

NEUROD1 VECTOR

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 63/084,908, filed September 29, 2020, and U.S. Provisional Patent Application No. 63/246,545, filed
5 September 21, 2021, the contents of which are incorporated herein by reference in their entireties.

INCORPORATION OF SEQUENCE LISTING

[0002] A sequence listing contained in the file named P34822WO00_SL.txt which is 21,632 bytes (measured in MS-Windows®) and created on September 27, 2021, is filed electronically herewith
10 and incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0003] The present disclosure includes methods and compositions using an AAV vector comprising a nucleic acid sequence encoding human NeuroD1 to convert glial cells to neurons.

BACKGROUND OF THE INVENTION

15 [0004] Neurons are often killed or damaged and unable to regenerate in subjects with a neurological condition or following an injury to the central nervous system (CNS) or peripheral nervous system (PNS).

[0005] Glial cells become reactive following an injury to the CNS or PNS such as a brain injury or neurological condition.

20 [0006] Currently there are no methods available to regenerate functional new neurons in human subjects having a neurological condition using adeno-associated viruses (AAVs).

SUMMARY OF THE INVENTION

[0007] In one aspect, this disclosure provides, and includes, an adeno-associated virus (AAV) vector comprising a human neurogenic differentiation 1 (hNeuroD1) sequence comprising the
25 nucleic acid sequence of SEQ ID NO: 6, where the hNeuroD1 sequence is operably linked to regulatory elements comprising: (a) a glial fibrillary acid protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15; (b) an enhancer from a human elongation factor-1 alpha (EF1- α) promoter comprising the nucleic acid

sequence of SEQ ID NO: 2 or a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11; (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18; and (e) a SV40 polyadenylation signal sequence comprising the nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

[0008] In one aspect, this disclosure provides, and includes, an adeno-associated virus (AAV) vector comprising a nucleic acid coding sequence encoding a human neurogenic differentiation 1 (hNeuroD1) protein comprising the amino acid sequence of SEQ ID NO: 10, where the coding sequence is operably linked to regulatory elements comprising: (a) a glial fibrillary acid protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15; (b) an enhancer from a human elongation factor-1 alpha (EF1- α) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11; (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18; (e) and a SV40 polyadenylation signal sequence with a nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

[0009] In an aspect, this disclosure provides, and includes, an adeno-associated virus (AAV) vector comprising a neurogenic differentiation 1 (NeuroD1) nucleic acid coding sequence encoding a NeuroD1 protein, where the coding sequence is operably linked to regulatory elements comprising: (a) a glial fibrillary acid protein (GFAP) promoter; (b) an enhancer; (c) a chimeric intron; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE); and (e) a polyadenylation signal sequence.

[0010] In an aspect, this disclosure provides, and includes, a composition comprising an adeno-associated virus (AAV) vector for converting glial cells to functional neurons in a human, where the AAV vector comprises a human neurogenic differentiation 1 (hNeuroD1) sequence having a nucleic acid sequence of SEQ ID NO: 6, and where the sequence is operably linked to regulatory

elements comprising: (a) a human glial fibrillary acid protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15; (b) an enhancer from the human elongation factor-1 alpha (EF-1 alpha) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11; (c) a chimeric intron comprising the nucleic sequence of SEQ ID NO: 5 or 16; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18; and (e) a SV40 polyadenylation signal sequence comprising the nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

[0011] In an aspect, this disclosure provides, and includes, a composition comprising an adeno-associated-virus (AAV) vector for converting glial cells to functional neurons in a human, where the AAV vector comprises a nucleic acid coding sequence encoding a human neurogenic differentiation 1 (hNeuroD1) protein comprising the amino acid sequence of SEQ ID NO: 10, and where the coding sequence is operably linked to regulatory elements comprising: (a) a human glial fibrillary acid protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15; (b) an enhancer from the human elongation factor-1 alpha (EF-1 alpha) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11; (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18; and (e) a SV40 polyadenylation signal sequence comprising the nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

[0012] In an aspect, this disclosure provides, and includes, a composition comprising an adeno-associated virus (AAV) vector for the treatment of a subject in need thereof, where the AAV vector comprises a neurogenic differentiation 1 (NeuroD1) sequence operably linked to expression control elements comprising: (a) a glial fibrillary acid protein (GFAP) promoter; (b) an enhancer; (c) a chimeric intron; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE); and (e) a polyadenylation signal.

[0013] In an aspect, this disclosure provides, and includes, a method of converting reactive astrocytes to functional neurons in a brain a living human comprising: injecting an adeno-associated virus (AAV) into a subject in need thereof, where the AAV comprises a DNA vector construct comprising a human neurogenic differentiation 1 (hNeuroD1) sequence comprising the nucleic acid sequence of SEQ ID NO: 6, where the sequence is operably linked to regulatory elements comprising: (a) a human glial fibrillary acid protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15; (b) an enhancer from the human elongation factor-1 alpha (EF-1 alpha) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11; (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NO: 7 and 18; and (e) a SV40 polyadenylation signal sequence comprising the nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

[0014] In an aspect, this disclosure provides, and includes, a method of converting reactive astrocytes to functional neurons in the brain of a living human brain comprising: injecting an adeno-associated virus (AAV) into a subject in need thereof, where the AAV comprises a DNA vector construct comprising a nucleic acid coding sequence encoding a human neurogenic differentiation 1 (hNeuroD1) protein comprising the amino acid sequence of SEQ ID NO: 10, where the coding sequence is operably linked to expression control elements comprising: (a) a human glial fibrillary acid protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15; (b) an enhancer from the human elongation factor-1 alpha (EF-1 alpha) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11; (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18; and (e) a SV40 polyadenylation signal sequence comprising the nucleic acid sequence of SEQ ID NO: 8, a hGH

polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

[0015] In an aspect, this disclosure provides, and includes, a method of converting glial cells to neurons in a subject in need thereof comprising: delivering an adeno-associated virus (AAV) to the subject in need thereof, where the AAV comprises a DNA vector construct comprising a neurogenic differentiation 1 (NeuroD1) sequence operably linked to expression control elements comprising: (a) a glial fibrillary acid protein (GFAP) promoter; (b) an enhancer; (c) a chimeric intron; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE); and (e) a polyadenylation signal sequence, where the vector is capable of converting at least one glial cell to a neuron in the subject in need thereof.

[0016] In an aspect, this disclosure provides, and includes, a method of treating a neurological condition in a subject in need thereof comprising: delivering an adeno-associated virus (AAV) to the subject, where the AAV comprises a DNA vector construct comprising a neurogenic differentiation 1 (NeuroD1) sequence operably linked to expression control elements comprising: (a) a glial fibrillary acid protein (GFAP) promoter; (b) an enhancer; (c) a chimeric intron; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE); and (e) a polyadenylation signal to the subject in need thereof.

[0017] In one aspect, this disclosure provides, and includes, an adeno-associated virus (AAV) vector comprising a human neurogenic differentiation 1 (hNeuroD1) sequence comprising the nucleic acid sequence of SEQ ID NO: 6, where the hNeuroD1 sequence is operably linked to regulatory elements comprising: (a) a glial fibrillary acidic protein (GFAP) promoter comprising the nucleic acid sequence of SEQ ID NO: 15; (b) an enhancer from a human elongation factor-1 alpha (EF1- α) promoter comprising the nucleic acid sequence of SEQ ID NO: 2; (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 16; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence of SEQ ID NO: 18; and (e) a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

[0018] In one aspect, this disclosure provides, and includes, an adeno-associated virus (AAV) vector comprising a human neurogenic differentiation 1 (hNeuroD1) sequence comprising the nucleic acid sequence of SEQ ID NO: 6, where the hNeuroD1 sequence is operably linked to regulatory elements comprising: (a) a glial fibrillary acidic protein (GFAP) promoter comprising

the nucleic acid sequence of SEQ ID NO: 15; (b) a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11; (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 16; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence of SEQ ID NO: 18; and (e) a
 5 bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

BRIEF DESCRIPTION OF THE DRAWINGS

- [0019] Figure 1A depicts a map of a EF-1 α :GfaABC1D:NeuroD1:WPRE:SV40 (P35).
 [0020] Figure 1B depicts a map of a EF-1 α :GfaABC1D:NeuroD1:WPRE:hGH.
 10 [0021] Figure 1C depicts a map of a CE:GfaABC1D:NeuroD1:WPRE:SV40 (P11).
 [0022] Figure 1D depicts a map of a CE:GfaABC1D:NeuroD1:WPRE:hGH.
 [0023] Figure 2A depicts a map of a EF-1 α :Gfa1.6:NeuroD1:WPRE:SV40 (P39).
 [0024] Figure 2B depicts a map of a CE:Gfa1.6:NeuroD1:WPRE:hGH.
 [0025] Figure 2C depicts a map of a CE:Gfa1.6:NeuroD1:WPRE:SV40 (P38).
 15 [0026] Figure 2D depicts a map of a EF-1 α :Gfa1.6:NeuroD1:WPRE:hGH.
 [0027] Figure 3A depicts a map of a EF-1 α :GFA2.2:NeuroD1:WPRE:SV40.
 [0028] Figure 3B depicts a map of a EF-1 α :GFA2.2:NeuroD1:WPRE:hGH.
 [0029] Figure 3C depicts a map of a CE:GFA2.2:NeuroD1:WPRE:SV40.
 [0030] Figure 3D depicts a map of a CE:GFA2.2:NeuroD1:WPRE:hGH.
 20 [0031] Figure 4 is a plot of measurements of AAV virus production of the P35 plasmid. Titer analysis is performed using gene of interest (GOI) primers, ITR region primers, and reverse packaging primers. Virus yield is calculated as vg/cell.
 [0032] Figure 5 depicts establishment of rat astrocyte primary culture from 3 day post-natal Sprague-Dawley rat brains. Upper left panel presents an image of GFAP stained cells. Upper
 25 right panel presents an image of SOX9 stained cells. Lower left panel presents an image of DAPI stained cells. Lower right panel presents a merge image of GFAP, SOX9, and DAPI stained cells.
 [0033] Figure 6 depicts transfection of primary rat astrocytes with plasmid P5 (pEF-1 α :hNeuroD1:GFP). Left panel presents an image of NeuroD1 stained cells. Middle left panel presents an image of GFP expressing cells. Middle right panel represents DAPI stained
 30 cells. Right panel represents a merge image of NeuroD1, GFP, and DAPI stained cells.

[0034] Figure 7 depicts comparison of NeuroD1 expression level of plasmid. Primary rat astrocytes are transfected with either the P6 (pEF-1 α :hNeuroD1:WPRE:SV40) expression vector, P11 (CE:GfaABC1D:NeuroD1:WPRE:SV40) expression vector, P35 (EF-1 α :GfaABC1D:NeuroD1:WPRE:SV40) expression vector, or P39 (EF-1 α :Gfa1.6:NeuroD1:WPRE:SV40). Top panels show NeuroD1 staining of cells, bottom panels show merged NeuroD1 and DAPI staining of cells.

[0035] Figure 8 depicts comparison of AAV virus particle transduction at different doses using AAV9-P12 (pGfaABC1D:GFP). Left panel shows a dose of 3×10^{10} vg/well. Middle panel shows a dose of 1×10^{10} vg/well. Right panel shows a dose of 2.5×10^9 vg/well.

[0036] Figure 9A and 9B depicts quantitative analysis of AAV particle transduction into primary rat astrocytes. Figure 9A presents the percentage transduction rate of AAV9-P12 (pGfaABC1D:GFP) and AAV5-P7 (pEF-1 α :GFP) at MOI of 5×10^5 vg/cell, 2×10^5 vg/cell, and 5×10^4 vg/cell. Figure 9B presents the percentage transduction rate of AAV9-P12 (pGfaABC1D:GFP) in cells seeded at a series of densities of 2×10^4 cell /well, 1.5×10^4 cell /well, 1×10^4 cell /well, and 5×10^3 cell /well and infected with virus at a series of amounts of 2 μ l, 1 μ l, 0.5 μ l, 0.25 μ l, 0.125 μ l of 1×10^{13} vg/ml virus in 100 μ l of medium.

[0037] Figure 10 depicts transduction of AAV virus particle comprising NeuroD1 into primary rat astrocytes. Primary rat astrocytes are transduced with AAV5-P1 (AAV5:pGfa2.2:cre) and AAV4-P4 (AAV5:pCAG:flex:hNeuroD1:GFP) (right panel), AAV9-P9 (CE:GfaABC1D:NeuroD1:GFP) (middle panel), or AAV9-P11 (CE:GfaABC1D:NeuroD1:WPRE:SV40) (left panel).

[0038] Figure 11 depicts RCAs three weeks post transduction with control plasmid AAV9-P21 (CE-pGFA681-CI-GFP-WPRE-SV40pA) at 2×10^{10} vg/ml. Cells are immunostained with antibodies against neuronal markers NeuN and MAP2, and with DAPI (nuclear stain). GFP fluorescence indicates the presence of cells transduced with the control plasmid.

[0039] Figure 12 depicts RCAs immunostained with an anti-NeuroD1(ND1) antibody and DAPI (nuclear stain) 24 hours post transfection with NXL-P134 (CE-pGfa681-CRGI-hND1-oPRE-bGHpA).

[0040] Figure 13 depicts RCAs immunostained with an anti-ND1 antibody and DAPI (nuclear stain) 6 days post transduction with AAV9-P134 (CE-pGfa681-CRGI-hND1-oPRE-bGHpA) at 2×10^{10} vg/ml.

- [0041] Figure 14 depicts RCAs immunostained with anti-NeuN and anti-MAP2 antibodies and DAPI (nuclear stain) 3 weeks post transduction with AAV9-P134 (CE-pGfa681-CRGI-hND1-oPRE-bGHpA) at 2×10^{10} vg/ml. Transduction with the ND1-containing vector generates neurons (NeuN//MAP2+) from the astrocyte culture.
- 5 [0042] Figure 15 depicts RCAs immunostained with an anti-ND1 antibody and DAPI (nuclear stain) 24 hours post transfection with NXL-P138 (EE-pGfa681-CRGI-hND1-oPRE-bGHpA).
- [0043] Figure 16 depicts RCAs immunostained with an anti-ND1 antibody and DAPI (nuclear stain) 6 days post transduction with AAV9-P138 (EE-pGfa681-CRGI-hND1-oPRE-bGHpA) at 2×10^{10} vg/ml).
- 10 [0044] Figure 17 depicts RCAs immunostained with anti-NeuN and anti-MAP2 antibodies and DAPI (nuclear stain) 3 weeks post transduction with AAV9-P138 (EE-pGfa681-CRGI-hND1-oPRE-bGHpA) at 2×10^{10} vg/ml). Transduction with the ND1-containing vector generates neurons (NeuN//MAP2+) from the astrocyte culture.
- [0045] Figure 18 depicts RCAs immunostained with an anti-ND1 antibody and DAPI (nuclear stain) 6 days post transduction with AAV9-P9 (CE-pGfa681-CI-hND1-p2A-GFP-WPRE-SV40pA) at 2×10^{10} vg/ml. GFP fluorescence indicates presence of transduced cells.
- 15 [0046] Figure 19 depicts RCAs immunostained with anti-NeuN and anti-MAP2 antibodies and DAPI (nuclear stain) 3 weeks post transduction with AAV9-P9 (CE-pGfa681-CI-hND1-p2A-GFP-WPRE-SV40pA) at 2×10^{10} vg/ml. Transduction with the ND1-containing vector generates neurons (NeuN//MAP2+) from the astrocyte culture.
- [0047] Figure 20 depicts RCAs immunostained with an anti-ND1 antibody and DAPI (nuclear stain) 24 hours post transfection with NXL-P22 (CE-pGfa681-CI-hND1-WPRE-SV40pA).
- [0048] Figure 21 depicts RCAs immunostained with an anti-ND1 antibody and DAPI (nuclear stain) 6 days post transduction with AAV9-P22 (CE-pGfa681-CI-hND1 WPRE-SV40pA) at
- 25 2×10^{10} vg/ml.
- [0049] Figure 22 depicts RCAs immunostained with anti-NeuN and anti-MAP2 antibodies and DAPI (nuclear stain) 3 weeks post transduction with AAV9-P22 (CE-pGfa681-CI-hND1-WPRE-SV40pA) at 2×10^{10} vg/ml. Transduction with the ND1-containing vector generates neurons (NeuN//MAP2+) from the astrocyte culture.
- 30 [0050] Figure 23 depicts RCAs immunostained with an anti-ND1 antibody and DAPI (nuclear stain) 24 hours post transfection with NXL-P35 (EE-pGfa681-CI-hND1-WPRE-SV40pA).

- [0051] Figure 24 depicts RCAs immunostained with an anti-ND1 antibody and DAPI (nuclear stain) 6 days post transduction with AAV9-P35 (EE-pGfa681-CI-hND1 WPRE-SV40pA) at 2×10^{10} vg/ml.
- [0052] Figure 25 depicts RCAs immunostained with an anti-NeuN antibody and DAPI (nuclear stain) 3 weeks post transduction with AAV9-P35 (EE-pGfa681-CI-hND1-WPRE-SV40pA) at 2×10^{10} vg/ml. Transduction with the ND1-containing vector generates neurons (NeuN+) from the astrocyte culture.
- [0053] Figure 26 depicts RCAs immunostained with an anti-ND1 antibody and DAPI (nuclear stain) 24 hours post transfection with NXL-P107 (CE-pGfa681-CI-hND1-bGHpA).
- 10 [0054] Figure 27 depicts RCAs immunostained with an anti-ND1 antibody and DAPI (nuclear stain) 24 hours post transfection with NXL-P108 (CE-pGfa681-CI-hND1-oPRE-bGHpA).
- [0055] Figure 28 depicts RCAs immunostained with an anti-ND1 antibody and DAPI (nuclear stain) 24 hours post transfection with NXL-P109 (CE-pGfa681-CRGI-hND1-bGHpA).
- [0056] Figure 29 depicts the brain cortex tissue of mice infected with AAV9-P12 (P12 control group), AAV9-P12 + AAV9-P134 (P134 group), and AAV9-P12 + AAV9-P138 (P138 group) at 15 10 days post infection (dpi).
- [0057] Figure 30 depicts the brain cortex tissue of mice infected with AAV9-P12 + AAV9-P134 (P134 group), and AAV9-P12 + AAV9-P138 (P138 group) at 30 days post infection (dpi).
- [0058] Figure 31 depicts the brain cortex tissue of mice (bilateral injury model) infected with 20 AAV9-P12 (P12 control group), and AAV9-P12 + AAV9-P134 (P134 group) at 10 dpi.
- [0059] Figure 32 is a plot of measurements of AAV virus production of the P134, P130, P138 and P21 plasmids. Titer analysis is performed by qPCR using primers amplifying gene of interest (GOI) and primers specific to the plasmids. Virus yield is calculated as vg/cell.
- [0060] Figure 33 depicts the brain cortex tissue of mice infected with AAV9-P12 (P12 control group), AAV9-P12 + AAV9-P134 (P134 group), and AAV9-P12 + AAV9-P138 (P138 group) at 25 10 days post infection (dpi). Cells are immunostained with antibodies against NeuroD1, GFAP, NeuN, and with DAPI (nuclear stain). GFP fluorescence indicates the presence of cells infected with the control virus.
- [0061] Figure 34 depicts the brain cortex tissue of mice infected with AAV9-P12 (P12 control group), AAV9-P12 + AAV9-P134 (P134 group), and AAV9-P12 + AAV9-P138 (P138 group) at 30 30 days post infection (dpi). Cells are immunostained with antibodies against GFAP, NeuN, and

with DAPI (nuclear stain). GFP fluorescence indicates the presence of cells infected with the control virus.

[0062] Figure 35 depicts the brain cortex tissue of mice (bilateral injury model) infected with AAV9-P12 (P12 control group), and AAV9-P12 + AAV9-P134 (P134 group) at 10 dpi. Cells are immunostained with antibodies against NeuroD1, GFAP, NeuN, and with DAPI (nuclear stain). GFP fluorescence indicates the presence of cells infected with the control virus.

[0063] Figure 36A and 36B depicts the brain cortex tissue of mice (bilateral injury model) infected with AAV9-P12 (P12 control group), and AAV9-P12 + AAV9-P134 (P134 group) at 30 dpi. Figure 36A depicts the cells that are immunostained with antibodies against NeuroD1, GFAP, NeuN, and with DAPI (nuclear stain). GFP fluorescence indicates the presence of cells infected with the control virus. Figure 36B is a quantification of the glial cell-to-neuron conversion rate at 30 dpi.

BRIEF DESCRIPTION OF SEQUENCES

[0064] A listing of nucleic acid sequences and amino acid sequences is provided in Table 1.

Table 1. Nucleic acid sequences

SEQ ID NO	Sequence Description	Sequence Type	Sequence
1	Upstream AAV2 ITR	Nucleic acid	TGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGG GCGTCGGGCGACCTTTGGTCGCCCCGGCCTCAGTGAGCGAGCG AGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTT CCT
2	Efla enhancer	Nucleic acid	TGCAAAGATGGATAAAGTTTAAACAGAGAGGAATCTTTGC AGCTAATGGACCTTCTAGGTCTTGAAAGGAGTGGGAATTGGC TCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCACAGTC CCCGAGAAGTTGGGGGGAGGGGTCGGCA
3	p2A	Nucleic acid	GGAAGCGGAGCTACTAACTTCAGCCTGCTGAAGCAGGCTGG AGACGTGGAGGAGAACCCTGGACCT
4	Gfa1.6 promoter	Nucleic acid	CTGCAAGCAGACCTGGCAGCATTGGGCTGGCCGCCCCCCAG GGCTCCTCTTCATGCCAGTGAATGACTCACCTTGGCACAG ACACAATGTTCTGGGGTGGGCACAGTGCCTGCTTCCCGCCGCA CCCAGCCCCCTCAAATGCCTTCCGAGAAGCCCATTTAGTA GGGGGCTTGCATTGCACCCAGCCTGACAGCCTGGCATCTTG GGATAAAAGCAGCACAGCCCCCTAGGGGCTGCCCTTGCTGTG TGGCGCCACCGGCGGTGGAGAACAAGGCTCTATTACGCCTGT GCCCAGGAAAGGGGATCAGGGGATGCCAGGCATGGACAGT GGGTGGCAGGGGGGGAGAGGAGGGCTGTCTGCTTCCCAGAA GTCCAAGGACACAAATGGGTGAGGGGACTGGGCAGGGTTCT

SEQ ID NO	Sequence Description	Sequence Type	Sequence
			GACCCCTGTGGGACCAGAGTGGAGGGCGTAGATGGACCTGAA GTCTCCAGGGACAAACAGGGCCCAAGTCTCAGGCTCCTAGTTG GGCCCAGTGGCTCCAGCGTTTCCAAACCCATCCATCCCCAGA GGTTCTTCCCATCTCTCCAGGCTGATGTGTGGGAACTCGAGG AAATAAATCTCCAGTGGGAGACGGAGGGGTGGCCAGGGAAA CGGGGCGCTGCAGGAATAAAGACGAGCCAGCACAGCCAGCT CATGCGTAACGGCTTTGTGGAGCTGTCAAGGCCTGGTCTCTG GGAGAGAGGCACAGGGAGGCCAGACAAGGAAGGGGTGACC TGGAGGGACAGATCCAGGGGCTAAAGTCCTGATAAGGCAAG AGAGTGCCGGCCCCCTCTTGCCCTATCAGGACCTCCACTGCC ACATAGAGGCCATGATTGACCCTTAGACAAAGGGCTGGTGTC CAATCCCAGCCCCCAGCCCCAGAACTCCAGGGAATGAATGG GCAGAGAGCAGGAATGTGGGACATCTGTGTTCAAGGGAAGG ACTCCAGGAGTCTGCTGGGAATGAGGCCTAGTAGGAAATGA GGTGGCCCTTGAGGGTACAGAACAGGTTTCATTCTTCGCCAAA TTCCCAGCACCTTGCAAGCACTTACAGCTGAGTGAGATAATG CCTGGGTTATGAAATCAAAAAGTTGGAAAGCAGGTCAGAGG TCATCTGGTACAGCCCTTCCCTTCCCTTTTTTTTTTTTTTTT GTGAGACAAGGTCTCTCTCTGTTGCCAGGCTGGAGTGGGCGC AAACACAGCTCACTGCAGCCTCAACCTACTGGGCTCAAGCAA TCCTCCAGCCTCAGCCTCCCAAAGTGCTGGGATTACAAGCAT GAGCCACCCCACTCAGCCCTTTCCTTCCCTTTTAAATTGATGCA TAATAATTGTAAGTATTCATCATGGTCCAACCAACCTTTCTT GACCCACCTTCTAGAGAGAGGGTCTCTTGATTGAGCGGTC AGGGCCCCCAGACCCATGGTCTGGCTCCAGGTACCACCTGCCT CATGCAGGAGTTGGCGTGCCCAGGAAGCTCTGCCTCTGGGCA CAGTGACCTCAGTGGGGTGAGGGGAGCTCTCCCATAGCTGG GCTGCGGCCCAACCCCAACCCCTCAGGCTATGCCAGGGGGTG TTGCCAGGGGCACCCGGGCATCGCCAGTCTAGCCCACTCTT CATAAAGCCCTCGCATCCAGGAGCGAGCAGACCCAGCT
5	Chimeric Intron	Nucleic acid	GTAAGTATCAAGGTTACAAGACAGGTTTAAGGAGACCAATA GAAACTGGGCTTGTGAGACAGAGAAGACTCTTGCGTTTCTG ATAGGCACCTATTGGTCTTACTGACATCCACTTTGCCTTCTC TCCACAG
6	hND1 (human NeuroD1)	Nucleic acid	ATGACCAAATCGTACAGCGAGAGTGGGCTGATGGGCGAGCC TCAGCCCCAAGGTCCTCCAAGCTGGACAGACGAGTGTCTCAG TTCTCAGGACGAGGAGCAGGAGGACAGACAAGAAGGAGGACG ACCTCGAAGCCATGAACGCAGAGGAGGACTCACTGAGGAAC GGGGGAGAGGAGGAGGACGAAGATGAGGACCTGGAAGAGG AGGAAGAAGAGGAAGAGGAGGATGACGATCAAAAGCCCAA GAGACGCGGCCCCAAAAGAAGAAGATGACTAAGGCTCGCC TGGAGCGTTTTAAATTGAGACGCATGAAGGCTAACGCCCGG GAGCGGAACCGCATGCACGGAAGTGAACGCGGCGCTAGACAA CCTGCGCAAGGTGGTGCCTTGCTATTCTAAGACGCAGAAGCT GTCCAAAATCGAGACTCTGCGCTTGCCCAAGAACTACATCTG GGCTCTGTGCGAGATCCTGCGCTCAGGCAAAAGCCCAGACCT GGTCTCCTTCGTTGAGACGCTTTGCAAGGGCTTATCCCAACC CACCACCAACCTGGTTGCGGGCTGCCTGCAACTCAATCCTCG

SEQ ID NO	Sequence Description	Sequence Type	Sequence
			GACTTTTCTGCCTGAGCAGAACCAGGACATGCCCCCCCACCT GCCGACGGCCAGCGCTTCCTTCCCTGTACACCCCTACTCCTA CCAGTCGCCTGGGCTGCCAGTCCGCCTTACGGTACCATGGA CAGCTCCCATGTCTTCCACGTTAAGCCTCCGCCGCACGCCTA CAGCGCAGCGCTGGAGCCCTTCTTTGAAAGCCCTCTGACTGA TTGCACCAGCCCTTCCTTTGATGGACCCCTCAGCCCGCCGCTC AGCATCAATGGCAACTTCTCTTTCAAACACGAACCGTCCGCC GAGTTTGAGAAAAATTATGCCTTTACCATGCACTATCCTGCA GCGACACTGGCAGGGGGCCCAAAGCCACGGATCAATCTTCTC AGGCACCGCTGCCCTCGCTGCGAGATCCCCATAGACAATAT TATGTCCTTCGATAGCCATTACATCATGAGCGAGTCATGAG TGCCCAGCTCAATGCCATATTTTCATGAT
7	WPRE (Woodchuck Hepatitis Virus Posttranscripti onal Regulatory Element)	Nucleic acid	AATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGT ATTCTTAACCTATGTTGCTCCTTTTACGCTATGTGGATACGCTG CTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTT CATTTTCTCCTCCTTGTATAAATCCTGGTTGCTGTCTCTTTATG AGGAGTTGTGGCCCGTTGTGTCAGGCAACGTGGCGTGGTGTGCA CTGTGTTTGTGACGCAACCCCCACTGGTTGGGGCATTGCCA CCACCTGTCAGCTCCTTTCCGGGACTTTCGCTTTCCCCCTCCC TATTGCCACGGCGGAACATCATCGCCGCCTGCCTTGCCCGCTG CTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGT GTTGTGCGGGAAATCATCGTCTTTCTTTGGCTGCTCGCCTGT GTTGCCACCTGGATTCTGCGCGGGACGTCCTTCTGCTACGTC CCTTCGGCCCTCAATCCAGCGGACCTTCCTTCCCGCGGCCTG CTGCCGCTCTGCGGCCTCTTCGCGCTCTTCGCCTTCGCCCTC AGACGAGTCGGATCTCCCTTTGGGCGCGCTCCCCGC
8	SV40 poly(A) signal	Nucleic acid	CGATCCACCGGATCTAGATAACTGATCATAATCAGCCATACC ACATTTGTAGAGGTTTTACTTGTCTTTAAAAAACCTCCACAC CTCCCCCTGAACCTGAAACATAAAATGAATGCAATTGTTGTT GTTAACTTGTTTATTGCAGCTTATAATGGTTACAAATAAAGC AATAGCATCACAAATTTACAAATAAAGCATTTTTTTTCATCG CATTCTAGTTGTGGTTTGTCCAAACTCATCAATGTATCTTA
9	Downstream AAV2 ITR	Nucleic acid	AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCG CTCGCTCGCTCACTGAGGCCGGGCGACCAAGGTGCCCCGAC GCCCCGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCG CGCAGCTGCCTGCA
10	hND1 (human NeuroD1)	Amino Acid	MTKSYSESLMGEPQPQGPSSWTDECLSSQDEEHEADKKEDDL EAMNAEEDSLRNGGEEDEDEDLEEEEEEEEEEDDDQKPKRRGP KKKKMTKARLERFKLRRMKANARERNRMHGLNAALDNLKRV VPCYSKTQKLSKIETLRLAKNYIWALSEILRSGKSPDLVSFVQTL CKGLSQPTTNLVAGCLQLNPRTFLPEQNQDMPPHLPPTASAFPV HPYSYQSPGLPSPPYGTMDSSHVFHVKPPPHAYSAALEPFESPL TDCTSPSFDGPLSPPLSINGNFSFKHEPSAEFEKNYAFTMHYPAA TLAGAQSHGSIFSHTAAPRCEIPIDNIMSFDSHSHHERVMSAQLN AIFHD
11	CMV enhancer ("CE")	Nucleic Acid	GACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGG GGTCATTAGTTCATAGCCCATATATGGAGTTCGCGGTTACAT

SEQ ID NO	Sequence Description	Sequence Type	Sequence
			AACCTACGGTAAATGGCCCCGCCTGGCTGACCGCCCAACGACC CCCGCCCATTTGACGTCAATAATGACGTATGTTCCCATAGTAA CGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGACTATT TACGGTAAACTGCCCACTTGGCAGTACATCAAGTGTATCATA TGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGC CCGCCTGGCATTATGCCCAGTACATGACCTTATGGGACTTTC CTACTTGGCAGTACATCTACGTATTAGTCATCGCTATTACCAT G
12	hGFA2.2 promoter	Nucleic Acid	CGCGTCCCACCTCCCTCTCTGTGCTGGGACTCACAGAGGGAG ACCTCAGGAGGCAGTCTGTCCATCACATGTCCAAATGCAGAG CATAACCTGGGCTGGGCGCAGTGGGCGCACAACCTGTAATTCCA GCACTTTGGGAGGCTGATGTGGAAGGATCACTTGAGCCAG AAGTTCTAGACCAGCCTGGGCAACATGGCAAGACCTATCTC TACAAAAAAGTTAAAAAATCAGCCACGTGTGGTGACACAC ACCTGTAGTCCCAGCTATTCAGGAGGCTGAGGTGAGGGGATC ACTTAAGGCTGGGAGGTTGAGGCTGCAGTGAGTCGTGGTTGC GCCACTGCACTCCAGCCTGGGCAACAGTGAGACCCTGTCTCA AAAGACAAAAAAAAAAAAAAAAAAAAAAAAAAGAACATATCCT GGTGTGGAGTAGGGGACGCTGCTCTGACAGAGGCTCGGGGG CCTGAGCTGGCTCTGTGAGCTGGGGAGGAGGCAGACAGCCA GGCCTTGTCTGCAAGCAGACCTGGCAGCATTGGGCTGGCCGC CCCCCAGGGCCTCCTCTTCATGCCCAGTGAATGACTCACCTT GGCACAGACACAATGTTTCGGGGTGGGCACAGTGCCTGCTTCC CGCCGCACCCAGCCCCCTCAAATGCCTTCCGAGAAGCCCA TTGAGCAGGGGGCTTGCATTGCACCCAGCCTGACAGCCTGG CATCTTGGGATAAAAGCAGCACAGCCCCCTAGGGGCTGCCCT TGCTGTGTGGCGCCACCGCGGTGGAGAACAAGGCTCTATTTC AGCCTGTGCCAGGAAAGGGGATCAGGGGATGCCAGGCAT GGACAGTGGGTGGCAGGGGGGGAGAGGAGGGCTGTCTGCTT CCCAGAAGTCCAAGGACACAAATGGGTGAGGGGACTGGGCA GGGTTCTGACCCTGTGGGACCAGAGTGGAGGGCGTAGATGG ACCTGAAGTCTCCAGGGACAACAGGGCCCAGGTCTCAGGCT CCTAGTTGGGCCCAGTGGCTCCAGCGTTTCCAAACCCATCCA TCCCCAGAGGTTCTTCCCATCTCTCCAGGCTGATGTGTGGGA ACTCGAGGAAATAAATCTCCAGTGGGAGACGGAGGGGTGGC CAGGGAAACGGGGCGCTGCAGGAATAAAGACGAGCCAGCAC AGCCAGCTCATGTGTAACGGCTTTGTGGAGCTGTCAAGGCCT GGTCTCTGGGAGAGAGGCACAGGGAGGCCAGACAAGGAAG GGGTGACCTGGAGGGACAGATCCAGGGGCTAAAGTCCTGAT AAGGCAAGAGAGTGCCGGCCCCCTCTTGCCCTATCAGGACCT CCACTGCCACATAGAGGCCATGATTGACCTTAGACAAAGG

