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(54) **RESCUING VOLTAGE-GATED SODIUM CHANNEL FUNCTION IN INHIBITORY NEURONS**

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§ 371 (c)(1),
(2) Date: **Sep. 30, 2020**

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C12N 15/86	(2006.01)
C07K 14/705	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 38/177*** (2013.01); ***A61K 48/0058*** (2013.01); ***A61K 9/0019*** (2013.01); *C12N 2830/008* (2013.01); ***C07K 14/705*** (2013.01); *C12N 2750/14143* (2013.01); ***C12N 15/86*** (2013.01)

(57) **ABSTRACT**

Selectively providing voltage-gated sodium channel function sufficient to rescue impaired Nav1.1 function to inhibitory neurons is described. Provided voltage-gated sodium channel function sufficient to rescue impaired Nav1.1 function in inhibitory neurons can be used to treat disorders such as epilepsy, and more particularly, Dravet Syndrome.

Specification includes a Sequence Listing.

FIG. 1A

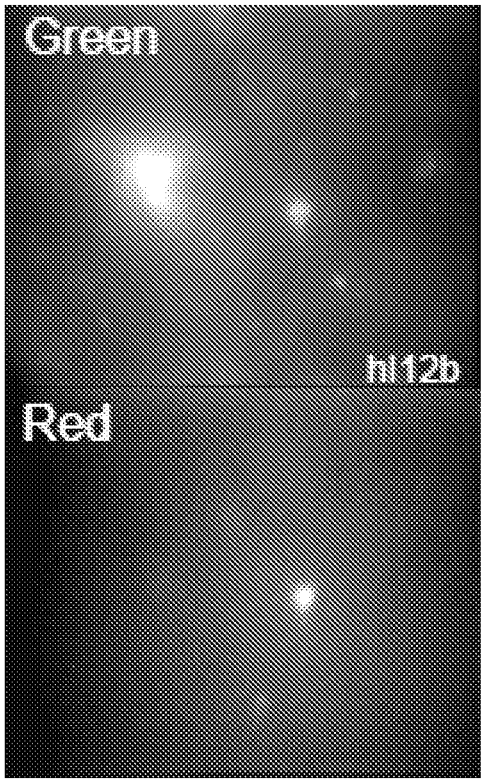

Green
hl12b
Red

FIG. 1B

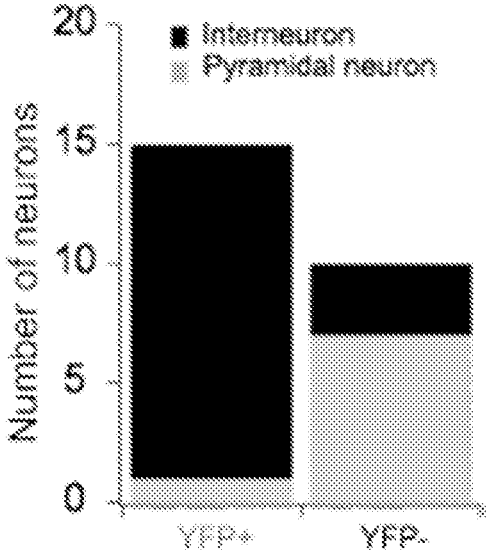

20
15
10
5
0
Number of neurons
Interneuron
Pyramidal neuron
YFP+
YFP-

FIG. 1C

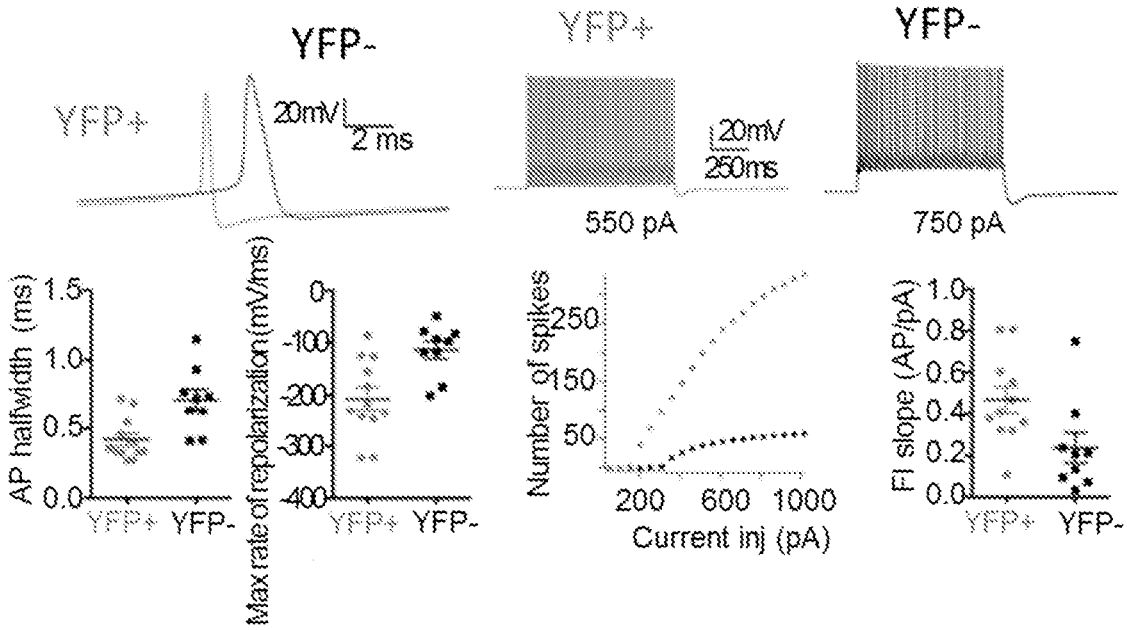

YFP-
YFP+
20mV
2 ms
YFP+
YFP-
20mV
250ms
550 pA
750 pA
AP halfwidth (ms)
1.5
1.0
0.5
0.0
YFP+ YFP-
Max rate of repolarization (mV/ms)
0
-100
-200
-300
-400
YFP+ YFP-
Number of spikes
250
150
50
200 600 1000
Current inj (pA)
FI slope (AP/pA)
1.0
0.8
0.6
0.4
0.2
0.0
YFP+ YFP-

FIG. 1D

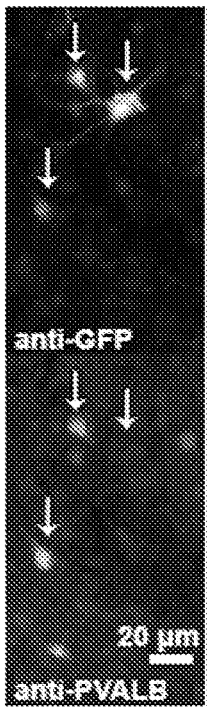

anti-CFP
20 µm
anti-PVALB

FIG. 2

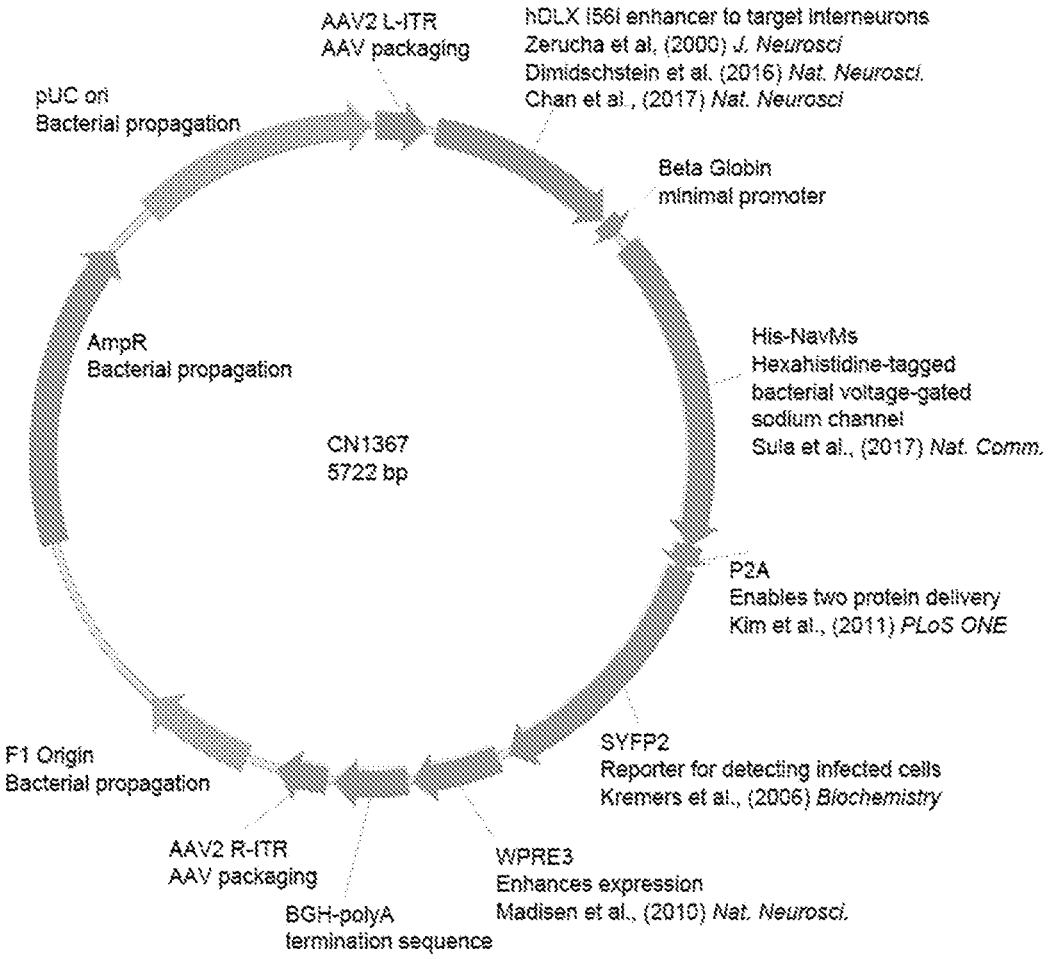

AAV2 L-ITR
AAV packaging
hDLX I56i enhancer to target interneurons
Zerucha et al, (2000) J. Neurosci
Dimidschstein et al. (2016) Nat. Neurosci.
Chan et al., (2017) Nat. Neurosci
pUC ori
Bacterial propagation
Beta Globin
minimal promoter
AmpR
Bacterial propagation
His-NavMs
Hexahistidine-tagged
bacterial voltage-gated
sodium channel
Sula et al., (2017) Nat. Comm.
CN1367
5722 bp
P2A
Enables two protein delivery
Kim et al., (2011) PLoS ONE
SYFP2
Reporter for detecting infected cells
Kremers et al., (2006) Biochemistry
F1 Origin
Bacterial propagation
AAV2 R-ITR
AAV packaging
WPRE3
Enhances expression
Madisen et al., (2010) Nat. Neurosci.
BGH-polyA
termination sequence

FIG. 3

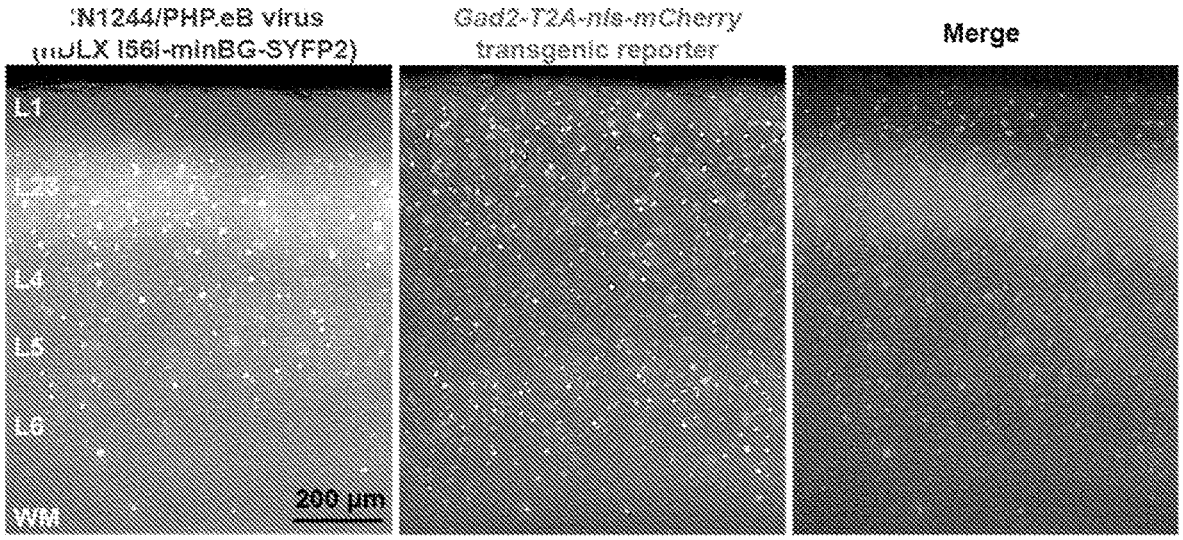

:N1244/PHP.eB virus
(mJLX I56i-minBG-SYFP2)
Gad2-T2A-nls-mCherry
transgenic reporter
Merge
L1
L2/3
L4
L5
L6
WM
200 µm

FIG. 4A

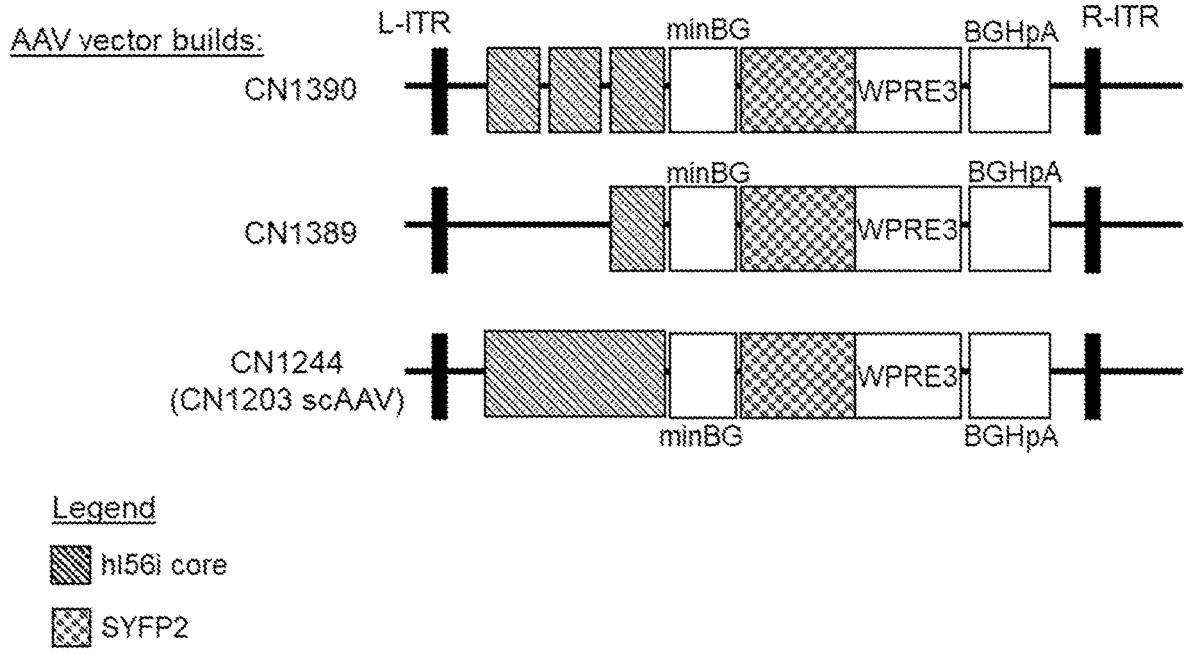

AAV vector builds:
L-ITR
minBG
BGHpA
R-ITR
CN1390
WPRE3
minBG
BGHpA
CN1389
WPRE3
CN1244
(CN1203 scAAV)
WPRE3
minBG
BGHpA
Legend
hl56i core
SYFP2

FIG. 4B

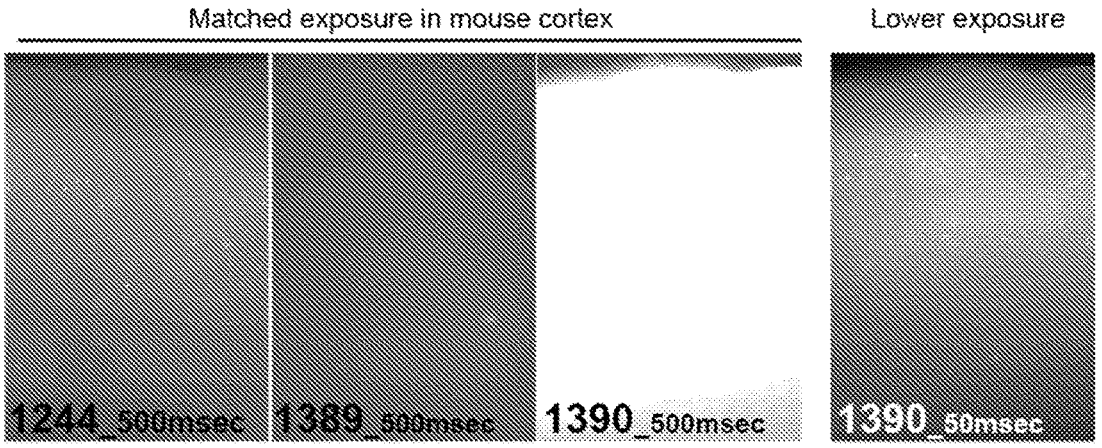

Matched exposure in mouse cortex
Lower exposure
1244_500msec
1389_500msec
1390_500msec
1390_50msec

FIG. 5

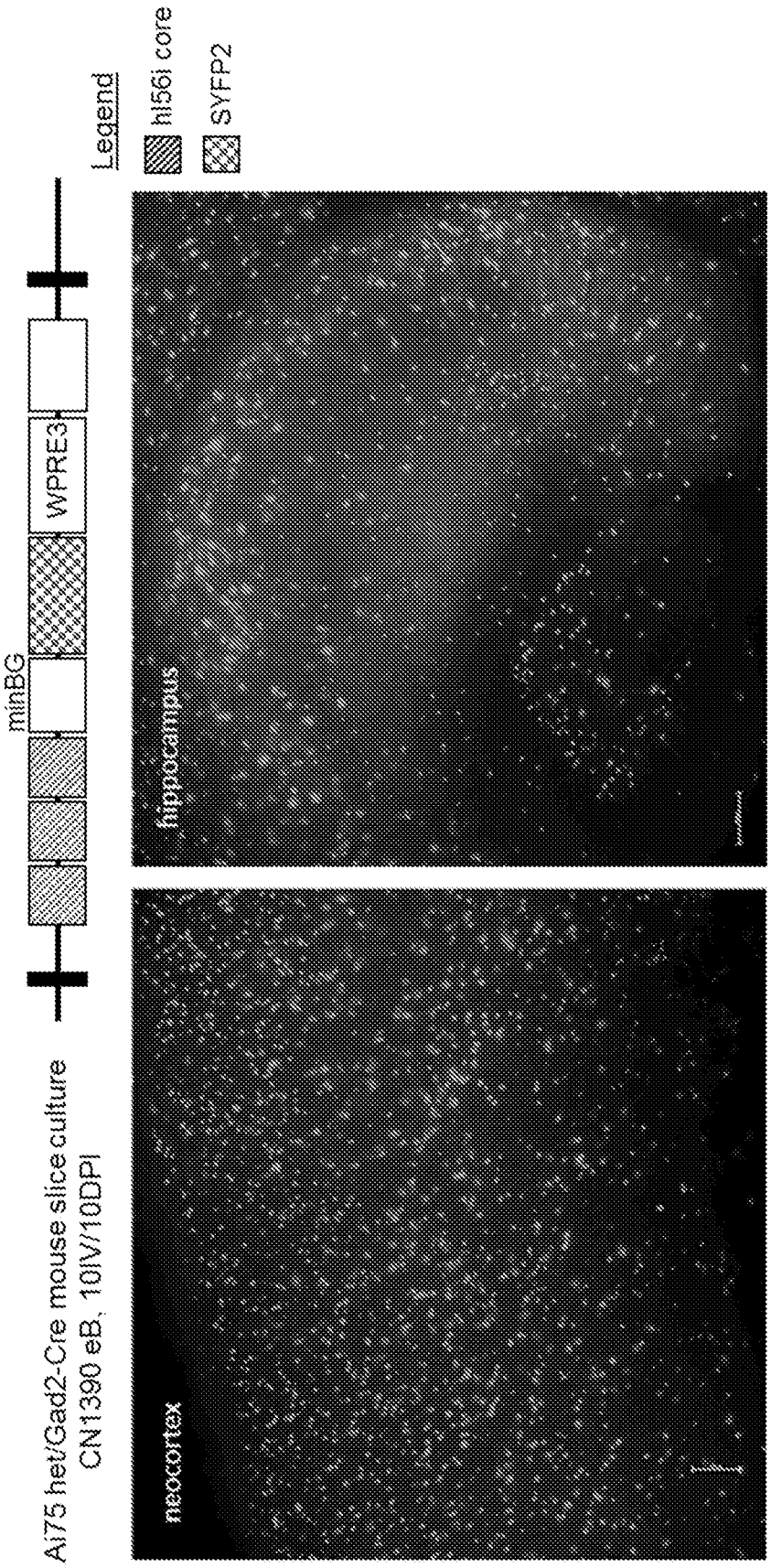

Legend
hl56i core
SYFP2
minBG
WPRE3
Ai75 het/Gad2-Cre mouse slice culture
CN1390 eB, 10IV//10DPI
neocortex
hippocampus

FIG. 6A

FIG. 6B

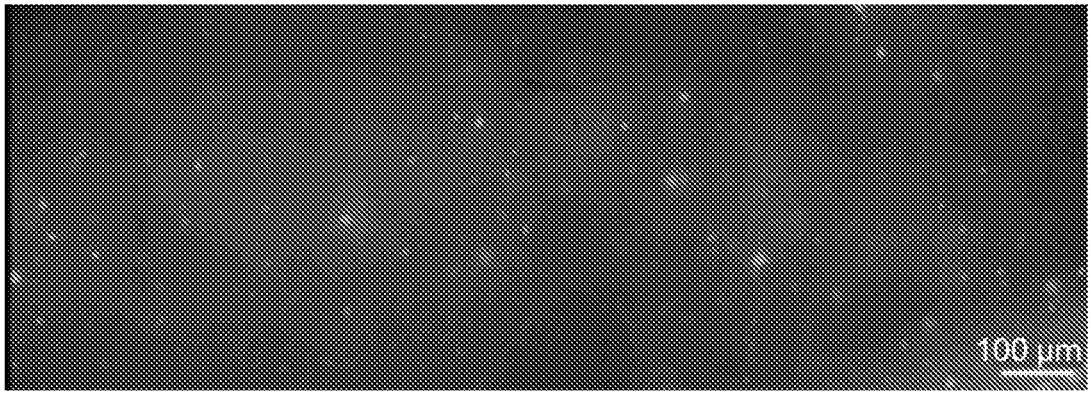


FIG. 6C

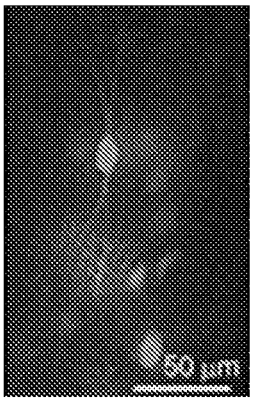

50 μm

FIG. 6D

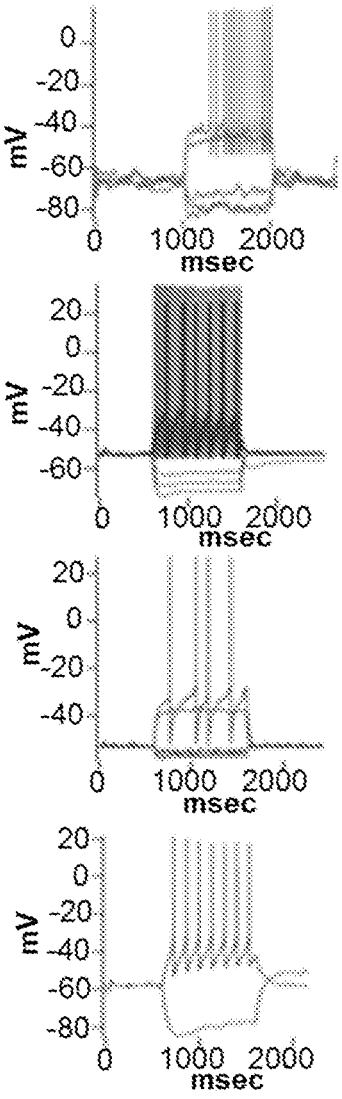

0
-20
-40
-60
-80
mV
0
1000
2000
msec
20
0
-20
-40
-60
mV
0
1000
2000
msec
20
0
-20
-40
mV
0
1000
2000
msec
20
0
-20
-40
-60
-80
mV
0
1000
2000
msec

FIG. 6E

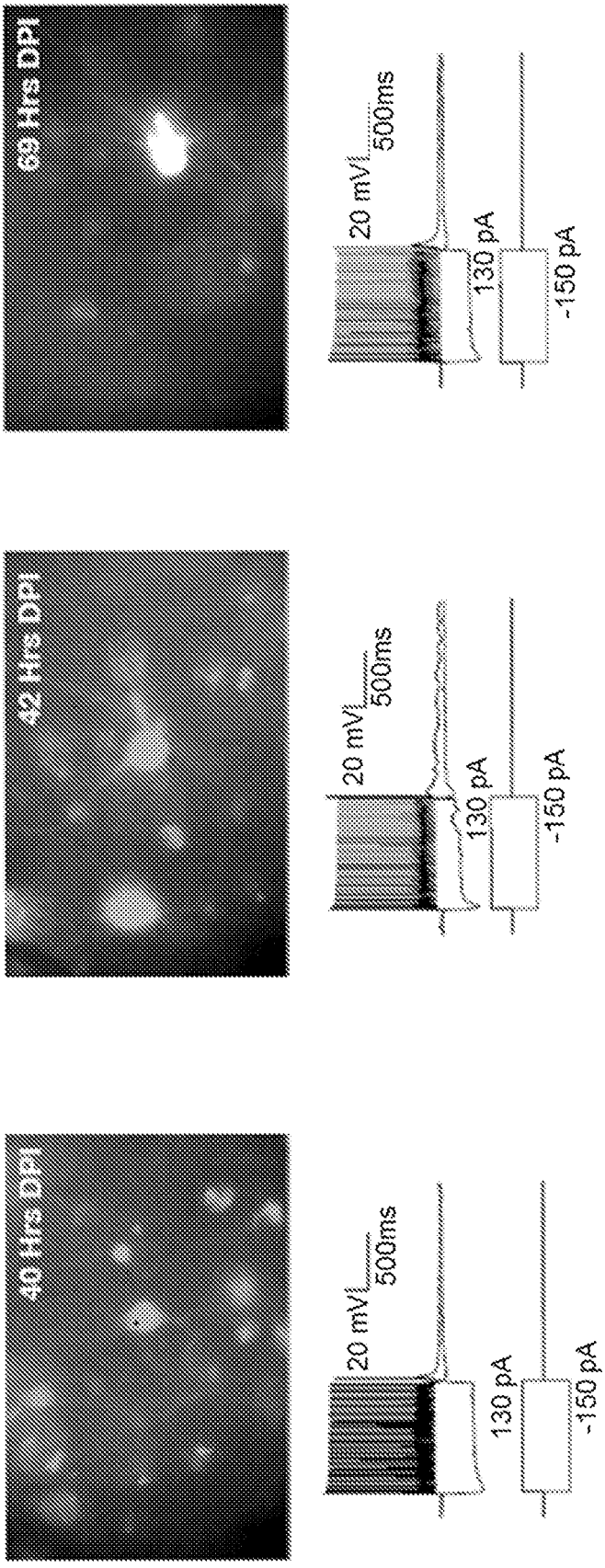

69 Hrs DPI
20 mV
500ms
130 pA
-150 pA
42 Hrs DPI
20 mV
500ms
130 pA
-150 pA
40 Hrs DPI
20 mV
500ms
130 pA
-150 pA

FIG. 7A

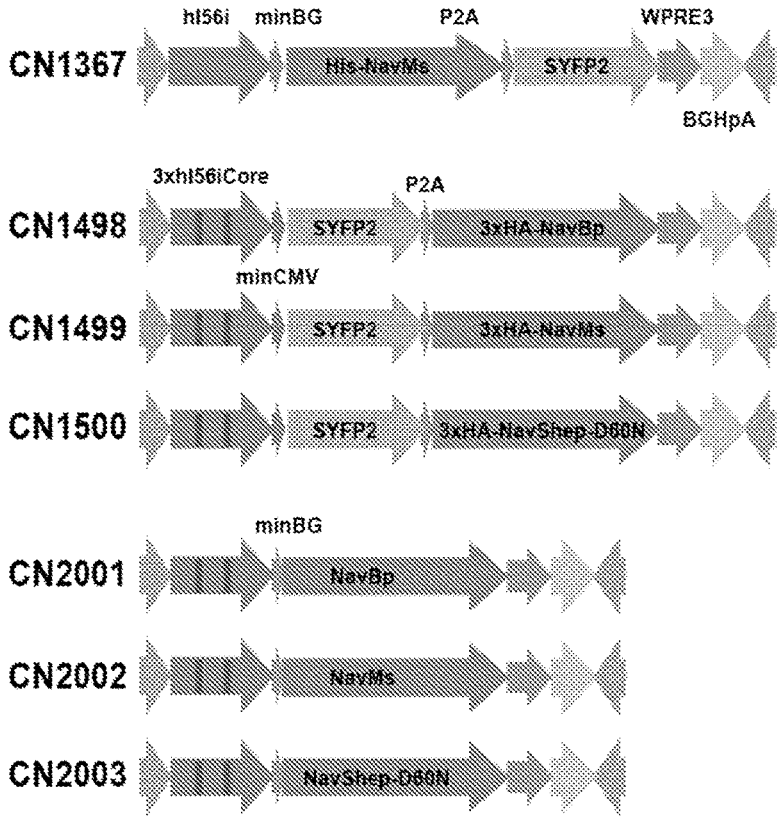

hI56i
minBG
P2A
WPRE3
CN1367
hIs-NavMs
SYFP2
BGHpA
3xhI56iCore
P2A
CN1498
SYFP2
3xHA-NavBp
minCMV
CN1499
SYFP2
3xHA-NavMs
CN1500
SYFP2
3xHA-NavShep-D60N
minBG
CN2001
NavBp
CN2002
NavMs
CN2003
NavShep-D60N

FIG. 7B

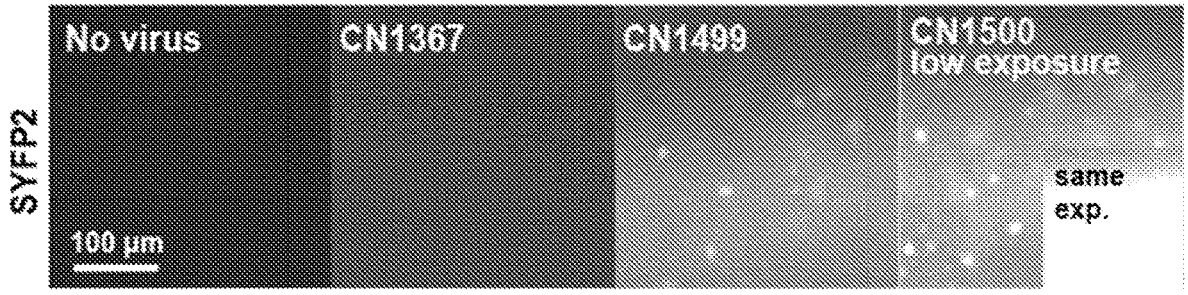

No virus
CN1367
CN1499
CN1500
low exposure
same
exp.
SYFP2
100 µm

FIG. 7C

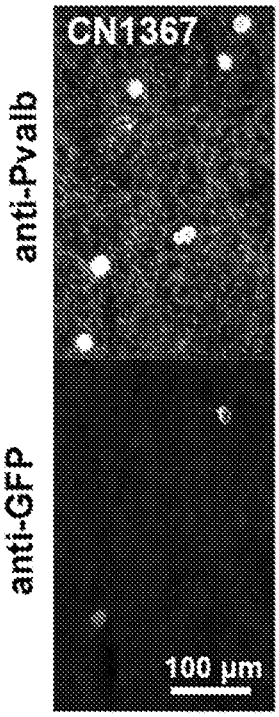


FIG. 7D

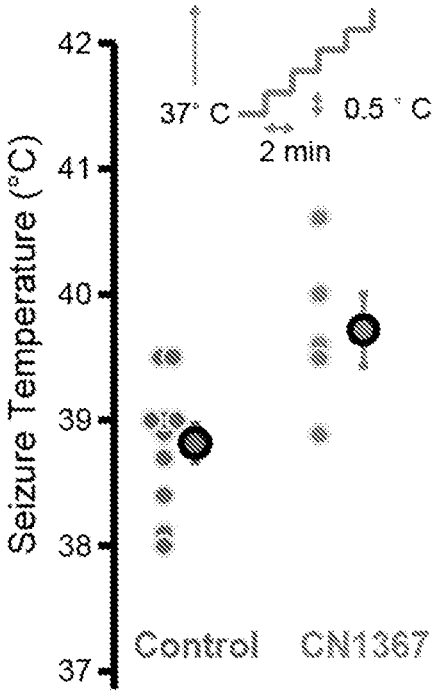


FIG. 7E

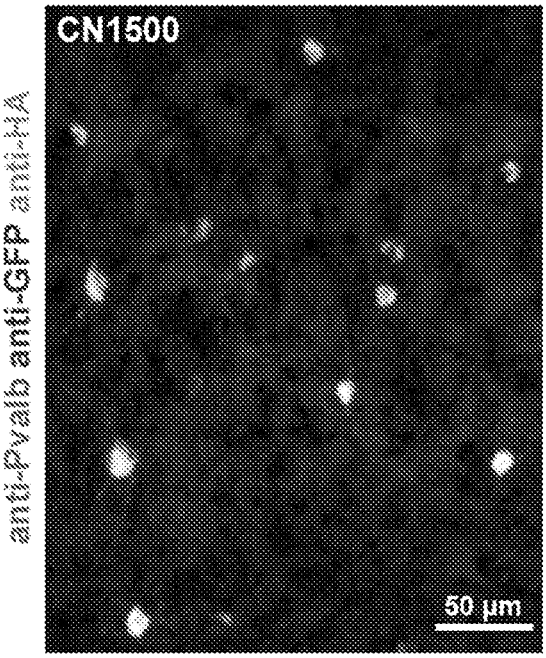


FIG. 7F

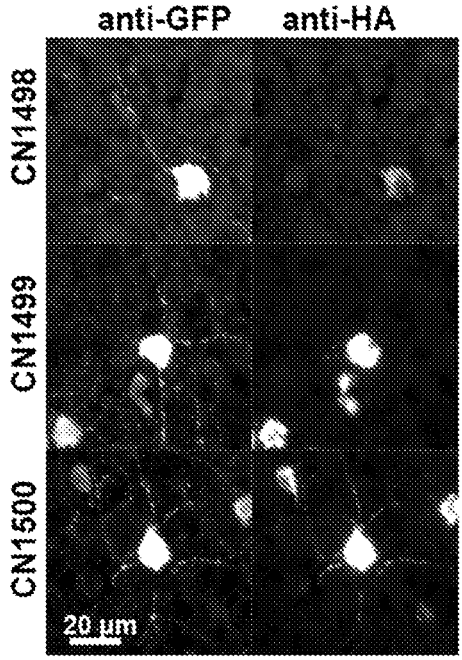


FIG. 8

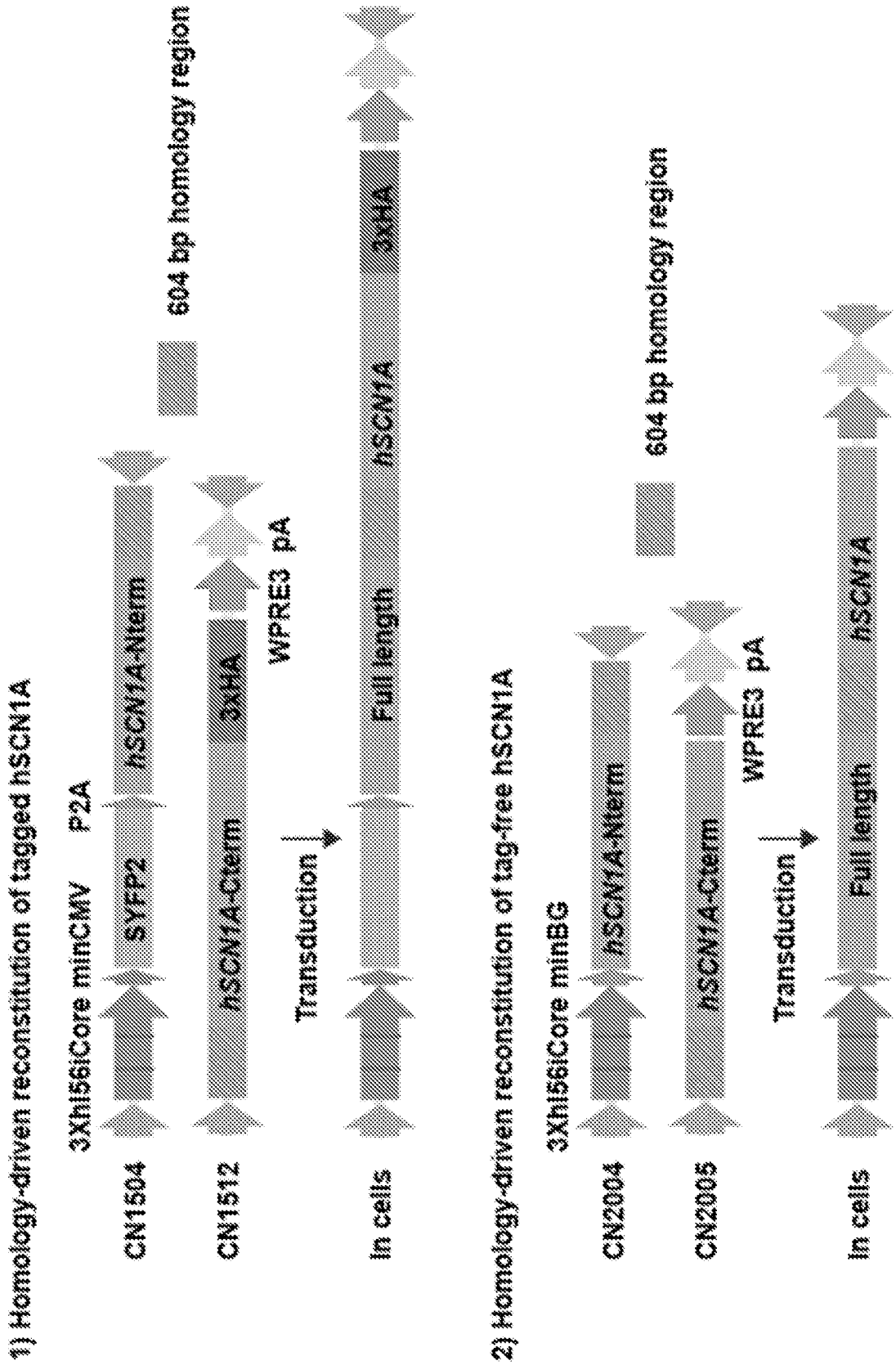

1) Homology-driven reconstitution of tagged hSCN1A
3Xhl56iCore minCMV
P2A
SYFP2
hSCN1A-Nterm
604 bp homology region
CN1504
CN1512
hSCN1A-Cterm
3xHA
WPRE3 pA
Transduction
In cells
Full length
hSCN1A
3xHA
2) Homology-driven reconstitution of tag-free hSCN1A
3Xhl56iCore minBG
hSCN1A-Nterm
604 bp homology region
CN2004
CN2005
hSCN1A-Cterm
WPRE3 pA
Transduction
In cells
Full length
hSCN1A

FIG. 8 cont'd

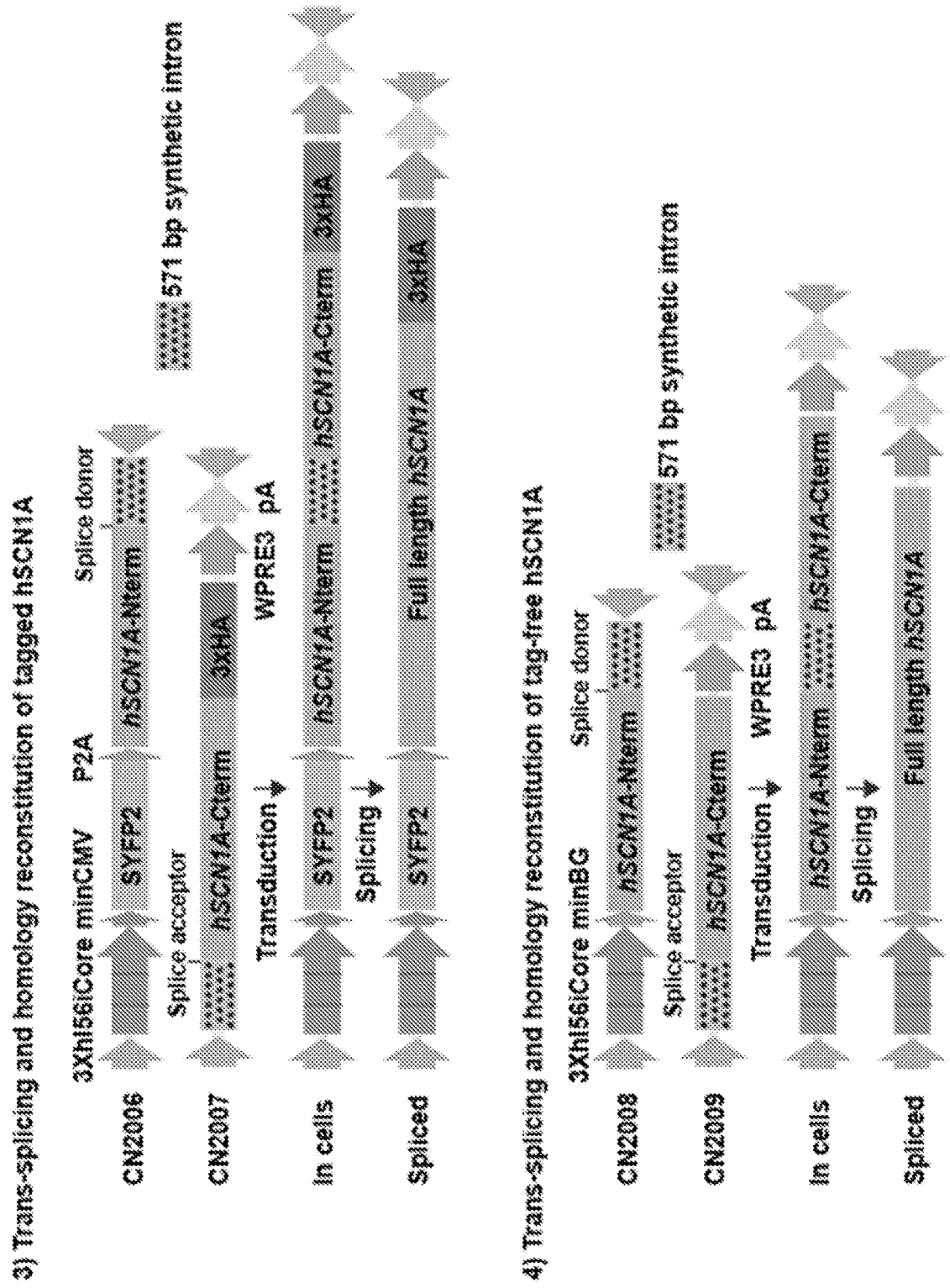

3) Trans-splicing and homology reconstitution of tagged hSCN1A
3Xhl56iCore minCMV
P2A
Splice donor
571 bp synthetic intron
CN2006
SYFP2
hSCN1A-Nterm
Splice acceptor
CN2007
hSCN1A-Cterm
3xHA
WPRE3
pA
Transduction
In cells
SYFP2
hSCN1A-Nterm
hSCN1A-Cterm
3xHA
Splicing
Spliced
SYFP2
Full length hSCN1A
3xHA
4) Trans-splicing and homology reconstitution of tag-free hSCN1A
3Xhl56iCore minBG
Splice donor
571 bp synthetic intron
CN2008
hSCN1A-Nterm
Splice acceptor
CN2009
hSCN1A-Cterm
Transduction
WPRE3
pA
In cells
hSCN1A-Nterm
hSCN1A-Cterm
Splicing
Spliced
Full length hSCN1A

FIG. 9

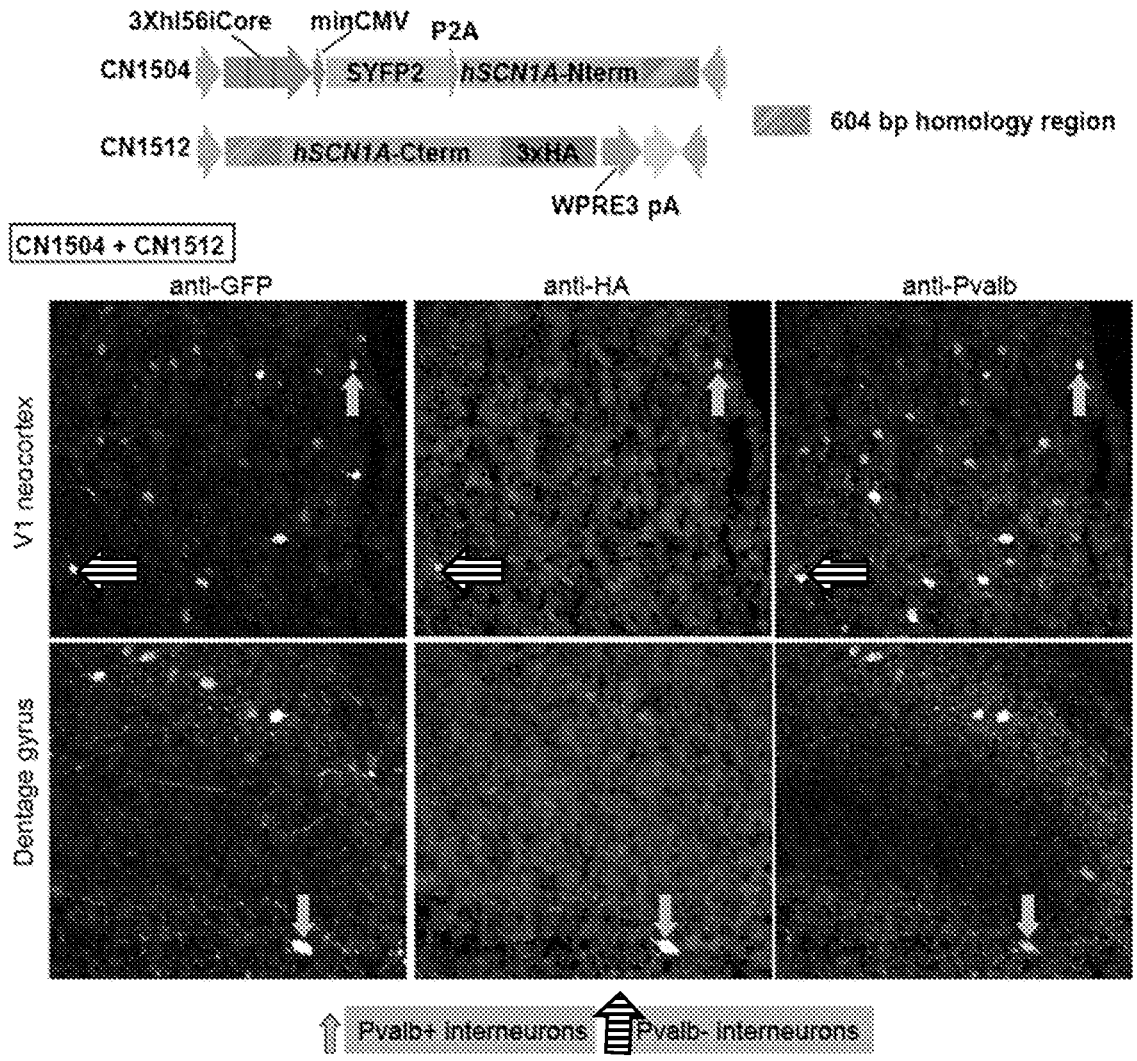
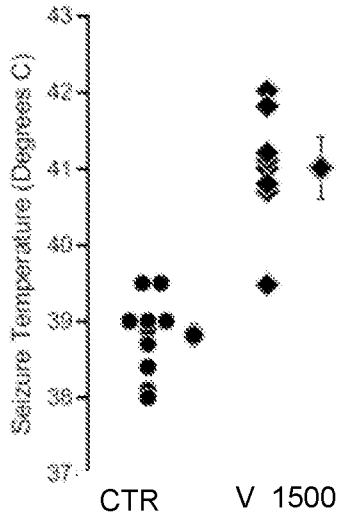

3XhI56iCore
minCMV
P2A
CN1504
SYFP2
hSCN1A-Nterm
CN1512
hSCN1A-Cterm
3xHA
WPRE3 pA
604 bp homology region
CN1504 + CN1512
anti-GFP
anti-HA
anti-Pvalb
V1 neocortex
Dentage gyrus
Pvalb+ interneurons
Pvalb- interneurons

FIG. 10


Seizure Temperature (Degrees C)
43
42
41
40
39
38
37
CTR
V 1500

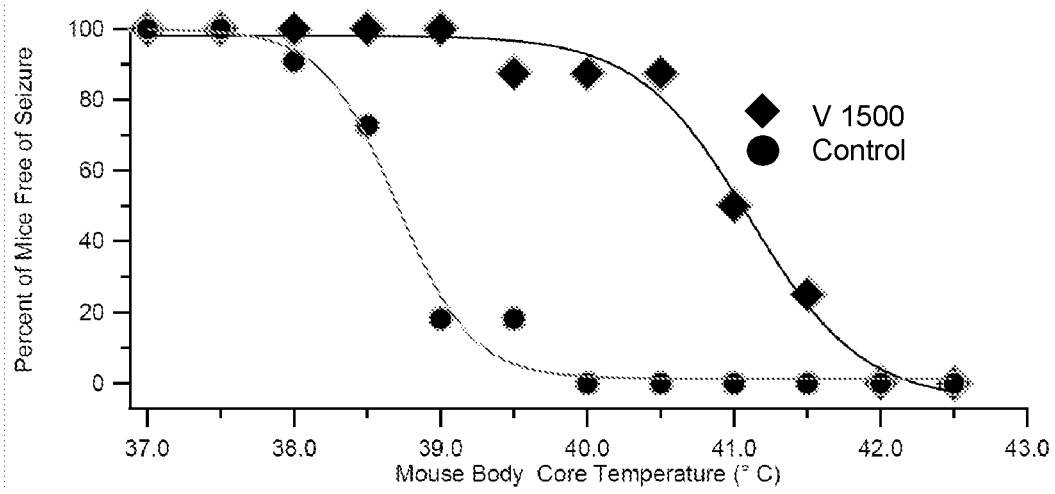

Percent of Mice Free of Seizure
100
80
60
40
20
0
37.0
38.0
39.0
40.0
41.0
42.0
43.0
Mouse Body Core Temperature (° C)
V 1500
Control

FIG. 11

hDLX I56i enhancer:
TATGCACTCACAGTGGTTTGGCATGCATCTGGTGAATTTTTTTTAACGAAAAATTAGTGTTG
GTTTCGATGTATGGTAGCATTCTCCCTAACGTAATTTGAATAATTCAGCAAAGCCCCACTAC
CAGCTGTACTTCTGCAGCCTCTTCCATTCTTTTCAGCATTATAATTTTGGTTAATTTTCAATT
TTAGGTCCTACGTCTCTGCAATTTGTGTATGAATAACAGAATAATTTCCCTCTTTTGTTTCGC
CTTTCCTGTTCCTGAATCTAAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACA
GGTAATTATCTTTGACGGTAAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACTCTAAT
TATGGCTGCATTTAAGAGAATGGAAAAAAACCTTCTTGTGGATAAAAACCTTAAATTGTCCC
CAATGTCTGCTTCAAATTGGATGGCACTGCAGCTGGAGGCTTTGTTCAGAATTGATCCTGG
GGAGCTACGAACCCAAAGTTTCACAGTAGG (SEQ ID NO: 1)

Core of the hDLX I56i enhancer:
CTAAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACG
GTAAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGA
GAATGG (SEQ ID NO: 2)

3xhI56iCore, Triply Concatamerized Core of the hDLX I56i enhancer:
CTAAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACG
GTAAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGA
GAATGGCTAAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATC
TTTGACGGTAAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCA
TTTAAGAGAATGGCTAAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGT
AATTATCTTTGACGGTAAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTAT
GGCTGCATTTAAGAGAATGG (SEQ ID NO: 3)

Murine I56i Enhancer (core is the same as human):
TATACACTCACAGTGGTTTGGCATATATTTGGTGAAATTTTTTAAGGAAAAATTAGTGTTGGT
TTCGATATATGGTAGCTTTTTCTCTAACATAATTTGAATAATTCAGCAAAGCCCTACTACCAG
CTGTACTTCTGCAGCCTCTTCCATTCTTTCCAGCATTATAATTTTGGTTAATTTTCAATTTTA
GGTCCTACGTCTCTGCAATTTGTGTATGAATAACAGAATAATTTCCCTCTTTTGTTTCGCCTT
TCCTGTTCCTGAATCTAAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGG
TAATTATCTTTGACGGTAAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTA
TGGCTGCATTTAAGAGAATGGAAAAAAACCTTCTTGTGGATAAAAACCTTAAATTGTCCCCA
ATGTCTGCTTCAAATTGGATGGCACTGCAGCTGGAGGCTTTGTTCAGAATTGATCCTGGGG
AGCTACGAACCCAAAGTTTCACAGTAGG (SEQ ID NO: 4)

Zebrafish I56i Enhancer:
ACATTGTAATTTTAGATAATATCCCAAGCGTTCACTCTCCTCGGCAATTTGTACATGAATAAC
CGAATAATTTCATCTTTTGTTTCGTCTTTGCCACTTCAAATCCAAATAAAGATGCCTTTTAGT
ATTAAAAGTGGTAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAATCAGCGG
GCTACATCAAAAATTACCCTAATTATGTCTGCATTTATGAGAATGGAAAAAAACCCTCTCTT
GGATAAAACCCATAAATTGTCCCAAATATCT (SEQ ID NO: 5)

Core of the Zebrafish I56i Enhancer:
CCAAATAAAGATGCCTTTTAGTATTAAAAGTGGTAGAAAATTACAGGTAATTATCTTTGACG
GTAAAAACGCTGTAATCAGCGGGCTACATCAAAAATTACCCTAATTATGTCTGCATTTATGA
GAATGG (SEQ ID NO: 6)

FIG. 11, cont'd

3x Concatamerized Core of the Zebrafish I56i Enhancer:
CCAAATAAAGATGCCTTTTAGTATTAAAAGTGGTAGAAAATTACAGGTAATTATCTTTGACG
GTAAAAACGCTGTAATCAGCGGGCTACATCAAAAATTACCCTAATTATGTCTGCATTTATGA
GAATGGCCAAATAAAGATGCCTTTTAGTATTAAAAGTGGTAGAAAATTACAGGTAATTATCT
TTGACGGTAAAAACGCTGTAATCAGCGGGCTACATCAAAAATTACCCTAATTATGTCTGCAT
TTATGAGAATGGCCAAATAAAGATGCCTTTTAGTATTAAAAGTGGTAGAAAATTACAGGTAA
TTATCTTTGACGGTAAAAACGCTGTAATCAGCGGGCTACATCAAAAATTACCCTAATTATGT
CTGCATTTATGAGAATGG (SEQ ID NO: 7)

hDLX I12b enhancer:
CAGCTGCAAACCCAAGAGGGTCAGCATCATTTCACTGTATTCTCTTCTTGATTACAAGCCG
GGCCCATCAAACACAACATAATTACAGTAATTTCAGGTTTATTTATTCTAATGCAGTTTCCCC
ATCTCTCTGGTAATTATGAGCAATTTTTTCGCCCAGGGAATCTTTTTGCATTAACAAAAGAG
ATAACGCACTGAAAGCCAAATTTGCTGTGCATTGAGAAAAGGAAAAAAAAAAAATCAAATAGG
TGCGAGCTGCCATCTCTGCAATTCTCTGGTACCGGAGCCGGCAAATTGCTTGCAGGTGTAT
GGAGCAAGCTTGTCAATGGCCAGGCCTCCAAATTAGCAAATGCACAGCAGCAAAGTAATG
AAGACAG (SEQ ID NO: 8)

NavSheP-D60N, codon optimized, with N-terminal 3x HA tag:
ATGGTTTACCCGTATGATGTCCCGGATTACGCTGGCAGCTACCCATACGATGTACCCGACT
ATGCCGGCAGTTATCCCTACGACGTCCCTGACTACGCATCTACGTCCCTTTTGAATGCGCC
TACCGGCCTTCAAGCTAGAGTCATTAATCTCGTCGAACAAAACTGGTTTGGACACTTTATAC
TGACTCTCATACTCATTAATGCTGTGCAGCTTGGAATGGAAACTAGCGCCAGCCTCATGGC
ACAATATGGCGCGCTGCTTATGTCCTTGAATAAGGTCCTTCTCTCTGTGTTCGTGGTCGAA
CTGCTGCTCCGGATTTATGCGTATCGGGGCAAGTTTTTTAAGGACCCGTGGAATGTGTTTG
ACTTCACTGTTATTGTTATTGCTCTGATTCCTGCATCTGGCCCATTGGCTGTCCTCCGCTCC
CTCCGAGTTCTCCGCGTCTTGAGGGTTCTGACGATTGTCCCCAGCATGAAAAGAGTAGTGT
CAGCACTGCTTGGGAGCTTGCCCGGGTTGGCCTCCATTGCAACCGTGCTTCTGTTGATCT
ATTACGTTTTCGCTGTGATCGCCACTAAAATTTTCGGGGATGCTTTTCCGGAATGGTTCGG
GACGATAGCGGACTCCTTCTATACCCTTTTTCAAATTATGACCTTGGAAAGTTGGTCTATGG
GGATCTCTAGGCCAGTGATGGAGGTGTACCCTTACGCTTGGGTATTCTTTGTGCCCTTTAT
TCTTGTTGCTACTTTTACCATGCTTAACCTTTTCATCGCCATCATAGTGAATACTATGCAGAC
ATTCTCTGACGAGGAACATGCTCTGGAGCGAGAGCAAGATAAACAGATCTTGGAACAGGA
GCAGAGACAAATGCACGAGGAACTGAAGGCCATTCGACTCGAGCTTCAGCAACTCCAAAC
CCTTTTGCGAAATGCGGCTGGGGACTCCTCCAATGTCTCCACAAAGGGCAATATCGGCTC
AGACTAA (SEQ ID NO: 9)

NavSheP endogenous sequence:
ATGAGTACATCTTTACTTAACGCGCCAACGGGTTTGCAGGCACGAGTGATTAACTTGGTTG
AGCAAAACTGGTTTGGTCATTTTATTTTGACATTGATTTTAATCAACGCGGTGCAGTTAGGT
ATGGAGACCTCAGCCAGCCTGATGGCGCAATACGGTGCTTTGTTGATGAGTCTTGATAAG
GTGCTGCTGAGTGTATTTGTGGTGGAGTTATTGCTGCGGATTTATGCCTACAGGGGGAAAT
TTTTTAAAGACCCTTGGAACGTGTTCGATTTTACCGTGATAGTGATAGCACTGATCCCTGCA
TCTGGGCCATTGGCTGTCCTGCGTTCGCTCAGGGTATTGCGGGTGCTGAGAGTGTTAACA
ATTGTGCCATCAATGAAACGGGTGGTGTCTGCGCTGTTGGGATCACTTCCTGGATTGGCAT
CGATCGCCACAGTATTACTGCTGATTTATTATGTGTTTGCGGTGATCGCTACCAAAATTTTT
GGCGATGCATTCCCTGAATGGTTTGGCACTATTGCTGACTCATTTTATACCCTATTTCAAAT
AATGACGCTTGAAAGCTGGTCTATGGGAATTTCGCGGCCAGTGATGGAAGTCTACCCTTAT
GCTTGGGTATTTTTCGTACCATTTATTCTGGTAGCGACTTTCACAATGCTAAATTTGTTTATT

