



(51) International Patent Classification:

CI2N 15/86 (2006.01) CI2N 15/11 (2006.01)
CI2N 7/02 (2006.01) CI2N 15/113 (2010.01)
C07K 14/11 (2006.01)

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(21) International Application Number:

PCT/US2024/052959

(22) International Filing Date:

25 October 2024 (25.10.2024)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

18/498,577 31 October 2023 (31.10.2023) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: ADENO-ASSOCIATED VIRUS (AAV) PRODUCER CELL LINES

(57) Abstract: The present disclosure relates to nucleic acids encoding helper genes and adeno-associated virus (AAV) genes, under the control of inducible promoters. The disclosure also relates to a mammalian cell line for producing AAV as well as methods of using the mammalian cells for producing AAVs.

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ADENO-ASSOCIATED VIRUS (AAV) PRODUCER CELL LINES

FIELD OF THE INVENTION

[0001] The present disclosure provides mammalian cell lines for producing adeno-associated virus (AAV). The cells suitably include isolated nucleic acids encoding helper genes and AAV genes, under the control of inducible promoters. The disclosure also relates to methods of producing AAVs using the mammalian cells and nucleic acids described herein.

BACKGROUND

[0002] Recombinant adeno-associated virus (rAAV) has emerged as an important gene therapy vector for broad clinical application due to its high safety profile and strong potency for delivering functional genes into a variety of tissues with long-term therapeutic benefits. Multiple AAV-based gene therapies have been approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). With 25 viral-vector therapeutics in late-stage development and approximately 120 in Phase II trials as of February 2022, the number of approved therapies is only expected to grow.

[0003] However, the challenges of current AAV manufacturing processes include low productivity and scalability, low batch-to-batch reproducibility, high cost and complex supply chain issues, which significantly limit the access to the gene delivery platform for the treatment of a variety of human diseases. Additionally, constitutive expression of both helper and Rep genes required for AAV production can be cytotoxic. AAV stable producer cell lines (PCLs) and vectors that are designed to tightly control the expression of helper and Rep genes can overcome these limitations and bolster large-scale current good manufacturing practice (cGMP) manufacturing for AAV gene therapy.

SUMMARY OF THE INVENTION

[0004] In some embodiments, the present disclosure is directed to an isolated nucleic acid molecule operably comprising a first inducible promoter with two tetracycline operator sequences (a TetO₂ sequence), an E2A gene under control of the first inducible promoter, a viral

associated (VA) non-coding RNA under control of a second inducible promoter, a third inducible promoter with a TetO₂ sequence, an E4 gene under control of the third inducible promoter, and an antibiotic resistance gene.

[0005] In further embodiments, the disclosure provides an isolated nucleic acid molecule operably comprising, a first inducible promoter with a TetO₂ sequence, an E2A gene under control of the first inducible promoter, a viral associated (VA) non-coding RNA under control of a second inducible promoter, a third inducible promoter with a TetO₂ sequence, an E4 gene under control of the third inducible promoter, an expression cassette encoding a protein ortholog of the VA RNA and a peptide protein tag under the control of a depressible promoter comprising a human Cytomegalovirus (CMV) promoter and a TetO₂ sequence, a termination sequence, and an antibiotic resistance gene.

[0006] In still further embodiments, the present disclosure is directed to an isolated nucleic acid molecule operably comprising a plasmid encoding a first inducible promoter with a TetO₂ sequence, a Rep78 gene, including a silenced p19 promoter located within the Rep78 gene coding region, wherein the silenced p19 promoter comprises mutations in SP1, TATA-1, and/or TATA-2 sites, a second inducible promoter and a TetO₂ sequence, a Rep52 gene under control of the second inducible promoter, termination sequence and an antibiotic resistance gene.

[0007] In still further embodiments, the present disclosure is directed to a mammalian cell for producing an adeno-associated virus (AAV), comprising any of isolated nucleic acid molecules disclosed herein integrated into its genome. In some embodiments, the mammalian cell further comprises a nucleic acid encoding a transcriptional repression domain in frame with a nucleic acid encoding a tetracycline repressor protein. In some embodiments, the mammalian cell comprises a nucleic acid molecule encoding a gene of interest.

[0008] In still further embodiments, the disclosure provides a method for producing an adeno-associated virus (AAV), comprising inducing production of the genomically integrated nucleic acid sequence of any of the mammalian cells disclosed herein, culturing the mammalian cell, and harvesting the AAV.

BRIEF DESCRIPTION OF THE FIGURES

[0009] **FIG. 1** shows a schematic of the use of the Tet-On inducible system utilizing the tetracycline repressor protein to repress and activate expression of a protein.

[0010] **FIGS. 2A and 2B** show an exemplary TetR and TetR-KRAB fusion system.

[0011] **FIGS. 3A-3I** show exemplary nucleic acid molecules for production of helper genes in accordance with embodiments hereof.

[0012] **FIGS. 4A and 4B** show exemplary nucleic acid molecules for production of helper genes in accordance with embodiments hereof.

[0013] **FIGS. 5A-5P** show exemplary nucleic acid molecules for production of Rep genes in accordance with embodiments hereof.

[0014] **FIGS. 6A-6E** show exemplary nucleic acid molecules for production of Cap genes and genes of interest in accordance with embodiments hereof.

[0015] **FIG. 7** shows the results of AAV titers using the Helper, Rep and Cap-GOI vectors, in accordance with embodiments hereof.

[0016] **FIG. 8** shows a Western Blot image of the expression of helper, Rep and Cap proteins in accordance with embodiments hereof.

[0017] **FIG. 9** shows the results of AAV production in 3 Liter single-use bioreactors in accordance with embodiments hereof.

[0018] **FIG. 10 shows comparative results of AAV production of PCL clones.**

[0019] **FIG. 11** shows the results of cell-based infectivity and potency assay of AAVs produced in accordance with embodiments hereof.

DETAILED DESCRIPTION OF THE INVENTION

[0020] Unless otherwise defined herein, scientific and technical terms used in the present disclosure shall have the meanings that are commonly understood by one of ordinary skill in the

art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. The use of the word “a” or “an” when used in conjunction with the term “comprising” in the claims and/or the specification may mean “one,” but it is also consistent with the meaning of “one or more,” “at least one,” and “one or more than one.”

[0021] Throughout this application, the term “about” is used to indicate that a value includes the inherent variation of error for the method/device being employed to determine the value. Typically, the term is meant to encompass approximately or less than 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19% or 20% variability depending on the situation.

[0022] The use of the term “or” in the claims is used to mean “and/or” unless explicitly indicated to refer only to alternatives or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and “and/or.”

[0023] As used in this specification and claim(s), the words “comprising” (and any form of comprising, such as “comprise” and “comprises”), “having” (and any form of having, such as “have” and “has”), “including” (and any form of including, such as “includes” and “include”) or “containing” (and any form of containing, such as “contains” and “contain”) are inclusive or open-ended and do not exclude additional, unrecited, elements or method steps. It is contemplated that any embodiment discussed in this specification can be implemented with respect to any method, system, host cells, expression vectors, and/or composition of the invention. Furthermore, compositions, systems, cells, and/or nucleic acids of the invention can be used to achieve any of the methods as described herein.

[0024] The use of the term “for example” and its corresponding abbreviation “e.g.” (whether italicized or not) means that the specific terms recited are representative examples and embodiments of the disclosure that are not intended to be limited to the specific examples referenced or cited unless explicitly stated otherwise.

[0025] As used herein, “between” is a range inclusive of the ends of the range. For example, a number between x and y explicitly includes the numbers x and y, and any numbers that fall within x and y.

[0026] As used herein, the term “adeno-associated virus (AAV)” refers to a small sized, replicative-defective nonenveloped virus containing a single stranded DNA of the family *Parvoviridae* and the genus *Dependoparvovirus*. Over 10 adeno-associated virus serotypes have been identified so far, with serotype AAV2 being the best characterized. Other non-limiting examples of AAV serotypes are ANC80, AAV1, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, and AAV11. In addition to these serotypes, AAV pseudotypes have been developed. An AAV pseudotype contains the capsid of a first serotype and the genome of a second serotype (e.g., the pseudotype AAV2/5 would correspond to an AAV with the genome of serotype AAV2 and the capsid of AAV5).

[0027] As referred to herein, the term “adenovirus” refers to a nonenveloped virus with an icosahedral nucleocapsid containing a double stranded DNA of the family *Adenoviridae*. Over 50 adenoviral subtypes have been isolated from humans and many additional subtypes have been isolated from other mammals and birds. Birds. See, e.g., Ishibashi et al., “Adenoviruses of animals,” In *The Adenoviruses*, Ginsberg, ed., Plenum Press, New York, N.Y., pp. 497-562 (1984); Strauss, “Adenovirus infections in humans,” In *The Adenoviruses*, Ginsberg, ed., Plenum Press, New York, N.Y., pp. 451-596 (1984). These subtypes belong to the family *Adenoviridae*, which is currently divided into two genera, namely *Mastadenovirus* and *Aviadenovirus*. All adenoviruses are morphologically and structurally similar. In humans, however, adenoviruses show diverging immunological properties and are, therefore, divided into serotypes. Two human serotypes of adenovirus, namely AV2 and AV5, have been studied intensively and have provided the majority of general information about adenoviruses.

[0028] Adeno-associated virus (AAV) has emerged as the vector of choice for gene therapy in over 120 clinical trials worldwide. The fast-growing demand of recombinant AAV requires highly efficient and robust manufacturing platforms. However, current methods for AAV production, including transient transfection and helper virus systems, are extremely costly and lab-intensive. Thus, described herein are isolated nucleic acid molecules for producing an adeno-associated virus (AAV) and plasmid/helper virus-free AAV producer cell lines, and methods of use thereof, that provide efficient AAV manufacturing for a long-term solution at significantly reduced cost. The AAV producer cell line described herein represents a next generation platform for both clinical and commercial AAV manufacturing.

[0029] As used herein, a “vector” or “expression vector” refers to a nucleic acid replicon, such as a plasmid, phage, virus, or cosmid, to which another nucleic acid segment may be attached to bring about the replication and/or expression of the attached nucleic acid segment in a host cell. The term “vector” includes episomal (e.g., plasmids) and non episomal vectors. The term “vector” may also include synthetic vectors. Non-limiting examples of vectors include baculovirus vectors, bacteriophage vectors, plasmids, phagemids, cosmids, fosmids, bacterial artificial chromosomes, viral vectors (e.g. viral vectors based on vaccinia virus, poliovirus, adenovirus, adeno-associated virus, SV40, herpes simplex virus, and the like), P1-based artificial chromosomes, yeast plasmids, yeast artificial chromosomes, and any other vectors specific for specific hosts of interest (e.g., mammalian cells such as the E1 complementary producer cells described herein, including but not limited to HEK293 cells, PER.C6 cells, CAP® cells, and derivatives thereof). Vectors may be introduced into the desired host cells, e.g., HEK293 cells, PER.C6 cells, CAP® cells, or derivatives thereof, by well-known methods, including, but not limited to, transfection, transduction, cell fusion, and lipofection. Vectors can comprise various regulatory elements including, e.g., constitutive and inducible promoters, transcription enhancers, transcription terminators, and the like.

[0030] As used herein an “isolated nucleic acid molecule” includes vectors and plasmids that can contain the isolated nucleic acid molecule, as well as similar structures where the isolated nucleic acid molecule can be manipulated, stored, shipped, and ultimately utilized in various cell transfection systems. The isolated nucleic acid molecules described herein can be used for production of AAVs as described herein, but can also be utilized in various non-AAV producing cell lines (including transient transfection systems). The isolated nucleic acid molecules described herein suitably further include various additional elements and sequences as required to allow for use in the cellular systems, including mammalian cells, described herein.

[0031] A “nucleic acid,” “nucleic acid molecule,” or “oligonucleotide” means a polymeric compound comprising covalently linked nucleotides. The term “nucleic acid” includes polyribonucleic acid (RNA) and polydeoxyribonucleic acid (DNA), both of which may be single- or double-stranded. DNA includes, but is not limited to, complimentary DNA (cDNA), genomic DNA, plasmid or vector DNA, and synthetic DNA. RNA includes, but is not limited to, mRNA, tRNA, rRNA, snRNA, microRNA, miRNA, or MIRNA.

[0032] A “gene” refers to an assembly of nucleotides that encode a polypeptide, and includes cDNA and genomic DNA nucleic acid molecules. “Gene” also refers to a nucleic acid fragment that can act as a regulatory sequence preceding (5' non-coding sequences) and following (3' non-coding sequences) the coding sequence. In some embodiments, genes are integrated with multiple copies. In some embodiments, genes are integrated at predefined copy numbers.

[0033] As referred to herein, the term “heterologous gene” or “HG” as it relates to nucleic acid sequences such as a coding sequence or a control sequence, denotes a nucleic acid sequence, e.g., a gene, that is not normally joined together, and/or are not normally associated with a particular cell. In some embodiments, a heterologous gene is a construct where the coding sequence itself is not found in nature (e.g., synthetic sequences having codons different from the native gene). Allelic variation or naturally occurring mutational events do not give rise to heterologous DNA, as used herein.

[0034] In the various embodiments described herein, the nucleic acid molecules are capable of encoding the various genes. That is the nucleic acid molecules, when transcribed, produce mRNA for the genes described herein, which is then translated to the desired or required proteins.

[0035] The various nucleic acid molecules encoding the various genes described herein are suitably under control of a promoter. As used herein “under control” refers to a gene being regulated by a “promoter,” “promoter sequence,” or “promoter region,” which refers to a DNA regulatory region/sequence capable of binding RNA polymerase and initiating transcription of a downstream coding or non-coding gene sequence. In other words, the promoter and the gene are in operable combination or operably linked. As referred to herein, the terms “in operable combination”, “in operable order”, “operably linked” and “operably” refer to the linkage of nucleic acid sequences in such a manner that a promoter capable of directing the transcription of a given gene and/or the synthesis of a desired protein molecule is produced.

[0036] In some examples of the present disclosure, the promoter sequence includes the transcription initiation site and extends upstream to include the minimum number of bases or elements necessary to initiate transcription at levels detectable above background. In some embodiments, the promoter sequence includes a transcription initiation site, as well as protein

binding domains responsible for the binding of RNA polymerase. Eukaryotic promoters will often, but not always, contain “TATA” boxes and “CAT” boxes. Various promoters, including inducible promoters, may be used to drive the gene expression, e.g., in the host cell or vectors of the present disclosure. In some embodiments, the promoter is not a leaky promoter, i.e., the promoter is not constitutively expressing any of the gene products as described herein. In other embodiments as described herein, the promoter is a constitutive promoter, which initiates mRNA synthesis independent of the influence of an external regulation.

[0037] Suitably, the promoters used to control the transcription of the various genes for producing the AAVs described herein are derepressible promoters. As used herein, a “derepressible promoter” refers to a structure that includes an inducible or a functional promoter and additional elements or sequences capable of binding to a repressor element to cause repression of the inducible or functional promoter. “Repression” refers to the decrease or inhibition of the initiation of transcription of a downstream coding or non-coding gene sequence by a promoter. A “repressor element” refers to a protein or polypeptide that is capable of binding to a promoter (or near a promoter) so as to decrease or inhibit the activity of the promoter. A repressor element can interact with a substrate or binding partner of the repressor element, such that the repressor element undergoes a conformation change. This conformation change in the repressor element takes away the ability of the repressor element to decrease or inhibit the promoter, resulting in the “derepression” of the promoter, thereby allowing the promoter to proceed with the initiation of transcription.

[0038] In some embodiments, the derepressible promoter comprises an inducible or functional promoter and one or more tetracycline operator sequences (TetO₂). An “inducible promoter” regulates (e.g., activates or inactivates) transcriptional activity of a nucleic acid to which it is operably linked when the promoter is influenced by or contacted by a corresponding regulatory protein or other external stimuli such as chemicals, stress, or biotic stimuli. A “functional promoter” refers to a promoter, that absent the action of the repressor element, would be capable of initiation transcription. Various inducible and functional promoters that can be used in the practice of the present invention are known in the art, and include for example, PCMV, PH1, P19, P5, P40 and promoters of Adenovirus helper genes (e.g., E1A, E1B, E2A, E4Orf6, and VA).

[0039] The term “Tet operator sequence”, “Tet operator sequence motif”, “Tet operator”, “TetO₂” or “TetO” as used herein is intended to encompass all classes of Tet operator sequences, e.g., TetO(A), TetO(B), TetO(C), TetO(D), TetO(E), TetO(G), TetO(H), TetO(J) and TetO(Z). The nucleotide sequences of Tet repressors of members of the A, B, C, D, E, G, H, J and Z classes, and their corresponding Tet operator sequences are well known in the art, see, for example, Waters 1983, *Nucl. Acids Res* 11:6089-6105, Hillen 1983, *Nucl. Acids Res.* 11:525-539, Postle 1984, *Nucl. Acids Res.* 12:4849-4863, Unger 1984, *Gene* 31: 103-108, Unger 1984, *Nucl Acids Res.* 12:7693-7703 and Tovar 1988, *Mol. Gen. Genet.* 215:76-80, which are incorporated herewith by reference with respect to the specifically disclosed Tet operator sequences and in their entirety. Tet operator sequences are also disclosed in U.S. Pat. No. 5,464,758.

[0040] Exemplary repressor elements and their corresponding binding partners that can be used as derepressible promoters are known in the art, and include systems such as the cumate gene-switch system (CuO operator, CymR repressor and cumate binding partner) (*see, e.g.,* Mullick *et al.*, “The cumate gene-switch: a system for regulated expression in mammalian cells,” *BMC Biotechnology* 6:43 (1-18) (2006), the disclosure of which is incorporated by reference herein in its entirety, including the disclosure of the derepressible promoter system described therein) and the TetO/TetR system described herein (*see, e.g.,* Yao *et al.*, “Tetracycline Repressor, tetR, rather than the tetR-Mammalian Cell Transcription Factor Fusion Derivatives, Regulates Inducible Gene Expression in Mammalian Cells,” *Human Gene Therapy* 9:1939-1950 (1998), the disclosure of which is incorporated by reference herein in its entirety).

[0041] VA (virus-associated) RNA is a non-coding type found in adenoviruses. It plays a role in the regulation of translation. There are two copies of this RNA called VAI or RNA I VA and VAII or RNA II VA. The two RNA VA genes are distinct genes in the adenovirus genome. RNA I VA is the main species with RNA II VA expressed at a lower level. Neither transcript is polyadenylated and both are transcribed by PolIII.

[0042] As described herein, the nucleic acid molecules suitably encode viral helper gene. Viral helper genes include various adenoviral virus genes, herpes virus genes and bocavirus genes (*see, e.g.,* Guido *et al.*, “Human bocavirus: Current knowledge and future challenges,”

World J. Gastroenterol 22:8684-8697, the disclosure of which is incorporated by reference herein in its entirety). In exemplary embodiments, the viral helper gene is an adenovirus helper gene. As referred to herein, the term “adenovirus helper gene” or “AV helper gene” refers to a gene that is composed of one or more nucleic acid sequences derived from one or more adenovirus subtypes or serotypes that contributes to Adeno-associated virus replication and packaging. In some embodiments, the Adenovirus helper gene is E1A, E1B, E2A, E4 (including E4Orf6), VA, or a combination thereof or any other adenovirus helper gene. In exemplary embodiments, the adenovirus helper gene comprises both E2A and E4Orf6 genes.

[0043] In still further embodiments, provided herein is an isolated nucleic acid molecule operably comprising a first inducible promoter and two tetracycline operator sequences (a TetO₂ sequence), an E2A gene under control of the first inducible promoter, a viral associated (VA) non-coding RNA under control of a second inducible promoter, a third inducible promoter and a TetO₂ sequence, an E4 gene under control of the third inducible promoter, and an antibiotic resistance gene.

[0044] In other embodiments, the present disclosure provides an isolated nucleic acid molecule operably comprising, a first inducible promoter and a TetO₂ sequence, an E2A gene under control of the first inducible promoter, a viral associated (VA) non-coding RNA under control of a second inducible promoter, a third inducible promoter and a TetO₂ sequence, an E4 gene under control of the third inducible promoter, an expression cassette encoding a protein ortholog of the VA RNA and a peptide protein tag under the control of a depressible promoter comprising a human Cytomegalovirus (CMV) promoter and a TetO₂ sequence, a termination sequence, and an antibiotic resistance gene.

[0045] As described herein, in exemplary embodiments, the E2A gene that is encoded by the nucleic acid molecules is suitably under the control of a first inducible promoter that is native to the E2A gene. In some embodiments, the VA non-coding RNA that is encoded by the nucleic acid molecules is suitably under the control of a second inducible promoter that is native to the VA non-coding RNA. In some embodiments, the second inducible promoter is an H1 promoter. In some embodiments, the E4 gene that is encoded by the nucleic acid molecules is suitably under the control of a third inducible promoter that is native to the E4 gene.

[0046] As used herein, protein orthologs refer to proteins that have the same specificity in different organisms, e.g., bind the same ligand and similar DNA sites in related genomes. Hence, orthologous proteins carry the same or similar specificity determining residues. In some embodiments, the isolated nucleic acid molecule described herein comprises a protein ortholog of the of the VA RNA. In some embodiments, the protein ortholog is an influenza non-structural 1 protein (NS1), Ebola viral protein 35 (VP35), orthoreovirus sigma 3 protein ($\sigma 3$), group C rotavirus non-structural protein 3 (NSP3), vaccinia virus E3L protein (E3L), herpes simplex virus type 1 US11 protein (US11), Epstein-Barr virus SM protein (SM), baculovirus PK2 protein (PK2), hepatitis C virus non-structural protein 5A protein (NS5A), human herpes virus-8 protein vIRF-2 (vIRF-2), human immunodeficiency virus protein Tat, vaccinia virus K3L protein (K3L), Herpes Simplex virus protein $\gamma 134.5$ /ICP34.5, or human papilloma virus-18 E6 protein (E6). In some embodiments, the protein ortholog is VP35. In some embodiments, the protein ortholog is SM.

[0047] Alternatively, or in addition, the protein ortholog of the VA RNA of any isolated nucleic acid molecule of the present invention may be operably linked to a peptide tag to assist in its isolation and detection, or to assist in the identification and expression of the encoded protein. A variety of peptide tags can be used in the context of the present invention, including PK tags, FLAG tags, MYC tags, hemagglutinin (HA) tags and polyhistidine tags. Peptide tags can be diagnosed by immunodetection tests, which use anti-tag antibodies. In some embodiments, the peptide tag is located individually at the N-terminus of the protein ortholog of the VA RNA. In some embodiments, the isolated nucleic acid molecule comprises a peptide protein tag. In some embodiments, the peptide protein tag is an HA tag. In some embodiments, the peptide protein tag is a FLAG-tag. In some embodiments, the FLAG-tag is an N-terminal flag tag.

