

PSEUDOTYPED VIRAL LIKE PARTICLE FOR IMMUNE CELLS TRANSDUCTION

FIELD OF INVENTION

- 5 [0001] The present invention relates to a pseudotyped viral-like particle (VLP) or viral vector that targets immune cells and has increased transduction efficiency.

BACKGROUND OF INVENTION

- 10 [0002] Pseudotyped viral like particles (VLP) and viral vectors represent a powerful tool for the delivery of payloads such as nucleic acids to specific populations of cells. In particular, the delivery to immune cells to modulate or reprogram the immune system enables the treatment of a broad range of pathologies such as cancer and auto-immune disorders, such as chimeric antigenic receptor – T (CAR-T) cell therapies. In particular, CAR-T cell therapies rely on the transfection of both CD4 and CD8 T cells for an efficient
15 treatment.

[0003] Such approaches require both a good efficiency of transduction to enable a therapeutic effect, but also a strong specificity of transduction to avoid off target adverse effects.

- 20 [0004] Current solution may, however, yield off target effects, such as VLP pseudotyped with VSV-G (see, *e.g.*, WO 2023114884 or US 9,249,426). In addition, when targeting CD4+ cells, some proteins are known to confer good specificity to VLP but yield very poor transduction efficiency. Besides, current solutions may be limited to *ex vivo* applications, limiting the target cell populations to circulating cells (*e.g.*, circulating T-cells), without the possibility to reach resident cells (*e.g.*, resident T-cells) which may be
25 improve by *in vivo* therapy.

[0005] There is thus an unmet need for improved solutions for the safe and efficient delivery of cargo molecules to specific population of cells, preferably *in vivo*, and in particular CD4+ immune cells, and avoiding delivery of other cell types.

[0006] The Applicant thereby provides pseudotyped VLP or viral vectors with improved
5 specificity and improved transduction efficiency, that can be used *in vivo* with limited off target effects.

SUMMARY

[0007] The present invention relates to a pseudotyped viral-like particle (VLP) or viral
10 vector that selectively targets CD4-positive cells, wherein said VLP or viral vector comprises an envelope protein comprising:

- a first protein comprising an amino acid sequence having at least one mutation compared to the amino acid sequence of sequence of SEQ ID NO: 1, wherein said at least one mutation is localized on the cytoplasmic domain of the first protein
15 and
- a second protein comprising an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 3.

[0008] In some embodiments, the first protein comprises an amino acid sequence having at least 70% sequence identity with an amino acid sequence selected from the group comprising SEQ ID NO: 2, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO:
20 9, SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12.

[0009] In some embodiments, the first protein comprises an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 2, preferably said first protein has the amino acid sequence of SEQ ID NO: 2.

25 [0010] In some embodiments, the envelope protein comprises an amino acid sequence having at least 70% sequence identity with an amino acid sequence selected from the

group comprising SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19.

[0011] In some embodiments, the envelope protein has an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 5, preferably said envelope protein has
5 the amino acid sequence of SEQ ID NO: 5.

[0012] In some embodiments, the first protein has the amino acid sequence of SEQ ID NO: 2.

[0013] In some embodiments, the envelope protein has an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 5.

10 [0014] In some embodiments, the amino acid sequence of the envelope protein is not SEQ ID NO: 4.

[0015] In some embodiments, the VLP or viral vector is a retroviral VLP or retroviral vector.

[0016] In some embodiments, the VLP further comprises at least one nucleic acid
15 molecule of interest or polypeptide of interest, preferably wherein said at least one nucleic acid molecule of interest encodes at least one polypeptide of interest.

[0017] In some embodiments, the nucleic acid molecule of interest encodes a gene editor.

[0018] In some embodiments, the nucleic acid molecule of interest encodes a chimeric
20 antigen receptor (CAR).

[0019] In some embodiments, the CD4-positive cells are immune cells.

[0020] In some embodiments, the CD4-positive cells are T cells.

[0021] In some embodiments, the second protein comprises an amino acid sequence selected from the group comprising SEQ ID NO: 3, SEQ ID NO: 36, SEQ ID NO: 37,
25 SEQ ID NO: 38, and SEQ ID NO: 39.

[0022] The present invention further relates to a pharmaceutical composition comprising the pseudotyped VLP or viral vector according to the invention, and at least one pharmaceutically acceptable excipient or carrier.

[0023] The present invention further relates to the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention, for use as a medicament.

[0024] The present invention further relates to the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention, for use for treating cancer or an autoimmune disease in a subject in need thereof.

[0025] In some embodiments, the disease is cancer.

[0026] The invention further relates to a pseudotyped viral-like particle (VLP) or viral vector that selectively targets CD4-positive cells, wherein said VLP or viral vector comprises an envelope protein comprising a first protein comprising an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 2 and a second protein comprising an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 3, wherein the amino acid sequence of the envelope protein is not SEQ ID NO: 4.

DEFINITIONS

[0027] In the present invention, the following terms have the following meanings:

[0028] “**About**”, when preceding a figure, means plus or less 10% of the value of said figure.

[0029] “**And/Or**” refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative (“**or**”).

[0030] “**At least one**” includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 25, 50, 75, 100, 250, 500, 750, 10^3 , 10^4 , 10^5 , 10^6 , 10^7 , 10^8 , 10^9 , 10^{10} , 10^{11} , 10^{12} , 10^{13} , 10^{14} , 10^{15} or more.

- [0031] “**At least 70% sequence identity**” encompasses at least 70% identity, at least 71% identity, at least 72% identity, at least 73% identity, at least 74% identity, at least 75% identity, at least 76% identity, at least 77% identity, at least 78% identity, at least 79% identity, at least 80% identity, at least 81% identity, at least 82% identity, at least 83% identity, at least 84% identity, at least 85% identity, at least 86% identity, at least 87% identity, at least 88% identity, at least 89% identity, at least 90% identity, at least 91% identity, at least 92% identity, at least 93% identity, at least 94% identity, at least 95% identity, at least 96% identity, at least 97% identity, at least 98% identity, at least 99% identity, at least 99.5% identity, at least 99.9% identity, and at least 100% identity.
- 10 [0032] “**Cargo**” or “**cargo molecule**” is meant to refer to any molecule that may be delivered by the VLP or viral vector of the invention. As non-limiting examples, “cargo” may refer to a DNA, a RNA, a siRNA, a shRNA, a peptide, a polypeptide, a protein, a viral payload, a viral genome, a small molecule or a combination thereof. In some embodiments, the polypeptide is a chimeric antigen receptor (“CAR”).
- 15 [0033] “**Chimeric antigen receptor**” or “**CAR**” as used herein refers to an antigen-binding domain that is fused to an intracellular signaling domain capable of activating or stimulating an immune cell. Most commonly, the CAR's extracellular binding domain is composed of a single chain variable fragment (scFv) derived from fusing the variable heavy and light regions of a murine or humanized monoclonal antibody. Alternatively,
- 20 scFvs may be used that are derived from Fab's (instead of from an antibody, e.g., obtained from Fab libraries). In various embodiments, this scFv is fused to a transmembrane domain and then to an intracellular signaling domain. However, the antigen binding domain can be any molecule that can bind to the target on the cell. For example, the antigen binding domain of a CAR can be an antibody, a scFv antibody, an antigen binding domain, an ankyrin repeat (e.g., DARPIN), a VHH domain antibody, a nanobody, single domain antibody, a FN3 domain, or any combination thereof. In various embodiments,
- 25 the CAR is selected to have high affinity or avidity for the antigen. These are merely illustrative in nature and are not limiting to the present embodiments and any chimeric antigen receptor can be delivered in conjunction with the VLPs or viral vectors provided
- 30 herein.

[0034] “**Comprising**”, “**comprises**” and “**comprised of**” are used herein are synonymous with “**including**”, “**includes**” or “**containing**”, “**contains**”, and are inclusive or open-ended and do not exclude additional, non-recited members, elements or method steps. These terms also encompass “**consisting of**”.

- 5 [0035] “**Gene**” typically refers to a DNA region encoding a protein (*i.e.*, a coding region). The term may also include DNA regions which do not *per se* encode a protein (*i.e.*, a non-coding region). The latter include, *e.g.*, regions transcribed into functional non-coding RNA molecules (*e.g.*, transfer RNA, ribosomal RNA, regulatory RNA, etc.). Other non-coding regions regulate the transcription and translation of coding regions (*i.e.*,
10 regulatory elements), or serve as architectural elements (*e.g.*, scaffold/matrix attachment region), as origins of DNA replication, as centromeres or telomeres, etc. Regulatory elements include, without limitations, promoter sequences, terminators, translational regulatory sequences (*e.g.*, ribosome binding sites [RBS] and internal ribosome entry sites [IRES]), enhancers, silencers, insulators, boundary elements, replication origins, matrix
15 attachment sites and locus control regions.

- [0036] “**Identity**” or “**identical**”, when used in a relationship between the sequences of two or more amino acid sequences, or of two or more nucleic acid sequences, refers to the degree of sequence relatedness between amino acid sequences or nucleic acid sequences, as determined by the number of matches between strings of two or more amino
20 acid residues or nucleic acid residues. “Identity” measures the percent of identical matches between the smaller of two or more sequences with gap alignments (if any) addressed by a particular mathematical model or computer program (*i.e.*, “algorithms”). Identity of related amino acid sequences or nucleic acid sequences can be readily calculated by known methods. Preferred methods for determining identity are designed
25 to give the largest match between the sequences tested. Methods of determining identity are described in publicly available computer programs. Preferred computer program methods for determining identity between two sequences include the GCG program package, including GAP, BLASTP, BLASTN, and FASTA. The BLASTX program is publicly available from the National Center for Biotechnology Information (NCBI) and
30 other sources. Illustratively, the percent identity between two nucleotide amino acid

sequences may also be determined using for example algorithms such as the BLASTN program for nucleic acid sequences using as defaults a word length (W) of 11, an expectation (E) of 10, M=5, N=4, and a comparison of both strands. The well-known Smith Waterman algorithm may also be used to determine identity. As used herein, the

5 “**percent identity**” between two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity = number of identical positions/total number of positions x 100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences

10 can be accomplished using a mathematical algorithm, as described herein.

[0037] “**Modified**” refers to a protein or nucleic acid sequence that is different than a corresponding unmodified protein or nucleic acid sequence.

[0038] “**Mutation**” refers to a substitution of a residue within a sequence, e.g., a nucleic acid or amino acid sequence, with another residue; and/or to a deletion or insertion of one

15 or more residues within a nucleic acid or amino acid sequence. Mutations are typically described herein by identifying the original residue followed by the position of the residue within the sequence, then the identity of the newly substituted residue. Various methods for making amino acid substitutions (mutations) provided herein are well known in the art. “**Mutated**”, in connection with a sequence (e.g., an amino acid sequence or a nucleic

20 acid sequence) means that the sequence is different than a reference sequence, such as a wild-type sequence. Typically, a mutated sequence comprises at least one of a substitution, an addition or a deletion of one or several residues by comparison to a reference sequence, such as a corresponding wild-type sequence.

[0039] “**Variant**” refers a peptide, polypeptide or protein that typically differs from a

25 peptide, polypeptide or protein specifically disclosed herein in one or more mutation, typically comprising substitutions, deletions, additions and/or insertions. In some embodiments, one or more mutation means 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more mutations. Such variants may be naturally occurring or may be synthetically generated, for example, by modifying one or more of the peptide, polypeptide or protein sequences and evaluating

30 one or more biological activities of the peptide, polypeptide or protein and/or using any

of a number of techniques well known in the art. Modifications may be made in the structure of the peptide, polypeptide or protein and still obtain a functional molecule with desirable characteristics. When it is desired to alter the amino acid sequence of a peptide, polypeptide or protein to create an equivalent, or even an improved, variant or portion of a peptide, polypeptide or protein, one skilled in the art will typically change one or more of the codons of the encoding DNA or RNA sequence. It is thus contemplated that various changes may be made in the peptide, polypeptide or protein sequences, or corresponding DNA or RNA sequences that encode said peptide, polypeptide or protein, with or without appreciable alteration of their biological utility or activity. In many instances, a peptide, polypeptide or protein variant will contain one or more conservative substitutions. A variant may also, or alternatively, contain nonconservative changes.

[0040] “**Nucleic acid (molecule/sequence)**” and “**nucleotide sequence**” may be used interchangeably to refer to any molecule composed of, or comprising, monomeric nucleotides. A nucleic acid may be an oligonucleotide or a polynucleotide; it can be a DNA, an RNA, or a mix thereof. It can be chemically modified or artificial; *e.g.*, it encompasses peptide nucleic acids (PNA), morpholinos and locked nucleic acids (LNA), as well as glycol nucleic acids (GNA) and threose nucleic acid (TNA). Each of these nucleic acids distinguish from naturally occurring DNA or RNA by changes in the backbone of the molecule.

[0041] “**Polypeptide**”, “**peptide**”, “**protein**” and “**amino acid sequence**” are used interchangeably to refer to a polymer of amino acid residues. Unless specified, a polymer of amino acid residues can be any length. The term also applies to amino acid polymers in which one or more amino acids are chemical analogues or modified derivatives of corresponding naturally-occurring amino acids.

[0042] “**Prevention**” and any declension thereof refers to prophylactic and preventative measures, wherein the object is to reduce the chances that a subject will develop a given pathologic condition or disorder over a given period of time. Such a reduction may be reflected, *e.g.*, in a delayed onset of at least one symptom of the pathologic condition or disorder in the subject.

[0043] “**Subject**” or “**individual**” refers to an animal individual, preferably a mammalian individual, more preferably a human individual. In some embodiments, an individual may be a mammalian individual. Mammalians include, but are not limited to, all primates (human and non-human), cattle (including cows), horses, pigs, sheep, goats, dogs, cats, and any other mammal which is awaiting the receipt of, or is receiving medical care or was/is/will be the object of a medical procedure, or is monitored for the development of a disease or condition. In some embodiments, an individual may be a “**patient**”, *i.e.*, a warm-blooded animal, more preferably a human, who/which is awaiting the receipt of, or is receiving medical care or was/is/will be the object of a medical procedure, or is monitored for the development of a disease or condition. In some embodiments, the individual is an adult (*e.g.*, an individual above the age of 18). In some embodiments, the individual is a child (*e.g.*, an individual below the age of 18). In some embodiments, the individual is a male. In some embodiments, the individual is a female.

[0044] “**Therapeutically effective amount**” refers to the level or amount of an agent that is aimed at, without causing significant negative or adverse side effects to the target, (1) delaying or preventing the onset of the disease or condition; (2) slowing down or stopping the progression, aggravation, or deterioration of one or more symptoms of the disease or condition; (3) bringing about ameliorations of the symptoms of the disease or condition; (4) reducing the severity or incidence of the disease or condition; or (5) curing the disease or condition. A therapeutically effective amount may be administered prior to the onset of the disease or condition, for a prophylactic or preventive action. Alternatively, or additionally, the therapeutically effective amount may be administered after initiation of the disease or condition, for a therapeutic action.

[0045] “**Transfection**”, “**Transduction**” and any declension thereof, used herein interchangeably, refers to the introduction of one or several molecule(s) of interest, otherwise referred to as “cargo molecule”, such as nucleic acid molecules (DNA and/or RNA), proteins, peptides, drugs and the like, preferably nucleic acid molecules, into one or more cells, whether *in vitro* or *in vivo*. In other words, “transfection” or “transduction” refers to any method, technique or vehicle that facilitates or increases expression of a nucleic acid and/or polypeptide, *e.g.*, facilitates or increases cytoplasmic transduction of

a nucleic acid molecule or cargo, in particular by a viral vector such as a lentiviral vector, or a Viral Like Particle (VLP).

[0046] “**Treatment**”, “**alleviation**”, “**curation**” and any declensions thereof refer to a therapeutic treatment, excluding prophylactic or preventative measures; wherein the object is to slow down, lessen, stop or even reverse (either partially or totally) the evolution of a targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well those suspected to have the disorder. A subject is successfully “treated” for the targeted pathologic condition or disorder if, after receiving treatment, they show observable and/or measurable reduction in or absence of one or more symptoms associated with the pathologic condition or disorder; relief to some extent; reduced morbidity and/or mortality; and/or improvement in quality-of-life issues. The above parameters for assessing successful treatment and improvement in the disease are readily measurable by routine procedures familiar to a physician.

[0047] “**Viral-like particle**”, “**virus-like particle**” or “**VLP**” refer to a particle formed by structural viral proteins that have inherent property for self-assembling and mimicking the morphology of a native virus exhibiting a repetitive array of antigens. In contrast to viruses, VLPs are non-infectious and non-replicating because they lack the genetic material therefor. VLP may be used for the delivery of any cargo molecule, *e.g.*, peptide, polypeptide, protein, DNA, RNA, small molecules, and the like. In other words, “viral-like particle”, “virus-like particle” or “VLP” refer to a nonreplicating, viral shell, derived from any of several viruses. VLPs are generally composed of one or more viral proteins, such as, but not limited to those proteins referred to as capsid, coat, shell, surface and/or envelope proteins, or particle-forming polypeptides derived from these proteins. VLPs can form spontaneously upon recombinant expression of the protein in an appropriate expression system. Methods for producing particular VLPs are known in the art. The presence of VLPs following recombinant expression of viral proteins can be detected using conventional techniques known in the art, such as by electron microscopy, biophysical characterization, and the like. For example, VLPs can be isolated by density gradient centrifugation and/or identified by characteristic density banding. Alternatively, cryoelectron microscopy can be performed on vitrified aqueous samples of the VLP

preparation in question, and images recorded under appropriate exposure conditions. The VLP may be a retroviral VLP, preferably a lentiviral VLP. Typically, lentiviral VLPs are not replicative/noninfectious but allow the transduction of the payload in target cells. These lentiviral VLPs do carry lentiviral DNA which has been removed of pathogenic sequences and replicative potential.

[0048] “**Viral vector**” or “**virus vector**” refers to a modified virus or fragment thereof, that lacks the ability to infect and/or replicate. Viral vectors may be used for the delivery of any cargo molecule, *e.g.*, peptide, polypeptide, protein, DNA, RNA, small molecules, and the like. The viral vector may be obtained from any virus such as, non limitatively,

10 *Retroviridae* (*e.g.*, human immunodeficiency viruses , such as HIV - 1 (also referred to as HDTV - III, LAVE or HTLV - III /LAV, or HIV - III; and other isolates, such as HIV – LP); *Picornaviridae* (*e.g.*, polio viruses , hepatitis A virus; enteroviruses , human Cocksackie viruses, rhinoviruses, echoviruses); *Calciviridae* (*e.g.* strains that cause gastroenteritis) ; *Togaviridae* (*e.g.*, equine encephalitis viruses, rubella viruses) ;

15 *Flaviridae* (*e.g.*, dengue viruses, encephalitis viruses, yellow feversviruses) ; *Coronaviridae* (*e.g.*, coronaviruses); *Rhabdoviridae* (*e.g.*, vesicular stomatitis viruses, rabies viruses); *Filoviridae* (*e.g.* ebola viruses) ; *Paramyxoviridae* (*e.g.*, parainfluenza viruses , mumps virus , measles virus , respiratory syncytialvirus) ; *Orthomyxoviridae* (*e.g.*, influenza viruses) ; *Bunyaviridae* (*e.g.* Hantaan viruses, bunya viruses, phleboviruses and Nairo viruses) ; *Arenaviridae* (hemorrhagic feversviruses) ; *Reoviridae* (*e.g.*, reoviruses, orbiviruses and rotaviruses); *Birnaviridae* ; *Hepadnaviridae* (Hepatitis B virus); *Parvoviridae* (parvoviruses); *Papovaviridae* (papillomaviruses, polyoma viruses); *Herpesviridae* (herpes simplex virus (HSV) 1 and 2, varicella zoster virus, cytomegalovirus (CMV) , herpesvirus ; *Poxviridae* (variola viruses, vaccinia viruses,

25 poxviruses) ; and *Iridoviridae* (*e.g.*, African swine fever virus) ; and unclassified viruses (*e.g.*, the agent of delta hepatitis (thought to be a defective satellite of hepatitis B virus) , the agents of non - A , non - B hepatitis (class 1 = internally transmitted ; class 2 = parenterally transmitted (*i.e.*, Hepatitis C ; Norwalk and related viruses , and astroviruses). The viral vector may be a retroviral vector, preferably a lentiviral vector.

30 Typically, lentiviral vectors are not replicative/noninfectious but allow the transduction

of the payload in target cells. These lentiviral vectors do carry lentiviral DNA which has been removed of pathogenic sequences and replicative potential.

[0049] “**Pseudotyped**”, “**pseudotyped VLP**” or “**pseudotyped viral vector**”, as used herein, refers to a VLP or viral vector bearing polypeptides, *e.g.*, proteins or glycoproteins, derived from at least one virus having envelopes or a viral vector encoding envelope glycoproteins from a virus that is different or identical from the parental virus. The host range of the vector particles can thus be expanded or altered depending on the type of cell surface receptor used by the glycoprotein. For example, a VLP can be pseudotyped with an envelope protein from any virus, such as HIV. For example, an HIV lentiviral vector can have the HIV envelope glycoprotein be replaced with another virus’s glycoprotein, or *vice versa*. In some embodiment, the VLP or virus vector is pseudotyped with a modified or mutated envelope protein. In some embodiment, the VLP or viral vector is pseudotyped with a variant or mutant of *env* (GP160) from HIV. For this purpose, the term “HIV pseudotyped” means that the VLP or viral vector is pseudotyped with at least one polypeptide, protein, or glycoprotein, derived from the human immunodeficiency virus, such as GP160 or subunits composing thereof (*i.e.*, GP41 and GP120). Typically, GP160 is cleaved into two subunits (GP41 and GP120) which are assembled together and shuttled to the membrane.

20 DETAILED DESCRIPTION

[0050] The present invention relates to a pseudotyped viral-like particle (VLP) or viral vector that selectively targets CD4-positive cells, wherein said VLP or viral vector comprises an envelope protein comprising:

- a first protein comprising an amino acid sequence having at least one mutation compared to the amino acid sequence of sequence of SEQ ID NO: 1, and
- a second protein comprising an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 3, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, and SEQ ID NO: 39.

[0051] The present invention also relates to a pseudotyped viral-like particle (VLP) or viral vector that selectively targets CD4-positive cells, wherein said VLP or viral vector comprises an envelope protein comprising:

- 5 - a first protein comprising an amino acid sequence having at least one mutation compared to the amino acid sequence of sequence of SEQ ID NO: 1, wherein said at least one mutation is localized on the cytoplasmic domain of the first protein, and
- a second protein comprising an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 3.

10 [0052] In certain embodiments, the invention relates to a pseudotyped viral-like particle (VLP) or viral vector that selectively targets CD4-positive cells, wherein said VLP or viral vector comprises an envelope protein comprising a first protein comprising an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 2 and a second protein comprising an amino acid sequence having at least 70% sequence identity with
15 SEQ ID NO: 3. In certain embodiments, the invention relates to a pseudotyped viral-like particle (VLP) or viral vector that selectively targets CD4-positive cells, wherein said VLP or viral vector comprises an envelope protein comprising a first protein comprising an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 2 and a second protein comprising an amino acid sequence having at least 70% sequence identity
20 with SEQ ID NO: 3, wherein the amino acid sequence of the first protein is not SEQ ID NO: 1.

[0053] It will be obvious for the person skilled in the art that the expression “selectively targets CD4-positive cells” is intended to mean that the pseudotyped viral-like particle (VLP) or viral vector of the invention does not substantially target cells that do not express
25 the CD4 protein. In some embodiments, the expression “selectively targets CD4-positive cells” means that the VLP or viral vector transduces or transfects or transduces CD4-positive cells with less than 20%, 10%, 5%, 1%, 0.1%, 0.01%, or less, of off-target effect. In some embodiments, the expression “selectively targets CD4-positive cells” means that the VLP or viral vector transduces or transfects or transduces less than 20%, 10%, 5%,
30 1%, 0.1%, 0.01%, or less, of cells that do not express CD4 (*i.e.*, CD4-negative cells). In

some embodiments, the expression “selectively targets CD4-positive cells” means that the VLP or viral vector transduces or transfects or transduces at most 20%, 10%, 5%, 1%, 0.1%, 0.01%, or less, of cells that do not express CD4 (*i.e.*, CD4-negative cells). In some
5 embodiments, the expression “selectively targets CD4-positive cells” means that the population of cells transduced or transfected by the VLP or viral vector comprises more than 80%, 90%, 95%, 99%, 99.9%, 99.99%, or more, of CD4-positive cells.

[0054] Methods to measure gene expression, at nucleic acid level and/or at protein level, are well known in the art and readily accessible to the person skilled in the art. Non-limitative examples of methods to measure gene expression at the nucleic acid level
10 include quantitative PCR (qPCR), Northern blotting, RNA sequencing (RNA-Seq), and in situ hybridization (ISH). Non-limitative examples of methods to measure gene expression at the protein level include methods such as Western blotting, Enzyme-linked immunosorbent assays (ELISA), Mass spectrometry, immunohistochemistry (IHC) and immunofluorescence.

15 [0055] In a preferred embodiment, the envelope protein or the modified envelope protein is a fusogen. Hence, in the present disclosure, the “envelope protein” or “modified envelope protein” may be interchangeably referred to as the “fusogen”.

[0056] In one embodiment, the invention relates to a pseudotyped VLP. In another embodiment, the invention relates to a pseudotyped viral vector.

20 [0057] The present invention also relates to a pseudotyped viral-like particle (VLP) or viral vector that selectively targets CD4-positive cells, wherein said VLP or viral vector comprises a modified envelope protein comprising:

- 25 - a mutant glycoprotein 41 (GP41) comprising an amino acid sequence having at least one mutation compared to the amino acid sequence of sequence of SEQ ID NO: 1, wherein said at least one mutation is localized on the cytoplasmic domain of the mutant glycoprotein 41 (GP41), and
- a glycoprotein 120 (GP120) comprising an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 3,

wherein the envelope protein does not comprise or consists of an amino acid sequence as set forth in SEQ ID NO: 95.