FIG. 11, cont'd

GCGATTATCGTCAATACCATGCAAACCTTCAGCGACGAAGAGCATGCATTAGAGCGTGAGC
AAGACAAACAAATCTTAGAGCAGGAACAAAGACAAATGCACGAGGAGTTGAAAGCCATCAG
ACTCGAGCTACAACAATTACAAACCTTGCTGCGCAATGCTGCTGGTGATTCTTCTAATGTGT
CGACAAAGGGAAACATTGGTTCTGACTAA (SEQ ID NO: 10)

NavBp, endogenous sequence:
ATGGAAAACAATCCAGCCGAACAACAAGTTCCACCATTAGTAGCCTTAGCTCAGCGTATCG
TCTTTCATAAGGCCTTTACCCCAACTATTATTACCTTGATTATCATTAATGCCATTATTGTAG
GCCTTGAAACATATCCTACTGTTTATCAAGGTTATAATGATTGGTTCTACGCAGCAGATTTA
GCCTTACTTTGGATTTTTACAATTGAGATTACACTGCGTTTTATCGCAGCGAGACCGACTAA
ATCTTTTTTTTAAAAGCAGCTGGAACTGGTTTGATTTATTAATCGTTCTTGCCGGTCATGTCTT
TGCCGGTGCTCATTTTGTAACGGTTCTTCGTATCCTGCGCGTTCTTCGCGTATTACGTGCC
ATTTCTGTCATTCCTTCTCTGCGTCGTTTAGTCGATGCTTTGCTGATGACCATCCCGGCTTT
AGGAAACATTATGATCCTGATGGGAATTATTTTCTATATTTTCGCTGTGATTGGAACGATGT
TATTTGCTTCTGTAGCACCTGAGTACTTTGGTAACTTACAGCTTTCTTTATTAACATTATTCC
AAGTTGTTACACTTGAATCTTGGGCAAGCGGTGTCATGAGGCCGATTTTTGCAGAGGTTTG
GTGGTCTTGGATTTATTTTGTCATCTTTATTTTAGTAGGGACATTTATTGTCTTTAACTTATTT
ATCGGTGTTATCGTTAATAACGTTGAAAAAGCAAACGAAGAAGAACTCAAATCAGAATTAGA
TGATAAAGAGGCAGATACAAAAGAAGAGCTTGCTTCTCTGCGTAATGAAGTAGCAGAGATG
AAAGACCTCATTAAACAAATGCATAAACAGCAAACAAAAAAAGGGTAA (SEQ ID NO: 11)

NavBp, codon optimized, with N-terminal 3x HA tag:
ATGGTTTACCCGTATGATGTCCCGGATTACGCTGGCAGCTACCCATACGATGTACCCGACT
ATGCCGGCAGTTATCCCTACGACGTCCCTGACTACGCAGAAAACAACCCAGCCGAACAGC
AAGTCCCACCCCTCGTGGCGCTCGCCCAACGCATAGTATTTCACAAGGCGTTTACGCCGA
CGATAATCACCCTCATCATTATTAATGCGATCATTGTGGGACTCGAGACATACCCAACGGTT
TACCAGGGTTACAATGATTGGTTCTATGCTGCCGACCTTGCTTTGTTGTGGATATTCACTAT
TGAAATCACGCTCCGATTCATCGCCGCCCGACCGACGAAGAGTTTCTTCAAGTCTAGCTGG
AACTGGTTTGATCTGCTTATCGTATTGGCGGGCCACGTCTTCGCTGGCGCCCATTTTGTTA
CGGTGCTTAGGATCCTCCGCGTCCTGAGGGTCCTCAGAGCTATCTCAGTCATACCCAGTC
TCCGGCGGCTGGTTGACGCACTTTTGATGACAATCCCAGCACTCGGTAACATCATGATACT
GATGGGGATTATTTTTTACATATTCGCGGTTATCGGGACGATGCTCTTTGCATCAGTAGCG
CCAGAATACTTTGGCAATTTGCAGCTGTCTCTGCTTACACTGTTCCAAGTGGTTACGCTGG
AAAGTTGGGCTAGTGGGGTTATGCGACCTATTTTTGCCGAAGTCTGGTGGTCTTGGATCTA
TTTTGTAATCTTTATTCTCGTGGGAACTTTCATAGTATTTAACCTTTTCATTGGCGTCATCGT
GAACAATGTGGAAAAAGCTAACGAAGAGGAACTGAAAAGCGAACTGGATGATAAAGAGGC
TGATACAAAAGAAGAACTGGCATCATTGCGAAACGAGGTGGCAGAAATGAAGGATCTCATA
AAACAGATGCATAAACAGCAAACAAAAAAGGGTTAA (SEQ ID NO: 12)

NavMs, endogenous sequence:
ATGTCACGCAAAATAAGAGATTTAATCGAATCCAAACGCTTTCAAAACGTCATCACCGCCAT
TATTGTGCTCAATGGCGCTGTGCTGGGTCTGCTGACCGATACAACCCTATCGGCCTCCAG
CCAAAACCTGCTGGAGCGTGTGGATCAACTTTGTCTGACTATCTTTATTGTTGAAATATCCC
TGAAAATATACGCCTATGGCGTGCGAGGCTTTTTCCGCAGCGGCTGGAATCTGTTTGATTT
TGTGATTGTGGCCATCGCGCTTATGCCCGCCCAGGGTAGCCTATCGGTGCTGCGAACCTT
CCGTATATTCCGCGTCATGCGGCTCGTATCGGTCATACCAACCATGCGAAGAGTGGTGCA
AGGCATGCTCTTGGCACTGCCCGGCGTGGGATCGGTAGCGGCACTGTTGACGGTGGTCT
TCTATATTGCGGCTGTCATGGCCACCAATCTCTACGGGGCAACCTTCCCTGAATGGTTTGG
TGATCTTAGCAAGAGCCTGTACACACTATTTCAGGTGATGACCTTAGAGTCATGGTCTATG

FIG. 11, cont'd

GGCATTGTGCGTCCAGTGATGAACGTTCATCCCAACGCATGGGTTTTTTTCATCCCCTTCA
TCATGCTCACCACCTTTACCGTGCTCAACCTGTTTATTGGCATTATTGTAGATGCCATGGCC
ATCACCAAGGAACAGGAGGAAGAGGCCAAAACCGGCCACCACCAAGAGCCTATTAGCCAA
ACATTGCTCCATCTGGGAGATCGCCTAGATAGGATCGAAAAGCAGCTTGCGCAAAACAAC
GAGCTCTTACAACGACAACAGCCGCAAAAAAAATAG (SEQ ID NO: 13)

NavMs, codon optimized, with N-terminal 3x HA tag and linker:
ATGGTTTATCCGTATGATGTTCCTGACTATGCAGGATCCTATCCTTATGATGTTCCCGATTA
CGCTGGTTCTTACCCTTACGATGTTCCCGATTATGCCAGTTCTGGATTGGTGCCACGAGGC
AGCCACATGAGCCGGAAGATCAGAGATCTTATCGAATCTAAGAGATTTCAGAATGTTATTAC
CGCGATAATCGTACTCAACGGGGCGGTGCTCGGTCTCCTCACCGATACCACATTGAGCGC
TTCTAGCCAGAACCTGCTCGAAAGGGTTGACCAACTGTGCCTGACAATTTTTATCGTGGAA
ATTAGCTTGAAAATTTACGCCTACGGCGTTCGCGGTTTTTTCCGGAGCGGTTGGAATCTTTT
TGACTTCGTTATCGTTGCCATCGCGCTCATGCCCGCACAGGGTTCTTTGTCTGTGTTGAGG
ACATTCCGAATATTTCGCGTGATGCGCTTGGTATCCGTGATCCCTACGATGCGCCGCGTCG
TACAAGGAATGTTGCTGGCTCTCCCCGGCGTCGGGAGCGTTGCTGCCCTCCTTACCGTGG
TATTTTACATAGCGGCGGTTATGGCTACTAATCTTTACGGAGCTACCTTCCCGGAGTGGTT
CGGGGATTTGTCCAAGAGCCTCTATACATTGTTTCAAGTTATGACCCTGGAGTCCTGGTCT
ATGGGCATTGTCCGGCCCGTAATGAACGTACACCCAAATGCGTGGGTGTTTTTCATTCCAT
TCATCATGCTGACTACCTTTACCGTGCTGAACTTGTTCATTGGGATTATCGTGGATGCGATG
GCCATCACTAAGGAGCAAGAAGAAGAGGCTAAAACTGGCCACCACCAAGAGCCAATTTCT
CAAACCCTCTTGCATCTCGGGGACCGACTGGACCGCATTGAGAAGCAACTCGCGCAGAAC
AATGAGCTGTTGCAGCGACAGCAACCTCAAAAAAAATAA (SEQ ID NO: 14)

NavMs, codon optimized, with N-terminal His tag and linker:
ATGGGCAGCAGCCATCATCATCATCATCACAGCAGCGGCCTGGTGCCGCGCGGCAGCCA
TATGTCACGCAAAATCCGCGATTTAATCGAATCCAAACGCTTTCAAAACGTCATCACCGCCA
TTATTGTGCTCAATGGCGCTGTGCTGGGTCTGCTGACCGATACAACCCTGTCGGCCTCCA
GCCAAAACCTGCTGGAGCGTGTGGATCAACTTTGTCTGACTATCTTTATTGTTGAAATCTCC
CTGAAAATCTACGCCTATGGCGTGCGCGGCTTTTTCCGCAGCGGCTGGAATCTGTTTGATT
TTGTGATTGTGGCCATCGCGCTTATGCCGGCCCAGGGTAGCCTGTCGGTGCTGCGTACCT
TCCGTATCTTCCGCGTCATGCGCCTCGTATCGGTCATCCCAACCATGCGCCGTGTGGTGC
AAGGCATGCTCTTGGCACTGCCGGGCGTGGGCTCGGTAGCGGCACTGTTGACGGTGGTC
TTCTATATTGCGGCTGTCATGGCCACCAATCTCTACGGGGCAACCTTCCCTGAATGGTTTG
GTGATCTTAGCAAGAGCCTGTACACACTGTTTCAGGTGATGACCTTAGAGTCATGGTCTAT
GGGCATTGTGCGTCCAGTGATGAACGTTCATCCGAACGCATGGGTTTTTTTCATCCCGTTC
ATCATGCTCACCACCTTTACCGTGCTCAACCTGTTTATTGGCATTATTGTAGATGCAATGGC
AATCACCAAGGAACAGGAGGAAGAGGCCAAAACCGGTCACCATCAAGAACCTATTTCTCAA
ACTCTTCTTCATCTTGGTGATCGTCTTGATCGTATTGAAAAACAACTTGCTCAAAATAATGAA
CTTCTTCAACGTCAACAACCTCAAAAAAAATAA (SEQ ID NO: 15)

Human SCN1A:
ATGGAGCAAACAGTGCTTGTACCACCAGGACCTGACAGCTTCAACTTCTTCACCAGAGAAT
CTCTTGCGGCTATTGAAAGACGCATTGCAGAAGAAAAGGCAAAGAATCCCAAACCAGACAA
AAAAGATGACGACGAAAATGGCCCAAAGCCAAATAGTGACTTGGAAGCTGGAAAGAACCTT
CCATTTATTTATGGAGACATTCCTCCAGAGATGGTGTCAGAGCCCCTGGAGGACCTGGACC
CCTACTATATCAATAAGAAAACTTTTATAGTATTGAATAAAGGGAAGGCCATCTTCCGGTTC
AGTGCCACCTCTGCCCTGTACATTTTAACTCCCTTCAATCCTCTTAGGAAAATAGCTATTAA
GATTTTGGTACATTCATTATTCAGCATGCTAATTATGTGCACTATTTTGACAAACTGTGTGTT

FIG. 11, cont'd

TATGACAATGAGTAACCCTCCTGATTGGACAAAGAATGTAGAATACACCTTCACAGGAATAT
ATACTTTTGAATCACTTATAAAAATTATTGCAAGGGGATTCTGTTTAGAAGATTTTACTTTCC
TTCGGGATCCATGGAACTGGCTCGATTTCACTGTCATTACATTTGCGTACGTCACAGAGTTT
GTGGACCTGGGCAATGTCTCGGCATTGAGAACATTCAGAGTTCTCCGAGCATTGAAGACG
ATTTCAGTCATTCCAGGCCTGAAAACCATTGTGGGAGCCCTGATCCAGTCTGTGAAGAAGC
TCTCAGATGTAATGATCCTGACTGTGTTCTGTCTGAGCGTATTTGCTCTAATTGGGCTGCAG
CTGTTCATGGGCAACCTGAGGAATAAATGTATACAATGGCCTCCCACCAATGCTTCCTTGG
AGGAACATAGTATAGAAAAGAATATAACTGTGAATTATAATGGTACACTTATAAATGAAACT
GTCTTTGAGTTTGACTGGAAGTCATATATTCAAGATTCAAGATATCATTATTTCCTGGAGGG
TTTTTTAGATGCACTACTATGTGGAAATAGCTCTGATGCAGGCCAATGTCCAGAGGGATATA
TGTGTGTGAAAGCTGGTAGAAATCCCAATTATGGCTACACAAGCTTTGATACCTTCAGTTG
GGCTTTTTTGTCCTTGTTTCGACTAATGACTCAGGACTTCTGGGAAAATCTTTATCAACTGA
CATTACGTGCTGCTGGGAAAACGTACATGATATTTTTTGTATTGGTCATTTTCTTGGGCTCA
TTCTACCTAATAAATTTGATCCTGGCTGTGGTGGCCATGGCCTACGAGGAACAGAATCAGG
CCACCTTGGAAGAAGCAGAACAGAAAGAGGCCGAATTTCAGCAGATGATTGAACAGCTTAA
AAAGCAACAGGAGGCAGCTCAGCAGGCAGCAACGGCAACTGCCTCAGAACATTCCAGAGA
GCCCAGTGCAGCAGGCAGGCTCTCAGACAGCTCATCTGAAGCCTCTAAGTTGAGTTCCAA
GAGTGCTAAGGAAAGAAGAAATCGGAGGAAGAAAAGAAAACAGAAAGAGCAGTCTGGTGG
GGAAGAGAAAGATGAGGATGAATTCCAAAAATCTGAATCTGAGGACAGCATCAGGAGGAA
AGGTTTTCGCTTCTCCATTGAAGGGAACCGATTGACATATGAAAAGAGGTACTCCTCCCCA
CACCAGTCTTTGTTGAGCATCCGTGGCTCCCTATTTTCACCAAGGCGAAATAGCAGAACAA
GCCTTTTCAGCTTTAGAGGGCGAGCAAAGGATGTGGGATCTGAGAACGACTTCGCAGATG
ATGAGCACAGCACCTTTGAGGATAACGAGAGCCGTAGAGATTCCTTGTTTGTGCCCCGAC
GACACGGAGAGAGACGCAACAGCAACCTGAGTCAGACCAGTAGGTCATCCCGGATGCTG
GCAGTGTTTCCAGCGAATGGGAAGATGCACAGCACTGTGGATTGCAATGGTGTGGTTTCC
TTGGTTGGTGGACCTTCAGTTCCTACATCGCCTGTTGGACAGCTTCTGCCAGAGGTGATAA
TAGATAAGCCAGCTACTGATGACAATGGAACAACCACTGAAACTGAAATGAGAAAGAGAAG
GTCAAGTTCTTTCCACGTTTCCATGGACTTTCTAGAAGATCCTTCCCAAAGGCAACGAGCA
ATGAGTATAGCCAGCATTCTAACAAATACAGTAGAAGAACTTGAAGAATCCAGGCAGAAAT
GCCCACCCTGTTGGTATAAATTTTCCAACATATTCTTAATCTGGGACTGTTCTCCATATTGG
TTAAAAGTGAAACATGTTGTCAACCTGGTTGTGATGGACCCATTTGTTGACCTGGCCATCA
CCATCTGTATTGTCTTAAATACTCTTTTCATGGCCATGGAGCACTATCCAATGACGGACCAT
TTCAATAATGTGCTTACAGTAGGAAACTTGGTTTTCACTGGGATCTTTACAGCAGAAATGTT
TCTGAAAATTATTGCCATGGATCCTTACTATTATTTCCAAGAAGGCTGGAATATCTTTGACG
GTTTTATTGTGACGCTTAGCCTGGTAGAACTTGGACTCGCCAATGTGGAAGGATTATCTGT
TCTCCGTTCATTTCGATTGCTGCGAGTTTTCAAGTTGGCAAAATCTTGGCCAACGTTAAATA
TGCTAATAAAGATCATCGGCAATTCCGTGGGGGCTCTGGGAAATTTAACCCTCGTCTTGGC
CATCATCGTCTTCATTTTTGCCGTGGTCGGCATGCAGCTCTTTGGTAAAAGCTACAAAGATT
GTGTCTGCAAGATCGCCAGTGATTGTCAACTCCCACGCTGGCACATGAATGACTTCTTCCA
CTCCTTCCTGATTGTGTTCCGCGTGCTGTGTGGGGAGTGGATAGAGACCATGTGGGACTG
TATGGAGGTTGCTGGTCAAGCCATGTGCCTTACTGTCTTCATGATGGTCATGGTGATTGGA
AACCTAGTGGTCCTGAATCTCTTTCTGGCCTTGCTTCTGAGCTCATTTAGTGCAGACAACCT
TGCAGCCACTGATGATGATAATGAAATGAATAATCTCCAAATTGCTGTGGATAGGATGCAC
AAAGGAGTAGCTTATGTGAAAAGAAAAATATATGAATTTATTCAACAGTCCTTCATTAGGAA
ACAAAAGATTTTAGATGAAATTAAACCACTTGATGATCTAAACAACAAGAAAGACAGTTGTA
TGTCCAATCATACAGCAGAAATTGGGAAAGATCTTGACTATCTTAAAGATGTAAATGGAACT
ACAAGTGGTATAGGAACTGGCAGCAGTGTTGAATACATTATTGATGAAAGTGATTACATGTC
ATTCATAAACAACCCCAGTCTTACTGTGACTGTACCAATTGCTGTAGGAGAATCTGACTTTG
AAAATTTAAACACGGAAGACTTTAGTAGTGAATCGGATCTGGAAGAAAGCAAAGAGAAACT

FIG. 11, cont'd

GAATGAAAGCAGTAGCTCATCAGAAGGTAGCACTGTGGACATCGGCGCACCTGTAGAAGA
ACAGCCCGTAGTGGAACCTGAAGAAACTCTTGAACCAGAAGCTTGTTTCACTGAAGGCTGT
GTACAAAGATTCAAGTGTTGTCAAATCAATGTGGAAGAAGGCAGAGGAAAACAATGGTGGA
ACCTGAGAAGGACGTGTTTCCGAATAGTTGAACATAACTGGTTTGAGACCTTCATTGTTTTC
ATGATTCTCCTTAGTAGTGGTGCTCTGGCATTTGAAGATATATATATTGATCAGCGAAAGAC
GATTAAGACGATGTTGGAATATGCTGACAAGGTTTTCACTTACATTTTCATTCTGGAAATGC
TTCTAAAATGGGTGGCATATGGCTATCAAACATATTTCACCAATGCCTGGTGTTGGCTGGA
CTTCTTAATTGTTGATGTTTCATTGGTCAGTTTAACAGCAAATGCCTTGGGTTACTCAGAAC
TTGGAGCCATCAAATCTCTCAGGACACTAAGAGCTCTGAGACCTCTAAGAGCCTTATCTCG
ATTTGAAGGGATGAGGGTGGTTGTGAATGCCCTTTTAGGAGCAATTCCATCCATCATGAAT
GTGCTTCTGGTTTGTCTTATATTCTGGCTAATTTTCAGCATCATGGGCGTAAATTTGTTTGCT
GGCAAATTCTACCACTGTATTAACACCACAACTGGTGACAGGTTTGACATCGAAGACGTGA
ATAATCATACTGATTGCCTAAAACTAATAGAAAGAAATGAGACTGCTCGATGGAAAAATGTG
AAAGTAAACTTTGATAATGTAGGATTTGGGTATCTCTCTTTGCTTCAAGTTGCCACATTCAAA
GGATGGATGGATATAATGTATGCAGCAGTTGATTCCAGAAATGTGGAACTCCAGCCTAAGT
ATGAAGAAAGTCTGTACATGTATCTTTACTTTGTTATTTTCATCATCTTTGGGTCCTTCTTCA
CCTTGAACCTGTTTATTGGTGTCATCATAGATAATTTCAACCAGCAGAAAAAGAAGTTTGGA
GGTCAAGACATCTTTATGACAGAAGAACAGAAGAAATACTATAATGCAATGAAAAAATTAGG
ATCGAAAAAACCGCAAAAGCCTATACCTCGACCAGGAAACAAATTTCAAGGAATGGTCTTT
GACTTCGTAACCAGACAAGTTTTTGACATAAGCATCATGATTCTCATCTGTCTTAACATGGT
CACAATGATGGTGGAAACAGATGACCAGAGTGAATATGTGACTACCATTTTGTCACGCATC
AATCTGGTGTTCATTGTGCTATTTACTGGAGAGTGTGTACTGAAACTCATCTCTCTACGCCA
TTATTATTTTACCATTGGATGGAATATTTTTGATTTTGTGGTTGTCATTCTCTCCATTGTAGG
TATGTTTCTTGCCGAGCTGATAGAAAAGTATTTCGTGTCCCCTACCCTGTTCCGAGTGATCC
GTCTTGCTAGGATTGGCCGAATCCTACGTCTGATCAAAGGAGCAAAGGGGATCCGCACGC
TGCTCTTTGCTTTGATGATGTCCCTTCCTGCGTTGTTTAACATCGGCCTCCTACTCTTCCTA
GTCATGTTCATCTACGCCATCTTTGGGATGTCCAACTTTGCCTATGTTAAGAGGGAAGTTG
GGATCGATGACATGTTCAACTTTGAGACCTTTGGCAACAGCATGATCTGCCTATTCCAAATT
ACAACCTCTGCTGGCTGGGATGGATTGCTAGCACCCATTCTCAACAGTAAGCCACCCGACT
GTGACCCTAATAAAGTTAACCCTGGAAGCTCAGTTAAGGGAGACTGTGGGAACCCATCTGT
TGGAATTTTCTTTTTTGTCAGTTACATCATCATATCCTTCCTGGTTGTGGTGAACATGTACAT
CGCGGTCATCCTGGAGAACTTCAGTGTTGCTACTGAAGAAAGTGCAGAGCCTCTGAGTGA
GGATGACTTTGAGATGTTCTATGAGGTTTGGGAGAAGTTTGATCCCGATGCAACTCAGTTC
ATGGAATTTGAAAAATTATCTCAGTTTGCAGCTGCGCTTGAACCGCCTCTCAATCTGCCACA
ACCAAACAAACTCCAGCTCATTGCCATGGATTTGCCCATGGTGAGTGGTGACCGGATCCAC
TGTCTTGATATCTTATTTGCTTTTACAAAGCGGGTTCTAGGAGAGAGTGGAGAGATGGATG
CTCTACGAATACAGATGGAAGAGCGATTCATGGCTTCCAATCCTTCCAAGGTCTCCTATCA
GCCAATCACTACTACTTTAAAACGAAAACAAGAGGAAGTATCTGCTGTCATTATTCAGCGTG
CTTACAGACGCCACCTTTTAAAGCGAACTGTAAAACAAGCTTCCTTTACGTACAATAAAAAC
AAAATCAAAGGTGGGGCTAATCTTCTTATAAAAGAAGACATGATAATTGACAGAATAAATGA
AAACTCTATTACAGAAAAAACTGATCTGACCATGTCCACTGCAGCTTGTCCACCTTCCTATG
ACCGGGTGACAAAGCCAATTGTGGAAAAACATGAGCAAGAAGGCAAAGATGAAAAAGCCA
AAGGGA (SEQ ID NO: 16)

FIG. 11, cont'd

SYFP2:
ATGGTCAGCAAGGGCGAGGAGCTGTTCACCGGGGTGGTGCCCATCCTGGTCGAGCTGGA
CGGCGACGTCAATGGCCACAAGTTCAGCGTGTCCGGCGAGGGCGAGGGCGATGCCACCT
ACGGCAAGCTGACCCTGAAGCTGATCTGCACCACCGGCAAGCTGCCCGTGCCCTGGCCC
ACCCTCGTGACCACCCTGGGCTACGGCGTGCAGTGCTTCGCCCGCTACCCCGACCACAT
GAAGCAGCACGACTTCTTCAAGTCCGCCATGCCCGAAGGCTACGTCCAGGAGCGCACCAT
CTTCTTCAAAGACGACGGCAACTACAAGACCCGCGCCGAGGTGAAGTTCGAGGGCGACAC
CCTGGTGAACCGCATCGAGCTGAAGGGCATCGACTTCAAGGAGGACGGCAACATCCTGG
GGCACAAGCTGGAGTACAACTACAACAGCCACAACGTCTATATCACCGCCGACAAGCAGA
AGAACGGCATCAAGGCCAACTTCAAGATCCGCCACAACATCGAGGACGGCGGCGTGCAG
CTCGCCGACCACTACCAGCAGAACACCCCCATCGGCGACGGCCCCGTGCTGCTGCCCGA
CAACCACTACCTGAGCTACCAGTCCAAGCTGAGCAAAGACCCCAACGAGAAGCGCGATCA
CATGGTCCTGCTGGAGTTCGTGACCGCCGCCGGGATCACTCTCGGCATGGACGAGCTGTA
CAAA (SEQ ID NO: 17)

P2A Encoding Sequence:
GGCAGCGGCGCCACCAACTTCAGCCTGCTGAAGCAGGCCGGCGACGTGGAGGAGAACCC
CGGCCCCGGAGCTAGCGGA (SEQ ID NO: 18)

WPRE3:
ATAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTATGTTGCTC
CTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTATG
GCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTAGTTCTTGCCACGGCGGAACTCATCGC
CGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGG
(SEQ ID NO: 19)

BGHpA:
CGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGAC
CCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGT
CTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGA
TTGGGAAGACAATAGCAGGCATG (SEQ ID NO: 20)

N-terminal 3XHA tag (Protein):
MVYPYDVPDYAGSYPYDVPDYAGSYPYDVPDYA (SEQ ID NO: 21)

N-terminal 3XHA tag (DNA):
ATGGTTTACCCGTATGATGTCCCGGATTACGCTGGCAGCTACCCATACGATGTACCCGACT
ATGCCGGCAGTTATCCCTACGACGTCCCTGACTACGCA (SEQ ID NO: 22)

hSCN1A N-term of two-part expression system:
ATGGAGCAAACAGTGCTTGTACCACCAGGACCTGACAGCTTCAACTTCTTCACCAGAGAAT
CTCTTGCGGCTATTGAAAGACGCATTGCAGAAGAAAAGGCAAAGAATCCCAAACCAGACAA
AAAAGATGACGACGAAAATGGCCCAAAGCCAAATAGTGACTTGGAAGCTGGAAAGAACCTT
CCATTTATTTATGGAGACATTCCTCCAGAGATGGTGTCAGAGCCCCTGGAGGACCTGGACC
CCTACTATATCAATAAGAAAACTTTTATAGTATTGAATAAAGGGAAGGCCATCTTCCGGTTC
AGTGCCACCTCTGCCCTGTACATTTTAACTCCCTTCAATCCTCTTAGGAAAATAGCTATTAA
GATTTTGGTACATTCATTATTCAGCATGCTAATTATGTGCACTATTTTGACAAACTGTGTGTT
TATGACAATGAGTAACCCTCCTGATTGGACAAAGAATGTAGAATACACCTTCACAGGAATAT
ATACTTTTGAATCACTTATAAAAATTATTGCAAGGGGATTCTGTTTAGAAGATTTTACTTTCC

FIG. 11, cont'd

TTCGGGATCCATGGAACTGGCTCGATTTCACTGTCATTACATTTGCGTACGTCACAGAGTTT
GTGGACCTGGGCAATGTCTCGGCATTGAGAACATTCAGAGTTCTCCGAGCATTGAAGACG
ATTTCAGTCATTCCAGGCCTGAAAACCATTGTGGGAGCCCTGATCCAGTCTGTGAAGAAGC
TCTCAGATGTAATGATCCTGACTGTGTTCTGTCTGAGCGTATTTGCTCTAATTGGGCTGCAG
CTGTTCATGGGCAACCTGAGGAATAAATGTATACAATGGCCTCCCACCAATGCTTCCTTGG
AGGAACATAGTATAGAAAAGAATATAACTGTGAATTATAATGGTACACTTATAAATGAAACT
GTCTTTGAGTTTGACTGGAAGTCATATATTCAAGATTCAAGATATCATTATTTCCTGGAGGG
TTTTTTAGATGCACTACTATGTGGAAATAGCTCTGATGCAGGCCAATGTCCAGAGGGATATA
TGTGTGTGAAAGCTGGTAGAAATCCCAATTATGGCTACACAAGCTTTGATACCTTCAGTTG
GGCTTTTTTGTCCTTGTTTCGACTAATGACTCAGGACTTCTGGGAAAATCTTTATCAACTGA
CATTACGTGCTGCTGGGAAAACGTACATGATATTTTTTGTATTGGTCATTTTCTTGGGCTCA
TTCTACCTAATAAATTTGATCCTGGCTGTGGTGGCCATGGCCTACGAGGAACAGAATCAGG
CCACCTTGGAAGAAGCAGAACAGAAAGAGGCCGAATTTCAGCAGATGATTGAACAGCTTAA
AAAGCAACAGGAGGCAGCTCAGCAGGCAGCAACGGCAACTGCCTCAGAACATTCCAGAGA
GCCCAGTGCAGCAGGCAGGCTCTCAGACAGCTCATCTGAAGCCTCTAAGTTGAGTTCCAA
GAGTGCTAAGGAAAGAAGAAATCGGAGGAAGAAAAGAAAACAGAAAGAGCAGTCTGGTGG
GGAAGAGAAAGATGAGGATGAATTCCAAAAATCTGAATCTGAGGACAGCATCAGGAGGAA
AGGTTTTCGCTTCTCCATTGAAGGGAACCGATTGACATATGAAAAGAGGTACTCCTCCCCA
CACCAGTCTTTGTTGAGCATCCGTGGCTCCCTATTTTCACCAAGGCGAAATAGCAGAACAA
GCCTTTTCAGCTTTAGAGGGCGAGCAAAGGATGTGGGATCTGAGAACGACTTCGCAGATG
ATGAGCACAGCACCTTTGAGGATAACGAGAGCCGTAGAGATTCCTTGTTTGTGCCCCGAC
GACACGGAGAGAGACGCAACAGCAACCTGAGTCAGACCAGTAGGTCATCCCGGATGCTG
GCAGTGTTTCCAGCGAATGGGAAGATGCACAGCACTGTGGATTGCAATGGTGTGGTTTCC
TTGGTTGGTGGACCTTCAGTTCCTACATCGCCTGTTGGACAGCTTCTGCCAGAGGTGATAA
TAGATAAGCCAGCTACTGATGACAATGGAACAACCACTGAAACTGAAATGAGAAAGAGAAG
GTCAAGTTCTTTCCACGTTTCCATGGACTTTCTAGAAGATCCTTCCCAAAGGCAACGAGCA
ATGAGTATAGCCAGCATTCTAACAAATACAGTAGAAGAACTTGAAGAATCCAGGCAGAAAT
GCCCACCCTGTTGGTATAAATTTTCCAACATATTCTTAATCTGGGACTGTTCTCCATATTGG
TTAAAAGTGAAACATGTTGTCAACCTGGTTGTGATGGACCCATTTGTTGACCTGGCCATCA
CCATCTGTATTGTCTTAAATACTCTTTTCATGGCCATGGAGCACTATCCAATGACGGACCAT
TTCAATAATGTGCTTACAGTAGGAAACTTGGTTTTCACTGGGATCTTTACAGCAGAAATGTT
TCTGAAAATTATTGCCATGGATCCTTACTATTATTTCCAAGAAGGCTGGAATATCTTTGACG
GTTTTATTGTGACGCTTAGCCTGGTAGAACTTGGACTCGCCAATGTGGAAGGATTATCTGT
TCTCCGTTCATTTCGATTGCTGCGAGTTTTCAAGTTGGCAAAATCTTGGCCAACGTTAAATA
TGCTAATAAAGATCATCGGCAATTCCGTGGGGGCTCTGGGAAATTTAACCCTCGTCTTGGC
CATCATCGTCTTCATTTTTGCCGTGGTCGGCATGCAGCTCTTTGGTAAAAGCTACAAAGATT
GTGTCTGCAAGATCGCCAGTGATTGTCAACTCCCACGCTGGCACATGAATGACTTCTTCCA
CTCCTTCCTGATTGTGTTCCGCGTGCTGTGTGGGGAGTGGATAGAGACCATGTGGGACTG
TATGGAGGTTGCTGGTCAAGCCATGTGCCTTACTGTCTTCATGATGGTCATGGTGATTGGA
AACCTAGTGGTCCTGAATCTCTTTCTGGCCTTGCTTCTGAGCTCATTTAGTGCAGACAACCT
TGCAGCCACTGATGATGATAATGAAATGAATAATCTCCAAATTGCTGTGGATAGGATGCAC
AAAGGAGTAGCTTATGTGAAAAGAAAAATATATGAATTTATTCAACAGTCCTTCATTAGGAA
ACAAAAGATTT (SEQ ID NO: 23)

hSCN1A C-term of two-part expression system with c-terminal 3XHA sequence:
CTGGTAGAACTTGGACTCGCCAATGTGGAAGGATTATCTGTTCTCCGTTCATTTCGATTGCT
GCGAGTTTTCAAGTTGGCAAAATCTTGGCCAACGTTAAATATGCTAATAAAGATCATCGGCA
ATTCCGTGGGGGCTCTGGGAAATTTAACCCTCGTCTTGGCCATCATCGTCTTCATTTTTGC
CGTGGTCGGCATGCAGCTCTTTGGTAAAAGCTACAAAGATTGTGTCTGCAAGATCGCCAGT

FIG. 11, cont'd

GATTGTCAACTCCCACGCTGGCACATGAATGACTTCTTCCACTCCTTCCTGATTGTGTTCC
GCGTGCTGTGTGGGGAGTGGATAGAGACCATGTGGGACTGTATGGAGGTTGCTGGTCAA
GCCATGTGCCTTACTGTCTTCATGATGGTCATGGTGATTGGAAACCTAGTGGTCCTGAATC
TCTTTCTGGCCTTGCTTCTGAGCTCATTTAGTGCAGACAACCTTGCAGCCACTGATGATGAT
AATGAAATGAATAATCTCCAAATTGCTGTGGATAGGATGCACAAAGGAGTAGCTTATGTGAA
AAGAAAAATATATGAATTTATTCAACAGTCCTTCATTAGGAAACAAAAGATTTTAGATGAAAT
TAAACCACTTGATGATCTAAACAACAAGAAAGACAGTTGTATGTCCAATCATACAGCAGAAA
TTGGGAAAGATCTTGACTATCTTAAAGATGTAAATGGAACTACAAGTGGTATAGGAACTGG
CAGCAGTGTTGAATACATTATTGATGAAAGTGATTACATGTCATTCATAAACAACCCCAGTC
TTACTGTGACTGTACCAATTGCTGTAGGAGAATCTGACTTTGAAAATTTAAACACGGAAGAC
TTTAGTAGTGAATCGGATCTGGAAGAAAGCAAAGAGAAACTGAATGAAAGCAGTAGCTCAT
CAGAAGGTAGCACTGTGGACATCGGCGCACCTGTAGAAGAACAGCCCGTAGTGGAACCTG
AAGAAACTCTTGAACCAGAAGCTTGTTTCACTGAAGGCTGTGTACAAAGATTCAAGTGTTGT
CAAATCAATGTGGAAGAAGGCAGAGGAAAACAATGGTGGAACCTGAGAAGGACGTGTTTC
CGAATAGTTGAACATAACTGGTTTGAGACCTTCATTGTTTTCATGATTCTCCTTAGTAGTGG
TGCTCTGGCATTTGAAGATATATATATTGATCAGCGAAAGACGATTAAGACGATGTTGGAAT
ATGCTGACAAGGTTTTCACTTACATTTTCATTCTGGAAATGCTTCTAAAATGGGTGGCATAT
GGCTATCAAACATATTTCACCAATGCCTGGTGTTGGCTGGACTTCTTAATTGTTGATGTTTC
ATTGGTCAGTTTAACAGCAAATGCCTTGGGTTACTCAGAACTTGGAGCCATCAAATCTCTCA
GGACACTAAGAGCTCTGAGACCTCTAAGAGCCTTATCTCGATTTGAAGGGATGAGGGTGG
TTGTGAATGCCCTTTTAGGAGCAATTCCATCCATCATGAATGTGCTTCTGGTTTGTCTTATA
TTCTGGCTAATTTTCAGCATCATGGGCGTAAATTTGTTTGCTGGCAAATTCTACCACTGTAT
TAACACCACAACTGGTGACAGGTTTGACATCGAAGACGTGAATAATCATACTGATTGCCTA
AAACTAATAGAAAGAAATGAGACTGCTCGATGGAAAAATGTGAAAGTAAACTTTGATAATGT
AGGATTTGGGTATCTCTCTTTGCTTCAAGTTGCCACATTCAAAGGATGGATGGATATAATGT
ATGCAGCAGTTGATTCCAGAAATGTGGAACTCCAGCCTAAGTATGAAGAAAGTCTGTACAT
GTATCTTTACTTTGTTATTTTCATCATCTTTGGGTCCTTCTTCACCTTGAACCTGTTTATTGG
TGTCATCATAGATAATTTCAACCAGCAGAAAAAGAAGTTTGGAGGTCAAGACATCTTTATGA
CAGAAGAACAGAAGAAATACTATAATGCAATGAAAAAATTAGGATCGAAAAAACCGCAAAA
GCCTATACCTCGACCAGGAAACAAATTTCAAGGAATGGTCTTTGACTTCGTAACCAGACAA
GTTTTTGACATAAGCATCATGATTCTCATCTGTCTTAACATGGTCACAATGATGGTGGAAAC
AGATGACCAGAGTGAATATGTGACTACCATTTTGTCACGCATCAATCTGGTGTTCATTGTGC
TATTTACTGGAGAGTGTGTACTGAAACTCATCTCTCTACGCCATTATTATTTTACCATTGGAT
GGAATATTTTTGATTTTGTGGTTGTCATTCTCTCCATTGTAGGTATGTTTCTTGCCGAGCTG
ATAGAAAAGTATTTCGTGTCCCCTACCCTGTTCCGAGTGATCCGTCTTGCTAGGATTGGCC
GAATCCTACGTCTGATCAAAGGAGCAAAGGGGATCCGCACGCTGCTCTTTGCTTTGATGAT
GTCCCTTCCTGCGTTGTTTAACATCGGCCTCCTACTCTTCCTAGTCATGTTCATCTACGCCA
TCTTTGGGATGTCCAACTTTGCCTATGTTAAGAGGGAAGTTGGGATCGATGACATGTTCAA
CTTTGAGACCTTTGGCAACAGCATGATCTGCCTATTCCAAATTACAACCTCTGCTGGCTGG
GATGGATTGCTAGCACCCATTCTCAACAGTAAGCCACCCGACTGTGACCCTAATAAAGTTA
ACCCTGGAAGCTCAGTTAAGGGAGACTGTGGGAACCCATCTGTTGGAATTTTCTTTTTTGT
CAGTTACATCATCATATCCTTCCTGGTTGTGGTGAACATGTACATCGCGGTCATCCTGGAG
AACTTCAGTGTTGCTACTGAAGAAAGTGCAGAGCCTCTGAGTGAGGATGACTTTGAGATGT
TCTATGAGGTTTGGGAGAAGTTTGATCCCGATGCAACTCAGTTCATGGAATTTGAAAAATTA
TCTCAGTTTGCAGCTGCGCTTGAACCGCCTCTCAATCTGCCACAACCAAACAAACTCCAGC
TCATTGCCATGGATTTGCCCATGGTGAGTGGTGACCGGATCCACTGTCTTGATATCTTATTT
GCTTTTACAAAGCGGGTTCTAGGAGAGAGTGGAGAGATGGATGCTCTACGAATACAGATG
GAAGAGCGATTCATGGCTTCCAATCCTTCCAAGGTCTCCTATCAGCCAATCACTACTACTTT
AAAACGAAAACAAGAGGAAGTATCTGCTGTCATTATTCAGCGTGCTTACAGACGCCACCTT

FIG. 11, cont'd

TTAAAGCGAACTGTAAAACAAGCTTCCTTTACGTACAATAAAAACAAAATCAAAGGTGGGGC
TAATCTTCTTATAAAAGAAGACATGATAATTGACAGAATAAATGAAAACTCTATTACAGAAAA
AACTGATCTGACCATGTCCACTGCAGCTTGTCCACCTTCCTATGACCGGGTGACAAAGCCA
ATTGTGGAAAAACATGAGCAAGAAGGCAAAGATGAAAAAGCCAAAGGGAAAGGAGGTGGT
GGTTCAGGTGGGGGCGGCTCAGAGTACCCCTATGATGTCCCTGATTATGCGGCGGAATAC
CCCTATGACGTGCCGGACTACGCGGCTGAATATCCGTATGACGTTCCCGATTATGCGGCT
AAGCTCGAATAATGA (SEQ ID NO: 24)

604 bp homology region of hSCN1A N term and C term that can be used in two-part expression system:
CTGGTAGAACTTGGACTCGCCAATGTGGAAGGATTATCTGTTCTCCGTTCATTTCGATTGCT
GCGAGTTTTCAAGTTGGCAAAATCTTGGCCAACGTTAAATATGCTAATAAAGATCATCGGCA
ATTCCGTGGGGGCTCTGGGAAATTTAACCCTCGTCTTGGCCATCATCGTCTTCATTTTTGC
CGTGGTCGGCATGCAGCTCTTTGGTAAAAGCTACAAAGATTGTGTCTGCAAGATCGCCAGT
GATTGTCAACTCCCACGCTGGCACATGAATGACTTCTTCCACTCCTTCCTGATTGTGTTCC
GCGTGCTGTGTGGGGAGTGGATAGAGACCATGTGGGACTGTATGGAGGTTGCTGGTCAA
GCCATGTGCCTTACTGTCTTCATGATGGTCATGGTGATTGGAAACCTAGTGGTCCTGAATC
TCTTTCTGGCCTTGCTTCTGAGCTCATTTAGTGCAGACAACCTTGCAGCCACTGATGATGAT
AATGAAATGAATAATCTCCAAATTGCTGTGGATAGGATGCACAAAGGAGTAGCTTATGTGAA
AAGAAAAATATATGAATTTATTCAACAGTCCTTCATTAGGAAACAAAAGATTT (SEQ ID NO: 25)

P2A Translation from CN1498:
(GSG)ATNFSLLKQAGDVEENPGPGASG (SEQ ID NO: 26)

T2A:
(GSG)EGRGSLLTCGDVEENPGP (SEQ ID NO: 27)

E2A:
(GSG)QCTNYALLKLAGDVESNPGPP (SEQ ID NO: 28)

F2A:
(GSG)VKQTLNFDLLKLAGDVESNPGP (SEQ ID NO: 29)

MinBglobin:
GGGCTGGGCATAAAAGTCAGGGCAGAGCCATCTATTGCTTACATTTGCTTCTG (SEQ ID NO: 30)

minCMV:
GAGGTAGGCGTGTACGGTGGGAGGCCTATATAAGCAGAGCTCGTTTAGTGAACCGTCAGA
TCGCCTGG (SEQ ID NO: 31)

PHP.eB capsid:
AAV9 capsid except that amino acids starting at residue 586: SAQA are changed to SDGTLAVPFKA (SEQ ID NO: 32)

FIG. 11, cont'd

CN1367 - The portion between L-ITR and R-ITR: positions 142-2984:
GCGGCCGCACGCGTATAGGTACCGAGCTCTATGCACTCACAGTGGTTTGGCATGCATCTG
GTGAATTTTTTTTAACGAAAAATTAGTGTTGGTTTCGATGTATGGTAGCATTCTCCCTAACGT
AATTTGAATAATTCAGCAAAGCCCCACTACCAGCTGTACTTCTGCAGCCTCTTCCATTCTTT
TCAGCATTATAATTTTGGTTAATTTTCAATTTTAGGTCCTACGTCTCTGCAATTTGTGTATGA
ATAACAGAATAATTTCCCTCTTTTGTTTCGCCTTTCCTGTTCCTGAATCTAAATAAAGATGGC
TTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAA
TCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGAAAAAAACC
TTCTTGTGGATAAAAACCTTAAATTGTCCCCAATGTCTGCTTCAAATTGGATGGCACTGCAG
CTGGAGGCTTTGTTCAGAATTGATCCTGGGGAGCTACGAACCCAAAGTTTCACAGTAGGGA
GCTCGGGCTGGGCATAAAAGTCAGGGCAGAGCCATCTATTGCTTACATTTGCTTCTGGGAT
CCAGATCTTTCGAAGCTAGCGCTACCGGTCGCCACCATGGGCAGCAGCCATCATCATCAT
CATCACAGCAGCGGCCTGGTGCCGCGCGGCAGCCATATGTCACGCAAAATCCGCGATTTA
ATCGAATCCAAACGCTTTCAAAACGTCATCACCGCCATTATTGTGCTCAATGGCGCTGTGC
TGGGTCTGCTGACCGATACAACCCTGTCGGCCTCCAGCCAAAACCTGCTGGAGCGTGTGG
ATCAACTTTGTCTGACTATCTTTATTGTTGAAATCTCCCTGAAAATCTACGCCTATGGCGTG
CGCGGCTTTTTCCGCAGCGGCTGGAATCTGTTTGATTTTGTGATTGTGGCCATCGCGCTTA
TGCCGGCCCAGGGTAGCCTGTCGGTGCTGCGTACCTTCCGTATCTTCCGCGTCATGCGCC
TCGTATCGGTCATCCCAACCATGCGCCGTGTGGTGCAAGGCATGCTCTTGGCACTGCCGG
GCGTGGGCTCGGTAGCGGCACTGTTGACGGTGGTCTTCTATATTGCGGCTGTCATGGCCA
CCAATCTCTACGGGGCAACCTTCCCTGAATGGTTTGGTGATCTTAGCAAGAGCCTGTACAC
ACTGTTTCAGGTGATGACCTTAGAGTCATGGTCTATGGGCATTGTGCGTCCAGTGATGAAC
GTTCATCCGAACGCATGGGTTTTTTTCATCCCGTTCATCATGCTCACCACCTTTACCGTGCT
CAACCTGTTTATTGGCATTATTGTAGATGCAATGGCAATCACCAAGGAACAGGAGGAAGAG
GCCAAAACCGGTCACCATCAAGAACCTATTTCTCAAACTCTTCTTCATCTTGGTGATCGTCT
TGATCGTATTGAAAAACAACTTGCTCAAAATAATGAACTTCTTCAACGTCAACAACCTCAAA
AAAAAGGCAGCGGCGCCACCAACTTCAGCCTGCTGAAGCAGGCCGGCGACGTGGAGGAG
AACCCCGGCCCCATGGTGAGCAAGGGCGAGGAGCTGTTCACCGGGGTGGTGCCCATCCT
GGTCGAGCTGGACGGCGACGTAAACGGCCACAAGTTCAGCGTGTCCGGCGAGGGCGAG
GGCGATGCCACCTACGGCAAGCTGACCCTGAAGCTGATCTGCACCACCGGCAAGCTGCC
CGTGCCCTGGCCCACCCTCGTGACCACCCTGGGCTACGGCGTGCAGTGCTTCGCCCGCT
ACCCCGACCACATGAAGCAGCACGACTTCTTCAAGTCCGCCATGCCCGAAGGCTACGTCC
AGGAGCGCACCATCTTCTTCAAGGACGACGGCAACTACAAGACCCGCGCCGAGGTGAAGT
TCGAGGGCGACACCCTGGTGAACCGCATCGAGCTGAAGGGCATCGACTTCAAGGAGGAC
GGCAACATCCTGGGGCACAAGCTGGAGTACAACTACAACAGCCACAACGTCTATATCACC
GCCGACAAGCAGAAGAACGGCATCAAGGCCAACTTCAAGATCCGCCACAACATCGAGGAC
GGCGGCGTGCAGCTCGCCGACCACTACCAGCAGAACACCCCCATCGGCGACGGCCCCGT
GCTGCTGCCCGACAACCACTACCTGAGCTACCAGTCCAAGCTGAGCAAAGACCCCAACGA
GAAGCGCGATCACATGGTCCTGCTGGAGTTCGTGACCGCCGCCGGGATCACTCTCGGCAT
GGACGAGCTGTACAAGTAAGTCGACGGCGCGCCGCGGCCGCGAATTCGATATCATAATCA
ACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTTAC
GCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCA
TTTTCTCCTCCTTGTATAAATCCTGGTTAGTTCTTGCCACGGCGGAACTCATCGCCGCCTG
CCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGCTCGAG
AGATCTTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTT
CCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAATAAAATGAGGAAATTGCATC
GCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGG
GGGAGGATTGGGAAGACAATAGCAGGCATGCACGTGCGGACCGAGCGGCCGC (SEQ ID
NO: 33)

FIG. 11, cont'd

CN1500 - The portion between L-ITR and R-ITR: positions 142-2976:
GCGGCCGCACGCGTGGTACCCTAAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAA
TTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACT
CTAATTATGGCTGCATTTAAGAGAATGGCTAAATAAAGATGGCTTTTTAGTATTAAAAGTGG
AAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAATCAGCGGGCTACATGAAA
AATTACTCTAATTATGGCTGCATTTAAGAGAATGGCTAAATAAAGATGGCTTTTTAGTATTAA
AAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAATCAGCGGGCTA
CATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGAGCTCGGGCTGGTCGACAC
AATTGGAGGTAGGCGTGTACGGTGGGAGGCCTATATAAGCAGAGCTCGTTTAGTGAACCG
TCAGATCGCCTGGAGGATCCTTCGAAAAGCTTGCTACCGGTCGCCACCATGGTCAGCAAG
GGCGAGGAGCTGTTCACCGGGGTGGTGCCCATCCTGGTCGAGCTGGACGGCGACGTCAA
TGGCCACAAGTTCAGCGTGTCCGGCGAGGGCGAGGGCGATGCCACCTACGGCAAGCTGA
CCCTGAAGCTGATCTGCACCACCGGCAAGCTGCCCGTGCCCTGGCCCACCCTCGTGACC
ACCCTGGGCTACGGCGTGCAGTGCTTCGCCCGCTACCCCGACCACATGAAGCAGCACGA
CTTCTTCAAGTCCGCCATGCCCGAAGGCTACGTCCAGGAGCGCACCATCTTCTTCAAAGAC
GACGGCAACTACAAGACCCGCGCCGAGGTGAAGTTCGAGGGCGACACCCTGGTGAACCG
CATCGAGCTGAAGGGCATCGACTTCAAGGAGGACGGCAACATCCTGGGGCACAAGCTGG
AGTACAACTACAACAGCCACAACGTCTATATCACCGCCGACAAGCAGAAGAACGGCATCAA
GGCCAACTTCAAGATCCGCCACAACATCGAGGACGGCGGCGTGCAGCTCGCCGACCACT
ACCAGCAGAACACCCCCATCGGCGACGGCCCCGTGCTGCTGCCCGACAACCACTACCTG
AGCTACCAGTCCAAGCTGAGCAAAGACCCCAACGAGAAGCGCGATCACATGGTCCTGCTG
GAGTTCGTGACCGCCGCCGGGATCACTCTCGGCATGGACGAGCTGTACAAAGGCAGCGG
CGCCACCAACTTCAGCCTGCTGAAGCAGGCCGGCGACGTGGAGGAGAACCCCGGCCCCG
GAGCTAGCGGAATGGTTTACCCGTATGATGTCCCGGATTACGCTGGCAGCTACCCATACG
ATGTACCCGACTATGCCGGCAGTTATCCCTACGACGTCCCTGACTACGCATCTACGTCCCT
TTTGAATGCGCCTACCGGCCTTCAAGCTAGAGTCATTAATCTCGTCGAACAAAACTGGTTT
GGACACTTTATACTGACTCTCATACTCATTAATGCTGTGCAGCTTGGAATGGAAACTAGCG
CCAGCCTCATGGCACAATATGGCGCGCTGCTTATGTCCTTGAATAAGGTCCTTCTCTCTGT
GTTCGTGGTCGAACTGCTGCTCCGGATTTATGCGTATCGGGGCAAGTTTTTTAAGGACCCG
TGGAATGTGTTTGACTTCACTGTTATTGTTATTGCTCTGATTCCTGCATCTGGCCCATTGGC
TGTCCTCCGCTCCCTCCGAGTTCTCCGCGTCTTGAGGGTTCTGACGATTGTCCCCAGCAT
GAAAAGAGTAGTGTCAGCACTGCTTGGGAGCTTGCCCGGGTTGGCCTCCATTGCAACCGT
GCTTCTGTTGATCTATTACGTTTTCGCTGTGATCGCCACTAAAATTTTCGGGGATGCTTTTC
CGGAATGGTTCGGGACGATAGCGGACTCCTTCTATACCCTTTTTCAAATTATGACCTTGGA
AAGTTGGTCTATGGGGATCTCTAGGCCAGTGATGGAGGTGTACCCTTACGCTTGGGTATTC
TTTGTGCCCTTTATTCTTGTTGCTACTTTTACCATGCTTAACCTTTTCATCGCCATCATAGTG
AATACTATGCAGACATTCTCTGACGAGGAACATGCTCTGGAGCGAGAGCAAGATAAACAGA
TCTTGGAACAGGAGCAGAGACAAATGCACGAGGAACTGAAGGCCATTCGACTCGAGCTTC
AGCAACTCCAAACCCTTTTGCGAAATGCGGCTGGGGACTCCTCCAATGTCTCCACAAAGG
GCAATATCGGCTCAGACTAATGACCGCGGCCGCGAATTCGATATCATAATCAACCTCTGGA
TTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGG
ATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCTC
CTTGTATAAATCCTGGTTAGTTCTTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCCCGC
TGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGCTCGAGAGATCTTCGAC
TGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGACCCTG
GAAGGTGCCACTCCCACTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGA
GTAGGTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGG
GAAGACAATAGCAGGCATGAGATCTCACGTGCGGACCGAGCGGCCGC (SEQ ID NO: 34)

FIG. 11, cont'd

CN1498 - The portion between L-ITR and R-ITR: positions 142-2943:
GCGGCCGCACGCGTGGTACCCTAAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAA
TTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACT
CTAATTATGGCTGCATTTAAGAGAATGGCTAAATAAAGATGGCTTTTTAGTATTAAAAGTGG
AAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAATCAGCGGGCTACATGAAA
AATTACTCTAATTATGGCTGCATTTAAGAGAATGGCTAAATAAAGATGGCTTTTTAGTATTAA
AAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAATCAGCGGGCTA
CATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGAGCTCGGGCTGGTCGACAC
AATTGGAGGTAGGCGTGTACGGTGGGAGGCCTATATAAGCAGAGCTCGTTTAGTGAACCG
TCAGATCGCCTGGAGGATCCTTCGAAAAGCTTGCTACCGGTCGCCACCATGGTCAGCAAG
GGCGAGGAGCTGTTCACCGGGGTGGTGCCCATCCTGGTCGAGCTGGACGGCGACGTCAA
TGGCCACAAGTTCAGCGTGTCCGGCGAGGGCGAGGGCGATGCCACCTACGGCAAGCTGA
CCCTGAAGCTGATCTGCACCACCGGCAAGCTGCCCGTGCCCTGGCCCACCCTCGTGACC
ACCCTGGGCTACGGCGTGCAGTGCTTCGCCCGCTACCCCGACCACATGAAGCAGCACGA
CTTCTTCAAGTCCGCCATGCCCGAAGGCTACGTCCAGGAGCGCACCATCTTCTTCAAAGAC
GACGGCAACTACAAGACCCGCGCCGAGGTGAAGTTCGAGGGCGACACCCTGGTGAACCG
CATCGAGCTGAAGGGCATCGACTTCAAGGAGGACGGCAACATCCTGGGGCACAAGCTGG
AGTACAACTACAACAGCCACAACGTCTATATCACCGCCGACAAGCAGAAGAACGGCATCAA
GGCCAACTTCAAGATCCGCCACAACATCGAGGACGGCGGCGTGCAGCTCGCCGACCACT
ACCAGCAGAACACCCCCATCGGCGACGGCCCCGTGCTGCTGCCCGACAACCACTACCTG
AGCTACCAGTCCAAGCTGAGCAAAGACCCCAACGAGAAGCGCGATCACATGGTCCTGCTG
GAGTTCGTGACCGCCGCCGGGATCACTCTCGGCATGGACGAGCTGTACAAAGGCAGCGG
CGCCACCAACTTCAGCCTGCTGAAGCAGGCCGGCGACGTGGAGGAGAACCCCGGCCCCG
GAGCTAGCGGAATGGTTTACCCGTATGATGTCCCGGATTACGCTGGCAGCTACCCATACG
ATGTACCCGACTATGCCGGCAGTTATCCCTACGACGTCCCTGACTACGCAGAAAACAACCC
AGCCGAACAGCAAGTCCCACCCCTCGTGGCGCTCGCCCAACGCATAGTATTTCACAAGGC
GTTTACGCCGACGATAATCACCCTCATCATTATTAATGCGATCATTGTGGGACTCGAGACAT
ACCCAACGGTTTACCAGGGTTACAATGATTGGTTCTATGCTGCCGACCTTGCTTTGTTGTG
GATATTCACTATTGAAATCACGCTCCGATTCATCGCCGCCCGACCGACGAAGAGTTTCTTC
AAGTCTAGCTGGAACTGGTTTGATCTGCTTATCGTATTGGCGGGCCACGTCTTCGCTGGCG
CCCATTTTGTTACGGTGCTTAGGATCCTCCGCGTCCTGAGGGTCCTCAGAGCTATCTCAGT
CATACCCAGTCTCCGGCGGCTGGTTGACGCACTTTTGATGACAATCCCAGCACTCGGTAA
CATCATGATACTGATGGGGATTATTTTTTACATATTCGCGGTTATCGGGACGATGCTCTTTG
CATCAGTAGCGCCAGAATACTTTGGCAATTTGCAGCTGTCTCTGCTTACACTGTTCCAAGT
GGTTACGCTGGAAAGTTGGGCTAGTGGGGTTATGCGACCTATTTTTGCCGAAGTCTGGTG
GTCTTGGATCTATTTTGTAATCTTTATTCTCGTGGGAACTTTCATAGTATTTAACCTTTTCATT
GGCGTCATCGTGAACAATGTGGAAAAAGCTAACGAAGAGGAACTGAAAAGCGAACTGGAT
GATAAAGAGGCTGATACAAAAGAAGAACTGGCATCATTGCGAAACGAGGTGGCAGAAATG
AAGGATCTCATAAAACAGATGCATAAACAGCAAACAAAAAAGGGTTAATGACCGCGGCCGC
GAATTCGATATCATAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTA
ACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATT
GCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTAGTTCTTGCCACGGC
GGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTG
ACAATTCCGTGGCTCGAGAGATCTTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTT
GCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAATA
AAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGTG
GGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCATGAGATCTCACGTGC
GGACCGAGCGGCCGC (SEQ ID NO: 35)

