that require limited access to the CSF space, a ventriculostomy can be employed. With this technique, the catheter is tunneled under the skin away from the burr hole. The catheter is usually connected to a sterile collection chamber. The catheter can be accessed sterilely as needed for administration of any of the vectors disclosed herein. In some aspects, the vector may be administered by injecting the solution into the most proximal port of the ventriculostomy and flushing the solution into the brain with a small amount of normal saline (3-5 ml). After this instillation, the ventriculostomy tubing is typically clamped for at least 15 minutes to allow for the injected solution to equilibrate in the CSF before reopening the drain. A ventriculostomy is advantageous for a condition that requires a limited time period for CSF drainage or intraventricular administration of any of the vector disclosed herein.

[00212] In some aspects, the nucleic acid or vector disclosed herein is administered to a subject (e.g., a primate) in combination with a contrast agent, e.g., gadolinium or gadoteridol. In other aspects, the nucleic acid or vector is not administered in combination with a contrast agent, e.g., gadolinium or gadoteridol.

[00213] The disclosure provides methods of administering the nucleic acid or vector disclosed herein by multiple routes of administration. For instance, the disclosure contemplates administration of the nucleic acid or vector via intracerebroventricular administration and also administering the nucleic acid or vector by intravenous administration. In some aspects, the disclosure provides methods of administering the nucleic acid or vector disclosed herein by

intrathecal administration and the same vector also by intravenous administration. In some aspects, the disclosure contemplates administering the nucleic acid or vector disclosed herein by one route of administration (e.g., intracerebroventricular administration) and an additional therapeutic agent (e.g., any of the additional therapeutic agents disclosed herein) by another route of administration (e.g., intravenous administration). For example, the disclosure provides for methods of administering the nucleic acid or vector disclosed herein by intracerebroventricular administration and administering an additional therapeutic agent intravenously, or administering the vector disclosed herein by intrathecal administration and administering an additional therapeutic agent intravenously. In some aspects, the disclosure provides for methods of administering the nucleic acid or vector disclosed herein by intravenous administration and administering an additional therapeutic agent by intracerebroventricular administration. Also provided is a method of administering the nucleic acid or vector disclosed herein by intravenous administration and administration of an additional therapeutic agent by intrathecal administration.

[00214] In some aspects, the disclosure provides for methods of administering the nucleic acid or vector disclosed herein to a subject, wherein the subject is a primate. In some aspects, the primate is a human. In some aspects, the primate is a non-human primate. In some aspects, the non-human primate is an old world monkey, an orangutan, a gorilla, a chimpanzee, a crab-eating macaque, a rhesus macaque, or a pig-tailed macaque. The present disclosure contemplates methods of treating a subject (e.g., a primate such as a human) in need thereof, comprising administering to the subject any of the nucleic acids, vectors, viral particles, and/or compositions disclosed herein.

[00215] The subject, in exemplary embodiments, is one diagnosed with a mutation or genetic aberration associated with a neurological disease or disorder, such as a mutation or genetic aberration associated with *ALDH7A1, ALG13, ARHGEF9, ARX, BRAT1, CACNA1A, CACNA1D, CACNB4, CDKL5, CHD2, CHRNA2, CHRNA4, CHRNB2, CLCN2, CLN, CLN2, CLN5, DEPDC5, DNM1, DOCK7, FGF13, FLNA, FMRI, FOLR1, FOXG1, GABRA1, GABRB3, GABRD, GABRG2, GBA1, GLI3, GNAO1, GRIN1, GRIN2A, GRIN2B, GRN, HCN1, HCN4, HNRNPU, KCNQ2, KCNQ3, KCNT1, KV3.1, KV3.2, KV3.3, LGI1, MAGI2, MECP2, MEF2C, Myoclonin1/EFHC1, NEDDL4, NDP, NPRL2, NXRN1, PCDH19, PIGASPTAN1, PLCB1, PNKP, POLG1, PPP3CASTXBP1, PRRT2, PTEN, SCA2TCF4, SCN1A, SCN1B, SCN2A, SCN2B, SCN8A, SETBP122q, SHANK3, SIK1Trisomy21, SLC13A5, SLC25A22, SLC2A1, SLC6A1, SLC6A8, SPTAN1, ST3GAL3, STRADA, STXBP1, SYNGAP1, TBC1D24, UBE3A,* and/or *WWOX*, although this is not required. Thus, in various aspects of the method of the disclosure, the method further comprising detecting

mutant ALDH7A1, ALG13, ARHGEF9, ARX, BRAT1, CACNA1A, CACNA1D, CACNB4, CDKL5, CHD2, CHRNA2, CHRNA4, CHRNB2, CLCN2, CLN, CLN2, CLN5, DEPDC5, DNM1, DOCK7, FGF13, FLNA, FMRI, FOLR1, FOXG1, GABRA1, GABRB3, GABRD, GABRG2, GBA1, GLI3, GNAO1, GRIN1, GRIN2A, GRIN2B, GRN, HCN1, HCN4, HNRNPU, KCNQ2, KCNQ3, KCNT1, KV3.1, KV3.2, KV3.3, LGI1, MAGI2, MECP2, MEF2C, Myoclonin1/EFHC1, NEDDL4, NDP, NPRL2, NXRN1, PCDH19, PIGASPTAN1, PLCB1, PNKP, POLG1, PPP3CASTXBP1, PRRT2, PTEN, SCA2TCF4, SCN1A, SCN1B, SCN2A, SCN2B, SCN8A, SETBP122q, SHANK3, SIK1Trisomy21, SLC13A5, SLC25A22, SLC2A1, SLC6A1, SLC6A8, SPTAN1, ST3GAL3, STRADA, STXBP1, SYNGAP1, TBC1D24, UBE3A, and/or WWOX in a biological sample (e.g., detecting mutant protein encoded by the referenced genes in the blood, plasma, CSF, or tissue (e.g., brain tissue)).

[00216] In various aspects of the disclosure, the subject is one diagnosed with a mutation or genetic aberration in a neurotransmitter regulator (e.g., STXBP1). In this regard, in various aspects of the method of the disclosure, the method optionally comprises detecting mutant STXBP1 in a biological sample (e.g., blood, plasma, CSF, or tissue (e.g., brain tissue)). Mutant STXBP1 may be detected by DNA or RNA sequencing (e.g., via Next Gen sequencing of a subject sample) or may be determined by detecting mutant STXBP1 protein in a sample.

[00217] It will be appreciated that disclosure herein relating to methods of treatment also apply to uses of the nucleic acid, vector, and composition described herein to treat the disease or disorders described herein; uses of the of the nucleic acid, vector, and composition described herein in the preparation of a medicament to treat the disease or disorders described herein; and the nucleic acid, vector, and composition described herein for use in treating the disease or disorders described herein. In this regard, the disclosure provides use of the nucleic acid or the expression vector described above in the manufacture of a medicament for the treatment of a neurological disease or disorder, wherein the nucleic acid or expression vector comprises a transgene encoding a protein associated with a neurological disease or disorder or a transcription factor that increases expression of a gene associated with a neural disease or disorder. In various aspects, the neurological condition or disorder is epilepsy or epileptic encephalopathy. Optionally, the neurological condition or disorder is an STXBP1-related neurological condition or disorder, and the transgene comprises the nucleic acid sequence of any one of SEQ ID NOS: 1-4, such as the nucleic acid sequence of SEQ ID NO: 3 or SEQ ID NO: 4.

[00218] Additionally, the disclosure provides the nucleic acid or the expression vector described herein for use in the treatment of a neurological disease or disorder, wherein the nucleic acid or expression vector comprises a transgene encoding a protein associated with a neurological disease

or disorder or a transcription factor that increases expression of a gene associated with a neural disease or disorder. Optionally, the neurological condition or disorder is an STXBP1-related neurological condition or disorder, and the transgene comprises the nucleic acid sequence of any one of SEQ ID NOS: 1-4, such as the nucleic acid sequence of SEQ ID NO: 3 or SEQ ID NO: 4.

[00219] PRODUCTION

[00220] Methods for generating recombinant AAVs are well known in the art. Typical methods used for production of rAAV virions include, but are not limited to, transfection, stable cell line production, and infectious hybrid virus production systems (e.g., adenovirus-AAV hybrids, herpesvirus-AAV hybrids, and baculovirus-AAV hybrids). rAAV production cultures for the production of rAAV virus particles involve suitable host cells, including, for example, human-derived cell lines such as HeLa, A549, or 293 cells, or insect-derived cell lines such as SF-9, in the case of baculovirus production systems; suitable helper virus function provided by adenovirus, herpes virus, baculovirus, or a plasmid construct providing helper functions; AAV rep and cap genes and gene products; a transgene flanked by AAV ITR sequences; and suitable media and media components to support cell growth and rAAV production.

[00221] Typically, production methods involve culturing a host cell which contains a nucleic acid sequence encoding an AAV capsid protein; a nucleic acid sequence encoding a functional rep gene; and a nucleic acid comprising a transgene and other regulatory elements flanked by ITRs, wherein the cell also offers sufficient helper functions to facilitate packaging of the AAV genome into capsid proteins. The helper/accessory functions include functions required for AAV replication, including (but not limited to) activation of AAV gene transcription, AAV mRNA splicing, AAV DNA replication, synthesis of cap expression products, and AAV capsid assembly. Viral-based accessory functions can be derived from any helper virus such as, e.g., adenovirus, herpesvirus (other than herpes simplex virus type-1), and vaccinia virus. Helper functions include, without limitation, adenovirus E1, E2a, VA, and E4 or herpesvirus UL5, ULB, UL52, and UL29, and herpesvirus polymerase. In a preferred embodiment, the proteins upon which AAV is dependent for replication are derived from adenovirus.

[00222] The AAV rep gene, AAV cap gene, and genes providing helper/accessory functions can be introduced into the cell via an expression vector(s) such as, e.g., a plasmid. The rep, cap and helper function genes may be present on the same expression vector or may be provided on different expression vectors (e.g., the AAV rep and cap genes may be present on one expression vector and helper function genes are provided on a different expression vector). Optionally, the recombinant AAV vector is produced using the triple transfection method wherein the AAV genome,

the rep and cap genes, and the genes providing the helper/accessory functions, are each provided on different vectors (see, e.g., U.S. Patent No. 6,001,650, hereby incorporated by reference). Preferably, the system employed offers efficient AAV vector production without generating detectable AAV virions containing functional rep and cap genes.

[00223] Optionally, a packaging cell is utilized which comprises the AAV rep and cap genes and/or one or more genes encoding helper/accessory functions stably integrated in the host cell genome.

[00224] Exemplary packaging cells may be derived from, e.g., 293 cells, A549 cells, or HeLa cells. Alternatively, an insect producer cell line may be used (typically Sf9 cells) that is infected with baculovirus expression vectors that provide rep and cap proteins. This system does not require adenovirus helper genes. See, e.g., Ayuso et al., Curr. Gene Ther. 10:423-436 (2010).

[00225] The production host cells may be cultured for a time and under conditions sufficient to achieve desired levels of expression vector replication and, if desired, packaging into viral virions. Generally, cells may be grown for about 24 hours, about 36 hours, about 48 hours, about 72 hours, about 4 days, about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, or up to about 10 days. After about 10 days (or sooner, depending on the culture conditions and the particular host cell used), the level of production generally decreases, though production still occurs. Generally, time of culture is measured from the point of viral production. For example, in the case of AAV, viral production generally begins upon supplying helper virus function in an appropriate host cell. Generally, cells are harvested about 48 to about 100, preferably about 48 to about 96, preferably about 72 to about 96, preferably about 68 to about 72 hours after helper virus infection (or after viral production begins).

[00226] rAAV production cultures can be grown under a variety of conditions (over a wide temperature range, for varying lengths of time, and the like) suitable to the particular host cell. rAAV production cultures include attachment-dependent cultures which can be cultured in suitable attachment-dependent vessels such as, for example, roller bottles, hollow fiber filters, microcarriers, and packed-bed or fluidized-bed bioreactors. rAAV vector production cultures may also include suspension-adapted host cells such as HeLa, 293, and SF-9 cells which can be cultured in a variety of ways including, for example, spinner flasks, stirred tank bioreactors, and disposable systems, such as the Wave bag system.

[00227] Any suitable media may be used for the production of expression vectors, including rAAV virions. These media include, without limitation, Modified Eagle Medium (MEM) and Dulbecco's Modified Eagle Medium (DMEM). Optionally, rAAV production culture media is supplemented with serum or serum-derived recombinant proteins at a level of 0.5%-20% (v/v or w/v). Alternatively,

rAAV vectors may be produced in serum-free conditions (i.e., media with no animal-derived products).

[00228] After culturing the host cells to allow AAV virion production, the resulting virions may then be harvested and purified. There are a variety of methods to harvest expression vectors. For instance, AAV virions may be obtained from culture medium after a period of time post-transfection (e.g., 72 hours), optionally with a cell lysis step to release vectors from host cells. Methods of lysing cells are known in the art and include, for example, multiple freeze/thaw cycles, sonication, microfluidization, and treatment with chemicals, such as detergents and/or proteases. rAAV virions may be harvested from spent media from the production culture, provided the cells are cultured under conditions that cause release of rAAV virions (see, e.g., U.S. Patent No. 6,566,118, incorporated herein by reference).

[00229] After harvesting, the expression vectors (e.g., rAAV virions) may be purified. "Purified" refers to a rAAV virions preparation devoid of at least some of the other components present where the rAAV virions naturally occur or are initially prepared from. Thus, for example, purified rAAV virions may be prepared using one or more isolation techniques to separate virions from a source mixture, such as a culture lysate or production culture supernatant. The result of the purification steps is, in various instances, an enriched preparation of expression vectors. Enrichment can be measured in a variety of ways, such as, for example, by the proportion of DNase-resistant particles (DRPs) or genome copies (gc) present in a preparation, or by infectivity, or it can be measured in relation to a second, potentially interfering substance present in the source mixture, such as contaminants, including production culture contaminants or in-process contaminants, including helper virus, media components, and the like.

[00230] If desired, the rAAV production culture harvest may be clarified to remove host cell debris. Clarification of production culture harvest may be achieved using any one or more of a variety of techniques, such as centrifugation or filtration through a filter of 0.2 μm or greater pore size (e.g., a cellulose acetate filter or a series of depth filters). Other methods include, but are not limited to, Cesium chloride (CsCl)- and iodixanol-based density gradient purification.

[00231] Alternatively or in addition, the rAAV production culture harvest may be treated with Benzonase™ to digest high molecular weight DNA present in the production culture. Benzonase™ digestion is typically performed under standard conditions, for example, a final concentration of 1-2.5 units/ml of Benzonase™ at a temperature ranging from ambient to 37°C for a period of 30 minutes to several hours.

[00232] The rAAV production harvest also may undergo heat inactivation of helper virus. Heat

inactivation of adenovirus is further described in, e.g., U.S. Patent No. 11,013,774, incorporated herein by reference in its entirety.

[00233] In various aspects, the rAAV virions are isolated or purified using one or more of the following purification steps: equilibrium centrifugation; flow-through anionic exchange filtration; tangential flow filtration (TFF) for concentrating the rAAV particles; rAAV capture by apatite chromatography; rAAV capture by hydrophobic interaction chromatography; buffer exchange by size exclusion chromatography (SEC); nanofiltration; and rAAV capture by anionic exchange chromatography, cationic exchange chromatography, or affinity chromatography. These steps may be used alone, in various combinations, or in different orders. Methods to purify rAAV particles are further described in, for example, Xiao et al., Journal of Virology 72:2224-2232 (1998); U.S. Patent Nos. 6,989,264 and 8,137,948; and International Patent Publication No. WO 2010/148143, all of which are incorporated by reference.

[00234] Optionally, purified AAV virions can be dialyzed against PBS, filtered and stored at –80°C. Titers of viral genomes can be determined by quantitative PCR using linearized plasmid DNA as standard curve (see e.g., Lock M, et al., Hum. Gene Ther., 21:1273-1285 (2010)).

[00235] The following examples are given merely to illustrate features of the present invention and not in any way to limit its scope

EXAMPLES

[00236] The disclosure below provides a description of materials and methods used throughout the Examples.

[00237] *STXBP1 vector design*: Vectors contained a selected promoter element, a codon optimized version of human *STXBP1*, a selected DRG-de-targeting 3'UTR element, a mutagenized woodchuck post-transcriptional regulatory element, and a synthetic poly-adenylation signal.

[00238] *Promoter screening (IHC):* Candidate promoter elements were cloned into a packaging plasmid containing a nuclear membrane-localized GFP reporter cassette to generate AAV9 vector. 3E10 vg/mouse of AAV9 vector was delivered by bilateral stereotaxic ICV injection at PND1 by Charles River Laboratories. Brain, left liver lobe, and spinal cord tissue were harvested 4 weeks post dosing by Charles River Laboratories. Tissues were fixed in NBF at room temperature for 24 hours then stored in 70% ethanol at 4˚C. The fraction of cells that expressed the reporter (activity) for a given cell type of each candidate element was measured in various cell types by IHC. Cell types were determined by co-staining with cell type specific markers.

[00239] *DRG de-targeting screening:* Candidate elements comprised of human 3'UTR sequence

and human miRNA binding site cognate sequences paired with unique molecular identifiers were synthesized (Twist Biosciences) and cloned into packaging plasmid libraries containing a GFP reporter cassette to generate an AAV9 library pool. AAV9 libraries were delivered via intrathecal injection at PND1, and DRG and brain tissue was harvested at four weeks post dosing. RNA was isolated from each tissue section, reverse transcribed, and sequence libraries were generated by PCR amplification of the resulting cDNA, or of the starting AAV9 pool. Amplicon libraries were sequenced (NextSeq2000, Illumina) and the resulting data was analyzed with DESEQ to identify elements that decreased mRNA levels in DRG tissue with minimal impact in brain tissue.

[00240] *AAV vector production*: Replication-incompetent, recombinant AAV9 (rAAV9) particles were produced in HEK293 via transient triple co-transfection: a transgene-containing plasmid, a packaging plasmid for Rep and Cap genes, and a plasmid containing adenoviral helper genes. For mouse studies, rAAV9 vectors were produced in an adherent HEK293 system, and were purified by CsCl centrifugation or iodixanol gradient followed by buffer exchange. Vector was formulated in phosphate-buffered saline (PBS) and stored at -80°C. For NHP studies, rAAV9 vectors were produced using a suspension-adapted HEK293 subclone. The cells and supernatant were harvested by detergent lysis, nuclease treatment, and filtration. rAAV vectors were purified using chromatography-based methods. Vectors were formulated in an artificial CSF solution including 0.005% w/v poloxamer 188, and stored at ≤60°C.

[00241] *Animals*: Heterozygous *Stxbp1*$^{+/-}$ mice generated by deletion of *STXBP1* exon 2 via LoxP/Cre recombination. Heterozygous animals were generated at Charles River Laboratories by fertilizing ova from C57BL/6N mice with sperm from *Stxbp1*$^{+/-}$ mice followed by transplantation of fertilized embryo into CD-1 surrogates. Animals were also supplemented internally by breeding *Stxbp1*$^{+/-}$ males with C57BL/6J females in a 1:2 breeding schema. IVF animals were used for all behavioral studies whereas internal breeding lines were used for vector optimization. Genotyping was performed by automated RT-PCR at TransnetYX, Inc. All mice were maintained on a 12:12-h light:dark cycle and had *ad libitum* access to food and water throughout the experiments.

[00242] Sera were screened for preexisting total anti-AAV9 antibodies and animals with titers from <1:100 to 1:800 were selected. NHPs with the highest anti-AAV9 antibody titers were evenly distributed among dosing groups and a minimum of two NHPs with total anti-AAV9 antibody levels ≤ 1:100 were assigned to each dosing group. Animals were group-housed in acclimatized holding rooms with water ad libitum. Animals were given meals of balanced composition and additional food was offered to provide environmental enrichment. Male and female juvenile cynomolgus macaques were 16.0–20.3 months old at dosing and weighed 1.58–2.60 kg.

[00243] *Intracerebroventricular injections*: Vector was thawed at 4°C and administered in a blinded fashion by bilateral ICV injection in mice on PND1. In anesthetized mice, Lambda and bregma skull sutures were referenced to determine the lateral and rostral/caudal location of the ventricle. The needle was lowered to a ventral depth of DV 1.7 mm to target the lateral ventricles and mice were injected with 2 µL of vector or vehicle at 8000 nL/min. After injection, mice were placed in a warming pad and returned to the mother in the cage.

[00244] For unilateral ICV administration in NHPs, presurgical MRI was performed to establish dosing coordinates within the anterior horn of the left lateral ventricle. A single burr hole was drilled over the target coordinates and a Tuohy guide needle (17 gauge) was advanced to the appropriate depth from pia using the established ventricular coordinates and stereotaxic guidance. A fiberoptic camera inserted through the lumen of the needle was used to confirm ventricular targeting via visualization of CSF flow. The vector or vehicle was delivered through a flexible 24 cm PEPU catheter (Part No. ICV-PEPU-24, SAI Infusion Technologies) tunneled through the Tuohy guide needle at a rate of 0.1 mL/min for a duration of 20 min (2 mL delivered in total). Following dosing, the craniotomy was covered with Gelfoam, and the muscle, subcutaneous layers, and skin were closed.

[00245] *In vivo assessment of STXBP1 phenotypes in mice*: Before all behavior assays, animals were single-housed for a minimum of 30 min with a 50bB white noise running in the background. Behaviors were performed on WT and *STXBP1* mutant mice that were age-matched and consisted of both males and females. Researchers were blinded to their genotypes and treatment groups. The individual home cage during acclimation of each animal was specific to that animal throughout completion of the behavioral tests conducted in each study.

[00246] *Open-field:* The open-field assay, to assess locomotor activity and anxiety, was conducted at 100–150 lumen lights and continuation of 50dB white noise in the background. At the beginning of the trial, the mouse was placed in the center of an opaque blue arena (40x 40 cm) and allowed to freely explore the empty area. The movement was recorded by a camera positioned directly above the arena and tracking was conducted using the EthoVision software. Four mice could be tested at the same time. After each trial, the animals were returned to home cages and the apparatus was cleaned with 70% ethanol. Using the video tracking system, the time spent by each animal in the center and periphery of the open-field, the total distance moved, and the velocity of the movement were determined. The percentage of time spent in the center of the open-field was calculated as an indicator of anxiety-like behavior. The total distance moved was used as an index of locomotor activity.

[00247] *Nesting:* The nest building tests examined the innate behavior by assessing the extent of nestlet shredding over a fixed duration. Day 0 began with the mouse single housed with an autoclave nestlet placed in the cage as the only form of enrichment prior to the initiation of the experiment. The quality of nest was observed at 24, 48, and 72 hours. Nestlet shredding was scored from 0 to 3, where 0 was minimally shredded to 3 where there was a completed formed nest.

[00248] *Hindlimb Clasping:* In their home cages, the hindlimb position of mice was observed for 10 s and the degree of clasping assessed using a four-point scoring system. A positive score resulted if the mouse clasped on and off or throughout for a minimum of 5 s. Mice were scored from 0 to 3: Score 0, Both hindlimbs consistently splayed outward, away from the abdomen; Score 1, One hindlimb retracted towards the abdomen for >50% of the time suspended; Score 2, Both hindlimbs partially retracted towards the abdomen for >50% of the time suspended; Score 3, Both hindlimbs fully retracted and touching the abdomen for >50% of the time suspended.

[00249] *Contextual Fear Conditioning*: Before contextual fear conditioning, mice were single-housed in an acclimation room separate from where the assay was conducted. There were three sessions: training, context (24 hours post training), and cue (4 hours post context). On the training day, mice were placed into a 7" x 7" x 12" (30 x 25 x 29 cm) enclosure with an electrified grid bottom (Context A). After 2 min of acclimation, mice were presented with a 15 s tone (conditioned stimulus (CS): 85–90 dB, 3 kHz tone). During the last two seconds of the tone, a 2 s footshock (unconditioned stimulus (US): 0.72 mA) was delivered. After a 60 s inter-trial interval, the procedure was repeated twice, for a total of three tone-shock pairings. Mice were removed from the assay enclosure and returned to their home cages post another minute in the cage. About twenty hours after training, retention of the contextual CS:US memory was assessed by measuring freezing behavior following placement into the original training chamber. Freezing behavior was evaluated for 5 min, and no stimuli was presented during this phase. Mice were then returned to their home cage. Retention of the tone CS:US memory was examined by placement of mice in a novel context. The animals were brought into the room with different lighting. The chamber was altered using plexiglass inserts and a different odor to create a new context for the cued fear test. Mice had a 3-min acclimation period to explore the chamber, during which baseline freezing behavior was scored. Immediately after, a 15 s tone was presented, then a 60 s interval of no stimulus. This was repeated for a total of three presentations of the tone. Upon completion, the mouse was removed and returned to its home cage. Time spent freezing during training and cued and contextual phases of the evaluation for each group was scored automatically via the Ethovision Software.

[00250] *PTZ assay*: PTZ is a chemoconvulsant drug that was used to induce tonic-clonic forebrain seizures in a terminal assay performed before necropsy. Mice were weighed and acclimated, then were induced with PTZ by subcutaneous injection. They were recorded for 30 min in their individual cage, and a six-point scoring system was used for recorded events: Score1: Hypoactivity with facial/ear twitching; Score 2: Partial clonus (head nodding, jerking, vocalization); Score 3: Forelimb clonus with Straub tail, repetitive movements; Score 4: Hindlimb clonus with righting reflex; Score 5: Tonic convulsions with loss of righting reflex; Score 6: Death.

[00251] *EEG implantation and video-EEG seizure analysis:* The fur at the back of the head was shaved between the ears to the bottom of the neck, and Rimadyl Working Solution was subcutaneously administered at a rate of 0.1 ml per 10 grams of body weight per mouse (25 mg/kg). The mouse was placed in an isoflurane chamber with an ISO level set at ~5%, achieving surgical anesthesia within 3–5 min. Isoflurane-anesthetized mice were secured in a stereotaxic frame with engagement of ear and bite bars to prevent head rotation, while isoflurane and oxygen were provided, and mouse breathing was closely monitored. A ~2–3 cm incision was made along the dorsal midline of the skull through the neck region, and a subcutaneous pocket was formed for the implantation of DSI's PhysioTel HD wireless telemetry implant device and the bi-potential lead wires. The leads were then exteriorized, and a procedure involving the perforation of the cervical trapezius muscles and insertion of leads through a needle was performed on both sides. Craniotomies were carried out using a 0.9 mm diameter micro-drill bit to perforate the skull at the coordinate of AP: 2.2, ML: -1 for the positive lead and AP: -6, ML: 1 for the ground lead. The craniotomies were ensured to pass completely through the skull but not perforate the dura membrane. Following screw placement, the exposed portion of the lead wires were wrapped around the corresponding screw. Dental cement was applied to completely encase the screws and exposed lead wires. The skin incision was then closed using 5–0 non-absorbable sutures. Post-surgery, mice were placed under a heat lamp for warm recovery until consciousness returned.