SEQ ID NO	Sequence Description	Sequence Type	Sequence
			GCTGGTGTCCAATCCCAGCCCCCAGCCCCAGAACTCCAGGGA ATGAATGGGCAGAGAGCAGGAATGTGGGACATCTGTGTTCA AGGGAAGGACTCCAGGAGTCTGCTGGGAATGAGGCCTAGTA GGAAATGAGGTGGCCCTTGAGGGTACAGAACAGGTTCAATTCT TCGCCAAATCCCAGCACCTTGACAGGCACTTACAGCTGAGTG AGATAATGCCTGGGTTATGAAATCAAAAAGTTGGAAAGCAG GTCAGAGGTCATCTGGTACAGCCCTTCCTTCCCTTTTTTTTTT TTTTTTTTTGTGAGACAAGGTCTCTCTCTGTTGCCAGGCTGG AGTGGCGCAAACACAGCTCACTGCAGCCTCAACCTACTGGGC TCAAGCAATCCTCCAGCCTCAGCCTCCCAAAGTGCTGGGATT ACAAGCATGAGCCACCCCACTCAGCCCTTTCCTTCCCTTTTAA TTGATGCATAATAATTGTAAGTATTCATCATGGTCCAACCAA CCCTTTCTTGACCCACCTTCCTAGAGAGAGGGTCTCTTGCTT CAGCGGTGAGGGCCCCAGACCCATGGTCTGGCTCCAGGTACC ACCTGCCTCATGCAGGAGTTGGCGTGCCAGGAAGCTCTGCC TCTGGGCACAGTGACCTCAGTGGGGTGAGGGGAGCTCTCCCC ATAGCTGGGCTGCGGCCCAACCCACCCCTCAGGCTATGCC AGGGGGTGTTGCCAGGGGCACCCGGGCATCGCCAGTCTAGC CCACTCCTTCATAAAGCCCTCGCATCCCAGGAGCGAGCAGAG CCAGAGCAGGTTGGAGAGGAGACGCATCACCTCCGCTGCTC GCCGGG
13	hGH poly(A) signal	Nucleic Acid	GGGTGGCATCCCTGTGACCCCTCCCCAGTGCTCTCTGGCC CTGGAAGTTGCCACTCCAGTGCCCAACAGCCTTGTCCTAATA AAATTAAGTTGCATCATTTTGTCTGACTAGGTGTCCTTCTATA ATATTATGGGGTGAGGGGGGTGGTATGGAGCAAGGGGCAA GTTGGGAAGACAACCTGTAGGGCCTGCGGGGTCTATTGGGA ACCAAGCTGGAGTGCAGTGGCACAATCTTGGCTCACTGCAAT CTCCGCCCTCTGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCC GAGTTGTTGGGATTCCAGGCATGCATGACCAGGCTCAGCTAA TTTTTGTTTTTTGGTAGAGACGGGGTTTCACCATATTGGCCA GGCTGGTCTCCAACCTCCTAATCTCAGGTGATCTACCCACCTT GGCCTCCCAAATTGCTGGGATTACAGGCGTGAACCACTGCTC CCTTCCCTGTCCTT
14	bGH poly (A) signal (bGHpA)	Nucleic acid	CTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCCTCCC CGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTT TCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGG TGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAA GGGGGAGGATTGGGAAGAGAATAGCAGGCATGCTGGGGA
15	pGfa681 promoter (also called	Nucleic acid	AACATATCCTGGTGTGGAGTAGGGGACGCTGCTCTGACAGA GGCTCGGGGGCCTGAGCTGGCTCTGTGAGCTGGGGAGGAGG CAGACAGCCAGGCCCTGTCTGCAAGCAGACCTGGCAGCATTG

SEQ ID NO	Sequence Description	Sequence Type	Sequence
	"GfaABC1D promoter")		GGCTGGCCGCCCCCAGGGCCTCCTCTTCATGCCCAGTGAAT GACTCACCTTGGCACAGACACAATGTTCTGGGGTGGGCACAGT GCCTGCTTCCCGCCGCACCCAGCCCCCTCAAATGCCTTCC GAGAAGCCCATTGAGCAGGGGGCTTGCAATGCACCCAGCCT GACAGCCTGGCATCTTGGGATAAAAGCAGCACAGCCCCCTA GGGGCTGCCCTTGCTGTGTGGCGCCACCGGCGGTGGAGAAC AAGGCTCTATTAGCCTGTGCCAGGAAAGGGGATCAGGGG ATGCCAGGCATGGACAGTGGGTGGCAGGGGGGAGAGGAG GGCTGTCTGCTTCCAGAAAGTCCAAGGACACAAATGGGTGA GGGAGAGCTCTCCCATAGCTGGGCTGCGGCCAACCCAC CCCTCAGGCTATGCCAGGGGGTGTGCCAGGGGCACCCGG GCATCGCCAGTCTAGCCCACTCCTTCATAAAGCCCTCGCATC CCAGGAGCGAGCAGAGCCAGAGCAGGTTGGAGAGGAGACG CATCACCTCCGCTGCTCGC
16	CRGI Chimeric Intron	Nucleic acid	GGAGTCGCTGCGTTGCCTTCGCCCCGTGCCCCGCTCCGCGCC GCCTCGCGCCGCCCGCCCCGGCTCTGACTGACCGCGTTACTC CCACAGGTGAGCGGGCGGGACGGCCCTTCTCCCTCCGGGCTG TAATTAGCGCTTGTTTAATGACGGCTCGTTTCTTTCTGTGG CTGCGTGAAAGCCTTAAAGGGCTCCGGGAGGGCCTTTGTGCG GGGGGAGCGGCTCGGGGGGTGCGTGCGTGTGTGTGCGT GGGAGCGCCGCTGCGGCCCGCGCTGCCCGGCGGCTGTGA GCGCTGCGGGCGCGGCGCGGGCTTTGTGCGCTCCGCGTGTG CGCGAGGGGAGCGCGGGCCGGGGCGGTGCCCGCGGTGCG GGGGGGCTGCGAGGGGAACAAAGGCTGCGTGCGGGGTGTGT GCGTGGGGGGGTGAGCAGGGGGTGTGGGCGCGGCGGTGCGG CTGTAAACCCCCCTGGCACCCCCCTCCCCAGTTGCTGAGC ACGGCCCCGGCTTCGGGTGCGGGGCTCCGTGCGGGGCGTGGC GCGGGGCTCGCCGTGCCGGGCGGGGGGTGGCGGCAGGTGGG GGTGCCGGGCGGGGCGGGGCCCGCTCGGGCCGGGAGGGCT CGGGGAGGGGCGCGGCGGCCCGGAGCGCCGGCGGCTGTC GAGGCGCGGCGAGCCGAGCCATTGCCTTTATGGTAATCGT GCGAGAGGGCGCAGGGACTTCCTTTGTCCCAAATCTGGCGGA GCCGAAATCTGGGAGGCGCCCGCCGACCCCCCTTAGCGGGC GCGGGCGAAGCGGTGCGGCGCCGGCAGGAAGGAAATGGGC GGGAGGGCCTTCGTGCGTCGCGCGCCGCGCTCCCTTCTC CATCTCCAGCCTCGGGGCTGCCGAGGGGGACGGCTGCCTTC GGGGGGACGGGGCAGGGCGGGGTTCGGCTTCTGGCGTGTG ACCGGCGGCTTTAGAGCCTCTGCTAACCATGTTTCATGCCTTCT TCTTTTCTACAGCTCCTGGGCAACGTGCTGGTTGTTGTGCT GTCTCATCATTTTGGCAAAGAT

SEQ ID NO	Sequence Description	Sequence Type	Sequence
17	GFAP first intron (GI)	Nucleic acid	GGCCACTGTGAGGCAGAAAGTGAGGAGGGGATGGGGAAGGG GGGCCTTGTGAGCAGAAGGGGCTGAATCCCCAAGAAGGAGT GCCCCGAGAAGTCTCAGGGAGGGGCGCAACCTCCCTGCTCCCT GGGCCTCCCTACCTCTTGATGGGGCACTATCCTTGCCCCCA ACATGATGGGAGGGACCAGAAACAGGCCAGGGCCCCGGGG ATCTGATGCCCCGCATGCCTTCTGCCAGGAGTCCAGGGTCCCC TCAGCACCTCCCTACTGGGGAAGCAGTGACAGGAGCAGCGG GGCCCCTGTGTTTCATTCATGGCTGGGCTTTGTGACTGTGGGC AGCGAGCTCACCTATTCTGAGCCTGTGTCCATATAAAGGAGG AGTTGGAAGCGGAGAAGGTTGATGTCCATGAGGGAGATTGG ATTCTGGGGTGAAGAAAGTGAGGGAAAGAGCAGGCAGGTCT GGGCGCAAAGCACAGGTGACTGCCTGCCACCAGCTTGTGAC CCCCATCAAGTTACTTTGACTTGCACAGCTGTGAAGCGGTGG TCATAATAAAATTCATTTCAAAAGGTGGTTACCTGGGATCAG AGGAATCCCCAGGGGCATGGCGCTTCACTGAGCTGACAGGA CATGCATGTGTGCCTTCAAGTGCAGGAGGACATGTGCGTGTG TGTGTGTGTGTGTGCAACAGTGAGTGTATGCTTGTGGATGCG CCTGTGTGAGCAGAAGCAGGTGCACCAACCCTGATAAGGCA CCTTAGTAATGAGTTAAGGCAAAAGCCCACATCTGCTCATCC TCCAGACAAGTCCTCTGTCTAAGGCCCCCCCAACCTTAATCC TCCTGCTGCTCTACTGGTCCTGGGTGGGGGTGGTCTCTGTGA CAGCTGCCTCAAGGGAGACTGAGGCAGGTATTCAAGTGCCT CAGAAGAGCCTGGACCCAGGAATGTGTCCCCCACTCCAGG CTCCAGGATGAAACCAACCTGA
18	Optimized version of WPRE (oPRE),	Nucleic acid	GAGCATCTTACCGCCATTTATACCCATATTTGTTCTGTTTTTC TTGATTTGGGTATACATTTAAATGTTAATAAAACAAAATGGT GGGGCAATCATTTACATTTTTAGGGATATGTAATTACTAGTT CAGGTGTATTGCCACAAGACAAACATGTTAAGAACTTTCCC GTTATTTACGCTCTGTTCCCTGTTAATCAACCTCTGGATTACAA AATTTGTGAAAGATTGACTGATATTCTTAACCTATGTTGCTCCT TTTACGCTGTGTGGATATGCTGCTTTATAGCCTCTGTATCTAG CTATTGCTTCCCGTACGGCTTTTCGTTTTCTCCTCCTTGTATAA ATCCTGGTTGCTGTCTCTTTTAGAGGAGTTGTGGCCCGTTGTC CGTCAACGTGGCGTGGTGTGCTCTGTGTTTGCTGACGCAACC CCCACTGGCTGGGGCATTGCCACCACCTGTCAACTCCTTTCT GGGACTTTCGCTTTCCCCCTCCCGATCGCCACGGCAGAACTC ATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTAGGTTG CTGGGCACTGATAATTCCGTGGTGTGTGTC
19	Forward ITR primer	Nucleic acid	GGAACCCCTAGTGATGGAGTT

SEQ ID NO	Sequence Description	Sequence Type	Sequence
20	Reverse ITR primer	Nucleic acid	CGGCCTCAGTGAGCGA

DETAILED DESCRIPTION

[0065] Unless defined otherwise, all technical and scientific terms used have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Where a term is provided in the singular, the inventors also contemplate aspects of the disclosure described by the plural of that term. Where there are discrepancies in terms and definitions used in references that are incorporated by reference, the terms used in this application shall have the definitions given herein. Other technical terms used have their ordinary meaning in the art in which they are used, as exemplified by various art-specific dictionaries, for example, “The American Heritage® Science Dictionary” (Editors of the American Heritage Dictionaries, 2011, Houghton Mifflin Harcourt, Boston and New York), the “McGraw-Hill Dictionary of Scientific and Technical Terms” (6th edition, 2002, McGraw-Hill, New York), or the “Oxford Dictionary of Biology” (6th edition, 2008, Oxford University Press, Oxford and New York).

[0066] Any references cited herein, including, *e.g.*, all patents, published patent applications, and non-patent publications, are incorporated herein by reference in their entirety.

[0067] When a grouping of alternatives is presented, any and all combinations of the members that make up that grouping of alternatives is specifically envisioned. For example, if an item is selected from a group consisting of A, B, C, and D, the inventors specifically envision each alternative individually (*e.g.*, A alone, B alone, etc.), as well as combinations such as A, B, and D; A and C; B and C; etc. The term “and/or” when used in a list of two or more items means any one of the listed items by itself or in combination with any one or more of the other listed items. For example, the expression “A and/or B” is intended to mean either or both of A and B – *i.e.*, A alone, B alone, or A and B in combination. The expression “A, B and/or C” is intended to mean A alone, B alone, C alone, A and B in combination, A and C in combination, B and C in combination, or A, B, and C in combination.

[0068] When a range of numbers is provided herein, the range is understood to be inclusive of the edges of the range as well as any number between the defined edges of the range. For example,

“between 1 and 10” includes any number between 1 and 10, as well as the number 1 and the number 10.

[0069] When the term “about” is used in reference to a number, it is understood to mean plus or minus 10%. For example, “about 100” would include from 90 to 110.

5 [0070] As used herein “hND1” refers to a human neuronal differentiation (NeuroD1) gene or protein.

[0071] As used herein “CE” refers to a cytomegalovirus (CMV) promoter enhancer sequence.

[0072] As used herein “EE” refers to an Efl alpha promoter enhancer sequence.

10 [0073] As used herein “pGfa681” refers to a human glial fibrillary acid protein (GFAP) promoter truncated sequence of 681 bp size.

[0074] As used herein “CI” refers to a chimeric intron composed of the 5’-donor site from the first intron of the human β -globin gene and the branch and 3’-acceptor site from the intron of an immunoglobulin gene heavy chain variable region.

15 [0075] As used herein “CRGI” refers to a chimeric intron of rabbit beta-globin and chicken beta actin similar in CAG promoter.

[0076] As used herein “GI” refers to a human glial fibrillary acid protein (GFAP) first intron.

[0077] As used herein “WPRE” refers to a Woodchuck Hepatitis Virus (WHV) Posttranscriptional Regulatory Element.

[0078] As used herein “oPRE” refers to an optimized version of WPRE.

20 [0079] As used herein “SV40pA” refers to a poly A signal of SV40 virus.

[0080] As used herein “bGHpA” refers to a poly A signal of bovine growth hormone.

[0081] As used herein “vg” refers to a viral genome.

[0082] As used herein “p2A” refers to a 2A self-cleavage peptide sequence from porcine teschovirus-1.

25 [0083] Any composition or vector provided herein is specifically envisioned for use with any method provided herein.

[0084] In an aspect, methods and compositions provided herein comprise a vector. As used herein, the term “vector” refers to a circular, double-stranded DNA molecule that is physically separate from chromosomal DNA. It should be noted that the term “vector” can be used interchangeably
30 with the term “plasmid.”

[0085] In an aspect, a vector provided herein is a recombinant vector. As used herein, the term “recombinant vector” refers to a vector that comprises a recombinant nucleic acid. As used herein, a “recombinant nucleic acid” refers to a nucleic acid molecule formed by laboratory methods of genetic recombination, such as, without being limiting, molecular cloning. A recombinant vector
5 can be formed by laboratory methods of genetic recombination, such as, without being limiting, molecular cloning. Also, without being limiting, one skilled in the art can create a recombinant vector *de novo* via synthesizing a plasmid by individual nucleotides, or by splicing together nucleic acid molecules from different pre-existing vectors.

[0086] Adeno-associated viruses (AAVs) are replication-defective, non-enveloped
10 *Dependoparvovirus* viruses that infect humans and additional primate species. AAVs are not known to cause disease in any species, although they can cause mild immune responses. AAVs can infect dividing and quiescent cells. AAVs are stably integrate into the human genome at a specific site in chromosome 19 termed the AAVS1 locus (nucleotides 7774-11429 of GenBank Accession No. AC010327.8), although random integrations at other loci in the human genome are
15 possible.

[0087] AAVs comprise a linear genome with a single-stranded DNA of about 4700 nucleotides in length. The genome of AAVs also includes a 145 nucleotide-long inverted terminal repeat (ITR) at each end of the genome. The ITRs flank two viral genes *rep* (for replication, encoding non-structural proteins) and *cap* (for capsid, encoding structural proteins). The ITRs contain all of the
20 *cis*-acting elements need for genome rescue, replication, and packaging of the AAV.

[0088] When used in gene therapy approaches, the *rep* and *cap* genes of the AAV genome sequence are removed and replaced with DNA of interest positioned between two AAV ITRs. As used herein, an “AAV vector construct” refers to a DNA molecule comprising a desired sequence inserted between two AAV ITR sequences. As used herein, an “AAV vector” refers to an AAV
25 packaged with a DNA vector construct.

[0089] As used herein, the term “AAV vector serotype” mainly refers to a variation within the *capsid* proteins of an AAV vector.

[0090] In an aspect, an AAV vector is selected from the group consisting of AAV vector serotype 1, AAV vector serotype 2, AAV vector serotype 3, AAV vector serotype 4, AAV vector serotype
30 5, AAV vector serotype 6, AAV vector serotype 7, AAV vector serotype 8, AAV vector serotype 9, AAV vector serotype 10, AAV vector serotype 11, and AAV vector serotype 12. In one aspect,

an AAV vector is selected from the group consisting AAV serotype 2, AAV serotype 5, and AAV serotype 9. In one aspect, an AAV vector is AAV serotype 1. In one aspect, an AAV vector is AAV serotype 2. In one aspect, an AAV vector is AAV serotype 3. In one aspect, an AAV vector is AAV serotype 4. In one aspect, an AAV vector is AAV serotype 5. In one aspect, an AAV vector is AAV serotype 6. In one aspect, an AAV vector is AAV serotype 7. In one aspect, an AAV vector is AAV serotype 8. In one aspect, an AAV vector is AAV serotype 9. In one aspect, an AAV vector is AAV serotype 10. In one aspect, an AAV vector is AAV serotype 11. In one aspect, an AAV vector is AAV serotype 12.

[0091] In an aspect, an AAV vector ITR is selected from the group consisting of an AAV serotype 1 ITR, an AAV serotype 2 ITR, an AAV serotype 3 ITR, an AAV serotype 4 ITR, an AAV serotype 5 ITR, an AAV serotype 6 ITR, an AAV serotype 7 ITR, an AAV serotype 8 ITR, an AAV serotype 9 ITR, an AAV serotype 10 ITR, an AAV serotype 11 ITR, and an AAV serotype 12 ITR. In one aspect, an AAV vector ITR is an AAV serotype 1 ITR. In one aspect, an AAV vector ITR is an AAV serotype 2 ITR. In one aspect, an AAV vector ITR is an AAV serotype 3 ITR. In one aspect, an AAV vector ITR is an AAV serotype 4 ITR. In one aspect, an AAV vector ITR is an AAV serotype 5 ITR. In one aspect, an AAV vector ITR is an AAV serotype 6 ITR. In one aspect, an AAV vector ITR is an AAV serotype 7 ITR. In one aspect, an AAV vector ITR is an AAV serotype 8 ITR. In one aspect, an AAV vector ITR is an AAV serotype 9 ITR. In one aspect, an AAV vector ITR is an AAV serotype 10 ITR. In one aspect, an AAV vector ITR is an AAV serotype 11 ITR. In one aspect, an AAV vector ITR is an AAV serotype 12 ITR.

[0092] In an aspect, at least one AAV vector ITR nucleic acid sequence is selected from the group consisting of SEQ ID NOs: 1 and 9. In one aspect, at least one AAV vector ITR nucleic acid sequence is SEQ ID NO: 1. In one aspect, at least one AAV vector ITR nucleic acid sequence is SEQ ID NO: 9.

[0093] In an aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 70% identical to SEQ ID NO: 1, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 75% identical to SEQ ID NO: 1, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 80% identical to SEQ ID NO: 1, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 85% identical to SEQ ID NO: 1, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 90% identical to SEQ ID

NO: 1, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 91% identical to SEQ ID NO: 1, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 92% identical to SEQ ID NO: 1, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 93% identical to SEQ ID NO: 1, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 94% identical to SEQ ID NO: 1, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 95% identical to SEQ ID NO: 1, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 96% identical to SEQ ID NO: 1, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 97% identical to SEQ ID NO: 1, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 98% identical to SEQ ID NO: 1, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 99% identical to SEQ ID NO: 1, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 99.5% identical to SEQ ID NO: 1, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 99.8% identical to SEQ ID NO: 1, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 99.9% identical to SEQ ID NO: 1, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence 100% identical to SEQ ID NO: 1, or the complement thereof.

[0094] In an aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 70% identical to SEQ ID NO: 9, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 75% identical to SEQ ID NO: 9, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 80% identical to SEQ ID NO: 9, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 85% identical to SEQ ID NO: 9, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 90% identical to SEQ ID NO: 9, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 91% identical to SEQ ID NO: 9, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 92% identical to SEQ ID NO: 9, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence

at least 93% identical to SEQ ID NO: 9, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 94% identical to SEQ ID NO: 9, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 95% identical to SEQ ID NO: 9, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 96% identical to SEQ ID NO: 9, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 97% identical to SEQ ID NO: 9, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 98% identical to SEQ ID NO: 9, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 99% identical to SEQ ID NO: 9, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 99.5% identical to SEQ ID NO: 9, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 99.8% identical to SEQ ID NO: 9, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence at least 99.9% identical to SEQ ID NO: 9, or the complement thereof. In one aspect, an AAV ITR nucleic acid sequence comprises a sequence 100% identical to SEQ ID NO: 9, or the complement thereof.

[0095] The terms “percent identity” or “percent identical” as used herein in reference to two or more nucleotide or amino acid sequences is calculated by (i) comparing two optimally aligned sequences (nucleotide or amino acid) over a window of comparison (the “alignable” region or regions), (ii) determining the number of positions at which the identical nucleic acid base (for nucleotide sequences) or amino acid residue (for proteins and polypeptides) occurs in both sequences to yield the number of matched positions, (iii) dividing the number of matched positions by the total number of positions in the window of comparison, and then (iv) multiplying this quotient by 100% to yield the percent identity. If the “percent identity” is being calculated in relation to a reference sequence without a particular comparison window being specified, then the percent identity is determined by dividing the number of matched positions over the region of alignment by the total length of the reference sequence. Accordingly, for purposes of the present application, when two sequences (query and subject) are optimally aligned (with allowance for gaps in their alignment), the “percent identity” for the query sequence is equal to the number of identical positions between the two sequences divided by the total number of positions in the query sequence over its length (or a comparison window), which is then multiplied by 100%.

[0096] When percentage of sequence identity is used in reference to amino acids it is recognized that residue positions which are not identical often differ by conservative amino acid substitutions, where amino acid residues are substituted for other amino acid residues with similar chemical properties (e.g., charge or hydrophobicity) and therefore do not change the functional properties of the molecule. When sequences differ in conservative substitutions, the percent sequence identity can be adjusted upwards to correct for the conservative nature of the substitution. Sequences that differ by such conservative substitutions are said to have “sequence similarity” or “similarity.”

[0097] For optimal alignment of sequences to calculate their percent identity, various pair-wise or multiple sequence alignment algorithms and programs are known in the art, such as ClustalW or Basic Local Alignment Search Tool® (BLAST™), etc., that can be used to compare the sequence identity or similarity between two or more nucleotide or amino acid sequences. Although other alignment and comparison methods are known in the art, the alignment and percent identity between two sequences (including the percent identity ranges described above) can be as determined by the ClustalW algorithm, *see, e.g.*, Chenna *et al.*, “Multiple sequence alignment with the Clustal series of programs,” *Nucleic Acids Research* 31: 3497-3500 (2003); Thompson *et al.*, “Clustal W: Improving the sensitivity of progressive multiple sequence alignment through sequence weighting, position-specific gap penalties and weight matrix choice,” *Nucleic Acids Research* 22: 4673-4680 (1994); Larkin *et al.*, “Clustal W and Clustal X version 2.0,” *Bioinformatics* 23: 2947-48 (2007); and Altschul *et al.*, “Basic local alignment search tool,” *J. Mol. Biol.* 215:403-410 (1990), the entire contents and disclosures of which are incorporated herein by reference.

[0098] The terms “percent complementarity” or “percent complementary” as used herein in reference to two nucleotide sequences is similar to the concept of percent identity but refers to the percentage of nucleotides of a query sequence that optimally base-pair or hybridize to nucleotides a subject sequence when the query and subject sequences are linearly arranged and optimally base paired without secondary folding structures, such as loops, stems or hairpins. Such a percent complementarity can be between two DNA strands, two RNA strands, or a DNA strand and a RNA strand. The “percent complementarity” can be calculated by (i) optimally base-pairing or hybridizing the two nucleotide sequences in a linear and fully extended arrangement (*i.e.*, without folding or secondary structures) over a window of comparison, (ii) determining the number of

positions that base-pair between the two sequences over the window of comparison to yield the number of complementary positions, (iii) dividing the number of complementary positions by the total number of positions in the window of comparison, and (iv) multiplying this quotient by 100% to yield the percent complementarity of the two sequences. Optimal base pairing of two sequences
5 can be determined based on the known pairings of nucleotide bases, such as G-C, A-T, and A-U, through hydrogen binding. If the “percent complementarity” is being calculated in relation to a reference sequence without specifying a particular comparison window, then the percent identity is determined by dividing the number of complementary positions between the two linear sequences by the total length of the reference sequence. Thus, for purposes of the present
10 application, when two sequences (query and subject) are optimally base-paired (with allowance for mismatches or non-base-paired nucleotides), the “percent complementarity” for the query sequence is equal to the number of base-paired positions between the two sequences divided by the total number of positions in the query sequence over its length, which is then multiplied by 100%.

15 [0099] The use of the term “polynucleotide,” “nucleic acid sequence,” or “nucleic acid molecule” is not intended to limit the present disclosure to polynucleotides comprising deoxyribonucleic acid (DNA). For example, ribonucleic acid (RNA) molecules are also envisioned. Those of ordinary skill in the art will recognize that polynucleotides and nucleic acid molecules can comprise ribonucleotides and combinations of ribonucleotides and deoxyribonucleotides. Such
20 deoxyribonucleotides and ribonucleotides include both naturally occurring molecules and synthetic analogues. The polynucleotides of the present disclosure also encompass all forms of sequences including, but not limited to, single-stranded forms, double-stranded forms, hairpins, stem-and-loop structures, and the like. In an aspect, a nucleic acid molecule provided herein is a DNA molecule. In one aspect, a nucleic acid molecule provided herein is an RNA molecule. In
25 one aspect, a nucleic acid molecule provided herein is single-stranded. In one aspect, a nucleic acid molecule provided herein is double-stranded. A nucleic acid molecule can encode a polypeptide or a small RNA.

[00100] As used herein, the term “polypeptide” refers to a chain of at least two covalently linked amino acids. Polypeptides can be encoded by polynucleotides provided herein. Proteins
30 provided herein can be encoded by nucleic acid molecules provided herein. Proteins can comprise polypeptides provided herein. As used herein, a “protein” refers to a chain of amino acid residues

that is capable of providing structure or enzymatic activity to a cell. As used herein, a “coding sequence” refers to a nucleic acid sequence that encodes a protein.

[00101] As used herein, the term “CpG site” or “CG site” refers to a region of DNA sequence where a cytosine and guanine is separated by only one phosphate group.

5 [00102] As used herein, the term “CpG island” or “CG island” refers to CpG sites that occur with a high frequency.

[00103] As used herein, the term “codon” refers to a sequence of three nucleotides.

[00104] As used herein, the term “codon optimized” refers to a code that is modified for enhanced expression in a host cell of interest by replacing at least one codon of a sequence with
10 codons that are more frequently or most frequently used in the genes of the host cell while maintaining the original amino acid sequence.

[00105] As used herein, the term “enhancer” refers to a region of DNA sequence that operates to initiate, assist, affect, cause, and/or promote the transcription and expression of the associated transcribable DNA sequence or coding sequence, at least in certain tissue(s),
15 developmental stage(s) and/or condition(s). In an aspect, an enhancer is a *cis* enhancer. In one aspect, an enhancer is a *trans* enhancer.

[00106] Enhancer sequences can be identified by utilizing genomic techniques well known in the art. Non-limiting examples include use of a reporter gene and next-generation sequencing methods such as chromatin immunoprecipitation sequencing (ChIP-seq), DNase I hypersensitivity
20 sequencing (DNase-seq), micrococcal nuclease sequencing (MNase-seq), formaldehyde-assisted isolation of regulatory elements sequencing (FAIRE-seq), and assay for transposase accessible chromatin sequencing (ATAC-seq).

[00107] As used herein, the term “operably linked” refers to a functional linkage between a promoter or other regulatory element and an associated transcribable DNA sequence or coding
25 sequence of a gene (or transgene), such that the promoter, etc., operates to initiate, assist, affect, cause, and/or promote the transcription and expression of the associated transcribable DNA sequence or coding sequence, at least in certain tissue(s), developmental stage(s) and/or condition(s). As used herein, “regulatory elements” refer to any sequence elements that regulate, positively or negatively, the expression of an operably linked sequence. “Regulatory elements”
30 include, without being limiting, a promoter, an enhancer, a leader, a transcription start site (TSS), a linker, 5’ and 3’ untranslated regions (UTRs), an intron, a polyadenylation signal, and a

termination region or sequence, etc., that are suitable, necessary or preferred for regulating or allowing expression of the gene or transcribable DNA sequence in a cell. Such additional regulatory element(s) can be optional and used to enhance or optimize expression of the gene or transcribable DNA sequence.

5 [00108] As used herein, the term “promoter” refers to a DNA sequence that contains an RNA polymerase binding site, a transcription start site, and/or a TATA box and assists or promotes the transcription and expression of an associated transcribable polynucleotide sequence and/or gene (or transgene). A promoter can be synthetically produced, varied, or derived from a known or naturally occurring promoter sequence or other promoter sequence. A promoter can also include
10 a chimeric promoter comprising a combination of two or more heterologous sequences. A promoter of the present application can thus include variants of promoter sequences that are similar in composition, but not identical to, other promoter sequence(s) known or provided herein.

[00109] As used herein, an “intron” refers to a nucleotide sequence that is removed by RNA splicing as a messenger RNA (mRNA) matures from a mRNA precursor.

15 [00110] As used herein, “mRNA” or “messenger RNA” refers to a single stranded RNA that corresponds to the genetic sequence of a gene.

[00111] Expression of mRNA can be measured using any suitable method known in the art. Non-limiting examples of measuring mRNA expression include quantitative reverse transcriptase polymerase chain reaction (qRT-PCR), RNA blot (*e.g.*, a Northern blot), and RNA sequencing.
20 Differences in expression can be described as an absolute quantification or a relative quantification. *See*, for example, Livak and Schmittgen, *Methods*, 25:402-408 (2001).

[00112] As used herein, the term “glial” or “glial cell” refers to a non-neuronal cell in the CNS or the PNS. In an aspect, at least one glial cell is selected from the group consisting of at least one oligodendrocyte, at least one astrocyte, at least one NG2 cell, at least one ependymal cell,
25 and at least one microglia. In one aspect, at least one glial cell is at least one oligodendrocyte. In one aspect, at least one glial cell is at least one NG2 cell. In one aspect, at least one glial cell is at least one ependymal cell. In one aspect, at least one glial cell is at least one microglia. In one aspect, at least one glial cell is at least one reactive astrocyte. In one aspect, at least one astrocyte is at least one reactive astrocyte.

30 [00113] As used herein, the term “astrocyte” refers to a glial cell that is an important component of the brain. An astrocyte is involved in supporting neuronal functions such as synapse

formation and plasticity, potassium buffering, nutrient supply, the secretion and absorption of neural or glial transmitters, and maintenance of the blood–brain barrier. As used herein, the term “reactive astrocytes” refers to an abnormal status of astrocytes after injury or disease.

[00114] As used herein, the term “NG2 cell” or “polydendrocyte” refers to a glial cell that expresses chondroitin sulfate proteoglycan (CSPG4) and the alpha receptor for platelet-derived growth factor (PDGFRA).

[00115] As used herein, the term “neuron” or “neuronal cell” refers to an electrically excitable cell that communicates with other neurons via synapses. In an aspect, a neuron is selected from the group consisting of an unipolar neuron, a bipolar neuron, a pseudounipolar neuron, and a multipolar neuron. In one aspect, a neuron is an unipolar neuron. In one aspect, a neuron is a bipolar neuron. In one aspect, a neuron is apseudounipolar neuron. In one aspect, a neuron is a bipolar neuron. In one aspect, a neuron is selected from the group consisting of a sensory neuron, a motor neuron, and an interneuron. In one aspect, a neuron is a sensory neuron. In one aspect, a neuron is a motor neuron. In one aspect, a neuron is an interneuron.

[00116] As used herein, the term “functional neuron” refers to a neuron that can perform biological process. Without being limiting, examples of biological processes include processing and transmission of information and communication via chemical and electrical synapses.

[00117] As used herein, the term “glutamatergic neurons” refers to a subclass of neurons that produce glutamate and establish excitatory synapses. As used herein, the term “excitatory synapse” refers to a synapse in which an action potential in a presynaptic neuron increases the probability of an action potential occurring in a postsynaptic cell. As used herein, the term “action potential” or “nerve impulse” refers to an electrical impulse across the membrane of an axon. As used herein, the term “axon” or “nerve fiber” refers to a neuron that conducts action potentials. As used herein, the term “GABAergic neurons” refers to a subset of neurons that produce GABA and establish inhibitory synapses. As used herein, the term “GABA” or “*gamma*-Aminobutyric acid” refers to a compound that opens ion channels to allow the flow of negatively charged chloride ions into the cell or positively charged potassium ions out of the cell. As used herein, the term “inhibitory synapse” refers to a synapse that moves the membrane potential of a postsynaptic neuron away from the threshold for generating action potentials. As used herein, the term “dopaminergic neuron” refers to a subset of neurons that produce dopamine. As used herein, the term “dopamine” refers to a type of neurotransmitter. As used herein, the term “neurotransmitter”

refers to a class of endogenous chemicals that activate neurotransmissions. As used herein, the term “neurotransmission” refers to a process where neurotransmitters are released by the axon terminal of a neuron. As used herein, the term “acetyl cholinergic neuron” or “cholinergic neuron” refers to a subset of neurons that secrete acetylcholine. As used herein, the term “acetylcholine” refers to a type of neurotransmitter. As used herein, the term “serotonergic neuron” refers to a subset of neurons that synthesizes serotonin. As used herein, the term “serotonin” refers to a type of neurotransmitter. As used herein, an “epinephrinergic neuron” refers to a neuron that releases epinephrine as the neurotransmitter. As used herein, the term “motor neuron” refers to a subset of neurons where the cell body is located in the motor cortex, brainstem, or the spinal cord and the axon projects to the spinal cord or outside the spinal cord and directly or indirectly controls muscles and glands. As used herein, the term peptidergic neuron refers to a subset of neurons that utilize small peptide molecules as their neurotransmitter.

