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(54) VIRAL VECTORS FOR TREATING PARKINSON'S DISEASE

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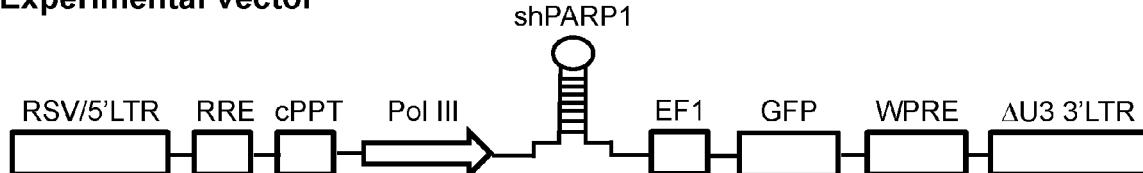
CPC *A61K 35/76* (2013.01); *A61K 31/7105* (2013.01); *A61K 45/06* (2013.01); *C12N 9/1077* (2013.01); *C12N 15/86* (2013.01); *C12N 15/1137* (2013.01)

(57) ABSTRACT

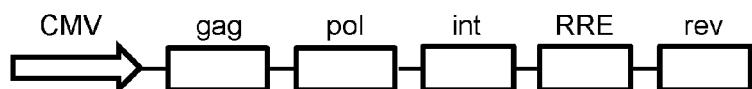
A lentiviral vector system for expressing a lentiviral particle is disclosed. The lentiviral vector system includes a therapeutic vector, an envelope plasmid, and at least one helper plasmid. The lentiviral vector system can produce a lentiviral particle for inhibiting PARP expression in neuron cells of a subject afflicted with Parkinson's disease.

Specification includes a Sequence Listing.

Experimental Vector



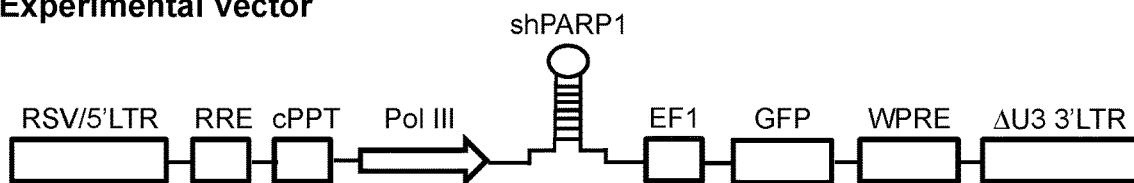
Helper Plasmid



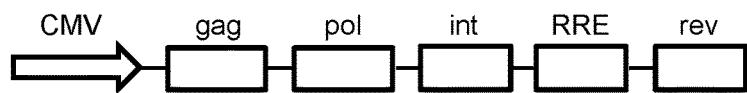
Envelope Plasmid



Experimental Vector



Helper Plasmid



Envelope Plasmid

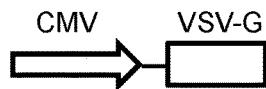


FIG. 1A

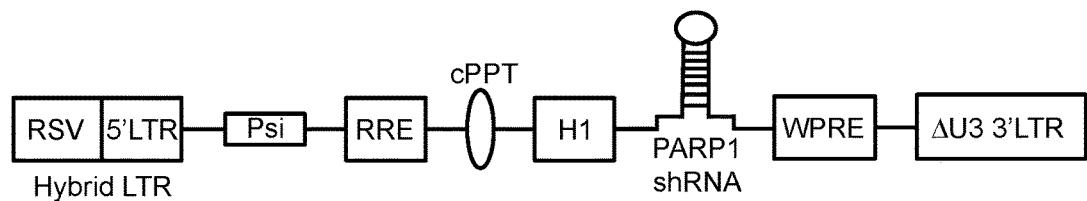
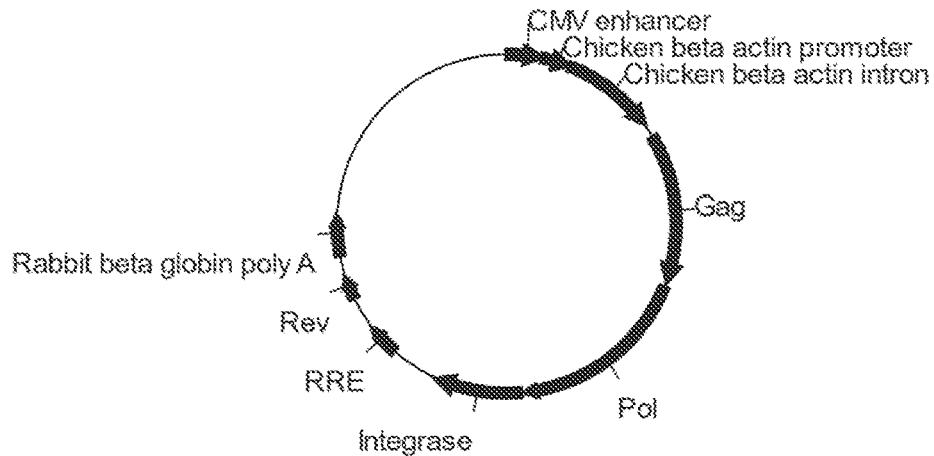
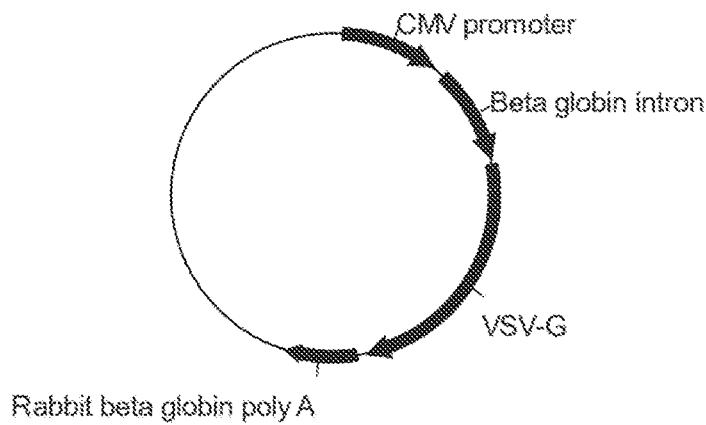
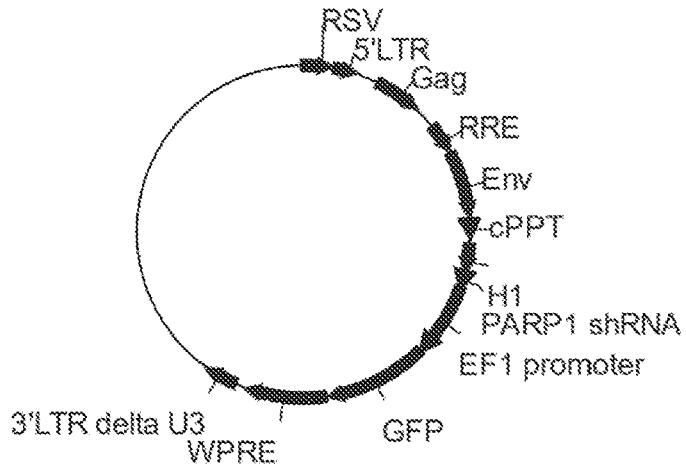
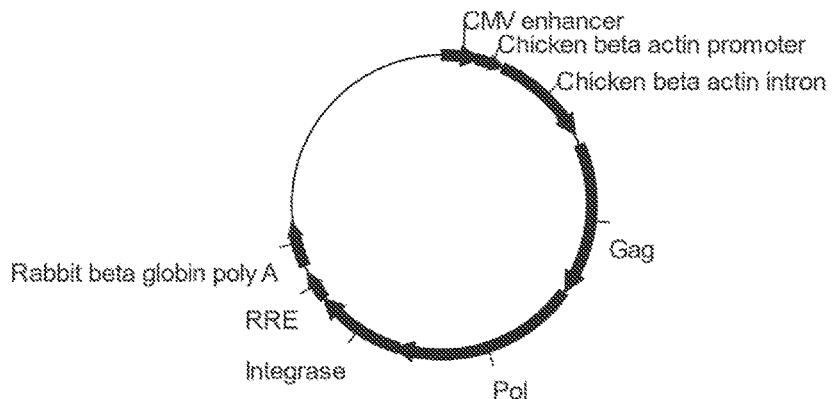


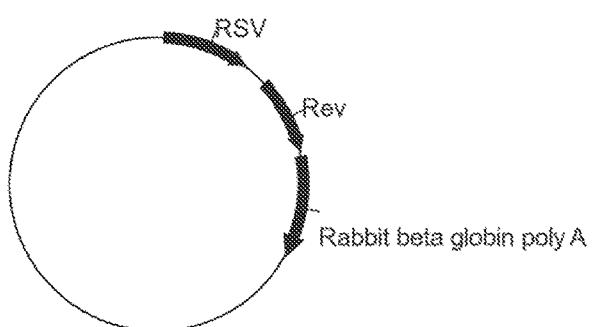
FIG. 1B

AGT Helper plus Rev plasmid**AGT Envelope plasmid****Lentiviral vector expressing PARP1 shRNA and GFP****FIG. 1C**

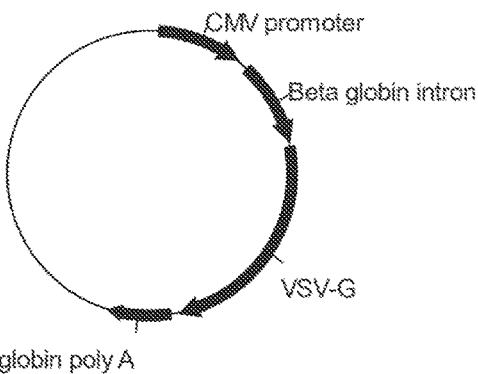
AGT Helper plasmid



AGT Rev plasmid



AGT Envelope plasmid



Lentiviral vector expressing PARP1 shRNA and GFP

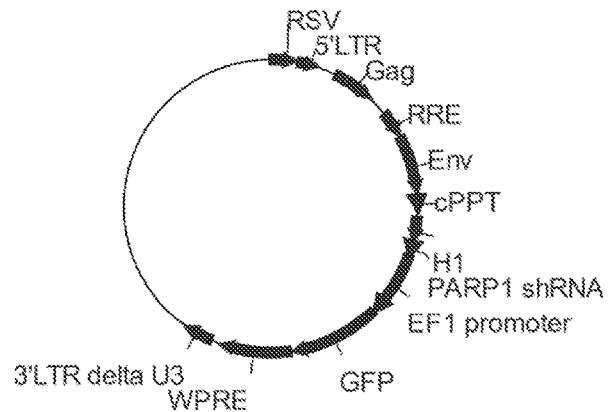
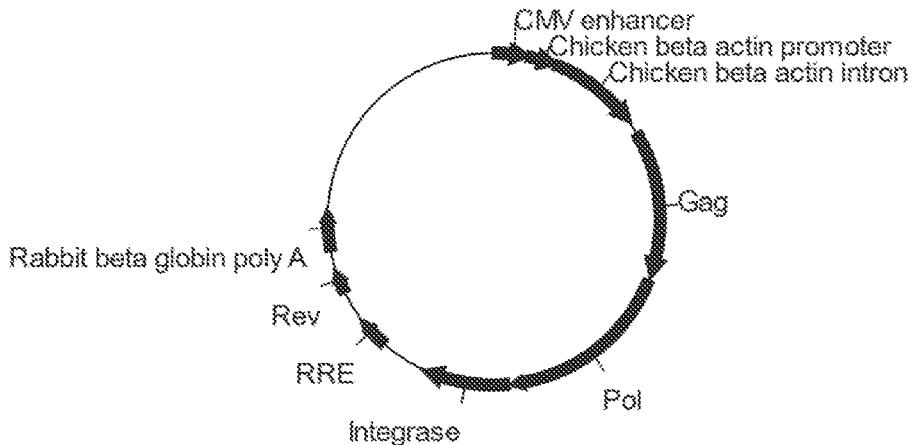
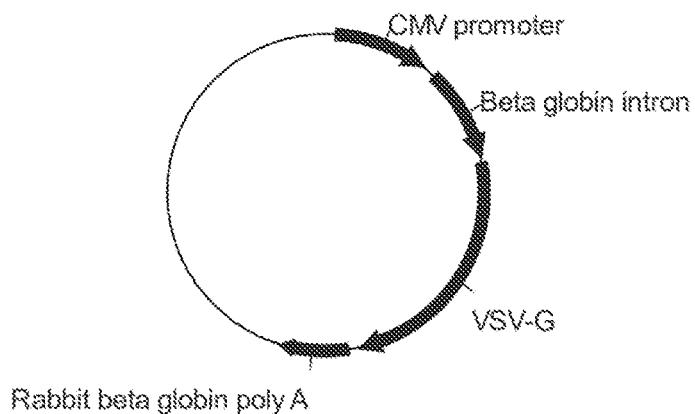


FIG. 1D

AGT Helper plus Rev plasmid



AGT Envelope plasmid



Lentiviral vector expressing PARP1 shRNA

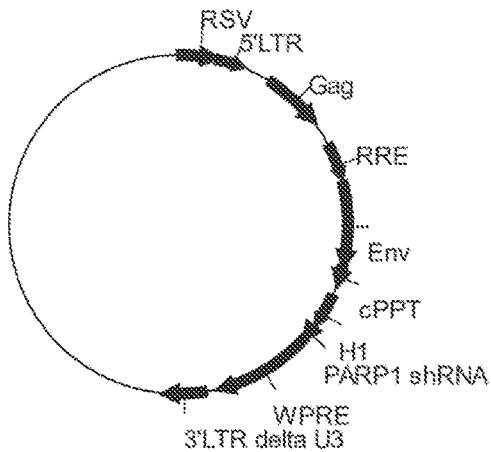
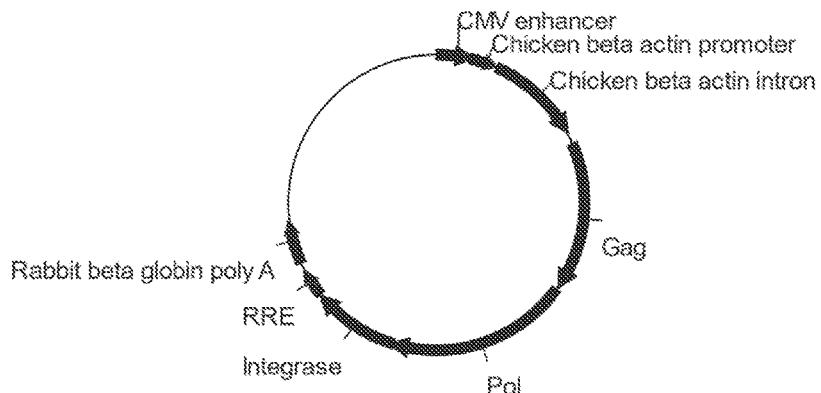
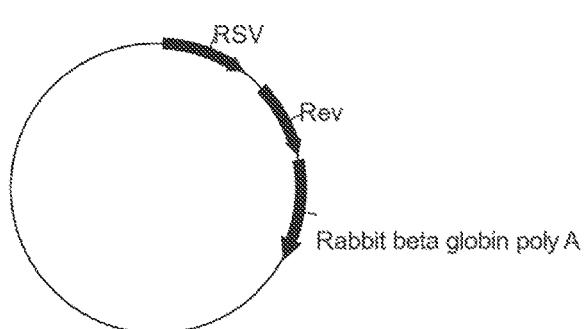


FIG. 1E

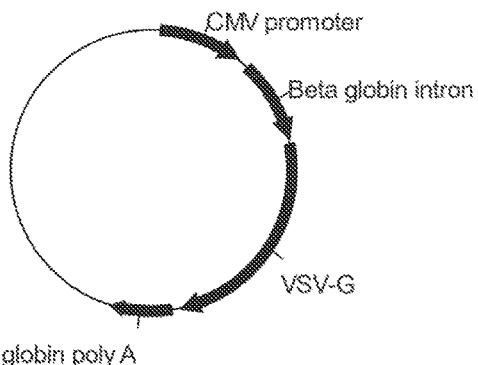
AGT Helper plasmid



AGT Rev plasmid



AGT Envelope plasmid



Lentiviral vector expressing PARP1 shRNA

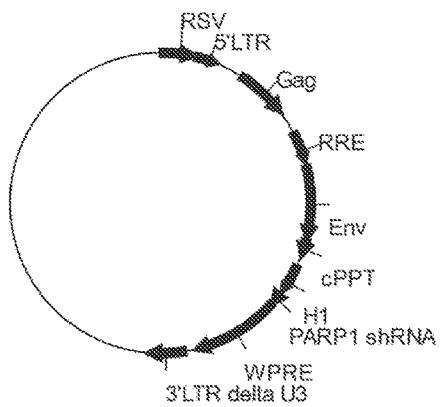


FIG. 1F

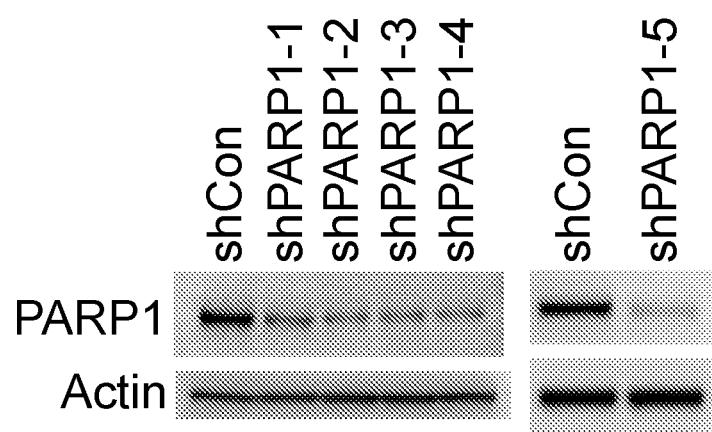


FIG. 2

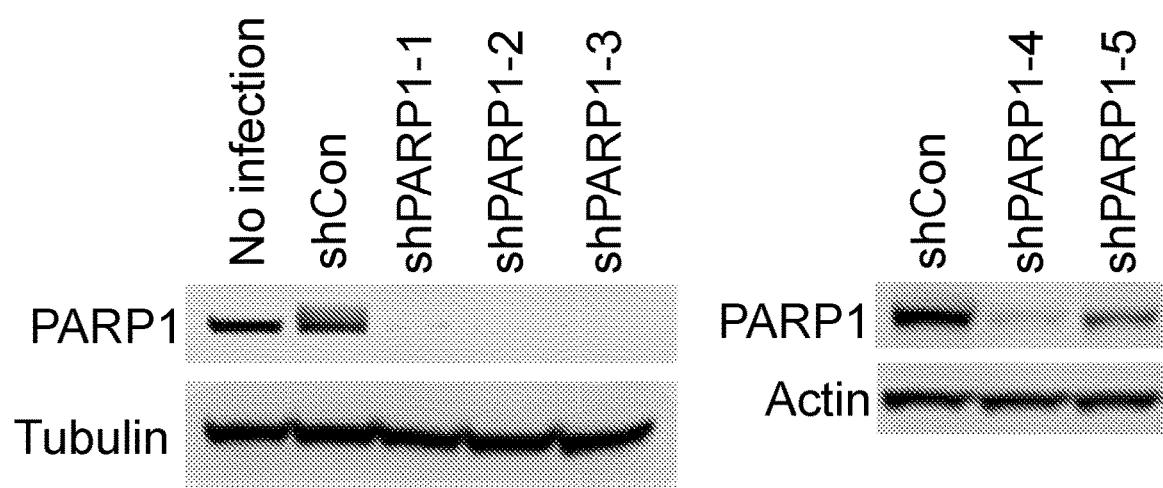


FIG. 3

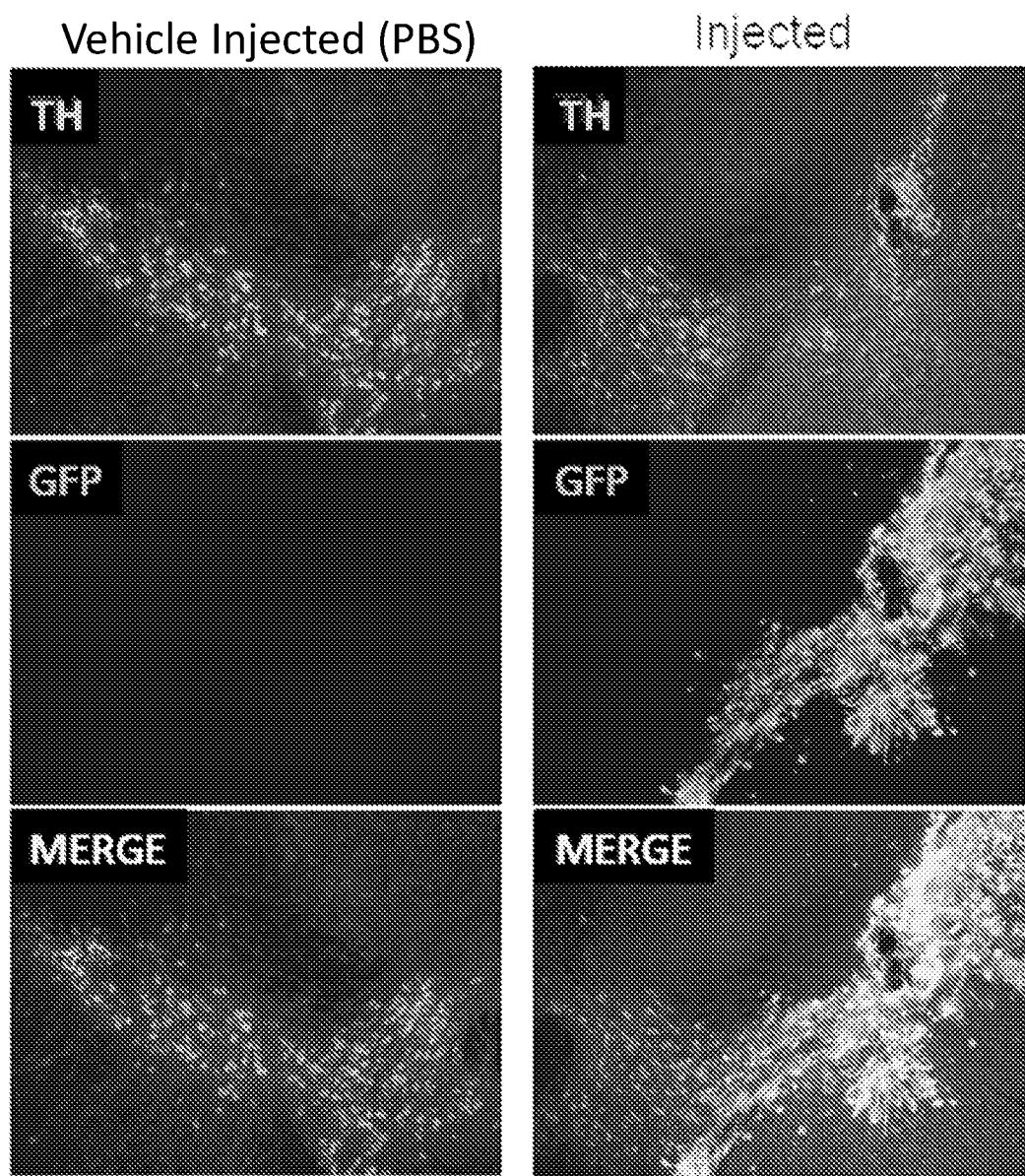


FIG. 4

VIRAL VECTORS FOR TREATING PARKINSON'S DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to: U.S. Provisional Patent Application No. 62/365,316 filed on Jul. 21, 2016 entitled "VIRAL VECTORS FOR TREATING PARKINSON'S DISEASE", the disclosure of which is incorporated herein by reference.

FIELD

[0002] Aspects of the invention relate to using vectors to treat Parkinson's disease. More specifically, aspects of the invention relate to using lentiviral vectors, including PARP-containing lentiviral vectors, to treat Parkinson's disease.

BACKGROUND

[0003] Parkinson's disease ("PD") is the second most common neurodegenerative disorder in the United States. Approximately 1 million Americans are afflicted with PD, with more than 60,000 new cases diagnosed each year. See, e.g., Fahn, S., 991 *Ann. N.Y. Acad. Sci.* 1-14 (2003). The incidence is expected to double by 2030. See, e.g., Dorsey, E. R., et al., 68(5) *Neurology*, 384-6 (2007). PD is a chronic progressive condition that generally appears late in life. PD is caused by the degeneration and death of dopamine producing neurons in the substantia nigra region of the basal ganglia. The deteriorated neurons and reduced dopamine result in abnormal neural activity and a chronic, progressive deterioration of motor function control. Patients with PD suffer from significant quality-of-life issues due to symptoms that include bradykinesia, rigidity, tremor, and postural instability. Additional complications due to PD include non-motor symptoms, such as dysphagia, and neuropsychiatric effects. See, e.g., Weintraub, D. et al., 14(2 Suppl) *Am. J Manag. Care*, S40-8 (2008).

[0004] PD can be treated with L-DOPA or dopamine agonists, but there are significant side effects and the continuous neuronal death results in an increasing requirement for L-DOPA or dopamine agonists. Gene therapy has the potential to modify the behavior of neurons in the substantia nigra. Consequently, gene therapy has been considered as a possibility for effectively treating PD.

[0005] Initial clinical studies on PD gene therapy attempted to increase dopamine production in the substantia nigra by elevating the level of dopamine-synthesizing enzymes, particularly aromatic L-amino acid decarboxylase (AADC). Adeno-associated viral vectors (AAV) carrying the complementary DNA sequence for AADC were injected into the substantia nigra of patients afflicted with PD. In one study, delivery of AADC using adeno-associated virus (AAV) was well tolerated, but the clinical outcomes trended to only modest improvement. See, e.g., Eberling et al., 70(21) *Neurology*, 1989-93 (2008). After longer (e.g., 4-year) follow-up, the clinical impact was largely lost, and it was concluded that the dosing was insufficient for sustained clinical improvement.

[0006] An alternate approach sought to treat PD using gene therapy to increase expression of neurturin, a neurotrophic growth factor, in the substantia nigra. Results from AAV delivery of the neurturin gene to the brains of patients

afflicted with PD showed no improvement over sham controls. See, e.g., Marks Jr. et al., 9(12) *Lancet Neurol.*, 1164-72 (2010).

[0007] Gene therapy trials designed to increase dopamine production or provide neurotrophic growth factors have not provided a significant, durable objective clinical response in patients with PD. See, e.g., Eberling et al., supra. Part of the reason why treatment for PD is complex and challenging is that disease progression is due to the accelerated death of dopaminergic neurons that eventually reduces dopamine below survivable levels.

[0008] Accordingly, current treatments for PD symptoms include drugs, ablative surgical intervention, and neural stimulation.

SUMMARY

[0009] In an aspect of the present disclosure, a lentiviral vector system is provided for expressing a lentiviral particle. The system includes a therapeutic vector which encodes a short hairpin RNA ("shRNA") for inhibiting Poly(ADP-ribose) polymerase ("PARP") expression. The system also includes an envelope plasmid comprising a neuron-specific sequence for targeting the shRNA to a neuron; and at least one helper plasmid comprising gag, pol, and rev genes. When the therapeutic vector, the envelope plasmid, and the at least one helper plasmid are transfected into a packaging cell line, a neuron-specific lentiviral particle optimized for inhibiting PARP expression is produced by the packaging cell line.

[0010] In embodiments, the shRNA comprises a PARP-specific shRNA. In embodiments, the shRNA comprises a PARP1-specific shRNA. In embodiments, the shRNA comprises at least 80% sequence identity with any one of SEQ ID NOs: 6-10. In embodiments, the shRNA comprises a shRNA having at least 85% sequence identity with any one of SEQ ID NOs: 6-10. In embodiments, the shRNA comprises a shRNA having at least 90% sequence identity with any one of SEQ ID NOs: 6-10. In embodiments, the shRNA comprises a shRNA having at least 95% sequence identity with any one of SEQ ID NOs: 6-10. In embodiments, the shRNA comprises any one of SEQ ID NOs: 6-10.

[0011] In embodiments, the shRNA comprises a shRNA having at least 80% sequence identity with any one of SEQ ID NOs: 16-20. In embodiments, the shRNA comprises a shRNA having at least 85% sequence identity with any one of SEQ ID NOs: 16-20. In embodiments, the shRNA comprises a shRNA having at least 90% sequence identity with any one of SEQ ID NOs: 16-20. In embodiments, the shRNA comprises a shRNA having at least 95% sequence identity with any one of SEQ ID NOs: 16-20. In embodiments, the shRNA comprises any one of SEQ ID NOs: 16-20. In embodiments, the neuron-specific sequence encodes VSV-G, FUG-C, or gp64, or a variant thereof. Optionally, the neuron-specific sequence encodes only VSV-G, or a variant thereof. The neuron-specific sequence may encode a protein that improves transduction into a neuron. The neuron-specific sequence may encode a protein that improves transduction into a neuron expressing tyrosine hydroxylase (TH+).