[00252] Video-EEG recordings were performed continuously for 20 hours beginning in the PM (~four hours before the lights off cycle) and ending in the AM (~four hours into the lights on cycle) using the Ponemah acquisition software. During the recording, mice in their home cage were placed on wireless receivers in a quiet room with ambient white noise. Individual cameras were mounted to capture activity in the home cage, and videos were synchronized with EEG recordings via the Ponemah software. SWD events were detected as spike trains through a semi-automated process using the NeuroScore software alongside manual scoring and correction as needed. Spikes were identified using an Absolute Threshold defined by an optimized threshold based on the basal

electrographic activity for each individual recording. Spike trains consisting of a clustering of ≥four spikes within a set spike interval and duration as well as amplitudes of >2x the basal electrographic activity were scored as a SWD event. SWD events that fell in the three-hour periods of 7–10 AM and 7–10 PM (the three hours following light cycle switches) were quantified. All assessments were performed by scorers blinded to treatment and genotype.

[00253] *Clinical assessments in NHPs*: Clinical observations were initiated before dosing and continued through the scheduled euthanasia on Day 50, including twice daily cage-side observations and weekly detailed clinical observations, body weight, and qualitative food consumption measurements. A functional observational battery evaluated neurologic parameters such as locomotor activity, behavioral changes, reflexes, and coordination, and was conducted once before dosing and again on Day 50.

[00254] Samples for clinical pathology and biomarker evaluations were collected prior to dosing (serum clinical chemistry, hematology, CSF pathology, serum biomarker), on Days 3, 8, 15, 30, and 45 of the observation period (serum clinical chemistry and serum biomarker only), and prior to the scheduled euthanasia on Day 50 (serum clinical chemistry, hematology, CSF pathology, serum biomarker).

[00255] *Nerve conduction electrophysiology in NHPs*: Nerve conduction assessments were performed in all animals before dosing and 7-weeks post-dosing. During all recording sessions animals were lightly anesthetized according to the NBR standard operating procedure, and placed on a temperature-controlled warm pad, such that normal physiological temperature was maintained during collections. All signal collections and post-collection data analyses were performed with a calibrated and certified clinical pediatric electromyography (EMG) machine (Natus Neurology System with Synergy software). Metea et al., J Pharmacol Toxicol Methods. 2022 Jul-Aug:116:107187. Standard subdermal needle electrodes (7 mm x 0.3 mm) or equivalent were used for recording. To sample conduction velocity at different spinal levels that were likely to be affected differently due to level-specific ganglionic size and morphology, sensory nerve conduction was assessed in multiple nerves including the sural, peroneal, saphenous, radial, and median nerves.

[00256] Motor nerve conduction was assessed for the tibial motor nerve and included the F-wave test for ascending motor pathways. Positions for nerve stimulation and recording were consistently located relative to anatomical landmarks, except where anastomoses were present requiring customization. Sensory nerve action potentials were generated by positioning the recording electrodes over the nerve, increasing the stimulus strength until a response was evoked, and subsequently eliciting 5–10 supramaximal responses. To account for delays introduced by the

neuromuscular junction, motor nerve function was assessed by eliciting compound muscle action potentials (CMAPs or M-waves) from distal muscles innervated by the tibial nerve, following orthodromic stimulation of the nerve at two locations along its course. F-waves were elicited for the motor pathways related to plantar flexors, via tibial branches. Stimulations were elicited at the popliteal fossa, using the same recording montage as for the tibial motor nerve. Onset latency was measured from the stimulus artifact to the initiation of the depolarization to the nearest 0.01 ms, and amplitude was measured from baseline to the peak of the depolarization to the nearest 0.01 μV for sensory responses and to the nearest 0.01 mV for motor responses. The nerve conduction velocity (NCV) was calculated using the onset latency of the response (sensory nerves) or the difference in latency (motor nerves) of the supramaximal response, and the distance from the recording electrode to the stimulation cathode.

[00257] *Takedown and terminal tissue collection*: Mouse cortical brain tissues were collected, flash frozen, and stored at -80°C for protein analysis or stored in *RNALater* at 4°C and transferred 24 hours later to -80°C for VCN and transcript analysis. For IHC analysis, brains were collected and preserved in 10% neutral buffered formalin (NBF) for 24 hours, then switched to 70% ethanol and stored at 4–8°C until histopathologic processing. Spinal columns were fixed in NBF for 48 hours before being transferred to 70% ethanol. For DRG collection, the mouse postmortem trunk was obtained, and the spinal column was surgically removed. The mouse spinal cord was subjected to hydraulic extrusion, as required. The cervical spinal column was pinned down, and both sides of the last rib (number thirteen) were identified and pinned down. After the thoracic spinal column was pinned down, the lumbar region was fully exposed. The muscles covering the lumbar spine were removed to expose the lumbar vertebrae. The lumbar vertebrae were equally center-cut through L1-L6 with a surgical razor blade. Scissors were used for the extension action to open the lumbar spinal cavity. Fine forceps and fine spring scissors were used to trace the location of spinal roots containing the DRGs. Ipsilateral and contralateral lumbar DRGs were carefully dissected out and placed into *RNALater* solution or snap frozen in liquid nitrogen.

[00258] For NHPs, NBR personnel performed all necropsies. Following euthanasia, animals received transcardial perfusion with 0.001% sodium nitrite in saline until clear of blood. A subset of peripheral tissues, brain tissue from 11 distinct brain regions, and spinal cord and DRG samples from cervical, thoracic, lumbar, and sacral vertebral regions were collected in *RNAlater* for transcript and/or VCN analysis, or were flash-frozen for protein analysis. For the neurohistopathology evaluation, representative samples of brain, spinal cord, DRG with spinal nerve roots (SNR) were collected. The brain was removed from the skull, weighed, placed in a chilled metal brain matrix,

and cut into 4 mm thick coronal slabs, which were sequentially numbered from rostral to caudal. The ICV injection slab, all odd-numbered slabs, and all even-numbered slabs (after fresh tissue collection) were split into two hemispheres, placed in 4% paraformaldehyde for 24 to 48 hours at 2–8°C, and then transferred to 70% ethanol (stored at 2–8°C). Transverse segments of spinal cord with attached SNR and DRG from cervical (C6), thoracic (T4 and T11), lumbar (L3 and L5), and sacral (S1) levels were collected, placed in 4% PFA for 24–48 hours at 2–8°C, and then transferred to 70% ethanol (stored at 2–8°C). Following ethanol transfer, tissues were shipped overnight under refrigerated conditions (2–8°C) to Experimental Pathology Laboratories (EPL®), Inc., Sterling, VA.

[00259] *Immunohistochemistry and histopathology*: Mouse brain tissue was embedded in coronal orientation, and vertebral columns were decalcified before embedding in formalin-fixed paraffin in a longitudinal orientation. After de-wax and heat retrieval, primary antibody incubation followed by secondary antibodies conjugated to horse radish peroxidase (HRP) followed by TSA-conjugated fluorophores was performed. Antibodies included rabbit anti-munc-18 (M2694; Sigma Aldrich), rabbit anti-GFP (ab290; Abcam), mouse anti-calcium/calmodulin-dependent protein kinase II alpha (MA1-048; Invitrogen), rabbit anti-somatostatin (T-4102; Peninsula Laboratories), mouse anti-PV (PV235; Swant) and mouse anti-fox-3 (MAB 377; Millipore). Slides were stained with DAPI and whole slide images were captured at 20x using an Akoya Biosciences Polaris instrument. Image exposures were determined for each fluorochrome.

[00260] NHP tissue samples were submitted by NBR on behalf of Encoded Therapeutics, South San Francisco, CA, to EPL. At EPL, all brain slabs were gross trimmed to fit the tissue cassette and processed to paraffin, cut to slide along the coronal plane using a 5-micron block advance, and then stained with Hemoxylin and Eosin (H&E). The spinal cord segments were trimmed into transverse and longitudinal oblique sections, embedded in paraffin, cut to slide using a 5-micron block advance, and stained with H&E. The DRG with SNR were embedded longitudinally in paraffin, cut to slide using a 5-micron block advance, and stained with H&E. All tissues were embedded within 14 days from date of placement in 70% ethanol. The study pathologist examined all slides for brain, spinal cord, and DRG (including SNR) by brightfield microscopy. Brain sampling, processing, and evaluation were in accordance with current industry best practices.[28] Findings were graded semi-quantitatively from one to five, depending upon severity.

[00261] *In situ hybridization of STXBP1-Co4 in mice*: A custom probe set Codon-*STXBP1*-Co4-C1 (1107241-C1, RNAScope 11zz pairs, ACD) was designed to target 278–1710 of human *STXBP1* (Isoforms 1 & 2, common region) with codon optimization. This antisense probe set was developed to detect the presence of AAV vector expressed mRNA and vector DNA. Wang et al., Appl

Microbiol Biotechnol 93, 1853-1863 (2012). RNAscope™ assay protocol conditions were optimized for the detection of *STXBP1*-Co4 signal in FFPE tissues and performed by Encoded Therapeutics. Regions of 1 mm^2 were selected from the somatosensory cortex dorsal to the hippocampus from both hemispheres for each animal. A StarDist nuclei segmentation model trained on Encoded images was used within Fiji to find nuclei in DAPI-stained images. Nuclei were then classified as marker positive or negative using a random forest classifier trained in Ilastik. Percent marker-positive nuclei were found for multiple routes of administration per animal.

[00262] *Vector count number (ddPCR*): VCN was assessed in mice and NHPs using DNA isolated from tissue using the Allprep Universal Kit (Qiagen) according to the manufacturer's instructions. The VCN evaluation for DNA samples was conducted in 96-well plates using a QX200-AutoDG Droplet Digital PCR system and C-1000 Touch Thermo Cycler followed by QX200 Droplet Digital Reader (Bio-Rad Laboratories). Tissue genomic DNA samples and non-template controls (NTC) were processed for droplet generation and PCR amplification in triplicate of master ddPCR mix containing: ddPCR Supermix for Probes (2X), Taqman primers/probes (FAM Dye) against the transgene (codon-optimized *STXBP1*, *STXBP1*_co4), primer/probe against reference gene with two copies per cell (Mus musculus transferrin receptor gene, MmTfrc, or *Macaca fascicularis* albumin gene, MfAlb) primers/probes (VIC Dye)), and DdeI restriction enzyme, which cut genomic DNA into fragments. The VCN was reported as copy number per diploid genome, which was calculated based on the ratio of the *STXBP1* transgene to the reference gene.

[00263] *Endogenous STXBP1 expression (RT-ddPCR):* Endogenous *STXBP1* expression was assessed in mice and NHPs using RNA isolated from tissue using Allprep Universal Kit (Qiagen) according to the manufacturer's instructions. For the RNA transcript, a reverse transcriptase (RT) ddPCR-based assay was performed on 96-well plates in a QX200-AutoDG Droplet Digital PCR system and C-1000 Touch Thermo Cycler followed by QX200 Droplet Digital Reader (Bio-Rad Laboratories). Isolated RNA samples were converted to cDNA using SuperScript IV VILO kit (Thermo Fisher) with additional DNase treatment step. Tissue cDNA samples, no RT-control and non-template controls (NTC) were analyzed in triplicate of master ddPCR mix containing: ddPCR Supermix for Probes (2X), Taqman primers/probes (FAM Dye) against the transgene (codon-optimized *STXBP1*, *STXBP1*_co4), and primers/probe against reference housekeeping gene (Macaca fascicularis ADP Ribosylation Factor GTPase Activating Protein 2 gene, MfARFGAP2, or Mus musculus beta-glucuronidase gene, MmGUSB) (VIC Dye). The transcript levels were reported as copies per microgram of RNA.

[00264] *STXBP1 expression*

[00265] *MSD ELISA*: MSD assays for total STXBP1 (pan-isoform) were conducted on mouse and NHP brain and peripheral tissues that were homogenized using a Qiagen TissueLyser II, according to the manufacturer's instructions, followed by 4°C centrifugation to pellet insoluble material. Total protein concentration was determined using the Pierce™ BCA Protein Assay Kit or Pierce™ Rapid Gold BCA Assay Kit (Thermo Fisher Scientific, Inc. #23225 and #A53225) and total protein from 0.04–1 mg/mL, depending on the specific tissue analyzed, was loaded onto a MULTI-ARRAY standard 96-well plate (Meso Scale Diagnostics #L15XA-6) for measurement via an ECL-based sandwich immunoassay.

[00266] Total STXBP1 was detected with a mouse anti-STXBP1 mAb against a human STXBP1 fusion protein (clone 1B5B3, ProteinTech #67137-1-Ig) as capture antibody and a rabbit mAb against a fragment of human STXBP1 (clone EPR4850, Abcam #ab124920) as detection antibody. To specifically detect isoform 2 of STXBP1 the same capture antibody as for total STXBP1 detection was used, and the detection antibody was replaced with a rabbit pAB (Sigma # M2694) directed against a synthetic peptide corresponding to the C-terminus of rat STXBP1 isoform 2. In both assay formats, the signal was detected using a SULFO-TAG anti-rabbit pAb as secondary antibody (Meso Scale Diagnostics #R32AB-1) and MSD read buffer T (Meso Scale Diagnostics #R92TC-2). For quantification, a purified recombinant human isoform 1 STXBP1 protein (GenScript # U591WGG200-9) was used as the standard for the total STXBP1 assay and a purified recombinant isoform 2 STXBP1 protein (Sino Biological #11751-H20B) was used for the isoform 2 assay. The level of total STXBP1 or isoform 2 STXBP1 in the sample was normalized by total protein loaded in each well.

[00267] *Western blotting*: In mice and NHPs, Western blots were performed using protein lysates from brain samples, which were loaded into Mini-PROTEAN® TGX™ Precast Gels (4–15%) (Bio-Rad: 4561086). The SDS-PAGE was run at 200V for 40 min. Gels were blotted using Trans-Blot Turbo Mini 0.2 µm PVDF Transfer Packs (Bio-Rad: 1704156). The membranes were washed in Tris-buffered saline plus Tween-20 (TBST) and blocked in Intercept® (TBS) Blocking Buffer (LI-COR Biosciences, 927-60001) for one hour at room temperature. The membrane was incubated with anti-*STXBP1* (Abcam: ab124920, SYSY:116002) and anti-tubulin (Invitrogen: MA5-16308) antibodies for overnight at 4°C with shaking. The membrane was washed in TBST and incubated with IRDye® 800CW Donkey anti-Rabbit IgG Secondary Antibody (LI-COR Biosciences: 926-32213) and IRDye® 680RD Donkey anti-Mouse IgG Secondary Antibody (LI-COR Biosciences: 926-68072). The signals were acquired by Odyssey (LI-COR Biosciences) and the protein

quantification was analyzed by EmpiriaStudio (LI-COR Biosciences). The intensity value of the band corresponding to *STXBP1* was normalized to the intensity value of the tubulin band.

[00268] *Neurofilament light chain biomarker assay in NHPs*: Serum concentrations of neurofilament light chain (Nf-L) were determined using the single molecule array (Simoa®) technology and performed on the Simoa® HD-1 Analyzer (Quanterix, Billerica, Massachusetts). The assay was conducted using the NF-Light™ Advantage Assay Kit, containing an anti-Nf-L human monoclonal antibody (UmanDiagnostics, Umeå, Sweden). Nf-L was measured from serum collected pre-study, and at Day 15, Day 30, Day 50. Quality control checks were performed using control samples provided in the kit to ensure assay accuracy and reproducibility. Nf-L data was acquired using the Simoa® software and further quantified (pg/mL) and plotted using *Microsoft Excel* or *GraphPad Prism*.

Example 1: Improved WPRE element

[00269] The WPRE fragment is derived from Woodchuck hepatitis virus and enhances gene expression in a cis-acting manner. The 3' region of WPRE includes an enhancer sequence (We1), a promoter for the WHV X-protein and the first 60 amino acids of the X-protein. This protein may have adverse effects in mammalian cells and has led to concerns about the safety of the WPRE element in therapeutic vectors. To mitigate this risk a mutant WPRE element, SEQ ID NO: 22, was developed which lacks the transcription start site.

[00270] To test the efficacy of SEQ ID NO: 22, HEK293 cells were transiently transfected with plasmids expressing STXBP1 under the control of an EF1a promoter with either no WPRE element, a wildtype WPRE element or SEQ ID NO: 22. As shown in FIG. 1, inclusion of either the wildtype WPRE element or SEQ ID NO: 22 resulted in an equivalent increase in STXBP1 protein expression compared to no WPRE element.

Example 2: Pan-neuronal promoters for gene therapy

[00271] Commonly-used ubiquitous and pan-neuronal vectors often do not produce strong expression in inhibitory neuronal populations. There is a need for promoters with strong expression in both excitatory and inhibitory neuronal populations.

[00272] Single-cell RNAseq data was used to identify a shortlist of human genes showing high levels of expression in neuronal populations and limited expression in non-neuronal populations. Next, a panel of human regulatory genomic data, including single-cell ATACseq data (Ref ATACseq datasets), conservation data, DNase accessibility in neuronal cell lines, transcription factor motifs, and Genehancer interactions, was used to identify putative cell-selective regulatory

sequence regions surrounding the transcription start sites. Each promoter candidate was operably linked to a nuclear membrane-tethered eGFP reporter gene and packed into AAV9 vectors delivered via ICV to WT mice. Brain sections were collected at four weeks and co-stained for pan-neuronal (NeuN+), excitatory (CamKII+), and inhibitory (PV+, VIP+, SST+) neuronal markers. FIG. 9 shows a representative image showing expression of eGFP in neurons. FIGs. 10 and 11 show quantification of the percentage of excitatory and inhibitory neurons expressing eGFP in representative cortical regions. This quantification identified two lead promoters: SEQ ID NO: 13 and SEQ ID NO: 11. These promoter candidates demonstrated comparable or improved expression in CamKII+ populations compared to control pan-neuronal (Syn1) or ubiquitous (CB) promoters (FIGs. 10 and 11), with broader expression in inhibitory (PV/VIP/SST) populations.

[00273] To further investigate the neuronal selectivity of the candidate promoters, brain sections were evaluated for co-localization of expression with the neuronal marker NeuN.
As shown in FIG. 39, Candidate 1 (SEQ ID NO: 13) and Candidate 2 (SEQ ID NO: 11) promoters showed significantly higher neuronal selectivity (95+/-, 96+/- %NeuN+eGFP+/%eGFP+) compared to the CB control (90+/- %NeuN+eGFP+/%eGFP+).

[00274] As AAV9 is liver-trophic, liver sections from candidate promoter arms were analyzed for off-target eGFP expression as a measure of selectivity. Whereas the ubiquitous promoter (CB) showed detectable eGFP+ expression in the liver hepatocytes despite targeted cerebrospinal fluid (CSF) delivery, no eGFP expression was detected in the liver of mice dosed with these pan-neuronal promoter candidates. Representative images of liver hepatocytes after treatment with the different constructs are shown in FIG. 40.

[00275] CNS delivery of AAV capsids has been demonstrated, in some cases, to produce high levels of expression in Dorsal Root Ganglion neurons, which may result in off-target DRG toxicity and impairments in neuronal function. This is a key limiting factor to dose and safety for CNS-targeted AAV therapeutics. In this study, eGFP was expressed under the control of SEQ ID NO: 7, with or without the DRG de-targeting sequence of SEQ ID NO: 30. Strong staining was observed in the DRG of neurons without SEQ ID NO: 30, however only background staining was observed from vectors carrying the SEQ ID NO: 30 element, as shown in FIG. 12A. As expected, no reduction in staining was observed in central brain sections, as shown in FIG. 12B.

[00276] These promoter candidates were then incorporated into vectors expressing a codon-optimized STXBP1 transgene, and delivered to wildtype and Stxbp1 heterozygous mice via ICV delivery on PND1. Protein expression analysis by MSD showed that vector candidates driven by SEQ ID NO: 13 and SEQ ID NO: 11 promoters resulted in significantly less STXBP1

overexpression in the liver than the ubiquitous benchmark EF1a promoter (FIG. 52A), with no significant differences in STXBP1 expression observed in the brain, as measured in hippocampal tissue (FIG. 52B). All vectors expressing STXBP1 under the control of EF1α, SEQ ID NO: 13, or SEQ ID NO: 11 promoters were well tolerated. At necropsy, no differences in body weight were observed in Stxbp1+/+ and Stxbp1+/- mice dosed with vehicle+ or vector, see FIG. 53. Taken together, these new promoters achieved comparable potency to ubiquitous promoters such as CB and EF1a in CNS, a selectivity profile similar to Syn1, and improved expression in inhibitory neurons.

Example 3: Epilepsy expansion

[00277] 6Hz is an electroshock induced acute seizure model as well as a model of refractory epilepsy for which many anti-seizure medications do not show efficacy at clinically relevant doses. WT C57Bl6 mice were administered AAVs comprising SEQ ID NO: 77 or SEQ ID NO: 78 at a dose of 6E10. SEQ ID NO: 77 comprises STXBP1 under the control of SEQ ID NO: 15 with the de-targeting element of SEQ ID NO: 28. SEQ ID NO: 78 comprises STXBP1 under the control of SEQ ID NO: 13 with the de-targeting element of SEQ ID NO: 28. A positive control was provided by administering valproate by IP injection at 400 mg/kg dose. Electrical stimulus (32mA, 6Hz, 0.2ms pulse width, 3s duration) was given to mice via corneal electrodes to produce psychomotor seizure defined as the expression of at least one of the following behaviors: stun/immobility, forelimb clonus, straub tail, or lateral head movement in >95% of control animals within 30 s of stimulus delivery. Seizure score is a sum of the presence of the four seizure phenotypes: stun, forelimb clonus, Straub tail, and lateral head movement. Protection was defined as complete absence of any of the four seizure phenotypes within 30 s of stimulus delivery. As shown in FIG. 3, 30% of the animals in the SEQ ID NO: 78 group did not experience seizures. Further the seizure score for these animals was also lower, as seen in FIG. 4.

[00278] The PTZ assay was also used to assess the efficacy of AAVs at a dose of 6E10 expressing STXBP1 under the control of SEQ ID NO: 15 or SEQ ID NO: 13, each with the de-targeting element of SEQ ID NO: 28. Treatment with the AAV comprising SEQ ID NO: 78 decreased seizure incidence (FIG. 5), and highest racine score (FIG. 7), while increasing latency to seizure (FIG. 8). Total seizure time was not significantly altered (FIG. 6).

[00279] A PTZ assay was also conducted with a Syn1-STXBP1 construct in STXBP1 het and STXBP1 WT mice. As shown in FIG. 2, administration of an AAV comprising Syn1-STXBP1 decreased the number of WT animals experiencing seizures in response to PTZ.

Example 4: AAV9-STXBP1 gene replacement rescues multiple phenotypes in an STXBP1 mouse

model

[00280] To determine the validity of a gene replacement approach for treating STXBP1 disorder STXBP1 +/+ (WT) mice and STXBP1 +/- (HET), littermates were dosed at PND1 (post-natal day 1) via bilateral ICV injection with an AAV9 expressing EF1a-STXBP1-WPRE-sPA at 1E11 vg/mouse.

[00281] For evaluation of efficacy, a battery of behavior tests as well as electro-encephalogram (EEG) were conducted between 6 and 12 weeks of age. The study design is outlined in FIG. 13. The behavioral battery consisted of elevated plus maze (7wks), open field (8wks), nesting (9wks), fear conditioning(10wks), hindlimb (10.5wks) clasping and PTZ induced seizures (11wks) to assess a variety of phenotypes. The baseline phenotypes and sequence for all these assays was determined in a separate study with unmanipulated/vehicle dosed animals. Additionally, a subset of animals that did not go through behavior were evaluated for cortical spike wave discharges via single channel EEG. In the open field assay used to assess mouse locomotion, exploration and anxiety, vehicle dosed STX HET mice show hyperactivity and increased anxiety-like behavior as compared to STX WT mice (FIG. 14). Upon treatment, a significant decrease in hyperactivity was observed for animals dosed with EF1a-STXBP1 (FIG. 14). Nesting examines the innate nest building capabilities. As shown in FIG. 15 STXBP1 HET vehicle dosed animals built significantly worse nests than counterpart WT animals and EF1a-STXBP1 dosed HET mice. One of the core features of STXBP1 encephalopathy is intellectual disability, reported in about 95% of patients. This is recapitulated as cognitive deficits in mice and was assessed via fear conditioning assay. In both contextual and cued fear conditioning STXBP1 HET mice displayed severe impairments in associative memory and learning when compared to WT mice. A significant dose-dependent correction of the phenotype was observed in vector dosed animals across both assays (FIG. 16). Hindlimb clasping is a feature of dystonia in mice. The WT vehicle animals showed no hindlimb clasping as compared to STXBP1 HET animals (FIG. 17). Once again, a dose dependent correction of the phenotype was observed with treatment (FIG. 17).

[00282] Epileptic activity in the form of spike-wave discharges (SWD) from frontal cortex was determined using electroencephalography (EEG). HET vehicle dosed control mice show a higher number of SWDs score as compared to *Stxbp1*$^{+/+}$ (WT) vehicle dosed control mice ($p=0.001$) within a 3-hour window between 7 and 10 am (FIG. 18). HET mice dosed with AAV9-EF1a-STXBP1 at 1E11 vg/animal showed a decrease in the SWDs when compared to HET control within the same time window (FIG. 18). The final assay was a PTZ induced seizure assay. Generally, PTZ is a GABA antagonist that binds non-competitively to the $GABA_A$-receptor and blocks the chloride channel. This results in convulsions due to continued depolarization of the neurons. STXBP1

haploinsufficiency further aggravates these seizures.

[00283] As seen in FIG. 19, HET mice dosed with AAV9-EF1a-STXBP1 at 1E11 vg/animal showed a significant reduction in seizure susceptibility as compared to HET vehicle dosed mise (p=0.003). WT mice dosed with AAV9-EF1a-STXBP1 at 1E11 vg/animal showed no difference when compared to WT control. PTZ is a terminal assay and animals were euthanized for biodistribution and expression. Post necropsy, MSD assay was conducted to determine protein levels in hippocampus from vehicle and vector dosed STXBP1 WT and HET animals. HET vehicle dosed animals showed about 50% protein as compared to the WT vehicle group (FIG. 20). A significant increase in STXBP1 expression in both WT and HET vector dosed animals was also observed (FIG. 20).

Example 5: AAV9-STXBP1 gene replacement rescues multiple phenotypes in an STXBP1 mouse model

[00284] The next experiment involved dosing STXBP1 HET and WT animals with an EF1a-STXBP1+DRG-de-targeting vector at three different doses (6E10, 3E10, and 1E10) at P1 via bilateral ICV and with behavior and EEG testing from 8 weeks post injection. A similar rescue was observed as previously. A dose dependent rescue was seen in our motor coordination (hindlimb clasping) and cognition (fear conditioning) assays with significance achieved until the 1E10 dose (FIGs. 21 and 22 respectively). EEG, one of the most sensitive assays, also continued to show the same trend with 1E10, 3E10 and 6E10 dosed HET animals being significantly rescued (FIG. 23).

[00285] A second set of studies focused on comparing SEQ ID NOs: 11 and 13 to EF1a at the 1E11 dose via P1 ICV injections, a schematic of the experiment is provided in FIG. 24C. Similar rescue was observed across both promoters for distance moved in open field (FIG. 24A), ability to build nests (FIG. 24B), hindlimb clasping (FIG. 26) as well as associated memory in fear conditioning assays (FIG. 25). The vector dosed animals also showed similar reductions in seizure susceptibility in the PTZ assay with SEQ ID NO: 13 showing close to a complete rescue (FIG. 27). The SWD incidence in Stxbp1$_{+/-}$ mice dosed with AAV9-EF1α-STXBP1 and AAV9-SEQ ID NO: 13-STXBP1 decreased to <5 events within the same time window (FIGs. 47A and 47B).This shows that the pan-neuronal promoters are as potent as EF1a when dosed via ICV. Another advantage of these pan-neuronal promoters is the reduced liver expression as compared to EF1a.