[00118] In an aspect, a neuron is a functional neuron. In one aspect, a functional neuron is selected from the group consisting of glutamatergic neurons, GABAergic neurons, dopaminergic neurons, cholinergic neurons, serotonergic neurons, epinephrinergic neurons, motor neurons, and peptidergic neurons. In one aspect, a functional neuron is a glutamatergic neuron. In one aspect, a functional neuron is a GABAergic neuron. In one aspect, a functional neuron is a dopaminergic neuron. In one aspect, a functional neuron is a cholinergic neuron. In one aspect, a functional neuron is a serotonergic neuron. In one aspect, a functional neuron is an epinephrinergic neuron. In one aspect, a functional neuron is a motor neuron. In one aspect, a functional neuron is a peptidergic neuron.

[00119] As used herein, the term “converting” or “converted” refers to a cell type changing its physical morphology and/or biological function into a different physical morphology and/or different biological function. In an aspect, this disclosure provides the conversion of at least one glial cell into at least one neuron. In one aspect, conversion of at least one glial cell to at least one neuron occurs in the CNS or PNS. In one aspect, conversion of at least one glial cell to at least one neuron occurs in the CNS. In one aspect, conversion of at least one glial cell to at least one neuron occurs in the PNS.

[00120] In an aspect, this disclosure provides, and includes, an adeno-associated virus (AAV) vector comprising a human neurogenic differentiation 1 (hNeuroD1) sequence comprising the nucleic acid sequence of SEQ ID NO: 6, where the hNeuroD1 sequence is operably linked to

regulatory elements comprising: (a) a glial fibrillary acid protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15; (b) an enhancer from a human elongation factor-1 alpha (EF1- α) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11; (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NO: 7 and 18; and (e) a SV40 polyadenylation signal sequence comprising the nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

[00121] In an aspect, this disclosure provides an adeno-associated virus (AAV) vector comprising a nucleic acid coding sequence encoding a human neurogenic differentiation 1 (hNeuroD1) protein comprising the amino acid sequence of SEQ ID NO: 10, where the coding sequence is operably linked to regulatory elements comprising: (a) a glial fibrillary acid protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15; (b) an enhancer from a human elongation factor-1 alpha (EF-1 alpha) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11; (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16; a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18; and a SV40 polyadenylation signal sequence with a nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

[00122] In an aspect, this disclosure provides, and includes, an adeno-associated virus (AAV) vector comprising a neurogenic differentiation 1 (NeuroD1) nucleic acid coding sequence encoding a NeuroD1 protein, where the coding sequence is operably linked to regulatory elements comprising: (a) a glial fibrillary acid protein (GFAP) promoter; (b) an enhancer; (c) a chimeric intron; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE); and (e) a polyadenylation signal sequence.

[00123] In an aspect, this disclosure provides, and includes, a composition comprising an adeno-associated virus (AAV) vector for converting glial cells to functional neurons in a human, where the AAV vector comprises a human neurogenic differentiation 1 (hNeuroD1) sequence having a nucleic acid sequence of SEQ ID NO: 6, and where the sequence is operably linked to regulatory elements comprising: (a) a human glial fibrillary acid protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15; (b) an enhancer from the human elongation factor-1 alpha (EF-1 alpha) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11; (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18; and (e) a SV40 polyadenylation signal sequence comprising the nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

[00124] In an aspect, this disclosure provides, and includes, a composition comprising an adeno-associated virus (AAV) vector for converting glial cells to functional neurons in a human, where the AAV vector comprises a nucleic acid coding sequence encoding a human neurogenic differentiation 1 (hNeuroD1) protein comprising the amino acid sequence of SEQ ID NO: 10, and where the coding sequence is operably linked to regulatory elements comprising: (a) a human glial fibrillary acid protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15; (b) an enhancer from the human elongation factor-1 alpha (EF-1 alpha) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11; (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18; and (e) a SV40 polyadenylation signal sequence comprising the nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

[00125] In an aspect, this disclosure provides, and includes, a composition comprising an adeno-associated virus (AAV) vector for the treatment of a subject in need thereof, where the AAV vector comprises a neurogenic differentiation 1 (NeuroD1) sequence operably linked to expression control elements comprising: (a) a glial fibrillary acid protein (GFAP) promoter; (b) an enhancer; 5 (c) a chimeric intron; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE); and (e) a polyadenylation signal.

[00126] In an aspect, an AAV vector comprises a nucleic acid sequence encoding an AAV protein. In one aspect, an AAV vector comprises a nucleic acid sequence encoding a viral protein. Non-limiting examples of AAV proteins and viral proteins include *rep* and *cap* proteins.

10 [00127] Neurogenic differentiation 1 (NeuroD1; also referred to as $\beta 2$) is a basic helix-loop-helix (bHLH) transcription factor that forms heterodimers with other bHLH proteins to activate transcription of genes that contain a DNA sequence known as an E-box.

[00128] In an aspect, a NeuroD1 sequence is a human NeuroD1 (hNeuroD1) sequence. In one aspect, a NeuroD1 sequence is selected from the group consisting of a chimpanzee NeuroD1 15 sequence, a bonobo NeuroD1 sequence, an orangutan NeuroD1 sequence, a gorilla NeuroD1 sequence, a macaque NeuroD1 sequence, a marmoset NeuroD1 sequence, a capuchin NeuroD1 sequence, a baboon NeuroD1 sequence, a gibbon NeuroD1 sequence, and a lemur NeuroD1 sequence. In one aspect, a NeuroD1 sequence is a chimpanzee NeuroD1 sequence. In one aspect, a NeuroD1 sequence is a bonobo NeuroD1 sequence. In one aspect, a NeuroD1 sequence is an orangutan NeuroD1 sequence. In one aspect, a NeuroD1 sequence is a gorilla NeuroD1 sequence. In one aspect, a NeuroD1 sequence is a macaque NeuroD1 sequence. In one aspect, a NeuroD1 20 sequence is a marmoset NeuroD1 sequence. In one aspect, a NeuroD1 sequence is a capuchin NeuroD1 sequence. In one aspect, a NeuroD1 sequence is a baboon NeuroD1 sequence. In one aspect, a NeuroD1 sequence is a gibbon NeuroD1 sequence. In one aspect, a NeuroD1 sequence is a lemur NeuroD1 sequence. 25

[00129] In an aspect, a NeuroD1 nucleic acid sequence comprises a sequence at least 70% identical to SEQ ID NO: 6, or the complement thereof. In one aspect, a NeuroD1 nucleic acid sequence comprises a sequence at least 75% identical to SEQ ID NO: 6, or the complement thereof. In one aspect, a NeuroD1 nucleic acid sequence comprises a sequence at least 80% identical to 30 SEQ ID NO: 6, or the complement thereof. In one aspect, a NeuroD1 nucleic acid sequence comprises a sequence at least 85% identical to SEQ ID NO: 6, or the complement thereof. In one

aspect, a NeuroD1 nucleic acid sequence comprises a sequence at least 90% identical to SEQ ID NO: 6, or the complement thereof. In one aspect, a NeuroD1 nucleic acid sequence comprises a sequence at least 91% identical to SEQ ID NO: 6, or the complement thereof. In one aspect, a NeuroD1 nucleic acid sequence comprises a sequence at least 92% identical to SEQ ID NO: 6, or the complement thereof. In one aspect, a NeuroD1 nucleic acid sequence comprises a sequence at least 93% identical to SEQ ID NO: 6, or the complement thereof. In one aspect, a NeuroD1 nucleic acid sequence comprises a sequence at least 94% identical to SEQ ID NO: 6, or the complement thereof. In one aspect, a NeuroD1 nucleic acid sequence comprises a sequence at least 95% identical to SEQ ID NO: 6, or the complement thereof. In one aspect, a NeuroD1 nucleic acid sequence comprises a sequence at least 96% identical to SEQ ID NO: 6, or the complement thereof. In one aspect, a NeuroD1 nucleic acid sequence comprises a sequence at least 97% identical to SEQ ID NO: 6, or the complement thereof. In one aspect, a NeuroD1 nucleic acid sequence comprises a sequence at least 98% identical to SEQ ID NO: 6, or the complement thereof. In one aspect, a NeuroD1 nucleic acid sequence comprises a sequence at least 99% identical to SEQ ID NO: 6, or the complement thereof. In one aspect, a NeuroD1 nucleic acid sequence comprises a sequence at least 99.5% identical to SEQ ID NO: 6, or the complement thereof. In one aspect, a NeuroD1 nucleic acid sequence comprises a sequence at least 99.8% identical to SEQ ID NO: 6, or the complement thereof. In one aspect, a NeuroD1 nucleic acid sequence comprises a sequence at least 99.9% identical to SEQ ID NO: 6, or the complement thereof. In one aspect, a NeuroD1 nucleic acid sequence comprises a sequence 100% identical to SEQ ID NO: 6, or the complement thereof.

[00130] In an aspect, a nucleic acid coding sequence encodes a NeuroD1 protein comprising an amino acid sequence at least 70% identical or similar to SEQ ID NO: 10. In one aspect, a nucleic acid coding sequence encodes a NeuroD1 protein comprising an amino acid sequence at least 75% identical or similar to SEQ ID NO: 10. In one aspect, a nucleic acid coding sequence encodes a NeuroD1 protein comprising an amino acid sequence at least 80% identical or similar to SEQ ID NO: 10. In one aspect, a nucleic acid coding sequence encodes a NeuroD1 protein comprising an amino acid sequence at least 85% identical or similar to SEQ ID NO: 10. In one aspect, a nucleic acid coding sequence encodes a NeuroD1 protein comprising an amino acid sequence at least 90% identical or similar to SEQ ID NO: 10. In one aspect, a nucleic acid coding sequence encodes a NeuroD1 protein comprising an amino acid sequence at least 91% identical or

similar to SEQ ID NO: 10. In one aspect, a nucleic acid coding sequence encodes a NeuroD1 protein comprising an amino acid sequence at least 92% identical or similar to SEQ ID NO: 10. In one aspect, a nucleic acid coding sequence encodes a NeuroD1 protein comprising an amino acid sequence at least 93% identical or similar to SEQ ID NO: 10. In one aspect, a nucleic acid coding sequence encodes a NeuroD1 protein comprising an amino acid sequence at least 94% identical or similar to SEQ ID NO: 10. In one aspect, a nucleic acid coding sequence encodes a NeuroD1 protein comprising an amino acid sequence at least 95% identical or similar to SEQ ID NO: 10. In one aspect, a nucleic acid coding sequence encodes a NeuroD1 protein comprising an amino acid sequence at least 96% identical or similar to SEQ ID NO: 10. In one aspect, a nucleic acid coding sequence encodes a NeuroD1 protein comprising an amino acid sequence at least 97% identical or similar to SEQ ID NO: 10. In one aspect, a nucleic acid coding sequence encodes a NeuroD1 protein comprising an amino acid sequence at least 98% identical or similar to SEQ ID NO: 10. In one aspect, a nucleic acid coding sequence encodes a NeuroD1 protein comprising an amino acid sequence at least 99% identical or similar to SEQ ID NO: 10. In one aspect, a nucleic acid coding sequence encodes a NeuroD1 protein comprising an amino acid sequence at least 99.5% identical or similar to SEQ ID NO: 10. In one aspect, a nucleic acid coding sequence encodes a NeuroD1 protein comprising an amino acid sequence at least 99.8% identical or similar to SEQ ID NO: 10. In one aspect, a nucleic acid coding sequence encodes a NeuroD1 protein comprising an amino acid sequence at least 99.9% identical or similar to SEQ ID NO: 10. In one aspect, a nucleic acid coding sequence encodes a NeuroD1 protein comprising an amino acid sequence 100% identical or similar to SEQ ID NO: 10.

[00131] Glial fibrillary acid protein (GFAP); also referred to as glial fibrillary acidic protein is a member of the type III intermediate filament family of proteins that is expressed in the central nervous system and plays a role in cell communication and the functioning of the blood-brain barrier.

[00132] In an aspect, the promoter is selected from the group consisting of GFAP promoter, Sox9 promoter, S100b promoter, Aldh1l1 promoter, Lipocalin 2 (Lcn2) promoter, glutamine synthetase promoter, Aquaporin-4 (AQP4) promoter, oligodendrocyte transcription factor (Olig2) promoter, and synapsin promoter, NG2 promoter, ionized calcium binding adaptor molecule 1 (Iba1) promoter, cluster of differentiation 86 (CD86) promoter, platelet-derived growth factor receptor alpha (PDGFRA) promoter, platelet-derived growth factor receptor beta (PDGFRB)

promoter, elongation factor 1-alpha (EF1a) promoter, CAG promoter, cytomegalovirus (CMV) promoter, ubiquitin promoter. In one aspect, the promoter is GFAP promoter. In one aspect, the promoter is a truncated GFAP promoter. In one aspect, the promoter is Sox9 promoter. In one aspect, the promoter is S100b promoter. In one aspect, the promoter is Aldhl1 promoter. In one aspect, the promoter is Lcn2 promoter. In one aspect, the promoter is glutamine synthetase promoter. In one aspect, the promoter is AQP4 promoter. In one aspect, the promoter is Olig2 promoter. In one aspect, the promoter is synapsin promoter. In one aspect, the promoter is Iba1 promoter. In one aspect, the promoter is CD86 promoter. In one aspect, the promoter is PDGFRA promoter. In one aspect, the promoter is PDGFRB promoter. In one aspect, the promoter is EF1a promoter. In one aspect, the promoter is CAG promoter. In one aspect, the promoter is CMV promoter. In one aspect, the promoter is ubiquitin promoter.

[00133] In an aspect, a GFAP promoter is a promoter directing astrocyte-specific expression of a protein called glial fibrillary acidic protein (GFAP) in cells. In one aspect, a GFAP promoter sequence is a human GFAP (hGFAP) promoter sequence. In one aspect, a GFAP promoter is selected from the group consisting of GfaABC1D, Gfa1.6, and hGFA2.2. In one aspect, a GFAP promoter is selected from the group consisting of GfaABC1D, Gfa1.6, hGFA2.2, and pGfa681. In one aspect, a GFAP promoter is GfaABC1D. In one aspect, a GFAP promoter is Gfa1.6. In one aspect, a GFAP promoter is hGFA2.2. In one aspect, a GFAP promoter is pGfa681. In one aspect, pGfa681 is SEQ ID NO: 15. In one aspect, GFAP GfaABC1D is SEQ ID NO: 15. In one aspect, GFAP Gfa1.6 is SEQ ID NO: 4. In one aspect, hGfa2.2 is SEQ ID NO: 12. In one aspect, a GFAP promoter is selected from the group consisting of SEQ ID NOs: 4, 12, and 15. In one aspect, a GFAP promoter is SEQ ID NO: 15. In one aspect, a GFAP promoter is SEQ ID NO: 4. In one aspect, a GFAP promoter is SEQ ID NO: 12.

[00134] In one aspect, a GFAP promoter sequence is selected from the group consisting of a chimpanzee GFAP promoter sequence, a bonobo GFAP promoter sequence, an orangutan GFAP promoter sequence, a gorilla GFAP promoter sequence, a macaque GFAP promoter sequence, a marmoset GFAP promoter sequence, a capuchin GFAP promoter sequence, a baboon GFAP promoter sequence, a gibbon GFAP promoter sequence, and a lemur GFAP promoter sequence. In one aspect, a GFAP promoter sequence is a chimpanzee GFAP promoter sequence. In one aspect, a GFAP promoter sequence is a bonobo GFAP promoter sequence. In one aspect, a GFAP promoter sequence is an orangutan GFAP promoter sequence. In one aspect, a GFAP promoter

sequence is a gorilla GFAP promoter sequence. In one aspect, a GFAP promoter sequence is a macaque GFAP promoter sequence. In one aspect, a GFAP promoter sequence is a marmoset GFAP promoter sequence. In one aspect, a GFAP promoter sequence is a capuchin GFAP promoter sequence. In one aspect, a GFAP promoter sequence is a baboon GFAP promoter sequence. In one aspect, a GFAP promoter sequence is a gibbon GFAP promoter sequence. In one aspect, a GFAP promoter sequence is a lemur GFAP promoter sequence.

[00135] In an aspect, a GFAP promoter sequence comprises at least 100 nucleotides. In one aspect, a GFAP promoter comprises at least 500 nucleotides. In a further aspect, a GFAP promoter comprises at least 1000 nucleotides. In still another aspect, a GFAP promoter comprises at least 1500 nucleotides.

[00136] It is appreciated in the art that a fragment of a promoter sequence can function to drive transcription of an operably linked nucleic acid molecule. For example, without being limiting, if a 1000 nucleotides promoter is truncated to 500 nucleotides, and the 500 nucleotides fragment is capable of driving transcription, the 500 nucleotides fragment is referred to as a “functional fragment.”

[00137] In an aspect, a promoter comprises at least 10 nucleotides. In one aspect, a promoter comprises at least 50 nucleotides. In one aspect, a promoter comprises at least 100 nucleotides. In one aspect, an intron comprises at least 150 nucleotides. In one aspect, a promoter comprises at least 200 nucleotides. In one aspect, a promoter comprises at least 250 nucleotides. In one aspect, a promoter comprises at least 300 nucleotides. In one aspect, a promoter comprises at least 350 nucleotides. In one aspect, a promoter comprises at least 400 nucleotides. In one aspect, a promoter comprises at least 450 nucleotides. In one aspect, a promoter comprises at least 500 nucleotides. In one aspect, a promoter comprises between 50 nucleotides and 7500 nucleotides. In one aspect, a promoter comprises between 50 nucleotides and 5000 nucleotides. In one aspect, a promoter comprises between 50 nucleotides and 2500 nucleotides. In one aspect, a promoter comprises between 50 nucleotides and 1000 nucleotides. In one aspect, a promoter comprises between 50 nucleotides and 500 nucleotides. In one aspect, a promoter comprises between 10 nucleotides and 7500 nucleotides. In one aspect, a promoter comprises between 10 nucleotides and 5000 nucleotides. In one aspect, a promoter comprises between 10 nucleotides and 2500 nucleotides. In one aspect, a promoter comprises between 10 nucleotides and 1000 nucleotides. In one aspect, a promoter comprises between 10 nucleotides and 500 nucleotides.

[00138] In an aspect, a GFAP promoter nucleic acid sequence comprises a sequence at least 70% identical to a sequence selected from the group consisting of SEQ ID NOs: 4, 12, 15, and functional fragment thereof. In one aspect, a GFAP promoter nucleic acid sequence comprises a sequence at least 75% identical to a sequence selected from the group consisting of SEQ ID NOs: 4, 12, 15, and functional fragment thereof. In one aspect, a GFAP promoter nucleic acid sequence comprises a sequence at least 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 4, 12, 15, and functional fragment thereof. In one aspect, a GFAP promoter nucleic acid sequence comprises a sequence at least 85% identical to a sequence selected from the group consisting of SEQ ID NOs: 4, 12, 15, and functional fragment thereof. In one aspect, a GFAP promoter nucleic acid sequence comprises a sequence at least 90% identical to a sequence selected from the group consisting of SEQ ID NOs: 4, 12, 15, and functional fragment thereof. In one aspect, a GFAP promoter nucleic acid sequence comprises a sequence at least 91% identical to a sequence selected from the group consisting of SEQ ID NOs: 4, 12, 15, and functional fragment thereof. In one aspect, a GFAP promoter nucleic acid sequence comprises a sequence at least 92% identical to SEQ ID NOs: 4, 12, 15, and functional fragment thereof. In one aspect, a GFAP promoter nucleic acid sequence comprises a sequence at least 93% identical to a sequence selected from the group consisting of SEQ ID NOs: 4, 12, 15, and functional fragment thereof. In one aspect, a GFAP promoter nucleic acid sequence comprises a sequence at least 94% identical to a sequence selected from the group consisting of SEQ ID NOs: 4, 12, 15, and functional fragment thereof. In one aspect, a GFAP promoter nucleic acid sequence comprises a sequence at least 95% identical to a sequence selected from the group consisting of SEQ ID NOs: 4, 12, 15, and functional fragment thereof. In one aspect, a GFAP promoter nucleic acid sequence comprises a sequence at least 96% identical to a sequence selected from the group consisting of SEQ ID NOs: 4, 12, 15, and functional fragment thereof. In one aspect, a GFAP promoter nucleic acid sequence comprises a sequence at least 97% identical to a sequence selected from the group consisting of SEQ ID NOs: 4, 12, 15, and functional fragment thereof. In one aspect, a GFAP promoter nucleic acid sequence comprises a sequence at least 98% identical to a sequence selected from the group consisting of SEQ ID NOs: 4, 12, 15, and functional fragment thereof. In one aspect, a GFAP promoter nucleic acid sequence comprises a sequence at least 99% identical to a sequence selected from the group consisting of SEQ ID NOs: 4, 12, 15, and functional fragment thereof. In one aspect, a GFAP promoter nucleic acid sequence comprises a sequence at least 99.5% identical to a sequence

selected from the group consisting of SEQ ID NOs: 4, 12, 15, and functional fragment thereof. In one aspect, a GFAP promoter nucleic acid sequence comprises a sequence at least 99.8% identical to a sequence selected from the group consisting of SEQ ID NOs: 4, 12, 15, and functional fragment thereof. In one aspect, a GFAP promoter nucleic acid sequence comprises a sequence at least 99.9% identical to a sequence selected from the group consisting of SEQ ID NOs: 4, 12, 15, and functional fragment thereof. In one aspect, a GFAP promoter nucleic acid sequence comprises a sequence 100% identical to a sequence selected from the group consisting of SEQ ID NOs: 4, 12, 15, and functional fragment thereof.

[00139] In an aspect, a nucleic acid sequence as provided herein is codon optimized.

10 [00140] In an aspect, a nucleic acid sequence as provided herein is CpG site depleted.

[00141] As used herein, the term “brain” refers to an organ that functions as the center of the nervous system. In an aspect, a brain comprises a cerebrum, a cerebral cortex, a cerebellum, and/or a brain stem.

[00142] As used herein, the term “cerebral cortex” refers to the outer layer of neural tissue of the cerebrum.

[00143] As used herein, the term “striatum” or “corpus striatum” refers to a cluster of neurons in the subcortical basal ganglia of the forebrain and comprises the ventral striatum and dorsal striatum.

[00144] As used herein, the term “substantia nigra” refers to a cluster of neurons in the subcortical basal ganglia of the midbrain and comprises the pars compacta and the pars reticulata.

[00145] As used herein, the term “forebrain” refers to the forward-most portion of the brain.

[00146] As used herein, the term “putamen” refers to a round structure at the base of the forebrain and is a component of the dorsal striatum.

[00147] As used herein, the term “caudate nucleus” refers to a structure at the base of the forebrain and is a component of the dorsal striatum.

[00148] As used herein, the term “subcortical basal ganglia” refers to a cluster of neurons in the deep cerebral hemispheres of the brain.

[00149] As used herein, the term “spinal cord” refers to a structure that functions in the transmission of nerve signals from the motor cortex to the body.

30 [00150] As used herein, the term “motor cortex” refers to a region in the frontal lobe of the cerebral cortex that is involved in the planning, control, and execution of voluntary movements.

[00151] In one aspect, a method provided herein converts reactive astrocytes to functional neurons in the brain. In an aspect, a method provided herein converts reactive astrocytes to functional neurons in a cerebral cortex of the brain. In one aspect, a method provided herein converts reactive astrocytes to functional neurons in a striatum of the brain. In one aspect, a method provided herein converts reactive astrocytes to functional neurons in a dorsal striatum of the brain. In one aspect, a method provided herein converts reactive astrocytes to functional neurons in a spinal cord of the brain. In one aspect, a method provided herein converts reactive astrocytes to functional neurons in a putamen of the brain. In one aspect, a method provided herein converts reactive astrocytes to functional neurons in a caudate nucleus of the brain. In one aspect, a method provided herein converts reactive astrocytes to functional neurons in a substantia nigra of the brain.

[00152] Elongation factor-1 alpha (EF-1 alpha; also referred to as eEF1a1) is an isoform of the alpha subunit of the elongation factor 1 complex. The complex is involved in the enzymatic delivery of aminoacyl tRNAs to the ribosome. The EF-1 alpha isoform is expressed in the brain, placenta, lung, liver, kidney, and pancreas.

[00153] In an aspect, an enhancer sequence from the EF-1 alpha promoter is a human enhancer sequence from the EF-1 alpha promoter. In one aspect, an enhancer sequence from the EF-1 alpha promoter is selected from the group consisting of a chimpanzee enhancer sequence from the EF-1 alpha promoter, a bonobo enhancer sequence from the EF-1 alpha promoter, an orangutan enhancer sequence from the EF-1 alpha promoter, a gorilla enhancer sequence from the EF-1 alpha promoter, a macaque enhancer sequence from the EF-1 alpha promoter, a marmoset enhancer sequence from the EF-1 alpha promoter, a capuchin enhancer sequence from the EF-1 alpha promoter, a baboon enhancer sequence from the EF-1 alpha promoter, a gibbon enhancer sequence from the EF-1 alpha promoter, and a lemur enhancer sequence from the EF-1 alpha promoter. In one aspect, an enhancer sequence from the EF-1 alpha promoter is a chimpanzee enhancer sequence from the EF-1 alpha promoter. In one aspect, an enhancer sequence from the EF-1 alpha promoter is a bonobo enhancer sequence from the EF-1 alpha promoter. In one aspect, an enhancer sequence from the EF-1 alpha promoter is an orangutan enhancer sequence from the EF-1 alpha promoter. In one aspect, an enhancer sequence from the EF-1 alpha promoter is a gorilla enhancer sequence from the EF-1 alpha promoter. In one aspect, an enhancer sequence from the EF-1 alpha promoter is a macaque enhancer sequence from the EF-1 alpha promoter. In one aspect, an enhancer sequence from the EF-1 alpha promoter is a marmoset enhancer sequence

from the EF-1 alpha promoter. In one aspect, enhancer sequence from the EF-1 alpha promoter is a capuchin enhancer sequence from the EF-1 alpha promoter. In one aspect, enhancer sequence from the EF-1 alpha promoter is a baboon enhancer sequence from the EF-1 alpha promoter. In one aspect, enhancer sequence from the EF-1 alpha promoter is a gibbon enhancer sequence from the EF-1 alpha promoter. In one aspect, enhancer sequence from the EF-1 alpha promoter is a lemur enhancer sequence from the EF-1 alpha promoter.

[00154] In an aspect, an enhancer from the EF-1 alpha promoter nucleic acid sequence comprises a sequence at least 70% identical to SEQ ID NO: 2, or the complement thereof. In one aspect, an enhancer from the EF-1 alpha promoter nucleic acid sequence comprises a sequence at least 75% identical to SEQ ID NO: 2, or the complement thereof. In one aspect, an enhancer from the EF-1 alpha promoter nucleic acid sequence comprises a sequence at least 80% identical to SEQ ID NO: 2, or the complement thereof. In one aspect, an enhancer from the EF-1 alpha promoter nucleic acid sequence comprises a sequence at least 85% identical to SEQ ID NO: 2, or the complement thereof. In one aspect, an enhancer from the EF-1 alpha promoter nucleic acid sequence comprises a sequence at least 90% identical to SEQ ID NO: 2, or the complement thereof. In one aspect, an enhancer from the EF-1 alpha promoter nucleic acid sequence comprises a sequence at least 91% identical to SEQ ID NO: 2, or the complement thereof. In one aspect, an enhancer from the EF-1 alpha promoter nucleic acid sequence comprises a sequence at least 92% identical to SEQ ID NO: 2, or the complement thereof. In one aspect, an enhancer from the EF-1 alpha promoter nucleic acid sequence comprises a sequence at least 93% identical to SEQ ID NO: 2, or the complement thereof. In one aspect, an enhancer from the EF-1 alpha promoter nucleic acid sequence comprises a sequence at least 94% identical to SEQ ID NO: 2, or the complement thereof. In one aspect, an enhancer from the EF-1 alpha promoter nucleic acid sequence comprises a sequence at least 95% identical to SEQ ID NO: 2, or the complement thereof. In one aspect, an enhancer from the EF-1 alpha promoter nucleic acid sequence comprises a sequence at least 96% identical to SEQ ID NO: 2, or the complement thereof. In one aspect, an enhancer from the EF-1 alpha promoter nucleic acid sequence comprises a sequence at least 97% identical to SEQ ID NO: 2, or the complement thereof. In one aspect, an enhancer from the EF-1 alpha promoter nucleic acid sequence comprises a sequence at least 98% identical to SEQ ID NO: 2, or the complement thereof. In one aspect, an enhancer from the EF-1 alpha promoter nucleic acid sequence comprises a sequence at least 99% identical to SEQ ID NO: 2, or the complement thereof. In one aspect, an

enhancer from the EF-1 alpha promoter nucleic acid sequence comprises a sequence at least 99.5% identical to SEQ ID NO: 2, or the complement thereof. In one aspect, an enhancer from the EF-1 alpha promoter nucleic acid sequence comprises a sequence at least 99.8% identical to SEQ ID NO: 2, or the complement thereof. In one aspect, an enhancer from the EF-1 alpha promoter nucleic acid sequence comprises a sequence at least 99.9% identical to SEQ ID NO: 2, or the complement thereof. In one aspect, an enhancer from the EF-1 alpha promoter nucleic acid sequence comprises a sequence 100% identical to SEQ ID NO: 2, or the complement thereof.

[00155] Cytomegalovirus (CMV) is a genus of viruses in the order *Herpesvirale*.

[00156] In an aspect, an enhancer sequence from the CMV is a human enhancer sequence from the CMV. In one aspect, an enhancer sequence from the CMV is selected from the group consisting of a chimpanzee enhancer sequence from the CMV, a bonobo enhancer sequence from the CMV, an orangutan enhancer sequence from the CMV, a gorilla enhancer sequence from the CMV, a macaque enhancer sequence from the CMV, a marmoset enhancer sequence from the CMV, a capuchin enhancer sequence from the CMV, a baboon enhancer sequence from the CMV, a gibbon enhancer sequence from the CMV, and a lemur enhancer sequence from the CMV. In one aspect, an enhancer sequence from the CMV is a chimpanzee enhancer sequence from the CMV. In one aspect, an enhancer sequence from the CMV is a bonobo enhancer sequence from the CMV. In one aspect, an enhancer sequence from the CMV is an orangutan enhancer sequence from the CMV. In one aspect, an enhancer sequence from the CMV is a gorilla enhancer sequence from the CMV. In one aspect, an enhancer sequence from the CMV is a macaque enhancer sequence from the CMV. In one aspect, an enhancer sequence from the CMV is a marmoset enhancer sequence from the CMV. In one aspect, an enhancer sequence from the CMV is a capuchin enhancer sequence from the CMV. In one aspect, an enhancer sequence from the CMV is a baboon enhancer sequence from the CMV. In one aspect, an enhancer sequence from the CMV is a gibbon enhancer sequence from the CMV. In one aspect, an enhancer sequence from the CMV is a lemur enhancer sequence from the CMV.

[00157] In an aspect, an enhancer from the CMV nucleic acid sequence comprises a sequence at least 70% identical to SEQ ID NO: 11, or the complement thereof. In one aspect, an enhancer from the CMV nucleic acid sequence comprises a sequence at least 75% identical to SEQ ID NO: 11, or the complement thereof. In one aspect, an enhancer from the CMV nucleic acid sequence comprises a sequence at least 80% identical to SEQ ID NO: 11, or the complement

thereof. In one aspect, an enhancer from the CMV nucleic acid sequence comprises a sequence at least 85% identical to SEQ ID NO: 11, or the complement thereof. In one aspect, an enhancer from the CMV nucleic acid sequence comprises a sequence at least 90% identical to SEQ ID NO: 11, or the complement thereof. In one aspect, an enhancer from the CMV nucleic acid sequence comprises a sequence at least 91% identical to SEQ ID NO: 11, or the complement thereof. In one aspect, an enhancer from the CMV nucleic acid sequence comprises a sequence at least 92% identical to SEQ ID NO: 11, or the complement thereof. In one aspect, an enhancer from the CMV nucleic acid sequence comprises a sequence at least 93% identical to SEQ ID NO: 11, or the complement thereof. In one aspect, an enhancer from the CMV nucleic acid sequence comprises a sequence at least 94% identical to SEQ ID NO: 11, or the complement thereof. In one aspect, an enhancer from the CMV nucleic acid sequence comprises a sequence at least 95% identical to SEQ ID NO: 11, or the complement thereof. In one aspect, an enhancer from the CMV nucleic acid sequence comprises a sequence at least 96% identical to SEQ ID NO: 11, or the complement thereof. In one aspect, an enhancer from the CMV nucleic acid sequence comprises a sequence at least 97% identical to SEQ ID NO: 11, or the complement thereof. In one aspect, an enhancer from the CMV nucleic acid sequence comprises a sequence at least 98% identical to SEQ ID NO: 11, or the complement thereof. In one aspect, an enhancer from the CMV nucleic acid sequence comprises a sequence at least 99% identical to SEQ ID NO: 11, or the complement thereof. In one aspect, an enhancer from the CMV nucleic acid sequence comprises a sequence at least 99.5% identical to SEQ ID NO: 11, or the complement thereof. In one aspect, an enhancer from the CMV nucleic acid sequence comprises a sequence at least 99.8% identical to SEQ ID NO: 11, or the complement thereof. In one aspect, an enhancer from the CMV nucleic acid sequence comprises a sequence at least 99.9% identical to SEQ ID NO: 11, or the complement thereof. In one aspect, an enhancer from the CMV nucleic acid sequence comprises a sequence 100% identical to SEQ ID NO: 11, or the complement thereof.

[00158] In an aspect, an enhancer is selected from the group consisting of an enhancer from EF1- α promoter and CMV enhancer. In one aspect, an enhancer is from EF1- α promoter. In one aspect, an enhancer is an CMV enhancer.