[0012] In another aspect, a method of treating a subject suffering from Parkinson's disease is disclosed. The method involves administering to the subject a therapeutic vector comprising a shRNA for inhibiting PARP expression; an envelope plasmid comprising a neuron-specific sequence for

targeting the shRNA to a neuron; and at least one helper plasmid comprising gag, pol, and rev genes. When the therapeutic vector, the envelope plasmid, and the at least one helper plasmid are transfected into at least one packaging cell, a neuron-specific lentiviral particle optimized for inhibiting PARP expression is produced by the packaging cell, and lentiviral particle is administered to the subject in need thereof. In embodiments, the lentiviral particle transduces a host cell to deliver the PARP shRNA. In embodiments, the shRNA comprises a PARP-specific shRNA. In embodiments, the shRNA comprises a PARP1-specific shRNA. In embodiments, the shRNA comprises a shRNA having at least 80% sequence identity with any one of SEQ ID NOS: 6-10. In embodiments, the shRNA comprises a shRNA having at least 85% sequence identity with any one of SEQ ID NOS: 6-10. In embodiments, the shRNA comprises a shRNA having at least 90% sequence identity with any one of SEQ ID NOS: 6-10. In embodiments, the shRNA comprises a shRNA having at least 95% sequence identity with any one of SEQ ID NOS: 6-10. In embodiments, the shRNA comprises any one of SEQ ID NOS: 6-10. In embodiments, the shRNA comprises a shRNA having at least 80% sequence identity with any one of SEQ ID NOS: 16-20. In embodiments, the shRNA comprises a shRNA having at least 85% sequence identity with any one of SEQ ID NOS: 16-20. In embodiments, the shRNA comprises a shRNA having at least 90% sequence identity with any one of SEQ ID NOS: 16-20. In embodiments, the shRNA comprises a shRNA having at least 95% sequence identity with any one of SEQ ID NOS: 16-20. In embodiments, the shRNA comprises any one of SEQ ID NOS: 16-20. The neuron-specific sequence may encode VSV-G, FUG-C, or gp64, or variants thereof. The neuron-specific sequence may encode only VSV-G, or variants thereof. The neuron-specific sequence may encode a protein that improves transduction into a neuron of the subject. The neuron-specific sequence may encode a protein that improves transduction into a neuron expressing tyrosine hydroxylase (TH+) of the subject.

[0013] In another aspect, a method of treating a subject suffering from Parkinson's disease is disclosed. The method involves administering to the subject a therapeutically effective amount of a lentiviral particle expressed by the lentiviral vector system as described herein. The method may also include a second therapeutic regimen. The second therapeutic regimen may include ablative surgical intervention, neural stimulation, L-DOPA administration, or dopamine agonist administration.

[0014] In another aspect, use of a therapeutic vector, an envelope plasmid, and at least one helper plasmid is disclosed for treating a subject suffering from Parkinson's disease. The therapeutic vector includes a shRNA to inhibit PARP expression. The envelope plasmid includes a neuron-specific sequence to target the shRNA to a neuron. One or more helper plasmids include at least one or more of a gag, pol, or rev gene.

[0015] By suppressing PARP levels, the lentiviral vector system disclosed herein reduces rates for neuronal death, preserves the capacity for normal dopamine production and delay or prevent the onset of Parkinson's disease. The lentiviral vector system disclosed herein, unlike AAVs, has a higher capacity for transducing resting cells, can be optimized to efficiently transduce neurons, and can generate a permanent modification by inserting a transgene into cellular DNA. Additionally, the lentiviral vector system

disclosed herein is less inflammatory than AAVs, which allows for greater dose escalation, and allows for greater flexibility in vector design when testing for alternate envelope glycoproteins, vector composition, doses, and associated delivery methods.

[0016] Other aspects and advantages of the inventions described herein will become apparent from the following detailed description, taken in conjunction with the accompanying drawings, which illustrate by way of example the aspects of the inventions.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] The patent application or application file contains at least one drawing executed in color. If applicable, copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0018] FIG. 1A depicts an exemplary lentiviral vector system comprised of an experimental therapeutic vector, an envelope plasmid, and a helper plasmid. The experimental therapeutic vector detailed in FIG. 1A contains GFP. FIG. 1B depicts an exemplary therapeutic vector designed to reduce expression of PARP1 in substantia nigra neurons in patients afflicted with PD. The therapeutic vector detailed in FIG. 1B does not contain GFP. FIG. 1C depicts an exemplary 3-vector lentiviral vector system in a circularized form that includes the experimental therapeutic vector detailed in FIG. 1A. FIG. 1D depicts an exemplary 4-vector lentiviral vector system in a circularized form that includes the experimental therapeutic vector detailed in FIG. 1A. FIG. 1E depicts an exemplary 3-vector lentiviral vector system in a circularized form that includes the therapeutic vector detailed in FIG. 1B. FIG. 1F depicts an exemplary 4-vector lentiviral vector system in a circularized form that includes the therapeutic vector detailed in FIG. 1B.

[0019] FIG. 2 depicts results from a knockdown experiment involving PARP1 in human cells.

[0020] FIG. 3 depicts results from a knockdown experiment involving PARP1 in mouse cells.

[0021] FIG. 4 depicts neurons transduced with an exemplary lentiviral vector.

DETAILED DESCRIPTION

Overview of the Disclosure

[0022] Aspects of the present invention describe the development of a lentiviral vector system for treating PD. The lentiviral vector system includes a therapeutic vector that includes an inhibitory RNA construct for reducing the expression of PARP. The PARP1 protein has been implicated for its role in PD.

Definitions and Interpretation

[0023] Unless otherwise defined herein, scientific and technical terms used in connection with the present disclosure shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclature used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well-

known and commonly used in the art. The methods and techniques of the present disclosure are generally performed according to conventional methods well-known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. See, e.g.: Sambrook J. & Russell D. Molecular Cloning: A Laboratory Manual, 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2000); Ausubel et al., Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology, Wiley, John & Sons, Inc. (2002); Harlow and Lane Using Antibodies: A Laboratory Manual; Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1998); and Coligan et al., Short Protocols in Protein Science, Wiley, John & Sons, Inc. (2003). Any enzymatic reactions or purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The nomenclature used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art.

[0024] As used herein, the term "includes" means includes without limitation.

[0025] As used herein, the term "lentiviral vector" is synonymous with the term "therapeutic vector." The term "experimental therapeutic vector" means a therapeutic vector that includes an experimental feature such as GFP.

[0026] As used herein, the term "miRNA" means a micro-RNA.

[0027] As used herein, the term "packaging cell line" refers to any cell line that can be used to express a lentiviral particle.

[0028] As used herein, the term "Parkinson's disease," which is also referred to herein as "PD," refers to the known neurodegenerative disease, as well as all symptoms related thereto. Treatment of "Parkinson's disease," therefore, may relate to treatment of all or some of the symptoms associated with Parkinson's disease.

[0029] As used herein, the term "PARP" stands for poly ADP ribose polymerase and includes all PARP-family members, and includes the specific PARP-family member, PARP1 (accession number NM_001618.3) and variants thereof.

[0030] The term "percent identity," which is also referred to herein as "sequence identity," in the context of two or more nucleic acid or polypeptide sequences, refer to two or more sequences or subsequences that have a specified percentage of nucleotides or amino acid residues that are the same, when compared and aligned for maximum correspondence, as measured using one of the sequence comparison algorithms described below (e.g., BLASTP and BLASTN or other algorithms available to persons of skill) or by visual inspection. Depending on the application, the "percent identity" can exist over a region of the sequence being compared, e.g., over a functional domain, or, alternatively, exist over the full length of the two sequences to be compared. For sequence comparison, typically one sequence acts as a reference sequence to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are input into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. The sequence

comparison algorithm then calculates the percent sequence identity for the test sequence(s) relative to the reference sequence, based on the designated program parameters.

[0031] Optimal alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith & Waterman, *Adv. Appl. Math.* 2:482 (1981), by the homology alignment algorithm of Needleman & Wunsch, *J. Mol. Biol.* 48:443 (1970), by the search for similarity method of Pearson & Lipman, *Proc. Natl. Acad. Sci. U.S.A.* 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, Wis.), or by visual inspection (see generally Ausubel et al., *infra*).

[0032] One example of an algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described in Altschul et al., *J. Mol. Biol.* 215:403-410 (1990). Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information website.

[0033] The percent identity between two nucleotide sequences can be determined using the GAP program in the GCG software package (available at <http://www.gcg.com>), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. The percent identity between two nucleotide or amino acid sequences can also be determined using the algorithm of E. Meyers and W. Miller (*CABIOS*, 4:11-17 (1989)) which has been incorporated into the ALIGN program (Version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (*J. Mol. Biol.* (48):444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available at <http://www.gcg.com>), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

[0034] The nucleic acid and/or protein sequences of the present disclosure can further be used as a "query sequence" to perform a search against public databases to, for example, identify related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul et al. (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score=100, word length=12 to obtain nucleotide sequences homologous to the nucleic acid molecules provided in the disclosure. BLAST protein searches can be performed with the XBLAST program, score=50, word-length=3 to obtain amino acid sequences homologous to the protein molecules of the disclosure. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., (1997) *Nucleic Acids Res.* 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. See <http://www.ncbi.nlm.nih.gov>.

[0035] As used herein, the term "plasmid" is synonymous with the term "vector."

[0036] As used herein, the term "SEQ ID NO" is synonymous with the term "Sequence ID No."

[0037] As used herein, the term "shRNA" refers to a short hairpin RNA.

[0038] As used herein, the term "subject" includes a human patient but also includes other mammals.

[0039] As used herein, the term "TH" refers to tyrosine hydroxylase.

Description of Aspects of the Disclosure

[0040] In an aspect of the disclosure, the present disclosure provides a lentiviral vector system for expressing a lentiviral particle. The system includes a therapeutic vector which includes a shRNA for inhibiting PARP-family member expression. There are numerous PARP family members and this disclosure is not limited to any one particular PARP-family member. However, in embodiments, the lentiviral vector system specifically inhibits PARP1.

[0041] The system includes at least one helper plasmid comprising at least one of a gag, pol, or rev gene. Each of the gag, pol and rev genes may be provided on individual plasmids, or one or more genes may be provided together on the same plasmid. In embodiments, the gag, pol, and rev genes are provided on the same plasmid (e.g., FIG. 1C). In embodiments, the gag and pol genes are provided on a first plasmid and the rev gene is provided on a second plasmid (e.g., FIG. 1D). In further embodiments, 3-vector and 4-vector systems are provided herein.

[0042] As detailed herein, the therapeutic vector, the envelope plasmid and at least one helper plasmid are transfected into a packaging cell line. A non-limiting example of a packaging cell line is the 293T/17 HEK cell line. When the therapeutic vector, the envelope plasmid, and at least one helper plasmid are transfected into the packaging cell line, a lentiviral particle is produced. Under the experimental conditions described herein, the lentiviral particle produced by the lentiviral vector system can be a neuron-specific lentiviral particle which is optimized for inhibiting PARP expression.

[0043] In embodiments, the shRNA comprises a PARP-specific shRNA. In embodiments, the shRNA comprises a PARP1-specific shRNA. In embodiments, the shRNA comprises a shRNA having at least 80%, or at least 81%, or at least 82%, or at least 83%, or at least 84% sequence identity with any one of SEQ ID NOs: 6-10. In embodiments, the shRNA comprises a shRNA having at least 85%, or at least 86%, or at least 87%, or at least 88%, or at least 89% sequence identity with any one of SEQ ID NOs: 6-10. In embodiments, the shRNA comprises a shRNA having at least 90%, or at least 91%, or at least 92%, or at least 93%, or at least 94% sequence identity with any one of SEQ ID NOs: 6-10. In embodiments, the shRNA comprises a shRNA having at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99% with any one of SEQ ID NOs: 6-10. In embodiments, the shRNA comprises any one of SEQ ID NOs: 6-10.

[0044] In embodiments, the shRNA comprises a shRNA having at least 80%, or at least 81%, or at least 82%, or at least 83%, or at least 84% sequence identity with any one of SEQ ID NOs: 16-20. In embodiments, the shRNA comprises a shRNA having at least 85%, or at least 86%, or at least 87%, or at least 88%, or at least 89% sequence identity with any one of SEQ ID NOs: 16-20. In embodiments, the shRNA comprises a shRNA having at least 90%, or at least 91%, or at least 92%, or at least 93%, or at least 94% sequence identity with any one of SEQ ID NOs: 16-20. In embodiments, the shRNA comprises a shRNA having at least 95%, or at least 96%, or at least 97%, or at least 98%,

or at least 99% sequence identity with any one of SEQ ID NOs: 16-20. In embodiments, the shRNA comprises any one of SEQ ID NOs: 16-20. In embodiments, any of the foregoing shRNAs can be replaced with a suitable miRNA. In embodiments, the neuron-specific sequence encodes VSV-G, FUG-C, or gp64 or any other sequence that confers tropic specificity to neuron cells. Optionally, the neuron-specific sequence encodes only VSV-G. In embodiments, the neuron-specific sequence encodes a protein that improves transduction into a neuron. In embodiments, the neuron-specific sequence encodes a protein that improves transduction into a TH+ neuron.

[0045] In another aspect of the disclosure, a method of treating a subject suffering from PD is disclosed. In embodiments, the subject is a human being afflicted with mild, moderate, or severe PD. In embodiments, the subject is a human being afflicted with any symptom commonly or uncommonly associated with PD.

[0046] The method involves administering to the subject a lentiviral therapeutic vector comprising a shRNA for inhibiting PARP expression. In embodiments, the lentiviral vector is packaged as a lentiviral particle that transduces a host cell to deliver the PARP shRNA.

[0047] In embodiments, the shRNA comprises a PARP-specific shRNA. In embodiments, the shRNA comprises a PARP1-specific shRNA. In embodiments, the shRNA comprises a shRNA having at least 80%, or at least 81%, or at least 82%, or at least 83%, or at least 84% sequence identity with any one of SEQ ID NOs: 6-10. In embodiments, the shRNA comprises a shRNA having at least 85%, or at least 86%, or at least 87%, or at least 88%, or at least 89% sequence identity with any one of SEQ ID NOs: 6-10. In embodiments, the shRNA comprises a shRNA having at least 90%, or at least 91%, or at least 92%, or at least 93%, or at least 94% sequence identity with any one of SEQ ID NOs: 6-10. In embodiments, the shRNA comprises a shRNA having at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99% sequence identity with any one of SEQ ID NOs: 6-10. In embodiments, the shRNA comprises any one of SEQ ID NOs: 6-10.

[0048] In embodiments, the shRNA comprises a shRNA having at least 80%, or at least 81%, or at least 82%, or at least 83%, or at least 84% sequence identity with any one of SEQ ID NOs: 16-20. In embodiments, the shRNA comprises a shRNA having at least 85%, or at least 86%, or at least 87%, or at least 88%, or at least 89% sequence identity with any one of SEQ ID NOs: 16-20. In embodiments, the shRNA comprises a shRNA having at least 90%, or at least 91%, or at least 92%, or at least 93%, or at least 94% sequence identity with any one of SEQ ID NOs: 16-20.

[0049] SEQ ID NOs: 16-20. In embodiments, the shRNA comprises a shRNA having at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99% sequence identity with any one of SEQ ID NOs: 16-20. In embodiments, the shRNA comprises any one of SEQ ID NOs: 16-20. In embodiments, any of the foregoing shRNAs can be replaced with a suitable miRNA. In embodiments, the neuron-specific sequence encodes VSV-G, FUG-C, or gp64 or any other sequence that confers tropic specificity to neuron cells. Optionally, the neuron-specific sequence encodes only VSV-G. In embodiments, the neuron-specific sequence encodes a protein that improves transduction into

a neuron of the subject. In embodiments, the neuron-specific sequence encodes a protein that improves transduction into a TH⁺ neuron of the subject.

[0050] In another aspect, a method of treating a subject suffering from PD is disclosed. The method involves administering to the subject a therapeutically effective amount of a lentiviral particle expressed by the lentiviral vector system as described herein. In embodiments, the method includes a second therapeutic regimen. In embodiments, the second therapeutic regimen includes, but is not limited to: ablative surgical intervention, neural stimulation, L-DOPA administration, dopamine agonist administration, or any other known Parkinson's disease treatment. In embodiments, the system disclosed herein can be used to treat PD while eliminating the need for increasing doses of L-DOPA.

Lentiviral Vector System

[0051] A lentiviral virion (particle) is expressed by a vector system encoding the necessary viral proteins to produce a virion (viral particle). There is at least one vector containing a nucleic acid sequence encoding the lentiviral pol proteins necessary for reverse transcription and integration, operably linked to a promoter. In another embodiment, the pol proteins are expressed by multiple vectors.

[0052] In another aspect, use of a therapeutic vector, an envelope plasmid, and at least one helper plasmid is disclosed for treating a subject suffering from PD. The therapeutic vector includes a shRNA to inhibit PARP expression. In embodiments, the envelope plasmid includes a neuron-specific sequence to target the shRNA to a neuron and at least one helper plasmid that includes gag, pol, and rev genes.

[0053] By suppressing PARP levels, the lentiviral vector system disclosed herein will reduce rates for neuronal death, preserve the capacity for normal dopamine production and delay and/or prevent the onset of PD. The lentiviral vector system disclosed herein, unlike AAV systems known in the art, has a higher capacity for transducing resting cells, can be optimized to efficiently transduce neurons, and can generate a permanent modification by inserting a transgene into cellular DNA. Additionally, the lentiviral vector system disclosed herein is less inflammatory than AAV systems, which allows for greater dose escalation, and allows for greater flexibility in vector design when testing for alternate envelope glycoproteins, vector composition, doses and associated delivery methods.

[0054] The disclosed lentiviral vector system can be optimized for short, medium, or long-term suppression of PARP expression in subjects afflicted with PD. Accordingly, dosing regimens may vary based upon the severity of the PD, or the associated PD symptoms. The lentiviral particles disclosed herein may be administered to a subject in need thereof in varying doses. A subject may be administered $\geq 10^6$ transducing units of lentiviral particle suspension (where 1 dose is needed on average to transduce 1 target cell). A subject may be administered $\geq 10^6$, $\geq 10^7$, $\geq 10^8$, $\geq 10^9$, or $\geq 10^{10}$ transducing units. Upper dosing limits will be determined by a variety of factors understood by those persons skilled in the art.

[0055] The vector(s) forming the lentiviral particle preferably do not contain a nucleic acid sequence from the lentiviral genome that expresses an envelope protein. Preferably, a separate vector that contains a nucleic acid sequence encoding an envelope protein operably linked to a

promoter is used. This env vector also does not contain a lentiviral packaging sequence. In one embodiment, the env nucleic acid sequence encodes a lentiviral envelope protein.

[0056] In another embodiment, the envelope protein is not from the lentivirus, but from a different virus. The resultant particle is referred to as a pseudotyped particle. By appropriate selection of envelopes one can "infect" virtually any cell. For example, one can use an env gene that encodes an envelope protein that targets an endocytic compartment such as that of the influenza virus, VSV-G, alpha viruses (Semliki forest virus, Sindbis virus), arenaviruses (lymphocytic choriomeningitis virus), flaviviruses (tick-home encephalitis virus, Dengue virus, hepatitis C virus, GB virus), rhabdoviruses (vesicular stomatitis virus, rabies virus), paramyxoviruses (mumps or measles), picornaviruses (Mengo, Polio, and Coxsackie), and orthomyxoviruses (influenza virus). Other envelopes that can preferably be used include those from Moloney Leukemia Virus such as MLV-E, MLV-A and GALV. These latter envelopes are particularly preferred where the host cell is a primary cell. Other envelope proteins can be selected depending upon the desired host cell. For example, targeting specific receptors such as a dopamine receptor can be used for brain delivery. Another target can be vascular endothelium. These cells can be targeted using a filovirus envelope. For example, the GP of Ebola., which by post-transcriptional modification become the GP, and GP₂ glycoproteins. In another embodiment, one can use different lentiviral capsids with a pseudotyped envelope (for example, Hy or SHIV [U.S. Pat. No. 5,654,195]). A SHIV pseudotyped vector can readily be used in animal models such as monkeys.

[0057] As detailed herein, a lentiviral vector system typically includes at least one helper plasmid comprising at least one of a gag, pol, or rev gene. Each of the gag, pol and rev genes may be provided on individual plasmids, or one or more genes may be provided together on the same plasmid. In one embodiment, the gag, pol, and rev genes are provided on the same plasmid (e.g., FIG. 1C). In another embodiment, the gag and pol genes are provided on a first plasmid and the rev gene is provided on a second plasmid (e.g., FIG. 1D). Accordingly, both 3-vector and 4-vector systems can be used to produce a lentivirus as described in the Examples section and elsewhere herein. The therapeutic vector, the envelope plasmid and at least one helper plasmid are transfected into a packaging cell line. A non-limiting example of a packaging cell line is the 293T/17 HEK cell line. When the therapeutic vector, the envelope plasmid, and at least one helper plasmid are transfected into the packaging cell line, a lentiviral particle is produced.

[0058] In another aspect, a lentiviral vector system for expressing a lentiviral particle is disclosed. The system includes a lentiviral vector as described herein; an envelope plasmid for expressing an envelope protein optimized for infecting a cell; and at least one helper plasmid for expressing gag, pol, and rev genes, wherein when the lentiviral vector, the envelope plasmid, and the at least one helper plasmid are transfected into a packaging cell line, a lentiviral particle is produced by the packaging cell line, wherein the lentiviral particle is capable of inhibiting production of PARP1.

[0059] In another aspect, and as detailed in FIG. 1C, the lentiviral vector, which is also referred to herein as a therapeutic vector, includes the following elements: a hybrid 5' long terminal repeat (RSV/5'LTR) (SEQ ID NOS: 21-22),

a HIV gag (SEQ ID NO: 23), a RRE (Rev-response element) (SEQ ID NO: 24), a Env element (SEQ ID NO: 25), a cPPT (SEQ ID NO: 26), a H1 promoter (SEQ ID NO: 27), a shRNA targeting PARP1 (shPARP1) (SEQ ID NOS: 6-10), a EF1 promoter (SEQ ID NO: 28), a GFP element (SEQ ID NO: 29), a Woodchuck Post-Transcriptional Regulatory Element (WPRE) (SEQ ID NO: 30), and a 3' LTR delta U3 (SEQ ID NO: 31). In another aspect, sequence variation, by way of substitution, deletion, addition, or mutation can be used to modify the sequences references herein.

[0060] In another aspect, and as detailed herein for example in FIG. 1C, a helper plasmid has been designed to include the following elements: CMV enhancer (SEQ ID NO: 32); a chicken beta actin promoter (SEQ ID NO: 33); a chicken beta actin intron (SEQ ID NO: 34); a HIV gag (SEQ ID NO: 23); a HIV Pol (SEQ ID NO: 35); a HIV Int (SEQ ID NO: 36); a HIV RRE (SEQ ID NO: 24); a HIV Rev (SEQ ID NO: 37); and a rabbit beta globin poly A (SEQ ID NO: 38). In another aspect, the helper plasmid may be modified to include a first helper plasmid for expressing the gag and pol genes, and a second and separate plasmid for expressing the rev gene. In another aspect, sequence variation, by way of substitution, deletion, addition, or mutation can be used to modify the sequences references herein.

[0061] In another aspect, and as detailed herein for example in FIG. 1C, an envelope plasmid has been designed to include the following elements being from left to right: a CMV promoter (SEQ ID NO: 39); a beta globin intron (SEQ ID NO: 40); a VSV-G (SEQ ID NO:

[0062] 25); and a rabbit beta globin poly A (SEQ ID NO: 38). In another aspect, sequence variation, by way of substitution, deletion, addition, or mutation can be used to modify the sequences references herein.

[0063] In another aspect, the plasmids used for lentiviral packaging can be modified with similar elements and the intron sequences can potentially be removed without loss of vector function. For example, the following elements can replace similar elements in the plasmids that comprise the packaging system: Elongation Factor-1 (EF-1), phosphoglycerate kinase (PGK), and ubiquitin C (UbC) promoters can replace the CMV or CAG promoter. SV40 poly A and bGH poly A can replace the rabbit beta globin poly A. The HIV sequences in the helper plasmid can be constructed from different HIV strains or clades. The VSV-G glycoprotein can be substituted with membrane glycoproteins from feline endogenous virus (RD114), gibbon ape leukemia virus (GALV), Rabies (FUG), lymphocytic choriomeningitis virus (LCMV), influenza A fowl plague virus (FPV), Ross River alphavirus (RRV), murine leukemia virus 10A1 (MLV), or Ebola virus (EboV).

[0064] Of note, lentiviral packaging systems can be acquired commercially (e.g., Lenti-vpak packaging kit from OriGene Technologies, Inc., Rockville, Md.), and can also be designed as described herein. Moreover, it is within the skill of a person skilled in the art to substitute or modify aspects of a lentiviral packaging system to improve any number of relevant factors, including the production efficiency of a lentiviral particle.

Doses and Dosage Forms

[0065] Dosing may occur once per day or several times per day. Dosing may occur with intervals in between dosing. For example, a subject may be treated on a first day, and then treated every other day, or every second day, or every third

day, or every fourth day, or every fifth day, or every sixth day, or every seventh day, or every second week, or every month, etc. However, dosing can also occur once, twice, or several times per year, and such a dosing schedule can be repeated on a yearly basis. A lentiviral particle can be delivered by any method suitable for treating symptoms associated with PD. For example, dosing can be made via direct injection into the brain stem using a guided needle. This will likely occur in conjunction with deep brain stimulation.

[0066] In another aspect, a pharmaceutical composition comprising a lentiviral particle as described herein can be formulated in a solid dosage form. The solid dosage form can include excipients known to those skilled in the art. The lentiviral particle as described herein can be formulated in a gel form, a foam form, a biodegradable capsule form, a nanoparticle form, or can be formulated with liposomes or other structures known to those skilled in the art. The solid dosage form can be formulated for immediate release or a modified release. Modified release dosage forms include controlled or extended release forms.

[0067] The following examples are given for the purpose of illustrating various embodiments of the invention and are not meant to limit the invention in any fashion. The present examples, along with the methods described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. Changes therein, and other uses which are encompassed within the spirit of the invention as defined by the scope of the claims, will occur to those persons skilled in the art.

EXAMPLES

Example 1

Development of a Lentiviral Vector System

[0068] A lentiviral vector system was developed as summarized generally in FIG. 1. Lentiviral particles were produced in 293T/17 HEK cells (purchased from American Type Culture Collection, Manassas, Va.) following transfection with the therapeutic vector, the envelope plasmid, and the helper plasmid. The transfection of 293T/17 HEK cells, which produced functional viral particles, employed the reagent Poly(ethylenimine) (PEI) to increase the efficiency of plasmid DNA uptake. The plasmids and DNA were initially added separately in culture medium without serum in a ratio of 3:1 (mass ratio of PEI to DNA). After 2-3 days, cell medium was collected and lentiviral particles were purified by high-speed centrifugation and/or filtration followed by anion-exchange chromatography. The concentration of lentiviral particles can be expressed in terms of transducing units/ml (TU/ml). The determination of TU was accomplished by measuring HIV p24 levels in culture fluids (p24 protein is incorporated into lentiviral particles), measuring the number of viral DNA copies per cell by quantitative PCR, or by infecting cells and using light (if the vectors encode luciferase or fluorescent protein markers).

[0069] A 3-vector system (i.e., a 2-vector lentiviral packaging system) was designed for the production of lentiviral particles. A schematic of the 3-vector system is shown in FIGS. 1A, 1C, and 1E. Briefly, and with reference to FIGS. 1C and 1E, the top-most vector is a helper plasmid, which, in this case, includes Rev. The vector appearing in the

middle of FIGS. 1C and 1E is the envelope plasmid. The bottom-most vector is the therapeutic vector, as described herein.

[0070] Referring to FIGS. 1C and 1E, the Helper plus Rev plasmid includes a CMV enhancer (SEQ ID NO: 32); a chicken beta actin promoter (SEQ ID NO: 33); a chicken beta actin intron (SEQ ID NO: 34); a HIV gag (SEQ ID NO: 23); a HIV Pol (SEQ ID NO: 35); a HIV Int (SEQ ID NO: 36); a HIV RRE (SEQ ID NO: 24); a HIV Rev (SEQ ID NO: 37); and a rabbit beta globin poly A (SEQ ID NO: 38). The Helper plus Rev plasmid is also shown in a linear form in FIG. 1A.

[0071] Referring to FIGS. 1C and 1E, the Envelope plasmid includes a CMV promoter (SEQ ID NO: 39); a beta globin intron (SEQ ID NO: 40); a VSV-G (SEQ ID NO: 25); and a rabbit beta globin poly A (SEQ ID NO: 38). The Envelope plasmid is also shown in a linear form in FIG. 1A.

[0072] Synthesis of a 2-Vector Lentiviral Packaging System including Helper (plus Rev) and Envelope Plasmids.

[0073] Materials and Methods:

[0074] Construction of the helper plasmid: The helper plasmid was constructed by initial PCR amplification of a DNA fragment from the pNL4-3 HIV plasmid (NIH Aids Reagent Program) containing Gag, Pol, and Integrase genes. Primers were designed to amplify the fragment with EcoRI and NotI restriction sites which could be used to insert at the same sites in the pCDNA3 plasmid (Invitrogen). The forward primer was (5'-TAAGCAGAACATC ATGAATTG-CAGGAAGAT-3') (SEQ ID NO: 41) and reverse primer was (5'-CCATACAAATGAATGGACACTAGGC CGGCCGCA-GAAT-3') (SEQ ID NO: 42).