- [0058] The present invention also relates to a pseudotyped viral-like particle (VLP) or viral vector that selectively targets CD4-positive cells, wherein said VLP or viral vector
- 5 comprises a modified envelope protein comprising:
- a mutant glycoprotein 41 (GP41) comprising an amino acid sequence having at least one mutation compared to the amino acid sequence of sequence of SEQ ID NO: 1, wherein said at least one mutation is localized on the cytoplasmic domain of the mutant glycoprotein 41 (GP41), and
 - 10 - a glycoprotein 120 (GP120) comprising an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 3.

[0059] The present invention also relates to a pseudotyped viral-like particle (VLP) or viral vector that selectively targets CD4-positive cells, wherein said viral VLP or viral vector comprises a modified envelope protein comprising:

- 15 - a mutant glycoprotein 41 (GP41) comprising at least one mutation of the cytoplasmic domain, wherein said mutant GP41 comprises an amino acid sequence having at least 70% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 2 , SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID
- 20 NO: 12, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, and SEQ ID NO: 26, and
- a glycoprotein 120 (GP120) second protein comprising an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 3.

- [0060] The present invention also relates to a pseudotyped viral-like particle (VLP) or
- 25 viral vector that selectively targets CD4-positive cells, wherein said viral VLP or viral vector comprises a modified envelope protein having an amino acid sequence having at least 70% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 27, SEQ ID

NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 81, and SEQ ID NO: 87, wherein the envelope protein does not comprise or consists
5 of an amino acid sequence as set forth in SEQ ID NO: 95.

[0061] The present invention also relates to a pseudotyped viral-like particle (VLP) or viral vector that selectively targets CD4-positive cells, wherein said viral VLP or viral vector comprises a modified envelope protein having an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID
10 NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 81, and SEQ ID NO: 87. The present invention also relates to a
15 pseudotyped viral-like particle (VLP) or viral vector that selectively targets CD4-positive cells, wherein said viral VLP or viral vector is pseudotyped a modified envelope protein having an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID
20 NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 81, and SEQ ID NO: 87.

[0062] The present invention also relates to a pseudotyped viral-like particle (VLP) or viral vector that selectively targets CD4-positive cells, wherein said viral VLP or viral
25 vector comprises a modified envelope protein having an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 76, and SEQ ID NO: 77.

[0063] The present invention also relates to a pseudotyped viral-like particle (VLP) or viral vector that selectively targets CD4-positive cells, wherein said viral VLP or viral
30 vector comprises a modified fusogen having an amino acid sequence selected from the

group consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 81, and SEQ ID NO: 87, preferably selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 76, and SEQ ID NO: 77.

[0064] The present invention also relates to a pseudotyped viral vector that selectively targets CD4-positive cells, wherein said VLP or viral vector comprises a modified envelope protein comprising:

- a mutant glycoprotein 41 (GP41) comprising an amino acid sequence having at least one mutation compared to the amino acid sequence of sequence of SEQ ID NO: 1, wherein said at least one mutation is localized on the cytoplasmic domain of the mutant glycoprotein 41 (GP41), and
- a glycoprotein 120 (GP120) comprising an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 3,

wherein the envelope protein does not comprise or consists of an amino acid sequence as set forth in SEQ ID NO: 95.

[0065] The present invention also relates to a pseudotyped viral vector that selectively targets CD4-positive cells, wherein said VLP or viral vector comprises a modified envelope protein comprising:

- a mutant glycoprotein 41 (GP41) comprising an amino acid sequence having at least one mutation compared to the amino acid sequence of sequence of SEQ ID NO: 1, wherein said at least one mutation is localized on the cytoplasmic domain of the mutant glycoprotein 41 (GP41), and
- a glycoprotein 120 (GP120) comprising an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 3.

[0066] The present invention also relates to a pseudotyped viral vector that selectively targets CD4-positive cells, wherein said viral VLP or viral vector comprises a modified envelope protein comprising:

- 5 - a mutant glycoprotein 41 (GP41) comprising at least one mutation of the cytoplasmic domain, wherein said mutant GP41 comprises an amino acid sequence having at least 70% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, and SEQ ID NO: 26, and
- 10 - a glycoprotein 120 (GP120) second protein comprising an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 3.

[0067] The present invention also relates to a pseudotyped viral vector that selectively targets CD4-positive cells, wherein said viral VLP or viral vector comprises a modified envelope protein having an amino acid sequence having at least 70% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 81, and SEQ ID NO: 87, wherein the envelope protein does not comprise or consists of an amino acid sequence as set forth in SEQ ID NO: 95.

[0068] The present invention also relates to a pseudotyped viral vector that selectively targets CD4-positive cells, wherein said viral VLP or viral vector comprises a modified envelope protein having an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID

NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 81, and SEQ ID NO: 87. NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 81, and SEQ ID NO: 87.

[0069] The present invention also relates to a pseudotyped viral vector that selectively targets CD4-positive cells, wherein said viral VLP or viral vector comprises a modified envelope protein having an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 76, and SEQ ID NO: 77.

[0070] The present invention also relates to a pseudotyped viral vector that selectively targets CD4-positive cells, wherein said viral VLP or viral vector comprises a modified fusogen having an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 81, and SEQ ID NO: 87, preferably selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 76, and SEQ ID NO: 77.

[0071] The present invention also relates to a pseudotyped retroviral-like particle (VLP) or retroviral vector, preferably a pseudotyped lentiviral-like particle (VLP) or lentiviral

vector, that selectively targets CD4-positive cells, wherein said retroviral VLP or retroviral vector comprises a modified envelope protein comprising:

- a mutant glycoprotein 41 (GP41) comprising an amino acid sequence having at least one mutation compared to the amino acid sequence of sequence of SEQ ID NO: 1, wherein said at least one mutation is localized on the cytoplasmic domain of the mutant glycoprotein 41 (GP41), and
- a glycoprotein 120 (GP120) comprising an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 3.

[0072] The present invention also relates to a pseudotyped retroviral viral-like particle (VLP) or retroviral vector, preferably a pseudotyped lentiviral-like particle (VLP) or lentiviral vector, that selectively targets CD4-positive cells, wherein said retroviral VLP or retroviral vector comprises a modified envelope protein comprising:

- a mutant glycoprotein 41 (GP41) comprising at least one mutation of the cytoplasmic domain, wherein said mutant GP41 comprises an amino acid sequence having at least 70% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, and SEQ ID NO: 26, and
- a glycoprotein 120 (GP120) second protein comprising an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 3.

[0073] The present invention also relates to a pseudotyped retroviral viral-like particle (VLP) or retroviral vector that selectively targets CD4-positive cells, wherein said retroviral VLP or retroviral vector comprises a modified envelope protein having an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 59, SEQ ID NO: 61,

SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 81, and SEQ ID NO: 87.

[0074] The present invention also relates to a pseudotyped retroviral viral-like particle (VLP) or retroviral vector that selectively targets CD4-positive cells, wherein said retroviral VLP or retroviral vector comprises a modified envelope protein having an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 76, and SEQ ID NO: 77.

[0075] The present invention also relates to a pseudotyped retroviral viral-like particle (VLP) or retroviral vector that selectively targets CD4-positive cells, wherein said retroviral VLP or retroviral vector comprises a modified fusogen having an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 81, and SEQ ID NO: 87, preferably selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 76, and SEQ ID NO: 77.

[0076] The present invention also relates to a pseudotyped retroviral-like particle (VLP) or retroviral vector that selectively targets CD4-positive cells, wherein said retroviral VLP or retroviral vector comprises a modified envelope protein comprising:

- a mutant glycoprotein 41 (GP41) comprising an amino acid sequence having at least one mutation compared to the amino acid sequence of sequence of SEQ ID NO: 1, wherein said at least one mutation is localized on the cytoplasmic domain of the mutant glycoprotein 41 (GP41), and
- a glycoprotein 120 (GP120) comprising an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 3.

[0077] The present invention also relates to a pseudotyped lentiviral vector that selectively targets CD4-positive cells, wherein said retroviral VLP or retroviral vector comprises a modified envelope protein comprising:

- 5 - a mutant glycoprotein 41 (GP41) comprising at least one mutation of the cytoplasmic domain, wherein said mutant GP41 comprises an amino acid sequence having at least 70% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, and SEQ ID NO: 26, and
- 10 - a glycoprotein 120 (GP120) second protein comprising an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 3.

[0078] The present invention also relates to a pseudotyped lentiviral vector that selectively targets CD4-positive cells, wherein said retroviral VLP or retroviral vector
15 comprises a modified envelope protein having an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 81, and SEQ ID NO: 87.

[0079] The present invention also relates to a pseudotyped lentiviral vector that selectively targets CD4-positive cells, wherein said retroviral VLP or retroviral vector comprises a modified envelope protein having an amino acid sequence selected from the
25 group consisting of SEQ ID NO: 5, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 76, and SEQ ID NO: 77.

[0080] The present invention also relates to a pseudotyped lentiviral vector that selectively targets CD4-positive cells, wherein said retroviral VLP or retroviral vector comprises a modified fusogen having an amino acid sequence selected from the group

consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 81, and SEQ ID NO: 87, preferably selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 76, and SEQ ID NO: 77.

[0081] The present invention also relates to a pseudotyped viral-like particle (VLP) or viral vector that selectively targets CD4-positive cells, wherein said VLP or viral vector is pseudotyped with a modified envelope protein comprising:

- a mutant glycoprotein 41 (GP41) comprising an amino acid sequence having at least one mutation compared to the amino acid sequence of sequence of SEQ ID NO: 1, wherein said at least one mutation is localized on the cytoplasmic domain of the mutant glycoprotein 41 (GP41), and
- a glycoprotein 120 (GP120) comprising an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 3,

wherein the envelope protein does not comprise or consists of an amino acid sequence as set forth in SEQ ID NO: 95.

[0082] The present invention also relates to a pseudotyped viral-like particle (VLP) or viral vector that selectively targets CD4-positive cells, wherein said VLP or viral vector is pseudotyped with a modified envelope protein comprising:

- a mutant glycoprotein 41 (GP41) comprising an amino acid sequence having at least one mutation compared to the amino acid sequence of sequence of SEQ ID NO: 1, wherein said at least one mutation is localized on the cytoplasmic domain of the mutant glycoprotein 41 (GP41), and
- a glycoprotein 120 (GP120) comprising an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 3.

[0083] In some embodiments, the pseudotyped retroviral viral-like particle (VLP) or retroviral vector is a HIV-pseudotyped VLP or viral vector.

[0084] Provided herein are pseudotyped VLP and viral vectors. In the present disclosure, they may be simply referred to as “VLP and viral vectors”, however it will be understood
5 that the pseudotyping is an essential feature of the invention, therefore the term refers to pseudotyped VLP and pseudotyped viral vectors. Hence, it will be apparent that the expression “a pseudotyped viral-like particle (VLP) or viral vector” refers to a pseudotyped VLP or a pseudotyped viral vector.

[0085] The inventors surprisingly demonstrated that pseudotyping VLP or viral vectors
10 with a modified envelop protein comprising at least one mutation localized on its cytoplasmic domain increases the transduction efficiency of the VLP or viral vectors, and increases cell selectivity for such transductions.

[0086] In certain embodiments the VLP or viral vector of the invention are enveloped viral particles. In some embodiments, the VLP or viral vector comprise a glycoprotein
15 derived from an envelope glycoprotein of a virus, or a mutant thereof, or a variant thereof, and/or a fragment thereof.

[0087] In some embodiments, the VLP or viral vector of the invention is a particle composed of structural viral proteins with an ability to self-assemble and replicate the morphology of a native virus, displaying a repetitive array of antigens. In some
20 embodiments, the VLP or viral vector of the invention is non-infectious and non-replicating. In some embodiments, the VLP or viral vector of the invention is a modified virus or its fragment lacking the ability to infect and/or replicate.

[0088] In some embodiments, the VLP or viral vector of the invention comprises or consists of a nonreplicating viral shell, or is derived from different viruses, or comprises
25 or consists of viral components or variants or mutants or fragments thereof, such as structural components. In some embodiments, the VLP or viral vector of the invention comprises or consists of one or more viral proteins selected from the group comprising or consisting of capsid, coat, shell, surface, and/or envelope proteins, or particle-forming polypeptides derived from these proteins. In some embodiments, the VLP or viral vector

of the invention can be derived from various viruses, including but not limited to Retroviridae (e.g., human immunodeficiency viruses like HIV-1), Picornaviridae (e.g., polio viruses, hepatitis A virus), Calciviridae (e.g., strains causing gastroenteritis), Togaviridae (e.g., equine encephalitis viruses, rubella viruses), Flaviridae (e.g., dengue
5 viruses, yellow fever viruses), Coronaviridae (e.g., coronaviruses), Rhabdoviridae (e.g., vesicular stomatitis viruses, rabies viruses), Filoviridae (e.g., Ebola viruses), Paramyxoviridae (e.g., parainfluenza viruses, mumps virus, measles virus), Orthomyxoviridae (e.g., influenza viruses), Bunyaviridae (e.g., Hantaan viruses, bunya
10 viruses, phleboviruses, and Nairoviruses), Arenaviridae (hemorrhagic fever viruses), Reoviridae (e.g., reoviruses, orbiviruses, and rotaviruses), Birnaviridae, Hepadnaviridae (Hepatitis B virus), Parvoviridae (parvoviruses), Papovaviridae (papillomaviruses, polyoma viruses), Herpesviridae (herpes simplex virus 1 and 2, varicella-zoster virus, cytomegalovirus), Poxviridae (variola viruses, vaccinia viruses, poxviruses), Iridoviridae (e.g., African swine fever virus), and unclassified viruses (e.g., the agent of delta hepatitis,
15 thought to be a defective satellite of hepatitis B virus, agents of non-A, non-B hepatitis, including Hepatitis C, Norwalk and related viruses, and astroviruses).

[0089] In some embodiments, the VLP or viral vector of the invention can be utilized for delivering various cargo molecules, such as peptides, polypeptides, proteins, DNA, RNA, small molecules, and the like.

20 [0090] In some embodiments, the VLP or viral vector of the invention can spontaneously form through recombinant expression of the protein in a suitable expression system. Established methods for producing specific VLPs are known in the art, and the presence of VLPs can be detected using standard techniques like electron microscopy and biophysical characterization, isolation can be achieved through density gradient
25 centrifugation, and identification can be done via characteristic density banding or cryoelectron microscopy on vitrified aqueous samples.

[0091] In some embodiments, the VLP or viral vector is a retroviral VLP or retroviral vector. In some embodiments, the VLP or viral vector is a lentiviral VLP or lentiviral vector. In some embodiments, the VLP or viral vector is a recombinant lentivirus. It will
30 be understood that a “retroviral VLP” or “retroviral vector” refers to a VLP or vector

derived from a retrovirus, *i.e.*, comprising at least one structural and/or functional element of a retrovirus. Likewise, a “lentiviral VLP” or “lentiviral vector” refers to a VLP or vector derived from a lentivirus, *i.e.*, comprising at least one structural and/or functional element of a lentivirus.

- 5 [0092] In some embodiments, the VLP or viral vector is a HIV-derived VLP or HIV-derived vector.

[0093] In some embodiments, VLP or viral vector is not selected from the group comprising or consisting of vaccinia Ankara VLP or vectors, modified vaccinia Ankara (MVA) VLP or vectors, murine leukemia virus (MuLV) VLP or vectors, and vesicular
10 stomatitis virus VLP or vectors.

[0094] In some embodiments, the VLP or viral vector is an engineered or modified VLP or viral vector.

[0095] In some embodiments, the envelope protein is derived from any enveloped virus, preferably the envelope protein is modified or mutated. In some embodiments, the
15 envelope protein is derived from an HIV envelope protein (env), or part thereof. In a preferred embodiment, the envelope protein comprises a modified or mutated HIV envelope protein, or part thereof, preferably the envelope protein is a modified or mutated HIV envelope protein, or part thereof. In some embodiments, the envelope protein is not from vaccinia Ankara, murine leukemia virus, or vesicular stomatitis virus.

20 [0096] In some embodiments, the envelope protein is a glycoprotein. In some embodiments, the first protein and the second protein are glycoproteins. In some embodiments, the first protein and the second protein are viral glycoproteins.

[0097] In some embodiments, the first protein and the second protein are subunits of the envelope protein. In some embodiments, the envelope protein comprises the first protein
25 and the second protein. In certain embodiments, the envelope protein comprises one or more additional proteins. In some embodiments, the envelope protein consists of the first protein and the second protein. In some embodiments, the envelope protein may be cleaved into the first protein and the second protein, and optionally into one or more

additional proteins. In some embodiments, the envelope protein is a mutant or variant of GP160, preferably a mutant or variant of GP160 from HIV, wherein the first protein is a mutant or variant of GP41, preferably a mutant or variant of GP41 from HIV, and wherein the second protein is GP120, preferably GP120 from HIV, optionally mutated GP120.

5 [0098] In some embodiments, the first protein is glycoprotein 41 (GP41), or a variant, mutant and/or fragment thereof. In a preferred embodiment, the first protein is a variant, mutant and/or fragment of GP41.

[0099] In some embodiments, the first protein is a modified or mutant GP41 comprising at least one mutation compared to the wild-type amino acid sequence of GP41. The person skilled in the art knows that various isolates of GP41 exist, such as isolate HXB2. Wild-type GP41 isolate HXB2 typically has the amino acid sequence as set forth in SEQ ID NO: 1.

	SEQ ID NO: 1
15	AVGIGALFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQNNLLRAIEAQQH LLQLTVWGIKQLQARILAVEYLKDDQLLGIWGC SGKLICTTAVPWNASWSNK SLEQIWNHTTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLW NWFNITNWLWYIKLFIMIVGGLVGLRIVFAVLSIVNRVRQGYSPLSFQTHLPTPR GPDRPEGIEEEGGERDRDRSIRLVNGSLALIWDDLRLCLFSYHRLRDL LLIVTRI VELLGRRGWEALKYWWNLLQYWSQELKNSAVSLLNATAIAVAEGTDRVIEVV 20 QGACRAIRHIPRRIRQGLERILL

[0100] Hence, in some embodiments, the amino acid sequence of the first protein comprises at least one mutation compared to the amino acid sequence as set forth in SEQ ID NO: 1. Therefore, in some embodiments, the amino acid sequence of the first protein is not SEQ ID NO: 1. In some embodiments, the amino acid sequence of the first protein is not the sequence of wild-type GP41.

[0101] As used herein, “at least one” means 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more.

[0102] As used herein, the term “mutation” is meant to broadly encompass all types of mutations in a sequence, preferably an amino acid sequence. Non-limitative examples of mutations include a substitution, a deletion, an insertion, an inversion, or a truncation. The mutation may affect 1, 2, 3, 4 or more amino acids; alternatively, the mutation may
5 a large number of amino acids (*e.g.*, an epitope, a domain, etc.). Illustratively, the mutation may be one or more amino acid substitution, one or more deletion, one or more insertion, one or more truncation, or combinations thereof.

[0103] In some embodiments, the at least one mutation is a substitution, a deletion, an insertion, an inversion, a truncation (*e.g.*, caused by the introduction of a stop codon in
10 the coding nucleic acid sequence), or a combination thereof. In some embodiments, the at least one mutation is one or more amino acid substitution, one or more deletion, one or more insertion, one or more truncation, or combinations thereof.

[0104] In a preferred embodiment, the at least one mutation is localized on the cytoplasmic domain of the first protein. Hence, in some embodiments, the first protein is
15 a modified or mutant GP41 comprising at least one mutation, modification or alteration of the cytoplasmic domain. In some embodiments, the first protein comprises an amino acid sequence having at least one mutation compared to the amino acid sequence of sequence of SEQ ID NO: 1, wherein said at least one mutation is localized on the cytoplasmic domain of the first protein.

20 [0105] As used herein, the term “cytoplasmic domain” is interchangeable with the term “cytoplasmic tail”.

[0106] In some embodiments, the first protein is a modified or mutant GP41 comprising at least one mutation of the cytoplasmic domain. In some embodiments, the first protein is a modified or mutant GP41 comprising a partial or complete truncation of the
25 cytoplasmic domain. In some embodiments, the first protein is a modified or mutant GP41 comprising a partial truncation of the cytoplasmic domain. In some embodiments, the first protein is a modified or mutant GP41 comprising a complete truncation of the cytoplasmic domain. In some embodiments, the first protein is a modified or mutant GP41 comprising one or more amino acid substitution, insertion and/or deletion substitution on

the cytoplasmic domain. In some embodiments, the first protein is a modified or mutant GP41 comprising a partial truncation of the cytoplasmic domain and one or more amino acid substitution, insertion and/or deletion substitution on the cytoplasmic domain. In some embodiments, the first protein comprises a mutation on the endocytosis motif.

- 5 [0107] It will be understood that the Applicant provides herein mutants or variants of GP41. It was surprisingly found by the Applicant that VLPs or viral vectors pseudotyped with mutants or variants of GP41 enabled improved transfection or transduction efficacy than VLPs or viral vectors pseudotyped with wild-type GP41.

[0108] In some embodiments, the first protein comprises or consists of an amino acid
10 sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group comprising or consisting of SEQ ID NO: 2 , SEQ ID NO: 6, SEQ ID NO:
15 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, and SEQ ID NO: 26.

[0109] In some embodiments, the first protein comprises or consists of an amino acid
20 sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group comprising or consisting of SEQ ID NO: 2 , SEQ ID NO: 6, SEQ ID NO: 9, SEQ ID NO: 20, and SEQ ID NO: 23.

25 [0110] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected

from the group comprising or consisting of SEQ ID NO: 2 , SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12.

[0111] In some embodiments, the first protein comprises or consists of an amino acid
5 sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80
%, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected
10 NO: 9.

[0112] Table 1: GP41 mutants

GP41 mutant	SEQ ID NO:
GP41 TM1 (<i>i.e.</i> , GP41 +SIV Y712I Δ139)	2
GP41 WT (isolate HXB2) Δ147	6
GP41 WT (isolate HXB2) Δ139	8
GP41 WT (isolate HXB2) Y712I	9
GP41 WT (isolate HXB2) Y712I Δ139	10
GP41WT (isolate HXB2) +SIV	11
GP41 WT (isolate HXB2) +SIV Y712I	12
GP41WT (isolate HXB2) +SIV Δ139	13

5

SEQ ID NO: 2

AVGIGAVFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQNNLLRAIEAQQQ
LLKLTVWGIKQLQARVLAVERYLKDQQLGIWGCSGKLICTTNVPWNTSWSN
KSMHQIWDNMTWMQWEREIDNYTGLIYSLIEESQNQQEKNEQELLALDEWAS
LWNWFDITKWLWYIKIFIMIVGGLIGLRIVFTVLSIVNRVRQGIRPVFSSPPSYF

10

SEQ ID NO: 6

AVGIGALFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQNNLLRAIEAQQH
LLQLTVWGIKQLQARILAVERYLKDQQLGIWGCSGKLICTTAVPWNASWSNK
SLEQIWNHTTWMEWDREINNYTSLIHSLEESQNQQEKNEQELLELDKWASLW
NWFNITNWLWYIKLFIMIVGGLVGLRIVFAVLSIVNRVR

15

SEQ ID NO: 7

AVGIGALFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQNNLLRAIEAQQH
LLQLTVWGIKQLQARILAVERYLKDQQLGIWGCSGKLICTTAVPWNASWSNK
SLEQIWNHTTWMEWDREINNYTSLIHSLEESQNQQEKNEQELLELDKWASLW
NWFNITNWLWYIKLFIMIVGGLVGLRIVFAVLSIVNRVRKGYSPLSF

20

SEQ ID NO: 8

AVGIGALFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQNNLLRAIEAQQH
LLQLTVWGIKQLQARILAVERYLKDQQLGIWGCSGKLICTTAVPWNASWSNK
SLEQIWNHTTWMEWDREINNYTSLIHSLEESQNQQEKNEQELLELDKWASLW
NWFNITNWLWYIKLFIMIVGGLVGLRIVFAVLSIVNRVRKGISPLSFQTRLPTPR
GPDRPGGIEEEGGERDRDTS DPLVTGFLALIWVDLRSFLYSYHHLRDFLLIVAR

IVELLGRRGWEALKYWWNLLQYWSQELKSSAVSLLNATAIAVAEGTDRIIEVV
QRTCRAILHIPRRIRQGLERALQ

SEQ ID NO: 9

5 AVGIGALFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQNNLLRAIEAQQH
LLQLTVWGIKQLQARILAVEYLKDQQLGIWGCSGKLICTTAVPWNASWSNK
SLEQIWNHTTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLW
NWFNITNWLWYIKLFIMIVGGLVGLRIVFAVLSIVNRVRKGISPLSF

SEQ ID NO: 10

10 AVGIGALFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQNNLLRAIEAQQH
LLQLTVWGIKQLQARILAVEYLKDQQLGIWGCSGKLICTTAVPWNASWSNK
SLEQIWNHTTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLW
NWFNITNWLWYIKLFIMIVGGLVGLRIVFAVLSIVNRVRQGYRPVFSSPPSYFQT
15 RLPTPRGPDRPGGIEEEGGERDRDTS DPLVTGFLALIWVDLRSFLYSYHHLRDF
LLIVARIVELLGRRGWEALKYWWNLLQYWSQELKSSAVSLLNATAIAVAEGTD
RIIEVVQRTCRAILHIPRRIRQGLERALQ

SEQ ID NO: 11

20 AVGIGALFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQNNLLRAIEAQQH
LLQLTVWGIKQLQARILAVEYLKDQQLGIWGCSGKLICTTAVPWNASWSNK
SLEQIWNHTTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLW
NWFNITNWLWYIKLFIMIVGGLVGLRIVFAVLSIVNRVRQGIRPVFSSPPSYFQT
RLPTPRGPDRPGGIEEEGGERDRDTS DPLVTGFLALIWVDLRSFLYSYHHLRDF
25 LLIVARIVELLGRRGWEALKYWWNLLQYWSQELKSSAVSLLNATAIAVAEGTD
RIIEVVQRTCRAILHIPRRIRQGLERALQ

SEQ ID NO: 12

AVGIGALFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQNNLLRAIEAQQH
LLQLTVWGIKQLQARILAVEYLKDQQLLGIWGC SGKLICTTAVPWNASWSNK
SLEQIWNHTTWMEWDREINNYTSLIHS LIEESQNQQEKNEQELLELDKWASLW
NWFNITNWLWYIKLFIMIVGGLVGLRIVFAVLSIVNRVRQGYRPVFSSPPSYF

[0113] In some embodiments, the first protein comprises or consists of an amino acid sequence having one or more of the following mutations:

- an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the first protein, preferably 13 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 35;
- a deletion of the last 147 amino acids relative to the amino acid numbering of SEQ ID NO: 1;
- a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 1;
- a substitution at position 201, preferably a substitution at position Y201, more preferably a tyrosine to isoleucine substitution (Y201I), relative to the amino acid sequence of SEQ ID NO: 1; or
- any combination thereof.