[00159] In an aspect, a vector of the present disclosures comprises a chimeric intron. In an aspect the chimeric intron is composed of the 5'-donor site from the first intron of the human β -globin gene and the branch and 3'-acceptor site from the intron of an immunoglobulin gene heavy

chain variable region. In an aspect, the chimeric intron is a chimeric intron of a rabbit beta-globin and a chicken beta actin similar in CAG promoter. In an aspect, a vector of the present disclosure comprises a glial fibrillary acid protein (GFAP) intron. In an aspect, a vector of the present disclosure comprises a glial fibrillary acid protein (GFAP) first intron.

5 [00160] Introns can be grouped into at least five classes, including: spliceosomal introns; transfer RNA introns; group I introns; group II introns; and group III introns. An intron can be synthetically produced, varied, or derived from a known or naturally occurring intron sequence or other intron sequence. An intron can also include a chimeric intron comprising a combination of two or more heterologous sequences. An intron of the present application can thus include variants
10 of intron sequences that are similar in composition, but not identical to, other intron sequence(s) known or provided herein. In an aspect, an intron comprises at least 10 nucleotides. In one aspect, an intron comprises at least 50 nucleotides. In one aspect, an intron comprises at least 100 nucleotides. In one aspect, an intron comprises at least 150 nucleotides. In one aspect, an intron comprises at least 200 nucleotides. In one aspect, an intron comprises at least 250 nucleotides. In
15 one aspect, an intron comprises at least 300 nucleotides. In one aspect, an intron comprises at least 350 nucleotides. In one aspect, an intron comprises at least 400 nucleotides. In one aspect, an intron comprises at least 450 nucleotides. In one aspect, an intron comprises at least 500 nucleotides. In one aspect, an intron comprises between 50 nucleotides and 7500 nucleotides. In one aspect, an intron comprises between 50 nucleotides and 5000 nucleotides. In one aspect, an
20 intron comprises between 50 nucleotides and 2500 nucleotides. In one aspect, an intron comprises between 50 nucleotides and 1000 nucleotides. In one aspect, an intron comprises between 50 nucleotides and 500 nucleotides. In one aspect, an intron comprises between 10 nucleotides and 7500 nucleotides. In one aspect, an intron comprises between 10 nucleotides and 5000 nucleotides. In one aspect, an intron comprises between 10 nucleotides and 2500 nucleotides. In one aspect,
25 an intron comprises between 10 nucleotides and 1000 nucleotides. In one aspect, an intron comprises between 10 nucleotides and 500 nucleotides.

[00161] In an aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 70% identical to SEQ ID NO: 5, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 75% identical to SEQ ID NO: 5, or the
30 complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 80% identical to SEQ ID NO: 5, or the complement thereof. In one aspect, a chimeric

intron nucleic acid sequence comprises a sequence at least 85% identical to SEQ ID NO: 5, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 90% identical to SEQ ID NO: 5, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 91% identical to SEQ ID NO: 5, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 92% identical to SEQ ID NO: 5, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 93% identical to SEQ ID NO: 5, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 94% identical to SEQ ID NO: 5, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 95% identical to SEQ ID NO: 5, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 96% identical to SEQ ID NO: 5, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 97% identical to SEQ ID NO: 5, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 98% identical to SEQ ID NO: 5, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 99% identical to SEQ ID NO: 5, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 99.5% identical to SEQ ID NO: 5, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 99.8% identical to SEQ ID NO: 5, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 99.9% identical to SEQ ID NO: 5, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence 100% identical to SEQ ID NO: 5, or the complement thereof.

[00162] In an aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 70% identical to SEQ ID NO: 16, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 75% identical to SEQ ID NO: 16, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 80% identical to SEQ ID NO: 16, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 85% identical to SEQ ID NO: 16, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 90% identical to SEQ ID NO: 16, or the complement thereof. In one aspect, a

chimeric intron nucleic acid sequence comprises a sequence at least 91% identical to SEQ ID NO: 16, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 92% identical to SEQ ID NO: 16, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 93% identical to SEQ ID NO: 16, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 94% identical to SEQ ID NO: 16, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 95% identical to SEQ ID NO: 16, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 96% identical to SEQ ID NO: 16, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 97% identical to SEQ ID NO: 16, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 98% identical to SEQ ID NO: 16, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 99% identical to SEQ ID NO: 16, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 99.5% identical to SEQ ID NO: 16, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 99.8% identical to SEQ ID NO: 16, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence at least 99.9% identical to SEQ ID NO: 16, or the complement thereof. In one aspect, a chimeric intron nucleic acid sequence comprises a sequence 100% identical to SEQ ID NO: 16, or the complement thereof.

[00163] In an aspect, an intron nucleic acid sequence comprises a sequence at least 70% identical to SEQ ID NO: 17, or the complement thereof. In one aspect, an intron nucleic acid sequence comprises a sequence at least 75% identical to SEQ ID NO: 17, or the complement thereof. In one aspect, an intron nucleic acid sequence comprises a sequence at least 80% identical to SEQ ID NO: 17, or the complement thereof. In one aspect, an intron nucleic acid sequence comprises a sequence at least 85% identical to SEQ ID NO: 17, or the complement thereof. In one aspect, an intron nucleic acid sequence comprises a sequence at least 90% identical to SEQ ID NO: 17, or the complement thereof. In one aspect, an intron nucleic acid sequence comprises a sequence at least 91% identical to SEQ ID NO: 17, or the complement thereof. In one aspect, an intron nucleic acid sequence comprises a sequence at least 92% identical to SEQ ID NO: 17, or the complement thereof. In one aspect, an intron nucleic acid sequence comprises a sequence at

least 93% identical to SEQ ID NO: 17, or the complement thereof. In one aspect, an intron nucleic acid sequence comprises a sequence at least 94% identical to SEQ ID NO: 17, or the complement thereof. In one aspect, an intron nucleic acid sequence comprises a sequence at least 95% identical to SEQ ID NO: 17, or the complement thereof. In one aspect, an intron nucleic acid sequence comprises a sequence at least 96% identical to SEQ ID NO: 17, or the complement thereof. In one aspect, an intron nucleic acid sequence comprises a sequence at least 97% identical to SEQ ID NO: 17, or the complement thereof. In one aspect, an intron nucleic acid sequence comprises a sequence at least 98% identical to SEQ ID NO: 17, or the complement thereof. In one aspect, an intron nucleic acid sequence comprises a sequence at least 99% identical to SEQ ID NO: 17, or the complement thereof. In one aspect, an intron nucleic acid sequence comprises a sequence at least 99.5% identical to SEQ ID NO: 17, or the complement thereof. In one aspect, an intron nucleic acid sequence comprises a sequence at least 99.8% identical to SEQ ID NO: 17, or the complement thereof. In one aspect, an intron nucleic acid sequence comprises a sequence at least 99.9% identical to SEQ ID NO: 17, or the complement thereof. In one aspect, an intron nucleic acid sequence comprises a sequence 100% identical to SEQ ID NO: 17, or the complement thereof.

[00164] The woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) is a DNA sequence that creates a tertiary structure enhancing expression of genes that are delivered in viral vectors.

[00165] In an aspect, a WPRE nucleic acid sequence is an optimized version of WPRE.

[00166] In an aspect, a WPRE nucleic acid sequence is selected from the group consisting of SEQ ID NOs: 7 and 18. In one aspect, a WPRE nucleic acid sequence is SEQ ID NO: 7. In one aspect, a WPRE nucleic acid sequence is SEQ ID NO: 18.

[00167] In an aspect, a WPRE nucleic acid sequence comprises a sequence at least 70% identical to SEQ ID NO: 7, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 75% identical to SEQ ID NO: 7, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 80% identical to SEQ ID NO: 7, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 85% identical to SEQ ID NO: 7, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 90% identical to SEQ ID NO: 7, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 91% identical to SEQ ID NO: 7, or the complement thereof. In one aspect, a WPRE nucleic acid

sequence comprises a sequence at least 92% identical to SEQ ID NO: 7, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 93% identical to SEQ ID NO: 7, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 94% identical to SEQ ID NO: 7, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 95% identical to SEQ ID NO: 7, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 96% identical to SEQ ID NO: 7, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 97% identical to SEQ ID NO: 7, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 98% identical to SEQ ID NO: 7, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 99% identical to SEQ ID NO: 7, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 99.5% identical to SEQ ID NO: 7, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 99.8% identical to SEQ ID NO: 7, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 99.9% identical to SEQ ID NO: 7, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence 100% identical to SEQ ID NO: 7, or the complement thereof.

[00168] In an aspect, a WPRE nucleic acid sequence comprises a sequence at least 70% identical to SEQ ID NO: 18, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 75% identical to SEQ ID NO: 18, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 80% identical to SEQ ID NO: 18, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 85% identical to SEQ ID NO: 18, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 90% identical to SEQ ID NO: 18, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 91% identical to SEQ ID NO: 18, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 92% identical to SEQ ID NO: 18, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 93% identical to SEQ ID NO: 18, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 94% identical to SEQ ID NO: 18, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 95% identical

to SEQ ID NO: 18, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 96% identical to SEQ ID NO: 18, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 97% identical to SEQ ID NO: 18, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 98% identical to SEQ ID NO: 18, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 99% identical to SEQ ID NO: 18, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 99.5% identical to SEQ ID NO: 18, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 99.8% identical to SEQ ID NO: 18, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence at least 99.9% identical to SEQ ID NO: 18, or the complement thereof. In one aspect, a WPRE nucleic acid sequence comprises a sequence 100% identical to SEQ ID NO: 18, or the complement thereof.

[00169] SV40 polyadenylation signal sequence (also refer as SV40 PolyA; Simian virus 40 PolyA; and PolyA) is a DNA sequence that can terminate transcription and add a PolyA tail to the 3' end of a messenger RNA (mRNA).

[00170] hGH polyadenylation signal sequence (also refer as hGH PolyA) is a DNA sequence the can terminate transcription and add a PolyA tail to the 3' end of a messenger RNA (mRNA).

[00171] bGH polyadenylation signal sequence (also refer as bGH PolyA or bGHpA) refers to a Poly A signal or PolyA tail of a bovine growth hormone.

[00172] As used herein, a "PolyA tail" refers to a stretch of RNA that only contains the nucleobase adenine. In an aspect, an RNA molecule transcribed from an AAV vector construct provided herein comprises a PolyA tail. In one aspect, a PolyA tail comprises at least two adenines. In one aspect, a PolyA tail comprises at least ten adenines. In one aspect, a PolyA tail comprises at least 50 adenines. In one aspect, a PolyA tail comprises at least 100 adenines. In one aspect, a PolyA tail comprises at least 150 adenines. In one aspect, a PolyA tail comprises at least 200 adenines. In one aspect, a PolyA tail comprises at least 250 adenines. In one aspect, a PolyA tail comprises between 50 adenines and 300 adenines.

[00173] In an aspect, a SV40 polyadenylation signal nucleic acid sequence comprises a sequence at least 70% identical to SEQ ID NO: 8, or the complement thereof. In one aspect, a SV40 polyadenylation signal nucleic acid sequence comprises a sequence at least 75% identical to

SEQ ID NO: 8, or the complement thereof. In one aspect, a SV40 polyadenylation signal nucleic acid sequence comprises a sequence at least 80% identical to SEQ ID NO: 8, or the complement thereof. In one aspect, a SV40 polyadenylation signal nucleic acid sequence comprises a sequence at least 85% identical to SEQ ID NO: 8, or the complement thereof. In one aspect, a SV40 polyadenylation signal nucleic acid sequence comprises a sequence at least 90% identical to SEQ ID NO: 8, or the complement thereof. In one aspect, a SV40 polyadenylation signal nucleic acid sequence comprises a sequence at least 91% identical to SEQ ID NO: 8, or the complement thereof. In one aspect, a SV40 polyadenylation signal nucleic acid sequence comprises a sequence at least 92% identical to SEQ ID NO: 8, or the complement thereof. In one aspect, a SV40 polyadenylation signal nucleic acid sequence comprises a sequence at least 93% identical to SEQ ID NO: 8, or the complement thereof. In one aspect, a SV40 polyadenylation signal nucleic acid sequence comprises a sequence at least 94% identical to SEQ ID NO: 8, or the complement thereof. In one aspect, a SV40 polyadenylation signal nucleic acid sequence comprises a sequence at least 95% identical to SEQ ID NO: 8, or the complement thereof. In one aspect, a SV40 polyadenylation signal nucleic acid sequence comprises a sequence at least 96% identical to SEQ ID NO: 8, or the complement thereof. In one aspect, a SV40 polyadenylation signal nucleic acid sequence comprises a sequence at least 97% identical to SEQ ID NO: 8, or the complement thereof. In one aspect, a SV40 polyadenylation signal nucleic acid sequence comprises a sequence at least 98% identical to SEQ ID NO: 8, or the complement thereof. In one aspect, a SV40 polyadenylation signal nucleic acid sequence comprises a sequence at least 99% identical to SEQ ID NO: 8, or the complement thereof. In one aspect, a SV40 polyadenylation signal nucleic acid sequence comprises a sequence at least 99.5% identical to SEQ ID NO: 8, or the complement thereof. In one aspect, a SV40 polyadenylation signal nucleic acid sequence comprises a sequence at least 99.8% identical to SEQ ID NO: 8, or the complement thereof. In one aspect, a SV40 polyadenylation signal nucleic acid sequence comprises a sequence at least 99.9% identical to SEQ ID NO: 8, or the complement thereof. In one aspect, a SV40 polyadenylation signal nucleic acid sequence comprises a sequence 100% identical to SEQ ID NO: 8, or the complement thereof.

[00174] In an aspect, a hGH polyadenylation signal nucleic acid sequence comprises a sequence at least 70% identical to SEQ ID NO: 13, or the complement thereof. In one aspect, a hGH polyadenylation signal nucleic acid sequence comprises a sequence at least 75% identical to SEQ ID NO: 13, or the complement thereof. In one aspect, a hGH polyadenylation signal nucleic

acid sequence comprises a sequence at least 80% identical to SEQ ID NO: 13, or the complement thereof. In one aspect, a hGH polyadenylation signal nucleic acid sequence comprises a sequence at least 85% identical to SEQ ID NO: 13, or the complement thereof. In one aspect, a hGH polyadenylation signal nucleic acid sequence comprises a sequence at least 90% identical to SEQ ID NO: 13, or the complement thereof. In one aspect, a hGH polyadenylation signal nucleic acid sequence comprises a sequence at least 91% identical to SEQ ID NO: 13, or the complement thereof. In one aspect, a hGH polyadenylation signal nucleic acid sequence comprises a sequence at least 92% identical to SEQ ID NO: 13, or the complement thereof. In one aspect, a hGH polyadenylation signal nucleic acid sequence comprises a sequence at least 93% identical to SEQ ID NO: 13, or the complement thereof. In one aspect, a hGH polyadenylation signal nucleic acid sequence comprises a sequence at least 94% identical to SEQ ID NO: 13, or the complement thereof. In one aspect, a hGH polyadenylation signal nucleic acid sequence comprises a sequence at least 95% identical to SEQ ID NO: 13, or the complement thereof. In one aspect, a hGH polyadenylation signal nucleic acid sequence comprises a sequence at least 96% identical to SEQ ID NO: 13, or the complement thereof. In one aspect, a hGH polyadenylation signal nucleic acid sequence comprises a sequence at least 97% identical to SEQ ID NO: 13, or the complement thereof. In one aspect, a hGH polyadenylation signal nucleic acid sequence comprises a sequence at least 98% identical to SEQ ID NO: 13, or the complement thereof. In one aspect, a hGH polyadenylation signal nucleic acid sequence comprises a sequence at least 99% identical to SEQ ID NO: 13, or the complement thereof. In one aspect, a hGH polyadenylation signal nucleic acid sequence comprises a sequence at least 99.5% identical to SEQ ID NO: 13, or the complement thereof. In one aspect, a hGH polyadenylation signal nucleic acid sequence comprises a sequence at least 99.13% identical to SEQ ID NO: 13, or the complement thereof. In one aspect, a hGH polyadenylation signal nucleic acid sequence comprises a sequence at least 99.9% identical to SEQ ID NO: 13, or the complement thereof. In one aspect, a hGH polyadenylation signal nucleic acid sequence comprises a sequence 100% identical to SEQ ID NO: 13, or the complement thereof

[00175] In an aspect, a bGH polyadenylation signal nucleic acid sequence comprises a sequence at least 70% identical to SEQ ID NO: 14, or the complement thereof. In one aspect, a bGH polyadenylation signal nucleic acid sequence comprises a sequence at least 75% identical to SEQ ID NO: 14, or the complement thereof. In one aspect, a bGH polyadenylation signal nucleic acid sequence comprises a sequence at least 80% identical to SEQ ID NO: 14, or the complement

thereof. In one aspect, a bGH polyadenylation signal nucleic acid sequence comprises a sequence at least 85% identical to SEQ ID NO: 14, or the complement thereof. In one aspect, a bGH polyadenylation signal nucleic acid sequence comprises a sequence at least 90% identical to SEQ ID NO: 14, or the complement thereof. In one aspect, a bGH polyadenylation signal nucleic acid sequence comprises a sequence at least 91% identical to SEQ ID NO: 14, or the complement thereof. In one aspect, a bGH polyadenylation signal nucleic acid sequence comprises a sequence at least 92% identical to SEQ ID NO: 14, or the complement thereof. In one aspect, a bGH polyadenylation signal nucleic acid sequence comprises a sequence at least 93% identical to SEQ ID NO: 14, or the complement thereof. In one aspect, a bGH polyadenylation signal nucleic acid sequence comprises a sequence at least 94% identical to SEQ ID NO: 14, or the complement thereof. In one aspect, a bGH polyadenylation signal nucleic acid sequence comprises a sequence at least 95% identical to SEQ ID NO: 14, or the complement thereof. In one aspect, a bGH polyadenylation signal nucleic acid sequence comprises a sequence at least 96% identical to SEQ ID NO: 14, or the complement thereof. In one aspect, a bGH polyadenylation signal nucleic acid sequence comprises a sequence at least 97% identical to SEQ ID NO: 14, or the complement thereof. In one aspect, a bGH polyadenylation signal nucleic acid sequence comprises a sequence at least 98% identical to SEQ ID NO: 14, or the complement thereof. In one aspect, a bGH polyadenylation signal nucleic acid sequence comprises a sequence at least 99% identical to SEQ ID NO: 14, or the complement thereof. In one aspect, a bGH polyadenylation signal nucleic acid sequence comprises a sequence at least 99.5% identical to SEQ ID NO: 14, or the complement thereof. In one aspect, a bGH polyadenylation signal nucleic acid sequence comprises a sequence at least 99.13% identical to SEQ ID NO: 14, or the complement thereof. In one aspect, a bGH polyadenylation signal nucleic acid sequence comprises a sequence at least 99.9% identical to SEQ ID NO: 14, or the complement thereof. In one aspect, a bGH polyadenylation signal nucleic acid sequence comprises a sequence 100% identical to SEQ ID NO: 14, or the complement thereof.

[00176] In an aspect, a vector of the present disclosure comprises a 2A self-cleavage peptide sequence. In an aspect, a vector of the present disclosure comprises a 2A self-cleavage peptide sequence from porcine teschovirus-1. In an aspect, a vector of the present disclosure comprises a nucleic acid sequence comprising SEQ ID NO: 3. In an aspect, a vector of the present disclosure comprises a nucleic acid sequence at least 70% identical to SEQ ID NO: 3. In an aspect, a vector of the present disclosure comprises a nucleic acid sequence at least 75% identical to SEQ ID NO:

3. In an aspect, a vector of the present disclosure comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 3. In an aspect, a vector of the present disclosure comprises a nucleic acid sequence at least 85% identical to SEQ ID NO: 3. In an aspect, a vector of the present disclosure comprises a nucleic acid sequence at least 90% identical to SEQ ID NO: 3. In an aspect, a vector of the present disclosure comprises a nucleic acid sequence at least 91% identical to SEQ ID NO: 3. In an aspect, a vector of the present disclosure comprises a nucleic acid sequence at least 92% identical to SEQ ID NO: 3. In an aspect, a vector of the present disclosure comprises a nucleic acid sequence at least 93% identical to SEQ ID NO: 3. In an aspect, a vector of the present disclosure comprises a nucleic acid sequence at least 94% identical to SEQ ID NO: 3. In an aspect, a vector of the present disclosure comprises a nucleic acid sequence at least 95% identical to SEQ ID NO: 3. In an aspect, a vector of the present disclosure comprises a nucleic acid sequence at least 96% identical to SEQ ID NO: 3. In an aspect, a vector of the present disclosure comprises a nucleic acid sequence at least 97% identical to SEQ ID NO: 3. In an aspect, a vector of the present disclosure comprises a nucleic acid sequence at least 98% identical to SEQ ID NO: 3. In an aspect, a vector of the present disclosure comprises a nucleic acid sequence at least 99% identical to SEQ ID NO: 3. In an aspect, a vector of the present disclosure comprises a nucleic acid sequence 100% identical to SEQ ID NO: 3.

[00177] As used herein, the term “central nervous system” or “CNS” refers to the brain and spinal cord of a bilaterally symmetric animal. The CNS also includes the retina, the optic nerve, olfactory nerves, and olfactory epithelium.

[00178] As used herein, the term “peripheral nervous system” or “PNS” refers to nerves and ganglia outside of the brain and spinal cord, excluding the retina, the optic nerve, olfactory nerves, and olfactory epithelium. In an aspect, the peripheral nervous system is divided into the somatic nervous system and the autonomic nervous system.

[00179] As used herein, the term “somatic nervous system” refers to the parts of the PNS that are associated with voluntary control of body movements.

[00180] As used herein, the term “autonomic nervous system” refers to the parts of the PNS that regulate the function of internal organs

[00181] As used herein, the term “GFAP positive” refers to a cell having detectable protein accumulation of human glial fibrillary acid protein (GFAP) or detectable accumulation of GFAP mRNA expression using techniques standard in the art. In one aspect, a glial cell is GFAP positive.

[00182] As used herein, the term “detectable” refers to protein or mRNA accumulation that is identifiable.

[00183] Protein accumulation can be identified using antibodies. Non limiting examples of measuring protein accumulation include Western blots, enzyme linked immunosorbent assays (ELISAs), immunoprecipitations and immunofluorescence. An antibody provided herein can be a polyclonal antibody or a monoclonal antibody. An antibody having specific binding affinity for a protein provided herein can be generated using methods well known in the art. An antibody provided herein can be attached to a solid support such as a microtiter plate using methods known in the art.

[00184] As used herein, the term “multiplicity of infection” and “MOI” refers to a the number of virions that are added per cell during infection.

[00185] As used herein, the term “virion” refers to the infective form of a virus outside a host cell.

[00186] As used herein, the term “neurological condition” refers to a disorder, illness, sickness, injury, or disease, in the central nervous system or the peripheral nervous system. Non-limiting examples of neurological conditions can be found in Neurological Disorders: course and treatment, 2nd Edition (2002) (Academic Press Inc.) and Christopher Goetz, Textbook of Clinical Neurology, 3rd Edition (2007) (Saunders).

[00187] As used herein, the term “injury” refers to damage to the central nervous system or peripheral nervous system.

[00188] In one aspect, a neurological condition is selected from the group consisting of Alzheimer’s Disease, Parkinson’s Disease, amyotrophic lateral sclerosis (ALS), Huntington’s Disease, epilepsy, physical injury, stroke, cerebral aneurysm, traumatic brain injury, concussion, a tumor, inflammation, infection, ataxia, brain atrophy, spinal cord atrophy, multiple sclerosis, traumatic spinal cord injury, ischemic or hemorrhagic myelopathy (myelopathy), global ischemia, hypoxic ischemic encephalopathy, embolism, fibrocartilage embolism myelopathy, thrombosis, nephropathy, chronic inflammatory disease, meningitis, and cerebral venous sinus thrombosis. In one aspect, a neurological condition is Alzheimer’s Disease. In one aspect, a neurological condition is Parkinson’s Disease. In one aspect, a neurological condition is ALS. In one aspect, a neurological condition is Huntington’s Disease. In one aspect, a neurological condition is epilepsy. In one aspect, a neurological condition is a physical injury. In one aspect, a neurological

condition is stroke. In one aspect, a neurological condition is ischemic stroke. In one aspect, a neurological condition is hemorrhagic stroke. In one aspect, a neurological condition is cerebral aneurysm. In one aspect, a neurological condition is traumatic brain injury. In one aspect, a neurological condition is concussion. In one aspect, a neurological condition is a tumor. In one aspect, a neurological condition is inflammation. In one aspect, a neurological condition is infection. In one aspect, a neurological condition is ataxia. In, one aspect, a neurological condition is brain atrophy. In, one aspect, a neurological condition is spinal cord atrophy. In one aspect, a neurological condition is multiple sclerosis. In one aspect, a neurological condition is traumatic spinal cord injury. In one aspect, a neurological condition is ischemic or hemorrhagic myelopathy (myelopathy). In one aspect, a neurological condition is global ischemia. In one aspect, a neurological condition is hypoxic ischemic encephalopathy. In one aspect, a neurological condition is embolism. In one aspect, a neurological condition is fibrocartilage embolism myelopathy. In one aspect, a neurological condition is thrombosis. In one aspect, a neurological condition is nephropathy. In one aspect, a neurological condition is chronic inflammatory disease. In one aspect, a neurological condition is meningitis. In one aspect, a neurological condition is cerebral venous sinus thrombosis.

[00189] In an aspect, a neurological condition comprises an injury to the CNS or to the PNS. In one aspect, a neurological condition comprises an injury to the CNS. In one aspect, a neurological condition comprises an injury to the PNS.

[00190] In an aspect, this disclosure provides, and includes, a method of converting reactive astrocytes to functional neurons in a brain of a living human brain comprising: injecting an adeno-associated virus (AAV) into a subject in need thereof, where the AAV comprises a DNA vector construct comprising a human neurogenic differentiation 1 (hNeuroD1) sequence comprising the nucleic acid sequence of SEQ ID NO: 6, where the sequence is operably linked to regulatory elements comprising: (a) a human glial fibrillary acid protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO: 4, 12, and 15; (b) an enhancer from the human elongation factor-1 alpha (EF-1 alpha) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11; (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs:

7 and 18; and (e) a SV40 polyadenylation signal sequence comprising the nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising that nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

5 [00191] In an aspect, this disclosure, and includes, provides a method of converting reactive astrocytes to functional neurons in a brain of a living human brain comprising: injecting an adeno-associated virus (AAV) into a subject in need thereof, where the AAV comprises a DNA vector construct comprising a nucleic acid coding sequence encoding a human neurogenic differentiation 1 (hNeuroD1) protein comprising the amino acid sequence of SEQ ID NO: 10, where the coding
10 sequence is operably linked to expression control elements comprising: (a) human glial fibrillary acid protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15; (b) an enhancer from the human elongation factor-1 alpha (EF-1 alpha) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11; (c) a
15 chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18; and (e) a SV40 polyadenylation signal sequence comprising the nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising that nucleic acid sequence of SEQ ID NO: 13, or a bGH
20 polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

[00192] In an aspect, this disclosure provides, and includes, a method of converting glial cells to neurons in a subject in need thereof comprising: delivering an adeno-associated virus (AAV) to the subject in need thereof, where the AAV comprises a DNA vector construct comprising a neurogenic differentiation 1 (NeuroD1) sequence operably linked to expression
25 control elements comprising: (a) a glial fibrillary acid protein (GFAP) promoter; (b) an enhancer; (c) a chimeric intron; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE); and (e) a polyadenylation signal sequence, where the AAV vector is capable of converting at least one glial cell to a neuron in the subject in need thereof.

[00193] In an aspect, this disclosure provides, and includes, a method of treating a
30 neurological condition in a subject in need thereof comprising: delivering an adeno-associated virus (AAV) to the subject, where the AAV comprises a DNA vector construct comprising a

neurogenic differentiation 1 (NeuroD1) sequence operably linked to expression control elements comprising: (a) a glial fibrillary acid protein (GFAP) promoter; (b) an enhancer; (c) a chimeric intron; (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE); and (e) a polyadenylation signal to the subject in need thereof.

5 [00194] In an aspect, a method as provided herein, is capable of converting at least one glial cell to a neuron. In one aspect, a method as provided herein converts at least one glial cell to a neuron.

[00195] Distal-less homeobox 2 (Dlx2; also referred to as TES1) is a member of the Dlx gene family and is a homeobox containing gene that plays a role in forebrain and craniofacial
10 development.

[00196] Achaete-scute family BHLH transcription factor 1 (Ascl1; also referred to as ASH1, HASH1, MASH-1, and bHLHa46) encodes a member of the basic helix-loop-helix family of transcription factors and is a gene that plays a role in neuronal commitment and differentiation..

[00197] Insulin gene enhancer protein (ISL1; also known as ISL LIM homeobox-1 and
15 ISLET1) is a gene that encodes a transcription factor containing two N-terminal LIM domains and one C-terminal homeodomain. The encoded protein plays a role in the embryogenesis of pancreatic islets of Langerhans.

[00198] LIM-homeobox 3 (LHX3; also known as LIM3 and CPHD3) gene encodes for a protein from a family of proteins with a unique cysteine-rich zinc-binding domain (LIM domain).

20 [00199] In an aspect, a method as provided herein uses an AAV vector comprising a NeuroD1 coding sequence in accordance with the present disclosure. In one aspect, a method as provided herein uses an AAV vector comprising a NeuroD1 coding sequence in combination with a second AAV vector comprising a second transcription factor coding sequence. In one aspect, a method as provided herein uses an AAV vector comprising a NeuroD1 coding sequence and a
25 second transcription factor coding sequence. In one aspect, a second transcription factor is selected from the group consisting of Dlx2, Ascl1, ISL1, and LHX3. In one aspect, a second transcription factor is Dlx2. In one aspect, a second transcription factor is Ascl1. In one aspect, a second transcription factor is ISL1. In one aspect, a second transcription factor is LHX3. In one aspect, a method as provided herein uses an AAV vector comprising a NeuroD1 coding sequence and
30 second NeuroD1 coding sequence. In one aspect, a method as provided herein uses an AAV vector

comprising a NeuroD1 coding sequence in combination with a second AAV vector comprising a NeuroD1 coding sequence.

[00200] In an aspect, an AAV vector as provided herein, is measured for functionality by assessing transcription levels and protein levels of NeuN, doublecortin (DCX), β 3-tubulin, (neurofilament 200) NF-200, (microtubule-associated protein 2) MAP2, ionized calcium binding adaptor molecule (Iba1).

[00201] As used herein, the term “NeuN” or “Fox-3” or “Rbfox2” or “Hexaribonucleotide Binding Protein-3” refers to a protein which is a homologue to the protein product of a sex-determining gene in *Caenorhabditis elegans* and is a neuronal nuclear antigen.

[00202] As used herein, the term “DCX” or “doubling” or “lissencephalin-X” refers to a microtubule-associated protein expressed by neuronal precursor cells and immature neurons in embryonic and adult cortical structures.

[00203] As used herein, the term “ β 3-tubulin” or “Class III β -tubulin” or “ β -tubulin III” refers to a microtubule element of the tubulin family found in neurons.

[00204] As used herein, the term “NF-200” refers to a class of protein that is a type IV intermediate filaments found in the cytoplasm of neurons.

[00205] As used herein, the term “MAP2” refers to a protein that belongs to the microtubule-associated protein family and play a role in determining and stabilizing neuronal morphology during neuron development.

[00206] As used herein, the term “Iba1” refers to a microglia macrophage-specific calcium binding protein.

[00207] In an aspect, a composition as provided herein, is capable of converting at least one glial cell to a neuron. In one aspect, a composition as provided herein converts at least one glial cell to a neuron

[00208] As used herein, the term “mammal” refers to any species classified in the class Mammalia.

[00209] As used herein, the term “human” refers to a *Homo sapiens*. In an aspect, a human has a neurological disorder.

[00210] As used herein, the term “living human” refers to a human that has heart, respiration and brain activity.

[00211] As used herein, the term “non-human primate” refers to any species or subspecies classified in the order Primates that are not *Homo sapiens*. Non-limiting examples of non-human primates include chimpanzee, bonobo, orangutan, gorilla, macaque, marmoset, capuchin, baboon, gibbon, and lemur.

5 [00212] As used herein, the term “delivering” or “delivery” refers to treating a mammal with an AAV vector or composition as provided herein. In an aspect, an AAV vector or composition as provided herein is delivered to a subject in need thereof. In one aspect, an AAV vector or composition as provided herein is formulated to be delivered to a subject in need thereof. In one aspect, delivering comprises local delivery. In one aspect, an AAV vector or composition
10 as provided herein is formulated for local delivery. In one aspect, delivering comprises systemic delivery. In one aspect, an AAV vector or composition as provided herein is formulated for systemic delivery. In one aspect, delivery comprises injecting an AAV vector or composition as provided herein into a subject in need thereof. In one aspect, delivering is selected from the group consisting of intraperitoneal, intramuscular, intravenous, intrathecal, intracerebral, intracranial,
15 intra lateral ventricle of the brain, intra cisterna magna, intra vitreous, intra-subretina, intraparenchymal, intranasal, or oral administration. In one aspect, delivery comprises intraperitoneal delivery. In one aspect, delivery comprises intramuscular delivery. In one aspect, delivery comprises intravenous delivery. In one aspect, delivery comprises intrathecal delivery. In one aspect, delivery comprises intracerebral delivery. In one aspect, delivery comprises intracranial delivery. In one aspect, delivery comprises intra lateral ventricle of the brain delivery. In one aspect, delivery comprises intra cisterna magna delivery. In one aspect, delivery comprises intra vitreous delivery. In one aspect, delivery comprises intra-subretina delivery. In one aspect, delivery comprises intraparenchymal delivery. In one aspect, delivery comprises intranasal delivery. In one aspect, delivery comprises oral administration.

25 [00213] As used herein, the term “injecting” refers to delivering an AAV vector or composition as provided herein under pressure and with force. As a non-limiting example, injecting can comprise the use of a syringe and needle.

[00214] In an aspect, an AAV vector or composition as provided herein is injected into a brain of a subject. In one aspect, an AAV vector or composition is injected into a cerebral cortex
30 of a subject. In one aspect, an AAV vector or composition as provided herein is injected in to a spinal cord or a subject. In one aspect, an AAV vector or composition is injected in the striatum

of a subject. In one aspect, an AAV vector or composition is injected in the dorsal striatum of a subject. In one aspect, an AAV vector or composition is injected in the putamen of a subject. In one aspect, an AAV vector or composition is injected in the caudate nucleus of a subject. In one aspect, an AAV vector or composition is injected in the substantia nigra of a subject.