[0075] The sequence for the Gag, Pol, Integrase fragment was as follows:

(SEQ ID NO: 43)
GAATTCATGAATTGCCAGGAAGATGGAAACAAAAATGATAGGGGAAT-TGGA

GTTTTATCAAAGTAAGACAGTATGATCAGATACTCATAGAAATCTGCG-GACATA

AAGCTATAGGTACAGTATTAGTAGGACCTACACCTGTCAACATAATTG-GAAGAA

ATCTGTTGACTCAGATTGGCTGCACTTAAATTTCCTATTAGCCTATT-GAGACT

GTACCAAGAAAATTAAAGCCAGGAATGGATGCCAAAAGTTAAACAATG-GCCA

TTGACAGAAGAAAAATAAAAGCATTAGTAGAAATTGTACAGAAATG-GAAAAG

GAAGGAAAATTCAAAATTGGGCTGAAAATCCATACAATACTCCAGT-ATT

GCCATAAGAAAAAGCAGTACTAAATGGAGAAAATTAGTAGATTCA-GAGAA

CTTAAATAAGAGAACTCAAGATTCTGGGAAGTCAATTAGGAATACCA-CATCCIG

CAGGGTTAAAACAGAAAAATCAGTAACAGTACTGGATGTGGCGATG-CATATT

TTTCAGTTCCCTTAGATAAAGACTTCAGGAAGTACTGCATTACCAT-ACCTAG

TATAAACATGAGACACCAGGGATTAGATATCAGTACAATGTGCTTC-CACAGGG

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ATGGAAAGGATCACCAATATTCCAGTGTAGCATGACAAAATCTTA-GAGCC

TTTTAGAAAACAAAATCCAGACATAGTCATCTATCAATACATGGAT-GATTTGTAT

GTAGGATCTGACTTAGAAAATAGGGCAGCATAGAACAAAAATAGAGGAAC-TGAG

ACAAACATCTGTTGAGGTGGGATTACACACCAGAACAAAAACATCA-GAAAGA

ACCTCCATTCTTGATGGGTATGAACTCCATCCTGATAATGGACAG-TACAG

CCTATACTGCTGCCAGAAAAGGACAGCTGGACTGTCAATGACATACA-GAAATTA

GTGGAAATGAAATTGGCAAGTCAGATTATGCAGGGATTAAAG-TAAGGCA

TTATGTAAACTCTTAGGGAACCAAGCACTAACAGAAAGTAGTAC-CACTAAC

GAAGAACGAGAGCTAGAACTGGCAGAAAACAGGGAGATTCTAAAAGAAC-CCGT

ACATGGAGTGTATTATGACCCATCAAAAGACTTAATAGCAGAAATACA-GAAGCA

GGGCAAGGCCATGGACATATCAAATTATCAAGAGGCCATT-TAAAATCTGAA

AACAGGAAAGTATGCAAGAATGAAGGGTGCACACTAATGATGT-GAAACAAATT

AACAGAGGCAGTACAAAAATGCCACAGAAAGCATA-GTAATATGGGAAAGA

CTCTAAATTAAATTACCCATACAAAGGAAACATGGAAAGCATGGT-GACAG

AGTATTGGCAAGCCACCTGGATTCTGAGTGGAGTTGTCAATAC-CCCTCCCT

AGTGAAGTTATGGTACCAAGTTAGAGAAAAGAACCCATAATAGGAGCA-GAAACTT

CTATGTAGATGGGCAGCCAATAGGAAACTAAATTAGGAAAGCAGGA-TATGT

AACTGACAGAGGAAGACAAAAAGTTGTCCCCCCTAACGGACA-CAACAAATCGAA

GAETGAGTTACAAGCAATTCTAGCTTGCAGGATTGGGATTAGAAG-TAAAC

ATAGTGACAGACTCACAATATGCATTGGAACTATTCAAGCACAAACAGA-TAAG

AGTGAATCAGAGTTAGTCAGTCAAATAATAGAGCAGT-TAATAAAAAGGAAAAA

GTCTACCTGGCATGGTACAGCACACAAAGGAATTGGAGGAAAT-GAACAGTA

GATAAAATTGGTCAGTGTGGAATCAGGAAAGTACTATTTTAGATG-GAATAGATA

AGGCCAAGAACATGAGAAATATCACAGTAATTGGAGAGCAATG-GCTAGTG

ATTTTAACCTACCACTGTAGTAGCAGAACAAATAGTAGCCAGCTGTGA-TAAATG

TCAGCTAAAGGGAAAGCCATGCATGGACAAGTAGACTGTAGCCCAG-GAACATG

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GCCAGTGGATATAGAACAGAAGTAATTCCAGCAGAGACA-
GGCAAGAAC

AGCATACTTCCTCTAAATTAGCAGGAAGATGGCCAGTAAAACAGTA-
CATAC

AGACAATGGCAGCAATTCAACCAAGTACTACAGTTAAGGCCGCTGTTG-
GTGGC

GGGGATCAAGCAGGAATTGGCATTCCCTACAATCCCCAAAGTCAGGAG-
TAAT

AAATCTATGAATAAAGAATTAAAGAAAATTATAGCACAGGTAAGA-
GATCAGGC

TGAACATCTAACAGACAGCAGTACAAATGGCAGTATTCACTCCACAATT-
TAAAGA

AAAGGGGGATTGGGGTACAGTCAGGGAAAGAATAGTAGA-
CATATAGC

AACAGACATACAAACTAAAGAATTACAAAACAAATTACAAAAT-
TCAAAATT

TCGGGTTTATTACAGGGACAGCAGAGATCCAGTTGGAAAGGACCAG-
CAAAGCT

CCTCTGGAAAGGTGAAGGGCAGTAGTAATACAAGATAATAGT-
GACATAAAAGT

AGTGCCAAGAAGAAAAGCAAGATCATCAGGGATTATGGAAAACAGATG-
GCAG

GTGATGATTGTGCGCAAGTAGACAGGATGAGGATTAA

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[0076] Next, a DNA fragment containing the Rev, RRE, and rabbit beta globin poly A sequence with XbaI and XmaI flanking restriction sites was synthesized by MWG Operon. The DNA fragment was then inserted into the plasmid at the XbaI and XmaI restriction sites. The DNA sequence was as follows:

(SEQ ID NO: 44)

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TCTAGAATGGCAGGAAGAAGCGGAGACAGCGACGAAGAGCTCATCAGAA
CAGTCAGACTCATCAAGCTCTATCAAAGCAACCCACCTCCCAATCC
CGAGGGACCCGACAGGCCGAGGAAGATAAGAAGAAGGTGGAGAGAG
AGACAGAGACAGATCCATTGATTAGTGAACGGATCCTGGCACTTATC
TGGGACGATCTCGGGAGCCTGCGCTTTCAGCTACCACCGCTTGAGAG
ACTTACTCTTGATGTAACGAGGATTGTGGAACCTCTGGGACGCCAGGG
GTGGGAAGCCCTCAAATATTGGTGGAACTCTCTACAAATATTGGAGTCAG
GAGCTAAAGAATAGAGGAGCTTGTCTGGGTTCTGGGAGCAGCAG
GAAGCACTATGGCGCAGCGTCAATGACGCTGACGGTACAGGCCAGACA
ATTATTGTCGTTGATAGTGCAGCAGCAGAACAAATTGCTGAGGGCTATT
GAGGCCAACACCATCTGTTGCAACTCACAGCTGGGCATCAAGCAGC
TCCAGGCAAGAACATCTGGCTGTGGAAAGATACTAAAGGATCAACAGCT
CCTAGATCTTCCCTCTGCCAAAAATTATGGGACATCATGAAGCCC
CTTGAGCATCTGACTCTGGCTAATAAGGAAATTATTTCTTGCAGGAG
TAGTGTGTTGAAATTGGTCTCTCACTCGAAGGACATATGGGAG
GGCAAACTATTTAAACATCAGAATGAGTATTGGTTAGAGTTGGCA
ACATATGCCATATGCTGGCTGCCATGAACAAAGGTGGCTATAAGAGGT

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CATCAGTATATGAAACAGCCCCCTGCTGTCCATTCCCTTATTCCATAGAA
AAGCCTTGACTTGAGGTTAGATTTTTTATTTTGTGTTATT
TTTTCTTAAACATCCCTAAATTTCCTTACATGTTTACTAGCCAGA
TTTTCTCCTCTCCTGACTACTCCCAGTCATAGCTGCCCTTCTCT
TATGAAGATCCCTCGACCTGCAAGCTTGGCGTAATCATGGTCA
AGCTGTTCTGTGAAATTGTTATCCGCTACAATTCCACACAACAT
ACGAGCCGAAAGCATAAAGTGTAAAGCCTGGGTGCTTAATGAGTGA
TAACTCACATTAATTGCGTTGCGCTACTGCCGCTTCCAGTCGGAA
ACCTGCTGTGCCAGCGGATCCGATCTCAATTAGTCAGCAACCATAGTC
CCGCCCTAACTCCGCCATCCGCCCTAACTCCGCCAGTCCGCC
ATTCTCCGCCCATGGCTGACTAATTTTTTATTGAGGAGGCTTTT
GGAGGCCTAGGCTTTGCAAAAGCTAACTTGTGTTATTGAGCTTATAA
TGGTTACAATAAAGCAATAGCATCACAAATTTCACAATAAAGCATT
TTTCACTGCATTCTAGTTGTGGTTGTCCAAACTCATCAATGTATCTT
ATCAGCGGCCGCCCGGG

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[0077] Finally, the CMV promoter of pCDNA3.1 was replaced with the CAG enhancer/promoter plus a chicken beta actin intron sequence. A DNA fragment containing the CAG enhancer/promoter/intron sequence with MluI and EcoRI flanking restriction sites was synthesized by MWG Operon. The DNA fragment was then inserted into the plasmid at the MluI and EcoRI restriction sites. The DNA sequence was as follows:

(SEQ ID NO: 45)

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ACGCGTTAGTTATAATAGTAATCAATTACGGGTCTTGTGTTCAAG
CCATATGGAGTTCCCGCTTACATAACTTACGGTAAATGGCCGCTG
GCTGACGCCAACGACCCCCGCCATTGACGTCAATAATGACGTATGT
TCCCATAGTAACGCCAATAGGACTTCCATTGACGTCAATGGTGAC
TATTTACGGTAAACTGCCACTGGCAGTACATCAAGTGTATCATATG
CAAGTACGCCCTATTGACGTCAATGACGGTAAATGCCCGCTGGCA
TTATGCCAGTACATGACCTTATGGACTTCCACTGGCAGTACATC
TACGTATTAGTCATCGCTTACCATGGTCAGGGTGGCCCCACGTT
TGCTTCACTCTCCCATCTCCCCCCCCCCCCACCCCCAATTGTTATT
TATTATTTTAAATTGGTGCAGCGATGGGGCGGGGGGGGGGGGGGG
GGCGCGGCCAGGCAGGGCGGGCGAGGGCGGGGGCGGGGGCGAG
GCGGAGAGGTGCGGCCAGCCAATCAGAGCGGCCGCGCTCCGAAAGTT
CCTTTATGGCGAGGCCGCGGCCGCGCCCTATAAAAGCGAAGCG
CGCGGCCGGCGGGAGTCGCTGCGTTGCCCTGCCCGCTCCG
CGCCGCCCTCGCGCCGCCGCCGGCTCTGACTGACCGCTTACTCCCA
CAGGTGAGCGGGCGGGACGGCCCTCTCCCTCGGGCTGTAATTAGCGCT

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TGGTTTAATGACGGCTCGTTCTTCTGTGGCTGCGTGAAAGCCTAA
AGGGCTCCGGAGGGCCCTTGTGCGGGGGAGCGGCTCGGGGGTGC
GTGCGTGTGTGCGTGGGAGCGCGCGTGCGCCGCGCTGCCG
GCCGCTGTGAGCCGTCGGGGCGCGCGCGGGCTTGTGCCCTCCCGT
GTGCGCAGGGGAGCGCGCGGGCGGTGCCCGCGGTGCCGG
CTGCGAGGGAACAAAGCTGCGTGCAGGGTGTGCGTGAGGGGGTGA
GCAGGGGTGTGGCGCGGGCGGTGCGGCTGAACCCCCCTGCACCCC
CCTCCCGAGTTGCTGAGCACGGCCGGCTCGGGTGCAGGGCTCCGTG
CGGGCGTGGCGCGGGCTCGCGTGCAGGGGGTGGCGCAGGT
GGGGGTGCCGGCGGGCGGGCGCTCGGGCGGGAGGGCTCGGG
GAGGGCGCGGGCGCCCGAGCGCGCGCGTGTGAGGCGCGCGAG
CCGCAGCCATTGCCCTTATGTAATCGTGCAGAGGGCGCAGGGACTT
CCTTGTCCCAAATCTGGCGAGGCCAAATCTGGAGGCGCCGCCAC
CCCCCTAGCGGGCGGGCGAAGCGGTGCAGGGCAGGAAGGAAA
TGGCGGGGAGGGCTTCGTGCGTCGCCCGCGCTCCCCCTCC
TCTCCAGCCTCGGGCTGCCAGGGGACGGCTGCCCTCGGGGGGAC
GGGCAGGGGGGTTCTGGCTGTGACCGGGGAAATT
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[0078] Construction of the VSV-G Envelope Plasmid:

[0079] The vesicular stomatitis Indiana virus glycoprotein (VSV-G) sequence was synthesized by MWG Operon with flanking EcoRI restriction sites. The DNA fragment was then inserted into the pCDNA3.1 plasmid (Invitrogen) at the EcoRI restriction site and the correct orientation was determined by sequencing using a CMV specific primer. The DNA sequence was as follows:

(SEQ ID NO: 46)

```
GAATTCAATGAACTGCCTTTGTACTTAGCCTTTATTCAATGGGTGA
ATTGCAAGTTACCATACTGGTCTTCCACACAACCAAAAGGAAACTGGAA
AAATGTTCTCTAATTACCATATTGCCGTCAAGCTCAGATTAAAT
TGGCATAATGACTTAATAGGCACAGCCTTACAAGTCAGGAAAGGAAA
GTCACAAGGCTATTCAAGCAGACGGTGGATGTCATGCTTCAAATG
GGTCACTACTGTGATTCCGCTGGTATGGACCGAAGTATAACACAT
TCCATCCGATCCTCACTCCATCTGTAGAACATGCAAGGAAAGCATTG
AACAAACGAAACAAGGAACTGGCTGAATCAGGCTCCCTCTCAAAG
TTGTGGATATGCAACTGTGACGGATGCCAAGCAGTGATTGTCAGGTG
ACTCCTCACCATGTGCTGGTGTGATGAAATACACAGGAGAATGGGTTGATT
CACAGTTCATCAACGGAAATGCAAGCAATTACATATGCCCACTGTCCA
TAACTCTACAACCTGGCATTCTGACTATAAGGTCAGGGCTATGTGAT
TCTAACCTCATTCATGGACATCACCTCTCTCAGAGGACGGAGAGC
TATCATCCCTGGGAAAGGAGGGCACAGGGTTCAGAGTAACTACTTGC
TTATGAAACTGGAGGCAAGGCCTGAAAATGCAACTTGCAAGCATTGG
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GGAGTCAGACTCCCATCAGGTGCTGGTCAGAGATGGCTGATAAGGATC
TCTTGTGCTGCAGCCAGATTCCCTGAATGCCAGAAGGGTCAAGTATCTC
TGCTCCATCTCAGACCTCAGTGGATGTAAGCTAATTCAAGGAGCTGAG
AGGATCTGGATTATTCCTCTGCCAGAAACCTGGAGCAAATCAGAG
CGGGCTTCCAATCTCCAGTGGATCTCAGCTATCTGCTCTAAAAA
CCCAGGAACCGGTCTGCTTCACCATATAATCAATGGTACCCCTAAATAC
TTTGGAGACAGATACTCAGAGTCGATATTGCTGCTTACATCCTCTCAA
GAATGGTGGAAATGATCAGTGGAACTACACAGAAAGGAACTGTGGGA
TGACTGGGACCCATATGAGACGTGGAAATTGGACCAATGGAGTTCTG
AGGACCAAGTCAGGATAAGTTCTTATACATGATTGGACATGGTA
TGTGACTCCGATCTTCATCTTAGCTCAAAGGCTCAGGTGTTGAAACA
TCCCTCACATTCAAGACGCTGCTCGAACCTCTGATGATGAGAGTTA
TTTTTGGTGTGAACTGGCTATCCAAAATCCAATCGAGCTGTGAGAAG
GTTGGTTCACTGGTGTGAAAGCTCTATTGCCCTTTTCTTATCAT
AGGGTTAACATTGGACTATTCTGGTCTCCAGTTGGTATCCATCTT
TGCATTAATTAAGCACCCAAGAAAAGACAGATTATACAGACATAG
AGATGAGAATT
```

[0080] A 4-vector system (i.e., a 3-vector lentiviral packaging system) has also been designed and produced using the methods and materials described herein. A schematic of the 4-vector system is shown in FIGS. 1D and 1F. Briefly, and with reference to FIGS. 1D and 1F, the top-most vector is a helper plasmid, which, in this case, does not include Rev. The vector second from the top, oriented at the left aspect of the page, is a separate Rev plasmid. The vector second from the bottom, oriented at the right aspect of the page, is the envelope plasmid. The bottom-most vector is an experimental therapeutic vector.

[0081] Referring to FIGS. 1D and 1F, the Helper plasmid includes a CMV enhancer (SEQ ID NO: 32); a chicken beta actin promoter (SEQ ID NO: 33); a chicken beta actin intron (SEQ ID NO: 34); a HIV gag (SEQ ID NO: 23); a HIV Pol (SEQ ID NO: 35); a HIV Int (SEQ ID NO: 36); a HIV RRE (SEQ ID NO: 24); and a rabbit beta globin poly A (SEQ ID NO: 38).

[0082] Referring to FIGS. 1D and 1F, the Rev plasmid includes a RSV promoter (SEQ ID NO: 47); a HIV Rev (SEQ ID NO: 37); and a rabbit beta globin poly A (SEQ ID NO: 38).

[0083] Referring to FIGS. 1D and 1F, the Envelope plasmid includes a CMV promoter (SEQ ID NO: 39); a beta globin intron (SEQ ID NO: 40); a VSV-G (SEQ ID NO: 25); and a rabbit beta globin poly A (SEQ ID NO: 38). The Envelope plasmid is also shown in a linear form in FIG. 1A.

[0084] Synthesis of a 3-Vector Lentiviral Packaging System including Helper, Rev, and Envelope Plasmids.

[0085] Materials and Methods:

[0086] Construction of the Helper Plasmid without Rev:

[0087] The Helper plasmid without Rev was constructed by inserting a DNA fragment containing the RRE and rabbit beta globin poly A sequence. This sequence was synthesized by MWG Operon with flanking XbaI and XmaI restriction sites. The RRE/rabbit poly A beta globin sequence was then

inserted into the Helper plasmid at the XbaI and XmaI restriction sites. The DNA sequence is as follows:

(SEQ ID NO: 44)

```
TCTAGAAGGAGCTTGTCCCTGGTTCTGGGAGCAGCAGGAAGCACT
ATGGGCGCAGCGCTCAATGACGCTGACGGTACAGGCCAGACAATTATTG
CTGGTATACTGAGCAGCAGAACAAATTGCTGAGGGCTATTGAGGCAGCA
ACAGCATCTGTCACACTCACAGTCTGGGCATCAAGCAGCTCCAGGCA
AGAATCCTGGCTGTGGAAAGATACTAAAGGATCAACAGCTCTAGATC
TTTTCCCTCTGCCAAAATTATGGGCACATCATGAAGCCCTTGAGCA
TCGACTTCTGGCTAAATAAGGAAATTATTTCAATTGCAATTAGTGTGT
TCCAATTTGGTGTCTCTACTCGGAAGGACATATGGGAGGGCAACATC
ATTTAAACATCAGAATGAGTATTGGTTAGAGTTGGCAACATATGC
CATATGCTGGCTGCCATGAACAAAGGTGGCTAAAGAGGTCACTAGTA
TATGAAACAGCCCCCTGCTGTCCTATTCCATTCCATAGAAAAGCCTG
ACTTGAGGTTAGATTTTTATATTTGTTTGTGTATTTTTTCTT
TAACATCCCTAAAATTCCTTACATGTTTACTAGCCAGATTTCCCT
CCTCTCTGACTACTCCCAGTCATAGCTGTCCCTTCTTATGAAGA
TCCCTCGACCTGCAGCCCAAGCTTGGCGTAATCATGGTCATAGCTGTT
CCTGTGTGAAATTGTTATCCGCTCACAATTCCACACAATCAGGCCG
GAAGCATAAAGTGTAAAGCCTGGGGTGCCTAATGAGTGAACACTCAC
ATTAATTGCGTTGCGCTCACTGCCCGCTTCCAGTCGGGAACTGTCG
TGCCAGCGGATCCGCATCTCAATTAGTCAGCAACCATACTCCGCCCT
AACTCCGCCATCCGCCCTAACTCCGCCAGTCGGCCATTCTCCG
CCCCATGGCTGACTAATTTTTATTATGCAGAGGCCAGGCCCT
CGGCCTCTGAGCTATTCCAGAAGTAGTGAAGGAGGTTTTGGAGGCCT
AGGCTTTGCAAAAGCTAATTGTTATTGAGCTTATAATGGTTACA
ATAAAAGCAATGCACTACAAATTTCACAAATAAGCATTTCCTCACT
GCATTCTAGTTGTGGTTGTCCAAACTCATCAATGTATCTTATCACCG
GG
```

[0088] Construction of the Rev Plasmid:

[0089] The RSV promoter and HIV Rev sequence was synthesized as a single DNA fragment by MWG Operon with flanking MfeI and XbaI restriction sites. The DNA fragment was then inserted into the pCDNA3.1 plasmid (Invitrogen) at the MfeI and XbaI restriction sites in which the CMV promoter is replaced with the RSV promoter. The DNA sequence was as follows:

(SEQ ID NO: 48)

```
CAATTGCGATGTACGGGCCAGATATACGCGTATCTGAGGGGACTAGGGT
GTGTTTAGGCAGAAAGCGGGCTTCGGTTGACCGGTTAGGAGTCCCC
TCAGGATATAGTAGTTGCTTGCATAGGGAGGGAAATGTAGTCT
TATGCAATACACTTGAGTCTGCAACATGGTAACGATGAGTTAGCAAC
ATGCCTTACAAGGAGAGAAAAGCACCGTGCATGCCGATTGGTGGAAAGT
```