[0048] As used herein, the role of the termination sequence is to define the end of a transcriptional unit (such as a gene) and initiate the process of releasing the newly synthesized RNA from the transcription machinery. Terminators are found downstream of the gene to be transcribed, and typically occur directly after any 3' regulatory elements, such as the polyadenylation or poly(A) signal. In some embodiments, any of the nucleic acid molecules disclosed herein comprise a termination sequence. In some embodiments, the termination sequence is a bovine growth hormone polyadenylation (bgh-PolyA) signal.

[0049] As referred to herein, a “reporter gene” is a gene whose expression confers a phenotype upon a cell that can be easily identified and measured. In some embodiments, the reporter gene comprises a fluorescent protein gene. In some embodiments, the reporter gene comprises a selection gene.

[0050] In some embodiments, the isolated nucleic acid molecules comprise a selection gene. As referred to herein, the term “selection gene” refers to the use of a gene which encodes an enzymatic activity that confers the ability to grow in medium lacking what would otherwise be an essential nutrient; in addition, a selection gene may confer resistance to an antibiotic or drug upon the cell in which the selection gene is expressed. A selection gene may be used to confer a particular phenotype upon a host cell. When a host cell must express a selection gene to grow in selective medium, the gene is said to be a positive selection gene. A selection gene can also be used to select against host cells containing a particular gene; a selection gene used in this manner is referred to as a negative selection gene. In some embodiments, the selection gene is an antibiotic resistance gene. In some embodiments, the antibiotic resistance gene is a puromycin resistance gene. In some embodiments, the antibiotic resistance gene is a blasticidin resistance gene. In some embodiments, the antibiotic resistance gene is a hygromycin resistance gene. In some embodiments, the antibiotic resistance gene is a zeocin resistance gene.

[0051] In exemplary embodiments, the nucleic acid molecules include two inverted terminal repeat (ITR) sequences. As known in the art, these ITR sequences (i.e., AAV2 ITR) are single stranded sequence of nucleotides, followed downstream by its reverse complement. ITR sequences represent the minimal sequence required for replication, rescue, packaging and integration of the AAV genome. Suitably, these ITR sequences flank a gene of interest. Thus, in embodiments, the nucleic acid molecules further encode a gene of interest. This gene of interest can be, for example, a reporter gene, a selection gene, or a gene of therapeutic interest, for example. In some embodiments, the nucleic acid sequence is flanked on both the 5′ and 3′ ends by transposon-specific inverted terminal repeats (ITR).

[0052] As used herein, “core insulator” refers to a gene boundary element that blocks the interaction between an enhancer and a promoter. The presence of the core insulator between the enhancer and the promoter allows the insulator to block subsequent interactions. The core

insulator can determine the set of genes that the enhancer can influence. Insulators are required when two adjacent genes on a chromosome have very different transcriptional patterns and it is necessary to induce or suppress one mechanism without inhibiting the adjacent genes. In some embodiments, any of the nucleic acid sequences disclosed herein comprise a core insulator sequence inserted downstream of the ITR on the 3' end and upstream of the ITR on the 5' end. In some embodiments, the nucleic acid molecule comprises a core insulator sequence inserted between the termination sequence and the antibiotic resistance gene.

[0053] As referred to herein, the term “Rep” gene refers to the art-recognized region of the AAV genome which encodes the replication proteins of the virus which are collectively required for replicating the viral genome, or functional homologues thereof such as the human herpesvirus 6 (HHV-6) rep gene which is also known to mediate AAV2 DNA replication. Thus, the Rep coding region can include the genes encoding for AAV Rep78 and Rep68 (the “long forms of Rep”), and Rep52 and Rep40 (the “short forms of Rep”), or functional homologues thereof. The Rep coding region, as used herein, can be derived from any viral serotype, such as the AAV serotypes described herein. The region need not include all wild-type genes but may be altered, (e.g., by insertion, deletion or substitution of nucleotides), so long as the Rep genes present provide for sufficient integration functions when expressed in a suitable target cell. See, e.g., Muzyczka, N., *Current Topics in Microbiol. and Immunol.* 158:97-129 (1992); and Kotin, R. M., *Human Gene Therapy* 5:793-801 (1994).

[0054] In still further embodiments, provided herein is an isolated nucleic acid molecule comprising a plasmid encoding a first inducible promoter and a TetO₂ sequence, a Rep78 gene, including a silenced p19 promoter located within the Rep78 gene coding region, wherein the silenced p19 promoter comprises mutations in SP1, TATA-1, and/or TATA-2 sites, a second inducible promoter and a TetO₂ sequence, a Rep52 gene under control of the second inducible promoter, termination sequence and an antibiotic resistance gene.

[0055] The terms “sequence identity” or “% identity” in the context of nucleic acid sequences described herein refer to the percentage of residues in the compared sequences that are the same when the sequences are aligned over a specified comparison window. A comparison window can be a segment of at least 10 to over 1000 residues in which the sequences can be aligned and

compared. Methods of alignment for determination of sequence identity are well-known and can be performed using publicly available databases such as BLAST (blast.ncbi.nlm.nih.gov/Blast.cgi).

[0056] The Kozak consensus sequence, Kozak consensus or Kozak sequence, is known as a sequence which occurs on eukaryotic mRNA and has the consensus (gcc)gccRccAUGG, where R is a purine (adenine or guanine) three bases upstream of the start codon (AUG), which is followed by another "G." In some embodiments, the isolated nucleic acid molecules disclosed herein comprise a Kozak consensus sequence. In some embodiments, the nucleic acid molecules comprise a consensus sequence that has at least about 70%, at least about 80%, at least about 90% sequence identity, or more identity to the Kozak consensus sequence. In some embodiments, the isolated nucleic acid molecule includes a Kozak consensus sequence after the gene cassette encoding one or more proteins of interest is inserted into the vector, e.g., at the restriction site downstream of the promoter. For example, the isolated nucleic acid molecule can include a nucleotide sequence of GCCGCCATG, where the ATG is the start codon of the protein of interest. In some embodiments, the isolated nucleic acid molecule comprises a nucleotide sequence of GCGGCCGCCATG, where the ATG is the start codon of the protein of interest. In some embodiments, the Rep78 gene of the isolated nucleic acid molecule further comprises a Kozak consensus sequence. In some embodiments, the Rep52 gene of the isolated nucleic acid molecule further comprises a Kozak consensus sequence.

[0057] To control the production of Rep proteins more effectively, non-canonical start codons or non-canonical translational initiation codons can be used. In some embodiments, the Rep78 gene of the isolated nucleic acid molecules further comprises a non-canonical start codon. In some embodiments, the Rep52 gene of the isolated nucleic acid molecule further comprises a non-canonical start codon. In some embodiments, the non-canonical translation initiation codon is GTG, CTG, ACG or TTG. In some embodiments, the non-canonical translation initiation codon is CTG.

[0058] Non-limiting examples of gene modifications that can be used in the present invention include codon optimization aimed at, for example, modifying a non-CTG leucine codon to CTG, or modifying a non-AAG lysine codon to AAG. Another example of a nucleic acid codon-

optimizing modification is to increase GC content. To increase the vector stability and Rep52 expression, the DNA sequence of coding region of Rep52 was optimized for human cell codon usage while retaining the same protein sequence, which significantly reduced the DNA sequence identity of the Rep52 coding sequence to the Rep78 coding sequence, from 100% sequence identity to 80.1% sequence identity. In some embodiments, the Rep52 of any of the nucleic acid molecules disclosed herein is codon optimized. In some embodiments, the VP1 gene of any of the nucleic acid molecules disclosed herein, excluding the first 439 bp of the coding region, is optimized.

[0059] In further embodiments, the first inducible promoter of the nucleic acid molecules disclosed herein is a human cytomegalovirus (CMV) immediate early enhancer-promoter, CMV immediate early enhancer fused chicken β -actin promoter (CAG), human ubiquitin C (UbC) promoter or Rous sarcoma virus (RSV) promoter. In some embodiments, the first inducible promoter is an RSV promoter. In some embodiments, the first inducible promoter is an UbC promoter. As described herein, the use of an artificial intron allows for removal of an inducible promoter following induction of the promoter and prior to the producing the AAV. In some embodiments, the nucleic acid molecule further comprises an intron of the UbC promoter inserted upstream of the UbC promoter.

[0060] In some embodiments, the second inducible promoter of the nucleic acid molecules disclosed herein is human CMV immediate early enhancer-promoter, CMV immediate early enhancer fused chicken β -actin promoter (CAG), human ubiquitin C (UbC) promoter or Rous sarcoma virus (RSV) promoter. In some embodiments, the second inducible promoter is a CAG promoter. In some embodiments, the second inducible promoter is a CMV promoter.

[0061] As referred to herein, the term “Cap” gene refers to the art-recognized region of the AAV genome which encodes the capsid proteins of the virus. Illustrative (non-limiting) examples of these capsid proteins are the AAV capsid proteins VP1, VP2, and VP3. Cap genes used in this disclosure can come from any AAV serotype or a combination of AAV serotypes.

[0062] In still further embodiments, the present disclosure provides an isolated nucleic acid molecule operably comprising a first inducible promoter and a TetO₂ sequence, a VP1 gene, a second inducible promoter and a TetO₂ sequence, a VP2 gene and a VP3 gene, and an antibiotic

resistance gene. In some embodiments, the nucleic acid sequence comprises a core insulator sequence inserted between the 1) VP1 gene and 2) the second inducible promoter and TetO₂ sequence. In some embodiments, the nucleic acid sequence comprises a core insulator sequence inserted between 1) the VP2 and VP3 gene and 2) the antibiotic resistance gene.

[0063] As referred to herein, the term “gene of interest”, or “gene of therapeutic interest” or “GOI” is used to describe a heterologous gene. The GOI of the present disclosure can comprise any desired gene that encodes a protein that is defective or missing from a target cell genome or that encodes a non-native protein having a desired biological or therapeutic effect (e.g., an antiviral function), or the sequence can correspond to a molecule having an antisense or ribozyme function. Representative (non-limiting) examples of suitable genes of therapeutic interest include those used for the treatment of inflammatory diseases, autoimmune, chronic and infectious diseases, including such disorders as AIDS, cancer, neurological diseases, cardiovascular disease, hypercholesterolemia; various blood disorders including various anemias, thalassemias and hemophilia; genetic defects such as cystic fibrosis, Gaucher's Disease, adenosine deaminase (ADA) deficiency, emphysema, etc. Several antisense oligonucleotides (e.g., short oligonucleotides complementary to sequences around the translational initiation site (AUG codon) of an mRNA) that are useful in antisense therapy for cancer and for viral diseases have been described in the art and are also examples of suitable genes of therapeutic interest.

[0064] In further embodiments, the nucleic acid molecule comprises a gene of interest (GOI) downstream of the VP2 and VP3 gene and upstream of the antibiotic resistance gene. In some embodiments, the nucleic acid molecule comprises a core insulator sequence inserted between the VP3 gene and the GOI. In some embodiments, the nucleic acid molecule comprises a core insulator sequence inserted between the GOI and the antibiotic resistance gene. In some embodiments, the nucleic acid molecule comprises a core insulator sequence inserted between the VP3 gene and the GOI, and between the GOI and the antibiotic resistance gene. In some embodiments, the GOI is a therapeutic gene.

[0065] In some embodiments, the present disclosure provides a mammalian cell for producing an adeno-associated virus (AAV), comprising any of the isolated nucleic acid molecules disclosed herein integrated into its genome. In some embodiments, the mammalian cell further

comprises a nucleic acid encoding a transcriptional repression domain in frame with a nucleic acid encoding a tetracycline repressor protein. In some embodiments, the mammalian cell disclosed herein further comprises a nucleic acid molecule encoding a gene of interest.

[0066] The AAV producer cells described herein provide a long-term and cost-effective solution for large scale AAV manufacturing. As constitutive expression of either helper or Rep proteins can be cytotoxic, the strategies described herein allow for control of their expression by engineered, derepressible promoters.

[0067] As used herein, the term “mammalian cell” includes cells from any member of the order Mammalia, such as, for example, human cells, mouse cells, rat cells, monkey cells, hamster cells, and the like. In some embodiments, the cell is a mouse cell, a human cell, a Chinese hamster ovary (CHO) cell, a CHOK1 cell, a CHO-DXB11 cell, a CHO-DG44 cell, a CHOK1SV cell including all variants (e.g., POTELLIGENT®, Lonza, Slough, UK), a CHOK1SV GS-KO (glutamine synthetase knockout) cell including all variants (e.g., XCEED™ Lonza, Slough, UK). In some embodiments, the mammalian cell is a Chinese hamster ovary (CHO) cell. In some embodiments, the mammalian cell is a human cell.

[0068] Exemplary human cells include human embryonic kidney (HEK) cells, such as HEK293, a HeLa cell, or a HT1080 cell. As used herein, the term “human embryonic kidney 293 (HEK293) cell” refers to a cell line originally derived from human embryonic kidney cells and containing approximately 4.5 kb of Ad5 genome. Variants of HEK293 cells have been developed and include, e.g., HEK293S, HEK293T, HEK293F, HEK293FT, HEK293FTM, HEK293SG, HEK293SGGD, HEK293H, HEK293E, HEK293MSR, and HEK293A. The term “HEK293 cell” as used herein encompasses all HEK293 cell variants and derivatives, including but not limited to the variants described herein. *See, e.g.,* Yuan et al., “The Scattered Twelve Tribes of HEK293,” *Biomed Pharmacol J* 2018; 11(2). In some embodiments, the human cell is an HEK cell. In some embodiments, the HEK cell is an HEK293 cell.

[0069] As described herein, suitably the mammalian cells are mammalian cell cultures, and in embodiments, can be suspension cultures. As described herein, the use of suspension cell cultures allows for increased scalability and production of AAV. Adherent cultures refer to cells that are grown on a substrate surface, for example a plastic plate, dish or other suitable cell

culture growth platform, and may be anchorage dependent. Suspension cultures refer to cells that can be maintained in, for example, culture flasks or large suspension vats, which allows for a large surface area for gas and nutrient exchange. Suspension cell cultures often utilize a stirring or agitation mechanism to provide appropriate mixing. Media and conditions for maintaining cells in suspension are generally known in the art. An exemplary suspension cell culture includes human HEK293 clonal cells.

[0070] “Transfection” as used herein means the introduction of an exogenous nucleic acid molecule, including a vector, into a cell. A “transfected” cell comprises an exogenous nucleic acid molecule inside the cell and a “transformed” cell is one in which the exogenous nucleic acid molecule within the cell induces a phenotypic change in the cell. The transfected nucleic acid molecule can be integrated into the host cell's genomic DNA and/or can be maintained by the cell, temporarily or for a prolonged period of time, extra-chromosomally. Host cells or organisms that express exogenous nucleic acid molecules or fragments are referred to as “recombinant,” “transformed,” or “transgenic” organisms. A number of transfection techniques are generally known in the art. See, e.g., Graham et al., *Virology*, 52:456 (1973); Sambrook et al., *Molecular Cloning*, a laboratory manual, Cold Spring Harbor Laboratories, New York (1989); Davis et al., *Basic Methods in Molecular Biology*, Elsevier (1986); and Chu et al., *Gene* 13:197 (1981). Such techniques can be used to introduce one or more exogenous DNA moieties, such as an AAV vector cassette, AAV helper constructs, and other nucleic acid molecules, into suitable host cells.

[0071] Various methods of transfecting the mammalian cells with the isolated nucleic acid molecules described herein (i.e., vectors), are known in the art and include various chemical and physical methods, for example, electroporation, cell injection, calcium phosphate exposure, liposome or polymer-based carrier systems, etc.

[0072] In still further embodiments, the present disclosure provides a method for producing an adeno-associated virus (AAV), comprising inducing production of the genomically integrated nucleic acid sequence of any of the mammalian cells disclosed herein, culturing the mammalian cell, and harvesting the AAV.

[0073] As discussed herein, the methods of producing and the mammalian cells of the present disclosure advantageously provide a high titer of the AAV produced by the mammalian cells. In

some embodiments, the amount of the AAV produced is about 10^{10} to about 10^{11} viral genomes per mL (vg/mL). In some embodiments, the amount of the AAV produced is at least about 10^{10} viral genomes per mL (vg/mL). In some embodiments, the amount of the AAV produced is at least about 10^{11} viral genomes per mL (vg/mL).

[0074] In some embodiments, the mammalian cells provided herein are substantially free of helper virus. As referred to herein, a “helper virus” is any non-AAV virus that is added to enable the replication and packaging of adeno-associated virus. Representative (non-limiting) examples of helper viruses are adenovirus and herpes virus. In some embodiments, the term substantially free of helper virus refers to a cell that has fewer than 100, fewer than 10, or fewer than 1 helper virus per cell. In some embodiments, the term substantially free of helper virus refers to a cell in which no helper viruses are present or to a population of cells in which no helper viruses are present using detection methods known to those skilled in the art. In some embodiments, no wild-type helper virus is in the cell. In some embodiments, the term wild-type virus refers to any complete-non-AAV virus that can replicate in the cell independently of any other virus.

[0075] The methods of producing the AAVs can be used in a continuous manufacturing system. In exemplary embodiments, the use of a suspension cell culture allows for the production of large volumes of AAV, with high productivity and prolonged culture conditions to allow for multiple harvests of AAV for each batch of starting cells.

[0076] Production methods can utilize any suitable reactor(s) including but not limited to stirred tank, airlift, fiber, microfiber, hollow fiber, ceramic matrix, fluidized bed, fixed bed, and/or spouted bed bioreactors. As used herein, “reactor” can include a fermenter or fermentation unit, or any other reaction vessel and the term “reactor” is used interchangeably with “fermenter.” The term fermenter or fermentation refers to both microbial and mammalian cultures. For example, in some aspects, an example bioreactor unit can perform one or more, or all, of the following: feeding of nutrients and/or carbon sources, injection of suitable gas (e.g., oxygen), inlet and outlet flow of fermentation or cell culture medium, separation of gas and liquid phases, maintenance of temperature, maintenance of oxygen and CO₂ levels, maintenance of pH level, agitation (e.g., stirring), and/or cleaning/sterilizing. Example reactor units, such as a fermentation unit, may contain multiple reactors within the unit, for example the unit can have 1,

2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, or 100, or more bioreactors in each unit and/or a facility may contain multiple units having a single or multiple reactors within the facility. In various embodiments, the bioreactor can be suitable for batch, semi fed-batch, fed-batch, perfusion, and/or a continuous fermentation processes. Any suitable reactor diameter can be used. In embodiments, the bioreactor can have a volume between about 100 mL and about 50,000 L. Non-limiting examples include a volume of 100 mL, 250 mL, 500 mL, 750 mL, 1 liter, 2 liters, 3 liters, 4 liters, 5 liters, 6 liters, 7 liters, 8 liters, 9 liters, 10 liters, 15 liters, 20 liters, 25 liters, 30 liters, 40 liters, 50 liters, 60 liters, 70 liters, 80 liters, 90 liters, 100 liters, 150 liters, 200 liters, 250 liters, 300 liters, 350 liters, 400 liters, 450 liters, 500 liters, 550 liters, 600 liters, 650 liters, 700 liters, 750 liters, 800 liters, 850 liters, 900 liters, 950 liters, 1000 liters, 1500 liters, 2000 liters, 2500 liters, 3000 liters, 3500 liters, 4000 liters, 4500 liters, 5000 liters, 6000 liters, 7000 liters, 8000 liters, 9000 liters, 10,000 liters, 15,000 liters, 20,000 liters, and/or 50,000 liters. Additionally, suitable reactors can be multi-use, single-use, disposable, or non-disposable and can be formed of any suitable material including metal alloys such as stainless steel (e.g., 316L or any other suitable stainless steel) and Inconel, plastics, and/or glass.

Additional Exemplary Embodiments

[0077] Embodiment 1 is an isolated nucleic acid molecule operably comprising a first inducible promoter and two tetracycline operator sequences (a TetO₂ sequence), an E2A gene under control of the first inducible promoter, a viral associated (VA) non-coding RNA under control of a second inducible promoter, a third inducible promoter and a TetO₂ sequence, an E4 gene under control of the third inducible promoter, and an antibiotic resistance gene.

[0078] Embodiment 2 includes the nucleic acid molecule of embodiment 1, wherein the first inducible promoter is native to the E2A gene.

[0079] Embodiment 3 includes the nucleic acid molecule of embodiment 1 or 2, wherein the second inducible promoter is a promoter native to the VA non-coding RNA.

[0080] Embodiment 4 includes the nucleic acid molecule of any one of embodiments 1 to 3, wherein the second inducible promoter is an H1 promoter.

[0081] Embodiment 5 includes the nucleic acid molecule of any one of embodiments 1 to 4, wherein the third inducible promoter is native to the E4 gene.

[0082] Embodiment 6 includes the nucleic acid molecule of any one of embodiments 1 to 5, wherein the antibiotic resistance gene is a puromycin resistance gene.

[0083] Embodiment 7 includes the nucleic acid molecule of any one of embodiments 1 to 6, wherein the nucleic acid sequence comprises a core insulator sequence inserted between the E4 gene and the antibiotic resistance gene.

[0084] Embodiment 8 includes the nucleic acid molecule of any one of embodiments 1 to 7, wherein the nucleic acid sequence is flanked on both the 5' and 3' ends by transposon-specific inverted terminal repeats (ITR).

[0085] Embodiment 9 includes the nucleic acid molecule of embodiment 8, wherein the nucleic acid sequence comprises a core insulator sequence inserted downstream of the ITR on the 3' end and upstream of the ITR on the 5' end.

[0086] Embodiment 10 includes the nucleic acid molecule of any one of embodiments 1 to 9, further comprising multiple copies of VA non-coding RNA.

[0087] Embodiment 11 is an isolated nucleic acid molecule operably comprising a first inducible promoter and a TetO₂ sequence, an E2A gene under control of the first inducible promoter, a viral associated (VA) non-coding RNA under control of a second inducible promoter, a third inducible promoter and a TetO₂ sequence, an E4 gene under control of the third inducible promoter, an expression cassette encoding a protein ortholog of the VA RNA and a peptide protein tag under the control of a depressible promoter comprising a human Cytomegalovirus (CMV) promoter and a TetO₂ sequence, a termination sequence, and an antibiotic resistance gene.

[0088] Embodiment 12 includes the nucleic acid molecule of embodiment 11, wherein the first inducible promoter is native to the E2A gene.

[0089] Embodiment 13 includes the nucleic acid molecule of embodiment 11 or 12, wherein the second inducible promoter is a promoter native to the VA non-coding RNA.

[0090] Embodiment 14 includes the nucleic acid molecule of any one of embodiments 11 to 13, wherein the second inducible promoter is an H1 promoter.

[0091] Embodiment 15 includes the isolated nucleic acid molecule of any one of embodiments 12 to 14, wherein the third inducible promoter is native to the E4 gene.