5 [00215] In an aspect, an AAV vector or composition as provided herein has spread in the brain between about 1% and about 100%. In one aspect, an AAV vector or composition as provided herein has spread in the brain between about 1% and about 10%, between 1% and about 20%, between 1% and about 30%, between 10% and about 20%, between 10% and about 30%, between about 10% and about 40%, between about 20% and about 30%, between about 20% and
10 about 40%, between about 20% and about 50%, between about 30% and about 40%, between about 30% and about 50%, between about 30% and about 60%, between about 40% and about 50%, between about 40% and about 60%, between about 40% and about 70%, between about 50% and about 60%, between about 50% and about 70%, between about 50% and about 80%, between about 60% and about 70%, between about 60% and about 80%, between about 60% and about
15 90%, between about 70% and about 80%, between about 70% and about 90%, between about 70% and about 100%, between about 80% and about 90%, between about 80% and about 100%, or between about 90% and about 100%.

[00216] In an aspect, an AAV vector or composition as provided herein has spread in the cerebral cortex between about 1% and about 100%. In one aspect, an AAV vector or composition
20 as provided herein has spread in the cerebral cortex between about 1% and about 10%, between 1% and about 20%, between 1% and about 30%, between 10% and about 20%, between 10% and about 30%, between about 10% and about 40%, between about 20% and about 30%, between about 20% and about 40%, between about 20% and about 50%, between about 30% and about 40%, between about 30% and about 50%, between about 30% and about 60%, between about 40%
25 and about 50%, between about 40% and about 60%, between about 40% and about 70%, between about 50% and about 60%, between about 50% and about 70%, between about 50% and about 80%, between about 60% and about 70%, between about 60% and about 80%, between about 60% and about 90%, between about 70% and about 80%, between about 70% and about 90%, between about 70% and about 100%, between about 80% and about 90%, between about 80% and about
30 100%, or between about 90% and about 100%.

[00217] In an aspect, an AAV vector or composition as provided herein has spread in the spinal cord between about 1% and about 100%. In one aspect, an AAV vector or composition as provided herein has spread in the spinal cord between about 1% and about 10%, between 1% and about 20%, between 1% and about 30%, between 10% and about 20%, between 10% and about 30%, between about 10% and about 40%, between about 20% and about 30%, between about 20% and about 40%, between about 20% and about 50%, between about 30% and about 40%, between about 30% and about 50%, between about 30% and about 60%, between about 40% and about 50%, between about 40% and about 60%, between about 40% and about 70%, between about 50% and about 60%, between about 50% and about 70%, between about 50% and about 80%, between about 60% and about 70%, between about 60% and about 80%, between about 60% and about 90%, between about 70% and about 80%, between about 70% and about 90%, between about 70% and about 100%, between about 80% and about 90%, between about 80% and about 100%, or between about 90% and about 100%.

[00218] In an aspect, an AAV vector or composition as provided herein has spread in the striatum between about 1% and about 100%. In one aspect, an AAV vector or composition as provided herein has spread in the striatum between about 1% and about 10%, between 1% and about 20%, between 1% and about 30%, between 10% and about 20%, between 10% and about 30%, between about 10% and about 40%, between about 20% and about 30%, between about 20% and about 40%, between about 20% and about 50%, between about 30% and about 40%, between about 30% and about 50%, between about 30% and about 60%, between about 40% and about 50%, between about 40% and about 60%, between about 40% and about 70%, between about 50% and about 60%, between about 50% and about 70%, between about 50% and about 80%, between about 60% and about 70%, between about 60% and about 80%, between about 60% and about 90%, between about 70% and about 80%, between about 70% and about 90%, between about 70% and about 100%, between about 80% and about 90%, between about 80% and about 100%, or between about 90% and about 100%.

[00219] In an aspect, an AAV vector or composition as provided herein has spread in the dorsal striatum between about 1% and about 100%. In one aspect, an AAV vector or composition as provided herein has spread in the dorsal striatum between about 1% and about 10%, between 1% and about 20%, between 1% and about 30%, between 10% and about 20%, between 10% and about 30%, between about 10% and about 40%, between about 20% and about 30%, between

about 20% and about 40%, between about 20% and about 50%, between about 30% and about 40%, between about 30% and about 50%, between about 30% and about 60%, between about 40% and about 50%, between about 40% and about 60%, between about 40% and about 70%, between about 50% and about 60%, between about 50% and about 70%, between about 50% and about 80%, between about 60% and about 70%, between about 60% and about 80%, between about 60% and about 90%, between about 70% and about 80%, between about 70% and about 90%, between about 70% and about 100%, between about 80% and about 90%, between about 80% and about 100%, or between about 90% and about 100%.

[00220] In an aspect, an AAV vector or composition as provided herein has spread in the putamen between about 1% and about 100%. In one aspect, an AAV vector or composition as provided herein has spread in the putamen between about 1% and about 10%, between 1% and about 20%, between 1% and about 30%, between 10% and about 20%, between 10% and about 30%, between about 10% and about 40%, between about 20% and about 30%, between about 20% and about 40%, between about 20% and about 50%, between about 30% and about 40%, between about 30% and about 50%, between about 30% and about 60%, between about 40% and about 50%, between about 40% and about 60%, between about 40% and about 70%, between about 50% and about 60%, between about 50% and about 70%, between about 50% and about 80%, between about 60% and about 70%, between about 60% and about 80%, between about 60% and about 90%, between about 70% and about 80%, between about 70% and about 90%, between about 70% and about 100%, between about 80% and about 90%, between about 80% and about 100%, or between about 90% and about 100%.

[00221] In an aspect, an AAV vector or composition as provided herein has spread in the caudate nucleus between about 1% and about 100%. In one aspect, an AAV vector or composition as provided herein has spread in the caudate nucleus between about 1% and about 10%, between 1% and about 20%, between 1% and about 30%, between 10% and about 20%, between 10% and about 30%, between about 10% and about 40%, between about 20% and about 30%, between about 20% and about 40%, between about 20% and about 50%, between about 30% and about 40%, between about 30% and about 50%, between about 30% and about 60%, between about 40% and about 50%, between about 40% and about 60%, between about 40% and about 70%, between about 50% and about 60%, between about 50% and about 70%, between about 50% and about 80%, between about 60% and about 70%, between about 60% and about 80%, between about 60%

and about 90%, between about 70% and about 80%, between about 70% and about 90%, between about 70% and about 100%, between about 80% and about 90%, between about 80% and about 100%, or between about 90% and about 100%.

[00222] In and aspect, an AAV vector or composition as provided herein has a spread at
5 from injection site between about 1% and about 100%. In one aspect, an AAV vector or composition as provided herein has a spread from injection site between about 1% and about 10%, between 1% and about 20%, between 1% and about 30%, between 10% and about 20%, between 10% and about 30%, between about 10% and about 40%, between about 20% and about 30%, between about 20% and about 40%, between about 20% and about 50%, between about 30% and
10 about 40%, between about 30% and about 50%, between about 30% and about 60%, between about 40% and about 50%, between about 40% and about 60%, between about 40% and about 70%, between about 50% and about 60%, between about 50% and about 70%, between about 50% and about 80%, between about 60% and about 70%, between about 60% and about 80%, between about 60% and about 90%, between about 70% and about 80%, between about 70% and about
15 90%, between about 70% and about 100%, between about 80% and about 90%, between about 80% and about 100%, or between about 90% and about 100%.

[00223] In an aspect, an AAV vector or composition as provided herein has spread in the substantia nigra between about 1% and about 100%. In one aspect, an AAV vector or composition as provided herein has spread in the putamen between about 1% and about 10%, between 1% and
20 about 20%, between 1% and about 30%, between 10% and about 20%, between 10% and about 30%, between about 10% and about 40%, between about 20% and about 30%, between about 20% and about 40%, between about 20% and about 50%, between about 30% and about 40%, between about 30% and about 50%, between about 30% and about 60%, between about 40% and about 50%, between about 40% and about 60%, between about 40% and about 70%, between about 50%
25 and about 60%, between about 50% and about 70%, between about 50% and about 80%, between about 60% and about 70%, between about 60% and about 80%, between about 60% and about 90%, between about 70% and about 80%, between about 70% and about 90%, between about 70% and about 100%, between about 80% and about 90%, between about 80% and about 100%, or between about 90% and about 100%.

30 [00224] As used herein, the term “AAV particle” refers to packaged capsid forms of the AAV virus that transmits its nucleic acid genome to cells.

[00225] In an aspect, a composition comprising an AAV particle encoded by an AAV vector as provided herein is injected at a concentration between 10^{10} AAV particles/mL and 10^{14} AAV particles/mL. In one aspect, a composition comprising an AAV particle encoded by an AAV vector as provided herein is injected at a concentration between 10^{10} AAV particles/mL and 10^{11} AAV particles/mL, between 10^{10} AAV particles/mL and 10^{12} AAV particles/mL, between 10^{10} AAV particles/mL and 10^{13} AAV particles/mL, between 10^{11} AAV particles/mL and 10^{12} AAV particles/mL, between 10^{11} AAV particles/mL and 10^{13} AAV particles/mL, between 10^{11} AAV particles/mL and 10^{14} AAV particles/mL, between 10^{12} AAV particles/mL and 10^{13} AAV particles/mL, between 10^{12} AAV particles/mL and 10^{14} AAV particles/mL, or between 10^{13} AAV particles/mL and 10^{14} AAV particles/mL.

[00226] In an aspect, a composition comprising an AAV particle encoded by an AAV vector as provided herein is injected at volume between 10 μ l and 1000 μ l. In one aspect, a composition comprising an AAV particle encoded by an AAV vector as provided herein is injected at volume between 10 μ l and 100 μ l, between 10 μ l and 200 μ l, between 10 μ l and 300 μ l, between 100 μ l and 200 μ l, between 100 μ l and 300 μ l, between 100 μ l and 400 μ l, between 200 μ l and 300 μ l, between 200 μ l and 400 μ l, between 200 μ l and 500 μ l, between 300 μ l and 400 μ l, between 300 μ l and 500 μ l, between 300 μ l and 600 μ l, between 400 μ l and 500 μ l, between 400 μ l and 600 μ l, between 400 μ l and 700 μ l, between 500 μ l and 600 μ l, between 500 μ l and 700 μ l, between 500 μ l and 800 μ l, between 600 μ l and 700 μ l, between 600 μ l and 800 μ l, between 600 μ l and 900 μ l, between 700 μ l and 800 μ l, between 700 μ l and 900 μ l, between 700 μ l and 1000 μ l, between 800 μ l and 900 μ l, between 800 μ l and 1000 μ l, or between 900 μ l and 1000 μ l.

[00227] As used herein, the term “subject” refers to any animal subject. Non-limiting examples of animal subjects include humans, laboratory animals (*e.g.*, non-human primates, rats, mice), livestock (*e.g.*, cows, sheep, goats, pigs, turkeys, chickens), and household pets (*e.g.*, dogs, cats, rodents, etc.).

[00228] As used herein, “a subject in need thereof” refers to a subject with a neurological condition. In an aspect, a subject in need thereof has a neurological condition selected from the group consisting of Alzheimer’s Disease, Parkinson’s Disease, amyotrophic lateral sclerosis (ALS), Huntington’s Disease, epilepsy, physical injury, stroke, cerebral aneurysm, traumatic brain injury, concussion, a tumor, inflammation, infection, ataxia, brain atrophy, spinal cord atrophy, multiple sclerosis, traumatic spinal cord injury, ischemic or hemorrhagic myelopathy

(myelopathy), global ischemia, hypoxic ischemic encephalopathy, embolism, fibrocartilage embolism myelopathy, thrombosis, nephropathy, chronic inflammatory disease, meningitis, and cerebral venous sinus thrombosis. In one aspect, a subject in need thereof has Alzheimer's Disease. In one aspect, a subject in need thereof has Parkinson's Disease. In one aspect, a subject
5 in need thereof has ALS. In one aspect, a subject in need thereof has Huntington's Disease. In one aspect, a subject in need thereof has epilepsy. In one aspect, a subject in need thereof has a physical injury. In one aspect, a subject in need thereof has a stroke. In one aspect, a subject in need thereof has ischemic stroke. In one aspect, a subject in need thereof has hemorrhagic stroke. In one aspect, a subject in need thereof has a cerebral aneurysm. In one aspect, a subject in need
10 thereof has traumatic brain injury. In one aspect, a subject in need thereof has concussion. In one aspect, a subject in need thereof has a tumor. In one aspect, a subject in need thereof has inflammation. In one aspect, a subject in need thereof has an infection. In, one aspect, a subject in need thereof has ataxia. In, one aspect, a subject in need thereof has brain atrophy. In one aspect, a subject in need thereof has spinal cord atrophy. In one aspect, a subject in need thereof
15 has multiple sclerosis. In one aspect, a subject in need thereof has a traumatic spinal cord injury. In one aspect, a subject in need thereof has ischemic or hemorrhagic myelopathy (myelopathy). In one aspect, a subject in need thereof has global ischemia. In one aspect, a subject in need thereof has hypoxic ischemic encephalopathy. In one aspect, a subject in need thereof has an embolism. In one aspect, a subject in need thereof has fibrocartilage embolism myelopathy. In one aspect, a
20 subject in need thereof has thrombosis. In one aspect, a subject in need thereof has nephropathy. In one aspect, a subject in need thereof has chronic inflammatory disease. In one aspect, a subject in need thereof has meningitis. In one aspect, a subject in need thereof has cerebral venous sinus thrombosis.

[00229] In an aspect, a subject in need thereof is a mammal. In one aspect, a subject in need
25 thereof is a human. In one aspect, a subject in need thereof is a non-human primate. In one aspect, a subject in need thereof is selected from the group consisting of chimpanzee, bonobo, orangutan, gorilla, macaque, marmoset, capuchin, baboon, gibbon, and lemur. In one aspect, a subject in need thereof is a chimpanzee. In one aspect, a subject in need thereof is a bonobo. In one aspect, a
30 subject in need thereof is orangutan. In one aspect, a subject in need thereof is gorilla. In one aspect, a subject in need thereof is a macaque. In one aspect, a subject in need thereof is marmoset. In one aspect, a subject in need thereof is a capuchin. In one aspect, a subject in need thereof is a

baboon. In one aspect, a subject in need thereof is a gibbon. In one aspect, a subject in need thereof is lemur.

[00230] In one aspect, a subject in need thereof is a male. In one aspect, a subject in need thereof is a female. In one aspect, a subject in need thereof is gender neutral. In one aspect, a
5 subject in need thereof is a premature newborn. In one aspect, a premature newborn is born before 36 weeks gestation. In one aspect, a subject in need thereof is a term newborn. In one aspect, a term newborn is below about 2 months old. In one aspect, a subject in need thereof is a neonate. In one aspect, a neonate is below about 1 month old. In one aspect, a subject in need thereof is an infant. In one aspect, an infant is between 2 months and 24 months old. In one aspect, an infant
10 is between 2 months and 3 months, between 2 months and 4 months, between 2 months and 5 months, between 3 months and 4 months, between 3 months and 5 months, between 3 months and 6 months, between 4 months and 5 months, between 4 months and 6 months, between 4 months and 7 months, between 5 months and 6 months, between 5 months and 7 months, between 5 months and 8 months, between 6 months and 7 months, between 6 months and 8 months, between 6 months
15 and 9 months, between 7 months and 8 months, between 7 months and 9 months, between 7 months and 10 months, between 8 months and 9 months, between 8 months and 10 months, between 8 months and 11 months, between 9 months and 10 months, between 9 months and 11 months, between 9 months and 12 months, between 10 months and 11 months, between 10 months and 12 months, between 10 months and 13 months, between 11 months and 12 months, between 11
20 months and 13 months, between 11 months and 14 months, between 12 months and 13 months, between 12 months and 14 months, between 12 months and 15 months, between 13 months and 14 months, between 13 months and 15 months, between 13 months and 16 months, between 14 months and 15 months, between 14 months and 16 months, between 14 months and 17 months, between 15 months and 16 months, between 15 months and 17 months, between 15 months and
25 18 months, between 16 months and 17 months, between 16 months and 18 months, between 16 months and 19 months, between 17 months and 18 months, between 17 months and 19 months, between 17 months and 20 months, between 18 months and 19 months, between 18 months and 20 months, between 18 months and 21 months, between 19 months and 20 months, between 19 months and 21 months, between 19 months and 22 months, between 20 months and 21 months,
30 between 20 months and 22 months, between 20 months and 23 months, between 21 months and 22 months, between 21 months and 23 months, between 21 months and 24 months, between 22

months and 23 months, between 22 months and 24 months, and between 23 months and 24 months old. In one aspect, a subject in need thereof is a toddler. In one aspect, a toddler is between 1 year and 4 years old. In one aspect, a toddler is between 1 year and 2 years, between 1 year and 3 years, between 1 year and 4 years, between 2 years and 3 years, between 2 years and 4 years, and between
5 3 years and 4 years old. In one aspect, a subject in need thereof is a young child. In one aspect, a young child is between 2 years and 5 years old. In one aspect, a young child is between 2 years and 3 years, between 2 years and 4 years, between 2 years and 5 years, between 3 years and 4 years, between 3 years and 5 years, and between 4 years and 5 years old. In one aspect, a subject in need thereof is a child. In one aspect, a child is between 6 years and 12 years old. In one aspect,
10 a child is between 6 years and 7 years, between 6 years and 8 years, between 6 years and 9 years, between 7 years and 8 years, between 7 years and 9 years, between 7 years and 10 years, between 8 years and 9 years, between 8 years and 10 years, between 8 years and 11 years, between 9 years and 10 years, between 9 years and 11 years, between 9 years and 12 years, between 10 years and 11 years, between 10 years and 12 years, and between 11 years and 12 years old. In one aspect, a
15 subject in need thereof is an adolescent. In one aspect, an adolescent is between 13 years and 19 years old. In one aspect, an adolescent is between 13 years and 14 years, between 13 years and 15 years, between 13 years and 16 years, between 14 years and 15 years, between 14 years and 16 years, between 14 years and 17 years, between 15 years and 16 years, between 15 years and 17 years, between 15 years and 18 years, between 16 years and 17 years, between 16 years and 18
20 years, between 16 years and 19 years, between 17 years and 18 years, between 17 years and 19 years, and between 18 years and 19 years old. In one aspect, a subject in need thereof is a pediatric subject. In one aspect, a pediatric subject between 1 day and 18 years old. In one aspect, a pediatric subject is between 1 day and 1 year, between 1 day and 2 years, between 1 day and 3 years, between 1 year and 2 years, between 1 year and 3 years, between 1 year and 4 years, between 2 years and
25 3 years, between 2 years and 4 years, between 2 years and 5 years, between 3 years and 4 years, between 3 years and 5 years, between 3 years and 6 years, between 4 years and 5 years, between 4 years and 6 years, between 4 years and 7 years, between 5 years and 6 years, between 5 years and 7 years, between 5 years and 8 years, between 6 years and 7 years, between 6 years and 8 years, between 6 years and 9 years, between 7 years and 8 years, between 7 years and 9 years,
30 between 7 years and 10 years, between 8 years and 9 years, between 8 years and 10 years, between 8 years and 11 years, between 9 years and 10 years, between 9 years and 11 years, between 9 years

and 12 years, between 10 years and 11 years, between 10 years and 12 years, between 10 years and 13 years, between 11 years and 12 years, between 11 years and 13 years, between 11 years and 14 years, between 12 years and 13 years, between 12 years and 14 years, between 12 years and 15 years, between 13 years and 14 years, between 13 years and 15 years, between 13 years and 16 years, between 14 years and 15 years, between 14 years and 16 years, between 14 years and 17 years, between 15 years and 16 years, between 15 years and 17 years, between 15 years and 18 years, between 16 years and 17 years, between 16 years and 18 years, and between 17 years and 18 years old. In one aspect, a subject in need thereof is a geriatric subject. In one aspect, a geriatric subject is between 65 years and 95 or more years old. In one aspect, a geriatric subject is between 65 years and 70 years, between 65 years and 75 years, between 65 years and 80 years, between 70 years and 75 years, between 70 years and 80 years, between 70 years and 85 years, between 75 years and 80 years, between 75 years and 85 years, between 75 years and 90 years, between 80 years and 85 years, between 80 years and 90 years, between 80 years and 95 years, between 85 years and 90 years, and between 85 years and 95 years old. In one aspect, a subject in need thereof is an adult. In one aspect, an adult subject is between 20 years and 95 or more years old. In one aspect, an adult subject is between 20 years and 25 years, between 20 years and 30 years, between 20 years and 35 years, between 25 years and 30 years, between 25 years and 35 years, between 25 years and 40 years, between 30 years and 35 years, between 30 years and 40 years, between 30 years and 45 years, between 35 years and 40 years, between 35 years and 45 years, between 35 years and 50 years, between 40 years and 45 years, between 40 years and 50 years, between 40 years and 55 years, between 45 years and 50 years, between 45 years and 55 years, between 45 years and 60 years, between 50 years and 55 years, between 50 years and 60 years, between 50 years and 65 years, between 55 years and 60 years, between 55 years and 65 years, between 55 years and 70 years, between 60 years and 65 years, between 60 years and 70 years, between 60 years and 75 years, between 65 years and 70 years, between 65 years and 75 years, between 65 years and 80 years, between 70 years and 75 years, between 70 years and 80 years, between 70 years and 85 years, between 75 years and 80 years, between 75 years and 85 years, between 75 years and 90 years, between 80 years and 85 years, between 80 years and 90 years, between 80 years and 95 years, between 85 years and 90 years, and between 85 years and 95 years old. In one aspect, a subject in need thereof is between 1 year and 5 years, between 2 years and 10 years, between 3 years and 18 years, between 21 years and 50 years, between 21

years and 40 years, between 21 years and 30 years, between 50 years and 90 years, between 60 years and 90 years, between 70 years and 90 years, between 60 years and 80 years, or between 65 years and 75 years old. In one aspect, a subject in need thereof is a young old subject (65 to 74 years old). In one aspect, a subject in need thereof is a middle old subject (75 to 84 years old). In one aspect, a subject in need thereof is an old subject (>85 years old).

[00231] As used herein, the term “flow rate” refers to the rate of delivery of an AAV vector or composition. In an aspect, the flow rate is between 0.1 $\mu\text{L}/\text{minute}$ and 5.0 $\mu\text{L}/\text{minute}$. In one aspect, the flow rate is between 0.1 $\mu\text{L}/\text{minute}$ and 0.2 $\mu\text{L}/\text{minute}$, between 0.1 $\mu\text{L}/\text{minute}$ and 0.3 $\mu\text{L}/\text{minute}$, between 0.1 $\mu\text{L}/\text{minute}$ and 0.4 $\mu\text{L}/\text{minute}$, between 0.2 $\mu\text{L}/\text{minute}$ and 0.3 $\mu\text{L}/\text{minute}$, between 0.2 $\mu\text{L}/\text{minute}$ and 0.4 $\mu\text{L}/\text{minute}$, between 0.2 $\mu\text{L}/\text{minute}$ and 0.5 $\mu\text{L}/\text{minute}$, between 0.3 $\mu\text{L}/\text{minute}$ and 0.4 $\mu\text{L}/\text{minute}$, between 0.3 $\mu\text{L}/\text{minute}$ and 0.5 $\mu\text{L}/\text{minute}$, between 0.3 $\mu\text{L}/\text{minute}$ and 0.6 $\mu\text{L}/\text{minute}$, between 0.4 $\mu\text{L}/\text{minute}$ and 0.5 $\mu\text{L}/\text{minute}$, between 0.4 $\mu\text{L}/\text{minute}$ and 0.6 $\mu\text{L}/\text{minute}$, between 0.4 $\mu\text{L}/\text{minute}$ and 0.7 $\mu\text{L}/\text{minute}$, between 0.5 $\mu\text{L}/\text{minute}$ and 0.6 $\mu\text{L}/\text{minute}$, between 0.5 $\mu\text{L}/\text{minute}$ and 0.7 $\mu\text{L}/\text{minute}$, between 0.5 $\mu\text{L}/\text{minute}$ and 0.8 $\mu\text{L}/\text{minute}$, between 0.6 $\mu\text{L}/\text{minute}$ and 0.7 $\mu\text{L}/\text{minute}$, between 0.6 $\mu\text{L}/\text{minute}$ and 0.8 $\mu\text{L}/\text{minute}$, between 0.6 $\mu\text{L}/\text{minute}$ and 0.9 $\mu\text{L}/\text{minute}$, between 0.7 $\mu\text{L}/\text{minute}$ and 0.8 $\mu\text{L}/\text{minute}$, between 0.7 $\mu\text{L}/\text{minute}$ and 0.9 $\mu\text{L}/\text{minute}$, between 0.7 $\mu\text{L}/\text{minute}$ and 1.0 $\mu\text{L}/\text{minute}$, between 0.8 $\mu\text{L}/\text{minute}$ and 0.9 $\mu\text{L}/\text{minute}$, between 0.8 $\mu\text{L}/\text{minute}$ and 1.0 $\mu\text{L}/\text{minute}$, between 0.8 $\mu\text{L}/\text{minute}$ and 1.1 $\mu\text{L}/\text{minute}$, between 0.9 $\mu\text{L}/\text{minute}$ and 1.0 $\mu\text{L}/\text{minute}$, between 0.9 $\mu\text{L}/\text{minute}$ and 1.1 $\mu\text{L}/\text{minute}$, between 0.9 $\mu\text{L}/\text{minute}$ and 1.2 $\mu\text{L}/\text{minute}$, between 1.0 $\mu\text{L}/\text{minute}$ and 1.1 $\mu\text{L}/\text{minute}$, between 1.0 $\mu\text{L}/\text{minute}$ and 1.2 $\mu\text{L}/\text{minute}$, between 1.0 $\mu\text{L}/\text{minute}$ and 1.3 $\mu\text{L}/\text{minute}$, between 1.1 $\mu\text{L}/\text{minute}$ and 1.2 $\mu\text{L}/\text{minute}$, between 1.1 $\mu\text{L}/\text{minute}$ and 1.3 $\mu\text{L}/\text{minute}$, between 1.1 $\mu\text{L}/\text{minute}$ and 1.4 $\mu\text{L}/\text{minute}$, between 1.2 $\mu\text{L}/\text{minute}$ and 1.3 $\mu\text{L}/\text{minute}$, between 1.2 $\mu\text{L}/\text{minute}$ and 1.4 $\mu\text{L}/\text{minute}$, between 1.2 $\mu\text{L}/\text{minute}$ and 1.5 $\mu\text{L}/\text{minute}$, between 1.3 $\mu\text{L}/\text{minute}$ and 1.4 $\mu\text{L}/\text{minute}$, between 1.3 $\mu\text{L}/\text{minute}$ and 1.5 $\mu\text{L}/\text{minute}$, between 1.3 $\mu\text{L}/\text{minute}$ and 1.6 $\mu\text{L}/\text{minute}$, between 1.4 $\mu\text{L}/\text{minute}$ and 1.5 $\mu\text{L}/\text{minute}$, between 1.4 $\mu\text{L}/\text{minute}$ and 1.6 $\mu\text{L}/\text{minute}$, between 1.4 $\mu\text{L}/\text{minute}$ and 1.7 $\mu\text{L}/\text{minute}$, between 1.5 $\mu\text{L}/\text{minute}$ and 1.6 $\mu\text{L}/\text{minute}$, between 1.5 $\mu\text{L}/\text{minute}$ and 1.7 $\mu\text{L}/\text{minute}$, between 1.5 $\mu\text{L}/\text{minute}$ and 1.8 $\mu\text{L}/\text{minute}$, between 1.6 $\mu\text{L}/\text{minute}$ and 1.7 $\mu\text{L}/\text{minute}$, between 1.6 $\mu\text{L}/\text{minute}$ and 1.8 $\mu\text{L}/\text{minute}$, between 1.6 $\mu\text{L}/\text{minute}$ and 1.9 $\mu\text{L}/\text{minute}$, between 1.7 $\mu\text{L}/\text{minute}$ and 1.8 $\mu\text{L}/\text{minute}$, between 1.7 $\mu\text{L}/\text{minute}$ and 1.9 $\mu\text{L}/\text{minute}$, between 1.7 $\mu\text{L}/\text{minute}$ and 2.0 $\mu\text{L}/\text{minute}$, between 1.8 $\mu\text{L}/\text{minute}$ and 1.9 $\mu\text{L}/\text{minute}$, between 1.8

[illegible]

and 4.2 $\mu\text{L}/\text{minute}$, between 4.1 $\mu\text{L}/\text{minute}$ and 4.3 $\mu\text{L}/\text{minute}$, between 4.1 $\mu\text{L}/\text{minute}$ and 4.4 $\mu\text{L}/\text{minute}$, between 4.2 $\mu\text{L}/\text{minute}$ and 4.3 $\mu\text{L}/\text{minute}$, between 4.2 $\mu\text{L}/\text{minute}$ and 4.4 $\mu\text{L}/\text{minute}$, between 4.2 $\mu\text{L}/\text{minute}$ and 4.5 $\mu\text{L}/\text{minute}$, between 4.3 $\mu\text{L}/\text{minute}$ and 4.4 $\mu\text{L}/\text{minute}$, between 4.3 $\mu\text{L}/\text{minute}$ and 4.5 $\mu\text{L}/\text{minute}$, between 4.3 $\mu\text{L}/\text{minute}$ and 4.6 $\mu\text{L}/\text{minute}$, between 4.4 $\mu\text{L}/\text{minute}$ and 4.5 $\mu\text{L}/\text{minute}$, between 4.4 $\mu\text{L}/\text{minute}$ and 4.6 $\mu\text{L}/\text{minute}$, between 4.4 $\mu\text{L}/\text{minute}$ and 4.7 $\mu\text{L}/\text{minute}$, between 4.5 $\mu\text{L}/\text{minute}$ and 4.6 $\mu\text{L}/\text{minute}$, between 4.5 $\mu\text{L}/\text{minute}$ and 4.7 $\mu\text{L}/\text{minute}$, between 4.5 $\mu\text{L}/\text{minute}$ and 4.8 $\mu\text{L}/\text{minute}$, between 4.6 $\mu\text{L}/\text{minute}$ and 4.7 $\mu\text{L}/\text{minute}$, between 4.6 $\mu\text{L}/\text{minute}$ and 4.8 $\mu\text{L}/\text{minute}$, between 4.6 $\mu\text{L}/\text{minute}$ and 4.9 $\mu\text{L}/\text{minute}$, between 4.7 $\mu\text{L}/\text{minute}$ and 4.8 $\mu\text{L}/\text{minute}$, between 4.7 $\mu\text{L}/\text{minute}$ and 4.9 $\mu\text{L}/\text{minute}$, between 4.7 $\mu\text{L}/\text{minute}$ and 5.0 $\mu\text{L}/\text{minute}$, 4.8 $\mu\text{L}/\text{minute}$ and 4.9 $\mu\text{L}/\text{minute}$, between 4.8 $\mu\text{L}/\text{minute}$ and 5.0 $\mu\text{L}/\text{minute}$, or between 4.9 $\mu\text{L}/\text{minute}$ and 5.0 $\mu\text{L}/\text{minute}$.

[00232] As used herein, the term “therapeutically effective dose” or “pharmaceutically active dose” refers to an amount of AAV particles or composition as provided herein which is effective in treating a neurological condition. In an aspect, an AAV particle or composition as provided herein can be provided together with a pharmaceutically acceptable carrier. As used herein, a “pharmaceutically acceptable carrier” refers to a non-toxic solvent, dispersant, excipient, adjuvant, or other material which is mixed with an AAV particles or composition as provided herein.

[00233] Non-limiting examples of a pharmaceutically acceptable carrier include a liquid (e.g., saline), gel, nanoparticles, exosomes, lipid vesicles, or solid form of diluents, adjuvant, excipients or an acid resistant encapsulated ingredient. Non-limiting examples of suitable diluents and excipients include pharmaceutical grades of physiological saline, dextrose, glycerol, mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, magnesium carbonate, and the like, and combinations thereof. In an aspect, a therapeutic effective dose contains auxiliary substances such as wetting or emulsifying agents, stabilizing or pH buffering agents. In one aspect, a therapeutically effective dose of an AAV particle or composition as provided herein is injected to a subject. In one aspect, a therapeutically effective dose of an AAV particle or composition as provided herein is delivered into a subject. In one aspect, a therapeutically effective dose is administered with at least one pharmaceutically acceptable carrier. In one aspect, a therapeutic effective dose contains between about 1% and about 5%, between about 5% and about 10%, between about 10% and about 15%, between about 15% and about 20%, between about 20% and

about 25%, between about 25% and about 30%, between about 30% and about 35%, between about 40 and about 45%, between about 50% and about 55%, between about 1% and about 95%, between about 2% and about 95%, between about 5% and about 95%, between about 10% and about 95%, between about 15% and about 95%, between about 20% and about 95%, between about 25% and about 95%, between about 30% and about 95%, between about 35% and about 95%, between about 40% and about 95%, between about 45% and about 95%, between about 50% and about 95%, between about 55% and about 95%, between about 60% and about 95%, between about 65% and about 95%, between about 70% and about 95%, between about 45% and about 95%, between about 80% and about 95%, or between about 85% and about 95% of AAV particle or composition as provided herein.

[00234] In an aspect, a therapeutically effective dose is delivered to subject in need thereof at least once daily or at least once weekly for at least two consecutive days or weeks. In one aspect, a therapeutically effective dose is delivered to subject in need thereof at least once daily or at least once weekly for at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 consecutive days or weeks. In one aspect, a therapeutically effective dose is delivered to subject in need thereof at least once daily or at least once weekly for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 consecutive weeks. In one aspect, a therapeutically effective dose is delivered to subject in need thereof at least once daily or at least once weekly for at most 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 consecutive days or weeks. In one aspect, a therapeutically effective dose is delivered to subject in need thereof at least once daily or at least once weekly for at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 consecutive weeks or months. In one aspect, a therapeutically effective dose is delivered to subject in need thereof is administered at least once for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 consecutive months or years, chronically for a subject's entire life span, or an indefinite period of time. In one aspect, a therapeutically effective dose is delivered to subject in need thereof once a year for 2 consecutive years, 3 consecutive years, or 5 consecutive years. In one aspect, a therapeutically effective dose is delivered to subject in need thereof once a year for 2 consecutive years. In one aspect, a therapeutically effective dose is delivered to subject in need thereof once a year for 3 consecutive years. In one aspect, a therapeutically effective dose is delivered to subject in need thereof once a year for 5 consecutive years.