-continued

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AAGGTGGTACGATCGTCCTTATTAGGAAGGAAACAGACAGGTCTGACA
TGGATTGGACGAACCACTGAATTCCGATTGCAGAGATAATTGTATTAA
AGTGCCTAGCTGATACAATAACGCCATTGACCATTCAACCACATTGG
TGTGACACCTCAAGCTCGAGCTCGTTAGTGAACCGTCAGATCGCCTGG
AGACGCCATCCACGCTGTTTGACCTCATAGAAGACACCGGGACCGAT
CCAGCCTCCCTCGAAGCTAGCGATTAGGCATCTCTATGGCAGGAAGA
AGCGGAGACAGCGACGAAGAACTCCTCAAGGCAGTCAGACTCATCAAGT
TTCTCTATCAAAGCAACCCACCTCCCAATCCCGAGGGGACCCGACAGGC
CCGAAGGAATAGAAGAAGAGGTGGAGAGAGACAGAGACAGATCCAT
TCGATTAGTGAACGGATCCTTAGCACTTATCTGGGACGATCTGGAGC
CTGTGCCTCTCAGCTACCACCGCTTGAGAGACTACTCTTGATTGAA
CGAGGATTGTTGAACTCTGGGACGCAAGGGGTTGGGAAGCCCTCAAATA
TTGGTGGAACTCCTACAATATTGGAGTCAGGAGCTAAGAATAGTCTA
GA
```

[0090] The plasmids for the 3-vector and 4-vector packaging systems can be modified with similar elements and the intron sequences could potentially be removed without loss of vector function. For example, the following elements could replace similar elements in the 3-vector and 4-vector packaging system:

[0091] Promoters: Elongation Factor-1 (EF-1) (SEQ ID NO: 28), phosphoglycerate kinase

[0092] (PGK) (SEQ ID NO: 49), and ubiquitin C (UbC) (SEQ ID NO: 50) can replace the CMV or CAG promoter (SEQ ID NO: 39). These sequences can also be further varied by addition, substitution, deletion or mutation.

[0093] Poly A sequences: SV40 poly A (SEQ ID NO: 51) and bGH poly A (SEQ ID NO: 52) can replace the rabbit beta globin poly A (SEQ ID NO: 38). These sequences can also be further varied by addition, substitution, deletion or mutation.

[0094] HIV Gag, Pol, and Integrase sequences: the HIV sequences in the Helper plasmid can be constructed from different HIV strains or clades. For example, HIV Gag (SEQ ID NO: 23); HIV Pol (SEQ ID NO: 35); and HIV Int (SEQ ID NO: 36) from the Bal strain can be interchanged with the gag, pol, and int sequences contained in the helper/helper plus Rev plasmids as outlined herein. These sequences can also be further varied by addition, substitution, deletion or mutation.

[0095] Envelope: The VSV-G glycoprotein can be substituted with membrane glycoproteins from feline endogenous virus (RD114) (SEQ ID NO: 53), gibbon ape leukemia virus (GALV) (SEQ ID NO: 54), Rabies (FUG) (SEQ ID NO: 55), lymphocytic choriomeningitis virus (LCMV) (SEQ ID NO: 56), influenza A fowl plague virus (FPV) (SEQ ID NO: 57), Ross River alphavirus (RRV) (SEQ ID NO: 58), murine leukemia virus 10A1 (MLV) (SEQ ID NO: 59), or Ebola virus (EboV) (SEQ ID NO: 60). Sequences for these envelopes are identified in the sequence portion herein. Further, these sequences can also be further varied by addition, substitution, deletion or mutation.

[0096] In summary, the 3-vector versus 4-vector systems can be compared and contrasted, in part, as follows. The

3-vector lentiviral vector system contains: 1. Helper plasmid: HIV Gag, Pol, Integrase, and Rev/Tat; 2. Envelope plasmid: VSV-G envelope; and 3. Therapeutic vector: RSV/5'LTR, HIV Gag, RRE, Env, cPPT, H1, shPARP1, EF1, GFP, WPRE, and a 3'LTR Δ U3. The 4-vector lentiviral vector system contains: 1. Helper plasmid: HIV Gag, Pol, and Integrase; 2. Rev plasmid: Rev; 3. Envelope plasmid: VSV-G envelope; and 4. Therapeutic vector: RSV/5'LTR, HIV Gag, RRE, Env, a cPPT, a H1 element, shPARP1, EF1, GFP, WPRE, and a 3'Δ LTR. Sequences corresponding with the above elements are identified in the sequence listings portion herein.

Example 2

Development of PARP1 Inhibitory RNA for use in a Lentiviral Vector in the Lentiviral Vector System

[0097] The purpose of this Example was to develop a PARP1 inhibitor RNA lentivirus vector.

[0098] Inhibitory RNA Design. The sequence of *Homo sapiens* poly ADP-ribose polymerase (PARP1) mRNA (NM_001618) or *Mus musculus* Parp1 mRNA (NM_007415) was used to search for potential siRNA or shRNA candidates to knock-down PARP1 levels in human or mouse cells. Potential RNA interference sequences were chosen from candidates selected by siRNA or shRNA design programs such as those from the Broad Institute (MIT) Genetic Perturbation Platform (GPP) Web Portal or the BLOCK-iT™ RNAi Designer from ThermoFisher Scientific. Potential RNA interference sequences were chosen from candidates selected by siRNA or shRNA design programs such as from GPP Web Portal hosted by the Broad Institute (<http://portals.broadinstitute.org/gpp/public/>) or the BLOCK-iT RNAi Designer from Thermo Scientific (<https://rnaidesigner.thermofisher.com/rnaiexpress/>).

[0099] Vector Construction. For PARP1 shRNAs, oligonucleotide sequences containing BamHI and EcoRI restriction sites were synthesized by MWG operon. Oligonucleotide sequences were annealed by incubation at 70 degrees Celsius and cooling to room temperature. Annealed oligonucleotides were digested with the restriction enzymes BamHI and EcoRI for one hour at 37 degrees Celsius and then the enzymes were heat-inactivated at 70 degrees Celsius for 20 minutes. In parallel, a lentiviral vector was digested with the restriction enzymes BamHI and EcoRI for one hour at 37 degrees Celsius. The digested lentiviral vector was purified by agarose gel electrophoresis and extracted from the gel using a DNA gel extraction kit from Invitrogen. The DNA concentration was determined by spectrophotometry at the absorbance wavelength of 260 nm. The vector and oligonucleotide sequences were ligated in the ratio 3:1 (insert to vector). The ligation reaction was carried out with T4 DNA ligase for 30 minutes at room temperature. 2.5 microliters of the ligation mixture was added to 25 microliters of STBL3 competent bacterial cells. Transformation was carried out by heat-shock at 42 degrees Celsius. Bacterial cells were streaked onto agar plates containing ampicillin and then colonies were expanded in LB broth. To check for insertion of the oligo sequences, plasmid DNA was extracted from harvested bacteria cultures with the Invitrogen DNA mini prep kit. Insertion of the shRNA sequence in the lentiviral vector was verified by DNA sequencing using a specific primer for which ever promoter is used to regulate shRNA expression. The lentiviral vectors

containing a correct PARP1 sequence were then used to package lentiviral particles to test for their ability to knock-down PARP1. Mammalian cells were transduced with lentiviral particles either in the presence or absence of polybrene. Cells were collected after 2-4 days and protein was analyzed by western blot for PARP1 expression.

[0100] The *Homo sapiens* PARP1 target sequences summarized in Table 1 were identified in respect of these experiments and in relation to the shRNA oligonucleotide sequences outlined in Table 2 herein.

TABLE 1

<i>Homo sapiens</i> PARP1 Target Sequences	
SEQ ID NO.:	Sequence
1	CTTCGTTAGAATGTCTGCCTT
2	GCAGCTTCATAACCGAAGATT
3	CCGAGAAATCTCTTACCTCAA
4	CGACCTGATCTGGAACATCAA
5	GTTGCTGATGGGTAGTACC

[0101] The following *Homo sapiens* PARP1 shRNA oligonucleotide sequences summarized in Table 2 were used in these experiments:

TABLE 2

<i>Homo sapiens</i> PARP1 shRNA Oligonucleotide Sequences	
SEQ ID NO.:	Sequence
6	CTTCGTTAGAATGTCTGCCTTCAGACATTCAACG AAGTTTT
7	GCAGCTTCATAACCGAAGATTCTCGAGAACATT CGCTTTT
8	CCGAGAAATCTTACCTCAACTCGAGTTGAGGA CGGTTTT
9	CGACCTGATCTGGAACATCAACTCGAGTTGAT TCGTTTT
10	GTTGCTGATGGGTAGTACCTCAAGAGAGGTACT ACCCATCAGCA ACTTTT

[0102] The *Mus musculus* PARP1 target sequences summarized in Table 3 were identified in respect of these experiments and in relation to the shRNA oligonucleotide sequences outlined in Table 4 herein:

TABLE 3

<i>Mus musculus</i> PARP1 Target Sequences	
SEQ ID NO.:	Sequence
11	GCACCTCATGAAGCTGTATGA
12	GCACAGTTATCGGCAGTAACA
13	GGAGGCAAGTTGACAGGATCT

TABLE 3 -continued

<i>Mus musculus</i> PARP1 Target Sequences	
SEQ ID NO.:	Sequence
14	TCGACGTCAACTACCGAGAAC
15	GCCCTTGGAAACATGTATGAA

[0103] The following *Mus musculus* PARP1 shRNA oligonucleotide sequences summarized in Table 4 were used in these experiments:

TABLE 4

<i>Mus musculus</i> PARP1 shRNA Oligonucleotide Sequences	
SEQ ID NO.:	Sequence
16	GCACTTCATGAAGCTGTATGACTCGAGTCATACAGCTTC ATGAAGTGCTTTT
17	GCACAGTTATCGCAGTAACACTCGAGTGTACTGCCGA TAACTGTGCTTTT
18	GGAGGCAAGTTGACAGGATCTCTCGAGAGATCCTGTCAA CTTGCCCTCTTTT
19	TGCAGTCAACTACAGAGAACCTCGAGGTTCTCGTAGT TGACGTCGATTTT
20	GCCCTTGGAAACATGTATGAACTCGAGTTCATACATGTT TCCAAGGGCTTTT

[0104] The *Homo sapiens* and *Mus musculus* PARP1 shRNA oligonucleotide sequences outlined in this Example were used in conjunction with the lentiviral vector system discussed herein.

[0105] An experimental therapeutic vector was designed as shown in FIG. 1A (linear form), and FIGS. 1C and 1D (circularized forms). Referring to the circularized vector map shown in FIGS. 1C and 1D, the experimental therapeutic vector includes: a hybrid 5' long terminal repeat (RSV/5' LTR) (SEQ ID NOS: 21-22), a HIV gag (SEQ ID NO: 23), a RRE (Rev-response element) (SEQ ID NO: 24), a Env element (SEQ ID NO: 25), a cPPT (SEQ ID NO: 26), a H1 promoter (SEQ ID NO: 27), a shRNA targeting PARP1 (shPARP1) (SEQ ID NOS: 6-10), a EF1 promoter (SEQ ID NO: 28), a GFP element (SEQ ID NO: 29), a Woodchuck Post-Transcriptional Regulatory Element (WPRE) (SEQ ID NO: 30), and a 3' LTR delta U3 (SEQ ID NO: 31). The presence of GFP is for experimental purposes due to its usefulness in demonstrating transduction in *in vitro* and *in vivo* model systems.

[0106] Further, referring to circularized vector maps shown in FIGS. 1E and 1F, a therapeutic or lentiviral vector has been designed which includes: a hybrid 5' long terminal repeat (RSV/5' LTR) (SEQ ID NOS: 21-22), a HIV gag (SEQ ID NO: 23), a RRE (Rev-response element) (SEQ ID NO: 24), a Env element (SEQ ID NO: 25), a cPPT (SEQ ID NO: 26), a H1 promoter (SEQ ID NO: 27), a shRNA targeting PARP1 (shPARP1) (SEQ ID NOS: 6-10), a Woodchuck Post-Transcriptional Regulatory Element (WPRE)

(SEQ ID NO: 30), and a 3' LTR delta U3 (SEQ ID NO: 31). The therapeutic or lentiviral vector detailed in FIGS. 1E and 1F does not contain GFP.

Example 3

shRNA-Mediated Decrease of PARP1 Protein Expression

[0107] shRNAs designed against *Homo sapiens* PARP1 were tested for their ability to downregulate PARP1 gene expression. The lentiviral vector containing human PARP1 shRNA was packaged as lentiviral particles. Lentiviral particles at a MOI of 1-10 were added to human U251 glioblastoma cells. After 48 hours, cells were lysed and PARP1 expression was measured by immunoblot analysis with a PARP1 specific antibody.

[0108] As shown in Table 5 below, five of the shRNAs designed against PARP1 showed an ability to downregulate PARP1 protein expression. Compared to a 100% control shRNA sequence: Sequence 6 (SEQ ID NO: 6) resulted in 57.1% of PARP1 protein expression; Sequence 7 (SEQ ID NO: 7) resulted in 45.8% of PARP1 protein expression; Sequence 8 (SEQ ID NO: 8) resulted in 47.2% of PARP1 protein expression; Sequence 9 (SEQ ID NO: 9) resulted in 48.8% of PARP1 protein expression; and Sequence 10 (SEQ ID NO: 10) resulted in 27.1% of PARP1 protein expression.

TABLE 5

shRNA-mediated downregulation of <i>Homo sapiens</i> PARP1	
shRNA against <i>Homo sapiens</i> PARP1	Percentage protein expression (Control shRNA = 100%) after transduction with lentivirus expressing shRNA
Control shRNA Sequence (SEQ ID NO: 61)	100
Human PARP1 Sequence 6 (SEQ ID NO: 6)	57.1
Human PARP1 Sequence 7 (SEQ ID NO: 7)	45.8
Human PARP1 Sequence 8 (SEQ ID NO: 8)	47.2
Human PARP1 Sequence 9 (SEQ ID NO: 9)	48.8
Human PARP1 Sequence 10 (SEQ ID NO: 10)	27.1

shRNAs designed against *Mus musculus* PARP1 were tested for their ability to downregulate PARP1 gene expression. The lentiviral vector containing mouse PARP1 shRNA was packaged as lentiviral particles. Lentiviral particles at a MOI of 1-10 was added to mouse Hepal-6 hepatoma cells. After 48 hours, cells were lysed and PARP1 expression was measured by immunoblot analysis with a PARP1 specific antibody. As shown in Table 6 below, five of the shRNAs designed against PARP1 showed an ability to downregulate PARP1 protein expression. Compared to a 100% control shRNA sequence: Sequence 16 (SEQ ID NO: 16) resulted in 22.8% of PARP1 protein expression; Sequence 17 (SEQ ID NO: 17) resulted in 47.7% of PARP1 protein expression; Sequence 18 (SEQ ID NO: 18) resulted in 2% of PARP1 protein expression; Sequence 19 (SEQ ID NO: 19) resulted in 0.2% of PARP1 protein expression; and Sequence 20 (SEQ ID NO: 20) resulted in 2% of PARP1 protein expression.

TABLE 6

shRNA-mediated downregulation of <i>Mus musculus</i> PARP1	
	Percentage protein expression (Control shRNA = 100%) after transduction with lentivirus expressing shRNA
Control shRNA Sequence (SEQ ID NO: 61)	100
Mouse PARP1 Sequence 16 (SEQ ID NO: 16)	22.8
Mouse PARP1 Sequence 17 (SEQ ID NO: 17)	47.7
Mouse PARP1 Sequence 18 (SEQ ID NO: 18)	2
Mouse PARP1 Sequence 19 (SEQ ID NO: 19)	0.2
Mouse PARP1 Sequence 20 (SEQ ID NO: 20)	2

[0109] PARP1 protein expression was found to be reduced in human and mouse cells following shRNA administration. Referring first to FIG. 2, a reduction in PARP1 protein in U251 human glioblastoma cell lines is demonstrated following treatment with lentivirus vectors expressing shRNA. The cell line U251 contains measurable PARP1 protein in cell lysates as indicated in the lanes identified as shCon (i.e., a lentivirus vector containing an irrelevant shRNA sequence that does not affect PARP1 protein expression). Individual shRNA sequences 6-10 (as referred to in Table 2 herein) were cloned into lentivirus vectors, expressed as infectious virus particles and used to transduce U251 cells. 48 hours after transduction, cells were lysed, proteins were separated by polyacrylamide gel electrophoresis and detected by immunoblot assay using anti-PARP1 antibody (Cell Signaling Technology).

[0110] Still referring to FIG. 2, Sequence 6 corresponds with lane shPARP1-1; Sequence 7 corresponds with lane shPARP1-2; Sequence 8 corresponds with lane shPARP1-3; Sequence 9 corresponds with lane shPARP1-4; and Sequence 10 corresponds with lane shPARP1-5. The house-keeping protein Actin was detected with Anti-Actin antibody (Sigma-Aldrich) to confirm that similar amounts of protein were analyzed in each lane of the gel. Sequence 10 was identified as being the most effective for reducing PARP1 protein in human U251 cells.

[0111] Turning to mouse cell experiments, and with reference to FIG. 3, a reduction in PARP1 protein levels in Hepal-6 mouse hepatoma cells was observed following administration of lentivirus vectors expressing shRNAs. The cell line Hepal-6 contains measurable PARP1 protein in cell lysates as indicated in lanes identified as No infection (no lentivirus used) or shCon (lentivirus vector containing an irrelevant shRNA sequence that does not affect PARP1 protein expression). Individual shRNA constructs 16-20 (as referred to in Table 4 herein) were cloned into lentivirus vectors, expressed as infectious virus particles and used to transduce Hepal-6 cells. 48 hours after transduction, cells were lysed, proteins were separated by polyacrylamide gel electrophoresis and detected by immunoblot assay using anti-PARP1 antibody (Cell Signaling Technology). Still referring to FIG. 3, Sequence 16 corresponds with lane shPARP1-1; Sequence 17 corresponds with lane shPARP1-2; Sequence 18 corresponds with lane shPARP1-3; Sequence 19 corresponds with lane shPARP1-4; and Sequence 20 corresponds with lane shPARP1-5. The house-

keeping proteins Actin or Tubulin were detected with antibody reagents (Sigma-Aldrich) as controls for the amount of protein loaded in each lane of the gel. shRNA 16, 17 and 18 were potent for inhibiting PARP1 protein expression. Sequence 19 was identified as being most effective for reducing PARP1 protein in murine Hepal-6.

Example 4

Lentiviral Vector Transduction in Mouse Neurons

[0112] The lentiviral vector system outlined herein has been found to be capable of transduction in mouse neurons. With reference to FIG. 4, wild-type mice were injected with mock (no lentivirus) in the left column of micrographs or LV-shPARP1 also expressing green fluorescence protein in the right column of micrographs, via a steel needle inserted into the substantia nigra region of the mouse brain. The LV-shPARP1-GFP was dosed at 0.1 ml containing approximately 1×10^8 transducing units. 14 days later, mice were sacrificed and the substantia nigra region was excised from the brain, fixed in formaldehyde, and embedded in paraffin. Thin sections were mounted on glass slides and visualized with a fluorescence microscope. TH+ neurons (expressing high levels of tyrosine hydroxylase) generally identify the substantia nigra region and appear red (or white in gray-scale photographs) in FIG. 4. The middle panels depict cells that were transduced with mock (left column) or LV-shPARP1-GFP (see: green [or white in gray-scale photographs] staining in right column). Due to the high intensity of light emitted by GFP, indicating efficient transduction and transgene expression, positively transduced neurons appeared black in this figure and were not present, as expected, in the sham control (left column). The lower panels merge the TH+ neuron staining and GFP+ neuron staining from lentivirus transductions to demonstrate the presence of transduced cells within the substantia nigra including within TH+ neurons.

Example 5

Therapeutic Treatment of Neuronal Death Using Lentiviral Vector System

[0113] The chemical neurotoxin 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes severe and irreversible motor abnormalities in mice, and is widely used to model human PD. See, e.g., Kopin & Markey, 11 *Annu. Rev. Neurosci.*, 81-96 (1988). Treating mice with MPTP lowers the levels of striatal dopamine and its metabolites, because drug neurotoxicity reduces the number of dopamine producing cells in the substantia nigra. The model has been used to test the protective effects of compounds including nitric oxide, which prevent neuronal death after MPTP exposure. See, e.g., Przedborski et al., 93 *Proc. Natl. Acad. Sci. USA.*, 44565-4571 (1996). This model can be employed to measure the potential for preventing death of dopaminergic neurons by pretreating mice with lentivirus vector designed to express a short hairpin RNA sequence (sh) that will reduce neuronal cell expression of PARP (LV-shPARP). The vector can be further modified to express the green fluorescence protein marker that will identify transduced cells (LV-shPARP-GFP) and is compared to a vector that does not express shPARP (LV-GFP).

[0114] Suspensions of LV-shPARP-GFP or LV-GFP are injected into the substantia nigra of healthy adult mice.

Doses are escalated until a toxic level is reached, which results in severe motor impairment or death of the mouse. Using the maximum tolerated dose, mice are treated with LV-shPARP-GFP or control vector. Two weeks later, sentinel animals from each group are sacrificed to confirm transduction of neurons in the substantia nigra. The remaining animals (in groups of 10) are treated with MPTP-HCl, 20 mg/kg dose in saline given four times via intraperitoneal injection with 2 hour intervals. Between 2 and 7 days later, groups of mice are sacrificed, the brain is removed, fixed and embedded in paraffin for sectioning. The substantia nigra region is identified by staining for tyrosine hydroxylase-expressing neurons (TH+) and transduced neurons are identified by expression of GFP. Therapeutic impact of LV-shPARP-GFP is determined by counting the numbers of TH+ or GFP+ neurons in substantia nigra from mice treated with LV-shPARP-GFP or control vector. MPTP is expected to destroy much of the substantia nigra TH+ cells and LV-shPARP-GFP is expected to protect these cells and preserve normal appearance of the substantia nigra. In additional groups of mice treated in the same way with both LV vectors and MPTP, the brains are removed at 7 days after MPTP dosing, the substantia nigra region is isolated by dissection and tissue is frozen at -80 degrees Celsius. Subsequently, the tissue specimens are thawed and dopamine is extracted according to published methods (see: Przedborski et al., infra). LV-shPARP-GFP is expected to preserve normal levels of dopamine production after MPTP treatment, and dopamine levels will be significantly higher in mice treated with LV-shPARP-GFP than mice treated with control vector.

Example 6

Lentiviral Targeting to Neurons using Variants of Envelope Glycoproteins

[0115] Properties of individual envelope glycoproteins impact tissue tropism and the efficiency of delivery of therapeutic genes to the sites of disease. To treat PD, a target for gene therapy is a TH+ cell of the substantia nigra. To optimize targeting to a TH+ cell, various envelope glycoproteins will be compared for their role in improving transduction efficiencies in the TH+ cells of the mouse substantia nigra. As described above in Example 1, an envelope plasmid has been designed and produced which contains the vesicular stomatitis virus G glycoprotein (VSV-G). This envelope plasmid can be compared to other designed envelope plasmids which, in place of VSV-G, includes FUG-C (N-terminal region of rabies virus glycoprotein), gp64 envelope glycoprotein from baculovirus, envelope glycoprotein from baboon endogenous virus or other suitable alternatives for packaging lentivirus particles. In each case, using the envelope plasmid variants, lentivirus vector stocks are produced, injected into mouse brains, and the efficiency of transduction into TH+ cells of the mouse substantia nigra is examined.

Example 7

Testing PARP Genes for Therapeutic Effect of PD

[0116] The studies described herein include a focus on PARP1 and how its modulation can be used to therapeutically treat PD. However, PARP1 is only 1 of approximately 16 closely related PARP genes with similar functions. Using