[00286] Next, the promoter of SEQ ID NO: 13 was assessed at three different doses (6E10, 3E10 and 1E10) as well as an arm that had the DRG de-targeting element, DT-A (RNA sequence of SEQ ID NO: 46) added at the 3E10 dose. A subset of animals was taken down for analysis of VCN and transgene expression prior to initiating behavior. A dose dependent change in expression was

observed across the three doses in both WT and STXBP1 HET animals, FIG. 28A and 28B respectively, as well as comparable transduction and expression across the +/- DRG arms. FIG. 54 shows dose dependent increase in VCN in hippocampus (FIG. 54A), DRG (FIG. 54B) and Forebrain/midbrain (FIG. 54C). FIG. 55 shows dose dependent increase in Stxbp1 transcript, and FIG. 56 shows a reduction in spinal cord STXBP1 expression with inclusion of the detargeting element. Quantification of mean intensity of STXBP1-iso2 IHC in mouse DRG and brain demonstrated that of SEQ ID NO: 13-STXBP1-iso2 increases STXBP1-iso2 expression in DRG compared to vehicle while the of SEQ ID NO: 13-STXBP1-iso2+DT-A (FIG. 28C) staining was similar to vehicle treatment. Brain expression in the hippocampus was not decreased and was similar in both (FIG. 28D). On evaluation of efficacy, dose dependent rescue and similar rescue across the +/-DRG arms was observed in the hindlimb clasping assay (FIG. 29), fear conditioning assay (FIG. 30), and PTZ seizure assay (FIG. 31). This data demonstrates that the pan-neuronal promoters work similarly to EF1a at even lower doses and that the DRG de-targeting arm has no impact on brain expression or efficacy but reduces expression in DRG.

[00287] As an additional test that inclusion of the DRG de-targeting element did not affect phenotypic rescue, it was also incorporated it into the positive control vector (AAV9-EF1a-STXBP1), and the efficacy in rescuing the EEG seizure phenotype of Stxbp1+/- mice treated with or without the DT-A element was compared. As seen in FIG. 51 no difference was observed between Stxbp1+/- mice with or without the DT-A sequence, confirming that inclusion of the DRG-detargeting element did not reduce vector potency. To further confirm that the DRG de-targeting did not impact the efficacy of the treatment, the promoter of SEQ ID NO: 11 was used to express STXBP1 and combined with the detargeting element. This construct was administered to STXBP1 heterozygous mice at a dose of 1E10 vg/animal. As seen in FIG. 41 this construct resulted in significant rescue of freezing in a fear conditioning assay. FIG. 42 shows rescue of hindlimb clasping and FIG. 43 shows rescue of SWDs in an EEG assay. In conclusion, compared with vehicle-dosed STXBP1+/- mice, there was significant rescue with AAV9-SEQ ID NO: 11-STXBP1+DT-A at low dose in hindlimb clasping, fear conditioning, and EEG phenotypes.

Example 6: Non-Human Primate data

[00288] Post validation of novel promoters in mice, the same promoters were tested in non-human primates for safety as well as protein upregulation. Juvenile cynomolgus macaques received a single unilateral ICV injection of vehicle (Group 1), AAV9-SEQ ID NO: 13-STXBP1 (Group 3, SEQ ID NO: 73), AAV9-SEQ ID NO: 11-STXBP1 (Group 4, SEQ ID NO: 74), or AAV9-SEQID NO: 13-

STXBP1-Detargeting (Group 5, SEQ ID NO: 75), or AAV9-EF1a-STXBP1 (Group 2, SEQ ID NO: 76) as a ubiquitous benchmark candidate, each at a dose of 1E14 vg/animal. All vector candidates were well-tolerated in male and female NHPs for the duration of the 50-day study. As expected following AAV delivery, mild transient elevations in serum alanine aminotransferase (ALT, FIG. 32A) and aspartate aminotransferase (AST, FIG. 32B) were observed within 1-2 weeks post-dosing and resolved for all groups by day 30 post-dosing. In the AAV9-EF1a-STXBP1 group, there was additionally a mild ~2-fold increase over baseline in glutamate dehydrogenase (GLDH) levels that persisted through the 50-day necropsy timepoint (FIG. 32C). Across all dose groups, there were no treatment-related clinical signs, neurological findings as assessed by a functional observational battery, changes in body weights, changes in hematology parameters, changes in CSF total cell count or chemistry, nor macroscopic observations noted in any organs examined during the full necropsy 50 days post-dosing. Necropsies were performed 50 ± 3 days post ICV injection and tissues were collected and frozen in RNA*later* for analysis. Genomic DNA (gDNA) and RNA were isolated from multiple tissues including various brain regions, including disease relevant cortical and hippocampal region, four levels of SC and DRG, as well as eight peripheral organs. Extracted gDNA was used for vector copy number (VCN) analysis by a restriction enzyme-treated digital droplet PCR-based method. Isolated RNA was used to measure human codon-optimized transgene expression and the cynomolgus monkey endogenous STXBP1 expression corresponding to both isoform 1 and 2, by a reverse-transcription droplet digital polymerase chain reaction (RT-ddPCR) based method.

[00289] The vector biodistribution and transgene RNA expression were widespread throughout multiple brain regions for all four candidates (FIGs. 33 and 34). As seen in FIG. 34, the transgene RNA expression levels driven by EF1a promotor (Group 2) were comparable to SEQ ID NO: 11 promoter (Group 4), which were 3-5-fold higher than the expression levels driven by the SEQ ID NO: 13 promoter (Group 3,) and SEQ ID NO: 13 promoter with DRG-de-targeting element (Group 5). Vector biodistribution was detected in most peripheral tissues examined, including liver, heart, kidney, lung, adrenal gland, spleen, gonads, and optic nerve. The mean VCN was similar across all candidates in peripheral tissues, with the highest transduction in liver, as seen in FIG. 57.

[00290] Within the spinal cord and DRG, vector biodistribution was comparable across all promoter candidates, showing highest vector transduction in sacral sections (FIGs. 35 and 59). For the promoter candidates without the DRG-de-targeting element, exogenous the transgene transcript levels in the spinal cord (SC) and DRG were highly expressed (FIG. 36). In contrast, the transgene transcript levels in the SC and DRG for AAV9-SEQ ID NO: 13-STXBP1-DT-A dosed animals were

3- to 13-fold lower than for the control AAV9-SEQ ID NO: 13-STXBP1 arm, with no difference in brain expression (FIG. 37). Resulting STXBP1 protein expression as measured by MSD-ELISA or IHC was indistinguishable from endogenous expression AAV9-SEQ ID NO: 13-STXBP1-DT-A in DRG and SC sections. FIG. 44 shows representative IHC images of STXBP1 Iso2 expression in sacral DRG from NHP, from left to right group 1 (vehicle), group 4 (SEQ ID NO: 11) and group 5 (SEQ ID NO: 11 and DRG detargeting) showing reduced expression in group 5 compared to group 4. FIG. 45 shows mean transcripts/VCN for group 4 (SEQ ID NO: 11) and group 5 (SEQ ID NO: 11 and DRG detargeting) in cortex and hippocampus, DRG and spinal cord. Mean transcripts/VCN are not affected by the presence of the DRG detargeting element in the Cortex and hippocampus but are significantly decreased in DRG and spinal cord.

[00291] Following necropsy, brain, SC, DRG, and a panel of peripheral tissues were stained using H&E and submitted for independent histopathological evaluation. No treatment-related observations were identified in the brain or any peripheral organs (data not shown). As expected, microscopic examination of neural tissues in the spinal cord (cervical, thoracic, lumbar) and DRG (cervical, thoracic, lumbar, sacral) showed vector-related findings, consistent with sensory ganglia damage, a known class effect of AAV delivery (FIG. 38). Findings that were characterized as potentially adverse included decreased neuron cellularity (i.e., neuron cell loss) and neuron necrosis in the DRG. Nerve fiber degeneration in the spinal cord of mild or greater severity also was considered potentially adverse given the limited regenerative capacity in the CNS. All other microscopic findings were considered non-adverse due to the limited severity and/or character of the changes, which were considered unlikely to impact function or ability to respond to an additional challenge. Notably, the frequency and severity of these findings appeared to be mitigated in the AAV9-SEQ ID NO: 13-STXBP1-DT-A arm compared to all other arms of the study, with no findings considered potentially adverse (FIG. 38). Nerve conduction assessments were performed pre-dosing and at 7 weeks post-dosing to evaluate peripheral neuropathies. Vector-related peripheral sensory axonopathies were observed in 2/4 animals administered AAV9-SEQ ID 13-STXBP1 and in 2/3 animals administered AAV9-SEQ ID 11-STXBP1. These functional changes were mild, with no expected adverse clinical correlates (FIG. 64, and summarized in FIG. 38). Consistent with histopathological and NfL observations, no functional changes were observed in animals dosed with AAV9-SEQ ID 13-STXBP1-DT-A, indicating improved functionality and reduced DRG and SC toxicity with the inclusion of DT-A detargeting element.

[00292] Assessment of nerve conduction velocities found a minor test article-related peripheral sensory axonopathies with no expected adverse clinical correlates in Group 3 (2/4 animals) Group

4 (2/3 animals) and no motor neuropathies, as investigated by electrophysiological techniques at Week 7 post-dose.

[00293] Assessment of serum levels of Serum Neurofilament light chain (Nf-L) showed transient Increases in Nf-L levels in subset of NHPs Dosed with AAV9 Vector Candidates with no significant differences across groups, as shown in FIG. 63.

[00294] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[00295] The use of the terms "a" and "an" and "the" and similar referents in the context of describing the disclosure (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context; the terms "a" (or "an"), "one or more," and "at least one" can be used interchangeably herein. The term "or" should be understood to encompass items in the alternative or together, unless context unambiguously requires otherwise. The term "and/or" should be understood to encompass each item in a list (individually), any combination of items a list, and all items in a list together. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted. The disclosure contemplates embodiments described as "comprising" a feature to include embodiments which "consist of" or "consist essentially of" the feature. The term "about" or "approximately" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. For example, "about" can mean within one or more than one standard deviation, per the practice in the art. Alternatively, "about" can mean a range of up to 10%, up to 5%, or up to 1% of a given value.

[00296] Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range and each endpoint, unless otherwise indicated herein, and each separate value and endpoint is incorporated into the specification as if it were individually recited herein. In any of the ranges described herein, the endpoints of the range are included in the range. However, the description also contemplates the same ranges in which the lower and/or the higher endpoint is excluded.

[00297] All method steps described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as" and "optionally") provided herein, is intended merely to better

illuminate the disclosure and does not pose a limitation on the scope of the disclosure unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the disclosure.

SEQUENCE TABLE

SEQ ID NO:	Sequence
1.	ATGGCCCCCATTGGCCTCAAAGCTGTTGTCGGAGAGAAGATTATGCATGATGTGAT AAAGAAGGTCAAGAAGAAGGGGGGAATGGAAGGTGCTGGTGGTGGATCAGTTAAGC ATGAGGATGCTGTCCTCCTGCTGCAAGATGACAGACATCATGACCGAGGGCATAAC GATTGTGGAAGATATCAATAAGCGCAGAGAGCCGCTCCCCAGCCTGGAGGCTGTGT ATCTCATCACTCCATCCGAGAAGTCCGTCCACTCTCTCATCAGTGACTTTAAGGACC CGCCGACTGCTAAATACCGGGCTGCACACGTCTTCTTCACTGACTCTTGTCCAGAT GCCCTGTTTAATGAACTGGTAAAATCCCGAGCAGCCAAAGTCATCAAAACTCTGACG GAAATCAATATTGCATTTCTCCCGTATGAATCCCAGGTCTATTCCTTGGACTCTGCTG ACTCTTTCCAAAGCTTCTACAGTCCCCACAAGGCTCAGATGAAGAATCCTATACTGG AGCGCCTGGCAGAGCAGATCGCGACCCTTTGTGCCACCCTGAAGGAGTACCCGGC TGTGCGGTATCGGGGGGGAATACAAGGACAATGCCCTGCTGGCTCAGCTAATCCAG GACAAGCTCGATGCCTATAAAGCTGATGATCCAACAATGGGGGAGGGCCCAGACAA GGCACGCTCCCAGCTCCTGATCCTGGATCGAGGCTTTGACCCCAGCTCCCCTGTGC TCCATGAATTGACTTTTCAGGCTATGAGTTATGATCTGCTGCCTATCGAAAATGATGT ATACAAGTATGAGACCAGCGGCATCGGGGAGGCACGGGTGAAGGAGGTGCTCCTG GACGAGGACGACGACCTGTGGATAGCACTGCGCCACAAGCACATCGCAGAGGTGT CCCAGGAAGTCACCCGGTCTCTGAAAGATTTTTCTTCTAGCAAGAGAATGAATACTG GAGAGAAGACCACCATGCGGGACCTGTCCCAGATGCTGAAGAAGATGCCTCAGTAC CAGAAAGAGCTCAGCAAGTACTCCACCCACCTGCACCTTGCTGAGGACTGTATGAA GCATTACCAAGGCACCGTAGACAAACTCTGCCGAGTGGAGCAGGACCTGGCCATG GGCACAGATGCTGAGGGAGAGAAGATCAAGGACCCTATGCGAGCCATCGTCCCCA TTCTGCTGGATGCCAATGTCAGCACTTATGACAAAATCCGCATCATCCTTCTCTACAT CTTTTTGAAGAATGGCATCACGGAGGAAAACCTGAACAAACTGATCCAGCACGCCC AGATACCCCCGGAGGATAGTGAGATCATCACCAACATGGCTCACCTCGGCGTGCCC ATCGTCACCGATTCCACGCTGCGTCGCCGGAGCAAGCCGGAGCGGAAGGAACGCA TCAGCGAGCAGACCTACCAGCTCTCACGGTGGACTCCGATTATCAAGGACATCATG GAGGACACTATTGAGGACAAACTTGACACCAAACACTACCCTTATATCTCTACCCGT TCCTCTGCCTCCTTCAGCACCACCGCCGTCAGCGCCCGCTATGGGCACTGGCATAA GAACAAGGCCCCAGGCGAGTACCGCAGTGGCCCCCGCCTCATCATTTTCATCCTTG GGGGTGTGAGCCTGAATGAGATGCGCTGCGCCTACGAGGTGACCCAGGCCAACGG AAAGTGGGAGGTGCTGATAGGTTCTACTCACATTCTTACTCCCACCAAATTTCTCAT GGACCTGAGACACCCCGACTTCAGGGAGTCCTCTAGGGTATCTTTTGAGGATCAGG CTCCAACAATGGAGTGA
2.	ATGGCCCCCATTGGCCTCAAAGCTGTTGTCGGAGAGAAGATTATGCATGATGTGAT AAAGAAGGTCAAGAAGAAGGGGGGAATGGAAGGTGCTGGTGGTGGATCAGTTAAGC ATGAGGATGCTGTCCTCCTGCTGCAAGATGACAGACATCATGACCGAGGGCATAAC GATTGTGGAAGATATCAATAAGCGCAGAGAGCCGCTCCCCAGCCTGGAGGCTGTGT ATCTCATCACTCCATCCGAGAAGTCCGTCCACTCTCTCATCAGTGACTTTAAGGACC CGCCGACTGCTAAATACCGGGCTGCACACGTCTTCTTCACTGACTCTTGTCCAGAT GCCCTGTTTAATGAACTGGTAAAATCCCGAGCAGCCAAAGTCATCAAAACTCTGACG GAAATCAATATTGCATTTCTCCCGTATGAATCCCAGGTCTATTCCTTGGACTCTGCTG ACTCTTTCCAAAGCTTCTACAGTCCCCACAAGGCTCAGATGAAGAATCCTATACTGG AGCGCCTGGCAGAGCAGATCGCGACCCTTTGTGCCACCCTGAAGGAGTACCCGGC TGTGCGGTATCGGGGGGGAATACAAGGACAATGCCCTGCTGGCTCAGCTAATCCAG GACAAGCTCGATGCCTATAAAGCTGATGATCCAACAATGGGGGAGGGCCCAGACAA

	GGCACGCTCCCAGCTCCTGATCCTGGATCGAGGCTTTGACCCCAGCTCCCCTGTGC TCCATGAATTGACTTTTCAGGCTATGAGTTATGATCTGCTGCCTATCGAAAATGATGT ATACAAGTATGAGACCAGCGGCATCGGGGAGGCACGGGTGAAGGAGGTGCTCCTG GACGAGGACGACGACCTGTGGATAGCACTGCGCCACAAGCACATCGCAGAGGTGT CCCAGGAAGTCACCCGGTCTCTGAAAGATTTTTCTTCTAGCAAGAGAATGAATACTG GAGAGAAGACCACCATGCGGGACCTGTCCCAGATGCTGAAGAAGATGCCTCAGTAC CAGAAAGAGCTCAGCAAGTACTCCACCCACCTGCACCTTGCTGAGGACTGTATGAA GCATTACCAAGGCACCGTAGACAAACTCTGCCGAGTGGAGCAGGACCTGGCCATG GGCACAGATGCTGAGGGAGAGAAGATCAAGGACCCTATGCGAGCCATCGTCCCCA TTCTGCTGGATGCCAATGTCAGCACTTATGACAAAATCCGCATCATCCTTCTCTACAT CTTTTTGAAGAATGGCATCACGGAGGAAAACCTGAACAAACTGATCCAGCACGCCC AGATACCCCCGGAGGATAGTGAGATCATCACCAACATGGCTCACCTCGGCGTGCCC ATCGTCACCGATTCCACGCTGCGTCGCCGGAGCAAGCCGGAGCGGAAGGAACGCA TCAGCGAGCAGACCTACCAGCTCTCACGGTGGACTCCGATTATCAAGGACATCATG GAGGACACTATTGAGGACAAACTTGACACCAAACACTACCCTTATATCTCTACCCGT TCCTCTGCCTCCTTCAGCACCACCGCCGTCAGCGCCCGCTATGGGCACTGGCATAA GAACAAGGCCCCAGGCGAGTACCGCAGTGGCCCCCGCCTCATCATTTTCATCCTTG GGGGTGTGAGCCTGAATGAGATGCGCTGCGCCTACGAGGTGACCCAGGCCAACGG AAAGTGGGAGGTGCTGATAGGATCCACACACATCCTCACCCCACAGAAACTGCTGG ACACACTGAAGAAACTGAATAAAACAGATGAAGAAATAAGCAGT
3.	ATGGCCCCCATTGGCCTGAAGGCTGTGGTGGGAGAGAAGATCATGCATGATGTGAT CAAGAAGGTGAAGAAGAAGGGAGAGTGGAAGGTGCTGGTGGTGGACCAGCTGAGC ATGAGAATGCTGAGCAGCTGCTGCAAGATGACAGACATCATGACAGAGGGCATCAC CATTGTGGAGGACATCAACAAGAGAAGAGAGCCCCTGCCCAGCCTGGAGGCTGTG TACCTGATCACCCCCTCTGAGAAGTCTGTGCACAGCCTGATCTCTGACTTCAAGGAC CCCCCCACAGCCAAGTACAGAGCTGCCCATGTGTTCTTCACAGACAGCTGCCCTGA TGCCCTGTTCAATGAGCTGGTGAAGAGCAGAGCTGCCAAGGTGATCAAGACCCTGA CAGAGATCAACATTGCCTTCCTGCCCTATGAGAGCCAGGTGTACAGCCTGGACTCT GCTGACAGCTTCCAGAGCTTCTACAGCCCCCACAAGGCCCAGATGAAGAACCCCAT CCTGGAGAGACTGGCTGAGCAGATTGCCACCCTGTGTGCCACCCTGAAGGAGTAC CCTGCTGTGAGATACAGAGGAGAGTACAAGGACAATGCCCTGCTGGCCCAGCTGAT CCAGGACAAGCTGGATGCCTACAAGGCTGATGACCCCACCATGGGAGAGGGCCCT GACAAGGCCAGAAGCCAGCTGCTGATCCTGGACAGAGGCTTTGACCCCAGCAGCC CTGTGCTGCATGAGCTGACCTTCCAGGCCATGAGCTATGACCTGCTGCCCATTGAG AATGATGTGTACAAGTATGAGACCTCTGGCATTGGAGAGGCCAGAGTGAAGGAGGT GCTGCTGGATGAGGATGATGACCTGTGGATTGCCCTGAGACACAAGCACATTGCTG AGGTGAGCCAGGAGGTGACCAGAAGCCTGAAGGACTTCAGCAGCAGCAAGAGAAT GAACACAGGAGAGAAGACCACCATGAGAGACCTGAGCCAGATGCTGAAGAAGATG CCCCAGTACCAGAAGGAGCTGAGCAAGTACAGCACCCACCTGCACCTGGCTGAGG ACTGCATGAAGCACTACCAGGGCACAGTGGACAAGCTGTGCAGAGTGGAGCAGGA CCTGGCCATGGGCACAGATGCTGAGGGAGAGAAGATCAAGGACCCCATGAGAGCC ATTGTGCCCATCCTGCTGGATGCCAATGTGAGCACCTATGACAAGATCAGAATCATC CTGCTGTACATCTTCCTGAAGAATGGCATCACAGAGGAGAACCTGAACAAGCTGAT CCAGCATGCCCAGATCCCCCCTGAGGACTCTGAGATCATCACCAACATGGCCCACC TGGGAGTGCCCATTGTGACAGACAGCACCCTGAGAAGAAGAAGCAAGCCTGAGAG AAAGGAGAGAATCTCTGAGCAGACCTACCAGCTGAGCAGATGGACCCCCATCATCA AGGACATCATGGAGGACACCATTGAGGACAAGCTGGACACCAAGCACTACCCCTAC ATCAGCACCAGAAGCTCTGCCAGCTTCAGCACCACAGCTGTGTCTGCCAGATATGG CCACTGGCACAAGAACAAGGCCCCTGGAGAGTACAGATCTGGCCCCAGACTGATCA

	TCTTCATCCTGGGAGGAGTGAGCCTGAATGAGATGAGATGTGCCTATGAGGTGACC CAGGCCAATGGCAAGTGGGAGGTGCTGATTGGCAGCACCCACATCCTGACCCCCC AGAAGCTGCTGGACACCCTGAAGAAGCTGAACAAGACAGATGAGGAGATCAGCAG CTGA
4.	ATGGCTCCTATAGGGTTGAAGGCAGTTGTAGGAGAGAAAATCATGCATGACGTCAT CAAAAAAGTAAAGAAGAAAGGTGAGTGGAAGGTTCTTGTGGTAGACCAGCTCTCTAT GCGGATGTTGTCCAGTTGCTGTAAGATGACCGATATCATGACCGAGGGTATTACAAT CGTGGAGGATATCAATAAACGACGAGAGCCTCTCCCTTCCCTGGAGGCAGTGTACC TCATCACCCCCTCCGAAAAATCTGTACACAGTTTGATCTCAGATTTCAAGGATCCAC CAACTGCAAAATACAGGGCCGCACACGTTTTCTTCACCGACAGTTGTCCCGACGCT CTTTTCAACGAGTTGGTCAAGTCTAGGGCTGCTAAGGTAATTAAGACACTGACTGAG ATTAACATCGCTTTTCTGCCATACGAATCTCAGGTGTACAGCCTTGACAGTGCTGAT AGCTTCCAGTCATTTTATAGTCCCCACAAAGCCCAAATGAAGAACCCCATCTTGGAG CGGCTTGCAGAGCAAATAGCCACACTCTGTGCAACCCTCAAAGAGTATCCAGCCGT CAGGTATCGAGGGGAATATAAGGACAATGCACTGTTGGCTCAGCTCATACAAGACA AGTTGGATGCATACAAGGCTGACGACCCAACTATGGGAGAGGGCCCAGACAAGGC TAGGAGCCAACTCTTGATCCTCGACCGGGGCTTTGACCCTTCCTCTCCAGTTCTCCA TGAATTGACCTTCCAGGCTATGTCCTATGATCTCTTGCCTATAGAGAATGACGTTTAC AAGTACGAAACCAGCGGCATTGGTGAAGCCCGCGTCAAAGAGGTATTGCTGGACGA AGACGATGACCTTTGGATTGCCCTCCGACACAAGCATATTGCCGAGGTGAGCCAGG AGGTGACCCGATCCTTGAAGGATTTTTCATCCTCCAAGAGAATGAACACAGGAGAG AAAACCACTATGCGCGATCTTAGTCAAATGCTGAAGAAGATGCCCCAATACCAAAAG GAACTCAGTAAATATAGCACCCATCTTCATCTGGCAGAAGACTGTATGAAACATTAC CAGGGAACAGTGGATAAGCTCTGTCGAGTTGAACAAGACTTGGCCATGGGCACTGA CGCAGAAGGGGAAAAGATAAAGGACCCCATGCGCGCCATTGTACCAATTCTTCTTG ACGCAAATGTCTCTACATATGATAAGATAAGGATTATCTTGTTGTATATATTCCTTAA GAATGGCATTACTGAAGAAAACTTGAACAAACTCATCCAGCATGCACAAATTCCCCC CGAGGATTCCGAGATAATCACCAATATGGCCCATCTTGGGGTTCCCATTGTGACAG ATTCTACTCTCCGGCGGCGGTCCAAGCCTGAGCGCAAAGAGAGGATAAGTGAACAG ACTTATCAATTGAGTCGATGGACTCCAATAATTAAAGACATAATGGAAGACACAATAG AAGATAAACTCGATACTAAACACTATCCCTATATAAGCACTAGATCCTCAGCATCATT CTCCACCACAGCTGTCAGTGCTAGATATGGACACTGGCACAAAAATAAGGCACCTG GTGAATACCGCAGTGGACCTAGACTCATAATCTTTATTCTGGGCGGAGTTTCCCTGA ACGAGATGCGCTGCGCTTACGAGGTCACACAGGCAAATGGGAAATGGGAGGTGTT GATTGGCTCCACACACATTCTTACACCCACCAAGTTTCTGATGGACCTCAGGCACCC TGATTTCCGGGAGTCAAGTAGAGTATCCTTCGAGGATCAGGCCCCAACTATGGAG