FIG. 11, cont'd

CN1499 - The portion between L-ITR and R-ITR: positions 142-2946:
GCGGCCGCACGCGTGGTACCCTAAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAA
TTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACT
CTAATTATGGCTGCATTTAAGAGAATGGCTAAATAAAGATGGCTTTTTAGTATTAAAAGTGG
AAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAATCAGCGGGCTACATGAAA
AATTACTCTAATTATGGCTGCATTTAAGAGAATGGCTAAATAAAGATGGCTTTTTAGTATTAA
AAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAATCAGCGGGCTA
CATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGAGCTCGGGCTGGTCGACAC
AATTGGAGGTAGGCGTGTACGGTGGGAGGCCTATATAAGCAGAGCTCGTTTAGTGAACCG
TCAGATCGCCTGGAGGATCCTTCGAAAAGCTTGCTACCGGTCGCCACCATGGTCAGCAAG
GGCGAGGAGCTGTTCACCGGGGTGGTGCCCATCCTGGTCGAGCTGGACGGCGACGTCAA
TGGCCACAAGTTCAGCGTGTCCGGCGAGGGCGAGGGCGATGCCACCTACGGCAAGCTGA
CCCTGAAGCTGATCTGCACCACCGGCAAGCTGCCCGTGCCCTGGCCCACCCTCGTGACC
ACCCTGGGCTACGGCGTGCAGTGCTTCGCCCGCTACCCCGACCACATGAAGCAGCACGA
CTTCTTCAAGTCCGCCATGCCCGAAGGCTACGTCCAGGAGCGCACCATCTTCTTCAAAGAC
GACGGCAACTACAAGACCCGCGCCGAGGTGAAGTTCGAGGGCGACACCCTGGTGAACCG
CATCGAGCTGAAGGGCATCGACTTCAAGGAGGACGGCAACATCCTGGGGCACAAGCTGG
AGTACAACTACAACAGCCACAACGTCTATATCACCGCCGACAAGCAGAAGAACGGCATCAA
GGCCAACTTCAAGATCCGCCACAACATCGAGGACGGCGGCGTGCAGCTCGCCGACCACT
ACCAGCAGAACACCCCCATCGGCGACGGCCCCGTGCTGCTGCCCGACAACCACTACCTG
AGCTACCAGTCCAAGCTGAGCAAAGACCCCAACGAGAAGCGCGATCACATGGTCCTGCTG
GAGTTCGTGACCGCCGCCGGGATCACTCTCGGCATGGACGAGCTGTACAAAGGCAGCGG
CGCCACCAACTTCAGCCTGCTGAAGCAGGCCGGCGACGTGGAGGAGAACCCCGGCCCCG
GAGCTAGCGGAATGGTTTATCCGTATGATGTTCCTGACTATGCAGGATCCTATCCTTATGAT
GTTCCCGATTACGCTGGTTCTTACCCTTACGATGTTCCCGATTATGCCAGTTCTGGATTGGT
GCCACGAGGCAGCCACATGAGCCGGAAGATCAGAGATCTTATCGAATCTAAGAGATTTCA
GAATGTTATTACCGCGATAATCGTACTCAACGGGGCGGTGCTCGGTCTCCTCACCGATACC
ACATTGAGCGCTTCTAGCCAGAACCTGCTCGAAAGGGTTGACCAACTGTGCCTGACAATTT
TTATCGTGGAAATTAGCTTGAAAATTTACGCCTACGGCGTTCGCGGTTTTTTCCGGAGCGG
TTGGAATCTTTTTGACTTCGTTATCGTTGCCATCGCGCTCATGCCCGCACAGGGTTCTTTGT
CTGTGTTGAGGACATTCCGAATATTTCGCGTGATGCGCTTGGTATCCGTGATCCCTACGAT
GCGCCGCGTCGTACAAGGAATGTTGCTGGCTCTCCCCGGCGTCGGGAGCGTTGCTGCCC
TCCTTACCGTGGTATTTTACATAGCGGCGGTTATGGCTACTAATCTTTACGGAGCTACCTTC
CCGGAGTGGTTCGGGGATTTGTCCAAGAGCCTCTATACATTGTTTCAAGTTATGACCCTGG
AGTCCTGGTCTATGGGCATTGTCCGGCCCGTAATGAACGTACACCCAAATGCGTGGGTGT
TTTTCATTCCATTCATCATGCTGACTACCTTTACCGTGCTGAACTTGTTCATTGGGATTATCG
TGGATGCGATGGCCATCACTAAGGAGCAAGAAGAAGAGGCTAAAACTGGCCACCACCAAG
AGCCAATTTCTCAAACCCTCTTGCATCTCGGGGACCGACTGGACCGCATTGAGAAGCAACT
CGCGCAGAACAATGAGCTGTTGCAGCGACAGCAACCTCAAAAAAAATAATGACCGCGGCC
GCGAATTCGATATCATAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTC
TTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTA
TTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTAGTTCTTGCCACG
GCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTTGGGCAC
TGACAATTCCGTGGCTCGAGAGATCTTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGT
TTGCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAA
TAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGG
TGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCATGAGATCTCACGT
GCGGACCGAGCGGCCGC (SEQ ID NO: 36)

FIG. 11, cont'd

CN1244 - The portion between L-ITR and R-ITR: positions 142-2042:
GCGGCCGCACGCGTATAGGTACCGAGCTCTATGCACTCACAGTGGTTTGGCATGCATCTG
GTGAATTTTTTTTAACGAAAAATTAGTGTTGGTTTCGATGTATGGTAGCATTCTCCCTAACGT
AATTTGAATAATTCAGCAAAGCCCCACTACCAGCTGTACTTCTGCAGCCTCTTCCATTCTTT
TCAGCATTATAATTTTGGTTAATTTTCAATTTTAGGTCCTACGTCTCTGCAATTTGTGTATGA
ATAACAGAATAATTTCCCTCTTTTGTTTCGCCTTTCCTGTTCCTGAATCTAAATAAAGATGGC
TTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAA
TCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGAAAAAAACC
TTCTTGTGGATAAAAACCTTAAATTGTCCCCAATGTCTGCTTCAAATTGGATGGCACTGCAG
CTGGAGGCTTTGTTCAGAATTGATCCTGGGGAGCTACGAACCCAAAGTTTCACAGTAGGGA
GCTCGGGCTGGGCATAAAAGTCAGGGCAGAGCCATCTATTGCTTACATTTGCTTCTGGGAT
CCAGATCTTTCGAAGCTAGCGCTACCGGTCGCCACCATGGTGAGCAAGGGCGAGGAGCT
GTTCACCGGGGTGGTGCCCATCCTGGTCGAGCTGGACGGCGACGTAAACGGCCACAAGT
TCAGCGTGTCCGGCGAGGGCGAGGGCGATGCCACCTACGGCAAGCTGACCCTGAAGCTG
ATCTGCACCACCGGCAAGCTGCCCGTGCCCTGGCCCACCCTCGTGACCACCCTGGGCTA
CGGCGTGCAGTGCTTCGCCCGCTACCCCGACCACATGAAGCAGCACGACTTCTTCAAGTC
CGCCATGCCCGAAGGCTACGTCCAGGAGCGCACCATCTTCTTCAAGGACGACGGCAACTA
CAAGACCCGCGCCGAGGTGAAGTTCGAGGGCGACACCCTGGTGAACCGCATCGAGCTGA
AGGGCATCGACTTCAAGGAGGACGGCAACATCCTGGGGCACAAGCTGGAGTACAACTACA
ACAGCCACAACGTCTATATCACCGCCGACAAGCAGAAGAACGGCATCAAGGCCAACTTCA
AGATCCGCCACAACATCGAGGACGGCGGCGTGCAGCTCGCCGACCACTACCAGCAGAAC
ACCCCCATCGGCGACGGCCCCGTGCTGCTGCCCGACAACCACTACCTGAGCTACCAGTC
CAAGCTGAGCAAAGACCCCAACGAGAAGCGCGATCACATGGTCCTGCTGGAGTTCGTGAC
CGCCGCCGGGATCACTCTCGGCATGGACGAGCTGTACAAGTAAGTCGACGGCGCGCCGC
GGCCGCGAATTCGATATCATAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGT
ATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCAT
GCTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTAGTTCTTGCC
ACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTTGGG
CACTGACAATTCCGTGGCTCGAGAGATCTTCGACTGTGCCTTCTAGTTGCCAGCCATCTGT
TGTTTGCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCC
TAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTG
GGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCATGAGATCTCA
CGTGCGGACCGAGCGGCCGC (SEQ ID NO: 37)

CN1389 - The portion between L-ITR and R-ITR corresponds to positions 142-1897:
CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCG
TCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTG
GCCAACTCCATCACTAGGGGTTCCTGCGGCCGCACGCGTGGTACCCTAAATAAAGATGGC
TTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAA
TCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCTAAATAAA
GATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAAC
GCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCT
AAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGT
AAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGA
ATGGAGCTCGGGCTGGGCATAAAAGTCAGGGCAGAGCCATCTATTGCTTACATTTGCTTCT
GGGATCCAGATCTTTCGAAGCTAGCGCTACCGGTCGCCACCATGGTGAGCAAGGGCGAG
GAGCTGTTCACCGGGGTGGTGCCCATCCTGGTCGAGCTGGACGGCGACGTAAACGGCCA
CAAGTTCAGCGTGTCCGGCGAGGGCGAGGGCGATGCCACCTACGGCAAGCTGACCCTGA
AGCTGATCTGCACCACCGGCAAGCTGCCCGTGCCCTGGCCCACCCTCGTGACCACCCTG

FIG. 11, cont'd

GGCTACGGCGTGCAGTGCTTCGCCCGCTACCCCGACCACATGAAGCAGCACGACTTCTTC
AAGTCCGCCATGCCCGAAGGCTACGTCCAGGAGCGCACCATCTTCTTCAAGGACGACGGC
AACTACAAGACCCGCGCCGAGGTGAAGTTCGAGGGCGACACCCTGGTGAACCGCATCGA
GCTGAAGGGCATCGACTTCAAGGAGGACGGCAACATCCTGGGGCACAAGCTGGAGTACA
ACTACAACAGCCACAACGTCTATATCACCGCCGACAAGCAGAAGAACGGCATCAAGGCCA
ACTTCAAGATCCGCCACAACATCGAGGACGGCGGCGTGCAGCTCGCCGACCACTACCAG
CAGAACACCCCCATCGGCGACGGCCCCGTGCTGCTGCCCGACAACCACTACCTGAGCTA
CCAGTCCAAGCTGAGCAAAGACCCCAACGAGAAGCGCGATCACATGGTCCTGCTGGAGTT
CGTGACCGCCGCCGGGATCACTCTCGGCATGGACGAGCTGTACAAGTAAGTCGACGGCG
CGCCGCGGCCGCGAATTCGATATCATAATCAACCTCTGGATTACAAAATTTGTGAAAGATT
GACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTT
TGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTAG
TTCTTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGG
CTGTTGGGCACTGACAATTCCGTGGCTCGAGAGATCTTCGACTGTGCCTTCTAGTTGCCAG
CCATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTG
TCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTG
GGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCATG
AGATCTCACGTGCGGACCGAGCGGCCGCAGGAACCCCTAGTGATGGAGTTGGCCACTCC
CTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGG
GCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGCTGCCTGCAGGGGCGCCT
GATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTCACACCGCATACGTCAAAGCAAC
CATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGC
GTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCTTTC
TCGCCACGTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCC
GATTTAGTGCTTTACGGCACCTCGACCCCAAAAAACTTGATTTGGGTGATGGTTCACGTAG
TGGGCCATCGCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAAT
AGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATCTCGGGCTATTCTTTTGATTT
ATAAGGGATTTTGCCGATTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTA
ACGCGAATTTTAACAAAATATTAACGTTTACAATTTTATGGTGCACTCTCAGTACAATCTGCT
CTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCCTGA
CGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGC
ATGTGTCAGAGGTTTTCACCGTCATCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATA
CGCCTATTTTTATAGGTTAATGTCATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTT
CGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAATATGTATCC
GCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTA
TTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTC
ACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTT
ACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTCGCCCCGAAGAACGTTT
TCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCC
GGGCAAGAGCAACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCAC
CAGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCAT
AACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGA
GCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCG
GAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCA
ACAACGTTGCGCAAACTATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAAT
AGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTG
GCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAG
CACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGG
CAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTG

FIG. 11, cont'd

GTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAAACTTCATTTTTAATTT
AAAAGGATCTAGGTGAAGATCCTTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGAGTT
TTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTT
TTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTT
GCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATA
CCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCAC
CGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTC
GTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTG
AACGGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATA
CCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGT
ATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAA
CGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTG
TGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACG
GTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGT (SEQ ID NO: 38)

CN1390 - The portion between L-ITR and R-ITR corresponds to positions 142-1660:
CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCG
TCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTG
GCCAACTCCATCACTAGGGGTTCCTGCGGCCGCACGCGTTCGCCTTTCCTGTTCCTGAAT
CTAAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACG
GTAAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGA
GAATGGACCTGCAGGGAGCTCGGGCTGGGCATAAAAGTCAGGGCAGAGCCATCTATTGCT
TACATTTGCTTCTGGGATCCAGATCTTTCGAAGCTAGCGCTACCGGTCGCCACCATGGTGA
GCAAGGGCGAGGAGCTGTTCACCGGGGTGGTGCCCATCCTGGTCGAGCTGGACGGCGAC
GTAAACGGCCACAAGTTCAGCGTGTCCGGCGAGGGCGAGGGCGATGCCACCTACGGCAA
GCTGACCCTGAAGCTGATCTGCACCACCGGCAAGCTGCCCGTGCCCTGGCCCACCCTCG
TGACCACCCTGGGCTACGGCGTGCAGTGCTTCGCCCGCTACCCCGACCACATGAAGCAG
CACGACTTCTTCAAGTCCGCCATGCCCGAAGGCTACGTCCAGGAGCGCACCATCTTCTTC
AAGGACGACGGCAACTACAAGACCCGCGCCGAGGTGAAGTTCGAGGGCGACACCCTGGT
GAACCGCATCGAGCTGAAGGGCATCGACTTCAAGGAGGACGGCAACATCCTGGGGCACA
AGCTGGAGTACAACTACAACAGCCACAACGTCTATATCACCGCCGACAAGCAGAAGAACG
GCATCAAGGCCAACTTCAAGATCCGCCACAACATCGAGGACGGCGGCGTGCAGCTCGCC
GACCACTACCAGCAGAACACCCCCATCGGCGACGGCCCCGTGCTGCTGCCCGACAACCA
CTACCTGAGCTACCAGTCCAAGCTGAGCAAAGACCCCAACGAGAAGCGCGATCACATGGT
CCTGCTGGAGTTCGTGACCGCCGCCGGGATCACTCTCGGCATGGACGAGCTGTACAAGTA
AGTCGACGGCGCGCCGCGGCCGCGAATTCGATATCATAATCAACCTCTGGATTACAAAATT
TGTGAAAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGC
TTTAATGCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTATAA
ATCCTGGTTAGTTCTTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGAC
AGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGCTCGAGAGATCTTCGACTGTGCCTT
CTAGTTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGC
CACTCCCACTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTC
ATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAAT
AGCAGGCATGAGATCTCACGTGCGGACCGAGCGGCCGCAGGAACCCCTAGTGATGGAGT
TGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCC
CGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGCTGCCTGC
AGGGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTCACACCGCATACG
TCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTT
ACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTC

FIG. 11, cont'd

CCTTCCTTTCTCGCCACGTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTT
TAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAAACTTGATTTGGGTGATGG
TTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACG
TTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATCTCGGGCTATTC
TTTTGATTTATAAGGGATTTTGCCGATTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACA
AAAATTTAACGCGAATTTTAACAAAATATTAACGTTTACAATTTTATGGTGCACTCTCAGTAC
AATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGC
GCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGG
GAGCTGCATGTGTCAGAGGTTTTCACCGTCATCACCGAAACGCGCGAGACGAAAGGGCCT
CGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATAATGGTTTCTTAGACGTCAGGTG
GCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAAT
ATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAG
TATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGT
TTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGA
GTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTCGCCCCGAAG
AACGTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATT
GACGCCGGGCAAGAGCAACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAG
TACTCACCAGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTG
CTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACC
GAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGG
GAACCGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCA
ATGGCAACAACGTTGCGCAAACTATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAAC
AATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTC
CGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCA
TTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGA
GTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAA
GCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAAACTTCATTT
TTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAACG
TGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGAT
CCTTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGG
TTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGC
GCAGATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCT
GTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGC
GATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGG
TCGGGCTGAACGGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGA
ACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGC
GGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAG
GGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTC
GATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCT
TTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGT (SEQ ID NO: 39)

CN1203 - The portion between L-ITR and R-ITR corresponds to positions 183-2052:
AAAGCTTCCCGGGGGGATCTGGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGG
CCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGA
GCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTGGAGGGGTGGAG
TCGTGACCTAGGACGCGTATAGGTACCGAGCTCTATGCACTCACAGTGGTTTGGCATGCAT
CTGGTGAATTTTTTTTAACGAAAAATTAGTGTTGGTTTCGATGTATGGTAGCATTCTCCCTAA
CGTAATTTGAATAATTCAGCAAAGCCCCACTACCAGCTGTACTTCTGCAGCCTCTTCCATTC
TTTTCAGCATTATAATTTTGGTTAATTTTCAATTTTAGGTCCTACGTCTCTGCAATTTGTGTAT

FIG. 11, cont'd

GAATAACAGAATAATTTCCCTCTTTTGTTTCGCCTTTCCTGTTCCTGAATCTAAATAAAGATG
GCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTG
TAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGAAAAAA
ACCTTCTTGTGGATAAAAACCTTAAATTGTCCCCAATGTCTGCTTCAAATTGGATGGCACTG
CAGCTGGAGGCTTTGTTCAGAATTGATCCTGGGGAGCTACGAACCCAAAGTTTCACAGTAG
GGAGCTCGGGCTGGGCATAAAAGTCAGGGCAGAGCCATCTATTGCTTACATTTGCTTCTG
GGATCCAGATCTTTCGAAGCTAGCGCTACCGGTCGCCACCATGGTGAGCAAGGGCGAGG
AGCTGTTCACCGGGGTGGTGCCCATCCTGGTCGAGCTGGACGGCGACGTAAACGGCCAC
AAGTTCAGCGTGTCCGGCGAGGGCGAGGGCGATGCCACCTACGGCAAGCTGACCCTGAA
GCTGATCTGCACCACCGGCAAGCTGCCCGTGCCCTGGCCCACCCTCGTGACCACCCTGG
GCTACGGCGTGCAGTGCTTCGCCCGCTACCCCGACCACATGAAGCAGCACGACTTCTTCA
AGTCCGCCATGCCCGAAGGCTACGTCCAGGAGCGCACCATCTTCTTCAAGGACGACGGCA
ACTACAAGACCCGCGCCGAGGTGAAGTTCGAGGGCGACACCCTGGTGAACCGCATCGAG
CTGAAGGGCATCGACTTCAAGGAGGACGGCAACATCCTGGGGCACAAGCTGGAGTACAAC
TACAACAGCCACAACGTCTATATCACCGCCGACAAGCAGAAGAACGGCATCAAGGCCAAC
TTCAAGATCCGCCACAACATCGAGGACGGCGGCGTGCAGCTCGCCGACCACTACCAGCA
GAACACCCCCATCGGCGACGGCCCCGTGCTGCTGCCCGACAACCACTACCTGAGCTACC
AGTCCAAGCTGAGCAAAGACCCCAACGAGAAGCGCGATCACATGGTCCTGCTGGAGTTCG
TGACCGCCGCCGGGATCACTCTCGGCATGGACGAGCTGTACAAGTAAGTCGACGGCGCG
CCGCGGCCGCGAATTCGATATCATAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGA
CTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGT
ATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTAGTTC
TTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTG
TTGGGCACTGACAATTCCGTGGCTCGAGCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTG
TTTGCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTA
ATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGG
GTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCATGACTAGTCCAC
TCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCC
CGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGACAGATCCG
GGCCCGCATGCGTCGACAATTCACTGGCCGTCGTTTTACAACGTCGTGACTGGGAAAACC
CTGGCGTTACCCAACTTAATCGCCTTGCAGCACATCCCCCTTTCGCCAGCTGGCGTAATAG
CGAAGAGGCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATGGC
GCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTCACACCGCATATGGTGCAC
TCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACC
CGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGAC
CGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTCACCGTCATCACCGAAACGCGCGAGACG
AAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATAATGGTTTCTTAGA
CGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATA
CATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAA
AGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTG
CCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTG
GGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTC
GCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATT
ATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTCGCCGCATACACTATTCTCAGAATGA
CTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAA
TTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGA
TCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCC
TTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGA
TGCCTGTAGCAATGGCAACAACGTTGCGCAAACTATTAACTGGCGAACTACTTACTCTAGC

FIG. 11, cont'd

TTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCG
CTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTC
TCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTAC
ACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTGCC
TCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTA
AAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAA
ATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGAT
CTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTA
CCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAACTGGCT
TCAGCAGAGCGCAGATACCAAATACTGTTCTTCTAGTGTAGCCGTAGTTAGGCCACCACTT
CAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCT
GCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAG
GCGCAGCGGTCGGGCTGAACGGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGA
CCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAG
GGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAG
GGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTG
ACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAG
CAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGTTCTTTCCTG
CGTTATCCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCG
CCGCAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGCGAGGAAGCGGAAGAGCGCCCA
ATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTAATGCAGCTGGCACGACAGG
TTTCCCGACTGGAAAGCGGGCAGTGAGCGCAACGCAATTAATGTGAGTTAGCTCACTCATT
AGGCACCCCAGGCTTTACACTTTATGCTTCCGGCTCGTATGTTGTGTGGAATTGTGAGCGG
ATAACAATTTCACACAGGAAACAGCTATGACCATGATTACGCCAAGCTCTCGAGATCTAG
(SEQ ID NO: 40)

CN1180 - The portion between L-ITR and R-ITR corresponds to positions 183-1891:
AAAGCTTCCCGGGGGGATCTGGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGG
CCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGA
GCGAGCGCGCAGAGAGGGAGTGGCCAACTCCATCACTAGGGGTTCCTGGAGGGGTGGAG
TCGTGACCTAGGACGCGTCAGCTGCAAACCCAAGAGGGTCAGCATCATTTCACTGTATTCT
CTTCTTGATTACAAGCCGGGCCCATCAAACACAACATAATTACAGTAATTTCAGGTTTATTT
ATTCTAATGCAGTTTCCCCATCTCTCTGGTAATTATGAGCAATTTTTTCGCCCAGGGAATCT
TTTTGCATTAACAAAAGAGATAACGCACTGAAAGCCAAATTTGCTGTGCATTGAGAAAAGGA
AAAAAAAAAATCAAATAGGTGCGAGCTGCCATCTCTGCAATTCTCTGGTACCGGAGCCGGC
AAATTGCTTGCAGGTGTATGGAGCAAGCTTGTCAATGGCCAGGCCTCCAAATTAGCAAATG
CACAGCAGCAAAGTAATGAAGACAGGAGCTCGGGCTGGGCATAAAAGTCAGGGCAGAGC
CATCTATTGCTTACATTTGCTTCTGGGATCCAGATCTTTCGAAGCTAGCGCTACCGGTCGC
CACCATGGTGAGCAAGGGCGAGGAGCTGTTCACCGGGGTGGTGCCCATCCTGGTCGAGC
TGGACGGCGACGTAAACGGCCACAAGTTCAGCGTGTCCGGCGAGGGCGAGGGCGATGCC
ACCTACGGCAAGCTGACCCTGAAGCTGATCTGCACCACCGGCAAGCTGCCCGTGCCCTG
GCCCACCCTCGTGACCACCCTGGGCTACGGCGTGCAGTGCTTCGCCCGCTACCCCGACC
ACATGAAGCAGCACGACTTCTTCAAGTCCGCCATGCCCGAAGGCTACGTCCAGGAGCGCA
CCATCTTCTTCAAGGACGACGGCAACTACAAGACCCGCGCCGAGGTGAAGTTCGAGGGCG
ACACCCTGGTGAACCGCATCGAGCTGAAGGGCATCGACTTCAAGGAGGACGGCAACATCC
TGGGGCACAAGCTGGAGTACAACTACAACAGCCACAACGTCTATATCACCGCCGACAAGC
AGAAGAACGGCATCAAGGCCAACTTCAAGATCCGCCACAACATCGAGGACGGCGGCGTG
CAGCTCGCCGACCACTACCAGCAGAACACCCCCATCGGCGACGGCCCCGTGCTGCTGCC
CGACAACCACTACCTGAGCTACCAGTCCAAGCTGAGCAAAGACCCCAACGAGAAGCGCGA

FIG. 11, cont'd

TCACATGGTCCTGCTGGAGTTCGTGACCGCCGCCGGGATCACTCTCGGCATGGACGAGCT
GTACAAGTAAGTCGACGGCGCGCCGCGGCCGCGAATTCGATATCATAATCAACCTCTGGA
TTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGG
ATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCTC
CTTGTATAAATCCTGGTTAGTTCTTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCCCGC
TGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGCTCGAGCGACTGTGCC
TTCTAGTTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGT
GCCACTCCCACTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGT
GTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGAC
AATAGCAGGCATGACTAGTGCATGCCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAG
GCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCG
AGCGAGCGCGCAGAGAGGGAGACAGATCCGGGCCCGCATGCGTCGACAATTCACTGGCCGT
CGTTTTACAACGTCGTGACTGGGAAAACCCTGGCGTTACCCAACTTAATCGCCTTGCAGCA
CATCCCCCTTTCGCCAGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAA
CAGTTGCGCAGCCTGAATGGCGAATGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGT
GCGGTATTTCACACCGCATATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTT
AAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCC
CGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTT
CACCGTCATCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGG
TTAATGTCATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCG
CGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATA
ACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTG
TCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTG
GTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGAT
CTCAACAGCGGTAAGATCCTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCA
CTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACT
CGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAG
CATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATA
ACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTT
GCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGC
CATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAA
ACTATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAG
GCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCT
GATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGAT
GGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAA
CGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACC
AAGTTTACTCATATATACTTTAGATTGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGT
GAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAG
CGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATC
TGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGC
TACCAACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTTCTT
CTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCG
CTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTT
GGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGT
GCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGC
TATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGC
AGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTA
TAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGG
GGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGC

FIG. 11, cont'd

TGGCCTTTTGCTCACATGTTCTTTCCTGCGTTATCCCCTGATTCTGTGGATAACCGTATTAC
CGCCTTTGAGTGAGCTGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAGCGAGTCAG
TGAGCGAGGAAGCGGAAGAGCGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCG
ATTCATTAATGCAGCTGGCACGACAGGTTTCCCGACTGGAAAGCGGGCAGTGAGCGCAAC
GCAATTAATGTGAGTTAGCTCACTCATTAGGCACCCCAGGCTTTACACTTTATGCTTCCGG
CTCGTATGTTGTGTGGAATTGTGAGCGGATAACAATTTCACACAGGAAACAGCTATGACCA
TGATTACGCCAAGCTCTCGAGATCTAG (SEQ ID NO: 41)

CN2001 - The portion between L-ITR and R-ITR corresponds to positions 142-2023:
CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCG
TCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTG
GCCAACTCCATCACTAGGGGTTCCTGCGGCCGCACGCGTGGTACCCTAAATAAAGATGGC
TTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAA
TCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCTAAATAAA
GATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAAC
GCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCT
AAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGT
AAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGA
ATGGAGCTCGGGCTGGGCATAAAAGTCAGGGCAGAGCCATCTATTGCTTACATTTGCTTCT
GGGATCCAGATCTTTCGAAGCTAGCGCTACCACCATGGAAAACAACCCAGCCGAACAGCA
AGTCCCACCCCTCGTGGCGCTCGCCCAACGCATAGTATTTCACAAGGCGTTTACGCCGAC
GATAATCACCCTCATCATTATTAATGCGATCATTGTGGGACTCGAGACATACCCAACGGTTT
ACCAGGGTTACAATGATTGGTTCTATGCTGCCGACCTTGCTTTGTTGTGGATATTCACTATT
GAAATCACGCTCCGATTCATCGCCGCCCGACCGACGAAGAGTTTCTTCAAGTCTAGCTGG
AACTGGTTTGATCTGCTTATCGTATTGGCGGGCCACGTCTTCGCTGGCGCCCATTTTGTTA
CGGTGCTTAGGATCCTCCGCGTCCTGAGGGTCCTCAGAGCTATCTCAGTCATACCCAGTC
TCCGGCGGCTGGTTGACGCACTTTTGATGACAATCCCAGCACTCGGTAACATCATGATACT
GATGGGGATTATTTTTTACATATTCGCGGTTATCGGGACGATGCTCTTTGCATCAGTAGCG
CCAGAATACTTTGGCAATTTGCAGCTGTCTCTGCTTACACTGTTCCAAGTGGTTACGCTGG
AAAGTTGGGCTAGTGGGGTTATGCGACCTATTTTTGCCGAAGTCTGGTGGTCTTGGATCTA
TTTTGTAATCTTTATTCTCGTGGGAACTTTCATAGTATTTAACCTTTTCATTGGCGTCATCGT
GAACAATGTGGAAAAAGCTAACGAAGAGGAACTGAAAAGCGAACTGGATGATAAAGAGGC
TGATACAAAAGAAGAACTGGCATCATTGCGAAACGAGGTGGCAGAAATGAAGGATCTCATA
AAACAGATGCATAAACAGCAAACAAAAAAGGGTTAATGACGGCGCGCCGCGGCCGCGAAT
TCGATATCATAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTA
TGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTT
CCCGTATGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTAGTTCTTGCCACGGCGGAA
CTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAA
TTCCGTGGCTCGAGAGATCTTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCC
CTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAATAAAAT
GAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGTGGGG
CAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCATGAGATCTCACGTGCGGA
CCGAGCGGCCGCAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGC
TCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGG
CCTCAGTGAGCGAGCGAGCGCGCAGCTGCCTGCAGGGGCGCCTGATGCGGTATTTTCTC
CTTACGCATCTGTGCGGTATTTCACACCGCATACGTCAAAGCAACCATAGTACGCGCCCTG
TAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTG
CCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTCGCCGG
CTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGG

FIG. 11, cont'd

CACCTCGACCCCAAAAAACTTGATTTGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGAT
AGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAA
ACTGGAACAACACTCAACCCTATCTCGGGCTATTCTTTTGATTTATAAGGGATTTTGCCGAT
TTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAAT
ATTAACGTTTACAATTTTATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAA
GCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCG
GCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTCA
CCGTCATCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTA
ATGTCATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGG
AACCCCTATTTGTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACC
CTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCG
CCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTG
AAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCA
ACAGCGGTAAGATCCTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTT
TAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGG
TCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCAT
CTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACA
CTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCA
CAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCAT
ACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACT
ATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCG
GATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATA
AATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGT
AAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGA
AATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAG
TTTACTCATATATACTTTAGATTGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAA
GATCCTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGT
CAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGC
TGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTAC
CAACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCT
AGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCT
CTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTG
GACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGTG
CACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCT
ATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCA
GGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTAT
AGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGG
GGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCT
GGCCTTTTGCTCACATGT (SEQ ID NO: 42)

CN2002 - The portion between L-ITR and R-ITR corresponds to positions 142-1993:
CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCG
TCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTG
GCCAACTCCATCACTAGGGGTTCCTGCGGCCGCACGCGTGGTACCCTAAATAAAGATGGC
TTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAA
TCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCTAAATAAA
GATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAAC
GCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCT
AAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGT

FIG. 11, cont'd

AAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGA
ATGGAGCTCGGGCTGGGCATAAAAGTCAGGGCAGAGCCATCTATTGCTTACATTTGCTTCT
GGGATCCAGATCTTTCGAAGCTAGCGCTACCACCATGAGCCGGAAGATCAGAGATCTTATC
GAATCTAAGAGATTTCAGAATGTTATTACCGCGATAATCGTACTCAACGGGGCGGTGCTCG
GTCTCCTCACCGATACCACATTGAGCGCTTCTAGCCAGAACCTGCTCGAAAGGGTTGACCA
ACTGTGCCTGACAATTTTTATCGTGGAAATTAGCTTGAAAATTTACGCCTACGGCGTTCGCG
GTTTTTTCCGGAGCGGTTGGAATCTTTTTGACTTCGTTATCGTTGCCATCGCGCTCATGCC
CGCACAGGGTTCTTTGTCTGTGTTGAGGACATTCCGAATATTTCGCGTGATGCGCTTGGTA
TCCGTGATCCCTACGATGCGCCGCGTCGTACAAGGAATGTTGCTGGCTCTCCCCGGCGTC
GGGAGCGTTGCTGCCCTCCTTACCGTGGTATTTTACATAGCGGCGGTTATGGCTACTAATC
TTTACGGAGCTACCTTCCCGGAGTGGTTCGGGGATTTGTCCAAGAGCCTCTATACATTGTT
TCAAGTTATGACCCTGGAGTCCTGGTCTATGGGCATTGTCCGGCCCGTAATGAACGTACAC
CCAAATGCGTGGGTGTTTTTCATTCCATTCATCATGCTGACTACCTTTACCGTGCTGAACTT
GTTCATTGGGATTATCGTGGATGCGATGGCCATCACTAAGGAGCAAGAAGAAGAGGCTAA
AACTGGCCACCACCAAGAGCCAATTTCTCAAACCCTCTTGCATCTCGGGGACCGACTGGA
CCGCATTGAGAAGCAACTCGCGCAGAACAATGAGCTGTTGCAGCGACAGCAACCTCAAAA
AAAATAATGACGGCGCGCCGCGGCCGCGAATTCGATATCATAATCAACCTCTGGATTACAA
AATTTGTGAAAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACG
CTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGT
ATAAATCCTGGTTAGTTCTTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCT
GGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGCTCGAGAGATCTTCGACTGTG
CCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAG
GTGCCACTCCCACTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAG
GTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAG
ACAATAGCAGGCATGAGATCTCACGTGCGGACCGAGCGGCCGCAGGAACCCCTAGTGAT
GGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGG
TCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGCTG
CCTGCAGGGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTCACACCGC
ATACGTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTG
GTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCT
TTCTTCCCTTCCTTTCTCGCCACGTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGC
TCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAAACTTGATTTGGG
TGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAG
TCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATCTCGGG
CTATTCTTTTGATTTATAAGGGATTTTGCCGATTTCGGCCTATTGGTTAAAAAATGAGCTGAT
TTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGTTTACAATTTTATGGTGCACTCT
CAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACCCGC
TGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGT
CTCCGGGAGCTGCATGTGTCAGAGGTTTTCACCGTCATCACCGAAACGCGCGAGACGAAA
GGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATAATGGTTTCTTAGACGT
CAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACAT
TCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAG
GAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCC
TTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGG
TGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTCGC
CCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATC
CCGTATTGACGCCGGGCAAGAGCAACTCGGTCGCCGCATACACTATTCTCAGAATGACTT
GGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTA
TGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCG

FIG. 11, cont'd

GAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTG
ATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGC
CTGTAGCAATGGCAACAACGTTGCGCAAACTATTAACTGGCGAACTACTTACTCTAGCTTC
CCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTC
GGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCG
CGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACAC
GACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTGCCTC
ACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAA
ACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAAT
CCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCT
TCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACC
AGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAACTGGCTTC
AGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCA
AGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGC
CAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGC
GCAGCGGTCGGGCTGAACGGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCT
ACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGA
GAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGA
GCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTT
GAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAAC
GCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGT (SEQ ID NO: 43)

CN2003 - The portion between L-ITR and R-ITR corresponds to positions 142-2056:
CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCG
TCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTG
GCCAACTCCATCACTAGGGGTTCCTGCGGCCGCACGCGTGGTACCCTAAATAAAGATGGC
TTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAA
TCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCTAAATAAA
GATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAAC
GCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCT
AAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGT
AAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGA
ATGGAGCTCGGGCTGGGCATAAAAGTCAGGGCAGAGCCATCTATTGCTTACATTTGCTTCT
GGGATCCAGATCTTTCGAAGCTAGCGCTACCACCATGTCTACGTCCCTTTTGAATGCGCCT
ACCGGCCTTCAAGCTAGAGTCATTAATCTCGTCGAACAAAACTGGTTTGGACACTTTATACT
GACTCTCATACTCATTAATGCTGTGCAGCTTGGAATGGAAACTAGCGCCAGCCTCATGGCA
CAATATGGCGCGCTGCTTATGTCCTTGAATAAGGTCCTTCTCTCTGTGTTCGTGGTCGAAC
TGCTGCTCCGGATTTATGCGTATCGGGGCAAGTTTTTTAAGGACCCGTGGAATGTGTTTGA
CTTCACTGTTATTGTTATTGCTCTGATTCCTGCATCTGGCCCATTGGCTGTCCTCCGCTCCC
TCCGAGTTCTCCGCGTCTTGAGGGTTCTGACGATTGTCCCCAGCATGAAAAGAGTAGTGTC
AGCACTGCTTGGGAGCTTGCCCGGGTTGGCCTCCATTGCAACCGTGCTTCTGTTGATCTAT
TACGTTTTCGCTGTGATCGCCACTAAAATTTTCGGGGATGCTTTTCCGGAATGGTTCGGGA
CGATAGCGGACTCCTTCTATACCCTTTTTCAAATTATGACCTTGGAAAGTTGGTCTATGGGG
ATCTCTAGGCCAGTGATGGAGGTGTACCCTTACGCTTGGGTATTCTTTGTGCCCTTTATTCT
TGTTGCTACTTTTACCATGCTTAACCTTTTCATCGCCATCATAGTGAATACTATGCAGACATT
CTCTGACGAGGAACATGCTCTGGAGCGAGAGCAAGATAAACAGATCTTGGAACAGGAGCA
GAGACAAATGCACGAGGAACTGAAGGCCATTCGACTCGAGCTTCAGCAACTCCAAACCCT
TTTGCGAAATGCGGCTGGGGACTCCTCCAATGTCTCCACAAAGGGCAATATCGGCTCAGA
CTAATGACGGCGCGCCGCGGCCGCGAATTCGATATCATAATCAACCTCTGGATTACAAAAT

FIG. 11, cont'd

TTGTGAAAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTG
CTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTATA
AATCCTGGTTAGTTCTTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGA
CAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGCTCGAGAGATCTTCGACTGTGCCT
TCTAGTTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTG
CCACTCCCACTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGT
CATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAA
TAGCAGGCATGAGATCTCACGTGCGGACCGAGCGGCCGCAGGAACCCCTAGTGATGGAG
TTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGC
CCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGCTGCCTG
CAGGGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTCACACCGCATAC
GTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGG
TTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCT
TCCCTTCCTTTCTCGCCACGTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCC
TTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAAACTTGATTTGGGTGAT
GGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCC
ACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATCTCGGGCTA
TTCTTTTGATTTATAAGGGATTTTGCCGATTTCGGCCTATTGGTTAAAAAATGAGCTGATTTA
ACAAAAATTTAACGCGAATTTTAACAAAATATTAACGTTTACAATTTTATGGTGCACTCTCAG
TACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGA
CGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTC
CGGGAGCTGCATGTGTCAGAGGTTTTCACCGTCATCACCGAAACGCGCGAGACGAAAGGG
CCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATAATGGTTTCTTAGACGTCAG
GTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCA
AATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAA
GAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTC
CTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGC
ACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTCGCCCC
GAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCC
GTATTGACGCCGGGCAAGAGCAACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGG
TTGAGTACTCACCAGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATG
CAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGA
GGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTGATC
GTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTG
TAGCAATGGCAACAACGTTGCGCAAACTATTAACTGGCGAACTACTTACTCTAGCTTCCCG
GCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGC
CCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGG
TATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACG
GGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTG
ATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAAACTT
CATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCCCT
TAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTT
GAGATCCTTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGC
GGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAACTGGCTTCAGC
AGAGCGCAGATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGA
ACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAG
TGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCA
GCGGTCGGGCTGAACGGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACA
CCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAA

FIG. 11, cont'd

AGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCT
TCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAG
CGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCG
GCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGT (SEQ ID NO: 44)

CN1504 - The portion between L-ITR and R-ITR corresponds to positions 142-4489:
CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCG
TCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTG
GCCAACTCCATCACTAGGGGTTCCTGCGGCCGCACGCGTGGTACCCTAAATAAAGATGGC
TTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAA
TCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCTAAATAAA
GATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAAC
GCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCT
AAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGT
AAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGA
ATGGAGCTCGGGCTGGTCGACACAATTGGAGGTAGGCGTGTACGGTGGGAGGCCTATATA
AGCAGAGCTCGTTTAGTGAACCGTCAGATCGCCTGGAGGATCCTTCGAAAAGCTTGCTAC
CGGTGCCACCATGGTCAGCAAGGGCGAGGAGCTGTTCACCGGGGTGGTGCCCATCCTGG
TCGAGCTGGACGGCGACGTCAATGGCCACAAGTTCAGCGTGTCCGGCGAGGGCGAGGGC
GATGCCACCTACGGCAAGCTGACCCTGAAGCTGATCTGCACCACCGGCAAGCTGCCCGTG
CCCTGGCCCACCCTCGTGACCACCCTGGGCTACGGCGTGCAGTGCTTCGCCCGCTACCC
CGACCACATGAAGCAGCACGACTTCTTCAAGTCCGCCATGCCCGAAGGCTACGTCCAGGA
GCGCACCATCTTCTTCAAAGACGACGGCAACTACAAGACCCGCGCCGAGGTGAAGTTCGA
GGGCGACACCCTGGTGAACCGCATCGAGCTGAAGGGCATCGACTTCAAGGAGGACGGCA
ACATCCTGGGGCACAAGCTGGAGTACAACTACAACAGCCACAACGTCTATATCACCGCCG
ACAAGCAGAAGAACGGCATCAAGGCCAACTTCAAGATCCGCCACAACATCGAGGACGGCG
GCGTGCAGCTCGCCGACCACTACCAGCAGAACACCCCCATCGGCGACGGCCCCGTGCTG
CTGCCCGACAACCACTACCTGAGCTACCAGTCCAAGCTGAGCAAAGACCCCAACGAGAAG
CGCGATCACATGGTCCTGCTGGAGTTCGTGACCGCCGCCGGGATCACTCTCGGCATGGA
CGAGCTGTACAAAGGCAGCGGCGCCACCAACTTCAGCCTGCTGAAGCAGGCCGGCGACG
TGGAGGAGAACCCCGGCCCCGGAACTAGTGGTATGGAGCAAACAGTGCTTGTACCACCAG
GACCTGACAGCTTCAACTTCTTCACCAGAGAATCTCTTGCGGCTATTGAAAGACGCATTGC
AGAAGAAAAGGCAAAGAATCCCAAACCAGACAAAAAAGATGACGACGAAAATGGCCCAAA
GCCAAATAGTGACTTGGAAGCTGGAAAGAACCTTCCATTTATTTATGGAGACATTCCTCCA
GAGATGGTGTCAGAGCCCCTGGAGGACCTGGACCCCTACTATATCAATAAGAAAACTTTTA
TAGTATTGAATAAAGGGAAGGCCATCTTCCGGTTCAGTGCCACCTCTGCCCTGTACATTTT
AACTCCCTTCAATCCTCTTAGGAAAATAGCTATTAAGATTTTGGTACATTCATTATTCAGCAT
GCTAATTATGTGCACTATTTTGACAAACTGTGTGTTTATGACAATGAGTAACCCTCCTGATT
GGACAAAGAATGTAGAATACACCTTCACAGGAATATATACTTTTGAATCACTTATAAAAATTA
TTGCAAGGGGATTCTGTTTAGAAGATTTTACTTTCCTTCGGGATCCATGGAACTGGCTCGAT
TTCACTGTCATTACATTTGCGTACGTCACAGAGTTTGTGGACCTGGGCAATGTCTCGGCAT
TGAGAACATTCAGAGTTCTCCGAGCATTGAAGACGATTTCAGTCATTCCAGGCCTGAAAAC
CATTGTGGGAGCCCTGATCCAGTCTGTGAAGAAGCTCTCAGATGTAATGATCCTGACTGTG
TTCTGTCTGAGCGTATTTGCTCTAATTGGGCTGCAGCTGTTCATGGGCAACCTGAGGAATA
AATGTATACAATGGCCTCCCACCAATGCTTCCTTGGAGGAACATAGTATAGAAAAGAATATA
ACTGTGAATTATAATGGTACACTTATAAATGAAACTGTCTTTGAGTTTGACTGGAAGTCATAT
ATTCAAGATTCAAGATATCATTATTTCCTGGAGGGTTTTTTAGATGCACTACTATGTGGAAAT
AGCTCTGATGCAGGCCAATGTCCAGAGGGATATATGTGTGTGAAAGCTGGTAGAAATCCCA
ATTATGGCTACACAAGCTTTGATACCTTCAGTTGGGCTTTTTTGTCCTTGTTTCGACTAATG

FIG. 11, cont'd

ACTCAGGACTTCTGGGAAAATCTTTATCAACTGACATTACGTGCTGCTGGGAAAACGTACA
TGATATTTTTTGTATTGGTCATTTTCTTGGGCTCATTCTACCTAATAAATTTGATCCTGGCTG
TGGTGGCCATGGCCTACGAGGAACAGAATCAGGCCACCTTGGAAGAAGCAGAACAGAAAG
AGGCCGAATTTCAGCAGATGATTGAACAGCTTAAAAAGCAACAGGAGGCAGCTCAGCAGG
CAGCAACGGCAACTGCCTCAGAACATTCCAGAGAGCCCAGTGCAGCAGGCAGGCTCTCAG
ACAGCTCATCTGAAGCCTCTAAGTTGAGTTCCAAGAGTGCTAAGGAAAGAAGAAATCGGAG
GAAGAAAAGAAAACAGAAAGAGCAGTCTGGTGGGGAAGAGAAAGATGAGGATGAATTCCA
AAAATCTGAATCTGAGGACAGCATCAGGAGGAAAGGTTTTCGCTTCTCCATTGAAGGGAAC
CGATTGACATATGAAAAGAGGTACTCCTCCCCACACCAGTCTTTGTTGAGCATCCGTGGCT
CCCTATTTTCACCAAGGCGAAATAGCAGAACAAGCCTTTTCAGCTTTAGAGGGCGAGCAAA
GGATGTGGGATCTGAGAACGACTTCGCAGATGATGAGCACAGCACCTTTGAGGATAACGA
GAGCCGTAGAGATTCCTTGTTTGTGCCCCGACGACACGGAGAGAGACGCAACAGCAACCT
GAGTCAGACCAGTAGGTCATCCCGGATGCTGGCAGTGTTTCCAGCGAATGGGAAGATGCA
CAGCACTGTGGATTGCAATGGTGTGGTTTCCTTGGTTGGTGGACCTTCAGTTCCTACATCG
CCTGTTGGACAGCTTCTGCCAGAGGTGATAATAGATAAGCCAGCTACTGATGACAATGGAA
CAACCACTGAAACTGAAATGAGAAAGAGAAGGTCAAGTTCTTTCCACGTTTCCATGGACTTT
CTAGAAGATCCTTCCCAAAGGCAACGAGCAATGAGTATAGCCAGCATTCTAACAAATACAG
TAGAAGAACTTGAAGAATCCAGGCAGAAATGCCCACCCTGTTGGTATAAATTTTCCAACATA
TTCTTAATCTGGGACTGTTCTCCATATTGGTTAAAAGTGAAACATGTTGTCAACCTGGTTGT
GATGGACCCATTTGTTGACCTGGCCATCACCATCTGTATTGTCTTAAATACTCTTTTCATGG
CCATGGAGCACTATCCAATGACGGACCATTTCAATAATGTGCTTACAGTAGGAAACTTGGT
TTTCACTGGGATCTTTACAGCAGAAATGTTTCTGAAAATTATTGCCATGGATCCTTACTATTA
TTTCCAAGAAGGCTGGAATATCTTTGACGGTTTTATTGTGACGCTTAGCCTGGTAGAACTTG
GACTCGCCAATGTGGAAGGATTATCTGTTCTCCGTTCATTTCGATTGCTGCGAGTTTTCAAG
TTGGCAAAATCTTGGCCAACGTTAAATATGCTAATAAAGATCATCGGCAATTCCGTGGGGG
CTCTGGGAAATTTAACCCTCGTCTTGGCCATCATCGTCTTCATTTTTGCCGTGGTCGGCAT
GCAGCTCTTTGGTAAAAGCTACAAAGATTGTGTCTGCAAGATCGCCAGTGATTGTCAACTC
CCACGCTGGCACATGAATGACTTCTTCCACTCCTTCCTGATTGTGTTCCGCGTGCTGTGTG
GGGAGTGGATAGAGACCATGTGGGACTGTATGGAGGTTGCTGGTCAAGCCATGTGCCTTA
CTGTCTTCATGATGGTCATGGTGATTGGAAACCTAGTGGTCCTGAATCTCTTTCTGGCCTT
GCTTCTGAGCTCATTTAGTGCAGACAACCTTGCAGCCACTGATGATGATAATGAAATGAATA
ATCTCCAAATTGCTGTGGATAGGATGCACAAAGGAGTAGCTTATGTGAAAAGAAAAATATAT
GAATTTATTCAACAGTCCTTCATTAGGAAACAAAAGATCTCACGTGCGGACCGAGCGGCCG
CAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAG
GCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCG
AGCGAGCGCGCAGCTGCCTGCAGGGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGT
GCGGTATTTCACACCGCATACGTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATT
AAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAG
CGCCCGCTCCTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTCGCCGGCTTTCCCCGTCA
AGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCC
AAAAAACTTGATTTGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTC
GCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAAC
ACTCAACCCTATCTCGGGCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTCGGCCTATT
GGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGTTTA
CAATTTTATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCG
ACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTA
CAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTCACCGTCATCACC
GAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATA
ATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTT

FIG. 11, cont'd

GTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGC
TTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCC
TTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGA
TGCTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAA
GATCCTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCTGC
TATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTCGCCGCATAC
ACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACGGATGG
CATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAAC
TTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGG
GATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGAC
GAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACTATTAACTGGC
GAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTG
CAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAG
CCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCC
CGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGA
TCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATAT
ATACTTTAGATTGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTG
ATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTA
GAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAAC
AAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTT
CCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTGTAGCCGT
AGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCT
GTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACG
ATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGTGCACACAGCCCA
GCTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCG
CCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACA
GGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGG
GTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCT
ATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCT
CACATGT (SEQ ID NO: 45)

CN1512 - The portion between L-ITR and R-ITR corresponds to positions 142-4165:
CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCG
TCGGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTG
GCCAACTCCATCACTAGGGGTTCCTGCGGCCGCACGCGTATAGGTACCCTGGTAGAACTT
GGACTCGCCAATGTGGAAGGATTATCTGTTCTCCGTTCATTTCGATTGCTGCGAGTTTTCAA
GTTGGCAAAATCTTGGCCAACGTTAAATATGCTAATAAAGATCATCGGCAATTCCGTGGGG
GCTCTGGGAAATTTAACCCTCGTCTTGGCCATCATCGTCTTCATTTTTGCCGTGGTCGGCA
TGCAGCTCTTTGGTAAAAGCTACAAAGATTGTGTCTGCAAGATCGCCAGTGATTGTCAACT
CCCACGCTGGCACATGAATGACTTCTTCCACTCCTTCCTGATTGTGTTCCGCGTGCTGTGT
GGGGAGTGGATAGAGACCATGTGGGACTGTATGGAGGTTGCTGGTCAAGCCATGTGCCTT
ACTGTCTTCATGATGGTCATGGTGATTGGAAACCTAGTGGTCCTGAATCTCTTTCTGGCCTT
GCTTCTGAGCTCATTTAGTGCAGACAACCTTGCAGCCACTGATGATGATAATGAAATGAATA
ATCTCCAAATTGCTGTGGATAGGATGCACAAAGGAGTAGCTTATGTGAAAAGAAAAATATAT
GAATTTATTCAACAGTCCTTCATTAGGAAACAAAAGATTTTAGATGAAATTAAACCACTTGAT
GATCTAAACAACAAGAAAGACAGTTGTATGTCCAATCATACAGCAGAAATTGGGAAAGATCT
TGACTATCTTAAAGATGTAAATGGAACTACAAGTGGTATAGGAACTGGCAGCAGTGTTGAA
TACATTATTGATGAAAGTGATTACATGTCATTCATAAACAACCCCAGTCTTACTGTGACTGTA
CCAATTGCTGTAGGAGAATCTGACTTTGAAAATTTAAACACGGAAGACTTTAGTAGTGAATC

FIG. 11, cont'd

GGATCTGGAAGAAAGCAAAGAGAAACTGAATGAAAGCAGTAGCTCATCAGAAGGTAGCAC
TGTGGACATCGGCGCACCTGTAGAAGAACAGCCCGTAGTGGAACCTGAAGAAACTCTTGA
ACCAGAAGCTTGTTTCACTGAAGGCTGTGTACAAAGATTCAAGTGTTGTCAAATCAATGTG
GAAGAAGGCAGAGGAAAACAATGGTGGAACCTGAGAAGGACGTGTTTCCGAATAGTTGAA
CATAACTGGTTTGAGACCTTCATTGTTTTCATGATTCTCCTTAGTAGTGGTGCTCTGGCATT
TGAAGATATATATATTGATCAGCGAAAGACGATTAAGACGATGTTGGAATATGCTGACAAG
GTTTTCACTTACATTTTCATTCTGGAAATGCTTCTAAAATGGGTGGCATATGGCTATCAAAC
ATATTTCACCAATGCCTGGTGTTGGCTGGACTTCTTAATTGTTGATGTTTCATTGGTCAGTT
TAACAGCAAATGCCTTGGGTTACTCAGAACTTGGAGCCATCAAATCTCTCAGGACACTAAG
AGCTCTGAGACCTCTAAGAGCCTTATCTCGATTTGAAGGGATGAGGGTGGTTGTGAATGCC
CTTTTAGGAGCAATTCCATCCATCATGAATGTGCTTCTGGTTTGTCTTATATTCTGGCTAATT
TTCAGCATCATGGGCGTAAATTTGTTTGCTGGCAAATTCTACCACTGTATTAACACCACAAC
TGGTGACAGGTTTGACATCGAAGACGTGAATAATCATACTGATTGCCTAAAACTAATAGAAA
GAAATGAGACTGCTCGATGGAAAAATGTGAAAGTAAACTTTGATAATGTAGGATTTGGGTAT
CTCTCTTTGCTTCAAGTTGCCACATTCAAAGGATGGATGGATATAATGTATGCAGCAGTTGA
TTCCAGAAATGTGGAACTCCAGCCTAAGTATGAAGAAAGTCTGTACATGTATCTTTACTTTG
TTATTTTCATCATCTTTGGGTCCTTCTTCACCTTGAACCTGTTTATTGGTGTCATCATAGATA
ATTTCAACCAGCAGAAAAAGAAGTTTGGAGGTCAAGACATCTTTATGACAGAAGAACAGAA
GAAATACTATAATGCAATGAAAAAATTAGGATCGAAAAAACCGCAAAAGCCTATACCTCGAC
CAGGAAACAAATTTCAAGGAATGGTCTTTGACTTCGTAACCAGACAAGTTTTTGACATAAGC
ATCATGATTCTCATCTGTCTTAACATGGTCACAATGATGGTGGAAACAGATGACCAGAGTG
AATATGTGACTACCATTTTGTCACGCATCAATCTGGTGTTCATTGTGCTATTTACTGGAGAG
TGTGTACTGAAACTCATCTCTCTACGCCATTATTATTTTACCATTGGATGGAATATTTTTGAT
TTTGTGGTTGTCATTCTCTCCATTGTAGGTATGTTTCTTGCCGAGCTGATAGAAAAGTATTT
CGTGTCCCCTACCCTGTTCCGAGTGATCCGTCTTGCTAGGATTGGCCGAATCCTACGTCTG
ATCAAAGGAGCAAAGGGGATCCGCACGCTGCTCTTTGCTTTGATGATGTCCCTTCCTGCGT
TGTTTAACATCGGCCTCCTACTCTTCCTAGTCATGTTCATCTACGCCATCTTTGGGATGTCC
AACTTTGCCTATGTTAAGAGGGAAGTTGGGATCGATGACATGTTCAACTTTGAGACCTTTG
GCAACAGCATGATCTGCCTATTCCAAATTACAACCTCTGCTGGCTGGGATGGATTGCTAGC
ACCCATTCTCAACAGTAAGCCACCCGACTGTGACCCTAATAAAGTTAACCCTGGAAGCTCA
GTTAAGGGAGACTGTGGGAACCCATCTGTTGGAATTTTCTTTTTTGTCAGTTACATCATCAT
ATCCTTCCTGGTTGTGGTGAACATGTACATCGCGGTCATCCTGGAGAACTTCAGTGTTGCT
ACTGAAGAAAGTGCAGAGCCTCTGAGTGAGGATGACTTTGAGATGTTCTATGAGGTTTGGG
AGAAGTTTGATCCCGATGCAACTCAGTTCATGGAATTTGAAAAATTATCTCAGTTTGCAGCT
GCGCTTGAACCGCCTCTCAATCTGCCACAACCAAACAAACTCCAGCTCATTGCCATGGATT
TGCCCATGGTGAGTGGTGACCGGATCCACTGTCTTGATATCTTATTTGCTTTTACAAAGCG
GGTTCTAGGAGAGAGTGGAGAGATGGATGCTCTACGAATACAGATGGAAGAGCGATTCAT
GGCTTCCAATCCTTCCAAGGTCTCCTATCAGCCAATCACTACTACTTTAAAACGAAAACAAG
AGGAAGTATCTGCTGTCATTATTCAGCGTGCTTACAGACGCCACCTTTTAAAGCGAACTGT
AAAACAAGCTTCCTTTACGTACAATAAAAACAAAATCAAAGGTGGGGCTAATCTTCTTATAA
AAGAAGACATGATAATTGACAGAATAAATGAAAACTCTATTACAGAAAAAACTGATCTGACC
ATGTCCACTGCAGCTTGTCCACCTTCCTATGACCGGGTGACAAAGCCAATTGTGGAAAAAC
ATGAGCAAGAAGGCAAAGATGAAAAAGCCAAAGGGAAAGGAGGTGGTGGTTCAGGTGGG
GGCGGCTCAGAGTACCCCTATGATGTCCCTGATTATGCGGCGGAATACCCCTATGACGTG
CCGGACTACGCGGCTGAATATCCGTATGACGTTCCCGATTATGCGGCTAAGCTCGAATAAT
GATGAGAATTCATCATAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTC
TTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTA
TTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTAGTTCTTGCCACG
GCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTTGGGCAC

FIG. 11, cont'd

TGACAATTCCGTGGCTCGAGAGATCTTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGT
TTGCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAA
TAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGG
TGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCATGAGATCTCACGT
GCGGACCGAGCGGCCGCAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCG
CTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGG
GCGGCCTCAGTGAGCGAGCGAGCGCGCAGCTGCCTGCAGGGGCGCCTGATGCGGTATTT
TCTCCTTACGCATCTGTGCGGTATTTCACACCGCATACGTCAAAGCAACCATAGTACGCGC
CCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACA
CTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTCG
CCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTT
ACGGCACCTCGACCCCAAAAAACTTGATTTGGGTGATGGTTCACGTAGTGGGCCATCGCC
CTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGT
TCCAAACTGGAACAACACTCAACCCTATCTCGGGCTATTCTTTTGATTTATAAGGGATTTTG
CCGATTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAA
CAAAATATTAACGTTTACAATTTTATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCAT
AGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTG
CTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGG
TTTTCACCGTCATCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTAT
AGGTTAATGTCATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGT
GCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGAC
AATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCC
GTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACG
CTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTG
GATCTCAACAGCGGTAAGATCCTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGA
GCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCA
ACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAA
AAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTG
ATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTT
TTTGCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAA
GCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGC
AAACTATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGA
GGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGC
TGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGA
TGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGA
ACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGAC
CAAGTTTACTCATATATACTTTAGATTGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGG
TGAAGATCCTTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCACTGA
GCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAAT
CTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAG
CTACCAACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCC
TTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCT
CGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGG
GTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTT
CGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTG
AGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGC
GGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCT
TTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCA

FIG. 11, cont'd

GGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTT
TGCTGGCCTTTTGCTCACATGT (SEQ ID NO: 46)