the techniques for target identification, shRNA production and conversion into lentivirus-delivered miRNA as described herein, the other PARP genes can be tested for their ability to be effective therapeutic vectors in treating PD. Briefly, lentiviral vectors containing the other PARP genes can be injected into a mouse to test for PD correction using the methods, techniques and materials described herein.

Example 8

Method of Designing Synthetic miRNAs for Insertion into a Lentiviral Vector System

[0117] Target short-hairpin sequences that are 19-22 nucleotides long are chosen from a shRNA design program such as, for example, the Invitrogen Block-iT RNAi designer or the RNAi design program from the Broad Institute (MIT). Several sequences are tested for efficient knockdown of a particular gene, such as, for example, PARP. A shRNA sequence that decreases the target gene expression at least 80% is then inserted within a defined microRNA hairpin backbone. MicroRNA (miRNA) hairpin structures can be obtained from the miRBase.org website.

[0118] The chosen shRNA sequence is then inserted within the hairpin structure while leaving the loop sequence unchanged. The antisense shRNA sequence is inserted within the 5-prime sequence of the miRNA hairpin to become the seed sequence for gene targeting. The sense shRNA sequence is modified according to the particular miRNA hairpin structure chosen. As an example, nucleotides 9 and 10 of the sense strand are removed for the miR30 hairpin structure. A miR sequence containing a target sequence such as PARP and a backbone sequence are synthesized with BsrGI and NotI restriction sites by either MWG Operon or IDT. This sequence is inserted into the BsrGI and NotI sites of the miR-acceptor lentiviral vector.

Example 9

Treatment of Human Patients with PD

[0119] Twelve patients aged 35-75 years at least 5 years after initial diagnosis of PD receive bilateral, stereotactic, intraputaminal injections of LV-shPARP compositions (based, for example, on the lentiviral construct shown in FIG. 1B) as described herein (cGMP grade) in a dose escalation study. The likely dose range is 10⁸ transducing units of LV-shPARP in 5 ml of sterile saline [1 transducing unit is the amount of LV-shPARP required to achieve on average, 1 copy of the transgene integrated into the chromosome of a single target cell]. The upper range is expected to be approximately 10¹⁰ transducing units of LV-shPARP. Treated patients are followed for at least 1 year and up to 5 years for changes in locomotor status.

[0120] Changes in clinical status are determined using the Unified Parkinson's Disease Rating Scale, comparing LV-treated to off medication status for a matched group of patients with PD. Patients are also asked to record clinical status in terms of time without troubling dyskinesia, and may also undergo testing with the Purdue pegboard test of hand dexterity, and activities of daily living score. See, e.g., Marks Jr., et al., 9(12) *Lancet Neurol.*, 1164-72 (2010). Patient outcomes after LV-shPARP therapy are compared to previous gene therapy trials testing Adeno-associated virus delivery of glutamic acid decarboxylase gene or aromatic

L-amino acid decarboxylase to increase L-DOPA production or studies using Adeno-associated virus delivery of the neurotrophic growth factor neurturin. See, e.g., Kaplitt et al. 369 (9579) *Lancet Neurol.* 2097-105 (2007); see also Christine et al., 73(20) *Neurology*, 1662-9, (2009). It is rationally predicted that subjects receiving LV-shPARP compositions show improvements in PD and PD-related symptoms.

[0121] The disclosure of the above example embodiments is intended to be illustrative, but not limiting, of the scope of

the inventions, which are set forth in the following claims and their equivalents. Although exemplary embodiments of the inventions have been described in some detail for purposes of clarity of understanding, it will be apparent that certain changes and modifications can be practiced within the scope of the following claims. In the following claims, elements and/or steps do not imply any particular order of operation, unless explicitly stated in the claims or implicitly required by the disclosure.

		Sequences	
SEQ	ID	NO : Description	Sequence
1	<i>Homo sapiens</i>	PARP1 Target Sequence 1	CTTCGTTAGAATGTCTGCCTT
2	<i>Homo sapiens</i>	PARP1 Target Sequence 2	GCAGCTTCATAACCGAAGATT
3	<i>Homo sapiens</i>	PARP1 Target Sequence 3	CCGAGAAATCTCTTACCTCAA
4	<i>Homo sapiens</i>	PARP1 Target Sequence 4	CGACCTGATCTGGAACATCAA
5	<i>Homo sapiens</i>	PARP1 Target Sequence 5	GTTGCTGATGGGTAGTACC
6	<i>Homo sapiens</i>	PARP1 shRNA Oligonucleotide Sequence 1	CTTCGTTAGAATGTCTGCCTTCTCGAGAACGGCAGACAT TCTAACGAAGTTTTT
7	<i>Homo sapiens</i>	PARP1 shRNA Oligonucleotide Sequence 2	GCAGCTTCATAACCGAAGATTCTCGAGAACATCTCGGTT ATGAAGCTGCTTTTT
8	<i>Homo sapiens</i>	PARP1 shRNA Oligonucleotide Sequence 3	CCGAGAAATCTCTTACCTCAACTCGAGTTGAGGTAAAGA GATTCTCGGTTTTT
9	<i>Homo sapiens</i>	PARP1 shRNA Oligonucleotide Sequence 4	CGACCTGATCTGGAACATCAACTCGAGTTGATGTTCCA GATCAGGTCGTTTTT
10	<i>Homo sapiens</i>	PARP1 shRNA Oligonucleotide Sequence 5	GTTGCTGATGGGTAGTACCTCAAGAGAGGTACTACCC ATCAGCAACTTTTT
11	<i>Mus musculus</i>	PARP1 Target Sequence 1	GCACTTCATGAAGCTGTATGA
12	<i>Mus musculus</i>	PARP1 Target Sequence 2	GCACAGTTATCGGCAGTAACA
13	<i>Mus musculus</i>	PARP1 Target Sequence 3	GGAGGCAAGTTGACAGGATCT
14	<i>Mus musculus</i>	PARP1 Target Sequence 4	TCGACGTCAACTACGAGAAC

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<u>Sequences</u>	
SEQ ID NO: Description	Sequence
15 <i>Mus musculus</i> PARP1 Target Sequence 5	GCCCTTGGAAACATGTATGAA
16 <i>Mus musculus</i> PARP1 shRNA Oligonucleotide Sequence 1	GCACTTCATGAAGCTGTATGACTCGAGTCATACAGCTT CATGAAGTGCTTTTT
17 <i>Mus musculus</i> PARP1 shRNA Oligonucleotide Sequence 2	GCACAGTTATCGGCAGTAACACTCGAGTGTTACTGCCG ATAACTGTGCTTTTT
18 <i>Mus musculus</i> PARP1 shRNA Oligonucleotide Sequence 3	GGAGGCAAGTTGACAGGATCTCGAGAGATCCTGTC AACTTGCCTCCTTTTT
19 <i>Mus musculus</i> PARP1 shRNA Oligonucleotide Sequence 4	TCGACGTCAACTACGAGAAACCTCGAGGTTCTCGTAG TTGACGTCGATTTTT
20 <i>Mus musculus</i> PARP1 shRNA Oligonucleotide Sequence 5	GCCCTTGGAAACATGTATGAACTCGAGTTCATACATGT TTCCAAGGGCTTTTT
21 <i>Rous Sarcoma virus</i> (RSV) promoter	GTAGTCTTATGCAATACTCTTGTAGTCTTGCACATGGT AACGATGAGTTAGCAACATGCCTTACAAGGAGAGAAA AAGCACCGTGCATGCCATTGGTGGAAAGTAAGGTGGTA CGATCGCTTATTAGGAAGGCAACAGACGGGCTGGA CATGGATTGGACGAACCACTGAATTGCGCATTGCGA GATATTGATTTAAGTGCCTAGCTCGATACAATAACG
22 5' Long terminal repeat (LTR)	GGTCTCTCTGGTTAGACCAGATCTGAGCCTGGGAGCTC TCTGGCTAACTAGGGAAACCCACTGCTTAAGCCTAATA AAGCTTGCCTTGTAGTCTCAAGTAGTGTGTGCCGTCT GTTGTGTGACTCTGTTAACTAGAGATCCCTCAGACCCCT TTAGTCAGTGGAATCTCTAGCA
23 Helper/Rev; HIV Gag; Viral capsid	ATGGGTGCGAGAGCGTCAGTATTAAGGGGGGAGAAT TAGATCGATGGAAAAAAATTGGTTAAGGCCAGGGGG AAAGAAAAAAATATAAATAAAACATATAAGTATGGCA AGCAGGGAGCTAGAACGATTGCGAGTTAATCCTGGCCT GTTAGAAACATCAGAAGGCTGTAGACAATAACTGGGA CAGCTACAACCCATCCCTCAGACAGGATCAGAAGAAC TAGATCATTATATAACAGTAGCAACCCCTTATTGGGT GCATCAAAGGATAGAGATAAAAGACACCAAGGAAGCT TTAGACAAGATAGAGGAAGAGCAAAACAAAAGTAAGA AAAAAGCACAGCAAGCAGCAGCTGACACAGGACACAG CAATCAGGTAGCCTAAATTACCCCTATAGTGCAGAAC TCCAGGGCAATGGTACATCAGGCCATATCACCTAGA ACTTTAAATGCATGGTAAAGTAGTGTAGAAGAGAAGG CTTTCAGCCCCAGAAGTGTACCCATTTTCAGCATTAT CAGAAGGGAGCCACCCCACAAGATTAAACACCATGCTA AACACAGTGGGGGACATCAAGCAGCAGCATGCAAATGT TAAAAGAGACCATCAATGAGGAAGCTGAGAATGGGA TAGAGTGCATCCAGTGCATGCAGGGCTATTGCACCA GCCAGATGAGAGAACCAAGGGGAAGTGTACATAGCAGG AACTACTAGTACCCCTCAGGAACAAATAGGATGGATGA CACATAATCCACCTATCCAGTAGGAGAAATCTATAAA AGATGGATAATCTGGGATTAATAAAATAGTAAGAAT GTATAGCCCTACCCAGCATCTGGACATAAGACAAGGAC CAAAGGAACCCCTTGTAGGACTATGTAGACCGATTCTAT AAAACCTAAGAGCCGAGCAAGCTTCACAAGAGGTAA AAAATTGGATGACAGAAACCTTGTGTCAAAATGCG ACCCAGATTGTAAGACTATTTAAAAGCATTGGGAC

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		Sequences	
SEQ	ID	NO: Description	Sequence
			AGGAGCGCACACTAGAAGAAAATGATGACAGCATGTCAG GGAGTGCCCCGGGACCCGGCCATAAAGCAAGAGTTTGG CTGAAGCAATGAGCCAAGTAACAAATCCAGTACCCATA ATGATACAGAAAGGCAATTAGGAAACCAAGAAGAAGA CTGTTAAGTGTTCATTGTGCAAAGAAGGGCACATA GCCAAAAATTGCAAGGCCCTAGGAAAAAGGGCTGTT GGAAATGTGAAAGGAAGGGACACCAAATGAAAGAGATTG TACTGAGAGACAGGCTAATTAGGAAAGATCTGGC CTTCCACAAAGGAAGGCCAGGGAAATTCTTCAGAGC AGACCAGAGCCAACAGCCCCACCAGAAGAGAGCTTCA GGTTTGGGAAGAGACAACAACTCCCTCTAGAACAGCAG GAGCCGATAGACAAGGAACTGTATCCTTAGCTTCCCT CAGATCACTTTGGCAGCGACCCCTCGTCACAATAA
24	Rev response element (RRE)		AGGAGCTTGTCCCTGGGTTCTGGGAGCAGCAGGAA GCACTATGGGGCAGCCTCAATGACGCTGACGGTACAG GCCAGACAATTATGTCGTTAGTGCAGCAGCAGAA CAATTGCTGAGGGCTATTGAGGCGCACAGCATCTGT TGCAACTCACAGTCTGGGCATCAAGCAGCTCCAGGCA AGAATCTGGCTGTGAAAGATAACCTAAAGGATCAACA GCTCC
25	Envelope; VSV-G; Glycoprotein envelope-cell entry		ATGAAGTGCCTTTGTACTTAGCCTTTTATTCAATTGGG GTGAATTGCAAGTTCACCATAGTTTCCACACAAACCA AAAAGGAAACTGGAAAATGTTCCCTTAATTACCAT ATTGCCGTCAAGCTCAGATTAAATTGGCATAATGAC TTAATAGGCACAGCCTACAAGTCAAATGCCAAGAG TCACAAGGCTATTCAAGCAGACGGTTGGATGTGTCATG CTTCAAATGGGTCACTACTTGTGATTTCGCTGGTATG GACCGAAGTATAAACACATCCATCCGATCCTTCACT CCATCTGAGAACATGCAAGGAAAGCATTGAACAAA CGAAACAAGGAACCTGGCTGAATCAGGCTCCCTCCT CAAAGTTGGATATGCAACTGTGACGGATGCCGAAGC AGTATTGTCAGGTGACTCTCACCATGTGCTGGTTG ATGAATACACAGGAGAATGGGTGATTACAGTTCATC AACGGAAAATGAGCAATTACATATGCCCACTGTCCA TAACTCTAACACCTGGCATTCTGACTATAAGGTCAAAG GGCTATGTGATTCTAACCTCATTTCCATGGACATCACCT TCTTCAGAGGACGGAGCTATCATCCCTGGGAAAG GAGGGCACAGGGTTCAGAAGTAACTACTTGCTTATGA AACTGGGGCAAGGCTGCAAATGCAATACTGCAAG CATTGGGGAGTCAGACTCCCATCAGGGTCTGGGTTG GATGGCTGATAAGGATCTTGCTGCAAGCAGATTCC CTGAATGCCAGAAGGGCTAAGTATCTGCTCCATCT CAGACCTCAGTGGATGTAAGTCTAATTCAAGCAGTGA GAGGATCTGGATTATCCCTCTGCCAAGAACCTGGA GCAAAATCAGAGCGGGCTTCCAATCTCCAGTGGAT CTCAGCTATCTGCTCTTAAACCCAGGAACCGGTCC TGCTTTCACCATATACTGGTACCTTAAATCTTGGA GACCAGATACATCAGAGTCGATATTGCTGCTCCATCC TCTCAAGAATGGTCGGAATGATCAGTGGAACTACCACA GAAAGGGAACTGTGGGATGACTGGGCACCATATGAAG ACGTGGAAATTGGACCCATGGAGTTCTGAGGACAGT TCAGGATATAAGTTCTTATACATGATTGACATGGT ATGTTGGACTCGATCTCATCTTAGCTCAAAGGCTCAG GTGTTGAAACATCCTCACATTCAAGACGCTGCTTCGCA ACTTCTGATGATGAGAGTTATTGGTGTACTGG GCTATCCAAAATCCAATCGAGCTTGTAGAAGGGTGGT TCAGTAGTTGAAAAGCTCTATTGCTCTTTTCTTAA TCATAGGTTAATCATGGACTATTCTGTTCTCCGAG TTGGTATCCATTTGCAATTAAATTAAAGCACACCAAG AAAAGACAGATTATACAGACATAGAGATGA
26	Central polypurine tract (cPPT)		TTTTAAAAGAAAAGGGGGATTGGGGGTACAGTGC GGGGAAAGAATAGTAGACATAATAGCAACAGACATAC AAACTAAAGAATTACAAAACAAATTACAAAATTCAA AATTTTA

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<u>Sequences</u>	
SEQ ID NO: Description	Sequence
27 Polymerase III shRNA promoters; H1 promoter	GAACGCTGACGTCATCAACCGCTCCAAGGAATCGCG GCCAGTGTCACTAGGGGGAACACCCAGCGCGTGC GCCCTGGCAGGAAGATGGCTGTGAGGGACAGGGGAGT GGCGCCCTGCAATATTTCGATGTCCTATGTGTTCTGG AAATCACCATAAACGTGAAATGTCTTGGATTGGAA TCTTATAAGTCTGTATGAGACCAC
28 EF1	GCTCCGGTCCCCGTCACTGGGAGAGCGCACATGCC ACAGTCCCAGAGAAGTTGGGGAGGGCGGGTAAACTG GAACGGGTGCTAGAGAAGGTGGCGCGGGTAAACTG GGAAAGTGTGCTGTACTGGCTCCGCCCTTTCCCGA GGGTGGGGAGAACCGTATAAAGTGCACTGTGCGC GTGAACGTTCTTTCGCAACGGGTTGCGCCAGAAC ACAGCTGAAAGCTTCGAGGGCTCGCATCTCCCTAC GCGCCCGCCGCCCTACCTGAGGCCCATCCACGCC TTGAGTCGCGCTCGCCGCTAGGTAAAGTCAAG TGAACCTGCGTCGCCGCTAGGTAAAGTCAAG GTCAAGACCGGGCTTGTCCGGCGCCCTTGAGCC TACCTAGACTCAGCCGCTCTCCACGCCCTGCGTAC TGCTTGCTCAACTCTACGTTGCTTGTGTTCTGTTCT GCGCCGTTACAGATCCAAGCTGTGACCGGCCCTAC ATGGAGAGCGACGAGAGCGGCCATGGAGA TCGAGTGGCGCATCACGGCACCCCTGAACGGCGTGGAG TTCGAGCTGGTGGCCGGAGAGGGCACCCCCAACG AGGGCCGCAATGACCAACAGATGAAGAGCACCAAAGG CGCCCTGACCTTCAGCCCCTACCTGAGCCACCTG TGGGCTACGGCTCTACCACTTCGGAACCTACCCAGC GGCTACGAGAACCCCTCCCTGCACGCCATCAACACGG CGGCTACACCAACACCCGATCGAGAAGTACGAGGAC GGCGCCGTGCTGACGTGAGCTTCAGCTACCGCTACGA GGCCGGCCGGCTGATGGGACTTCAGGTGGTGGCA CCGGCTTCCCGAGGACAGCGTGTCTCACCGACAAG ATCATCCGCAGAACGCCACCGTGGAGCACCTG CATGGGGATAACAGTGTGGTGGAGCTTCGCCCC CCTTCAGCCCTGGGAGCCGGCTACTACAGCTTGTG GTGGACGCCATGCACTTCAGAGGCCATCCACCC CAGCATCTGCAAGACGGGGCCCATGTTGCTTCC GCCGCGTGGAGGAGCTGCAAGCAACACCGAGCTGG CATCGTGGAGTACACGACAGCCTTAAGACCCCC CCTTCGCGAGATCCGGCTCAGTGTCCAATTCTGCG TGGACGGCACCGCCGGACCCGGCTCCACCGATCTCG TAA
29 GFP	AATCAACCTCTGATTACAAAATTGTGAAAGATTGACT GGTATTCCTAACATATGTGCTCTTTACGCTATGTGA TACGCTGCTTAAATGCCCTTGATCATGCTATTGCTTCC CGTATGCGTTCAATTCTCTCTTGATAAATCTGG TTGCTGCTCTTATGAGGAGTTGTGGCCGTTGT CAACGTGGCGTGGTGCACGTGTGTTGCTGACGCAAC CCCCACTGGTGGGCAATTGCCACACCTGTCAGCTCT TTCCGGGACTTCGCTTCCCTCCCTATTGCCACGGC GGAACCTCATGCCGCTGCCCTGCCGCTGTGGACAG GGGCTCGCTGGGGCACTGACAATTCCGTGGTGTG TCGGGAAATCATGTCCTTCCCTTGCTGCTCGCTG GTTGCCACCTGGATTCTGCCGGGAGCTTCTGCTAC GTCCTCTGGGCTCAATCCAGCGGACCTTCCTTCCCG GGCCTGCTGCCGGCTCTGCCCTTCCGGCTTCTCG CTTCGCCCTCAGACGAGTCGGATCTCCCTTGGCG TCCCCGCCT
30 Long WPRE sequence	AATCAACCTCTGATTACAAAATTGTGAAAGATTGACT GGTATTCCTAACATATGTGCTCTTTACGCTATGTGA TACGCTGCTTAAATGCCCTTGATCATGCTATTGCTTCC CGTATGCGTTCAATTCTCTCTTGATAAATCTGG TTGCTGCTCTTATGAGGAGTTGTGGCCGTTGT CAACGTGGCGTGGTGCACGTGTGTTGCTGACGCAAC CCCCACTGGTGGGCAATTGCCACACCTGTCAGCTCT TTCCGGGACTTCGCTTCCCTCCCTATTGCCACGGC GGAACCTCATGCCGCTGCCCTGCCGCTGTGGACAG GGGCTCGCTGGGGCACTGACAATTCCGTGGTGTG TCGGGAAATCATGTCCTTCCCTTGCTGCTCGCTG GTTGCCACCTGGATTCTGCCGGGAGCTTCTGCTAC GTCCTCTGGGCTCAATCCAGCGGACCTTCCTTCCCG GGCCTGCTGCCGGCTCTGCCCTTCCGGCTTCTCG CTTCGCCCTCAGACGAGTCGGATCTCCCTTGGCG TCCCCGCCT
31 3' delta LTR	TGGAAGGGCTAATTCACTCCAACGAGATAAGATCTG CTTTTGCTTGTACTGGCTCTCTGGTAGACCGAGATC TGAGCCTGGGAGCTCTGGCTAACTAGGGAACCCACT GCTTAAGCCTCAATAAAGCTGCTGTGACTCTGTTAACTAGA TAGTGTGTGCCGTCTGGTGACTCTGTTAACTAGA GATCCCTCAGACCCCTTTAGTCAGTGTGAAATCTCTA GCAGTAGTAGTTCATGTC

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<u>Sequences</u>	
SEQ ID NO: Description	Sequence
32 Helper/Rev; CMV early (CAG) enhancer; Enhance Transcription	TAGTTATTAATAGTAATTACGGGTCAATTAGTTCA TAGCCCATATATGGAGTCCCGGTTACATAACTTACGG TAAATGCCCGCTGGCTGACCGCCCAACGACCCCCGC CCATTGACGTCAATAATGACGTATGTCATAGTAAAC GCCAATAGGACTTTCAATTGACGTCAATGGTGGACT ATTACGGTAAACTGCCACTTGGCAGTACATCAAGTG TATCATATGCCAAGTACGCCCTATTGACGTCAATGA CGGTAATGCCGCTGGCATTATGCCAGTACATGA CCTTATGGGACTTCTACTTGGCAGTACATCTACGTAT TAGTCATC
33 Helper/Rev; Chicken beta actin (CAG) promoter; Transcription	GCTATTACCATGGTCGAGGTGAGCCCCACGTTCTGCT TCACTCTCCCATCTCCCCCCCCTCCCACCCCCAATT TGTATTATTATTTTAATTATTTGTGCAGCGATGG GGCGGGGGGGGGGGGGGGCGCGCCAGGGGGGGGG GGCGGGGGCGAGGGGGGGGGCGAGGGGGAGAG GTGCGCGGGCAGCCAATCAGAGCGGCCGCTCCGAAA GTTTCCTTTATGGCAGGGCGGGCGGGCGGGCGGGCCCT ATAAAAAGCGAAGCGCGCGGGCGGGCG
34 Helper/Rev; Chicken beta actin intron; Enhance gene expression	GGAGTCGCTGCGTTGCCTTCGCCCGTGCCTCGCG GCCGCTCGCGGCCGCCGCCGGCTCTGACTGACCGC GTTACTCCCACAGGTGAGCGGGCGGGACCGCCCTTC CTCGGGCTGTAATTAGCGCTGGTTAATGACGGCTC GTTCTTTCTGTGGCTGCGTGAACCTTAAGGGCTC CGGGAGGGCCCTTGTGCGGGGGGAGCGGCTCGGG GGTGCCTGCGTGTGTGCGGTGGGGAGCGGCCGCGT CGGCGCGCGCTGGCTCGCGTGTGAGCGCTGCGGGCG CGGCGCGGGCTTGTGCGCTCGCGTGTGCGGAGGG GAGCGCGCCGGGGCGGTGCCCGCGGTGCGGGGGGG GCTGCAGGGAAACAAGGTGCGTGCCTGGGGTGTG CGTGGGGGGGTGAGCAGGGGTGTGGCGCGGCCG GGGCTGTAACCCCCCTGCACCCCTCCCGAGTTG CTGAGCACGGCCGGCTCGGGTGCCTGGCTCCGTGCG GGGCGTGGCGCGGGCTCGCGTGCCTGGCGGGGG GGCGGAGGTGGGGTGCCTGGCGGGCGGGCGCC TCGGGCGGGGGGGCTCGGGGAGGGGCGGGCG CCCAGCAGCGCCGGCGCTGTGAGCGGCCGAGCG CAGCCATTGCTTTATGGTAATCGTGCAGAGGGCGC AGGGACTCTCTTGTCCAATCTGGCGAGGCCAAAT CTGGAGGGCGCCGCCACCCCTTAGCGGGCGCG CGAAGGGCTTCTGCGTGCCTGCCCGCGCCGTC TCCATCTCCAGCCTCGGGCTGCCAGGGGACGGCT GCCCTCGGGGGGAGGGCAGGGCGGGGTTCGC TGGCGTGTGACCGGGCG
35 Helper/Rev; HIV Pol; Protease and reverse transcriptase	ATGAATTGCCAGGAAGATGGAAACCAAAATGATAG GGGAATTGGAGGTTTATCAAAGTAGGACAGTATGAT CAGATACTCATAGAAATCTGGGACATAAAAGCTATAG TACAGTATTAGTAGGACACTACACCTGTCAACATAATT GAAGAAATCTGTTGACTCAGATTGGCTGCACTTTAAAT TTTCCCATAGTCTATTGAGACTGTACAGTAAATTA AAGCCAGGAATGGATGCCAAAGTTAAACATGCG CATTGACAGAAGAAAAATAAAAGCATAGTAAAT TTGTACAGAAATGGAAAAGGAAGGAAAAATTCAAAA ATTGGGCCTGAAAAATCCATACAATACTCCAGTATTG CATAAAGAAAAAAAGACAGTACTAAATGGAGAAAATTA GTAGATTCAAGAGACTTAATAAGAGAACTCAAGATT CTGGGAAGTTCATTAGGAATACACATCCTGCAGGGT AAAAACAGAAAAATCAGTAACAGTACTGGATGTGG CGATGCATATTTCAGTCCCTAGATAAGAGACTTCAG GAAGTATACTGCATTACCATACCTAGTATAAACATG AGACACCAAGGGATTAGATATCAGTACAATGTGCTTCCA CAGGGATGGAAGGATCACCAGCAATTCCAGTGTAG CATGACAATACTTAGAGCTTGTAGAAAACAAATC CAGACATAGTCATCTATCAATACATGGATGTTGTAT GTAGGATCTGACTTAGAAATAGGGCAGCATAGAACAA AAATAGGAAACTGAGACAAACATCTGTGAGGTGGGG

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Sequences	
SEQ ID NO: Description	Sequence
	ATTTACACACAGACAAAAACATCAGAAAGAACCTC CATCCTTGGATGGGTTATGAACCTCATCTGTAAAT GGACAGTACAGCTATAGTCTGCCAGAAAAGGACAG CTGGACTGTCATGACATACAGAAATTAGTGGGAAAAT TGAATTGGCAAGTCAGATTATGCAGGGATTAAAGTA AGGAATATGTAAACTCTTAGGGAACCAAAGCACT AACAGAAGTAGTACCACTAACAGAAGAAGCAGAGCTA GAACCTGGCAGAAAACAGGGAGATTCTAAAAGAACCGG TACATGGAGTGATTATGACCCATCAAAGACTTAATA GCAGAAATACAGAACGGGCAAGGCCATGGACAT ATCAAATTATCAAGAGCCATTAAAAATCTGAAACA GGAAAATATGCAAGAATGAAGGGTCCCCACACTAATG ATGTGAAACAATTAAACAGAGGCAGTACAAAAAAATAGC CACAGAAAGCATAGTAATATGGGAAAGACTCCTAAA TTTAAATTACCCATACAAAAGGAAACATGGGAGCATG GTGGACAGAGTATTGCCAAGGCCACCTGGATTCCCTGAGT GGGAGTTGTCAATACCCCTCCCTTAGTGAAGTTATGGT ACCAGTTAGAAGAACCCATAATAGGACAGCAGAAC TTTCTATGTAGATGGGCAGCCAATAGGGAAACTAAAT TAGGAAAAGCAGGATATGTAACTGACAGAGGAAGACA AAAAGTTGCCCCCTAACGGACACAAACAAATCAGAAG ACTGAGTTACAAGCAATTCTAGCTTGCAGGATT GGGATTAGAAGTAAACATAGTGCAGACACTCACAAATATG CATTGGGAAATCATTCAAGCAACACAGATAAGAGTGA TCAGAGTTAGTCAGTCAAATAATAGGAGCTTAATAAA AAAGGAAAAGTCTACTGGCATGGTACCGCACAC AAAGGAATTGGAGGAATGAACAAGTAGATGGTTGG TCAGTGCTGGAATCAGGAAGTACTA
36 Helper Rev; HIV Integrase; Integration of viral RNA	TTTTTAGATGGAATAGATAAGGCCAAGAAGAACATGA GAAATATCACAGTAATTGGAGAGCAATGGTAGTGATT TTAACCTACACCTGTAGTAGCAGAAATAGTAGGC AGCTGTGATAAATGTGAGCTAAAGGGGAAGGCCATGC ATGGACAAGTAGACTGTAGCCAGGAATATGGCAGCTA GATTGATCACATTAGAAGGAAAGTTATCTGGTAGC AGTTCATGTAGCCAGTGGATATAGAAGCAGAACTAA TTCCAGCAGACAGGCCAGAAAACAGCATACTTCCTC TTAAAATTAGCAGGAAGATGGCCAGTAAACACAGTAC ATACAGACATGGCAGCAATTTCACCACTACAGTT AAGGCCGCTGTTGGCGGGGATCAAGCAGGAATT TGGCATTCCCTACACATCCCAGTCAAGGAGTAATAG AATCTATGAAATAAGAAATTAAAGAAAATTATAGACA GGTAAGAGATCAGGTGAACATCTAACAGCAGCTAC AAATGGCAGTATTCTACACATTTAAAGAAAAGGG GGGATTGGGGGTACAGTGAGGGAAAGAATAGTAG ACATAATAGAACACACATACAAACTAAAGAATTACA AAAACAAATTACAAAATTCAAAATTTCGGTTTATT ACAGGGACAGCAGAGATCCAGTTGGAAAGGACAGC AAAGCTCCTCTGGAAAGGTGAAGGGGCAGTAGTAATA CAAGATAATAGTGACATAAAAGTAGTGCCTAAGAAGAA AAGCAAGATCATCAGGATTATGGAAAACAGATGCC AGGTGATGATTGTGTGGCAAGTAGACAGGATGAGGATT AA
37 Helper/Rev; HIV Rev; Nuclear export and stabilize viral mRNA	ATGGCAGGAAGAAGCGGAGACAGCGACGAAGAACTCC TCAAGGCAGTCAGACTCATCAAGTTCTCTATCAAAGC AACCCACCTCCCAATCCCGAGGGGACCGACAGGCCG AAGGAATAGAAGAAGAAGGTGGAGAGAGACAGAG ACAGATCATTGAGTAGTGAACGGATCCTTAGCACT ATCTGGGACGATCTGGGAGGCCTGTGCTCTTCAGCTA CCACCGCTTGAGAGACTACTCTGATGTAAACGAGGA TTGTGGAACTCTGGGACGCAAGGGGTTGGAAAGCCTC AAATATTGGTGAATCTCCCTACAAATTGGAGTCAGGA GCTAAAGAATAG
38 Helper/Rev; Rabbit beta globin poly A; RNA stability	AGATTTTCCCTGCCAAAAATTATGGGACATCAT GAAGCCCCCTTGAGCATCTGACTTCTGCTAATAAAGGA AATTTATTTCAATTGCAATAGTGTGGAAATTGGT GTCTCTCACTCGGAAGGACATATGGGAGGGCAAATCAT TTAAACATCAGAAATGAGTATTGGTTAGAGTTGGC

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<u>Sequences</u>	
SEQ ID NO: Description	Sequence
	AACATATGCCATATGCTGGCTGCCATGAACAAAGGTGG CTATAAAGAGGTCACTAGTATATGAACACGCCCTGC TGTCCCATCCTTATTCCATAGAAAAGCCTTGACTTGAGG TTAGATTTTTTATTTTGTGTTATTTTTCTTCT TAACATCCTAAAAATTTCCTTACATGTTTACTAGCCA GATTTTCCCTCTCTCTGACTACTCCAGTCATAGCTG TCCCTCTCTTATGAAGATC
39 Envelope; CMV promoter; Transcription	ACATTGATTATTGACTAGTTATAATAGTAATCAATTAC GGGGTCATTAGTTCATAGCCCATATATGGAGTTCCCG TTACATAACTACCGTAAATGGCCCGCCTGGCTGACCG CCCAACGACCCCCGCCCATTGACGTCATAATGACGTA TGTCCCCATAGTAACGCCAATAGGGACTTCCATTGAC GTCATGGGTGGAGTATTACGGTAAACTGCCCACTTG GCAGTACATCAAGTGTATCATATGCCAAGTACGCC TATTGACGTCATTGACGGTAAATGCCCGCCTGGCATT ATGCCAGTACATGACCTTATGGGACTTCCACTTG AGTACATCTACGTATTAGTCATCGTATTACCATGGTGA TGCGGTTTGGCAGTACATCAATGGCGTGGATAGCGG TTTGACTCACGGGGATTCCAAGTCTCACCCATTGAC GTCAATGGGAGTTTGGCACCAAATCAACGGGA CTTCCAAATGTCGTAAACAACTCGCCCAATTGACGC AAATGGCGGTAGGCGTGTACGGTGGAGGTCTATATA AGC
40 Envelope; Beta globin intron; Enhance gene expression	GTGAGTTGGGGACCCTGATTGTTCTTCTTTCGCT ATTGAAATTCATGTTATGGAGGGGAAAGTTT CAGGGTGTGTTAGAATGGGAAGATGTCCCTTGATC ACCATGGACCCCTCATGATAATTGGTTCTTCACTT TACTCTGGTACACAATTGCTCCTCTTATTCTTTTC ATTTCCTGTAACCTTCTGTTAACATTAGCTGATTG TAACGAATTTTAAATTCACCTTTGTTATTGTCAGAT TGTAAGTACTTCTCATTCATCATTTCACAGGCAAT CAGGGTATATTATGTAATTTCAGCACAGTTAGAG AACATTGTTATAATTAAATGATAAGGTAGAATATT TGCATATAAACTGCGCTGGGTGAAATTCTTATTG GTAGAAACAACCTACACCCCTGGTCATCATCTGCC CTTATGGTTACAATGATATAACTGTTGAGATGAGG ATAAAATACTGAGTCACCGGCCCTCTGCTAA CCATGTTCATGCCCTCTCTTCTACAG
41 Primer	TAAGCAGAATTCATGAATTGCCAGGAAGAT
42 Primer	CCATACAAATGAATGGACACTAGGCGGCCACGAAT
43 Gag, Pol, Integrase fragment	GAATTCTGAAATTGCCAGGAAGATGGAAACCAAAAT GATAGGGGAATTGGAGGTTTATCAAAGTAAGACAGT ATGATCAGAACTCATGAAATCTGCGACATAAAGCT ATAGGTACAGTATTAGTAGGACCTACACCTGTCAACAT AATTGGAAAGAAATCTGTGACTCAGATTGGCTGCACTT TAAATTCTCCATTAGTCTTATTGAGACTGTACCAAGTAA AATTAAAGCCAGGAATGGATGGCCAAAGTTAAC ATGGCCATTGACAGAAGAAAAAATAAAAGCATTAGTA GAAATTGTCAGAAATGGAAAGGAAGGAAAGGAAATT CAAAATGGGCTGAAATCCATACATACTCCAGTA TTTGCCATAAGAAAAAGCAGTACTAAATGGAGAA AATTAGTAGATTTCAGAGAACTTAATAAGAGAACTCAA GATTTCGGGAAGTTCAATTAGGAATACCCACATCTGC AGGGTTAAACAGAAAAAATCAGTAACAGTACTGGAT GTGGGGATGTCATATTTCAGTCCCTTAGATAAAGA CTTCAGGAAGTACTGCAATTACCATACCTAGTATAA ACAATGAGACACCAGGGATTAGATACTAGTACAATGTG CTTCCACAGGGATGGAAGGATCACCGAATATTCCA GTGTAGCATGACAAAAATCTTAGAGCCTTTAGAAAAAC AAAATCCAGACATAGTCATCTATCAATACATGGATGAT TTGTATGTAGGATCTGACTTAGAAATAGGGCAGCATAG AACAAAATAGAGGAACGACACAATCTGTTGAGG TGGGGATTACCAACCCAGACAAAAACATCAGAAAG AACCTCCATTCTTGGATGGTTATGAACCTCCATCTG ATAAAATGGACAGTACAGCCTATAGTGTGCCAGAAAAG

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Sequences	
SEQ ID NO: Description	Sequence