[0092] Embodiment 16 includes the isolated nucleic acid molecule of any one of embodiments 11 to 15, wherein the protein ortholog is an influenza non-structural 1 protein (NS1), Ebola viral protein 35 (VP35), orthoreovirus sigma 3 protein ($\sigma 3$), group C rotavirus non-structural protein 3 (NSP3), vaccinia virus E3L protein (E3L), herpes simplex virus type 1 US11 protein (US11), Epstein-Barr virus SM protein (SM), baculovirus PK2 protein (PK2), hepatitis C virus non-structural protein 5A protein (NS5A), human herpes virus-8 protein vIRF-2 (vIRF-2), human immunodeficiency virus protein Tat, vaccinia virus K3L protein (K3L), Herpes Simplex virus protein $\gamma 134.5$ /ICP34.5, and human papilloma virus-18 E6 protein (E6).

[0093] Embodiment 17 includes the isolated nucleic acid molecule of embodiment 16, wherein the protein ortholog is VP35.

[0094] Embodiment 18 includes the isolated nucleic acid molecule of embodiment 16, wherein the protein ortholog is SM.

[0095] Embodiment 19 includes the isolated nucleic acid molecule of any one of embodiments 11 to 18, wherein the peptide protein tag is a FLAG-tag.

[0096] Embodiment 20 includes the isolated nucleic acid molecule of embodiment 19, wherein the FLAG-tag is a N-terminal Flag tag.

[0097] Embodiment 21 includes the isolated nucleic acid molecule of any one of embodiments 11 to 20, wherein the termination sequence is a bovine growth hormone polyadenylation (bgh-PolyA) signal.

[0098] Embodiment 22 includes the nucleic acid molecule of any one of embodiments 11 to 21, wherein the antibiotic resistance gene is a puromycin resistance gene.

[0099] Embodiment 23 includes the nucleic acid molecule of any one of embodiments 11 to 22, wherein the nucleic acid sequence comprises a core insulator sequence inserted between the E4 gene and the expression cassette.

[00100] Embodiment 24 includes the nucleic acid molecule of any one of embodiments 11 to 23, wherein the nucleic acid sequence is flanked on both the 5' and 3' ends by transposon-specific inverted terminal repeats (ITR).

[00101] Embodiment 25 includes the nucleic acid molecule of embodiment 24, wherein the nucleic acid sequence comprises a core insulator sequence inserted downstream of the ITR on the 3' end and upstream of the ITR on the 5' end.

[00102] Embodiment 26 is an isolated nucleic acid molecule operably comprising a plasmid encoding a first inducible promoter and a TetO₂ sequence, a Rep78 gene, including a silenced p19 promoter located within the Rep78 gene coding region, wherein the silenced p19 promoter comprises mutations in SP1, TATA-1, and/or TATA-2 sites, a second inducible promoter and a TetO₂ sequence, a Rep52 gene under control of the second inducible promoter, termination sequence and, an antibiotic resistance gene.

[00103] Embodiment 27 includes the isolated nucleic acid molecule of embodiment 26, wherein the Rep78 gene further comprises a Kozak consensus sequence or a non-canonical start codon.

[00104] Embodiment 28 includes the nucleic acid molecule of embodiment 26, wherein the Rep52 gene further comprises a Kozak consensus sequence or a non-canonical start codon.

[00105] Embodiment 29 includes the isolated nucleic acid molecule of any one of embodiments 26 to 28, wherein the first inducible promoter is human cytomegalovirus (CMV) immediate early enhancer-promoter, CMV immediate early enhancer fused chicken β -actin promoter (CAG), human ubiquitin C (UbC) promoter or Rous sarcoma virus (RSV) promoter.

[00106] Embodiment 30 includes the isolated nucleic acid molecule of embodiment 29, wherein the first inducible promoter is an RSV promoter.

[00107] Embodiment 31 includes the isolated nucleic acid molecule of any one of embodiments 26 to 30, wherein the second inducible promoter is human CMV immediate early enhancer-

promoter, CMV immediate early enhancer fused chicken β -actin promoter (CAG), human ubiquitin C (UbC) promoter or Rous sarcoma virus (RSV) promoter.

[00108] Embodiment 32 includes the isolated nucleic acid molecule of embodiment 31, wherein the second inducible promoter is a CAG promoter.

[00109] Embodiment 33 includes the isolated nucleic acid molecule of any one of embodiments 26 to 32, wherein the termination sequence is a bovine growth hormone polyadenylation (bgh-PolyA) signal.

[00110] Embodiment 34 includes the nucleic acid molecule of any one of embodiments 26 to 33, wherein the antibiotic resistance gene is a blasticidin resistance gene.

[00111] Embodiment 35 includes the nucleic acid molecule of any one of embodiments 26 to 34, wherein the nucleic acid sequence comprises a core insulator sequence inserted between the termination sequence and the antibiotic resistance gene.

[00112] Embodiment 36 includes the nucleic acid molecule of any one of embodiments 26 to 35, wherein the Rep52 is codon optimized.

[00113] Embodiment 37 includes the nucleic acid molecule of any one of embodiments 26 to 36, wherein the nucleic acid sequence is flanked on both the 5' and 3' ends by transposon-specific inverted terminal repeats (ITR).

[00114] Embodiment 38 includes the nucleic acid molecule of embodiment 37, wherein the nucleic acid sequence comprises a core insulator sequence inserted downstream of the ITR on the 3' end and upstream of the ITR on the 5' end.

[00115] Embodiment 39 is an isolated nucleic acid molecule operably comprising a first inducible promoter and a TetO₂ sequence, a VP1 gene, a second inducible promoter and a TetO₂ sequence, a VP2 gene and a VP3 gene, and an antibiotic resistance gene.

[00116] Embodiment 40 includes the isolated nucleic acid molecule of embodiment 39, wherein the VP1 gene, excluding the first 439 bp of the coding region, is optimized.

[00117] Embodiment 41 includes the isolated nucleic acid molecule of embodiment 39 or 40, wherein the first inducible promoter is human cytomegalovirus (CMV) immediate early enhancer-promoter, CMV immediate early enhancer fused chicken β -actin promoter (CAG), human ubiquitin C (UbC) promoter or Rous sarcoma virus (RSV) promoter.

[00118] Embodiment 42 includes the isolated nucleic acid molecule of embodiment 41, wherein the first inducible promoter is an UbC promoter.

[00119] Embodiment 43 includes the isolated nucleic acid molecule of embodiment 42, further comprising an intron of the UbC promoter inserted upstream of the UbC promoter.

[00120] Embodiment 44 includes the isolated nucleic acid molecule of any one of embodiments 37 to 43, wherein the second inducible promoter is human CMV immediate early enhancer-promoter, CMV immediate early enhancer fused chicken β -actin promoter (CAG), human ubiquitin C (UbC) promoter or Rous sarcoma virus (RSV) promoter.

[00121] Embodiment 45 includes the isolated nucleic acid molecule of embodiment 44, wherein the second inducible promoter is a CMV promoter.

[00122] Embodiment 46 includes the isolated nucleic acid molecule of any one of embodiments 39 to 45, further comprising a gene of interest (GOI) downstream of the VP3 gene and upstream of the antibiotic resistance gene.

[00123] Embodiment 47 includes the isolated nucleic acid molecule of embodiment 46, wherein the nucleic acid molecule comprises a core insulator sequence inserted between the VP3 gene and the GOI and between the GOI and the antibiotic resistance gene.

[00124] Embodiment 48 includes the isolated nucleic acid molecule of embodiment 47, wherein the GOI is a therapeutic gene.

[00125] Embodiment 49 includes the nucleic acid molecule of any one of embodiments 39 to 48, wherein the nucleic acid sequence comprises a core insulator sequence inserted between the VP1 gene and the second inducible promoter and TetO2 sequence.

[00126] Embodiment 50 includes the nucleic acid molecule of any one of embodiments 39 to 49, wherein the nucleic acid sequence comprises a core insulator sequence inserted between the VP2 and VP3 gene of d) and the antibiotic resistance gene of e).

[00127] Embodiment 51 includes the nucleic acid molecule of any one of embodiments 39 to 50, wherein the nucleic acid sequence is flanked on both the 5' and 3' ends by transposon-specific inverted terminal repeats (ITR).

[00128] Embodiment 52 includes the nucleic acid molecule of embodiment 51, wherein the nucleic acid sequence comprises a core insulator sequence inserted downstream of the ITR on the 3' end and upstream of the ITR on the 5' end.

[00129] Embodiment 53 includes the mammalian cell for producing an adeno-associated virus (AAV), comprising the isolated nucleic acid molecule of any one of embodiments 1 to 52 integrated into its genome.

[00130] Embodiment 54 includes the mammalian cell of embodiment 53, further comprising a nucleic acid encoding a transcriptional repression domain in frame with a nucleic acid encoding a tetracycline repressor protein.

[00131] Embodiment 55 includes the mammalian cell of embodiment 53 or 54, wherein the mammalian cell is a mammalian cell culture.

[00132] Embodiment 56 includes the mammalian cell any one of embodiments 53 to 55, wherein the mammalian cell is a Chinese hamster ovary (CHO) cell.

[00133] Embodiment 57 includes the mammalian cell of any one of embodiments 53 to 55, wherein the mammalian cell is a human cell.

[00134] Embodiment 58 includes the mammalian of embodiment 57, wherein the human cell is a human embryonic kidney (HEK) cell.

[00135] Embodiment 59 includes the mammalian cell of embodiment 58, wherein the HEK cell is an HEK293 cell.

[00136] Embodiment 60 includes the mammalian cell of any one of embodiments 53 to 59, further comprising a nucleic acid molecule encoding a gene of interest.

[00137] Embodiment 61 includes a method for producing an adeno-associated virus (AAV), comprising inducing production of the genomically integrated nucleic acid sequence of any of the mammalian cells of embodiments 53 to 60, culturing the mammalian cell, and harvesting the AAV.

[00138] Embodiment 62 includes the method of embodiment 61, wherein an amount of the AAV produced is about 10^{10} to about 10^{11} viral genomes per mL (vg/mL).

[00139] Embodiment 63 includes the method of embodiment 62, wherein an amount of the AAV produced is at least about 10^{10} viral genomes per mL (vg/mL).

EXAMPLES

Example 1: Preparation of HEK293 stable clonal cells for TetR-KRAB expression

[00140] One of the original Tet-On inducible systems utilizes the tetracycline repressor protein (TetR) to silence the human cytomegalovirus (CMV) promoter with an insertion of two tetracycline operator sequences (TetO₂) between the TATA box and transcriptional start site (TSS) (Yao et al., “Tetracycline repressor, tetR, rather than the tetR-mammalian cell transcription factor fusion derivatives, regulates inducible gene expression in mammalian cells,” Hum Gene Ther. 9(13):1939-50 (1998)). In the absence of doxycycline, transcription initiation is blocked by the binding of TetR on the TetO₂ sites. When doxycycline is added into the medium, it competitively binds to TetR and changes its conformation. This leads to the release of TetR and derepression/activation of the CMV promoter and results in induced gene expression (See FIG. 1). However, the high level of leaky expression of toxic proteins before induction in the original system poses a major challenge for the stability of the generated inducible cell lines and limits its application for an AAV producer cell line.

[00141] Improvements of the Tet-On inducible system were implemented to minimize the leakiness level. First, an enhanced version of TetR was applied as described in Suzlc et al., “A versatile tool for conditional gene expression and knockdown,” Nat Methods 3(2):109-16 (2006). Briefly, a strong repressive domain of KRAB was fused in-frame to the C-terminus of original TetR, which dramatically improved its repressive activity and minimized basal gene expression before induction. An SV40 nuclear localization signal (NLS) was inserted as well to facilitate the nuclear entry of the larger TetR-KRAB fusion protein (See FIG. 2A and 2B). Second, the expression cassette was optimized for high level expression of TetR-KRAB protein, including the strong human CMV promoter to drive a high level of mRNA expression, the consensus Kozak sequence to boost the initiation of the protein translation, and the rabbit beta-globin intron to increase mRNA level. The expression cassette was further protected on both ends by two chicken hypersensitive site-4 (cHS4) extended core chromatin insulators, which can prevent undesired silencing of the CMV promoter from the spreading of neighboring heterochromatin. An SV40 promoter driven Zeocin antibiotic resistance gene was included for stable selection. Third, a stable TetR-KRAB overexpression clonal HEK293 cell line, C20, was established using

this optimized construct by plasmid random integration. When compared to a commercially available TetR stable HEK293 cell line in a transient transfection test, the C20 cell line reduced the leaky production of AAV by approximately 200-fold.

Sequence Listings

[00142] Any nucleic acid and amino acid sequences listed herein or in the accompanying sequence listing are shown using standard letter abbreviations for nucleotide bases and amino acids, as defined in 37 C.F.R. § 1.822. In at least some cases, only one strand of each nucleic acid sequence is shown, but the complementary strand is understood as included by any reference to the displayed strand.

[00143] The sequence of the pcDNA-TetR-Ins vector is provided below:

[00144] pcDNA-TetR-Ins (7147 bp) (SEQ ID NO: 1)

[00145] gacggatcgggagatctgagctcacggggacagccccccccaaagccccagggatgtaattacgtccctccccgcta
gggggcagcagcgagccgcccggggtccgctccggcgctccccgcacccccgagccggcagcgtgcggggacagccc
gggcacggggaaggtggcacgggatcgcttctctgaacgcttctcgctgctctttgagcctgcagacacctggggggatacggggaaa
aagcttaggctgaaagagagattagaatgacagaatcatagaacggcctgggttgcaaaggagcacagtgtcatccagatccaacccc
ctgctatgtgcagggtcatcaaccagcagcccaggctgccagagccacatccagcctggccttgaatgcctgcaggccccgatcccctat
ggtcgactctcagtacaatctgctctgatgcccatagttaagccagtatctgctccctgcttgtgttgagggtcgctgagtagtgcgcgag
caaaatttaagctacaacaaggcaaggcttgaccgacaattgcatgaagaatctgcttaggggttaggcgtttgcgctgcttcgcatgtacg
ggccagatatacgcgttgacattgattattgactagttattaatagtaaatcaattacggggtcattagttcatagcccatataggagttccgcgtt
acataacttacggtaaatggcccgctggctgaccgccaacgacccccgccattgacgtcaataatgacgtatgttcccatagtaacgcc
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[00146] The sequence of the pcDNA-TetR-KRAB-Ins vector is provided below:

[00147] pcDNA-TetR-KRAB-Ins (7493 bp) (SEQ ID NO: 2)

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Example 2: Design and Validation of Derepressible Helper Genes

pPBBG-iHelper2.0-HA vector

[00148] To drive the expression of Adenovirus Helper Genes E2A and E4Orf6, two tetracycline operator sequences (TetO₂) were inserted between the TATA box and transcriptional start site (TSS) in the native promoters of the E2A and E4 genes. Expression of the VA RNA is driven by its native promoter or H1 promoter with or without TetO₂ insertion. The VA gene promoter is embedded in the gene body of the non-coding RNA, and the TetO₂ sequences were added upstream of the VA gene. To facilitate the detection of E4orf6 protein expression, an HA tag was fused in frame to the N-terminus of E4orf6 coding sequence. The expression cassettes of

inducible E2A, E4 and VA as one gene block was flanked by core insulator sequences, long-range regulatory sequences to prevent the activation or silencing of the gene promoters from neighboring distal enhancers or spreading heterochromatin, respectively. The sequence was fully synthesized and subcloned into a *piggyBac* transposon vector between the transposon-specific ITRs on 5' and 3' ends. To allow the antibiotic selection of the recombinant transposon in cells, the puromycin antibiotic resistance gene driven by a CMV promoter was also included and flanked by core insulators inside the ITRs, which resulted in the pPBBG-iHelper2.0-HA vector (See Figure 3A).

[00149] To enhance the VA RNA expression of the pPBBG-iHelper2.0-HA vector design, a series of modifications were applied to the VA cassettes in the pPBBG-iHelper2.0-HA vector design.

[00150] In the iHelper2.1 vector, both the TetO₂ and VAI regions originally in the pPBBG-iHelper2.0-HA vector design were removed (see Figure 3B). In the iHelper2.2 vector, the VAI cassette in iHelper2.1 was relocated between E2A and E4 cassettes to achieve inducibility from neighboring TetO₂ sequences (See Figure 3C). In the iHelper2.3 vector, the constitutive H1 promoter was added upstream of VAI cassette in the iHelper2.1 to increase the VA expression (see Figure 3D). In iHelper2.4 vector, the VAI and H1 promoter in iHelper2.3 was relocated between E2A and E4 cassettes (see Figure 3E). To further augment the VA expression, the VA cassette was increased from a single copy in the iHelper 2.1, 2.2, 2.3 and 2.4 vectors to four tandem repeats in the iHelper 2.5, 2.6, 2.7 and 2.8, accordingly. The addition of further promoters (H1) in various locations was also investigated. (See Figures 3F – 3I).

[00151] To further enhance the helper function, functional protein orthologs to VA RNA were screened to enhance AAV production. These protein-encoding genes are derived from different viruses with reported function as inhibitors of protein kinase R (PKR), a key function of VA RNA (Langland et al., “Inhibition of PKR by RNA and DNA viruses,” *Virus Res.* 119(1):100-10 (2006) and Feng et al., “The VP35 protein of Ebola virus inhibits the antiviral effect mediated by double-stranded RNA-dependent protein kinase PKR,” *J Virol.* 81(1):182-92 (2007). Two candidates boosted AAV production, VP35 from Ebola virus and SM from Epstein-Barr virus. To incorporate the protein orthologs into the iHelper2.2 vector, a VP35 or SM gene was fused in

frame to an N-terminal Flag tag, and placed under an inducible human CMV promoter with an insertion of TetO₂, followed by a BGH Poly(A) signal. The expression cassette was then inserted into the region between E4 and puromycin resistance gene in the iHelper2.2, flanked by core insulators. The iHelper3.1 vector with a VP35 gene is shown in Figure 4A and the iHelper3.2 vector with a SM gene is shown in Figure 4B.

Sequence Listings

[00152] The sequence of the pPBBG-iHelper2.0-HA vector is provided below:

[00153] pPBBG-iHelper2.0-HA (16,549 bp) (SEQ ID NO: 3)

[00154] ACTCTTCCTTTTCAATATTATTGAAGCATTATCAGGGTTATTGTCTCATGA
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CGCAAAAAGGGAATAAGGGCGACACGGAAATGTTGAATACTCAT

[00155] The sequence of the pPBBG-iHelper2.1-HA vector is provided below:

[00156] pPBBG-iHelper2.1-HA (15,878 bp) (SEQ ID NO: 4)

[00157] ACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATTGTCTCATGA
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ACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACACGGAAATGTTGAA
TACTCAT

[00158] The sequence of the pPBBG-iHelper2.2-HA vector is provided below:

[00159] pPBBG-iHelper2.2-HA (15,878 bp) (SEQ ID NO: 5)

[00160] ACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATTGTCTCATGA
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ACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACACGGAAATGTTGAA
TACTCAT

[00161] The sequence of the pPBBG-iHelper2.3-HA vector is provided below:

[00162] pPBBG-iHelper2.3-HA (15,992 bp) (SEQ ID NO: 6)

[00163] ACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATTGTCTCATGA
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GCACCCA ACTGATCTTCAGCATCTTTTACTTTTACCAGCGTTTCTGGGTGAGCAAAA
ACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACACGGAAATGTTGAA
TACTCAT

[00164] The sequence of the pPBBG-iHelper2.4-HA vector is provided below:

[00165] pPBBG-iHelper2.4-HA (15, 992 bp) (SEQ ID NO: 7)

[00166] ACTCTTCCTTTTTCAATATTATTGAAGCATTATCAGGGTTATTGTCTCATGA
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ACCGCGCCACATAGCAGAACTTTAAAAGTGCTCATCATTGGAAAACGTTCTTCGGGG
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GCACCCAACTGATCTTCAGCATCTTTTACTTTACCAGCGTTTCTGGGTGAGCAAAA
ACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACACGGAAATGTTGAA
TACTCAT

[00167] The sequence of the pPBBG-iHelper2.5-HA vector is provided below:

[00168] pPBBG-iHelper2.5-HA (16, 658 bp) (SEQ ID NO: 8)

[00169] ACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATTGTCTCATGA
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GCGAGCGGTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGG
ATAACGCAGGAAAGAACATGTGAGCAAAAGGCCAGCAAAAGGCCAGGAACCGTAA
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CGCAAAAAGGGAATAAGGGCGACACGGAAATGTTGAATACTCAT

[00170] The sequence of the pPBBG-iHelper2.6-HA vector is provided below:

[00171] pPBBG-iHelper2.6-HA (16,658 bp) (SEQ ID NO: 9)

[00172] ACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATTGTCTCATGA
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[00173] The sequence of the pPBBG-iHelper2.7-HA vector is provided below:

[00174] pPBBG-iHelper2.7-HA (17,114 bp) (SEQ ID NO: 10)

[00175] ACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATTGTCTCATGA
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[00176] The sequence of the pPBBG-iHelper2.8-HA vector is provided below:

[00177] pPBBG-iHelper2.8-HA (17,114 bp) (SEQ ID NO: 11)

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[00179] The sequence of the pPBBG-iHelper3.1-HA vector is provided below:

[00180] pPBBG-iHelper3.1-HA (18, 311 bp) (SEQ ID NO: 12)

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[00182] The sequence of the pPBBG-iHelper3.2-HA vector is provided below:

[00183] pPBBG-iHelper3.2-HA (18, 728 bp) (SEQ ID NO: 13)

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TTGACTGGATTCTTTTTTTAGGGCCCATTTGGTATGGCTTTTTTCCCGTATCCCCCAG
GTGTCTGCAGGCTCAAAGAGCAGCGAGAAGCGTTCAGAGGAAAGCGATCCCGTGCC
ACCTTCCCCGTGCCCGGGCTGTCCCCGCACGCTGCCGGCTCGGGGATGCGGGGGGA

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GACGTAATTACATCCCTGGGGGCTTTGGGGGGGGGCTGTCCCTCTAGAGCGGCCGCC
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 GATTATCAAAAAGGATCTTCACCTAGATCCTTTTAAATTAAAAATGAAGTTTTAAAT
 CAATCTAAAGTATATATGAGTAAACTTGGTCTGACAGTTACCAATGCTTAATCAGTG
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 TACCGCTGTTGAGATCCAGTTCGATGTAACCCACTCGTGCACCCAACTGATCTTCAG
 CATCTTTTACTTTTACCAGCGTTTCTGGGTGAGCAAAAACAGGAAGGCAAAATGCCG
 CAAAAAAGGGAATAAGGGCGACACGGAAATGTTGAATACTCAT

Example 3: Design and Validation of inducible Rep Genes

[00185] Producing inducible Rep proteins can be challenging due to the critical maintenance of the ratio of Rep78 and Rep52 protein expression needed for high titer AAV quality and quantity. In addition, the p19 promoter required for Rep52 expression is embedded in the coding region of Rep78, which is difficult for direct promoter engineering. To overcome these challenges, two strategies were developed.