5.	gagtaattcatacaaaaggactcgcccctgccttggggaatcccagggaccgtcgttaaactcccactaacgtagaaccca gagatcgctgcgttcccgccccctcacccgcccgctctcgtcatcactgaggtggagaagagcatgcgtgaggctccggtg cccgtcagtgggcagagcgcacatcgcccacagtccccgagaagttgggggggaggggtcggcaattgaaccggtgcct agagaaggtggcgcggggtaaactgggaaagtgatgtcgtgtactggctccgccttttcccgagggtgggggagaaccgt atataagtgcagtagtcgccgtgaacgttcttttcgcaacgggtttgccgccagaacacaggtaagtgccgtgtgtggttccc gcgggcctggcctctttacgggttatggcccttgcgtgccttgaattacttccacgcccctggctgcagtacgtgattcttgatcc cgagcttcgggttggaagtgggtgggagagttcgaggccttgcgcttaaggagccccttcgcctcgtgcttgagttgaggcct ggcttgggcgctggggccgccgcgtgcgaatctggtggcaccttcgcgcctgtctcgctgctttcgataagtctctagccattta aaatttttgatgacctgctgcgacgctttttttctggcaagatagtcttgtaaatgcgggccaagatctgcacactggtatttcggtt ttggggccgcgggcggcgacggggcccgtgcgtcccagcgcacatgttcggcgaggcggggcctgcgagcgcggcca ccgagaatcggacgggggtagtctcaagctggccggcctgctctggtgcctggcctcgccgccgcgtgtatcgccccgccc tgggcggcaaggctggcccggtcggcaccagttgcgtgagcggaaagatggccgcttcccggccctgctgcagggagct caaaatggaggacgcggcgctcgggagagcgggcgggtgagtcacccacacaaaggaaaagggcctttccgtcctca gccgtcgcttcatgtgactccacggagtaccgggcgccgtccaggcacctcgattagttctcgagcttttggagtacgtcgtctt taggttgggggagggttttatgcgatggagtttccccacactgagtgggtggagactgaagttaggccagcttggcacttg atgtaattctccttggaatttgccctttttgagtttggatcttggttcattctcaagcctcagacagtggttcaaagttttttttcttccattt caggtgtcgtga
6.	gtctaacaaaaaagccaaaaacggccagaatttagcggacaatttactagtctaacactgaaaattacatattgacccaaa tgattacatttcaaaaggtgcctaaaaaacttcacaaaacacactcgccaaccccgagcgcatagttcaaaaccggagctt cagctacttaagaagataggtacataaaaccgaccaaagaaactgacgcctcacttatccctcccctcaccagaggtccg gcgcctgtcgattcaggagagcctaccctaggcccgaaccctgcgtcctgcgacggagaaaagcctaccgcacacctac cggcaggtggccccaccctgcattataagccaacagaacgggtgacgtcacgacacgacgagggcgcgcgctcccaa aggtacgggtgcactgcccaacggcaccgccataactgccgcccccgcaacagacgacaaaccgagttctccagtcagt gacaaacttcacgtcagggtccccagatggtgccccagcccatctcacccgaataagagctttcccgcattagcgaaggc ctcaagaccttgggttcttgccgcccaccatgccccccaccttgtttcaacgacctcacagcccgcctcacaagcgtcttccat tcaagactcgggaacagccgccattttgctgcgctccccccaaccccccagttcagggcaaccttgctcgcggacccagact acagcccttggcggtctctccacacgcttccgtcccaccgagcggcccggcggccacgaaagccccggccagcccagc agcccgctactcaccaagtgacgatcacagcgatccacaaacaagaaccgcgacccaaatcccggctgcgacggaac tagctgtgccacacccggcgcgtccttatataatcatcggcgttcaccgccccacggagatccctccgcagaatcgccgag aagggactacttttcctcgcctgttccgctctctggaaagaaaaccagtgccctagagtcacccaagtcccgtcctaaaatgt ccttctgctgatactgggttctaaggccgagtcttatgagcagcgggccgctgtcctgagcgtccgggcggaaggatcagg acgctcgctgcgcccttcgtctgacgtggcagcgctcgccgtgaggaggggggcgcccgcgggaggcgccaaaacccg gcgcggaggcc
7.	tagtatctgcagagggccctgcgtatgagtgcaagtgggttttaggaccaggatgaggcggggtgggggtgcctacctgac gaccgaccccgacccactggacaagcacccaaccccattccccaaattgcgcatcccctatcagagaggggggagggg aaacaggatgcggcgaggcgcgtgcgcactgccagcttcagcaccgcggacagtgccttcgccccgcctggcggcgc gcgccaccgccgcctcagcactgaaggcgcgctgacgtcactcgccggtcccccgcaaactcccctccccggccaccttg gtcgcgtccgcgccgccgccggcccagccggaccgcaccacgcgaggcgcgagataggggggcacgggcgcgacc atctgcgctgcggcgccggcgactcagcgctgcctcagtctgcggtgggcagcggaggagtcgtgtcgtgcctgagagcg cagctgtgctcctgggcaccgcgcagtccgccccgcggctcctggccagaccacccctaggacccccctgccccaagtc gcagcc
8.	
9.	
10.	CCTTCCCCCGACTCCTGCAACAGCTCAGAGAGCCTGGCTCTGACGTAGTTCAAAAT AACGTGCGCCAGCCTCGCTGCCCGGCTGACCACAGCAACGAGAGCCACAAGCCCT CGACGCTGCTTCGATAACATGAAGCAATCACTCATAAAAATAGCAACCCACGTAGCC

	TGGCCATATATGGAGCTGGCGAGGGTGGACGGGGATGCCCCTACGGACCCTCTTC GGAGAAAACAAATCGCCGCTGAAATTTCCCCCACCCCTCCCATCACTACCTTTTACC CCTCCTCTGCCTTCCCCTCTCCTTAGATGACTCAACCACAGATTCCACTGAAAGGGG GTGGGGGTGGGGGTGGGGGGGAATATATACACATACACACAAATTATACATATATT ATACATGTATTATAAAATATACACACACATACATATATACATACACACACATATACACA TATGTACACACACACGCACACACACCAAAGAACATCAGGAATGCAGTTGCGGGATG AAGCCGTTTGCCCAAGACCGAGTGTTAAAATGGAGTCATAAGAGTCGCCCCGTGCG GGTGTTTATAGAAGGTGAAAACACGCAGGTTTGCAGGCCAGCGCACTGGGAACCGA GTCAAGCGCGCCGCAGCCCGGGCCCCGCCCCCGCCCCCGCCGTGCCCCGCCCCC ACTTCCTCCCGCCCCTCGCTGGGCGGCTATTAAAAGCTGCTGACGTCAAAACGGAC GGCCATCTTTGATGAGGGCAGAGCTCACGTTGCATTGAAGACGAAACCTCGGGGAG GTCAGGCGCTGTCTTTCCTTCCCTCCCTGCTCGGCGGCTCCACCACAGTTGCAACC TGCAGAGGCCCGGAGAACACAACCCTCCCGAGAAGCCCAGGTAAGAAC
11.	AAAGCTTTCAGAGGCTTGAATTATCACAGTGTAAATATCCATCTAGCAGAGCAGGTA ATTTTCTCGTTACTCATCCTAAGCATTAGATACTCTGTGTGTTAGTTCTTTGCAGAAA TAACCCATAGCAGCTGAACCATTTTGGAACAAATTTTCCATCACCTTCCTTCCCTGTG TGGTTCAGGCCTTTGCAAACCCTGAGTATCATGAATCTGCTGGTTCTCTACTGGCAA AGATGATGACGTTTTCTTGTTTGTTTTTGTTTTGCTTTAATCATGCCGTGAGAAAATC CTAAGGGAAAAAAATCTCATTATCCTATTCAAAATACATTTAGGGTTATCTGGTCATC CCTAGCAGATTTTTATGTACCCAATGTTTATGTATCTCAAATTACACTCTGTTACCTTT CCCAGAGCAAGATGAAGAACCTCTAAGAACCTCTCAAACAGCATCATTTTCACAACA AGCACTAGCAATGGAAAACATTGTCACCACCACCAGCTAATCTTGTAGGGTCCATGG TATTTTCTGTAATGCCTTGAAACAGTCTGCCTCTCTCTTCTTGTCTGTCATTTTTATAG ATGTCAGTGTGGGGCATCAGCAGTTGAAAACTCAGAATACCAAGCCAGTCCTTCCC TGTGACTGCTACATAGCTTTTGCCTGCAGGATAAGCCTCCATCACTGACGTAGTTGC TTTTTAACTTCTTTTTTTTTTTTTAACTTGGAAAATCCCCCACCTCCTCCATTCCTTCAC AAAACTTTCTGCCTGAATGATTTCTAGTCTGAGGGCCATACACACATTTTTTTTTCTC CCTCTGCAGGTTTTTTTTTCTCTTCAAACTTCCGCATGCTGCCTTTTTTTAAAGTGTC ACACTTTGGCCTTCCCCCGACTCCTGCAACAGCTCAGAGAGCCTGGCTCTGACGTA GTTCAAAATAACGTGCGCCAGCCTCGCTGCCCGGCTGACCACAGCAACGAGAGCC ACAAGCCCTCGACGCTGCTTCGATAACATGAAGCAATCACTCATAAAAATAGCAACC CACGTAGCCTGGCCATATATGGAGCTGGCGAGGGTGGACGGGGATGCCCCTACGG ACCCTCTTCGGAGAAAACAAATCGCCGCTGAAATTTCCCCCACCCCTCCCATCACTA CCTTTTACCCCTCCTCTGCCTTCCCCTCTCCTTAGATGACTCAACCACAGATTCCAC TGAAAGGGGGTGGGGGTGGGGGTGGGGGGGAATATATACACATACACACAAATTA TACATATATTATACATGTATTATAAAATATACACACACATACATATATACATACACACA CATATACACATATGTACACACACACGCACACACACCAAAGAACATCAGGAATGCAGT TGCGGGATGAAGCCGTTTGCCCAAGACCGAGTGTTAAAATGGAGTCATAAGAGTCG CCCCGTGCGGGTGTTTATAGAAGGTGAAAACACGCAGGTTTGCAGGCCAGCGCACT GGGAACCGAGTCAAGCGCGCCGCAGCCCGGGCCCCGCCCCCGCCCCCGCCGTGC CCCGCCCCCACTTCCTCCCGCCCCTCGCTGGGCGGCTATTAAAAGCTGCTGACGTC AAAACGGACGGCCATCTTTGATGAGGGCAGAGCTCACGTTGCATTGAAGACGAAAC CTCGGGGAGGTCAGGCGCTGTCTTTCCTTCCCTCCCTGCTCGGCGGCTCCACCAC AGTTGCAACCTGCAGAGGCCCGGAGAACACAACCCTCCCGAGAAGCCCAGGTAAG AAC
12.	CGGAAAATGGAGATTAAAAATAATGCCCATAGGTATGAGCTAAGAGGAGTGTAAACA AAACAAAATAAAAAGCAATGCCCAGTGATTGGAGGATTTGATGAGATGATGCCCGC GAGGTGCTTGGCACGGAGTTTGACACAAGAACTCAGTGTTGGTGAATGCACGAATG CAGGTACCCAGCGACAGGGAGGTGCTGTGGGTGGATTCACCCTGGCTTCGCTGCG

	GCTGGGAGTGGGCGCTGCTAGTAAGAGATCTCGCCTCCAAGCTCCTTCCGTGGGC AGGAAAAAACGGAAGCTCCCAGAAAGAGGAAAGACAGGACCCGAGCGGGGTTTCA GGCAGATGGAGCGCGTCGGTAGCCTGTGGCCAGGGATCCCAGCACCGACGGGAA AGAGGAGGCCTGGGTACCCTGCGCCCCGGGCGCGCGCGGCGCGTGAGGTGAGG GGGAGGGCGCGGCTCCGCACCAGCCAGCGGCCGCCTGGCGCCCAGCCGCATCTC GGGGGGCGGGGTTGAGCCTCCGGGCCGCAGTGCGATTGGCGGAGGCGAGTGGGT GACGCCAACGGCCGGCGCGAGGCCCCGCCCCCGGCTTGCCCCGCCCCCGCGCG CGCCGGCGGCGGGGCAGCCTCGCTCTGGCTCGCGCCGCGCCCCCGCGCCCAGTC CGCGCGTCAGTCGGTCCCTAGCGCGGCTGCGGGGCGGAGAGCTGCGGCTGGCCC AGCGCGCCCACCTGAGGAGGCGGCGGGGTCCGCAGGCGTCGCGGGACGAGGAG ATCGGAGCCGGGAGACTCGCGCAGCGCC
13.	CCAGGTTCCCAGTCCTGGATAAAGTACCTTATAAATATTATCTTGTTGATCTTTAGAA ACTGCTCCTAAAGGAGTGTCGCAGAATCAAACGGCCCAGAGGCTAGGAGGAGGGG ATGTGGGTGAACACAGAACACCGCAGCTGATGATGCAGCTTAAAAGCAGAAGGGAG GGAGGTGCAGCCCGAGGCTGTCGGAGAAGCGGCCCAGACTGGCCCCAGGGCTCT GCAACAGGCTCCAGTTGTGCAGGGAGGGGACAAGCTTGTGATACCGCGTGAAGGA CTCAGGAGGTCCGGTGGAGGGGTGGCCTCTCTCCCGCTGGTTGGCTCCATTGCTA TTTCTGTCTCCTCGTTCTCGGTCTCTCCAGGCCGCTCCCTCTCCATCTGTCCTGATC GCCAGCCTCTCCCCCGCTCCTCTCCGCAGCGGTCGGCCCACCTGGAGCACTCCCC GCCGCCACGTGACCCGTGCGTAAATCGCAGTACTCTTCCCACCCCTGCGCTGGGC CAGCACCCGGCTCTGCGGAGGCTGCAGGCCGCGCATGCGCAGCTGTGGACGCAC CTGCGCGCCCCGGAAAATGGAGATTAAAAATAATGCCCATAGGTATGAGCTAAGAG GAGTGTAAACAAAACAAAATAAAAAGCAATGCCCAGTGATTGGAGGATTTGATGAGA TGATGCCCGCGAGGTGCTTGGCACGGAGTTTGACACAAGAACTCAGTGTTGGTGAA TGCACGAATGCAGGTACCCAGCGACAGGGAGGTGCTGTGGGTGGATTCACCCTGG CTTCGCTGCGGCTGGGAGTGGGCGCTGCTAGTAAGAGATCTCGCCTCCAAGCTCC TTCCGTGGGCAGGAAAAAACGGAAGCTCCCAGAAAGAGGAAAGACAGGACCCGAG CGGGGTTTCAGGCAGATGGAGCGCGTCGGTAGCCTGTGGCCAGGGATCCCAGCAC CGACGGGAAAGAGGAGGCCTGGGTACCCTGCGCCCCGGGCGCGCGCGGCGCGT GAGGTGAGGGGGAGGGCGCGGCTCCGCACCAGCCAGCGGCCGCCTGGCGCCCA GCCGCATCTCGGGGGGCGGGGTTGAGCCTCCGGGCCGCAGTGCGATTGGCGGAG GCGAGTGGGTGACGCCAACGGCCGGCGCGAGGCCCCGCCCCCGGCTTGCCCCGC CCCCGCGCGCGCCGGCGGCGGGGCAGCCTCGCTCTGGCTCGCGCCGCGCCCCC GCGCCCAGTCCGCGCGTCAGTCGGTCCCTAGCGCGGCTGCGGGGCGGAGAGCTG CGGCTGGCCCAGCGCGCCCACCTGAGGAGGCGGCGGGGTCCGCAGGCGTCGCG GGACGAGGAGATCGGAGCCGGGAGACTCGCGCAGCGCC
14.	GGAGGAAGCCATCAACTAAACTACAATGACTGTAAGATACAAAATTGGGAATGGTAA CATATTTTGAAGTTCTGTTGACATAAAGAATCATGATATTAATGCCCATGGAAATGAA AGGGCGATCAACACTATGGTTTGAAAAGGGGGAAATTGTAGAGCACAGATGTGTTC GTGTGGCAGTGTGCTGTCTCTAGCAATACTCAGAGAAGAGAGAGAACAATGAAATT CTGATTGGCCCCAGTGTGAGCCCAGATGAGGTTCAGCTGCCAACTTTCTCTTTCACA TCTTATGAAAGTCATTTAAGCACAACTAACTTTTTTTTTTTTTTTTTTTTTTTGAGACAG

	AGTCTTGCTCTGTTGCCCAGGACAGAGTGCAGTAGTGACTCAATCTCGGCTCACTG CAGCCTCCACCTCCTAGGCTCAAACGGTCCTCCTGCATCAGCCTCCCAAGTAGCTG GAATTACAGGAGTGGCCCACCATGCCCAGCTAATTTTTGTATTTTTAATAGATACGG GGGTTTCACCATATCACCCAGGCTGGTCTCGAACTCCTGGCCTCAAGTGATCCACC TGCCTCGGCCTCCCAAAGTGCTGGGATTATAGGCGTCAGCCACTATGCCCAACCCG ACCAACCTTTTTTAAAATAAATATTTAAAAAATTGGTATTTCACATATATACTAGTATTT ACATTTATCCACACAAAACGGACGGGCCTCCGCTGAACCAGTGAGGCCCCAGACGT GCGCATAAATAACCCCTGCGTGCTGCACCACCTGGGGAGAGGGGGAGGACCACGG TAAATGGAGCGAGCGCATAGCAAAAGGGACGCGGGGTCCTTTTCTCTGCCGGTGG CACTGGGTAGCTGTGGCCAGGTGTGGTACTTTGATGGGGCCCAGGGCTGGAGCTC AAGGAAGCGTCGCAGGGTCACAGATCTGGGGGAACCCCGGGGAAAAGCACTGAGG CAAAACCGCCGCTCGTCTCCTACAATATATGGGAGGGGGAGGTTGAGTACGTTCTG GATTACTCATAAGACCTTTTTTTTTTCCTTCCGGGCGCAAAACCGTGAGCTGGATTTA TAATCGCCCTATAAAGCTCCAGAGGCGGTCAGGCACCTGCAGAGGAGCCCCGCCG CTCCGCCGACTAGCTGCCCCCGCGAGCAACGGCCTCGTGATTTCCCCGCCGATCC GGTCCCCGCCTCCCCACTCTGCCCCCGCCTACCCCGGAGCCGTGCAGCCGCCTCT CCGAATCTCTCTCTTCTCCTGGCGCTCGCGTGCGAGAGGGAACTAGCGAGAACGA GGAAGCAGCTGGAGGTGACGCCGGGCAGATTACGCCTGTCAGGGCCGAGCCGAG CGGATCGCTGGGCGCTGTGCAGAGGAAAGGCGGGAGTGCCCGGCTCGCTGTCGC AGAGCCGAGGTGGGTAAGCTAGCGACCACCTGGACTTCCCAGCGCCCAACCGTGG CTTTTCAGCCAGGTCCTCTCCTCCCGCGGCTTCTCAACCAACCCCATCCCAGCGCC GGCCACCCAACCTCCCGAAATGAGTGCTTCCTGCCCCAGCAGCCGAAGGCGCTAC TAGGAACGGTAACCTGTTACTTTTCCAGGGGCCGTAGTCGACCCGCTGCCCGAGTT GCTGTGCGACTGCGCGCGCGGGGCTAGAGTGCAAGGTGACTGTGGTTCTTCTCTG GCCAAGTCCGAGGGAGAACGTAAAGATATGGGCCTTTTTCCCCCTCTCACCTTGTC TCACCAAAGTCCCTAGTCCCCGGAGCAGTTAGCCTCTTTCTTTCCAGGGAATTAGCC AGACACAACAACGGGAACCAGACACCGAACCAGACATGCCCGCCCCGTGCGCCCT CCCCGCTCGCTGCCTTTCCTCCCTCTTGTCTCTCCAGAGCCGGATCTTCAAGGGGA GCCTCCGTGCCCCCGGCTGCTCAGTCCCTCCGGTGTGCAGGACCCCGGAAGTCCT CCCCGCACAGCTCTCGCTTCTCTTTGCAGCCTGTTTCTGCGCCGGACCAGTCGAGG ACTCTGGACAGTAGAGGCCCCGGGACGACCGAGCTG
15.	TTGAGTACGTTCTGGATTACTCATAAGACCTTTTTTTTTTCCTTCCGGGCGCAAAACC GTGAGCTGGATTTATAATCGCCCTATAAAGCTCCAGAGGCGGTCAGGCACCTGCAG AGGAGCCCCGCCGCTCCGCCGACTAGCTGCCCCCGCGAGCAACGGCCTCGTGATT TCCCCGCCGATCCGGTCCCCGCCTCCCCACTCTGCCCCCGCCTACCCCGGAGCCG TGCAGCCGCCTCTCCGAATCTCTCTCTTCTCCTGGCGCTCGCGTGCGAGAGGGAAC TAGCGAGAACGAGGAAGCAGCTGGAGGTGACGCCGGGCAGATTACGCCTGTCAGG GCCGAGCCG
16.	CGGACCTGGAGCGGGTCAGACCCCGACTTCCGCCCCTGACTCCCCAGGCGGTCAC ATGACCGAAGCGGCTGGGAGCAGGGAGGGGCATCATGTGACCACTCGCCGGCGA CGGCTGATGACGCAAGAGCCCGCTCTCACTTTTCAGCGGCAGGCGAAGGGGGCTG AGGAAAGGAGGTGGGTCTAGGCAGGGGAAATTGGGGTGCCACCAGACGGAGACA GCTTGGACTACCAGGTAGGGAAGA
17.	GGAGGAAGCCATCAACTAAACTACAATGACTGTAAGATACAAAATTGGGAATGGTAA CATATTTTGAAGTTCTGTTGACATAAAGAATCATGATATTAATGCCCATGGAAATGAA AGGGCGATCAACACTATGGTTTGAAAAGGGGGAAATTGTAGAGCACAGATGTGTTC GTGTGGCAGTGTGCTGTCTCTAGCAATACTCAGAGAAGAGAGAGAACAATGAAATT CTGATTGGCCCCAGTGTGAGCCCAGATGAGGTTCAGCTGCCAACTTTCTCTTTCACA

	TCTTATGAAAGTCATTTAAGCACAACTAACTTTTTTTTTTTTTTTTTTTTTTTGAGACAG AGTCTTGCTCTGTTGCCCAGGACAGAGTGCAGTAGTGACTCAATCTCGGCTCACTG CAGCCTCCACCTCCTAGGCTCAAACGGTCCTCCTGCATCAGCCTCCCAAGTAGCTG GAATTACAGGAGTGGCCCACCATGCCCAGCTAATTTTTGTATTTTTAATAGATACGG GGGTTTCACCATATCACCCAGGCTGGTCTCGAACTCCTGGCCTCAAGTGATCCACC TGCCTCGGCCTCCCAAAGTGCTGGGATTATAGGCGTCAGCCACTATGCCCAACCCG ACCAACCTTTTTTAAAATAAATATTTAAAAAATTGGTATTTCACATATATACTAGT
18.	AAAGCTTTCAGAGGCTTGAATTATCACAGTGTAAATATCCATCTAGCAGAGCAGGTA ATTTTCTCGTTACTCATCCTAAGCATTAGATACTCTGTGTGTTAGTTCTTTGCAGAAA TAACCCATAGCAGCTGAACCATTTTGGAACAAATTTTCCATCACCTTCCTTCCCTGTG TGGTTCAGGCCTTTGCAAACCCTGAGTATCATGAATCTGCTGGTTCTCTACTGGCAA AGATGATGACGTTTTCTTGTTTGTTTTTGTTTTGCTTTAATCATGCCGTGAGAAAATC CTAAGGGAAAAAAATCTCATTATCCTATTCAAAATACATTTAGGGTTATCTGGTCATC CCTAGCAGATTTTTATGTACCCAATGTTTATGTATCTCAAATTACACTCTGTTACCTTT CCCAGAGCAAGATGAAGAACCTCTAAGAACCTCTCAAACAGCATCATTTTCACAACA AGCACTAGCAATGGAAAACATTGTCACCACCACCAGCTAATCTTGTAGGGTCCATGG TATTTTCTGTAATGCCTTGAAACAGTCTGCCTCTCTCTTCTTGTCTGTCATTTTTATAG ATGTCAGTGTGGGGCATCAGCAGTTGAAAACTCAGAATACCAAGCCAGTCCTTCCC TGTGACTGCTACATAGCTTTTGCCTGCAGGATAAGCCTCCATCACTGACGTAGTTGC TTTTTAACTTCTTTTTTTTTTTTTAACTTGGAAAATCCCCCACCTCCTCCATTCCTTCAC AAAACTTTCTGCCTGAATGATTTCTAGTCTGAGGGCCATACACACATTTTTTTTTCTC CCTCTGCAGGTTTTTTTTTCTCTTCAAACTTCCGCATGCTGCCTTTTTTTAAAGTGTC ACACTTTGG
19.	CCAGGTTCCCAGTCCTGGATAAAGTACCTTATAAATATTATCTTGTTGATCTTTAGAA ACTGCTCCTAAAGGAGTGTCGCAGAATCAAACGGCCCAGAGGCTAGGAGGAGGGG ATGTGGGTGAACACAGAACACCGCAGCTGATGATGCAGCTTAAAAGCAGAAGGGAG GGAGGTGCAGCCCGAGGCTGTCGGAGAAGCGGCCCAGACTGGCCCCAGGGCTCT GCAACAGGCTCCAGTTGTGCAGGGAGGGGACAAGCTTGTGATACCGCGTGAAGGA CTCAGGAGGTCCGGTGGAGGGGTGGCCTCTCTCCCGCTGGTTGGCTCCATTGCTA TTTCTGTCTCCTCGTTCTCGGTCTCTCCAGGCCGCTCCCTCTCCATCTGTCCTGATC GCCAGCCTCTCCCCCGCTCCTCTCCGCAGCGGTCGGCCCACCTGGAGCACTCCCC GCCGCCACGTGACCCGTGCGTAAATCGCAGTACTCTTCCCACCCCTGCGCTGGGC CAGCACCCGGCTCTGCGGAGGCTGCAGGCCGCGCATGCGCAGCTGTGGACGCAC CTGCGCGCCC
20.	GTGTGTATGCTCAGGGGCTGGGAAAGGAGGGGAGGGAGCTCCGGCTCAG
21.	GTTTTCGAAACAAATAAAACAGAAAAGCGAACCTAAACA
22.	AATCAACCTCTGGATTACAAAATTTGTGAAAGATAGACTGGTATTCTTAACTATGTTG CTCCTTTTACGCTATGTGGATACGCTGCTTTATAGCCTTTGTATCTAGCTATTGCTTC CCGTTAGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTGCTGTCTCTTTTAGAG GAGTTGTGGCCCGTTGTCAGGCAACGTGGCGTGGTGTGCACTGTGTTTGCTGACG CAACCCCCACTGGTTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTC GCTTTCCCCCTCCCTATTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTG CTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGTGTTGTCGGGGAAA TCATCGTCCTTTCCTTGGCTGCTCGCCTTAGTTGCCACCTGGATTCTGCGCGGGAC GTCCTTCTGCTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCC TGCTGCCGGCTCTGCGGCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGACGAGTCG GATCTCCCTTTGGGCCGCCTCCCCGC