	GACAGCTGGACTGTCAATGACATAACAGAAATTAGTGGGAAAATTGAATTGGCAAGTCAGATTATGCAGGGATTA AAGTAAGGCAATTATGTAACATTCTTAGGGAACAAA GCACTAACAGAAGTAGTACCACTAACAGAAGAACAG AGCTAGAAACTGCCAGAAAACAGGGAGATTCTAAAAGA ACCGGTACATGGAGTGTATTATGACCCATAAAAGACT TAATAGCAGAAAATACAGAACAGCAGGGCAAGGCCATG GACATATCAAATTATCAAGAGGCCATTAAAAATCTGA AAACAGGAAAGTATGCAAGAATGAAGGGTCCCCACAC TAATGATGTAAAATTAACAGAGGCCAGTACAAAAAA ATAGCCACAGAAAGCATAGTAATATGGGAAAGACTC CTAAATTAAATTACCCATACAAAAGGAAACATGGGAA GCATGGGGACAGAGTATTGGCAAGCCACCTGGATTCC TGAGTGGAAGTTGTCAATACCCCTCCATTAGTGAAGTT ATGGTACCACTAGTAGAGAAAAGAACCCATAATAGGAGCA GAAACTTCTATGTAGATGGGCAGCCAATAGGGAAAC TAAATTAGGAAAAGCAGGATATGTAACCTGACAGAGGA AGACAAAAGTTGTCCTCTAACGGACACAACAAATCA GAAGACTGAGTTACAAGCAATTCTAGCTAGTTGCAGG ATTGGGATTAGAAGTAAACATAGTGACAGACTCACAA TATGCATTGGGAATCATCAAGCACAAACCGAGATAAGAG TGAATCAGAGTTAGTCAGTCAAATAATAGAGCAGTTAA TAAAAAAGGAAAAGTCTACCTGGATGGGTACCCAGC ACACAAAGGAAATTGGAGGAAATGAAAGTAGATAAA TTGGTCAGTGGAATCTAGGAAAGTACTATTTTAA TGGAAATGATAAGGCCAAGAAGAACATGAGAAATAT CACAGTAATTGGAGAGCAATGGCTAGTGATTTAACCT ACCACCTGTAGTAGCAAAGAAATAGTAGCCAGCTGTG ATAAAATGTCAGCTAAAGGGGAAGCCATGCGATGGACAA AGTAGACTGTAGCCCAGGAATATGGCAGCTAGTTGTA CACATTAGAAGGAAAGTTATCTGGTAGCAGTTCAT GTAGCCAGTGGATATATAAGAAGCAGAAAGTAATTCCAGC AGAGACAGGGCAAGAACAGCATACTTCCCTTAAAT TAGCAGGAAGATGGCCAGTAAAACAGTACATAACAGA CAATGGCAGCAATTCCACCACTTCAAGCTACTACAGTTAAGGCCG CCTGTGGTGGCGGGGATCAAGCAGGAATTGGCATT CCCTACATCCCCAAGTCAGGACTATAGAATCTAT GAATAAGAAATTAAAGAAAATTATAGGACAGGTAAGA GATCAGGCTAACATCTTAAGACAGCAGTACAAATGGC AGTATTCTACACAAATTAAAAGAAAAGGGGGGATTG GGGGTACAGTGAGGGAAAGAATAGTAGACATAAT AGCAACAGACATACAACATAAGAATTACAAAACAA ATTACAAAATTCAAAATTTCGGTTTATTACAGGGA CAGCAGAGATCCAGTTGGAAAGGACCAGCAAAGCTC CTCTGGAAAGGTGAAGGGCAGTACTAATACAAGATA ATAGTGACATAAAAGTAGTGCAAGAAGAAAAGCAA GATCATCAGGATTATGGAAAACAGATGGCAGGTGAT GATTGTGGCAAGTAGACAGGATGAGGATTAA
44 DNA Fragment containing Rev, RRE and rabbit beta globin poly A	TCTAGAAATGGCAGGAAGAAGCGGAGACAGCAGCAAG AGCTCATCAGAACAGTCAGACTCATCAAGCTTCTAT CAAAGCAACCCACCTCCCAATCCCGAGGGACCCGACA GGCCCGAGGAATAGAAGAAGAGGTGGAGAGAG ACAGAGACAGTCATTGAGTAGTGACAGGGATCTTG GCACCTATCTGGACGATCTGGAGCCTGTGCTCTTC AGCTACCAACCCTGAGAGACTTACTCTTGATTGTAAC GAGGATTGTGGAACTCTGGGACGAGGGGTGGAA GCCCTCAAAATTGGTGGAACTCTCTACAATATTGGAG TCAGGAGCTAAAGAAATAGAGGAGCTTGTCTTGGGT TCTTGGGAGCAGCAGGAAGCACTATGGGCCAGCGCTCA ATGACGCTGACGGTACAGGCCAGACAATTATGCTGG TATAGTGACGAGCAAGAACATTGCTGAGGGCTATTG AGGCACACAGCATCTGGCAACTCAGCTGGGG ATCAAGCAGCTCCAGGCAAGAACCTGGCTGTGAAAG ATACCTAAAGGATCAACAGCTCTAGATCTTTTCCCTC TGCCAAAATTATGGGACATCATGAAGGCCCTTGAGC ATCTGACTCTGGCTAATAAGGAAATTATTTTATTG CAATAGTGTTGGAAATTGGTGTCTCACTCGGAA GGACATATGGGAGGGCAATCATTAAAACATCAGAAT GAGTATTGGTTAGGTTGGCAACATATGCCATATG

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Sequences	
SEQ ID NO: Description	Sequence
	CTGGCTGCCATGAACAAAGGTGGCTATAAGAGGTCA CAGTATGAAACAGCCCCCTGCTGCTCATCCCTTATT CATAGAAAAGCCTGACTTGAGGTTAGATTTTTTATA TTTGTTTTGTGTTATTTCCTTAACTCCCTAAAT TTCCCTAACATGTTACTAGCCAGATTTCCCTCTCT CTGACTACTCCCAGTCATAGCTGTCCTCTCTTATG AAGATCCCTGCACCTGAGCCAAGCTGGCGTAATCA TGGTCATAGCTGTTCTGTGAAATTGTTATCCGCTC ACAATTCCACACAAACATACGAGCCGGAAGCATAAAGT GTAAGCCTGGGTGCTTAATGAGTGAGCTAACTCACA TTAATTGCGTTGCGCTACTGCCGTTTCAGTCGGGA AACCTGCGTGCAGGGGATCCGATCTCAATTAGTC GCAACCATAGTCCCAGCCCTAACCTCCGCCATCCGCC CCTAACCTCCGCCAGTCCGCCATTCTCCGCCCATGG CTGACTAATTTTTTATTATGAGAGGGCGAGGCC CTCGGCCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCT TTTTGGAGGGCTAGGCTTTGCAAAAAGCTAACATTGTT TATTGAGCTTATAATGGTTACAAATAAGCAATAGCA TCACAAATTTCACAATAAAAGCATTTCACTGCATT CTAGTTGTTGTTGTCCTAAACTCATCAATGATCTTATC AGCGGGCCGCCCGGG
45 DNA fragment containing the CAG enhancer/promoter/ intron sequence	ACGCGTTAGTTAATAGTAATCAATTACGGGGTCA TAGTTCATAGCCCATAATGGAGTTCCGGCTTACATAA CTTACGGTAAATGGCCCGCTGGCTGACCGCCAACGA CCCCGCCCATTGACGTCATAATGACGTATGTTCCAT AGTAACGCCAATAGGGACTTCCATTGACGTCATGGG TGGACTATTACGGTAAACTGCCACTTGGCAGTACAT CAAGTGTATCATATGCCAAGTACGCCCTATTGACGT CAATGACGGTAAATGCCGCCCTGGCATTATGCCAGT ACATGACCTTATGGACTTTCTACTTGGCAGTACATCT ACGTTATTAGTCATCGTATTACCATGGTCGAGGTGAG CCCCACGTTCTGCTTCACTCTCCCATCTCCCCCCCCCTC CCCACCCCCATTGTTGATTATTATTATTAAATTATT TGTGCAGCGATGGGGGGGGGGGGGGGGGGGGCGCG CCAGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG CGAGGGGGAGAGGTGGCGCAGCCATCAGAGCGG CGCGCTCCGAAAGTTCCTTTATGGCGAGGGCGCG GGCGGGGCCCTATAAAAGCGAACCGCGCGCG GGGAGTCGCTGCGTTGCCTCGCCCCGTGCCCCGTCC GCGCCGCCCTCGCGCCGCCGCCGCCCTGACTGAC CGCTTACTCCCCACAGGTGAGCGGGGGGACGCCCTTC TCCCTGGGCTGTAATTAGCCTTGGTTAATGACGGCT CGTTTCTTCTGTCGTGCGTGAAGCCTAAAGGCT CGGGGAGGGGCCCTTGTGGGGGGAGCGGCTCGGG GGGTGCGTGCCTGTTGCGTGGGGAGCGCCGCG GGGGCGCGCTGCCCCGGCGCTGTGAGCGCTCGCG GCGGCGCGGGGCTTGTGCGCTCCGCGTGTGCGCGAG GGAGCGCGGGGGGGGGGGGGGGGGGGGGGGGG GGCTGCGAGGGGAACAAAGGCTGCGTGCGGGTGTG GGCTGGGGGGGTGAGCAGGGGGTGTGCGCGGGCG CGGGCTGTAACCCCCCTGACCCCCCTCCCCGAGTT GCTGAGCACGCCCGGCCCTCGGGTGGGGCTCCGTG GGGGCGTGGCGGGGGCTCGCCGTGCGGGGGGG TGGCGGCAGGTGGGGGTGCGGGCGGGGGGGCG CTCGGGCGGGGAGGGCTCGGGGGAGGGGGCGGG CCCCGGAGCGCGGCCGCTGCGAGGGCGGGCGAGCC GCAGCCATTGCTTTATGGTAATGCGAGAGGGCG CAGGGACTTCCCTTGCCCAAATCTGGCGAGCCGAAA TCTGGGGGGCCGCCGCACCCCCCTTAGGGGGCG GCGAAGCGGTGCGGCCGCCGGCAGGAAGGAATGGGCG GGGAGGGGCTTGTGCGTGCCTGCGCGCCGCTCCCT CTCCATCTCCAGCCTCGGGGCTGCGCAGGGGACGGC TGCCCTCGGGGGGAGGGCAGGGCGGGGTTCGGCTT CTGGCGTGTGACCGGGGAAATT
46 DNA fragment containing VSV-G	GAATTCATGAAGTGCCTTTGACTTAGCCTTTATT ATTGGGGTGAATTGCAAGTTCACCATAGTTTCCACAC AACCAAAAAGGAAACTGAAAAATGTTCCCTTAATT CCATTATGCCCCGTCAAGCTCAGATTAAATTGGCATA

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		Sequences
SEQ ID NO: Description	Sequence	
	ATGACTTAATAGGCACAGCCTTACAAGTCAAAATGCCA AAGAGTCACAAGGTATTCAAGCAGACGGTTGGATGTG TCATGCTCCAAATGGGTCACTACTTGTGATTCCGCTG GTATGGACCGAAGTATAACACATTCATCCGATCCT TCACTCCATCTGAGAACATGCAAGGAAGCATTGAA CAAACGAAACAAGGAACCTGGCTGAATCCAGGCTTCCC TCCTCAAAGTTGGATATGCAACTGTGACGGATGCCG AAGCACTGATTGTCCAGGTGACTCTCACCATGTGCTG GTTGATGAATAACAGGAGAATGGGTGATTCAAGTT CATCAACGGAAAATGCAGCAATTACATATGCCCACTG TCCATAACTCTACAACCTGGCATTGACTATAAGGTC AAAGGGCTATGTGATTCTAACCTCATTTCCATGGACAT CACCTCTTCTCAGAGGACGGAGAGCTATCATCCCTGG GAAAGGGGGCACAGGGTTCAGAAGTAACACTTTGCT TATGAAACTTGAGGGCAAGGCTGCAAATGCAACTG CAAGCATGGGGAGTCAGACTCCCATCAGGTGTCAGG TCGAGATGGGCTGATAAGGATCTTGTGTCAGGCCAGA TTCCCTGAATGCCAGAGGGTCAAGTATCTCTGCTC ATCTCAGACCTCAGTGGATGTAAGTCTAAATCAGGACG TTGAGAGGATCTGGATTATCCCTCTGCAAGAAC TGGAGCAAAATCAGAGCGGGCTTCCAATCTCTCAG GGATCTCAGTATCTGCTCTAAACCCAGGAACCG GTCCTGCTTCAACCATAAATCAATGGTACCTTAAACT TTGAGACACAGATACTCAGAGTCGATATTGCTGCTCA ATCCTCTCAAGAATGGTGGAAATGATCAGTGGAACTAC CACAGAAAGGAACCTGGGATGACTGGGACCCATAT GAAGACGTGAAATTGGACCAATGGAGTTCTGAGGA CCAGTTCAAGGATAAACTGGGACTTATACATGATTGGAC ATGGTATGGGACTCCGATCTTACATTTAGCTCAAAGG CTCAGGTGTTGCAACATCCCTCACATTCAAGACGCTGCT CGCAACTCTCTGATGATGAGAGTTATTGGTGTGATA CTGGGCTATCCAAAATCCAATCGAGCTTAGAAGGT TGGTTCAAGTAGTTGGAAAGCTCTATTGCTCTTTTC TTTATCATAGGGTAAATCATGGACTATTCTGGTCTC CGAGTTGGTATCCATTTGCAATTAAAGCACAC CAAGAAAAGACAGATTATACAGACATAGAGATGAGA ATTC	
47 Rev; RSV promoter; Transcription	ATGGCAGGAAGAAGCGGGAGACAGCGACGAAGAACTCC TCAAGGCAGTCAGACTCATCAAGTTCTCTATCAAAGC AACCACCTCCCAATCCCGAGGGGACCCGACAGGCCCG AAGGAATAGAAGAAGAAGGTGGAGAGAGAGACAGAG ACAGATCATTGATTAGTGAACGGATCCTTAGCACTT ATCTGGGACGATCTGCGAGCCTGTGCTCTTCAGCTA CCACCGCTTGAGAGACTACTCTTGTATTGTAACGAGGA TTGTGGAACCTTGGGACCGCAGGGGGTGGGAAGCCCTC AAATATTGGTGAATCTCTACAAATTGAGTCAGGA GCTAAAGAATAG	
48 RSV promoter and HIV Rev	CAATTGCGATGTACGGGCCAGATATACCGTATCTGAG GGGACTAGGGTGTGTTAGGGAAAGCGGGCTTCGG TTGTCAGCGGTTAGGAGTCCCTCAGGATATAGTAGTT TCGCTTTGATAGGGGGAAATGTAGTCTTATGC AATACACTTGTAGTCTGCAACATGGTAACGATGAGTT AGCAACATGCTTACAAGGAGAGAAAAGCACCGTGC ATGCCATTGGTGGAAAGTAAGGTGGTACGATCGTGCCT TATTAGGAAGGCAACAGACAGTCGACATGGATTGGA CGAACCCACTGAATTCCGATITGCAGAGATAATTGTATT TAAGTGCTAGTCGATACAATAAACGCCATTGACCA TTCACCACTGGTGTGCACTTCAAGCTCGAGCTCGTT TAGTGAACTGTCAGATGCCCTGGAGACGCCATCACGC TGTTTGACCTCCATAGAAGACACCCGGACCGATCCAG CCTCCCCCTGAAGCTAGCGATTAGGCATCTCCTATGGC AGGAAGAAGCGGGAGACAGCGACGAAGAACTCCTCAAG GCAGTCAGACTCATCAAGTTCTCTATCAAAGCAACCC ACCTCCCAATCCCGAGGGGACCCGACAGGCCAGGG AATAGAAGAAGAGTGGAGAGAGACAGAGACAG ATCCATTGCAAGTAGTGAACGGATCTTAGCACTTATCTG GGACGATCTGCGGAGCCTGTGCTCTTCAGCTACCAC GCTTGAGAGACTTACTCTTGATTGTAACGAGGATTGT	

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<u>Sequences</u>	
SEQ ID NO: Description	Sequence
	GAACCTCTGGGACGCAGGGGTGGGAAGCCCTCAAAT ATTGGTGAATCTCTACAATATTGGAGTCAGGAGCTA AAGAATAGTCTAGA
49 Promoter; PGK	GGGGTTGGGTTGGCCTTTCCAAGGCAGCCCTGGGT TTGGCAGGGACGCCCTGCTCTGGCGTGTTCCGGG AAACGCAGCGGCCGACCCCTGGGTCTCGCACATTCTT CACGTCGGTTCGCAGGGTCAACCGGATCTCGCCGCTA CCCTTGTGGGCCCCCGCGACGCTTCTGCTCCGCC TAAGTCGGGAAGGTTCTTGGGTTGCGGGTGC ACGTGACAACAGGAAGCCGACGTCTCACTAGTACCT CGCAGACGGACAGGCCAGGGAGCAATGGCAGCGC CGACCGCGATGGGCTGGGCAATAGCGGCTGCTCAGC AGGGCGCGCAGAGCAGCGCCGGGAAGGGCGGTG CGGGAGGGGGGTGTGGGGCGGTAGTGTGGCC CCTGCCCAGCGGGTGTCCCGATTCTGCAAGCCTCGG AGCGCACGTCGGCAGTCGGCTCCCTCGTTGACCGAATC ACCGACCTCTCCCCAG
50 Promoter; Ubc	GCGCCGGGTTTGGCGCCTCCCGGGCGCCCCCTCC TCACGGCGAGCCGCTGCCACGTCAAGCAAGGGCGCAG GAGCGTTCCGTATCCTCCGCCGACGCTCAGGACAG CGGCCCGCTGCTCATAAAGACTCGGCCTAGAACCCAG TATCAGCAGAAGGACATTAGGACGGGACTTGGGTGA CTCTAGGGCACTGGTTCTTCCAGAGAGCGGAACAG GCGAGGAAAAGTAGTCCCTCTCGGGATTCTGGGAG GGATCTCGTGGGGCGGTGAACGCCATGATTATAA GGACGGCCGGGTGTGCCACAGCTAGTCCGTCGAGC CGGGATTGGGTGCGGTTCTTGTGGATCGCTGTG ATCGTCACTTGGTAGTGGGGCTGCTGGCTGGCG GGGCTTCGTGGCGCCGGCCGCTCGTGGGACGGAA GCGTGTGGAGAGACCCCAAGGGCTGTAGTCTGGGT GCGAGCAAGGTTGCCCTGAACTGGGGTTGGGGGG CGCACAAAATGGCGGTGTTCCCGACTTGAATGAA GACGTTGAAAGCGGGCTGTGAGTCGTTGAAACAA GTGGGGGCAATGGTGGCGGAAGAACCAAGGTCT GAGGCTTCGCTAATGGGAAAGCTTATTGGGT AGATGGGCTGGGCACCATCTGGGACCTGACGTGA GTTTGTCACTGAGGAACCTGGGTTTGTGCTGTT TGCGGGGCGGCAGTTATGCGGTGCCGGTGGGAGTGC ACCCGTAACCTTGGGAGCGCCGCTCGTGTG ACGTACCCGTCTGGGTTATAATGCAAGGTGGG CCACCTGGCGTAGGTGTGGCTAGGCTTCTCGT CAGGACGCAAGGGTCCGGCCTAGGGTAGGCTCTCTGA ATCGACAGGGCCGGACCTGGTAGGGGGAGGGATA AGTGAGGCGTCAGTTCTGGTGGTTATGTACCTA TCTCTTAAGTAGCTGAAGTCCGGTTTGAACTATGCG CTCGGGGTGGCAGGTGTGTTGTGAAGTTTGTACCTA ACCTTTGAAATGTAATCATTTGGGCAATATGTAATT TCAGTGTAGACTAGTAA
51 Poly A; SV40	GTTTATTGCACTTATAATGGTTACAATAAGCAATA GCATCACAAATTCAAAATAAGCATTTTCACTGC ATTCTAGTTGTGGTTGTCAAACATCAATGTATCTT ATCA
52 Poly A; bGH	GACTGTGCCCTCTAGTTGCCAGCCATCTGGTTGCC CTCCCCCGTGCCTTCTGACCCCTGGAGGTGCCACTCC CACTGTCCTTCTAATAAAATGAGGAATTGCATCGC ATTGTCGAGTAGGTGTCATTCTATTCTGGGGGTGG GTGGGGCAGGACAGCAAGGGGGAGGATGGGAAGACA ATAGCAGGCATGCTGGGATGCCGTGGCTATGG
53 Envelope; RD114	ATGAAACTCCCAACAGGAATGGTCAATTATGTAGCCT ATAATAAGTTCGGGAGGGTTGACGACCCCGCAAGG CTATCGCATTAGTACAAAAACACATGGTAAACCATGC GAATGAGCGGGAGGGCAGGTATCGAGGCCACCGA ACTCCATCCAACAGGTAACTGCCAGGCAAGACGGC TACTTAATGACCAACAAAAATGAAATGAGAGTCAC TCCAAAAATCTCACCCCTAGCGGGGAGAACTCCAGA

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Sequences	
SEQ ID NO: Description	Sequence
	ACTGCCCTGTAAACACTTCCAGGACTCGATGCACAGT TCTGTTATACTGAATACCGCAATCGAGGGCAATAA TAAGACATACTACACGCCACCTTGCTAAAATACGGT CTGGAGCCCTCAACGAGGTACAGATATTACAAAACCC AATCAGCTCTACAGTCCCCCTGTAGGGCTCTATAAA TCAGCCGTTGGCTGGAGGTACAGATATTACAAAACCC TCTCCGATGGTGGAGGACCCCTCGATACTAAGAGAGT TGGACAGTCCAAAAAAAGGCTAGAACAAATTCTATAAGG CTATGCATCCTGAACCTCAATACCACCCCTAGGCCGC CCAAAGTCAGAGATGACCTTAGCCTTGATGCACGGACT TTTGATATCCTGAATACCACTTTAGGTTACTCCAGATG TCCAATTAGCCCTGCCAAGATTGTTGGCTCTGTTA AAACTAGGTACCCCTACCCCTTGCAGTACCCACTCCC TCTTTAACCTACTCCCTAGCAGACTCCCTAGCGAATGCC TCCGTGCAAGATTATACTCCCTCTTGGTCAACCGATG CAGTTCTCCAACCTCGTCCTGTTTACTTCCCTTCTTCA ACGATACGGAACAAATAGACTTAGGTGCAGTCACCTT ACTAATGCACTCTGTAGCCAATGTCAGTAGTCCTT TGTGCCCTAAACGGGTCACTTCCCTCTGTGGAAATAA CATGGCATACACCTATTACCCAAAACTGGACAGGAC TTTGGCTCCAAGGCTCCCTCTCCCGACATTGACATCA TCCCGGGGATGAGCCAGTCCCCATTCTGCATTGAT CATTATATACATAGACCTAACGAGCTGAGCTCAT CCCTTTACTAGCTGGACTGGGAATCACCGCAGCATCA CCACCGGAGCTACAGGCTAGGGTGTCTCGTCACCCAG TATAAAAATTATCCCATCAGTTAATATCTGATGTC GTCTTATCCGGTACCATACAAGATTACAAGACAGG AGACTCGTTAGCTGAAGTAGTTCTCCAAAATAGGAGGG GAATGGACCTACTAACGGCAGAACAAAGGAGGAATTG TTAGCTTACAAGAAAATGCTGTTTTATGCTAACAA GTCAGGAATTGTGAGAACAAAATAAGAACCCCTACAA GAAGAAATTACAAAACGCAAGGAAAGCCTGGCATTCA ACCCTCTCTGGACCGGGCTGCAGGGCTTCTCCGTAC TCCTACCTCTCTGGACCCCTACTCACCTCTACTCA TACTAACCATGGGCATGCGTTTCAATGATTGGTCC AATTGTTAAAGACAGGATCTCAGTGTCAGGCTCTG GTTTGACTCAGCAATATCACCGCTAAACCCATAGA GTACGAGCCATGA
54 Envelope; GALV	ATGCTTCACCTCAAGCCCGCACACCTCGGCACCA GATGAGTCTGGAGCTGGAAAAGACTGATCATCTCT TAAGCTCGTATTGGAGACGGAAAACGAGTCTGCA GAATAAGAACCCCAACAGCTGTGACCCCTACCTGGC AGGTAAGTCCAAACTGGGACGTTGCTGGACAAA AAGGAGTCCAGGCCCTTGGAACTTGGTGGCCCTCT TACACCTGATGTATGCCCTGGCGCCGGTCTGAGT CCTGGGATATCCGGGATCCGATGATCTCGTCTCTAA AGAGTTAGACCTCTGATTCAAGACTATACTGCCGCTT TAAGCAAATCACCTGGGAGGCCATAGGGTGCAGCTAC CCTCGGGCTAGGACAGGATGGCAGGAAATTCCCTCT CGTGTCTCCCGAGCTGGCGAACCCATTAGAAAGCTA GGAGGTGTTGGGGCTAGAATCCCTATACTGTAAGA ATGGAGTTGAGACCCAGGGTACCGTTATTGGCAC CCAAGTCTCATGGGACCTCTAAACTGTAAAATGGGAC AAAAATGTGAAATGGGAGAAAATTCTCAAAGTGTG AACAAACCGCTGGTGTAAACCCCTCAAGATAGACTTC ACAGAAAAGGAAAACCTCCAGAGATTGGATAACCG AAAAAACCTGGGAAATTAGGTTCTATGTTATGGACAC CCAGGCATACAGTGTGACTATCGCTTAGAGGTCACTAA CATGCCGGTTGTGGCAGTGGCCAGACCCCTGTCCTG CGGAACAGGGACCTCTAGCAAGCCCTCACTCCCT CTCTCCACCGAAAGGCCGCCACCCCTTACCCCC GGCGGCTAGTGAGCAACCCCTGCGGTGATGGAGAA ACTGTTACCCCTAAACTCTCGCCTCCACCGATGGCGA CCGACTCTTGGCCTGTGAGGGGCCCTCTAACCTT GAATGCTACCAACCCAGGGGCCACTAAGTCTGCTGGC TCTGTTGGGATGAGCCCTTATTATGAAGGGATA GCCTCTCAGGAGAGGTGCGTTATACCTCAACCATAC CCGATGCCACTGGGGGCCAAGGAAAGCTTACCCCTCA CTGAGGTCTCCGGACTGGGTATGCATAGGAAGGTG

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<u>Sequences</u>	
SEQ ID NO: Description	Sequence
	CCTCTTACCCATCAACATCTTGCAACCAGACCTTACCC ATCAATTCTCTAAAACCATCAGTATCTGCTCCCTCA AACCATAGCTGGTGGGCCTGCAGCACTGGCCTCACCC CTGCCCTCTCACCCTCAGTTTTAATCAGCTAAAGACTT CTGTGTCAGGTCCAGCTGATCCCCCGCATCTATTAC ATTCTGAAGAAACCTTGTGACAAGCTATGACAAATCA CCCCCCAGGTTAAAAGAGAGCCTGCCTCACTTACCC AGCTGCTCTGGGTTAGGGATTGCGGAGGTATAG GTACTGGCTCAACCAGCCCTAATTAAAGGGCCCATAGAC CTCCAGCAAGGCCAACCGCTCCAATGCCATTGAC CGCTGACCTCCGGGCCCCCTCAGGACTCAATCAGCAAGC TAGAGGACTCACTGACTCCCTATCTGAGGTTAGTACTC CAAATAGGAGAGGCCTTGACTTACTATTCTTAAAGA AGGAGGCCCTGCGCGCCCTAAAAGAGAGTGTGTT TTTATGTAGACCACTCAGGTGCACTGAGACTCCATG AAAAAACTTAAAGAAAGACTAGATAAAAGACAGTTAG AGCGCCAGAAAACCAAACCTGGTATGAAGGGTGGTT CAAAATCCTCCCTGTTTACTACCTACTATCAACCAT CGCTGGGCCCTATTGCTCCCTTTGTTACTCACT TGGGCCCTGCATCATCAAAATTAATCCAAATTCA ATGATAGGATAAGTGCAGTCAAAATTGTCCTTAA CAGAAATATCAGACCCTAGATAACGAGGAAAACCTT AA
55 Envelope; FUG	ATGGTTCCGCAGGTTCTTTGTTGACTCCTCTGGGT TTTCGTGTTTCGGAAGTTCCCATTTACACGATA CCAGACGAACTTGGTCCCTGGAGCCATTGACATACA CCATCTCAGCTGTCCAAATAACCTGGTTGAGGATG AAGGATGTAACCAACCTGTCGAGGTCTCCATATGGAA CTCAAAGTGGGATACTCAGCCATCAAAGTGAACGG GTTCACTGCACAGGTTGTGACAGAGGGAGAGCCT ACACCAACTTGTGTTGACTCACAACCAATTCAAG AGAAAAGCATTTCGCCCCACCCAGACGATGTAGAGC CGCGTATAACTGGAAGATGGCGGTGACCCAGATATG AAGAGTCCCTACACAATCCATACCCGACTACCACTGG CTTCGAACCTGTAAGAACCCAAAAGAGTCCCTATTAT CATATCCTAACAGTGTGACAGATTGGACCCATATGACA AATCCCTCACTCAAGGGCTTCCCTGGCGGAAAGTGC TCAGGAATAACGGTGTCTTACCTACTGCTCAACTAA CCATGATTACACCAATTGGATGCCGAGAATCCGAGAC CAAGGACACCTTGTGACATTTCACCAATAGCAGAGGG AAGAGAGCATCCAAACGGGAACAGACTTGGGCTTGG TGGATGAAAGAGGCCCTGATAAGTCTTAAAGGAGC ATGCAGGCTCAAGTTATGTGGAGTTCTGGACTTAGAC TTATGGATGGAACATGGTCCGATGCAAACATCAGAT GAGACCAATGGTGCCTCCAGATCAGTTGGTGAATT GCACGACTTGCAGACGAGATCGAGCATCTCGTTG TGGAGGAGTTAGTTAAGAAAAGAGAGGAATGTCTGGA TGCATTAGAGTCCATCATGACCCAAAGTCAGTAAGTT TCAGACGCTCAGTCACCTGAGAAAACATTGTCCTCAGGG TTTGGAAAAGCATATACCATATTCAACAAAACCTTGAT GGAGGCTGATGCTCACTACAAGTCAGTCCGGACCTGGA ATGAGATCATCCCTCAAAAGGGTGTGAAAGTGGGA GGAAGGGGCCATCCTCATGTGAACAGGGGTGTTTCAA TGGTATAATAATTAGGGCTGACGACCATGTCCTAATCC CAGAGATGCAATCATCCCTCCTCCAGCAACATATGGAG TTGTTGGAATCTTCAGTTATCCCTGATGCCACCCCTG GCAGACCCCTTCACTGAAAGAAGGTGATGAGGC TGAGGATTTGTAAGGTTCACCTCCCCGATGTGTACA AACAGATCTCAGGGTTGACCTGGGCTCCCGAAGTGG GGAAAGTATGATTGATGACTGCAGGGCCATGATTGG CCTGGTGTGATAATTCCCTAATGACATGGTGCAGAG TTGGTATCCATCTTGCAATTAAAGCACACCAAG AAAAGACAGATTATACAGACATAGAGATGAACCGAC TTGGAAAGTAA
56 Envelope; LCMV	ATGGGTCAAGATTGTGACAATGTTGAGGCTCTGCCTCA CATCATCGATGAGGTGATCAACATTGTCATTATTGTC TTATCGTGTACACGGGTATCAAGGCTGTCACAATT GCCACCTGTGGGATATTGCGATTGATCAGTTCCCTACTT

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<u>Sequences</u>	
SEQ ID NO: Description	Sequence
	CTGGCTGGCAGGTCCCTGTCATGTACGGTCTTAAGGG ACCCGACATTACAAGGAGTTACCAATTAAAGTCAG TGGAGTTGATATGTCACATCTGAACCTGACCAGGCC AACGCATGTTCAAGCCAACAACTCCCACATTACATCAG TATGGGGACTCTTGACTAGAATTGACCTTCACCAATG ATTCCCATCATCAGTCACAACTTTGCAATCTGACCTCTG CCTTCACAAAAAGACCTTTGACCACACACTCATGAGT ATAGTTCGAGCCTACACCTCAGTATCAGAGGGAACTC CAACTATAAGGCAGTATCCTGCGACTTCACAAATGGCA TAACCATCCAAATACAACTTGACATTCTCAGATGACAA AGTGCTCAGAGCAGTGTAGAACCTTCAGAGGTAGAGT CCTAGATATGTTAGAACCTGCCTTCGGGGGAAATACA TGAGGAGTGGCTGGGGCTGGACAGGCTCAGATGGCAA GACCACCTGGTGTAGCCAGCGAGTTACCAATACCTGA TTATACAAAATAGAACCTGGGAAACCACTGCACATAT GCAGGGTCTTTGGGATGTCAGGATTCTCTTTCCCAA GAGAAGACTAATTCTTCACTAGGAGACTAGCGGGCA CATTCACTGGACATTGTCAGACTCTTCAGGGGTGGAG AATCCAGGTGGTTATTGCGCTGACCAAATGGATGATTCT TGCTGCAGGCTTAAGTGTTCGGAAACACAGCAGTTG CGAAATGCAATGAAATCATGATGCCGAATTCTGTGAC ATGCTGGCACTAATTGACTACAACAAAGGCTGCTTTGAG TAAGTCAAAGAGGAGCTAGAATCTGCTTGCACTTAT TCAAAACAAACAGTGAATTCTTGATTTCACTGAACTA CTGATGAGGAACCACTTGAGAGATCTGATGGGGTGCC ATATTGCAATTACTCAAAGTTTGTTGACCTAGAACATG CAAAGACCGCGAAACTAGTGTCCCCAAGTGTGGCTT GTCACCAATGTTCTACTTAAATGAGACCCACTTCAG TGATGAGGAACAGGATCAACATGATTACA GAGATGTTGAGGAAGGATTACATAAAAGAGGAGGGGA GTACCCCCCTAGCATTGATGCCATTCTGATGTTTCA CATCTGCATATCTAGTCAGCATCTCTGACCTTGTC AAATACCCAAACACAGGCACATAAAAGGTGGCTCATG TCCAAAGCCACACCGATAACCAACAAAGGAATTGTA GTTGTGGTGCATTAAAGGTGCCCTGGTGTAAAACCGTC TGGAAAAGACGCTGA
57 Envelope; FPV	ATGAACACTCAAATCTGGTTTCGCCCTTGGCAGT CATCCCCACAAATGCAGACAAAATTGTCCTGGACATC ATGCTGTATCAAATGGCACCAAGTAACACACTCACT GAGAGAGGAGTAGAAGTGTCAATGCAACCGGAAACAG TGGAGCGGACAAACATCCCCAAATTGCTCAAAGG GAAAGAAACCACTGATCTGCCAATGCCACTGTAG GGACCATACCGGACCCCTCAATGCCACCAATTCTA GAATTTCACTGATCTAATAATCAGAGGAGCGAGAAG AAATGATGTTGTTACCCGGGAAGTTGTTAATGAAAG AGGCATTGCGACAAATCTCAGAGGATCAGGTGGGATT GACAAAGAAACATGGGATTACATATAGTGAATAA GGACCAACGGAACAACTAGTGCATGAGAAGATCAGG GTCTTCATTCTATGCGAAATGGAGTGGCTCTGTCAA ATACAGACAATGCTGTTCCACAAATGACAAATCA TACAAAAACACAGGAGAGAACGCTCTGATAGTCT GGGAATCCCACCATTCAGGATCAACCCGAACAGAC CAAACATATGGGAGTGGAAATAACTGATAACAGTC GGGAGTCCAAATATCATCAATCTTGTGCCGAGTCC AGGAACACGACCGAGATAATGCCAGTGGGAGGG ATTGATTTATTGGTGTGATCTGGATCCAAATGATA GTTACTTTAGTTCAATGGGCTTCATAGCTCAAAT CGTGCAGCCTTGTGAGGGAAAGTCATGGGATCCA GAGCGATGTCAGGTTGATGCCAATTGCGAAGGGGAA TGCTACACAGTGGAGGGACTATAACAGCAGATTG TTTCAAAACATCAATAGCAGAGCAATTGCAAATGCC CAAGATATGAAAACAGGAAAGTTATTATGGAAC GGGATGAGGAACAGTCCCGAACCTTCCAAAAAGGA AAAAAGAGGCTGTTGGCCTATAGCAGGGTTATT GAAAATGTTGGGAAGGCTGGTCGACGGGTGGTAC GTTTCAGGATCAGAATGCAACAGGAGAAGGAAC AGCAGACATACAAAAGCACCAATCGCAATTGATCAG ATAACCGGAAAGTTAAATAGACTCATTGAGAAA ACCAGCAATTGAGCTAATAGATAATGAATTCACTGAG

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<u>Sequences</u>	
SEQ ID NO: Description	Sequence
	<pre>GTGGAAAAGCAGATTGCGAATTAACTTAAGTGGACCAA AGACTCCATCACAGAAAGTATGCTTACAATGCTGAAC TTCTTGCGCAATGGAAAACCAGCACACTATTGATTG GCTGATTTCAGAGATGAAACAAGCTGTATGACCGAGTGA GGAAACAAATTAAAGGAAAATGCTGAAGAGGATGGCAC TGGTTGCTTTGAAATTTCATAAATGTGACGATGATTG TATGGCTAGTATAAGGACAATACTTATGATCACAGCA AATACAGAGAGAAGGAGATGCAAAATAGAATACAAT TGACCCAGTCAAATTGAGTAGTGGCTACAAGATGTGA TACTTTGGTTTAGCTCGGGCATCATGCTTTGCTTC TTGCCATTGCAATGGGCTTGTGTTCATATGTGTAAGA ACGGAAACATCGCGGTGCACTATTGTATATAA</pre>
58 Envelope; RRV	<pre>AGTGTAAACAGAGCACTTAATGTGATAAGGCTACTAG ACCATACCTAGCACATTGCGCCATTGCGGGACGGGT ACTTCTGCTATAGCCCCAGTTGCTATCGAGGAGATCGGA GATGAGGGCGTCTGATGGCATGCTTAAGATCCAAGTCTC CGCCCAAATAGTCTGGACAAGGCAGGCACCCACGCC CACACGAAGCTCCGATATATGGCTGGCATGATGTTCA GGAATCTAAGAGAGATTCCCTGAGGGTGTACACGTCG CAGCGTGTCCCATACTGGGACGATGGGACACTTCATC GTCGCACACTGTCACCCAGGACTACCTCAAGGTTTC GTTCGAGGAGCGCAGATTGCGACGTGAAGGATGTAAG GTCCAAATACAAGCACAATCCATTGCCGGTGGGTAGAGA GAAGTTCTGGTTAGACCAACTTGGCGTAGAGCTGC CATGCACTCATACAGACTGACAACCGCTCCACCGAC GAGGAGATTGACATGCATACACCGCAGATAACCGG ATCGCACCCCTGCTATCACAGACGGCGGAAACGTAAA ATAACAGCAGGCGGAGGACTATCAGGTACAACGTGA CCTGCGGGCGTGTGACAACGTTAGGCACCTACCGTACTGAC AAGACCATCAACACATGCAAGATTGACCAATGCCATGC TGCCGTACACAGCATGACAATGGCAATTACCTCTC CATTTGTTCCAGGGCTGATCAGACAGCTAGGAAAGGC AAGGTACACGTCTCCATTCTGACTAACGTCACTTG CCGAGTGGCGTGGCTCGAGCGCCGGATGCCACCTATG GTAAGAAGGAGGTGACCTGAGATTACACCCAGATCA TCGAGCGCTCTCTATAGGAGTTAGGAGCGGAAAC CGCACCCGTACAGGAATGGGTGACAAGTCTCTGAG CGCATCATCCCAAGTGAAGGAGAAGGGATTGAGTAC AGTGGGCAACAACCCGGCGGTCTGCTGTGGGCCA ACTGACGACCGAGGGCAAAACCCATGGCTGCCACAT GAAATATTCACTATTATGGACTATAACCCGCC CACTATTGCCCGAGTATCCGGGGCAGTCTGATGCC TCCTAACTCTGGCGGCCACATGCTGATGCTGGCCACC GCGAGGGAGAAAGTGCCTAACACCGTACGCCCTGACCC CAGGAGCGGTGGTACCGTTGACACTGGGCTGTTGC TGCACCGAGGGCAATGCA</pre>
59 Envelope; MLV 10A1	<pre>AGTGTAAACAGAGCACTTAATGTGATAAGGCTACTAG ACCATACCTAGCACATTGCGCCATTGCGGGACGGGT ACTTCTGCTATAGCCCCAGTTGCTATCGAGGAGATCGGA GATGAGGGCGTCTGATGGCATGCTTAAGATCCAAGTCTC CGCCCAAATAGTCTGGACAAGGCAGGCACCCACGCC CACACGAAGCTCCGATATATGGCTGGCATGATGTTCA GGAATCTAAGAGAGATTCCCTGAGGGTGTACACGTCG CAGCGTGTCCCATACTGGGACGATGGGACACTTCATC GTCGCACACTGTCACCCAGGAGCTACCTCAAGGTTTC GTTCGAGGAGCGCAGATTGCGACGTTAGGAGCTGTAAG GTCCAATACAAGCACAATCCATTGCCGGTGGGTAGAGA GAAGTTCTGGTTAGACCAACTTGGCTAGAGCTGC CATGCACTCATACAGCTGACAACGGCTCCACCGAC GAGGAGATTGACATGCATACACCGCAGATAACCGG ATCGCACCCCTGCTATCACAGACGGCGGAAACGTAAA ATAACAGCAGGCGGAGGACTATCAGGTACAACGTGA CCTGCGGGCGTGTGACAACGTTAGGCACCTACCGTACTGAC AAGACCATCAACACATGCAAGATTGACCAATGCCATGC TGCCGTACACAGCATGACAATGGCAATTACCTCTC CATTTGTTCCAGGGCTGATCAGACAGCTAGGAAAGGC AAGGTACACGTCTCCATTCTGACTAACGTCACTTG CCGAGTGGCGTGGCTGGCTGAGCGCCGGATGCCACCTATG</pre>

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<u>Sequences</u>	
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Sequences

SEQ ID NO:Description	Sequence
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ctagaacat tcgcagttaa tcctggctcg tttagaaacat cagaaggctg tagacaata	180
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ccgtcaagct cagattttaa ttggcataat gacttaatag gcacagcctt acaagtcaaa	180
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tccactccat ctgtagaaca atgcaaggaa agcattgaac aaacgaaaca aggaacttgg	360
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agcctcaata	aagcttgctc	tgagtgcctt	aagtagtgtg	tgcccgctg	ttgtgtact	180
ctggtaacta	gagatccc	tc agacccttt	agtca	gtgtg	gaaaatctct	240
gttcatgtca						250

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<210> SEQ ID NO 32
<211> LENGTH: 352
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Helper/Rev CMV early (CAG) enhancer DNA
construct
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<400> SEQUENCE: 32  
  
tagtttattaa tagtaatcaa ttacgggttc attagttcat agcccatata tggagttcg 60  
  
cgttacataa cttacgttaa atggggcacc tgacttaaccg cccaaacgacc ccccccatt 120
```