[00235] As used herein, the term “remission”, “cure,” or “resolution rate” refers to the percentage of subjects in need thereof that are cured or obtain remission or complete resolution of a neurological condition in response to a therapeutically effective dose.

[00236] As used herein, the term “response rate” refers to the percentage of subjects in need thereof that respond positively (*e.g.*, reduced severity or frequency of one or more symptoms) to a therapeutically effective dose.

[00237] In one aspect, a therapeutically effective dose achieves a remission, cure, response rate, or resolution rate of a neurological condition of at least about 50%. In one aspect, a therapeutically effective dose eliminates, reduces, slows, or delays, one or more neurological condition symptoms. Non-limiting examples of neurological condition symptoms include tremor, slowed movement (bradykinesia), rigid muscles, impaired posture and balance, loss of automatic movements, uncoordinated movement, uncontrolled movement, spontaneous jerking movement, speech changes, numbness, and writing changes. In an aspect, a neurological condition symptom is a movement symptom. Non-limiting examples of movement symptoms include impairment of an involuntary movement or an impairment of a voluntary movement. In one aspect, a neurological condition symptom is a cognitive symptom. Non-limiting examples of cognitive symptoms include fine motor skills, tremors, seizures, chorea, dystonia, dyskinesia, slow or abnormal eye movements, impaired gait, impaired posture, impaired balance, difficulty with speech, difficulty with swallowing, difficulty organizing, difficulty prioritizing, difficulty focusing on tasks, lack of flexibility, lack of impulse control, outbursts, lack of awareness of one's own behaviors and/or abilities, slowness in processing thoughts, difficulty in learning new information, difficulty in remember things, difficulty in communications, difficulty in following orders, difficulty in executing tasks.

[00238] In an aspect, neurological condition symptom is a psychiatric symptom. Non-limiting examples of psychiatric symptoms include depression, irritability, sadness or apathy, social withdrawal, insomnia, fatigue, lack of energy, obsessive-compulsive disorder, mania, bipolar disorder, and weight loss. In one aspect, a neurological condition symptom is at least one damaged blood vessel. In one aspect, a neurological condition symptom is a damaged blood brain barrier. In one aspect, a neurological condition symptom is damaged blood flow. Non-limiting examples of tests to evaluate the elimination, reduction, slow, or delay, of neurological condition symptoms include the unified Huntington's disease rating scale (UHDRS) score, UHDRS Total

Functional Capacity (TFC), UHDRS Functional Assessment, UHDRS Gait score, UHDRS Total Motor Score (TMS), Hamilton depression scale (HAM-D), Columbia-suicide severity rating scale (C-SSRS), Montreal cognitive assessment (MoCA), modified Rankin Scale (mRS), National Institutes of Health Stroke Scale (NIHSS), and Barthel Index (BI), Timed Up and Go Test (TUG),
 5 Chedoke Arm and Hand Activity Inventory (CAHAI), Symbol Digit Modalities Test, Controlled Oral Word Association tasks, magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET) scanning.

[00239] In an aspect, a therapeutically effective dose achieves remission, cure, response rate, or resolution rate of a neurological condition of between about 10% and about 100% or more.

10 In one aspect, a therapeutically effective dose achieves remission, cure, response rate, or resolution rate of a neurological condition between 10% and 100%, such as between 10% and 15 %, between 10% and 20%, between 10% and 25%, between 15% and 20%, between 15% and 25 %, between 15% and 30%, between 20% and 25%, between 20% and 30%, between 20% and 35%, between 25% and 30%, between 25% and 35%, between 25% and 40%, between 30% and 35%, between
 15 30% and 40%, between 35% and 45%, between 35% and 50%, between 40% and 45%, between 40% and 50%, between 40% and 55%, between 45% and 50%, between 45% and 55%, between 45% and 60%, between 50% and 55%, between 50% and 60%, between 50% and 65%, between 55% and 60%, between 55% and 65%, between 55% and 70%, between 60% and 65%, between 60% and 70%, between 60% and 75%, between 65% and 70%, between 65% and 75%, between
 20 65% and 80%, between 70% and 75%, between 70% and 80%, between 70% and 85%, between 75% and 80%, between 75% and 85%, between 75% and 90%, between 80% and 85%, between 80% and 90%, between 80% and 95%, between 85% and 90%, between 85% and 95%, between 85%and 100%, between 90% and 95%, between 90% and 100%, or between 95% and 100%.

[00240] In an aspect, a therapeutically effective dose eliminates, reduces, slows, or delays,
 25 one or more neurological condition symptoms between 10% and 100%, such as between 10% to about 15%, between 10% and 20%, between 10% and 25%, between 15% and 20%, between 15% and 25 %, between 15% and 30%, between 20% and 25%, between 20% and 30%, between 20% and 35%, between 25 and 30%, between 25% and 35%, between 25% and 40%, between 30% and 35%, between 30% and 40%, between 35% and 45%, between 35% and 50%, between 40% and
 30 45%, between 40% and 50%, between 40% and 55%, between 45% and 50%, between 45% and 55%, between 45% and 60%, between 50% and 55%, between 50% and 60%, between 50% and

65%, between 55% and 60%, between 55% and 65%, between 55% and 70%, between 60% and 65%, between 60% and 70%, between 60% and 75%, between 65% and 70%, between 65% and 75%, between 65% and 80%, between 70% and 75%, between 70% and 80%, between 70% and 85%, between 75% and 80%, between 75% and 85%, between 75% and 90%, between 80% and 85%, between 80% and 90%, between 80% and 95%, between 85% and 90%, between 85% and 95%, between 85% and 100%, between 90% and 95%, between 90% and 100%, or between 95% and 100%.

[00241] In an aspect, a neurological condition symptom is assessed on the day of treatment, 1 day post treatment, 3 months post treatment, 6 months post treatment, 1 year post treatment and every year thereafter post treatment.

[00242] In an aspect, a neurological condition symptom is assessed between 1 day post treatment and 7 days post treatment. In one aspect, symptoms can be assessed between 1 day post treatment and 2 days post treatment, between 1 day post treatment and 3 days post treatment, between 1 day post treatment and 4 days post treatment, between 2 days post treatment and 3 days post treatment, between 2 days post treatment and 4 days post treatment, between 2 days post treatment and 5 days post treatment, between 3 days post treatment and 4 days post treatment, between 3 days post treatment and 5 days post treatment, 3 days post treatment and 6 days post treatment, between 4 days post treatment and 5 days post treatment, between 4 days post treatment and 6 days post treatment, between 4 days post treatment and 7 days post treatment, between 5 days post treatment and 6 days post treatment, between 5 days post treatment and 7 days post treatment, or between 6 days post treatment and 7 days post treatment. In one aspect, symptoms can be assessed between 1 week post treatment and 4 weeks post treatment. In one aspect, symptoms can be assessed between 1 week post treatment and 2 weeks post treatment, between 1 week post treatment and 3 weeks post treatment, between 1 week post treatment and 4 weeks post treatment, between 2 weeks post treatment and 3 weeks post treatment, between 2 weeks post treatment and 4 weeks post treatment, or between 3 weeks post treatment and 4 weeks post treatment. In one aspect, symptoms can be assessed between 1 month post treatment and 12 months post treatment. In one aspect, symptoms can be assessed between 1 month post treatment and 2 months post treatment, between 1 month post treatment and 3 months post treatment, between 1 month post treatment and 4 months post treatment, between 2 months post treatment and 3 months post treatment, between 2 months post treatment and 4 months post treatment,

between 2 months post treatment and 5 months post treatment, between 3 months post treatment and 4 months post treatment, between 3 months post treatment and 5 months post treatment, between 3 months post treatment and 6 months post treatment, between 4 months post treatment and 5 months post treatment, between 4 months post treatment and 6 months post treatment, between 4 months post treatment and 7 months post treatment, between 5 months post treatment and 6 months post treatment, between 5 months post treatment and 7 months post treatment, between 5 months post treatment and 8 months post treatment, between 6 months post treatment and 7 months post treatment, between 6 months post treatment and 8 months post treatment, between 6 months post treatment and 9 months post treatment, between 7 months post treatment and 8 months post treatment, between 7 months post treatment and 9 months post treatment, between 7 months post treatment and 10 months post treatment, between 8 months post treatment and 9 months post treatment, between 8 months post treatment and 10 months post treatment, between 8 months post treatment and 11 months post treatment, between 9 months post treatment and 10 months post treatment, between 9 months post treatment and 11 months post treatment, between 9 months post treatment and 12 months post treatment, between 10 months post treatment and 11 months post treatment, between 10 months post treatment and 12 months post treatment, or between 11 months post treatment and 12 months post treatment. In one aspect, symptoms can be assessed between 1 year post treatment and about 20 years post treatment. In one aspect symptoms can be assessed between 1 year post treatment and 5 years post treatment, between 1 year post treatment and 10 years post treatment, between 1 year post treatment and 15 years post treatment, between 5 years post treatment and 10 years post treatment, between 5 years post treatment and 15 years post treatment, between 5 years post treatment and 20 years post treatment, between 10 years post treatment and 15 years post treatment, between 10 years post treatment and 20 years post treatment, or between 15 years post treatment and 20 years post treatment.

[00243] As used herein, the term “survival rate” refers to a cohort of subjects in a treatment group still alive after a given period of time after diagnosis of a neurological condition.

[00244] In an aspect, a therapeutically effective dose achieves increase survival rate of between about 10% and 100% or more. In one aspect, a therapeutically effective dose achieves an increase in survival rate of between 10% and 100%, such as between 10% and 15%, between 10% and 20%, between 10% and 25%, between 15% and 20%, between 15% and 25%, between 15% and 30%, between 20% and 25%, between 20% and 30%, between 20% and 35%, between

25% and 30%, between 25% and 35%, between 25% and 40%, between 30% and 35%, between 30% and 40%, between 35% and 45%, between 35% and 50%, between 40% and 45%, between 40% and 50%, between 40% and 55%, between 45% and 50%, between 45% and 55%, between 45% and 60%, between 50% and 55%, between 50% and 60%, between 50% and 65%, between 55% and 60%, between 55% and 65%, between 55% and 70%, between 60% and 65%, between 60% and 70%, between 60% and 75%, between 65% and 70%, between 65% and 75%, between 65% and 80%, between 70% and 75%, between 70% and 80%, between 70% and 85%, between 75% and 80%, between 75% and 85%, between 75% and 90%, between 80% and 85%, between 80% and 90%, between 80% and 95%, between 85% and 90%, between 85% and 95%, between 85% and 100%, between 90% and 95%, between 90% and 100%, or between 95% and 100%.

[00245] As used herein, the term “life expectancy” refers to a period of time a subject is expected to live.

[00246] In an aspect, a therapeutically effective dose increases life expectancy of between about 10% and 100% or more. In one aspect, a therapeutically effective dose increases life expectancy of between 10% and 100%, such as between 10% and 15%, between 10% and 20%, between 10% and 25%, between 15% and 20%, between 15% and 25%, between 15% and 30%, between 20% and 25%, between 20% and 30%, between 20% and 35%, between 25% and 30%, between 25% and 35%, between 25% and 40%, between 30% and 35%, between 30% and 40%, between 35% and 45%, between 35% and 50%, between 40% and 45%, between 40% and 50%, between 40% and 55%, between 45% and 50%, between 45% and 55%, between 45% and 60%, between 50% and 55%, between 50% and 60%, between 50% and 65%, between 55% and 60%, between 55% and 65%, between 55% and 70%, between 60% and 65%, between 60% and 70%, between 60% and 75%, between 65% and 70%, between 65% and 75%, between 65% and 80%, between 70% and 75%, between 70% and 80%, between 70% and 85%, between 75% and 80%, between 75% and 85%, between 75% and 90%, between 80% and 85%, between 80% and 90%, between 80% and 95%, between 85% and 90%, between 85% and 95%, between 85% and 100%, between 90% and 95%, between 90% and 100%, or between 95% and 100%.

[00247] In an aspect, a therapeutically effective dose reduces the amount of atrophy within the brain of a subject in need thereof between about 10% and 100% or more. In one aspect, a therapeutically effective dose reduces the amount of atrophy within the brain of a subject in need thereof between 10% and 100%, such as between 10% and 15%, between 10% and 20%, between

10% and 25%, between 15% and 20%, between 15% and 25%, between 15% and 30%, between
20% and 25%, between 20% and 30%, between 20% and 35%, between 25% and 30%, between
25% and 35%, between 25% and 40%, between 30% and 35%, between 30% and 40%, between
35% and 45%, between 35% and 50%, between 40% and 45%, between 40% and 50%, between
5 40% and 55%, between 45% and 50%, between 45% and 55%, between 45% and 60%, between
50% and 55%, between 50% and 60%, between 50% and 65%, between 55% and 60%, between
55% and 65%, between 55% and 70%, between 60% and 65%, between 60% and 70%, between
60% and 75%, between 65% and 70%, between 65% and 75%, between 65% and 80%, between
70% and 75%, between 70% and 80%, between 70% and 85%, between 75% and 80%, between
10 75% and 85%, between 75% and 90%, between 80% and 85%, between 80% and 90%, between
80% and 95%, between 85% and 90%, between 85% and 95%, between 85% and 100%, between
90% and 95%, between 90% and 100%, or between 95% and 100%.

[00248] In an aspect, the amount of atrophy within the brain of a subject in need thereof is
assessed on the day of treatment, 1 day post treatment, 3 months post treatment, 6 months post
15 treatment, 1 year post treatment and every year thereafter post treatment.

[00249] In an aspect, the amount of atrophy within the brain of a subject in need thereof is
assessed between 1 day post treatment and 7 days post treatment. In one aspect, symptoms can be
assessed between 1 day post treatment and 2 days post treatment, between 1 day post treatment
and 3 days post treatment, between 1 day post treatment and 4 days post treatment, between 2 days
20 post treatment and 3 days post treatment, between 2 days post treatment and 4 days post treatment,
between 2 days post treatment and 5 days post treatment, between 3 days post treatment and 4 days
post treatment, between 3 days post treatment and 5 days post treatment, 3 days post treatment and
6 days post treatment, between 4 days post treatment and 5 days post treatment, between 4 days
post treatment and 6 days post treatment, between 4 days post treatment and 7 days post treatment,
25 between 5 days post treatment and 6 days post treatment, between 5 days post treatment and 7 days
post treatment, or between 6 days post treatment and 7 days post treatment. In one aspect,
symptoms can be assessed between 1 week post treatment and 4 weeks post treatment. In one
aspect, symptoms can be assessed between 1 week post treatment and 2 weeks post treatment,
between 1 week post treatment and 3 weeks post treatment, between 1 week post treatment and 4
30 weeks post treatment, between 2 weeks post treatment and 3 weeks post treatment, between 2
weeks post treatment and 4 weeks post treatment, or between 3 weeks post treatment and 4 weeks

post treatment. In one aspect, symptoms can be assessed between 1 month post treatment and 12 months post treatment. In one aspect, symptoms can be assessed between 1 month post treatment and 2 months post treatment, between 1 month post treatment and 3 months post treatment, between 1 month post treatment and 4 months post treatment, between 2 months post treatment and 3 months post treatment, between 2 months post treatment and 4 months post treatment, between 2 months post treatment and 5 months post treatment, between 3 months post treatment and 4 months post treatment, between 3 months post treatment and 5 months post treatment, between 3 months post treatment and 6 months post treatment, between 4 months post treatment and 5 months post treatment, between 4 months post treatment and 6 months post treatment, between 4 months post treatment and 7 months post treatment, between 5 months post treatment and 6 months post treatment, between 5 months post treatment and 7 months post treatment, between 5 months post treatment and 8 months post treatment, between 6 months post treatment and 7 months post treatment, between 6 months post treatment and 8 months post treatment, between 6 months post treatment and 9 months post treatment, between 7 months post treatment and 8 months post treatment, between 7 months post treatment and 9 months post treatment, between 7 months post treatment and 10 months post treatment, between 8 months post treatment and 9 months post treatment, between 8 months post treatment and 10 months post treatment, between 8 months post treatment and 11 months post treatment, between 9 months post treatment and 10 months post treatment, between 9 months post treatment and 11 months post treatment, between 9 months post treatment and 12 months post treatment, between 10 months post treatment and 11 months post treatment, between 10 months post treatment and 12 months post treatment, or between 11 months post treatment and 12 months post treatment. In one aspect, symptoms can be assessed between 1 year post treatment and about 20 years post treatment. In one aspect symptoms can be assessed between 1 year post treatment and 5 years post treatment, between 1 year post treatment and 10 years post treatment, between 1 year post treatment and 15 years post treatment, between 5 years post treatment and 10 years post treatment, between 5 years post treatment and 15 years post treatment, between 5 years post treatment and 20 years post treatment, between 10 years post treatment and 15 years post treatment, between 10 years post treatment and 20 years post treatment, or between 15 years post treatment and 20 years post treatment.

[00250] Non-limiting examples of tests to evaluate the amount of atrophy within the brain of a subject in need thereof include Nissle staining, MRI, functional magnetic resonance fMRI, and PET scanning

[00251] While the present disclosure has been described with reference to preferred
5 embodiments, it will be understood by those skilled in the art that various changes may be made and equivalents may be substituted for elements thereof to adapt to particular situations without departing from the scope of the present disclosure. Therefore, it is intended that the present disclosure not be limited to the particular embodiments disclosed as the best mode contemplated for carrying out the present disclosure, but that the present disclosure will include all embodiments
10 falling within the scope and spirit of the appended claims.

[00252] The examples set out herein illustrate several embodiments of the present disclosure but should not be construed as limiting the scope of the present disclosure in any manner.

EXAMPLES

Example 1. AAV vector constructs

[00253] Twelve AAV vector constructs,

- EF-1 α :GfaABC1D:NeuroD1:WPRE:SV40 (P35) (Figure 1A);
- 5 EF-1 α :Gfa1.6:NeuroD1:WPRE:SV40 (P39) (Figure 2A),
- EF-1 α :GFA2.2:NeuroD1:WPRE:SV40 (Figure 3A),
- EF-1 α :GfaABC1D:NeuroD1:WPRE:hGH (Figure 1B),
- EF-1 α :Gfa1.6:NeuroD1:WPRE:hGH (Figure 2D),
- EF-1 α :GFA2.2:NeuroD1:WPRE:hGH (Figure 3B),
- 10 CE:GfaABC1D:NeuroD1:WPRE:SV40 (P11) (Figure 1C),
- CE:Gfa1.6:NeuroD1:WPRE:SV40 (P38) (Figure 2C),
- CE:GFA2.2:NeuroD1:WPRE:SV40 (Figure 3C),
- CE:GfaABC1D:NeuroD1:WPRE:hGH (Figure 1D),
- CE:Gfa1.6:NeuroD1:WPRE:hGH (Figure 2B), and
- 15 CE:GFA2.2:NeuroD1:WPRE:hGH are constructed (Figure 3D).

[00254] All 12 vector constructs utilize pHSG-299 (Takara, Mountain View, CA), a pUC based vector construct which contains an origin of replication, a Kanamycin resistance gene and a multiple cloning site (MSC) with lacZ gene as backbone.

- [00255] The 5' end of the expression cassette is an enhancer from a human elongation factor-1 alpha promoter (EF-1 alpha enhancer; SEQ ID NO: 2) or the cytomegalovirus enhancer (CMV enhancer; SEQ ID NO: 11) placed 5' to either a 681-nucleotide GFAP promoter (GfaABC1D; SEQ ID NO: 15), a 1667-nucleotide GFAP promoter (Gfa1.6; SEQ ID NO: 4), or a 2214-nucleotide GFAP promoter (GFA2.2 SEQ ID NO: 12).

- [00256] Following (*e.g.*, 3' to) the enhancer/GFAP promoter, several additional sequences are introduced into the expression cassette in 5' to 3' direction, including: a chimeric intron (SEQ ID NO: 5); a human NeuroD1 coding sequence (hNeuroD1; SEQ ID NO: 6); and a modified woodchuck hepatitis virus posttranscriptional regulatory element (WPRE; SEQ ID NO: 7 or SEQ ID NO: 18). These sequences are all operably linked to an SV40 poly(A) signal (SEQ ID NO: 8) or hGH poly (A) signal (SEQ ID NO: 13) or bGH poly (A) signal (SEQ ID NO: 14). The enhancer,

GFAP promoter, chimeric intron, hNeuroD1 coding sequence, WPRE, and poly(A) signal are flanked by two AAV ITR sequences.

Example 2. AAV virus production

[00257] Each of the twelve plasmids is co-transfected into 293AAV cells using polyethylenimine along with Rep-Cap plasmid (a plasmid comprising a promoter driving the expression of AAV *rep* and *cap* genes) and Helper plasmid (a plasmid comprising a promoter driving the expression of E2A, E4, and VA RNA (of Adenovirus) to produce recombinant AAV virus particles.

[00258] Transfected cells are scraped and centrifuged at 72 hours after transfection. Cell pellets are frozen and thawed being placed in a dry ice/ethanol mixture followed by being placed in a 37°C water bath. The freeze/thaw cycle is repeated three additional times. An AAV lysate is purified (e.g., cellular debris is removed) by ultra-centrifugation at 350,000 g for 1 hour in discontinuous iodixanol gradients. The virus-containing layer is collected and then concentrated by using Millipore Amicon Ultra Centrifugal Filters. Virus titers are then determined by qPCR using primers amplifying ITR region or gene/expression cassette specific sequences.

Example 3. Astrocyte cell cultures

[00259] Human cortical astrocytes (HA1800; ScienCell Research Laboratories, Inc., Carlsbad, California) are subcultured when they are over 90% confluent. For subculture, cells are trypsinized using TrypLE™ Select (Invitrogen, Carlsbad, California), centrifuged for 5 minutes at 200× g, then resuspended and plated on a medium comprising DMEM/F12 (Gibco); 10% fetal bovine serum (Gibco); penicillin/streptomycin (Gibco); 3.5 mM glucose (Sigma-Aldrich); B27 (Gibco); 10 ng/mL epidermal growth factor (Invitrogen); and 10 ng/mL fibroblast growth factor 2 (Invitrogen). The astrocytes are cultured on poly-D-lysine (Sigma-Aldrich) coated coverslips (12 mm) at a density of approximately 20,000 cells per coverslip in 24-well plates (BD Biosciences).

[00260] Rat primary astrocytes (isolated from Sprague Dawley Rat cortex or striatum) are cultured in media comprising DMEM/F12 (Gibco); 10% fetal bovine serum (Gibco), penicillin/streptomycin (Gibco); 3.5 mM glucose (Gibco).

[00261] All cells are maintained at 37°C in humidified air with 5% carbon dioxide.

Example 4. Testing AAV vector in astrocyte cell cultures (*in vitro*)

[00262] Recombinant AAV obtained from the method of Example 2 are used to infect human cortical astrocytes and rat primary astrocytes from Example 3 at a concentration range of 10^{10} particles/mL and 10^{14} particles/mL. Twenty-four hours after infection of the cells, the culture medium is replaced by differentiation medium comprising DMEM/F12 (Gibco); N2 supplement (Gibco); and 20 ng/mL brain-derived neurotrophic factor (Invitrogen). The differentiation medium is added to the cell cultures every four days. *See Song et al., Nature, 417:39-44 (2002).*

[00263] Empty space in the cell cultures is filled with additional human astrocytes to support the functional development of converted neurons as astrocytes or rat primary astrocytes convert to neurons.

Example 5. Testing of AAV vector potency

[00264] Recombinant AAV obtained from the method of Example 2 are used to infect human cortical astrocytes and rat primary astrocytes from Example 3 (or astrocytes from other brain regions or the spinal cord) at passage number 4 to 7 at a concentration range of 10^{10} particles/mL and 10^{14} particles/mL. qPCR, enzyme-linked immunosorbent (ELISA), and western blot are performed to determine expression of NeuroD1 transcript and protein levels.

[00265] Expression of NeuN, doublecortin (DCX), β 3-tubulin, NF-200, and MAP2, are assessed by qPCR, ELISA, western blot, and immunostaining to determine functional output of recombinant AAV.

Example 6. Testing of AAV vector titration and infection rate.

[00266] A purified AAV vector is treated with DNaseI to eliminate remnant plasmid contamination. A series of AAV vector dilutions are performed at 100 times, 500 times, 2500 times, and 12500 times. The AAV plasmid backbone is diluted to generate a standard curve by serial dilutions. The plasmid is diluted 10^4 , 10^5 , 10^6 , 10^7 , and 10^8 molecules/ μ l. qPCR is performed on the diluted AAV vectors and the diluted AAV plasmid. The primers used are against the ITR region (Forward ITR primer, 5'-GGAACCCCTAGTGATGGAGTT, reverse ITR primer, 5'-CGGCCTCAGTGAGCGA). The qPCR mix comprises 10 μ l Universal SYBR Master Mix 2X, 2 μ l of 5 μ M forward ITR primer, 2 μ l of 5 μ M reverse ITR primer, 5 μ l of tested sample or diluted standard and 1 μ l H₂O. The qPCR program is 95 °C for 10 minutes followed by 40 cycles of 95

°C for 15 seconds, 60 °C for 30 seconds followed by a melt curve. The data is analyzed using the qPCR cyclers software. The physical titer of the AAV sample (viral genomes (vg)/ml) is calculated based on the standard curve.

[00267] The AAV vector infection rate is tested by using the 50% tissue culture infection dose (TCID₅₀) assay performed using a standard protocol from the American Type Culture Collection (ATCC; Manassas, VA).

Example 7. Testing of AAV dose range (*in vivo*).

[00268] Recombinant AAV obtained from the method of Example 2 is injected into C57/BL6 mice by bilateral intracranial injection into the motor cortex. Each AAV is injected at a dosage of 1×10^{11} , 3×10^{11} , 1×10^{12} , 3×10^{12} , 1×10^{13} viral genomes/mL at 1 μ l of volume. Each dosage is assessed at 4 days, 20 days, and 60 days post injection to determine the optimal effective dose (OED), maximum tolerable dose (MTD), and minimum effective dose (MED) at a cell and tissue level. There are three mice per time point. The OED, MTD, and MED, are determined by assessment of astrocyte-to-neuron conversion efficiency and potential toxicity via immunostaining of NeuroD1, GFAP, NeuN, and Iba1. If the first dose range is not sufficient to determine the OED, MTD, and MED, a second dosage range is performed at 1×10^{10} GC/mL to 1×10^{14} GC/mL, at 1 μ l of volume.

Example 8. Dose Scale Assay in non-human primates

[00269] The volume of brain tissue expressing NeuroD1 from Example 7 is divided by the number of vector genomes (mm³/vector genomes) is used to determine the viral infection rate of brain tissue. The volume (mm³) of specific brain region to be treated in non-human primates is calculated and a dose range of vector genomes is according to the infection rate obtained in Example 7. A dose range study is performed as in Example 7 and the OED, MTD, and MED are determine by assessment of astrocyte-to-neuron conversion efficiency and potential toxicity via immunostaining of NeuroD1, GFAP, NeuN, and Iba1.

Example 9. Testing AAV vector in human subjects (*in vivo*)

[00270] Recombinant AAV obtained from the method of Example 2 are used to infect human brain or spinal cord astrocytes *in vivo*. Recombinant AAV is injected at a concentration range of 10^{10} particles/mL and 10^{14} particles/mL with a volume ranging from 10 μ l to 1 mL into

the cerebral cortex of a human subject with a neurological condition. The human subject's neurological condition symptoms, brain or spinal cord imaging including MRI, PET scan, or combination of MRI and PET, and behavioral metrics are observed before, during, and post injection. Post injection observations are performed once a week until the first month post injection. After the first month post injection, observations are performed once a month for the next 11 months, and may be extended to 2 years following viral injection.

Example 10. Treatment of a subject in need thereof with Stroke (*in vivo*)

[00271] A subject with Stroke is treated with recombinant AAV obtained from the method of Example 2. The subject's neurological symptoms include speech changes, numbness, and writing changes. Recombinant AAV is injected at a concentration range of 10^{10} particles/mL and 10^{14} particles/mL with a volume ranging from 10 μ l to 1000 μ l into the cerebral cortex of a human subject with a neurological condition. The human subject's neurological condition symptoms, brain imaging including MRI, PET scan, or combination of MRI and PET, and behavioral metrics are observed before, during, and post injection. Post injection observations are performed once a week until the first month post injection. After the first month post injection, observations are performed once a month for the next 11 months, and may be extended to 2 years following viral injection.

Example 11. AAV virus production of P35

[00272] Recombinant AAV is obtained as described in Example 2. The P35 plasmid is co-transfected into AAV293 cells with a Rep-Cap plasmid expressing serotype 9 capsid protein and the Helper plasmid P40Helper (P40H) or pALD-X80 (X80) to produce recombinant AAV virus particles (P35-P40H or P35-X80). Virus yields are determined by qPCR using primers amplifying gene of interest (GOI) primers specific to the P34 plasmid and the ITR region. Reverse packaging primers are used to evaluate nonspecific packaging. Increased viral production is observed with the X80 helper plasmid compared to the P40H helper plasmid (Figure 4).

Example 12. Successful establishment of rat astrocytes primary culture

[00273] Cortical and striatum tissue is isolated from 3-day post-natal Sprague-Dawley rat brains. Tissue is treated with papain to generate single cell suspension and seeded in flasks coated with poly-D-lysine. Cells are subcultured when 90% confluent. Cells of passage 6 are

immunostained with GFAP antibody and SOX9 antibody. Cells are counter stained with DAPI antibody. More than 95% of cells are astrocytes identified by GFAP and SOX9 staining (Figure 5). Upper left panel presents an image of GFAP stained cells. Upper right panel presents an image of SOX9 stained cells. Lower left panel presents an image of DAPI stained cells. Lower right panel presents a merge image of GFAP, SOX9, and DAPI stained cells.

Example 13. Successful transfection of rat astrocytes

[00274] Primary rat astrocytes are seeded in 24-well plates with glass coverslip coated with poly-D-lysine and transfected with plasmid P5 (pEF-1 α :hNeuroD1:GFP), a control plasmid, and Lipofectamine LTX reagent using a standard protocol from Thermo Fisher Scientific. Forty eight hours post transfection, cells are fixed and immunostained with anti-NeuroD1 antibody followed by a secondary antibody tagged with Alexa-568. Cells are counter stained with DAPI to show all cell nuclei (Figure 6). Left panel presents an image of NeuroD1 stained cells. Middle left panel presents an image of GFP expressing cells. Middle right panel represent DAPI stained cells. Right panel represents a merge image of NeuroD1, GFP, and DAPI stained cells.

Example 14. Comparison of plasmid transfection

[00275] Primary rat astrocytes are seeded and transfected as described in Example 11 with expression vectors P6 (pEF-1 α :hNeuroD1:WPRE:SV40), P11 (CE:GfaABC1D:NeuroD1:WPRE:SV40), P35 (EF-1 α :GfaABC1D:NeuroD1:WPRE:SV40), and P39 (EF-1 α :Gfa1.6:NeuroD1:WPRE:SV40) to test the transfection efficiency of NeuroD1 into cells. P11 resulted in the highest NeuroD1 expression shown by NeuroD1 staining of cells (Figure 7; top panels show NeuroD1 staining of cells, bottom panels show merged NeuroD1 and DAPI staining of cells).

Example 15. Successful transduction of AAV virus particles into primary rat astrocytes

[00276] Recombinant AAV obtained from the method of Example 2 is transduced into primary rat astrocytes using control virus particles from AAV9-P12 (pGfaABC1D:GFP) at a transduction of either 3×10^{10} vg/well, 1×10^{10} vg/well, 2.5×10^{19} vg/well in 100 μ l media in a 96 well plate. RCAs of passage 5-7 are seeded on glass cover slips coated with poly-D-lysine (PDL) in 24-well plates at 30-50% confluency 24-48 hours prior to transduction. Cells are transduced with virus in fresh astrocyte media at the designated titer. Media are refreshed the next day and

every 3-4 days. Images acquired six days post transduction of GFP positives cells show that the transduction rate is higher when virus titer is higher (Figure 8).

Example 16. Quantitative analysis of transduction of AAV virus particles into primary rat astrocytes.

5 [00277] Recombinant AAV obtained from the method of Example 2 is transduced into primary rat astrocytes seeded in 24-well plates or 96-well plates with viral particles AAV9-P12 (pGfaABC1D:GFP). and AAV5-P7 (pEF-1 α :GFP). Cells are harvested seven days post-infection by trypsinization. The cells are fixed, washed, and suspended in PBS. The viral transduction rate is analyzed using flow cytometry to count GFP positive cells compared with all cells (Figure 9A-
10 9B). Figure 9A shows the % transduction rate at different MOI. Cells seeded in 24-well plates at 1×10^5 cells/well are infected at MOI of either 5×10^5 vg/cell, 2×10^5 vg/cell and 5×10^4 vg/cell. The viral transduction rate decreases as the MOI decreases. Figure 9B shows the transduction rate of AAV viral particles in cells seeded in 96 well plates at a series of densities of 2×10^4 cells/well, 1.5×10^4 cells/well, 1×10^4 cells/well, and 5×10^3 cells/well, and infected with virus at a series of
15 amounts of 2 μ l, 1 μ l, 0.5 μ l, 0.25 μ l, 0.125 μ l of 1×10^{13} vg/ml virus in 100 μ l of medium. This is equivalent to 2×10^{10} vg, 1×10^{10} vg, 5×10^9 vg, 2.5×10^9 vg, and 1.25×10^9 vg each well respectively. The viral transduction rate is unchanged as the number of cells per well decreases.

Example 17. Successful transduction of AAV virus particles containing NeuroD1 into primary rat astrocytes.

20 [00278] Recombinant AAV obtained from the method of Example 2 is transduced into primary rat astrocytes seeded in 24-well plates with viral particles 1) AAV5-P1 (AAV5:pGfa2.2:cre) and AAV4-P4 (AAV5:pCAG:flex:hNeuroD1:GFP); 2) AAV9-P9 (CE:GfaABC1D:NeuroD1:GFP); and 3) AAV9-P11 (CE:GfaABC1D:NeuroD1:WPRE:SV40). RCAs of passage 5-7 are seeded on glass cover slips coated with poly-D-lysine (PDL) in 24-well
25 plates at 30-50% confluency 24-48 hours prior to transduction. Cells are transduced with virus in fresh astrocyte media at the titer of 2×10^{10} vg/ml (MOI of 1×10^6 vg/cell). Media are refreshed the next day and every 3-4 days. Cells are fixed at six days post infection and immunostained for NeuroD1. The cells are counter stained with DAPI to identify the cell nuclei (Figure 10). Cells transduced with the P1+P4 combination, P9 and P11 all show NeuroD1 expression.

Example 18. *In vitro* transgene expression and astrocyte-to-neuron conversion induced by NeuroD1 vectors.