23.	AAAGAGACCGGUUCACUGUGA
24.	GAAACCCAGCAGACAAUGUAGCU
25.	ACCCAGUAGCCAGAUGUAGCU
26.	AAAGAGACCGGUUCACUGUGACAGUAAAAGAGACCGGUUCACUGUGAGAAUGAAA GAGACCGGUUCACUGUGAUCGGAAAAGAGACCGGUUCACUGUGAGCGGCCUUGA AACCCAGCAGACAAUGUAGCUCAGUAGAAACCCAGCAGACAAUGUAGCUGAAUGG AAACCCAGCAGACAAUGUAGCUUCGGAGAAACCCAGCAGACAAUGUAGCU
27.	GAAACCCAGCAGACAAUGUAGCUAGACCCAGUAGCCAGAUGUAGCUAAAGAGACC GGUUCACUGUGA
28.	GAAACCCAGCAGACAAUGUAGCUAGACCCAGUAGCCAGAUGUAGCUAAAGAGACC GGUUCACUGUGAGAAACCCAGCAGACAAUGUAGCUAGACCCAGUAGCCAGAUGUA GCUAAAGAGACCGGUUCACUGUGA
29.	CCCAACAACAGGAAACUACCUA
30.	CACAAAUUCGGUUCUACAGGGUA
31.	CUGUGUUUCAGCUCAGUAGGCA
32.	UUAUGGCCCUUCGGUAAUUCAC
33.	CCCAACAACAUGAAACUACCUA
34.	GAGGUUUCCCGUGUAUGUUUCA
35.	AAAAGCAAAUGCUGACUGCUGCUCACGCCCUGGCUGUGGAUGCCAAAAACUUACU CGAUGUCAUUGACCAAGCAAGACUGAAAAUGCUUGGGCAGACGAGACCACACUGA GCCUCCCCUAGGAGCACGUCUUGCUACCCUCUUUUGAAGAUGUUCUCUAGCCUU CCACCAGCAGCGAGGAAUUAACCCUGUGUCCUCAGUCGCCAGCACUUACAGCUC CAACUUU
36.	UUACUCGAUGUCAUUGACCAAGCAAGACUGAAAAUGCUUGGGCAGACGAGACCAC ACUGAGCCUCCCCUAGGAGCACGUCUUGCUACCCUCUUUUGAAGAUGUUCUCUA GCCUUCCACCAGCAGC
37.	UCUGGAUGGAAUAACUCUUCUUUUGAUGAUGAUCAUAAAAUUAAAUUUCAGACUU CACUAGUUCUGCGUAACACGACAGGUUGCCUAAGGAACCUCAGCUCCGCGGGGG AAGAAGCUCGGAAGCAAAUGCGGUCCUGCGAGGGGCUGGUAGACUCACUGUUGU AUGUGAUCCACACGUGUGUGAACACAUCCGAUUACGACAGCAAGACGGUGGAGA ACUGCGUG
38.	GACUUCACUAGUUCUGCGUAACACGACAGGUUGCCUAAGGAACCUCAGCUCCGC GGGGGAAGAAGCUCGGAAGCAAAUGCGGUCCUGCGAGGGGCUGGUAGACUCACU GUUGUAUGUGAUCCACA
39.	CCCAACAACAGGAAACUACCUA
40.	AGUGUGAGUUCUACCAUUGCCAAA
41.	
42.	
43.	CCCAACAACAGGAAACUACCUAUGGCGAGACCUCCACCCCUCCUCCCAACAACAG GAAACUACCUAGUUGAUAAGUCGGGGACAAUCUCCCAACAACAGGAAACUACCUA GCCGUCAUGAACGCACCAGUCCCCCAACAACAGGAAACUACCUA

44.	UUAUGGCCCUUCGGUAAUUCACUGGCGAGACCUCCACCCCUCCUUUAUGGCCCU UCGGUAAUUCACGUUGAUAAGUCGGGGACAAUCUUUAUGGCCCUUCGGUAAUUC ACGCCGUCAUGAACGCACCAGUCCUUAUGGCCCUUCGGUAAUUCAC
45.	CUGUGUUUCAGCUCAGUAGGCAUGGCGAGACCUCCACCCCUCCUCUGUGUUUCA GCUCAGUAGGCAGUUGAUAAGUCGGGGACAAUCUCUGUGUUUCAGCUCAGUAGG CAGCCGUCAUGAACGCACCAGUCCCUGUGUUUCAGCUCAGUAGGCA
46.	CACAAAUUCGGUUCUACAGGGUAGGCGAGACCUCCACCCCUCCUCACAAAUUCG GUUCUACAGGGUAUUGAUAAGUCGGGGACAAUCUCACAAAUUCGGUUCUACAGG GUACCGUCAUGAACGCACCAGUCCCACAAAUUCGGUUCUACAGGGUA
47.	CUGUGUUUCAGCUCAGUAGGCAUGGCGAGACCUCCACCCCUCCUCACAAAUUCG GUUCUACAGGGUAGUUGAUAAGUCGGGGACAAUCUCUGUGUUUCAGCUCAGUAG GCAGCCGUCAUGAACGCACCAGUCCCACAAAUUCGGUUCUACAGGGUA
48.	CCCAACAACAGGAAACUACCUAUGGCGAGACCUCCACCCCUCCUCACAAAUUCGG UUCUACAGGGUAUUGAUAAGUCGGGGACAAUCUACCCAACAACAGGAAACUACCU ACCGUCAUGAACGCACCAGUCCUCACAAAUUCGGUUCUACAGGGUA
49.	ACAGUUCUUCAACUGGCAGCUU
50.	CCACGACCUAAUCCUAACU
51.	GGGAGCUAGGUUGCCAUGUGC
52.	CUACCUGCACUGUAAGCACUUUG
53.	CUAGUGGUCCUAAACAUUUCAC
54.	AUUUAGUGUGAUAAUGGCGU
55.	CAAACACCAUUGUCACACUCCA
56.	CUACCUGCACGAACAGCACUUUG
57.	UCAGUUUUGCAUAGAUUUGCACA
58.	GAGAUCAUAUGCAUAUGUGUAGGGCUGGAGCGUGUGUGUGUCUUGAGAUUGUG UGUGUUGCAGUCAUCAUAUCUAUGUGUUACAGAUUGUGUAUGUUAGCCUUGUGU AUGUGUGCUUGAUUGAGGUGGUGUAUUUGGGUUGAAAUUGUGUCAUAUGUGUG UGCUAUCCAUCUCGUGU
59.	GCAGAAGAGGUAAGGGAGUGAGGCACUCCUAUCCCAGUCUCCCAGGUUUGGUUG AGGGCUCCCCAAGGCAGGGCAAGAUAGCGGCCCUGUCACUGACCCUGGCCUGUG GUGGUCUGAGCUGGGGAGGGAAGGACACCAAUGAAUCAGCUUGGGACCUCUUUA GGCCUUCCCCUUUUCCUC
60.	GCAUUAAAACACACAUACAAACAAAAUCAAAAACACUGCGGACUUUCACUCAAGCU GGUCUUUCUUCCCCAGUGUAAGGCAAUCCUGCCUACUAACAACACCAACAACAAA ACACUCCAUCUGUGAAAGCUGACGCAGUUAAGGGGGCUAGGCAGGGCAUUUGUG CCAACUAAGAAUCACCAGAUACCCACCAUAAGUACCUAUCGCAGUUUUGAAGUCG UUUCUCCC
61.	CAACCAUCACGUCAGGCUGCCCAUCCAAUAGACUCCUGGGAUGGGGCAGCCAAC CCUGGCUCAUCUCAUCUGCCGCUUGGUGCGUGUGCGUGUGCGUGCAUGUGCGU GUGCGUGUGUGCAGGGGUGAGAAUCUGGCAGAUGGUGCCUCUGCCUGCUCUUC UUCGCCUCCUUUAUUUA
62.	UGGCCCUGCGCAUGCUGAAAUAACUGGAACCCAGCCUCUCCUCCUACACCGGCC UACCCAUCUGGGCCCAAGAGCUGCACUCACACUCCUACAACGAAGGACAAACUGU CCAGGUCGGAGGGAUCACGAGACACAGAACCUGGAGGGGUGUG

63.	UCUGACUUGAGAGCUCCCCCAGUCAGAUCUCAGGCUUGUCCCCCUGUCAGCUGC CUCCAGAAGGGAAGGUAGCCAGUGCCUGAGAAGACAGUCCCUUUUCUACCCACC GCACUCCAUAACCUCCAUCUUCUCCCACACUGAUGGCGAGCAGCCCCUGAGCAC UUUCUGGGACUGGGAGACUGCUUGGUGUUCCCUGAGGACAAGAGACAUCCUGAC AGUGUUGGGCA
64.	UAUUUAGUGUGAUAAUGGCGUUaaugguccUAUUUAGUGUGAUAAUGGCGUUcgaccg cgUAUUUAGUGUGAUAAUGGCGUU
65.	acaccauugucacacuccacaccauugucacacuccacaccauugucacacucc
66.	UCAGUUUUGCAUAGAUUUGCACAaaugguccgcacauggcaaccUAGCUCCcgaccgcgCCA CGACCUAAUCCUAACUacuuucuuCUACCUGCACUGUAAGCACUUUGuagagcaugaaag caccugucuaUCAGUUUUGCAUAGAUUUGCACAaaugguccgcacauggcaaccUAGCUCCcg accgcgCCACGACCUAAUCCUAACUacuuucuuCUACCUGCACUGUAAGCACUUUG
67.	CCCAACAACAGGAAACUACCUAAUUAUUUAGUGUGAUAAUGGCGUUAUCCCAACA ACAGGAAACUACCUAGUAUUUAGUGUGAUAAUGGCGUUUUACUCGAUGUCAUUGA CCAAGCAAGACUGAAAAUGCUUGGGCAGACGAGACCACACUGAGCCUCCCCUAG GAGCACGUCUUGCUACCCUCUUUUGAAGAUGUUCUCUAGCCUUCCACCAGCAGC CCCAACAACAGGAAACUACCUAGGUAUUUAGUGUGAUAAUGGCGUUGUCCCAACA ACAGGAAACUACCUAGAUAUUUAGUGUGAUAAUGGCGUUUGGCCCUGCGCAUGC UGAAAUAACUGGAACCCAGCCUCUCCUCCUACACCGGCCUACCCAUCUGGGCCCA AGAGCUGCACUCACACUCCUACAACGAAGGACAAACUGUCCAGGUCGGAGGGAU CACGAGACACAGAACCUGGAGGGGUGUGACUAGU
68.	CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCGTCGGGCG ACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCC AACTCCATCACTAGGGGTTCCTGCGGCCGCACGCGTCCAGGTTCCCAGTCCTGGAT AAAGTACCTTATAAATATTATCTTGTTGATCTTTAGAAACTGCTCCTAAAGGAGTGTC GCAGAATCAAACGGCCCAGAGGCTAGGAGGAGGGGATGTGGGTGAACACAGAACA CCGCAGCTGATGATGCAGCTTAAAAGCAGAAGGGAGGGAGGTGCAGCCCGAGGCT GTCGGAGAAGCGGCCCAGACTGGCCCCAGGGCTCTGCAACAGGCTCCAGTTGTGC AGGGAGGGGACAAGCTTGTGATACCGCGTGAAGGACTCAGGAGGTCCGGTGGAGG GGTGGCCTCTCTCCCGCTGGTTGGCTCCATTGCTATTTCTGTCTCCTCGTTCTCGGT CTCTCCAGGCCGCTCCCTCTCCATCTGTCCTGATCGCCAGCCTCTCCCCCGCTCCT CTCCGCAGCGGTCGGCCCACCTGGAGCACTCCCCGCCGCCACGTGACCCGTGCGT AAATCGCAGTACTCTTCCCACCCCTGCGCTGGGCCAGCACCCGGCTCTGCGGAGG CTGCAGGCCGCGCATGCGCAGCTGTGGACGCACCTGCGCGCCCCGGAAAATGGA GATTAAAAATAATGCCCATAGGTATGAGCTAAGAGGAGTGTAAACAAAACAAAATAA AAAGCAATGCCCAGTGATTGGAGGATTTGATGAGATGATGCCCGCGAGGTGCTTGG CACGGAGTTTGACACAAGAACTCAGTGTTGGTGAATGCACGAATGCAGGTACCCAG CGACAGGGAGGTGCTGTGGGTGGATTCACCCTGGCTTCGCTGCGGCTGGGAGTGG GCGCTGCTAGTAAGAGATCTCGCCTCCAAGCTCCTTCCGTGGGCAGGAAAAAACGG AAGCTCCCAGAAAGAGGAAAGACAGGACCCGAGCGGGGTTTCAGGCAGATGGAGC GCGTCGGTAGCCTGTGGCCAGGGATCCCAGCACCGACGGGAAAGAGGAGGCCTG GGTACCCTGCGCCCCGGGCGCGCGCGGCGCGTGAGGTGAGGGGGAGGGCGCGG CTCCGCACCAGCCAGCGGCCGCCTGGCGCCCAGCCGCATCTCGGGGGGCGGGGT TGAGCCTCCGGGCCGCAGTGCGATTGGCGGAGGCGAGTGGGTGACGCCAACGGC CGGCGCGAGGCCCCGCCCCCGGCTTGCCCCGCCCCCGCGCGCGCCGGCGGCGG GGCAGCCTCGCTCTGGCTCGCGCCGCGCCCCCGCGCCCAGTCCGCGCGTCAGTC GGTCCCTAGCGCGGCTGCGGGGCGGAGAGCTGCGGCTGGCCCAGCGCGCCCACC

	TGAGGAGGCGGCGGGGTCCGCAGGCGTCGCGGGACGAGGAGATCGGAGCCGGG AGACTCGCGCAGCGCCGAATTCGCCACCATGGCCCCCATTGGCCTGAAGGCTGTG GTGGGAGAGAAGATCATGCATGATGTGATCAAGAAGGTGAAGAAGAAGGGAGAGT GGAAGGTGCTGGTGGTGGACCAGCTGAGCATGAGAATGCTGAGCAGCTGCTGCAA GATGACAGACATCATGACAGAGGGCATCACCATTGTGGAGGACATCAACAAGAGAA GAGAGCCCCTGCCCAGCCTGGAGGCTGTGTACCTGATCACCCCCTCTGAGAAGTCT GTGCACAGCCTGATCTCTGACTTCAAGGACCCCCCCACAGCCAAGTACAGAGCTGC CCATGTGTTCTTCACAGACAGCTGCCCTGATGCCCTGTTCAATGAGCTGGTGAAGA GCAGAGCTGCCAAGGTGATCAAGACCCTGACAGAGATCAACATTGCCTTCCTGCCC TATGAGAGCCAGGTGTACAGCCTGGACTCTGCTGACAGCTTCCAGAGCTTCTACAG CCCCCACAAGGCCCAGATGAAGAACCCCATCCTGGAGAGACTGGCTGAGCAGATT GCCACCCTGTGTGCCACCCTGAAGGAGTACCCTGCTGTGAGATACAGAGGAGAGTA CAAGGACAATGCCCTGCTGGCCCAGCTGATCCAGGACAAGCTGGATGCCTACAAG GCTGATGACCCCACCATGGGAGAGGGCCCTGACAAGGCCAGAAGCCAGCTGCTGA TCCTGGACAGAGGCTTTGACCCCAGCAGCCCTGTGCTGCATGAGCTGACCTTCCAG GCCATGAGCTATGACCTGCTGCCCATTGAGAATGATGTGTACAAGTATGAGACCTCT GGCATTGGAGAGGCCAGAGTGAAGGAGGTGCTGCTGGATGAGGATGATGACCTGT GGATTGCCCTGAGACACAAGCACATTGCTGAGGTGAGCCAGGAGGTGACCAGAAG CCTGAAGGACTTCAGCAGCAGCAAGAGAATGAACACAGGAGAGAAGACCACCATGA GAGACCTGAGCCAGATGCTGAAGAAGATGCCCCAGTACCAGAAGGAGCTGAGCAA GTACAGCACCCACCTGCACCTGGCTGAGGACTGCATGAAGCACTACCAGGGCACA GTGGACAAGCTGTGCAGAGTGGAGCAGGACCTGGCCATGGGCACAGATGCTGAGG GAGAGAAGATCAAGGACCCCATGAGAGCCATTGTGCCCATCCTGCTGGATGCCAAT GTGAGCACCTATGACAAGATCAGAATCATCCTGCTGTACATCTTCCTGAAGAATGGC ATCACAGAGGAGAACCTGAACAAGCTGATCCAGCATGCCCAGATCCCCCCTGAGGA CTCTGAGATCATCACCAACATGGCCCACCTGGGAGTGCCCATTGTGACAGACAGCA CCCTGAGAAGAAGAAGCAAGCCTGAGAGAAAGGAGAGAATCTCTGAGCAGACCTAC CAGCTGAGCAGATGGACCCCCATCATCAAGGACATCATGGAGGACACCATTGAGGA CAAGCTGGACACCAAGCACTACCCCTACATCAGCACCAGAAGCTCTGCCAGCTTCA GCACCACAGCTGTGTCTGCCAGATATGGCCACTGGCACAAGAACAAGGCCCCTGG AGAGTACAGATCTGGCCCCAGACTGATCATCTTCATCCTGGGAGGAGTGAGCCTGA ATGAGATGAGATGTGCCTATGAGGTGACCCAGGCCAATGGCAAGTGGGAGGTGCT GATTGGCAGCACCCACATCCTGACCCCCCAGAAGCTGCTGGACACCCTGAAGAAG CTGAACAAGACAGATGAGGAGATCAGCAGCTGACTCGAGCACAAATTCGGTTCTAC AGGGTAGGCGAGACCTCCACCCCTCCTCACAAATTCGGTTCTACAGGGTATTGATA AGTCGGGGACAATCTCACAAATTCGGTTCTACAGGGTACCGTCATGAACGCACCAG TCCCACAAATTCGGTTCTACAGGGTACCTCGAGAATCAACCTCTGGATTACAAAATT TGTGAAAGATAGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACG CTGCTTTATAGCCTTTGTATCTAGCTATTGCTTCCCGTTAGGCTTTCATTTTCTCCTC CTTGTATAAATCCTGGTTGCTGTCTCTTTTAGAGGAGTTGTGGCCCGTTGTCAGGCA ACGTGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGGTTGGGGCATTG CCACCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCCTATTGCCACG GCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTTGG GCACTGACAATTCCGTGGTGTTGTCGGGGAAATCATCGTCCTTTCCTTGGCTGCTC GCCTTAGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTGCTACGTCCCTTCGGC CCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCCGGCTCTGCGGCCTCTTC CGCGTCTTCGCCTTCGCCCTCAGACGAGTCGGATCTCCCTTTGGGCCGCCTCCCC GCACTAGTTCGAGaataaaagatctttattttcattagatctgtgtgttggtttttgtgtgCACGTGCGGACCGA GCGGCCGCAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGC TCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGG

	GCGGCCTCAGTGAGCGAGCGAGCGCGCAGCTGCCTGCAGG
69.	CCAGGTTCCCAGTCCTGGATAAAGTACCTTATAAATATTATCTTGTTGATCTTTAGAA ACTGCTCCTAAAGGAGTGTCGCAGAATCAAACGGCCCAGAGGCTAGGAGGAGGGG ATGTGGGTGAACACAGAACACCGCAGCTGATGATGCAGCTTAAAAGCAGAAGGGAG GGAGGTGCAGCCCGAGGCTGTCGGAGAAGCGGCCCAGACTGGCCCCAGGGCTCT GCAACAGGCTCCAGTTGTGCAGGGAGGGGACAAGCTTGTGATACCGCGTGAAGGA CTCAGGAGGTCCGGTGGAGGGGTGGCCTCTCTCCCGCTGGTTGGCTCCATTGCTA TTTCTGTCTCCTCGTTCTCGGTCTCTCCAGGCCGCTCCCTCTCCATCTGTCCTGATC GCCAGCCTCTCCCCCGCTCCTCTCCGCAGCGGTCGGCCCACCTGGAGCACTCCCC GCCGCCACGTGACCCGTGCGTAAATCGCAGTACTCTTCCCACCCCTGCGCTGGGC CAGCACCCGGCTCTGCGGAGGCTGCAGGCCGCGCATGCGCAGCTGTGGACGCAC CTGCGCGCCCCGGAAAATGGAGATTAAAAATAATGCCCATAGGTATGAGCTAAGAG GAGTGTAAACAAAACAAAATAAAAAGCAATGCCCAGTGATTGGAGGATTTGATGAGA TGATGCCCGCGAGGTGCTTGGCACGGAGTTTGACACAAGAACTCAGTGTTGGTGAA TGCACGAATGCAGGTACCCAGCGACAGGGAGGTGCTGTGGGTGGATTCACCCTGG CTTCGCTGCGGCTGGGAGTGGGCGCTGCTAGTAAGAGATCTCGCCTCCAAGCTCC TTCCGTGGGCAGGAAAAAACGGAAGCTCCCAGAAAGAGGAAAGACAGGACCCGAG CGGGGTTTCAGGCAGATGGAGCGCGTCGGTAGCCTGTGGCCAGGGATCCCAGCAC CGACGGGAAAGAGGAGGCCTGGGTACCCTGCGCCCCGGGCGCGCGCGGCGCGT GAGGTGAGGGGGAGGGCGCGGCTCCGCACCAGCCAGCGGCCGCCTGGCGCCCA GCCGCATCTCGGGGGGCGGGGTTGAGCCTCCGGGCCGCAGTGCGATTGGCGGAG GCGAGTGGGTGACGCCAACGGCCGGCGCGAGGCCCCGCCCCCGGCTTGCCCCGC CCCCGCGCGCGCCGGCGGCGGGGCAGCCTCGCTCTGGCTCGCGCCGCGCCCCC GCGCCCAGTCCGCGCGTCAGTCGGTCCCTAGCGCGGCTGCGGGGCGGAGAGCTG CGGCTGGCCCAGCGCGCCCACCTGAGGAGGCGGCGGGGTCCGCAGGCGTCGCG GGACGAGGAGATCGGAGCCGGGAGACTCGCGCAGCGCCGAATTCGCCACCATGG CCCCCATTGGCCTGAAGGCTGTGGTGGGAGAGAAGATCATGCATGATGTGATCAAG AAGGTGAAGAAGAAGGGAGAGTGGAAGGTGCTGGTGGTGGACCAGCTGAGCATGA GAATGCTGAGCAGCTGCTGCAAGATGACAGACATCATGACAGAGGGCATCACCATT GTGGAGGACATCAACAAGAGAAGAGAGCCCCTGCCCAGCCTGGAGGCTGTGTACC TGATCACCCCCTCTGAGAAGTCTGTGCACAGCCTGATCTCTGACTTCAAGGACCCC CCCACAGCCAAGTACAGAGCTGCCCATGTGTTCTTCACAGACAGCTGCCCTGATGC CCTGTTCAATGAGCTGGTGAAGAGCAGAGCTGCCAAGGTGATCAAGACCCTGACAG AGATCAACATTGCCTTCCTGCCCTATGAGAGCCAGGTGTACAGCCTGGACTCTGCT GACAGCTTCCAGAGCTTCTACAGCCCCCACAAGGCCCAGATGAAGAACCCCATCCT GGAGAGACTGGCTGAGCAGATTGCCACCCTGTGTGCCACCCTGAAGGAGTACCCT GCTGTGAGATACAGAGGAGAGTACAAGGACAATGCCCTGCTGGCCCAGCTGATCCA GGACAAGCTGGATGCCTACAAGGCTGATGACCCCACCATGGGAGAGGGCCCTGAC AAGGCCAGAAGCCAGCTGCTGATCCTGGACAGAGGCTTTGACCCCAGCAGCCCTG TGCTGCATGAGCTGACCTTCCAGGCCATGAGCTATGACCTGCTGCCCATTGAGAAT GATGTGTACAAGTATGAGACCTCTGGCATTGGAGAGGCCAGAGTGAAGGAGGTGCT GCTGGATGAGGATGATGACCTGTGGATTGCCCTGAGACACAAGCACATTGCTGAGG TGAGCCAGGAGGTGACCAGAAGCCTGAAGGACTTCAGCAGCAGCAAGAGAATGAA CACAGGAGAGAAGACCACCATGAGAGACCTGAGCCAGATGCTGAAGAAGATGCCC CAGTACCAGAAGGAGCTGAGCAAGTACAGCACCCACCTGCACCTGGCTGAGGACT GCATGAAGCACTACCAGGGCACAGTGGACAAGCTGTGCAGAGTGGAGCAGGACCT GGCCATGGGCACAGATGCTGAGGGAGAGAAGATCAAGGACCCCATGAGAGCCATT

	GTGCCCATCCTGCTGGATGCCAATGTGAGCACCTATGACAAGATCAGAATCATCCT GCTGTACATCTTCCTGAAGAATGGCATCACAGAGGAGAACCTGAACAAGCTGATCC AGCATGCCCAGATCCCCCCCTGAGGACTCTGAGATCATCACCAACATGGCCCACCTG GGAGTGCCCATTGTGACAGACAGCACCCTGAGAAGAAGAAGCAAGCCTGAGAGAA AGGAGAGAATCTCTGAGCAGACCTACCAGCTGAGCAGATGGACCCCCATCATCAAG GACATCATGGAGGACACCATTGAGGACAAGCTGGACACCAAGCACTACCCCTACAT CAGCACCAGAAGCTCTGCCAGCTTCAGCACCACAGCTGTGTCTGCCAGATATGGCC ACTGGCACAAGAACAAGGCCCCTGGAGAGTACAGATCTGGCCCCAGACTGATCATC TTCATCCTGGGAGGAGTGAGCCTGAATGAGATGAGATGTGCCTATGAGGTGACCCA GGCCAATGGCAAGTGGGAGGTGCTGATTGGCAGCACCCACATCCTGACCCCCCAG AAGCTGCTGGACACCCTGAAGAAGCTGAACAAGACAGATGAGGAGATCAGCAGCTG ACTCGAGAATCAACCTCTGGATTACAAAATTTGTGAAAGATAGACTGGTATTCTTAAC TATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTATAGCCTTTGTATCTAGCTA TTGCTTCCCGTTAGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTGCTGTCTCT TTTAGAGGAGTTGTGGCCCGTTGTCAGGCAACGTGGCGTGGTGTGCACTGTGTTTG CTGACGCAACCCCCACTGGTTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGG ACTTTCGCTTTCCCCCTCCCTATTGCCACGGCGGAACTCATCGCCGCCTGCCTTGC CCGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGTGTTGTCG GGGAAATCATCGTCCTTTCCTTGGCTGCTCGCCTTAGTTGCCACCTGGATTCTGCG CGGGACGTCCTTCTGCTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCCTTCCC GCGGCCTGCTGCCGGCTCTGCGGCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGAC GAGTCGGATCTCCCTTTGGGCCGCCTCCCCGCACTAGTaataaaagatctttattttcattagatct gtgtgttggttttttgtgtg
70.	CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCGTCGGGCG ACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCC AACTCCATCACTAGGGGTTCCTGCGGCCGCACGCGTGGCGCGCCGTTTAAACTTAA TTAAGCTAGCgagtaattcatacaaaaggactcgcccctgccttggggaatcccagggaccgtcgttaaactcccac taacgtagaacccagagatcgctgcgttcccgccccctcacccgcccgctctcgtcatcactgaggtggagaagagcatgc gtgaggctccggtgcccgtcagtgggcagagcgcacatcgcccacagtccccgagaagttgggggggaggggtcggcaa ttgaaccggtgcctagagaaggtggcgcggggtaaactgggaaagtgatgtcgtgtactggctccgcctttttcccgagggt ggggggagaaccgtatataagtgcagtagtcgccgtgaacgttcttttcgcaacgggtttgccgccagaacacaggtaagtg ccgtgtgtggttcccgcgggcctggcctctttacgggttatggcccttgcgtgccttgaattacttccacgcccctggctgcagta cgtgattcttgatcccgagcttcgggttggaagtgggtgggagagttcgaggccttgcgcttaaggagccccttcgcctcgtgc ttgagttgaggcctggcttgggcgctggggccgccgcgtgcgaatctggtggcaccttcgcgcctgtctcgctgctttcgataa gtctctagccatttaaaatttttgatgacctgctgcgacgcttttttctggcaagatagtcttgtaaatgcgggccaagatctgca cactggtatttcggttttggggccgcgggcggcgacggggcccgtgcgtcccagcgcacatgttcggcgaggcggggcct gcgagcgcggccaccgagaatcggacgggggtagtctcaagctggccggcctgctctggtgcctggcctcgcgccgccg tgtatcgccccgccctgggcggcaaggctggcccggtcggcaccagttgcgtgagcggaaagatggccgcttcccggcc ctgctgcagggagctcaaaatggaggacgcggcgctcgggagagcgggcgggtgagtcacccacacaaaggaaaag ggcctttccgtcctcagccgtcgcttcatgtgactccacggagtaccgggcgccgtccaggcacctcgattagttctcgagcttt tggagtacgtcgtctttaggttgggggggagggggttttatgcgatggagtttccccacactgagtgggtggagactgaagttagg ccagcttggcacttgatgtaattctccttggaatttgccctttttgagtttggatcttggttcattctcaagcctcagacagtggttcaa agtttttttcttccatttcaggtgtcgtgaGGTACCGAATTCGCCACCATGGCCCCCATTGGCCTGAA GGCTGTGGTGGGAGAGAAGATCATGCATGATGTGATCAAGAAGGTGAAGAAGAAG GGAGAGTGGAAGGTGCTGGTGGTGGACCAGCTGAGCATGAGAATGCTGAGCAGCT GCTGCAAGATGACAGACATCATGACAGAGGGCATCACCATTGTGGAGGACATCAAC AAGAGAAGAGAGCCCCTGCCCAGCCTGGAGGCTGTGTACCTGATCACCCCCTCTG AGAAGTCTGTGCACAGCCTGATCTCTGACTTCAAGGACCCCCCCACAGCCAAGTAC AGAGCTGCCCATGTGTTCTTCACAGACAGCTGCCCTGATGCCCTGTTCAATGAGCT