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gacgtcaata atgacgtatg ttcccatagt aacgccaata gggacttcc attgacgtca	180
atgggtggac tatttacggt aaactgccc cttggcagta catcaagtgt atcatatgcc	240
aagtaacgccc cctattgacg tcaatgacgg taaatggccc gcctggcatt atgcccagta	300
catgacctta tgggacttc ctacttggca gtacatctac gtattagtca tc	352

<210> SEQ ID NO 33	
<211> LENGTH: 290	
<212> TYPE: DNA	
<213> ORGANISM: artificial sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Helper/Rev Chicken beta actin (CAG) promoter DNA construct	

<400> SEQUENCE: 33	
gttattacca tgggtcgagg tgagccccac gttctgtttc actctccccca tctccccccc	60
ctccccccccc ccaattttgt atttattttat ttttaatta ttttgtgcag cgatggggc	120
gggggggggg ggggcgcgcg ccaggcgggg cggggcgggg cgagggggcg ggccggggcga	180
ggcggagagg tgcggcggca gccaatcaga gcggcgcgcgt ccgaaagttt cctttatgg	240
cgaggcggcg gcggcggcg ccctataaaa agcgaagcgc gcggcggggcg	290

<210> SEQ ID NO 34	
<211> LENGTH: 960	
<212> TYPE: DNA	
<213> ORGANISM: artificial sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Helper/Rev Chicken beta actin intron DNA construct	

<400> SEQUENCE: 34	
ggagtcgtc cgttgccttc gccccgtgcc cgcgtccgcg cgcctcgcg ccgcggccc	60
cggctctgac tgaccgcgtt actccccacag gtgagcgggc gggacggccc ttctctccg	120
ggctgtatt agcgttttgtt ttaatgacgg ctgcgtttctt ttctgtggct gcgtgaaagc	180
cttaaaggc tccgggaggg ccctttgtgc gggggggagc ggctgggggg gtgcgtgcgt	240
gtgtgtgtgc gtggggagcg ccgegtgegg cccgcgtgc cggcggcgtg tgagegctgc	300
gggcgeggcg cggggctttg tgcgctccgc gtgtgcgcga gggagcgcg gccggggcg	360
gtgcggccgc gtgcgggggg gctgcgaggg gaacaaaggc tgcggtgggg gtgtgtgcgt	420
gggggggtga gcaggggggtg tggcgccggc ggtcggtgtg taacccccc ctgcacccccc	480
ctccccgagt tgctgagcac ggccggcgtt cgggtgcggg gtcggcgtgc gggcgtgcgc	540
cgggggtcgc cgtgcgggc ggggggtggc ggcagggtgg ggtgcgggc gggcggggc	600
cgccctcgggc cggggagggc tcggggggagg ggcgcggcgc cccggagcg cggcggcgt	660
tgcaggcgcgc gcgagccgca gccattgcct tttatggtaa tcgtgcgaga gggcgcaggg	720
acttcctttg tcccaaatct ggccggagccg aaatctggga ggcgcgcgcg caccctct	780
agcggggcgc ggcgaagcgg tgccggcgcgc gcaggaagga aatgggggg gagggccttc	840
gtgcgtgcgc ggcggccgt cccctctcc atctccagcc tcggggcgtgc cgcaggggga	900
cggctgcctt cgggggggac ggggcaggc ggggttcggc ttctggcgtg tgaccggcgg	960

<210> SEQ ID NO 35	
<211> LENGTH: 1872	
<212> TYPE: DNA	

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<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Helper/Rev HIV Pol DNA construct

<400> SEQUENCE: 35
atgaatttgc caggaagatg gaaaccaaaa atgatagggg gaattggagg ttttatcaaa      60
gttaggacagt atgatcagat actcatagaa atctgcggac ataaagctat aggtacagta     120
ttatggac ctacacctgt caacataatt ggaagaatac tggtgactca gattggctgc     180
actttaaatt ttccatttag tcctatttag actgtaccag taaaattaaa gccaggaatg     240
gatggcccaa aagttaaaca atggccattt acagaagaaa aaataaaagc attagtagaa     300
atttgtagac aatggaaaa ggaaggaaaa atttcaaaaa ttgggcctga aaatccatac     360
aatactccag tatttgcatt aaagaaaaaa gacagtacta aatggagaaa attagtagat     420
ttcagagaac ttaataagag aactcaagat ttctggaaat ttcaatttagg aataccacat     480
cctgcagggt taaaacagaa aaaatcagta acagtactgg atgtggcgta tgcatattt     540
tcagttccct tagataaaga cttcaggaag tatactgcatt ttaccatacc tagtataaac     600
aatgagacac cagggattag atatcagta aatgtgttc cacaggatg gaaaggatca     660
ccagcaatat tccagtgttag catgacaaaa atcttagagc ctttttagaaa acaaaatcca     720
gacatagtc tctatcaata catggatgtat ttgtatgttag gatctgactt agaaataggg     780
cagcatagaa caaaaataga ggaactgaga caacatctgt tgaggtgggg atttaccaca     840
ccagacaaaa aacatcagaa agaacctcca ttcccttggg tgggttatga actccatcct     900
gataaatggc cagtagcgtc tatagtgtcg ccagaaaagg acagctggac tgtcaatgac     960
atacagaaat tagtggaaa attgaattgg gcaagtcaga tttatgcagg gattaaagta     1020
aggcaattt gtaaaacttct taggggaacc aaagcactaa cagaagtagt accactaaca     1080
gaagaagcag agctagaact ggcagaaaaac agggagattc taaaagaacc ggtacatgga     1140
gtgttattatg acccatcaaa agacttaata gcagaaatac agaagcaggg gcaaggccaa     1200
tggacatatc aaatttatca agagccattt aaaaatctgtt aaacaggaaa atatgcaaga     1260
atgaagggtc cccacactaa tgatgtgaaa caattaacag aggcagtaca aaaaatagcc     1320
acagaaagca tagtaatatg gggaaagact cctaaatttta aattaccat acaaaaggaa     1380
acatggaaag catgggtggac agagtattgg caagccaccc ggattcctgt gttggagttt     1440
gtcaatacccc ctccttagt gaagttatgg taccagttttag agaaagaacc cataatagga     1500
gcagaaacctt tctatgttaga tggggcagcc aataggaaa ctaaatttagg aaaagcagga     1560
tatgttaactg acagagggaaag acaaaaagtt gtccccctaa cggcacacaac aaatcagaag     1620
actgagttac aagcaattca tctagcttg caggattcgg gatttagaagt aaacatagtg     1680
acagactcac aatatgcatt gggaaatcattt caagcacaac cagataagag tgaatcagag     1740
ttatgtcagtc aaataataga gcagttataa aaaaaggaaa aagtctaccc ggcattggta     1800
ccagcacaca aagggattgg agggaaatgaa caagtagatg ggttgggtcag tgcttggaaatc     1860
aggaaaatgtac ta                                         1872

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<210> SEQ ID NO 36
<211> LENGTH: 867
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Helper Rev HIV Integrase DNA construct

<400> SEQUENCE: 36

tttttagatg gaatagataa ggcccaagaa gaacatgaga aatatcacag taattggaga	60
gcaatggcta gtgatttaa cctaccacct gtagtagcaa aagaaatagt agccagctgt	120
gataaatgtc agctaaaagg ggaagccatg catggacaag tagactgtag cccaggaata	180
tggcagctag attgtacaca tttagaagga aaagttatct tggtagcagt tcatgtagcc	240
agtggatata tagaaggcaga agtaattcca gcagagacag ggcaagaaac agcatacttc	300
ctcttaaaat tagcaggaag atggccagta aaaacagtac atacagacaa tggcagcaat	360
ttcaccagta ctacagttaa ggccgcctgt tggtggcggg ggatcaagca ggaatttggc	420
attccctaca atccccaaag tcaaggagta atagaatcta tgaataaaga attaaagaaa	480
attataggac aggtaaagaga tcaggctgaa catcttaaga cagcagttaca aatggcagta	540
ttcatccaca attttaaaag aaaagggggg attggggggg acagtgcagg ggaaagaata	600
gtagacataa tagcaacaga catacaaact aaagaattac aaaaacaat tacaaaaatt	660
caaaattttc gggtttatta cagggacacg agagatccag tttggaaagg accagcaaag	720
ctcctctgga aagggtgaagg ggcagtagta atacaagata atagtgcacat aaaagttagtg	780
ccaagaagaa aagcaaagat catcaggat tatggaaaac agatggcagg tcatgtatgt	840
gtggcaagta gacaggatga ggattaa	867

<210> SEQ ID NO 37

<211> LENGTH: 351

<212> TYPE: DNA

<213> ORGANISM: artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Helper/Rev HIV Rev DNA construct

<400> SEQUENCE: 37

atggcaggaa gaageggaga cagcgaccaa gaactcctca aggcaagtca actcatcaag	60
tttctctatc aaagcaaccc acctccaaat cccgagggga cccgacaggc ccgaaggaaat	120
agaagaagaa ggtggagaga gagacagaga cagatccatt cgattagtga acggatcctt	180
agcacttatac tgggacgatc tgccggaccc gtgcctttc agtaccacc gcttgagaga	240
cttactcttg attgtaacga ggattgtgga acttctggaa cgcagggggt gggaaaggccc	300
caaatatgg tggaatctcc tacaatattg gagtcaggag ctaaagaata g	351

<210> SEQ ID NO 38

<211> LENGTH: 448

<212> TYPE: DNA

<213> ORGANISM: artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Helper/Rev Rabbit beta globin poly A DNA construct

<400> SEQUENCE: 38

agatctttt ccctctgcca aaaattatgg ggacatcatg aagcccttg agcatctgac	60
ttctggctaa taaaggaaat ttatttcat tgcaatagtg tggatattttgtct	120
ctcactcgaa aggacatatg ggaggccaa tcatttaaaa catcagaatg agtattttgt	180
ttagagttt gcaacatatg ccatatgtg gctgccatga acaaagggtgg ctataaagag	240
gtcatcagta tatgaaacag cccctgtct tccatccctt attccataga aaagccttga	300

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cttgaggta gatTTTTT atATTTGTT ttGTGTTATT ttttCTTta acATCCtaa	360
aATTTcCTT acATGTTTA cTAGCCAGAT tttCCTCCT cTCCTGACTA CTCCCAGTCa	420
tagCTGTCCTC TCTTCtTTA tGAAGATC	448

<210> SEQ ID NO 39
<211> LENGTH: 577
<212> TYPE: DNA
<213> ORGANISM: Cytomegalovirus

<400> SEQUENCE: 39

acattgatta ttGACTAGTT attaatAGTA atcaattACG gggTCATTAG ttCATAGCCC	60
atataatGGAG ttCCGCGTTA cataactTAC ggtAAATGGC CGCCTGGCT gaccGCCAA	120
cgacCCCCGC ccATTGACGT caataATGAC gtATGTTCCC ATAGTAACGC CAATAGGGAC	180
tttCCATTGA CGTCAATGGG tggAGTATTAC acGGTAAACT GCCCACtTGG CAGTACATCA	240
agtGTATCAT ATGCCAAGTA CGCCCCCTAT TGACGTCAAT GACGGTAAAT GGCCCGCTG	300
gcATTATGCC CAGTACATGA CCTTATGGGA CTTTCTACT TGGCAGTACA TCTACGTATT	360
agtCATCGCT ATTACCATGG tGATGCGGTT ttGGCAGTAC ATCAATGGC GTGGATAcG	420
gtttGACTCA CGGGGATTTc CAAGTCTCCA CCCATTGAC GTCAATGGGA GTTTGTTTG	480
gcacaaaaAT CAACGGGACT TTCCAAAATG TCGTAACAAc TCCGCCCAT TGACGCAAAT	540
gggcGGTAGG CGTGTACGGT GGGAGGTCTA TATAAGC	577

<210> SEQ ID NO 40
<211> LENGTH: 573
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

gtgagTTTGG ggACCCTTGA ttGTTCTTC tttTCGCTA ttGTAaaATT catGTTATAT	60
ggAGGGGGCA aAGTTTCAg ggtGTTGTTT agaATGGAA gatGTCCTT gtATCACCAT	120
ggACCCtCAT gataATTTG tttCTTtAC tttCTACTCT gttGACAACC attGTCTCCT	180
cttATTTCT tttCATTTc tGTAACtTTT tcGTTAAACT ttagCTGCA tttGTAACGA	240
atTTTAAAT tcACTTTGT ttATTTGTCA gattGTAAGT acTTTCTCTA atCACTTTT	300
tttCAAGGCA atCAGGGTAT attATATTGT acTTCAgCAC agTTTtAGAG aacaATTGTT	360
ataATTTAAAT gataAGGTAG aATATTCTG catATAAATT ctGGCTGGCG tggAAATATT	420
cttATTTGGTA gaaACAACtA caccCTGGTC atcatCCTGC ctttCTCTT atGGTTACAA	480
tGATATAACAC tGTTTGAGAT gaggATAAA TACTCTGAGT ccaaACCGGG cccCTCTGCT	540
aaccATGTTC atGCCTTCTT CTCTTCtCTA cAG	573

<210> SEQ ID NO 41
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer DNA fragment

<400> SEQUENCE: 41

taAGCAGAAT tCATGAAATTt GCCAGGAAGA t	31
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<210> SEQ ID NO 42
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Primer DNA fragment

<400> SEQUENCE: 42

ccataacaatg aatggacact aggccgcgc acgaat 36

<210> SEQ ID NO 43
<211> LENGTH: 2745
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Gag, Pol, Integrase DNA fragment

<400> SEQUENCE: 43

gaattcatga atttgccagg aagatggaaa ccaaaaatga tagggggaat tggagggttt 60
atcaaagtaa gacagtatga tcagatactc atagaaatct gcggacataa agctataggt 120
acagtattag taggacctac acctgtcaac ataattggaa gaaatctgtt gactcagatt 180
ggctgcacctt taaatttcc cattagtcctt attgagactg taccagtaaa attaaagcca 240
ggaatggatg gccccaaagt taaacaatgg ccattgacag aaaaaaaaaat aaaagcatta 300
gtagaaattt gtacagaaat ggaaaaggaa ggaaaaattt caaaaattgg gcctgaaaat 360
ccatacaata ctccagtatt tgccataaaag aaaaaagaca gtactaaatg gagaaaattt 420
gtagatttca gagaacttaa taagagaact caagatttctt gggaaagtca atttaggaata 480
ccacatcctg cagggttaaa acagaaaaaa tcaagtaacag tactggatgt gggcgatgca 540
tatTTTcag ttcccttaga taaagacttc aggaagtata ctgcatttac catacctagt 600
ataaacaatg agacaccagg gattagatat cagtacaatg tgcttccaca gggatggaaa 660
ggatcaccag caatattcca gtgttagcatg acaaaaatct tagagcctt tagaaaacaa 720
aatccagaca tagtcatcta tcaatacatg gatgatttgt atgttaggatc tgacttagaa 780
atagggcagc atagaacaaa aatagaggaa ctgagacaac atctgttgag gtggggattt 840
accacaccag aaaaaaaaaa tcagaaagaa cttccattcc ttggatggg ttatgacttc 900
catcctgata aatggacagt acagcctata gtgctgccag aaaaggacag ctggactgtc 960
aatgacatac agaaaatttg gggaaaattt aattggcaaa gtcagattt tgcaggattt 1020
aaagtaaggc aattatgtaa acttcttagg ggaaccaaag cactaacaga agtagtacca 1080
ctaacagaag aagcagagct agaactggca gaaaacaggag agattctaaa agaaccggta 1140
catggagtgt attatgaccc atcaaaagac ttaatagcag aaatacagaa gcagggca 1200
ggccaaatgga catatcaaattt ttatcaagag ccattttaaa atctgaaaac aggaaaagtat 1260
gcaagaatga agggtgccca cactaatgtat gtgaaacaat taacagaggc agtacaaaa 1320
atagccacag aaagcatagt aatatggga aagactccta aattttaaatt acccataaa 1380
aaggaaacat gggaaagcatg gtggacagag tattggcaag ccacctggat tcctgagtgg 1440
gagtttgtaa ataccctcc ctttagtgaag ttatggtacc agtttagagaa agaaccata 1500
ataggagcag aaactttcta ttttagatggg gcagccaata gggaaactaa atttagaaaa 1560
gcaggatatg taactgacag aggaagacaa aaagttgtcc ccctaacgga cacaacaaat 1620
cagaagactg agttacaagc aattcatcta gcttgcagg attcgggatt agaagtaac 1680

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atagtacag actcacaata tgcattggga atcattcaag cacaaccaga taagagtcaa	1740
ttagttag tcagtcaat aatagagcg ttaataaaaa agaaaaagt ctacctggca	1800
tgggtaccag cacacaaagg aattggagga aatgaacaag tagataatt ggtcagtgct	1860
ggaatcagga aagtactatt tttagatgga atagataagg cccaagaaga acatgagaaa	1920
tatcacagta attggagagc aatggctagt gatTTAACCTGAGTAGCAAAA	1980
gaaaatgttag ccagctgtga taaatgtcg ctaaaagggg aagccatgca tggacaagta	2040
gactgtagcc caggaatatg gcagctagat tgtacacatt tagaaggaaa agttatcttgc	2100
gtagcgttc atgttagccag tggatatata gaagcagaag taattccagc agagacaggg	2160
caagaaacag catacttcct cttaaaatta gcaggaagat ggccagtaaa aacagtacat	2220
acagacaatg gcagcaattt caccagtact acagtttaagg ccgcctgttg gtggcgcccc	2280
atcaaggcagg aattttggcat tccctacaat ccccaaagtgc aaggagtaat agaatctatg	2340
aataaaagaat taaagaaaat tataggacag gtaagagatc aggctgaaca tcttaagaca	2400
gcagtacaaa tggcgttatt catccacaat tttaaaaagaa aaaaaaaaaaaaaatgggggtac	2460
agtgcagggg aaagaatagt agacataata gcaacagaca tacaaactaa agaattacaa	2520
aaacaaatta caaaaattca aaattttcggttttattaca gggacagcag agatccagtt	2580
tggaaaggac cagcaagct cctctggaaa ggtgaagggg cagtagtaat acaagataat	2640
agtgcacataa aagtatgtgcc aagaagaaaa gcaaagatca tcagggatata tggaaaacag	2700
atggcaggtg atgattgtgt ggcaagtata caggatgagg attaa	2745

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<210> SEQ ID NO 44
<211> LENGTH: 1586
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Rev, RRE and rabbit beta globin poly A DNA
      fragment

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<400> SEQUENCE: 44

tctagaatgg caggaagaag cggagacagc gacgaagagc tcatacagaac agtcagactc       60
atcaagcttc tctatcaag caacccacct cccaatcccg aggggaccgg acaggccgaa       120
aggaatagaa gaagaagggtg gagagagaga cagagacaga tccattcgat tagtgaacgg       180
atccttggca cttatctggg acgtatctgcg gggcctgtgc ctcttcagct accaccgtt       240
gagagactta ctcttgattt taacgaggat tgtgaaactt ctgggacgca ggggggtggaa       300
ggccctcaaa tattgggtgga atctcctaca atattggagt caggagctaa agaatagagg       360
agctttgttc cttgggttct tggggcagc aggaagcact atggggcgcag cgtcaatgac       420
gctgacggta caggccagac aattattgtc tggatagtg cagcagcaga acaatttgc       480
gagggctatt gaggcgcaac agcatctgtt gcaactcaca gtctggggca tcaagcagct       540
ccaggcaaga atcctggctg tggaaagata cctaaaggat caacagctcc tagatcttt       600
tccctctgcc aaaaattatg gggacatcat gaagcccctt gagcatctga cttctggcta       660
ataaaaggaaa ttatTTTCA ttgcaatagt gtgttggaaat tttttgtgtc tctcactcggt       720
aaggacatata gggagggcaa atcattaaa acatcagaat gagtatttgg ttttagatgtt       780
ggcaacatata gccatatgtt ggctgccatg aacaaagggtg gctataaaga ggtcatcagt       840

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atatgaaaca gccccctgct gtccattct tatccatag aaaaggcttg acttgagggtt	900
agatttttt tatattttgt tttgtgttat tttttcttt aacatcccta aaatttcct	960
tacatgtttt actagccaga ttttcctcc tctcctgact actcccagtc atagctgtcc	1020
ctttctctt atgaagatcc ctcgacctgc agcccaagct tggcgtaatc atggcatag	1080
ctgtttcctg tgtgaaattt ttatccgctc acaattccac acaacatacg agccggaagc	1140
ataaaagtgtta aagctgggg tgcctaatga gtgagctaac tcacattaat tgcgttgcgc	1200
tcactgccc ctttcagtc gggaaacctg tctgtgccagc ggatccgcattt ctcaatttttgc	1260
cagcaaccat agtcccgcccc ctaactccgc ccatcccgcc cctaactccg cccagttccg	1320
cccatttctcc gccccatggc tgactaattt tttttattha tgcagaggcc gaggeccgcct	1380
cggcctctga gctattccag aagtagtgag gaggctttt tggaggccctt ggcttttgc	1440
aaaagctaac ttgtttattt cagttataaa ttgttacaaa taaagcaataa gcatcacaaa	1500
tttcacaaat aaagcatttt ttctactgca ttctagttgt ggtttgtcca aactcatcaa	1560
tgatcttat cagcggccgc cccggg	1586

<210> SEQ ID NO 45
<211> LENGTH: 1614
<212> TYPE: DNA
<213> ORGANISM: artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: CAG enhancer/promoter/intron sequence DNA fragment