[00186] First, the expression cassettes of Rep78 and Rep52 were split from overlapped genes into two separate ones, each of which was driven by one of the following viral or non-viral promoters with diverse strength, including human cytomegalovirus (CMV) immediate early enhancer-promoter, CMV immediate early enhancer fused chicken β -actin promoter (CAG), human ubiquitin C (UbC) promoter and Rous sarcoma virus (RSV) promoter. To convert these constitutive promoters into inducible versions, two tetracycline operator sequences (TetO₂) were inserted between the TATA box and transcriptional start site (TSS).

[00187] The original p19 promoter in the Rep78 open reading frame (ORF) was silenced by changing six nucleotides in three core regulatory elements required for p19 activity (SP1, TATA-1, and TATA-2 sites). These changes did not alter the Rep78 protein sequence. To increase vector stability and Rep52 expression, the DNA sequence of coding region of Rep52 was optimized for human cell codon usage while retaining the same protein sequence, which significantly reduced the sequence identity of the Rep52 sequence with the Rep78 sequence, from 100% to 80.1%.

[00188] To improve the expression of Rep genes, a Kozak sequence or non-canonical start codon ACG was applied to enhance or reduce the protein expression, respectively. Sixteen inducible Rep vectors were designed in piggyBac transposon vectors with core insulators flanking the Rep78 and Rep52 cassettes, as well as an expression cassette for human PGK promoter driven blasticidin antibiotic resistance gene (BSD) (See Figure 5A – 5P). A summary of the inducible promoter designs for Rep genes are shown in Table 1.

Table 1

		iCMV	iCMV/no Kozak	iCMV/ACG	iCAG	iUbC	iRSV
PB-hiRep-1	Rep78		x				
	Rep52	x					
PB-hiRep-2	Rep78			x			
	Rep52	x					

PB- hiRep-3	Rep78					x	
	Rep52	x					
PB- hiRep-4	Rep78						x
	Rep52	x					
PB- hiRep-5	Rep78		x				
	Rep52		x				
PB- hiRep-6	Rep78			x			
	Rep52		x				
PB- hiRep-7	Rep78					x	
	Rep52		x				
PB- hiRep-8	Rep78						x
	Rep52		x				
PB- hiRep-9	Rep78			x			
	Rep52			x			
PB- hiRep-10	Rep78					x	
	Rep52			x			
PB- hiRep-11	Rep78						x
	Rep52			x			
PB- hiRep-12	Rep78		x				
	Rep52				x		
PB- hiRep-13	Rep78			x			
	Rep52				x		

PB- hiRep-14	Rep78					x	
	Rep52				x		
PB- hiRep-15	Rep78						x
	Rep52				x		
PB- hiRep-16	Rep78						x
	Rep52					x	

[00189] The sequence of the PB-hiRep-1# (11,866 bp) vector is provided below:

[00190] PB-hiRep-1# (11,866 bp) (SEQ ID NO: 14)

[00191] actcttccttttcaatattattgaagcatttatcagggttattgtctcatgagcggatacatattgaatgtatttagaaaaataaca
aataggggtccgcgcacattccccgaaaagtgccacctaattgaagcgtaataattttgttaaaattcgcgttaattttgttaaatcagctc
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[00195] The sequence of the PB-hiRep-3# vector is provided below:

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[00198] The sequence of the PB-hiRep-4# vector is provided below:

[00199] PB-hiRep-4# (11,702 bp) (SEQ ID NO: 17)

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[00201] The sequence of the PB-hiRep-5# vector is provided below:

[00202] PB-hiRep-5# (11,865 bp) (SEQ ID NO: 18)

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[00210] The sequence of the PB-hiRep-8# vector is provided below:

[00211] PB-hiRep-8# (11,701 bp) (SEQ ID NO: 21)

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[00213] The sequence of the PB-hiRep-9# vector is provided below:

[00214] PB-hiRep-9# (11, 861 bp) (SEQ ID NO: 22)

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[00216] The sequence of the PB-hiRep-10# vector is provided below:

[00217] PB-hiRep-10# (11,580 bp) (SEQ ID NO: 23)

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[00219] The sequence of the PB-hiRep-11# vector is provided below:

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[00222] The sequence of the PB-hiRep-12# vector is provided below:

[00223] PB-hiRep-12# (11,589 bp) (SEQ ID NO: 25)

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[00225] The sequence of the PB-hiRep-13# vector is provided below:

[00226] PB-hiRep-13# (11, 854 bp) (SEQ ID NO: 26)

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[00228] The sequence of the PB-hiRep-14# vector is provided below:

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[00231] The sequence of the PB-hiRep-15# vector is provided below:

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[00234] The sequence of the PB-hiRep-16# vector is provided below:

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Example 4: Design and Validation of inducible Cap Genes and Gene of Interest

[00237] Two strategies were implemented for the inducible Cap gene expression. In the first strategy, the Cap genes were split into two cassettes, one for the VP1 expression, and the other for VP2 and VP3. To reduce the DNA sequence homology between VP1 and VP2/3 genes in order to increase the vector stability, the DNA sequence of VP1 coding region was optimized for human cell codon usage without change of protein sequence. To maintain the protein coding sequence of membrane-associated accessory protein (MAAP), the first 439 bp of VP1 coding region that included the MAAP gene was excluded for codon optimization. The DNA sequence identity between the optimized VP1 and the original VP2/3 gene was reduced to 80.7%.

[00238] An AAV ITR flanked transgene expression cassette, such as the GFP gene driven by CMV promoter, was also included in the vector as a representative of a gene of interest (GOI) inserted into the vector. In addition, the third antibiotic resistance gene for hygromycin driven by human PGK promoter was included. All the gene cassettes were subcloned into the *piggyBac* transposon vectors, and flanked by core insulators.

[00239] In the PB-iCapsplit-ITRGFP-hygro-1 vector, the previously described inducible CMV promoter was used to drive the VP1 gene expression without the Kozak sequence before ATG start codon of VP1, while the same promoter was also used for the expression of VP2 and VP3 gene expression by the native leader sequence (ggcgctaag) before the original ACG start codon (See FIG. 6A). In the PB-iCapsplit-ITRGFP-hygro-2 vector, the VP1 cassette was modified with the native VP2 leader sequence followed by the ACG start codon, while no other changes compared to PB-iCapsplit-ITRGFP-hygro-1 vector (See FIG. 6B). In the PB-iCapsplit-ITRGFP-hygro-3 vector, the promoter for VP1 cassette was switched to the inducible UbC promoter, and the Kozak sequence was added before the ATG start codon of VP1 gene, without other changes compared to PB-iCapsplit-ITRGFP-hygro-1 vector (See FIG. 6C). To increase the expression of VP1 protein, the 814 bp UbC intron that was identified as an enhancer (Bianchi et al., "A potent enhancer element in the 5'-UTR intron is crucial for transcriptional regulation of the human ubiquitin C gene," *Gene* 448(1):88-101 (2009)) was inserted before the inducible UbC promoter

in the PB-iCapsplit-ITRGFP-hygro-3 vector, and resulted in the PB-iCapsplit-ITRGFP-hygro-4 vector (See FIG. 6D).

[00240] In the second strategy, the VP1, VP2 and VP3 genes remained in the original architecture in a single native DNA sequence. The strong inducible CMV promoter was applied to drive the Cap gene expression. To enhance the expression level of VP proteins, the original suboptimal splicing donor site for the VP genes was optimized to the conserved donor sequence (caggtAGT from 2309 to 2317 bp) without affecting the ratios of VP proteins (Farris and Pintel, “Improved splicing of Adeno-associated viral (AAV) capsid protein-supplying pre-mRNAs leads to increased recombinant AAV vector production,” Hum Gene Ther. 19(12): 1421–1427 (2008). The pPBBG-iCap8cd-ITRGFP-hygro vector is shown in FIG. 6E.

[00241] The sequence of the PB-iCap8split-ITRGFP-hygro-1 vector is provided below:

[00242] PB-iCap8split-ITRGFP-hygro-1 (17,121 bp) (SEQ ID NO: 30)

[00243] ACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATTGTCTCATGA
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TTTCCCCGAAAAGTGCCACCTAAATTGTAAGCGTTAATATTTTGTAAATTCGCGTT
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[00244] The sequence of the PB-iCap8split-ITRGFP-hygro-2 vector is provided below:

[00245] PB-iCap8split-ITRGFP-hygro-2 (17,119 bp) (SEQ ID NO: 31)

[00246] ACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATTGTCTCATGA
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TTGCTACAGGCATCGTGGTGTACGCTCGTCGTTTGGTATGGCTTCATTCAGCTCCGG
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CTCCTTCGGTCCTCCGATCGTTGTCAGAAGTAAGTTGGCCGCAGTGTTATCACTCATG
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TGA CTGGT GAGTACTCAACCAAGTCATTCTGAGAATAGTGTATGCGGCGACCGAGTT
GCTCTTGCCCCGGCGTCAATACGGGATAATACCGCGCCACATAGCAGAACTTTAAAA
GTGCTCATCATTGGAAAACGTTCTTCGGGGCGAAAACCTCTCAAGGATCTTACCGCTG
TTGAGATCCAGTTCGATGTAACCCACTCGTGCACCCA ACTGATCTTCAGCATCTTTTA
CTTTCACCAGCGTTTCTGGGTGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAAG
GGAATAAGGGCGACACGGAAATGTTGAATACTCAT

[00247] The sequence of the PB-iCap8split-ITRGFP-hygro-3 vector is provided below:

[00248] PB-iCap8split-ITRGFP-hygro-3 (16,835 bp) (SEQ ID NO: 32)

[00249] ACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATTGTCTCATGA
GCGGATACATATTTGAATGTATTTAGAAAAATAAACAAATAGGGGTTCCGCGCACA
TTTCCCCGAAAAGTGCCACCTAAATTGTAAGCGTTAATATTTTGT TAAAATTCGCGTT
AAATTTTGT TAAATCAGCTCATTTTTTTAAACCAATAGGCCGAAATCGGCAAAAATCCC
TTATAAATCAAAAGAATAGACCGAGATAGGGTTGAGTGT TGTTCAGTTTGGAAACA
AGAGTCCACTATTAAAGAACGTGGACTCCAACGTCAAAGGGCGAAAAACCGTCTAT
CAGGGCGATGGCCCACTACGTGAACCATCACCTAATCAAGTTTTTTGGGGTTCGAGG
TGCCGTAAAGCACTAAATCGGAACCCTAAAGGGAGCCCCCGATTTAGAGCTTGACG
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CGCTTAATGCGCCGCTACAGGGCGCGTCCCATTCGCCATTCAGGCTGCGCAACTGTT
GGGAAGGGCGATCGGTGCGGGCCTCTTCGCTATTACGCCAGCTGGCGAAAGGGGGA
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[00250] The sequence of the PB-iCap8split-ITRGFP-hygro-4 vector is provided below:

[00251] PB-iCap8split-ITRGFP-hygro-4 (17,649 bp) (SEQ ID NO: 33)

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[00253] The sequence of the pPBBG-iCap8cd-ITRGFP-hygro vector is provided below:

[00254] pPBBG-iCap8cd-ITRGFP-hygro (14,262 bp) (SEQ ID NO: 34)

[00255] ACTCTTCCTTTTTCAATATTATTGAAGCATTTATCAGGGTTATTGTCTCATGA
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CCCGACAGGACTATAAAGATACCAGGCGTTTCCCCCTGGAAGCTCCCTCGTGCGCTC
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GTGGCGCTTTCTCATAGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTGCT
CCAAGCTGGGCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCG
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TTACCATCTGGCCCCAGTGCTGCAATGATACCGCGAGACCCACGCTCACCGGCTCCA
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 TGAGCAAAAACAGGAAGGCAAAATGCCGCAAAAAAGGGAATAAGGGCGACACGGA
 AATGTTGAATACTCAT

Example 5: Performance of AAV stable producer cell lines

[00256] To generate stable AAV producer cell lines, one transposon from each group of iHelper, iRep and iCap-GOI was used to integrate into the genome of stable HEK293-TetR-KRAB C20 cell lines through a “cut and paste” mechanism by the co-transfection of these three transposon plasmids with mRNA encoding super *piggyBac* transposase (SPB-100). After transfection, three antibiotics including puromycin, blasticidin and hygromycin were added into the cell culture medium to select the transposon integrated cells. After stable cell pool generation and screening, one highly productive cell pool was selected to monitor the long-term stability of cells for AAV productivity. The suspension pool was left untreated or induced by doxycycline from cell passage 5 to passage 25 over three months. As shown in FIG. 7, the productivity of polyclonal pool of AAV producer cell line is stable for 25 passages upon induction by Dox. AAV production without Dox induction showed extremely low basal/leaky levels of AAVs.

[00257] To evaluate the performance of AAV stable producer cell lines, multiple single cell clones were isolated by single cell printing and expanded for testing. First, the viral protein expression was evaluated by western blot analysis. Top three clonal cells (Clone A, B and C) were uninduced or induced by doxycycline for AAV production. Whole cell lysates were harvested three days post induction and prepared for the Western blot analysis. The whole cell lysate produced from a triple plasmid transfection process was used as positive control. The results show the robust induction of protein expression of helper, Rep and Cap genes in these clonal AAV producer cell lines, at the level similar or higher than the control samples, while showing undetectable level of leakiness protein expression in uninduced cells (See FIG. 8).

[00258] The AAV productivity of the top three clones expressing Green Fluorescent Protein (GFP), a gene of interest, was examined in 3 Liter single-use bioreactors. The AAV genomic titer by ddPCR titer assay showed strong induction of AAV production in all clones in the range

from 4.3×10^{10} vg/mL to 2.8×10^{11} vg/mL on day 5 harvest, which was comparable or higher than the AAV productivity using conventional triple transfection method (See FIG. 9).

[00259] The productivity of Clones A, B and C expressing GFP was further compared to three representative clonal cells (Clone 1, Clone 2 and Clone 3) uninduced or induced by doxycycline. Clone 1, Clone 2 and Clone 3 comprise nucleic acid sequences disclosed in US Patent No. 11,739,347 B2 that were designed using E2A and E4 genes under control of an inducible CMV promoter, VA RNA under control of an H1 promoter, and Rep and Cap genes under control of a native promoter. The AAV productivity of Clones A, B and C was significantly higher than Clone 1, Clone 2 and Clone 3 after Dox induction (See FIG. 10).

[00260] The functionality of the AAV produced from the bioreactors was tested by the cell-based infectivity and potency assay. The purified AAV was serially diluted and transduced to HT1080 cells in 96-well plates. The percentage of GFP-positive cells from transduced AAV was quantified by flow cytometry analysis and used to calculate the transduction unit (TU). The normalized viral genome per TU result suggests that the AAV produced from AAV producer cell lines are functional in infecting cells and expressing a gene of interest, such as GFP (See FIG. 11).

[00261] It will be readily apparent to one of ordinary skill in the relevant arts that other suitable modifications and adaptations to the methods and applications described herein can be made without departing from the scope of any of the embodiments.

[00262] It is to be understood that while certain embodiments have been illustrated and described herein, the claims are not to be limited to the specific forms or arrangement of parts described and shown. In the specification, there have been disclosed illustrative embodiments and, although specific terms are employed, they are used in a generic and descriptive sense only and not for purposes of limitation. Modifications and variations of the embodiments are possible in light of the above teachings. It is therefore to be understood that the embodiments may be practiced otherwise than as specifically described.

[00263] All references cited herein, including patents, patent applications, papers, textbooks and the like, and the references cited therein, to the extent that they are not already, are hereby incorporated herein by reference in their entirety.

CLAIMS

1. An isolated nucleic acid molecule operably comprising:
 - a. a first inducible promoter and two tetracycline operator sequences (a TetO₂ sequence);
 - b. an E2A gene under control of the first inducible promoter;
 - c. a viral associated (VA) non-coding RNA under control of a second inducible promoter;
 - d. a third inducible promoter and a TetO₂ sequence;
 - e. an E4 gene under control of the third inducible promoter; and
 - f. an antibiotic resistance gene.
2. The isolated nucleic acid molecule of claim 1, wherein the first inducible promoter is native to the E2A gene.
3. The nucleic acid molecule of claim 1, wherein the second inducible promoter is a promoter native to the VA non-coding RNA.
4. The nucleic acid molecule of claim 1, wherein the second inducible promoter is an H1 promoter.
5. The isolated nucleic acid molecule of claim 1, wherein the third inducible promoter is native to the E4 gene.
6. The nucleic acid molecule of claim 1, wherein the nucleic acid sequence comprises a core insulator sequence inserted between the E4 gene and the antibiotic resistance gene.
7. The nucleic acid molecule of claim 1, wherein the nucleic acid sequence is flanked on both the 5' and 3' ends by transposon-specific inverted terminal repeats (ITR), and wherein the nucleic acid sequence comprises a core insulator sequence inserted downstream of the ITR on the 3' end and upstream of the ITR on the 5' end.
8. An isolated nucleic acid molecule operably comprising:
 - a. a first inducible promoter and a TetO₂ sequence;
 - b. an E2A gene under control of the first inducible promoter;
 - c. a viral associated (VA) non-coding RNA under control of a second inducible promoter;
 - d. a third inducible promoter and a TetO₂ sequence;

- e. an E4 gene under control of the third inducible promoter;
 - f. an expression cassette encoding a protein ortholog of the VA RNA and a peptide protein tag under the control of a depressible promoter comprising a human Cytomegalovirus (CMV) promoter and a TetO₂ sequence;
 - g. a termination sequence; and
 - h. an antibiotic resistance gene.
9. The isolated nucleic acid molecule of claim 8, wherein the first inducible promoter is native to the E2A gene.
10. The nucleic acid molecule of claim 8, wherein the second inducible promoter is a promoter native to the VA non-coding RNA.
11. The nucleic acid molecule of claim 8, wherein the second inducible promoter is an H1 promoter.
12. The isolated nucleic acid molecule of claim 8, wherein the third inducible promoter is native to the E4 gene.
13. The isolated nucleic acid molecule of claim 8, wherein the protein ortholog is an influenza non-structural 1 protein (NS1), Ebola viral protein 35 (VP35), orthoreovirus sigma 3 protein (σ 3), group C rotavirus non-structural protein 3 (NSP3), vaccinia virus E3L protein (E3L), herpes simplex virus type 1 US11 protein (US11), Epstein-Barr virus SM protein (SM), baculovirus PK2 protein (PK2), hepatitis C virus non-structural protein 5A protein (NS5A), human herpes virus-8 protein vIRF-2 (vIRF-2), human immunodeficiency virus protein Tat, vaccinia virus K3L protein (K3L), Herpes Simplex virus protein γ 134.5/ICP34.5, and human papilloma virus-18 E6 protein (E6).
14. The nucleic acid molecule of claim 8, wherein the nucleic acid sequence comprises a core insulator sequence inserted between the E4 gene and the expression cassette.
15. The nucleic acid molecule of claim 8, wherein the nucleic acid sequence is flanked on both the 5' and 3' ends by transposon-specific inverted terminal repeats (ITR), and wherein the nucleic acid sequence comprises a core insulator sequence inserted downstream of the ITR on the 3' end and upstream of the ITR on the 5' end.
16. An isolated nucleic acid molecule operably comprising a plasmid encoding:
- a. a first inducible promoter and a TetO₂ sequence;

- b. a Rep78 gene, including a silenced p19 promoter located within the Rep78 gene coding region, wherein the silenced p19 promoter comprises mutations in SP1, TATA-1, and/or TATA-2 sites;
 - c. a second inducible promoter and a TetO₂ sequence;
 - d. a Rep52 gene under control of the second inducible promoter;
 - e. termination sequence and;
 - f. an antibiotic resistance gene.
17. The isolated nucleic acid molecule of claim 16, wherein the first inducible promoter is human cytomegalovirus (CMV) immediate early enhancer-promoter, CMV immediate early enhancer fused chicken β -actin promoter (CAG), human ubiquitin C (UbC) promoter or Rous sarcoma virus (RSV) promoter.
18. The isolated nucleic acid molecule of claim 16, wherein the second inducible promoter is human CMV immediate early enhancer-promoter, CMV immediate early enhancer fused chicken β -actin promoter (CAG), human ubiquitin C (UbC) promoter or Rous sarcoma virus (RSV) promoter.
19. The nucleic acid molecule of claim 16, wherein the nucleic acid sequence comprises a core insulator sequence inserted between the termination sequence and the antibiotic resistance gene.
20. The nucleic acid molecule of claim 16, wherein the nucleic acid sequence is flanked on both the 5' and 3' ends by transposon-specific inverted terminal repeats (ITR), and wherein the nucleic acid sequence comprises a core insulator sequence inserted downstream of the ITR on the 3' end and upstream of the ITR on the 5' end.
21. An isolated nucleic acid molecule operably comprising:
- a. a first inducible promoter and a TetO₂ sequence;
 - b. a VP1 gene;
 - c. a second inducible promoter and a TetO₂ sequence;
 - d. a VP2 gene and a VP3 gene; and
 - e. an antibiotic resistance gene.
22. The isolated nucleic acid molecule of claim 21, wherein the first inducible promoter is human cytomegalovirus (CMV) immediate early enhancer-promoter, CMV immediate early

enhancer fused chicken β -actin promoter (CAG), human ubiquitin C (UbC) promoter or Rous sarcoma virus (RSV) promoter.

23. The isolated nucleic acid molecule of claim 21, wherein the second inducible promoter is human CMV immediate early enhancer-promoter, CMV immediate early enhancer fused chicken β -actin promoter (CAG), human ubiquitin C (UbC) promoter or Rous sarcoma virus (RSV) promoter.
24. The isolated nucleic acid molecule of claim 21, further comprising a gene of interest (GOI) downstream of the VP3 gene and upstream of the antibiotic resistance gene.
25. The isolated nucleic acid molecule of claim 24, wherein the nucleic acid molecule comprises a core insulator sequence inserted between the VP3 gene and the GOI and between the GOI and the antibiotic resistance gene.
26. The nucleic acid molecule of claim 21, wherein the nucleic acid sequence comprises a core insulator sequence inserted between the VP1 gene and the second inducible promoter and TetO2 sequence.
27. The nucleic acid molecule of claim 21, wherein the nucleic acid sequence comprises a core insulator sequence inserted between the VP2 and VP3 gene of d) and the antibiotic resistance gene of e).
28. The nucleic acid molecule of claim 21, wherein the nucleic acid sequence is flanked on both the 5' and 3' ends by transposon-specific inverted terminal repeats (ITR), and wherein the nucleic acid sequence comprises a core insulator sequence inserted downstream of the ITR on the 3' end and upstream of the ITR on the 5' end.