SEQ ID NO: 34

QGYRPVFSSPPSY

SEQ ID NO: 35

QGIRPVFSSPPSY

- [0114] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group comprising SEQ ID NO: 2, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12, and comprises or consists of an amino acid sequence having one or more of the following mutations:
- an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the first protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 35;
 - a deletion of the last 147 amino acids relative to the amino acid numbering of SEQ ID NO: 1;
 - a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 1;

- a substitution at position 201, preferably a substitution at position Y201, more preferably a tyrosine to isoleucine substitution (Y201I), relative to the amino acid sequence of SEQ ID NO: 1; or
- any combination thereof.

5 [0115] In some embodiments, the first protein has the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12. In some embodiments, the first protein has the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 6, and SEQ ID NO: 9.

10 [0116] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 2.

15 [0117] In some embodiments, the first protein comprises one or more of the following mutations:

20 - an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the first protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 35;

25 - a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 1; or

- a substitution at position 201, preferably a substitution at position Y201, more preferably a tyrosine to isoleucine substitution (Y201I), relative to the amino acid sequence of SEQ ID NO: 1.

[0118] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 2, and comprises one or more of the following mutations:

- 10 - an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the first protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %,
15 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 35;
- 20 - a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 1; or
- a substitution at position 201, preferably a substitution at position Y201, more preferably a tyrosine to isoleucine substitution (Y201I), relative to the amino acid sequence of SEQ ID NO: 1.

[0119] In some embodiments, the first protein has the amino acid sequence of SEQ ID NO: 2.

[0120] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 2, and comprises one or more of the following mutations:

94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 6.

[0121] In some embodiments, the first protein comprises a deletion of the last 147 amino acids relative to the amino acid numbering of SEQ ID NO: 1.

- 5 [0122] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 6, and comprises
10 a deletion of the last 147 amino acids relative to the amino acid numbering of SEQ ID NO: 1.

[0123] In some embodiments, the first protein has the amino acid sequence of SEQ ID NO: 6.

- [0124] In some embodiments, the first protein comprises or consists of an amino acid
15 sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 7.

- [0125] In some embodiments, the first protein comprises a deletion of the last 139 amino
20 acids relative to the amino acid numbering of SEQ ID NO: 1.

- [0126] In some embodiments, the first protein comprises or consists of an amino acid
sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 7, and comprises
25 a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 1.

[0127] In some embodiments, the first protein has the amino acid sequence of SEQ ID NO: 7.

[0128] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80
5 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 8.

[0129] In some embodiments, the first protein comprises a substitution at position 201, preferably a substitution at position Y201, more preferably a tyrosine to isoleucine
10 substitution (Y201I), relative to the amino acid sequence of SEQ ID NO: 1.

[0130] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80
%, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 8, and comprises
15 a substitution at position 201, preferably a substitution at position Y201, more preferably a tyrosine to isoleucine substitution (Y201I), relative to the amino acid sequence of SEQ ID NO: 1.

[0131] In some embodiments, the first protein has the amino acid sequence of SEQ ID
20 NO: 8.

[0132] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80
%, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 9.
25

[0133] In some embodiments, the first protein comprises one or more of the following mutations:

- a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 1;
- a substitution at position 201, preferably a substitution at position Y201, more preferably a tyrosine to isoleucine substitution (Y201I), relative to the amino acid sequence of SEQ ID NO: 1.

[0134] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 9, and comprises one or more of the following mutations:

- a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 1;
- a substitution at position 201, preferably a substitution at position Y201, more preferably a tyrosine to isoleucine substitution (Y201I), relative to the amino acid sequence of SEQ ID NO: 1.

[0135] In some embodiments, the first protein has the amino acid sequence of SEQ ID NO: 9.

[0136] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 10.

[0137] In some embodiments, the first protein comprises an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the first protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95

%, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34.

- 5 [0138] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 10, and comprises
- 10 an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the first protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34.
- 15

- [0139] In some embodiments, the first protein has the amino acid sequence of SEQ ID NO: 10.
- 20

- [0140] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 11.
- 25

[0141] In some embodiments, the first protein comprises one or more of the following mutations:

- an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the first protein, preferably

14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 35;

- a substitution at position 201, preferably a substitution at position Y201, more preferably a tyrosine to isoleucine substitution (Y201I), relative to the amino acid sequence of SEQ ID NO: 1.

[0142] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 11, and comprises one or more of the following mutations:

- an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the first protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 35;
- a substitution at position 201, preferably a substitution at position Y201, more preferably a tyrosine to isoleucine substitution (Y201I), relative to the amino acid sequence of SEQ ID NO: 1.

[0143] In some embodiments, the first protein has the amino acid sequence of SEQ ID NO: 11.

[0144] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80
5 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 12.

[0145] In some embodiments, the first protein comprises one or more of the following mutations:

- 10 - an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the first protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1
15 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34;
- 20 - a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 1.

[0146] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 12, and comprises
25 one or more of the following mutations:

- an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the first protein, preferably

- 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34;
- 5
- a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 1.
- 10 [0147] In some embodiments, the first protein has the amino acid sequence of SEQ ID NO: 12.
- [0148] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group comprising or consisting of SEQ ID NO: 2, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, and SEQ ID NO: 26.
- 15
- 20 [0149] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group comprising or consisting of SEQ ID NO: 2, SEQ ID NO: 20, and SEQ ID NO: 23.
- 25

[0150] Table 2: GP41 mutants

GP41 mutant	SEQ ID NO:
GP41 R3A Δ147	20
GP41 R3A Δ139	21
GP41 R3A Y712I	22
GP41 R3A Y712I Δ139	23
GP41 R3A +SIV	24
GP41 R3A +SIV Y712I	25
GP41 R3A +SIV Δ139	26

5

SEQ ID NO: 20

AVGIGAVFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQNNLLRAIEAQQQ
LLKLTVWGIKQLQARVLAVERYLKDQQLLGIWGCSGKLICTTNVPWNTSWSN
KSMHQIWDNMTWMQWEREIDNYTGLIYSLIEESQNQQEKNEQELLALDEWAS
LWNWFDITKWLWYIKIFIMIVGGLIGLRIVFTVLSIVNRVR

10

SEQ ID NO: 21

AVGIGAVFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQNNLLRAIEAQQQ
LLKLTVWGIKQLQARVLAVERYLKDQQLLGIWGCSGKLICTTNVPWNTSWSN
KSMHQIWDNMTWMQWEREIDNYTGLIYSLIEESQNQQEKNEQELLALDEWAS
LWNWFDITKWLWYIKIFIMIVGGLIGLRIVFTVLSIVNRVRKGYSPLSF

5 **SEQ ID NO: 22**

AVGIGAVFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQNNLLRAIEAQQQ
LLKLTVWGIKQLQARVLAVERYLKDQQLGIWGCSGKLICTTNVPWNTSWSN
KSMHQIWDNMTWMQWEREIDNYTGLIYSLIEESQNQQEKNEQELLALDEWAS
LWNWFDITKWLWYIKIFIMIVGGLIGLRIVFTVLSIVNRVRKGISPLSFQTRLPTP
RGPDRPGGIEEEGGERDRDTS DPLVTGFLALIWVDLRSLFLYSYHHLRD FLLIVA
RIVELLGRRGWEALKYWWNLLQYWSQELKSSAVSLLNATAIAVAEGTDRIIEV
VQRTCRAILHIPRRIRQGLERALQ

10 **SEQ ID NO: 23**

AVGIGAVFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQNNLLRAIEAQQQ
LLKLTVWGIKQLQARVLAVERYLKDQQLGIWGCSGKLICTTNVPWNTSWSN
KSMHQIWDNMTWMQWEREIDNYTGLIYSLIEESQNQQEKNEQELLALDEWAS
LWNWFDITKWLWYIKIFIMIVGGLIGLRIVFTVLSIVNRVRKGISPLSF

15

20 **SEQ ID NO: 24**

AVGIGAVFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQNNLLRAIEAQQQ
LLKLTVWGIKQLQARVLAVERYLKDQQLGIWGCSGKLICTTNVPWNTSWSN
KSMHQIWDNMTWMQWEREIDNYTGLIYSLIEESQNQQEKNEQELLALDEWAS
LWNWFDITKWLWYIKIFIMIVGGLIGLRIVFTVLSIVNRVRQGYRPVFSSPPSYFQ
TRLPTPRGPDRPGGIEEEGGERDRDTS DPLVTGFLALIWVDLRSLFLYSYHHLRD
FLLIVARIVELLGRRGWEALKYWWNLLQYWSQELKSSAVSLLNATAIAVAEGT
DRIIEVVQRTCRAILHIPRRIRQGLERALQ

SEQ ID NO: 25

AVGIGAVFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQNNLLRAIEAQQQ
LLKLTVWGIKQLQARVLAVEYLKDQQLLGIWGCSGKLICTTNVPWNTSWSN
5 KSMHQIWDNMTWMQWEREIDNYTGLIYSLIEESQNQQEKNEQELLALDEWAS
LWNWFDITKWLWYIKIFIMIVGGLIGLRIVFTVLSIVNRVRQGIRPVFSSPPSYFQ
TRLPTPRGPDRPGGIEEEGGERDRDTS DPLVTGFLALIWVDLRSFLYSYHHLRD
FLLIVARIVELLGRRGWEALKYWWNLLQYWSQELKSSAVSLLNATAIAVAEGT
DRIIEVVQRTCRAILHIPRRIRQGLERALQ

10

SEQ ID NO: 26

AVGIGAVFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQNNLLRAIEAQQQ
LLKLTVWGIKQLQARVLAVEYLKDQQLLGIWGCSGKLICTTNVPWNTSWSN
KSMHQIWDNMTWMQWEREIDNYTGLIYSLIEESQNQQEKNEQELLALDEWAS
15 LWNWFDITKWLWYIKIFIMIVGGLIGLRIVFTVLSIVNRVRQGYRPVFSSPPSYF

[0151] In some embodiments, the first protein comprises or consists of an amino acid sequence having one or more of the following mutations:

- an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the first protein, preferably 13 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 35;

- a deletion of the last 147 amino acids relative to the amino acid numbering of SEQ ID NO: 1;
- a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 1;
- 5 - a substitution at position 201, preferably a substitution at position Y201, more preferably a tyrosine to isoleucine substitution (Y201I), relative to the amino acid sequence of SEQ ID NO: 1; or
- any combination thereof.

[0152] In some embodiments, the first protein comprises or consists of an amino acid
 10 sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80
 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group comprising SEQ ID NO: 2, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID
 15 NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, and SEQ ID NO: 26, and comprises or consists of an amino acid sequence having one or more of the following mutations:

- an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17
 20 amino acids, or more, in the cytoplasmic domain of the first protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75
 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1
 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably
 25 having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 35;
- a deletion of the last 147 amino acids relative to the amino acid numbering of SEQ ID NO: 1;

- a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 1;
- a substitution at position 201, preferably a substitution at position Y201, more preferably a tyrosine to isoleucine substitution (Y201I), relative to the amino acid sequence of SEQ ID NO: 1; or
- any combination thereof.

[0153] In some embodiments, the first protein has the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, or SEQ ID NO: 26. In some embodiments, the first protein has the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 20, and SEQ ID NO: 23.

[0154] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 20.

[0155] In some embodiments, the first protein comprises a deletion of the last 147 amino acids relative to the amino acid numbering of SEQ ID NO: 1.

[0156] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 20, and comprises a deletion of the last 147 amino acids relative to the amino acid numbering of SEQ ID NO: 1.

[0157] In some embodiments, the first protein has the amino acid sequence of SEQ ID NO: 20.

[0158] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 21.

[0159] In some embodiments, the first protein comprises a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 1.

[0160] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 21, and comprises a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 1.

[0161] In some embodiments, the first protein has the amino acid sequence of SEQ ID NO: 21.

[0162] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 22.

[0163] In some embodiments, the first protein comprises a substitution at position 201, preferably a substitution at position Y201, more preferably a tyrosine to isoleucine substitution (Y201I), relative to the amino acid sequence of SEQ ID NO: 1.

[0164] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 23.

99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 22, and comprises a substitution at position 201, preferably a substitution at position Y201, more preferably a tyrosine to isoleucine substitution (Y201I), relative to the amino acid sequence of SEQ ID NO: 1.

- 5 [0165] In some embodiments, the first protein has the amino acid sequence of SEQ ID NO: 22.

[0166] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 10 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 23.

[0167] In some embodiments, the first protein comprises one or more of the following mutations:

- 15 - a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 1;
- a substitution at position 201, preferably a substitution at position Y201, more preferably a tyrosine to isoleucine substitution (Y201I), relative to the amino acid sequence of SEQ ID NO: 1.

[0168] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 20 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 23, and comprises one or more of the following mutations:

- 25 - a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 1;

- a substitution at position 201, preferably a substitution at position Y201, more preferably a tyrosine to isoleucine substitution (Y201I), relative to the amino acid sequence of SEQ ID NO: 1.

[0169] In some embodiments, the first protein has the amino acid sequence of SEQ ID
5 NO: 23.

[0170] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 24.

[0171] In some embodiments, the first protein comprises an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the first protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34.

[0172] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 24, and comprises an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the first protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 24.

99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34.

- 5 [0173] In some embodiments, the first protein has the amino acid sequence of SEQ ID NO: 24.

[0174] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 10 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 25.

[0175] In some embodiments, the first protein comprises one or more of the following mutations:

- 15 - an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the first protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 35;
- 20 - a substitution at position 201, preferably a substitution at position Y201, more preferably a tyrosine to isoleucine substitution (Y201I), relative to the amino acid sequence of SEQ ID NO: 1.
- 25

[0176] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 25.

94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 25, and comprises one or more of the following mutations:

- 5 - an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the first protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 35;
- 10
- a substitution at position 201, preferably a substitution at position Y201, more preferably a tyrosine to isoleucine substitution (Y201I), relative to the amino acid sequence of SEQ ID NO: 1.
- 15

[0177] In some embodiments, the first protein has the amino acid sequence of SEQ ID NO: 25.

- [0178] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 26.
- 20

[0179] In some embodiments, the first protein comprises one or more of the following mutations:

- 25 - an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the first protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 25, and comprises one or more of the following mutations:

88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34;

- a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 1.

[0180] In some embodiments, the first protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 26, and comprises one or more of the following mutations:

- an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the first protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34;
- a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 1.

[0181] In some embodiments, the first protein has the amino acid sequence of SEQ ID NO: 26.

[0182] In some embodiments, the amino acid sequence of the first protein does not comprise or consist of SEQ ID NO: 54 or SEQ ID NO: 55. In some embodiments, the

first protein is not SEQ ID NO: 54 nor SEQ ID NO: 55. In some embodiments, the first protein is not SEQ ID NO: 54. In some embodiments, the first protein is not SEQ ID NO: 55.

SEQ ID NO: 54

5 GVFVLGFLGFLATAGSAMGAASLTTLTAQSRTLLAGIVQQQQQLLDVVKRQQEL
LRLTVWGTKNLQTRVTAIEKYLDQAQLNAWGCAFRQVCHTTVPWPNASLTP
DWNNDTWQEWERKVDFLEENITALLEEAQIQKEKNMYELQKLSWDVFGNW
FDLASWIKYIQYGIYVVVGVILLRIVYIVQMLAKLRQGYRPVFSSPPSYFQHTT
10 QQDPALPTREGKEGDGGEGGGNSSWPWQIEYIHFLIRQLIRLLTWLFSNCRTLLS
RAYQILQPILQRLSATLRRVREVLRTELTYLQYGWSYFHEAVQAGWRSATETL
AGAWRDLWETLRRGGRWILAIPRRIRQGLELTLL

SEQ ID NO: 55

15 AVGIGALFLGFLGAAGSTMGAASMTLTVQARQLLSGIVQQQNNLLRAIEAQQH
LLQLTVWGIKQLQARILAVEYLKDQQLLGIWGCSGKLICTTAVPWNASWSNK
SLEQIWNNMTWMEWDREINNYTSLIHSLIEESQNQQEKNEQELLELDKWASLW
NWFNITNWLWYIKIFIMIVGGLVGLRIVFAVLSIVNRVRQGYSPLSFQTHLPTPR
GPDRPEGIEEEGGERDRDRSIRLVNGSLALIWDDLRLSLCLFSYHRLRDLLLIVTRI
20 VELLGRRGWEALKYWWNLLQYWSQELKNSAVSLLNATAIAVAEGTDRVIEVV
QGACRAIRHIPRRIRQGLERILL

[0183] In some embodiments, the first protein binds or otherwise recognizes the protein cluster of differentiation 4 (CD4), preferably the first protein binds or otherwise recognizes selectively or specifically the protein CD4. Hence, the VLP or viral vector of the invention selectively targets cells expressing CD4 at their surface. In some
25 embodiments, the VLP or viral vector of the invention enables transfection or transduction of CD4-positive cells, preferably the VLP or viral vector of the invention enables selective or specific transfection or transduction of CD4-positive cells.

[0184] In some embodiments, the first protein comprises or consists of 100 to 1000 amino acids, 150 to 500 amino acids, or 200 to 400 amino acids.

[0185] In some embodiments, the second protein is glycoprotein 120 (GP120), or a variant, mutant and/or fragment thereof.

5 [0186] In some embodiments, the second protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected
10 from the group comprising or consisting of SEQ ID NO: 3, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, and SEQ ID NO: 39.

[0187] In some embodiments, the second protein is wild type GP120. In some embodiments, the second protein is a variant of GP120.

[0188] The person skilled in the art knows that various isolate of GP120 exist, such as
15 isolate HXB2. Wild-type GP120 isolate HXB2 typically has the amino acid sequence as set forth in SEQ ID NO: 3. Hence, in some embodiments, the second protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ
20 ID NO: 3.

SEQ ID NO: 3

MRVKEKYQHLWRWGWGWGTMLLGMLMICSATEKLWVTVYYGVPVWKEAT
TTLFCASDAKAYDTEVHNVWATHACVPTDPNPQEVVLNVNVTENFNMWKNDM
25 VEQMHEDIISLWDQSLKPCVKLTPLCVSLKCTDLKNDTNTNSSSGRMIMEKGEI
KNCSFNISTSIRGKVQKEYAFFYKLDIIPIDNDTTSYKLTSCNTSVITQACPKVSFE
PIPIHYCAPAGFAILKCNKTFNGTGPCTNVSTVQCTHGIRPVVSTQLLNGSLA
EEEVVIRSVNFTDNAKTIIVQLNTSVEINCTRPNNNTRKRIRIQRGPGRAFTIGKI

GNMRQAHCNISRAKWNNTLKQIASKLREQFGNNKTIIFKQSSGGDPEIVTHSFN
CGGEFFYCNSTQLFNSTWFNSTWSTEGSNNTEGSDTITLPCRIKQIINMWQKVG
KAMYAPPISGQIRCSSNITGLLLTRDGGNSNNESEIFRPGGGDMRDNRSELYK
YKVVKIEPLGVAPTKAKRRVVQREKR

5 [0189] In some embodiments, the second protein has the amino acid sequence of SEQ ID NO: 3.

[0190] In some embodiments, the second protein is a modified or mutant GP120 comprising at least one mutation compared to the wild-type amino acid sequence of GP120. In some embodiments, the amino acid sequence of the second protein comprises
10 at least one mutation compared to the amino acid sequence as set forth in SEQ ID NO: 3.

[0191] As used herein, “at least one” means 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more.

[0192] In some embodiments, the at least one mutation is a substitution, a deletion, an insertion, an inversion, or a truncation (*e.g.*, caused by the introduction of a stop codon in the coding nucleic acid sequence).

15 [0193] In some embodiments, the second protein is a mutant of GP120.

[0194] In some embodiments, the second protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group comprising or consisting of SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, and SEQ ID NO: 39.

SEQ ID NO: 36

MRVKGIRRNCRWWKWGIMLLGILMICNAEQLWVTVYYGVPVWKEATTTLF
25 CASDAKGHDTEAHNVWATHACVPTDPNPQEIVLENTENFNMWKNMVEQM
HEDVISLWDQSLKPCVKLTPLCVTLNCTDVMNNVNTTTNSSERMIEKGEIKNCS
FNINTNMRNKVQKEHALFYKLDVVPIDNTTKNNYTSYRLISCNTSVITQACPKV

5 SFEPPIHYCAPAGFAILKCRDKKFNGTGPCTNVSTVQCTHGIRPVVSTQLLFNGLAEEDVVIRSANFSDNAKTILVQLNETVVMNCTRPGNNTRKRVTLGPRVYYT
TGQIIGDIRKAHCNLSRAGWNNTLERIAIKLREQFQNKTIAFNQSSGGDPEITTIS
FNCGGEFFYCNSTQLFNGTWNGTWLDVKQGNGTITLPCRIKQIINLWQEVGKA
MYAPPISGQIRCSSNITGLLLTRDGGTSNETTTTETFRPGGGNMKDNWRSELYR
YKVIKIEPLGVAPTKARRRVVQREKR

10 **SEQ ID NO: 37**
MRVKGIRKSYQYLWKG GTLLL GILMICS AVEKLWVT VYYGVPVWKEATTTLF
CASDAKAYDTEVHNVWATHACVPTDPNPQEVVLE NVTEHFNMWKNNMVEQ
MQEDIISLWDQSLKPCVKLTPLCVTLNCKDVNATNTTNDSEGTMERGEIKNCSF
NITTSIRDEVQKEYALFYKLDVVPIDNNNTSYRLISCDTSVITQACPKISFEPIPIH
YCAPAGFAILKCNDKTFNGKGPCKNVSTVQCTHGIRPVVSTQLLLNGSLAEEEV
15 VIRSDNFTNNAKTIIVQLKESVEINCTRPNNNTRKSIHIGPGRAFYTTGEIIGDIRQ
AHCNISRAKWNDTLKQIVIKLREQFENKTIVFNHSSGGDPEIVMHSFNCGGEFFY
CNSTQLFNSTWNNNTEGSNNTEGNTITLPCRIKQIINMWQEVGKAMYAPPIRGQ
IRCSSNITGLLLTRDGGINENGTEIFRPGGGDMRDNWRSELYKYKVVKIEPLGV
APTKAKRRRVVQREKR

20 **SEQ ID NO: 38**
MRVKEIRKNWQH LRGGILL GMLMICS AAKEKTWVTIYYGVPVWREATTTLF
CASDAKAYDTEVHNVWATHACVPTDPNPQEVVLGNVTENFNMWKNNMV DQ
MHEDIISLWDESLKPCVKLTPLCVTLNCTNLNITKNNTNPTSSSWGMM EKGEIK
NCSFYITTSIRNKVKKEYALFNRLDVVPIENTNNTKYRLISCNTSVITQACPKVSF
25 QPIPIHYCVPAGFAM LKCNKTFNGSGPCTNVSTVQCTHGIRPVVSTQLLLNGS
LAEEDIVIRSENFTDNAKTIIVQLNESVVINCTRPNNNTRRRLSIGPGRFYARRN
IIGDIRQAHCNISRAKWNN TLQQIVIKLREKFRNKTI AFNQSSGGDPEIVMHSFNC
GGEFFYCNTAQLFNSTWNV TGGTNGTEGNDIITLQCR IKQIINMWQKV GKAMY

APPITGQIRCSSNITGLLLTRDGGNSTETETEIFRPGGGDMRDNWRSELYKYKV
VRIEPIGVAPTRAKRRTVQREKR

SEQ ID NO: 39

5 MRVKEIRKNWQHRLRGGILLGMLMICSAAKEKTWVTIYYGVPVWREATTTLF
CASDAKAYDTEVHNWATHACVPTDPNPQEVVLGNVTENFNMWKNMVDQ
MHEDIISLWDESLKPCVKLTPLCVTLNCTNLNITKNTTNPTSSSWGMMEKGEIK
NCSFYITTSIRNKVKKEYALFNRLDVVPIENTNNTKYRLISCQTSVITQACPKVSF
QPIPIHYCVPAGFAMLKCNNKTFNGSGPCTNVSTVQCTHGIRPVVSTQLLNGS
10 LAEEDIVIRSENFTDNAKTIIVQLNESVVINCTRPNNNTRRRLSIGPGRAFYARRN
IIGDIRQAHCNISRAKWNNTLQQIVIKLREKFRNKTIAFNQSSGGDPEIVMHSFNC
GGEFFYCNTAQLFNSTWNVTGGTNGTEGNDIITLQCRIKQIINMWQKV GKAMY
APPITGQIRCSSNITGLLLTRDGGNSTETETEIFRPGGGDMRDNWRSELYKYKV
VRIEPIGVAPTRAKRRTVQREKRAVGIGAVFLGFLGAAGSTMGAASVTLTVQARL
15 LLSGIVQQQNNLLRAIEAQQHMLQLTVWGIKQLQARVLALERYLRDQQLMGI
WGCSGKLICTTSVPWNVSWSNKSVDIWNMTWMEWEREIDNYTDYIDLLE
KSQTQQEKNEKELLELDKWASLWNWFDITNWLWYIRLFIMIVGGLIGLRIVFA
VLSIVNRVRQGYSPFSFQTLLPASRGPDPEGTEEEGGERDRDRSGPLVNGFLAL
FWVDLRNLCLFLYHLLRNLLIVTRIVELLGRRGWEALKYWWNLLQYWSQEL
20 KNSAVSLLNATAIAVAEGTDRVIKIVQRACRAIRNIPTRIRQGLERALL

[0195] In some embodiments, the second protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group comprising or consisting of SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, and SEQ ID NO: 39.