	GGTGAAGAGCAGAGCTGCCAAGGTGATCAAGACCCTGACAGAGATCAACATTGCCT TCCTGCCCTATGAGAGCCAGGTGTACAGCCTGGACTCTGCTGACAGCTTCCAGAGC TTCTACAGCCCCCACAAGGCCCAGATGAAGAACCCCATCCTGGAGAGACTGGCTGA GCAGATTGCCACCCTGTGTGCCACCCTGAAGGAGTACCCTGCTGTGAGATACAGAG GAGAGTACAAGGACAATGCCCTGCTGGCCCAGCTGATCCAGGACAAGCTGGATGC CTACAAGGCTGATGACCCCACCATGGGAGAGGGCCCTGACAAGGCCAGAAGCCAG CTGCTGATCCTGGACAGAGGCTTTGACCCCAGCAGCCCTGTGCTGCATGAGCTGAC CTTCCAGGCCATGAGCTATGACCTGCTGCCCATTGAGAATGATGTGTACAAGTATGA GACCTCTGGCATTGGAGAGGCCAGAGTGAAGGAGGTGCTGCTGGATGAGGATGAT GACCTGTGGATTGCCCTGAGACACAAGCACATTGCTGAGGTGAGCCAGGAGGTGA CCAGAAGCCTGAAGGACTTCAGCAGCAGCAAGAGAATGAACACAGGAGAGAAGAC CACCATGAGAGACCTGAGCCAGATGCTGAAGAAGATGCCCCAGTACCAGAAGGAG CTGAGCAAGTACAGCACCCACCTGCACCTGGCTGAGGACTGCATGAAGCACTACCA GGGCACAGTGGACAAGCTGTGCAGAGTGGAGCAGGACCTGGCCATGGGCACAGAT GCTGAGGGAGAGAAGATCAAGGACCCCATGAGAGCCATTGTGCCCATCCTGCTGG ATGCCAATGTGAGCACCTATGACAAGATCAGAATCATCCTGCTGTACATCTTCCTGA AGAATGGCATCACAGAGGAGAACCTGAACAAGCTGATCCAGCATGCCCAGATCCCC CCTGAGGACTCTGAGATCATCACCAACATGGCCCACCTGGGAGTGCCCATTGTGAC AGACAGCACCCTGAGAAGAAGAAGCAAGCCTGAGAGAAAGGAGAGAATCTCTGAG CAGACCTACCAGCTGAGCAGATGGACCCCCATCATCAAGGACATCATGGAGGACAC CATTGAGGACAAGCTGGACACCAAGCACTACCCCTACATCAGCACCAGAAGCTCTG CCAGCTTCAGCACCACAGCTGTGTCTGCCAGATATGGCCACTGGCACAAGAACAAG GCCCCTGGAGAGTACAGATCTGGCCCCAGACTGATCATCTTCATCCTGGGAGGAGT GAGCCTGAATGAGATGAGATGTGCCTATGAGGTGACCCAGGCCAATGGCAAGTGG GAGGTGCTGATTGGCAGCACCCACATCCTGACCCCCCAGAAGCTGCTGGACACCC TGAAGAAGCTGAACAAGACAGATGAGGAGATCAGCAGCTGAGCACAAATTCGGTTC TACAGGGTAGGCGAGACCTCCACCCCTCCTCACAAATTCGGTTCTACAGGGTATTG ATAAGTCGGGGACAATCTCACAAATTCGGTTCTACAGGGTACCGTCATGAACGCAC CAGTCCCACAAATTCGGTTCTACAGGGTACCTCGAGAATCAACCTCTGGATTACAAA ATTTGTGAAAGATAGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGAT ACGCTGCTTTATAGCCTTTGTATCTAGCTATTGCTTCCCGTTAGGCTTTCATTTTCTC CTCCTTGTATAAATCCTGGTTGCTGTCTCTTTTAGAGGAGTTGTGGCCCGTTGTCAG GCAACGTGGCGTGGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGGTTGGGGC ATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCCTATTGCC ACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGT TGGGCACTGACAATTCCGTGGTGTTGTCGGGGAAATCATCGTCCTTTCCTTGGCTG CTCGCCTTAGTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTGCTACGTCCCTTC GGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTGCTGCCGGCTCTGCGGCCT CTTCCGCGTCTTCGCCTTCGCCCTCAGACGAGTCGGATCTCCCTTTGGGCCGCCTC CCCGCACTAGTaataaaagatctttattttcattagatctgtgtgttggtttttgtgtgCACGTGCGGACCGAGC GGCCGCAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTC GCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGC GGCCTCAGTGAGCGAGCGAGCGCGCAGCTGCCTGCAGG
71.	CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCG GGCGTCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAG AGGGAGTGGCCAACTCCATCACTAGGGGTTCCTGCGGCCGCACGCGTAAAGCTTT CAGAGGCTTGAATTATCACAGTGTAAATATCCATCTAGCAGAGCAGGTAATTTTCTC GTTACTCATCCTAAGCATTAGATACTCTGTGTGTTAGTTCTTTGCAGAAATAACCCAT AGCAGCTGAACCATTTTGGAACAAATTTTCCATCACCTTCCTTCCCTGTGTGGTTCA

	GGCCTTTGCAAACCCTGAGTATCATGAATCTGCTGGTTCTCTACTGGCAAAGATGAT GACGTTTTCTTGTTTGTTTTTGTTTTGCTTTAATCATGCCGTGAGAAAATCCTAAGGG AAAAAAATCTCATTATCCTATTCAAAATACATTTAGGGTTATCTGGTCATCCCTAGCA GATTTTTATGTACCCAATGTTTATGTATCTCAAATTACACTCTGTTACCTTTCCCAGAG CAAGATGAAGAACCTCTAAGAACCTCTCAAACAGCATCATTTTCACAACAAGCACTA GCAATGGAAAACATTGTCACCACCACCAGCTAATCTTGTAGGGTCCATGGTATTTTC TGTAATGCCTTGAAACAGTCTGCCTCTCTCTTCTTGTCTGTCATTTTTATAGATGTCA GTGTGGGGCATCAGCAGTTGAAAACTCAGAATACCAAGCCAGTCCTTCCCTGTGAC TGCTACATAGCTTTTGCCTGCAGGATAAGCCTCCATCACTGACGTAGTTGCTTTTTA ACTTCTTTTTTTTTTTTTAACTTGGAAAATCCCCCACCTCCTCCATTCCTTCACAAAACT TTCTGCCTGAATGATTTCTAGTCTGAGGGCCATACACACATTTTTTTTTCTCCCTCTG CAGGTTTTTTTTTCTCTTCAAACTTCCGCATGCTGCCTTTTTTTTAAAGTGTCACACTTT GGCCTTCCCCCGACTCCTGCAACAGCTCAGAGAGCCTGGCTCTGACGTAGTTCAAA ATAACGTGCGCCAGCCTCGCTGCCCGGCTGACCACAGCAACGAGAGCCACAAGCC CTCGACGCTGCTTCGATAACATGAAGCAATCACTCATAAAAATAGCAACCCACGTAG CCTGGCCATATATGGAGCTGGCGAGGGTGGACGGGGATGCCCCTACGGACCCTCT TCGGAGAAAACAAATCGCCGCTGAAATTTCCCCCACCCCTCCCATCACTACCTTTTA CCCCTCCTCTGCCTTCCCCTCTCCTTAGATGACTCAACCACAGATTCCACTGAAAGG GGGTGGGGGTGGGGGTGGGGGGGGAATATATACACATACACACAAATTATACATATA TTATACATGTATTATAAAATATACACACACATACATATATACATACACACACATATACA CATATGTACACACACACGCACACACACCAAAGAACATCAGGAATGCAGTTGCGGGA TGAAGCCGTTTGCCCAAGACCGAGTGTTAAAATGGAGTCATAAGAGTCGCCCCGTG CGGGTGTTTATAGAAGGTGAAAACACGCAGGTTTGCAGGCCAGCGCACTGGGAAC CGAGTCAAGCGCGCCGCAGCCCGGGCCCCGCCCCCGCCCCCGCCGTGCCCCGCC CCCACTTCCTCCCGCCCCTCGCTGGGCGGCTATTAAAAGCTGCTGACGTCAAAACG GACGGCCATCTTTGATGAGGGCAGAGCTCACGTTGCATTGAAGACGAAACCTCGGG GAGGTCAGGCGCTGTCTTTCCTTCCCTCCCTGCTCGGCGGCTCCACCACAGTTGCA ACCTGCAGAGGCCCGGAGAACACAACCCTCCCGAGAAGCCCAGGTAAGAACGAAT TCGCCACCATGGCCCCCATTGGCCTGAAGGCTGTGGTGGGAGAGAAGATCATGCA TGATGTGATCAAGAAGGTGAAGAAGAAGGGAGAGTGGAAGGTGCTGGTGGTGGAC CAGCTGAGCATGAGAATGCTGAGCAGCTGCTGCAAGATGACAGACATCATGACAGA GGGCATCACCATTGTGGAGGACATCAACAAGAGAAGAGAGCCCCTGCCCAGCCTG GAGGCTGTGTACCTGATCACCCCCTCTGAGAAGTCTGTGCACAGCCTGATCTCTGA CTTCAAGGACCCCCCCACAGCCAAGTACAGAGCTGCCCATGTGTTCTTCACAGACA GCTGCCCTGATGCCCTGTTCAATGAGCTGGTGAAGAGCAGAGCTGCCAAGGTGATC AAGACCCTGACAGAGATCAACATTGCCTTCCTGCCCTATGAGAGCCAGGTGTACAG CCTGGACTCTGCTGACAGCTTCCAGAGCTTCTACAGCCCCCACAAGGCCCAGATGA AGAACCCCATCCTGGAGAGACTGGCTGAGCAGATTGCCACCCTGTGTGCCACCCTG AAGGAGTACCCTGCTGTGAGATACAGAGGAGAGTACAAGGACAATGCCCTGCTGGC CCAGCTGATCCAGGACAAGCTGGATGCCTACAAGGCTGATGACCCCACCATGGGA GAGGGCCCTGACAAGGCCAGAAGCCAGCTGCTGATCCTGGACAGAGGCTTTGACC CCAGCAGCCCTGTGCTGCATGAGCTGACCTTCCAGGCCATGAGCTATGACCTGCTG CCCATTGAGAATGATGTGTACAAGTATGAGACCTCTGGCATTGGAGAGGCCAGAGT GAAGGAGGTGCTGCTGGATGAGGATGATGACCTGTGGATTGCCCTGAGACACAAG CACATTGCTGAGGTGAGCCAGGAGGTGACCAGAAGCCTGAAGGACTTCAGCAGCA GCAAGAGAATGAACACAGGAGAGAAGACCACCATGAGAGACCTGAGCCAGATGCT GAAGAAGATGCCCCAGTACCAGAAGGAGCTGAGCAAGTACAGCACCCACCTGCAC CTGGCTGAGGACTGCATGAAGCACTACCAGGGCACAGTGGACAAGCTGTGCAGAG TGGAGCAGGACCTGGCCATGGGCACAGATGCTGAGGGAGAGAAGATCAAGGACCC CATGAGAGCCATTGTGCCCATCCTGCTGGATGCCAATGTGAGCACCTATGACAAGA

	TCAGAATCATCCTGCTGTACATCTTCCTGAAGAATGGCATCACAGAGGAGAACCTGA ACAAGCTGATCCAGCATGCCCAGATCCCCCCTGAGGACTCTGAGATCATCACCAAC ATGGCCCACCTGGGAGTGCCCATTGTGACAGACAGCACCCTGAGAAGAAGAAGCA AGCCTGAGAGAAAGGAGAGAATCTCTGAGCAGACCTACCAGCTGAGCAGATGGAC CCCCATCATCAAGGACATCATGGAGGACACCATTGAGGACAAGCTGGACACCAAGC ACTACCCCTACATCAGCACCAGAAGCTCTGCCAGCTTCAGCACCACAGCTGTGTCT GCCAGATATGGCCACTGGCACAAGAACAAGGCCCCTGGAGAGTACAGATCTGGCC CCAGACTGATCATCTTCATCCTGGGAGGAGTGAGCCTGAATGAGATGAGATGTGCC TATGAGGTGACCCAGGCCAATGGCAAGTGGGAGGTGCTGATTGGCAGCACCCACA TCCTGACCCCCCAGAAGCTGCTGGACACCCTGAAGAAGCTGAACAAGACAGATGAG GAGATCAGCAGCTGACTCGAGCACAAATTCGGTTCTACAGGGTATATTTAGTGTGAT AATGGCGTTCACAAATTCGGTTCTACAGGGTATATTTAGTGTGATAATGGCGTTCAC AAATTCGGTTCTACAGGGTATATTTAGTGTGATAATGGCGTTCACAAATTCGGTTCTA CAGGGTACCTCGAGAATCAACCTCTGGATTACAAAATTTGTGAAAGATAGACTGGTA TTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTATAGCCTTTGTA TCTAGCTATTGCTTCCCGTTAGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTG CTGTCTCTTTTAGAGGAGTTGTGGCCCGTTGTCAGGCAACGTGGCGTGGTGTGCAC TGTGTTTGCTGACGCAACCCCCACTGGTTGGGGCATTGCCACCACCTGTCAGCTCC TTTCCGGGACTTTCGCTTTCCCCCTCCCTATTGCCACGGCGGAACTCATCGCCGCC TGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGG TGTTGTCGGGGAAATCATCGTCCTTTCCTTGGCTGCTCGCCTTAGTTGCCACCTGGA TTCTGCGCGGGACGTCCTTCTGCTACGTCCCTTCGGCCCTCAATCCAGCGGACCTT CCTTCCCGCGGCCTGCTGCCGGCTCTGCGGCCTCTTCCGCGTCTTCGCCTTCGCC CTCAGACGAGTCGGATCTCCCTTTGGGCCGCCTCCCCGCACTAGTaataaaagatctttattt tcattagatctgtgtgttggttttttgtgtgCACGTGCGGACCGAGCGGCCGCAGGAACCCCTAGTGA TGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACC AAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGC GCGCAGCTGCCTGCAGG

72.	CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCGTCGGGCG ACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTGGCC AACTCCATCACTAGGGGTTCCTGCGGCCGCACGCGTAAAGCTTTCAGAGGCTTGAA TTATCACAGTGTAAATATCCATCTAGCAGAGCAGGTAATTTTCTCGTTACTCATCCTA AGCATTAGATACTCTGTGTGTTAGTTCTTTGCAGAAATAACCCATAGCAGCTGAACC ATTTTGGAACAAATTTTCCATCACCTTCCTTCCCTGTGTGGTTCAGGCCTTTGCAAAC CCTGAGTATCATGAATCTGCTGGTTCTCTACTGGCAAAGATGATGACGTTTTCTTGTT TGTTTTTGTTTTGCTTTAATCATGCCGTGAGAAAATCCTAAGGGAAAAAAATCTCATT ATCCTATTCAAAATACATTTAGGGTTATCTGGTCATCCCTAGCAGATTTTTATGTACC CAATGTTTATGTATCTCAAATTACACTCTGTTACCTTTCCCAGAGCAAGATGAAGAAC CTCTAAGAACCTCTCAAACAGCATCATTTTCACAACAAGCACTAGCAATGGAAAACA TTGTCACCACCACCAGCTAATCTTGTAGGGTCCATGGTATTTTCTGTAATGCCTTGA AACAGTCTGCCTCTCTCTTCTTGTCTGTCATTTTTATAGATGTCAGTGTGGGGCATCA GCAGTTGAAAACTCAGAATACCAAGCCAGTCCTTCCCTGTGACTGCTACATAGCTTT TGCCTGCAGGATAAGCCTCCATCACTGACGTAGTTGCTTTTTAACTTCTTTTTTTTTT TTAACTTGGAAAATCCCCCACCTCCTCCATTCCTTCACAAAACTTTCTGCCTGAATGA TTTCTAGTCTGAGGGCCATACACACATTTTTTTTTCTCCCTCTGCAGGTTTTTTTTTCT CTTCAAACTTCCGCATGCTGCCTTTTTTTAAAGTGTCACACTTTGGCCTTCCCCCGA CTCCTGCAACAGCTCAGAGAGCCTGGCTCTGACGTAGTTCAAAATAACGTGCGCCA GCCTCGCTGCCCGGCTGACCACAGCAACGAGAGCCACAAGCCCTCGACGCTGCTT CGATAACATGAAGCAATCACTCATAAAAATAGCAACCCACGTAGCCTGGCCATATAT GGAGCTGGCGAGGGTGGACGGGGATGCCCCTACGGACCCTCTTCGGAGAAAACAA ATCGCCGCTGAAATTTCCCCCACCCCTCCCATCACTACCTTTTACCCCTCCTCTGCC TTCCCCTCTCCTTAGATGACTCAACCACAGATTCCACTGAAAGGGGGTGGGGGTGG GGGTGGGGGGGGAATATATACACATACACACAAATTATACATATATTATACATGTATTA TAAAATATACACACACATACATATATACATACACACACATATACACATATGTACACAC ACACGCACACACACCAAAGAACATCAGGAATGCAGTTGCGGGATGAAGCCGTTTGC CCAAGACCGAGTGTTAAAATGGAGTCATAAGAGTCGCCCCGTGCGGGTGTTTATAG AAGGTGAAAACACGCAGGTTTGCAGGCCAGCGCACTGGGAACCGAGTCAAGCGCG CCGCAGCCCGGGCCCCGCCCCCGCCCCCGCCGTGCCCCGCCCCCACTTCCTCCC GCCCCTCGCTGGGCGGCTATTAAAAGCTGCTGACGTCAAAACGGACGGCCATCTTT GATGAGGGCAGAGCTCACGTTGCATTGAAGACGAAACCTCGGGGAGGTCAGGCGC TGTCTTTCCTTCCCTCCCTGCTCGGCGGCTCCACCACAGTTGCAACCTGCAGAGGC CCGGAGAACACAACCCTCCCGAGAAGCCCAGGTAAGAACGAATTCGCCACCATGG CCCCCATTGGCCTGAAGGCTGTGGTGGGAGAGAAGATCATGCATGATGTGATCAAG AAGGTGAAGAAGAAGGGAGAGTGGAAGGTGCTGGTGGTGGACCAGCTGAGCATGA GAATGCTGAGCAGCTGCTGCAAGATGACAGACATCATGACAGAGGGCATCACCATT GTGGAGGACATCAACAAGAGAAGAGAGCCCCTGCCCAGCCTGGAGGCTGTGTACC TGATCACCCCCTCTGAGAAGTCTGTGCACAGCCTGATCTCTGACTTCAAGGACCCC CCCACAGCCAAGTACAGAGCTGCCCATGTGTTCTTCACAGACAGCTGCCCTGATGC CCTGTTCAATGAGCTGGTGAAGAGCAGAGCTGCCAAGGTGATCAAGACCCTGACAG AGATCAACATTGCCTTCCTGCCCTATGAGAGCCAGGTGTACAGCCTGGACTCTGCT GACAGCTTCCAGAGCTTCTACAGCCCCCACAAGGCCCAGATGAAGAACCCCATCCT GGAGAGACTGGCTGAGCAGATTGCCACCCTGTGTGCCACCCTGAAGGAGTACCCT GCTGTGAGATACAGAGGAGAGTACAAGGACAATGCCCTGCTGGCCCAGCTGATCCA GGACAAGCTGGATGCCTACAAGGCTGATGACCCCACCATGGGAGAGGGCCCTGAC AAGGCCAGAAGCCAGCTGCTGATCCTGGACAGAGGCTTTGACCCCAGCAGCCCTG TGCTGCATGAGCTGACCTTCCAGGCCATGAGCTATGACCTGCTGCCCATTGAGAAT GATGTGTACAAGTATGAGACCTCTGGCATTGGAGAGGCCAGAGTGAAGGAGGTGCT GCTGGATGAGGATGATGACCTGTGGATTGCCCTGAGACACAAGCACATTGCTGAGG

	TGAGCCAGGAGGTGACCAGAAGCCTGAAGGACTTCAGCAGCAGCAAGAGAATGAA CACAGGAGAGAAGACCACCATGAGAGACCTGAGCCAGATGCTGAAGAAGATGCCC CAGTACCAGAAGGAGCTGAGCAAGTACAGCACCCACCTGCACCTGGCTGAGGACT GCATGAAGCACTACCAGGGCACAGTGGACAAGCTGTGCAGAGTGGAGCAGGACCT GGCCATGGGCACAGATGCTGAGGGAGAGAAGATCAAGGACCCCATGAGAGCCATT GTGCCCATCCTGCTGGATGCCAATGTGAGCACCTATGACAAGATCAGAATCATCCT GCTGTACATCTTCCTGAAGAATGGCATCACAGAGGAGAACCTGAACAAGCTGATCC AGCATGCCCAGATCCCCCCTGAGGACTCTGAGATCATCACCAACATGGCCCACCTG GGAGTGCCCATTGTGACAGACAGCACCCTGAGAAGAAGAAGCAAGCCTGAGAGAA AGGAGAGAATCTCTGAGCAGACCTACCAGCTGAGCAGATGGACCCCCATCATCAAG GACATCATGGAGGACACCATTGAGGACAAGCTGGACACCAAGCACTACCCCTACAT CAGCACCAGAAGCTCTGCCAGCTTCAGCACCACAGCTGTGTCTGCCAGATATGGCC ACTGGCACAAGAACAAGGCCCCTGGAGAGTACAGATCTGGCCCCAGACTGATCATC TTCATCCTGGGAGGAGTGAGCCTGAATGAGATGAGATGTGCCTATGAGGTGACCCA GGCCAATGGCAAGTGGGAGGTGCTGATTGGCAGCACCCACATCCTGACCCCCCAG AAGCTGCTGGACACCCTGAAGAAGCTGAACAAGACAGATGAGGAGATCAGCAGCTG ACTCGAGAATCAACCTCTGGATTACAAAATTTGTGAAAGATAGACTGGTATTCTTAAC TATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTATAGCCTTTGTATCTAGCTA TTGCTTCCCGTTAGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTGCTGTCTCT TTTAGAGGAGTTGTGGCCCGTTGTCAGGCAACGTGGCGTGGTGTGCACTGTGTTTG CTGACGCAACCCCCACTGGTTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGG ACTTTCGCTTTCCCCCTCCCTATTGCCACGGCGGAACTCATCGCCGCCTGCCTTGC CCGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGTGTTGTCG GGGAAATCATCGTCCTTTCCTTGGCTGCTCGCCTTAGTTGCCACCTGGATTCTGCG CGGGACGTCCTTCTGCTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCCTTCCC GCGGCCTGCTGCCGGCTCTGCGGCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGAC GAGTCGGATCTCCCTTTGGGCCGCCTCCCCGCACTAGTaataaaagatctttattttcattagatct gtgtgttggttttttgtgtgCACGTGCGGACCGAGCGGCCGCAGGAACCCCTAGTGATGGAGTT GGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTC GCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGC TGCCTGCAGG
73.	CCAGGTTCCCAGTCCTGGATAAAGTACCTTATAAATATTATCTTGTTGATCTTTAGAA ACTGCTCCTAAAGGAGTGTCGCAGAATCAAACGGCCCAGAGGCTAGGAGGAGGGG ATGTGGGTGAACACAGAACACCGCAGCTGATGATGCAGCTTAAAAGCAGAAGGGAG GGAGGTGCAGCCCGAGGCTGTCGGAGAAGCGGCCCAGACTGGCCCCAGGGCTCT GCAACAGGCTCCAGTTGTGCAGGGAGGGGACAAGCTTGTGATACCGCGTGAAGGA CTCAGGAGGTCCGGTGGAGGGGTGGCCTCTCTCCCGCTGGTTGGCTCCATTGCTA TTTCTGTCTCCTCGTTCTCGGTCTCTCCAGGCCGCTCCCTCTCCATCTGTCCTGATC GCCAGCCTCTCCCCCGCTCCTCTCCGCAGCGGTCGGCCCACCTGGAGCACTCCCC GCCGCCACGTGACCCGTGCGTAAATCGCAGTACTCTTCCCACCCCTGCGCTGGGC CAGCACCCGGCTCTGCGGAGGCTGCAGGCCGCGCATGCGCAGCTGTGGACGCAC CTGCGCGCCCCGGAAAATGGAGATTAAAAATAATGCCCATAGGTATGAGCTAAGAG GAGTGTAAACAAAACAAAATAAAAAGCAATGCCCAGTGATTGGAGGATTTGATGAGA TGATGCCCGCGAGGTGCTTGGCACGGAGTTTGACACAAGAACTCAGTGTTGGTGAA TGCACGAATGCAGGTACCCAGCGACAGGGAGGTGCTGTGGGTGGATTCACCCTGG CTTCGCTGCGGCTGGGAGTGGGCGCTGCTAGTAAGAGATCTCGCCTCCAAGCTCC TTCCGTGGGCAGGAAAAAACGGAAGCTCCCAGAAAGAGGAAAGACAGGACCCGAG CGGGGTTTCAGGCAGATGGAGCGCGTCGGTAGCCTGTGGCCAGGGATCCCAGCAC