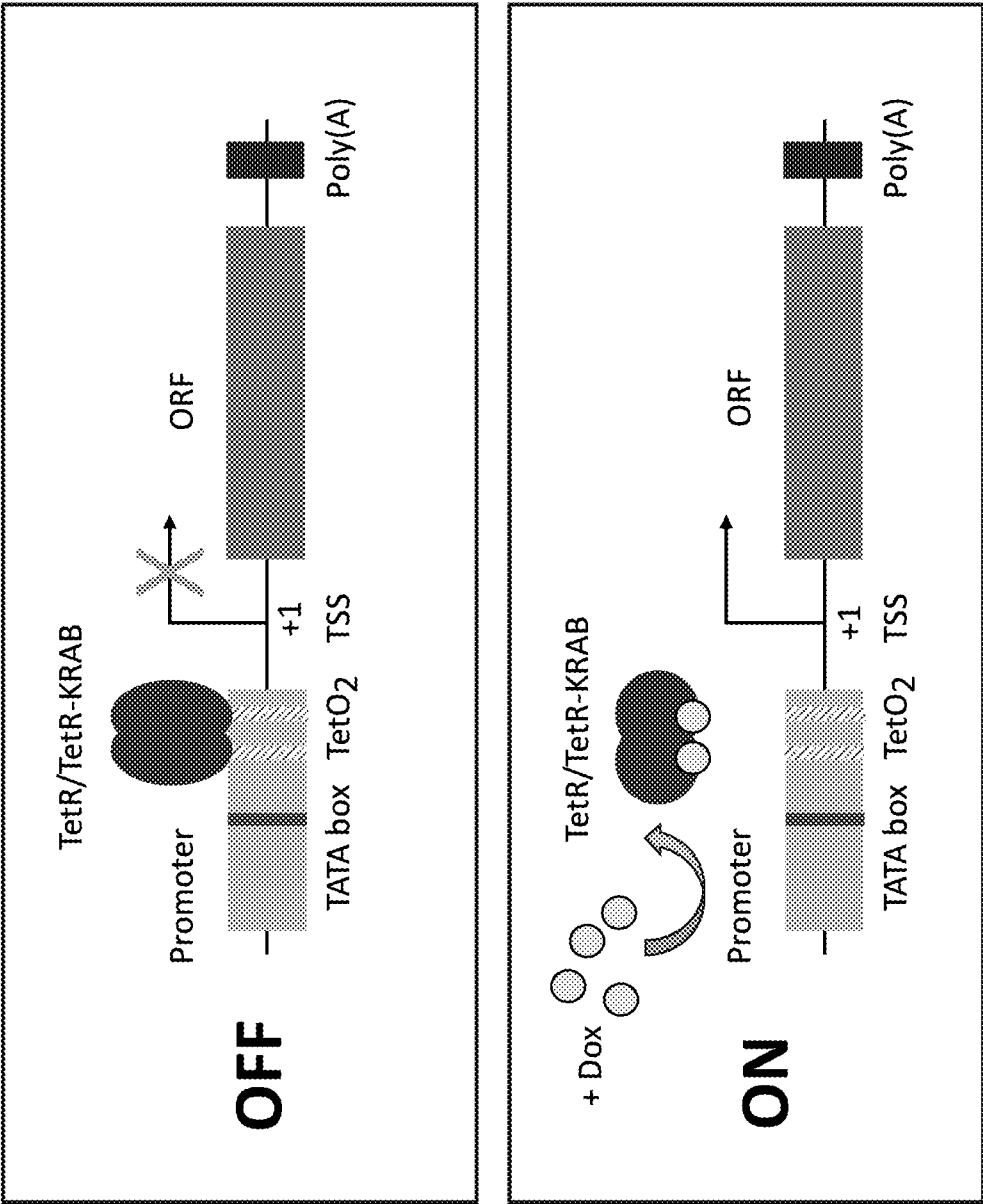


FIG. 1

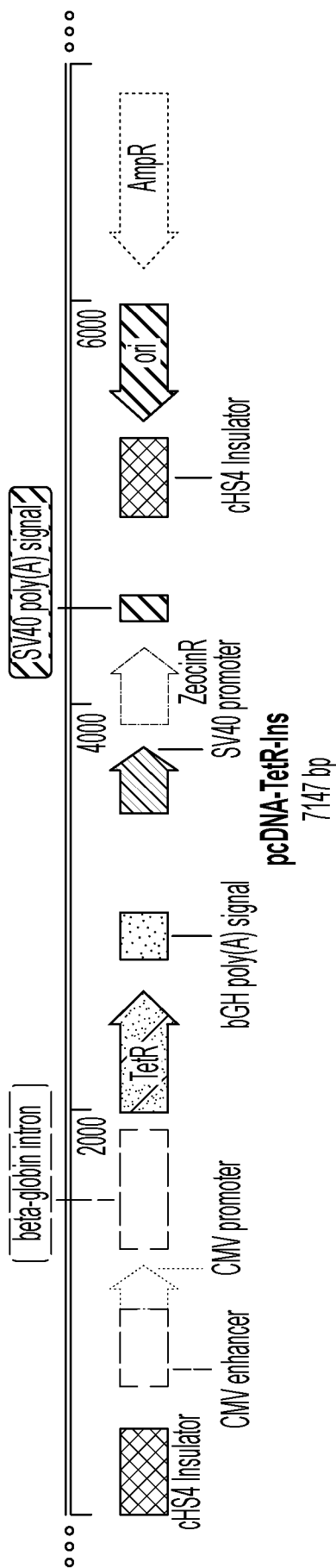


FIG. 2A

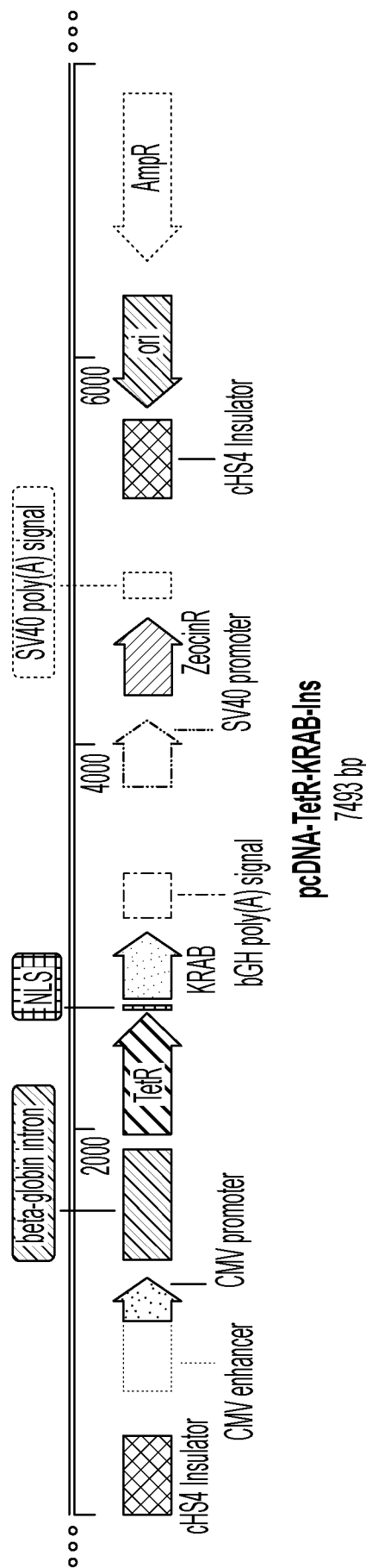


FIG. 2B

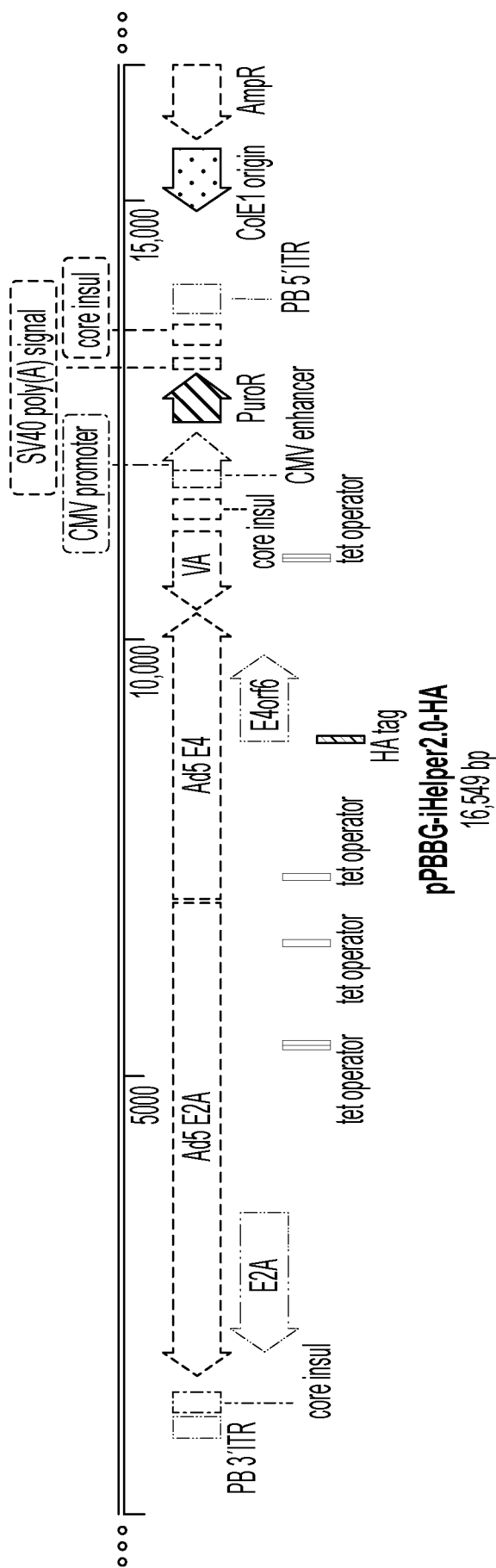


FIG. 3A

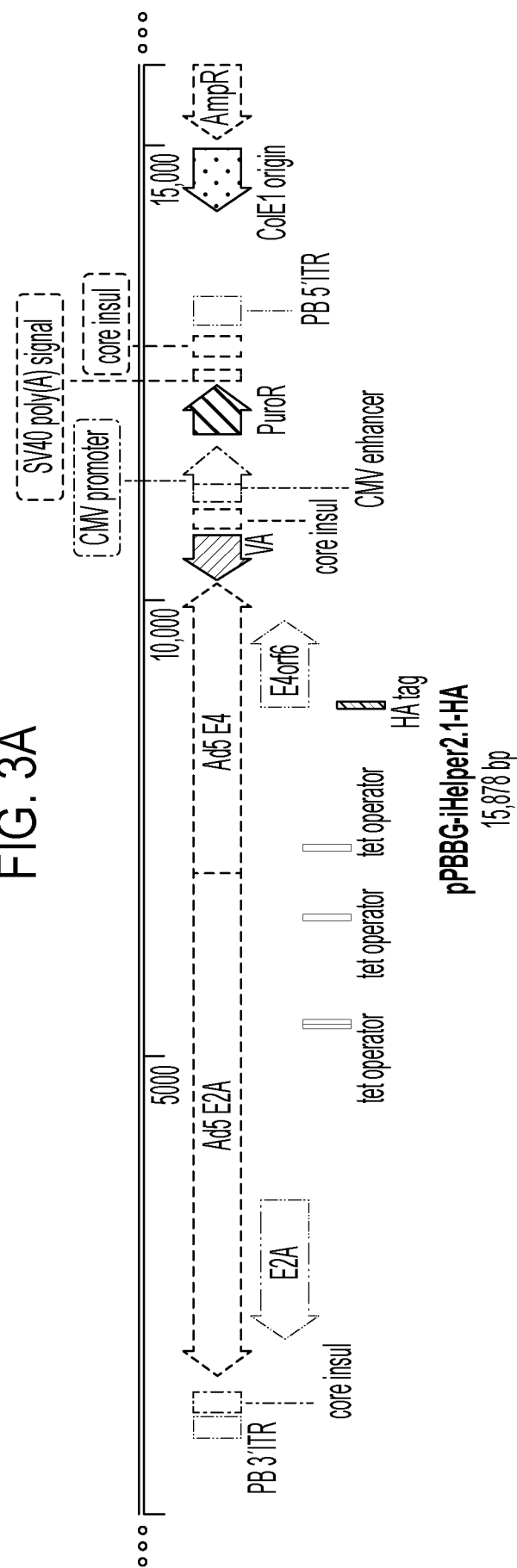
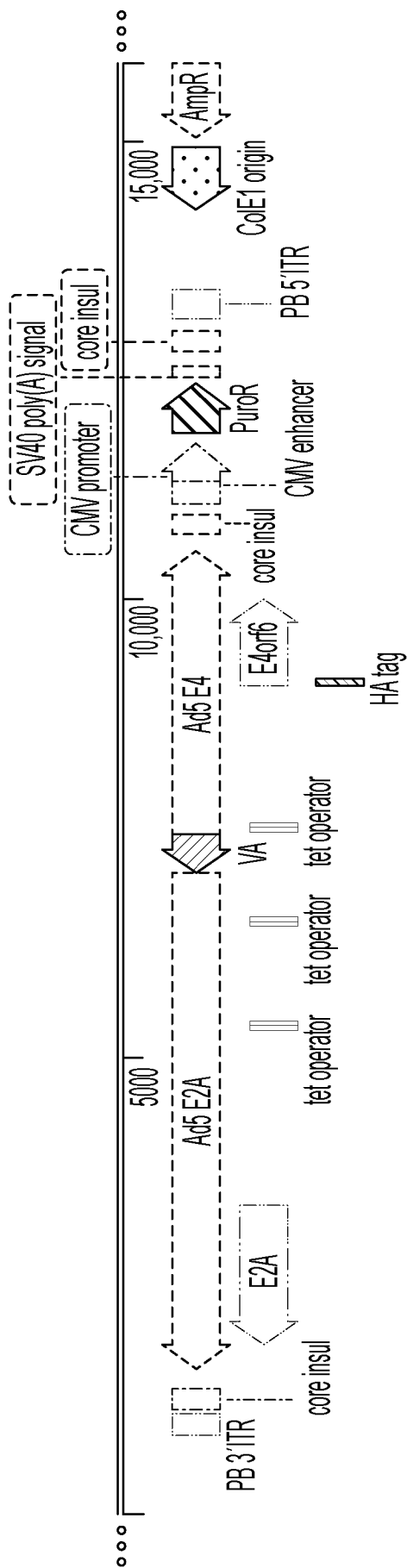