[0196] In some embodiments, the second protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 36. In some
5 embodiments, the second protein has the amino acid sequence of SEQ ID NO: 36.

[0197] In some embodiments, the second protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 37. In some
10 embodiments, the second protein has the amino acid sequence of SEQ ID NO: 37.

[0198] In some embodiments, the second protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 38. In some
15 embodiments, the second protein has the amino acid sequence of SEQ ID NO: 38.

[0199] In some embodiments, the second protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 39. In some
20 embodiments, the second protein has the amino acid sequence of SEQ ID NO: 39.

[0200] In some embodiments, the amino acid sequence of the second protein does not comprise or consist of SEQ ID NO: 52 or SEQ ID NO: 53. In some embodiments, the second protein is not SEQ ID NO: 52 nor SEQ ID NO: 53. In some embodiments, the second protein is not SEQ ID NO: 52. In some embodiments, the second protein is not
25 SEQ ID NO: 53.

SEQ ID NO: 52

MGCLGNQLLIAILLLSVYGIYCTQYVTVFYGVPAPWRNATIPLFCATKNRDTWG
 TTQCLPDNGDYSELALNVTESFDAWENTVTEQAIEDVWQLFETSIKPCVKLSPL
 CITMRCNKSETDRWGLTKSSTTITTAAPTSAPVSEKIDMVNETSSCIAQNNCTGL
 5 EQEQMISCKFTMTGLKRDKTKEYNETWYSTDLVCEQGNSTDNESRCYMNHCN
 TSVIQESCDKHYYWDTIRFRYCAPPGYALLRCNDTNYSGFMPKCSKVVSCTR
 MMETQTSTWFGFNGTRAENRTYIYWHGRDNRTIISLNKYYNLTMKCRPGNK
 TVLPVTIMSGLVFHSQPINDRPKQAWCWFGGKWKDAIKEVKQTIVKHPRYTGT
 NNTDKINLTAPGGGDPEVTFMWTNCRGEFLYCKMNWFLNWVEDRDVTTQRP
 10 KERHRRNYVPCHIRQIINTWHKVGKNVYLPREGDLTCNSTVTSLIANIDWTDG
 NQTSITMSAEVAELYRLELGDYKLVEITPIGLAPTDVKRYTTGGTSRNRK

SEQ ID NO: 53

MRVKEKYQHLWRWGWKWGTMLLGILMICSATEKLWVTVYYGVPVWKEATT
 15 TLFCASDAKAYDTEVHNVWATHACVPTDPNPQEVVLNVNVTENFNMWKNDMV
 EQMHEDIISLWDQSLKPCVKLTPLCVSLKCTDLGNATNTNSSNTNSSSGEMMM
 EKGEIKNCSFNISTSIRGKVQKEYAFFYKLDIIPIDNDTTSYTLTSCNTSVITQACP
 KVSFEPIPIHYCAPAGFAILKCNNKTFNGTGPCTNVSTVQCTHGIRPVVSTQLLL
 NGLAEEEVVIRSANFTDNAKTIIVQLNQSVINCTRPNNNTRKSIRIQRGPGRAF
 20 VTIGKIGNMRQAHCNISRAKWNATLKQIASKLREQFGNNKTIIFKQSSGGDPEIV
 THSFNCGGEFFYCNSTQLFNSTWFNSTWSTEGSNNTEGSDTITLPCRIKQFINMW
 QEVGKAMYAPPISGQIRCSSNITGLLLTRDGGNNNNGSEIFRPGGGDMRDNWS
 ELYKYKVVKIEPLGVAPTKAKRRVVQREKR

[0201] In some embodiments, the second protein binds or otherwise recognizes the
 25 protein C-C chemokine receptor type 5 (CCR5) and/or the protein C-X-C chemokine
 receptor type 4 (CXCR-4). Hence, the VLP or viral vector of the invention enables
 transfection or transduction in cells expressing CCR5 and/or CXCR4.

[0202] In some embodiments, the second protein comprises or consists of 100 to 1000 amino acids, 300 to 800 amino acids, or 400 to 600 amino acids.

[0203] It is known in the art that GP41 and GP120 are the two sub-units of the glycoprotein 160 (GP160), herein interchangeably referred to as envelope protein, or *env*.

- 5
- [0204] In some embodiments, the envelope protein is GP160, or a variant, mutant and/or fragment thereof. In a preferred embodiment, the envelope protein is a variant, mutant and/or fragment of GP160. In some embodiments, the modified envelope protein is GP160, or a variant, mutant and/or fragment thereof. In a preferred embodiment, the modified envelope protein is a variant, mutant and/or fragment of GP160.
- 10
- [0205] In some embodiments, the envelope protein is a modified or mutant GP160 comprising at least one mutation compared to the wild-type amino acid sequence of GP160. The person skilled in the art knows that various isolates of GP160 exist, such as isolate HXB2. Wild-type GP160 isolate HXB2 typically has the amino acid sequence as set forth in SEQ ID NO: 4.

15	SEQ ID NO: 4
	MRVKEKYQHLWRWGWRWGTMLLGMLMICSATEKLWVTVYYGVPVWKEAT
	TTLFCASDAKAYDTEVHNVWATHACVPTDPNPQEVVLNVNVTENFNMWKNDM
	VEQMHEDIISLWDQSLKPCVKLTPLCVSLKCTDLKNDTNTNSSSGRMIMEKGEI
	KNCSFNISTSIRGKVQKEYAFFYKLDIIPIDNDTTSYKLTSCNTSVITQACPKVSFE
20	PIPIHYCAPAGFAILKCNKTFNGTGPCTNVSTVQCTHGIRPVVSTQLLNGSLA
	EEEVVIRSVNFTDNAKTIIVQLNTSVEINCTRPNNNTRKRIRIQRGPGRAFTIGKI
	GNMRQAHCNISRAKWNNLTKQIASKLREQFGNNKTIIFKQSSGGDPEIVTHSFN
	CGGEFFYCNSTQLFNSTWFNSTWSTEGSNNTGSDTITLPCRIKQIINMWQKVG
	KAMYAPPISGQIRCSSNITGLLLTRDGGNSNNESEIFRPGGGDMRDNRSELYK
25	YKVVKIEPLGVAPTKAKRRVVQREKRAVGIGALFLGFLGAAGSTMGAASMTLT
	VQARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQQ
	LLGIWGCSGKLICTTAVPWNASWSNKSLEQIWNHTTWMEWDREINNYTSLIHS
	LIEESQNQQEKNEQELLELDKWASLWNWFNITNWLWYIKLFIMIVGGLVGLRI
	VFAVLSIVNRVRQGYSPLSFQTHLPTPRGPDRPEGIEEGGERDRDRSIRLVNGS

LALIWDLLRSLCLFSYHRLRDLLLVTRIVELLGRRGWEALKYWWNLLQYWSQ
ELKNSAVSLLNATAIAVAEGTDRVIEVVQGACRAIRHIPRRIRQGLERILL

[0206] Hence, in some embodiments, the amino acid sequence of the envelope protein comprises at least one mutation compared to the amino acid sequence as set forth in SEQ ID NO: 4. Therefore, in some embodiments, the amino acid sequence of the envelope protein is not SEQ ID NO: 4. In some embodiments, the amino acid sequence of the envelope protein is not the sequence of wild-type GP160.

[0207] As used herein, “at least one” means 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more.

[0208] As used herein, the term “mutation” is meant to broadly encompass all types of mutations in a sequence, preferably an amino acid sequence. Non-limitative examples of mutations include a substitution, a deletion, an insertion, an inversion, or a truncation. The mutation may affect 1, 2, 3, 4 or more amino acids; alternatively, the mutation may affect a large number of amino acids (*e.g.*, an epitope, a domain, etc.). Illustratively, the mutation may be one or more amino acid substitution, one or more deletion, one or more insertion, one or more truncation, or combinations thereof.

[0209] In some embodiments, the at least one mutation is a substitution, a deletion, an insertion, an inversion, a truncation (*e.g.*, caused by the introduction of a stop codon in the coding nucleic acid sequence), or a combination thereof. In some embodiments, the at least one mutation is one or more amino acid substitution, one or more deletion, one or more insertion, one or more truncation, or combinations thereof.

[0210] In a preferred embodiment, the at least one mutation is localized on the cytoplasmic domain of the envelope protein. Hence, in some embodiments, the envelope protein is a modified or mutant GP160 comprising at least one mutation, modification or alteration of the cytoplasmic domain. In some embodiments, the envelope protein comprises an amino acid sequence having at least one mutation compared to the amino acid sequence of sequence of SEQ ID NO: 4, wherein said at least one mutation is localized on the cytoplasmic domain of the first protein.

[0211] As used herein, the term “cytoplasmic domain” is interchangeable with the term “cytoplasmic tail”.

[0212] In some embodiments, the envelope protein is a modified or mutant GP160 comprising at least one mutation of the cytoplasmic domain. In some embodiments, the envelope protein is a modified or mutant GP160 comprising a partial or complete truncation of the cytoplasmic domain. In some embodiments, the envelope protein is a modified or mutant GP160 comprising a partial truncation of the cytoplasmic domain. In some embodiments, the envelope protein is a modified or mutant GP160 comprising a complete truncation of the cytoplasmic domain. In some embodiments, the envelope protein is a modified or mutant GP160 comprising one or more amino acid substitution, insertion and/or deletion substitution on the cytoplasmic domain. In some embodiments, the envelope protein is a modified or mutant GP160 comprising a partial truncation of the cytoplasmic domain and one or more amino acid substitution, insertion and/or deletion substitution on the cytoplasmic domain. In some embodiments, the envelope protein comprises a mutation on the endocytosis motif.

[0213] It will be understood that the Applicant provide herein mutants or variants of GP160. It was surprisingly found by the Applicant that VLPs or viral vectors pseudotyped with mutants or variants of GP160 enabled improved transfection or transduction efficacy than VLPs or viral vectors pseudotyped with wild-type GP160.

[0214] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 81, and SEQ ID NO: 87.

[0215] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 5 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 16, SEQ ID NO: 27, SEQ ID NO: 30, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 81, and SEQ ID NO: 87.

10 [0216] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence
15 selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 81, and SEQ ID NO: 87.

20 [0217] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence
25 selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 16, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 81, and SEQ ID NO: 87.

[0218] In some embodiments, the envelope protein comprises or consists of an amino
30 acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79

%, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 76, and SEQ ID NO: 77.

[0219] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 16, SEQ ID NO: 27, SEQ ID NO: 30, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 76, and SEQ ID NO: 77.

[0220] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 76, and SEQ ID NO: 77.

[0221] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence

selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 16, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 76, and SEQ ID NO: 77.

[0222] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group comprising or consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, and SEQ ID NO: 33.

[0223] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group comprising or consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 16, SEQ ID NO: 27, and SEQ ID NO: 30.

[0224] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group comprising or consisting of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19.

[0225] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79

%, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group comprising or consisting of SEQ ID NO: 5, SEQ ID NO: 13, and
5 SEQ ID NO: 16.

[0226] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 10 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 81, and SEQ ID NO: 87.

[0227] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 15 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 81, and SEQ ID NO: 87.
20

[0228] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 25 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, and SEQ ID NO: 67.

[0229] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 5 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, and SEQ ID NO: 67.

[0230] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 10 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 76, and SEQ ID NO: 77.

15 [0231] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence 20 selected from the group consisting of SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 76, and SEQ ID NO: 77.

[0232] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 25 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 59, SEQ ID NO: 65, and SEQ ID NO: 67.

[0233] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 5 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 65, and SEQ ID NO: 67.

[0234] In a preferred embodiment, the envelope protein does not comprise the amino acid sequence as set forth in SEQ ID NO: 95. In a preferred embodiment, the envelope 10 protein does not consist of SEQ ID NO: 95.

[0235] Table 3: GP160 mutants

GP160 mutant	SEQ ID NO:
GP160 TM1 (<i>i.e.</i> , GP160 +SIV Y712I Δ139)	5
GP160 WT (isolate HXB2) Δ147	13
GP160 WT (isolate HXB2) Δ139	14
GP160 WT (isolate HXB2) Y712I	15
GP160 WT (isolate HXB2) Y712I Δ139	16
GP160 WT (isolate HXB2) +SIV	17
GP160 WT (isolate HXB2) +SIV Y712I	18
GP160WT (isolate HXB2) +SIV Δ139	19
F04	61
F28	59
F29	70

F67	75
F71	71
F75	76
F76	77
F80	67
F81	81
F82	65
F85	87

	SEQ ID NO: 5
	MRVKGIRRNCQRWWKWGIMLLGILMICNAEQLWVTVYYGVPVWKEATTTLF
	CASDAKGHDTEAHNVWATHACVPTDPNPQEIVLENTENFNMWKNMVEQM
5	HEDVISLWDQSLKPCVKLTPLCVTLNCTDVMNNVNTTTNSSERMIEKGEIKNCS
	FNINTNMRNKVQKEHALFYKLDVVPIDNTTKNNYTSYRLISCNTSVITQACPKV
	SFEPIPIHYCAPAGFAILKCRDKKFNGTGPCTNVSTVQCTHGIRPVVSTQLLFNGS
	LAEEDVVIRSANFSDNAKTILVQLNETVVMNCTRPGNNTRKRVTLGPRVYYT
	TGQIIGDIRKAHCNLSRAGWNNTLERIAIKLREQFQNKTIAFNQSSGGDPEITTIS
10	FNCGGEFFYCNSTQLFNGTWNGTWLDVKQGNGTITLPCRIKQIINLWQEVGKA
	MYAPPISGQIRCSSNITGLLLTRDGGTSNETTTTETFRPGGGNMKDNWRSELYR
	YKVIKIEPLGVAPTKARRRVVQREKRAVGIGAVFLGFLGAAGSTMGAASMTLT
	VQARQLLSGIVQQQNNLLRAIEAQQQLLKLTVWGIKQLQARVLAVERYLKDQ
	QLLGIWGCSGKLICTTNVPWNTSWSNKSMHQIWDNMTWMQWEREIDNYTGLI
15	YSLIEESQNQQEKNEQELLALDEWASLWNWFDITKWLWYIKIFIMIVGGLIGLRI
	VFTVLSIVNRVRQGIRPVFSSPPSYF

SEQ ID NO: 13

MRVKEKYQHLWRWGWRWGTMLLGMLMICSATEKLWVTVYYGVPVWKEAT
TTLFCASDAKAYDTEVHNVWATHACVPTDPNPQEVVLNVVTENFNMWKNDM
5 VEQMHEDIISLWDQSLKPCVKLTPLCVSLKCTDLKNDTNTNSSSSGRMIMEKGEI
KNCSFNISTSIRGKVQKEYAFFYKLDIIPIDNDTTSYKLTSCNTSVITQACPKVSFE
PIPIHYCAPAGFAILKCNNKTFNGTGPCTNVSTVQCTHGIRPVVSTQLLLNGSLA
EEEVVIRSVNFTDNAKTIIVQLNTSVEINCTRPNNNTRKRIRIQRGPGRAFVTIGKI
GNMRQAHCNISRAKWNNTLKQIASKLREQFGNNKTIIFKQSSGGDPEIVTHSFN
10 CGGEFFYCNSTQLFNSTWFNSTWSTEGSNNTSGSDTITLPCRIKQIINMWQKVG
KAMYAPPISGQIRCSSNITGLLLTRDGGNSNNESEIFRPGGGDMRDNRSELYK
YKVVKIEPLGVAPTKAKRRVVQREKRAVGIGALFLGFLGAAGSTMGAASMTLT
VQARQLLSGIVQQQNNLLRAIEAQHLLQLTVWGIKQLQARILAVERYLKDQQ
LLGIWGCSGKLICTTAVPWNASWSNKSLEQIWNHTTWMEWDREINNYTSLIHS
15 LIEESQNQQEKNEQELLELDKWASLWNWFNITNWLWYIKLFIMIVGGLVGLRI
VFAVLSIVNRVR

SEQ ID NO: 14

MRVKEKYQHLWRWGWRWGTMLLGMLMICSATEKLWVTVYYGVPVWKEAT
20 TTLFCASDAKAYDTEVHNVWATHACVPTDPNPQEVVLNVVTENFNMWKNDM
VEQMHEDIISLWDQSLKPCVKLTPLCVSLKCTDLKNDTNTNSSSSGRMIMEKGEI
KNCSFNISTSIRGKVQKEYAFFYKLDIIPIDNDTTSYKLTSCNTSVITQACPKVSFE
PIPIHYCAPAGFAILKCNNKTFNGTGPCTNVSTVQCTHGIRPVVSTQLLLNGSLA
EEEVVIRSVNFTDNAKTIIVQLNTSVEINCTRPNNNTRKRIRIQRGPGRAFVTIGKI
25 GNMRQAHCNISRAKWNNTLKQIASKLREQFGNNKTIIFKQSSGGDPEIVTHSFN
CGGEFFYCNSTQLFNSTWFNSTWSTEGSNNTSGSDTITLPCRIKQIINMWQKVG
KAMYAPPISGQIRCSSNITGLLLTRDGGNSNNESEIFRPGGGDMRDNRSELYK
YKVVKIEPLGVAPTKAKRRVVQREKRAVGIGALFLGFLGAAGSTMGAASMTLT

VQARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQQ
LLGIWGCSGKLICTTAVPWNASWSNKSLEQIWNHTTWMEWDREINNYTSLIHS
LIEESQNQQEKNEQELLELDKWASLWNWFNITNWLWYIKLFIMIVGGLVGLRI
VFAVLSIVNRVRKGYSPLSF

5

SEQ ID NO: 15

MRVKEKYQHLWRWGWRWGTMLLGMLMICSATEKLWVTVYYGVPVWKEAT
TTLFCASDAKAYDTEVHNVWATHACVPTDPNPQEVVLNVNVTENFNMWKNDM
VEQMHEDIISLWDQSLKPCVKLTPLCVSLKCTDLKNDTNTNSSSGRMIMEKGEI
10 KNCFSNISTSIRGKVQKEYAFFYKLDIIPIDNDTTSYKLTSCNTSVITQACPKVSFE
PIPIHYCAPAGFAILKCNKTFNGTGPCTNVSTVQCTHGIRPVVSTQLLLNGSLA
EEEVVIRSVNFTDNAKTIIVQLNTSVEINCTRPNNNTRKRIRIQRGPGRAFTIGKI
GNMRQAHCNISRAKWNNTLKQIASKLREQFGNNKTIIFKQSSGGDPEIVTHSFN
CGGEFFYCNSTQLFNSTWFNSTWSTEGSNNTSGSDTITLPCRIKQIINMWQKVG
15 KAMYAPPISGQIRCSSNITGLLLTRDGGNSNNESEIFRPGGGDMRDNRSELYK
YKVVKIEPLGVAPTKAKRRVVQREKRAVGIGALFLGFLGAAGSTMGAASMTLT
VQARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQQ
LLGIWGCSGKLICTTAVPWNASWSNKSLEQIWNHTTWMEWDREINNYTSLIHS
LIEESQNQQEKNEQELLELDKWASLWNWFNITNWLWYIKLFIMIVGGLVGLRI
20 VFAVLSIVNRVRKGISPLSFQTRLPTPRGPDRPGGIEEEGGERDRDTS DPLVTGFL
ALIWVDLRSLFLYSYHHLRDFLLIVARIVELLGRRGWEALKYWWNLLQYWSQ
ELKSSAVSLLNATAIAVAEGTDRIIEVVQRTCRAILHIPRRIRQGLERALQ

25

SEQ ID NO: 16

MRVKEKYQHLWRWGWRWGTMLLGMLMICSATEKLWVTVYYGVPVWKEAT
TTLFCASDAKAYDTEVHNVWATHACVPTDPNPQEVVLNVNVTENFNMWKNDM
VEQMHEDIISLWDQSLKPCVKLTPLCVSLKCTDLKNDTNTNSSSGRMIMEKGEI
KNCFSNISTSIRGKVQKEYAFFYKLDIIPIDNDTTSYKLTSCNTSVITQACPKVSFE

PIPIHYCAPAGFAILKCNNKTFNGTGPCTNVSTVQCTHGIRPVVSTQLLLNGSLA
EEEVVIRSVNFTDNAKTIIVQLNTSVEINCTRPNNNTRKRIRIQRGPGRAFVTIGKI
GNMRQAHCNISRAKWNNTLKQIASKLREQFGNNKTIIFKQSSGGDPEIVTHSFN
CGGEFFYCNSTQLFNSTWFNSTWSTEGSNNTGSDTITLPCRICKIINMWQKVG
5 KAMYAPPISGQIRCSSNITGLLLTRDGGNSNNESEIFRPGGGDMRDNRSELYK
YKVVKIEPLGVAPTKAKRRVVQREKRAVGIGALFLGFLGAAGSTMGAASMTLT
VQARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVEERYLKDQQ
LLGIWGCSGKLICTTAVPWNASWSNKSLEQIWNHTTWMEWDREINNYTSLIHS
LIEESQNQQEKNEQELLELDKWASLWNWFNITNWLWYIKLFIMIVGGLVGLRI
10 VFAVLSIVNRVRKGISPLSF

SEQ ID NO: 17

MRVKEKYQHLWRWGWWRWGTMLLGMLMICSATEKLWVTVYYGVPVWKEAT
TTLFCASDAKAYDTEVHNVWATHACVPTDPNPQEVVLNVNVTENFNMWKNDM
15 VEQMHEDIISLWDQSLKPCVKLTPLCVSLKCTDLKNDTNTNSSSGRMIMEKGEI
KNCSFNISTSIRGKVQKEYAFFYKLDIIPIDNDTTSYKLTSCNTSVITQACPKVSFE
PIPIHYCAPAGFAILKCNNKTFNGTGPCTNVSTVQCTHGIRPVVSTQLLLNGSLA
EEEVVIRSVNFTDNAKTIIVQLNTSVEINCTRPNNNTRKRIRIQRGPGRAFVTIGKI
GNMRQAHCNISRAKWNNTLKQIASKLREQFGNNKTIIFKQSSGGDPEIVTHSFN
20 CGGEFFYCNSTQLFNSTWFNSTWSTEGSNNTGSDTITLPCRICKIINMWQKVG
KAMYAPPISGQIRCSSNITGLLLTRDGGNSNNESEIFRPGGGDMRDNRSELYK
YKVVKIEPLGVAPTKAKRRVVQREKRAVGIGALFLGFLGAAGSTMGAASMTLT
VQARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVEERYLKDQQ
LLGIWGCSGKLICTTAVPWNASWSNKSLEQIWNHTTWMEWDREINNYTSLIHS
25 LIEESQNQQEKNEQELLELDKWASLWNWFNITNWLWYIKLFIMIVGGLVGLRI
VFAVLSIVNRVRQGYRPVFSSPPSYFQTRLPTPRGPDRPGGIEEGGERDRDTS
PLVTGFLALIWVDLRSFLYSYHHLRDFLLIVARIVELLGRRGWEALKYWWNL
LQYWSQELKSSAVSLLNATAIAVAEGTDRIIEVVQRTCRAILHIPRRIRQGLERA
LQ

SEQ ID NO: 18

MRVKEKYQHLWRWGWRWGTMLLGMLMICSATEKLWVTVYYGVPVWKEAT
TTLFCASDAKAYDTEVHNVWATHACVPTDPNPQEVVLNVVTENFNMWKNDM
5 VEQMHEDIISLWDQSLKPCVKLTPLCVSLKCTDLKNDTNTNSSSSGRMIMEKGEI
KNCSFNISTSIRGKVQKEYAFFYKLDIIPIDNDTTSYKLTSCNTSVITQACPKVSFE
PIPIHYCAPAGFAILKCNNKTFNGTGPCTNVSTVQCTHGIRPVVSTQLLLNGSLA
EEEVVIRSVNFTDNAKTIIVQLNTSVEINCTRPNNNTRKRIRIQRGPGRAFTIGKI
GNMRQAHCNISRAKWNNTLKQIASKLREQFGNNKTIIFKQSSGGDPEIVTHSFN
10 CGGEFFYCNSTQLFNSTWFNSTWSTEGSNNTSGSDTITLPCRIKQIINMWQKVG
KAMYAPPISGQIRCSSNITGLLLTRDGGNSNNESEIFRPGGGDMRDNRSELYK
YKVVKIEPLGVAPTKAKRRVVQREKRAVGIGALFLGFLGAAGSTMGAASMTLT
VQARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQQ
LLGIWGCSGKLICTTAVPWNASWSNKSLEQIWNHTTWMEWDREINNYTSLIHS
15 LIEESQNQQEKNEQELLELDKWASLWNWFNITNWLWYIKLFIMIVGGLVGLRI
VFAVLSIVNRVRQGIRPVFSSPPSYFQTRLPTPRGPDRPGGIEEGGERDRDTS
LVTGFLALIWVDLRSFLYSYHHLRDFLLIVARIVELLGRRGWEALKYWWNLL
QYWSQELKSSAVSLLNATAIAVAEGTDRIIEVVQRTCRAILHIPRRIRQGLERAL
Q

20

SEQ ID NO: 19

MRVKEKYQHLWRWGWRWGTMLLGMLMICSATEKLWVTVYYGVPVWKEAT
TTLFCASDAKAYDTEVHNVWATHACVPTDPNPQEVVLNVVTENFNMWKNDM
VEQMHEDIISLWDQSLKPCVKLTPLCVSLKCTDLKNDTNTNSSSSGRMIMEKGEI
25 KNCSFNISTSIRGKVQKEYAFFYKLDIIPIDNDTTSYKLTSCNTSVITQACPKVSFE
PIPIHYCAPAGFAILKCNNKTFNGTGPCTNVSTVQCTHGIRPVVSTQLLLNGSLA
EEEVVIRSVNFTDNAKTIIVQLNTSVEINCTRPNNNTRKRIRIQRGPGRAFTIGKI
GNMRQAHCNISRAKWNNTLKQIASKLREQFGNNKTIIFKQSSGGDPEIVTHSFN

5

CGGEFFYCNSTQLFNSTWFNSTWSTEGSNNTEGSDTITLPCRIKQIINMWQKVG
KAMYAPPISGQIRCSSNITGLLLTRDGGNSNNESEIFRPGGGDMRDNWRSELYK
YKVVKIEPLGVAPTKAKRRVVQREKRAVGIGALFLGFLGAAGSTMGAASMTLT
VQARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYLKDQQ
LLGIWGCSGKLICTTAVPWNASWSNKSLEQIWNHTTWMEWDREINNYTSLIHS
LIEESQNQQEKNEQELLELDKWASLWNWFNITNWLWYIKLFIMIVGGLVGLRI
VFAVLSIVNRVRQGYRPVFSSPPSYF

[0236] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having one or more of the following mutations:

- 10
- an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the envelope protein, preferably 13 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 35;
- 15
- a deletion of the last 147 amino acids relative to the amino acid numbering of SEQ ID NO: 4;
- 20
- a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 4;
- a substitution at position 712, preferably a substitution at position Y712, more preferably a tyrosine to isoleucine substitution (Y712I), relative to the amino acid sequence of SEQ ID NO: 4; or
- 25
- any combination thereof.