	CGACGGGAAAGAGGAGGCCTGGGTACCCTGCGCCCCGGGCGCGCGCGGCGCGT GAGGTGAGGGGGAGGGCGCGGCTCCGCACCAGCCAGCGGCCGCCTGGCGCCCA GCCGCATCTCGGGGGGGCGGGGTTGAGCCTCCGGGCCGCAGTGCGATTGGCGGAG GCGAGTGGGTGACGCCAACGGCCGGCGCGAGGCCCCGCCCCCGGCTTGCCCCGC CCCCGCGCGCGCCGGCGGCGGGGCAGCCTCGCTCTGGCTCGCGCCGCGCCCCC GCGCCCAGTCCGCGCGTCAGTCGGTCCCTAGCGCGGCTGCGGGGCGGAGAGCTG CGGCTGGCCCAGCGCGCCCACCTGAGGAGGCGGCGGGGTCCGCAGGCGTCGCG GGACGAGGAGATCGGAGCCGGGAGACTCGCGCAGCGCCGAATTCGCCACCATGG CCCCCATTGGCCTGAAGGCTGTGGTGGGAGAGAAGATCATGCATGATGTGATCAAG AAGGTGAAGAAGAAGGGAGAGTGGAAGGTGCTGGTGGTGGACCAGCTGAGCATGA GAATGCTGAGCAGCTGCTGCAAGATGACAGACATCATGACAGAGGGCATCACCATT GTGGAGGACATCAACAAGAGAAGAGAGCCCCTGCCCAGCCTGGAGGCTGTGTACC TGATCACCCCCTCTGAGAAGTCTGTGCACAGCCTGATCTCTGACTTCAAGGACCCC CCCACAGCCAAGTACAGAGCTGCCCATGTGTTCTTCACAGACAGCTGCCCTGATGC CCTGTTCAATGAGCTGGTGAAGAGCAGAGCTGCCAAGGTGATCAAGACCCTGACAG AGATCAACATTGCCTTCCTGCCCTATGAGAGCCAGGTGTACAGCCTGGACTCTGCT GACAGCTTCCAGAGCTTCTACAGCCCCCACAAGGCCCAGATGAAGAACCCCATCCT GGAGAGACTGGCTGAGCAGATTGCCACCCTGTGTGCCACCCTGAAGGAGTACCCT GCTGTGAGATACAGAGGAGAGTACAAGGACAATGCCCTGCTGGCCCAGCTGATCCA GGACAAGCTGGATGCCTACAAGGCTGATGACCCCACCATGGGAGAGGGCCCTGAC AAGGCCAGAAGCCAGCTGCTGATCCTGGACAGAGGCTTTGACCCCAGCAGCCCTG TGCTGCATGAGCTGACCTTCCAGGCCATGAGCTATGACCTGCTGCCCATTGAGAAT GATGTGTACAAGTATGAGACCTCTGGCATTGGAGAGGCCAGAGTGAAGGAGGTGCT GCTGGATGAGGATGATGACCTGTGGATTGCCCTGAGACACAAGCACATTGCTGAGG TGAGCCAGGAGGTGACCAGAAGCCTGAAGGACTTCAGCAGCAGCAAGAGAATGAA CACAGGAGAGAAGACCACCATGAGAGACCTGAGCCAGATGCTGAAGAAGATGCCC CAGTACCAGAAGGAGCTGAGCAAGTACAGCACCCACCTGCACCTGGCTGAGGACT GCATGAAGCACTACCAGGGCACAGTGGACAAGCTGTGCAGAGTGGAGCAGGACCT GGCCATGGGCACAGATGCTGAGGGAGAGAAGATCAAGGACCCCATGAGAGCCATT GTGCCCATCCTGCTGGATGCCAATGTGAGCACCTATGACAAGATCAGAATCATCCT GCTGTACATCTTCCTGAAGAATGGCATCACAGAGGAGAACCTGAACAAGCTGATCC AGCATGCCCAGATCCCCCCTGAGGACTCTGAGATCATCACCAACATGGCCCACCTG GGAGTGCCCATTGTGACAGACAGCACCCTGAGAAGAAGAAGCAAGCCTGAGAGAA AGGAGAGAATCTCTGAGCAGACCTACCAGCTGAGCAGATGGACCCCCATCATCAAG GACATCATGGAGGACACCATTGAGGACAAGCTGGACACCAAGCACTACCCCTACAT CAGCACCAGAAGCTCTGCCAGCTTCAGCACCACAGCTGTGTCTGCCAGATATGGCC ACTGGCACAAGAACAAGGCCCCTGGAGAGTACAGATCTGGCCCCAGACTGATCATC TTCATCCTGGGAGGAGTGAGCCTGAATGAGATGAGATGTGCCTATGAGGTGACCCA GGCCAATGGCAAGTGGGAGGTGCTGATTGGCAGCACCCACATCCTGACCCCCCAG AAGCTGCTGGACACCCTGAAGAAGCTGAACAAGACAGATGAGGAGATCAGCAGCTG ACTCGAGAATCAACCTCTGGATTACAAAATTTGTGAAAGATAGACTGGTATTCTTAAC TATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTATAGCCTTTGTATCTAGCTA TTGCTTCCCGTTAGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTGCTGTCTCT TTTAGAGGAGTTGTGGCCCGTTGTCAGGCAACGTGGCGTGGTGTGCACTGTGTTTG CTGACGCAACCCCCACTGGTTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGG ACTTTCGCTTTCCCCCTCCCTATTGCCACGGCGGAACTCATCGCCGCCTGCCTTGC CCGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGTGTTGTCG GGGAAATCATCGTCCTTTCCTTGGCTGCTCGCCTTAGTTGCCACCTGGATTCTGCG CGGGACGTCCTTCTGCTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCCTTCCC GCGGCCTGCTGCCGGCTCTGCGGCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGAC

	GAGTCGGATCTCCCTTTGGGCCGCCTCCCCGCACTAGTaataaaagatctttattttcattagatct gtgtgttggttttttgtgtg
74.	AAAGCTTTCAGAGGCTTGAATTATCACAGTGTAAATATCCATCTAGCAGAGCAGGTA ATTTTCTCGTTACTCATCCTAAGCATTAGATACTCTGTGTGTTAGTTCTTTGCAGAAA TAACCCATAGCAGCTGAACCATTTTGGAACAAATTTTCCATCACCTTCCTTCCCTGTG TGGTTCAGGCCTTTGCAAACCCTGAGTATCATGAATCTGCTGGTTCTCTACTGGCAA AGATGATGACGTTTTCTTGTTTGTTTTTGTTTTGCTTTAATCATGCCGTGAGAAAATC CTAAGGGAAAAAAATCTCATTATCCTATTCAAAATACATTTAGGGTTATCTGGTCATC CCTAGCAGATTTTTATGTACCCAATGTTTATGTATCTCAAATTACACTCTGTTACCTTT CCCAGAGCAAGATGAAGAACCTCTAAGAACCTCTCAAACAGCATCATTTTCACAACA AGCACTAGCAATGGAAAACATTGTCACCACCACCAGCTAATCTTGTAGGGTCCATGG TATTTTCTGTAATGCCTTGAAACAGTCTGCCTCTCTCTTCTTGTCTGTCATTTTTATAG ATGTCAGTGTGGGGCATCAGCAGTTGAAAACTCAGAATACCAAGCCAGTCCTTCCC TGTGACTGCTACATAGCTTTTGCCTGCAGGATAAGCCTCCATCACTGACGTAGTTGC TTTTTAACTTCTTTTTTTTTTTTAACTTGGAAAATCCCCCACCTCCTCCATTCCTTCAC AAAACTTTCTGCCTGAATGATTTCTAGTCTGAGGGCCATACACACATTTTTTTTTCTC CCTCTGCAGGTTTTTTTTTCTCTTCAAACTTCCGCATGCTGCCTTTTTTTAAAGTGTC ACACTTTGGCCTTCCCCCGACTCCTGCAACAGCTCAGAGAGCCTGGCTCTGACGTA GTTCAAAATAACGTGCGCCAGCCTCGCTGCCCGGCTGACCACAGCAACGAGAGCC ACAAGCCCTCGACGCTGCTTCGATAACATGAAGCAATCACTCATAAAAATAGCAACC CACGTAGCCTGGCCATATATGGAGCTGGCGAGGGTGGACGGGGATGCCCCTACGG ACCCTCTTCGGAGAAAACAAATCGCCGCTGAAATTTCCCCCACCCCTCCCATCACTA CCTTTTACCCCTCCTCTGCCTTCCCCTCTCCTTAGATGACTCAACCACAGATTCCAC TGAAAGGGGGTGGGGGTGGGGGTGGGGGGGAATATATACACATACACACAAATTA TACATATATTATACATGTATTATAAAATATACACACACATACATATATACATACACACA CATATACACATATGTACACACACACGCACACACACCAAAGAACATCAGGAATGCAGT TGCGGGATGAAGCCGTTTGCCCAAGACCGAGTGTTAAAATGGAGTCATAAGAGTCG CCCCGTGCGGGTGTTTATAGAAGGTGAAAACACGCAGGTTTGCAGGCCAGCGCACT GGGAACCGAGTCAAGCGCGCCGCAGCCCGGGCCCCGCCCCCGCCCCCGCCGTGC CCCGCCCCCACTTCCTCCCGCCCCTCGCTGGGCGGCTATTAAAAGCTGCTGACGTC AAAACGGACGGCCATCTTTGATGAGGGCAGAGCTCACGTTGCATTGAAGACGAAAC CTCGGGGAGGTCAGGCGCTGTCTTTCCTTCCCTCCCTGCTCGGCGGCTCCACCAC AGTTGCAACCTGCAGAGGCCCGGAGAACACAACCCTCCCGAGAAGCCCAGGTAAG AACGAATTCGCCACCATGGCCCCCATTGGCCTGAAGGCTGTGGTGGGAGAGAAGA TCATGCATGATGTGATCAAGAAGGTGAAGAAGAAGGGAGAGTGGAAGGTGCTGGTG GTGGACCAGCTGAGCATGAGAATGCTGAGCAGCTGCTGCAAGATGACAGACATCAT GACAGAGGGCATCACCATTGTGGAGGACATCAACAAGAGAAGAGAGCCCCTGCCC AGCCTGGAGGCTGTGTACCTGATCACCCCCTCTGAGAAGTCTGTGCACAGCCTGAT CTCTGACTTCAAGGACCCCCCCACAGCCAAGTACAGAGCTGCCCATGTGTTCTTCA CAGACAGCTGCCCTGATGCCCTGTTCAATGAGCTGGTGAAGAGCAGAGCTGCCAAG GTGATCAAGACCCTGACAGAGATCAACATTGCCTTCCTGCCCTATGAGAGCCAGGT GTACAGCCTGGACTCTGCTGACAGCTTCCAGAGCTTCTACAGCCCCCACAAGGCCC AGATGAAGAACCCCATCCTGGAGAGACTGGCTGAGCAGATTGCCACCCTGTGTGCC ACCCTGAAGGAGTACCCTGCTGTGAGATACAGAGGAGAGTACAAGGACAATGCCCT GCTGGCCCAGCTGATCCAGGACAAGCTGGATGCCTACAAGGCTGATGACCCCACC ATGGGAGAGGGCCCTGACAAGGCCAGAAGCCAGCTGCTGATCCTGGACAGAGGCT TTGACCCCAGCAGCCCTGTGCTGCATGAGCTGACCTTCCAGGCCATGAGCTATGAC CTGCTGCCCATTGAGAATGATGTGTACAAGTATGAGACCTCTGGCATTGGAGAGGC CAGAGTGAAGGAGGTGCTGCTGGATGAGGATGATGACCTGTGGATTGCCCTGAGA

	CACAAGCACATTGCTGAGGTGAGCCAGGAGGTGACCAGAAGCCTGAAGGACTTCA GCAGCAGCAAGAGAATGAACACAGGAGAGAAGACCACCATGAGAGACCTGAGCCA GATGCTGAAGAAGATGCCCCAGTACCAGAAGGAGCTGAGCAAGTACAGCACCCAC CTGCACCTGGCTGAGGACTGCATGAAGCACTACCAGGGCACAGTGGACAAGCTGT GCAGAGTGGAGCAGGACCTGGCCATGGGCACAGATGCTGAGGGAGAGAAGATCAA GGACCCCATGAGAGCCATTGTGCCCATCCTGCTGGATGCCAATGTGAGCACCTATG ACAAGATCAGAATCATCCTGCTGTACATCTTCCTGAAGAATGGCATCACAGAGGAGA ACCTGAACAAGCTGATCCAGCATGCCCAGATCCCCCCTGAGGACTCTGAGATCATC ACCAACATGGCCCACCTGGGAGTGCCCATTGTGACAGACAGCACCCTGAGAAGAA GAAGCAAGCCTGAGAGAAAGGAGAGAATCTCTGAGCAGACCTACCAGCTGAGCAG ATGGACCCCCATCATCAAGGACATCATGGAGGACACCATTGAGGACAAGCTGGACA CCAAGCACTACCCCTACATCAGCACCAGAAGCTCTGCCAGCTTCAGCACCACAGCT GTGTCTGCCAGATATGGCCACTGGCACAAGAACAAGGCCCCTGGAGAGTACAGATC TGGCCCCAGACTGATCATCTTCATCCTGGGAGGAGTGAGCCTGAATGAGATGAGAT GTGCCTATGAGGTGACCCAGGCCAATGGCAAGTGGGAGGTGCTGATTGGCAGCAC CCACATCCTGACCCCCCAGAAGCTGCTGGACACCCTGAAGAAGCTGAACAAGACAG ATGAGGAGATCAGCAGCTGACTCGAGAATCAACCTCTGGATTACAAAATTTGTGAAA GATAGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTT ATAGCCTTTGTATCTAGCTATTGCTTCCCGTTAGGCTTTCATTTTCTCCTCCTTGTAT AAATCCTGGTTGCTGTCTCTTTTAGAGGAGTTGTGGCCCGTTGTCAGGCAACGTGG CGTGGTGTGCACTGTGTTTGCTGACGCAACCCCCACTGGTTGGGGCATTGCCACCA CCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCCTATTGCCACGGCGGAA CTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTG ACAATTCCGTGGTGTTGTCGGGGAAATCATCGTCCTTTCCTTGGCTGCTCGCCTTAG TTGCCACCTGGATTCTGCGCGGGACGTCCTTCTGCTACGTCCCTTCGGCCCTCAAT CCAGCGGACCTTCCTTCCCGCGGCCTGCTGCCGGCTCTGCGGCCTCTTCCGCGTC TTCGCCTTCGCCCTCAGACGAGTCGGATCTCCCTTTGGGCCGCCTCCCCGCACTAG Taataaaagatctttattttcattagatctgtgtgttggtttttgtgtg
75.	CCAGGTTCCCAGTCCTGGATAAAGTACCTTATAAATATTATCTTGTTGATCTTTAGAA ACTGCTCCTAAAGGAGTGTCGCAGAATCAAACGGCCCAGAGGCTAGGAGGAGGGG ATGTGGGTGAACACAGAACACCGCAGCTGATGATGCAGCTTAAAAGCAGAAGGGAG GGAGGTGCAGCCCGAGGCTGTCGGAGAAGCGGCCCAGACTGGCCCCAGGGCTCT GCAACAGGCTCCAGTTGTGCAGGGAGGGGACAAGCTTGTGATACCGCGTGAAGGA CTCAGGAGGTCCGGTGGAGGGGTGGCCTCTCTCCCGCTGGTTGGCTCCATTGCTA TTTCTGTCTCCTCGTTCTCGGTCTCTCCAGGCCGCTCCCTCTCCATCTGTCCTGATC GCCAGCCTCTCCCCCGCTCCTCTCCGCAGCGGTCGGCCCACCTGGAGCACTCCCC GCCGCCACGTGACCCGTGCGTAAATCGCAGTACTCTTCCCACCCCTGCGCTGGGC CAGCACCCGGCTCTGCGGAGGCTGCAGGCCGCGCATGCGCAGCTGTGGACGCAC CTGCGCGCCCCGGAAAATGGAGATTAAAAATAATGCCCATAGGTATGAGCTAAGAG GAGTGTAAACAAAACAAAATAAAAAGCAATGCCCAGTGATTGGAGGATTTGATGAGA TGATGCCCGCGAGGTGCTTGGCACGGAGTTTGACACAAGAACTCAGTGTTGGTGAA TGCACGAATGCAGGTACCCAGCGACAGGGAGGTGCTGTGGGTGGATTCACCCTGG CTTCGCTGCGGCTGGGAGTGGGCGCTGCTAGTAAGAGATCTCGCCTCCAAGCTCC TTCCGTGGGCAGGAAAAAACGGAAGCTCCCAGAAAGAGGAAAGACAGGACCCGAG CGGGGTTTCAGGCAGATGGAGCGCGTCGGTAGCCTGTGGCCAGGGATCCCAGCAC CGACGGGAAAGAGGAGGCCTGGGTACCCTGCGCCCCGGGCGCGCGCGGCGCGT GAGGTGAGGGGGAGGGCGCGGCTCCGCACCAGCCAGCGGCCGCCTGGCGCCCA GCCGCATCTCGGGGGGCGGGGTTGAGCCTCCGGGCCGCAGTGCGATTGGCGGAG GCGAGTGGGTGACGCCAACGGCCGGCGCGAGGCCCCGCCCCCGGCTTGCCCCGC

	CCCCGCGCGCGCCGGCGGCGGGGCAGCCTCGCTCTGGCTCGCGCCGCGCCCCC GCGCCCAGTCCGCGCGTCAGTCGGTCCCTAGCGCGGCTGCGGGGCGGAGAGCTG CGGCTGGCCCAGCGCGCCCACCTGAGGAGGCGGCGGGGTCCGCAGGCGTCGCG GGACGAGGAGATCGGAGCCGGGAGACTCGCGCAGCGCCGAATTCGCCACCATGG CCCCCATTGGCCTGAAGGCTGTGGTGGGAGAGAAGATCATGCATGATGTGATCAAG AAGGTGAAGAAGAAGGGAGAGTGGAAGGTGCTGGTGGTGGACCAGCTGAGCATGA GAATGCTGAGCAGCTGCTGCAAGATGACAGACATCATGACAGAGGGCATCACCATT GTGGAGGACATCAACAAGAGAAGAGAGCCCCTGCCCAGCCTGGAGGCTGTGTACC TGATCACCCCCTCTGAGAAGTCTGTGCACAGCCTGATCTCTGACTTCAAGGACCCC CCCACAGCCAAGTACAGAGCTGCCCATGTGTTCTTCACAGACAGCTGCCCTGATGC CCTGTTCAATGAGCTGGTGAAGAGCAGAGCTGCCAAGGTGATCAAGACCCTGACAG AGATCAACATTGCCTTCCTGCCCTATGAGAGCCAGGTGTACAGCCTGGACTCTGCT GACAGCTTCCAGAGCTTCTACAGCCCCCACAAGGCCCAGATGAAGAACCCCATCCT GGAGAGACTGGCTGAGCAGATTGCCACCCTGTGTGCCACCCTGAAGGAGTACCCT GCTGTGAGATACAGAGGAGAGTACAAGGACAATGCCCTGCTGGCCCAGCTGATCCA GGACAAGCTGGATGCCTACAAGGCTGATGACCCCACCATGGGAGAGGGCCCTGAC AAGGCCAGAAGCCAGCTGCTGATCCTGGACAGAGGCTTTGACCCCAGCAGCCCTG TGCTGCATGAGCTGACCTTCCAGGCCATGAGCTATGACCTGCTGCCCATTGAGAAT GATGTGTACAAGTATGAGACCTCTGGCATTGGAGAGGCCAGAGTGAAGGAGGTGCT GCTGGATGAGGATGATGACCTGTGGATTGCCCTGAGACACAAGCACATTGCTGAGG TGAGCCAGGAGGTGACCAGAAGCCTGAAGGACTTCAGCAGCAGCAAGAGAATGAA CACAGGAGAGAAGACCACCATGAGAGACCTGAGCCAGATGCTGAAGAAGATGCCC CAGTACCAGAAGGAGCTGAGCAAGTACAGCACCCACCTGCACCTGGCTGAGGACT GCATGAAGCACTACCAGGGCACAGTGGACAAGCTGTGCAGAGTGGAGCAGGACCT GGCCATGGGCACAGATGCTGAGGGAGAGAAGATCAAGGACCCCATGAGAGCCATT GTGCCCATCCTGCTGGATGCCAATGTGAGCACCTATGACAAGATCAGAATCATCCT GCTGTACATCTTCCTGAAGAATGGCATCACAGAGGAGAACCTGAACAAGCTGATCC AGCATGCCCAGATCCCCCCTGAGGACTCTGAGATCATCACCAACATGGCCCACCTG GGAGTGCCCATTGTGACAGACAGCACCCTGAGAAGAAGAAGCAAGCCTGAGAGAA AGGAGAGAATCTCTGAGCAGACCTACCAGCTGAGCAGATGGACCCCCATCATCAAG GACATCATGGAGGACACCATTGAGGACAAGCTGGACACCAAGCACTACCCCTACAT CAGCACCAGAAGCTCTGCCAGCTTCAGCACCACAGCTGTGTCTGCCAGATATGGCC ACTGGCACAAGAACAAGGCCCCTGGAGAGTACAGATCTGGCCCCAGACTGATCATC TTCATCCTGGGAGGAGTGAGCCTGAATGAGATGAGATGTGCCTATGAGGTGACCCA GGCCAATGGCAAGTGGGAGGTGCTGATTGGCAGCACCCACATCCTGACCCCCCAG AAGCTGCTGGACACCCTGAAGAAGCTGAACAAGACAGATGAGGAGATCAGCAGCTG ACTCGAGCACAAATTCGGTTCTACAGGGTAGGCGAGACCTCCACCCCTCCTCACAA ATTCGGTTCTACAGGGTATTGATAAGTCGGGGACAATCTCACAAATTCGGTTCTACA GGGTACCGTCATGAACGCACCAGTCCCACAAATTCGGTTCTACAGGGTACCTCGAG AATCAACCTCTGGATTACAAAATTTGTGAAAGATAGACTGGTATTCTTAACTATGTTG CTCCTTTTACGCTATGTGGATACGCTGCTTTATAGCCTTTGTATCTAGCTATTGCTTC CCGTTAGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTGCTGTCTCTTTTAGAG GAGTTGTGGCCCGTTGTCAGGCAACGTGGCGTGGTGTGCACTGTGTTTGCTGACG CAACCCCCACTGGTTGGGGCATTGCCACCACCTGTCAGCTCCTTTCCGGGACTTTC GCTTTCCCCCTCCCTATTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTG CTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGTGTTGTCGGGGAAA TCATCGTCCTTTCCTTGGCTGCTCGCCTTAGTTGCCACCTGGATTCTGCGCGGGAC GTCCTTCTGCTACGTCCCTTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCC TGCTGCCGGCTCTGCGGCCTCTTCCGCGTCTTCGCCTTCGCCCTCAGACGAGTCG GATCTCCCTTTGGGCCGCCTCCCCGCACTAGTTCGAGaataaaagatctttattttcattagatctgt

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77.	TTGAGTACGTTCTGGATTACTCATAAGACCTTTTTTTTTTCCTTCCGGGCGCAAAACC GTGAGCTGGATTTATAATCGCCCTATAAAGCTCCAGAGGCGGTCAGGCACCTGCAG AGGAGCCCCGCCGCTCCGCCGACTAGCTGCCCCCGCGAGCAACGGCCTCGTGATT TCCCCGCCGATCCGGTCCCCGCCTCCCCACTCTGCCCCCGCCTACCCCGGAGCCG TGCAGCCGCCTCTCCGAATCTCTCTCTTCTCCTGGCGCTCGCGTGCGAGAGGGAAC TAGCGAGAACGAGGAAGCAGCTGGAGGTGACGCCGGGCAGATTACGCCTGTCAGG GCCGAGCCGGAATTCGCCACCATGGCCCCCATTGGCCTGAAGGCTGTGGTGGGAG AGAAGATCATGCATGATGTGATCAAGAAGGTGAAGAAGAAGGGAGAGTGGAAGGTG CTGGTGGTGGACCAGCTGAGCATGAGAATGCTGAGCAGCTGCTGCAAGATGACAG ACATCATGACAGAGGGCATCACCATTGTGGAGGACATCAACAAGAGAAGAGAGCCC CTGCCCAGCCTGGAGGCTGTGTACCTGATCACCCCCTCTGAGAAGTCTGTGCACAG CCTGATCTCTGACTTCAAGGACCCCCCCACAGCCAAGTACAGAGCTGCCCATGTGT TCTTCACAGACAGCTGCCCTGATGCCCTGTTCAATGAGCTGGTGAAGAGCAGAGCT GCCAAGGTGATCAAGACCCTGACAGAGATCAACATTGCCTTCCTGCCCTATGAGAG CCAGGTGTACAGCCTGGACTCTGCTGACAGCTTCCAGAGCTTCTACAGCCCCCACA AGGCCCAGATGAAGAACCCCATCCTGGAGAGACTGGCTGAGCAGATTGCCACCCT GTGTGCCACCCTGAAGGAGTACCCTGCTGTGAGATACAGAGGAGAGTACAAGGACA ATGCCCTGCTGGCCCAGCTGATCCAGGACAAGCTGGATGCCTACAAGGCTGATGAC CCCACCATGGGAGAGGGCCCTGACAAGGCCAGAAGCCAGCTGCTGATCCTGGACA GAGGCTTTGACCCCAGCAGCCCTGTGCTGCATGAGCTGACCTTCCAGGCCATGAG CTATGACCTGCTGCCCATTGAGAATGATGTGTACAAGTATGAGACCTCTGGCATTGG AGAGGCCAGAGTGAAGGAGGTGCTGCTGGATGAGGATGATGACCTGTGGATTGCC CTGAGACACAAGCACATTGCTGAGGTGAGCCAGGAGGTGACCAGAAGCCTGAAGG ACTTCAGCAGCAGCAAGAGAATGAACACAGGAGAGAAGACCACCATGAGAGACCTG AGCCAGATGCTGAAGAAGATGCCCCAGTACCAGAAGGAGCTGAGCAAGTACAGCA CCCACCTGCACCTGGCTGAGGACTGCATGAAGCACTACCAGGGCACAGTGGACAA GCTGTGCAGAGTGGAGCAGGACCTGGCCATGGGCACAGATGCTGAGGGAGAGAAG ATCAAGGACCCCATGAGAGCCATTGTGCCCATCCTGCTGGATGCCAATGTGAGCAC CTATGACAAGATCAGAATCATCCTGCTGTACATCTTCCTGAAGAATGGCATCACAGA GGAGAACCTGAACAAGCTGATCCAGCATGCCCAGATCCCCCCTGAGGACTCTGAGA TCATCACCAACATGGCCCACCTGGGAGTGCCCATTGTGACAGACAGCACCCTGAGA AGAAGAAGCAAGCCTGAGAGAAAGGAGAGAATCTCTGAGCAGACCTACCAGCTGAG CAGATGGACCCCCATCATCAAGGACATCATGGAGGACACCATTGAGGACAAGCTGG ACACCAAGCACTACCCCTACATCAGCACCAGAAGCTCTGCCAGCTTCAGCACCACA GCTGTGTCTGCCAGATATGGCCACTGGCACAAGAACAAGGCCCCTGGAGAGTACA GATCTGGCCCCAGACTGATCATCTTCATCCTGGGAGGAGTGAGCCTGAATGAGATG AGATGTGCCTATGAGGTGACCCAGGCCAATGGCAAGTGGGAGGTGCTGATTGGCA