5 Materials and Methods

[00279] Primary Rat Astrocyte Culture: Rat cortical astrocytes (RCA) are isolated from 3-day postnatal Sprague Dawley rat cortical tissue. Cells are maintained in astrocyte media (AM) composed of DMEM supplemented with 10% FBS, 2.5 mM Glutamine, 3.5 mM Glucose, penn/strep. Cells are sub-cultured at 1:3-1:4 ratio for first two passages at low cell density to promote residual progenitor differentiation. Subsequent sub-cultures are at 1:2 or 1:3 ratio when reaching 90-100% confluent. Cells at passage 5-7 are used for transfection and transduction. Immunostaining with a GFAP antibody shows that >90% cells are GFAP positive astrocytes. Culture astrocytes are immunostained with astrocyte markers GFAP and Sox9 at passage 6 (Figure 5).

15 [00280] Vectors: AAVs are produced with selected vectors and tested *in vitro* using rat astrocytes;

- NXL-P9 (CE-pGfa681-CI-hND1-p2A-GFP-WPRE-SV40pA)
- NXL-P22 (CE-pGfa681-CI-hND1-WRPE-SV40pA)
- NXL-P35 (EE-pGfa681-CI-hND1-WRPE-SV40pA)
- 20 • NXL-P37 (EE-pGfa681-CI-hND1-p2A-GFP-WPRE-SV40pA)
- NXL-P107 (CE-pGfa681-CI-hND1-bGHpA)
- NXL-P108 (CE-pGfa681-CI-hND1-oPRE-bGHpA)
- NXL-P109 (CE-pGfa681-CRGI-hND1-bGHpA)
- NXL-P130 (CE-pGfa681-GI-hND1-oPRE-bGHpA)
- 25 • NXL-P134 (CE-pGfa681-CRGI-hND1-oPRE-bGHpA)
- NXL-P136 (EE-Gfa681-CRGI-hND1-bGHpA)
- NXL-P138 (EE-Gfa681-CRGI-hND1-oPRE-bGHpA)

[00281] Viral Production: Virus used for *in vitro* studies are produced using adherent AAV293 cells by triple transfections (GOI, helper, and Rep/Cap plasmids) with polyethylenimine

(PEI). Virus recovery and purification is achieved via ultra-centrifugation or the use of commercial purification kits.

[00282] Specifically, AAV293 cells (Cell Biolabs, Cat# AAV-100) are seeded in 15-cm culture dishes 24 hours prior to transfection. Cells at 70-85% confluency are transfected per dish with 10 µg GOI, 10 µg of Rep/Cap, and 14 µg of pALD-X80 (Aldevron) or pHelper (Cell Biolabs) using polyethylenimine (PEI) at a DNA:PEI ratio of 1:4. Multiple dishes are transfected for production based on the scale needed. Culture media is refreshed daily. Seventy-two hours post transfection, cells are collected and lysed to harvest the virus using an AAVpro purification kit (Takara, Cat# 6666, 6675, 6235) following the manufacturer's protocol.

[00283] Viral titers are determined by real-time quantitative PCR using a primer pair in the ITR region, primers amplifying a gene of interest (GOI), or vector specific primers. Plasmid DNA is used as a standard. The production yield is $\sim 10^3$ - 10^4 vg/cell level. Figure 32 depicts how each of the P134, P130, P138 and P21 plasmids co-transfected into AAV293 cells with a Rep-Cap plasmid expressing a serotype 9 capsid protein and the Helper plasmid pALD-X80 (X80) produced recombinant AAV virus particles as measured by qPCR.

[00284] Transfection and Immunofluorescence: Rat cortical astrocytes (RCAs) of passage 5-7 are seeded on glass cover slips coated with poly-D-lysine (PDL) in 24-well plates at 30-50% confluency 24-48 hours prior to transfection. Cells are transfected with 300 ng of vector DNA using Lipofectamine reagent (Thermo Fisher Cat# 15338) following the manufacturer's protocol. At 24-48 hours post transfection, cells are fixed with 4% paraformaldehyde in PBS and subsequently washed and immunostained with anti-NeuroD1 (anti-ND1) antibody (Abcam Cat# ab60704) and followed with secondary antibodies conjugated with fluorescent dyes (Invitrogen, Alexa Fluor). Images are captured under a fluorescent microscope (Zeiss Axiovert A1, Zen Blue). Gene expression levels are assessed by comparing the fluorescence intensity.

[00285] Transduction and Immunofluorescence: RCAs of passage 5-7 are seeded on glass cover slips coated with poly-D-lysine (PDL) in 24-well plates at 30-50% confluency 24-48 hours prior to transduction. Cells are transduced with AAVs at $2-6 \times 10^{10}$ viral genome (vg)/ml in fresh astrocyte media. Media are refreshed the next day and every 3-4 days. Three to six days post transduction, cells are fixed with 4% paraformaldehyde in PBS and subsequently washed and immunostained with anti-ND1 antibody (Abcam Cat# ab60704) and followed with secondary antibodies conjugated with fluorescent dyes (Invitrogen, Alexafluor) for observation and image

capturing under a fluorescent microscope (Zeiss Axiovert A1, Zen Blue). Gene expression levels are assessed by comparing the fluorescence intensity.

[00286] *Astrocyte-to-neuron conversion assessment* RCAs of passage 5-7 are seeded on glass cover slips coated with poly-D-lysine (PDL) in 24-well plates at 30-50% confluency 24-48
 5 hours prior to transduction. Cells are transduced with virus at $2-6 \times 10^{10}$ vg/ml in 500 μ l of fresh astrocyte media (DMEM supplemented with 10% FBS, 2.5 mM Glutamine, 3.5 mM Glucose, penn/strep). At 48 hours post transduction, media is replaced with 5% FBS astrocyte media. Subsequently, 100 μ l of conversion media (DMEM/F12 + 1% FBS + B27 + N2 and 1 μ M Rock inhibitor and 10 ng/ml BDNF) is added daily for 4 days. After the 4 days, the media is completely
 10 replaced with conversion media.

[00287] Cells are fixed with 4% paraformaldehyde in PBS at various desired time points (three days, one to five weeks post transduction) and subsequently washed and immunostained with antibodies against ND1 (Abcam Cat# ab60704), NeuN (Millipore, Cat# ABN78), Map2 (Invitrogen, Cat# PA5-17646), followed with secondary antibodies conjugated with fluorescent
 15 dyes (Invitrogen, Alexafluor) for observation and imaging under a fluorescent microscope (Zeiss Axiovert A1, Zen Blue).

In Vitro Studies Results:

[00288] All tested NeuroD1 (ND1) plasmids are effective in driving the expression of
 20 NeuroD1 (Figures 12-28). The expression level of NeuroD1 is affected by the elements in the vector. Among three versions of the GFA promoter, the 681bp promoter shows the highest NeuroD1 expression level and the 1.6 kb promoter shows the weakest NeuroD1 expression level. Promoter enhancer elements significantly affect the expression level of NeuroD1. The CMV enhancer increases the expression level of NeuroD1 more than the efl α enhancer. Chimeric introns and WPREs also increase the expression level of NeuroD1.
 25

[00289] All tested ND1-containing AAVs are effective in driving the expression of ND1 and inducing an astrocyte-to-neuron conversion in cultured rat astrocytes as shown by positive staining of NeuN and/or MAP2 (Figures 14, 17, 19, 22, and 25). The conversion rate is higher when astrocytes are transduced by the vectors driving a higher ND1 expression. Vectors NXL-
 30 P134 and NXL-P138, and the viruses generated using these vectors, i.e., AAV9-P134 and AAV9-P138 respectively, are the most effective in driving expression of ND1 and inducing astrocyte-to-

neuron conversion, with AAV-P134 being the most effective (Figures 12-17). Plasmid AAV9-P21 (CE-pGFA681-CI-GFP-WPRE-SV40pA), which does not contain an ND1 sequence, is used as a control, and it does not induce an astrocyte-to-neuron conversion, as shown by the lack of positive staining for NeuN and/or Map2 (Figure 11).

- 5 [00290] NeuN/RBFOX3 (Neuronal nuclear protein) is a neuron differentiation marker, which stains nuclei and perinuclear cytoplasm in neurons. MAP2 (microtubule associated protein 2) is another neuronal marker which stains cytoplasm microtubules including dendrites in neurons.
- [00291] One week post transduction by ND1-containing AAVs, small number of NeuN and MAP2 positive cells (neurons) are observed. By two and three weeks, more NeuN/MAP2 positive
- 10 cells are observed. Some NeuN/MAP2 positive cells show typical neuronal morphology.

Example 19. *In vivo* transgene expression and astrocyte-to-neuron conversion induced by NeuroD1 viral vectors.

- [00292] AAV9-P134 and AAV9-P138 viruses are used for the *in vivo* studies. AAV9-P12, which drives the expression of GFP alone (no ND1) under a GFAP promoter, is used for the control
- 15 and to identify cells expressing GFAP (astrocytes).

- [00293] Single strand adenovirus-associated viral (ssAAV, AAV for short) vectors NXL-P12, NXL-P134 and NXL-P138 are packaged into AAV, serotype 9 (AAV9), followed by a subsequent iodixanol gradient ultracentrifuge and concentration. Purified AAV viruses are titered
- 20 using a quantitative PCR-based method. All AAV used in this study is prepared in 0.001% Pluronic F-68 (Poloxamer 188 Solution, PFL01-100ML, Caisson Laboratories, Smithfield, UT, USA) in PBS (pH 7.4).

- [00294] Normal C57BL/6J mice older than 8 weeks are injected with AAV9-P134, AAV-P138, and AAV9-P12 viruses as follows:
- 25
- P12 control group: AAV9-P12 5×10^{11} GC/ml, 1 μ L, 1 injection in cortex (unilateral) (n=6)
 - P134 group: AAV9-P12 2.5×10^{11} GC/ml + AAV9-P134 2.5×10^{11} GC/ml, 1 μ L, 1 injection in cortex (unilateral) (n=6)
 - P138 group: AAV9-P12 2.5×10^{11} GC/ml + AAV9-P138 2.5×10^{11} GC/ml, 1 μ L, 1 injection in cortex (unilateral) (n=6)

- 30 [00295] Mice are sacrificed and brain cortex tissue analyzed at 10 days post infection (dpi) and at 30 dpi. The animals are anesthetized with 1.25 % Avertin and then sequentially perfused

intracardially first with saline solution (0.9 % NaCl) and then with 4 % paraformaldehyde (PFA). The brains are collected and post-fixed in 4 % PFA overnight and sequentially placed in 20 % and 30 % sucrose at 4 °C until the tissue sank. The dehydrated brains are embedded in Optimal Cutting Temperature (Tissue-Tek® O.C.T. Compound, Sakura® Finetek, Torrance, CA, USA), and then serially sectioned at the coronal plane on the cryostat (Thermo Scientific, Shanghai, China) at 30 µm thickness. For immunofluorescence, free floating brain sections are first washed with PBS and blocked for 1 hour at room temperature (RT) in 5 % normal donkey serum, 3 % bovine serum albumin and 0.3 % TritonX-100 prepared in PBS, and then incubated overnight at 4° C with primary antibodies diluted in blocking solution. After additional washing with 0.2 % PBST (0.2 % tween-20 in PBS), the samples are incubated with 0.5 µg/µL 4',6-diamidino-2-phenylindole (DAPI; F. Hoffmann-La Roche, Natley, NJ, USA) and appropriate donkey anti-mouse/rabbit secondary antibodies conjugated to Alexa Fluor 555, goat anti-chicken secondary antibodies conjugated to Alexa Fluor 488 (1:1000, Life technologies, Carlsbad, CA, USA), and goat anti-rat (Life technologies)/guinea pig (Jackson immune research) secondary antibodies conjugated to Alexa Fluor 647(1:500) for 2 hours at room temperature, followed by extensive washing with PBS. Samples are finally mounted with VECTASHIELD® mounting medium (VECTOR Laboratories, Burlingame, CA, USA) and sealed with nail polish. Representative Images are taken with a confocal microscope (LSM880, Zeiss, Jena, Germany). Primary antibodies used are as follow: rat anti-GFAP (a marker for astrocytes, 1:1000, Cat# 13-0300, Invitrogen), guinea pig anti-NeuN (a marker for neurons 1:1000, Cat# ABN90, Millipore), mouse anti-NeuroD1 (1:500, Cat# ab60704, Abcam), and chicken anti-GFP (1:1000, Cat# ab13970, Abcam). Representative images are captured by either Zeiss Axioplan fluorescent microscope (Axio Imager Z2, Zeiss, Göttingen, Germany) or confocal microscope (LSM880, Zeiss, Jena, Germany). Quantitative analysis is performed based on 4 randomly chosen fields (212 µm x 212 µm, acquired at 400 magnification from LSM880 confocal microscope) from 3 brain slices per mouse (3 mice per group). The data is shown as mean ± SEM.

[00296] Control virus P12, which expresses GFP reporter alone, is first compared with NeuroD1-expressing viruses P134 and P138 (both added P12 together to trace converted neurons). When the control virus P12 is injected in the uninjured mouse cortex, the infected cells are primarily astrocytes without NeuroD1 expression at 10 dpi (days post injection, Figure 33). In contrast, NeuroD1 expression is detected clearly in both P134 and P138 groups. While most

NeuroD1-expressing cells in the P138 group at 10 dpi are still astrocytes, a portion of NeuroD1-expressing cells in P134 group are NeuN+ neurons already (Figure 33), suggesting that P134 might have better conversion capability than P138. Additionally at 10 dpi, analysis of the cortex brain tissue of the mice in the P134 group shows a high level of conversion of astrocytes into neurons, as demonstrated by the morphological changes, such as the presence of long processes, in GFP positive cells (Figure 29). The P138 group shows a lower level of conversion.

[00297] At 30 days after virus injection, the infected cells in the control group (P12) remain as astrocytes, but most GFP positive cells in the P134 group are neurons expressing NeuN (Figure 34). However, the conversion rate of the P138 group is lower than the P134. Most infected cells in the P138 group at this stage are still astrocytes, and the GFP signal in the converted neurons is weak (Figure 34). Additionally, at 30 dpi, analysis of the cortex brain tissue of the mice in the P134 group shows an even higher level of conversion of astrocytes into neurons, as demonstrated by the presence of long processes in GFP positive cells (Figure 30).

[00298] The AAV9-P134 virus is also effective in a bilateral injury mouse model. Ischemic stroke is induced in normal C57BL/6J mice (older than 8 weeks) by injecting 1 μ L of Endophilin 1, 1-31 aa (1 μ g/ μ L) in each side of the cortex. Mice are anesthetized with 20 mg/kg 1.25 % Avertin (a mixture of 12.5 mg/mL of 2,2,2-Tribromoethanol and 25 μ L/mL 2-Methyl-2-butanol, Sigma, St. Louis, MO, USA) through intraperitoneal injection and then placed in a prone position in the stereotaxic frame. Endothelin-1 (ET-1) and virus is injected through glass pipette into motor cortex at the coordinate +0.2 mm anterior-posterior (AP from Bregma), -1.5 mm medial-lateral (ML from Bregma, left side), -0.7 mm dorsal-lateral (DV from dura). The injection speed is 80 nL/min. The pipette is kept in place after injection for about 10 minutes and then slowly withdrawn. Seven days after injection of Endothelin-1, mice are injected with the AAV9-P12 and AAV9-P134 viruses as follow:

- P12 Group: AAV9-P12 5 $\times 10^{11}$ GC/ml, 1 μ L, 1 injection in each side of cortex (bilateral)
- P134 Group: AAV9-P12 2.5 $\times 10^{11}$ GC/ml + AAV9-P134 2.5 $\times 10^{11}$ GC/ml, 1 μ L, 1 injection in each side of cortex (bilateral)

[00299] Mice are sacrificed at 10 days post injection (dpi) of the viruses and the brain cortex tissue analyzed. When the control virus P12 is injected in the ET-1 lesioned mouse cortex, the infected cells are primarily astrocytes without NeuroD1 expression at 10 dpi (days post injection, Figure 35). In contrast, NeuroD1 expression is detected in the P134 group (Figure 35).

Additionally, at 10 dpi, analysis of the cortex brain tissue of the mice in the P134 group shows a high level of conversion of astrocytes into neurons, as demonstrated by the morphological changes observed in GFP positive cells, such as the presence of long processes (Figure 31).

[00300] At 30 days after viral injection in the ET-1-injured mouse cortex, the infected cells
 5 in the control group (P12) remain as astrocytes, but most GFP positive cells in the P134 group become converted neurons expressing NeuN (Figure 36A). The conversion rate of P134 in the ET-1 lesioned mouse cortex at 30 dpi is around 64% (Figure 36B, NeuN⁺GFP⁺/GFP⁺: P12, 1.0 ± 0.2%; P12+P134, 63.8 ± 1.2%, **P* < 0.0001, unpaired Student's *t* test). These studies demonstrate that P134 is a vector that can efficiently convert astrocytes into neurons in the ischemic injured mouse
 10 cortex *in vivo*.

[00301] A variety of further modifications and improvements in and to the compositions and methods of the present disclosure will be apparent to those skilled in the art based. The following non-limiting embodiments are envisioned:

1. An adeno-associated virus (AAV) vector comprising a human neurogenic differentiation 1
 15 (hNeuroD1) sequence comprising the nucleic acid sequence of SEQ ID NO: 6, where the hNeuroD1 sequence is operably linked to regulatory elements comprising:
 - (a) a glial fibrillary acidic protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15;
 - (b) an enhancer from a human elongation factor-1 alpha (EF1- α) promoter comprising
 20 the nucleic acid sequence of SEQ ID NO: 2 or a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11;
 - (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16;
 - (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ
 25 ID NOs: 7 and 18; and
 - (e) a SV40 polyadenylation signal sequence comprising the nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

2. An adeno-associated virus (AAV) vector comprising a nucleic acid coding sequence encoding a human neurogenic differentiation 1 (hNeuroD1) protein comprising the amino acid sequence of SEQ ID NO: 10, wherein said coding sequence is operably linked to regulatory elements comprising:
 - 5 (a) a glial fibrillary acidic protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15;
 - (b) an enhancer from a human elongation factor-1 alpha (EF1- α) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11;
 - 10 (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16;
 - (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18; and
 - (e) a SV40 polyadenylation signal sequence with a nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.
3. An adeno-associated virus (AAV) vector comprising a neurogenic differentiation 1 (NeuroD1) nucleic acid coding sequence encoding a NeuroD1 protein, wherein said coding sequence is operably linked to regulatory elements comprising:
 - 20 (a) a glial fibrillary acidic protein (GFAP) promoter;
 - (b) an enhancer;
 - (c) a chimeric intron;
 - (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE); and
 - 25 (e) a polyadenylation signal sequence.
4. A composition comprising an adeno-associated virus (AAV) vector for converting glial cells to functional neurons in a human, wherein said AAV vector comprises a human neurogenic differentiation 1 (hNeuroD1) sequence having a nucleic acid sequence of SEQ ID NO: 6, and wherein said sequence is operably linked to regulatory elements comprising:
 - 30

- (a) a human glial fibrillary acidic protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15;
 - (b) an enhancer from the human elongation factor-1 alpha (EF-1 alpha) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11;
 - (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16;
 - (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18; and
 - (e) a SV40 polyadenylation signal sequence comprising the nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.
5. A composition comprising an adeno-associated-virus (AAV) vector for converting glial cells to functional neurons in a human, wherein said AAV vector comprises a nucleic acid sequence encoding a human neurogenic differentiation 1 (hNeuroD1) protein comprising the amino acid coding sequence of SEQ ID NO: 10, and wherein said coding sequence is operably linked to regulatory elements comprising:
- (a) a human glial fibrillary acidic protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15;
 - (b) an enhancer from the human elongation factor-1 alpha (EF-1 alpha) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11;
 - (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16;
 - (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18; and
 - (e) a SV40 polyadenylation signal sequence comprising the nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid

sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

6. A composition comprising an adeno-associated virus (AAV) vector for the treatment of a subject in need thereof, wherein said AAV vector comprises a neurogenic differentiation 1 (NeuroD1) sequence operably linked to expression control elements comprising:
 - (a) a glial fibrillary acidic protein (GFAP) promoter;
 - (b) an enhancer;
 - (c) a chimeric intron;
 - (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE); and
 - (e) a polyadenylation signal.
7. The AAV vector of any one of embodiments 1-3, or the composition of any one of embodiments 4-6, wherein said AAV vector is selected from the group consisting of AAV serotype 2, AAV serotype 5, and AAV serotype 9.
8. The AAV vector or composition of embodiment 7, wherein said AAV vector is AAV serotype 2.
9. The AAV vector or composition of embodiment 7, wherein said AAV vector is AAV serotype 5.
10. The AAV vector or composition of embodiment 7, wherein said AAV vector is AAV serotype 9.
11. The composition of embodiment 4 or 5, wherein said glial cells are reactive astrocytes.
12. The composition of embodiment 4 or 5, wherein said functional neurons are selected from the group consisting of glutamatergic neurons, GABAergic neurons, dopaminergic neurons, cholinergic neurons, serotonergic neurons, epinephrinergic neurons, motor neurons, and peptidergic neurons.
13. The composition of embodiment 4 or 5, wherein said human has a neurological condition.

14. The AAV vector of embodiment 3, or the composition of embodiment 6, wherein said NeuroD1 is a human NeuroD1 (hNeuroD1).
15. The AAV vector of embodiment 3, or the composition of embodiment 6, wherein said NeuroD1 is selected from the group consisting of a chimpanzee NeuroD1, a bonobo
5 NeuroD1, an orangutan NeuroD1, a gorilla NeuroD1, a macaque NeuroD1, a marmoset NeuroD1, a capuchin NeuroD1, a baboon NeuroD1, a gibbon NeuroD1, and a lemur NeuroD1.
16. The AAV vector or composition of embodiment 14, wherein said hNeuroD1 comprises a nucleic acid coding sequence encoding an amino acid sequence at least 80% identical or
10 similar to SEQ ID NO: 10.
17. The AAV vector or composition of embodiment 14, wherein said hNeuroD1 sequence comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 6, or the complement thereof.
18. The AAV vector of embodiment 3, or the composition of embodiment 6, wherein said
15 GFAP promoter is a human GFAP (hGFAP) promoter.
19. The AAV vector of embodiment 3, or the composition of embodiment 6, wherein said GFAP promoter is selected from the group consisting of a chimpanzee GFAP promoter, a bonobo GFAP promoter, an orangutan GFAP promoter, a gorilla GFAP promoter, a
20 macaque GFAP promoter, a marmoset GFAP promoter, a capuchin GFAP promoter, a baboon GFAP promoter, a gibbon GFAP promoter, and a lemur GFAP promoter.
20. The AAV vector or composition of any one of the preceding embodiments, wherein the AAV vector further comprises a 2A self-cleavage peptide sequence at least 80% identical to SEQ ID NO: 3 or the complement thereof.
21. The AAV vector or composition of embodiment 18, wherein said hGFAP promoter
25 comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 4 or the complement thereof.

22. The AAV vector or composition of embodiment 18, wherein said hGFAP promoter comprises a nucleic acid sequence at least 80% identical to SEQ ID NOs: 12 or the complement thereof.
23. The AAV vector or composition of embodiment 18, wherein said hGFAP promoter
5 comprises a nucleic acid sequence at least 80% identical to SEQ ID NOs: 15 or the complement thereof.
24. The AAV vector of embodiment 3, or the composition of embodiment 6, wherein said enhancer is selected from the group consisting of an enhancer from human elongation factor-1 alpha (EF1- α) promoter and cytomegalovirus (CMV) enhancer.
- 10 25. The AAV vector or composition of embodiment 24, wherein said EF1- α comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 2, or the complement thereof.
26. The AAV vector or composition of embodiment 24, wherein said CMV enhancer
15 comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 11, or the complement thereof.
27. The AAV vector of embodiment 3, or the composition of embodiment 6, wherein said chimeric intron comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 5 or the complement thereof.
28. The AAV vector of embodiment 3, or the composition of embodiment 6, wherein said
20 chimeric intron comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 16 or the complement thereof.
29. The AAV vector of embodiment 3, or the composition of embodiment 6, wherein said WPRE comprises a nucleic acid sequence at least 80% identical to a nucleic acid
25 sequence selected from the group consisting of SEQ ID NOs: 7 and 18, or the complement thereof.

30. The AAV vector of embodiment 3, or the composition of embodiment 6, wherein said polyadenylated signal is selected from the group consisting of SV40 polyadenylation signal and a hGH polyadenylation signal.
- 5 31. The AAV vector or composition of embodiment 30, wherein said SV40 polyadenylated signal comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 8, or the complement thereof.
32. The AAV vector or composition of embodiment 30, wherein said hGH polyadenylated signal comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 13, or the complement thereof.
- 10 33. The AAV vector or composition of embodiment 30, wherein said bGH polyadenylated signal comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 14, or the complement thereof.
34. The AAV vector of embodiment 3, or the composition of embodiment 6, wherein said AAV vector further comprises a nucleic acid sequence encoding an AAV protein
15 sequence.
35. The AAV vector of any one of embodiments 1-3, or the composition of any one of embodiments 4-6, wherein said AAV vector comprises AAV serotype 2 inverted terminal repeats (ITRs).
36. The AAV vector of any one of embodiments 1-3, or the composition of any one of
20 embodiments 4-6, wherein said AAV vector comprises AAV serotype 5 inverted terminal repeats (ITRs).
37. The AAV vector of any one of embodiments 1-3, or the composition of any one of embodiments 4-6, wherein said AAV vector comprises AAV serotype 9 inverted terminal repeats (ITRs).

38. The AAV vector of any one of embodiments 1-3, or the composition of any one of
embodiments 4-6, wherein said AAV vector comprises at least one ITR nucleic acid
sequence at least 80% identical to SEQ ID NO: 1.
39. The AAV vector of any one of embodiments 1-3, or the composition of any one of
embodiments 4-6, wherein said AAV vector comprises at least one ITR nucleic acid
sequence at least 80% identical to SEQ ID NO: 9.
40. The composition of embodiment 6, wherein said subject in need thereof is a mammal.
41. The composition of embodiment 40, wherein said mammal is a human.
42. The composition of embodiment 40, wherein said mammal is a non-human primate.
43. The composition of embodiment 6, wherein said subject in need thereof has a
neurological condition.
44. The composition of embodiment 13 or 43, wherein said neurological condition comprises
an injury to the central nervous system (CNS) or peripheral nervous system.
45. The composition of embodiment 13 or 43, wherein said wherein said neurological
condition comprises an injury to the CNS.
46. The composition of embodiment 13 or 43, wherein said neurological condition is selected
from the group consisting of Alzheimer's Disease, Parkinson's Disease, amyotrophic
lateral sclerosis (ALS), Huntington's Disease, epilepsy, physical injury, stroke, cerebral
aneurysm, traumatic brain injury, concussion, a tumor, inflammation, infection, ataxia,
brain atrophy, spinal cord atrophy, multiple sclerosis, traumatic spinal cord injury,
ischemic or hemorrhagic myelopathy (myelopathy), global ischemia, hypoxic ischemic
encephalopathy, embolism, fibrocartilage embolism myelopathy, thrombosis,
nephropathy, chronic inflammatory disease, meningitis, and cerebral venous sinus
thrombosis.

47. The composition of embodiment 13 or 43, wherein said neurological condition is Alzheimer's Disease.
48. The composition of embodiment 13 or 43, wherein said neurological condition is Parkinson's Disease.
- 5 49. The composition of embodiment 13 or 43, wherein said neurological condition is ALS.
50. The composition of embodiment 13 or 43, wherein said neurological condition is Huntington's Disease.
51. The composition of embodiment 13 or 43, wherein said neurological condition is a stroke.
- 10 52. The composition of embodiment 51, wherein said stroke is an ischemic stroke.
53. The composition of embodiment 51, wherein said stroke is a hemorrhagic stroke.
54. The composition of embodiment 43, wherein said composition is capable of converting at least one glial cell to a neuron.
55. The composition of embodiment 54, wherein said glial cells are selected from the group consisting of astrocytes and NG2 cells.
- 15 56. The composition of embodiment 54, wherein said glial cells are astrocytes.
57. The composition of embodiment 56, wherein said astrocytes are reactive astrocytes.
58. The composition of embodiment 54, wherein said glial cells are GFAP positive.
59. The composition of embodiment 54, wherein said neurons are functional neurons.
- 20 60. The composition of embodiment 54, wherein said functional neurons are selected from the group consisting of glutamatergic neurons, GABAergic neurons, dopaminergic neurons, cholinergic neurons, serotonergic neurons, epinephrinergic neurons, motor neurons, and peptidergic neurons..

61. The composition of embodiment 60, wherein said functional neurons are glutamatergic neurons.
62. The composition of embodiment 6, wherein said composition is formulated to be delivered to a subject in need thereof.
- 5 63. The composition of embodiment 62, wherein said composition is formulated for local delivery.
64. The composition of embodiment 62, wherein said composition is formulated for systemic delivery.
- 10 65. The composition of any one of embodiments 62-64, wherein said composition is formulated for delivery via intraperitoneal, intramuscular, intravenous, intrathecal, intracerebral, intracranial, intra lateral ventricle of the brain, intra cisterna magna, intra vitreous, intra-subretina, intraparenchymal, intranasal, or oral administration.
66. A method comprising delivering the composition of embodiment 6 to said subject in need thereof.
- 15 67. The method of embodiment 66, wherein said composition is formulated to be delivered to a subject in need thereof.
68. The method of embodiment 66, wherein said delivering comprises local administration.
69. The method of embodiment 66, wherein said delivering comprises systemic administration.
- 20 70. The method of any one of embodiments 66-69, wherein said delivering comprises an intraperitoneal, intramuscular, intravenous, intrathecal, intracerebral, intracranial, intra lateral ventricle of the brain, intra cisterna magna, intra vitreous, intra-subretina, intraparenchymal, intranasal, or oral administration.
- 25 71. A method of converting reactive astrocytes to functional neurons in a brain of a living human comprising: injecting an adeno-associated virus (AAV) into a subject in need

thereof, wherein said AAV comprises a DNA vector construct comprising a human neurogenic differentiation 1 (hNeuroD1) sequence comprising the nucleic acid sequence of SEQ ID NO: 6, wherein said sequence is operably linked to regulatory elements comprising:

- 5 (a) a human glial fibrillary acid protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15;
- (b) an enhancer from the human elongation factor-1 alpha (EF-1 alpha) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11;
- 10 (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16;
- (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18; and
- (e) a SV40 polyadenylation signal sequence comprising the nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.
- 15

72. A method of converting reactive astrocytes to functional neurons in a brain of a living human comprising: injecting an adeno-associated virus (AAV) into a subject in need thereof, wherein said AAV comprises a DNA vector construct comprising a nucleic acid sequence encoding a human neurogenic differentiation 1 (hNeuroD1) protein comprising the amino acid coding sequence of SEQ ID NO: 10, wherein said coding sequence is operably linked to expression control elements comprising:

- 20 (a) a human glial fibrillary acid protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15;
- (b) an enhancer from the human elongation factor-1 alpha (EF-1 alpha) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11;
- 25 (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16;

- (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18; and
- (e) a SV40 polyadenylation signal sequence comprising the nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

73. A method of converting glial cells to neurons in a subject in need thereof comprising: delivering an adeno-associated virus (AAV) to said subject in need thereof, wherein said AAV comprises a DNA vector construct comprising a neurogenic differentiation 1 (NeuroD1) sequence operably linked to expression control elements comprising:

- (a) a glial fibrillary acid protein (GFAP) promoter;
- (b) an enhancer;
- (c) a chimeric intron;
- (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE); and
- (e) and a polyadenylation signal sequence,

wherein said vector is capable of converting at least one glial cell to a neuron in said subject in need thereof.

74. A method of treating a neurological condition in a subject in need thereof comprising: delivering an adeno-associated virus (AAV) to said subject, wherein said AAV comprises a DNA vector construct comprising a neurogenic differentiation 1 (NeuroD1) sequence operably linked to expression control elements comprising:

- (a) a glial fibrillary acid protein (GFAP) promoter;
- (b) an enhancer;
- (c) a chimeric intron;
- (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE); and
- (e) a polyadenylation signal to said subject in need thereof.

75. The method of any one of embodiments 71-74, wherein said AAV is selected from the group consisting of AAV serotype 2, AAV serotype 5, and AAV serotype 9.

76. The method of embodiment 75, wherein said AAV is AAV serotype 2.
77. The method of embodiment 75, wherein said AAV is AAV serotype 5.
78. The method of embodiment 75, wherein said AAV is AAV serotype 9.
79. The method of embodiments 71 or 72, wherein said functional neurons are glutamatergic
5 neurons, GABAergic neurons, dopaminergic neurons, cholinergic neurons, serotonergic
neurons, epinephrinergic neurons, motor neurons, and peptidergic neurons.
80. The method of embodiments 73 or 74, wherein said NeuroD1 is human NeuroD1
(hNeuroD1).
81. The method of embodiments 73 or 74, wherein said NeuroD1 is selected from the group
10 consisting of a chimpanzee NeuroD1, a bonobo NeuroD1, an orangutan NeuroD1, a
gorilla NeuroD1, a macaque NeuroD1, a marmoset NeuroD1, a capuchin NeuroD1, a
baboon NeuroD1, a gibbon NeuroD1, and a lemur NeuroD1.
82. The method of embodiment 80, wherein said hNeuroD1 comprises a amino acid
sequence encoding an amino acid coding sequence at least 80% identical or similar to
15 SEQ ID NO: 10.
83. The method of embodiment 80, wherein said hNeuroD1 sequence comprises a nucleic
acid sequence at least 80% identical to SEQ ID NO: 6, or the complement thereof.
84. The method of embodiments 73 or 74, wherein said GFAP promoter is a human GFAP
(hGFAP) promoter.
85. The method of embodiments 73 or 74, wherein said GFAP promoter is selected from the
20 group consisting of a chimpanzee GFAP promoter, a bonobo GFAP promoter, an
orangutan GFAP promoter, a gorilla GFAP promoter, a macaque GFAP promoter, a
marmoset GFAP promoter, a capuchin GFAP promoter, a baboon GFAP promoter, a
gibbon GFAP promoter, and a lemur GFAP promoter.