[0237] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group comprising SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, and SEQ ID NO: 19, and comprises or consists of an amino acid sequence having one or more of the following mutations:

- 10 - an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the envelope protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 35;
- 15 - a deletion of the last 147 amino acids relative to the amino acid numbering of SEQ ID NO: 4;
- 20 - a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 4;
- 25 - a substitution at position 712, preferably a substitution at position Y712, more preferably a tyrosine to isoleucine substitution (Y712I), relative to the amino acid sequence of SEQ ID NO: 4; or
- any combination thereof.

[0238] In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 5, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID

NO: 17, SEQ ID NO: 18, or SEQ ID NO: 19. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 5, SEQ ID NO: 13, and SEQ ID NO: 16.

[0239] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79
 5 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 5.

[0240] In some embodiments, the envelope protein comprises one or more of the following mutations:

- 10 - an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the envelope protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 35;
- 15 - a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 4; or
- 20 - a substitution at position 712, preferably a substitution at position Y712, more preferably a tyrosine to isoleucine substitution (Y712I), relative to the amino acid sequence of SEQ ID NO: 4.

[0241] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79
 25 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 5.

99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 5, and comprises one or more of the following mutations:

- 5 - an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the envelope protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 35;
- 10 - a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 4; or
- 15 - a substitution at position 712, preferably a substitution at position Y712, more preferably a tyrosine to isoleucine substitution (Y712I), relative to the amino acid sequence of SEQ ID NO: 4.

[0242] In some embodiments, the envelope protein has an amino acid sequence having at least 70% sequence identity with SEQ ID NO: 5. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 5.

- 20 [0243] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 13.

- 25 [0244] In some embodiments, the envelope protein comprises a deletion of the last 147 amino acids relative to the amino acid numbering of SEQ ID NO: 4.

[0245] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79

%, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 13, and comprises a deletion of the last 147 amino acids relative to the amino acid numbering of SEQ ID NO: 4.

[0246] In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 13.

[0247] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 14.

[0248] In some embodiments, the envelope protein comprises a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 4.

[0249] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 14, and comprises a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 4.

[0250] In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 14.

[0251] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 15.

[0252] In some embodiments, the envelope protein comprises a substitution at position 712, preferably a substitution at position Y712, more preferably a tyrosine to isoleucine substitution (Y712I), relative to the amino acid sequence of SEQ ID NO: 4.

[0253] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 15, and comprises a substitution at position 712, preferably a substitution at position Y712, more preferably a tyrosine to isoleucine substitution (Y712I), relative to the amino acid sequence of SEQ ID NO: 4.

[0254] In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 15.

[0255] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 16.

[0256] In some embodiments, the envelope protein comprises one or more of the following mutations:

- a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 4;
- a substitution at position 712, preferably a substitution at position Y712, more preferably a tyrosine to isoleucine substitution (Y712I), relative to the amino acid sequence of SEQ ID NO: 4.

[0257] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 16.

93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 16, and comprises one or more of the following mutations:

- 5 - a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 4;
- a substitution at position 712, preferably a substitution at position Y712, more preferably a tyrosine to isoleucine substitution (Y712I), relative to the amino acid sequence of SEQ ID NO: 4.

10 [0258] In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 16.

15 [0259] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 17.

20 [0260] In some embodiments, the envelope protein comprises an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the envelope protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34.

25 [0261] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 36 or SEQ ID NO: 37, even more preferably having the amino acid sequence of SEQ ID NO: 36 or SEQ ID NO: 37, even more preferably having the amino acid sequence of SEQ ID NO: 36.

99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 17, and comprises an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the envelope protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76
 5 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence
 10 of SEQ ID NO: 34.

[0262] In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 17.

[0263] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79
 15 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 18.

[0264] In some embodiments, the envelope protein comprises one or more of the following mutations:

- 20 - an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the envelope protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 35;
- 25

- a substitution at position 712, preferably a substitution at position Y712, more preferably a tyrosine to isoleucine substitution (Y712I), relative to the amino acid sequence of SEQ ID NO: 4.

[0265] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 18, and comprises one or more of the following mutations:

- 10 - an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the envelope protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 35;
- 20 - a substitution at position 712, preferably a substitution at position Y712, more preferably a tyrosine to isoleucine substitution (Y712I), relative to the amino acid sequence of SEQ ID NO: 4.

[0266] In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 18.

[0267] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 19.

[0268] In some embodiments, the envelope protein comprises one or more of the following mutations:

- 5 - an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the envelope protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more
10 preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34;
- a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 4.

[0269] In some embodiments, the envelope protein comprises or consists of an amino
15 acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 19, and comprises one or more of the following mutations:

- 20 - an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the envelope protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more
25 preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34;

- a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 4.

[0270] In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 19.

- 5 [0271] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 81, and SEQ ID NO: 87.

- 10 [0272] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having an amino acid sequence selected from the group consisting of SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 81, and SEQ ID NO: 87.

- 15 [0273] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, and SEQ ID NO: 67.

[0274] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having an amino acid sequence selected from the group consisting of SEQ

- 20 ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 65, and SEQ ID NO: 67.

[0275] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 76, and SEQ ID NO: 77.

- 25 [0276] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having an amino acid sequence selected from the group consisting of SEQ ID NO: 65, SEQ ID NO: 67, SEQ ID NO: 76, and SEQ ID NO: 77.

[0277] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 59, SEQ ID NO: 65, and SEQ ID NO: 67.

5 [0278] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 65, and SEQ ID NO: 67.

[0279] In a preferred embodiment, the envelope protein does not comprise the amino acid sequence as set forth in SEQ ID NO: 95. In a preferred embodiment, the envelope protein does not consist of SEQ ID NO: 95.

10 [0280] In a preferred embodiment, the envelope protein has the amino acid sequence of SEQ ID NO: 59. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 61. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 65. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 67. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 70. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 71. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 75. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 76. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 77. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 81. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 87.

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[0281] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group comprising or consisting of SEQ ID NO: 5, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, and SEQ ID NO: 33.

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[0282] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 5 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group comprising or consisting of SEQ ID NO: 5, SEQ ID NO: 27, SEQ ID NO: 30.

[0283] Table 4: GP160 mutants

GP160 mutant	SEQ ID NO:
GP160 R3A Δ147	27
GP160 R3A Δ139	28
GP160 R3A Y712I	29
GP160 R3A Y712I Δ139	30
GP160 R3A +SIV	31
GP160 R3A +SIV Y712I	32
GP160 R3A +SIV Δ139	33

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SEQ ID NO: 27

MRVKGIRRNCQRWWKWGIMLLGILMICNAEQLWVTVYYGVPVWKEATTTLF
CASDAKGHDTEAHNVWATHACVPTDPNPQEIVLENTENFNMWKNNMVEQM
HEDVISLWDQSLKPCVKLTPLCVTLNCTDVMNNVNTTTNSSERMIEKGEIKNCS
FNINTNMRNKVQKEHALFYKLDVVPIDNTTKNNYTSYRLISCNTSVITQACPKV
SFEPPIHYCAPAGFAILKCRDKKFNGTGPCTNVSTVQCTHGIRPVVSTQLLFNGS
LAEEDVVIRSANFSDNAKTILVQLNETVVMNCTRPGNNTRKRVTLGPGRVYYT

5 TGQIIGDIRKAHCNLSRAGWNNTLERIAIKLREQFQNKTIAFNQSSGGDPEITTIS
FNCGGEFFYCNSTQLFNGTWNGTWLDVKQGNGTITLPCRIKQIINLWQEVGKA
MYAPPISGQIRCSSNITGLLLTRDGGTSNETTTTETFRPGGGNMKDNWRSELYR
YKVIKIEPLGVAPTKARRRVVQREKRAVGIGAVFLGFLGAAGSTMGAASMTLT
VQARQLLSGIVQQQNNLLRAIEAQQQLLKLTVWGIKQLQARVLAVERYLKDQ
QLLGIWGCSGKLICTTNVPWNTSWSNKS MHQIWDNMTWMQWEREIDNYTGLI
YSLIEESQNQQEKNEQELLALDEWASLWNWFDITKWLWYIKIFIMIVGGLIGLRI
VFTVLSIVNRVR

10 **SEQ ID NO: 28**
MRVKGIRRNCQRWWKWGIMLLGILMICNAEQLWVTVYYGVPVWKEATTTLF
CASDAKGHDTEAHNVWATHACVPTDPNPQEIVLENTENFNMWKNNMVEQM
HEDVISLWDQSLKPCVKLTPLCVTLNCTDVMNNVNTTTNSSERMIEKGEIKNCS
FNINTNMRNKVQKEHALFYKLDVVPIDNTTKNNYTSYRLISCNTSVITQACPKV
15 SFEPIPIHYCAPAGFAILKCRDKKFNGTGPCTNVSTVQCTHGIRPVVSTQLLFNGS
LAEEDVVIRSANFSDNAKTILVQLNETVVMNCTRPGNNTRKRVTLGPRVYYT
TGQIIGDIRKAHCNLSRAGWNNTLERIAIKLREQFQNKTIAFNQSSGGDPEITTIS
FNCGGEFFYCNSTQLFNGTWNGTWLDVKQGNGTITLPCRIKQIINLWQEVGKA
MYAPPISGQIRCSSNITGLLLTRDGGTSNETTTTETFRPGGGNMKDNWRSELYR
20 YKVIKIEPLGVAPTKARRRVVQREKRAVGIGAVFLGFLGAAGSTMGAASMTLT
VQARQLLSGIVQQQNNLLRAIEAQQQLLKLTVWGIKQLQARVLAVERYLKDQ
QLLGIWGCSGKLICTTNVPWNTSWSNKS MHQIWDNMTWMQWEREIDNYTGLI
YSLIEESQNQQEKNEQELLALDEWASLWNWFDITKWLWYIKIFIMIVGGLIGLRI
VFTVLSIVNRVRKGYSPLSF

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SEQ ID NO: 29
MRVKGIRRNCQRWWKWGIMLLGILMICNAEQLWVTVYYGVPVWKEATTTLF
CASDAKGHDTEAHNVWATHACVPTDPNPQEIVLENTENFNMWKNNMVEQM

HEDVISLWDQSLKPCVKLTPLCVTLNCTDVMNNVNNTTTNSSERMIEKGEIKNCS
FNINTNMRNKVQKEHALFYKLDVVPIDNTTKNNYTSYRLISCNTSVITQACPKV
SFEPPIHYCAPAGFAILKCRDKKFNGTGPCTNVSTVQCTHGIRPVVSTQLLFNCS
LAEEDVVIRSANFSDNAKTILVQLNETVVMNCTRPGNNTRKRVTLGPRVYYT
5 TGQIIGDIRKAHCNLSRAGWNNTLERIAIKLREQFQNKTIAFNQSSGGDPEITTIS
FNCGGEFFYCNSTQLFNGTWNGTWLDVKQGNGTITLPCRIKQIINLWQEVGKA
MYAPPISGQIRCSSNITGLLLTRDGGTSNETTTTETFRPGGGNMKDNWRSELYR
YKVIKIEPLGVAPTKARRRVVQREKRAVGIGAVFLGFLGAAGSTMGAASMTLT
VQARQLLSGIVQQQNNLLRAIEAQQQLLKLTVWGIKQLQARVLAVERYLKDQ
10 QLLGIWGCSGKLICTTNVPWNTSWSNKSMSHQIWDNMTWMQWEREIDNYTGLI
YSLIEESQNQQEKNEQELLALDEWASLWNWFDITKWLYYIKIFIMIVGGLIGLRI
VFTVLSIVNRVRKGISPLSFQTRLPTPRGPDRPGGIEEGGERDRDTSPLVTGFL
ALIWVDLRSLFLYSYHHLRDFLLIVARIVELLGRRGWEALKYWWNLLQYWSQ
ELKSSAVSLLNATAIAVAEGTDRIIEVVQRTCRAILHIPRRIRQGLERALQ

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SEQ ID NO: 30

MRVKGIRRNQCQRWWKWGIMLLGILMICNAEQLWVTVYYGVPVWKEATTTLF
CASDAKGHDTEAHNVWATHACVPTDPNPQEIVLENTENFNMWKNMVEQM
HEDVISLWDQSLKPCVKLTPLCVTLNCTDVMNNVNNTTTNSSERMIEKGEIKNCS
20 FNINTNMRNKVQKEHALFYKLDVVPIDNTTKNNYTSYRLISCNTSVITQACPKV
SFEPPIHYCAPAGFAILKCRDKKFNGTGPCTNVSTVQCTHGIRPVVSTQLLFNCS
LAEEDVVIRSANFSDNAKTILVQLNETVVMNCTRPGNNTRKRVTLGPRVYYT
TGQIIGDIRKAHCNLSRAGWNNTLERIAIKLREQFQNKTIAFNQSSGGDPEITTIS
FNCGGEFFYCNSTQLFNGTWNGTWLDVKQGNGTITLPCRIKQIINLWQEVGKA
25 MYAPPISGQIRCSSNITGLLLTRDGGTSNETTTTETFRPGGGNMKDNWRSELYR
YKVIKIEPLGVAPTKARRRVVQREKRAVGIGAVFLGFLGAAGSTMGAASMTLT
VQARQLLSGIVQQQNNLLRAIEAQQQLLKLTVWGIKQLQARVLAVERYLKDQ
QLLGIWGCSGKLICTTNVPWNTSWSNKSMSHQIWDNMTWMQWEREIDNYTGLI
YSLIEESQNQQEKNEQELLALDEWASLWNWFDITKWLYYIKIFIMIVGGLIGLRI
30 VFTVLSIVNRVRKGISPLSF

SEQ ID NO: 31

MRVKGIRRNCQRWWKWGIMLLGILMICNAEQLWVTVYYGVPVWKEATTTLF
CASDAKGHDTEAHNVWATHACVPTDPNPQEIVLENTENFNMWKNNMVEQM
5 HEDVISLWDQSLKPCVKLTPLCVTLNCTDVMNNVNNTTTNSSERMIEKGEIKNCS
FNINTNMRNKVQKEHALFYKLDVVPIDNTTKNNYTSYRLISCNTSVITQACPKV
SFEPPIHYCAPAGFAILKCRDKKFNGTGPCTNVSTVQCTHGIRPVVSTQLLFNCS
LAEEDVVIRSANFSDNAKTILVQLNETVVMNCTRPGNNTRKRVTLGPGRVYYT
TGQIIGDIRKAHCNLSRAGWNNTLERIAIKLREQFQNKTIAFNQSSGGDPEITTIS
10 FNCCGGEFFYCNSTQLFNGTWNGTWLDVKQGNGTITLPCRQIINLWQEVGKA
MYAPPISGQIRCSSNITGLLLTRDGGTSNETTTTETFRPGGGNMKDNWRSELYR
YKVIKIEPLGVAPTARRRVVQREKRAVGIGAVFLGFLGAAGSTMGAASMTLT
VQARQLLSGIVQQQNNLLRAIEAQQQLLKLTVWGIKQLQARVLAVERYLKDQ
QLLGIWGCSGKLICTTNVPWNTSWSNKSMSHQIWDNMTWMQWEREIDNYTGLI
15 YSLIEESQNQQEKNEQELLALDEWASLWNWFDITKWLYYIKIFIMIVGGLIGLRI
VFTVLSIVNRVRQGYRPVFSSPPSYFQTRLPTPRGPDRPGGIEEGGERDRDTS
PLVTGFLALIWDLRSLFLYSYHHLRDFLLIVARIVELLGRRGWEALKYWWNL
LQYWSQELKSSAVSLLNATAIAVAEGTDRIIEVVQRTCRAILHIPRRIRQGLERA
LQ

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SEQ ID NO: 32

MRVKGIRRNCQRWWKWGIMLLGILMICNAEQLWVTVYYGVPVWKEATTTLF
CASDAKGHDTEAHNVWATHACVPTDPNPQEIVLENTENFNMWKNNMVEQM
HEDVISLWDQSLKPCVKLTPLCVTLNCTDVMNNVNNTTTNSSERMIEKGEIKNCS
25 FNINTNMRNKVQKEHALFYKLDVVPIDNTTKNNYTSYRLISCNTSVITQACPKV
SFEPPIHYCAPAGFAILKCRDKKFNGTGPCTNVSTVQCTHGIRPVVSTQLLFNCS
LAEEDVVIRSANFSDNAKTILVQLNETVVMNCTRPGNNTRKRVTLGPGRVYYT
TGQIIGDIRKAHCNLSRAGWNNTLERIAIKLREQFQNKTIAFNQSSGGDPEITTIS

FNCGGEFFYCNSTQLFNGTWNGTWLDVKQGNGTITLPCRIKQIINLWQEVGKA
 MYAPPISGQIRCSSNITGLLLTRDGGTSNETTTTETFRPGGGNMKDNWRSELYR
 YKVIKIEPLGVAPTKARRRVVQREKRAVGIGAVFLGFLGAAGSTMGAASMTLT
 VQARQLLSGIVQQQNNLLRAIEAQQQLLKLTVWGIKQLQARVLAVERYLKDQ
 5 QLLGIWGCSGKLICTTNVPWNTSWSNKS MHQIWDNMTWMQWEREIDNYTGLI
 YSLIEESQNQQEKNEQELLALDEWASLWNWFDITKWLYYIKIFIMIVGGLIGLRI
 VFTVLSIVNRVRQGIRPVFSSPPSYFQTRLPTPRGPDRPGGIEEGGERDRDTS DP
 LVTGFLALIWDLRSLFLYSYHHLRDFLLIVARIVELLGRRGWEALKYWWNLL
 QYWSQELKSSAVSLLNATAIAVAEGTDRIIEVVQRTCRAILHIPRRIRQGLERAL
 10 Q

SEQ ID NO: 33

MRVKGIRRNCQRWWKWGIMLLGILMICNAEQLWVTVYYGVPVWKEATTTLF
 CASDAKGHDTEAHNVWATHACVPTDPNPQEIVLENTENFNMWKNMVEQM
 15 HEDVISLWDQSLKPCVKLTPLCVTLNCTDVMNNVNTTTNSSERMIEKGEIKNCS
 FNINTNMRNKVQKEHALFYKLDVVPIDNTTKNNYTSYRLISCNTSVITQACPKV
 SFEPIPIHYCAPAGFAILKCRDKKFNGTGPCTNVSTVQCTHGIRPVVSTQLLFNGS
 LAEEDVVIRSANFSDNAKTILVQLNETVVMNCTRPGNNTRKRVTLGPRVYYT
 TGQIIGDIRKAHCNLSRAGWNNTLERIAIKLREQFQNKTI AFNQSSGGDPEITTIS
 20 FNCGGEFFYCNSTQLFNGTWNGTWLDVKQGNGTITLPCRIKQIINLWQEVGKA
 MYAPPISGQIRCSSNITGLLLTRDGGTSNETTTTETFRPGGGNMKDNWRSELYR
 YKVIKIEPLGVAPTKARRRVVQREKRAVGIGAVFLGFLGAAGSTMGAASMTLT
 VQARQLLSGIVQQQNNLLRAIEAQQQLLKLTVWGIKQLQARVLAVERYLKDQ
 QLLGIWGCSGKLICTTNVPWNTSWSNKS MHQIWDNMTWMQWEREIDNYTGLI
 25 YSLIEESQNQQEKNEQELLALDEWASLWNWFDITKWLYYIKIFIMIVGGLIGLRI
 VFTVLSIVNRVRQGYRPVFSSPPSYF

[0284] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having one or more of the following mutations:

- an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the envelope protein, preferably 13 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 35;
- a deletion of the last 147 amino acids relative to the amino acid numbering of SEQ ID NO: 4;
- a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 4;
- a substitution at position 712, preferably a substitution at position Y712, more preferably a tyrosine to isoleucine substitution (Y712I), relative to the amino acid sequence of SEQ ID NO: 4; or
- any combination thereof.

[0285] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group comprising SEQ ID NO: 5, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, and SEQ ID NO: 33, and comprises or consists of an amino acid sequence having one or more of the following mutations:

- an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the envelope protein,

- preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 35;
- 5 - a deletion of the last 147 amino acids relative to the amino acid numbering of SEQ ID NO: 4;
- 10 - a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 4;
- a substitution at position 712, preferably a substitution at position Y712, more preferably a tyrosine to isoleucine substitution (Y712I), relative to the amino acid sequence of SEQ ID NO: 4; or
- 15 - any combination thereof.

[0286] In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 5, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, or SEQ ID NO: 33. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 5, SEQ ID NO: 27, and SEQ ID NO: 30.

- 20 [0287] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 27.

- 25 [0288] In some embodiments, the envelope protein comprises a deletion of the last 147 amino acids relative to the amino acid numbering of SEQ ID NO: 4.

[0289] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 5 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 27, and comprises a deletion of the last 147 amino acids relative to the amino acid numbering of SEQ ID NO: 4.

[0290] In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 27.

10 [0291] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 28.

15 [0292] In some embodiments, the envelope protein comprises a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 4.

[0293] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 20 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 28, and comprises a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 4.

[0294] In some embodiments, the envelope protein has the amino acid sequence of SEQ 25 ID NO: 28.

[0295] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 28, and comprises a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 4.

93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 29.

[0296] In some embodiments, the envelope protein comprises a substitution at position 712, preferably a substitution at position Y712, more preferably a tyrosine to isoleucine substitution (Y712I), relative to the amino acid sequence of SEQ ID NO: 4.

[0297] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 29, and comprises a substitution at position 712, preferably a substitution at position Y712, more preferably a tyrosine to isoleucine substitution (Y712I), relative to the amino acid sequence of SEQ ID NO: 4.

[0298] In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 29.

[0299] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 30.

[0300] In some embodiments, the envelope protein comprises one or more of the following mutations:

- a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 4;
- a substitution at position 712, preferably a substitution at position Y712, more preferably a tyrosine to isoleucine substitution (Y712I), relative to the amino acid sequence of SEQ ID NO: 4.

[0301] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 5 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 30, and comprises one or more of the following mutations:

- a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 4;
- a substitution at position 712, preferably a substitution at position Y712, more preferably a tyrosine to isoleucine substitution (Y712I), relative to the amino acid 10 sequence of SEQ ID NO: 4.

[0302] In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 30.

[0303] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 15 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 31.

[0304] In some embodiments, the envelope protein comprises an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the 20 cytoplasmic domain of the envelope protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 25 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34.

[0305] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 5 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 31, and comprises an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the envelope protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 10 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34.

15 [0306] In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 31.

[0307] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 20 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 32.

[0308] In some embodiments, the envelope protein comprises one or more of the following mutations:

- an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 25 amino acids, or more, in the cytoplasmic domain of the envelope protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %,

or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 35;

- a substitution at position 712, preferably a substitution at position Y712, more preferably a tyrosine to isoleucine substitution (Y712I), relative to the amino acid sequence of SEQ ID NO: 4.

[0309] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 32, and comprises one or more of the following mutations:

- an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the envelope protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 35;
- a substitution at position 712, preferably a substitution at position Y712, more preferably a tyrosine to isoleucine substitution (Y712I), relative to the amino acid sequence of SEQ ID NO: 4.

[0310] In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 32.

[0311] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79

%, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 33.

[0312] In some embodiments, the envelope protein comprises one or more of the
5 following mutations:

- an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the envelope protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86
10 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34;
- 15 - a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 4.

[0313] In some embodiments, the envelope protein comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79
20 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 33, and comprises one or more of the following mutations:

- an insertion or substitution of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 amino acids, or more, in the cytoplasmic domain of the envelope protein, preferably 14 amino acids, more preferably having at least 70%, 71%, 72%, 73%,
25 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 34 or SEQ ID NO: 35, even more

preferably having the amino acid sequence of SEQ ID NO: 34 or SEQ ID NO: 35, even more preferably having the amino acid sequence of SEQ ID NO: 34;

- a deletion of the last 139 amino acids relative to the amino acid numbering of SEQ ID NO: 4.

5 [0314] In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 33.

[0315] In some embodiments, the amino acid sequence of the envelope protein does not comprise or consist of SEQ ID NO: 50 or SEQ ID NO: 51. In some embodiments, the envelope protein is not SEQ ID NO: 50 nor SEQ ID NO: 51. In some embodiments, the
10 envelope protein is not SEQ ID NO: 50. In some embodiments, the envelope protein is not SEQ ID NO: 51.