<400> SEQUENCE: 45

acgcgttagt tattaatagt aatcaattac ggggtcatta gttcatagcc catatatggaa	60
gttcccggtt acataactta cggtaatgg cccgcctggc tgaccgccc acgaccggc	120
cccatttgcgt tcaataatga cgtatgttcc catagttaacg ccaataggaa ctttttgc	180
acgtcaatgg gtggactatt tacggtaaac tgcccacttg gcagtgatc aagtgtatca	240
tatgccaagt acgcccccta ttgacgtcaa tgacggtaaa tggccgcctt ggcattatgc	300
ccagtacatg accttatggg actttctac ttggcgtac atctacgtat tagtcatcgc	360
tattaccatg ggtcgagggtg agccccacgt tctgcttcac tctcccccac tccccccctt	420
ccccaccccc aattttgtat ttatattttt ttaattttt ttgtgcagcg atggggcg	480
gggggggggggg ggcgegcgcg aggccccccg gggccggggcg aggggggggg cggggcgagg	540
cggagaggtg cggcgccgcg caatcagagc ggccgcgtcc gaaagttcc ttttatggcg	600
aggccggccgcg ggccggccgc ctataaaaag cgaagcgcgcg ggccggccgg agtcgctgcg	660
ttgccttcgc cccgtcccccc gctccgcgcg gctcgcgcg gcccgcggc gctctgactg	720
accgcgttac tcccacaggt gageggccgg gacggccctt ctctcgggg ctgttaatttt	780
cgcttggttt aatgacggct cgtttctttt ctgtggctgc gtgaaagctt taaaggctc	840
cgggaggccc ctttgcgggg gggggagccgg ctgggggggtt gctgtgcgtgt gtgtgtgcgt	900
ggggagccgcg ccgtgcggcc cgccgtgcggcc ggccggctgtg agcgctgcgg ggcggccgcg	960
ggggcttgcgt gctccgcgt gtgcgcgcgg ggagcgcggc cggggggggt gccccggcgt	1020
ggggggggggc tgcgaggggaa acaaaggctg cgtgcgggggtt gtgtgcgtgg ggggggtgagc	1080
aggggggtgtg ggcgeggccgg tcgggctgtta accccccccctt gcaaaaaacccctt ccccgagttt	1140
ctgagcacgg cccggcttcg ggtgcggggc tccgtgcggg gctggccgcg gggctgcgg	1200

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tgccggggcg	gggtggcg	caggtgggg	tgcggggcg	ggggggccg	cctggggcg	1260
ggggggctc	gggggggg	cgcggggcc	ceggagegc	gggggtgtc	gagggcgcc	1320
gagccgcgc	cattgcctt	tatggtaatc	gtgcgagagg	gogcaggggac	ttcccttgc	1380
ccaaatctgg	cgagccgaa	atctggagg	cgccgcgc	ccccctctag	cgggcgccc	1440
cgaagcggtg	cggcgccggc	aggaaggaaa	tggcggggg	gggccttcgt	gcgtgcgcgc	1500
gccgcgtcc	ccttcctcat	ctccagcctc	ggggctgcgc	cagggggacgc	gctgcctcg	1560
ggggggacgg	ggcagggcg	ggttcggctt	ctggcgtgtc	accggcggg	attc	1614

<210> SEQ_ID NO 46

<211> LENGTH: 1531

<212> TYPE: DNA

<213> ORGANISM: Vesicular Stomatitis Indiana Virus

<400> SEQUENCE: 46

gaattcatga	agtgcctttt	gtacttagcc	tttttattca	ttggggtgaa	ttgcaagttc	60
accatagttt	ttccacacaa	ccaaaaagga	aactggaaaa	atgttccttc	taattaccat	120
tattgcccgt	caagctcaga	ttaaaattgg	cataatgact	taataggcac	agccttacaa	180
gtcaaaaatgc	ccaagagtca	caaggctatt	caagcagacg	gttggatgtg	tcatgcttcc	240
aaatgggtca	ctacttgta	tttccgctgg	tatggaccga	agtatataac	acattccatc	300
cgatccttca	ctccatctgt	agaacaatgc	aaggaaagca	ttgaacaaac	gaaacaagga	360
acttggctga	atccaggctt	ccctcctcaa	agttgtggat	atgcaactgt	gacggatgcc	420
gaagcagtga	ttgtccaggt	gactcctcac	catgtgtgg	ttgatgaata	cacaggagaa	480
tgggttGatt	cacagttcat	caacggaaaa	tgcagcaatt	acatatgccc	cactgtccat	540
aactctacaa	cctggcattc	tgactataag	gtcaaagggc	tatgtgatcc	taacctcatt	600
tccatggaca	tcaccttctt	ctcagaggac	ggagagctat	catccctggg	aaaggaggc	660
acagggttca	aaagtaacta	ctttgcttat	gaaactggag	gcaaggctg	caaaaatgcaa	720
tactgcaagc	attggggagt	cagactccca	tcaggtgtct	ggttcgagat	ggctgataag	780
gatctcttg	ctgcagccag	attccctgaa	tgcggcagaag	ggtcaagtat	ctctgctcca	840
tctcagacct	cagtggatgt	aagtctaatt	caggacgttg	agaggatctt	ggattattcc	900
ctctgccaag	aaacctggag	caaaaatcaga	gccccgtttc	caatctctcc	agtggatctc	960
agctatcttg	ctcctaaaaaa	cccgagaaacc	ggtcctgttt	tcaccataat	caatggtacc	1020
ctaaaatact	ttgagaccag	atacatcaga	gtcgatattg	ctgctccaat	cctctcaaga	1080
atggtcggaa	tgatcagtgg	aactaccaca	gaaaggaaac	tgtggatga	ctgggcacca	1140
tatgaagacg	tggaaattgg	acccaatgga	gttctggag	ccagttcagg	atataagttt	1200
cctttataca	tgattggaca	tggtatgtt	gactccgatc	ttcatcttag	ctcaaaggct	1260
cagggttgc	aacatcctca	cattcaagac	gctgcttcgc	aacttcctga	tgtatggatgt	1320
ttatTTTGTG	gtgatactgg	gctatccaaa	aatccaaatcg	agcttgcata	aggttgggtc	1380
agtagttgga	aaagctctat	tgcctttttt	ttctttatca	tagggtaat	cattggacta	1440
ttcttgggtc	tccgagttgg	tatccatctt	tgcattaaat	taaagcacac	caagaaaaga	1500
cagatttata	cagacataga	gatgagaatt	c			1531

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<210> SEQ ID NO 47
 <211> LENGTH: 351
 <212> TYPE: DNA
 <213> ORGANISM: Rous Sarcoma Virus

<400> SEQUENCE: 47

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atggcaggaa gaagcgaga cagcgacaa gaactcctca aggtagtcg actcatcaag 60
tttctctata aaagcaaccc acctccaaat cccgagggga cccgacaggc cccgaaaggaaat 120
agaagaagaa ggtggagaga gagacagaga cagatccatt cgattagtga acggatcctt 180
agcacatttc tgggacgatc tgccggaccc gtgcctcttc agtaccacc gcttgagaga 240
cttactcttg attgttaacga ggattgtgga acttctggaa cgcaggggtt gggaaaggccct 300
caaataattgg tggaaatctcc tacaatattg gagtcaggag ctaaaaataa g 351
  
```

<210> SEQ ID NO 48
 <211> LENGTH: 884
 <212> TYPE: DNA
 <213> ORGANISM: artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Rous Sarcoma Virus (RSV) promoter and Human Immunodeficiency Virus (HIV) Rev DNA fragment

<400> SEQUENCE: 48

```

caattgcgt gtacgggcca gatatacgcg tatctgaggg gactagggtg tgtttaggcg 60
aaaagcgccc cttcggttgt acgcggtagt gagtcccccc agatataatg agtttcgctt 120
ttgcataagg agggggaaat gtatgtttt gcaataacact tttttttttt caatcggtt 180
acatgtttttt agcaacatgc cttacaagga gaaaaaaagg accgtgcattt ccgtttttttt 240
gaagtaagg ggtacgatcg tgcccttata ggaaggcaac agacagggtct gacatggatt 300
ggacgaacca ctgaattccg cattgcagag ataattgtat ttaagtgcctt agctcgatac 360
aataaaacgcg atttgaccat tcaccacatt ggtgtgcacc tccaaatcg agctcgatcc 420
gtgaaccgtc agatcgccctg gagacgcctt ccacgcgttt ttgaccccca tagaagacac 480
cgggaccgtt ccagccccc ctcgaagctt ggcattttttt atctccatgg gcaggaaagaa 540
geggagacag cgacgaagaa ctcccaagg cagtcagact catcaagttt ctctatcaaa 600
gcaacccacc tcccaatccc gaggggaccc gacaggcccg aaggaataga agaagaaggtt 660
ggagagagag acagagacag atccattcga ttatgttgcg gatcccttagc acttatctgg 720
gacgatctgc ggacgcctgtt cctcttcagc taccaccgtt tgagagactt actcttgattt 780
gtaacggaga ttgttggaaact tctgggacgc aggggggtttt aagccctcaa atattgggtttt 840
aatctccatc aatattggag tcaggagcta aagaatagtc taga 884
  
```

<210> SEQ ID NO 49
 <211> LENGTH: 511
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

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ggggttgggg ttgcgcctt tccaaggcag ccctgggtt ggcgcgggac ggggtgtctc 60
tggggcgtgtt tccgggaaac gcagcggcgc cggccctggg tctcgcacat tcttcacgtc 120
cgttcgcaggc gtcacccggc tcttcgcgc tacccttgcg gggcccccgg cgacgttcc 180
tgctccggccctt ctaatgtcggtt aaggttccctt ggcgggttgcg ggtgtccggc cgtgcacaaac 240
  
```

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ggaaagccgca cgtctcacta gtaccctcg	agacggacag cgccaggagg	caatggcagc	300
gccccgaccg ccatgggctg tggccaaatag	cggctgtca gcagggcg	ccgagagcag	360
cgcccccggaa ggggggggtgc	gggaggcggg	gtgtggggcg	420
gccccggcgg tggccgcatt	tctgcaagcc	tccggagcgc acgtcggcag	480
cgttgaccga atcaccgacc	tctctccca	g	511

<210> SEQ ID NO 50
<211> LENGTH: 1162
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

gcgcggggtt ttggggcctc	ccggggcgc ccccttcctc	acggcgagcg ctgccacgtc	60
agacgaaggg cgcaggagcg	ttccctgatcc	ttccggccgg acgctcagga	120
ctgctataa gactcggcct	tagaacccca	gtatcagcag aaggacattt	180
cttgggtgac tctaggcac	tggttttctt	tccagagagc ggaacaggcg	240
gtcccttctc ggcgattctg	cgaggggatc	tccgtgggc ggtgaacgcc	300
taaggacgcg ccgggtgtgg	cacagctagt	tccgtcgcag cccggattt	360
cttgggtgtg gatcgctgt	atcgtaactt	ggtgagttgc	420
gttttgtgg ccgcggggcc	gctcggtgg	acggaagcgt	480
tgttgtgtt gtcgcgagc	aaggttgccc	tgaactgggg	540
tggccgtgt tcccagatct	tgaatggaa	acgcttgtaa	600
aaacaaggtg gggggcatgg	tggcgccaa	gaacccaagg	660
cgggaaagct cttatccgg	tgagatgggc	tggggcacca	720
gtttgtact gactggagaa	ctcggttttgc	tgcgtcggt	780
gtgcgcgtgg	gcagtcacc	cgtaccttgc	840
acccgttctg ttgggtata	atgcagggtg	ggcccacctg	900
tttctccgt cgcaaggacgc	agggttcggg	cctaggtag	960
gccccaccc	tggtaggggg	aggataagt	1020
tacatatctt cttaaatgc	tgaagctccg	ttttgtact	1080
tgtgtttgt gaagttttt	aggcacctt	tgaatgtaa	1140
tttctcgatgt	tagactagta	aa	1162

<210> SEQ ID NO 51
<211> LENGTH: 120
<212> TYPE: DNA
<213> ORGANISM: Simian virus 40

<400> SEQUENCE: 51

gtttattgca gttataatg	gttacaaata	aagcaatgc	atcacaaatt	tcacaaataa	60
agcattttttt	tcactgcatt	ctagttgtgg	tttgcacaaa	ctcatcaatg	120

<210> SEQ ID NO 52
<211> LENGTH: 227
<212> TYPE: DNA
<213> ORGANISM: Bos taurus

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<210> SEQ ID NO 54
<211> LENGTH: 2013
<212> TYPE: DNA
<213> ORGANISM: Gibbon Ape Leukemia Virus
<400> SEQUENCE: 54

atgcttctca cctcaagccc gcaccacatt cggcaccaga tgagtctgg gagctggaaa	60
agactgatca tcctttaag ctgcgttattc ggagacggca aaacgatct gcagaataag	120
aaccccccacc agcctgtgac cctcacctgg caggtactgt cccaaactgg ggacgttgtc	180
tgggacaaaa aggcagtcca gccccttgg acttggtggc cctctttac acctgtatgt	240
tgtgccttgg oggccccgtct tgagtctgg gatatcccg gatccgatgt atcgctct	300
aaaagaggtt gaccccttga ttcagactat actgccgtt ataagcaaat cacctgggaa	360
gcacatagggt gcaagctaccc tggggcttagg accaggatgg caaattcccc cttctacgt	420
tgtccccgag ctggccgaac ccattcagaa gctaggaggt gtggggggct agaatcccta	480
tactgttaag aatggagttt tgagaccacg ggtaccgtt attggcaacc caagtctca	540
tgggacactca taactgtaaa atggaccaa aatgtgaaat gggagcaaaa atttcaaaag	600
tgtgaacaaa cccggctggtg taaccccttc aagatagact tcacagaaaa aggaaaactc	660
tccagagatt ggataacgga aaaaacctgg gaattaagggt ttatgtata tggacaccca	720
ggcatacagt tgactatccg ctttagaggtc actaacatgc cgggtgtggc agtggggcca	780
gaccctgtcc ttgcggaaaca gggacctct agcaagcccc tcactctccc tctctccca	840
cggaaagcgc cgcccccccc tctacccccc gcccgtatgt agcaaaaccc tgccgtgc	900
ggagaaactg ttaccctaaa ctctccgcct cccaccatgt gcaacccact ctttggcctt	960
gtgcaggggg ctttcttaac cttgaatgtt accaaccacg gggccactaa gtcttgctgg	1020
ctctgtttgg gcatgagccc cccttattat gaaggatag cctcttcagg agaggctcgct	1080
tataacctcca accatacccg atgcactgg gggcccaag gaaagttac ctcactgag	1140
gtctccggac tcgggtcatg cataggaaag gtgccttta cccatcaaca tctttgcaac	1200
cagacccatcc ccatcaattt ctctaaaaac catcagtatc tgctccccctc aaaccatagc	1260
tggtgggcct gcagcactgg cctcaccccc tgcctctcca cctcagttt taatcgtct	1320
aaagacttct gtgtccaggt ccagctgatc ccccgcatct attaccatc tgaagaaacc	1380
ttgttacaag cctatgacaa atcaccgggg aggtttaaaa gagagcctgc ctcacttacc	1440
ctagctgtct tcctgggggtt agggattgcg gcaggtatag gtactggctc aaccgcctt	1500
ataaaagggc ccatagaccc ccagcaaggc ctaaccagcc tccaaatcgc cattgacgct	1560
gacctccggg cccttcagga ctcaatcgc aagcttaggg actcactgac ttccctatct	1620
gaggttagtac tccaaaatag gagaggcctt gacttactat tccttaaaga aggaggcctc	1680
tgcgcggccc taaaagaaga gtgcgtttt tatgttagacc actcaggtgc agtacgagac	1740
tccatgaaaa aacttaaaga aagacttagat aaaagacagt tagagcgc gaaaaaccaa	1800
aactggatgt aagggtgggtt caataactcc cttgggtta ctaccctact atcaaccatc	1860
gctggggccc tattgtctt cttttgtta ctcacttgc gcccctgc catcaataaa	1920
ttaatccaat tcatcaatga taggataagt gcagtcaaaa ttttagtct tagacagaaaa	1980
tatcagaccc tagataacga gaaaaacctt taa	2013

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<210> SEQ ID NO 56
<211> LENGTH: 1497
<212> TYPE: DNA
<213> ORGANISM: Lymphocytic Choriomeningitis Virus

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<400> SEQUENCE: 56  
  
atgggtcaga ttgtgacaat gtttgaggct ctgcctcaca tcatcgatga ggtgtatcaac 60  
  
attgtcatta ttgtgcattt cgtgatcagc ggatcaagg ctgtctacaa ttttgcacc 120  
  
tgtgggatat tcgcattgtat cagttcccta cttctggctg gcaggctctg tggcatgtac 180  
  
qgtcttaaqg qacccgacat ttacaaaqqa qtttaccaat ttaaqtcagt qqaqttqat 240
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atgtcacatc tgaacctgac catgccccaaac gcatgttcag ccaacaactc ccaccattac	300
atcagtatgg ggacttctgg actagaattt accttcacca atgattccat catcagtcac	360
aacttttgc aatctgaccc tcgccttcaac aaaaagaccc ttgaccacac actcatgagt	420
atagtttcga gcctacaccc cagtatcaga gggaaactcca actataaggc agtattctgc	480
gacttcaaca atggcataaac catccaataac aacttgacat tctcagatcg acaaagtgc	540
cagagccagt gtagaacctt cagaggtaga gtccttagata tgtttagaac tgccctcgg	600
gggaaataca tgaggagtgg ctggggctgg acaggctcag atggcaagac cacctgggt	660
agccagacga gttaccaata cctgattata caaaatagaa cctggaaaaa ccactgcaca	720
tatgcaggc ottttggat gtccaggatt ctcccttccc aagagaagac taagttttc	780
actaggagac tagcgggcac attcacctgg actttgtcag actcttcagg ggtggagaat	840
ccaggggtt attgcgtac caaatggatg attctgtctg cagagcttaa gtgtttcgg	900
aacacagcag ttgcgaaatg caatgtaaat catgatgccg aattctgtga catgtgcga	960
ctaatttact acaacaaggc tgctttgagt aagttcaaaag aggacgtaga atctgccttgc	1020
cacttattca aaacaacagt gaattctttg atttcagatc aactactgtat gaggaaccac	1080
ttgagagatc tgatgggggt gccatattgc aattactcaa agttttggta cctagaacat	1140
gcaaagaccc gcgaaactag tgccccaaag tgctggcttgc accaaatgg ttcttactta	1200
aatgagaccc acttcgtga tcaaatcgaa caggaagccg ataacatgtat tacagagatg	1260
ttgaggaagg attacataaa gaggcagggg agtacccccc tagcattgtat ggaccttctg	1320
atgttttccca catctgcata tctagtcgc atcttcgtc accttgcata aataccaaca	1380
cacaggcaca taaaaggtgg ctcatgtcca aagccacacc gattaaccaa caaaggaaatt	1440
tgttagttgtg gtgcatttaa ggtgcctggt gtaaaaaccc tctggaaaag acgctga	1497

<210> SEQ ID NO 57
<211> LENGTH: 1692
<212> TYPE: DNA
<213> ORGANISM: Fowl Plague virus

<400> SEQUENCE: 57

atgaacactc aaatcctggt ttccgcctt gtggcagtca tccccacaaa tgcagacaaa	60
atttgcattt gacatcatgc tgtatcaaattt ggcacccaaag taaacacact cactgagaga	120
ggagtagaaag ttgtcaatgc aacggaaaca gtggagcggaa caaacatccc caaaatttgc	180
tcaaaaggaa aaagaaccac tgcattttggc caatgcggac tgtagggac cattaccggaa	240
ccacccatgc ggcaccaattt tctagaattt tcagctgatc taataatcgaa gagacgagaa	300
ggaaatgtatc ttgttaccc gggaaagttt gttaatgaag aggacattgc acaaatcctc	360
agaggatcgtg tgggatttgc caaagaaaca atgggatttca catatagtgg aataaggacc	420
aacggaaacaa ctatgtcatg tagaagatca gggcttcattt tctatgcaga aatggatgg	480
ctccctgtcaaa atacagacaa tgcgttccat ccacaaatgtca caaaatcata caaaaacaca	540
aggagagaat cagctctgtatc agtctggggaa atccaccattt caggatcaac caccgaacag	600
acccaaactat atggggatgg aaataaaactg ataacagtgc ggagttccaa atatcatcaa	660
tcttttgc cggatccagg aacacgaccg cagataaaatg ggcagtcgg acggattgtatc	720
tttcattggat tgcattttggat tccaaatgtatc acagttactt ttagttccaa tgcccttc	780

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atagctccaa atcgccagg cttcttgggg gaaaaatcca tggggatcca gagcgatgtg	840
cagggttgcata ccaattgcga agggaaatgc taccacagtg gagggactat aacaagcaga	900
ttgccttttc aaaacatcaa tagcagagca gttggcaaat gcccaagata tgtaaaacag	960
gaaagtttat tattggcaac tgggatgaag aacgttcccg aacccatccaa aaaaaggaaa	1020
aaaagaggcc tggggcgc tatagcaggg ttattgaaa atgggtggga aggtctggc	1080
gacgggtggt acggtttcag gcatcagaat gcacaaggag aaggaaactgc agcagactac	1140
aaaagccccc aatcgccaat tgatcagata accggaaagt taaatagact cattgagaaa	1200
accaaccaggc aatttgagct aatagataat gaattcactg aggtggaaaa gcagattgc	1260
aatttaatta actggaccat agactccatc acagaagtat ggtcttacaa tgctgaactt	1320
cttgtggcaa tggaaaacca gcacactatt gattggctg attcagagat gaacaagctg	1380
tatgagcggatg tgagggaaataa attagggaa aatgctgaag aggatggcac tgggtgc	1440
gaaatttttc ataaatgtga cgatgattgt atggcttagta taaggaacaa tacttatgt	1500
cacagccaaat acagagaaga agcgtatgc aatagaatac aaattgaccc agtcaaattg	1560
agtagtggct acaaagatgt gatactttgg tttagcttcg gggcatcatg cttttgc	1620
cttgccattt ccattggccct tggggccata tgggtgcata acggaaacat gcgggtgc	1680
atttgtatataa	1692

<210> SEQ ID NO 58

<211> LENGTH: 1266

<212> TYPE: DNA

<213> ORGANISM: Ross River Virus

<400> SEQUENCE: 58

agtgtaacatg agcactttaa tgggtataag gctactagac catacctagc acattgcgc	60
gattgcgggg acgggtactt ctgtatagc ccagttgcta tcgaggagat ccgagatgag	120
gcgtctgatg gcatgtttaa gatccaaatc tccggccaaat taggtctgga caaggcaggc	180
acccacgccc acacgaagct ccgtatatgc gctggcataat atgttcagga atctaagaga	240
gattccatgtt ggggtgtacac gtccgcageg tgccatccatac atgggcacat gggacactc	300
atcgtegcac actgtccacc aggcgactac ctcaagggtt cggtcgagga cgcagatcg	360
cacgtgttggt catgttgggtt ccaatatacg cacaatccat tgccgggtgg tagagagaag	420
tgcgtggtaa gaccacactt tggcgtagag ctgcctatgca cctcataccca gctgacaacg	480
gttcccccaccc acggaggatg tgacatgcat acaccgcacat atataccgga tcgcaccctg	540
ctatcacaga cggcgccaa cgtcaaaata acagcaggcg gcaggactat caggtacaac	600
tgtacctgcg gccgtgacaa cgtaggactc accagttactg acaagaccat caacacatgc	660
aagattgacc aatgccatgc tgccgtcacc agccatgaca aatggcaatt tacctcttca	720
tttggccatca gggctgtatca gacagctagg aaaggcaagg tacacgttcc gttccctctg	780
actaacgtca octgcggagt gccgtgggt cgagcgcggg atgcccacca tggtaagaag	840
gagggtgaccc tgagattaca cccagatcat ccgacgcgtct tctccatag gagtttagga	900
gcggaaaccgc acccgatcga ggaatgggtt gacaagttct ctgagcgcataatccactg	960
acggaaagaag ggattgagta ccagtggggc aacaacccgc cggctgcct gtgggc	1020
ctgacgaccg agggcaaaacc ccatggctgg ccacatgaaa tcattcagta ctattatgga	1080

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ctatacccg ccgcccactat tgccgcagta tccggggcga gtctgatggc cctcctaact	1140
ctggcggcca catgctgcat gctggccacc gcgaggagaa agtgcctaac accgtacgcc	1200
ctgacgcccag gagcgggttgtt accggttgaca ctggggctgc tttgctgcgc accgagggcg	1260
aatgca	1266

<210> SEQ ID NO 59
<211> LENGTH: 1266
<212> TYPE: DNA
<213> ORGANISM: Murine Leukemia virus

<400> SEQUENCE: 59

agtgttaacag agcactttaa tgtgtataag gctactagac cataccttagc acattgcgcc	60
gattgcgggg acgggtactt ctgctatagc ccagttgcta tcgaggagat ccgagatgag	120
gctgtctgat gcatgtttaa gatccaaatgc tccgccccaa taggtctgga caaggcaggc	180
acccacgccc acacgaagct ccgatatatg gctggtcatg atgttcagga atctaagaga	240
gattccttga gggtgtacac gtccgcagcg tgctccatac atgggacgat gggacacttc	300
atcggtcgac actgtccacc agggactac ctcaagggtt cgttcgagga cgccgatcg	360
cacgtgaagg catgtttagt ccaatacacaag cacaatccat tgccgggtgg tagagagaag	420
ttcgtgggta gaccacactt tggcgtagag ctgcccattc ctcataccca gctgacaacg	480
gttcccccaccc acgaggagat tgacatgcat acaccgcac atataccggc tcgcacctg	540
ctatcacaga cggcgggcaa cgtaaaata acagcaggcg gcaggactat caggtacaac	600
tgtacctgcg gccgtacaa cgtaggactc accagtaactg acaagaccat caacacatgc	660
aagattgacc aatgcctatgc tgccgtcacc agccatgaca aatggcaatt tacctctca	720
tttggccca gggctgtatca gacagctagg aaaggcaagg tacacgttcc gttccctctg	780
actaacgtca cctgcggagt gcccgtggct cgagcgcgg atgcccacta tggtaagaag	840
gagggtgaccc tggattaca cccagatcat cccacgtct tctccatag gagtttagga	900
gccgaaccgc acccgtaacg ggaatgggtt gacaaggctt ctgagccat catcccagt	960
acggaaagaag ggattgagta ccagtgggc aacaaccgc eggtctgcct gtggcgcac	1020
ctgacgaccg agggcaaaacc ccatggctgg ccacatgaaa tcattcagta ctattatgga	1080
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<210> SEQ ID NO 60
<211> LENGTH: 2030
<212> TYPE: DNA
<213> ORGANISM: Ebola virus

<400> SEQUENCE: 60

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<210> SEQ ID NO 61
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<223> OTHER INFORMATION: Control shRNA sequence

<400> SEQUENCE: 61

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What is claimed is:

1. A lentiviral vector system for expressing a lentiviral particle, the system comprising:
 - a. a therapeutic vector comprising a shRNA for inhibiting PARP expression;
 - b. an envelope plasmid comprising a neuron-specific sequence for targeting the shRNA to a neuron; and
 - c. at least one helper plasmid comprising gag, pol, and rev genes, wherein when the therapeutic vector, the envelope plasmid and the at least one helper plasmid are transfected into a packaging cell line, a neuron-specific lentiviral particle capable of inhibiting PARP expression is produced by the packaging cell line.
2. The lentiviral vector system of claim 1, wherein the shRNA comprises a PARP-specific shRNA.
3. The lentiviral vector system of claim 1, wherein the shRNA comprises a PARP1-specific shRNA.
4. The lentiviral vector system of claim 1, wherein the shRNA comprises a shRNA having at least 80%, or at least 85%, or at least 90%, or at least 95% sequence identity with any one of SEQ ID NOs: 6-10.
5. The lentiviral vector system of claim 1, wherein the shRNA comprises any one of SEQ ID NOs: 6-10.
6. The lentiviral vector system of claim 1, wherein the neuron-specific sequence encodes VSV-G, FUG-C, or gp64, or a variant thereof.
7. The lentiviral vector system of claim 1, wherein the neuron-specific sequence encodes VSV-G or a variant thereof.
8. The lentiviral vector system of claim 1, wherein the neuron-specific sequence encodes a protein that improves transduction into a neuron.
9. The lentiviral vector system of claim 1, wherein the neuron-specific sequence encodes a protein that improves transduction into a TH+ neuron.
10. A lentiviral particle produced by a packaging cell and capable of infecting a cell, the lentiviral particle comprising:
 - a. an envelope protein capable of infecting the cell; and
 - b. a shRNA for inhibiting PARP expression.
11. The lentiviral particle of claim 10, wherein the cell comprises a neuron.
12. The lentiviral particle of claim 10, wherein the cell comprises a TH+ neuron.
13. The lentiviral particle of claim 10, wherein the shRNA comprises a PARP-specific shRNA.
14. The lentiviral particle of claim 10, wherein the shRNA comprises a PARP1-specific shRNA.
15. The lentiviral particle of claim 10, wherein the shRNA comprises a shRNA having at least 80%, or at least 85%, or at least 90%, or at least 95% sequence identity with any one of SEQ ID NOs: 6-10.
16. The lentiviral particle of claim 10, wherein the shRNA comprises any one of SEQ ID NOs: 6-10.
17. A method of treating a subject suffering from Parkinson's disease, the method comprising administering to the subject a lentiviral particle, wherein the lentiviral particle comprises:
 - a. an envelope protein capable of infecting a cell in the subject; and
 - b. a shRNA for inhibiting PARP expression.
18. The method of claim 17, wherein the cell comprises a neuron.
19. The method of claim 17, wherein the cell comprises a TH+ neuron.
20. The method of claim 17, wherein the shRNA comprises a PARP-specific shRNA.
21. The method of claim 17, wherein the shRNA comprises a PARP1-specific shRNA.
22. The method of claim 17, wherein the shRNA comprises a shRNA having at least 80%, or at least 85%, or at least 90%, or at least 95% sequence identity with any one of SEQ ID NOs: 6-10.
23. The method of claim 17, wherein the shRNA comprises any one of SEQ ID NOs: 6-10.
24. The method of claim 17, further comprising a second therapeutic regimen.
25. The method of claim 17, further comprising a second therapeutic regime, wherein the second therapeutic regimen comprises ablative surgical intervention, neural stimulation, L-DOPA administration, or dopamine agonist administration.

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