CN2004 - The portion between L-ITR and R-ITR corresponds to positions 142-3792:
CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCG
TCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTG
GCCAACTCCATCACTAGGGGTTCCTGCGGCCGCACGCGTGGTACCCTAAATAAAGATGGC
TTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAA
TCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCTAAATAAA
GATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAAC
GCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCT
AAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGT
AAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGA
ATGGAGCTCGGGCTGGGCATAAAAGTCAGGGCAGAGCCATCTATTGCTTACATTTGCTTCT
GGGATCCAGATCTTTCGAAGCTAGCGCTAATGGAGCAAACAGTGCTTGTACCACCAGGAC
CTGACAGCTTCAACTTCTTCACCAGAGAATCTCTTGCGGCTATTGAAAGACGCATTGCAGA
AGAAAAGGCAAAGAATCCCAAACCAGACAAAAAAGATGACGACGAAAATGGCCCAAAGCC
AAATAGTGACTTGGAAGCTGGAAAGAACCTTCCATTTATTTATGGAGACATTCCTCCAGAGA
TGGTGTCAGAGCCCCTGGAGGACCTGGACCCCTACTATATCAATAAGAAAACTTTTATAGT
ATTGAATAAAGGGAAGGCCATCTTCCGGTTCAGTGCCACCTCTGCCCTGTACATTTTAACT
CCCTTCAATCCTCTTAGGAAAATAGCTATTAAGATTTTGGTACATTCATTATTCAGCATGCTA
ATTATGTGCACTATTTTGACAAACTGTGTGTTTATGACAATGAGTAACCCTCCTGATTGGAC
AAAGAATGTAGAATACACCTTCACAGGAATATATACTTTTGAATCACTTATAAAAATTATTGC
AAGGGGATTCTGTTTAGAAGATTTTACTTTCCTTCGGGATCCATGGAACTGGCTCGATTTCA
CTGTCATTACATTTGCGTACGTCACAGAGTTTGTGGACCTGGGCAATGTCTCGGCATTGAG
AACATTCAGAGTTCTCCGAGCATTGAAGACGATTTCAGTCATTCCAGGCCTGAAAACCATT
GTGGGAGCCCTGATCCAGTCTGTGAAGAAGCTCTCAGATGTAATGATCCTGACTGTGTTCT
GTCTGAGCGTATTTGCTCTAATTGGGCTGCAGCTGTTCATGGGCAACCTGAGGAATAAATG
TATACAATGGCCTCCCACCAATGCTTCCTTGGAGGAACATAGTATAGAAAAGAATATAACTG
TGAATTATAATGGTACACTTATAAATGAAACTGTCTTTGAGTTTGACTGGAAGTCATATATTC
AAGATTCAAGATATCATTATTTCCTGGAGGGTTTTTTAGATGCACTACTATGTGGAAATAGC
TCTGATGCAGGCCAATGTCCAGAGGGATATATGTGTGTGAAAGCTGGTAGAAATCCCAATT
ATGGCTACACAAGCTTTGATACCTTCAGTTGGGCTTTTTTGTCCTTGTTTCGACTAATGACT
CAGGACTTCTGGGAAAATCTTTATCAACTGACATTACGTGCTGCTGGGAAAACGTACATGA
TATTTTTTGTATTGGTCATTTTCTTGGGCTCATTCTACCTAATAAATTTGATCCTGGCTGTGG
TGGCCATGGCCTACGAGGAACAGAATCAGGCCACCTTGGAAGAAGCAGAACAGAAAGAGG
CCGAATTTCAGCAGATGATTGAACAGCTTAAAAAGCAACAGGAGGCAGCTCAGCAGGCAG
CAACGGCAACTGCCTCAGAACATTCCAGAGAGCCCAGTGCAGCAGGCAGGCTCTCAGACA
GCTCATCTGAAGCCTCTAAGTTGAGTTCCAAGAGTGCTAAGGAAAGAAGAAATCGGAGGAA
GAAAAGAAAACAGAAAGAGCAGTCTGGTGGGGAAGAGAAAGATGAGGATGAATTCCAAAA
ATCTGAATCTGAGGACAGCATCAGGAGGAAAGGTTTTCGCTTCTCCATTGAAGGGAACCGA
TTGACATATGAAAAGAGGTACTCCTCCCCACACCAGTCTTTGTTGAGCATCCGTGGCTCCC
TATTTTCACCAAGGCGAAATAGCAGAACAAGCCTTTTCAGCTTTAGAGGGCGAGCAAAGGA
TGTGGGATCTGAGAACGACTTCGCAGATGATGAGCACAGCACCTTTGAGGATAACGAGAG
CCGTAGAGATTCCTTGTTTGTGCCCCGACGACACGGAGAGAGACGCAACAGCAACCTGAG
TCAGACCAGTAGGTCATCCCGGATGCTGGCAGTGTTTCCAGCGAATGGGAAGATGCACAG
CACTGTGGATTGCAATGGTGTGGTTTCCTTGGTTGGTGGACCTTCAGTTCCTACATCGCCT
GTTGGACAGCTTCTGCCAGAGGTGATAATAGATAAGCCAGCTACTGATGACAATGGAACAA
CCACTGAAACTGAAATGAGAAAGAGAAGGTCAAGTTCTTTCCACGTTTCCATGGACTTTCTA

FIG. 11, cont'd

GAAGATCCTTCCCAAAGGCAACGAGCAATGAGTATAGCCAGCATTCTAACAAATACAGTAG
AAGAACTTGAAGAATCCAGGCAGAAATGCCCACCCTGTTGGTATAAATTTTCCAACATATTC
TTAATCTGGGACTGTTCTCCATATTGGTTAAAAGTGAAACATGTTGTCAACCTGGTTGTGAT
GGACCCATTTGTTGACCTGGCCATCACCATCTGTATTGTCTTAAATACTCTTTTCATGGCCA
TGGAGCACTATCCAATGACGGACCATTTCAATAATGTGCTTACAGTAGGAAACTTGGTTTTC
ACTGGGATCTTTACAGCAGAAATGTTTCTGAAAATTATTGCCATGGATCCTTACTATTATTTC
CAAGAAGGCTGGAATATCTTTGACGGTTTTATTGTGACGCTTAGCCTGGTAGAACTTGGAC
TCGCCAATGTGGAAGGATTATCTGTTCTCCGTTCATTTCGATTGCTGCGAGTTTTCAAGTTG
GCAAAATCTTGGCCAACGTTAAATATGCTAATAAAGATCATCGGCAATTCCGTGGGGGCTC
TGGGAAATTTAACCCTCGTCTTGGCCATCATCGTCTTCATTTTTGCCGTGGTCGGCATGCA
GCTCTTTGGTAAAAGCTACAAAGATTGTGTCTGCAAGATCGCCAGTGATTGTCAACTCCCA
CGCTGGCACATGAATGACTTCTTCCACTCCTTCCTGATTGTGTTCCGCGTGCTGTGTGGGG
AGTGGATAGAGACCATGTGGGACTGTATGGAGGTTGCTGGTCAAGCCATGTGCCTTACTG
TCTTCATGATGGTCATGGTGATTGGAAACCTAGTGGTCCTGAATCTCTTTCTGGCCTTGCTT
CTGAGCTCATTTAGTGCAGACAACCTTGCAGCCACTGATGATGATAATGAAATGAATAATCT
CCAAATTGCTGTGGATAGGATGCACAAAGGAGTAGCTTATGTGAAAAGAAAAATATATGAAT
TTATTCAACAGTCCTTCATTAGGAAACAAAAGATCTGTGCGGACCGAGCGGCCGCAGGAAC
CCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGG
CGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAG
CGCGCAGCTGCCTGCAGGGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTA
TTTCACACCGCATACGTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGC
GGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCG
CTCCTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTCGCCGGCTTTCCCCGTCAAGCTCTA
AATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAAAC
TTGATTTGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGCCCTTT
GACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAAC
CCTATCTCGGGCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTCGGCCTATTGGTTAAA
AAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGTTTACAATTTTA
TGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCG
CCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAA
GCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTCACCGTCATCACCGAAACGC
GCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATAATGG
TTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTT
TTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAA
TATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGC
GGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAA
GATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTT
GAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTG
GCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTCGCCGCATACACTATT
CTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACGGATGGCATGAC
AGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTT
CTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCAT
GTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGACGAGCGT
GACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACTATTAACTGGCGAACTAC
TTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACC
ACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGA
GCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGT
AGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGA
GATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTT

FIG. 11, cont'd

AGATTGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCT
CATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAG
ATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAA
ACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAG
GTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAG
GCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACC
AGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTT
ACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGTGCACACAGCCCAGCTTGG
AGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGC
TTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAG
CGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGC
CACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAA
AACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGT
(SEQ ID NO: 47)

CN2005 - The portion between L-ITR and R-ITR corresponds to positions 142-4160:
CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCG
TCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTG
GCCAACTCCATCACTAGGGGTTCCTGCGGCCGCACGCGTATAGGTACCCTGGTAGAACTT
GGACTCGCCAATGTGGAAGGATTATCTGTTCTCCGTTCATTTCGATTGCTGCGAGTTTTCAA
GTTGGCAAAATCTTGGCCAACGTTAAATATGCTAATAAAGATCATCGGCAATTCCGTGGGG
GCTCTGGGAAATTTAACCCTCGTCTTGGCCATCATCGTCTTCATTTTTGCCGTGGTCGGCA
TGCAGCTCTTTGGTAAAAGCTACAAAGATTGTGTCTGCAAGATCGCCAGTGATTGTCAACT
CCCACGCTGGCACATGAATGACTTCTTCCACTCCTTCCTGATTGTGTTCCGCGTGCTGTGT
GGGGAGTGGATAGAGACCATGTGGGACTGTATGGAGGTTGCTGGTCAAGCCATGTGCCTT
ACTGTCTTCATGATGGTCATGGTGATTGGAAACCTAGTGGTCCTGAATCTCTTTCTGGCCTT
GCTTCTGAGCTCATTTAGTGCAGACAACCTTGCAGCCACTGATGATGATAATGAAATGAATA
ATCTCCAAATTGCTGTGGATAGGATGCACAAAGGAGTAGCTTATGTGAAAAGAAAAATATAT
GAATTTATTCAACAGTCCTTCATTAGGAAACAAAAGATTTTAGATGAAATTAAACCACTTGAT
GATCTAAACAACAAGAAAGACAGTTGTATGTCCAATCATACAGCAGAAATTGGGAAAGATCT
TGACTATCTTAAAGATGTAAATGGAACTACAAGTGGTATAGGAACTGGCAGCAGTGTTGAA
TACATTATTGATGAAAGTGATTACATGTCATTCATAAACAACCCCAGTCTTACTGTGACTGTA
CCAATTGCTGTAGGAGAATCTGACTTTGAAAATTTAAACACGGAAGACTTTAGTAGTGAATC
GGATCTGGAAGAAAGCAAAGAGAAACTGAATGAAAGCAGTAGCTCATCAGAAGGTAGCAC
TGTGGACATCGGCGCACCTGTAGAAGAACAGCCCGTAGTGGAACCTGAAGAAACTCTTGA
ACCAGAAGCTTGTTTCACTGAAGGCTGTGTACAAAGATTCAAGTGTTGTCAAATCAATGTG
GAAGAAGGCAGAGGAAAACAATGGTGGAACCTGAGAAGGACGTGTTTCCGAATAGTTGAA
CATAACTGGTTTGAGACCTTCATTGTTTTCATGATTCTCCTTAGTAGTGGTGCTCTGGCATT
TGAAGATATATATATTGATCAGCGAAAGACGATTAAGACGATGTTGGAATATGCTGACAAG
GTTTTCACTTACATTTTCATTCTGGAAATGCTTCTAAAATGGGTGGCATATGGCTATCAAAC
ATATTTCACCAATGCCTGGTGTTGGCTGGACTTCTTAATTGTTGATGTTTCATTGGTCAGTT
TAACAGCAAATGCCTTGGGTTACTCAGAACTTGGAGCCATCAAATCTCTCAGGACACTAAG
AGCTCTGAGACCTCTAAGAGCCTTATCTCGATTTGAAGGGATGAGGGTGGTTGTGAATGCC
CTTTTAGGAGCAATTCCATCCATCATGAATGTGCTTCTGGTTTGTCTTATATTCTGGCTAATT
TTCAGCATCATGGGCGTAAATTTGTTTGCTGGCAAATTCTACCACTGTATTAACACCACAAC
TGGTGACAGGTTTGACATCGAAGACGTGAATAATCATACTGATTGCCTAAAACTAATAGAAA
GAAATGAGACTGCTCGATGGAAAAATGTGAAAGTAAACTTTGATAATGTAGGATTTGGGTAT
CTCTCTTTGCTTCAAGTTGCCACATTCAAAGGATGGATGGATATAATGTATGCAGCAGTTGA
TTCCAGAAATGTGGAACTCCAGCCTAAGTATGAAGAAAGTCTGTACATGTATCTTTACTTTG

FIG. 11, cont'd

TTATTTTCATCATCTTTGGGTCCTTCTTCACCTTGAACCTGTTTATTGGTGTCATCATAGATA
ATTTCAACCAGCAGAAAAAGAAGTTTGGAGGTCAAGACATCTTTATGACAGAAGAACAGAA
GAAATACTATAATGCAATGAAAAAATTAGGATCGAAAAAACCGCAAAAGCCTATACCTCGAC
CAGGAAACAAATTTCAAGGAATGGTCTTTGACTTCGTAACCAGACAAGTTTTTGACATAAGC
ATCATGATTCTCATCTGTCTTAACATGGTCACAATGATGGTGGAAACAGATGACCAGAGTG
AATATGTGACTACCATTTTGTCACGCATCAATCTGGTGTTCATTGTGCTATTTACTGGAGAG
TGTGTACTGAAACTCATCTCTCTACGCCATTATTATTTTACCATTGGATGGAATATTTTTGAT
TTTGTGGTTGTCATTCTCTCCATTGTAGGTATGTTTCTTGCCGAGCTGATAGAAAAGTATTT
CGTGTCCCCTACCCTGTTCCGAGTGATCCGTCTTGCTAGGATTGGCCGAATCCTACGTCTG
ATCAAAGGAGCAAAGGGGATCCGCACGCTGCTCTTTGCTTTGATGATGTCCCTTCCTGCGT
TGTTTAACATCGGCCTCCTACTCTTCCTAGTCATGTTCATCTACGCCATCTTTGGGATGTCC
AACTTTGCCTATGTTAAGAGGGAAGTTGGGATCGATGACATGTTCAACTTTGAGACCTTTG
GCAACAGCATGATCTGCCTATTCCAAATTACAACCTCTGCTGGCTGGGATGGATTGCTAGC
ACCCATTCTCAACAGTAAGCCACCCGACTGTGACCCTAATAAAGTTAACCCTGGAAGCTCA
GTTAAGGGAGACTGTGGGAACCCATCTGTTGGAATTTTCTTTTTTGTCAGTTACATCATCAT
ATCCTTCCTGGTTGTGGTGAACATGTACATCGCGGTCATCCTGGAGAACTTCAGTGTTGCT
ACTGAAGAAAGTGCAGAGCCTCTGAGTGAGGATGACTTTGAGATGTTCTATGAGGTTTGGG
AGAAGTTTGATCCCGATGCAACTCAGTTCATGGAATTTGAAAAATTATCTCAGTTTGCAGCT
GCGCTTGAACCGCCTCTCAATCTGCCACAACCAAACAAACTCCAGCTCATTGCCATGGATT
TGCCCATGGTGAGTGGTGACCGGATCCACTGTCTTGATATCTTATTTGCTTTTACAAAGCG
GGTTCTAGGAGAGAGTGGAGAGATGGATGCTCTACGAATACAGATGGAAGAGCGATTCAT
GGCTTCCAATCCTTCCAAGGTCTCCTATCAGCCAATCACTACTACTTTAAAACGAAAACAAG
AGGAAGTATCTGCTGTCATTATTCAGCGTGCTTACAGACGCCACCTTTTAAAGCGAACTGT
AAAACAAGCTTCCTTTACGTACAATAAAAACAAAATCAAAGGTGGGGCTAATCTTCTTATAA
AAGAAGACATGATAATTGACAGAATAAATGAAAACTCTATTACAGAAAAAACTGATCTGACC
ATGTCCACTGCAGCTTGTCCACCTTCCTATGACCGGGTGACAAAGCCAATTGTGGAAAAAC
ATGAGCAAGAAGGCAAAGATGAAAAAGCCAAAGGGAAATAATGACATCATAATCAACCTCT
GGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATG
TGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTC
CTCCTTGTATAAATCCTGGTTAGTTCTTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCC
CGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGCTCGAGAGATCTTC
GACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGACC
CTGGAAGGTGCCACTCCCACTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTC
TGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGAT
TGGGAAGACAATAGCAGGCATGAGATCTCACGTGCGGACCGAGCGGCCGCAGGAACCCC
TAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGA
CCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGC
GCAGCTGCCTGCAGGGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTT
CACACCGCATACGTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGC
GGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTC
CTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTCGCCGGCTTTCCCCGTCAAGCTCTAAAT
CGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAAACTTG
ATTTGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGCCCTTTGAC
GTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTA
TCTCGGGCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTCGGCCTATTGGTTAAAAAAT
GAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGTTTACAATTTTATGG
TGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAA
CACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTG
TGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTCACCGTCATCACCGAAACGCGCGA

FIG. 11, cont'd

GACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATAATGGTTTCT
TAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCT
AAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATT
GAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCA
TTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCA
GTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAG
TTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCG
GTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTCGCCGCATACACTATTCTCAGA
ATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAG
AGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACA
ACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACT
CGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACC
ACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACTATTAACTGGCGAACTACTTACTC
TAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCT
GCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGG
GTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTAT
CTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGG
TGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTG
ATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGA
CCAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAA
AGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCAC
CGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAAC
TGGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCAC
CACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGG
CTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGG
ATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGA
ACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCC
GAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCA
CGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACC
TCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACG
CCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGT (SEQ
ID NO: 48)

CN2006 - The portion between L-ITR and R-ITR corresponds to positions 142-4790:
CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCG
TCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTG
GCCAACTCCATCACTAGGGGTTCCTGCGGCCGCACGCGTGGTACCCTAAATAAAGATGGC
TTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAA
TCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCTAAATAAA
GATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAAC
GCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCT
AAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGT
AAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGA
ATGGAGCTCGGGCTGGTCGACACAATTGGAGGTAGGCGTGTACGGTGGGAGGCCTATATA
AGCAGAGCTCGTTTAGTGAACCGTCAGATCGCCTGGAGGATCCTTCGAAAAGCTTGCTAC
CGGTGCCACCATGGTCAGCAAGGGCGAGGAGCTGTTCACCGGGGTGGTGCCCATCCTGG
TCGAGCTGGACGGCGACGTCAATGGCCACAAGTTCAGCGTGTCCGGCGAGGGCGAGGGC
GATGCCACCTACGGCAAGCTGACCCTGAAGCTGATCTGCACCACCGGCAAGCTGCCCGTG
CCCTGGCCCACCCTCGTGACCACCCTGGGCTACGGCGTGCAGTGCTTCGCCCGCTACCC

FIG. 11, cont'd

CGACCACATGAAGCAGCACGACTTCTTCAAGTCCGCCATGCCCGAAGGCTACGTCCAGGA
GCGCACCATCTTCTTCAAAGACGACGGCAACTACAAGACCCGCGCCGAGGTGAAGTTCGA
GGGCGACACCCTGGTGAACCGCATCGAGCTGAAGGGCATCGACTTCAAGGAGGACGGCA
ACATCCTGGGGCACAAGCTGGAGTACAACTACAACAGCCACAACGTCTATATCACCGCCG
ACAAGCAGAAGAACGGCATCAAGGCCAACTTCAAGATCCGCCACAACATCGAGGACGGCG
GCGTGCAGCTCGCCGACCACTACCAGCAGAACACCCCCATCGGCGACGGCCCCGTGCTG
CTGCCCGACAACCACTACCTGAGCTACCAGTCCAAGCTGAGCAAAGACCCCAACGAGAAG
CGCGATCACATGGTCCTGCTGGAGTTCGTGACCGCCGCCGGGATCACTCTCGGCATGGA
CGAGCTGTACAAAGGCAGCGGCGCCACCAACTTCAGCCTGCTGAAGCAGGCCGGCGACG
TGGAGGAGAACCCCGGCCCCGGAACTAGTGGTATGGAGCAAACAGTGCTTGTACCACCAG
GACCTGACAGCTTCAACTTCTTCACCAGAGAATCTCTTGCGGCTATTGAAAGACGCATTGC
AGAAGAAAAGGCAAAGAATCCCAAACCAGACAAAAAAGATGACGACGAAAATGGCCCAAA
GCCAAATAGTGACTTGGAAGCTGGAAAGAACCTTCCATTTATTTATGGAGACATTCCTCCA
GAGATGGTGTCAGAGCCCCTGGAGGACCTGGACCCCTACTATATCAATAAGAAAACTTTTA
TAGTATTGAATAAAGGGAAGGCCATCTTCCGGTTCAGTGCCACCTCTGCCCTGTACATTTT
AACTCCCTTCAATCCTCTTAGGAAAATAGCTATTAAGATTTTGGTACATTCATTATTCAGCAT
GCTAATTATGTGCACTATTTTGACAAACTGTGTGTTTATGACAATGAGTAACCCTCCTGATT
GGACAAAGAATGTAGAATACACCTTCACAGGAATATATACTTTTGAATCACTTATAAAAATTA
TTGCAAGGGGATTCTGTTTAGAAGATTTTACTTTCCTTCGGGATCCATGGAACTGGCTCGAT
TTCACTGTCATTACATTTGCGTACGTCACAGAGTTTGTGGACCTGGGCAATGTCTCGGCAT
TGAGAACATTCAGAGTTCTCCGAGCATTGAAGACGATTTCAGTCATTCCAGGCCTGAAAAC
CATTGTGGGAGCCCTGATCCAGTCTGTGAAGAAGCTCTCAGATGTAATGATCCTGACTGTG
TTCTGTCTGAGCGTATTTGCTCTAATTGGGCTGCAGCTGTTCATGGGCAACCTGAGGAATA
AATGTATACAATGGCCTCCCACCAATGCTTCCTTGGAGGAACATAGTATAGAAAAGAATATA
ACTGTGAATTATAATGGTACACTTATAAATGAAACTGTCTTTGAGTTTGACTGGAAGTCATAT
ATTCAAGATTCAAGATATCATTATTTCCTGGAGGGTTTTTTAGATGCACTACTATGTGGAAAT
AGCTCTGATGCAGGCCAATGTCCAGAGGGATATATGTGTGTGAAAGCTGGTAGAAATCCCA
ATTATGGCTACACAAGCTTTGATACCTTCAGTTGGGCTTTTTTGTCCTTGTTTCGACTAATG
ACTCAGGACTTCTGGGAAAATCTTTATCAACTGACATTACGTGCTGCTGGGAAAACGTACA
TGATATTTTTTGTATTGGTCATTTTCTTGGGCTCATTCTACCTAATAAATTTGATCCTGGCTG
TGGTGGCCATGGCCTACGAGGAACAGAATCAGGCCACCTTGGAAGAAGCAGAACAGAAAG
AGGCCGAATTTCAGCAGATGATTGAACAGCTTAAAAAGCAACAGGAGGCAGCTCAGCAGG
CAGCAACGGCAACTGCCTCAGAACATTCCAGAGAGCCCAGTGCAGCAGGCAGGCTCTCAG
ACAGCTCATCTGAAGCCTCTAAGTTGAGTTCCAAGAGTGCTAAGGAAAGAAGAAATCGGAG
GAAGAAAAGAAAACAGAAAGAGCAGTCTGGTGGGGAAGAGAAAGATGAGGATGAATTCCA
AAAATCTGAATCTGAGGACAGCATCAGGAGGAAAGGTTTTCGCTTCTCCATTGAAGGGAAC
CGATTGACATATGAAAAGAGGTACTCCTCCCCACACCAGTCTTTGTTGAGCATCCGTGGCT
CCCTATTTTCACCAAGGCGAAATAGCAGAACAAGCCTTTTCAGCTTTAGAGGGCGAGCAAA
GGATGTGGGATCTGAGAACGACTTCGCAGATGATGAGCACAGCACCTTTGAGGATAACGA
GAGCCGTAGAGATTCCTTGTTTGTGCCCCGACGACACGGAGAGAGACGCAACAGCAACCT
GAGTCAGACCAGTAGGTCATCCCGGATGCTGGCAGTGTTTCCAGCGAATGGGAAGATGCA
CAGCACTGTGGATTGCAATGGTGTGGTTTCCTTGGTTGGTGGACCTTCAGTTCCTACATCG
CCTGTTGGACAGCTTCTGCCAGAGGTGATAATAGATAAGCCAGCTACTGATGACAATGGAA
CAACCACTGAAACTGAAATGAGAAAGAGAAGGTCAAGTTCTTTCCACGTTTCCATGGACTTT
CTAGAAGATCCTTCCCAAAGGCAACGAGCAATGAGTATAGCCAGCATTCTAACAAATACAG
TAGAAGAACTTGAAGAATCCAGGCAGAAATGCCCACCCTGTTGGTATAAATTTTCCAACATA
TTCTTAATCTGGGACTGTTCTCCATATTGGTTAAAAGTGAAACATGTTGTCAACCTGGTTGT
GATGGACCCATTTGTTGACCTGGCCATCACCATCTGTATTGTCTTAAATACTCTTTTCATGG
CCATGGAGCACTATCCAATGACGGACCATTTCAATAATGTGCTTACAGTAGGAAACTTGGT

FIG. 11, cont'd

TTTCACTGGGATCTTTACAGCAGAAATGTTTCTGAAAATTATTGCCATGGATCCTTACTATTA
TTTCCAAGAAGGCTGGAATATCTTTGACGGTTTTATTGTGACGCTTAGCCTGGTAGAACTTG
GACTCGCCAATGTGGAAGGATTATCTGTTCTCCGTTCATTTCGATTGCTGCGAGTTTTCAAG
TTGGCAAAATCTTGGCCAACGTTAAATATGCTAATAAAGATCATCGGCAATTCCGTGGGGG
CTCTGGGAAATTTAACCCTCGTCTTGGCCATCATCGTCTTCATTTTTGCCGTGGTCGTGAGT
TTGGGGACCCTTGATTGTTCTTTCTTTTTCGCTATTGTAAAATTCATGTTATATGGAGGGGG
CAAAGTTTTCAGGGTGTTGTTTAGAATGGGAAGATGTCCCTTGTATCACCATGGACCCTCA
TGATAATTTTGTTTCTTTCACTTTCTACTCTGTTGACAACCATTGTCTCCTCTTATTTTCTTTT
CATTTTCTGTAACTTTTTCGTTAAACTTTAGCTTGCATTTGTAACGAATTTTTAAATTCACTTT
TGTTTATTTGTCAGATTGTAAGTACTTTCTCTAATCACTTTTTTTTCAAGGCAATCAGGGTAT
ATTATATTGTACTTCAGCACAGTTTTAGAGAACAATTGTTATAATTAAATGATAAGGTAGAAT
ATTTCTGCATATAAATTCTGGCTGGCGTGGAAATATTCTTATTGGTAGAAACAACTACACCC
TGGTCATCATCCTGCCTTTCTCTTTATGGTTACAATGATATACACTGTTTGAGATGAGGATA
AAATACTCTGAGTCCAAACCGGGCCCCTCTGCTAACCATGTTCATGCCTTCTTCTCTTTCCT
ACTCACGTGCGGACCGAGCGGCCGCAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTC
TCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCT
TTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGCTGCCTGCAGGGGCGCCTGAT
GCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTCACACCGCATACGTCAAAGCAACCAT
AGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTG
ACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCTTTCTCG
CCACGTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGAT
TTAGTGCTTTACGGCACCTCGACCCCAAAAAACTTGATTTGGGTGATGGTTCACGTAGTGG
GCCATCGCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGT
GGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATCTCGGGCTATTCTTTTGATTTATA
AGGGATTTTGCCGATTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACG
CGAATTTTAACAAAATATTAACGTTTACAATTTTATGGTGCACTCTCAGTACAATCTGCTCTG
ATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCCTGACGG
GCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATG
TGTCAGAGGTTTTCACCGTCATCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGC
CTATTTTTATAGGTTAATGTCATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCG
GGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAATATGTATCCGC
TCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATT
CAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCA
CCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTA
CATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTCGCCCCGAAGAACGTTTT
CCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCG
GGCAAGAGCAACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACC
AGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATA
ACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAG
CTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGG
AGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAA
CAACGTTGCGCAAACTATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATA
GACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGG
CTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGC
ACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGC
AACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGG
TAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAAACTTCATTTTTAATTTA
AAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTT
TCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTT

FIG. 11, cont'd

TCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTG
CCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATAC
CAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACC
GCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCG
TGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGA
ACGGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATA
CCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGT
ATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAA
CGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTG
TGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACG
GTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGT (SEQ ID NO: 49)

CN2007 - The portion between L-ITR and R-ITR corresponds to positions 142-4671:
CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCG
TCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTG
GCCAACTCCATCACTAGGGGTTCCTGCGGCCGCAGAGTTTGGGGACCCTTGATTGTTCTTT
CTTTTTCGCTATTGTAAAATTCATGTTATATGGAGGGGGCAAAGTTTTCAGGGTGTTGTTTA
GAATGGGAAGATGTCCCTTGTATCACCATGGACCCTCATGATAATTTTGTTTCTTTCACTTT
CTACTCTGTTGACAACCATTGTCTCCTCTTATTTTCTTTTCATTTTCTGTAACTTTTTCGTTAA
ACTTTAGCTTGCATTTGTAACGAATTTTTAAATTCACTTTTGTTTATTTGTCAGATTGTAAGTA
CTTTCTCTAATCACTTTTTTTTCAAGGCAATCAGGGTATATTATATTGTACTTCAGCACAGTT
TTAGAGAACAATTGTTATAATTAAATGATAAGGTAGAATATTTCTGCATATAAATTCTGGCTG
GCGTGGAAATATTCTTATTGGTAGAAACAACTACACCCTGGTCATCATCCTGCCTTTCTCTT
TATGGTTACAATGATATACACTGTTTGAGATGAGGATAAAATACTCTGAGTCCAAACCGGGC
CCCTCTGCTAACCATGTTCATGCCTTCTTCTCTTTCCTACAGGGCATGCAGCTCTTTGGTAA
AAGCTACAAAGATTGTGTCTGCAAGATCGCCAGTGATTGTCAACTCCCACGCTGGCACATG
AATGACTTCTTCCACTCCTTCCTGATTGTGTTCCGCGTGCTGTGTGGGGAGTGGATAGAGA
CCATGTGGGACTGTATGGAGGTTGCTGGTCAAGCCATGTGCCTTACTGTCTTCATGATGGT
CATGGTGATTGGAAACCTAGTGGTCCTGAATCTCTTTCTGGCCTTGCTTCTGAGCTCATTTA
GTGCAGACAACCTTGCAGCCACTGATGATGATAATGAAATGAATAATCTCCAAATTGCTGT
GGATAGGATGCACAAAGGAGTAGCTTATGTGAAAAGAAAAATATATGAATTTATTCAACAGT
CCTTCATTAGGAAACAAAAGATTTTAGATGAAATTAAACCACTTGATGATCTAAACAACAAG
AAAGACAGTTGTATGTCCAATCATACAGCAGAAATTGGGAAAGATCTTGACTATCTTAAAGA
TGTAAATGGAACTACAAGTGGTATAGGAACTGGCAGCAGTGTTGAATACATTATTGATGAAA
GTGATTACATGTCATTCATAAACAACCCCAGTCTTACTGTGACTGTACCAATTGCTGTAGGA
GAATCTGACTTTGAAAATTTAAACACGGAAGACTTTAGTAGTGAATCGGATCTGGAAGAAAG
CAAAGAGAAACTGAATGAAAGCAGTAGCTCATCAGAAGGTAGCACTGTGGACATCGGCGC
ACCTGTAGAAGAACAGCCCGTAGTGGAACCTGAAGAAACTCTTGAACCAGAAGCTTGTTTC
ACTGAAGGCTGTGTACAAAGATTCAAGTGTTGTCAAATCAATGTGGAAGAAGGCAGAGGAA
AACAATGGTGGAACCTGAGAAGGACGTGTTTCCGAATAGTTGAACATAACTGGTTTGAGAC
CTTCATTGTTTTCATGATTCTCCTTAGTAGTGGTGCTCTGGCATTTGAAGATATATATATTGA
TCAGCGAAAGACGATTAAGACGATGTTGGAATATGCTGACAAGGTTTTCACTTACATTTTCA
TTCTGGAAATGCTTCTAAAATGGGTGGCATATGGCTATCAAACATATTTCACCAATGCCTGG
TGTTGGCTGGACTTCTTAATTGTTGATGTTTCATTGGTCAGTTTAACAGCAAATGCCTTGGG
TTACTCAGAACTTGGAGCCATCAAATCTCTCAGGACACTAAGAGCTCTGAGACCTCTAAGA
GCCTTATCTCGATTTGAAGGGATGAGGGTGGTTGTGAATGCCCTTTTAGGAGCAATTCCAT
CCATCATGAATGTGCTTCTGGTTTGTCTTATATTCTGGCTAATTTTCAGCATCATGGGCGTA
AATTTGTTTGCTGGCAAATTCTACCACTGTATTAACACCACAACTGGTGACAGGTTTGACAT
CGAAGACGTGAATAATCATACTGATTGCCTAAAACTAATAGAAAGAAATGAGACTGCTCGAT

FIG. 11, cont'd

GGAAAAATGTGAAAGTAAACTTTGATAATGTAGGATTTGGGTATCTCTCTTTGCTTCAAGTT
GCCACATTCAAAGGATGGATGGATATAATGTATGCAGCAGTTGATTCCAGAAATGTGGAAC
TCCAGCCTAAGTATGAAGAAAGTCTGTACATGTATCTTTACTTTGTTATTTTCATCATCTTTG
GGTCCTTCTTCACCTTGAACCTGTTTATTGGTGTCATCATAGATAATTTCAACCAGCAGAAA
AAGAAGTTTGGAGGTCAAGACATCTTTATGACAGAAGAACAGAAGAAATACTATAATGCAAT
GAAAAAATTAGGATCGAAAAAACCGCAAAAGCCTATACCTCGACCAGGAAACAAATTTCAA
GGAATGGTCTTTGACTTCGTAACCAGACAAGTTTTTGACATAAGCATCATGATTCTCATCTG
TCTTAACATGGTCACAATGATGGTGGAAACAGATGACCAGAGTGAATATGTGACTACCATTT
TGTCACGCATCAATCTGGTGTTCATTGTGCTATTTACTGGAGAGTGTGTACTGAAACTCATC
TCTCTACGCCATTATTATTTTACCATTGGATGGAATATTTTTGATTTTGTGGTTGTCATTCTC
TCCATTGTAGGTATGTTTCTTGCCGAGCTGATAGAAAAGTATTTCGTGTCCCCTACCCTGTT
CCGAGTGATCCGTCTTGCTAGGATTGGCCGAATCCTACGTCTGATCAAAGGAGCAAAGGG
GATCCGCACGCTGCTCTTTGCTTTGATGATGTCCCTTCCTGCGTTGTTTAACATCGGCCTC
CTACTCTTCCTAGTCATGTTCATCTACGCCATCTTTGGGATGTCCAACTTTGCCTATGTTAA
GAGGGAAGTTGGGATCGATGACATGTTCAACTTTGAGACCTTTGGCAACAGCATGATCTGC
CTATTCCAAATTACAACCTCTGCTGGCTGGGATGGATTGCTAGCACCCATTCTCAACAGTA
AGCCACCCGACTGTGACCCTAATAAAGTTAACCCTGGAAGCTCAGTTAAGGGAGACTGTG
GGAACCCATCTGTTGGAATTTTCTTTTTTGTCAGTTACATCATCATATCCTTCCTGGTTGTG
GTGAACATGTACATCGCGGTCATCCTGGAGAACTTCAGTGTTGCTACTGAAGAAAGTGCAG
AGCCTCTGAGTGAGGATGACTTTGAGATGTTCTATGAGGTTTGGGAGAAGTTTGATCCCGA
TGCAACTCAGTTCATGGAATTTGAAAAATTATCTCAGTTTGCAGCTGCGCTTGAACCGCCTC
TCAATCTGCCACAACCAAACAAACTCCAGCTCATTGCCATGGATTTGCCCATGGTGAGTGG
TGACCGGATCCACTGTCTTGATATCTTATTTGCTTTTACAAAGCGGGTTCTAGGAGAGAGT
GGAGAGATGGATGCTCTACGAATACAGATGGAAGAGCGATTCATGGCTTCCAATCCTTCCA
AGGTCTCCTATCAGCCAATCACTACTACTTTAAAACGAAAACAAGAGGAAGTATCTGCTGTC
ATTATTCAGCGTGCTTACAGACGCCACCTTTTAAAGCGAACTGTAAAACAAGCTTCCTTTAC
GTACAATAAAAACAAAATCAAAGGTGGGGCTAATCTTCTTATAAAAGAAGACATGATAATTG
ACAGAATAAATGAAAACTCTATTACAGAAAAAACTGATCTGACCATGTCCACTGCAGCTTGT
CCACCTTCCTATGACCGGGTGACAAAGCCAATTGTGGAAAAACATGAGCAAGAAGGCAAA
GATGAAAAAGCCAAAGGGAAAGGAGGTGGTGGTTCAGGTGGGGGCGGCTCAGAGTACCC
CTATGATGTCCCTGATTATGCGGCGGAATACCCCTATGACGTGCCGGACTACGCGGCTGA
ATATCCGTATGACGTTCCCGATTATGCGGCTAAGCTCGAATAATGATGAGAATTCATCATAA
TCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTATGTTGCTCCTTT
TACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTATGGCTT
TCATTTTCTCCTCCTTGTATAAATCCTGGTTAGTTCTTGCCACGGCGGAACTCATCGCCGCC
TGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTGGCTCG
AGAGATCTTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCC
TTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAATAAAATGAGGAAATTGCAT
CGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAG
GGGGAGGATTGGGAAGACAATAGCAGGCATGAGATCTCACGTGCGGACCGAGCGGCCGC
AGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGG
CCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGA
GCGAGCGCGCAGCTGCCTGCAGGGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTG
CGGTATTTCACACCGCATACGTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAA
GCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCG
CCCGCTCCTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTCGCCGGCTTTCCCCGTCAAG
CTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAA
AAAACTTGATTTGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGC
CCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACT

FIG. 11, cont'd

CAACCCTATCTCGGGCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTCGGCCTATTGGT
TAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGTTTACAA
TTTTATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACA
CCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACA
GACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTCACCGTCATCACCGA
AACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAAT
AATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGT
TTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTT
CAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTT
TTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATG
CTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGA
TCCTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTA
TGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTCGCCGCATACAC
TATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACGGATGGCA
TGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTT
ACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGA
TCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGACGA
GCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACTATTAACTGGCGA
ACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCA
GGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCC
GGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTCCCG
TATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATC
GCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATAT
ACTTTAGATTGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGAT
AATCTCATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAG
AAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACA
AAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTC
CGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTGTAGCCGTA
GTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTG
TTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGA
TAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGTGCACACAGCCCAG
CTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGC
CACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAG
GAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGT
TTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTAT
GGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCA
CATGT (SEQ ID NO: 50)

CN2008 - The portion between L-ITR and R-ITR corresponds to positions 142-3995:
CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCG
TCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTG
GCCAACTCCATCACTAGGGGTTCCTGCGGCCGCACGCGTGGTACCCTAAATAAAGATGGC
TTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAA
TCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCTAAATAAA
GATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAAC
GCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCT
AAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGT
AAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGA
ATGGAGCTCGGGCTGGTCGACACAATTGGAGGTAGGCGTGTACGGTGGGAGGCCTATATA

FIG. 11, cont'd

AGCAGAGCTCGTTTAGTGAACCGTCAGATCGCCTGGAGGATCCTTCGAAAAGCTTGCTAC
CGGTGCCACCATGGAGCAAACAGTGCTTGTACCACCAGGACCTGACAGCTTCAACTTCTTC
ACCAGAGAATCTCTTGCGGCTATTGAAAGACGCATTGCAGAAGAAAAGGCAAAGAATCCCA
AACCAGACAAAAAAGATGACGACGAAAATGGCCCAAAGCCAAATAGTGACTTGGAAGCTG
GAAAGAACCTTCCATTTATTTATGGAGACATTCCTCCAGAGATGGTGTCAGAGCCCCTGGA
GGACCTGGACCCCTACTATATCAATAAGAAAACTTTTATAGTATTGAATAAAGGGAAGGCCA
TCTTCCGGTTCAGTGCCACCTCTGCCCTGTACATTTTAACTCCCTTCAATCCTCTTAGGAAA
ATAGCTATTAAGATTTTGGTACATTCATTATTCAGCATGCTAATTATGTGCACTATTTTGACA
AACTGTGTGTTTATGACAATGAGTAACCCTCCTGATTGGACAAAGAATGTAGAATACACCTT
CACAGGAATATATACTTTTGAATCACTTATAAAAATTATTGCAAGGGGATTCTGTTTAGAAGA
TTTTACTTTCCTTCGGGATCCATGGAACTGGCTCGATTTCACTGTCATTACATTTGCGTACG
TCACAGAGTTTGTGGACCTGGGCAATGTCTCGGCATTGAGAACATTCAGAGTTCTCCGAGC
ATTGAAGACGATTTCAGTCATTCCAGGCCTGAAAACCATTGTGGGAGCCCTGATCCAGTCT
GTGAAGAAGCTCTCAGATGTAATGATCCTGACTGTGTTCTGTCTGAGCGTATTTGCTCTAAT
TGGGCTGCAGCTGTTCATGGGCAACCTGAGGAATAAATGTATACAATGGCCTCCCACCAAT
GCTTCCTTGGAGGAACATAGTATAGAAAAGAATATAACTGTGAATTATAATGGTACACTTAT
AAATGAAACTGTCTTTGAGTTTGACTGGAAGTCATATATTCAAGATTCAAGATATCATTATTT
CCTGGAGGGTTTTTTAGATGCACTACTATGTGGAAATAGCTCTGATGCAGGCCAATGTCCA
GAGGGATATATGTGTGTGAAAGCTGGTAGAAATCCCAATTATGGCTACACAAGCTTTGATA
CCTTCAGTTGGGCTTTTTTGTCCTTGTTTCGACTAATGACTCAGGACTTCTGGGAAAATCTT
TATCAACTGACATTACGTGCTGCTGGGAAAACGTACATGATATTTTTTGTATTGGTCATTTTC
TTGGGCTCATTCTACCTAATAAATTTGATCCTGGCTGTGGTGGCCATGGCCTACGAGGAAC
AGAATCAGGCCACCTTGGAAGAAGCAGAACAGAAAGAGGCCGAATTTCAGCAGATGATTG
AACAGCTTAAAAAGCAACAGGAGGCAGCTCAGCAGGCAGCAACGGCAACTGCCTCAGAAC
ATTCCAGAGAGCCCAGTGCAGCAGGCAGGCTCTCAGACAGCTCATCTGAAGCCTCTAAGT
TGAGTTCCAAGAGTGCTAAGGAAAGAAGAAATCGGAGGAAGAAAAGAAAACAGAAAGAGC
AGTCTGGTGGGGAAGAGAAAGATGAGGATGAATTCCAAAAATCTGAATCTGAGGACAGCAT
CAGGAGGAAAGGTTTTCGCTTCTCCATTGAAGGGAACCGATTGACATATGAAAAGAGGTAC
TCCTCCCCACACCAGTCTTTGTTGAGCATCCGTGGCTCCCTATTTTCACCAAGGCGAAATA
GCAGAACAAGCCTTTTCAGCTTTAGAGGGCGAGCAAAGGATGTGGGATCTGAGAACGACT
TCGCAGATGATGAGCACAGCACCTTTGAGGATAACGAGAGCCGTAGAGATTCCTTGTTTGT
GCCCCGACGACACGGAGAGAGACGCAACAGCAACCTGAGTCAGACCAGTAGGTCATCCC
GGATGCTGGCAGTGTTTCCAGCGAATGGGAAGATGCACAGCACTGTGGATTGCAATGGTG
TGGTTTCCTTGGTTGGTGGACCTTCAGTTCCTACATCGCCTGTTGGACAGCTTCTGCCAGA
GGTGATAATAGATAAGCCAGCTACTGATGACAATGGAACAACCACTGAAACTGAAATGAGA
AAGAGAAGGTCAAGTTCTTTCCACGTTTCCATGGACTTTCTAGAAGATCCTTCCCAAAGGC
AACGAGCAATGAGTATAGCCAGCATTCTAACAAATACAGTAGAAGAACTTGAAGAATCCAG
GCAGAAATGCCCACCCTGTTGGTATAAATTTTCCAACATATTCTTAATCTGGGACTGTTCTC
CATATTGGTTAAAAGTGAAACATGTTGTCAACCTGGTTGTGATGGACCCATTTGTTGACCTG
GCCATCACCATCTGTATTGTCTTAAATACTCTTTTCATGGCCATGGAGCACTATCCAATGAC
GGACCATTTCAATAATGTGCTTACAGTAGGAAACTTGGTTTTCACTGGGATCTTTACAGCAG
AAATGTTTCTGAAAATTATTGCCATGGATCCTTACTATTATTTCCAAGAAGGCTGGAATATCT
TTGACGGTTTTATTGTGACGCTTAGCCTGGTAGAACTTGGACTCGCCAATGTGGAAGGATT
ATCTGTTCTCCGTTCATTTCGATTGCTGCGAGTTTTCAAGTTGGCAAAATCTTGGCCAACGT
TAAATATGCTAATAAAGATCATCGGCAATTCCGTGGGGGCTCTGGGAAATTTAACCCTCGT
CTTGGCCATCATCGTCTTCATTTTTGCCGTGGTCGTGAGTTTGGGGACCCTTGATTGTTCTT
TCTTTTTCGCTATTGTAAAATTCATGTTATATGGAGGGGGCAAAGTTTTCAGGGTGTTGTTT
AGAATGGGAAGATGTCCCTTGTATCACCATGGACCCTCATGATAATTTTGTTTCTTTCACTT
TCTACTCTGTTGACAACCATTGTCTCCTCTTATTTTCTTTTCATTTTCTGTAACTTTTTCGTTA

FIG. 11, cont'd

AACTTTAGCTTGCATTTGTAACGAATTTTTAAATTCACTTTTGTTTATTTGTCAGATTGTAAGT
ACTTTCTCTAATCACTTTTTTTTTCAAGGCAATCAGGGTATATTATATTGTACTTCAGCACAGT
TTTAGAGAACAATTGTTATAATTAAATGATAAGGTAGAATATTTCTGCATATAAATTCTGGCT
GGCGTGGAAATATTCTTATTGGTAGAAACAACTACACCCTGGTCATCATCCTGCCTTTCTCT
TTATGGTTACAATGATATACACTGTTTGAGATGAGGATAAAATACTCTGAGTCCAAACCGGG
CCCCTCTGCTAACCATGTTCATGCCTTCTTCTCTTTCCTACTCACGTGCGGACCGAGCGGC
CGCAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCACTG
AGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTGAG
CGAGCGAGCGCGCAGCTGCCTGCAGGGGCGCCTGATGCGGTATTTTCTCCTTACGCATCT
GTGCGGTATTTCACACCGCATACGTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCGCA
TTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCT
AGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTCGCCGGCTTTCCCCGT
CAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGACC
CCAAAAAACTTGATTTGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTT
TCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAA
CACTCAACCCTATCTCGGGCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTCGGCCTAT
TGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGTTT
ACAATTTTATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCC
GACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGCT
TACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTCACCGTCATCA
CCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGA
TAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTAT
TTGTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAAT
GCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTC
CCTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAA
GATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGT
AAGATCCTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCT
GCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTCGCCGCAT
ACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACGGAT
GGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCA
ACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGG
GGATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGA
CGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACTATTAACTGG
CGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTT
GCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGA
GCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTC
CCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACA
GATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCA
TATATACTTTAGATTGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTT
TTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCC
GTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCA
AACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTT
TTTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTGTAGC
CGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAAT
CCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAG
ACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGTGCACACAGC
CCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAA
GCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGA
ACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTC

FIG. 11, cont'd

GGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGC
CTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTG
CTCACATGT (SEQ ID NO: 51)

CN2009 - The portion between L-ITR and R-ITR corresponds to positions 142-4525:
CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCG
TCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTG
GCCAACTCCATCACTAGGGGTTCCTGCGGCCGCAGAGTTTGGGGACCCTTGATTGTTCTTT
CTTTTTCGCTATTGTAAAATTCATGTTATATGGAGGGGGCAAAGTTTTCAGGGTGTTGTTTA
GAATGGGAAGATGTCCCTTGTATCACCATGGACCCTCATGATAATTTTGTTTCTTTCACTTT
CTACTCTGTTGACAACCATTGTCTCCTCTTATTTTCTTTTCATTTTCTGTAACTTTTTCGTTAA
ACTTTAGCTTGCATTTGTAACGAATTTTTAAATTCACTTTTGTTTATTTGTCAGATTGTAAGTA
CTTTCTCTAATCACTTTTTTTTTCAAGGCAATCAGGGTATATTATATTGTACTTCAGCACAGTT
TTAGAGAACAATTGTTATAATTAAATGATAAGGTAGAATATTTCTGCATATAAATTCTGGCTG
GCGTGGAAATATTCTTATTGGTAGAAACAACTACACCCTGGTCATCATCCTGCCTTTCTCTT
TATGGTTACAATGATATACACTGTTTGAGATGAGGATAAAATACTCTGAGTCCAAACCGGGC
CCCTCTGCTAACCATGTTCATGCCTTCTTCTCTTTCCTACAGGGCATGCAGCTCTTTGGTAA
AAGCTACAAAGATTGTGTCTGCAAGATCGCCAGTGATTGTCAACTCCCACGCTGGCACATG
AATGACTTCTTCCACTCCTTCCTGATTGTGTTCCGCGTGCTGTGTGGGGAGTGGATAGAGA
CCATGTGGGACTGTATGGAGGTTGCTGGTCAAGCCATGTGCCTTACTGTCTTCATGATGGT
CATGGTGATTGGAAACCTAGTGGTCCTGAATCTCTTTCTGGCCTTGCTTCTGAGCTCATTTA
GTGCAGACAACCTTGCAGCCACTGATGATGATAATGAAATGAATAATCTCCAAATTGCTGT
GGATAGGATGCACAAAGGAGTAGCTTATGTGAAAAGAAAAATATATGAATTTATTCAACAGT
CCTTCATTAGGAAACAAAAGATTTTAGATGAAATTAAACCACTTGATGATCTAAACAACAAG
AAAGACAGTTGTATGTCCAATCATACAGCAGAAATTGGGAAAGATCTTGACTATCTTAAAGA
TGTAAATGGAACTACAAGTGGTATAGGAACTGGCAGCAGTGTTGAATACATTATTGATGAAA
GTGATTACATGTCATTCATAAACAACCCCAGTCTTACTGTGACTGTACCAATTGCTGTAGGA
GAATCTGACTTTGAAAATTTAAACACGGAAGACTTTAGTAGTGAATCGGATCTGGAAGAAAG
CAAAGAGAAACTGAATGAAAGCAGTAGCTCATCAGAAGGTAGCACTGTGGACATCGGCGC
ACCTGTAGAAGAACAGCCCGTAGTGGAACCTGAAGAAACTCTTGAACCAGAAGCTTGTTTC
ACTGAAGGCTGTGTACAAAGATTCAAGTGTTGTCAAATCAATGTGGAAGAAGGCAGAGGAA
AACAATGGTGGAACCTGAGAAGGACGTGTTTCCGAATAGTTGAACATAACTGGTTTGAGAC
CTTCATTGTTTTCATGATTCTCCTTAGTAGTGGTGCTCTGGCATTTGAAGATATATATATTGA
TCAGCGAAAGACGATTAAGACGATGTTGGAATATGCTGACAAGGTTTTCACTTACATTTTCA
TTCTGGAAATGCTTCTAAAATGGGTGGCATATGGCTATCAAACATATTTCACCAATGCCTGG
TGTTGGCTGGACTTCTTAATTGTTGATGTTTCATTGGTCAGTTTAACAGCAAATGCCTTGGG
TTACTCAGAACTTGGAGCCATCAAATCTCTCAGGACACTAAGAGCTCTGAGACCTCTAAGA
GCCTTATCTCGATTTGAAGGGATGAGGGTGGTTGTGAATGCCCTTTTAGGAGCAATTCCAT
CCATCATGAATGTGCTTCTGGTTTGTCTTATATTCTGGCTAATTTTCAGCATCATGGGCGTA
AATTTGTTTGCTGGCAAATTCTACCACTGTATTAACACCACAACTGGTGACAGGTTTGACAT
CGAAGACGTGAATAATCATACTGATTGCCTAAAACTAATAGAAAGAAATGAGACTGCTCGAT
GGAAAAATGTGAAAGTAAACTTTGATAATGTAGGATTTGGGTATCTCTCTTTGCTTCAAGTT
GCCACATTCAAAGGATGGATGGATATAATGTATGCAGCAGTTGATTCCAGAAATGTGGAAC
TCCAGCCTAAGTATGAAGAAAGTCTGTACATGTATCTTTACTTTGTTATTTTCATCATCTTTG
GGTCCTTCTTCACCTTGAACCTGTTTATTGGTGTCATCATAGATAATTTCAACCAGCAGAAA
AAGAAGTTTGGAGGTCAAGACATCTTTATGACAGAAGAACAGAAGAAATACTATAATGCAAT
GAAAAAATTAGGATCGAAAAAACCGCAAAAGCCTATACCTCGACCAGGAAACAAATTTCAA
GGAATGGTCTTTGACTTCGTAACCAGACAAGTTTTTGACATAAGCATCATGATTCTCATCTG
TCTTAACATGGTCACAATGATGGTGGAAACAGATGACCAGAGTGAATATGTGACTACCATTT

FIG. 11, cont'd

TGTCACGCATCAATCTGGTGTTCATTGTGCTATTTACTGGAGAGTGTGTACTGAAACTCATC
TCTCTACGCCATTATTATTTTACCATTGGATGGAATATTTTTGATTTTGTGGTTGTCATTCTC
TCCATTGTAGGTATGTTTCTTGCCGAGCTGATAGAAAAGTATTTCGTGTCCCCTACCCTGTT
CCGAGTGATCCGTCTTGCTAGGATTGGCCGAATCCTACGTCTGATCAAAGGAGCAAAGGG
GATCCGCACGCTGCTCTTTGCTTTGATGATGTCCCTTCCTGCGTTGTTTAACATCGGCCTC
CTACTCTTCCTAGTCATGTTCATCTACGCCATCTTTGGGATGTCCAACTTTGCCTATGTTAA
GAGGGAAGTTGGGATCGATGACATGTTCAACTTTGAGACCTTTGGCAACAGCATGATCTGC
CTATTCCAAATTACAACCTCTGCTGGCTGGGATGGATTGCTAGCACCCATTCTCAACAGTA
AGCCACCCGACTGTGACCCTAATAAAGTTAACCCTGGAAGCTCAGTTAAGGGAGACTGTG
GGAACCCATCTGTTGGAATTTTCTTTTTTGTCAGTTACATCATCATATCCTTCCTGGTTGTG
GTGAACATGTACATCGCGGTCATCCTGGAGAACTTCAGTGTTGCTACTGAAGAAAGTGCAG
AGCCTCTGAGTGAGGATGACTTTGAGATGTTCTATGAGGTTTGGGAGAAGTTTGATCCCGA
TGCAACTCAGTTCATGGAATTTGAAAAATTATCTCAGTTTGCAGCTGCGCTTGAACCGCCTC
TCAATCTGCCACAACCAAACAAACTCCAGCTCATTGCCATGGATTTGCCCATGGTGAGTGG
TGACCGGATCCACTGTCTTGATATCTTATTTGCTTTTACAAAGCGGGTTCTAGGAGAGAGT
GGAGAGATGGATGCTCTACGAATACAGATGGAAGAGCGATTCATGGCTTCCAATCCTTCCA
AGGTCTCCTATCAGCCAATCACTACTACTTTAAAACGAAAACAAGAGGAAGTATCTGCTGTC
ATTATTCAGCGTGCTTACAGACGCCACCTTTTAAAGCGAACTGTAAAACAAGCTTCCTTTAC
GTACAATAAAAACAAAATCAAAGGTGGGGCTAATCTTCTTATAAAAGAAGACATGATAATTG
ACAGAATAAATGAAAACTCTATTACAGAAAAAACTGATCTGACCATGTCCACTGCAGCTTGT
CCACCTTCCTATGACCGGGTGACAAAGCCAATTGTGGAAAAACATGAGCAAGAAGGCAAA
GATGAAAAAGCCAAAGGGAAATAATGACATCATAATCAACCTCTGGATTACAAAATTTGTGA
AAGATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAAT
GCCTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTATAAATCCTG
GTTAGTTCTTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGG
CTCGGCTGTTGGGCACTGACAATTCCGTGGCTCGAGAGATCTTCGACTGTGCCTTCTAGTT
GCCAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTC
CCACTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCT
ATTCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCA
GGCATGAGATCTCACGTGCGGACCGAGCGGCCGCAGGAACCCCTAGTGATGGAGTTGGC
CACTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGAC
GCCCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGCTGCCTGCAGGG
GCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTCACACCGCATACGTCAA
AGCAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACG
CGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTCCCT
TCCTTTCTCGCCACGTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAG
GGTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAAACTTGATTTGGGTGATGGTTC
ACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTC
TTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATCTCGGGCTATTCTTT
TGATTTATAAGGGATTTTGCCGATTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACAAA
AATTTAACGCGAATTTTAACAAAATATTAACGTTTACAATTTTATGGTGCACTCTCAGTACAA
TCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGC
CCTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGA
GCTGCATGTGTCAGAGGTTTTCACCGTCATCACCGAAACGCGCGAGACGAAAGGGCCTCG
TGATACGCCTATTTTTATAGGTTAATGTCATGATAATAATGGTTTCTTAGACGTCAGGTGGC
ACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAATATG
TATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTAT
GAGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTTT
TGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGT

FIG. 11, cont'd

GGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTCGCCCCGAAGAA
CGTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGA
CGCCGGGCAAGAGCAACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTA
CTCACCAGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCT
GCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCG
AAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGG
AACCGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAA
TGGCAACAACGTTGCGCAAACTATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAACA
ATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCC
GGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCAT
TGCAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAG
TCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAG
CATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAAACTTCATTTTT
AATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAACGT
GAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATC
CTTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGT
TTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCG
CAGATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTG
TAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCG
ATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGT
CGGGCTGAACGGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAA
CTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCG
GACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGG
GGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGA
TTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTT
TTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGT (SEQ ID NO: 52)

AVV9 VP1 capsid protein:
MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPGNGLDK
GEPVNAADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAVFQAKK
RLLEPLGLVEEAAKTAPGKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTESVPDP
QPIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDRVITTSTRT
WALPTYNNHLYKQISNSTSGGSSNDNAYFGYSTPWGYFDFNRFHCHFSPRDWQRLINNNWG
FRPKRLNFKLFNIQVKEVTDNNGVKTIANNLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADV
FMIPQYGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQFSYEFENVPFHSSYAHSQSLD
RLMNPLIDQYLYYLSKTINGSGQNQQTLKFSVAGPSNMAVQGRNYIPGPSYRQQRVSTTVTQN
NNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVDADK
VMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDRDVYLQGPIW
AKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDKLNSFITQYSTGQVSVEIE
WELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL (SEQ ID NO:
57)