SEQ ID NO: 50

MGCLGNQLLIAILLLSVYGIYCTQYVTVFYGVPAWRNATIPFCATKNRDTWG
TTQCLPDNGDYSELALNVTESFDAWENTVTEQAIEDVWQLFETSIKPCVKLSPL
15 CITMRCNKSETDRWGLTKSSTTITTAAPTSAPVSEKIDMVNETSSCIAQNNCTGL
EQEQMISCKFTMTGLKRDKTKEYNETWYSTDLVCEQGNSTDNESRCYMNHCN
TSVIQESCDKHWDITIRFYCAPPGYALLRCNDTNYSGFMPKCSKVVVSSCTR
MMETQTSTWFGFNGTRAENRTYIYWHGRDNRTIISLNKYYNLTMKCRPGNK
TVLPVTIMSGLVFHSQPINDRPKQAWCWFGGKWKDAIKEVKQTIVKHPRYTGT
20 NNTDKINLTAPGGGDPEVTFMWTNCRGEFLYCKMNWFLNWVEDRDVTTQRP
KERHRRNYVPCHIRQIINTWHKVGKNVYLPPREGDLTCNSTVTSLIANIDWTDG
NQTSITMSAEVAELYRLELGDYKLVEITPIGLAPTDVKRYTTGGTSRNKRGV
LGFLGFLATAGSAMGAASLTLTAQSRLLAGIVQQQQQLLDVVKRQQELLRLT
VWGTKNLQTRVTAIEKYLKDQAQLNAWGCAFRQVCHTTVPWPNASLTPDWN
25 NDTWQEWERKVDFLEENITALLEEAQIQQEKNMYELQKLNSWDVFGNWFDLA
SWIKYIQYGIYVVVGVILLRIVYIVQMLAKLRQGYRPVFSSPPSYFQHTTQQDP
ALPTREGKEGDGGEGGNSSWPWQIEYIHFLIRQLIRLLTWLFSNCRTLTSRAY
QILQPILQRLSATLRRVREVLRTETYLQYGWSYFHEAVQAGWRSATETLAGA
WRDLWETLRRGGRWILAIPRRIRQGLELTLL

SEQ ID NO: 51

MRVKEKYQHLWRWGWKWGTMLLGILMICSATEKLWVTVYYGVPVWKEATT
TLFCASDAKAYDTEVHNWVATHACVPTDPNPQEVVLVNVTENFNMWKNDMV
5 EQMHEDIISLWDQSLKPCVKLTPLCVSLKCTDLGNATNTNSSNTNSSSGEMMM
EKGEIKNCFSNISTSIRGKVQKEYAFFYKLDIIPIDNDTTSYTLTSCNTSVITQACP
KVSFEPIPIHYCAPAGFAILKCNNKTFNGTGPCTNVSTVQCTHGIRPVVSTQLLL
NGSLAEEEVVIRSANFTDNAKTIIVQLNQSVEINCTRPNNNTRKSIRIQRGPGRAF
VTIGKIGNMRQAHCNISRAKWNATLKQIASKLREQFGNNKTIIFKQSSGGDPEIV
10 THSFNCGGEFFYCNSTQLFNSTWFNSTWSTEGSNNTGSDTITLPCRKQFINMW
QEVGKAMYAPPISGQIRCSSNITGLLLTRDGGNNNNGSEIFRPGGGDMRDNWS
ELYKYKVVKIEPLGVAPTKAKRRVVQREKRAVGIGALFLGFLGAAGSTMGAAS
MTLTVQARQLLSGIVQQQNNLLRAIEAQQHLLQLTVWGIKQLQARILAVERYL
KDQQLLGIWGCSGKLICTTAVPWNASWSNKSLEQIWNNMTWMEWDREINNY
15 TSLIHSLEEESQNQQEKNEQELLELDKWASLWNWFNITNWLWYIKIFIMIVGGL
VGLRIVFAVLSIVNRVRQGYSPLSFQTHLPTPRGPDRPEGIEEEGGERDRDRSIRL
VNGSLALIWDRLSLCLFSYHRLRDLILLIVTRIVELLGRRGWEALKYWWNLLQ
YWSQELKNSAVSLLNATAIAVAEGTDRVIEVVQGACRAIRHIPRRIRQGLERILL

[0316] In some embodiments, the envelope protein binds or otherwise recognizes the protein cluster of differentiation 4 (CD4), preferably the envelope protein binds or otherwise recognizes selectively or specifically the protein CD4. Hence, the VLP or viral vector of the invention selectively targets cells expressing CD4 at their surface. In some embodiments, the VLP or viral vector of the invention enables transfection or transduction of CD4-positive cells, preferably the VLP or viral vector of the invention enables selective or specific transfection or transduction of CD4-positive cells. In some embodiments, the envelope protein further binds or otherwise recognizes CCR5 and CXCR4.

[0317] In some embodiments, the envelope protein comprises or consists of 100 to 1500 amino acids, 300 to 1000 amino acids, or 500 to 900 amino acids.

[0318] In some embodiments, the envelope protein is a fusogen.

[0319] In some embodiments, the first protein and/or the envelope protein comprise a mutated cytoplasmic tail or cytoplasmic domain. The person skilled in the art knows what domain corresponds to the cytoplasmic domain (i.e., cytoplasmic tail) of the envelope protein, preferably GP160, or its subunit comprising thereof, preferably GP41 (i.e., the first protein).

[0320] In some embodiments, the mutated cytoplasmic tail or cytoplasmic domain comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with an amino acid sequence selected from the group comprising or consisting of SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, and SEQ ID NO: 49.

15 **SEQ ID NO: 42**

RVR

SEQ ID NO: 43

RVRKGYSPLSF

20

SEQ ID NO: 44

RVRKGISPLSFQTRLPTPRGPDRPGGIEEEGGERDRDTS DPLVTGFLALIWVDLR
SLFLYSYHHLRDFLLIVARIVELLGRRGWEALKYWWNLLQYWSQELKSSAVSL
LNATAIAVAEGTDRIIEVVQRTCRAILHIPRRIRQGLERALQ

25

SEQ ID NO: 45

RVRKGISPLSF

SEQ ID NO: 46

5 RVRQGYRPFSSPPSYFQTRLPTPRGPDRPGGIEEEGGERDRDTS DPLVTGFLALI
WVDLRSLFLYSYHHLRD FLLIVARIVELLGRRGWEALKYWWNLLQYWSQELK
SSAVSLLNATAIAVAEGTDRIIEVVQRTCRAILHIPRRIRQGLERALQ

SEQ ID NO: 47

10 RVRQGIRPVFSSPPSYFQTRLPTPRGPDRPGGIEEEGGERDRDTS DPLVTGFLALI
WVDLRSLFLYSYHHLRD FLLIVARIVELLGRRGWEALKYWWNLLQYWSQELK
SSAVSLLNATAIAVAEGTDRIIEVVQRTCRAILHIPRRIRQGLERALQ

SEQ ID NO: 48

15 RVRQGYRPFSSPPSYF

SEQ ID NO: 49

RVRQGIRPVFSSPPSYF

20 [0321] In some embodiments, the mutated cytoplasmic tail or cytoplasmic domain
comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%,
74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87
%, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence

identity with SEQ ID NO: 42. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 42.

[0322] In some embodiments, the mutated cytoplasmic tail or cytoplasmic domain comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%,
5 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 43. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 43.

10 [0323] In some embodiments, the mutated cytoplasmic tail or cytoplasmic domain comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence
15 identity with SEQ ID NO: 44. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 44.

[0324] In some embodiments, the mutated cytoplasmic tail or cytoplasmic domain comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%,
20 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 45. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 45.

[0325] In some embodiments, the mutated cytoplasmic tail or cytoplasmic domain
25 comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence

identity with SEQ ID NO: 46. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 46.

[0326] In some embodiments, the mutated cytoplasmic tail or cytoplasmic domain comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%,
5 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 47. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 47.

10 [0327] In some embodiments, the mutated cytoplasmic tail or cytoplasmic domain comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%, 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence
15 identity with SEQ ID NO: 48. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 48.

[0328] In some embodiments, the mutated cytoplasmic tail or cytoplasmic domain comprises or consists of an amino acid sequence having at least 70%, 71%, 72%, 73%,
20 74 %, 75 %, 76 %, 77 %, 78 %, 79 %, 80 %, 81 %, 82 %, 83 %, 84 %, 85 %, 86 %, 87 %, 88 %, 89 %, 90 %, 91 %, 92 %, 93 %, 94 %, 95 %, 96 %, 97 %, 98 %, 99 %, 99.1 %, 99.2 %, 99.3 %, 99.4 %, 99.5 %, 99.6 %, 99.7 %, 99.8 %, 99.9 %, or 100% sequence identity with SEQ ID NO: 49. In some embodiments, the envelope protein has the amino acid sequence of SEQ ID NO: 49.

[0329] In some embodiments, the amino acid sequence of the mutated cytoplasmic tail
25 or cytoplasmic domain does not comprise or consist of SEQ ID NO: 40 or SEQ ID NO: 41. In some embodiments, the mutated cytoplasmic tail or cytoplasmic domain is not SEQ ID NO: 40 nor SEQ ID NO: 41. In some embodiments, the mutated cytoplasmic tail or cytoplasmic domain is not SEQ ID NO: 40. In some embodiments, the mutated cytoplasmic tail or cytoplasmic domain is not SEQ ID NO: 41.

SEQ ID NO: 40

RVRQGYSPFSFQTHLPTPRGPDRPEGIEEEGGERDRDRSIRLVNGSLALIWDLLR
SLCLFSYHRLRDLLIVTRIVELLGRRGWEALKYWWNLLQYWSQELKNSAVSL
LNATAIAVAEGTDRVIEVVQGACRAIRHPRRIRQGLERILL

5

SEQ ID NO: 41

RVRKGYSPLSFQTRLPTPRGPDRPGGIEEEGGERDRDTSDDLVTGFLALIWDLLR
SLFLYSYHHLRDFLLIVARIVELLGRRGWEALKYWWNLLQYWSQELKSSAVSL
LNATAIAVAEGTDRIIEVVQRTCRAILHPRRIRQGLERALQ

10

[0330] In some embodiments, the VLP or viral vector is pseudotyped with the envelope protein. In some embodiments, the envelope protein as defined hereinabove is expressed at the surface of the VLP or viral vector. In some embodiments, at least 1 copy, at least 10 copies, at least 100 copies, at least 10³ copies, at least 10⁴ copies, at least 10⁵ copies, at least 10⁶ copies, at least 10⁷ copies, at least 10⁸ copies, or more, of the envelope protein are at the surface of the VLP or viral vector.

[0331] Typically, the VLPs are produced by growing host cells transformed by an expression vector under conditions whereby the particle-forming polypeptide is expressed and VLPs can be formed. Similarly, a viral vector is produced by growing host cells transformed by an expression vector encoding the viral vector. The selection of the appropriate growth conditions is within the skill of the art. If the VLPs or viral vectors are formed intracellularly, the cells are then disrupted, using chemical, physical or mechanical means, which lyse the cells yet keep the VLPs substantially intact. Such methods are known to those of skill in the art. Host cells may be, non-limitatively, HEK-293 cells.

[0332] The expression vector may be any vector known in the art, and the transformation of host cells (*e.g.*, producer cells) is performed by any means known in the art.

[0333] In some embodiments, the transformation of host cells to produce the VLP or viral vector of the invention is achieved by contacting the population of cells with an expression vector suitable for production of the VLP or viral vector of the invention. In some embodiments, the expression vector comprises at least one nucleic acid molecule.

- 5 In some embodiments, said at least one nucleic acid encodes the VLP or viral vector, and the envelope protein. As used herein, at least one means 1, 2, 3, 4, 5, 6, 7, 8, 9, or more.

[0334] In some embodiments, the expression vector is an integrating vector or a non-integrating vector.

- [0335] In some embodiments, the vector is an integrating vector. In some embodiments, the integrating vector is selected from the group comprising or consisting of integrating virus, integrating plasmids, enzymes including engineered transposase or engineered integrase, or genome editing methods including CRISPR-Cas9.

- [0336] In some embodiments, the integrating vector is an integrating virus selected from the group comprising or consisting of *Retroviridae*, *Adenoviridae*, *Flaviviridae*, *Herpesviridae*, *Hepadnaviridae*, *Papillomaviridae*, *Polyomaviridae*, *Parvoviridae*, *Arenaviridae*, *Bornaviridae*, *Bunyaviridae*, *Filoviridae* and *Paramyxoviridae* families of viruses, preferably selected from the group comprising or consisting of *Retroviridae*, *Adenoviridae* and *Flaviviridae* families of viruses. In some embodiments, the integrating virus belongs to the family of *Retroviridae* family. In some embodiments, the integrating virus is a lentivirus.

- [0337] In some embodiments, a genome editing method is used to transform host cells to produce the VLP or viral vector of the invention. Non limitative examples of genome editing methods include CRISPR-Cas9, zinc finger nucleases (ZFN), transcription activator-like effector nuclease (TALEN), and the like. Means to implement these methods are well known in the art.

[0338] In some embodiments, the expression vector is a non-integrating vector. In some embodiments, the non-integrating vector is viral vector or a non-viral vector.

[0339] In some embodiments, the expression vector is a non-integrating viral vector selected from the group comprising or consisting of adenoviral vector, adeno-associated virus (AAV) vector, integration-deficient lentiviral vector (IDLVs), poxviral vector, herpes simplex virus vector.

- 5 [0340] In some embodiments, the expression vector is a non-integrating non-viral vector selected from the group comprising or consisting of plasmid, fosmid, cosmid, artificial chromosome (*e.g.*, human artificial chromosome), nanoparticle (*e.g.*, polymer-based nanoparticle, proteoliposome or lentiviral-like particle), minicircle DNA, and the like. In some embodiments, the non-integrating non-viral vector is a plasmid or a nanoparticle.
- 10 In some embodiments, the non-integrating non-viral vector is a plasmid.

[0341] In some embodiments, the VLP or viral vector further comprises at least one cargo molecule, *i.e.*, any molecule that is to be delivered in a cell. The at least one cargo molecule may be, non-imitatively, a protein, polypeptide, peptide, nucleic acid molecule (*e.g.*, DNA, RNA), a small molecule, a drug, a lipid, or any combination thereof.

- 15 [0342] In some embodiments, the VLP or viral vector further comprises at least one nucleic acid molecule of interest or polypeptide of interest. In some embodiments, the VLP or viral vector further comprises at least one nucleic acid molecule of interest and at least one polypeptide of interest, or a combination thereof (*e.g.*, a nucleoprotein).

- [0343] In one embodiment, the VLP or viral vector further comprises at least one
20 polypeptide of interest. As used herein, the term “polypeptide” is intended to encompass proteins, polypeptides, and peptides.

- [0344] In another embodiment, the VLP or viral vector further comprises at least one nucleic acid molecule of interest. In certain embodiment, the at least one nucleic acid molecule of interest is a DNA molecule, a RNA molecule, or a combination thereof. In
25 certain embodiment, the at least one nucleic acid molecule of interest is a DNA molecule. In certain embodiment, the at least one nucleic acid molecule of interest is a RNA molecule. In some embodiments, the RNA molecule is preferably selected from the list comprising or consisting of mRNA, tRNA, shRNA, snRNA, siRNA, miRNA, and the like.

[0345] In some embodiments, the at least one nucleic acid molecule of interest is single stranded (ss) or double stranded (ds). In some embodiments, the at least one nucleic acid molecule of interest is single stranded. In some embodiments, the at least one nucleic acid molecule of interest is double stranded.

- 5 [0346] It will be understood that the nucleic acid molecule of interest may be useful for modulating the expression of a target gene. In some embodiments, the nucleic acid molecule of interest modulates expression of at least one gene.

[0347] In one embodiment, the nucleic acid molecule of interest decreases expression of at least one gene. In this case, siRNA or shRNA are exemplary suitable embodiments for
10 the at least one nucleic acid molecule of interest. The term “decreases expression”, as used herein, means that the quantity, number of copies and/or biological activity of the products of the gene (*i.e.*, transcripts such as mRNA and/or polypeptides or proteins) are decreased 1.1-fold, 1.2-fold, 1.3-fold, 1.4-fold, 1.5-fold, 1.6-fold, 1.7-fold, 1.8-fold, 1.9-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 100-fold, or
15 more, compared to basal expression of said gene.

[0348] In one embodiment, the nucleic acid molecule of interest decreases expression of at least one oncogene.

[0349] In one embodiment, the nucleic acid molecule of interest increases expression of at least one gene. In this case, mRNA or cDNA are exemplary suitable embodiments for
20 the at least one nucleic acid molecule of interest. The term “increases expression”, as used herein, means that the quantity, number of copies and/or biological activity of the products of the gene (*i.e.*, transcripts such as mRNA and/or polypeptides or proteins) are increased 1.1-fold, 1.2-fold, 1.3-fold, 1.4-fold, 1.5-fold, 1.6-fold, 1.7-fold, 1.8-fold, 1.9-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 100-fold, or
25 more, compared to basal expression of said gene.

[0350] In some embodiments, the nucleic acid molecule of interest increases expression of at least one gene defective in a genetic disease.

[0351] In some embodiments, the nucleic acid molecule of interest increases expression of at least one tumor suppressor gene or antitumor gene.

[0352] In one embodiment, the nucleic acid molecule of interest modulates expression of one or more surface protein in a cell. In one embodiment, the nucleic acid molecule of interest decreases expression of one or more surface protein in a cell. In some
5 embodiments, the one or more surface protein is a protein used for binding, attachment and/or entry of one or more pathogen, preferably virus. In one embodiment, the nucleic acid molecule of interest decreases expression of CXCR4, CCR5, and/or CD4.

[0353] In some embodiments, the at least one nucleic acid molecule of interest encodes
10 at least one polypeptide of interest or at least one nucleic acid molecule of interest. In certain embodiments, the at least one nucleic acid molecule of interest comprises or consists of at least one coding region or sequence, typically a gene or a portion thereof, therefore in some embodiments, the nucleic acid molecule of interest comprises or consists of a transgene. In certain embodiments, the at least one nucleic acid molecule of
15 interest may comprise at least one non-coding region or sequence, such as, *e.g.*, a regulatory region.

[0354] In a preferred embodiment, the at least one nucleic acid molecule of interest encodes at least one polypeptide of interest.

[0355] It will be understood that polypeptides of interest may be delivered to a cell
20 directly by the VLP or viral vector of the invention, or be encoded in the cell by a nucleic acid molecule delivered by the VLP or viral vector of the invention. The present invention thus further relates to a nucleic acid encoding the VLP or viral vector of the invention.

[0356] In some embodiments, the at least one polypeptide of interest is selected from the list comprising or consisting of a membrane protein, a chimeric antigen receptor, a tumor
25 antigen, an antibody, a monobody, an enzyme, a nuclear receptor, a transporter, a ribosomal protein, a cytoplasmic protein, a G-protein coupled receptor, a voltage gated ion channel, a secretory protein, a mitochondria protein, a cytokine, a gene editor or a portion or chimeric species thereof.

[0357] In some embodiments, the at least one polypeptide of interest is selected from the list comprising or consisting of a chimeric antigen receptor or portion thereof, or a tumor antigen or a portion thereof. In some embodiments, the polypeptide of interest is a CAR, CCR or TCR or combination thereof. In some embodiments, the polypeptide of interest
5 is a chimeric antigen receptor (CAR), or a portion thereof. In some embodiments, the polypeptide of interest is a tumor antigen, or a portion thereof. In some embodiments, the nucleic acid molecule of interest encodes a CAR, CCR or TCR or combination thereof. In some embodiments, the nucleic acid molecule of interest encodes a CAR.

[0358] In some embodiments, the at least one polypeptide of interest is an antibody, or
10 a fragment of an antibody, optionally which can then be secreted by the cell that is infected with the VLP or viral vector of the invention.

[0359] In some embodiments, the at least one polypeptide of interest is selected from the list comprising or consisting of an enzyme, a nuclear receptor, a transporter, a ribosomal protein, a membrane bound protein, a cytoplasmic protein, a G-protein coupled receptor,
15 a voltage gated ion channel, a secretory protein, a mitochondria protein, a cytokine, a chimeric antigen receptor, a tumor antigen, or a portion or chimeric species thereof.

[0360] In some embodiments, the at least one polypeptide of interest is a gene editor. In some embodiments, the nucleic acid molecule of interest encodes a gene editor. Gene editors are known in the art, and non-limitative examples of gene editors comprise zinc
20 finger nucleases (ZFN), transcription activator-like effector nuclease (TALEN), CRISPR/Cas systems, engineered nucleases, engineered nickases, engineered transposases, engineered integrases, and/or any combination thereof.

[0361] In some embodiments, the at least one polypeptide of interest is a membrane protein. In some embodiments, the membrane protein is a chimeric antigen receptor, a
25 chimeric costimulatory receptor, chimeric T-cell receptor, or a combination of thereof.

[0362] In some embodiments, the at least one polypeptide of interest is a cytoplasmic protein or a secreted protein.

[0363] In some embodiments, the at least one polypeptide of interest is a cytokine, a nuclease, an enzyme, a fluorochrome, a growth hormone, a cytoplasmic protein, or a secreted protein.

5 [0364] In some embodiments, the at least one polypeptide of interest is selected from the group comprising or consisting of therapeutic molecules, antigens, surface receptor, or combinations thereof.

[0365] In some embodiments, the at least one nucleic acid molecule of interest, or the polypeptide encoded by the at least one nucleic acid molecule of interest, is a therapeutic gene. In some embodiments, the therapeutic gene can correct of a single-gene disorder.

10 In some embodiments, the therapeutic gene can also encode a tumor suppressor, enzyme, antibody, receptor or hormone.

[0366] In some embodiments, the cargo molecule is a therapeutic cargo molecule.

[0367] As described hereinabove, the VLP or viral vector of the invention is pseudotyped with an envelope protein that confers selectivity for CD4-positive cells.

15 Hence, in some embodiments, the VLP or viral vector of the invention selectively targets CD4-positive cells. In some embodiments, the fusogen GP160 confers selectivity for CD4 positive cells.

[0368] In some embodiments, the CD4-positive cells are CD4-positive immune cells.

[0369] In some embodiments, the CD4-positive cells further express CCR5 and/or CXCR4. In some embodiments, the CD4-positive cells express CD4 and CCR5,

20 preferably at the surface of the cell. In some embodiments, the CD4-positive cells express CD4 and CXCR4, preferably at the surface of the cell.

[0370] In some embodiments, the CD4-positive cells are selected from the group comprising or consisting of T cells, B cells, plasma cells, natural killer (NK) cells, granulocytes, monocytes, macrophages, Hofbauer cells, Kupffer cells, dendritic cells, and

25 Langerhans cells. In some embodiments, the CD4-positive cells are selected from the group comprising or consisting of T cells, NK cells, granulocytes, monocytes, macrophages, and dendritic cells. In some embodiments, the CD4-positive cells are

selected from the group comprising or consisting of T cells, monocytes, macrophages, and dendritic cells.

[0371] In a preferred embodiment, the CD4-positive cells are CD4-positive T cells.

[0372] In some embodiments, the CD4-positive cells are CD4-positive NK cells. In
5 some embodiments, the CD4-positive cells are CD4-positive monocytes. In some
embodiments, the CD4-positive cells are CD4-positive macrophages. In some
embodiments, the CD4-positive cells are CD4-positive dendritic cells.

[0373] The present invention further relates to a pharmaceutical composition comprising
the pseudotyped VLP or viral vector according to the invention, and at least one
10 pharmaceutically acceptable vehicle, excipient or carrier.

[0374] In some embodiments, the pharmaceutically acceptable vehicle, excipient or
carrier is selected in a group comprising or consisting of a solvent, a diluent, a carrier, an
excipient, a dispersion medium, a coating, and any combinations thereof. The carrier,
diluent, solvent or excipient must be “acceptable” in the sense of being compatible with
15 human administration, and not be deleterious upon being administered to an individual.
Typically, the vehicle does not produce an adverse, allergic or other untoward reaction
when administered to an individual, preferably a human individual. The term
“pharmaceutical formulation” refers to a preparation which is in such form as to permit
the biological activity of an active ingredient contained therein to be effective, and which
20 contains no additional components which are unacceptably toxic to a subject to which the
formulation would be administered. Thus, in some embodiments, a “pharmaceutically
acceptable carrier” refers to an ingredient in a pharmaceutical formulation, other than an
active ingredient, which is nontoxic to a subject. A pharmaceutically acceptable carrier
includes, but is not limited to, a buffer, excipient, stabilizer, or preservative. In some
25 aspects, the choice of carrier is determined in part by the method of administration.
Illustratively, suitable preservatives may include, for example, methylparaben,
propylparaben, sodium benzoate, and benzalkonium chloride. In some aspects, a mixture
of two or more preservatives is used. The preservative or mixtures thereof are typically
present in an amount of about 0.0001% to about 2% by weight of the total composition.

Pharmaceutically acceptable carriers are generally nontoxic to recipients at the dosages and concentrations employed, and include, but are not limited to: buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; 5 hexamethonium chloride; benzalkonium chloride; benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, 10 glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g. Zn-protein complexes); and/or non-ionic surfactants such as polyethylene glycol (PEG).

15 [0375] In some embodiments, the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention is further administrated with a buffering agent. Buffering agents in some aspects are included in the compositions. Suitable buffering agents include, for example, citric acid, sodium citrate, phosphoric acid, potassium phosphate, and various other acids and salts. In some aspects, a mixture of two 20 or more buffering agents is used. The buffering agent or mixtures thereof are typically present in an amount of about 0.001% to about 4% by weight of the total composition. Methods for preparing administrable pharmaceutical compositions are known.

[0376] In some embodiments, the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention is administered parenterally. The term 25 “parenteral,” as used herein, includes intravenous, intramuscular, subcutaneous, rectal, vaginal, and intraperitoneal administration. In some embodiments, the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention is administered to the subject using peripheral systemic delivery by intravenous, intraperitoneal, or subcutaneous injection. the pseudotyped VLP or viral vector of the 30 invention, or the pharmaceutical composition of the invention is provided as sterile liquid

preparations, e.g., isotonic aqueous solutions, suspensions, emulsions, dispersions, or viscous compositions, which may in some aspects be buffered to a selected pH. Liquid or viscous compositions can comprise carriers, which can be a solvent or dispersing medium containing, for example, water, saline, phosphate buffered saline, polyol (for example, glycerol, propylene glycol, liquid polyethylene glycol) and suitable mixtures thereof. Sterile injectable solutions can be prepared by incorporating the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention in a solvent, such as in admixture with a suitable carrier, diluent, or excipient such as sterile water, physiological saline, glucose, dextrose, or the like. The pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention can contain auxiliary substances such as wetting, dispersing, or emulsifying agents (e.g., methylcellulose), pH buffering agents, gelling or viscosity enhancing additives, preservatives, flavoring agents, and/or colors, depending upon the route of administration and the preparation desired.