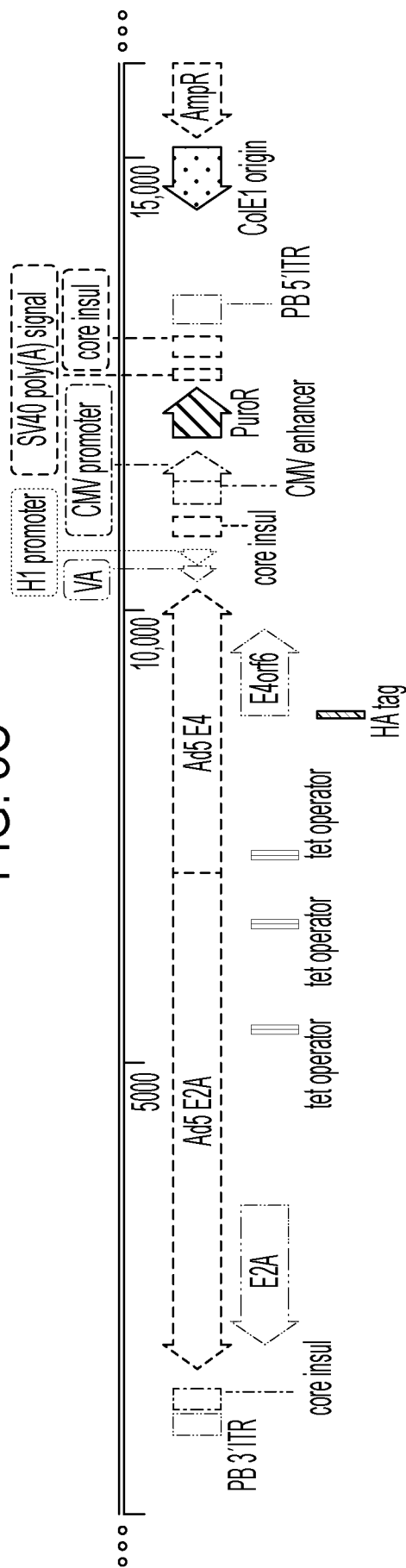
FIG. 3B



pPBBG-iHelper2.2-HA

15,878 bp

FIG. 3C



pPBBG-iHelper2.3-HA

15,992 bp

FIG. 3D

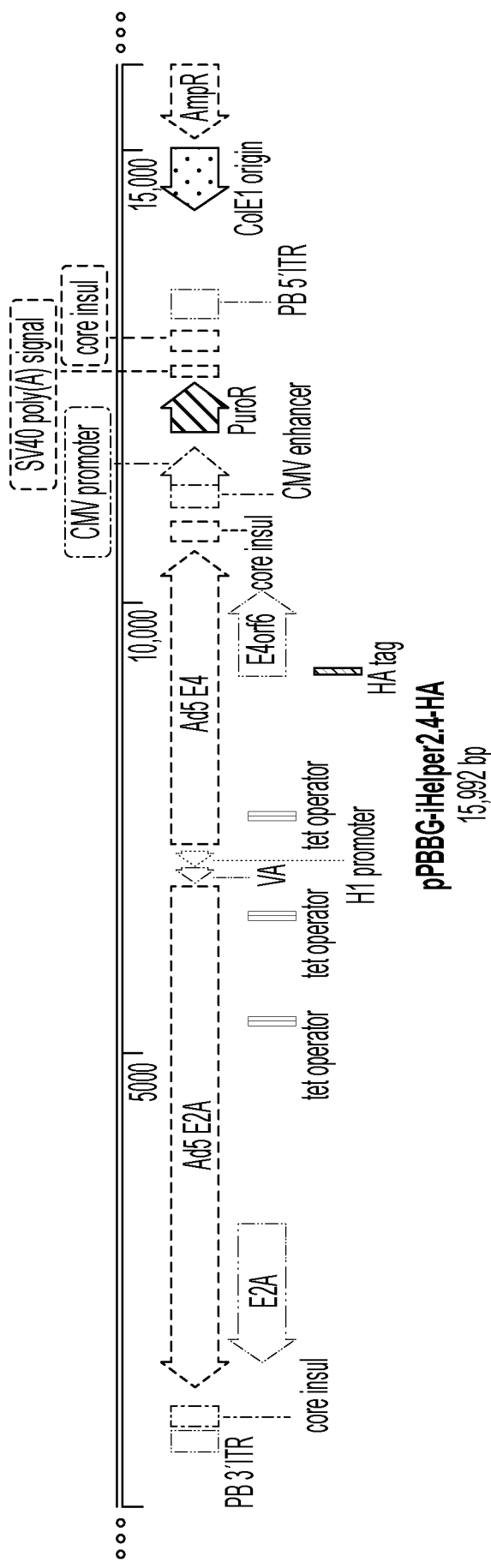


FIG. 3E

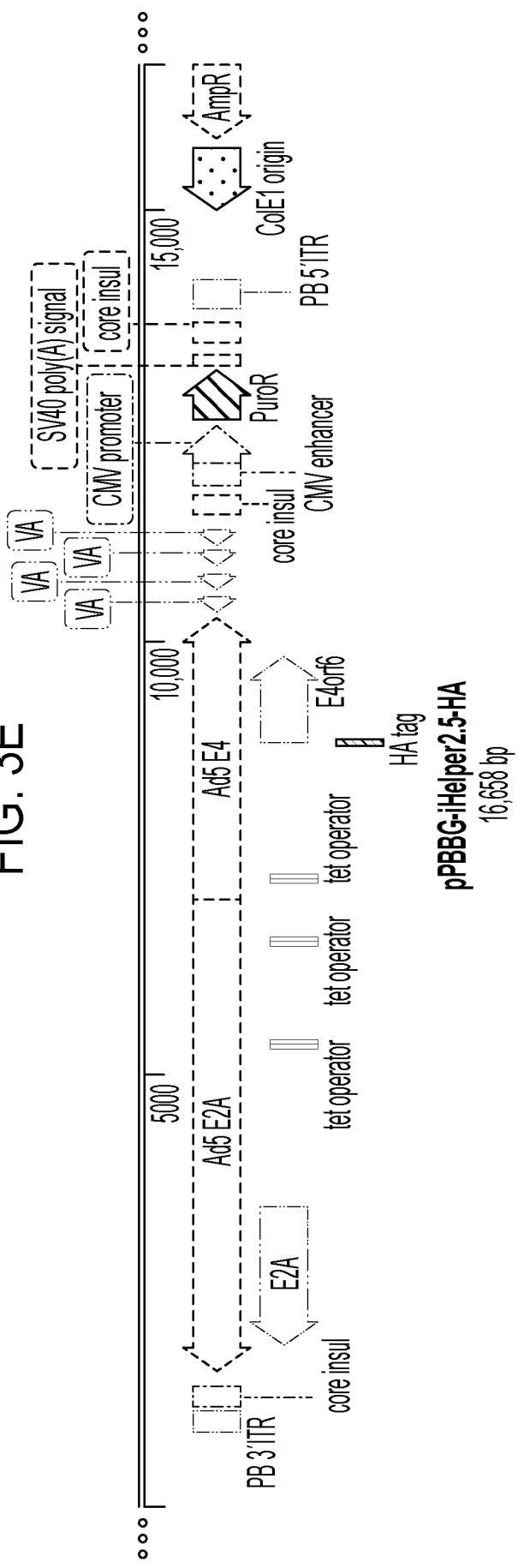


FIG. 3F

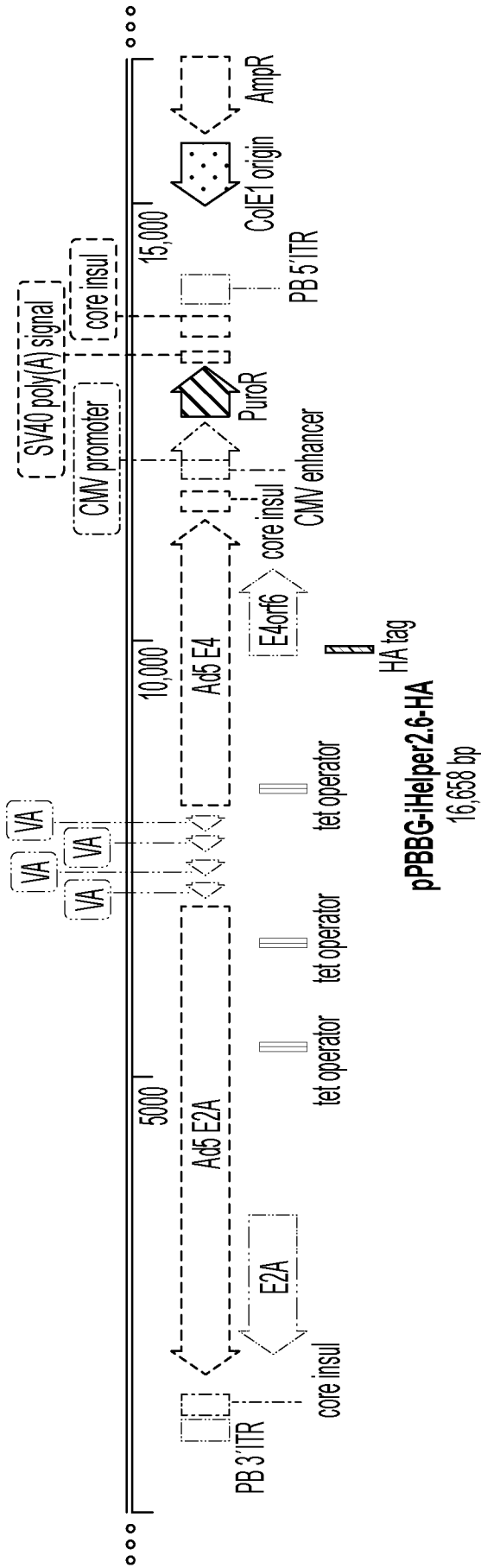


FIG. 3G

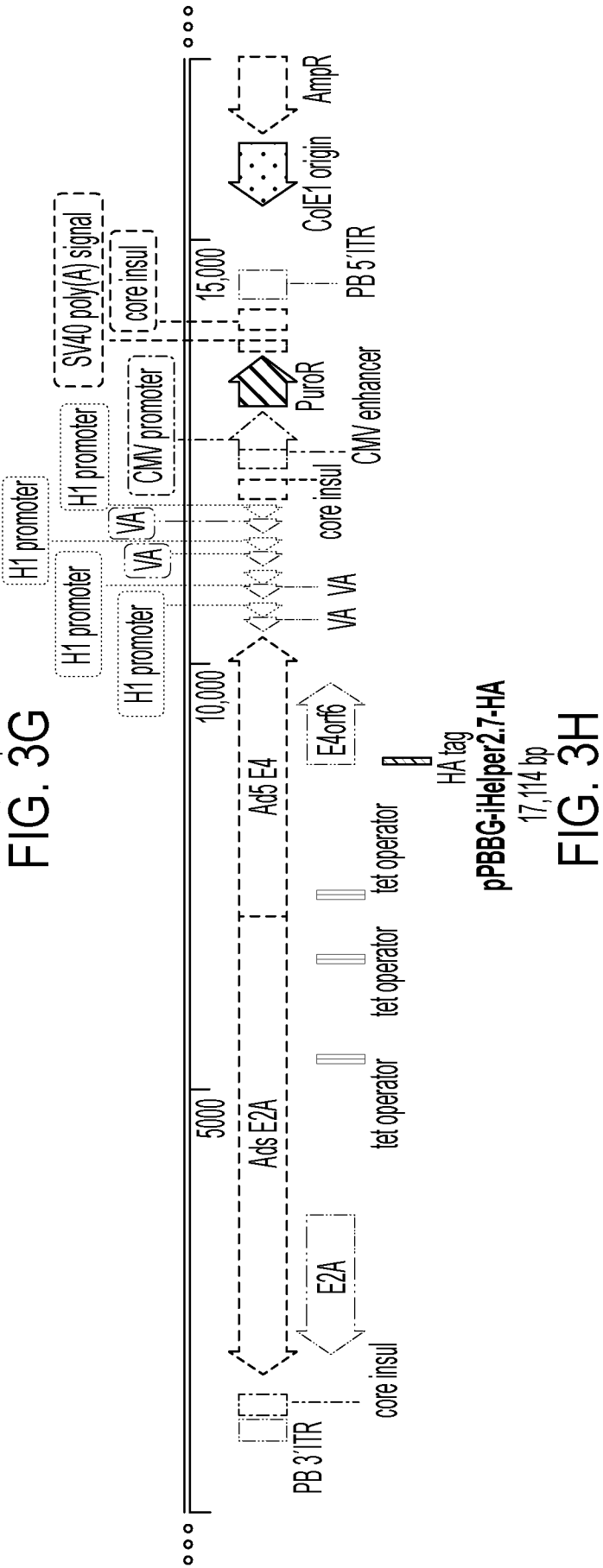
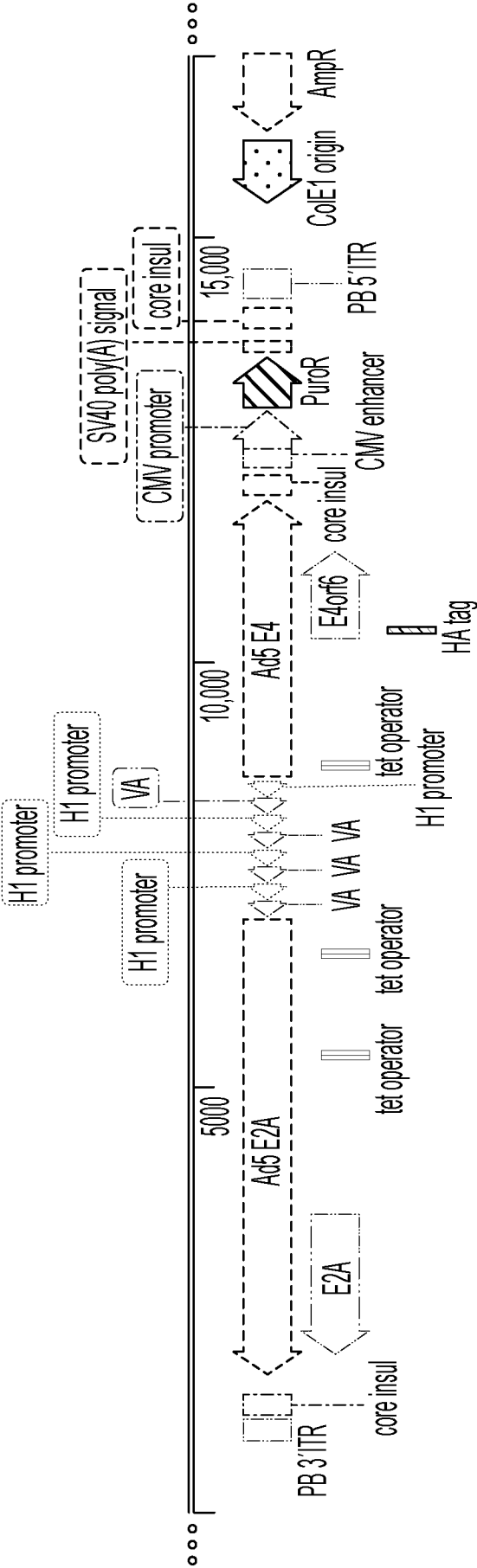
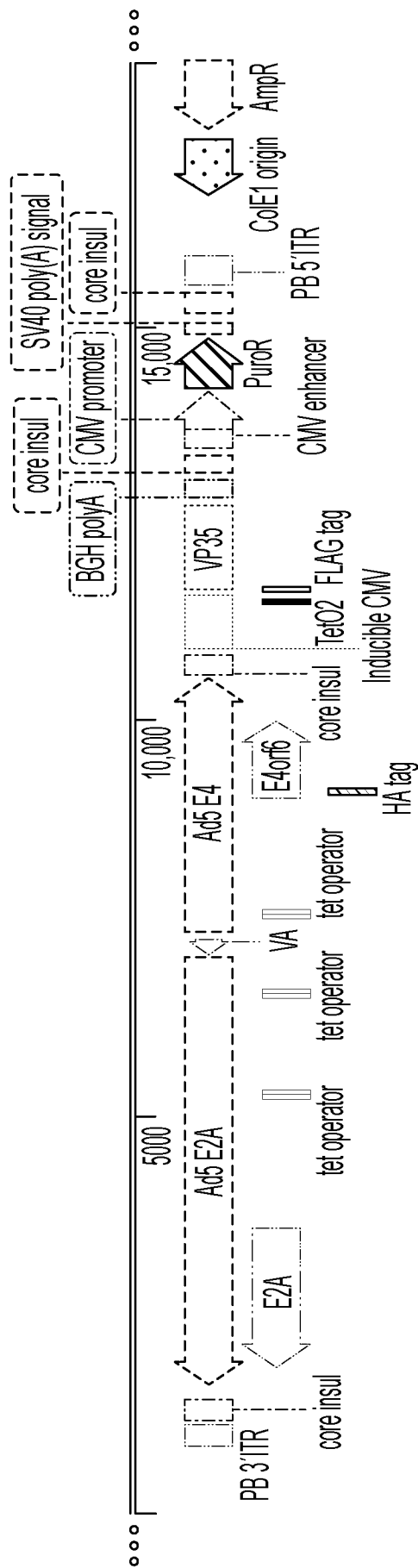