FIG. 11, cont'd

CN2026-rAAV-3xhl56i(core)-minBG-hSCN1A_Fragment1-WPRE3-BGHpA:
CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCG
TCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTG
GCCAACTCCATCACTAGGGGTTCCTGCGGCCGCACGCGTGGTACCCTAAATAAAGATGGC
TTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAA
TCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCTAAATAAA
GATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAAC
GCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCT
AAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGT
AAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGA
ATGGAGCTCGGGCTGGGCATAAAAGTCAGGGCAGAGCCATCTATTGCTTACATTTGCTTCT
GGGATCCAGATCTTTCGAAGCTAGCGCTACCACCATGGAGCAAACAGTGCTTGTACCACC
AGGACCTGACAGCTTCAACTTCTTCACCAGAGAATCTCTTGCGGCTATTGAAAGACGCATT
GCAGAAGAAAAGGCAAAGAATCCCAAACCAGACAAAAAAGATGACGACGAAAATGGCCCA
AAGCCAAATAGTGACTTGGAAGCTGGAAAGAACCTTCCATTTATTTATGGAGACATTCCTCC
AGAGATGGTGTCAGAGCCCCTGGAGGACCTGGACCCCTACTATATCAATAAGAAAACTTTT
ATAGTATTGAATAAAGGGAAGGCCATCTTCCGGTTCAGTGCCACCTCTGCCCTGTACATTT
TAACTCCCTTCAATCCTCTTAGGAAAATAGCTATTAAGATTTTGGTACATTCATTATTCAGCA
TGCTAATTATGTGCACTATTTTGACAAACTGTGTGTTTATGACAATGAGTAACCCTCCTGATT
GGACAAAGAATGTAGAATACACCTTCACAGGAATATATACTTTTGAATCACTTATAAAAATTA
TTGCAAGGGGATTCTGTTTAGAAGATTTTACTTTCCTTCGGGATCCATGGAACTGGCTCGAT
TTCACTGTCATTACATTTGCGTACGTCACAGAGTTTGTGGACCTGGGCAATGTCTCGGCAT
TGAGAACATTCAGAGTTCTCCGAGCATTGAAGACGATTTCAGTCATTCCAGGCCTGAAAAC
CATTGTGGGAGCCCTGATCCAGTCTGTGAAGAAGCTCTCAGATGTAATGATCCTGACTGTG
TTCTGTCTGAGCGTATTTGCTCTAATTGGGCTGCAGCTGTTCATGGGCAACCTGAGGAATA
AATGTATACAATGGCCTCCCACCAATGCTTCCTTGGAGGAACATAGTATAGAAAAGAATATA
ACTGTGAATTATAATGGTACACTTATAAATGAAACTGTCTTTGAGTTTGACTGGAAGTCATAT
ATTCAAGATTCAAGATATCATTATTTCCTGGAGGGTTTTTTAGATGCACTACTATGTGGAAAT
AGCTCTGATGCAGGCCAATGTCCAGAGGGATATATGTGTGTGAAAGCTGGTAGAAATCCCA
ATTATGGCTACACAAGCTTTGATACCTTCAGTTGGGCTTTTTTGTCCTTGTTTCGACTAATG
ACTCAGGACTTCTGGGAAAATCTTTATCAACTGACATTACGTGCTGCTGGGAAAACGTACA
TGATATTTTTTGTGTTGGTCATTTTCTTGGGCTCATTCTACCTAATAAATTTGATCCTGGCTG
TGGTGGCCATGGCCTACGAGGAACAGAATCAGGCCACCTTGGAAGAAGCAGAACAGAAAG
AGGCCGAATTTCAGCAGATGATTGAACAGCTTAAAAAGCAACAGGAGGCAGCTCAGCAGG
CAGCAACGGCAACTGCCTCAGAACATTCCAGAGAGCCCAGTGCAGCAGGCAGGCTCTCAG
ACAGCTCATCTGAAGCCTCTAAGTTGAGTTCCAAGAGTGCTAAGGAAAGAAGAAATCGGAG
GAAGAAAAGAAAACAGAAAGAGCAGTCTGGTGGGGAAGAGAAAGATGAGGATGAATTCCA
AAAATCTGAATCTGAGGACAGCATCAGGAGGAAAGGTTTTCGCTTCTCCATTGAAGGGAAC
CGATTGACATATGAAAAGAGGTACTCCTCCCCACACCAGTCTTTGTTGAGCATCCGTGGCT
CCCTATTTTCACCAAGGCGAAATAGCAGAACAAGCCTTTTCAGCTTTAGAGGGCGAGCAAA
GGATGTGGGATCTGAGAACGACTTCGCAGATGATGAGCACAGCACCTTTGAGGATAACGA
GAGCCGTAGAGATTCCTTGTTTGTGCCCCGACGACACGGAGAGAGACGCAACAGCAACCT
GAGTCAGACCAGTAGGTCATCCCGGTGATGACGGCGCGCCGCGGCCGCGAATTCGATAT
CATAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTATGTTGCT
CCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTAT
GGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTAGTTCTTGCCACGGCGGAACTCATCG
CCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGTG
GCTCGAGAGATCTTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCTCCCCC
GTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAATAAAATGAGGAAA

FIG. 11, cont'd

TTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGACA
GCAAGGGGGAGGATTGGGAAGACAATAGCAGGCATGAGATCTCACGTGCGGACCGAGCG
GCCGCAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCAC
TGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGTG
AGCGAGCGAGCGCGCAGCTGCCTGCAGGGGCGCCTGATGCGGTATTTTCTCCTTACGCAT
CTGTGCGGTATTTCACACCGCATACGTCAAAGCAACCATAGTACGCGCCCTGTAGCGGCG
CATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCC
CTAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTCGCCGGCTTTCCCC
GTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTCGA
CCCCAAAAAACTTGATTTGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTT
TTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAAC
AACACTCAACCCTATCTCGGGCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTCGGCCT
ATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGT
TTACAATTTTATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCC
CGACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATCCGC
TTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTCACCGTCATCA
CCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGA
TAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTAT
TTGTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGATAAAT
GCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTTATTC
CCTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAA
GATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGT
AAGATCCTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCT
GCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTCGCCGCAT
ACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACGGAT
GGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCA
ACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGG
GGATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGA
CGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACTATTAACTGG
CGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTT
GCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGA
GCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCCCTC
CCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACA
GATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCA
TATATACTTTAGATTGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTT
TTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACCCC
GTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTGCA
AACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTT
TTTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTGTAGC
CGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAAT
CCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAG
ACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGTGCACACAGC
CCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAA
GCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGA
ACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTC
GGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGC
CTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTG
CTCACATGT (SEQ ID NO: 58)

FIG. 11, cont'd

CN2027-rAAV-3xhl56i(core)-minBG-hSCN1A_Fragment2-WPRE3-BGHpA
CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCG
TCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTG
GCCAACTCCATCACTAGGGGTTCCTGCGGCCGCACGCGTGGTACCCTAAATAAAGATGGC
TTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAA
TCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCTAAATAAA
GATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAAC
GCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCT
AAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGT
AAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGA
ATGGAGCTCGGGCTGGGCATAAAAGTCAGGGCAGAGCCATCTATTGCTTACATTTGCTTCT
GGGATCCAGATCTTTCGAAGCTAGCGCTACCACCATGCTGGCAGTGTTTCCAGCGAATGG
GAAGATGCACAGCACTGTGGATTGCAATGGTGTGGTTTCCTTGGTTGGTGGACCTTCAGTT
CCTACATCGCCTGTTGGACAGCTTCTGCCAGAGGTGATAATAGATAAGCCAGCTACTGATG
ACAATGGAACAACCACTGAAACTGAAATGAGAAAGAGAAGGTCAAGTTCTTTCCACGTTTC
CATGGACTTTCTAGAAGATCCTTCCCAAAGGCAACGAGCAATGAGTATAGCCAGCATTCTA
ACAAATACAGTAGAAGAACTTGAAGAATCCAGGCAGAAATGCCCACCCTGTTGGTATAAAT
TTTCCAACATATTCTTAATCTGGGACTGTTCTCCATATTGGTTAAAAGTGAAACATGTTGTCA
ACCTGGTCGTGATGGACCCATTTGTTGACCTGGCCATCACCATCTGTATTGTCTTAAATACT
CTTTTCATGGCCATGGAGCACTATCCAATGACGGACCATTTCAATAATGTGCTTACAGTAG
GAAACTTGGTTTTCACTGGGATCTTTACAGCAGAAATGTTTCTGAAAATTATTGCCATGGAT
CCTTACTATTATTTCCAAGAAGGCTGGAATATCTTTGACGGTTTTATTGTGACGCTTAGCCT
GGTAGAACTTGGACTCGCCAATGTGGAAGGATTATCTGTTCTCCGTTCATTTCGATTGCTG
CGAGTTTTCAAGTTGGCAAAATCTTGGCCAACGTTAAATATGCTAATAAAGATCATCGGCAA
TTCCGTGGGGGCTCTGGGAAATTTAACCCTCGTCTTGGCCATCATCGTCTTCATTTTTGCC
GTGGTCGGCATGCAGCTCTTTGGTAAAAGCTACAAAGATTGTGTCTGCAAGATCGCCAGTG
ATTGTCAACTCCCACGCTGGCACATGAATGACTTCTTCCACTCCTTCCTGATTGTGTTCCGC
GTGCTGTGTGGGGAGTGGATAGAGACCATGTGGGACTGTATGGAGGTTGCTGGTCAAGCC
ATGTGCCTTACTGTCTTCATGATGGTCATGGTGATTGGAAACCTAGTGGTCCTGAATCTCTT
TCTGGCCTTGCTTCTGAGCTCATTTAGTGCAGACAACCTTGCAGCCACTGATGATGATAAT
GAAATGAATAATCTCCAAATTGCTGTGGATAGGATGCACAAAGGAGTAGCTTATGTGAAAA
GAAAAATATATGAATTTATTCAACAGTCCTTCATTAGGAAACAAAAGATTTTAGATGAAATTA
AACCACTTGATGATCTAAACAACAAGAAAGACAGTTGTTGATGACGGCGCGCCGCGGCCG
CGAATTCGATATCATAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTT
AACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATT
GCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTAGTTCTTGCCACGGC
GGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTG
ACAATTCCGTGGCTCGAGAGATCTTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTT
GCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAATA
AAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGTG
GGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCATGAGATCTCACGTGC
GGACCGAGCGGCCGCAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCT
CGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGG
CGGCCTCAGTGAGCGAGCGAGCGCGCAGCTGCCTGCAGGGGCGCCTGATGCGGTATTTT
CTCCTTACGCATCTGTGCGGTATTTCACACCGCATACGTCAAAGCAACCATAGTACGCGCC
CTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACAC
TTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTCGC
CGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTA
CGGCACCTCGACCCCAAAAAACTTGATTTGGGTGATGGTTCACGTAGTGGGCCATCGCCC

FIG. 11, cont'd

TGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTT
CCAAACTGGAACAACACTCAACCCTATCTCGGGCTATTCTTTTGATTTATAAGGGATTTTGC
CGATTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACA
AAATATTAACGTTTACAATTTTATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAG
TTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCT
CCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTT
TTCACCGTCATCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAG
GTTAATGTCATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGC
GCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAAT
AACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGT
GTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCT
GGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGA
TCTCAACAGCGGTAAGATCCTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGC
ACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAAC
TCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAA
GCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGAT
AACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTT
TGCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAG
CCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCA
AACTATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGA
GGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGC
TGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGA
TGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGA
ACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGAC
CAAGTTTACTCATATATACTTTAGATTGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGG
TGAAGATCCTTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCACTGA
GCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAAT
CTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAG
CTACCAACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCC
TTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCT
CGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGG
GTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTT
CGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTG
AGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGC
GGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCT
TTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCA
GGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTT
TGCTGGCCTTTTGCTCACATGT (SEQ ID NO: 59)

CN2028-rAAV-3xhI56i(core)-minBG-hSCN1A_Fragment3-WPRE3-BGHpA
CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCG
TCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTG
GCCAACTCCATCACTAGGGGTTCCTGCGGCCGCACGCGTGGTACCCTAAATAAAGATGGC
TTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAA
TCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCTAAATAAA
GATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAAC
GCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCT
AAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGT
AAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGA

FIG. 11, cont'd

ATGGAGCTCGGGCTGGGCATAAAAGTCAGGGCAGAGCCATCTATTGCTTACATTTGCTTCT
GGGATCCAGATCTTTCGAAGCTAGCGCTACCACCATGTCCAATCATACAACAGAAATTGGG
AAAGATCTTGACTATCTTAAAGATGTAAATGGAACTACAAGTGGTATAGGAACTGGCAGCA
GTGTTGAAAAATACATTATTGATGAAAGTGATTACATGTCATTCATAAACAACCCCAGTCTTA
CTGTGACTGTACCAATTGCTGTAGGAGAATCTGACTTTGAAAATTTAAACACGGAAGACTTT
AGTAGTGAATCGGATCTGGAAGAAAGCAAAGAGAAACTGAATGAAAGCAGTAGCTCATCAG
AAGGTAGCACTGTGGACATCGGCGCACCTGTAGAAGAACAGCCCGTAGTGGAACCTGAAG
AAACTCTTGAACCAGAAGCTTGTTTCACTGAAGGCTGTGTACAAAGATTCAAGTGTTGTCAA
ATCAATGTGGAAGAAGGCAGAGGAAAACAATGGTGGAACCTGAGAAGGACGTGTTTCCGA
ATAGTTGAACATAACTGGTTTGAGACCTTCATTGTTTTCATGATTCTCCTTAGTAGTGGTGC
TCTGGCATTTGAAGATATATATATTGATCAGCGAAAGACGATTAAGACGATGTTGGAATATG
CTGACAAGGTTTTCACTTACATTTTCATTCTGGAAATGCTTCTAAAATGGGTGGCATATGGC
TATCAAACATATTTCACCAATGCCTGGTGTTGGCTGGACTTCTTAATTGTTGATGTTTCATTG
GTCAGTTTAACAGCAAATGCCTTGGGTTACTCAGAACTTGGAGCCATCAAATCTCTCAGGA
CACTAAGAGCTCTGAGACCTCTAAGAGCCTTATCTCGATTTGAAGGGATGAGGGTGGTTGT
GAATGCCCTTTTAGGAGCAATTCCATCCATCATGAATGTGCTTCTGGTTTGTCTTATATTCT
GGCTAATTTTCAGCATCATGGGCGTAAATTTGTTTGCTGGCAAATTCTACCACTGTATTAAC
ACCACAACTGGTGACAGGTTTGACATCGAAGACGTGAATAATCATACTGATTGCCTAAAAC
TAATAGAAAGAAATGAGACTGCTCGATGGAAAAATGTGAAAGTAAACTTTGATAATGTAGGA
TTTGGGTATCTCTCTTTGCTTCAAGTTGCCACATTCAAAGGATGGATGGATATAATGTATGC
AGCAGTTGATTCCAGAAATGTGGAACTCCAGCCTAAGTATGAAGAAAGTCTGTACATGTAT
CTTTACTTTGTTATTTTCATCATCTTTGGGTCCTTCTTCACCTTGAACCTGTTTATTGGTGTC
ATCATAGATAATTTCAACCAGCAGAAAAAGAAGTTTGGAGGTCAAGACATCTTTTGATGACG
GCGCGCCGCGGCCGCGAATTCGATATCATAATCAACCTCTGGATTACAAAATTTGTGAAAG
ATTGACTGGTATTCTTAACTATGTTGCTCCTTTTACGCTATGTGGATACGCTGCTTTAATGC
CTTTGTATCATGCTATTGCTTCCCGTATGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGT
TAGTTCTTGCCACGGCGGAACTCATCGCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTC
GGCTGTTGGGCACTGACAATTCCGTGGCTCGAGAGATCTTCGACTGTGCCTTCTAGTTGC
CAGCCATCTGTTGTTTGCCCCTCCCCCGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCC
ACTGTCCTTTCCTAATAAAATGAGGAAATTGCATCGCATTGTCTGAGTAGGTGTCATTCTAT
TCTGGGGGGTGGGGTGGGGCAGGACAGCAAGGGGGAGGATTGGGAAGACAATAGCAGG
CATGAGATCTCACGTGCGGACCGAGCGGCCGCAGGAACCCCTAGTGATGGAGTTGGCCA
CTCCCTCTCTGCGCGCTCGCTCGCTCACTGAGGCCGGGCGACCAAAGGTCGCCCGACGC
CCGGGCTTTGCCCGGGCGGCCTCAGTGAGCGAGCGAGCGCGCAGCTGCCTGCAGGGGC
GCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTCACACCGCATACGTCAAAG
CAACCATAGTACGCGCCCTGTAGCGGCGCATTAAGCGCGGCGGGTGTGGTGGTTACGCG
CAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTCGCTTTCTTCCCTTC
CTTTCTCGCCACGTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGG
GTTCCGATTTAGTGCTTTACGGCACCTCGACCCCAAAAAACTTGATTTGGGTGATGGTTCA
CGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCT
TTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATCTCGGGCTATTCTTTT
GATTTATAAGGGATTTTGCCGATTTCGGCCTATTGGTTAAAAAATGAGCTGATTTAACAAAA
ATTTAACGCGAATTTTAACAAAATATTAACGTTTACAATTTTATGGTGCACTCTCAGTACAAT
CTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCC
CTGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAG
CTGCATGTGTCAGAGGTTTTCACCGTCATCACCGAAACGCGCGAGACGAAAGGGCCTCGT
GATACGCCTATTTTTATAGGTTAATGTCATGATAATAATGGTTTCTTAGACGTCAGGTGGCA
CTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAATATGT
ATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATG

FIG. 11, cont'd

AGTATTCAACATTTCCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTTTT
GCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTG
GGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTCGCCCCGAAGAAC
GTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGAC
GCCGGGCAAGAGCAACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTAC
TCACCAGTCACAGAAAAGCATCTTACGGATGGCATGACAGTAAGAGAATTATGCAGTGCTG
CCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACCGAA
GGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAA
CCGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATG
GCAACAACGTTGCGCAAACTATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAAT
TAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCGG
CTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTG
CAGCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTC
AGGCAACTATGGATGAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCA
TTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAAACTTCATTTTTAA
TTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGA
GTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCT
TTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTT
GTTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGCA
GATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTA
GCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGAT
AAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCG
GGCTGAACGGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACT
GAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGG
ACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGG
GGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGAT
TTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTT
TACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGT (SEQ ID NO: 60)

CN2029-rAAV-3xhl56i(core)-minBG-hSCN1A_Fragment4-WPRE3-BGHpA
CCTGCAGGCAGCTGCGCGCTCGCTCGCTCACTGAGGCCGCCCGGGCAAAGCCCGGGCG
TCGGGCGACCTTTGGTCGCCCGGCCTCAGTGAGCGAGCGAGCGCGCAGAGAGGGAGTG
GCCAACTCCATCACTAGGGGTTCCTGCGGCCGCACGCGTGGTACCCTAAATAAAGATGGC
TTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAACGCTGTAA
TCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCTAAATAAA
GATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGTAAAAAC
GCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGAATGGCT
AAATAAAGATGGCTTTTTAGTATTAAAAGTGGAAGAAAATTACAGGTAATTATCTTTGACGGT
AAAAACGCTGTAATCAGCGGGCTACATGAAAAATTACTCTAATTATGGCTGCATTTAAGAGA
ATGGAGCTCGGGCTGGGCATAAAAGTCAGGGCAGAGCCATCTATTGCTTACATTTGCTTCT
GGGATCCAGATCTTTCGAAGCTAGCGCTACCACCATGACAGAAGAACAGAAGAAATACTAT
AATGCAATGAAAAAATTAGGATCGAAAAAACCGCAAAAGCCTATACCTCGACCAGGAAACA
AATTTCAAGGAATGGTCTTTGACTTCGTAACCAGACAAGTTTTTGACATAAGCATCATGATT
CTCATCTGTCTTAACATGGTCACAATGATGGTGGAAACAGATGACCAGAGTGAATATGTGA
CTACCATTTTGTCACGCATCAATCTGGTGTTCATTGTGCTATTTACTGGAGAGTGTGTACTG
AAACTCATCTCTCTACGCCATTATTATTTTACCATTGGATGGAATATTTTTGATTTTGTGGTT
GTCATTCTCTCCATTGTAGGTATGTTTCTTGCCGAGCTGATAGAAAAGTATTTCGTGTCCCC
TACCCTGTTCCGAGTGATCCGTCTTGCTAGGATTGGCCGAATCCTACGTCTGATCAAAGGA
GCAAAGGGGATCCGCACGCTGCTCTTTGCTTTGATGATGTCCCTTCCTGCGTTGTTTAACA

FIG. 11, cont'd

TCGGCCTCCTACTCTTCCTAGTCATGTTCATCTACGCCATCTTTGGGATGTCCAACTTTGCC
TATGTTAAGAGGGAAGTTGGGATCGATGACATGTTCAACTTTGAGACCTTTGGCAACAGCA
TGATCTGCCTATTCCAAATTACAACCTCTGCTGGCTGGGATGGATTGCTAGCACCCATTCT
CAACAGTAAGCCACCCGACTGTGACCCTAATAAAGTTAACCCTGGAAGCTCAGTTAAGGGA
GACTGTGGGAACCCATCTGTTGGAATTTTCTTTTTTGTCAGTTACATCATCATATCCTTCCT
GGTTGTGGTGAACATGTACATCGCGGTCATCCTGGAGAACTTCAGTGTTGCTACTGAAGAA
AGTGCAGAGCCTCTGAGTGAGGATGACTTTGAGATGTTCTATGAGGTTTGGGAGAAGTTTG
ATCCCGATGCAACTCAGTTCATGGAATTTGAAAAATTATCTCAGTTTGCAGCTGCGCTTGAA
CCGCCTCTCAATCTGCCACAACCAAACAAACTCCAGCTCATTGCCATGGATTTGCCCATGG
TGAGTGGTGACCGGATCCACTGTCTTGATATCTTATTTGCTTTTACAAAGCGGGTTCTAGGA
GAGAGTGGAGAGATGGATGCTCTACGAATACAGATGGAAGAGCGATTCATGGCTTCCAAT
CCTTCCAAGGTCTCCTATCAGCCAATCACTACTACTTTAAAACGAAAACAAGAGGAAGTATC
TGCTGTCATTATTCAGCGTGCTTACAGACGCCACCTTTTAAAGCGAACTGTAAAACAAGCTT
CCTTTACGTACAATAAAAACAAAATCAAAGGTGGGGCTAATCTTCTTATAAAAGAAGACATG
ATAATTGACAGAATAAATGAAAACTCTATTACAGAAAAAACTGATCTGACCATGTCCACTGC
AGCTTGTCCACCTTCCTATGACCGGGTGACAAAGCCAATTGTGGAAAAACATGAGCAAGAA
GGCAAAGATGAAAAAGCCAAAGGGAAATAATGACGGCGCGCCGCGGCCGCGAATTCGATA
TCATAATCAACCTCTGGATTACAAAATTTGTGAAAGATTGACTGGTATTCTTAACTATGTTGC
TCCTTTTACGCTATGTGGATACGCTGCTTTAATGCCTTTGTATCATGCTATTGCTTCCCGTA
TGGCTTTCATTTTCTCCTCCTTGTATAAATCCTGGTTAGTTCTTGCCACGGCGGAACTCATC
GCCGCCTGCCTTGCCCGCTGCTGGACAGGGGCTCGGCTGTTGGGCACTGACAATTCCGT
GGCTCGAGAGATCTTCGACTGTGCCTTCTAGTTGCCAGCCATCTGTTGTTTGCCCCTCCCC
CGTGCCTTCCTTGACCCTGGAAGGTGCCACTCCCACTGTCCTTTCCTAATAAAATGAGGAA
ATTGCATCGCATTGTCTGAGTAGGTGTCATTCTATTCTGGGGGGTGGGGTGGGGCAGGAC
AGCAAGGGGGAGGATTGGGAAGACAATAGCAGGCATGAGATCTCACGTGCGGACCGAGC
GGCCGCAGGAACCCCTAGTGATGGAGTTGGCCACTCCCTCTCTGCGCGCTCGCTCGCTCA
CTGAGGCCGGGCGACCAAAGGTCGCCCGACGCCCGGGCTTTGCCCGGGCGGCCTCAGT
GAGCGAGCGAGCGCGCAGCTGCCTGCAGGGGCGCCTGATGCGGTATTTTCTCCTTACGC
ATCTGTGCGGTATTTCACACCGCATACGTCAAAGCAACCATAGTACGCGCCCTGTAGCGG
CGCATTAAGCGCGGCGGGTGTGGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCG
CCCTAGCGCCCGCTCCTTTCGCTTTCTTCCCTTCCTTTCTCGCCACGTTCGCCGGCTTTCC
CCGTCAAGCTCTAAATCGGGGGCTCCCTTTAGGGTTCCGATTTAGTGCTTTACGGCACCTC
GACCCCAAAAAACTTGATTTGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACG
GTTTTTCGCCCTTTGACGTTGGAGTCCACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGG
AACAACACTCAACCCTATCTCGGGCTATTCTTTTGATTTATAAGGGATTTTGCCGATTTCGG
CCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAA
CGTTTACAATTTTATGGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAG
CCCCGACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGTCTGCTCCCGGCATC
CGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTCACCGTC
ATCACCGAAACGCGCGAGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTC
ATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCC
CTATTTGTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATAACCCTGAT
AAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCCTT
ATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGT
AAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAG
CGGTAAGATCCTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAA
GTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCGGTCGC
CGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTAC
GGATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCG

FIG. 11, cont'd

GCCAACTTACTTCTGACAACGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACA
TGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAA
ACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACTATTAA
CTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAA
AGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCT
GGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGATGGTAAGCC
CTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGA
CAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACT
CATATATACTTTAGATTGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCT
TTTTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGTCAGACC
CCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTG
CAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTC
TTTTTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTGTA
GCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTA
ATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCA
AGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGTGCACACA
GCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGA
AAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCG
GAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTG
TCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGA
GCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTT
TGCTCACATGT (SEQ ID NO: 61)

hSCN1A_Fragment1_ProteinSequence
MEQTVLVPPGPDSFNFFTRESLAAIERRIAEEKAKNPKPDKKDDDENGPKPNSDLEAGKNLPFI
YGDIPPEMVSEPLEDLDPYYINKKTFIVLNKGKAIFRFSATSALYILTPFNPLRKIAIKILVHSLFSML
IMCTILTNCVFMTMSNPPDWTKNVEYTFTGIYTFESLIKIIARGFCLEDFTFLRDPWNWLDFTVIT
FAYVTEFVDLGNVSALRTFRVLRALKTISVIPGLKTIVGALIQSVKKLSDVMILTVFCLSVFALIGLQ
LFMGNLRNKCIQWPPTNASLEEHSIEKNITVNYNGTLINETVFEFDWKSYIQDSRYHYFLEGFLD
ALLCGNSSDAGQCPEGYMCVKAGRNPNYGYTSFDTFSWAFLSLFRLMTQDFWENLYQLTLRA
AGKTYMIFFVLVIFLGSFYLINLILAVVAMAYEEQNQATLEEAEQKEAEFQQMIEQLKKQQEAAQ
QAATATASEHSREPSAAGRLSDSSSEASKLSSKSAKERRNRRKKRKQKEQSGGEEKDEDEFQ
KSESEDSIRRKGFRFSIEGNRLTYEKRYSSPHQSLLSIRGSLFSPRRNSRTSLFSFRGRAKDVG
SENDFADDEHSTFEDNESRRDSLFVPRRHGERRNSNLSQTSRSSR* (SEQ ID NO: 62)

hSCN1A_Fragment2_ProteinSequence
MLAVFPANGKMHSTVDCNGVVSLVGGPSVPTSPVGQLLPEVIIDKPATDDNGTTTETEMRKRR
SSSFHVSMDFLEDPSQRQRAMSIASILTNTVEELEESRQKCPPCWYKFSNIFLIWDCSPYWLKV
KHVVNLVVMDPFVDLAITICIVLNTLFMAMEHYPMTDHFNNVLTVGNLVFTGIFTAEMFLKIIAMD
PYYYFQEGWNIFDGFIVTLSLVELGLANVEGLSVLRSFRLLRVFKLAKSWPTLNMLIKIIGNSVGA
LGNLTLVLAIIVFIFAVVGMQLFGKSYKDCVCKIASDCQLPRWHMNDFFHSFLIVFRVLCGEWIE
TMWDCMEVAGQAMCLTVFMMVMVIGNLVVLNLFLALLLSSFSADNLAATDDDNEMNNLQIAVD
RMHKGVAYVKRKIYEFIQQSFIRKQKILDEIKPLDDLNNKKDSC* (SEQ ID NO: 63)

hSCN1A_Fragment3_ProteinSequence
MSNHTTEIGKDLDYLKDVNGTTSGIGTGSSVEKYIIDESDYMSFINNPSLTVTVPIAVGESDFENL
NTEDFSSESDLEESKEKLNESSSSSEGSTVDIGAPVEEQPVVEPEETLEPEACFTEGCVQRFK
CCQINVEEGRGKQWWNLRRTCFRIVEHNWFETFIVFMILLSSGALAFEDIYIDQRKTIKTMLEYA
DKVFTYIFILEMLLKWVAYGYQTYFTNAWCWLDFLIVDVSLVSLTANALGYSELGAIKSLRTLRAL

FIG. 11, cont'd

RPLRALSRFEGMRVVVNALLGAIPSIMNVLLVCLIFWLIFSIMGVNLFAGKFYHCINTTTGDRFDI
EDVNNHTDCLKLIERNETARWKNVKVNFDNVGFGYLSLLQVATFKGWMDIMYAAVDSRNVEL
QPKYEESLYMYLYFVIFIIFGSFFTLNLFIGVIIDNFNQQKKKFGGQDIF* (SEQ ID NO: 64)

hSCN1A_Fragment4_ProteinSequence
MTEEQKKYYNAMKKLGSKKPQKPIPRPGNKFQGMVFDFVTRQVFDISIMILICLNMVTMMVETD
DQSEYVTTILSRINLVFIVLFTGECVLKLISLRHYYFTIGWNIFDFVVVILSIVGMFLAELIEKYFVSP
TLFRVIRLARIGRILRLIKGAKGIRTLLFALMMSLPALFNIGLLLFLVMFIYAIFGMSNFAYVKREVGI
DDMFNFETFGNSMICLFQITTSAGWDGLLAPILNSKPPDCDPNKVNPGSSVKGDCGNPSVGIFF
FVSYIIISFLVVVNMYIAVILENFSVATEESAEPLSEDDFEMFYEVWEKFDPDATQFMEFEKLSQF
AAALEPPLNLPQPNKLQLIAMDLPMVSGDRIHCLDILFAFTKRVLGESGEMDALRIQMEERFMA
SNPSKVSYQPITTTLKRKQEEVSAVIIQRAYRRHLLKRTVKQASFTYNKNKIKGGANLLIKEDMII
DRINENSITEKTDLTMSTAACPPSYDRVTKPIVEKHEQEGKDEKAKGK* (SEQ ID NO: 65)

Nucleotide sequences that can result in upregulation of SCN1A expression (described in Hsiao et al., EBioMedicine 9 (2016) 257-277):

TCGACTTTGAAAA (SEQ ID NO: 66)
CCTCTCCACGCGCAGTACATT (SEQ ID NO: 67)
T•C•G•G•T•G•T•C•C•A•C•T•C•T•G•G•C•A•G•T• (SEQ ID NO: 68)
T•G•C•A•C•T•G•T•G•G•G•A•G•C•C•T•G•T•C•T (SEQ ID NO: 69)
G•T•A•G•C•A•C•T•G•T•G•G•A•C•A•T•C•G•G•C (SEQ ID NO: 70)
G•T•A•G•A•A•G•A•A•C•A•G•C•C•C•G•T•A•G•T•G (SEQ ID NO: 71)
G•T•G•G•T•C•T•C•T•G•C•A•T•T•C•T•G•T•C•A (SEQ ID NO: 72)
G•T•G•G•T•A•T•A•G•G•A•A•C•T•G•G•C•A•G•C•A (SEQ ID NO: 73)
G•T•C•C•A•A•T•C•A•T•A•C•A•G•C•A•G•A•A (SEQ ID NO: 74)
G•T•G•A•C•T•G•T•A•C•C•A•A•T•T•G•C•T•G•T (SEQ ID NO: 75)
A•C•T•T•C•T•T•C•C•A•C•T•C•C•T•T•C•C•T (SEQ ID NO: 76)
G•A•T•G•T•C•C•C•T•T•C•C•T•G•C•G•T•T•G•T (SEQ ID NO: 77)
T•G•T•G•G•A•T•G•C•T•G•G•G•T•G•T•C•T•C•T•C (SEQ ID NO: 78)
T•C•C•C•A•G•T•G•A•C•T•C•C•C•G•A•T•G•C•T (SEQ ID NO: 79)
A•G•T•C•T•C•A•G•T•T•G•T•C•A•G•T•A•C•C•T•C (SEQ ID NO: 80)
G•T•T•A•T•T•G•A•A•T•G•C•C•C•T•G•G•T•G•T (SEQ ID NO: 81)
T•C•G•G•A•T•C•A•T•C•A•G•G•G•T•T•G•T•A•G•T (SEQ ID NO: 82)
G•T•G•G•T•A•T•A•G•G•A•A•C•T•G•G•C•A•G•C•A (SEQ ID NO: 83)
T•C•T•G•C•T•C•T•T•C•C•C•T•A•C•A•T•T•G•G (SEQ ID NO: 84)
G•T•A•A•T•C•T•G•C•T•C•T•T•C•C•C•T•A•C (SEQ ID NO: 85)
G•G•G•A•G•A•A•C•T•T•G•A•G•A•G•C•A•A•C•A•G (SEQ ID NO: 86)
G•C•C•A•G•T•C•A•C•A•A•A•T•T•C•A•G•A•T•C•A (SEQ ID NO: 87)
G•T•G•G•C•A•T•A•G•G•G•A•C•G•G•G•C•A•G•C•A (SEQ ID NO: 88)
G•T•A•G•C•A•C•T•G•T•G•G•A•C•A•T•C•G•G•C (SEQ ID NO: 89)
G•T•A•G•A•A•G•A•A•C•A•G•C•C•C•G•T•A•G•T•G (SEQ ID NO: 90)
G•T•C•C•A•A•T•C•A•T•A•C•A•G•C•A•G•A•A (SEQ ID NO: 91)
G•T•G•A•C•T•G•T•A•C•C•A•A•T•T•G•C•T•G•T (SEQ ID NO: 92)
A•C•T•T•C•T•T•C•C•A•C•T•C•C•T•T•C•C•T (SEQ ID NO: 93)
G•A•T•G•T•C•C•C•T•T•C•C•T•G•C•G•T•T•G•T (SEQ ID NO: 94)
T•G•T•G•G•A•T•G•C•T•G•G•G•T•G•T•C•T•C•T•C (SEQ ID NO: 95)

FIG. 11, cont'd

T•C•C•C•A•G•T•G•A•C•T•C•C•C•G•A•T•G•C•T (SEQ ID NO: 96)
A•G•T•C•T•C•A•G•T•T•G•T•C•A•G•T•A•C•C•T•C (SEQ ID NO: 97)
T•C•G•G•A•T•C•A•T•C•A•G•G•G•T•T•G•T•A•G•T (SEQ ID NO: 98)
G•T•G•G•T•A•T•A•G•G•A•A•C•T•G•G•C•A•G•C•A (SEQ ID NO: 99)
G•T•G•GAC•AGGAT•GCAC•AAAGG•A (SEQ ID NO: 100)
T•G•G•T•A•T•A•G•G•A•A•C•T•G•G•C•A•G•C•A (SEQ ID NO: 101)
G•T•G•G•C•A•T•A•G•G•G•A•C•G•G•G•C•A•G•C•A (SEQ ID NO: 102)
G•T•G•ACTGTGCCCATTG•C•T•G (SEQ ID NO: 103)
G•C•C•ACTT•GATGAT•CTA•A•A•C (SEQ ID NO: 104)
G•T•G•GAC•AGGAT•GCAC•AAAGG•A (SEQ ID NO: 105)
T•G•G•T•A•T•A•G•G•A•A•C•T•G•G•C•A•G•C•A (SEQ ID NO: 106)
*C•*C•A•C•G•C•G•C•G•A•G•T•*A•*C•*A (SEQ ID NO: 107)
*G•*T•A•T•A•G•G•A•A•C•T•G•*G•*C•*A (SEQ ID NO: 108)
*G•*T•G•G•T•A•*T•A•G•G•A•A•*C•*T•*G (SEQ ID NO: 109)
*A•*G•A•A•C•T•T•G•A•G•A•G•*C•*A•*A (SEQ ID NO: 110)
*G•*C•C•A•G•*T•C•A•*C•A•A•A•*T•*T•*C (SEQ ID NO: 111)
*C•*A•C•A•A•A•T•T•C•A•G•A•*T•*C•*A (SEQ ID NO: 112)
*G•*T•GGTA*T•AGGAA*C•*T•*G (SEQ ID NO: 113)
*G•*T•A•T•A•G•G•A•A•C•T•G•*G•*C•*A (SEQ ID NO: 114)
*G•*T•G•G•T•A•*T•A•G•G•A•A•*C•*T•*G (SEQ ID NO: 115)
*G•*C•CAGT•C•A*C•AAA*T•*T•*C (SEQ ID NO: 116)
*C•*A•CAAATTCAGA*T•*C•*A (SEQ ID NO: 117)
*G•*C•C•A•G•xU•C•A•xC•A•A•xA•xU•*T•*C (SEQ ID NO: 118)
*G•C•C•A•G•*T•C•A•*C•A•A•A•T•*T•*C (SEQ ID NO: 119)
*G•*C•xC•A•G•xU•C•A•xC•A•xA•*A•*T (SEQ ID NO: 120)
*G•*C•C•A•G•T•C•A•C•A•*A•*A•*T (SEQ ID NO: 121)
*G•C•C•A•G•T•C•A•*C•*A•*A (SEQ ID NO: 122)
*G•*C•C•A•G•T•C•A•C•*A•*A•*A (SEQ ID NO: 123)
*A•*T•T•G•A•G•C•C•A•*G•*T•*C (SEQ ID NO: 124)
*G•*T•GGTA*T•AGGAA*C•*T•*G (SEQ ID NO: 125)
xG•xC•C•A•G•xU•C•A•xC•A•A•A•xU•T•C•xA•xG (SEQ ID NO: 126)
xG•xC•C•A•G•xU•C•A•xC•A•A•A•xU•xU•xC (SEQ ID NO: 127)
xG•xU•xG•G•xU•A•xU•A•G•G•A•A•xC•T•G•G•xC•A•xG•xC•xA (SEQ ID NO: 128)
xG•xG•xG•A•G•A•A•xC•T•xU•G•A•G•A•G•xC•A•A•xC•xA•xG (SEQ ID NO: 129)
xG•xC•xC•A•G•T•xC•A•C•A•A•A•xU•T•xC•A•G•A•xU•xC•xA (SEQ ID NO: 130)
xG•xU•xG•GxU•AxU•AGGAAxC•TGGxC•AxG•xC•xA (SEQ ID NO: 131)
xG•xG•xU•A•xU•A•G•G•xA•A•C•xU•G•G•xC•A•G•xC•A•G•xU•G•xU•xU•xG (SEQ ID NO: 132)
xU•xG•xG•T•A•xU•A•G•xG•A•A•xC•T•G•G•xC•A•G•C•xA•xG•xU (SEQ ID NO: 133)
xG•G•T•A•xU•A•G•G•A•A•xC•T•G•G•xC•A•G•xC•A•G•T•G•T•T•xG (SEQ ID NO: 134)
xA•xA•G•xC•G•G•xU•A•T•A•G•G•A•A•xC•T•G•G•xC•A•G•xC•A•xG (SEQ ID NO: 135)
xG•xA•xG•C•C•A•G•xU•C•A•xC•A•A•A•xU•T•C•A•G•xA•T•C•A•xC•xC•xC (SEQ ID NO: 136)
xA•A•xU•G•G•G•A•G•A•A•xC•xU•xU•G•A•G•A•G•xC•xA•xA (SEQ ID NO: 137)
xG•TGACxU•GTGCCxC•ATTGCTxG (SEQ ID NO: 138)
xG•ACAAxC•CTTGxC•AGCCAxC•TGAxU•GATGxA (SEQ ID NO: 139)
xU•xG•G•xU•A•xU•A•G•G•A•A•xC•T•G•G•xC•A•xG•xC•xA (SEQ ID NO: 140)
xC•xC•A•G•T•xC•A•C•A•A•A•xU•T•xC•A•G•A•xU•xC•xA (SEQ ID NO: 141)
xU•xG•GxU•AxU•AGGAAxC•TGGxC•AxG•xC•xA (SEQ ID NO: 142)
xA•xG•C•C•A•G•xU•C•A•xC•A•A•A•xU•T•C•A•G•xA•T•C•A•xC•xC•xC (SEQ ID NO: 143)

FIG. 11, cont'd

xG•xU•xG•G•xU•A•xU•A•G•G•A•A•xC•T•G•G•xC•A•xG•xC•xA (SEQ ID NO: 144)
xG•xU•xG•GxU•AxU•AGGAAxC•TGGxC•AxG•xC•xA (SEQ ID NO: 145)
xG•xG•xU•A•xU•A•G•G•xA•A•C•xU•G•G•xC•A•G•xC•A•G•xU•G•xU•xU•xG (SEQ ID NO: 146)
xU•xG•xG•T•A•xU•A•G•xG•A•A•xC•T•G•G•xC•A•G•C•xA•xG•xU (SEQ ID NO: 147)
xG•G•T•A•xU•A•G•G•A•A•xC•T•G•G•xC•A•G•xC•A•G•T•G•T•T•xG (SEQ ID NO: 148)
xA•xA•G•xC•G•G•xU•A•T•A•G•G•A•A•xC•T•G•G•xC•A•G•xC•A•xG (SEQ ID NO: 149)
xG•xU•xG•G•xC•A•xU•A•G•xG•G•A•xC•G•G•G•xC•A•xG•xC•xA (SEQ ID NO: 150)
xA•xC•xA•xA•xG•xU•G•G•C•A•T•A•G•G•G•A•C•G•G•xG•xC•xA•xG•xC•xA (SEQ ID NO: 151)
xA•xC•A•A•G•xU•G•G•xC•A•T•A•xG•G•G•A•xC•G•G•G•xC•A•G•xC•xA (SEQ ID NO: 152)
xA•A•G•xU•G•G•xC•A•xU•A•G•xG•G•A•xC•G•G•G•xC•A•G•xC•A•G•xU (SEQ ID NO: 153)
xU•xG•G•xU•A•xU•A•G•G•A•A•xC•T•G•G•xC•A•xG•xC•xA (SEQ ID NO: 154)
xC•xC•xU•xA•xU•xC•T•T•T•C•C•C•C•C•C•C•C•T•xA•xC•xC•xU•xU•xU (SEQ ID NO: 155)
xA•xA•xG•xU•xG•G•C•A•T•A•G•G•G•A•C•G•G•G•C•A•xG•xC•xA•xG•xU (SEQ ID NO: 156)
xG•TGACxU•GTGCCxC•ATTGCTxG (SEQ ID NO: 157)
xG•TGACTGTGCCCATTGCTxG (SEQ ID NO: 158)
xC•CTCxU•TTCxU•GGCxC•TTGxC•TTxC (SEQ ID NO: 159)
xG•ACAAxC•CTTGxC•AGCCAxC•TGAxU•GATGxA (SEQ ID NO: 160)
rArUrUrUrArArArCrArCrGrGrArArGrArCrUrUrUrArGrUrArGrUrGrCrUrArCrUrArArArGrUrCrUrUr
CrCrGrUrGrUrUrUrArAAT (SEQ ID NO: 161)
rUrCrArCrArArArUrUrCrArGrArUrCrArCrCrCrArUrCrUrUrCrUrArGrArArGrArUrGrGrGrUrGrArUr
CrUrGrArArUrUrUrGrUGA (SEQ ID NO: 162)
rArUrUrUrArArArCrArCrGrGrArArGrArCrUrUrUrArGrUrArGrUrGrCrUrArCrUrArArArGrUrCrUrUr
CrCrGrUrGrUrUrUrArAAT (SEQ ID NO: 163)

[•]: phosphorothioate bond, *: LNA modification, x: 2′OXethylxodification, r: ribonucleotide.

RESCUING VOLTAGE-GATED SODIUM CHANNEL FUNCTION IN INHIBITORY NEURONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application Nos. 62/655,043, filed Apr. 9, 2018, 62/742,835, filed Oct. 8, 2018, and 62/810,281, filed Feb. 25, 2019, each of which is incorporated herein by reference in its entirety as if fully set forth herein.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with government support under grant RF1MH114126 awarded by the National Institutes of Health. The government has certain rights in the invention.

FIELD OF THE DISCLOSURE

[0003] The current disclosure describes the rescue of voltage-gated sodium channel function selectively in inhibitory neurons in need thereof. Rescued voltage-gated sodium channel function in inhibitory neurons can be used to treat disorders such as epilepsy, and more particularly, Dravet Syndrome.

BACKGROUND OF THE DISCLOSURE

[0004] There are numerous neurological disorders for which treatments are urgently needed. One class of such disorders arise due to dysfunctional Nav1.1 sodium channels in inhibitory neurons. For example, epilepsy, infantile spasms, migraine headaches, and autism spectrum disorders are associated with dysfunctional Nav1.1 sodium channels.

[0005] Epilepsy is a neurological disorder that occurs when the brain presents an enduring predisposition to generate two or more epileptic seizures. An epileptic seizure is a temporary disruption of brain function due to abnormal excessive or synchronous neuronal activity. Its manifestation may include periods of unusual behavior, sensations and sometimes loss of consciousness.

[0006] Dravet Syndrome (DS) particularly is a rare and catastrophic form of intractable epilepsy that begins in infancy. Initially, the patient experiences prolonged seizures. In their second year, additional types of seizure begin to occur and this typically coincides with a developmental decline. This leads to poor development of language and motor skills.

[0007] Children with DS are likely to experience multiple seizures per day. Epileptic seizures are far more likely to result in death in sufferers of DS; 10 to 16% of patients diagnosed with DS die in childhood, particularly between two and four years of age. Additionally, patients are at risk of numerous associated conditions including orthopedic developmental issues, impaired growth, sleep and circadian rhythm impairments, and chronic infections.

[0008] Of particular concern, children with DS are particularly susceptible to episodes of Status epilepticus. Status epilepticus is a condition in which a seizure lasts for more than 5 minutes or multiple seizures occur close together within a 5 minute-period without recovery of consciousness between them. This severe condition is categorized as a medical emergency requiring immediate medical intervention, typically involving hospitalization. Prolonged convulsive status epilepticus lasting >30 min can be fatal and lead to substantial brain damage. Frequent hospitalizations of children with DS are clearly distressing, not only to the patient but also to family and care givers. The cost of care for DS is also high as the affected children require constant supervision and many require institutionalization.

[0009] At present, although a number of anticonvulsant therapies can be employed to reduce the instance of seizures in patients with DS, the results obtained with such therapies are typically poor and those therapies only produce partial cessation of seizures in most patients. Many of these anticonvulsants such as clobazam and clonazepam have undesirable side effects, which are particularly acute in pediatric patients. Furthermore, certain anticonvulsants (particularly the sodium-channel blockers) exacerbate the seizures.

[0010] Cell-type or cell-class specific gene delivery using non-pathogenic viral delivery is showing increasing promise for the treatment of diverse diseases. Inclusion of particular gene regulatory elements, such as specific promoters or enhancers, within the delivered vector, has been beneficial to provide specificity for gene expression within particular targeted cell types. For example, Dimidschstein and colleagues (Nat Neurosci 19(12):1743-1749, 2016) developed a viral delivery gene construct based on the adeno-associated virus (AAV) that resulted in selective expression of a gene within gamma-aminobutyric acid (GABA)ergic interneurons within the telencephalon, a cell type important in the treatment of epilepsy. This construct included a 529 base pair (bp) enhancer sequence (referred to as mI56i or mDlx).

[0011] One significant drawback to using AAV as a selective gene-delivery system is the strictly restricted packaging limit of AAVs; this is particularly limiting to the inclusion of lengthy genetic control elements. In addition, existing interneuron-specific AAV expression constructs provide weak expression in certain applications, as well as for expression of transgenes (such as therapeutic genes) that are more poorly tolerated than other more commonly used proteins. Thus, there remains a need in the art for shorter enhancer sequences that are capable of providing rapid and strong expression of functional proteins within selected cell types.

SUMMARY OF THE DISCLOSURE

[0012] The current disclosure provides expression constructs that result in unexpectedly rapid and high levels of protein expression selectively within inhibitory neurons for the purpose of rescuing defective Nav1.1 channel function. In particular embodiments, the current disclosure provides a concatemerized core of the human I56i enhancer and a gene encoding a voltage-gated sodium channel protein or nucleotide sequence that can rescue impaired Nav1.1 sodium channel function. The expression constructs can be used to reverse or ameliorate the effects of Nav1.1 voltage-gated sodium channel dysfunction in inhibitory neurons. In particular embodiments, the current disclosure provides treatment of sodium channel disorders by selectively delivering a gene allowing for a functioning voltage-gated sodium channel to inhibitory neurons. Administration of viral vectors including these enhancers and genes results in selective expression of a protein or nucleotide sequence that rescues Nav1.1 sodium channel function in inhibitory interneurons. In particular embodiments, the therapeutic voltage-gated

sodium channel genes in these viral vectors can be of bacterial origin, which are small and can fit into a single AAV construct, or of human origin, which are larger and can use a dual construct AAV delivery technique, among other strategies. The Nav1.1 sodium channel disorders that can be treated include epilepsy, and more particularly, Dravet Syndrome (DS). For example, as disclosed herein, administration of the expression constructs results in therapeutic efficacy to treat DS in a well-established in vivo mouse model of the disease.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0013] Many of the drawings submitted herein are better understood in color. Applicant considers the color versions of the drawings as part of the original submission and reserve the right to present color images of the drawings in later proceedings.

[0014] FIGS. **1**A-**1**D. Pan-GABAergic viral enhancer labels fast spiking interneurons in human organotypic slice culture. (FIG. **1**A) Green fluorescence identifies cells expressing a CN1180/DJ viral vector at 7 DIV/DPI (DIV: days in vitro, DPI: days post infection). CN1180 includes a SYFP2 expression cassette under control of the human DLX (hDLX) 112b enhancer and a minimal beta-globin promoter. Neurons were patch-clamped and visualized post-hoc with Alexa 594 backfill in the red channel. (FIG. **1**B) Morphologies of patched cells from one human case, categorized by presence of YFP fluorescence, suggest that SYFP2-expressing cells are largely interneurons. (FIG. **1**C) Electrophysiological parameters of YFP+neurons suggest that these cells are predominantly fast-spiking interneurons. (FIG. **1**D) Post-hoc immuno-histochemistry demonstrates that many YFP+ cells (arrows) express Parvalbumin (PVALB), which suggests that these cells have molecular properties of fast-spiking interneurons.

[0015] FIG. **2** depicts an exemplary vector for targeted expression of a protein in inhibitory interneurons: CN1367-rAAV2-hI56i-minBglobin-His-NavMs-P2A-SYFP2-WPRE3-BGHpA. Key: hI56i—full-length human DLX I56i enhancer (SEQ ID NO: 1); minBglobin—minimal beta globin promoter; His-NavMs—Hexahistidine-tagged voltage-gated sodium channel from *Magnetococcus marinus;* P2A—self-cleaving peptide; SYFP2—super yellow fluorescent protein 2; WPRE3—woodchuck hepatitis virus post-transcriptional regulatory element 3 (SEQ ID NO: 19); BGHpA—bovine growth hormone polyA sequence.

[0016] FIG. **3**. Virus CN1244/PHP.eB. 10^{11} genome copies delivered intravenously (IV). PHP.eB encodes for a capsid originating from AAV9 that allows efficient AAV transit across the mouse blood brain barrier, which enables delivery of AAV vectors in a brain-wide fashion. This capsid differs from AAV9 such that amino acids starting at residue 586: SAQA are changed to SDGTLAVPFKA. The Gad2-T2A-nls-mCherry reporter marks nearly all inhibitory neurons in the mouse brain (here shown V1 visual cortex), and the delivered CN1244/PHP.eB virus drives specific SYFP2 reporter activity in forebrain inhibitory neurons.

[0017] FIGS. **4**A, **4**B. Comparison of CN1244 vs CN1389 vs CN1390. (FIG. **4**A) Schematic representations of three vector constructs, CN1244, CN1389, and CN1390 (CN1203 scAAV). Key: hI56i—full-length human DlxI56i enhancer (SEQ ID NO: 1); hI56iCore—human DlxI56i enhancer core (SEQ ID NO: 2); minBG—minimal beta globin promoter; SYFP2—super yellow fluorescent protein 2; WPRE3—woodchuck hepatitis virus posttranscriptional regulatory element 3; BGHpA—bovine growth hormone polyA sequence; L-ITR and R-ITR—Adeno-associated virus-2 (AAV2) inverted terminal repeats (ITRs). (FIG. **4**B) Fluorograph images showing relative expression of the SYFP2 from AAV vector constructs CN1244, CN1389, and CN1390.

[0018] FIG. **5**. CN1390 retains cell type specificity of reporter expression for the pan-GABAergic neuronal populations (marked with red fluorescence in these Ai75 het/Gad2-IRES-Cre mice) in the juvenile mouse cortex and hippocampus in slice culture. 10DIV/10DPI.

[0019] FIGS. **6**A-**6**E. CN1390 exhibits rapid onset of transgene expression in human ex vivo brain slices. (FIG. **6**A) Time course of virus-mediated YFP expression following human brain slice transduction with CN1390/PHP.eB (left panel: 1DIV/1DPI; middle panel: 3DIV/3DPI; right panel: 6DIV/6DPI). (FIG. **6**B) Expanded view of the boxed region in (FIG. **6**A, right panel). (FIG. **6**C) High magnification view of a virus labeled interneuron with bipolar morphology. (FIG. **6**D) Example whole cell recordings from four different virus-labeled YFP+ human interneurons and demonstrating diverse firing patterns to supra-threshold current injection. (FIG. **6**E) Functional analysis of human neocortical interneuron firing patterns and electrical properties by patch clamp recording was feasible as early as 40 hours post-infection with CN1390/PHP.eB virus.

[0020] FIGS. **7**A-**7**F. AAV vector reagents to reverse DS symptoms in $Scn1a^{+/-}$ mice. (**7**A) Vectors to deliver epitope-tagged Nav genes of bacterial origin (NavBacs). The Nav genes shown here are NavMs (from *Magnetococcus marinus*), NavBp (from *Bacillus pseudofirmus*), and NavSheP-D60N (from *Shewanella putrifaciens* with an engineered D60N mutation). These examples all have N-terminal epitope tags (hexahistidine in the case of CN1367, or 3×HA for CN1498, CN1499, and CN1500). hI56i refers to the full-length I56i enhancer of SEQ ID NO: 1; 3×hI56iCore refers to the concatemerized core of the I56i enhancer (SEQ ID NO: 3); (**7**B) Graded expression levels from NavBac vectors. (**7**C) Weak but detectable expression in few Pvalb interneurons from vector CN1367. (**7**D) Trend towards seizure protection with vector CN1367. (**7**E) Vector 1500 drives high-level expression in $Pvalb^{+}$ and $Pvalb^{-}$ interneurons throughout cortex. (**7**F) Abundant production of HA-tagged NavBacs in cell bodies and proximal processes with vectors 1498 and 1500, but not 1499.

[0021] FIG. **8**. Four exemplary strategies to encode and deliver full-length human SCN1A protein despite exceeding the AAV packaging limit. The human SCN1A gene (hSCN1A) has a 6030 bp open reading frame which exceeds the 4.7 kb packaging limit in AAV vectors. One approach to overcome this size limit is to split hSCN1A into two parts for delivery. Strategies 1 and 2 take advantage of homology-driven recombination between two separate AAV vector genomes (homologous regions indicated with hashed lines) to enable full open reading frame reconstitution in co-transduced cells. Strategies 3 and 4, in contrast, add trans-splicing elements (synthetic intron indicated by dots) to potentially increase the efficiency of open reading frame reconstitution and hence full-length protein expression. Strategies 1 and 3 utilize SYFP-P2A- and 3×HA-tagged hSCN1A protein to enable easy detection of both parts of the protein by fluorescence and immunohistochemistry, while

strategies 2 and 4 utilize untagged hSCN1A protein and a vertebrate promoter to ensure low immunogenicity of the delivered transgene and encoded proteins. Another strategy is to utilize multiple vectors, each encoding a different segment or subunit of the SCN1A protein. Protein subunits can then self-assemble after expression naturally or through the inclusion of engineered cysteines or other linking domains.

[0022] FIG. **9**. Full-length human SCN1A expression driven by a two-part AAV viral vector system. (Top panel): Model of two-part vector system. The top vector (1504) includes the concatemerized 3×hI56iCore (SEQ ID NO: 3) and promoter (minCMV) elements to drive expression in all inhibitory neurons (including both Pvalb+ and Pvalb− inhibitory neurons). The driven transgene includes a SYFP2 linked by a P2A tag to the N-terminal region of human SCN1A, which includes 604 bp homology to the C-terminal region included on the bottom vector 1512. The bottom vector 1512 also includes a C-terminal 3×HA tag and 3'UTR regulatory sequences (WPRE3 and polyA sites). (Bottom panel): Both AAV viral vectors were packaged into viral particles with PHP.eB capsid and both were delivered intravenously to a C57Bl/6 mouse. After 21 days the mouse brain was harvested, fixed, and processed for immunofluorescence with anti-GFP (targeting SYFP2), anti-HA, and anti-Pvalb antibodies to detect transgene-expressing cells and their overlap with $Pvalb^+$ inhibitory neurons (which are cells having particular importance in DS symptomology). Many inhibitory neurons were labeled with the N-terminal $SYFP2^+$ tag at high level, including both $Pvalb^+$ and $Pvalb^-$ inhibitory neurons. Some of these $SYFP2^+$ cells also express HA which indicates fully intact SCN1A protein product being expressed in these GFP^+HA^+ cells (arrows). The vertical arrows indicate $Pvalb^+$ interneurons expressing human SCN1A and the horizontal arrows indicate $Pvalb^-$ interneurons expressing human SCN1A. These SCN1A-expressing cells are found throughout the forebrain (both neocortex and hippocampus [here dentate gyrus]), which includes the brain region known to be important in many epilepsies and known to be dysfunctional in DS.

[0023] FIG. **10**. CN1500 rAAV vector substantially reverses febrile seizures in $Scn1a^{+/-}$ mice. Febrile seizure assay shown as internal temperature where a seizure is first detected. (Top) Circles show $Scn1a^{+/-}$ mice untransduced with AAVs, while the diamonds represent animal that were transduced with CN1500. The large dot and error bars represent the average +/− SEM for each group of animals. (Bottom) Trends of the same data are shown as the percentage of mice in each group that remain seizure free at different temperatures using a Kaplan-Meier curve.

[0024] FIG. **11**. Exemplary sequences supporting the disclosure.

DETAILED DESCRIPTION

[0025] In vertebrates, voltage gated sodium channels (Navs) are heteromeric protein complexes including a large central pore composed of alpha subunits, and smaller auxiliary subunits composed of beta subunits which modulate the kinetics and subcellular distribution of the pores. The alpha subunits are encoded by a family of 9 different genes (from SCN1A to SCN11A), and the beta subunits are encoded by 4 different genes (SCN1B to SCN4B), and these gene members show cell- and tissue-specific expression patterns. Each of the nine different alpha subunit genes seeds a distinct Nav channel complex, making 9 different subtypes (Nav1.1-Nav1.9), and these nine Nav channels display tissue specific localization and functional differences (See, Goldin, (2001) Annu Rev Physiol 63: 871-94; and Yu et al., (2003), J. Neurosci 23: 7577-758).

[0026] Navs are central for neuron function, being responsible for initiating the rapid upstroke of action potentials in excitable nervous system cells, and Nav1.1 drives this activity in many cells. The Nav1.1 channel includes the SCN1A alpha subunit, and is expressed in nearly all neurons and at high levels in GABAergic neurons. The Nav1.2 channel includes the SCN2A subunit; the Nav1.3 channel includes the SCN3A subunit, the Nav1.4 channel includes the SCN4A subunit, the Nav1.5 channel includes the SCN5A subunit, the Nav1.6 channel includes the SCN8A subunit, the Nav1.7 channel includes the SCN9A subunit, the Nav1.8 channel includes the SCN10A subunit, and the Nav1.9 channel includes the SCN11A subunit.

[0027] There are numerous neurological disorders for which treatments are urgently needed. One class of such disorders arise due to dysfunctional Nav1.1 sodium channels in inhibitory neurons. For example, the following disorders and conditions are associated with dysfunctional Nav1.1 sodium channels: epilepsy (including Dravet syndrome (DS), generalized epilepsy with febrile seizures plus (GEFS+), borderline DS, intractable childhood epilepsy with generalized tonic-clonic seizures (ICEGTC), cryptogenic focal and generalized epilepsies, myoclonic-astatic epilepsy (Doose syndrome), Lennox Gastaut syndrome, and severe infantile multifocal epilepsy (Gambardella A et al. Epilepsia. 2009, 50 Suppl 5:20-3)), West syndrome, also known as infantile spasms (Harkin L. A. et al. Brain, 2007, 130(3) 843-852), rare cases of familiar migraine such as familial hemiplegic migraine 3 (FHM3), Panayiotopoulos syndrome (Livingston J. H. et al. J Child Neurol. 2009, 24(4):503-8), familial autism (Weiss L. A et al. 2003, Molecular Psychiatry, 8(2), 186-194), sporadic autism spectrum disorders (ASDs) (Nat Genet. 2011 43(6):585-9), Rasmussens's encephalitis, also known as chronic focal encephalitis, or CFE (Ohmori I. et al, Epilepsia. 2008 49(3):521-6), Alzheimer's disease (Scharfman H. E. Epilepsy Curr. 2012 12(5): 178-183), and cerebral ischemia-reperfusion (Yao C. et al, Neurotox Res. 2002; 4(1):67).