[0377] Various additives which enhance the stability and sterility of the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention, including antimicrobial preservatives, antioxidants, chelating agents, and buffers, can be added. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, and sorbic acid. Prolonged absorption of the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0378] In some embodiments, the pharmaceutical composition further comprises at least one other therapeutic agent. Non-limitative examples of therapeutic agents include drugs, pharmaceutical agents, peptides, proteins, nanoparticles, cells, other VLPs or viral vectors, or the likes. In some embodiments, the other therapeutic agent is for treating a disease such as cancer, auto-immune disease, infectious disease (e.g., a virus such as HIV), genetic disease, and the like. Such therapeutic agents are known by the skilled in the art and are commonly used in medical practice. In some embodiments, the pharmaceutical composition further includes other pharmaceutically active agents or drugs selected from the group comprising or consisting of chemotherapeutic agents, e.g.,

asparaginase, busulfan, carboplatin, cisplatin, daunorubicin, doxorubicin, fluorouracil, gemcitabine, hydroxyurea, methotrexate, paclitaxel, rituximab, vinblastine, and/or vincristine. The pharmaceutical composition in some embodiments contains the composition in amounts effective to treat or prevent the disease or condition, such as a
5 therapeutically effective or prophylactically effective amount. Therapeutic or prophylactic efficacy in some embodiments is monitored by periodic assessment of treated subjects. The desired dosage can be delivered by a single bolus administration of the composition, by multiple bolus administrations of the composition, or by continuous infusion administration of the composition. In some embodiments, the pharmaceutical
10 composition does not include a chemotherapeutic.

[0379] In some embodiments, the other therapeutic agent is administered prior, concomitantly or after the VLP or viral vector according to the invention. In some embodiments, the other therapeutic agent is administered prior to the VLP or viral vector according to the invention, preferably between about 1 month and about 1 minute prior
15 to the VLP or viral vector according to the invention. In some embodiments, the other therapeutic agent is administered concomitantly with the VLP or viral vector according to the invention. In some embodiments, the other therapeutic agent is administered after the VLP or viral vector according to the invention, preferably between about 1 minute and about 1 month after the VLP or viral vector according to the invention.

20 [0380] In some embodiments, the other therapeutic agent is for treating cancer. In some embodiments, the other therapeutic agent is for treating an autoimmune disease. In some embodiments, the other therapeutic agent is for treating a genetic disease. In some embodiments, the other therapeutic agent is for treating an infectious disease.

[0381] For the particular purpose of human administration, the pharmaceutical
25 compositions should meet general safety and purity standards as required by regulatory offices, such as, for example, the Food and Drugs Administration (FDA) Office or the European Medicines Agency (EMA).

[0382] The present invention further relates to the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention, for use as a medicament.

5 [0383] The present invention further relates to the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention, for use for treating a disease or condition in a subject in need thereof. In some embodiments, the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention is for use for treating a disease or condition in a subject in need thereof, wherein said disease is selected from the group comprising or consisting of cancer, autoimmune
10 diseases, genetic diseases, and infectious diseases.

[0384] The present invention further relates to the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention, for use for treating cancer or an autoimmune disease in a subject in need thereof.

15 [0385] In some embodiments, the present invention relates to the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention, for use for treating cancer in a subject in need thereof. In some embodiments, the present invention relates to the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention, for use for treating an autoimmune disease in a subject in need thereof. In some embodiments, the present invention relates to the
20 pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention, for use for treating a genetic disease in a subject in need thereof. In some embodiments, the present invention relates to the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention, for use for treating an infectious disease in a subject in need thereof.

25 [0386] The present invention further relates to a method of treating and/or preventing a disease or condition in a subject in need thereof, comprising administering to said subject a therapeutically effective dose of the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention. In some embodiments, the present invention relates to a method of treating and/or preventing cancer in a subject in need

thereof, comprising administering to said subject a therapeutically effective dose of the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention. In some embodiments, the present invention relates to a method of treating and/or preventing an autoimmune disease in a subject in need thereof, comprising
5 administering to said subject a therapeutically effective dose of the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention. In some embodiments, the present invention relates to a method of treating and/or preventing a genetic disease in a subject in need thereof, comprising administering to said subject a therapeutically effective dose of the pseudotyped VLP or viral vector of the invention, or
10 the pharmaceutical composition of the invention. In some embodiments, the present invention relates to a method of treating and/or preventing an infectious disease in a subject in need thereof, comprising administering to said subject a therapeutically effective dose of the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention.

15 [0387] In some embodiments, the subject has been treated with a therapeutic agent targeting the disease or condition, *e.g.*, a tumor, prior to administration of the composition. In some aspects, the subject is refractory or non-responsive to the other therapeutic agent. In some embodiments, the subject has persistent or relapsed disease, *e.g.*, following treatment with another therapeutic intervention. In some embodiments,
20 the administration effectively treats the subject despite the subject having become resistant to another therapy.

[0388] In some embodiments, the subject is responsive to the other therapeutic agent, and treatment with the therapeutic agent reduces disease burden. In some aspects, the subject is initially responsive to the therapeutic agent, but exhibits a relapse of the disease
25 or condition over time. In some embodiments, the subject has not relapsed. In some such embodiments, the subject is determined to be at risk for relapse, such as at a high risk of relapse, and thus the composition is administered prophylactically, *e.g.*, to reduce the likelihood of or prevent relapse. In some aspects, the subject has not received prior treatment with another therapeutic agent.

[0389] The administration of the pseudotyped VLP or viral vector of the invention or the pharmaceutical composition of the invention may be carried out in any convenient manner known to those of skill in the art. For example, the pseudotyped VLP or viral vector of the invention or the pharmaceutical composition of the invention may be administered to a subject by aerosol inhalation, injection, ingestion, transfusion, implantation or transplantation. In some embodiments, the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention may be administered to a patient transarterially, subcutaneously, intradermally, intratumorally, intranodally, intramedullary, intramuscularly, by intravenous (i.v.) injection, or intraperitoneally. In some embodiments, the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention is injected directly into a site of a local disease site in the subject, a lymph node, an organ, a tumor, and the like.

[0390] For the prevention or treatment of disease, the appropriate dosage may depend on the type of disease to be treated, the severity and course of the disease, whether the composition is administered for preventive or therapeutic purposes, previous therapy, the subject's clinical history and response to the treatment, and the discretion of the attending physician. In some embodiments, the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention is suitably administered to the subject at one time or over a series of treatments.

[0391] In some embodiments, the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention is administered as part of a combination treatment, such as simultaneously with or sequentially with, in any order, another therapeutic intervention, such as, and non-imitatively, an antibody or produced cell or receptor or agent, such as a cytotoxic or therapeutic agent. In some embodiments, the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention is co-administered with one or more additional therapeutic agents or in connection with another therapeutic intervention, either simultaneously or sequentially in any order. In some embodiments, the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention is co-administered with another therapy sufficiently close in time such that the composition enhances the effect of one or

more additional therapeutic agents, or vice versa. In some embodiments, the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention is administered prior to the one or more additional therapeutic agents. In some embodiments, the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention is administered after the one or more additional therapeutic agents. In some embodiments, a chemotherapeutic agent is co-administered. In some embodiments, a chemotherapeutic agent is not co-administered.

[0392] In some embodiments, the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention is administered without a lymphodepletion step, such as the administration of cyclophosphamide and/or fludarabine.

[0393] In some embodiments, the subject can be administered a conditioning therapy after the administration of the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention, to kill certain immune cells that are not transduced with the CAR encoded by the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention. This can be done by including a selection marker that is encoded by the nucleic acid cargo of interest.

[0394] In some embodiments, a specific dosage regimen of the present disclosure includes a lymphodepletion step after the administration of the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention.

[0395] In some embodiments, the pseudotyped VLP or viral vector of the invention, or the pharmaceutical composition of the invention is administered following the diagnosis of CRS, appropriate CRS management strategies to mitigate the physiological symptoms of uncontrolled inflammation without dampening the antitumor efficacy of the in vivo generated cells (e.g., CAR T cells). CRS management strategies are known in the art. For example, systemic corticosteroids may be administered to rapidly reverse symptoms of sCRS (e.g., grade 3 CRS) without compromising initial antitumor response. CRS is generally managed based on the severity of the observed syndrome and interventions are

tailored as such. CRS management decisions may be based upon clinical signs and symptoms and response to interventions, not solely on laboratory values alone.

[0396] In some embodiments, the disease is cancer.

[0397] In some embodiments, the pseudotyped VLP or viral vector of the invention, or
5 the pharmaceutical composition of the invention can be used in methods for the treatment of any condition related to a cancer, such as a cell-mediated immune response against a tumor cell(s), where it is desirable to treat or alleviate the disease.

[0398] In some embodiments, the cancer is selected from the group comprising or consisting of carcinoma, blastoma, sarcoma, certain leukemia or lymphoid malignancies,
10 benign and malignant tumors, malignancies e.g., sarcomas, carcinomas, and melanomas.

[0399] In some embodiments, the cancer is selected from the group comprising or consisting of breast cancer, prostate cancer, ovarian cancer, cervical cancer, skin cancer, pancreatic cancer, colorectal cancer, renal cancer, liver cancer, brain cancer, lymphoma, leukemia, lung cancer, thyroid cancer, and the like.

[0400] In some embodiments, the cancer is selected from the group comprising or consisting of non-solid tumors (such as hematological tumors) or solid tumors. In some
15 embodiments, the cancer is selected from the group comprising or consisting of adult tumors/cancers and pediatric tumors/cancers. In one embodiment, the cancer is a hematological tumor. In one embodiment, the cancer is a carcinoma. In one embodiment,
20 the cancer is a sarcoma. In one embodiment, the cancer is a leukemia. In one embodiment the cancer is a solid tumor.

[0401] In some embodiments, the cancer is selected from the group comprising or consisting of fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon
25 carcinoma, lymphoid malignancy, pancreatic cancer, breast cancer, lung cancers, ovarian cancer, prostate cancer, hepatocellular carcinoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, medullary thyroid carcinoma, papillary thyroid carcinoma, pheochromocytomas sebaceous gland carcinoma, papillary

carcinoma, papillary adenocarcinomas, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, Wilms' tumor, cervical cancer, testicular tumor, seminoma, bladder carcinoma, melanoma, CNS tumors (such as a glioma (such as brainstem glioma and mixed gliomas), glioblastoma (also
5 known as glioblastoma multiforme) astrocytoma, CNS lymphoma, germinoma, medulloblastoma, Schwannoma craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, neuroblastoma, retinoblastoma and brain metastases).

[0402] In some embodiments, the cancer is selected from the group comprising or
10 consisting of esophageal carcinoma, hepatocellular carcinoma, basal cell carcinoma (a form of skin cancer), squamous cell carcinoma (various tissues), bladder carcinoma, including transitional cell carcinoma (a malignant neoplasm of the bladder), bronchogenic carcinoma, colon carcinoma, colorectal carcinoma, gastric carcinoma, lung carcinoma, including small cell carcinoma and non-small cell carcinoma of the lung,
15 adrenocortical carcinoma, thyroid carcinoma, pancreatic carcinoma, breast carcinoma, ovarian carcinoma, prostate carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinoma, cystadenocarcinoma, medullary carcinoma, renal cell carcinoma, ductal carcinoma in situ or bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's
20 tumor, cervical carcinoma, uterine carcinoma, testicular carcinoma, osteogenic carcinoma, epithelial carcinoma, and nasopharyngeal carcinoma.

[0403] In some embodiments, the cancer is selected from the group comprising or consisting of light chain myeloma, non-secretory myeloma, monoclonal gamopathy of undertermined significance (MGUS), plasmacytoma (e.g., solitary, multiple solitary,
25 extramedullary plasmacytoma), amyloidosis, and multiple myeloma. In some embodiments, methods of treating multiple myeloma are provided. In some embodiments, the multiple myeloma is refractory myeloma. In some embodiments, the multiple myeloma is relapsed myeloma.

[0404] In some embodiments, the cancer is selected from the group comprising or
30 consisting of superficial spreading melanoma, nodular melanoma, lentigo maligna

melanoma, acral lentiginous melanoma, amelanotic melanoma, or melanoma of the skin (e.g., cutaneous, eye, vulva, vagina, rectum melanoma). In some embodiments, the melanoma is cutaneous melanoma. In some embodiments, the melanoma is refractory melanoma. In some embodiments, the melanoma is relapsed melanoma.

- 5 [0405] In some embodiments, the cancer is selected from the group comprising or consisting of angiosarcoma, chondrosarcoma, chordoma, endothelial sarcoma, Ewing's sarcoma, fibrosarcoma, gastrointestinal stromal tumor, leiomyosarcoma, liposarcoma, lymphangiosarcoma, lymphangioendothelial sarcoma, mesothelioma, malignant peripheral nerve sheath tumor, myxosarcoma, osteogenic sarcoma, osteosarcoma, 10 pleomorphic sarcoma, rhabdomyosarcoma, synovial sarcoma, synovial sarcoma, and other soft tissue sarcomas. In some embodiments, the sarcoma is synovial sarcoma. In some embodiments, the sarcoma is liposarcoma such as myxoid/round cell liposarcoma, differentiated/dedifferentiated liposarcoma, or pleomorphic liposarcoma. In some embodiments, the sarcoma is myxoid/round cell liposarcoma. In some embodiments, the 15 sarcoma is refractory sarcoma. In some embodiments, the sarcoma is relapsed sarcoma.

- [0406] In some embodiments, the subject has been treated with a therapeutic agent targeting the disease or condition, e.g., the tumor, prior to administration of the composition. In some aspects, the subject is refractory or non-responsive to the other therapeutic agent. In some embodiments, the subject has persistent or relapsed disease, 20 e.g., following treatment with another therapeutic intervention, including chemotherapy, radiation, and/or hematopoietic stem cell transplantation (HSCT), e.g., allogeneic HSCT. In some embodiments, the administration effectively treats the subject despite the subject having become resistant to another therapy.

- [0407] In some embodiments, the subject is responsive to the other therapeutic agent, 25 and treatment with the therapeutic agent reduces disease burden. In some aspects, the subject is initially responsive to the therapeutic agent, but exhibits a relapse of the disease or condition over time. In some embodiments, the subject has not relapsed. In some such embodiments, the subject is determined to be at risk for relapse, such as at a high risk of relapse, and thus the composition is administered prophylactically, e.g., to reduce the

likelihood of or prevent relapse. In some aspects, the subject has not received prior treatment with another therapeutic agent.

[0408] In some embodiments, the disease is an autoimmune disease.

[0409] In some embodiments, the autoimmune disease is selected from the group
 5 comprising or consisting of Acromegaly, Acquired aplastic, Acquired hemophilia, Agammaglobulinemia, primary, Alopecia areata, Ankylosing spondylitis (AS), Anti-NMDA receptor encephalitis, Antiphospholipid syndrome (APS) , catastrophic antiphospholipid syndrome (CAPS)/Asherson's syndrome, Arteriosclerosis, Autoimmune Addison's disease (AAD), Autoimmune autonomic ganglionopathy
 10 (AAG)/autoimmune dysautonomia , autoimmune gastrointestinal dysmotility (AGID), Autoimmune encephalitis , acute disseminated encephalomyelitis (ADEM), Autoimmune gastritis, Autoimmune hemolytic anemia (AIHA), Autoimmune hepatitis (AIH), Autoimmune hyperlipidemia, Autoimmune hypophysitis/lymphocytic hypophysitis, Autoimmune inner ear disease (AIED), Autoimmune lymphoproliferative syndrome
 15 (ALPS), Autoimmune myelofibrosis, Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune pancreatitis (AIP), Autoimmune polyglandular syndromes, types I, II, & III (APS type 1, APS type 2, APS type 3, APECED), Autoimmune progesterone dermatitis, Autoimmune retinopathy (AIR), Autoimmune sudden sensorineural hearing loss (SNHL), Balo disease, Behçet's disease, Birdshot chorioretinopathy/birdshot uveitis,
 20 Bullous pemphigoid, Castleman disease, Celiac disease, Chagas disease, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic autoimmune urticaria, Churg-Strauss syndrome/eosinophilic granulomatosis with polyangiitis (EGPA), Cogan's syndrome, Cold agglutinin disease, CREST syndrome , limited cutaneous systemic sclerosis, Crohn's disease (CD), Cronkhite-Canada syndrome (CSS), Cryptogenic
 25 organizing pneumonia (COP), Dermatitis herpetiformis, Dermatomyositis, Diabetes, type 1, Discoid lupus, Dressler's syndrome/postmyocardial infarction/postpericardiotomy syndrome, Eczema/Atopic Dermatitis, Endometriosis, Eosinophilic esophagitis/eosinophilic gastroenteritis, Eosinophilic fasciitis, Erythema nodosum, Essential mixed cryoglobulinemia, Evans syndrome, Fibrosing alveolitis/Idiopathic
 30 pulmonary fibrosis (IPF), Giant cell arteritis/temporal arteritis/Horton's disease, Giant

Cell Myocarditis, Glomerulonephritis, Goodpasture's syndrome/anti-GBM/anti-TBM disease, Granulomatosis with polyangiitis (GPA)/Wegener's granulomatosis, Graves disease/thyroid eye disease, Guillain-Barré syndrome (GBS), Hashimoto's thyroiditis/chronic lymphocytic thyroiditis/autoimmune thyroiditis, Henoch-Schönlein purpura/IgA vasculitis, Hidradenitis suppurativa, Hurst's disease/acute hemorrhagic leukoencephalitis (AHLE), Hypogammaglobulinemia, IgA nephropathy/Berger's disease, Immune-mediated necrotizing myopathy (IMNM), Immune thrombocytopenia (ITP)/autoimmune thrombocytopenic purpura/autoimmune thrombocytopenia, Inclusion body myositis, IgG4-related sclerosing disease (ISD), Interstitial cystitis, Juvenile idiopathic arthritis/Adult-onset Still's disease, Juvenile polymyositis, Juvenile dermatomyositis, juvenile myositis, Kawasaki disease, Lambert-Eaton myasthenic syndrome (LEMS), Leukocytoclastic vasculitis, Lichen planus, Lichen planopilaris, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), linear IgA bullous dermatosis (LABD), Lupus nephritis, Lyme disease/chronic Lyme disease/post-treatment Lyme disease syndrome (PTLDS), Lymphocytic colitis/microscopic colitis, Lymphocytic hypophysitis/autoimmune hypophysitis, Ménière's disease, Microscopic polyangiitis (MPA)/ANCA-associated vasculitis, Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multifocal motor neuropathy, Multiple sclerosis (MS), Myalgic encephalomyelitis (ME)/ Chronic fatigue syndrome (CFS), Myasthenia gravis (MG), Narcolepsy, Neuromyelitis Optica/Devic's disease, Ocular cicatricial pemphigoid, Opsoclonus-myoclonus syndrome (OMS), Palindromic rheumatism, Paraneoplastic cerebellar degeneration, Paraneoplastic pemphigus, Parry-Romberg syndrome (PRS)/Hemifacial atrophy (HFA)/Progressive facial hemiatrophy, Paroxysmal nocturnal hemoglobinuria (PNH), Peripheral uveitis/pars planitis, PANS/PANDAS, Parsonage-Turner syndrome, Pemphigus gestationis/herpes gestationis, Pemphigus foliaceus, Pemphigus vulgaris, Pernicious anemia, POEMS syndrome, Polyarteritis nodosa, Polymyalgia rheumatica, Polymyositis, Postural orthostatic tachycardia syndrome (POTS), Primary biliary cirrhosis (PBC)/primary biliary cholangitis, Primary sclerosing cholangitis (PSC), Psoriasis, Palmoplantar Pustulosis, Psoriatic arthritis, Pulmonary fibrosis, idiopathic (IPF), Pure red cell aplasia (PRCA), Pyoderma gangrenosum, Rasmussen's encephalitis, Raynaud's syndrome/phenomenon, Reactive arthritis/Reiter's syndrome, Reflex sympathetic

dystrophy syndrome (RSD)/Complex regional pain syndrome (CRPS), Relapsing polychondritis, Restless leg syndrome (RLS)/Willis-Ekbom disease, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome/autoimmune polyendocrine syndrome type II, Scleritis, Scleroderma, Sclerosing Mesenteritis/Mesenteric Panniculitis, Serpiginous choroidopathy, Sjögren's syndrome, Stiff person syndrome (SPS), Small fiber sensory neuropathy, Systemic lupus erythematosus (SLE), Subacute bacterial endocarditis (SBE), Subacute cutaneous lupus, Susac syndrome, Sydenham's chorea, Sympathetic ophthalmia, Takayasu's arteritis (vasculitis), Testicular autoimmunity (vasculitis, orchitis), Tolosa-Hunt syndrome, Transverse myelitis (TM),
 5 Tubulointerstitial nephritis uveitis syndrome (TINU), Ulcerative colitis (UC), Undifferentiated connective tissue disease (UCTD), Uveitis , anterior/intermediate/posterior, Vasculitis, VEXAS Syndrome, Vitiligo, and Vogt-Koyanagi-Harada syndrome (VKH).

[0410] In some embodiments, the autoimmune disease is selected from the group comprising or consisting of Acquired aplastic, Agammaglobulinemia, primary, Alopecia areata, Ankylosing spondylitis (AS), Antiphospholipid syndrome (APS) , catastrophic antiphospholipid syndrome (CAPS)/Asherson's syndrome, Autoimmune Addison's disease (AAD), Autoimmune autonomic ganglionopathy (AAG)/autoimmune dysautonomia , autoimmune gastrointestinal dysmotility (AGID), Autoimmune
 20 encephalitis , acute disseminated encephalomyelitis (ADEM), Autoimmune gastritis, Autoimmune hemolytic anemia (AIHA), Autoimmune hepatitis (AIH), Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune pancreatitis (AIP), Autoimmune polyglandular syndromes, types I, II, & III (APS type 1, APS type 2, APS type 3, APECED), Autoimmune progesterone dermatitis, Balo disease, Behçet's disease,
 25 Bullous pemphigoid, Celiac disease, Chronic inflammatory demyelinating polyneuropathy (CIDP), Churg-Strauss syndrome/eosinophilic granulomatosis with polyangiitis (EGPA), CREST syndrome , limited cutaneous systemic sclerosis, Crohn's disease (CD), Dermatitis herpetiformis, Dermatomyositis, Diabetes, type 1, Discoid lupus, Evans syndrome, Fibrosing alveolitis/Idiopathic pulmonary fibrosis (IPF),
 30 Glomerulonephritis, Goodpasture's syndrome/anti-GBM/anti-TBM disease, Granulomatosis with polyangiitis (GPA)/Wegener's granulomatosis, Graves

disease/thyroid eye disease, Guillain-Barré syndrome (GBS), Hashimoto's thyroiditis/chronic lymphocytic thyroiditis/autoimmune thyroiditis, Henoch-Schönlein purpura/IgA vasculitis, Hurst's disease/acute hemorrhagic leukoencephalitis (AHLE), IgA nephropathy/Berger's disease, Immune thrombocytopenia (ITP)/autoimmune

5 thrombocytopenic purpura/autoimmune thrombocytopenia, Juvenile idiopathic arthritis/Adult-onset Still's disease, Lambert-Eaton myasthenic syndrome (LEMS), Linear IgA disease (LAD) , linear IgA bullous dermatosis (LABD), Lupus nephritis, Ménière's disease, Mixed connective tissue disease (MCTD), Multiple sclerosis (MS), Myasthenia gravis (MG), Neuromyelitis Optica/Devic's disease, Ocular cicatricial

10 pemphigoid, Palindromic rheumatism, Paraneoplastic cerebellar degeneration, Paraneoplastic pemphigus, Paroxysmal nocturnal hemoglobinuria (PNH), Pemphigus gestationis/herpes gestationis, Pemphigus foliaceus, Pemphigus vulgaris, POEMS syndrome, Polyarteritis nodosa, Polymyalgia rheumatica, Polymyositis, Primary biliary cirrhosis (PBC)/primary biliary cholangitis, Psoriasis, Palmoplantar Pustulosis, Psoriatic

15 arthritis, Pure red cell aplasia (PRCA), Raynaud's syndrome/phenomenon, Reactive arthritis/Reiter's syndrome, Relapsing polychondritis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome/autoimmune polyendocrine syndrome type II, Scleritis, Scleroderma, Sclerosing Mesenteritis/Mesenteric Panniculitis, Serpiginous choroidopathy, Sjögren's syndrome, Small fiber sensory neuropathy, Systemic lupus

20 erythematosus (SLE), Testicular autoimmunity (vasculitis, orchitis), Tolosa-Hunt syndrome, Ulcerative colitis (UC), Undifferentiated connective tissue disease (UCTD), and Vitiligo.

[0411] In some embodiments, the disease is a genetic disease.