86. The method of any one of embodiments 71-85, wherein the DNA vector construct further comprises a 2A self-cleavage peptide sequence at least 80% identical to SEQ ID NO: 3 or the complement thereof.
- 5 87. The method of embodiment 84, wherein said hGFAP promoter comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 4, or the complement thereof.
88. The method of embodiment 84, wherein said hGFAP promoter comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 12, or the complement thereof.
89. The method of embodiment 84, wherein said hGFAP promoter comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 15, or the complement thereof.
- 10 90. The method of embodiments 73 or 74, wherein said enhancer is selected from the group consisting of an enhancer from human elongation factor-1 alpha (EF1- α) promoter and cytomegalovirus (CMV) enhancer.
91. The method of embodiment 90, wherein said EF1- α comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 2, or the complement thereof.
- 15 92. The method of embodiment 90 wherein said CMV enhancer comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 11, or the complement thereof.
93. The method of embodiments 73 or 74, wherein said chimeric intron comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 5, or the complement thereof.
94. The method of embodiments 73 or 74, wherein said chimeric intron comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 16, or the complement thereof.
- 20 95. The method of embodiments 73 or 74, wherein said WPRE comprises a nucleic acid sequence at least 80% identical to a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18, or the complement thereof.

96. The method of embodiments 73 or 74, wherein said polyadenylated signal is selected from the group consisting of SV40 polyadenylation signal, a hGH polyadenylation signal, and a bGH polyadenylation signal.
- 5 97. The method of embodiments 73 or 74, wherein said SV40 polyadenylated signal comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 8, or the complement thereof.
98. The method of embodiments 73 or 74 wherein said hGH polyadenylated signal comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 13, or the complement thereof.
- 10 99. The method of embodiments 73 or 74 wherein said bGH polyadenylated signal comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 14, or the complement thereof.
100. The method of embodiments 73 or 74, wherein said vector further comprises a nucleic acid sequence encoding an AAV protein sequence.
- 15 101. The method of any one of embodiments 71-74, wherein said vector comprises AAV serotype 2 inverted terminal repeats (ITRs).
102. The method of any one of embodiments 71-74, wherein said vector comprises AAV serotype 5 inverted terminal repeats (ITRs).
103. The method of any one of embodiments 71-74, wherein said vector comprises
20 AAV serotype 9 inverted terminal repeats (ITRs).
104. The method of any one of embodiments 71-74, wherein said vector comprises at least one ITR nucleic acid sequence at least 80% identical to SEQ ID NO: 1.
105. The method of any one of embodiments 71-74, wherein said vector comprises at least one ITR nucleic acid sequence at least 80% identical to SEQ ID NO: 9.

106. The method of embodiment 71, wherein said converting occurs in the central nervous system (CNS) or peripheral nervous system.
107. The method of embodiment 73, wherein said converting occurs in the CNS.
108. The method of embodiment 73 or 74, wherein said subject in need thereof is a mammal.
109. The method of embodiment 108, wherein said mammal is a human.
110. The method of embodiment 108, wherein said mammal is a non-human primate.
111. The method of embodiment 73 or 74, wherein said delivering comprises a local administration.
112. The method of embodiment 73 or 74, wherein said delivering comprises systemic administration.
113. The method of embodiment 73 or 74, wherein said delivering comprises an administration selected from the group consisting of an intraperitoneal administration, intramuscular administration, intravenous administration, intrathecal administration, intracerebral administration, intracranial, intra lateral ventricle of the brain, intra cisterna magna, intra vitreous, intra-subretina, intraparenchymal administration, intranasal administration, and oral administration.
114. The method of embodiment 71 or 72, wherein said injecting comprises an injection selected from the group consisting of an intraperitoneal injection, intramuscular injection, intravenous injection, intrathecal injection, intracerebral injection, intracranial, intra lateral ventricle of the brain, intra cisterna magna, intra vitreous, intra-subretina, intraparenchymal injection, intranasal injection, and oral injection.
115. The method of embodiments 73 or 74, wherein said delivering comprises injecting.

116. The method of any one of embodiments 71, 72, or 115, wherein said injecting is performed at a concentration of between 10^{10} particles/mL and 10^{14} particles/mL.
117. The method of embodiment 116, wherein said injecting further comprises a flow rate of between 0.1 ul/minute and 5.0 ul/minute.
- 5 118. The method of embodiment 73, wherein said at least one glial cell is selected from the group consisting of at least one astrocyte and at least one NG2 cell.
119. The method of embodiment 71, wherein said at least one glial cell is at least one astrocyte.
120. The method of embodiment 118 or 119, wherein said at least one astrocyte is a
10 reactive astrocyte.
121. The method of embodiment 73, wherein said neuron is a functional neuron.
122. The method of any one of embodiments 71, 72, and 121, wherein said functional neurons are selected from the group consisting of glutamatergic neurons, GABAergic neurons, dopaminergic neurons, cholinergic neurons, serotonergic neurons,
15 epinephrinergic neurons, motor neurons, and peptidergic neurons.
123. The method of embodiment 73, wherein said subject exhibits an improvement of at least one neurological condition symptom as compared to said subject prior to said delivering.
124. The method of embodiment 123, wherein said improvement is measured within 1
20 year of said delivering.
125. The method of any one of embodiments 71, 72, or 115, wherein said method comprises directly injecting said AAV into the brain of said subject.
126. The method of any one of embodiments 71 or 72, wherein said converting is in the cerebral cortex of said brain.

127. The method of any one of embodiments 71, 72, or 115, wherein said method comprises directly injecting said AAV into the spinal cord of said subject.
128. The method of embodiment 74, wherein said neurological condition comprises an injury to the central nervous system (CNS) or peripheral nervous system.
- 5 129. The method of embodiment 74, wherein said neurological condition is selected from the group consisting of Alzheimer's Disease, Parkinson's Disease, amyotrophic lateral sclerosis (ALS), Huntington's Disease, epilepsy, physical injury, stroke, cerebral aneurysm, traumatic brain injury, concussion, a tumor, inflammation, infection, ataxia, brain atrophy, spinal cord atrophy, multiple sclerosis, traumatic spinal cord injury, 10 ischemic or hemorrhagic myelopathy (myelopathy), global ischemia, hypoxic ischemic encephalopathy, embolism, fibrocartilage embolism myelopathy, thrombosis, nephropathy, chronic inflammatory disease, meningitis, and cerebral venous sinus thrombosis.
130. The method of embodiment 74, wherein said neurological condition is 15 Alzheimer's Disease.
131. The method of embodiment 74, wherein said neurological condition is Parkinson's Disease.
132. The method of embodiment 74, wherein said neurological condition is ALS.
133. The method of embodiment 74, wherein said neurological condition is 20 Huntington's Disease.
134. The method of embodiment 74, wherein said neurological condition is a stroke.
135. The method of embodiment 134, wherein said stroke is an ischemic stroke.
136. The method of embodiment 134, wherein said stroke is a hemorrhagic stroke.
137. The method of embodiment 74, wherein said method is capable of converting at 25 least one glial cell into a neuron.

138. The method of embodiment 137, wherein said glial cells are selected from the group consisting of astrocytes and NG2 cells.
139. The method of embodiment 137, wherein said glial cells are astrocytes.
140. The method of embodiment 139, wherein said astrocytes are reactive astrocytes.
- 5 141. The method of embodiment 137, wherein said glial cells are GFAP positive.
142. The method of embodiment 137, wherein said neurons are functional neurons.
143. The method of embodiment 142, wherein said functional neurons are selected from the group consisting of glutamatergic neurons, GABAergic neurons, dopaminergic neurons, cholinergic neurons, serotonergic neurons, epinephrinergic neurons, motor
10 neurons, and peptidergic neurons..
144. The method of embodiments 71 or 72, wherein a therapeutically effective dose of said AAV vector is injected into said subject.
145. The method of embodiments 73 or 74, wherein a therapeutically effective dose of said AAV vector is delivered to said subject.
- 15 146. The method of embodiment 144 or 145, wherein said therapeutically effective dose is administered with a pharmaceutically acceptable carrier.
147. An adeno-associated virus (AAV) vector comprising a human neurogenic differentiation 1 (hNeuroD1) sequence comprising the nucleic acid sequence of SEQ ID NO: 6, where the hNeuroD1 sequence is operably linked to regulatory elements
20 comprising:
- (a) a glial fibrillary acidic protein (GFAP) promoter comprising the nucleic acid sequence of SEQ ID NO: 15;
 - (b) an enhancer from a human elongation factor-1 alpha (EF1- α) promoter comprising the nucleic acid sequence of SEQ ID NO: 2;
 - 25 (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 16;

- (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence of SEQ ID NO: 18; and
- (e) a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

5 148. An adeno-associated virus (AAV) vector comprising a human neurogenic differentiation 1 (hNeuroD1) sequence comprising the nucleic acid sequence of SEQ ID NO: 6, where the hNeuroD1 sequence is operably linked to regulatory elements comprising:

- 10 (a) a glial fibrillary acidic protein (GFAP) promoter comprising the nucleic acid sequence of SEQ ID NO: 15;
- (b) a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11;
- (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 16;
- (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence of SEQ ID NO: 18; and
- 15 (e) a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

20

25

CLAIMS:

1. An adeno-associated virus (AAV) vector comprising a human neurogenic differentiation 1 (hNeuroD1) sequence comprising the nucleic acid sequence of SEQ ID NO: 6, where the hNeuroD1 sequence is operably linked to regulatory elements comprising:
 - 5 (a) a glial fibrillary acidic protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15;
 - (b) an enhancer from a human elongation factor-1 alpha (EF1- α) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11;
 - 10 (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16;
 - (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18; and
 - (e) a SV40 polyadenylation signal sequence comprising the nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.
2. An adeno-associated virus (AAV) vector comprising a nucleic acid coding sequence encoding a human neurogenic differentiation 1 (hNeuroD1) protein comprising the amino acid sequence of SEQ ID NO: 10, wherein said coding sequence is operably linked to regulatory elements comprising:
 - 20 (a) a glial fibrillary acidic protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15;
 - (b) an enhancer from a human elongation factor-1 alpha (EF1- α) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11;
 - 25 (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16;
 - (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18; and
 - 30

- (e) a SV40 polyadenylation signal sequence with a nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.
- 5 3. An adeno-associated virus (AAV) vector comprising a neurogenic differentiation 1 (NeuroD1) nucleic acid coding sequence encoding a NeuroD1 protein, wherein said coding sequence is operably linked to regulatory elements comprising:
- 10 (a) a glial fibrillary acidic protein (GFAP) promoter;
- (b) an enhancer;
- (c) a chimeric intron;
- (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE); and
- (e) a polyadenylation signal sequence.
- 15 4. A composition comprising an adeno-associated virus (AAV) vector for converting glial cells to functional neurons in a human, wherein said AAV vector comprises a human neurogenic differentiation 1 (hNeuroD1) sequence having a nucleic acid sequence of SEQ ID NO: 6, and wherein said sequence is operably linked to regulatory elements comprising:
- 20 (a) a human glial fibrillary acidic protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15;
- (b) an enhancer from the human elongation factor-1 alpha (EF-1 alpha) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11;
- (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16;
- (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18; and
- 25 (e) a SV40 polyadenylation signal sequence comprising the nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.
- 30

5. A composition comprising an adeno-associated-virus (AAV) vector for converting glial cells to functional neurons in a human, wherein said AAV vector comprises a nucleic acid sequence encoding a human neurogenic differentiation 1 (hNeuroD1) protein comprising the amino acid coding sequence of SEQ ID NO: 10, and wherein said coding sequence is operably linked to regulatory elements comprising:
- (a) a human glial fibrillary acidic protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15;
 - (b) an enhancer from the human elongation factor-1 alpha (EF-1 alpha) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11;
 - (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16;
 - (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18; and
 - (e) a SV40 polyadenylation signal sequence comprising the nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.
6. A composition comprising an adeno-associated virus (AAV) vector for the treatment of a subject in need thereof, wherein said AAV vector comprises a neurogenic differentiation 1 (NeuroD1) sequence operably linked to expression control elements comprising:
- (a) a glial fibrillary acidic protein (GFAP) promoter;
 - (b) an enhancer;
 - (c) a chimeric intron;
 - (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE); and
 - (e) a polyadenylation signal.
7. The AAV vector of any one of claims 1-3, or the composition of any one of claims 4-6, wherein said AAV vector is selected from the group consisting of AAV serotype 2, AAV serotype 5, and AAV serotype 9.

8. The AAV vector or composition of claim 7, wherein said AAV vector is AAV serotype 2.
9. The AAV vector or composition of claim 7, wherein said AAV vector is AAV serotype 5.
- 5 10. The AAV vector or composition of claim 7, wherein said AAV vector is AAV serotype 9.
11. The composition of claim 4 or 5, wherein said glial cells are reactive astrocytes.
12. The composition of claim 4 or 5, wherein said functional neurons are selected from the group consisting of glutamatergic neurons, GABAergic neurons, dopaminergic neurons, 10 cholinergic neurons, serotonergic neurons, epinephrinergic neurons, motor neurons, and peptidergic neurons.
13. The composition of claim 4 or 5, wherein said human has a neurological condition.
14. The AAV vector of claim 3, or the composition of claim 6, wherein said NeuroD1 is a human NeuroD1 (hNeuroD1).
- 15 15. The AAV vector of claim 3, or the composition of claim 6, wherein said NeuroD1 is selected from the group consisting of a chimpanzee NeuroD1, a bonobo NeuroD1, an orangutan NeuroD1, a gorilla NeuroD1, a macaque NeuroD1, a marmoset NeuroD1, a capuchin NeuroD1, a baboon NeuroD1, a gibbon NeuroD1, and a lemur NeuroD1.
16. The AAV vector or composition of claim 14, wherein said hNeuroD1 comprises a nucleic acid coding sequence encoding an amino acid sequence at least 80% identical or similar 20 to SEQ ID NO: 10.
17. The AAV vector or composition of claim 14, wherein said hNeuroD1 sequence comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 6, or the complement thereof.

18. The AAV vector of claim 3, or the composition of claim 6, wherein said GFAP promoter is a human GFAP (hGFAP) promoter.
19. The AAV vector of claim 3, or the composition of claim 6, wherein said GFAP promoter is selected from the group consisting of a chimpanzee GFAP promoter, a bonobo GFAP promoter, an orangutan GFAP promoter, a gorilla GFAP promoter, a macaque GFAP promoter, a marmoset GFAP promoter, a capuchin GFAP promoter, a baboon GFAP promoter, a gibbon GFAP promoter, and a lemur GFAP promoter.
20. The AAV vector or composition of any one of the preceding claims, wherein the AAV vector further comprises a 2A self-cleavage peptide sequence at least 80% identical to SEQ ID NO: 3 or the complement thereof.
21. The AAV vector or composition of claim 18, wherein said hGFAP promoter comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 4 or the complement thereof.
22. The AAV vector or composition of claim 18, wherein said hGFAP promoter comprises a nucleic acid sequence at least 80% identical to SEQ ID NOs: 12 or the complement thereof.
23. The AAV vector or composition of claim 18, wherein said hGFAP promoter comprises a nucleic acid sequence at least 80% identical to SEQ ID NOs: 15 or the complement thereof.
24. The AAV vector of claim 3, or the composition of claim 6, wherein said enhancer is selected from the group consisting of an enhancer from human elongation factor-1 alpha (EF1- α) promoter and cytomegalovirus (CMV) enhancer.
25. The AAV vector or composition of claim 24, wherein said EF1- α comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 2, or the complement thereof.
26. The AAV vector or composition of claim 24, wherein said CMV enhancer comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 11, or the complement thereof.

27. The AAV vector of claim 3, or the composition of claim 6, wherein said chimeric intron comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 5 or the complement thereof.
28. The AAV vector of claim 3, or the composition of claim 6, wherein said chimeric intron
5 comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 16 or the complement thereof.
29. The AAV vector of claim 3, or the composition of claim 6, wherein said WPRE comprises a nucleic acid sequence at least 80% identical to a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18, or the complement thereof.
- 10 30. The AAV vector of claim 3, or the composition of claim 6, wherein said polyadenylated signal is selected from the group consisting of SV40 polyadenylation signal and a hGH polyadenylation signal.
31. The AAV vector or composition of claim 30, wherein said SV40 polyadenylated signal
15 comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 8, or the complement thereof.
32. The AAV vector or composition of claim 30, wherein said hGH polyadenylated signal comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 13, or the complement thereof.
33. The AAV vector or composition of claim 30, wherein said bGH polyadenylated signal
20 comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 14, or the complement thereof.
34. The AAV vector of claim 3, or the composition of claim 6, wherein said AAV vector further comprises a nucleic acid sequence encoding an AAV protein sequence.
35. The AAV vector of any one of claims 1-3, or the composition of any one of claims 4-6,
25 wherein said AAV vector comprises AAV serotype 2 inverted terminal repeats (ITRs).

36. The AAV vector of any one of claims 1-3, or the composition of any one of claims 4-6, wherein said AAV vector comprises AAV serotype 5 inverted terminal repeats (ITRs).
37. The AAV vector of any one of claims 1-3, or the composition of any one of claims 4-6, wherein said AAV vector comprises AAV serotype 9 inverted terminal repeats (ITRs).
- 5 38. The AAV vector of any one of claims 1-3, or the composition of any one of claims 4-6, wherein said AAV vector comprises at least one ITR nucleic acid sequence at least 80% identical to SEQ ID NO: 1.
39. The AAV vector of any one of claims 1-3, or the composition of any one of claims 4-6, wherein said AAV vector comprises at least one ITR nucleic acid sequence at least 80% identical to SEQ ID NO: 9.
- 10 40. The composition of claim 6, wherein said subject in need thereof is a mammal.
41. The composition of claim 40, wherein said mammal is a human.
42. The composition of claim 40, wherein said mammal is a non-human primate.
43. The composition of claim 6, wherein said subject in need thereof has a neurological condition.
- 15 44. The composition of claim 13 or 43, wherein said neurological condition comprises an injury to the central nervous system (CNS) or peripheral nervous system.
45. The composition of claim 13 or 43, wherein said wherein said neurological condition comprises an injury to the CNS.
- 20 46. The composition of claim 13 or 43, wherein said neurological condition is selected from the group consisting of Alzheimer's Disease, Parkinson's Disease, amyotrophic lateral sclerosis (ALS), Huntington's Disease, epilepsy, physical injury, stroke, cerebral aneurysm, traumatic brain injury, concussion, a tumor, inflammation, infection, ataxia, brain atrophy, spinal cord atrophy, multiple sclerosis, traumatic spinal cord injury,
- 25 ischemic or hemorrhagic myelopathy (myelopathy), global ischemia, hypoxic ischemic

encephalopathy, embolism, fibrocartilage embolism myelopathy, thrombosis, nephropathy, chronic inflammatory disease, meningitis, and cerebral venous sinus thrombosis.

- 5 47. The composition of claim 13 or 43, wherein said neurological condition is Alzheimer's Disease.
48. The composition of claim 13 or 43, wherein said neurological condition is Parkinson's Disease.
49. The composition of claim 13 or 43, wherein said neurological condition is ALS.
- 10 50. The composition of claim 13 or 43, wherein said neurological condition is Huntington's Disease.
51. The composition of claim 13 or 43, wherein said neurological condition is a stroke.
52. The composition of claim 51, wherein said stroke is an ischemic stroke.
53. The composition of claim 51, wherein said stroke is a hemorrhagic stroke.
- 15 54. The composition of claim 43, wherein said composition is capable of converting at least one glial cell to a neuron.
55. The composition of claim 54, wherein said glial cells are selected from the group consisting of astrocytes and NG2 cells.
56. The composition of claim 54, wherein said glial cells are astrocytes.
57. The composition of claim 56, wherein said astrocytes are reactive astrocytes.
- 20 58. The composition of claim 54, wherein said glial cells are GFAP positive.
59. The composition of claim 54, wherein said neurons are functional neurons.
60. The composition of claim 54, wherein said functional neurons are selected from the group consisting of glutamatergic neurons, GABAergic neurons, dopaminergic neurons,

cholinergic neurons, serotonergic neurons, epinephrinergic neurons, motor neurons, and peptidergic neurons..

61. The composition of claim 60, wherein said functional neurons are glutamatergic neurons.

5 62. The composition of claim 6, wherein said composition is formulated to be delivered to a subject in need thereof.

63. The composition of claim 62, wherein said composition is formulated for local delivery.

64. The composition of claim 62, wherein said composition is formulated for systemic delivery.

10 65. The composition of any one of claims 62-64, wherein said composition is formulated for delivery via intraperitoneal, intramuscular, intravenous, intrathecal, intracerebral, intracranial, intra lateral ventricle of the brain, intra cisterna magna, intra vitreous, intra-subretina, intraparenchymal, intranasal, or oral administration.

66. A method comprising delivering the composition of claim 6 to said subject in need thereof.

15 67. The method of claim 66, wherein said composition is formulated to be delivered to a subject in need thereof.

68. The method of claim 66, wherein said delivering comprises local administration.

69. The method of claim 66, wherein said delivering comprises systemic administration.

20 70. The method of any one of claims 66-69, wherein said delivering comprises an intraperitoneal, intramuscular, intravenous, intrathecal, intracerebral, intracranial, intra lateral ventricle of the brain, intra cisterna magna, intra vitreous, intra-subretina, intraparenchymal, intranasal, or oral administration.

71. A method of converting reactive astrocytes to functional neurons in a brain of a living human comprising: injecting an adeno-associated virus (AAV) into a subject in need

thereof, wherein said AAV comprises a DNA vector construct comprising a human neurogenic differentiation 1 (hNeuroD1) sequence comprising the nucleic acid sequence of SEQ ID NO: 6, wherein said sequence is operably linked to regulatory elements comprising:

- 5 (a) a human glial fibrillary acid protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15;
- (b) an enhancer from the human elongation factor-1 alpha (EF-1 alpha) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11;
- 10 (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16;
- (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18; and
- (e) a SV40 polyadenylation signal sequence comprising the nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.
- 15

72. A method of converting reactive astrocytes to functional neurons in a brain of a living human comprising: injecting an adeno-associated virus (AAV) into a subject in need thereof, wherein said AAV comprises a DNA vector construct comprising a nucleic acid sequence encoding a human neurogenic differentiation 1 (hNeuroD1) protein comprising the amino acid coding sequence of SEQ ID NO: 10, wherein said coding sequence is operably linked to expression control elements comprising:

- 20 (a) a human glial fibrillary acid protein (GFAP) promoter comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 4, 12, and 15;
- (b) an enhancer from the human elongation factor-1 alpha (EF-1 alpha) promoter comprising the nucleic acid sequence of SEQ ID NO: 2 or a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11;
- 25 (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 5 or 16;

- (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18; and
- (e) a SV40 polyadenylation signal sequence comprising the nucleic acid sequence of SEQ ID NO: 8, a hGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 13, or a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

73. A method of converting glial cells to neurons in a subject in need thereof comprising: delivering an adeno-associated virus (AAV) to said subject in need thereof, wherein said AAV comprises a DNA vector construct comprising a neurogenic differentiation 1 (NeuroD1) sequence operably linked to expression control elements comprising:

- (a) a glial fibrillary acid protein (GFAP) promoter;
- (b) an enhancer;
- (c) a chimeric intron;
- (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE); and
- (e) and a polyadenylation signal sequence,

wherein said vector is capable of converting at least one glial cell to a neuron in said subject in need thereof.

74. A method of treating a neurological condition in a subject in need thereof comprising: delivering an adeno-associated virus (AAV) to said subject, wherein said AAV comprises a DNA vector construct comprising a neurogenic differentiation 1 (NeuroD1) sequence operably linked to expression control elements comprising:

- (a) a glial fibrillary acid protein (GFAP) promoter;
- (b) an enhancer;
- (c) a chimeric intron;
- (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE); and
- (e) a polyadenylation signal to said subject in need thereof.

75. The method of any one of claims 71-74, wherein said AAV is selected from the group consisting of AAV serotype 2, AAV serotype 5, and AAV serotype 9.

76. The method of claim 75, wherein said AAV is AAV serotype 2.
77. The method of claim 75, wherein said AAV is AAV serotype 5.
78. The method of claim 75, wherein said AAV is AAV serotype 9.
79. The method of claims 71 or 72, wherein said functional neurons are glutamatergic
5 neurons, GABAergic neurons, dopaminergic neurons, cholinergic neurons, serotonergic
neurons, epinephrinergic neurons, motor neurons, and peptidergic neurons.
80. The method of claims 73 or 74, wherein said NeuroD1 is human NeuroD1 (hNeuroD1).
81. The method of claims 73 or 74, wherein said NeuroD1 is selected from the group
10 consisting of a chimpanzee NeuroD1, a bonobo NeuroD1, an orangutan NeuroD1, a
gorilla NeuroD1, a macaque NeuroD1, a marmoset NeuroD1, a capuchin NeuroD1, a
baboon NeuroD1, a gibbon NeuroD1, and a lemur NeuroD1.
82. The method of claim 80, wherein said hNeuroD1 comprises a amino acid sequence
encoding an amino acid coding sequence at least 80% identical or similar to SEQ ID NO:
10.
83. The method of claim 80, wherein said hNeuroD1 sequence comprises a nucleic acid
15 sequence at least 80% identical to SEQ ID NO: 6, or the complement thereof.
84. The method of claims 73 or 74, wherein said GFAP promoter is a human GFAP (hGFAP)
promoter.
85. The method of claims 73 or 74, wherein said GFAP promoter is selected from the group
20 consisting of a chimpanzee GFAP promoter, a bonobo GFAP promoter, an orangutan
GFAP promoter, a gorilla GFAP promoter, a macaque GFAP promoter, a marmoset
GFAP promoter, a capuchin GFAP promoter, a baboon GFAP promoter, a gibbon GFAP
promoter, and a lemur GFAP promoter.

86. The method of any one of claims 71-85, wherein the DNA vector construct further comprises a 2A self-cleavage peptide sequence at least 80% identical to SEQ ID NO: 3 or the complement thereof.
- 5 87. The method of claim 84, wherein said hGFAP promoter comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 4, or the complement thereof.
88. The method of claim 84, wherein said hGFAP promoter comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 12, or the complement thereof.
89. The method of claim 84, wherein said hGFAP promoter comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 15, or the complement thereof.
- 10 90. The method of claims 73 or 74, wherein said enhancer is selected from the group consisting of an enhancer from human elongation factor-1 alpha (EF1- α) promoter and cytomegalovirus (CMV) enhancer.
91. The method of claim 90, wherein said EF1- α comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 2, or the complement thereof.
- 15 92. The method of claim 90 wherein said CMV enhancer comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 11, or the complement thereof.
93. The method of claims 73 or 74, wherein said chimeric intron comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 5, or the complement thereof.
94. The method of claims 73 or 74, wherein said chimeric intron comprises a nucleic acid
20 sequence at least 80% identical to SEQ ID NO: 16, or the complement thereof.
95. The method of claims 73 or 74, wherein said WPRE comprises a nucleic acid sequence at least 80% identical to a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 7 and 18, or the complement thereof.

96. The method of claims 73 or 74, wherein said polyadenylated signal is selected from the group consisting of SV40 polyadenylation signal, a hGH polyadenylation signal, and a bGH polyadenylation signal.
- 5 97. The method of claims 73 or 74, wherein said SV40 polyadenylated signal comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 8, or the complement thereof.
98. The method of claims 73 or 74 wherein said hGH polyadenylated signal comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 13, or the complement thereof.
- 10 99. The method of claims 73 or 74 wherein said bGH polyadenylated signal comprises a nucleic acid sequence at least 80% identical to SEQ ID NO: 14, or the complement thereof.
100. The method of claims 73 or 74, wherein said vector further comprises a nucleic acid sequence encoding an AAV protein sequence.
- 15 101. The method of any one of claims 71-74, wherein said vector comprises AAV serotype 2 inverted terminal repeats (ITRs).
102. The method of any one of claims 71-74, wherein said vector comprises AAV serotype 5 inverted terminal repeats (ITRs).
103. The method of any one of claims 71-74, wherein said vector comprises AAV
20 serotype 9 inverted terminal repeats (ITRs).
104. The method of any one of claims 71-74, wherein said vector comprises at least one ITR nucleic acid sequence at least 80% identical to SEQ ID NO: 1.
105. The method of any one of claims 71-74, wherein said vector comprises at least one ITR nucleic acid sequence at least 80% identical to SEQ ID NO: 9.

106. The method of claim 71, wherein said converting occurs in the central nervous system (CNS) or peripheral nervous system.
107. The method of claim 73, wherein said converting occurs in the CNS.
108. The method of claim 73 or 74, wherein said subject in need thereof is a mammal.
- 5 109. The method of claim 108, wherein said mammal is a human.
110. The method of claim 108, wherein said mammal is a non-human primate.
111. The method of claim 73 or 74, wherein said delivering comprises a local administration.
112. The method of claim 73 or 74, wherein said delivering comprises systemic
10 administration.
113. The method of claim 73 or 74, wherein said delivering comprises an administration selected from the group consisting of an intraperitoneal administration, intramuscular administration, intravenous administration, intrathecal administration, intracerebral administration, intracranial, intra lateral ventricle of the brain, intra cisterna
15 magna, intra vitreous, intra-subretina, intraparenchymal administration, intranasal administration, and oral administration.
114. The method of claim 71 or 72, wherein said injecting comprises an injection selected from the group consisting of an intraperitoneal injection, intramuscular injection, intravenous injection, intrathecal injection, intracerebral injection, intracranial, intra
20 lateral ventricle of the brain, intra cisterna magna, intra vitreous, intra-subretina, intraparenchymal injection, intranasal injection, and oral injection.
115. The method of claims 73 or 74, wherein said delivering comprises injecting.
116. The method of any one of claims 71, 72, or 115, wherein said injecting is performed at a concentration of between 10^{10} particles/mL and 10^{14} particles/mL.

117. The method of claim 116, wherein said injecting further comprises a flow rate of between 0.1 ul/minute and 5.0 ul/minute.
118. The method of claim 73, wherein said at least one glial cell is selected from the group consisting of at least one astrocyte and at least one NG2 cell.
- 5 119. The method of claim 71, wherein said at least one glial cell is at least one astrocyte.
120. The method of claim 118 or 119, wherein said at least one astrocyte is a reactive astrocyte.
121. The method of claim 73, wherein said neuron is a functional neuron.
- 10 122. The method of any one of claims 71, 72, and 121, wherein said functional neurons are selected from the group consisting of glutamatergic neurons, GABAergic neurons, dopaminergic neurons, cholinergic neurons, serotonergic neurons, epinephrinergic neurons, motor neurons, and peptidergic neurons.
123. The method of claim 73, wherein said subject exhibits an improvement of at least
15 one neurological condition symptom as compared to said subject prior to said delivering.
124. The method of claim 123, wherein said improvement is measured within 1 year of said delivering.
125. The method of any one of claims 71, 72, or 115, wherein said method comprises directly injecting said AAV into the brain of said subject.
- 20 126. The method of any one of claims 71 or 72, wherein said converting is in the cerebral cortex of said brain.
127. The method of any one of claims 71, 72, or 115, wherein said method comprises directly injecting said AAV into the spinal cord of said subject.

128. The method of claim 74, wherein said neurological condition comprises an injury to the central nervous system (CNS) or peripheral nervous system.
129. The method of claim 74, wherein said neurological condition is selected from the group consisting of Alzheimer's Disease, Parkinson's Disease, amyotrophic lateral sclerosis (ALS), Huntington's Disease, epilepsy, physical injury, stroke, cerebral aneurysm, traumatic brain injury, concussion, a tumor, inflammation, infection, ataxia, brain atrophy, spinal cord atrophy, multiple sclerosis, traumatic spinal cord injury, ischemic or hemorrhagic myelopathy (myelopathy), global ischemia, hypoxic ischemic encephalopathy, embolism, fibrocartilage embolism myelopathy, thrombosis, nephropathy, chronic inflammatory disease, meningitis, and cerebral venous sinus thrombosis.
130. The method of claim 74, wherein said neurological condition is Alzheimer's Disease.
131. The method of claim 74, wherein said neurological condition is Parkinson's Disease.
132. The method of claim 74, wherein said neurological condition is ALS.
133. The method of claim 74, wherein said neurological condition is Huntington's Disease.
134. The method of claim 74, wherein said neurological condition is a stroke.
135. The method of claim 134, wherein said stroke is an ischemic stroke.
136. The method of claim 134, wherein said stroke is a hemorrhagic stroke.
137. The method of claim 74, wherein said method is capable of converting at least one glial cell into a neuron.
138. The method of claim 137, wherein said glial cells are selected from the group consisting of astrocytes and NG2 cells.

139. The method of claim 137, wherein said glial cells are astrocytes.
140. The method of claim 139, wherein said astrocytes are reactive astrocytes.
141. The method of claim 137, wherein said glial cells are GFAP positive.
142. The method of claim 137, wherein said neurons are functional neurons.
- 5 143. The method of claim 142, wherein said functional neurons are selected from the group consisting of glutamatergic neurons, GABAergic neurons, dopaminergic neurons, cholinergic neurons, serotonergic neurons, epinephrinergic neurons, motor neurons, and peptidergic neurons..
- 10 144. The method of claims 71 or 72, wherein a therapeutically effective dose of said AAV vector is injected into said subject.
145. The method of claims 73 or 74, wherein a therapeutically effective dose of said AAV vector is delivered to said subject.
146. The method of claim 144 or 145, wherein said therapeutically effective dose is administered with a pharmaceutically acceptable carrier.
- 15 147. An adeno-associated virus (AAV) vector comprising a human neurogenic differentiation 1 (hNeuroD1) sequence comprising the nucleic acid sequence of SEQ ID NO: 6, where the hNeuroD1 sequence is operably linked to regulatory elements comprising:
- 20 (a) a glial fibrillary acidic protein (GFAP) promoter comprising the nucleic acid sequence of SEQ ID NO: 15;
- (b) an enhancer from a human elongation factor-1 alpha (EF1- α) promoter comprising the nucleic acid sequence of SEQ ID NO: 2;
- (c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 16;
- 25 (d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence of SEQ ID NO: 18; and

(e) a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.

148. An adeno-associated virus (AAV) vector comprising a human neurogenic differentiation 1 (hNeuroD1) sequence comprising the nucleic acid sequence of SEQ ID NO: 6, where the hNeuroD1 sequence is operably linked to regulatory elements comprising:

(a) a glial fibrillary acidic protein (GFAP) promoter comprising the nucleic acid sequence of SEQ ID NO: 15;

(b) a cytomegalovirus (CMV) enhancer comprising the nucleic acid sequence of SEQ ID NO: 11;

(c) a chimeric intron comprising the nucleic acid sequence of SEQ ID NO: 16;

(d) a woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) comprising the nucleic acid sequence of SEQ ID NO: 18; and

(e) a bGH polyadenylation sequence comprising the nucleic acid sequence of SEQ ID NO: 14.