[0028] The underlying cause of epilepsy is believed to arise from a defect in the excitation-inhibition (E/I) balance of cortical circuits. Forebrain GABAergic interneurons are the primary source of inhibition in the telencephalon and various lines of evidence indicate their importance in epilepsy. DS particularly is a severe childhood epilepsy predominantly due to SCN1A haploinsufficiency. It is marked by severe and frequent seizures (sometimes hundreds a day), leads to developmental delay, and has a lethality rate of up to 16%. DS affects nearly 1 in 20,000 births in both the United States and Europe, and more than 10,000 people are estimated to suffer from DS on both continents (Wu et al., Pediatrics 136, e1310-e1315, 2015). Heterozygous loss-of-function mutations in SCN1A, the gene that encodes the pore forming subunit of the voltage-gated sodium channel Nav1.1 is the predominant cause of DS (Catterall et al., *J. Physiol.* 588, 1849-1859, 2010; Claes et al., *Hum. Mutat.* 21, 615-621, 2003; Fujiwara, *Epilepsy Res.* 70 Suppl 1, S223-230, 2006; Verbeek et al., *Epilepsy Behav. EB* 47, 39-44, 2015). Genetic models of DS have established the pathophysiology of this disease (Han et al., *Nature* 489, 385-390,

2012; Kalume et al., *J. Clin. Invest.* 123, 1798-1808, 2013; Kalume et al., *J. Neurosci.* 27, 11065-11074, 2007; Kalume et al., *Neurobiol. Dis.* 77, 141-154, 2015; Oakley et al., *Proc. Natl. Acad. Sci.* 106, 3994-3999, 2009; Cheah et al., *Proc. Natl. Acad. Sci.* 109, 14646-14651, 2012; Han et al., *Proc. Natl. Acad. Sci.* 109, E368-E377, 2012). Mouse models of DS have reduced Nav1.1 function due to heterozygous deletion of Scn1a and exhibit the key phenotypic traits of DS including: febrile seizures, anxiety, and sleep deficits (Han et al., *Nature* 489, 385-390, 2012; Kalume et al., *J. Clin. Invest.* 123, 1798-1808, 2013; Kalume et al., *Neurobiol. Dis.* 77, 141-154, 2015; Oakley et al., *Proc. Natl. Acad. Sci.* 106, 3994-3999, 2009; Tai et al., *Proc. Natl. Acad. Sci.* 111, E3139-E3148, 2014; Yu et al., *Nat. Neurosci.* 9, 1142-1149, 2006).

[0029] DS is a disease of forebrain interneurons. Global Scn1a deletion causes reduced sodium current and excitability of GABAergic interneurons with no detectable impact on excitatory neurons (Catterall et al., *J. Physiol.* 588, 1849-1859, 2010; Kalume et al., *J. Neurosci.* 27, 11065-11074, 2007; Cheah et al., *Proc. Natl. Acad. Sci.* 109, 14646-14651, 2012; Tai et al., *Proc. Natl. Acad. Sci.* 111, E3139-E3148, 2014; Yu et al., *Nat. Neurosci.* 9, 1142-1149, 2006; Ogiwara et al., *J. Neurosci.* 27, 5903-5914, 2007 Rubinstein et al., *Brain* 138, 2219-2233, 2015; Mistry et al., *Neurobiol. Dis.* 65, 1-11, 2014). Conditional deletion of Scn1a in forebrain or interneurons using specific Cre drivers qualitatively reproduced the key symptoms of DS, whereas excitatory neuron-specific deletion caused no detectable phenotype (Cheah et al., *Proc. Natl. Acad. Sci.* 109, 14646-14651, 2012). In addition, targeted deletion of Scn1a in $Pvalb^+$ or Sst^+ interneuron classes (separately or in combination) revealed that dysfunction in each class separately contributes to the multifaceted phenotypes of DS, with $Pvalb^+$ cells exerting a greater effect (Rubinstein et al., *Brain* 138, 2219-2233, 2015; Dutton et al., *Neurobiol. Dis.* 49, 211-220, 2013). Consistent with these mouse models, patients with DS demonstrated a reduced GABAergic inhibition, and no change in glutamatergic neuron excitability following transcranial stimulation testing (Stern et al., *Neurology* 88, 1659-1665, 2017). Thus, studies of both mouse and human strongly indicate that DS is a disease of forebrain interneurons, caused by pathogenic loss-of-function mutations in SCN1A. Based on this insight, it was hypothesized that targeted introduction of functional voltage gated sodium channel with properties similar to Nav1.1 in forebrain GABAergic interneurons would improve or eliminate DS symptoms via rescue of their physiology. For exemplary methods to electrophysiologically and phenotypically characterize DS in a mouse model, see FIG. **1** of Rubinstein et al., *Brain* 138(Pt 8):2219-33, 2015.

[0030] Cell type- or cell class-specific gene delivery using non-pathogenic recombinant adeno-associated virus (rAAV) is showing increasing promise for the treatment of diverse diseases. Inclusion within rAAVs of one or more cis-acting DNA-control elements, such as specific promoters or enhancers, has been beneficial to provide specificity for expression within particular target cells, including specific cell types or cell classes in the brain. For example, Dimidschstein and colleagues (*Nat Neurosci* 19(12):1743-1749, 2016) developed a rAAV that results in selective expression of a gene within GABAergic interneurons within the telencephalon. The rAAV includes a 529 base pair (bp) enhancer sequence (referred to as mI56i or mDlx) from the distal-less homeobox 5 and 6 (Dlx5/6) genes, which are naturally expressed by forebrain GABAergic interneurons during embryonic development (Zerucha et al., *J. Neurosci.* 20(2):709-721, 2000). A construct developed by Dimidschstein et al. is available on Addgene as ID #83900 (in which the enhancer drives eGFP expression). Additional constructs which employ the murine or human I56i enhancer to drive various transgenes are also available through Addgene, such as Plasmid ID #s 83899 (driving GCaMP6f expression), 83898 (driving ChR2-mCherry expression), 83895 (driving Cre recombinase-dependent eGFP expression), 89897 (driving bicistronic hM3Dq and nls-dTomato expression), 83896 (driving bicistronic hM4Di and nls-dTomato expression), and 83894 (driving cre recombinase-dependent tdTomato expression). See also U.S. Patent Publication No. US2018/0078658. Additionally, the mDlx enhancer has previously been used to reliably target reporter genes in a pattern very similar to the normal patterns of Dlx5/6 expression during embryonic development (Zerucha et al., *J Neuroscience* 20:709-721, 2000; Stühmer et al., *Cerebral Cortex* 12:75-85, 2002; Stenman et al., *J Neuroscience* 23:167-174, 2003; Monory et al., *Neuron.* 51:455-455, 2006; Miyoshi et al., *J Neuroscience* 30:1532-1594, 2010).

[0031] One significant drawback to using rAAVs as a selective gene-delivery system is the strictly restricted packaging limit of AAVs; this is particularly limiting to the inclusion of lengthy genetic control elements. In addition, existing interneuron-specific rAAV expression constructs provide weak expression in certain applications, as well as for expression of transgenes (such as therapeutic genes) that are more poorly tolerated than GFP. Thus, there remains a need in the art for even shorter enhancer sequences that are capable of providing cell-specific expression of Nav1.1 function-restoring proteins particularly in neurons such as inhibitory interneurons. There also remains a need for genetic elements that provide stronger expression, and/or that work with a wider selection of reporter or other target genes and in a wider array of expression contexts.

[0032] The current disclosure provides expression constructs that result in high levels of protein expression in inhibitory neurons for the purpose of rescuing voltage-gated sodium channel function. The protein expression is selective to targeted inhibitory neurons and results in therapeutic efficacy to treat DS in a well-established in vivo mouse model of the disease, particularly that described in Kalume et al., *J. Clin. Invest.* 123, 1798-1808, 2013; and Oakley et al., *Proc. Natl. Acad. Sci.* 106, 3994-3999, 2009. In this model, mice can be implanted with electroencephalography (EEG) and electromyography (EMG) electrodes using approaches described in Kalume et al., *J. Clin. Invest.* 123, 1798-1808, 2013; Kalume et al., *Neurobiol. Dis.* 77, 141-154, 2015; and Oakley et al., *Proc. Natl. Acad. Sci.* 106, 3994-3999, 2009). After recovery, animals can be continuously monitored by video, EEG, and EMG. During testing procedures, mouse body temperature can be increased in 0.5° C. steps until either a generalized tonic-clonic seizure occurs, or a core body temperature of 42° C. is achieved. For each treatment group, a Kaplan Meier curve for seizure susceptibility due to temperature can be generated and the average temperature of seizure occurrence can be computed. Chi-squared tests can contrast Kaplan Meier plots of seizure susceptibility, and unpaired 2-tailed t-tests ascertain differences among average temperatures of seizure occurrence.

[0033] In particular embodiments, the expression constructs include non-naturally occurring enhancer element sequences that demonstrate strong and rapid interneuron-specific expression when used to drive a heterologous encoding sequence to treat Nav1.1 associated sodium channel disorders. In particular embodiments, the non-naturally occurring enhancer element includes multiple copies of a shortened, core portion of the human or murine I56i enhancer (SEQ ID NO: 3). In fact, the present disclosure can include a concatemerized core of the I56i enhancer from any species, so long as the concatemerized core results in selective expression of a functional protein in inhibitory neurons. For example, the Zebrafish I56i enhancer is provided as SEQ ID NO: 5 and the core of the Zebrafish I56i enhancer is provided as SEQ ID NO: 6. Particular embodiments provide a non-naturally occurring enhancer element including a three-copy concatemer of the human, murine, or zebrafish I56i core, such as shown in SEQ ID NO: 3 and SEQ ID NO: 7. Additional embodiments include 2×, 4×, 5×, 6×, 7×, 8×, 9×, or 10× copies of I56i core sequence of SEQ ID NO: 2 or SEQ ID NO: 6, arranged for instance in tandem. Particular embodiments can include a concatemerized hybrid of SEQ ID NO: 2 and SEQ ID NO: 6 (e.g., 2-6-2, 6-2-6, 2-2-6, 6-6-2).

[0034] In particular embodiments, a concatemerized core of the I56i enhancer is used to minimize the size required to enhance expression of proteins or nucleotide sequences that rescue voltage-gated sodium channel function. The synthetic 3× human DLX I56i core enhancer (a.k.a., 3×hI56iCore; SEQ ID NO: 3) is shorter than the original full-length enhancer sequence reported in Dimidschstein et al. (*Nat Neurosci* 19(12):1743-1749, 2016), despite being a 3× concatemer of the strongly conserved core of the enhancer. When used to construct a heterologous expression cassette driving expression of proteins rescuing Nav1.1 sodium channel function, this concatemerized core enhancer provided more room for cargo genes linked to the enhancer, which is highly desirable in gene therapy vectors.

[0035] The compact size of the enhancer core, together with the multiple copies linked together as a concatemer, led to unexpectedly strong peak transgene expression in forebrain interneurons following viral transduction of mouse and human brain tissue (see FIGS. **4**B & **5**). The onset is also surprisingly rapid (see FIGS. **6**A, **6**B), leading to faster and higher expression in direct comparison to virus packaged with, for instance, the enhancer of Addgene plasmid #83900. The increase in expression is supra-linear and not simply three times the level driven by the full-length enhancer (SEQ ID NO: 1). Thus, the concatemerized I56i core enhancer also enables new and improved viral (and other) vectors such as those described herein with demonstrably better performance in the treatment of Nav1.1 sodium channel disorders. These are particularly useful for achieving transgene expression in inhibitory brain cell types such as neocortical GABAergic interneurons in diverse animal species.

[0036] Thus, the current disclosure provides expression constructs, vectors, and methods useful in reversing or ameliorating deficiency of function of the voltage-gated sodium channel Nav1.1. In particular embodiments, the current disclosure provides treatment of Nav1.1 channel disorders by selectively delivering a gene providing a protein or nucleotide sequence that allows for rescue of voltage-gated sodium channel function to inhibitory interneurons with impaired Nav1.1 activity.

[0037] In particular embodiments, genes encoding proteins that rescue voltage-gated sodium channel function when Nav1.1 is impaired, are Nav genes of bacterial origin (NavBac) that function in human cells (Nguyen et al., *Nat. Commun.* 7, 13132, 2016; Sula et al., *Nat. Commun.* 8, 14205, 2017; DeCaen et al., *eLife* 3, e04387, 2014). Particular exemplary NavBacs include NavSheP, NavBp, and NavMs, which are three Nav proteins from three separate bacterial species. For representative experimental protocols and data demonstrating that bacterial voltage-gated sodium channels can confer sodium conductance to non-excitable cells, see Nguyen et al., Nature Communications 18(7), 13132, 2016 and particularly Supplemental FIG. **8**.

[0038] NavBac proteins can also be engineered by mutagenesis to increase or alter activity as necessary, as in NavSheP-D60N. Additionally, these proteins can be engineered to incorporate tags or other fusion proteins for detection, as in His-NavMs (which contains an N-terminal hexahistidine tag), or with N-terminal 3×HA tags, or with other epitope tags or fluorescent protein tags or with any other protein tag as necessary. In particular embodiments, expression constructs do not encode immunogenic components. In particular embodiments, expression constructs do not include or encode immunogenic components.

[0039] In particular embodiments, the genes encoding proteins that restore voltage-gated sodium channel function are genes encoding SCNA1 (e.g., human SCNA1 or mouse Scna1).

[0040] In particular embodiments, therapeutic treatments are based on the intravenous, retro-orbital, intraspinal, and/or intrathecal administration of viral vectors result in selective expression within targeted inhibitory neurons.

[0041] In particular embodiments, provided herein is an AAV viral vector CN1500, a recombinant AAV that expresses the transgene SYFP2-P2A-NavSheP-D60N, which when translated is cleaved into two proteins: SYFP2 (reporter) and NavSheP-D60N. As indicated, NavSheP-D60N (Nguyen et al., *Nat. Comm.* 7:13132, 2016) is a modified voltage-gated sodium channel of bacterial origin that has been modified to improve the channel kinetics and codon-optimized for increased expression in mammalian cells. The transgene expression level is elevated by the addition of a WPRE3 element, and transcription is terminated with the bovine growth hormone poly adenylation sequence (BGHpA). Expression of the transgene is high and limited to inhibitory cells in forebrain structures including the cortex and the hippocampus, via the 3×hI56iCore synthetic enhancer directly 5' of a cytomegalovirus (CMV) minimal promoter. Furthermore, the therapeutic transgene NavSheP-D60N can be labeled by an HA epitope tag to verify protein expression and correct protein localization. Therapeutic efficacy in a mouse model of DS has been demonstrated. In particular embodiments, the HA epitope tag can be removed from CN1500 and other vector designs described herein.

[0042] The human SCNA1 gene is relatively large and can benefit from administration from a vector that accepts a larger cargo than AAV or by using a two-AAV vector administration strategy. Multiple different strategies can be utilized in order to split a large open reading frame among two AAV vectors. Four strategies to split the large hSCN1A open reading frame are depicted in FIG. **8**, but several more can be imagined.

[0043] In particular embodiments, a two-vector administration strategy can split a coding sequence between two vectors. In particular embodiments, the first vector can encode the N-terminal portion of a protein and include a promoter and an enhancer. The second vector can encode the C-terminal portion of the protein and include a termination signal and a polyA signal. The portions of the protein encoded by each vector overlap to create a region of homology. Example 2, FIG. **8** strategy 1, and FIG. **9** show an example of such a two-vector system that achieved selective expression of the human SCN1A protein in inhibitory neurons. The 604-base pair (bp) region of homology is depicted in FIG. **9** by diagonal hashing. However, as is understood by one of ordinary skill in the art, a wide range of number of homologous bp can be selected. In particular embodiments, bp regions of homology range from less than 75 to more than 1500 bp. Moreover, various other components and configurations can be appropriate in a two-vector system as described in relation to single vector systems in more detail elsewhere herein. Another possible configuration includes a synthetic intron element that provides a region of homology as well as splice donor and acceptor sites that make final reconstitution of the protein more efficient and lead to higher levels of protein expression.

[0044] Moreover, additional strategies can also be used to provide exogenous voltage-gated sodium channel activity to inhibitory neurons that are deficient in this activity. For example, particular embodiments can utilize expression constructs encoding an artificial transcription factor that increases the expression of the endogenous functional copy of SCN1A.

[0045] In particular embodiments, expression constructs can encode molecules that increase the prevalence of functional SCN1A mRNA molecules, for example through post-transcriptional positive regulation of splicing and or stability.

[0046] In particular embodiments, strategies can be employed that restore the full length hSCN1A transcript through trans-splicing the hSCN1A transcript separated into two parts.

[0047] In particular embodiments, expression constructs (e.g., AAV) can deliver hSCN1A protein as several (two or four) subunit ORFs delivered by two or four separate vectors.

[0048] Aspects of the disclosure are now described with the following additional options and detail: (i) Expression Constructs & Vectors; (ii) Compositions for Administration (iii) Methods of Use; (iv) Kits and Commercial Packages; (iv) Exemplary Embodiments; and (v) Experimental Examples.

[0049] (i) Expression Constructs & Vectors. Expression constructs disclosed herein include (i) a concatemerized core of the I56i enhancer sequence that leads to selective expression of a coding sequence within inhibitory neurons, (ii) a coding sequence that is expressed and results in a protein or nucleotide sequence that rescues voltage-gated sodium channel function in a cell in need thereof, and (iii) a promoter. The expression construct can also include other regulatory elements if necessary or beneficial. In particular embodiments, expression constructs are isolated polynucleotides.

[0050] In particular embodiments, an "enhancer" or an "enhancer element" is a cis-acting sequence that increases the level of transcription associated with a promoter, and can function in either orientation relative to the promoter and the coding sequence that is to be transcribed, and can be located upstream or downstream relative to the promoter or the coding sequence to be transcribed. There are art-recognized methods and techniques for measuring function(s) of enhancer element sequences. By way of example, specific methods for determining or measuring function(s) of a I56i enhancer are described in Dimidschstein et al. (Nat Neurosci 19(12):1743-1749, 2016) and U.S. Patent Publication No. US2018/0078658. Particular examples of enhancer sequences include the human full-length I56i enhancer (SEQ ID NO: 1), the h156 core (SEQ ID NO: 2), and the 3×hI56i core (SEQ ID NO: 3) as well as the murine and zebrafish orthologs thereof.

[0051] In particular embodiments, an inhibitory-neuron-specific enhancer is an enhancer that is uniquely or predominantly utilized in inhibitory neurons. An inhibitory-neuron-specific enhancer enhances expression of a gene in inhibitory neurons, but does not substantially affect expression of genes in other cell types, for example non-inhibitory neurons or glial cells, thus having neuronal specific transcriptional activity. In some instances there may be some low level expression in other cell types, but such expression is substantially lower than in inhibitory neurons, for example less than 1% or 1%, 2%, 3%, 5%, 10%, 15% or 20% of the expression levels in inhibitory neurons. In particular embodiments, interneurons are the only cell types that express the right combination of transcription factors that bind to the concatemerized core of the I56i enhancer to drive gene expression.

[0052] In particular embodiments, selective expression within inhibitory neurons is demonstrated by 10% more expression, 20% more expression, 30% more expression, 40% more expression; 50% more expression; 60% more expression, 70% more expression, 80% more expression, 90% more expression, 100% more expression or more over non-inhibitory neurons. In particular embodiments, selective expression within inhibitory neurons is demonstrated by expression within inhibitory neurons and no detectable expression within non-inhibitory neurons.

[0053] In particular embodiments, selective expression within GABAergic interneurons is demonstrated by 10% more expression, 20% more expression, 30% more expression, 40% more expression; 50% more expression; 60% more expression, 70% more expression, 80% more expression, 90% more expression, 100% more expression or more over non-GABAergic interneurons. In particular embodiments, selective expression within GABAergic interneurons is demonstrated by expression within GABAergic interneurons and no detectable expression within non-GABAergic interneurons.

[0054] In particular embodiments, one class of inhibitory neurons can be identified based on Pvalb expression as described in relation to FIGS. **1**, **7**C, **7**E, and **8**. In particular embodiments, GABAergic interneurons can be distinguished from other cell types by the expression of the genes Gad2 and Gad1; in the adult cortex, GABAergic interneurons can be distinguished from glutamatergic excitatory neurons by the presence of GABA. In the adult striatum, GABAergic interneurons can be distinguished from Medium Spiny Neurons by the expression of the gene Nkx2.1. (See, for example, Rudy et al., Devel Neurobio 71, 45-61 (2011)): Kepecs. & Fishell, Nature. 505, 318-326 (2014).

[0055] In particular embodiments, a coding sequence encodes a protein or nucleotide sequence that rescues voltage-gated sodium channel function. In particular embodiments, the coding sequence further encodes a reporter protein. If the coding sequence encodes a protein or nucleotide sequence that rescues voltage-gated sodium channel function and a reporter protein, it can further encode a skipping element such as a self-cleaving peptide or an internal ribosome entry site (IRES) sequence.

[0056] Exemplary proteins that restore voltage-gated sodium channel function include NavShep, NavShep-D60N, NavBp, NavMs, and hSCN1A, and their epitope-tagged variants 3×HA-NavShep-D60N, 3×HA-NavBp, 3×HA-NavMs, His-NavMs, and hSCN1A-3×HA.

[0057] Exemplary coding sequences that encode proteins that rescue voltage-gated sodium channel function include SEQ ID NOs: 9-16.

[0058] Further, as indicated above, there are additional strategies that can be used to provide exogenous voltage-gated sodium channel activity to inhibitory neurons that are deficient in this activity. For example, in particular embodiments, enhancer-vectors (e.g., AAV) can encode an artificial transcription factor that increases the expression of the endogenous functional copy of SCN1A (or other SCN_A family gene) in $SCN1A^{+/-}$ patients (e.g., Dravet patients) or other patients deficient in other voltage-gated sodium channels. This artificial transcription factor can contain a specific DNA-binding domain linked to a general transcription-activating domain. The DNA-binding domain can be engineered from a Cas9-related gene using CRISPR activation technology (as in Matharu et al., 2019, Science, 363(6424), 186-194 wherein Cas proteins are engineered to lack nuclease activity), or from other custom DNA-sensing proteins such as TALE-transcription factors (TFs) (Morbitzer et al., 2010, Proc. Nat. Acad. Sci., 107(50), 21617-21622) or zinc finger TFs (Gersbach et al., 2014, Acc. Chem. Res, 47(8), 2309-2318). Additional information and options regarding CRISPR and other targeted gene binding (and optionally editing) systems and components are provided below.

[0059] In particular embodiments, enhancer-vectors can encode molecules that increase the prevalence of functional SCN1A mRNA molecules, for example through post-transcriptional positive regulation of splicing and or stability, eventually leading to increases in functional voltage-gated sodium channel activity. This could be accomplished through AAV introduction of antisense RNA oligonucleotide molecules to increase splicing (Hsiao et al., 2016, EBioMedicine. 9, 257-277), or to prevent potential microRNA negative regulation.

[0060] In particular embodiments, strategies can be employed that restore the full length hSCN1A transcript through trans-splicing the hSCN1A transcript separated into two parts. This can be accelerated through the use of strong synthetic splice donors and splice acceptors in a two vector system, and through the use of different ITRs (ITR2 and ITR5) that induce proper juxtaposition of the two different genomes in cell after transduction (McClements M E, et al., 2017, Yale J. Biol Med. 90(4):611-623).

[0061] In particular embodiments, enhancer-vectors (e.g., AAV) can deliver hSCN1A protein as several (two or four) subunit ORFs delivered by two or four separate vectors. Nav channels display pseudo-four-fold internal symmetry, due to four similar internal domains within the alpha subunit (Shen et al., Science 363(6433), 1303-1308), demonstrating that this protein can be amenable to delivery in two or four pieces. As indicated previously, assembly of sub-units can occur naturally and/or can be facilitated by the inclusion of engineered cysteines or other linking domains.

[0062] In particular embodiments, due to its internal 4-domain pseudo-symmetry, hSCN1A can be delivered in four fragments encoded on four different vectors that can self-assemble into a tetramer that is functionally and chemically equivalent to the functional NaV1.1 alpha subunit, except with breakpoints in surface loops. Alternatively, a single fragment may be delivered on a single vector that may self-assemble into a homo-tetrameric complex resembling the NaV1.1 alpha subunit which consists entirely of human sequence. Either strategy can deliver human non-immunogenic biomolecules to inhibitory cells for the purpose of rescuing Nav1.1 channel function in neurons that are deficient in voltage-gated sodium channel activity.

[0063] Additional strategies could also be used to reduce the hSCN1A ORF into a smaller (e.g., AAV-compatible) size (<4.7 kb).

[0064] Exemplary reporter proteins include fluorescent proteins such as yellow fluorescent molecules such as SYFP2, Citrine, PhiYFP and ZsYellow1; red fluorescent molecules such as mCherry, mRuby, Jred, and AsRed2; green fluorescent molecules such as green fluorescent protein (GFP), enhanced green fluorescent protein (EGFP), avGFP, ZsGreen, and mAzamiGreen; orange fluorescent molecules such as mOrange and mKusabira-Orange; blue fluorescent molecules such as Sapphire, mKalamal, EBFP2 and Azurite; cyan fluorescent molecules such as Cerulean and mTurquoise; far red proteins such as mPlum and mNeptune.

[0065] GFP is composed of 238 amino acids (26.9 kDa), originally isolated from the jellyfish Aequorea victoria/Aequorea aequorea/Aequorea forskalea that fluoresces green when exposed to blue light. The GFP from A. victoria has a major excitation peak at a wavelength of 395 nm and a minor one at 475 nm. Its emission peak is at 509 nm which is in the lower green portion of the visible spectrum. The GFP from the sea pansy (*Renilla reniformis*) has a single major excitation peak at 498 nm. Due to the potential for widespread usage and the evolving needs of researchers, many different mutants of GFP have been engineered. The first major improvement was a single point mutation (S65T) reported in 1995 in Nature by Roger Tsien. This mutation dramatically improved the spectral characteristics of GFP, resulting in increased fluorescence, photostability and a shift of the major excitation peak to 488 nm with the peak emission kept at 509 nm. The addition of the 37° C. folding efficiency (F64L) point mutant to this scaffold yielded enhanced GFP (EGFP). EGFP has an extinction coefficient (denoted ε), also known as its optical cross section of 9.13E-21 m^2/molecule, also quoted as 55,000 L/(mol·cm). Superfolder GFP, a series of mutations that allow GFP to rapidly fold and mature even when fused to poorly folding peptides, was reported in 2006.

[0066] The "yellow fluorescent protein" (YFP) is a genetic mutant of green fluorescent protein, derived from Aequorea victoria. Its excitation peak is 514 nm and its emission peak is 527 nm.

[0067] Exemplary self-cleaving peptides include the 2A peptides which lead to the production of two proteins from one mRNA. The 2A sequences are short (e.g., 20 amino acids), allowing more use in size-limited constructs. Par-

ticular examples include P2A, T2A, E2A, and F2A. In particular embodiments, the expression constructs include an internal ribosome entry site (IRES) sequence. IRES allow ribosomes to initiate translation at a second internal site on a mRNA molecule, leading to production of two proteins from one mRNA.

[0068] Coding sequences encoding proteins described herein can be obtained from publicly available databases and publications. Coding sequences can further include various sequence polymorphisms, mutations, and/or sequence variants wherein such alterations do not affect the function of the encoded protein. The term "encode" or "encoding" refers to a property of sequences of nucleic acids, such as a vector, a plasmid, a gene, cDNA, mRNA, to serve as templates for synthesis of other molecules such as proteins.

[0069] The term "gene" may include not only coding sequences but also regulatory regions such as promoters, enhancers, and termination regions. The term further can include all introns and other DNA sequences spliced from the mRNA transcript, along with variants resulting from alternative splice sites. The sequences can also include degenerate codons of a reference sequence or sequences that may be introduced to provide codon preference in a specific organism or cell type.

[0070] Promoters can include general promoters, tissue-specific promoters, cell-specific promoters, and/or promoters specific for the cytoplasm. Promoters may include strong promoters, weak promoters, constitutive expression promoters, and/or inducible promoters. Inducible promoters direct expression in response to certain conditions, signals or cellular events. For example, the promoter may be an inducible promoter that requires a particular ligand, small molecule, transcription factor or hormone protein in order to effect transcription from the promoter. Particular examples of promoters include minBglobin, CMV, minCMV, SV40 immediately early promoter, and the Rous Sarcoma Virus (RSV) long-terminal repeat (LTR) promoter.

[0071] In particular embodiments, expression constructs are provided within vectors. The term vector refers to a nucleic acid molecule capable of transferring or transporting another nucleic acid molecule, such as an expression construct. The transferred nucleic acid is generally linked to, e.g., inserted into, the vector nucleic acid molecule. A vector may include sequences that direct autonomous replication in a cell, or may include sequences that permit integration into host cell DNA. Useful vectors include, for example, plasmids (e.g., DNA plasmids or RNA plasmids), transposons, cosmids, bacterial artificial chromosomes, and viral vectors.

[0072] Viral vector is widely used to refer to a nucleic acid molecule that includes virus-derived nucleic acid elements that facilitate transfer and expression of non-native nucleic acid molecules within a cell. The term adeno-associated viral vector refers to a viral vector or plasmid containing structural and functional genetic elements, or portions thereof, that are primarily derived from AAV. The term "retroviral vector" refers to a viral vector or plasmid containing structural and functional genetic elements, or portions thereof, that are primarily derived from a retrovirus. The term "lentiviral vector" refers to a viral vector or plasmid containing structural and functional genetic elements, or portions thereof, that are primarily derived from a lentivirus, and so on. The term "hybrid vector" refers to a vector including structural and/or functional genetic elements from more than one virus type.

[0073] Adenovirus. "Adenovirus vectors" refer to those constructs containing adenovirus sequences sufficient to (a) support packaging of an expression construct and (b) to express a coding sequence that has been cloned therein in a sense or antisense orientation. A recombinant Adenovirus vector includes a genetically engineered form of an adenovirus. Knowledge of the genetic organization of adenovirus, a 36 kb, linear, double-stranded DNA virus, allows substitution of large pieces of adenoviral DNA with foreign sequences up to 7 kb. In contrast to retrovirus, the adenoviral infection of host cells does not result in chromosomal integration because adenoviral DNA can replicate in an episomal manner without potential genotoxicity. Also, adenoviruses are structurally stable, and no genome rearrangement has been detected after extensive amplification.

[0074] Adenovirus is particularly suitable for use as a gene transfer vector because of its mid-sized genome, ease of manipulation, high titer, wide target-cell range and high infectivity. Both ends of the viral genome contain 100-200 base pair inverted repeats (ITRs), which are cis elements necessary for viral DNA replication and packaging. The early (E) and late (L) regions of the genome contain different transcription units that are divided by the onset of viral DNA replication. The E1 region (E1A and E1 B) encodes proteins responsible for the regulation of transcription of the viral genome and a few cellular genes. The expression of the E2 region (E2A and E2B) results in the synthesis of the proteins for viral DNA replication. These proteins are involved in DNA replication, late gene expression and host cell shut-off. The products of the late genes, including the majority of the viral capsid proteins, are expressed only after significant processing of a single primary transcript issued by the major late promoter (MLP). The MLP is particularly efficient during the late phase of infection, and all the mRNAs issued from this promoter possess a 5'-tripartite leader (TPL) sequence which makes them preferred mRNAs for translation.

[0075] Other than the requirement that an adenovirus vector be replication defective, or at least conditionally defective, the nature of the adenovirus vector is not believed to be crucial to the successful practice of particular embodiments disclosed herein. The adenovirus may be of any of the 42 different known serotypes or subgroups A-F. In particular embodiments, adenovirus type 5 of subgroup C is the preferred starting material in order to obtain a conditional replication-defective adenovirus vector for use in particular embodiments, since Adenovirus type 5 is a human adenovirus about which a great deal of biochemical and genetic information is known, and it has historically been used for most constructions employing adenovirus as a vector.

[0076] As indicated, the typical vector is replication defective and will not have an adenovirus E1 region. Thus, it will be most convenient to introduce the polynucleotide encoding the gene of interest at the position from which the E1-coding sequences have been removed. However, the position of insertion of the construct within the adenovirus sequences is not critical. The polynucleotide encoding the gene of interest may also be inserted in lieu of a deleted E3 region in E3 replacement vectors or in the E4 region where a helper cell line or helper virus complements the E4 defect.

[0077] Adeno-Associated Virus (AAV) is a parvovirus, discovered as a contamination of adenoviral stocks. It is a ubiquitous virus (antibodies are present in 85% of the US human population) that has not been linked to any disease.

It is also classified as a dependovirus, because its replication is dependent on the presence of a helper virus, such as adenovirus. Various serotypes have been isolated, of which AAV-2 is the best characterized. AAV has a single-stranded linear DNA that is encapsidated into capsid proteins VP1, VP2 and VP3 to form an icosahedral virion of 20 to 24 nm in diameter.

[0078] The AAV DNA is 4.7 kilobases long. It contains two open reading frames and is flanked by two ITRs. There are two major genes in the AAV genome: rep and cap. The rep gene codes for proteins responsible for viral replication, whereas cap codes for capsid protein VP1-3. Each ITR forms a T-shaped hairpin structure. These terminal repeats are the only essential cis components of the AAV for chromosomal integration. Therefore, the AAV can be used as a vector with all viral coding sequences removed and replaced by the cassette of genes for delivery. Three AAV viral promoters have been identified and named p5, p19, and p40, according to their map position. Transcription from p5 and p19 results in production of rep proteins, and transcription from p40 produces the capsid proteins.

[0079] AAVs stand out for use within the current disclosure because of their superb safety profile and rare integration into genomic DNA, and because their capsids and genomes can be tailored to allow expression in selected cell populations. scAAV refers to a self-complementary AAV. rAAV refers to a recombinant adeno-associated virus.

[0080] Other viral vectors may also be employed. For example, vectors derived from viruses such as vaccinia virus, polioviruses and herpes viruses may be employed. They offer several attractive features for various mammalian cells.

[0081] Retrovirus. Retroviruses are a common tool for gene delivery. "Retrovirus" refers to an RNA virus that reverse transcribes its genomic RNA into a linear double-stranded DNA copy and subsequently covalently integrates its genomic DNA into a host genome. Once the virus is integrated into the host genome, it is referred to as a "provirus." The provirus serves as a template for RNA polymerase II and directs the expression of RNA molecules which encode the structural proteins and enzymes needed to produce new viral particles.

[0082] Illustrative retroviruses suitable for use in particular embodiments, include: Moloney murine leukemia virus (M-MuLV), Moloney murine sarcoma virus (MoMSV), Harvey murine sarcoma virus (HaMuSV), murine mammary tumor virus (MuMTV), gibbon ape leukemia virus (GaLV), feline leukemia virus (FLV), spumavirus, Friend murine leukemia virus, Murine Stem Cell Virus (MSCV) and Rous Sarcoma Virus (RSV) and lentivirus.

[0083] "Lentivirus" refers to a group (or genus) of complex retroviruses. Illustrative lentiviruses include: HIV (human immunodeficiency virus; including HIV type 1, and HIV type 2); visna-maedi virus (VMV); the caprine arthritis-encephalitis virus (CAEV); equine infectious anemia virus (EIAV); feline immunodeficiency virus (FIV); bovine immune deficiency virus (BIV); and simian immunodeficiency virus (SIV). In particular embodiments, HIV based vector backbones (i.e., HIV cis-acting sequence elements) can be used.

[0084] "Self-inactivating" (SIN) vectors refer to replication-defective vectors in which the right (3') LTR enhancer-promoter region, known as the U3 region, has been modified (e.g., by deletion or substitution) to prevent viral transcription beyond the first round of viral replication. This is because the right (3') LTR U3 region is used as a template for the left (5') LTR U3 region during viral replication and, thus, the viral transcript cannot be made without the U3 enhancer-promoter. In a further embodiment, the 3' LTR is modified such that the U5 region is replaced, for example, with an ideal poly(A) sequence. It should be noted that modifications to the LTRs such as modifications to the 3' LTR, the 5' LTR, or both 3' and 5' LTRs, are also included in particular embodiments.

[0085] In particular embodiments, viral vectors include a TAR element. The term "TAR" refers to the "trans-activation response" genetic element located in the R region of lentiviral (e.g., HIV) LTRs. This element interacts with the lentiviral trans-activator (tat) genetic element to enhance viral replication. However, this element is not required in embodiments wherein the U3 region of the 5' LTR is replaced by a heterologous promoter.

[0086] The "R region" refers to the region within retroviral LTRs beginning at the start of the capping group (i.e., the start of transcription) and ending immediately prior to the start of the poly(A) tract. The R region is also defined as being flanked by the U3 and U5 regions. The R region plays a role during reverse transcription in permitting the transfer of nascent DNA from one end of the genome to the other.

[0087] In particular embodiments, expression of heterologous sequences in viral vectors is increased by incorporating posttranscriptional regulatory elements, efficient polyadenylation sites, and optionally, transcription termination signals into the vectors. A variety of posttranscriptional regulatory elements can increase expression of a heterologous nucleic acid at the protein, e.g., woodchuck hepatitis virus posttranscriptional regulatory element (WPRE; Zufferey et al., 1999, J. Virol., 73:2886); the posttranscriptional regulatory element present in hepatitis B virus (HPRE) (Huang et al., Mol. Cell. Biol., 5:3864); and the like (Liu et al., 1995, Genes Dev., 9:1766). In particular embodiments, vectors include a posttranscriptional regulatory element such as a WPRE or HPRE. In particular embodiments, vectors lack or do not include a posttranscriptional regulatory element such as a WPRE or HPRE.

[0088] Elements directing the efficient termination and polyadenylation of a heterologous nucleic acid transcript can increase heterologous gene expression. Transcription termination signals are generally found downstream of the polyadenylation signal. In particular embodiments, vectors include a polyadenylation sequence 3' of a polynucleotide encoding a polypeptide to be expressed. The term "poly(A) site" or "poly(A) sequence" denotes a DNA sequence which directs both the termination and polyadenylation of the nascent RNA transcript by RNA polymerase II. Polyadenylation sequences can promote mRNA stability by addition of a poly(A) tail to the 3' end of the coding sequence and thus, contribute to increased translational efficiency. Particular embodiments may utilize BGHpA or SV40pA. In particular embodiments, a preferred embodiment of an expression construct includes a terminator element. These elements can serve to enhance transcript levels and to minimize read through from the construct into other plasmid sequences.

[0089] Beyond the foregoing description, a wide range of suitable expression vector types will be known to a person of ordinary skill in the art. These can include commercially available expression vectors designed for general recombi-

nant procedures, for example plasmids that contain one or more reporter genes and regulatory elements required for expression of the reporter gene in cells. Numerous vectors are commercially available, e.g., from Invitrogen, Stratagene, Clontech, etc., and are described in numerous associated guides. In particular embodiments, suitable expression vectors include any plasmid, cosmid or phage construct that is capable of supporting expression of encoded genes in mammalian cell, such as pUC or Bluescript plasmid series.

[0090] Particular embodiments include:

Vector Name	Features
CN1367	rAAV2: hl56i-minBglobin-His-NavMs-P2A-SYFP2-WPRE3-BGHpA
CN1244	rAAV2: hl56i-minBglobin-SYFP2-WPRE3-BGHpA
CN1389	rAAV2: 1xhl56iCore-minBglobin-SYFP2-WPRE3-BGHpA
CN1390	rAAV2: 3xhl56iCore-minBglobin-SYFP2-WPRE3-BGHpA
CN1203	scAAV: hl56i-minBglobin-SYFP2-WPRE3-BGHpA
CN1180	scAAV: hl12b-minBglobin-SYFP2-WPRE3-BGHpA
CN1498	rAAV2: 3xhl56iCore-minCMV-SYFP2-P2A-3xHA-NavBp-WPRE3-BGHpA
CN1499	rAAV2: 3xhl56iCore-minCMV-SYFP2-P2A-3xHA-NavMs-WPRE3-BGHpA
CN1500	rAAV2: 3xhl56iCore-minCMV-SYFP2-P2A-3xHA-NavSheP-D60N-WPRE3-BGHpA
CN1504	rAAV2: 3xhlI56iCore-minCMV-SYFP2-P2A-hSCN1A-Nterm
CN1512	rAAV2: hSCN1A-Cterm-3xHA-WPRE3-BGHpA
CN2001	rAAV2: 3xhl56iCore-minBG-NavBp-WPRE3-BGHpA
CN2002	rAAV2: 3xhl56iCore-minBG-NavMs-WPRE3-BGHpA
CN2003	rAAV2: 3xhl56iCore-minBG-NavSheP-D60N-WPRE3-BGHpA
CN2004	rAAV2: 3xhl56iCore-minBG-hSCN1AFrontEnd
CN2005	rAAV2: hSCN1ABackEnd-WPRE3-BGHpA
CN2006	rAAV2: 3xhl56iCore-minBG-SYFP2ns-P2A-hSCN1AFrontEnd-IntronBridge
CN2007	rAAV2: IntronBridge-hSCN1ABackEnd-3xHA-WPRE3-BGHpA
CN2008	rAAV2: 3xhl56iCore-minBG-hSCN1AFrontEnd-IntronBridge
CN2009	rAAV2: IntronBridge-hSCN1ABackEnd-WPRE3-BGHpA
CN2026	rAAV-3xhl56i(core)-minBG-hSCN1A_Fragment1-WPRE3-BGHpA
CN2027	rAAV-3xhl56i(core)-minBG-hSCN1A_Fragment2-WPRE3-BGHpA
CN2028	rAAV-3xhl56i(core)-minBG-hSCN1A_Fragment3-WPRE3-BGHpA
CN2029	rAAV-3xhl56i(core)-minBG-hSCN1A_Fragment4-WPRE3-BGHp

[0091] In particular embodiments viral vectors with capsids that cross the blood-brain barrier (BBB) are selected. In particular embodiments, AAV are modified to include capsids that cross the BBB. Examples of AAV with viral capsids that cross the blood brain barrier include AAV9 (Gombash et al., Front Mol Neurosci. 2014; 7:81), AAVrh.10 (Yang, et al., Mol Ther. 2014; 22(7): 1299-1309), AAV1R6, AAV1R7 (Albright et al., Mol Ther. 2018; 26(2): 510), rAAVrh.8 (Yang, et al., supra), AAV-BR1(Marchio et al., EMBO Mol Med. 2016; 8(6): 592), AAV-PHP.S (Chan et al., Nat Neurosci. 2017; 20(8): 1172), AAV-PHP.B (Deverman et al., Nat Biotechnol. 2016; 34(2): 204), and AAV-PPS (Chen et al., Nat Med. 2009; 15: 1215).

[0092] AAV9 is a naturally occurring AAV serotype that, unlike many other naturally occurring serotypes, can cross the BBB following intravenous injection. It transduces large sections of the central nervous system (CNS), thus permitting minimally invasive treatments (Naso et al., BioDrugs. 2017; 31(4): 317), for example, as described in relation to the ongoing clinical trials for the treatment of superior mesenteric artery (SMA) syndrome by AveXis (AVXS-101, NCT03505099) and the treatment of CLN3 gene-Related Neuronal Ceroid-Lipofuscinosis (NCT03770572). In particular embodiments, a representative AAV9 capsid protein sequence can include the AAV9 VP1 capsid protein sequence (UniProt Accession number Q6JC40, SEQ ID NO: 57).

[0093] AAVrh.10, was originally isolated from rhesus macaques and shows low seropositivity in humans when compared with other common serotypes used for gene delivery applications (Selot et al., Front Pharmacol. 2017; 8: 441) and is currently being evaluated in clinical trials LYS-SAF302, LYSOGENE, and NCT03612869.

[0094] AAV1R6 and AAV1R7, two variants isolated from a library of chimeric AAV vectors (AAV1 capsid domains swapped into AAVrh.10), retain the ability to cross the BBB and transduce the CNS while showing significantly reduced hepatic and vascular endothelial transduction.

[0095] rAAVrh.8, also isolated from rhesus macaques, shows a global transduction of glial and neuronal cell types in regions of clinical importance following peripheral administration and also displays reduced peripheral tissue tropism compared to other vectors.

[0096] AAV-BR1 is an AAV2 variant displaying the NRGTEWD (SEQ ID NO: 53) epitope that was isolated during in vivo screening of a random AAV display peptide library. It shows high specificity accompanied by high transgene expression in the brain with minimal off-target affinity (including for the liver) (Körbelin et al., EMBO Mol Med. 2016; 8(6): 609).

[0097] AAV-PHP.S (Addgene, Watertown, Mass.) is a variant of AAV9 generated with the CREATE method that encodes the 7-mer sequence QAVRTSL (SEQ ID NO: 54), transduces neurons in the enteric nervous system, and strongly transduces peripheral sensory afferents entering the spinal cord and brain stem.

[0098] AAV-PHP.B (Addgene, Watertown, Mass.) is a variant of AAV9 generated with the CREATE method that encodes the 7-mer sequence TLAVPFK (SEQ ID NO: 55). It transfers genes throughout the CNS with higher efficiency than AAV9 and transduces the majority of astrocytes and neurons across multiple CNS regions.

[0099] AAV-PPS, an AAV2 variant crated by insertion of the DSPAHPS (SEQ ID NO: 56) epitope into the capsid of AAV2, shows a dramatically improved brain tropism relative to AAV2.

[0100] In particular embodiments, a capsid that results in brain-wide transduction of inhibitory cells in a primate following administration (e.g., i.v. administration) is chosen. In particular embodiments, a capsid that results in widespread transduction of tissue and cell types impacted by the loss of Scn1a following administration is chosen.

[0101] Compositions for Administration. Expression constructs and vectors of the present disclosure (referred to herein as physiologically active components) can be formulated with a carrier that is suitable for administration to human or animal subjects. Physiologically active components within compositions described herein can be prepared in neutral forms, as freebases, or as pharmacologically acceptable salts.

[0102] Pharmaceutically-acceptable salts include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

[0103] Carriers of physiologically active components can include solvents, dispersion media, vehicles, coatings, diluents, isotonic and absorption delaying agents, buffers, solutions, suspensions, colloids, and the like. The use of such carriers for physiologically active components is well known in the art. Except insofar as any conventional media or agent is incompatible with the physiologically active components, it can be used with compositions as described herein.

[0104] The phrase "pharmaceutically-acceptable carriers" refer to carriers that do not produce an allergic or similar untoward reaction when administered to a human, and in particular embodiments, when administered intravenously.

[0105] In particular embodiments, compositions can be formulated for intravenous, intraocular, intravitreal, parenteral, subcutaneous, intracerebro-ventricular, intramuscular, intrathecal, intraspinal, oral, intraperitoneal, oral or nasal inhalation, or by direct injection to one or more cells, tissues, or organs.

[0106] Compositions may include liposomes, lipids, lipid complexes, microspheres, microparticles, nanospheres, and/or nanoparticles.

[0107] The formation and use of liposomes is generally known to those of skill in the art. Liposomes have been developed with improved serum stability and circulation half-times (see, for instance, U.S. Pat. No. 5,741,516). Further, various methods of liposome and liposome like preparations as potential drug carriers have been described (see, for instance U.S. Pat. Nos. 5,567,434; 5,552,157; 5,565,213; 5,738,868; and 5,795,587).

[0108] Liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs). MLVs generally have diameters of from 25 nm to 4 μm. Sonication of MLVs results in the formation of small unilamellar vesicles (SUVs) with diameters in the range of 200 to 500 Å, containing an aqueous solution in the core.

[0109] Liposomes bear resemblance to cellular membranes and are widely suitable as both water- and lipid-soluble substances can be entrapped, i.e. in the aqueous spaces and within the bilayer itself, respectively.

[0110] Liposomes may also be employed for site-specific delivery of active agents by selectively modifying the liposomal formulation. Should specific targeting be desired, methods are available for this to be accomplished. For example, binding domains of antibodies may be used to bind to the liposome surface and to direct the antibody and its drug contents to specific antigenic receptors located on a particular cell-type surface. Carbohydrate determinants (glycoprotein or glycolipid cell-surface components that play a role in cell-cell recognition, interaction and adhesion) may also be used as recognition sites as they have potential in directing liposomes to particular cell types.

[0111] In addition to the teachings of Couvreur et al. (*FEBS Lett.* 84(2):323-326, 1977; *Crit Rev Ther Drug Carrier Syst.* 5(1)1-20, 1988), the following information may be utilized in generating liposomal formulations. Phospholipids can form a variety of structures other than liposomes when dispersed in water, depending on the molar ratio of lipid to water. At low ratios the liposome is the preferred structure. The physical characteristics of liposomes depend on pH, ionic strength and the presence of divalent cations. Liposomes can show low permeability to ionic and polar substances, but at elevated temperatures undergo a phase transition which markedly alters their permeability. The phase transition involves a change from a closely packed, ordered structure, known as the gel state, to a loosely packed, less-ordered structure, known as the fluid state. This occurs at a characteristic phase-transition temperature and results in an increase in permeability to ions, sugars and drugs.

[0112] The ability to trap solutes varies between different types of liposomes. For example, MLVs are moderately efficient at trapping solutes, but SUVs are extremely inefficient. SUVs offer the advantage of homogeneity and reproducibility in size distribution, however, and a compromise between size and trapping efficiency is offered by large unilamellar vesicles (LUVs). These are prepared by ether evaporation and are three to four times more efficient at solute entrapment than MLVs.

[0113] Alternatively, the disclosure provides for pharmaceutically acceptable nanocapsule formulations of the physiologically active components of the present disclosure. Nanocapsules can generally entrap compounds in a stable and reproducible way (Quintanar-Guerrero et al., *Drug Dev Ind Pharm* 24(12):1113-1128, 1998; Quintanar-Guerrero et al., *Pharm Res.* 15(7):1056-1062, 1998; Quintanar-Guerrero et al., J. *Microencapsul.* 15(1):107-119, 1998; Douglas et al., *Crit Rev Ther Drug Carrier Syst* 3(3):233-261, 1987). To avoid side effects due to intracellular polymeric overloading, ultrafine particles can be designed using polymers able to be degraded in vivo. Biodegradable polyalkyl-cyanoacrylate nanoparticles that meet these requirements are contemplated for use in the present disclosure. Such particles may be made as described in Couvreur et al., *J Pharm Sci* 69(2):199-202, 1980; Couvreur et al., *Crit Rev Ther Drug Carrier Syst.* 5(1)1-20, 1988; zur Muhlen et al., *Eur J Pharm Biopharm,* 45(2):149-155, 1998; Zambaux et al., *J Control Release* 50(1-3):31-40, 1998; and U.S. Pat. No. 5,145,684.

[0114] Injectable compositions can include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (U.S. Pat. No. 5,466,468). For delivery via injec-

tion, the form is sterile and fluid to the extent that it can be delivered by syringe. In particular embodiments, it is stable under the conditions of manufacture and storage, and optionally contains one or more preservative compounds against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion, and/or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and/or antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In various embodiments, the preparation will include an isotonic agent(s), for example, sugar(s) or sodium chloride. Prolonged absorption of the injectable compositions can be accomplished by including in the compositions of agents that delay absorption, for example, aluminum monostearate and gelatin. Injectable compositions can be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose.

[0115] Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. As indicated, under ordinary conditions of storage and use, these preparations can contain a preservative to prevent the growth of microorganisms.

[0116] Sterile compositions can be prepared by incorporating the physiologically active component in an appropriate amount of a solvent with other optional ingredients (e.g., as enumerated above), followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized physiologically active components into a sterile vehicle that contains the basic dispersion medium and the required other ingredients (e.g., from those enumerated above). In the case of sterile powders for the preparation of sterile injectable solutions, preferred methods of preparation can be vacuum-drying and freeze-drying techniques which yield a powder of the physiologically active components plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0117] Oral compositions may be in liquid form, for example, as solutions, syrups or suspensions, or may be presented as a drug product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). The compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinyl pyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). Tablets may be coated by methods well-known in the art.

[0118] Inhalable compositions can be delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0119] Compositions can also include microchip devices (U.S. Pat. No. 5,797,898), ophthalmic formulations (Bourlais et al., *Prog Retin Eye Res,* 17(1):33-58, 1998), transdermal matrices (U.S. Pat. No. 5,770,219 and U.S. Pat. No. 5,783,208) and feedback-controlled delivery (U.S. Pat. No. 5,697,899).

[0120] Supplementary active ingredients can also be incorporated into the compositions.

[0121] Typically, compositions can include at least 0.1% of the physiologically active components or more, although the percentage of the physiologically active components may, of course, be varied and may conveniently be between 1 or 2% and 70% or 80% or more or 0.5-99% of the weight or volume of the total composition. Naturally, the amount of physiologically active components in each physiologically-useful composition may be prepared is such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of compositions and dosages may be desirable.

[0122] In particular embodiments, for administration to humans, compositions should meet sterility, pyrogenicity, and the general safety and purity standards as required by United States Food and Drug Administration (FDA) or other applicable regulatory agencies in other countries.

[0123] Methods of Use. In particular embodiments, a composition including a physiologically active component described herein is administered to a subject to result in selective expression of a protein or nucleotide sequence that rescues voltage-gated sodium channel function within inhibitory neurons in the subject. In particular embodiments, rescuing voltage-gated sodium channel function includes converting a subject's interneurons lacking a sufficient quantity and/or activity of Nav1.1 sodium channels, into interneurons that express a sufficient quantity of exogenous voltage-gated sodium channels and activity, in order to recover neuronal function and to prevent epileptiform circuit activity.

[0124] In particular embodiments, rescued voltage-gated sodium channel function is evidenced by one or more of an increase in sodium channel current in and/or the increased excitability of an inhibitory neuron genetically-modified by the physiologically active component. In particular embodiments, rescued voltage-gated sodium channel function is evidenced by one or more of an increase in sodium channel conductance in and/or the sodium channel influx in response to voltage depolarization of an inhibitory neuron genetically-modified by the physiologically active component. An increase can be at least a 10% increase, at least a 20% increase, at least a 30% increase, at least a 40% increase, at

least a 50% increase, at least a 60% increase, at least a 70% increase, at least an 80% increase or at least a 90% increase. The output of inhibitory neurons can be measured using an electrophysiological method, such as a multi-electrode array or a patch-clamp.

[0125] In particular embodiments, the inhibitory neuron is an inhibitory interneuron, a GABAergic neuron, a GABAergic interneuron, a pan-GABAergic neuron, or an inhibitory neuron in the hippocampus or cortex.

[0126] In particular embodiments, rescued voltage-gated sodium channel function is evidenced by increased sodium current-dependent fast spiking in forebrain interneurons, for example, using a mouse model. In particular embodiments, rescued voltage-gated sodium channel function is evidenced by delayed or prevented temperature-induced seizing in a mouse model as described herein.

[0127] Particular embodiments include identifying a subject with reduced Nav1.1 sodium channel function in inhibitory neurons. Such subjects can be identified based on a diagnosis of a disorder associated with Nav1.1 sodium channel dysfunction. Such disorders include epilepsy, an SCN1A-related seizure disorder, simple febrile seizures (FS), GEFS+, DS, intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC), intractable infantile partial seizures, myoclonic-astatic epilepsy, Lennox-Gastaut syndrome (LGS), and infantile spasms. Intractable seizures (also referred to as "uncontrolled" or "refractory" seizures) are seizures that cannot be controlled to a satisfactory degree based on sound medical judgment with conventional treatments.

[0128] Regarding DS particularly, 80% of DS patients test positive for an SCN1A gene mutation, but the absence of an SCN1A mutation does not exclude a DS diagnosis. DS is associated with mutations in SCN1A (such as partial or total deletion mutations, truncating mutations and/or missense mutations e.g. in the voltage or pore regions S4 to S6), SCN1B (encoding the sodium channel β1 subunit), SCN2A, SCN3A, SCN9A, GABRG2 (encoding the γ2 subunit of GABA receptor), GABRD (encoding the delta subunit of GABA receptor) and/or PCDH19 genes.

[0129] In particular embodiments, a subject in need of a treatment described herein may not experience diagnosable seizures, but exhibits subclinical electrical discharges, which refers to a high rate of seizure-like activity when their brain waves are measured with an electroencephalogram. Epileptic syndromes associated with these seizure-like discharges include Landau-Kleffner Syndrome, and Continuous Spike-wave Activity during Slow-wave Sleep.

[0130] In particular embodiments, patients may have an intellectual developmental disability (IDD) such as an Autism Spectrum Disorders (ASD). In particular embodiments, the patient of the disclosed method has epilepsy and an IDD or ASD disorder. Common IDD and ASD that are comorbid with seizures and epilepsy include fragile X syndrome (FXS), Rett syndrome (RTT), Angelman syndrome, Prader-Willi syndrome, Velocardiofacial syndrome, Smith-Lemli-Opitz syndrome, neuroligin mutations and "interneuronopathies" resulting from aristaless-related homeobox, X-linked (ARX) and Neuropilin 2 (NRP2) gene mutations.

[0131] The methods described herein may be particularly useful for treating children and infants, and for treating disorders that onset during infancy or childhood. In particular embodiments, the patient of the disclosed method is a newborn, a baby, a toddler, a preschooler, a school-age child, a tween, or a teenager. In particular embodiments, the patient is 18 years old or younger, 12 years old or younger, 10 years old or younger, 8 years old or younger, 6 years old or younger, 4 years old or younger, 2 years old or younger, 1 year old or younger. In particular embodiments, the patient is an adult that is over eighteen years old.

[0132] In particular embodiments, the methods reduce or prevent seizures, or symptoms thereof in a patient in need thereof. In particular embodiments, the methods provided may reduce or prevent one or more different types of seizures. Ideally, the methods of the disclosure result in a total prevention of seizures. However, the disclosure also encompasses methods in which the instances of seizures are decreased by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80% or at least 90%.

[0133] Generally, a seizure can include convulsions, repetitive movements, unusual sensations, and combinations thereof. Seizures can be categorized as focal seizures (also referred to as partial seizures) and generalized seizures. Focal seizures affect only one side of the brain, while generalized seizures affect both sides of the brain. Specific types of focal seizures include simple focal seizures, complex focal seizures, and secondarily generalized seizures. Simple focal seizures can be restricted or focused on a particular lobe (e.g., temporal lobe, frontal lobe, parietal lobe, or occipital lobe). Complex focal seizures generally affect a larger part of one hemisphere than simple focal seizures, but commonly originate in the temporal lobe or the frontal lobe. When a focal seizure spreads from one side (hemisphere) to both sides of the brain, the seizure is referred to as a secondarily generalized seizure. Specific types of generalized seizures include absences (also referred to as petit mal seizures), tonic seizures, atonic seizures, myoclonic seizures, tonic clonic seizures (also referred to as grand mal seizures), and clonic seizures.

[0134] In particular embodiments, methods described herein may reduce the frequency of seizures, reduce the severity of seizures, change the type of seizures (e.g., from a more severe type to a less severe type), or a combination thereof in a patient after treatment compared to the absence of treatment (e.g., before treatment), or compared to treatment with an alternative conventional treatment.

[0135] Administration of compositions can be by any appropriate route. For example, in particular embodiments, administration may include administration to a cell or tissue slice for research purposes related to Nav1.1 sodium channel dysfunction.

[0136] In particular embodiments, administration is to a subject and can be intravenous, retro-orbital, intraocular, intravitreal, parenteral, subcutaneous, intracerebro-ventricular, intramuscular, intrathecal, intraspinal, oral, intraperitoneal, oral, nasal, or direct to a targeted site administration. Delivery can be accomplished by a needle or a cannula or by any other technique of expelling fluidic materials. The methods of administration may also include those modalities as described in U.S. Pat. Nos. 5,543,158; 5,641,515 and 5,399,363.

[0137] As is well known in the medical arts, dosages for any one subject depends upon many factors, including the subject's size, surface area, age, the particular compound to be administered, sex, time and route of administration, general health, and other drugs being administered concur-

rently. Dosages for the compounds of the disclosure will vary, but, in particular embodiments, a dose could be from 10^5 to 10^{10} copies of an expression construct of the disclosure. In particular embodiments, a patient receiving intravenous, intraspinal, retro-orbital, intracerebroventricular, or intrathecal administration can be infused with from 10^6 to 10^{22} copies of the expression construct.

[0138] Therapeutically effective amounts include those that provide effective amounts and/or therapeutic treatments.

[0139] An "effective amount" is the amount of a composition necessary to result in a desired physiological change in the subject. Effective amounts are often administered for research purposes. Effective amounts disclosed herein can cause a statistically-significant effect in an animal model or in vitro assay relevant to a disorder associated with Nav1.1 sodium channel dysfunction.

[0140] A "therapeutic treatment" includes a treatment administered to a subject who displays symptoms or signs of a disorder associated with Nav1.1 sodium channel dysfunction and is administered to the subject for the purpose of diminishing or eliminating those signs or symptoms of the disorder. The therapeutic treatment can reduce, control, or eliminate the presence or activity of the disorder, the cause of the disorder, and/or reduce control or eliminate side effects of the disorder.

[0141] In particular embodiments, the administration of therapeutically-effective amounts of the disclosed compositions may be achieved by a single administration, such as for example, a single injection of sufficient numbers of expression constructs to provide therapeutic benefit to the subject receiving the administration. Alternatively, in some circumstances, it may be desirable to provide multiple, or successive administrations of the compositions, either over a relatively short, or a relatively prolonged period of time.