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109.	ggaggaagccatcaactaaactacaatgactgtaagatacaaaattgggaatggtaacat attttgaagttctgttgacataaagaatcatgatattaatgcccatggaaatgaaagggc gatcaacactatggtttgaaaaggggaaattgtagagcacagatgtgttcgtgtggcag tgtgctgtctctagcaatactcagagaagagagagaacaatgaaattctgattggcccca gtgtgagcccagatgaggttcagctgccaactttctctttcacatcttatgaaagtcatt taagcacaactaacttttttttttttttttttttttgagacagagtcttgctctgttgc ccaggacagagtgcagtagtgactcaatctcggctcactgcagcctccacctcctaggct caaacggtcctcctgcatcagcctcccaagtagctggaattacaggagtggcccaccatg cccagctaatttttgtatttttaatagatacgggggtttcaccatatcacccaggctggt ctcgaactcctggcctcaagtgatccacctgcctcggcctcccaaagtgctgggattata ggcgtcagccactatgcccaacccgaccaacctttttaaaataaatatttaaaaaattg gtatttcacatatatactagtatttacatttatccacacaaaacggacgggcctccgctg aaccagtgaggccccagacgtgcgcataaataaccccctgcgtgctgcaccacctggggag agggggaggaccacggtaaatggagcgagcgcatagcaaaagggacgcggggtcctttttctctgccggtggcactgggtagctgtgg ccaggtgtggtactttgatggggcccagggctggagctcaaggaagcgtcgcagggtcacagatctgggggaaccccggggaaaag cactgaggcaaaaccgccgctcgtctcctacaatatatgggaggggggaggttgagtacgttctggattactcataagacctttttttttccttc cgggcgcaaaaccgtgagctggatttataatcgccctataaagctccagaggcggtcaggcacctgcagaggagccccgccgctccg ccgactagctgcccccgcgagcaacggcctcgtgatttccccgccgatccggtccccgcctccccactctgcccccgcctaccccggag ccgtgcagccgcctctccgaatctctctcttctcctggcgctcgcgtgcgagagggaactagcgagaacgaggaagcagctggaggtg acgccgggcagattacgcctgtcagggccgagccgagcggatcgctgggcgctgtgcagaggaaaggcgggagtgcccggctcgct gtcgcagagccgaggtgggtaagctagcgaccacctggacttcccagcgcccaaccgtggcttttcagccaggtcctctcctcccgcgg cttctcaaccaaccccatcccagccgccggccacccaacctcccgaaatgagtgcttcctgccccagcagccgaaggcgctactaggaa cggtaacctgttacttttccaggggccgtagtcgacccgctgcccgagttgctgtgcgactgcgcgcgcggggctagagtgcaaggtgac tgtggttcttctctggccaagtccgagggagaacgtaaagatatgggccttttccccctctcaccttgtctcaccaaagtccctagtccccgg agcagttagcctctttctttccagggaattagccagacacaacaacgggaaccagacaccgaaccagacatgcccgccccgtgcgcc ctccccgctcgctgcctttcctccctcttgtctctccagagccggatcttcaaggggagcctccgtgcccccggctgctcagtccctccggtgt gcaggaccccggaagtcctccccgcacagctctcgcttctctttgcagcctgtttctgcgccggaccagtcgaggactctggacagtaga ggccccgggacgaccgagctg
110.	tcaacaggggacacttgggaaagaaggatggggacagagccgagaggactgttacacat

	tagagaaacatcagtgactgtgccagctttggggtagactgcacaaaagccctgaggcag cacaggcaggatccagtctgctggtcccaggaagctaaccgtctcagacagagcacaaag caccgagacatgtgccacaaggcttgtgtagagaggtcagaggacagcgtacaggtccca gagatcaaactcaacctcaccaggcttggcagcaagcctttaccaacccacccccacccc acccaccctgcacgcgcccctctcccctcccatggtctcccatggctatctcacttggc cctaaaatgtttaaggatgacactggctgctgagtggaaatgagacagcagaagtcaaca gtagattttaggaaagccagagaaaaaggcttgtgctgtttttagaaagccaagggacaa gctaagatagggcccaagtaatgctagtatttacatttatccacacaaaacggacgggcc tccgctgaaccagtgaggccccagacgtgcgcataaataacccctgcgtgctgcaccacc tggggagaggggaggaccacggtaaatggagcgagcgcatagcaaaagggacgcggggtccttttctctgccggtggcactgggt agctgtggccaggtgtggtactttgatggggcccagggctggagctcaaggaagcgtcgcagggtcacagatctgggggaaccccgg ggaaaagcactgaggcaaaaccgccgctcgtctcctacaatatatgggaggggggaggttgagtacgttctggattactcataagacctttt ttttttccttccgggcgcaaaaccgtgagctggatttataatcgccctataaagctccagaggcggtcaggcacctgcagaggagccccg ccgctc cgccgactagctgcccccgcgagcaacggcctcgtgatttccccgccgatccggtccccg cctccccactctgcccccgcctaccccggagccgtgcagccgcctctccgaatctctctc ttctcctggcgctcgcgtgcgagagggaactagcgagaacgaggaagcagctggaggtga cgccgggcagattacgcctgtcagggccgagccgagcggatcgctgggcgctgtgcagag gaaaggcgggagtgcccggctcgctgtcgcagagccgaggtgggtaagctagcgaccacc tggacttcccagcgcccaaccgtggcttttcagccaggtcctctcctcccgcggcttctc aaccaaccccatcccagcgccggccacccaacctcccgaaatgagtgcttcctgccccag cagccgaaggcgctactaggaacggtaacctgttacttttccaggggccgtagtcgaccc gctgcccgagttgctgtgcgactgcgcgcgcggggctagagtgcaaggtgactgtggttc ttctctggccaagtccgagggagaacgtaaagatatgggccttttcccccctctcacctt gtctcaccaaagtccctagtccccggagcagttagcctctttctttccagggaattagcc agacacaacaacgggaaccagacaccgaaccagacatgcccgccccgtgcgccctccccg ctcgctgcctttcctccctcttgtctctccagagccggatcttcaaggggagcctccgtg cccccggctgctcagtccctccggtgtgcaggaccccggaagtcctccccgcacagctct cgcttctctttgcagcctgtttctgcgccggaccagtcgaggactctggacagtagaggc cccgggacgaccgagctg

CLAIMS

WHAT IS CLAIMED IS:

1. A nucleic acid comprising a regulatory element comprising a nucleic acid sequence having at least 80% identity to a sequence of SEQ ID NO: 10-13 or 16-19.

2. The nucleic acid of claim 1, wherein the regulatory element comprises a nucleic acid sequence having at least 85% identity to a sequence of SEQ ID NO: 10-13 or 16-19.

3. The nucleic acid of claim 1, wherein the regulatory element comprises a nucleic acid sequence having at least 90% identity to a sequence of SEQ ID NO: 10-13 or 16-19.

4. The nucleic acid of claim 1, wherein the regulatory element comprises a nucleic acid sequence having at least 95% identity to a sequence of SEQ ID NO: 10-13 or 16-19.

5. The nucleic acid of claim 1, wherein the regulatory element comprises a nucleic acid sequence having at least 98% identity to a sequence of SEQ ID NO: 10-13 or 16-19.

6. The nucleic acid of claim 1, wherein the regulatory element comprises a nucleic acid sequence having the sequence of SEQ ID NO: 10-13 or 16-19.

7. The nucleic acid of any one of claims 1-6, wherein the regulatory element is a promoter.

8. The nucleic acid of claim 7, wherein the regulatory element comprises a nucleic acid sequence of SEQ ID NO: 10.

9. The nucleic acid of claim 7, wherein the regulatory element comprises a nucleic acid sequence of SEQ ID NO: 12.

10. The nucleic acid of any one of claims 1-6, wherein the regulatory element is an enhancer.

11. The nucleic acid of claim 10, wherein the regulatory element comprises a nucleic acid sequence of SEQ ID NO: 16.

12. The nucleic acid of claim 10, wherein the regulatory element comprises a nucleic acid sequence of SEQ ID NO: 18.

13. The nucleic acid of claim 10, wherein the regulatory element comprises a nucleic acid sequence of SEQ ID NO: 19.

14. The nucleic acid of any one of claims 10-13, wherein the enhancer is operably linked to a promoter.

15. The nucleic acid of claim 14, wherein the regulatory element comprises a nucleic acid sequence of SEQ ID NO: 11.

16. The nucleic acid of claim 14, wherein the regulatory element comprises a nucleic acid sequence of SEQ ID NO: 13.

17. The nucleic acid of any one of claims 1-16, wherein the regulatory element is operably linked to a transgene.

18. The nucleic acid of claim 17, wherein the transgene is a therapeutic transgene.

19. The nucleic acid of claim 17, wherein the transgene encodes a protein associated with a neurological disease or disorder.

20. The nucleic acid of claim 19, wherein the transgene encodes STXBP1 or a functional fragment thereof.

21. The nucleic acid of claim 17, wherein the transgene comprises the nucleic acid sequence of any one of SEQ ID NOS: 1-4.

22. The nucleic acid of claim 21, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 1.

23. The nucleic acid of claim 21, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 2.

24. The nucleic acid of claim 21, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 3.

25. The nucleic acid of claim 21, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 4.

26. The nucleic acid of any one of claims 1-25, further comprising a regulatory element comprising the nucleic acid sequence of SEQ ID NO: 22.

27. The nucleic acid of any one of claims 1-26, further comprising a nucleic acid sequence encoding a de-targeting element.

28. The nucleic acid of claim 27, wherein the de-targeting element reduces expression of the transgene in excitatory neurons.

29. The nucleic acid of claim 28, wherein the de-targeting element comprises a nucleic acid sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to a sequence of SEQ ID NOS: 23-25.

30. The nucleic acid of claim 29, wherein the de-targeting element comprises a nucleic acid sequence of any one or more of SEQ ID NOS: 23-25 or combinations thereof.

31. The nucleic acid of claim 27, wherein the nucleic acid sequence encoding a de-targeting element comprises the nucleic acid sequence of any one or more of SEQ ID NOS: 26-28

32. The nucleic acid of claim 31, the nucleic acid sequence encoding a de-targeting element comprises the nucleic acid sequence of SEQ ID NO: 28.

33. The nucleic acid of claim 27, wherein the de-targeting element reduces expression of

the transgene in liver cells.

34. The nucleic acid of claim 33, wherein the de-targeting element comprises a nucleic acid sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to a sequence of SEQ ID NOS: 49-66.

35. The nucleic acid of claim 34, wherein the de-targeting element comprises a nucleic acid sequence of any one or more of SEQ ID NOS: 49-66 or combinations thereof.

36. The nucleic acid of claim 27, wherein the de-targeting element reduces expression of the transgene in Dorsal Root Ganglion cells.

37. The nucleic acid of claim 36, wherein the de-targeting element comprises a nucleic acid sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to a sequence of SEQ ID NOS: 29-48.

38. The nucleic acid of claim 37, wherein the de-targeting element comprises a nucleic acid sequence of any one or more of SEQ ID NOS: 29-48 or combinations thereof.

39. The nucleic acid of claim 27, wherein the de-targeting element reduces expression of the transgene in two or more tissues.

40. The nucleic acid of claim 27, wherein the de-targeting element comprises the sequence of SEQ ID NO: 67.

41. The nucleic acid of anyone of claims 1-40, wherein the nucleic acid comprises a poly-adenylation sequence.

42. The nucleic acid of any one of claims 1-41, comprising the nucleic acid sequence of SEQ ID NO: 11 or SEQ ID NO: 13

43. An expression vector comprising the nucleic acid of any one of claims 1-42.

44. The expression vector of claim 43, which is viral vector.

45. The expression vector of claim 44, which is an adeno-associated viral (AAV) vector.

46. The expression vector of claim 45, wherein the AAV vector is AAV1, AAV8, AAV9, scAAV1, scAAV8, or scAAV9.

47. The expression vector of claim 45, wherein the AAV vector is an AAV9 vector comprising AAV2 inverted terminal repeats (ITRs).

48. A composition comprising the nucleic acid of any one of claims 1-42 or the expression vector of any one of claims 43-47 and a physiologically acceptable carrier.

49. A method of delivering a transgene to a subject, the method comprising administering to the subject an expression vector of any one of claims 43-47 comprising a transgene.

50. A method of treating a neurological disease or disorder, the method comprising administering to a subject in need thereof the expression vector of any one of claims 35-47 comprising a transgene encoding a protein associated with a neurological disease or disorder or a transcription factor that increases expression of a gene associated with a neural disease or disorder.

51. The method of claim 50, wherein the neurological disease or disorder is epilepsy.

52. The method of claim 51, wherein the neurological disease or disorder is epileptic encephalopathy.

53. The method of claim 50, wherein the neurological disease or disorder is refractory epilepsy.

54. The method of claim 50, wherein the neurological disease or disorder is Benign familial neonatal epilepsy (BFNE), Early myoclonic encephalopathy (EME), Ohtahara syndrome, Epilepsy of infancy with migrating focal seizures, infantile spasms (West syndrome), Myoclonic epilepsy in infancy (MEI), Benign infantile epilepsy, Benign familial infantile epilepsy, Dravet syndrome, Myoclonic encephalopathy in nonprogressive disorders, Early onset epilepsy, Febrile seizures, Febrile seizures plus (FS+), Panayiotopoulos syndrome, Epilepsy with myoclonic atonic (previously astatic) seizures, Doose syndrome, Benign epilepsy with centrotemporal spikes (BECTS), frontal lobe epilepsy (e.g., Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)), Late onset childhood occipital epilepsy (Gastaut type), Epilepsy with myoclonic absences, Lennox-Gastaut syndrome, Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS), Landau-Kleffner syndrome (LKS), Childhood absence epilepsy (CAE), Juvenile absence epilepsy (JAE), Juvenile myoclonic epilepsy (JME), Epilepsy with generalized tonic-clonic seizures alone, Progressive myoclonic epilepsies (PME), Autosomal dominant epilepsy with auditory features (ADEAF), Focal epilepsy, Familial focal epilepsy with variable foci, Self-limited familial and non-familial neonatal infantile seizures, Reflex epilepsies, temporal lobe epilepsy (e.g., Mesial Temporal Lobe Epilepsy (MTLE)), Rasmussen syndrome, Gelastic seizures with hypothalamic hamartoma, Hemiconvulsion-hemiplegia-epilepsy, Benign Rolandic epilepsy, Genetic epilepsy with sleep-related hypermotor epilepsy (SHE), Epilepsy eyelid myoclonia (Jeavons syndrome), or Photosensitive epilepsy.

55. The method of claim 50, wherein the neurological disease or disorder is an STXBP1 (syntaxin-1B)-related disorder and the transgene encodes STXBP1.

56. The method of any one of claims 49-55, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 1.

57. The method of any one of claims 49-55, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 2.

58. The method of any one of claims 49-55, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 3.

59. The method of any one of claims 49-55, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 4.

60. A method for expressing Syntaxin-binding protein 1 (STXBP1) in a GABAergic neuron, the method comprising contacting a GABAergic neuron cell with the expression vector of any one of claims 43-47, wherein the expression vector comprises a transgene comprises the nucleic acid sequence of SEQ ID NO: 3 or SEQ ID NO: 4.

61. The method of claim 60, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 3.

62. The method of claim 60, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 4.

63. A nucleic acid comprising a transgene comprising the nucleic acid sequence of SEQ ID NO: 3 or SEQ ID NO: 4.

64. The nucleic acid of claim 63, wherein the transgene is operably linked to a regulatory element comprising any one or more of SEQ ID NOS: 5-21.

65. The nucleic acid of claim 63 or claim 64, further comprising nucleic acid sequence encoding a de-targeting element.

66. The nucleic acid of claim 65, wherein the de-targeting element reduces expression of the transgene in excitatory neurons.

67. The nucleic acid of claim 66, wherein the de-targeting element comprises a nucleic acid sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to a sequence of SEQ ID NOS: 23-25.

68. The nucleic acid of claim 67, wherein the de-targeting element comprises a nucleic acid sequence of any one or more of SEQ ID NOS: 23-25 or combinations thereof.

69. The nucleic acid of claim 68, wherein the nucleic acid sequence encoding the de-targeting element comprises the nucleic acid sequence of any one of SEQ ID NOS: 26-28.

70. The nucleic acid of claim 68, wherein the nucleic acid sequence encoding the de-targeting element comprises the nucleic acid sequence of SEQ ID NO: 28.

71. The nucleic acid of claim 65, wherein the de-targeting element reduces expression of the transgene in liver cells.

72. The nucleic acid of claim 71, wherein the de-targeting element comprises a nucleic acid sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to a sequence of SEQ ID NOS: 49-66.

73. The nucleic acid of claim 72, wherein the de-targeting element comprises a nucleic acid sequence of any one or more of SEQ ID NOS: 49-66 or combinations thereof.

74. The nucleic acid of claim 65, wherein the de-targeting element reduces expression of the transgene in Dorsal Root Ganglion cells.

75. The nucleic acid of claim 74, wherein the de-targeting element comprises a nucleic acid sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to a sequence of SEQ ID NOS: 29-48.

76. The nucleic acid of claim 75, wherein the de-targeting element comprises a nucleic acid sequence of any one or more of SEQ ID NOS: 29-48 or combinations thereof.

77. The nucleic acid of claim 65, wherein the de-targeting element reduces expression of the transgene in two or more tissues.

78. The nucleic acid of claim 77, wherein the de-targeting element comprises the sequence of SEQ ID NO: 67.

79. The nucleic acid of any one of claims 63-78, wherein the nucleic acid comprises a regulatory element of SEQ ID NO: 22.

80. An expression vector comprising the nucleic acid of any one of claims 63-79.

81. The expression vector of claim 80, wherein the vector is a viral vector.

82. The expression vector of claim 81, wherein the viral vector is an adeno-associated viral (AAV) vector.

83. The expression vector of claim 82, wherein the AAV vector is AAV1, AAV8, AAV9, scAAV1, scAAV8, or scAAV9.

84. The expression vector of claim 82, wherein the AAV vector is an AAV9 vector comprising AAV2 inverted terminal repeats (ITRs).

85. A composition comprising the nucleic acid of any one of claims 65-79 or the expression vector of any one of claims 80-84 and one or more physiologically acceptable carriers.

86. A method of treating a neurological disease or disorder, the method comprising administering to a subject in need thereof the expression vector of any one of claims 80-84.

87. The method of claim 86, wherein the neurological condition or disorder is epilepsy.

88. The method of claim 86, wherein the neurological condition or disorder is epileptic encephalopathy.

89. The method of claim 86, wherein the neurological disease or disorder is refractory epilepsy.

90. The method of claim 86, wherein the neurological disease or disorder is not STXBP1-related or is of unknown etiology.

91. The method of any one of claims 86-90, wherein the method further comprises detecting mutant STXBP1 in a biological sample of the subject.

92. A nucleic acid comprising a transgene and a posttranscriptional regulatory element comprising SEQ ID NO: 22.

93. The nucleic acid of claim 92, wherein the posttranscriptional regulatory element comprising SEQ ID NO: 22 is located in the 3' untranslated region (UTR) of the transgene.

94. The nucleic acid of claim 92 or claim 93, wherein the posttranscriptional regulatory element comprising SEQ ID NO: 22 is located proximal to a poly-adenylation signal.

95. The nucleic acid of any one of claims 92-94, wherein the nucleic acid further comprises a regulatory element comprising any one or more of SEQ ID NOs: 5-21.

96. The nucleic acid of any one of claims 92-95, further comprising a nucleic acid sequence encoding a de-targeting element.

97. The nucleic acid of claim 96, wherein the de-targeting element reduces expression of the transgene in excitatory neurons.

98. The nucleic acid of claim 97, wherein the de-targeting element comprises a nucleic acid sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to a sequence of SEQ ID NOS: 23-25.

99. The nucleic acid of claim 98, wherein the de-targeting element comprises a nucleic acid sequence of any one or more of SEQ ID NOS: 23-25 or combinations thereof.

100. The nucleic acid of claim 97, wherein the nucleic acid sequence encoding the de-targeting element comprises the nucleic acid sequence of any one or more of SEQ ID NOS: 26-28.

101. The nucleic acid of claim 100, wherein the nucleic acid sequence encoding the de-targeting element comprises the nucleic acid sequence of SEQ ID NO: 28.

102. The nucleic acid of claim 96, wherein the de-targeting element reduces expression of the transgene in liver cells.

103. The nucleic acid of claim 102, wherein the de-targeting element comprises a nucleic acid sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to a sequence of SEQ ID NOS: 49-66.

104. The nucleic acid of claim 103, wherein the de-targeting element comprises a nucleic

acid sequence of any one or more of SEQ ID NOS: 49-66 or combinations thereof.

105. The nucleic acid of claim 96, wherein the de-targeting element reduces expression of the transgene in Dorsal Root Ganglion cells.

106. The nucleic acid of claim 105, wherein the de-targeting element comprises a nucleic acid sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to a sequence of SEQ ID NOS: 29-48.

107. The nucleic acid of claim 106, wherein the de-targeting element comprises a nucleic acid sequence of any one or more of SEQ ID NOS: 29-48 or combinations thereof.

108. The nucleic acid of claim 96, wherein the de-targeting element reduces expression of the transgene in two or more tissues.

109. The nucleic acid of claim 108, wherein the de-targeting element comprises the sequence of SEQ ID NO: 67.

110. The nucleic acid of any one of claims 92-109, wherein the transgene is a therapeutic transgene.

111. The nucleic acid of claim 110, wherein the transgene encodes a protein associated with a neurological disease or disorder.

112. The nucleic acid of claim 110, wherein the transgene encodes STXBP1 or a functional fragment thereof.

113. The nucleic acid of claim 112, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 1.

114. The nucleic acid of claim 112, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 2.

115. The nucleic acid of claim 112, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 3.

116. The nucleic acid of claim 112, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 4.

117. An expression vector comprising the nucleic acid of any one of claims 92-116.

118. The expression vector of claim 117, which is viral vector.

119. The expression vector of claim 118, which is an adeno-associated viral (AAV) vector.

120. The expression vector of claim 119, wherein the AAV vector is AAV1, AAV8, AAV9, scAAV1, scAAV8, or scAAV9.

121. The expression vector of claim 119, wherein the AAV vector is an AAV9 vector comprising AAV2 inverted terminal repeats (ITRs).

122. A composition comprising the nucleic acid of any one of claims 92-116 or the expression vector of any one of claims 117-121 and a physiologically acceptable carrier.

123. A method of delivering a transgene to a subject, the method comprising administering to the subject an expression vector of any one of claims 117-121.

124. A method of treating a neurological disease or disorder, the method comprising administering to a subject in need thereof the expression vector of any one of claims 117-121 comprising a transgene encoding a protein associated with a neurological disease or disorder or a transcription factor that increases expression of a gene associated with a neural disease or disorder.

125. The method of claim 124, wherein the neurological disease or disorder is epilepsy.

126. The method of claim 124, wherein the neurological disease or disorder is epileptic encephalopathy.

127. The method of claim 124, wherein the neurological disease or disorder is refractory epilepsy.

128. The method of claim 124, wherein the neurological disease or disorder is Benign familial neonatal epilepsy (BFNE), Early myoclonic encephalopathy (EME), Ohtahara syndrome, Epilepsy of infancy with migrating focal seizures, infantile spasms (West syndrome), Myoclonic epilepsy in infancy (MEI), Benign infantile epilepsy, Benign familial infantile epilepsy, Dravet syndrome, Myoclonic encephalopathy in nonprogressive disorders, Early onset epilepsy, Febrile seizures, Febrile seizures plus (FS+), Panayiotopoulos syndrome, Epilepsy with myoclonic atonic (previously astatic) seizures, Doose syndrome, Benign epilepsy with centrotemporal spikes (BECTS), frontal lobe epilepsy (e.g., Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)), Late onset childhood occipital epilepsy (Gastaut type), Epilepsy with myoclonic absences, Lennox-Gastaut syndrome, Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS), Landau-Kleffner syndrome (LKS), Childhood absence epilepsy (CAE), Juvenile absence epilepsy (JAE), Juvenile myoclonic epilepsy (JME), Epilepsy with generalized tonic-clonic seizures alone, Progressive myoclonic epilepsies (PME), Autosomal dominant epilepsy with auditory features (ADEAF), Focal epilepsy, Familial focal epilepsy with variable foci, Self-limited familial and non-familial neonatal infantile seizures, Reflex epilepsies, temporal lobe epilepsy (e.g., Mesial Temporal Lobe Epilepsy (MTLE)), Rasmussen syndrome, Gelastic seizures with hypothalamic hamartoma, Hemiconvulsion-hemiplegia-epilepsy, Benign Rolandic epilepsy, Genetic epilepsy with sleep-related hypermotor epilepsy (SHE), Epilepsy eyelid myoclonia (Jeavons syndrome), or Photosensitive epilepsy.

129. The method of any one of claims 123-128, wherein the transgene encodes STXBP1 or a functional fragment thereof.

130. The method of claim 129, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 1.

131. The method of claim 129, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 2.

132. The method of claim 129, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 3.

133. The method of claim 129, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 4.

134. The method of claim 124, wherein the neurological disease or disorder is an STXBP1 (syntaxin-1B)-related disorder and the transgene encodes STXBP1.

135. The method of claim 134, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 1.

136. The method of claim 134, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 2.

137. The method of claim 134, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 3.

138. The method of claim 134, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 4.

139. A host cell comprising the nucleic acid of any one of claims 1-42, 63-79, and 92-116 or the expression vector of any one of claims 43-47, 80-84, and 117-120.

140. Use of the nucleic acid of any one of claims 1-42, 63-79, and 92-116 or the expression vector of any one of claims 43-47, 80-84, and 117-120, in the manufacture of a medicament for the treatment of a neurological disease or disorder, wherein the nucleic acid or expression vector comprises a transgene encoding a protein associated with a neurological disease or disorder or a transcription factor that increases expression of a gene associated with a neural disease or disorder.

141. The use of claim 140, wherein the neurological condition or disorder is epilepsy.

142. The use of claim 140, wherein the neurological condition or disorder is epileptic encephalopathy.

143. The use of claim 140, wherein the neurological condition or disorder is an STXBP1-related neurological condition or disorder, and the transgene comprises the nucleic acid sequence

of any one of SEQ ID NOS: 1-4.

144. The use of claim 140, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 3 or SEQ ID NO: 4.

145. The nucleic acid of any one of claims 1-42, 63-79, and 92-116 or the expression vector of any one of claims 43-47, 80-84, and 117-120, for use in the treatment of a neurological disease or disorder, wherein the nucleic acid or expression vector comprises a transgene encoding a protein associated with a neurological disease or disorder or a transcription factor that increases expression of a gene associated with a neural disease or disorder.

146. The nucleic acid or expression vector for use of claim 145, wherein the neurological condition or disorder is epilepsy.

147. The nucleic acid or expression vector for use of claim 145, wherein the neurological condition or disorder is epileptic encephalopathy.

148. The nucleic acid or expression vector for use of claim 145, wherein the neurological condition or disorder is an STXBP1-related neurological condition or disorder, and the transgene comprises the nucleic acid sequence of any one of SEQ ID NOS: 1-4.

149. The use of claim 145, wherein the transgene comprises the nucleic acid sequence of SEQ ID NO: 3 or SEQ ID NO: 4.