FIG. 3H



pPBBG-iHelper2.8-HA
17,114 bp

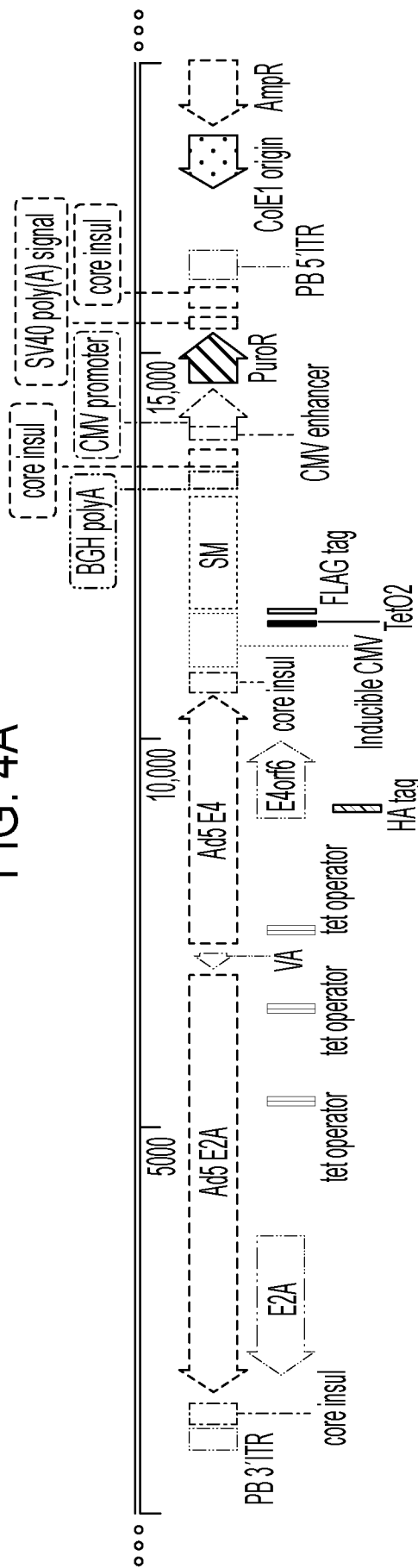
FIG. 3I



pPBBG-iHelper3.1-HA

18,311 bp

FIG. 4A



pPBBG-iHelper3.2-HA

18,728 bp

FIG. 4B

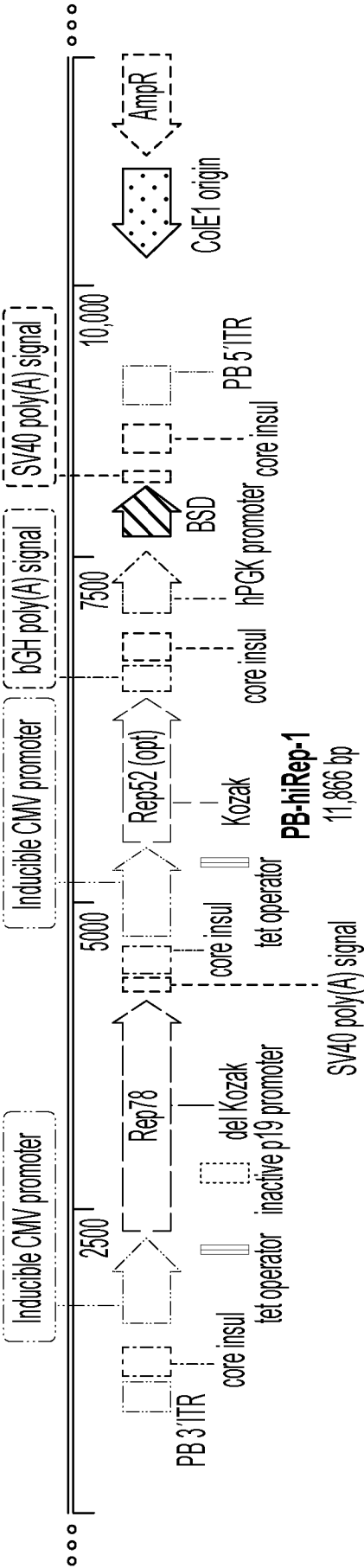


FIG. 5A

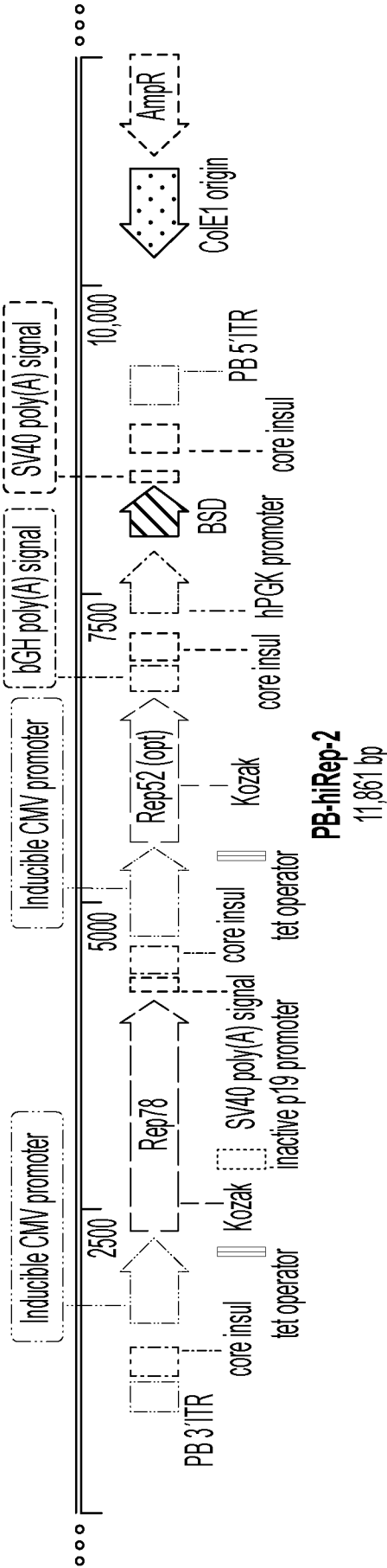


FIG. 5B

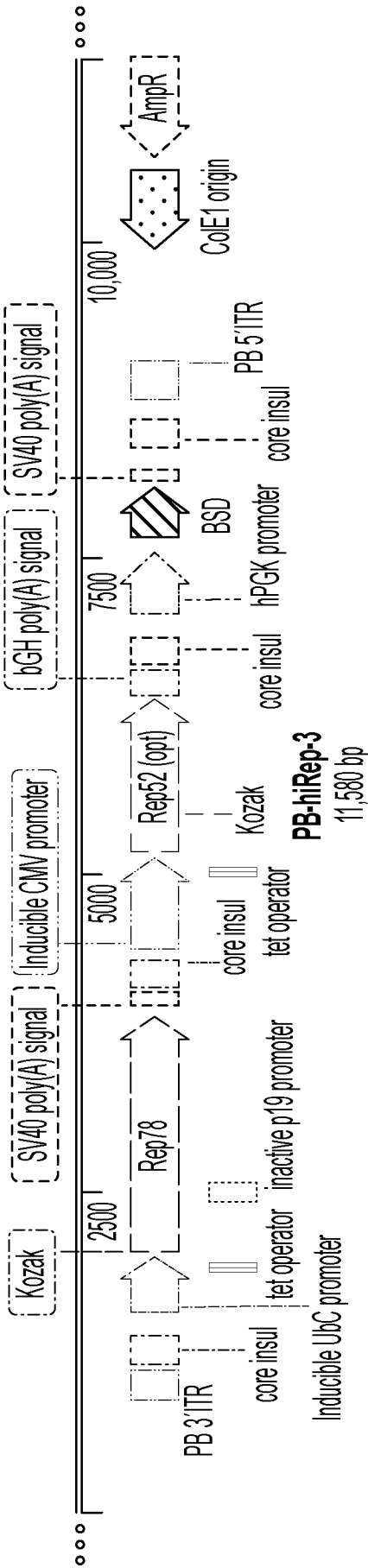


FIG. 5C

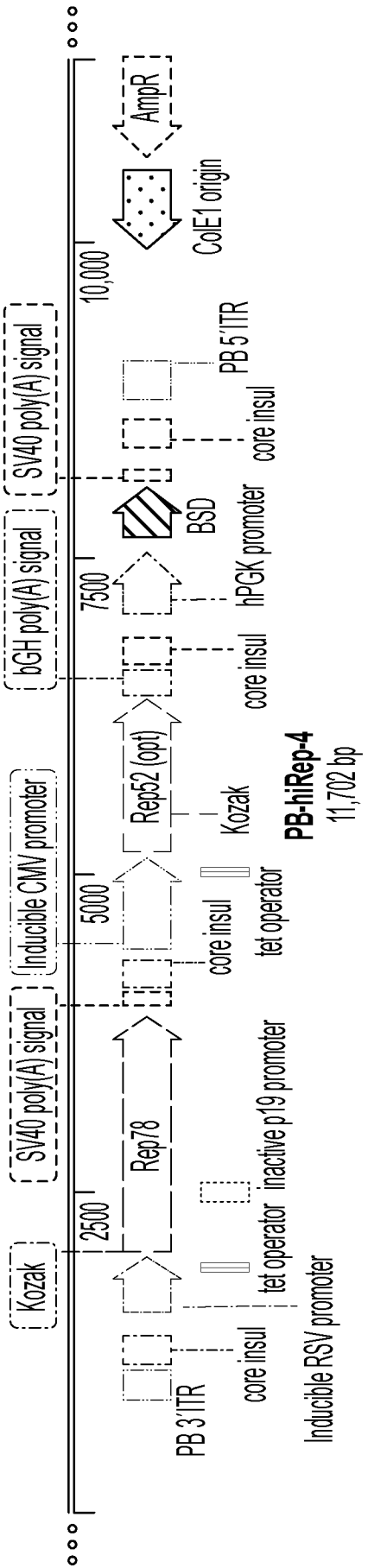


FIG. 5D

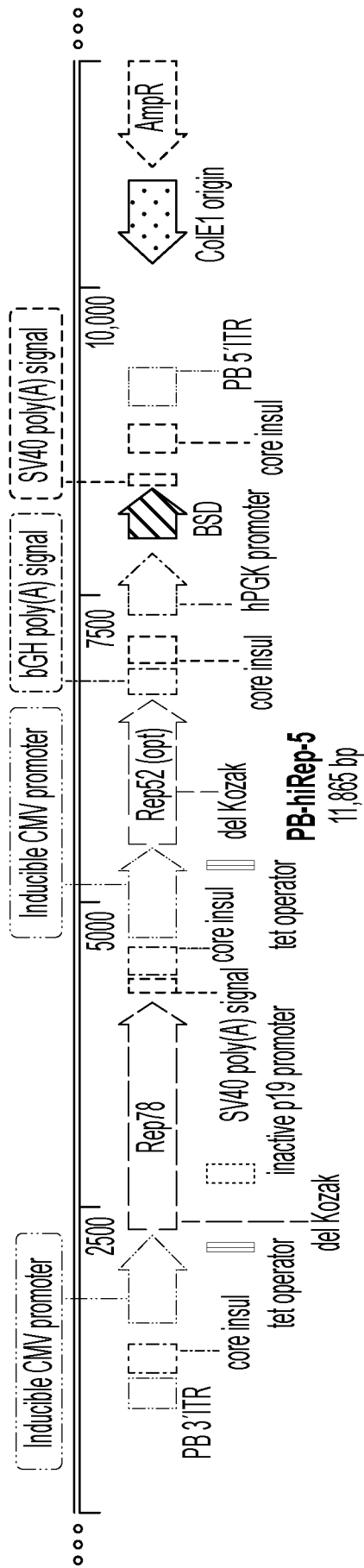


FIG. 5E

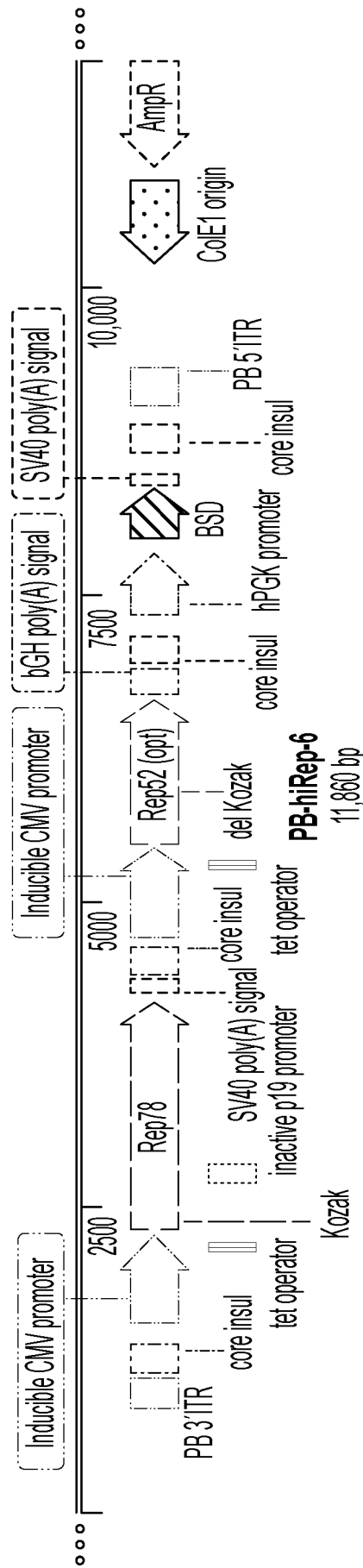


FIG. 5F

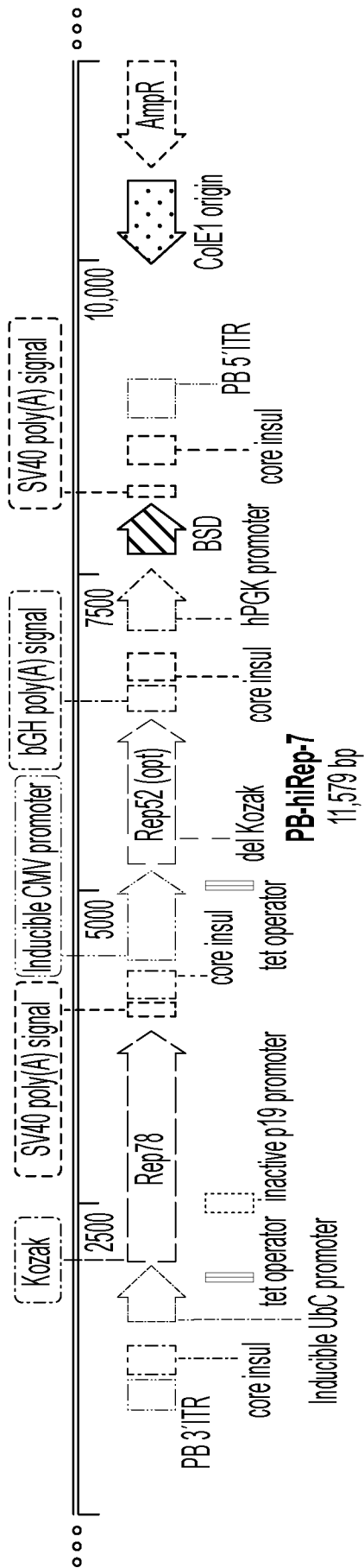


FIG. 5G

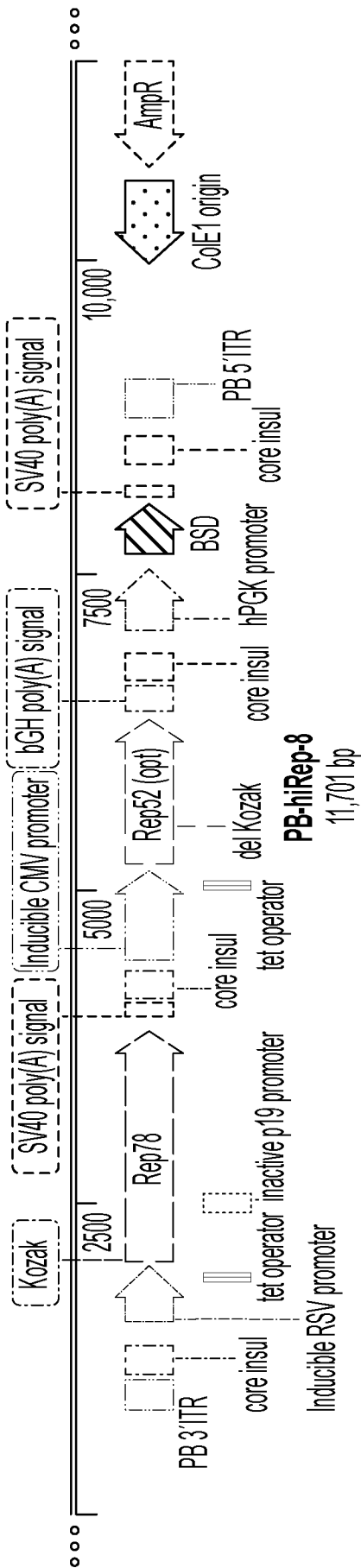


FIG. 5H

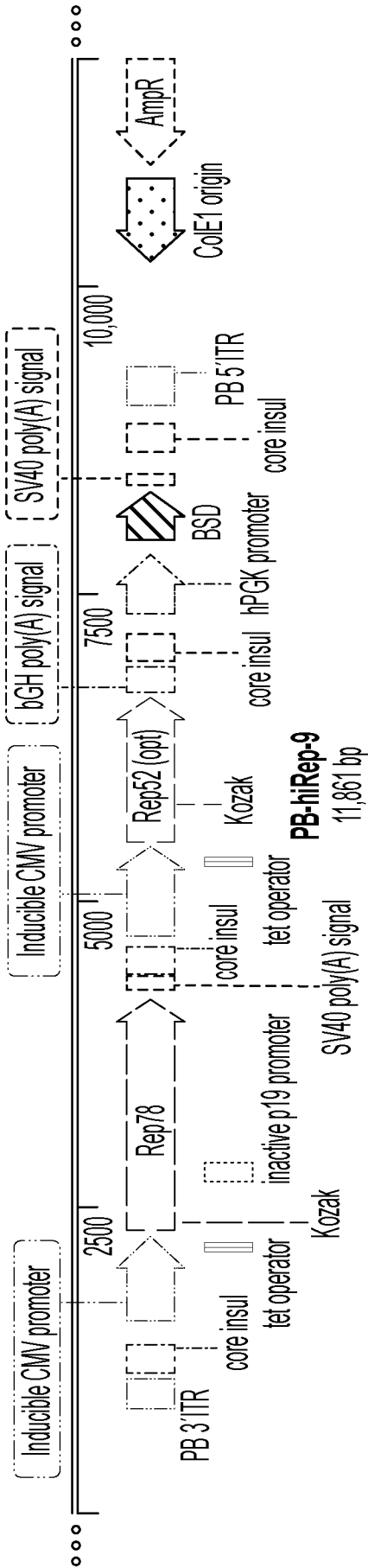


FIG. 5I

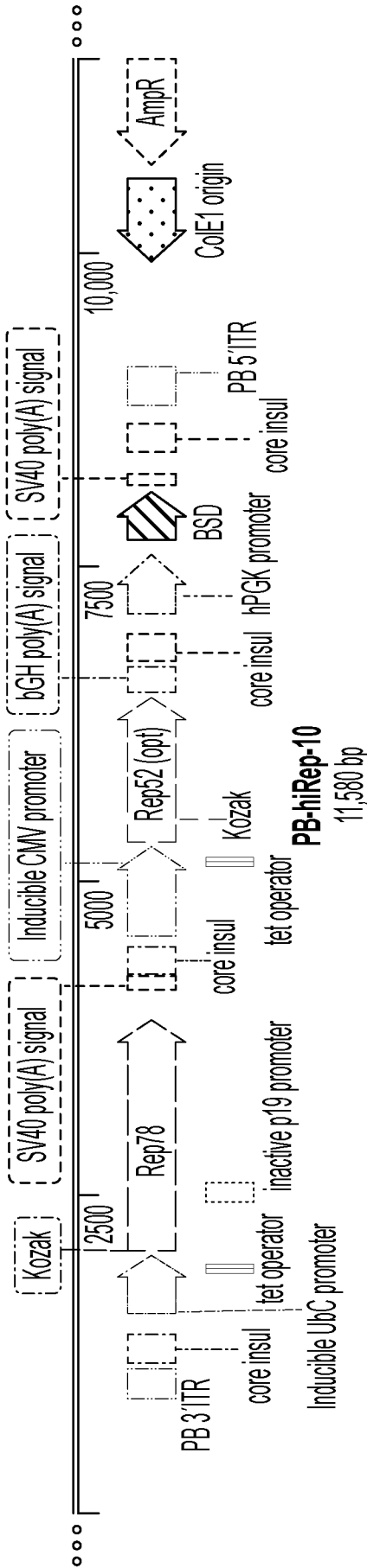


FIG. 5J

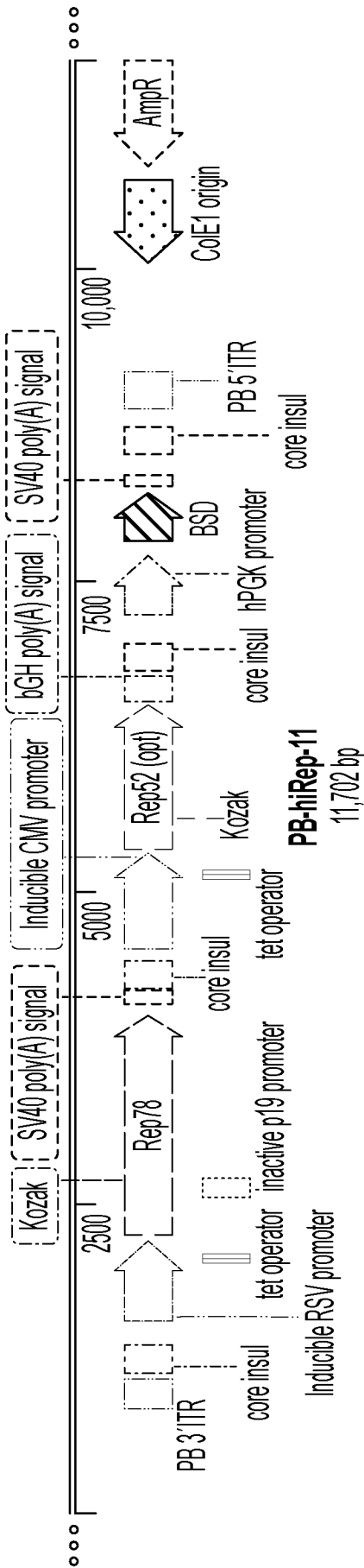


FIG. 5K

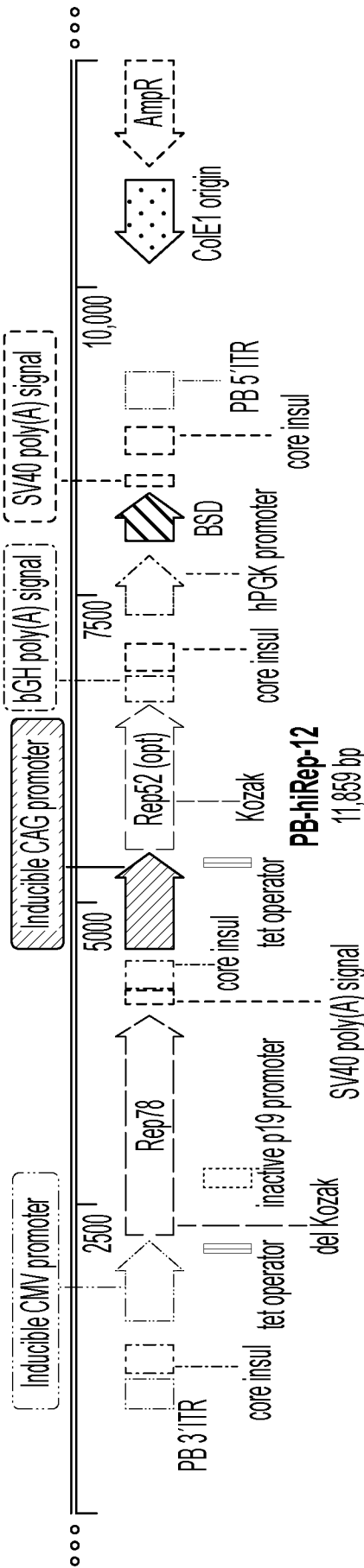


FIG. 5L

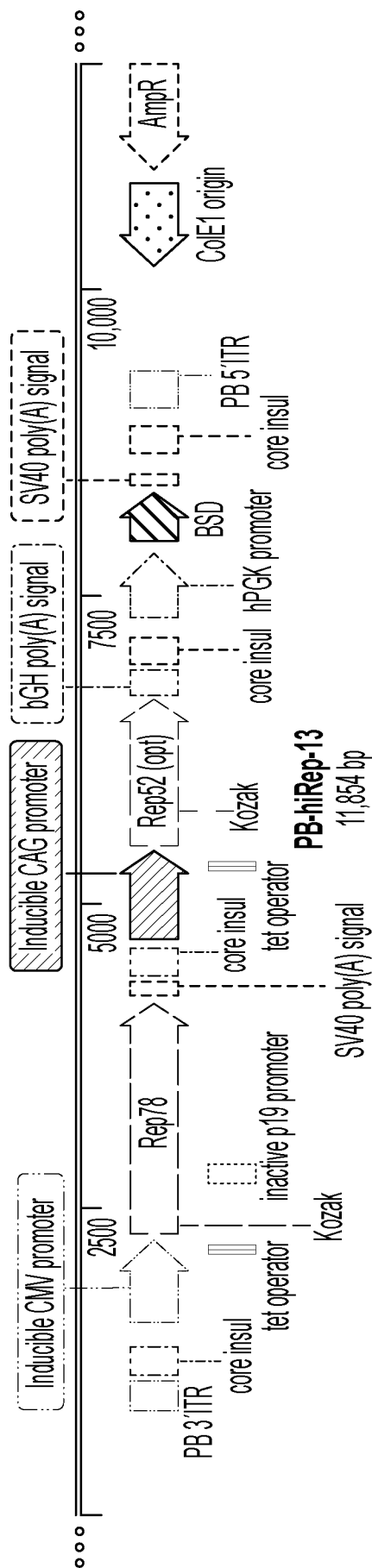


FIG. 5M

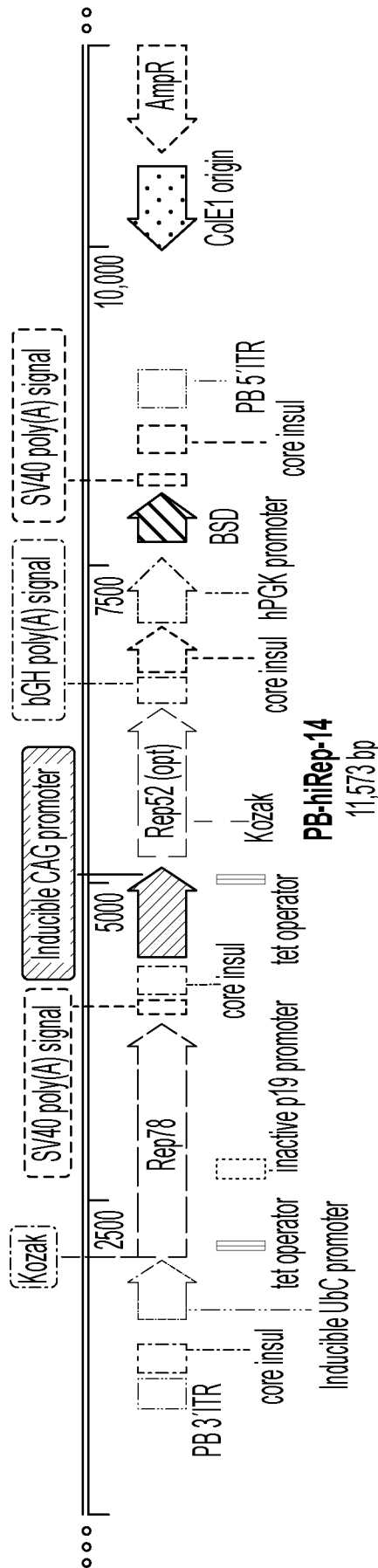


FIG. 5N

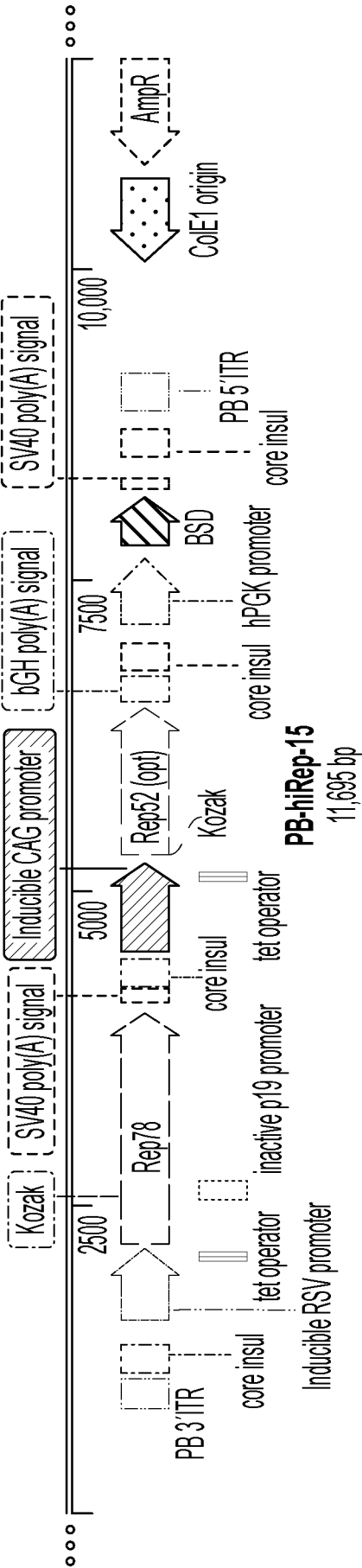


FIG. 50

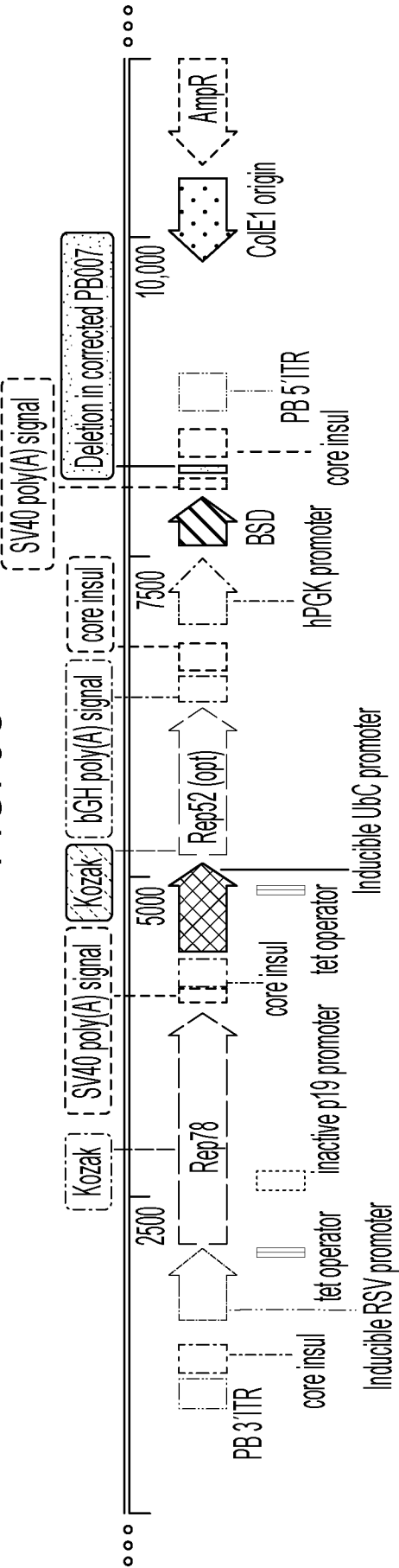


FIG. 5P

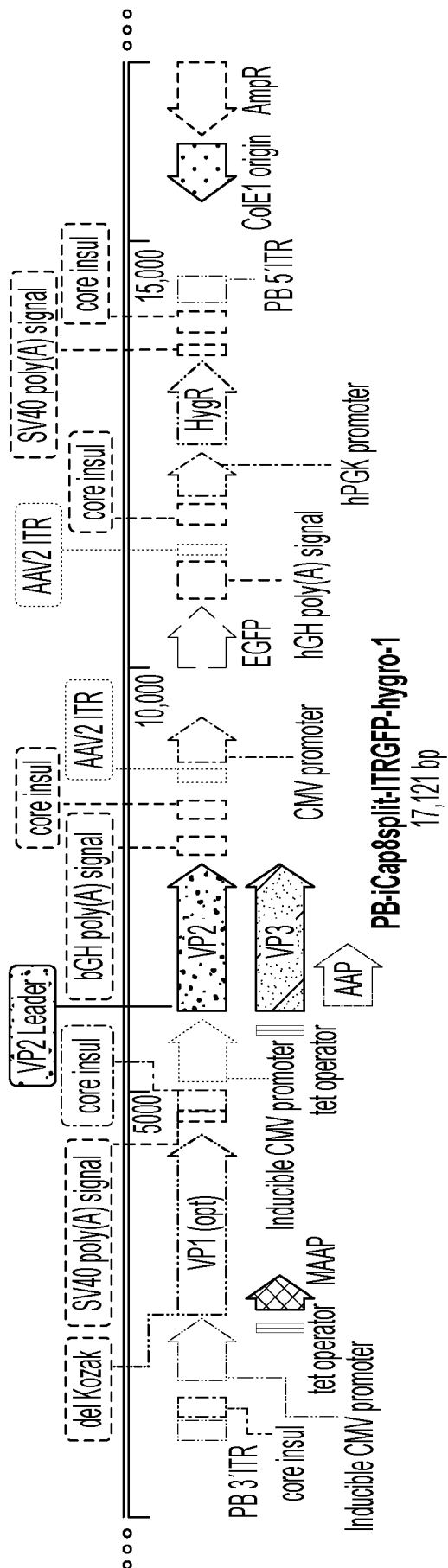


FIG. 6A

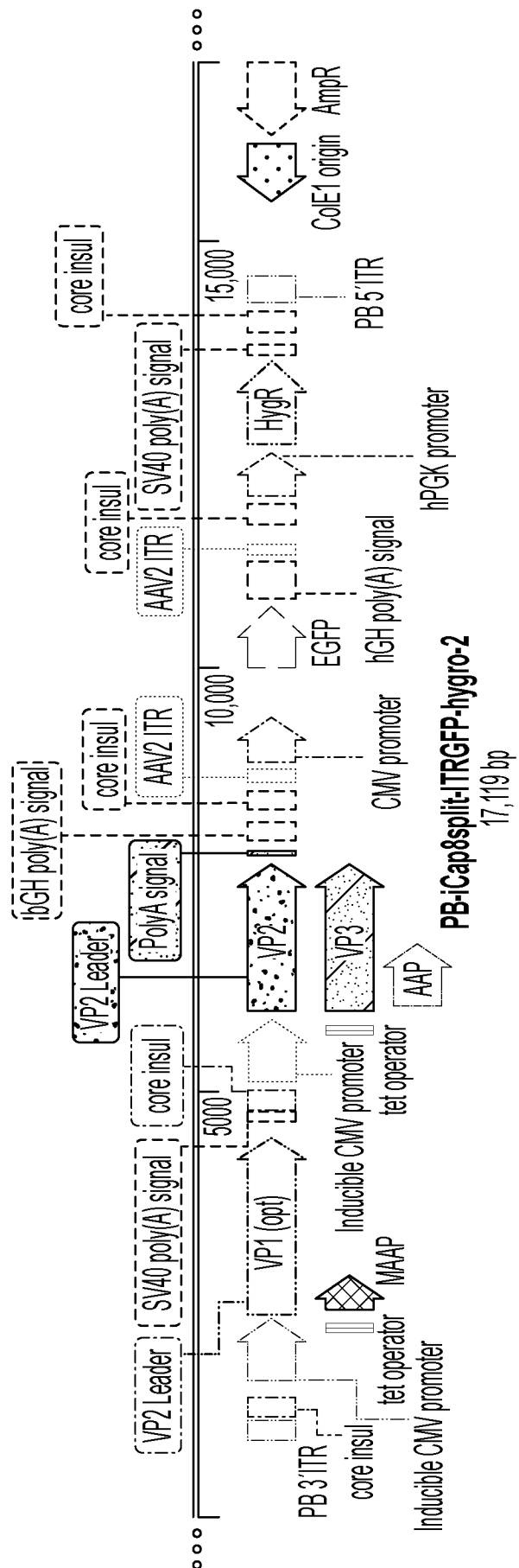


FIG. 6B

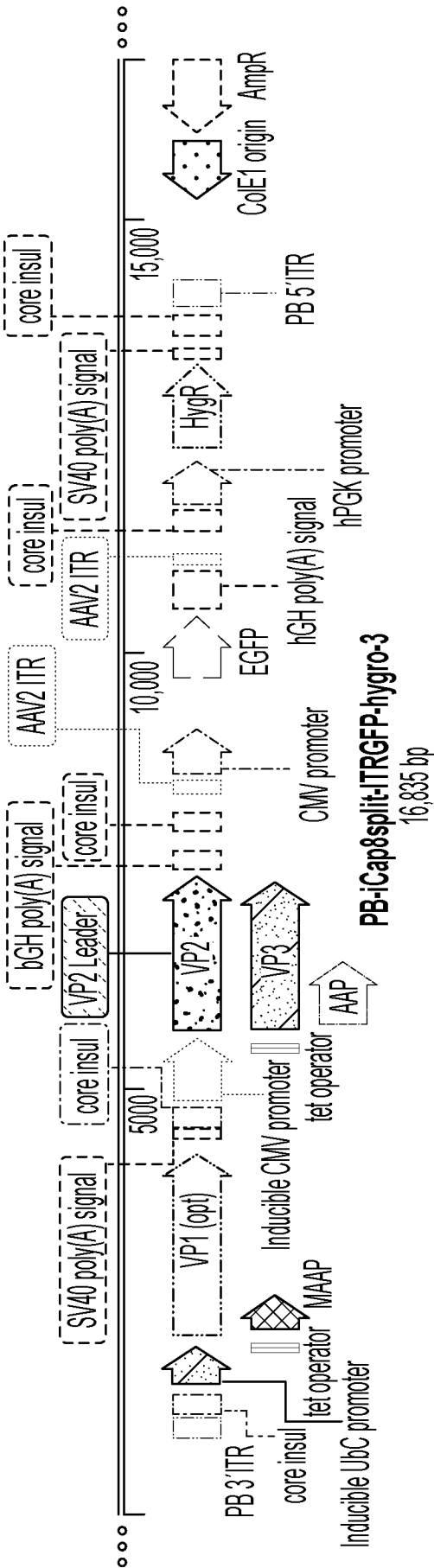


FIG. 6C

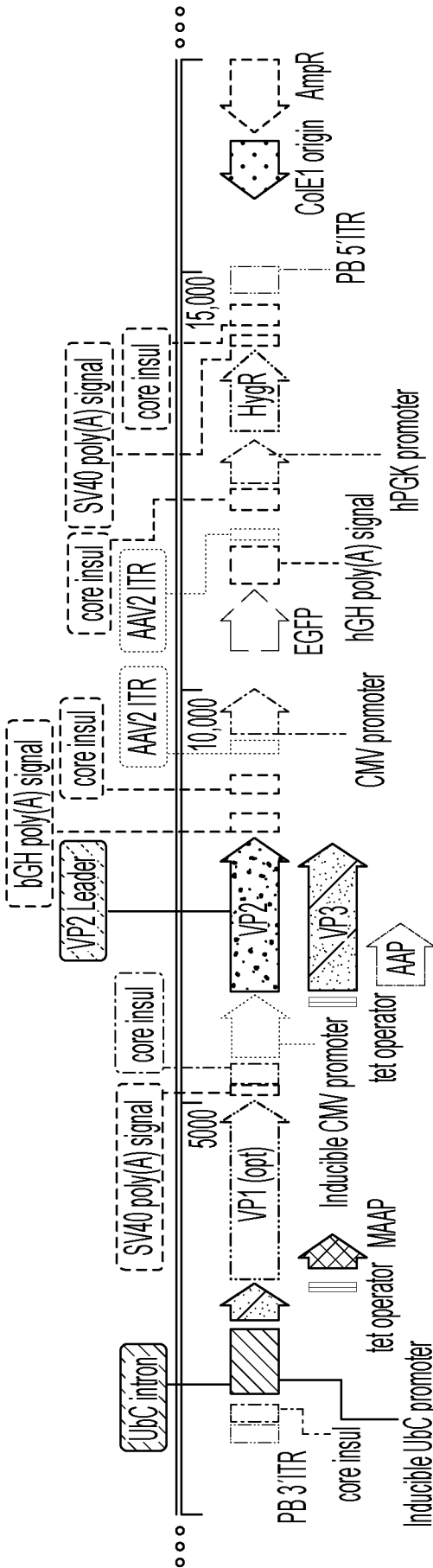
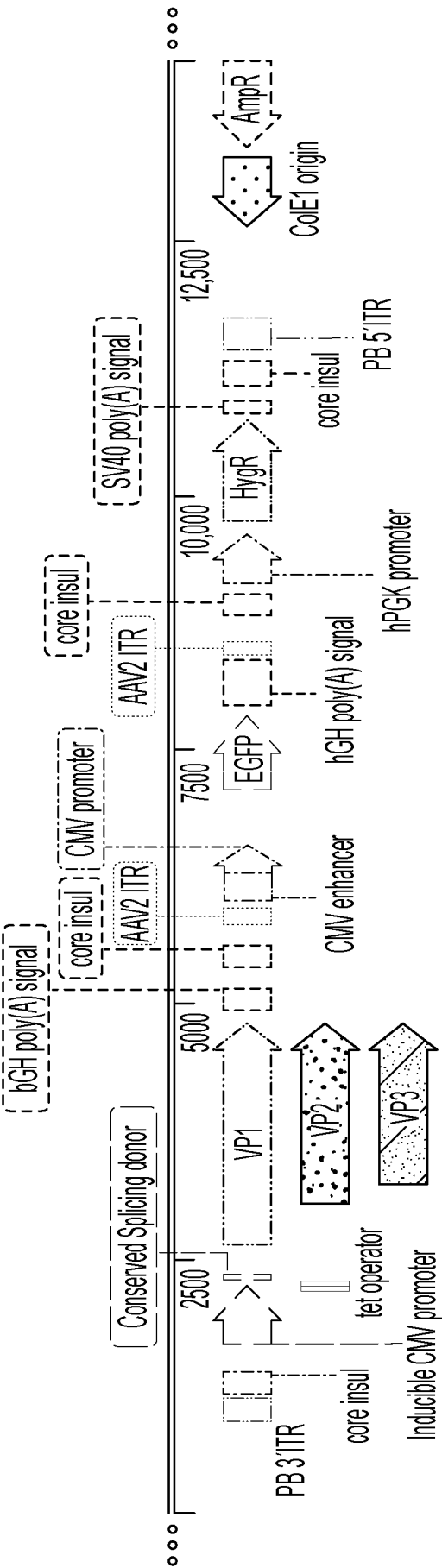


FIG. 6D



pPBBG-iCap&cd-ITRGFP-hygro
14,262 bp

FIG. 6E

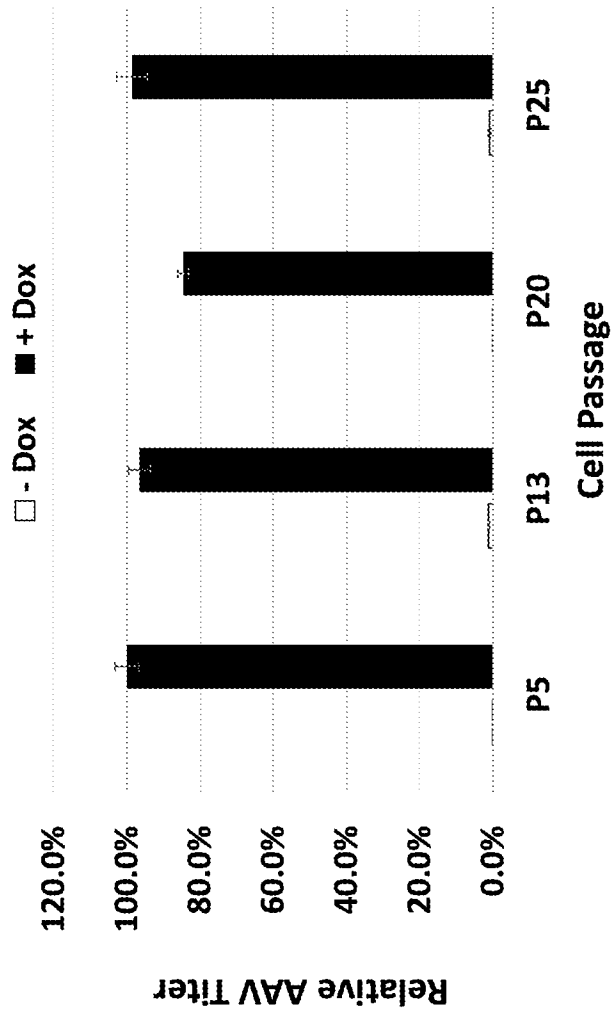


FIG. 7

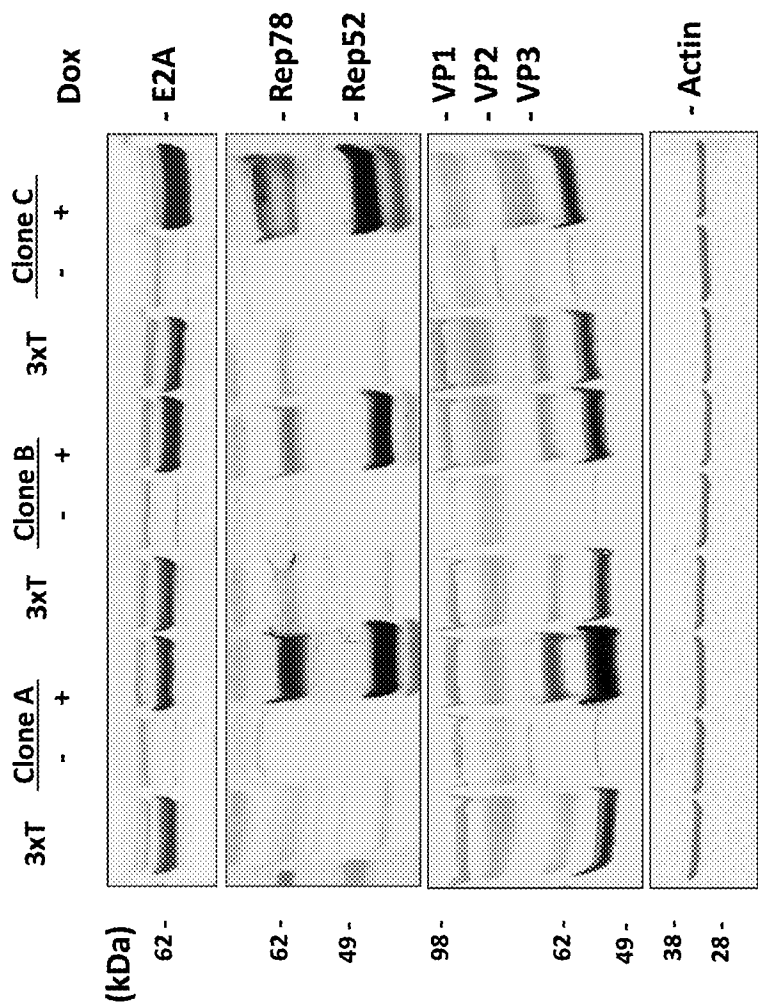


FIG. 8

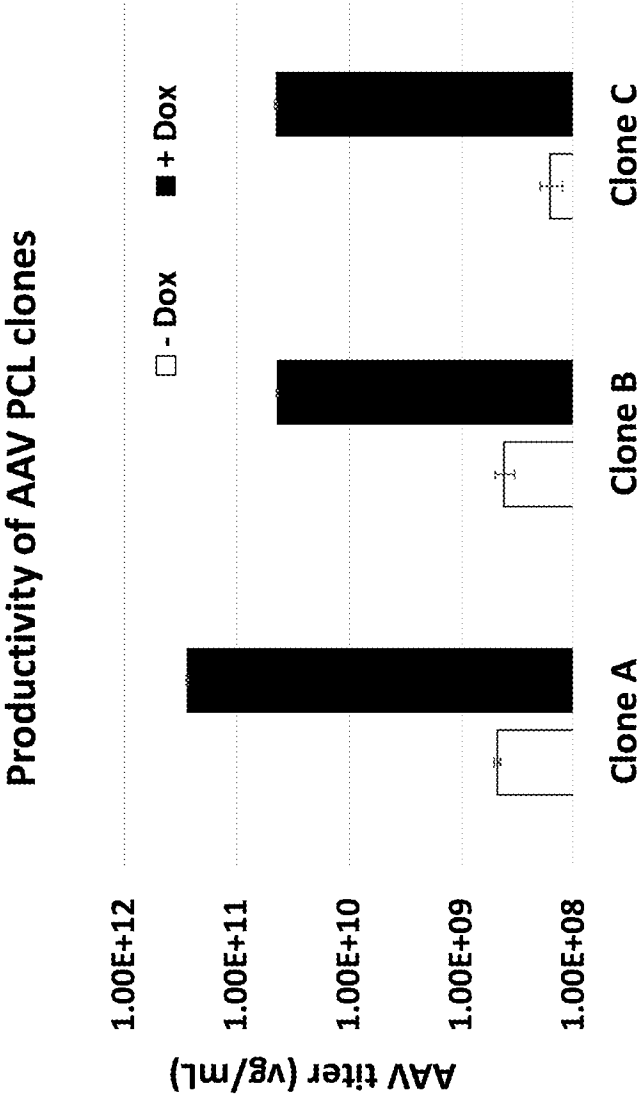


FIG. 9

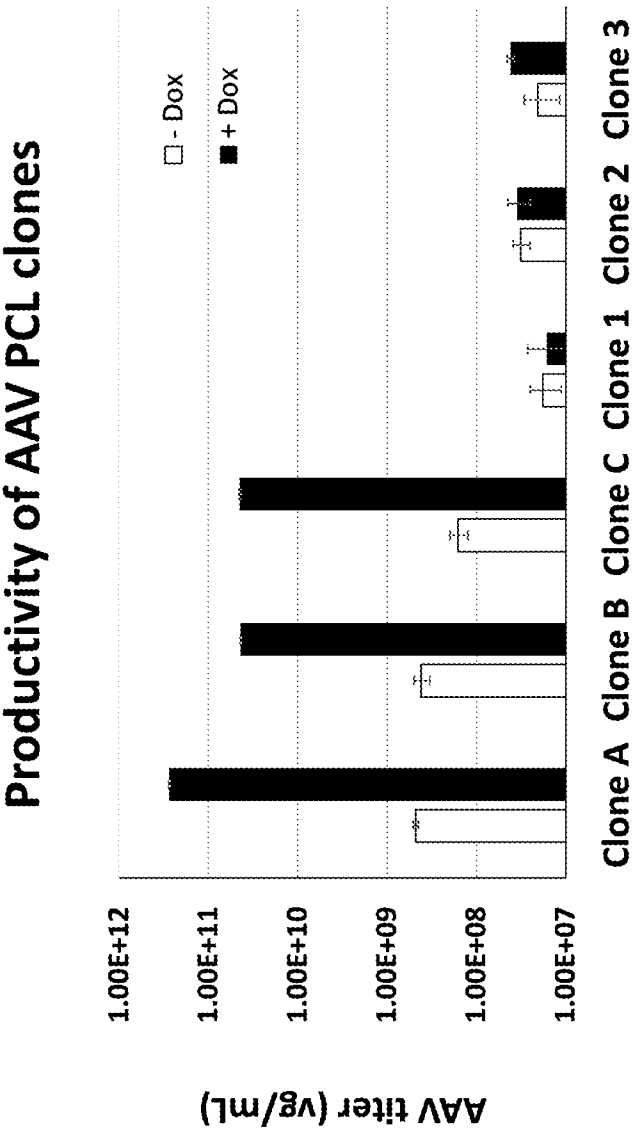


FIG. 10

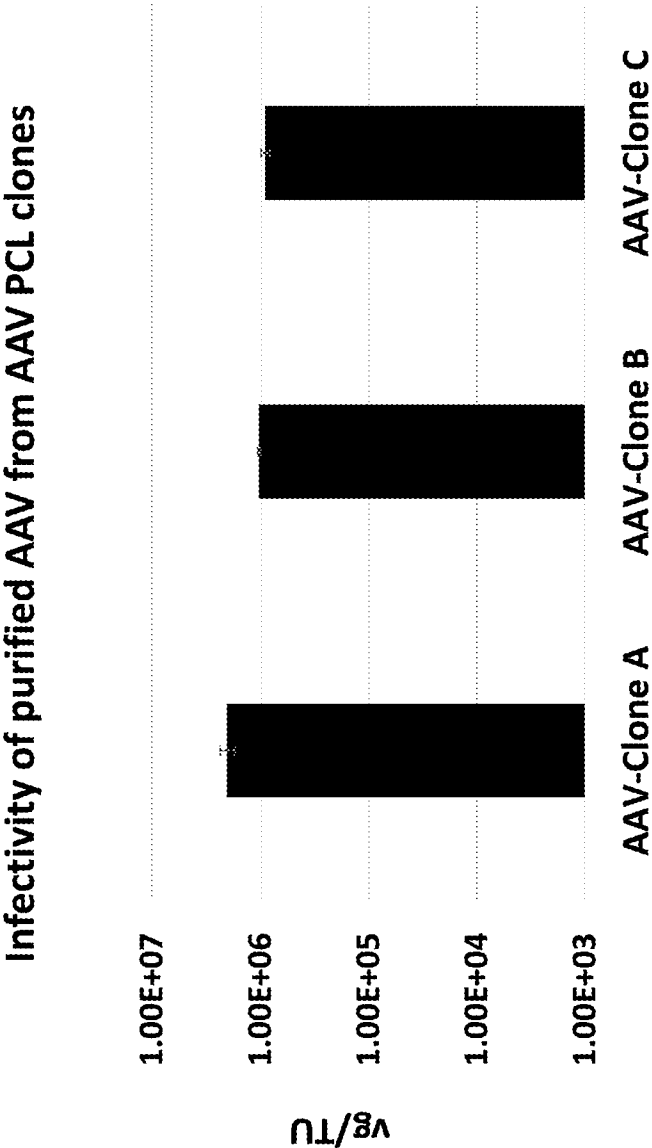


FIG. 11

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/052959

A. CLASSIFICATION OF SUBJECT MATTER

IPC: *C12N 15/86* (2025.01); *C12N 7/02* (2025.01); *C07K 14/11* (2025.01); *C12N 15/11* (2025.01); *C12N 15/113* (2025.01)
CPC: *C12N 15/86*; *C12N 15/113*; *C12N 7/02*; *C07K 14/11*; *C12N 15/111*; *C12N 2830/002*

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2020/0199627 A1 (LONZA WALKERSVILLE INC.) 25 June 2020 (25.06.2020) entire document	1-7
A	US 2019/0017033 A1 (APPLIED GENETIC TECHNOLOGIES CORPORATION) 17 January 2019 (17.01.2019) entire document	1-7
A	US 6,127,175 A (VIGNE et al.) 03 October 2000 (03.10.2000) entire document	1-7



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance
“D” document cited by the applicant in the international application
“E” earlier application or patent but published on or after the international filing date
“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
“O” document referring to an oral disclosure, use, exhibition or other means
“P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“&” document member of the same patent family

Date of the actual completion of the international search

07 January 2025 (07.01.2025)

Date of mailing of the international search report

28 February 2025 (28.02.2025)

Name and mailing address of the ISA/US

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TAINA MATOS

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Telephone No. **571-272-4300**

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/052959

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed.
 - b. ☒ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
☒ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I: claims 1-7 are drawn to isolated nucleic acid molecule operably comprising helper genes and AAV genes under the control of inducible promoters.

Group II: claims 8-15 are drawn to isolated nucleic acid molecule operably comprising helper genes and AAV genes under the control of inducible promoters.

Group III: claim 16-20 is drawn to isolated nucleic acid molecule operably comprising helper genes and AAV genes under the control of inducible promoters.

Group IV: claims 21-28 are drawn to isolated nucleic acid molecule operably comprising helper genes and AAV genes under the control of inducible promoters.