[0142] For example, the number of expression constructs administered to a subject may be 10^7, 10^8, 10^9, 10^{10}, 10^{11}, 10^{12}, 10^{13}, or even higher, expression constructs/ml given either as a single dose, or divided into two or more administrations as may be required to achieve a desired physiological outcome. In particular embodiments, it may be desirable to administer two or more different expression constructs, either alone, or in combination with one or more other therapeutic drugs to achieve the desired effects of a particular therapy regimen.

[0143] Particular dosing and timing of administration for a particular subject can be chosen by a treating physician, researcher, or veterinarian. In other words, the amount of compositions and/or expression constructs and time of administration will be within the purview of the skilled artisan having benefit of the present teachings.

[0144] In particular embodiments, treatments for Nav1.1 sodium channel disorders can be combined with another treatment. For example, common conventional therapies for seizures and epilepsy include antiepileptic drugs and non-antiepileptic drug treatments such as low carbohydrate diet (e.g., ketogenic diets, such as classical diet, medium chain triglyceride (MCT) diet, modified Atkins diet (MAD), and low glycemic index treatment (LGIT)), intravenous immunoglobulin, steroids, elimination diet, vagus nerve stimulation, corticetomy, and multiple subpial transections.

[0145] Common antiepileptic and anticonvulsive active compounds that may be used in combination with compositions described herein include acetazolamide, cannabidiol, carbamazepine, clobazam, clonazepam, eslicarbazepine acetate, ethosuximide, gabapentin, lacosamide, lamotrigine, levetiracetam, nitrazepam, oxcarbazepine, perampanel, piracetam, phenobarbital, phenytoin, pregabalin, primidone, retigabine, rufinamide, sodium valproate, stiripentol, tiagabine, topiramate, vigabatrin, and zonisamide.

[0146] Kits and Commercial Packages. Kits and commercial packages contain an expression construct described herein. The expression product can be isolated. In particular embodiments, the components of an expression product can be isolated from each other. In particular embodiments, the expression product can be within a vector, within a viral vector, within a cell, within a tissues slice or sample, and/or within a transgenic animal. In particular embodiments, an animal is transgenic following administration of a composition including the expression construct. In particular embodiments, a transgenic animal includes a genetic modification that renders the animal appropriate for use in an animal model of DS. For example, the transgenic animal such as a mouse can be $Scn1a^{+/-}$. Detailed methods for producing transgenic animals are described in U.S. Pat. No. 4,736,866. Transgenic animals may be of any nonhuman mammalian or avian species, but preferably include mice or nonhuman primates (NHPs). Sheep, horses, cattle, pigs, goats, dogs, cats, rabbits, chickens, and other rodents such as guinea pigs, hamsters, gerbils, rats, and ferrets are also included.

[0147] Embodiments of a kit or commercial package will also contain instructions regarding use of the included components, for example, in the research and/or treatment of disorders associated with Nav1.1 sodium channel dysfunction, such as epilepsy and/or DS. Such kits may further include one or more reagents, restriction enzymes, peptides, therapeutics, pharmaceutical compounds, or means for delivery of the compositions such as syringes, injectables, and the like.

[0148] The Exemplary Embodiments and Example below are included to demonstrate particular embodiments of the disclosure. Those of ordinary skill in the art should recognize in light of the present disclosure that many changes can be made to the specific embodiments disclosed herein and still obtain a like or similar result without departing from the spirit and scope of the disclosure.

Exemplary Embodiments

[0149] 1. An expression construct (e.g, isolated polynucleotide) including (i) a concatemerized enhancer of SEQ ID: NO: 2 or SEQ ID NO: 6, (ii) a promoter; and (iii) a coding sequence encoding a protein or nucleic acid that rescues voltage-gated sodium channel function in a cell or subject in need thereof.

[0150] 2. An expression construct of embodiment 1, wherein the concatemer includes a 3× concatemer of SEQ ID: NO: 2 or SEQ ID NO: 6.

[0151] 3. An expression construct of embodiment 1, wherein the concatemer includes SEQ ID: NO: 2 and SEQ ID NO: 6 arranged in tandem.

[0152] 4. An expression construct of embodiment 3, wherein the concatemer includes SEQ ID NO: 2-SEQ ID NO: 6-SEQ ID NO: 2; SEQ ID NO: 6-SEQ ID NO: 2-SEQ ID NO: 6; SEQ ID NO: 6-SEQ ID NO: 6-SEQ ID NO: 2; SEQ ID NO: 2-SEQ ID NO: 2-SEQ ID NO: 6; SEQ ID NO: 6-SEQ ID NO: 2-SEQ ID NO: 2; or SEQ ID NO: 2-SEQ ID NO: 6-SEQ ID NO: 6.

[0153] 5. An expression construct (e.g, isolated polynucleotide) including (i) SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and/or SEQ ID NO: 8, (ii) a promoter; and (iii) a coding sequence encoding a protein or nucleic acid that rescues voltage-gated sodium channel function in a cell or subject in need thereof.

[0154] 6. An expression construct of any of embodiments 1-5, wherein the coding sequence includes or encodes NavSheP-D60N, NavBp, NavMs, 3×HA-NavSheP-D60N, 3×HA-NavBp, 3×HA-NavMs, or His-NavMs.

[0155] 7. An expression construct of any of embodiments 1-6, wherein the coding sequence includes or encodes human SCN1A, mouse Scn1a, human SCN1A-3×HA, and/or mouse Scn1a-3×ha.

[0156] 8. An expression construct of any of embodiments 1-7, wherein the coding sequence includes or encodes an artificial transcription factor that increases expression of endogenous SCN1A wherein the artificial transcription factor includes a targeted DNA-binding domain linked to a transcription-activating domain.

[0157] 9. An expression construct of any of embodiments 1-8, wherein the coding sequence includes or encodes antisense RNA molecules that increase splicing or prevent microRNA negative regulation.

[0158] 10. An expression construct of any of embodiments 1-9, wherein the coding sequence includes or encodes a nucleotide sequence that upregulates SCN1A expression (e.g., SEQ ID NOs: 66-163).

[0159] 11. An expression construct of any of embodiments 1-10, wherein the coding sequence includes or encodes and/or one or more segments of SCN1A that assemble into full length SCN 1A after expression.

[0160] 12. An expression construct of embodiment 11 including the SCN1A coding sequence of SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, and SEQ ID NO: 61.

[0161] 13. An expression construct of embodiment 11 wherein the SCN1A segments include SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, and SEQ ID NO: 65.

[0162] 14. An expression construct any of embodiments 1-13, wherein the promoter includes minBglobin or minCMV.

[0163] 15. An expression construct of any of embodiments 1-14, wherein the expression construct is within an adeno-associated viral (AAV) vector.

[0164] 16. An expression construct of any of embodiments 1-15, wherein the expression construct includes a coding sequence for a reporter protein.

[0165] 17. An expression construct of embodiment 16, wherein the reporter protein includes a fluorescent reporter protein.

[0166] 18. An expression construct of any of embodiments 1-17, wherein the expression construct includes or encodes a skipping element.

[0167] 19. An expression construct of embodiment 18, wherein the skipping element includes a 2A peptide or an internal ribosome entry site (IRES).

[0168] 20. An expression construct of embodiment 19, wherein the 2A peptide includes T2A, P2A, E2A, and/or F2A.

[0169] 21. An expression construct of any of embodiments 1-20, wherein the construct includes the elements of CN1367, CN1244, CN1389, CN1390, CN1180, CN1203, CN1498, CN1499, CN1500, CN2001, CN2002, CN2003, CN1504 and CN1512, CN2004 and CN2005, CN2006 and CN2007, CN2008 and CN2009, or CN2026, CN2027, CN2028 and CN2029.

[0170] 22. An expression construct of any of embodiments 1-21, wherein the construct includes SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, and/or SEQ ID NO: 52.

[0171] 23. An expression construct of any of embodiments 1-22, wherein the construct includes SEQ ID NO: 45 and SEQ ID NO: 46, SEQ ID NO: 47 and SEQ ID NO: 48, SEQ ID NO: 49 and SEQ ID NO: 50, SEQ ID NO: 51, and SEQ ID NO: 52 or CN2026, CN2027, CN2028 and CN2029.

[0172] 24. An expression construct of any of embodiments 15-23, wherein the AAV vector is associated with a capsid that crosses the blood brain barrier.

[0173] 25. An expression construct of embodiment 24, wherein the capsid includes PHP.Eb.

[0174] 26. An expression construct of embodiment 24 or 25, wherein the capsid includes SEQ ID NO: 53.

[0175] 27. An expression construct of any of embodiments 24-26, wherein the capsid includes an AAV9 capsid with a SEQ ID NO: 54 or SEQ ID NO: 55 insert.

[0176] 28. An expression construct of any of embodiments 24-27, wherein the capsid includes an AAV2 capsid with a SEQ ID NO: 56 insert.

[0177] 29. A composition including the expression construct of any of embodiments 1-28.

[0178] 30. A cell including the expression construct of any of embodiments 1-28.

[0179] 31. A non-human animal including the expression construct of any of embodiments 1-28.

[0180] 32. A kit including the expression construct of any of embodiments 1-28.

[0181] 33. A method of rescuing voltage-gated sodium channel function in a defective cell in need thereof including administering a therapeutically effective amount of a composition of embodiment 29 to the cell.

[0182] 34. A method of rescuing voltage-gated sodium channel function in a subject in need thereof including administering a therapeutically effective amount of a composition of embodiment 29 to the subject.

[0183] 35. A method of embodiment 34, wherein the subject is need thereof due to a diagnosis of epilepsy, an SCN1A-related seizure disorder, simple febrile seizures (FS), generalized epilepsy with febrile seizures plus (GEFS+), Dravet Syndrome (DS), intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC), intractable infantile partial seizures, myoclonic-astatic epilepsy, Lennox-Gastaut syndrome (LGS), or infantile spasms.

[0184] 36. A method of embodiment 34 or 35, wherein the subject is a pediatric patient.

[0185] 37. A method of any of embodiments 34-36, wherein the subject is less than 4 years old.

[0186] 38. A method of embodiment 34, 35, or 37, wherein the subject is a transgenic $Scn1a^{+/-}$ mouse undergoing a temperature-induced febrile seizure test.

[0187] 39. A method of any of embodiments 34-38, wherein the composition is administered intravenously.

[0188] 40. A method of any of embodiments 34-39, wherein the composition is administered intrathecally into cerebrospinal fluid, via the lateral ventricles or cisterna magna or lumbar space or cannula into the foramen magnum.

[0189] 41. An expression construct (e.g, isolated polynucleotide) including:

[0190] (a) a non-naturally occurring enhancer sequence; and

[0191] (b) a nucleic acid encoding a protein or nucleotide sequence that rescues voltage-gated sodium channel function;

[0192] wherein the enhancer sequence:

[0193] (i) consists of the sequence of SEQ ID NO: 3;

[0194] (ii) includes two or more copies of SEQ ID NO: 2 or SEQ ID NO: 6 arranged in tandem (e.g, SEQ ID NO: 2-SEQ ID NO: 6-SEQ ID NO: 2; SEQ ID NO: 6-SEQ ID NO: 2-SEQ ID NO: 6; SEQ ID NO: 6-SEQ ID NO: 6-SEQ ID NO: 2; SEQ ID NO: 2-SEQ ID NO: 2-SEQ ID NO: 6; SEQ ID NO: 6-SEQ ID NO: 2-SEQ ID NO: 2; or SEQ ID NO: 2-SEQ ID NO: 6-SEQ ID NO: 6; SEQ ID NO: 6-SEQ ID NO: 6-SEQ ID NO: 6);

[0195] (iii) includes a sequence having at least 90% sequence identity with SEQ ID NO: 3 and maintaining interneuron-specific enhancer function; or

[0196] (iv) a sequence the complementary strand of which is capable of hybridizing to the sequence of (i), (ii), or (iii); and

[0197] wherein the enhancer promotes the transcription of the nucleic acid selectively within inhibitory neurons following administration to a sample or subject.

[0198] 42. An expression construct of embodiment 41, wherein nucleic acid includes or encodes NavSheP-D60N, NavBp, NavMs, 3×HA-NavSheP-D60N, 3×HA-NavBp, 3×HA-NavMs, or His-NavMs.

[0199] 43. An expression construct of embodiment 41 or 42, wherein the nucleic acid includes or encodes human SCN1A, mouse Scn1a, human SCN1A-3×HA, and/or mouse Scn1a-3×ha.

[0200] 44. An expression construct of any of embodiments 41-43, wherein the nucleic acid includes or encodes an artificial transcription factor that increases expression of endogenous SCN1A wherein the artificial transcription factor includes a targeted DNA-binding domain linked to a transcription-activating domain.

[0201] 45. An expression construct of any of embodiments 41-44, wherein the nucleic acid includes or encodes antisense RNA molecules that increase splicing or prevent microRNA negative regulation.

[0202] 46. An expression construct of any of embodiments 41-45, wherein the nucleic acid includes or encodes a nucleotide sequence that upregulates SCN1A expression (e.g., SEQ ID NOs: 66-163).

[0203] 47. An expression construct of any of embodiments 41-46, wherein the nucleic acid includes or encodes and/or one or more segments of SCN1A that assemble into full length SCN1A after expression.

[0204] 48. An expression construct of embodiment 47 including nucleic acid including the SCN1A coding sequence of SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, and SEQ ID NO: 61.

[0205] 49. An expression construct of embodiment 47 wherein the SCN1A segments include SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, and SEQ ID NO: 65.

[0206] 50. An expression construct of any of embodiment 41-49, including a promoter including minBglobin or minCMV.

[0207] 51. An expression construct of any of embodiments 41-50, wherein the expression construct is within an adeno-associated viral (AAV) vector.

[0208] 52. An expression construct of any of embodiments 41-51, wherein the expression construct includes a nucleic acid encoding a reporter protein.

[0209] 53. An expression construct of embodiment 52, wherein the reporter protein includes a fluorescent reporter protein.

[0210] 54. An expression construct of any of embodiments 41-53, wherein the expression construct includes or encodes a skipping element.

[0211] 55. An expression construct of embodiment 54, wherein the skipping element includes a 2A peptide or an internal ribosome entry site (IRES).

[0212] 56. An expression construct of embodiment 55, wherein the 2A peptide includes T2A, P2A, E2A, and/or F2A.

[0213] 57. An expression construct of any of embodiments 41-56, wherein the construct includes the elements of CN1367, CN1244, CN1389, CN1390, CN1180, CN1203, CN1498, CN1499, CN1500, CN2001, CN2002, CN2003, CN1504 and CN1512, CN2004 and CN2005, CN2006 and CN2007, or CN2008 and CN2009.

[0214] 58. An expression construct of any of embodiments 41-57, wherein the construct includes SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, and/or SEQ ID NO: 52.

[0215] 59. An expression construct of any of embodiments 41-58, wherein the construct includes SEQ ID NO: 45 and SEQ ID NO: 46, SEQ ID NO: 47 and SEQ ID NO: 48, SEQ ID NO: 49 and SEQ ID NO: 50, or SEQ ID NO: 51, and SEQ ID NO: 52

[0216] 60. An expression construct of any of embodiments 51-59, wherein the AAV vector is associated with a capsid that crosses the blood brain barrier.

[0217] 61. An expression construct of embodiment 60, wherein the capsid includes PHP.Eb.

[0218] 62. An expression construct of embodiment 60 or 61, wherein the capsid includes SEQ ID NO: 53.

[0219] 63. An expression construct of any of embodiments 60-62, wherein the capsid includes AAV9 capsid with a SEQ ID NO: 54 or SEQ ID NO: 55 insert.

[0220] 64. An expression construct of any of embodiments 60-63, wherein the capsid includes AAV2 capsid with a SEQ ID NO: 56 insert.

[0221] 65. A composition including the expression construct of any of embodiments 41-64.

[0222] 66. A cell including the expression construct of any of embodiments 41-64.

[0223] 67. A non-human animal including the expression construct of any of embodiments 41-64.

[0224] 68. A kit including the expression construct of any of embodiments 41-64.

[0225] 69. A method of rescuing voltage-gated sodium channel function in a defective cell in need thereof including administering a therapeutically effective amount of a composition of embodiment 65 to the cell.

[0226] 70. A method of rescuing voltage-gated sodium channel function in a subject in need thereof including administering a therapeutically effective amount of a composition of embodiment 65 to the subject.

[0227] 71. A method of embodiment 70, wherein the subject is need thereof due to a diagnosis of epilepsy, an SCN1A-related seizure disorder, simple febrile seizures (FS), generalized epilepsy with febrile seizures plus (GEFS+), Dravet Syndrome (DS), intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC), intractable infantile partial seizures, myoclonic-astatic epilepsy, Lennox-Gastaut syndrome (LGS), or infantile spasms.

[0228] 72. A method of embodiment 70 or 71, wherein the subject is a pediatric patient.

[0229] 73. A method of any of any of embodiments 70-72, wherein the subject is less than 4 years old.

[0230] 74. A method of any of embodiments 70, 71, or 73, wherein the subject is a transgenic Scn1a$^{+/-}$ mouse undergoing a temperature-induced febrile seizure test.

[0231] 75. A method of any of embodiments 70-74, wherein the composition is administered intravenously.

[0232] 76. A method of any of embodiments 70-75, wherein the composition is administered intrathecally into cerebrospinal fluid, via the lateral ventricles or cisterna magna or lumbar space or cannula into the foramen magnum.

[0233] 77. A vector system including two AAV vectors wherein the first vector encodes the N-terminal portion of a protein that rescues voltage-gated sodium channel activity in a cell in need thereof, and the second vector encodes the C-terminal portion of the protein, wherein the portion of the gene encoded by the two vectors overlaps to provide a region of homology for homologous recombination to produce the full-length Nav1.1 protein, and wherein the first vector includes a promoter and an enhancer that consists of SEQ ID NO: 3 but does not include a termination signal or a polyA signal and the second vector includes a termination signal and a polyA signal but does not include a promoter or an enhancer.

[0234] 78. A vector system of embodiment 77, wherein the protein includes human SCN1A.

[0235] 79. A vector system of embodiment 77 or 78, wherein the region of homology is 75-1000 base pairs.

[0236] 80. A vector system of embodiment 77 or 78, wherein the region of homology is 550-650 base pairs.

[0237] 81. A vector system of any of embodiments 77-80, wherein the vectors selectively express the protein in inhibitory neurons.

[0238] 82. A vector system of any of embodiments 77-81, wherein the region of homology further includes an intron element with a splice donor site on the first vector and a splice acceptor site on the second vector, so that trans-splicing across the homologous region drives more efficient full-length protein reconstitution following recombination.

[0239] 83. A vector system of any of embodiments 77-82, wherein the vector system includes the elements of CN1504, CN1512, CN2004, CN2005, CN2006, CN2007, CN2008, and/or CN2009.

[0240] 84. A vector system of any of embodiments 77-83, wherein the vector system includes the elements of CN1504 and CN1512, CN2004 and CN2005, CN2006 and CN2007, or CN2008 and CN2009.

[0241] 85. A vector system of any of embodiments 77-84, wherein the vector system includes SEQ ID NO: 45 and SEQ ID NO: 46, SEQ ID NO: 47 and SEQ ID NO: 48, SEQ ID NO: 49 and SEQ ID NO: 50, or SEQ ID NO: 51, and SEQ ID NO: 52.

[0242] 86. A viral vector including SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, or SEQ ID NO: 52.

[0243] 87. An expression construct including SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and/or SEQ ID NO: 8 and a coding sequence encoding an artificial transcription factor including a specific DNA-binding domain linked to a general transcription-activating domain wherein the artificial transcription factor increases the expression of the endogenous functional copy of SCN1A (or other SCN_A family gene).

[0244] 88. An expression construct including SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and/or SEQ ID NO: 8 and a coding sequence encoding an artificial transcription factor including a specific DNA-binding domain linked to a general transcription-activating domain wherein the artificial transcription factor increases the expression of the endogenous functional copy of SCN1A (or other SCN_A family gene).

[0245] 89. An expression construct including SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and/or SEQ ID NO: 8 and a coding sequence encoding antisense RNA molecules that increase splicing and/or prevent microRNA negative regulation of SCN1A expression.

[0246] 90. A set of expression constructs including SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and/or SEQ ID NO: 8 wherein the set of expression constructs delivers hSCN1A protein as two or four subunit ORFs delivered by two or four separate vectors.

[0247] 91. An isolated polynucleotide including an enhancer including the sequence of SEQ ID NO: 3, and further including a heterologous inducible promoter and a gene encoding a protein or nucleic acid sequence that rescues Nav1.1 channel function selectively in inhibitory neurons, wherein the enhancer and the heterologous inducible promoter are operably linked to the gene.

[0248] 92. A vector including the isolated polynucleotide of embodiment 91.

[0249] 93. A vector of embodiment 92, wherein the vector is a viral vector.

[0250] 94. A vector of embodiment 93, wherein the viral vector is an AAV viral vector.

[0251] 95. A human or non-human cell including the isolated polynucleotide of embodiment 91.

[0252] 96. A set of vectors for selectively driving expression of a protein or nucleic acid sequence that rescues Nav1.1 channel function in inhibitory neurons including

the vector of any of embodiment 92-94, and a second vector including an enhancer selected from SEQ ID NOS: 1, 2, 4, 5, 6, 7 or 8.

[0253] 97. A method for selectively driving expression of a protein or nucleic acid sequence that rescues Nav1.1 channel function in inhibitory neurons including (1) providing the vector of any of embodiments 92-94, (2) using the vector to generate a transgenic mouse, and (3) detecting rescued Nav1.1 channel function in the transgenic mouse.

[0254] 98. A method of embodiment 97, wherein the rescued Nav1.1 channel function is within inhibitory neurons.

[0255] 99. A set of coding sequences including the coding sequences of the hSCN1A_Fragments within SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, and SEQ ID NO: 61.

[0256] 100. A set of vectors including CN2026, CN2027, CN2028, and CN2029.

[0257] Example 1. In relation to FIG. **1**A, living human temporal cortex brain tissue was excised during neurosurgery to remove an epileptic focus. This tissue was dissected and sliced to 350-micron thick tissue slices, which were cultured on semipermeable membranes with semisynthetic culture medium as described by Ting et al. (*Scientific Reports* 8(1):8407, 2018). On the first day of culture, slices were infected with purified virus CN 1180/DJ (which labels inhibitory neurons) by applying purified virus directly to the brain slice. At 7 days post infection, the electrophysiology of $SYFP2^+$ (visible in the green channel) infected cells was assessed by patch-clamp recordings. The recorded cells were backfilled with Alexa 594 dye (visible in the red channel) to perform post-hoc visualization of their cell bodies and morphologies.

[0258] In relation to FIG. **1**B, patch-clamp recordings were performed on multiple $SYFP2^+$ and $SYFP2^-$ cells. Their backfilled morphologies were tabulated as being pyramidal (indicative of excitatory neurons) or non-pyramidal (indicative of inhibitory neurons). This analysis indicated that $SYFP2^+$ cells are largely of inhibitory neuron character.

[0259] In relation to FIG. **10**, the electrophysiological character of multiple $SYFP2^+$ and $SYFP2^-$ cells was analyzed. These analyses indicated that, compared to $SYFP2^-$ cells, the $SYFP2^+$ cells had shorter action potential (AP) half-widths, had greater firing rates, had faster rates of depolarization, and had faster rates of AP firing in response to injected current (FI slope). These metrics all suggest that $SYFP2^+$ cells are fast-spiking interneurons.

[0260] In relation to FIG. **1**D, after performing patch-clamp electrophysiology tissue was fixed and immunostained with anti-GFP and anti-Parvalbumin antibodies. This analysis indicated that many GFP^+ cells are $Parvalbumin^+$, which suggests that these cells have molecular identities consistent with fast-spiking interneurons.

[0261] In relation to FIG. **3**, a Gad2-T2A-nls-mCherry (Peron et al., *Neuron* 86:783-799, 2015) mouse was injected retro-orbitally with 1E11 genome copies of the virus CN1244/PHP.eB. After 3 weeks the brain was harvested, sliced into 350-micron thick slices, and then imaged for SYFP2 and mCherry expression to visualize virus-expressing cells and all interneurons, respectively.

[0262] In relation to FIGS. **4**A, **4**B, adult wild type mice were retro-orbitally injected with 1E+11 genome copies of the indicated viruses. Animals were maintained for 3-4 weeks, then euthanized, with brains extracted and sliced, followed by live tissue epifluorescence imaging of native fluorescence. Exposure times were matched to allow direct comparison of transgene expression levels. The first three panels are a 500 msec exposure for each of the indicated constructs; the fourth panel is a shorter (50 msec) exposure image of CN1390.

[0263] In relation to FIG. **5**, cortical/hippocampal brain slice cultures were prepared from P5-10 Gad2-IRES-Cre heterozygous;Ai75 heterozygous animals. These animals have Cre-mediated activation of a nuclear-tagged tdTomato transgene in Gad2-expressing cells, resulting in bright nuclear red fluorescence in inhibitory neurons. One hour after culturing, CN 1390 viral suspension was pipetted onto the slice surface to transduce brain cell types. At 10 DIV/10DPI, native fluorescence was imaged in green and red channels on a Nikon inverted microscope.

[0264] In relation to FIGS. **6**A-**6**E, human ex vivo neocortical brain slice cultures were prepared from live neurosurgical specimens (Ting et al., *Scientific Reports* 8(1):8407, 2018). One hour after culturing, CN1390 viral suspension was pipetted onto the slice surface to transduce brain cell types. At 1, 3, and 6DIV/DPI, native SYFP2 fluorescence was imaged using matched exposure times on aa Nikon microscope. FIGS. **6**A-**6**D illustrate rapid viral-genetic labeling of human neocortical interneurons for targeted patch clamp recording and analysis. At various times in culture, slices were taken for terminal patch clamp recording analysis to establish the firing properties of labeled neurons. Functional analysis of human neocortical interneuron firing patterns and electrical properties by patch clamp recording was feasible as early as 40 hours post-infection with CN1390 eB virus.

[0265] Referring to FIG. **9**, the top vector includes the enhancer of SEQ ID NO: 3 and promoter (minCMV) elements to drive expression in all inhibitory neurons (including both Pvalb+ and Pvalb− inhibitory neurons). The driven transgene includes a SYFP2 linked by a P2A tag to the N-terminal region of human SCN1A, which includes 604 bp homology to the C-terminal region included on the bottom vector. The bottom vector also includes a C-terminal 3×HA tag and 3'UTR regulatory sequences (WPRE3 and polyA sites).

[0266] Both AAV viral vectors were packaged into PHP.eB capsid and delivered both intravenously to a single C57BI/6 mouse. After 21 days the mouse brain was harvested, fixed, and processed for immunofluorescence with anti-GFP (targeting SYFP2), anti-HA, and anti-Pvalb antibodies to detect transgene-expressing cells and their overlap with Pvalb+ inhibitory neurons (which are cells having particular importance in DS symptomology). Many inhibitory neurons were labeled with the N-terminal SYFP2+ tag at high level, including both Pvalb+ and Pvalb− inhibitory neurons. Some of these SYFP2+ cells also express HA which indicates fully intact SCN1A protein product being expressed in these GFP+HA+ cells (arrows). The vertical arrows indicate Pvalb+ interneurons expressing human SCN1A and the horizontal arrows indicate Pvalb− interneurons expressing human SCN1A. These SCN1A-expressing cells are found throughout the forebrain (both neocortex and hippocampus [here dentate gyrus]), which includes the brain region known to be important for most epilepsies and known to be dysfunctional in DS.

[0267] Example 2. Dravet syndrome (DS) is a drug-resistant and life-threatening form of epilepsy. It typically begins in the first year of life, with fever- or temperature-induced seizures that evolve into generalized clonic, tonic-clonic, and unilateral seizures. These seizures are often resistant to current anti-epileptic drugs, the first-line therapies for this syndrome; complete seizure control is typically not achieved. As the disease progresses, most affected children also suffer from comorbid conditions including developmental delays, intellectual disabilities, impaired motor control and coordination, autistic behaviors, sleep disturbances, and many die prematurely.

[0268] Heterozygous loss-of-function mutations in SCN1A, the gene that encodes the pore-forming subunit of the voltage-gated sodium channel Nav1.1 are the most common cause of DS and occur in nearly $1/16{,}000$ newborns.

[0269] A mouse model, generated by knock-out of Scn1a, replicates the several key phenotypic features of this epilepsy including infantile (P21)-epilepsy onset, high susceptibility to thermal seizures, ataxia, spontaneous seizures, sleep impairments, autistic behaviors, and premature death. Seizures and several comorbidities arise from impaired interneuron function in these mice.

[0270] This mouse model was used to investigate the efficacy of a new viral vector for DS. The virus was delivered by retro-orbital injection using an insulin syringe and its ability to suppress seizure was evaluated using the thermal seizure test. In this test, the mouse body core temperature is elevated slowly, using a temperature controller and a heat lamp, until a seizure occurs, or 42.5° C. is attained. The temperature of seizure onset in treated and control mice are compared to determine the efficacy of the intervention. In additional tests, the efficacy of treatment on spontaneous seizure and premature mortality are assessed using video and electroencephalographic monitoring.

[0271] The viral vector is a new AAV viral vector named CN1500. This viral vector is a recombinant AAV that expresses the transgene SYFP2-P2A-NavSheP-D60N to rescue the loss of the voltage-gated sodium channel Nav1.1. NavSheP-D60N is a modified voltage-gated sodium channel of bacterial origin that has been modified to improve the kinetics and expression in mammalian cells. The transgene expression level is elevated by the addition of a WPRE3 element, and transcription is terminated with the bovine growth hormone poly adenylation sequence. Expression of the transgene is high and limited to inhibitory cells in forebrain structures including the cortex and the hippocampus, via the 3×hi56iCore synthetic enhancer (SEQ ID NO: 3) directly 5' of a CMV minimal promoter. Furthermore, the therapeutic transgene NavSheP-D60N is labeled by an HA epitope tag to verify correct protein localization.

[0272] To test the efficacy of the therapeutic AAV viral vector, CN1500 package using the PHP.eB serotype was used. A cohort of postnatal day 35 $Scn1a^{+/-}$ mice were either injected with 2×10^{11} vg per animal or were left un-injected. The AAV was introduced intravenously using the retro-orbital delivery route. Two weeks after viral administration, animals from the treatment and control groups were assessed for their susceptibility to febrile seizures. As indicated previously, febrile seizures were measured by steadily raising the mouse's temperature under a heat lamp 0.5 Celsius every two minutes and measuring the internal temperature of the mouse with a rectal probe. The temperature where the mouse experienced a seizure is recorded.

[0273] The new therapeutic vector CN1500 was both highly expressed in mouse cortical and hippocampal GABAergic cells, but also raised the average temperature where $Scn1a^{+/-}$ mice experienced febrile seizures from 38.7° C. to 41° C. These data show that CN1500 can substantially rescue the loss of Scn1a.

[0274] Example 2 references include: Catterall et al. (2010) The Journal of physiology 588:1849-1859; Cheah et al. (2012) Proceedings of the National Academy of Sciences of the United States of America 109:14646-14651; Kalume (2013) Respir Physiol Neurobiol. 189(2):324-8; Kalume et al., (2007) J Neurosci 27:11065-11074; Kalume et al., (2013) The Journal of clinical investigation 123:1798-1808; Oakley et al., (2009) Proceedings of the National Academy of Sciences of the United States of America 106:3994-3999.

DESCRIPTION OF SEQUENCES

[0275] Nucleic acid sequences described herein are shown using standard letter abbreviations for nucleotide bases, as defined in 37 C.F.R. §1.822. Only one strand of each nucleic acid sequence is shown, but the complementary strand is understood as included in embodiments where it would be appropriate.

[0276] SEQ ID NO: 1: nucleic acid sequence of the human (h)DLX I56i enhancer;

[0277] SEQ ID NO: 2: nucleic acid sequence of the hI56i core enhancer;

[0278] SEQ ID NO: 3: nucleic acid sequence of the 3×hI56iCore enhancer;

[0279] SEQ ID NO: 4: nucleic acid sequence of the murine DLX I56i enhancer;

[0280] SEQ ID NO: 5: nucleic acid sequence of the zebrafish DLX I56i enhancer;

[0281] SEQ ID NO: 6: nucleic acid sequence of the zebrafish I56i core;

[0282] SEQ ID NO: 7: nucleic acid sequence of the zebrafish 3×I56i core;

[0283] SEQ ID NO: 8: hDLX I12b enhancer;

[0284] SEQ ID NO: 9: NavSheP-D60N, codon optimized, with N-terminal 3× HA tag;

[0285] SEQ ID NO: 10: NavSheP endogenous sequence;

[0286] SEQ ID NO: 11: NavBp, endogenous sequence;

[0287] SEQ ID NO: 12: NavBp, codon optimized, with N-terminal 3× HA tag;

[0288] SEQ ID NO: 13: NavMs, endogenous sequence;

[0289] SEQ ID NO: 14: NavMs, codon optimized, with N-terminal 3× HA tag and linker;

[0290] SEQ ID NO: 15: NavMs, codon optimized, with N-terminal His tag and linker;

[0291] SEQ ID NO: 16: Human SCN1A;

[0292] SEQ ID NO: 17: SYFP2;

[0293] SEQ ID NO: 18: P2A Encoding Sequence;

[0294] SEQ ID NO: 19: WPRE3;

[0295] SEQ ID NO: 20: BGHpA;

[0296] SEQ ID NO: 21: N-terminal 3×HA tag (Protein);

[0297] SEQ ID NO: 22: N-terminal 3×HA tag (DNA);

[0298] SEQ ID NO: 23: hSCN1A N-term of two-part expression system;

[0299] SEQ ID NO: 24: hSCN1A C-term of two-part expression system with c-terminal 3×HA sequence;

[0300] SEQ ID NO: 25: 604 bp homology region of hSCN1A N term and C term that can be used in two-part expression system;

[0301] SEQ ID NO: 26: P2A Translation from CN1498;

[0302] SEQ ID NO: 27: T2A;
[0303] SEQ ID NO: 28: E2A;
[0304] SEQ ID NO: 29: F2A;
[0305] SEQ ID NO: 30: MinBglobin;
[0306] SEQ ID NO: 31: minCMV;
[0307] SEQ ID NO: 32: AAV9 PHP.eB capsid replacement sequence;
[0308] SEQ ID NO: 33: CN1367—portion between L-ITR and R-ITR: positions 142-2984;
[0309] SEQ ID NO: 34: CN1500—portion between L-ITR and R-ITR: positions 142-2976;
[0310] SEQ ID NO: 35: CN1498—portion between L-ITR and R-ITR: positions 142-2943;
[0311] SEQ ID NO: 36: CN1499—portion between L-ITR and R-ITR: positions 142-2946;
[0312] SEQ ID NO: 37: CN1244—portion between L-ITR and R-ITR: positions 142-2042;
[0313] SEQ ID NO: 38: CN1389—portion between L-ITR and R-ITR positions 142-1897;
[0314] SEQ ID NO: 39: CN1390—portion between L-ITR and R-ITR positions 142-1660;
[0315] SEQ ID NO: 40: CN1203—portion between L-ITR and R-ITR positions 183-2052;
[0316] SEQ ID NO: 41: CN1180—portion between L-ITR and R-ITR positions 183-1891;
[0317] SEQ ID NO: 42: CN2001—portion between L-ITR and R-ITR positions 142-2023;
[0318] SEQ ID NO: 43: CN2002—portion between L-ITR and R-ITR positions 142-1993;
[0319] SEQ ID NO: 44: CN2003—portion between L-ITR and R-ITR positions 142-2056;
[0320] SEQ ID NO: 45: CN 1504—portion between L-ITR and R-ITR positions 142-4489;
[0321] SEQ ID NO: 46: CN1512—portion between L-ITR and R-ITR positions 142-4165;
[0322] SEQ ID NO: 47: CN2004—portion between L-ITR and R-ITR positions 142-3792;
[0323] SEQ ID NO: 48: CN2005—portion between L-ITR and R-ITR positions 142-4160;
[0324] SEQ ID NO: 49: CN2006—portion between L-ITR and R-ITR positions 142-4790;
[0325] SEQ ID NO: 50: CN2007—portion between L-ITR and R-ITR positions 142-4671;
[0326] SEQ ID NO: 51: CN2008—portion between L-ITR and R-ITR positions 142-3995;
[0327] SEQ ID NO: 52: CN2009—portion between L-ITR and R-ITR positions 142-4525;
[0328] SEQ ID NO: 53: epitope isolated during in vivo screening of a random AAV display peptide library;
[0329] SEQ ID NO: 54: 7-mer sequence of AAV-PHP.S;
[0330] SEQ ID NO: 55: 7-mer sequence of AAV-PHP.B;
[0331] SEQ ID NO: 56: 7-mer sequence of AAV-PPS;
[0332] SEQ ID NO: 57: AAV9 VP1 capsid protein sequence (UniProt Accession number Q6JC40);
[0333] SEQ ID NO: 58: CN2026-rAAV-3×hI56i(core)-minBG-hSCN1A_Fragment1-WPRE3-BGHpA;
[0334] SEQ ID NO: 59: CN2027-rAAV-3×hI56i(core)-minBG-hSCN1A_Fragment2-WPRE3-BGHpA;
[0335] SEQ ID NO: 60: CN2028-rAAV-3×hI56i(core)-minBG-hSCN1A_Fragment3-WPRE3-BGHpA;
[0336] SEQ ID NO: 61: CN2029-rAAV-3×hI56i(core)-minBG-hSCN1A_Fragment4-WPRE3-BGHpA;
[0337] SEQ ID NO: 62: >hSCN1A_Fragment1_ProteinSequence;
[0338] SEQ ID NO: 63: hSCN1A_Fragment2_ProteinSequence;
[0339] SEQ ID NO: 64: hSCN1A_Fragment3_ProteinSequence;
[0340] SEQ ID NO: 65: hSCN1A_Fragment4_ProteinSequence;
[0341] SEQ ID NOs. 66-163: Nucleotide sequences that result in upregulation of SCNA1.
[0342] Variants of the sequences disclosed and referenced herein are also included. Guidance in determining which amino acid residues can be substituted, inserted, or deleted without abolishing biological activity can be found using computer programs well known in the art, such as DNASTAR™ software. Preferably, amino acid changes in the protein variants disclosed herein are conservative amino acid changes, i.e., substitutions of similarly charged or uncharged amino acids. A conservative amino acid change involves substitution of one of a family of amino acids which are related in their side chains.
[0343] In a peptide or protein, suitable conservative substitutions of amino acids are known to those of skill in this art and generally can be made without altering a biological activity of a resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (see, e.g., Watson et al. *Molecular Biology of the Gene,* 4th Edition, 1987, The Benjamin/Cummings Pub. Co., p. 224). Naturally occurring amino acids are generally divided into conservative substitution families as follows: Group 1: Alanine (Ala), Glycine (Gly), Serine (Ser), and Threonine (Thr); Group 2: (acidic): Aspartic acid (Asp), and Glutamic acid (Glu); Group 3: (acidic; also classified as polar, negatively charged residues and their amides): Asparagine (Asn), Glutamine (Gln), Asp, and Glu; Group 4: Gln and Asn; Group 5: (basic; also classified as polar, positively charged residues): Arginine (Arg), Lysine (Lys), and Histidine (His); Group 6 (large aliphatic, nonpolar residues): Isoleucine (Ile), Leucine (Leu), Methionine (Met), Valine (Val) and Cysteine (Cys); Group 7 (uncharged polar): Tyrosine (Tyr), Gly, Asn, Gln, Cys, Ser, and Thr; Group 8 (large aromatic residues): Phenylalanine (Phe), Tryptophan (Trp), and Tyr; Group 9 (non-polar): Proline (Pro), Ala, Val, Leu, Ile, Phe, Met, and Trp; Group 11 (aliphatic): Gly, Ala, Val, Leu, and Ile; Group 10 (small aliphatic, nonpolar or slightly polar residues): Ala, Ser, Thr, Pro, and Gly; and Group 12 (sulfur-containing): Met and Cys. Additional information can be found in Creighton (1984) Proteins, W. H. Freeman and Company.
[0344] In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, J. Mol. Biol. 157(1), 105-32). Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are: Ile (+4.5); Val (+4.2); Leu (+3.8); Phe (+2.8); Cys (+2.5); Met (+1.9); Ala (+1.8); Gly (−0.4); Thr (−0.7); Ser (−0.8); Trp (−0.9); Tyr (−1.3); Pro (−1.6); His (−3.2); Glutamate (−3.5); Gln (−3.5); aspartate (−3.5); Asn (−3.5); Lys (−3.9); and Arg (−4.5).
[0345] It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, i.e., still obtain a biological functionally

equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are within ±2 is preferred, those within ±1 are particularly preferred, and those within ±0.5 are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity.

[0346] As detailed in U.S. Pat. No. 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: Arg (+3.0); Lys (+3.0); aspartate (+3.0±1); glutamate (+3.0±1); Ser (+0.3); Asn (+0.2); Gln (+0.2); Gly (0); Thr (−0.4); Pro (−0.5±1); Ala (−0.5); His (−0.5); Cys (1.0); Met (−1.3); Val (−1.5); Leu (−1.8); Ile (−1.8); Tyr (−2.3); Phe (−2.5); Trp (−3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within ±2 is preferred, those within ±1 are particularly preferred, and those within ±0.5 are even more particularly preferred.

[0347] As outlined above, amino acid substitutions may be based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like.

[0348] As indicated elsewhere, variants of gene sequences can include codon optimized variants, sequence polymorphisms, splice variants, and/or mutations that do not affect the function of an encoded product to a statistically-significant degree.

[0349] Variants of the protein, nucleic acid, and gene sequences disclosed herein also include sequences with at least 70% sequence identity, 80% sequence identity, 85% sequence, 90% sequence identity, 95% sequence identity, 96% sequence identity, 97% sequence identity, 98% sequence identity, or 99% sequence identity to the protein, nucleic acid, or gene sequences disclosed herein.

[0350] "% sequence identity" refers to a relationship between two or more sequences, as determined by comparing the sequences. In the art, "identity" also means the degree of sequence relatedness between protein, nucleic acid, or gene sequences as determined by the match between strings of such sequences. "Identity" (often referred to as "similarity") can be readily calculated by known methods, including (but not limited to) those described in: Computational Molecular Biology (Lesk, A. M., ed.) Oxford University Press, NY (1988); Biocomputing: Informatics and Genome Projects (Smith, D. W., ed.) Academic Press, NY (1994); Computer Analysis of Sequence Data, Part I (Griffin, A. M., and Griffin, H. G., eds.) Humana Press, NJ (1994); Sequence Analysis in Molecular Biology (Von Heijne, G., ed.) Academic Press (1987); and Sequence Analysis Primer (Gribskov, M. and Devereux, J., eds.) Oxford University Press, NY (1992). Preferred methods to determine identity are designed to give the best match between the sequences tested. Methods to determine identity and similarity are codified in publicly available computer programs. Sequence alignments and percent identity calculations may be performed using the Megalign program of the LASERGENE bioinformatics computing suite (DNASTAR, Inc., Madison, Wis.). Multiple alignment of the sequences can also be performed using the Clustal method of alignment (Higgins and Sharp CABIOS, 5, 151-153 (1989) with default parameters (GAP PENALTY=10, GAP LENGTH PENALTY=10). Relevant programs also include the GCG suite of programs (Wisconsin Package Version 9.0, Genetics Computer Group (GCG), Madison, Wis.); BLASTP, BLASTN, BLASTX (Altschul, et al., J. Mol. Biol. 215:403-410 (1990); DNASTAR (DNASTAR, Inc., Madison, Wis.); and the FASTA program incorporating the Smith-Waterman algorithm (Pearson, Comput. Methods Genome Res., [Proc. Int. Symp.] (1994), Meeting Date 1992, 111-20. Editor(s): Suhai, Sandor. Publisher: Plenum, New York, N.Y. Within the context of this disclosure it will be understood that where sequence analysis software is used for analysis, the results of the analysis are based on the "default values" of the program referenced. As used herein "default values" will mean any set of values or parameters, which originally load with the software when first initialized.

[0351] Variants also include nucleic acid molecules that hybridizes under stringent hybridization conditions to a sequence disclosed herein and provide the same function as the reference sequence. Exemplary stringent hybridization conditions include an overnight incubation at 42° C. in a solution including 50% formamide, 5×SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5×Denhardt's solution, 10% dextran sulfate, and 20 μg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1×SSC at 50° C. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, moderately high stringency conditions include an overnight incubation at 37° C. in a solution including 6×SSPE (20×SSPE=3M NaCl; 0.2M NaH_2PO_4; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 μg/ml salmon sperm blocking DNA; followed by washes at 50° C. with 1×SSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5×SSC). Variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

[0352] In particular embodiments references to gene editing systems, such as CRISPR and Cas-9 (also known as Csnl and Csxl2) above should be interpreted to include additional options and developments, as is understood by one of ordinary skill in the art. For example, any gene editing system capable of precise genomic recognition and binding can be used. When nucleases are used for targeted genome binding without associated cutting and editing, the nucleases can lack cutting functionality.

[0353] In relation to the use of Cas-9, numerous other options for Cas proteins are available and appropriate for use. Cas-9 itself can refer to one or more catalytic domains of a Cas9 protein derived from bacteria such as Corynebacter, Sutterella, Legionella, Treponema, Filif actor, Eubacterium, Streptococcus, Lactobacillus, Mycoplasma, Bacteroides, Flaviivola, Flavobacterium, Sphaerochaeta, Azospirillum, Gluconacetobacter, Neisseria, Roseburia, Parvibaculum, Staphylococcus, Nitratifractor, and Campylobacter. In some embodiments, the Cas9 is a fusion protein,

e.g. the two catalytic domains are derived from different bacterial species. Additional exemplary Cas nucleases that can be used to bind DNA include Casl, CaslB, Cas2, Cas3, Cas4, Cas5, Cas6, Cas7, Cas8, Cas10, Cpfl, C2c3, C2c2 and C2clCsyl, Csy2, Csy3, Csel, Cse2, Cscl, Csc2, Csa5, Csn2, Csm2, Csm3, Csm4, Csm5, Csm6, Cmrl, Cmr3, Cmr4, Cmr5, Cmr6, Cpfl, Csbl, Csb2, Csb3, Csxl7, Csxl4, CsxlO, Csxl6, CsaX, Csx3, Csxl, Csxl5, Csfl, Csf2, Csf3, and Csf4.

[0354] The Cpf1 nuclease particularly can provide added flexibility in target site selection by means of a short, three base pair recognition sequence (TTN), known as the protospacer-adjacent motif or PAM. Particular embodiments can utilize engineered Cpf1s. For example, US 2018/0030425 describes engineered Cpf1 nucleases from Lachnospiraceae bacterium ND2006 and *Acidaminococcus* sp. BV3L6 with altered and improved target specificity.

[0355] Other Cpf1 variants include Cpf1 homologs and orthologs of the Cpf1 polypeptides disclosed in Zetsche et al. (2015) Cell 163: 759-771 as well as the Cpf1 polypeptides disclosed in U.S. 2016/0208243. Other engineered Cpf1 variants are known to those of ordinary skill in the art and included within the scope of the current disclosure (see, e.g., WO/2017/184768).

[0356] Additional information regarding CRISPR-Cas systems and components thereof are described in, U.S. Pat. Nos. 8,697,359, 8,771,945, 8,795,965, 8,865,406, 8,871,445, 8,889,356, 8,889,418, 8,895,308, 8,906,616, 8,932,814, 8,945,839, 8,993,233 and 8,999,641 and applications related thereto; and WO2014/018423, WO2014/093595, WO2014/093622, WO2014/093635, WO2014/093655, WO2014/093661, WO2014/093694, WO2014/093701, WO2014/093709, WO2014/093712, WO2014/093718, WO2014/145599, WO2014/204723, WO2014/204724, WO2014/204725, WO2014/204726, WO2014/204727, WO2014/204728, WO2014/204729, WO2015/065964, WO2015/089351, WO2015/089354, WO2015/089364, WO2015/089419, WO2015/089427, WO2015/089462, WO2015/089465, WO2015/089473 and WO2015/089486, WO2016205711, WO2017/106657, WO2017/127807 and applications related thereto.

[0357] Zinc finger nucleases (ZFNs) are synthesized by fusing a zinc finger DNA-binding domain to a DNA cleavage domain. Particular embodiments described herein can utilize zinc fingers to bind specific DNA sequences. The DNA-binding domain includes three to six zinc finger proteins which are similar to those found in transcription factors. The DNA cleavage domain includes the catalytic domain of, for example, Fokl endonuclease. The Fokl domain functions as a dimer requiring two constructs with unique DNA binding domains for sites on either side of the target site cleavage sequence. The Fokl cleavage domain cleaves within a five or six base pair spacer sequence separating the two inverted half-sites.

[0358] For additional information regarding ZFNs and ZFNs useful within the teachings of the current disclosure, see, e.g., U.S. Pat. Nos. 6,534,261; 6,607,882; 6,746,838; 6,794,136; 6,824,978; 6,866,997; 6,933,113; 6,979,539; 7,013,219; 7,030,215; 7,220,719; 7,241,573; 7,241,574; 7,585,849; 7,595,376; 6,903,185; 6,479,626; and U.S. Application Publication Nos. 2003/0232410 and 2009/0203140 as well as Gaj et al., Nat Methods, 2012, 9(8):805-7; Ramirez et al., Nucl Acids Res, 2012, 40(12):5560-8; Kim et al., Genome Res, 2012, 22(7): 1327-33; Urnov et al., Nature Reviews Genetics, 2010, 11:636-646; Miller, et al. Nature biotechnology 25, 778-785 (2007); Bibikova, et al. Science 300, 764 (2003); Bibikova, et al. Genetics 161, 1169-1175 (2002); Wolfe, et al. Annual review of biophysics and biomolecular structure 29, 183-212 (2000); Kim, et al. Proceedings of the National Academy of Sciences of the United States of America 93, 1156-1160 (1996); and Miller, et al. The EMBO journal 4, 1609-1614 (1985).

[0359] Particular embodiments can use transcription activator like effector nucleases (TALENs) as gene editing agents. TALENs have been engineered to bind a target genetic sequence and cut DNA at the location of the target sequence. The TALEs of TALENs are DNA binding proteins secreted by Xanthomonas bacteria. The DNA binding domain of TALEs include a highly conserved 33 or 34 amino acid repeat, with divergent residues at the 12th and 13th positions of each repeat. These two positions, referred to as the Repeat Variable Diresidue (RVD), show a strong correlation with specific nucleotide recognition. Accordingly, targeting specificity can be improved by changing the amino acids in the RVD and incorporating nonconventional RVD amino acids.

[0360] Examples of DNA cleavage domains that can be used in TALEN fusions are wild-type and variant Fokl endonucleases. For additional information regarding TALENs, see U.S. Pat. Nos. 8,440,431; 8,440,432; 8,450,471; 8,586,363; and 8,697,853; as well as Joung and Sander, Nat Rev Mol Cell Biot, 2013, 14(I):49-55; Beurdeley et al., Nat Commun, 2013, 4: 1762; Scharenberg et al., Curr Gene Ther, 2013, 13(4):291-303; Gaj et al., Nat Methods, 2012, 9(8):805-7; Miller, et al. Nature biotechnology 29, 143-148 (2011); Christian, et al. Genetics 186, 757-761 (2010); Boch, et al. Science 326, 1509-1512 (2009); and Moscou, & Bogdanove, Science 326, 1501 (2009).

[0361] Particular embodiments can utilize MegaTALs as gene editing agents. MegaTALs have a single chain rare-cleaving nuclease structure in which a TALE is fused with the DNA cleavage domain of a meganuclease. Meganucleases, also known as homing endonucleases, are single peptide chains that have both DNA recognition and nuclease function in the same domain. In contrast to the TALEN, the megaTAL only requires the delivery of a single peptide chain for functional activity.

[0362] Exemplary meganucleases include I-SceI, I-SceII, I-SceIII, I-SceIV, I-SceV, I-SceVI, I-SceVII, I-CeuI, I-CeuAIIP, I-CreI, I-CrepsbIP, I-CrepsbIIP, I-CrepsbIIIP, I-CrepsbIVP, I-TIiI, I-Ppol, PI-PspI, F-SceI, F-SceII, F-SuvI, F-TevI, F-TevII, I-AmaI, I-AniI, I-ChuI, I-CmoeI, I-CpaI, I-CpaII, I-CsmI, I-CvuI, I-CvuAIP, I-DdiI, I-DdiII, I-DirI, I-DmoI, I-HmuI, I-HmuII, I-HsNIP, I-LlaI, I-MsoI, I-NaaI, I-NanI, I-NcIIP, I-NgrIP, I-NitI, I-NjaI, I-Nsp236IP, I-PakI, I-PbolP, I-PcuIP, I-PcuAI, I-PcuVI, I-PgrIP, I-PobIP, I-Port, I-PorIIP, I-PbpIP, I-SpBetaIP, I-ScaI, I-SexIP, 1-SneIP, I-SpomI, I-SpomCP, I-SpomIP, I-SpomIIP, I-SquIP, I-Ssp6803I, I-SthPhiJP, I-SthPhiST3P, I-SthPhiSTe3bP, I-TdeIP, I-TevI, I-TevII, I-TevIII, I-UarAP, I-UarHGPAIP, I-UarHGPA13P, I-VinIP, 1-ZbiIP, PI-MtuI, PI-MtuHIP PI-MtuHIIP, PI-PfuI, PI-PfuII, PI-PkoI, PI-PkoII, PI-Rma438121P, PI-SpBetaIP, PI-SceI, PI-TfuI, PI-TfuII, PI-ThyI, PI-TIiI, and PI-THII.

[0363] Particular embodiments described herein can utilize gene editing systems to insert expression constructs within targeted genomic safe harbors. Methods for identifying genomic safe harbor sites are described in Sadelain et

al., Nature Reviews (2012); 12:51-58; and Papapetrou et al., Nat Biotechnol. (2011) January; 29(1):73-8.

[0364] In particular embodiments, expression constructs refer to isolated polynucleotide sequences that include no elements, portions, or nucleotides that are not described in relation to the construct.

[0365] As will be understood by one of ordinary skill in the art, each embodiment disclosed herein can comprise, consist essentially of or consist of its particular stated element, step, ingredient or component. Thus, the terms "include" or "including" should be interpreted to recite: "comprise, consist of, or consist essentially of." The transition term "comprise" or "comprises" means includes, but is not limited to, and allows for the inclusion of unspecified elements, steps, ingredients, or components, even in major amounts. The transitional phrase "consisting of" excludes any element, step, ingredient or component not specified. The transition phrase "consisting essentially of" limits the scope of the embodiment to the specified elements, steps, ingredients or components and to those that do not materially affect the embodiment. A material effect would cause a significantly significant reduction in the ability of a vector to reverse febrile seizures in Scn1a+/− mice according to the protocol of Example 2 and FIG. **10**.

[0366] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. When further clarity is required, the term "about" has the meaning reasonably ascribed to it by a person skilled in the art when used in conjunction with a stated numerical value or range, i.e. denoting somewhat more or somewhat less than the stated value or range, to within a range of ±20% of the stated value; ±19% of the stated value; ±18% of the stated value; ±17% of the stated value; ±16% of the stated value; ±15% of the stated value; ±14% of the stated value; ±13% of the stated value; ±12% of the stated value; ±11% of the stated value; ±10% of the stated value; ±9% of the stated value; ±8% of the stated value; ±7% of the stated value; ±6% of the stated value; ±5% of the stated value; ±4% of the stated value; ±3% of the stated value; ±2% of the stated value; or ±1% of the stated value.

[0367] Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

[0368] The terms "a," "an," "the" and similar referents used in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

[0369] Groupings of alternative elements or embodiments of the invention disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs, the specification is deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

[0370] Certain embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Of course, variations on these described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

[0371] Furthermore, numerous references have been made to patents, printed publications, journal articles and other written text throughout this specification (referenced materials herein). Each of the referenced materials are individually incorporated herein by reference in their entirety for their referenced teaching.

[0372] In closing, it is to be understood that the embodiments of the invention disclosed herein are illustrative of the principles of the present invention. Other modifications that may be employed are within the scope of the invention. Thus, by way of example, but not of limitation, alternative configurations of the present invention may be utilized in accordance with the teachings herein. Accordingly, the present invention is not limited to that precisely as shown and described.

[0373] The particulars shown herein are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of various embodiments of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for the fundamental understanding of the inven-

tion, the description taken with the drawings and/or examples making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

[0374] Definitions and explanations used in the present disclosure are meant and intended to be controlling in any future construction unless clearly and unambiguously modified in the following examples or when application of the meaning renders any construction meaningless or essentially meaningless. In cases where the construction of the term would render it meaningless or essentially meaningless, the definition should be taken from Webster's Dictionary, 3rd Edition or a dictionary known to those of ordinary skill in the art, such as the Oxford Dictionary of Biochemistry and Molecular Biology (Ed. Anthony Smith, Oxford University Press, Oxford, 2004).