The inventions listed in Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I, a first inducible promoter and two tetracycline operator sequences, are not present in Groups II, III, or IV; the special technical features of Group II, an expression cassette encoding a protein ortholog of the VA RNA and a peptide protein tag under the control of a depressible promoter comprising a human Cytomegalovirus (CMV) promoter and a TetO2 sequence; g. a termination sequence, are not present in Groups I, III, or IV; the special technical features of Group III, a Rep78 gene, including a silenced p19 promoter located within the Rep78 gene coding region, wherein the silenced p19 promoter comprises mutations in SP1, TATA-1, and/or TATA-2 sites, are not present in Groups I, II, or IV; and the special technical features of Group IV, a VP1 gene, are not present in Groups I-III.

Additionally, even if Groups I-IV were considered to share the technical features of an isolated nucleic acid molecule operably comprising: a. a first inducible promoter and a TetO2 sequence; b. an E2A gene under control of the first inducible promoter; c. a viral associated (VA) non-coding RNA under control of a second inducible promoter; d. a third inducible promoter and a TetO2 sequence; e. an E4 gene under control of the third inducible promoter; and f. an antibiotic resistance gene. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2020/0199627 A1 to Lonza Walkersville Inc. (hereinafter, "Lonza") discloses an isolated nucleic acid molecule (an isolated nucleic acid molecule, Para. [0009]) operably comprising: a. a first inducible promoter and a TetO2 sequence (the derepressible promoters comprise a functional promoter and two tetracycline operator sequences (TetO2). In embodiments, the functional promoter of the first derepressible promoter (i.e., controlling the expression of the adenovirus helper gene comprising E2A and E4Orf6 genes) is a cytomegalovirus (CMV) promoter, Para. [0074]); b. an E2A gene under control of the first inducible promoter (the derepressible promoters comprise a functional promoter and two tetracycline operator sequences (TetO2). In embodiments, the functional promoter of the first derepressible promoter (i.e., controlling the expression of the adenovirus helper gene comprising E2A and E4Orf6 genes) is a cytomegalovirus (CMV) promoter, Para. [0074]); c. a viral associated (VA) non-coding RNA under control of a second inducible promoter (a viral-associated, non-coding RNA under control of a third depressible promoter, Para. [0008]); d. a third inducible promoter and a TetO2 sequence (a third depressible promoter, Para. [0009]; the derepressible promoters comprise a functional promoter and two tetracycline operator sequences (TetO2). In embodiments, the functional promoter of the first derepressible promoter (i.e., controlling the expression of the adenovirus helper gene comprising E2A and E4Orf6 genes) is a cytomegalovirus (CMV) promoter, Para. [0074]); e. an E4 gene under control of the third inducible promoter (the Adenovirus helper gene is E1A, E1B, E2A, E4 (including E4Orf6), VA, or a combination thereof or any other adenovirus helper gene. In exemplary embodiments, the adenovirus helper gene comprises both E2A and E4Orf6 genes, Para. [0040]; a third depressible promoter, Para.

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Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

[0009]); and f. an antibiotic resistance gene (the mammalian cell further comprises a selection gene, such as a zeocin resistance gene, Para. [0126]).

The inventions listed in Groups I-IV therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-7**

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.