SEQUENCE LISTING

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ttcaatttta ggtcctacgt ctctgcaatt tgtgtatgaa taacagaata atttccctct 240

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gaagaaaatt acaggtaatt atctttgacg gtaaaaacgc tgtaatcagc gggctacatg 360

aaaaattact ctaattatgg ctgcatttaa gagaatggaa aaaaaccttc ttgtggataa 420

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ccccatctct ctggtaatta tgagcaattt tttcgcccag ggaatctttt tgcattaaca 180

aaagagataa cgcactgaaa gccaaatttg ctgtgcattg agaaaaggaa aaaaaaaaat 240

caaataggtg cgagctgcca tctctgcaat tctctggtac cggagccggc aaattgcttg 300

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3x HA tag

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gtcgaactgc tgctccggat ttatgcgtat cggggcaagt tttttaagga cccgtggaat 360

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ctccgctccc tccgagttct ccgcgtcttg agggttctga cgattgtccc cagcatgaaa 480

agagtagtgt cagcactgct tgggagcttg cccgggttgg cctccattgc aaccgtgctt 540

ctgttgatct attacgtttt cgctgtgatc gccactaaaa ttttcgggga tgcttttccg 600

gaatggttcg ggacgatagc ggactccttc tatacccttt ttcaaattat gaccttggaa 660

agttggtcta tggggatctc taggccagtg atggaggtgt acccttacgc ttgggtattc 720

tttgtgccct ttattcttgt tgctactttt accatgctta acctttttcat cgccatcata 780

gtgaatacta tgcagacatt ctctgacgag gaacatgctc tggagcgaga gcaagataaa 840

cagatcttgg aacaggagca gagacaaatg cacgaggaac tgaaggccat tcgactcgag 900

cttcagcaac tccaaaccct tttgcgaaat gcggctgggg actcctccaa tgtctccaca 960

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aagggcaata tcggctcaga ctaa 984

<210> SEQ ID NO 10
<211> LENGTH: 888
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: NavSheP endogenous sequence

<400> SEQUENCE: 10

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gagcaaaact ggtttggtca ttttattttg acattgattt taatcaacgc ggtgcagtta 120

ggtatggaga cctcagccag cctgatggcg caatacggtg ctttgttgat gagtcttgat 180

aaggtgctgc tgagtgtatt tgtggtggag ttattgctgc ggatttatgc ctacaggggg 240

aaatttttta aagacccttg gaacgtgttc gattttaccg tgatagtgat agcactgatc 300

cctgcatctg ggccattggc tgtcctgcgt tcgctcaggg tattgcgggt gctgagagtg 360

ttaacaattg tgccatcaat gaaacgggtg gtgtctgcgc tgttgggatc acttcctgga 420

ttggcatcga tcgccacagt attactgctg atttattatg tgtttgcggt gatcgctacc 480

aaaatttttg gcgatgcatt ccctgaatgg tttggcacta ttgctgactc attttatacc 540

ctatttcaaa taatgacgct tgaaagctgg tctatgggaa tttcgcggcc agtgatggaa 600

gtctaccctt atgcttgggt atttttcgta ccatttattc tggtagcgac tttcacaatg 660

ctaaatttgt ttattgcgat tatcgtcaat accatgcaaa ccttcagcga cgaagagcat 720

gcattagagc gtgagcaaga caaacaaatc ttagagcagg aacaaagaca aatgcacgag 780

gagttgaaag ccatcagact cgagctacaa caattacaaa ccttgctgcg caatgctgct 840

ggtgattctt ctaatgtgtc gacaaaggga aacattggtt ctgactaa 888

<210> SEQ ID NO 11
<211> LENGTH: 855
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: NavBp, endogenous sequence

<400> SEQUENCE: 11

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gtctttcata aggcctttac cccaactatt attaccttga ttatcattaa tgccattatt 120

gtaggccttg aaacatatcc tactgtttat caaggttata atgattggtt ctacgcagca 180

gatttagcct tactttggat ttttacaatt gagattacac tgcgttttat cgcagcgaga 240

ccgactaaat ctttttttaa aagcagctgg aactggtttg atttattaat cgttcttgcc 300

ggtcatgtct ttgccggtgc tcattttgta acggttcttc gtatcctgcg cgttcttcgc 360

gtattacgtg ccatttctgt cattccttct ctgcgtcgtt tagtcgatgc tttgctgatg 420

accatcccgg ctttaggaaa cattatgatc ctgatgggaa ttattttcta tattttcgct 480

gtgattggaa cgatgttatt tgcttctgta gcacctgagt actttggtaa cttacagctt 540

tctttattaa cattattcca agttgttaca cttgaatctt gggcaagcgg tgtcatgagg 600

ccgatttttg cagaggtttg gtggtcttgg atttattttg tcatctttat tttagtaggg 660

acatttattg tctttaactt atttatcggt gttatcgtta ataacgttga aaaagcaaac 720

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gaagaagaac tcaaatcaga attagatgat aaagaggcag atacaaaaga agagcttgct 780

tctctgcgta atgaagtagc agagatgaaa gacctcatta aacaaatgca taaacagcaa 840

acaaaaaaag ggtaa 855

<210> SEQ ID NO 12
<211> LENGTH: 951
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: NavBp, codon optimized, with N-terminal 3x HA tag

<400> SEQUENCE: 12

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tatgccggca gttatcccta cgacgtccct gactacgcag aaaacaaccc agccgaacag 120

caagtcccac ccctcgtggc gctcgcccaa cgcatagtat ttcacaaggc gtttacgccg 180

acgataatca ccctcatcat tattaatgcg atcattgtgg gactcgagac atacccaacg 240

gtttaccagg gttacaatga ttggttctat gctgccgacc ttgctttgtt gtggatattc 300

actattgaaa tcacgctccg attcatcgcc gcccgaccga cgaagagttt cttcaagtct 360

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cccagtctcc ggcggctggt tgacgcactt ttgatgacaa tcccagcact cggtaacatc 540

atgatactga tggggattat tttttacata ttcgcggtta tcgggacgat gctctttgca 600

tcagtagcgc cagaatactt tggcaatttg cagctgtctc tgcttacact gttccaagtg 660

gttacgctgg aaagttgggc tagtggggtt atgcgaccta tttttgccga agtctggtgg 720

tcttggatct attttgtaat ctttattctc gtgggaactt tcatagtatt taacctttc 780

attggcgtca tcgtgaacaa tgtggaaaaa gctaacgaag aggaactgaa aagcgaactg 840

gatgataaag aggctgatac aaaagaagaa ctggcatcat tgcgaaacga ggtggcagaa 900

atgaaggatc tcataaaaca gatgcataaa cagcaaacaa aaaagggtta a 951

<210> SEQ ID NO 13
<211> LENGTH: 825
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: NavMs, endogenous sequence

<400> SEQUENCE: 13

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attattgtgc tcaatggcgc tgtgctgggt ctgctgaccg atacaaccct atcggcctcc 120

agccaaaacc tgctggagcg tgtggatcaa ctttgtctga ctatctttat tgttgaaata 180

tccctgaaaa tatacgccta tggcgtgcga ggctttttcc gcagcggctg gaatctgttt 240

gattttgtga ttgtggccat cgcgcttatg cccgcccagg gtagcctatc ggtgctgcga 300

accttccgta tattccgcgt catgcggctc gtatcggtca taccaaccat gcgaagagtg 360

gtgcaaggca tgctcttggc actgcccggc gtgggatcgg tagcggcact gttgacggtg 420

gtcttctata ttgcggctgt catggccacc aatctctacg gggcaacctt ccctgaatgg 480

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tttggtgatc ttagcaagag cctgtacaca ctatttcagg tgatgacctt agagtcatgg 540

tctatgggca ttgtgcgtcc agtgatgaac gttcatccca acgcatgggt ttttttcatc 600

cccttcatca tgctcaccac ctttaccgtg ctcaacctgt ttattggcat tattgtagat 660

gccatggcca tcaccaagga acaggaggaa gaggccaaaa ccggccacca ccaagagcct 720

attagccaaa cattgctcca tctgggagat cgcctagata ggatcgaaaa gcagcttgcg 780

caaaacaacg agctcttaca acgacaacag ccgcaaaaaa aatag 825

<210> SEQ ID NO 14
<211> LENGTH: 954
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: NavMs, codon optimized, with N-terminal 3x HA tag and linker

<400> SEQUENCE: 14

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tacgctggtt cttaccctta cgatgttccc gattatgcca gttctggatt ggtgccacga 120

ggcagccaca tgagccggaa gatcagagat cttatcgaat ctaagagatt tcagaatgtt 180

attaccgcga taatcgtact caacggggcg gtgctcggtc tcctcaccga taccacattg 240

agcgcttcta gccagaacct gctcgaaagg gttgaccaac tgtgcctgac aatttttatc 300

gtggaaatta gcttgaaaat ttacgcctac ggcgttcgcg gttttttccg gagcggttgg 360

aatctttttg acttcgttat cgttgccatc gcgctcatgc ccgcacaggg ttctttgtct 420

gtgttgagga cattccgaat atttcgcgtg atgcgcttgg tatccgtgat ccctacgatg 480

cgccgcgtcg tacaaggaat gttgctggct ctccccggcg tcgggagcgt tgctgccctc 540

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caagagccaa tttctcaaac cctcttgcat ctcggggacc gactggaccg cattgagaag 900

caactcgcgc agaacaatga gctgttgcag cgacagcaac ctcaaaaaaa ataa 954

<210> SEQ ID NO 15
<211> LENGTH: 885
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: NavMs, codon optimized, with N-terminal His tag and linker

<400> SEQUENCE: 15

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atgtcacgca aaatccgcga tttaatcgaa tccaaacgct ttcaaaacgt catcaccgcc 120

attattgtgc tcaatggcgc tgtgctgggt ctgctgaccg atacaaccct gtcggcctcc 180

agccaaaacc tgctggagcg tgtggatcaa ctttgtctga ctatctttat tgttgaaatc 240

tccctgaaaa tctacgccta tggcgtgcgc ggctttttcc gcagcggctg gaatctgttt 300

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gattttgtga ttgtggccat cgcgcttatg ccggcccagg gtagcctgtc ggtgctgcgt 360

accttccgta tcttccgcgt catgcgcctc gtatcggtca tcccaaccat gcgccgtgtg 420

gtgcaaggca tgctcttggc actgccgggc gtgggctcgg tagcggcact gttgacggtg 480

gtcttctata ttgcggctgt catggccacc aatctctacg gggcaacctt ccctgaatgg 540

tttggtgatc ttagcaagag cctgtacaca ctgtttcagg tgatgacctt agagtcatgg 600

tctatgggca ttgtgcgtcc agtgatgaac gttcatccga acgcatgggt ttttttcatc 660

ccgttcatca tgctcaccac ctttaccgtg ctcaacctgt ttattggcat tattgtagat 720

gcaatggcaa tcaccaagga acaggaggaa gaggccaaaa ccggtcacca tcaagaacct 780

atttctcaaa ctcttcttca tcttggtgat cgtcttgatc gtattgaaaa acaacttgct 840

caaaataatg aacttcttca acgtcaacaa cctcaaaaaa aataa 885

<210> SEQ ID NO 16
<211> LENGTH: 6027
<212> TYPE: DNA
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 16

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aaaaaagatg acgacgaaaa tggcccaaag ccaaatagtg acttggaagc tggaaagaac 180

cttccattta tttatggaga cattcctcca gagatggtgt cagagcccct ggaggacctg 240

gacccctact atatcaataa gaaaactttt atagtattga ataaagggaa ggccatcttc 300

cggttcagtg ccacctctgc cctgtacatt ttaactccct tcaatcctct taggaaaata 360

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ttcacaggaa tatatacttt tgaatcactt ataaaaatta ttgcaagggg attctgttta 540

gaagatttta ctttccttcg ggatccatgg aactggctcg atttcactgt cattacattt 600

gcgtacgtca cagagtttgt ggacctgggc aatgtctcgg cattgagaac attcagagtt 660

ctccgagcat tgaagacgat ttcagtcatt ccaggcctga aaaccattgt gggagccctg 720

atccagtctg tgaagaagct ctcagatgta atgatcctga ctgtgttctg tctgagcgta 780

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cctcccacca atgcttcctt ggaggaacat agtatagaaa agaatataac tgtgaattat 900

aatggtacac ttataaatga aactgtcttt gagtttgact ggaagtcata tattcaagat 960

tcaagatatc attatttcct ggagggtttt ttagatgcac tactatgtgg aaatagctct 1020

gatgcaggcc aatgtccaga gggatatatg tgtgtgaaag ctggtagaaa tcccaattat 1080

ggctacacaa gctttgatac cttcagttgg gctttttttgt ccttgtttcg actaatgact 1140

caggacttct gggaaaatct ttatcaactg acattacgtg ctgctgggaa aacgtacatg 1200

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gaggccgaat ttcagcagat gattgaacag cttaaaaagc aacaggaggc agctcagcag 1380

gcagcaacgg caactgcctc agaacattcc agagagccca gtgcagcagg caggctctca 1440

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gacagctcat ctgaagcctc taagttgagt tccaagagtg ctaaggaaag aagaaatcgg 1500

aggaagaaaa gaaaacagaa agagcagtct ggtggggaag agaaagatga ggatgaattc 1560

caaaaatctg aatctgagga cagcatcagg aggaaaggtt ttcgcttctc cattgaaggg 1620

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ggaactacaa gtggtatagg aactggcagc agtgttgaat acattattga tgaaagtgat 3300

tacatgtcat tcataaacaa ccccagtctt actgtgactg taccaattgc tgtaggagaa 3360

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gaagaacaga agaaatacta taatgcaatg aaaaaattag gatcgaaaaa accgcaaaag 4560

cctatacctc gaccaggaaa caaatttcaa ggaatggtct ttgacttcgt aaccagacaa 4620

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acctctgctg gctgggatgg attgctagca cccattctca acagtaagcc acccgactgt 5220

gaccctaata aagttaaccc tggaagctca gttaagggag actgtgggaa cccatctgtt 5280

ggaattttct tttttgtcag ttacatcatc atatccttcc tggttgtggt gaacatgtac 5340

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attcagcgtg cttacagacg ccacctttta aagcgaactg taaaacaagc ttcctttacg 5820

tacaataaaa acaaaatcaa aggtggggct aatcttctta taaaagaaga catgataatt 5880

gacagaataa atgaaaactc tattacagaa aaaactgatc tgaccatgtc cactgcagct 5940

tgtccacctt cctatgaccg ggtgacaaag ccaattgtgg aaaaacatga gcaagaaggc 6000

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aaagatgaaa aagccaaagg gaaataa 6027

<210> SEQ ID NO 17
<211> LENGTH: 720
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: SYFP2

<400> SEQUENCE: 17

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ggcaagctga ccctgaagct gatctgcacc accggcaagc tgcccgtgcc ctggcccacc 180

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aagctggagt acaactacaa cagccacaac gtctatatca ccgccgacaa gcagaagaac 480

ggcatcaagg ccaacttcaa gatccgccac aacatcgagg acggcggcgt gcagctcgcc 540

gaccactacc agcagaacac ccccatcggc gacggccccg tgctgctgcc cgacaaccac 600

tacctgagct accagtccaa gctgagcaaa gaccccaacg agaagcgcga tcacatggtc 660

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<210> SEQ ID NO 18
<211> LENGTH: 78
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: P2A Encoding Sequence

<400> SEQUENCE: 18

ggcagcggcg ccaccaactt cagcctgctg aagcaggccg gcgacgtgga ggagaacccc 60

ggccccggag ctagcgga 78

<210> SEQ ID NO 19
<211> LENGTH: 246
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: WPRE3

<400> SEQUENCE: 19

ataatcaacc tctggattac aaaatttgtg aaagattgac tggtattctt aactatgttg 60

ctccttttac gctatgtgga tacgctgctt taatgccttt gtatcatgct attgcttccc 120

gtatggcttt cattttctcc tccttgtata aatcctggtt agttcttgcc acggcggaac 180

tcatcgccgc ctgccttgcc cgctgctgga caggggctcg gctgttgggc actgacaatt 240

ccgtgg 246

<210> SEQ ID NO 20
<211> LENGTH: 204
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:

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<223> OTHER INFORMATION: BGHpA

<400> SEQUENCE: 20

cgactgtgcc ttctagttgc cagccatctg ttgtttgccc ctccccgtg ccttccttga 60

ccctggaagg tgccactccc actgtccttt cctaataaaa tgaggaaatt gcatcgcatt 120

gtctgagtag gtgtcattct attctggggg gtggggtggg gcaggacagc aagggggagg 180

attgggaaga caatagcagg catg 204

<210> SEQ ID NO 21
<211> LENGTH: 33
<212> TYPE: PRT
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: N-terminal 3XHA tag (Protein)

<400> SEQUENCE: 21

Met Val Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Gly Ser Tyr Pro Tyr
1 5 10 15

Asp Val Pro Asp Tyr Ala Gly Ser Tyr Pro Tyr Asp Val Pro Asp Tyr
20 25 30

Ala

<210> SEQ ID NO 22
<211> LENGTH: 99
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: N-terminal 3XHA tag

<400> SEQUENCE: 22

atggtttacc cgtatgatgt cccggattac gctggcagct acccatacga tgtacccgac 60

tatgccggca gttatcccta cgacgtccct gactacgca 99

<210> SEQ ID NO 23
<211> LENGTH: 3133
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: hSCN1A N-term of two-part expression system

<400> SEQUENCE: 23

atggagcaaa cagtgcttgt accaccagga cctgacagct tcaacttctt caccagagaa 60

tctcttgcgg ctattgaaag acgcattgca gaagaaaagg caaagaatcc caaaccagac 120

aaaaaagatg acgacgaaaa tggcccaaag ccaaatagtg acttggaagc tggaaagaac 180

cttccattta tttatggaga cattcctcca gagatggtgt cagagcccct ggaggacctg 240

gacccctact atatcaataa gaaaactttt atagtattga ataaagggaa ggccatcttc 300

cggttcagtg ccacctctgc cctgtacatt ttaactccct tcaatcctct taggaaaata 360

gctattaaga ttttggtaca ttcattattc agcatgctaa ttatgtgcac tattttgaca 420

aactgtgtgt ttatgacaat gagtaaccct cctgattgga caaagaatgt agaatacacc 480

ttcacaggaa tatatacttt tgaatcactt ataaaaatta ttgcaagggg attctgttta 540

gaagatttta ctttccttcg ggatccatgg aactggctcg atttcactgt cattacattt 600

gcgtacgtca cagagtttgt ggacctgggc aatgtctcgg cattgagaac attcagagtt 660

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ctccgagcat tgaagacgat ttcagtcatt ccaggcctga aaaccattgt gggagccctg 720

atccagtctg tgaagaagct ctcagatgta atgatcctga ctgtgttctg tctgagcgta 780

tttgctctaa ttgggctgca gctgttcatg ggcaacctga ggaataaatg tatacaatgg 840

cctcccacca atgcttcctt ggaggaacat agtatagaaa agaatataac tgtgaattat 900

aatggtacac ttataaatga aactgtcttt gagtttgact ggaagtcata tattcaagat 960

tcaagatatc attatttcct ggagggtttt ttagatgcac tactatgtgg aaatagctct 1020

gatgcaggcc aatgtccaga gggatatatg tgtgtgaaag ctggtagaaa tcccaattat 1080

ggctacacaa gctttgatac cttcagttgg gctttttttgt ccttgtttcg actaatgact 1140

caggacttct gggaaaatct ttatcaactg acattacgtg ctgctgggaa aacgtacatg 1200

atatttttttg tattggtcat tttcttgggc tcattctacc taataaattt gatcctggct 1260

gtggtggcca tggcctacga ggaacagaat caggccacct tggaagaagc agaacagaaa 1320

gaggccgaat ttcagcagat gattgaacag cttaaaaagc aacaggaggc agctcagcag 1380

gcagcaacgg caactgcctc agaacattcc agagagccca gtgcagcagg caggctctca 1440

gacagctcat ctgaagcctc taagttgagt tccaagagtg ctaaggaaag aagaaatcgg 1500

aggaagaaaa gaaaacagaa agagcagtct ggtggggaag agaaagatga ggatgaattc 1560

caaaaatctg aatctgagga cagcatcagg aggaaaggtt ttcgcttctc cattgaaggg 1620

aaccgattga catatgaaaa gaggtactcc tccccacacc agtctttgtt gagcatccgt 1680

ggctccctat tttcaccaag gcgaaatagc agaacaagcc ttttcagctt tagagggcga 1740

gcaaaggatg tgggatctga gaacgacttc gcagatgatg agcacagcac ctttgaggat 1800

aacgagagcc gtagagattc cttgtttgtg ccccgacgac acggagagag acgcaacagc 1860

aacctgagtc agaccagtag gtcatcccgg atgctggcag tgtttccagc gaatgggaag 1920

atgcacagca ctgtggattg caatggtgtg gtttccttgg ttggtggacc ttcagttcct 1980

acatcgcctg ttggacagct tctgccagag gtgataatag ataagccagc tactgatgac 2040

aatggaacaa ccactgaaac tgaaatgaga aagagaaggt caagttcttt ccacgtttcc 2100

atggactttc tagaagatcc ttcccaaagg caacgagcaa tgagtatagc cagcattcta 2160

acaaatacag tagaagaact tgaagaatcc aggcagaaat gcccaccctg ttggtataaa 2220

ttttccaaca tattcttaat ctgggactgt tctccatatt ggttaaaagt gaaacatgtt 2280

gtcaacctgg ttgtgatgga cccatttgtt gacctggcca tcaccatctg tattgtctta 2340

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acagtaggaa acttggtttt cactgggatc tttacagcag aaatgtttct gaaaattatt 2460

gccatggatc cttactatta tttccaagaa ggctggaata tctttgacgg ttttattgtg 2520

acgcttagcc tggtagaact tggactcgcc aatgtggaag gattatctgt tctccgttca 2580

tttcgattgc tgcgagtttt caagttggca aaatcttggc caacgttaaa tatgctaata 2640

aagatcatcg gcaattccgt gggggctctg ggaaatttaa ccctcgtctt ggccatcatc 2700

gtcttcattt ttgccgtggt cggcatgcag ctctttggta aaagctacaa agattgtgtc 2760

tgcaagatcg ccagtgattg tcaactccca cgctggcaca tgaatgactt cttccactcc 2820

ttcctgattg tgttccgcgt gctgtgtggg gagtggatag agaccatgtg ggactgtatg 2880

gaggttgctg gtcaagccat gtgccttact gtcttcatga tggtcatggt gattggaaac 2940

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ctagtggtcc tgaatctctt tctggccttg cttctgagct catttagtgc agacaacctt 3000

gcagccactg atgatgataa tgaaatgaat aatctccaaa ttgctgtgga taggatgcac 3060

aaaggagtag cttatgtgaa aagaaaaata tatgaattta ttcaacagtc cttcattagg 3120

aaacaaaaga ttt 3133

<210> SEQ ID NO 24
<211> LENGTH: 3639
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: hSCN1A C-term of two-part expression system with c-terminal 3XHA sequence

<400> SEQUENCE: 24

ctggtagaac ttggactcgc caatgtggaa ggattatctg ttctccgttc atttcgattg 60

ctgcgagttt tcaagttggc aaaatcttgg ccaacgttaa atatgctaat aaagatcatc 120

ggcaattccg tgggggctct gggaaattta accctcgtct tggccatcat cgtcttcatt 180

tttgccgtgg tcggcatgca gctctttggt aaaagctaca aagattgtgt ctgcaagatc 240

gccagtgatt gtcaactccc acgctggcac atgaatgact tcttccactc cttcctgatt 300

gtgttccgcg tgctgtgtgg ggagtggata gagaccatgt gggactgtat ggaggttgct 360

ggtcaagcca tgtgccttac tgtcttcatg atggtcatgg tgattggaaa cctagtggtc 420

ctgaatctct ttctggcctt gcttctgagc tcatttagtg cagacaacct tgcagccact 480

gatgatgata atgaaatgaa taatctccaa attgctgtgg ataggatgca caaaggagta 540

gcttatgtga aaagaaaaat atatgaattt attcaacagt ccttcattag gaaacaaaag 600

attttagatg aaattaaacc acttgatgat ctaaacaaca agaaagacag ttgtatgtcc 660

aatcatacag cagaaattgg gaaagatctt gactatctta aagatgtaaa tggaactaca 720

agtggtatag gaactggcag cagtgttgaa tacattattg atgaaagtga ttacatgtca 780

ttcataaaca accccagtct tactgtgact gtaccaattg ctgtaggaga atctgacttt 840

gaaaatttaa acacggaaga ctttagtagt gaatcggatc tggaagaaag caaagagaaa 900

ctgaatgaaa gcagtagctc atcagaaggt agcactgtgg acatcggcgc acctgtagaa 960

gaacagcccg tagtggaacc tgaagaaact cttgaaccag aagcttgttt cactgaaggc 1020

tgtgtacaaa gattcaagtg ttgtcaaatc aatgtggaag aaggcagagg aaaacaatgg 1080

tggaacctga gaaggacgtg tttccgaata gttgaacata actggtttga gaccttcatt 1140

gttttcatga ttctccttag tagtggtgct ctggcatttg aagatatata tattgatcag 1200

cgaaagacga ttaagacgat gttggaatat gctgacaagg ttttcactta cattttcatt 1260

ctggaaatgc ttctaaaatg ggtggcatat ggctatcaaa catatttcac caatgcctgg 1320

tgttggctgg acttcttaat tgttgatgtt tcattggtca gtttaacagc aaatgccttg 1380

ggttactcag aacttggagc catcaaatct ctcaggacac taagagctct gagacctcta 1440

agagccttat ctcgatttga agggatgagg gtggttgtga atgccctttt aggagcaatt 1500

ccatccatca tgaatgtgct tctggtttgt cttatattct ggctaatttt cagcatcatg 1560

ggcgtaaatt tgtttgctgg caaattctac cactgtatta acaccacaac tggtgacagg 1620

tttgacatcg aagacgtgaa taatcatact gattgcctaa aactaataga aagaaatgag 1680

actgctcgat ggaaaaatgt gaaagtaaac tttgataatg taggatttgg gtatctctct 1740

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ttgcttcaag ttgccacatt caaaggatgg atggatataa tgtatgcagc agttgattcc 1800

agaaatgtgg aactccagcc taagtatgaa gaaagtctgt acatgtatct ttactttgtt 1860

attttcatca tctttgggtc cttcttcacc ttgaacctgt ttattggtgt catcatagat 1920

aatttcaacc agcagaaaaa gaagtttgga ggtcaagaca tctttatgac agaagaacag 1980

aagaaatact ataatgcaat gaaaaaatta ggatcgaaaa aaccgcaaaa gcctatacct 2040

cgaccaggaa acaaatttca aggaatggtc tttgacttcg taaccagaca agtttttgac 2100

ataagcatca tgattctcat ctgtcttaac atggtcacaa tgatggtgga aacagatgac 2160

cagagtgaat atgtgactac cattttgtca cgcatcaatc tggtgttcat tgtgctattt 2220

actggagagt gtgtactgaa actcatctct ctacgccatt attattttac cattggatgg 2280

aatatttttg attttgtggt tgtcattctc tccattgtag gtatgtttct tgccgagctg 2340

atagaaaagt atttcgtgtc ccctaccctg ttccgagtga tccgtcttgc taggattggc 2400

cgaatcctac gtctgatcaa aggagcaaag gggatccgca cgctgctctt tgctttgatg 2460

atgtcccttc ctgcgttgtt taacatcggc ctcctactct tcctagtcat gttcatctac 2520

gccatctttg ggatgtccaa ctttgcctat gttaagaggg aagttgggat cgatgacatg 2580

ttcaactttg agacctttgg caacagcatg atctgcctat tccaaattac aacctctgct 2640

ggctgggatg gattgctagc acccattctc aacagtaagc cacccgactg tgaccctaat 2700

aaagttaacc ctggaagctc agttaaggga gactgtggga acccatctgt tggaattttc 2760

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tttgaaaaat tatctcagtt tgcagctgcg cttgaaccgc ctctcaatct gccacaacca 3000

aacaaactcc agctcattgc catggatttg cccatggtga gtggtgaccg gatccactgt 3060

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ccaatcacta ctactttaaa acgaaaacaa gaggaagtat ctgctgtcat tattcagcgt 3240

gcttacagac gccacctttt aaagcgaact gtaaaacaag cttcctttac gtacaataaa 3300

aacaaaatca aaggtggggc taatcttctt ataaaagaag acatgataat tgacagaata 3360

aatgaaaact ctattacaga aaaaactgat ctgaccatgt ccactgcagc ttgtccacct 3420

tcctatgacc gggtgacaaa gccaattgtg gaaaaacatg agcaagaagg caaagatgaa 3480

aaagccaaag ggaaaggagg tggtggttca ggtgggggcg gctcagagta cccctatgat 3540

gtccctgatt atgcggcgga ataccctat gacgtgccgg actacgcggc tgaatatccg 3600

tatgacgttc ccgattatgc ggctaagctc gaataatga 3639

<210> SEQ ID NO 25
<211> LENGTH: 604
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: 604 bp homology region of hSCN1A N term and C term that can be used in two-part expression system

<400> SEQUENCE: 25

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ctggtagaac ttggactcgc caatgtggaa ggattatctg ttctccgttc atttcgattg 60

ctgcgagttt tcaagttggc aaaatcttgg ccaacgttaa atatgctaat aaagatcatc 120

ggcaattccg tgggggctct gggaaattta accctcgtct tggccatcat cgtcttcatt 180

tttgccgtgg tcggcatgca gctctttggt aaaagctaca aagattgtgt ctgcaagatc 240

gccagtgatt gtcaactccc acgctggcac atgaatgact tcttccactc cttcctgatt 300

gtgttccgcg tgctgtgtgg ggagtggata gagaccatgt gggactgtat ggaggttgct 360

ggtcaagcca tgtgccttac tgtcttcatg atggtcatgg tgattggaaa cctagtggtc 420

ctgaatctct ttctggcctt gcttctgagc tcatttagtg cagacaacct tgcagccact 480

gatgatgata atgaaatgaa taatctccaa attgctgtgg ataggatgca caaaggagta 540

gcttatgtga aaagaaaaat atatgaattt attcaacagt ccttcattag gaaacaaaag 600

attt 604

<210> SEQ ID NO 26
<211> LENGTH: 26
<212> TYPE: PRT
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: P2A Translation from CN1498

<400> SEQUENCE: 26

Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val
1 5 10 15

Glu Glu Asn Pro Gly Pro Gly Ala Ser Gly
20 25

<210> SEQ ID NO 27
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: T2A

<400> SEQUENCE: 27

Gly Ser Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu
1 5 10 15

Glu Asn Pro Gly Pro
20

<210> SEQ ID NO 28
<211> LENGTH: 24
<212> TYPE: PRT
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: E2A

<400> SEQUENCE: 28

Gly Ser Gly Gln Cys Thr Asn Tyr Ala Leu Leu Lys Leu Ala Gly Asp
1 5 10 15

Val Glu Ser Asn Pro Gly Pro Pro
20

<210> SEQ ID NO 29
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: artificial sequence
<220> FEATURE:

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<223> OTHER INFORMATION: F2A

<400> SEQUENCE: 29

Gly Ser Gly Val Lys Gln Thr Leu Asn Phe Asp Leu Leu Lys Leu Ala
1 5 10 15

Gly Asp Val Glu Ser Asn Pro Gly Pro
20 25

<210> SEQ ID NO 30
<211> LENGTH: 53
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: MinBglobin

<400> SEQUENCE: 30

gggctgggca taaaagtcag ggcagagcca tctattgctt acatttgctt ctg 53

<210> SEQ ID NO 31
<211> LENGTH: 68
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: minCMV

<400> SEQUENCE: 31

gaggtaggcg tgtacggtgg gaggcctata taagcagagc tcgtttagtg aaccgtcaga 60

tcgcctgg 68

<210> SEQ ID NO 32
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: PHP.eB capsid: Corresponds to the AAV9 VP1 capsid sequence with a modification that starts at amino acid residue 586 where S AQ A are changed to S DGTLAVPFK A.

<400> SEQUENCE: 32

Ser Asp Gly Thr Leu Ala Val Pro Phe Lys Ala
1 5 10

<210> SEQ ID NO 33
<211> LENGTH: 2843
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CN1367 - The portion between L-ITR and R-ITR: positions 142-2984

<400> SEQUENCE: 33

gcggccgcac gcgtataggt accgagctct atgcactcac agtggtttgg catgcatctg 60

gtgaattttt tttaacgaaa aattagtgtt ggtttcgatg tatggtagca ttctccctaa 120

cgtaatttga ataattcagc aaagccccac taccagctgt acttctgcag cctcttccat 180

tcttttcagc attataattt tggttaattt tcaattttag gtcctacgtc tctgcaattt 240

gtgtatgaat aacagaataa tttccctctt ttgtttcgcc tttcctgttc ctgaatctaa 300

ataaagatgg ctttttagta ttaaaagtgg aagaaaatta caggtaatta tctttgacgg 360

taaaaacgct gtaatcagcg ggctacatga aaaattactc taattatggc tgcatttaag 420

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agaatggaaa aaaaccttct tgtggataaa aaccttaaat tgtccccaat gtctgcttca 480

aattggatgg cactgcagct ggaggctttg ttcagaattg atcctgggga gctacgaacc 540

caaagtttca cagtagggag ctcgggctgg gcataaaagt cagggcagag ccatctattg 600

cttacatttg cttctgggat ccagatcttt cgaagctagc gctaccggtc gccaccatgg 660

gcagcagcca tcatcatcat catcacagca gcggcctggt gccgcgcggc agccatatgt 720

cacgcaaaat ccgcgattta atcgaatcca aacgctttca aaacgtcatc accgccatta 780

ttgtgctcaa tggcgctgtg ctgggtctgc tgaccgatac aaccctgtcg gcctccagcc 840

aaaacctgct ggagcgtgtg gatcaacttt gtctgactat ctttattgtt gaaatctccc 900

tgaaaatcta cgcctatggc gtgcgcggct ttttccgcag cggctggaat ctgtttgatt 960

ttgtgattgt ggccatcgcg cttatgccgg cccagggtag cctgtcggtg ctgcgtacct 1020

tccgtatctt ccgcgtcatg cgcctcgtat cggtcatccc aaccatgcgc cgtgtggtgc 1080

aaggcatgct cttggcactg ccgggcgtgg gctcggtagc ggcactgttg acggtggtct 1140

tctatattgc ggctgtcatg gccaccaatc tctacggggc aaccttccct gaatggtttg 1200

gtgatcttag caagagcctg tacacactgt ttcaggtgat gaccttagag tcatggtcta 1260

tgggcattgt gcgtccagtg atgaacgttc atccgaacgc atgggttttt ttcatcccgt 1320

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ctcaaactct tcttcatctt ggtgatcgtc ttgatcgtat tgaaaaacaa cttgctcaaa 1500

ataatgaact tcttcaacgt caacaacctc aaaaaaaagg cagcggcgcc accaacttca 1560

gcctgctgaa gcaggccggc gacgtggagg agaaccccgg ccccatggtg agcaagggcg 1620

aggagctgtt caccggggtg gtgcccatcc tggtcgagct ggacggcgac gtaaacggcc 1680

acaagttcag cgtgtccggc gagggcgagg gcgatgccac ctacggcaag ctgaccctga 1740

agctgatctg caccaccggc aagctgcccg tgccctggcc caccctcgtg accaccctgg 1800

gctacggcgt gcagtgcttc gcccgctacc ccgaccacat gaagcagcac gacttcttca 1860

agtccgccat gcccgaaggc tacgtccagg agcgcaccat cttcttcaag gacgacggca 1920

actacaagac ccgcgccgag gtgaagttcg agggcgacac cctggtgaac cgcatcgagc 1980

tgaagggcat cgacttcaag gaggacggca acatcctggg gcacaagctg gagtacaact 2040

acaacagcca caacgtctat atcaccgccg acaagcagaa gaacggcatc aaggccaact 2100

tcaagatccg ccacaacatc gaggacggcg gcgtgcagct cgccgaccac taccagcaga 2160

acaccccat cggcgacggc cccgtgctgc tgcccgacaa ccactacctg agctaccagt 2220

ccaagctgag caaagacccc aacgagaagc gcgatcacat ggtcctgctg gagttcgtga 2280

ccgccgccgg gatcactctc ggcatggacg agctgtacaa gtaagtcgac ggcgcgccgc 2340

ggccgcgaat tcgatatcat aatcaacctc tggattacaa aatttgtgaa agattgactg 2400

gtattcttaa ctatgttgct ccttttacgc tatgtggata cgctgcttta atgcctttgt 2460

atcatgctat tgcttcccgt atggctttca ttttctcctc cttgtataaa tcctggttag 2520

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tgttgggcac tgacaattcc gtggctcgag agatcttcga ctgtgccttc tagttgccag 2640

ccatctgttg tttgcccctc ccccgtgcct tccttgaccc tggaaggtgc cactcccact 2700

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gtcctttcct aataaaatga ggaaattgca tcgcattgtc tgagtaggtg tcattctatt 2760

ctgggggggtg gggtggggca ggacagcaag ggggaggatt gggaagacaa tagcaggcat 2820

gcacgtgcgg accgagcggc cgc 2843

<210> SEQ ID NO 34
<211> LENGTH: 2835
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CN1500 - The portion between L-ITR and R-ITR: positions 142-2976

<400> SEQUENCE: 34

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aactatggat gaacgaaata gacagatcgc tgagataggt gcctcactga ttaagcattg 4860

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cgaactgaga tacctacagc gtgagctatg agaaagcgcc acgcttcccg aagggagaaa 5460

ggcggacagg tatccggtaa gcggcagggt cggaacagga gagcgcacga gggagcttcc 5520

agggggaaac gcctggtatc tttatagtcc tgtcgggttt cgccacctct gacttgagcg 5580

tcgatttttg tgatgctcgt caggggggcg gagcctatgg aaaaacgcca gcaacgcggc 5640

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<210> SEQ ID NO 37
<211> LENGTH: 4780
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CN1244 - The portion between L-ITR and R-ITR:
positions 142-2042

<400> SEQUENCE: 37

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actccatcac taggggttcc tgcggccgca cgcgtatagg taccgagctc tatgcactca 180

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cagtggtttg gcatgcatct ggtgaatttt ttttaacgaa aaattagtgt tggtttcgat 240

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tacttctgca gcctcttcca ttctttttcag cattataatt ttggttaatt ttcaatttta 360

ggtcctacgt ctctgcaatt tgtgtatgaa taacagaata atttccctct tttgtttcgc 420

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acaggtaatt atctttgacg gtaaaaacgc tgtaatcagc gggctacatg aaaaattact 540

ctaattatgg ctgcatttaa gagaatggaa aaaaaccttc ttgtggataa aaaccttaaa 600

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gatcctgggg agctacgaac ccaaagtttc acagtaggga gctcgggctg ggcataaaag 720

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cgccctttga cgttggagtc cacgttcttt aatagtggac tcttgttcca aactggaaca 2580

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gatctcaaca gcggtaagat ccttgagagt tttcgccccg aagaacgttt tccaatgatg 3300

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caactcggtc gccgcataca ctattctcag aatgacttgg ttgagtactc accagtcaca 3420

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<210> SEQ ID NO 38
<211> LENGTH: 4398
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CN1389 - The portion between L-ITR and R-ITR corresponds to positions 142-1897

<400> SEQUENCE: 38

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actccatcac taggggttcc tgcggccgca cgcgttcgcc tttcctgttc ctgaatctaa 180

ataaagatgg ctttttagta ttaaaagtgg aagaaaatta caggtaatta tctttgacgg 240

taaaaacgct gtaatcagcg ggctacatga aaaattactc taattatggc tgcatttaag 300

agaatggacc tgcagggagc tcgggctggg cataaaagtc agggcagagc catctattgc 360

ttacatttgc ttctgggatc cagatctttc gaagctagcg ctaccggtcg ccaccatggt 420

gagcaagggc gaggagctgt tcaccggggt ggtgcccatc ctggtcgagc tggacggcga 480

cgtaaacggc cacaagttca gcgtgtccgg cgagggcgag ggcgatgcca cctacggcaa 540

gctgaccctg aagctgatct gcaccaccgg caagctgccc gtgccctggc ccaccctcgt 600

gaccaccctg ggctacggcg tgcagtgctt cgcccgctac cccgaccaca tgaagcagca 660

cgacttcttc aagtccgcca tgcccgaagg ctacgtccag gagcgcacca tcttcttcaa 720

ggacgacggc aactacaaga cccgcgccga ggtgaagttc gagggcgaca ccctggtgaa 780

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gagctaccag tccaagctga gcaaagaccc caacgagaag cgcgatcaca tggtcctgct 1080

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ccgctgacgc gccctgacgg gcttgtctgc tcccggcatc cgcttacaga caagctgtga 2460

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ggccttttgc tcacatgt 4398

<210> SEQ ID NO 39
<211> LENGTH: 4635
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CN1390 - The portion between L-ITR and R-ITR corresponds to positions 142-1660

<400> SEQUENCE: 39

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aacgctgtaa tcagcgggct acatgaaaaa ttactctaat tatggctgca tttaagagaa 420

tggctaaata aagatggctt tttagtatta aaagtggaag aaaattacag gtaattatct 480

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gaaaaaggaa gagtatgagt attcaacatt tccgtgtcgc ccttattccc ttttttgcgg 3000

cattttgcct tcctgttttt gctcacccag aaacgctggt gaaagtaaaa gatgctgaag 3060

atcagttggg tgcacgagtg ggttacatcg aactggatct caacagcggt aagatccttg 3120

agagttttcg ccccgaagaa cgttttccaa tgatgagcac ttttaaagtt ctgctatgtg 3180

gcgcggtatt atcccgtatt gacgccgggc aagagcaact cggtcgccgc atacactatt 3240

ctcagaatga cttggttgag tactcaccag tcacagaaaa gcatcttacg gatggcatga 3300

cagtaagaga attatgcagt gctgccataa ccatgagtga taacactgcg gccaacttac 3360

ttctgacaac gatcggagga ccgaaggagc taaccgcttt tttgcacaac atgggggatc 3420

atgtaactcg ccttgatcgt tgggaaccgg agctgaatga agccatacca aacgacgagc 3480

gtgacaccac gatgcctgta gcaatggcaa caacgttgcg caaactatta actggcgaac 3540

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ctctttttcc gaaggtaact ggcttcagca gagcgcagat accaaatact gtccttctag   4140

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cttttgctca catgt                                                    4635


<210> SEQ ID NO 40
<211> LENGTH: 4841
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CN1203 - The portion between L-ITR and R-ITR
      corresponds to positions 183-2052

<400> SEQUENCE: 40

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agcgcgcaga gagggagtgg ccaactccat cactaggggt tcctggaggg gtggagtcgt    180

gacctaggac gcgtataggt accgagctct atgcactcac agtggtttgg catgcatctg    240

gtgaattttt tttaacgaaa aattagtgtt ggtttcgatg tatggtagca ttctccctaa    300

cgtaatttga ataattcagc aaagccccac taccagctgt acttctgcag cctcttccat    360

tcttttcagc attataattt tggttaattt tcaattttag gtcctacgtc tctgcaattt    420

gtgtatgaat aacagaataa tttccctctt ttgtttcgcc tttcctgttc ctgaatctaa    480

ataaagatgg ctttttagta ttaaaagtgg aagaaaatta caggtaatta tctttgacgg    540

taaaaacgct gtaatcagcg ggctacatga aaaattactc taattatggc tgcatttaag    600

agaatggaaa aaaaccttct tgtggataaa aaccttaaat tgtccccaat gtctgcttca    660

aattggatgg cactgcagct ggaggctttg ttcagaattg atcctgggga gctacgaacc    720

caaagtttca cagtagggag ctcgggctgg gcataaaagt cagggcagag ccatctattg    780

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tcaaggccaa cttcaagatc cgccacaaca tcgaggacgg cggcgtgcag ctcgccgacc 1380

actaccagca gaacaccccc atcggcgacg gccccgtgct gctgcccgac aaccactacc 1440

tgagctacca gtccaagctg agcaaagacc ccaacgagaa gcgcgatcac atggtcctgc 1500

tggagttcgt gaccgccgcc gggatcactc tcggcatgga cgagctgtac aagtaagtcg 1560

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gccagccatc tgttgtttgc ccctcccccg tgccttcctt gaccctggaa ggtgccactc 1920

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cacaacatgg gggatcatgt aactcgcctt gatcgttggg aaccggagct gaatgaagcc 3300

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gcggataaag ttgcaggacc acttctgcgc tcggcccttc cggctggctg gtttattgct 3480

gataaatctg gagccggtga gcgtgggtct cgcggtatca ttgcagcact ggggccagat 3540

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aacagctatg accatgatta cgccaagctc tcgagatcta g 4841

<210> SEQ ID NO 41
<211> LENGTH: 4680
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CN1180 - The portion between L-ITR and R-ITR corresponds to positions 183-1891

<400> SEQUENCE: 41

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agcgcgcaga gagggagtgg ccaactccat cactaggggt tcctggaggg gtggagtcgt 180

gacctaggac gcgtcagctg caaacccaag agggtcagca tcatttcact gtattctctt 240

cttgattaca agccgggccc atcaaacaca acataattac agtaatttca ggtttattta 300

ttctaatgca gtttccccat ctctctggta attatgagca atttttcgc ccagggaatc 360

tttttgcatt aacaaaagag ataacgcact gaaagccaaa tttgctgtgc attgagaaaa 420

ggaaaaaaaa aaatcaaata ggtgcgagct gccatctctg caattctctg gtaccggagc 480

cggcaaattg cttgcaggtg tatggagcaa gcttgtcaat ggccaggcct ccaaattagc 540

aaatgcacag cagcaaagta atgaagacag gagctcgggc tgggcataaa agtcagggca 600

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gagctggacg gcgacgtaaa cggccacaag ttcagcgtgt ccggcgaggg cgagggcgat 780

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attaatagac tggatggagg cggataaagt tgcaggacca cttctgcgct cggcccttcc 3300

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<210> SEQ ID NO 42
<211> LENGTH: 4761
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CN2001 - The portion between L-ITR and R-ITR
corresponds to positions 142-2023

<400> SEQUENCE: 42

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actccatcac taggggttcc tgcggccgca cgcgtggtac cctaaataaa gatggctttt 180

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cagcgggcta catgaaaaat tactctaatt atggctgcat ttaagagaat ggctaaataa 300

agatggcttt ttagtattaa aagtggaaga aaattacagg taattatctt tgacggtaaa 360

aacgctgtaa tcagcgggct acatgaaaaa ttactctaat tatggctgca tttaagagaa 420

tggctaaata aagatggctt tttagtatta aaagtggaag aaaattacag gtaattatct 480

ttgacggtaa aaacgctgta atcagcgggc tacatgaaaa attactctaa ttatggctgc 540

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gccgaacagc aagtcccacc cctcgtggcg ctcgcccaac gcatagtatt tcacaaggcg 720

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gtgccactcc cactgtcctt tcctaataaa atgaggaaat tgcatcgcat tgtctgagta 1920

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atggttcacg tagtgggcca tcgccctgat agacggtttt tcgccctttg acgttggagt 2520

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gctattcttt tgatttataa gggattttgc cgatttcggc ctattggtta aaaaatgagc 2640

tgatttaaca aaaatttaac gcgaatttta acaaaatatt aacgtttaca attttatggt 2700

gcactctcag tacaatctgc tctgatgccg catagttaag ccagccccga cacccgccaa 2760

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atagtcctgt cgggtttcgc cacctctgac ttgagcgtcg atttttgtga tgctcgtcag 4680

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<210> SEQ ID NO 43
<211> LENGTH: 4732
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CN2002 - The portion between L-ITR and R-ITR corresponds to positions 142-1993

<400> SEQUENCE: 43

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actccatcac taggggttcc tgcggccgca cgcgtggtac cctaaataaa gatggctttt 180

tagtattaaa agtggaagaa aattacaggt aattatcttt gacggtaaaa acgctgtaat 240

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agatggcttt ttagtattaa aagtggaaga aaattacagg taattatctt tgacggtaaa 360

aacgctgtaa tcagcgggct acatgaaaaa ttactctaat tatggctgca tttaagagaa 420

tggctaaata aagatggctt tttagtatta aaagtggaag aaaattacag gtaattatct 480

ttgacggtaa aaacgctgta atcagcgggc tacatgaaaa attactctaa ttatggctgc 540

atttaagaga atggagctcg ggctgggcat aaaagtcagg gcagagccat ctattgctta 600

catttgcttc tgggatccag atctttcgaa gctagcgcta ccaccatgag ccggaagatc 660

agagatctta tcgaatctaa gagatttcag aatgttatta ccgcgataat cgtactcaac 720

ggggcggtgc tcggtctcct caccgatacc acattgagcg cttctagcca gaacctgctc 780

gaaagggttg accaactgtg cctgacaatt tttatcgtgg aaattagctt gaaaatttac 840

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aaggagcaag aagaagaggc taaaactggc caccaccaag agccaatttc tcaaaccctc 1380

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ccgggcaaga gcaactcggt cgccgcatac actattctca gaatgacttg gttgagtact 3360

caccagtcac agaaaagcat cttacggatg gcatgacagt aagagaatta tgcagtgctg 3420

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aggagctaac cgcttttttg cacaacatgg gggatcatgt aactcgcctt gatcgttggg 3540

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cttgagatcc ttttttttctg cgcgtaatct gctgcttgca aacaaaaaaa ccaccgctac 4140

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tcaagaactc tgtagcaccg cctacatacc tcgctctgct aatcctgtta ccagtggctg 4320

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ttgagcgtcg atttttgtga tgctcgtcag gggggcggag cctatggaaa aacgccagca 4680

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<210> SEQ ID NO 44
<211> LENGTH: 4794
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CN2003 - The portion between L-ITR and R-ITR corresponds to positions 142-2056

<400> SEQUENCE: 44

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actccatcac taggggttcc tgcggccgca cgcgtggtac cctaaataaa gatggctttt 180

tagtattaaa agtggaagaa aattacaggt aattatcttt gacggtaaaa acgctgtaat 240

cagcgggcta catgaaaaat tactctaatt atggctgcat ttaagagaat ggctaaataa 300

agatggcttt ttagtattaa aagtggaaga aaattacagg taattatctt tgacggtaaa 360

aacgctgtaa tcagcgggct acatgaaaaa ttactctaat tatggctgca tttaagagaa 420

tggctaaata aagatggctt tttagtatta aaagtggaag aaaattacag gtaattatct 480

ttgacggtaa aaacgctgta atcagcgggc tacatgaaaa attactctaa ttatggctgc 540

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catttgcttc tgggatccag atctttcgaa gctagcgcta ccaccatgtc tacgtccctt 660

ttgaatgcgc ctaccggcct tcaagctaga gtcattaatc tcgtcgaaca aaactggttt 720

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gccatcatag tgaatactat gcagacattc tctgacgagg aacatgctct ggagcgagag 1380

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caagataaac agatcttgga acaggagcag agacaaatgc acgaggaact gaaggccatt 1440

cgactcgagc ttcagcaact ccaaaccctt ttgcgaaatg cggctgggga ctcctccaat 1500

gtctccacaa agggcaatat cggctcagac taatgacggc gcgccgcggc cgcgaattcg 1560

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cggaccgagc ggccgcagga acccctagtg atggagttgg ccactccctc tctgcgcgct 2100

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gacttgagcg tcgatttttg tgatgctcgt caggggggcg gagcctatgg aaaaacgcca 4740

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<210> SEQ ID NO 45
<211> LENGTH: 7368
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CN1504 - The portion between L-ITR and R-ITR corresponds to positions 142-4489

<400> SEQUENCE: 45

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actccatcac taggggttcc tgcggccgca cgcgtggtac cctaaataaa gatggctttt 180

tagtattaaa agtggaagaa aattacaggt aattatcttt gacggtaaaa acgctgtaat 240

cagcgggcta catgaaaaat tactctaatt atggctgcat ttaagagaat ggctaaataa 300

agatggcttt ttagtattaa aagtggaaga aaattacagg taattatctt tgacggtaaa 360

aacgctgtaa tcagcgggct acatgaaaaa ttactctaat tatggctgca tttaagagaa 420

tggctaaata aagatggctt tttagtatta aaagtggaag aaaattacag gtaattatct 480

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<210> SEQ ID NO 47
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<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CN2004 - The portion between L-ITR and R-ITR
      corresponds to positions 142-3792

<400> SEQUENCE: 47

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<220> FEATURE:
<223> OTHER INFORMATION: CN2005 - The portion between L-ITR and R-ITR corresponds to positions 142-4160

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<210> SEQ ID NO 51
<211> LENGTH: 6733
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CN2008 - The portion between L-ITR and R-ITR corresponds to positions 142-3995

<400> SEQUENCE: 51

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<210> SEQ ID NO 52
<211> LENGTH: 7263
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CN2009 - The portion between L-ITR and R-ITR corresponds to positions 142-4525

<400> SEQUENCE: 52

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Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
35 40 45

Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
50 55 60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65 70 75 80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
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Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
100 105 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro
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Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
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Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
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Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
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Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
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Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
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385                 390                 395                 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
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Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
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Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
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Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
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Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
545                 550                 555                 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
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Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
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                645                 650                 655

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
            660                 665                 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
        675                 680                 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn
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Tyr Tyr Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Glu Gly Val
705                 710                 715                 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
                725                 730                 735
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1. A method of treating Dravet Syndrome in a subject in need thereof comprising intravenously administering a therapeutically effective amount of at least two adeno-associated viral (AAV) vectors wherein each viral vector comprises an expression construct comprising

(i) an enhancer consisting of SEQ ID NO: 3;

(ii) a promoter; and

(iii) a coding sequence that results in expression of a fragment of human SCN1A wherein the AAV vectors are associated with a capsid that crosses the blood brain barrier, and wherein the human SCN1A fragments encoded by the coding sequences are expressed selectively within inhibitory GABAergic interneurons and result in rescue of Nav1.1 channel function within inhibitory GABAergic interneurons in need thereof following the intravenous administering

thereby treating Dravet Syndrome in the subject in need thereof.

2. The method of claim **1**, wherein the viral vectors comprise SEQ ID NO: 47 and SEQ ID NO: 48; SEQ ID NO: 49 and SEQ ID NO: 50; or SEQ ID NO: 51 and SEQ ID NO: 52.

3. The method of claim **1**, wherein the viral vectors comprise SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, and SEQ ID NO: 61.

4. An expression construct comprising (i) an enhancer consisting of SEQ ID NO: 3; (ii) a promoter; and (iii) a coding sequence encoding a protein that rescues voltage-gated sodium channel function in a cell or subject in need thereof.

5. The expression construct of claim **4**, wherein the coding sequence comprises NavSheP-D60N, NavBp, NavMs, 3×HA-NavSheP-D60N, 3×HA-NavBp, 3×HA-NavMs, His-NavMs, human SCN1A, mouse Scn1a, human SCN1A-3×HA, and/or mouse Scn1a-3×HA.

6. The expression construct of claim **4**, wherein the promoter comprises minBglobin or minCMV.

7. The expression construct of claim **4**, wherein the expression construct is within an adeno-associated viral (AAV) vector.

8. The expression construct of claim **4**, wherein the expression construct comprises a coding sequence for a reporter protein.

9. The expression construct of claim **8**, wherein the reporter protein comprises a fluorescent reporter protein.

10. The expression construct of claim **4**, wherein the expression construct comprises or encodes a skipping element.

11. The expression construct of claim **10**, wherein the skipping element comprises a 2A peptide or an internal ribosome entry site (IRES).

12. The expression construct of claim **11**, wherein the 2A peptide comprises T2A, P2A, E2A, and/or F2A.

13. The expression construct of claim **7**, wherein the construct comprises the elements of CN1367, CN1244, CN1389, CN1390, CN1180, CN1203, CN1498, CN1499, CN1500, CN2001, CN2002, CN2003, CN1504 and CN1512, CN2004 and CN2005, CN2006 and CN2007, or CN2008 and CN2009.

14. The expression construct of claim **7**, wherein the construct comprises SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, and/or SEQ ID NO: 52.

15. The expression construct of claim **7**, wherein the construct comprises SEQ ID NO: 45 and SEQ ID NO: 46, SEQ ID NO: 47 and SEQ ID NO: 48, SEQ ID NO: 49 and SEQ ID NO: 50, or SEQ ID NO: 51, and SEQ ID NO: 52.

16. The expression construct of claim **7**, wherein the AAV vector is associated with a capsid that crosses the blood brain barrier.

17. The expression construct of claim **16**, wherein the capsid comprises PHP.Eb.

18. The expression construct of claim **16**, wherein the capsid comprises SEQ ID NO: 53.

19. The expression construct of claim **16**, wherein the capsid comprises AAV9 capsid with a SEQ ID NO: 54 or SEQ ID NO: 55 insert.

20. The expression construct of claim **16**, wherein the capsid comprises AAV2 capsid with a SEQ ID NO: 56 insert.

21. A composition comprising the expression construct of claim **4**.

22. A cell comprising the expression construct of claim **4**.

23. A non-human animal comprising the expression construct of claim **4**.

24. A kit comprising the expression construct of claim **4**.

25. A method of rescuing voltage-gated sodium channel function in a defective cell in need thereof comprising administering a therapeutically effective amount of a composition of claim **21** to the cell.

26. A method of rescuing voltage-gated sodium channel function in a subject in need thereof comprising administering a therapeutically effective amount of a composition of claim **21** to the subject.

27. The method of claim **26**, wherein the subject is in need thereof due to a diagnosis of epilepsy, an SCN1A-related seizure disorder, simple febrile seizures (FS), generalized epilepsy with febrile seizures plus (GEFS+), Dravet Syndrome (DS), intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC), intractable infantile partial seizures, myoclonic-astatic epilepsy, Lennox-Gastaut syndrome (LGS), or infantile spasms.

28. The method of claim **26**, wherein the subject is a pediatric patient.

29. The method of claim **26**, wherein the subject is less than 4 years old.

30. The method of claim **26**, wherein the subject is a transgenic $Scn1a^{+/-}$ mouse undergoing a temperature-induced febrile seizure test.

31. The method of claim **26**, wherein the composition is administered intravenously.

32. The method of claim **26**, wherein the composition is administered intrathecally into cerebrospinal fluid, via the lateral ventricles or cisterna magna or lumbar space or cannula into the foramen magnum.

33. An expression construct comprising:

(a) a non-naturally occurring enhancer sequence; and

(b) a nucleic acid encoding a protein that rescues voltage-gated sodium channel function;

wherein the enhancer sequence:

(i) consists of the sequence of SEQ ID NO: 3;

(ii) comprises two or more copies of SEQ ID NO: 2 arranged in tandem;

(iii) comprises a sequence having at least 90% sequence identity with SEQ ID NO: 3 and maintaining interneuron-specific enhancer function; or

(iv) a sequence the complementary strand of which is capable of hybridizing to the sequence of (i), (ii), or (iii); and

wherein the enhancer promotes the transcription of the nucleic acid selectively within inhibitory neurons following administration to a sample or subject.

34. The expression construct of claim **33**, wherein nucleic acid is selected from NavSheP-D60N, NavBp, NavMs, 3×HA-NavSheP-D60N, 3×HA-NavBp, 3×HA-NavMs, His-NavMs, human SCN1A, mouse Scn1a, human SCN1A-3×HA, or mouse Scn1a-3×HA.

35. The expression construct of claim **33**, comprising a promoter comprising minBglobin or minCMV.

36. The expression construct of claim **33**, wherein the expression construct is within an adeno-associated viral (AAV) vector.

37. The expression construct of claim **33**, wherein the expression construct comprises a nucleic acid encoding a reporter protein.

38. The expression construct of claim **37**, wherein the reporter protein comprises a fluorescent reporter protein.

39. The expression construct of claim **33**, wherein the expression construct comprises or encodes a skipping element.

40. The expression construct of claim **39**, wherein the skipping element comprises a 2A peptide or an internal ribosome entry site (IRES).

41. The expression construct of claim **40**, wherein the 2A peptide comprises T2A, P2A, E2A, and/or F2A.

42. The expression construct of claim **36**, wherein the construct comprises the elements of CN1367, CN1244, CN1389, CN1390, CN1180, CN1203, CN1498, CN1499, CN1500, CN2001, CN2002, CN2003, CN1504 and CN1512, CN2004 and CN2005, CN2006 and CN2007, or CN2008 and CN2009.

43. The expression construct of claim **36**, wherein the construct comprises SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, (Original) SEQ ID NO: 51, and/or SEQ ID NO: 52.

44. The expression construct of claim **36**, wherein the construct comprises SEQ ID NO: 45 and SEQ ID NO: 46, SEQ ID NO: 47 and SEQ ID NO: 48, SEQ ID NO: 49 and SEQ ID NO: 50, or SEQ ID NO: 51, and SEQ ID NO: 52

45. The expression construct of claim **36**, wherein the AAV vector is associated with a capsid that crosses the blood brain barrier.

46. The expression construct of claim **45**, wherein the capsid comprises PHP.Eb.

47. The expression construct of claim **45**, wherein the capsid comprises SEQ ID NO: 53.

48. The expression construct of claim **45**, wherein the capsid comprises AAV9 capsid with a SEQ ID NO: 54 or SEQ ID NO: 55 insert.

49. The expression construct of claim **45**, wherein the capsid comprises AAV2 capsid with a SEQ ID NO: 56 insert.

50. A composition comprising the expression construct of claim **33**.

51. A cell comprising the expression construct of claim **33**.

52. A non-human animal comprising the expression construct of claim **33**.

53. A kit comprising the expression construct of claim **33**.

54. A method of rescuing voltage-gated sodium channel function in a defective cell in need thereof comprising administering a therapeutically effective amount of a composition of claim **50** to the cell.

55. A method of rescuing voltage-gated sodium channel function in a subject in need thereof comprising administering a therapeutically effective amount of a composition of claim **50** to the subject.

56. The method of claim **55**, wherein the subject is need thereof due to a diagnosis of epilepsy, an SCN1A-related seizure disorder, simple febrile seizures (FS), generalized epilepsy with febrile seizures plus (GEFS+), Dravet Syndrome (DS), intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC), intractable infantile partial

seizures, myoclonic-astatic epilepsy, Lennox-Gastaut syndrome (LGS), or infantile spasms.

57. The method of claim **55**, wherein the subject is a pediatric patient.

58. The method of claim **55**, wherein the subject is less than 4 years old.

59. The method of claim **55**, wherein the subject is a transgenic Scn1a$^{+/-}$ mouse undergoing a temperature-induced febrile seizure test.

60. The method of claim **55**, wherein the composition is administered intravenously.

61. The method of claim **55**, wherein the composition is administered intrathecally into cerebrospinal fluid, via the lateral ventricles or cisterna magna or lumbar space or cannula into the foramen magnum.

62. A vector system comprising two AAV vectors wherein the first vector encodes the N-terminal portion of a protein that rescues voltage-gated sodium channel activity in a cell in need thereof, and the second vector encodes the C-terminal portion of the protein, wherein the portion of the gene encoded by the two vectors overlaps to provide a region of homology for homologous recombination to produce the full-length Nav1.1 protein, and wherein the first vector comprises a promoter and an enhancer that consists of SEQ ID NO: 3 but does not comprise a termination signal or a polyA signal and the second vector comprises a termination signal and a polyA signal but does not comprise a promoter or an enhancer.

63. The vector system of claim **62**, wherein the protein comprises human SCN1A.

64. The vector system of claim **62**, wherein the region of homology is 75-1000 base pairs.

65. The vector system of claim **62**, wherein the region of homology is 550-650 base pairs.

66. The vector system of claim **62**, wherein the vectors selectively express the protein in inhibitory neurons.

67. The vector system of claim **62**, wherein the region of homology further comprises an intron element with a splice donor site on the first vector and a splice acceptor site on the second vector, so that trans-splicing across the homologous region drives more efficient full-length protein reconstitution following recombination.

68. The vector system of claim **62**, wherein the vector system comprises the elements of CN1504, CN1512, CN2004, CN2005, CN2006, CN2007, CN2008, and/or CN2009.

69. The vector system of claim **62**, wherein the vector system comprises the elements of CN1504 and CN1512, CN2004 and CN2005, CN2006 and CN2007, or CN2008 and CN2009.

70. The vector system of claim **62**, wherein the vector system comprises SEQ ID NO: 45 and SEQ ID NO: 46, SEQ ID NO: 47 and SEQ ID NO: 48, SEQ ID NO: 49 and SEQ ID NO: 50, or SEQ ID NO: 51, and SEQ ID NO: 52.

71. A viral vector comprising SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, or SEQ ID NO: 52.

* * * * *