[0412] In some embodiments, the genetic disease is selected from the group comprising

25 or consisting of 21-hydroxylase deficiency, Alpha 1-antitrypsin deficiency, AAA syndrome (achalasia–addisonianism–alacrima syndrome), Aarskog–Scott syndrome, ABCD syndrome, Absence deformity of leg-cataract syndrome, Aceruloplasminemia, Acheiropodia, Achondrogenesis type II, Achondroplasia, Acute intermittent porphyria, Adenylosuccinate lyase deficiency, Adrenoleukodystrophy, Alagille syndrome, ADULT

30 syndrome, Aicardi–Goutières syndrome, Albinism, Alexander disease, Alfi's syndrome,

Alkaptonuria, Alport syndrome, Alternating hemiplegia of childhood, Aortic arch anomaly - peculiar facies - intellectual disability, Amish lethal microcephaly, Amyotrophic lateral sclerosis – Frontotemporal dementia, Angel-shaped phalangopiphyseal dysplasia, Alström syndrome, Alzheimer's disease, Amelogenesis imperfecta, 5 Aminolevulinic acid dehydratase deficiency porphyria, Androgen insensitivity syndrome, Angelman syndrome, Aphyalangy-syndactyly-microcephaly syndrome, Apert syndrome, Arthrogryposis–renal dysfunction–cholestasis syndrome, Ataxia telangiectasia, Axenfeld syndrome, Bainbridge–Ropers syndrome, Beare–Stevenson cutis gyrata syndrome, Beckwith–Wiedemann syndrome, Benjamin syndrome, biotinidase deficiency, Björnstad 10 syndrome, Blepharophimosis intellectual disability syndromes, Bloom syndrome, Birt–Hogg–Dubé syndrome, Brody myopathy, Brunner syndrome, CADASIL syndrome, Cat eye syndrome, CRASIL syndrome, Chronic granulomatous disorder, Campomelic dysplasia, Camptodactyly-aurinuria syndrome, Canavan disease, Carpenter Syndrome, CDKL5 deficiency disorder, Cerebral dysgenesis–neuropathy–ichthyosis–keratoderma 15 syndrome (CEDNIK), Cleft palate short stature vertebral anomalies syndrome, Combined malonic and methylmalonic aciduria (CMAMMA), Combined malonic and methylmalonic aciduria (CMAMMA), Congenital muscular dystrophy-infantile cataract-hypogonadism syndrome, Cystic fibrosis, Charcot–Marie–Tooth disease, CHARGE syndrome, Chédiak–Higashi syndrome, Chondrodysplasia, Grebe type, Cleidocranial 20 dysostosis, Cockayne syndrome, Coffin–Lowry syndrome, Cohen syndrome, Collagenopathy, types II and XI, Congenital insensitivity to pain with anhidrosis (CIPA), Congenital Muscular Dystrophy, Corneal dystrophy-perceptive deafness syndrome, Cornelia de Lange syndrome (CDLS), Cowden syndrome, CPO deficiency (coproporphyrin), Cranio-lenticulo-sutural dysplasia, Cri du chat, Crohn's disease, 25 Crouzon syndrome, Crouzonodermoskeletal syndrome (Crouzon syndrome with acanthosis nigricans), Currarino syndrome, Darier's disease, Dent's disease (Genetic hypercalciuria), Denys–Drash syndrome, De Grouchy syndrome, Dolichonychia, Down Syndrome, DiGeorge syndrome, Distal hereditary motor neuropathies, multiple types, Distal muscular dystrophy, Duchenne muscular dystrophy, Dravet syndrome, 30 Ectrodactyly-polydactyly syndrome, Edwards Syndrome, Ehlers–Danlos syndrome, Emanuel syndrome, Emery–Dreifuss syndrome, Epidermolysis bullosa, Erythropoietic protoporphyria, Fanconi anemia (FA), Fabry disease, Factor V Leiden thrombophilia,

Fatal familial insomnia, Familial adenomatous polyposis, Familial dysautonomia, Familial Creutzfeld–Jakob Disease, Familial episodic pain syndrome, Familial thoracic aortic aneurysm and aortic dissection, Feingold syndrome, FG syndrome, FBXW7 neurodevelopmental syndrome, Fibular aplasia-ectrodactyly syndrome, Fine-Lubinsky syndrome, Fragile X syndrome, Friedreich's ataxia, G6PD deficiency, Galactosemia, 5 Gaucher disease, Gerstmann–Sträussler–Scheinker syndrome, Gillespie syndrome, Glutaric aciduria, type 1 and type 2, GRACILE syndrome, GRIN2B-related neurodevelopmental disorder, Griscelli syndrome, Gustavson syndrome, Hailey–Hailey disease, Harlequin type ichthyosis, Hemochromatosis type 1, Hemochromatosis type 2A, 10 Hemochromatosis type 2B, Haemochromatosis type 3, Hemochromatosis type 4, Hemochromatosis type 5, Hemophilia, Hepatoerythropoietic porphyria, Hereditary coproporphyria, Hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu syndrome), Hereditary inclusion body myopathy, Hereditary multiple exostoses, Hereditary spastic paraplegia (infantile-onset ascending hereditary spastic paralysis), Hermansky–Pudlak 15 syndrome, Hereditary neuropathy with liability to pressure palsies (HNPP), Heterotaxy, Homocystinuria, Huntington's disease, Hunter syndrome, Hurler syndrome, Hutchinson–Gilford progeria syndrome, Hyperlysinemia, Hyperoxaluria, primary, Hyperphenylalaninemia, Hypoalphalipoproteinemia (Tangier disease), Hypochondrogenesis, Hypochondroplasia, Immunodeficiency–centromeric instability– 20 facial anomalies syndrome (ICF syndrome), Incontinentia pigmenti, Infantile cerebral and cerebellar atrophy with postnatal progressive microcephaly, Ischiopatellar dysplasia, Isodicentric 15, PRICKLE1-related progressive myoclonus epilepsy with ataxia, Jackson–Weiss syndrome, Jacobsen syndrome, Joubert syndrome, Juvenile-onset dystonia, Juvenile primary lateral sclerosis (JPLS), Keloid disorder, KIF1A-Associated 25 Neurological Disorder, Kleefstra syndrome, Kniest dysplasia, Kosaki overgrowth syndrome, Krabbe disease, Kufor–Rakeb syndrome, LCAT deficiency, Lesch–Nyhan syndrome, Li–Fraumeni syndrome, Limb-Girdle Muscular Dystrophy, Lynch syndrome, lipoprotein lipase deficiency, Malignant hyperthermia, Maple syrup urine disease, Marfan Syndrome, Maroteaux–Lamy syndrome, McCune–Albright syndrome, McLeod 30 syndrome, MEDNIK syndrome, Mediterranean fever, familial, Menkes disease, Methemoglobinemia, Methylmalonic acidemia, Micro syndrome, Microcephaly, Miller–Dieker syndrome, Morquio syndrome, Mowat–Wilson syndrome, Muenke syndrome,

Multiple endocrine neoplasia type 1 (Wermer's syndrome), Multiple endocrine neoplasia type 2, Muscular dystrophy, Muscular dystrophy, Duchenne and Becker type, Myostatin-related muscle hypertrophy, Myotonic dystrophy, Natowicz syndrome, Neurofibromatosis type I, Neurofibromatosis type II, Niemann–Pick disease, Nonketotic

5 hyperglycinemia, Nonsyndromic deafness, Noonan syndrome, Norman–Roberts syndrome, Ogden syndrome, Omenn syndrome, Osteogenesis imperfecta, Ostravik-Lindemann-Solberg syndrome, Pantothenate kinase-associated neurodegeneration, Patau syndrome (Trisomy 13), PCC deficiency (propionic acidemia), Porphyria cutanea tarda (PCT), Pendred syndrome, Peutz–Jeghers syndrome, Pfeiffer syndrome, Phelan-

10 McDermid syndrome, Phenylketonuria, Pipecolic acidemia, Pitt–Hopkins syndrome, Polycystic kidney disease, Polycystic ovary syndrome (PCOS), Porphyria, Prader–Willi syndrome, Primary ciliary dyskinesia (PCD), Primary pulmonary hypertension, Protein C deficiency, Protein S deficiency, Proximal 18q deletion syndrome, Pseudo-Gaucher disease, Pseudoxanthoma elasticum, Retinitis pigmentosa, Rett syndrome, Roberts

15 syndrome, Rubinstein–Taybi syndrome (RSTS), Sandhoff disease, Sanfilippo syndrome, Scheuermann's disease, Schwartz–Jampel syndrome, Sjogren-Larsson syndrome, Skin fragility-woolly hair-palmoplantar keratoderma syndrome, Spondyloepiphyseal dysplasia congenita (SED), Shprintzen–Goldberg syndrome, Sick cell anemia, Siderius X-linked mental retardation syndrome, Sideroblastic anemia, Sly syndrome, Smith–

20 Lemli–Opitz syndrome, Smith–Magenis syndrome, Snyder–Robinson syndrome, Spinal muscular atrophy, Spinocerebellar ataxia (types 1–29), Split hand split foot-nystagmus syndrome, SSB syndrome (SADDAN), Stargardt disease (macular degeneration), Stickler syndrome (multiple forms), Strudwick syndrome (spondyloepimetaphyseal dysplasia, Strudwick type), Tay–Sachs disease, Tetrahydrobiopterin deficiency,

25 Thanatophoric dysplasia, Thickened earlobes-conductive deafness syndrome, Treacher Collins syndrome, Tuberous sclerosis complex (TSC), Turner syndrome, Usher syndrome, Variegate porphyria, Viljoen-Kallis-Voges syndrome, von Hippel–Lindau disease, von Willebrand disease, Waardenburg syndrome, Warkany syndrome 2, Weissenbacher–Zweymüller syndrome, Weyer's ulnar ray/oligodactyly syndrome,

30 Williams syndrome, Wilson disease, Woodhouse–Sakati syndrome, Wolf–Hirschhorn syndrome, Xeroderma pigmentosum, X-linked intellectual disability and macroorchidism (fragile X syndrome), X-linked spinal-bulbar muscle atrophy (spinal and bulbar muscular

atrophy), X-linked severe combined immunodeficiency (X-SCID), X-linked sideroblastic anemia (XLSA), and Zellweger syndrome.

[0413] In some embodiments, the disease is an infectious disease.

[0414] In some embodiments, the infectious disease is selected from the group comprising or consisting of viral diseases, bacterial diseases, parasitic diseases, and the like. In some embodiments, the infectious disease is a viral disease. In some embodiments, the viral disease is selected from the group comprising or consisting of Acquired immunodeficiency syndrome (AIDS), Alkhurma haemorrhagic fever, Anaplasmosis, Anthrax, Arenavirus, Avian influenza virus, Babesiosis, Bordetella (pertussis), Borreliosis, Botulism, Brucellosis, Campylobacteriosis, Chickenpox (varicella), Chikungunya virus disease, Chlamydia infection, Cholera, Ciguatera fish poisoning (CFP), Clostridioides difficile infections, Congenital rubella, Congenital syphilis, Coronavirus, COVID-19, Cowpox, Coxsackievirus, Creutzfeldt-Jakob disease (CJD), Crimean-Congo haemorrhagic fever (CCHF), Cryptosporidiosis, Cutaneous warts, Dengue, DHF, Diphtheria, Ebola virus disease, Echinococcosis, Enteric fever, Enterohaemorrhagic Escherichia coli (EHEC) infection, Enterovirus, Epidemic louse-borne typhus, Escherichia coli infection, Febris recurrens, Flu, Food- and waterborne diseases, German measles (rubella), Giardiasis, Gonorrhoea, Haemophilus infection, Haemorrhagic fever, Haemorrhagic fever with renal syndrome, Hantavirus infection, Hepatitis, Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis E, HIV infection, Human papillomavirus infection (HPV), Influenza in humans, avian origin, Influenza in humans, pandemic, Influenza in humans, seasonal, Influenza in humans, swine origin, Invasive Haemophilus influenzae disease, Invasive meningococcal disease, Invasive pneumococcal disease, Japanese encephalitis virus, Lassa fever, Legionnaires' disease, Leishmaniasis, Leptospirosis, Listeriosis, Louse borne relapsing fever, Louse-borne diseases, Louse-borne typhus, Lyme disease (borreliosis), Lymphogranuloma venereum (LGV), Malaria, Marine biotoxins related diseases, Measles, Meningococcal disease, Middle East respiratory syndrome coronavirus, Mosquito-borne diseases, Mpox (Monkeypox), Mumps, Nephropathia epidemica, Nipah virus disease, Norovirus infection, Paratyphoid fever, Pertussis, Piroplasmosis, Plague, Pneumococcal disease,

Poliomyelitis, Q fever, Quintan fever, Rabies, Respiratory Syncytial Virus (RSV), Rickettsiosis, Rift Valley fever, Rotavirus infection, Rubella, S. pneumoniae, Salmonellosis, Sandfly-borne diseases, SARS-CoV-2, Schmallenberg virus (SBV), Seasonal influenza, Severe acute respiratory syndrome (SARS), Sexually transmitted infections, Shigellosis, Sindbis fever, Smallpox, Streptococcus pneumoniae, Swine-origin influenza, Syphilis, Syphilis, congenital, Tetanus, Tick-borne diseases, Tick-borne encephalitis (TBE), Tick-borne relapsing fever (TBRF), Toscana virus infection, Toxoplasmosis, congenital, Trench fever, Trichinellosis, Tuberculosis (TB), Tularaemia, Typhoid and paratyphoid fever, Vaccine-preventable diseases, Variant Creutzfeldt-Jakob disease (vCJD), Varicella, Viral haemorrhagic fever, Viral hepatitis, West Nile virus infection, Whooping cough (pertussis), Yellow fever, Yersiniosis, Zika virus disease, Zoonosis. In some embodiments, the viral disease is AIDS.

[0415] The present invention further relates to a nucleic acid molecule or a plurality of nucleic acid molecules encoding the pseudotyped VLP or viral vector of the invention.

15 The present invention further relates to a pharmaceutical composition comprising a nucleic acid molecule or a plurality of nucleic acid molecules encoding the pseudotyped VLP or viral vector of the invention.

[0416] The present invention further relates to the use of the nucleic acid molecule or the plurality of nucleic acid molecules encoding the pseudotyped VLP or viral vector of the invention, for use as a medicament. The present invention further relates to the use of the nucleic acid molecule or the plurality of nucleic acid molecules encoding the pseudotyped VLP or viral vector of the invention, for use for treating and/or preventing a disease selected from the group comprising or consisting of cancer, autoimmune diseases, genetic diseases, infectious diseases.

25 [0417] The present invention further relates to the use of the pseudotyped VLP or viral vector of the invention for transfecting or transducing a cell or a population of cells.

[0418] The present invention further relates to a method of transfecting or transducing a cell or a population of cells comprising contacting said cell or population of cells with the

pseudotyped VLP or viral vector of the invention. In some embodiments, the method is a method of delivering a cargo of interest into a cell or a population of cells.

[0419] In some embodiments, the method is an *in vitro* or *ex vivo* method.

[0420] In some embodiments, the method is an *in vivo* method. In some embodiments,
5 the method is a non-therapeutic *in vivo* method.

[0421] In some embodiments, the population of cells is heterogenous. In some embodiments, the population of cells is homogenous, *i.e.*, the population of cells comprise one unique cell type. In some embodiments, the population of cells is substantially free of contamination by other cell types and/or other biological or chemical contaminants.

10 [0422] In some embodiments, the cell or population of cells is an immune cell or a population of immune cells. In some embodiments, the cell or population of cells is a CD4-positive cell or a population of CD4-positive cells. In some embodiments, the cell or population of cells is a T cell or a population of T cells.

[0423] Hence, in some embodiments, the method is a method of modifying, delivering
15 a payload to, or transfecting or transducing immune cells, preferably CD4-positive cells, more preferably T cells, in an individual (*i.e.*, *in vivo*). In some embodiments, the method is a method of modifying, delivering a payload to, or transfecting or transducing immune cells, preferably CD4-positive cells, more preferably T cells, *in vitro* or *ex vivo*.

[0424] The present invention further relates to a cell or a population of cells transfected
20 or transduced by the pseudotyped VLP or viral vector of the invention. In some embodiments, the cell or population of cells comprises a cargo molecule delivered by the pseudotyped VLP or viral vector of the invention.

[0425] The present invention further relates to the use of the cell or population of cells transfected or transduced by the pseudotyped VLP or viral vector of the invention, for use
25 as a medicament. The present invention further relates to the use of the cell or population of cells transfected or transduced by the pseudotyped VLP or viral vector of the invention, for use for treating and/or preventing a disease selected from the group comprising or consisting of cancer, autoimmune diseases, genetic diseases, infectious diseases.

[0426] The present invention further relates to the pseudotyped VLP or viral vector of the invention, the pharmaceutical composition according to the invention, the nucleic acid molecule or the plurality of nucleic acid molecules encoding the pseudotyped VLP or viral vector of the invention, or the cell or population of cells transfected or transduced by the pseudotyped VLP or viral vector of the invention, for the manufacture of a medicament for treating cancer. The present invention further relates to the pseudotyped VLP or viral vector of the invention, the pharmaceutical composition according to the invention, the nucleic acid molecule or the plurality of nucleic acid molecules encoding the pseudotyped VLP or viral vector of the invention, or the cell or population of cells transfected or transduced by the pseudotyped VLP or viral vector of the invention, for the manufacture of a medicament for treating an autoimmune disease. The present invention further relates to the pseudotyped VLP or viral vector of the invention, the pharmaceutical composition according to the invention, the nucleic acid molecule or the plurality of nucleic acid molecules encoding the pseudotyped VLP or viral vector of the invention, or the cell or population of cells transfected or transduced by the pseudotyped VLP or viral vector of the invention, for the manufacture of a medicament for treating a genetic disease. The present invention further relates to the pseudotyped VLP or viral vector of the invention, the pharmaceutical composition according to the invention, the nucleic acid molecule or the plurality of nucleic acid molecules encoding the pseudotyped VLP or viral vector of the invention, or the cell or population of cells transfected or transduced by the pseudotyped VLP or viral vector of the invention, for the manufacture of a medicament for treating an infectious disease.

[0427] The present invention further relates to a method of treating and/or preventing a disease or condition in a subject in need thereof, comprising administering to said subject a therapeutically effective dose of the pseudotyped VLP or viral vector of the invention, the pharmaceutical composition according to the invention, the nucleic acid molecule or the plurality of nucleic acid molecules encoding the pseudotyped VLP or viral vector of the invention, or the cell or population of cells transfected or transduced by the pseudotyped VLP or viral vector of the invention. In some embodiments, the present invention relates to a method of treating and/or preventing cancer in a subject in need thereof, comprising administering to said subject a therapeutically effective dose of the

pseudotyped VLP or viral vector of the invention, the pharmaceutical composition according to the invention, the nucleic acid molecule or the plurality of nucleic acid molecules encoding the pseudotyped VLP or viral vector of the invention, or the cell or population of cells transfected or transduced by the pseudotyped VLP or viral vector of the invention. In some embodiments, the present invention relates to a method of treating and/or preventing an autoimmune disease in a subject in need thereof, comprising administering to said subject a therapeutically effective dose of the pseudotyped VLP or viral vector of the invention, the pharmaceutical composition according to the invention, the nucleic acid molecule or the plurality of nucleic acid molecules encoding the pseudotyped VLP or viral vector of the invention, or the cell or population of cells transfected or transduced by the pseudotyped VLP or viral vector of the invention. In some embodiments, the present invention relates to a method of treating and/or preventing a genetic disease in a subject in need thereof, comprising administering to said subject a therapeutically effective dose of the pseudotyped VLP or viral vector of the invention, the pharmaceutical composition according to the invention, the nucleic acid molecule or the plurality of nucleic acid molecules encoding the pseudotyped VLP or viral vector of the invention, or the cell or population of cells transfected or transduced by the pseudotyped VLP or viral vector of the invention. In some embodiments, the present invention relates to a method of treating and/or preventing an infectious disease in a subject in need thereof, comprising administering to said subject a therapeutically effective dose of the pseudotyped VLP or viral vector of the invention, the pharmaceutical composition according to the invention, the nucleic acid molecule or the plurality of nucleic acid molecules encoding the pseudotyped VLP or viral vector of the invention, or the cell or population of cells transfected or transduced by the pseudotyped VLP or viral vector of the invention.

[0428] In some embodiments, the method of treating and/or preventing a disease or condition as described herein comprises the steps of:

- (i) transfecting or transducing *ex vivo* a cell or population of cells isolated with the pseudotyped VLP or viral vector of the invention, the pharmaceutical composition according to the invention, or the nucleic acid molecule or the

plurality of nucleic acid molecules encoding the pseudotyped VLP or viral vector of the invention, and

- (ii) administering to the subject a therapeutically effective dose of the cell or population of cells obtained at step (i).

5 [0429] In some embodiments, the method of treating and/or preventing a disease or condition as described herein comprises the steps of:

- (i) isolating a cell or a population of cells from the subject;
- (ii) transfecting or transducing *ex vivo* the cell or population of cells isolated at
10 step (i) with the pseudotyped VLP or viral vector of the invention, the pharmaceutical composition according to the invention, or the nucleic acid molecule or the plurality of nucleic acid molecules encoding the pseudotyped VLP or viral vector of the invention, and
- (iii) administering to the subject a therapeutically effective dose of the cell or population of cells obtained at step (ii).

15 [0430] In some embodiments, the cells are cultured at step (i). In some embodiments, the cells are amplified at step (i).

[0431] In some embodiments, the present invention further relates to methods for of delivering a chimeric antigen receptor to an immune cell, preferably a CD4-positive cell, more preferably a T cell in a subject.

20 [0432] In some embodiments, the present invention is not for use as a vaccine. Thus, in some embodiment, the VLP or viral vector as described herein is not for use as a vaccine and/or is not comprised in a vaccine composition.

BRIEF DESCRIPTION OF THE DRAWINGS

- [0433] **Figure 1** is a FACS plot showing GFP expression in PBMC after transduction with VLP pseudotyped with wild type GP160.
- 5 [0434] **Figure 2** is a FACS plot showing GFP expression in PBMC after transduction with VLP pseudotyped with GP160 LAI.
- [0435] **Figure 3** is a FACS plot showing GFP expression in PBMC after transduction with VLP pseudotyped with GP160 SIV Mac251.
- [0436] **Figure 4** is a FACS plot showing GFP expression in NALM-6 cells after
10 transduction with VLP pseudotyped with GP160 TM1.
- [0437] **Figure 5** is a FACS plot showing GFP expression in NALM-6 after transduction with VLP pseudotyped with GP160 TM1.
- [0438] **Figure 6** is a histogram showing CD4+ cell transduction values, relative to HXB2 WT GFP %. Addition of cytoplasmic TM-1 tail leads to improvement in CD4+ cell
15 transduction. Effect is observed for WT but also generalizable for other sequences, with even more differences.
- [0439] **Figure 7A-7C** is a set of dot plots and histogram showing transduction efficiency. (**Fig. 7A**) CD4+ PMBCs cell transduction values, relative to HXB2-TM1 GFP %. Variants tested with TM1 background. (**Fig. 7B**) F06 WT HXB2, GFP%. (**Fig. 7C**)
20 F28 in CD4+ PBMCs, GFP%.
- [0440] **Figure 8A-8B** is a set of schemes showing sequence comparison (**Fig. 8A**) and phylogenetic tree (**Fig 8B**) of the tested variants.

EXAMPLES

[0441] The present invention is further illustrated by the following examples.

Example 1:

5 **Materials and Methods**

[0442] *Generation of DNA sequences*

[0443] Envelope, and fusogen sequences were cloned in CMV based expression vector scaled and sequence-verified using standard methods. Lentiviral transgene vectors, encoding GFP or CAR expressing constructs were cloned in to pCCL vector using
10 standard methods.

[0444] *Production and titration of pseudotyped viral-like particle (VLP) and lentiviral vectors*

[0445] Pseudotyped Lentiviral vectors (LVV) and VLPs were produced using HEK293T cells seeded in 10cm plates. Briefly, cells were transduced with 0.3-1.5 ug of plasmids encoding fusogen, Transgene (e.g. green fluorescent protein, CAR) and GAGPOL-TAT
15 REV (2nd generation packaging).

[0446] In some cases, up to 10ug Transgene and GAGPOL encoding plasmids were used. In some cases, viruses were packaged with 3rd generation lentiviral packaging system. In those cases, pspAX2 was substituted for 10ug of GAGPOL encoding plasmid
20 and 10ug of REV encoding plasmid. Plasmid quantities were scale proportionally as needed for larger preparations.

[0447] The physical titer of VLP/LLV was determined using p24 ELISA detection (performed+ according to the manufacturers' protocol, Takara bio, 631476 Lenti-X™ p24 Rapid Titer Kit).

25 [0448] Functional titer was measured by infecting 240000 cells of the corresponding

cell line (HEK293T or TMZ-1b) with serially diluted LV amounts and the following formula: Functional Titter (FT) expressed in Transducing Units per mL (TU/mL) is calculated according to the formula $FT = (\%GFP \text{ positive cells} / 100) * \text{number of infected cells} / \text{added LV volume in mL}$.

5 [0449] *Transduction of PBMCs*

[0450] PBMCs were isolated from human blood by Density Gradient Centrifugation using Ficoll. T cells (55000 per well) were seeded in wells of a 96-well plate and activated using CD3/CD28 magnetic dynabeads (Thermo Fisher) and supplemented with IL-2, IL-7 and IL-15. T-cells were infected with serially diluted LV 2 days after activation. The ability of LLVs or VLPs to infect various T cell subtypes was monitored over the course of a 2-week period using FACS to measure GFP positive cells. T cell subtype was assigned to each GFP-expressing and non-expressing cell using various subtype specific antibodies that were conjugated to a fluorophore: CD4 (CD4-APC-Vio770, human, REA623 Miltenyi), CD8: (CD8-PE-Vio770 human), CD3 (CD3-VioBlue, human, REA613, Miltenyi) and CD7 (CD7 Antibody, anti-human, APC, REAfinity™, Miltenyi). The MOI was calculated according to the formula: $MOI = FT * V / nb \text{ of cells}$, where FT corresponds to Functional Titter as defined above.

10
15

[0451] *Transduction of NALM-6 and HepG2 cells*

[0452] NALM-6 cells, a type of B cells, were used to document transduction of B cells by the exemplified VLPs. HepG2 cells, a type of hepatocytes, were used to document transduction of hepatocytes by the exemplified VLPs.

20

Results

[0453] A batch of VLPs pseudotyped with WT GP160 (isolate HXB2) (SEQ ID NO: 4) was produced according to the method described in the Material and Methods section.

25 [0454] The physical and functional titers of this batch were determined according to the methods described in the introduction of this section and the following values were obtained:

- Physical titer: 1.77E+11 p24 LP/mL
- Functional titer on TMZ-1b: 2.56E+06 TU/mL

[0455] Following this characterization, T cells were transduced with this VLP batch according to the method described in the Material and Methods section. T cells were then
5 analyzed by FACS to determine the percentage of C4+ cells transduced by Ex#1 VLP that are GFP+ (see **Figure 1**).

[0456] The percentage of CD4+ GFP+ cells is 6.05%.

[0457] In conclusion, VLP pseudotyped with WT GP160 only transduce a small percentage of CD3+ cells with a strong tropism towards CD4+ rather than CD8+ T cells.

10

Example 2:

Materials and Methods

[0458] See Example 1.

Results

15 [0459] A batch of VLPs pseudotyped with gp160 LAI (SEQ ID NO: 51) was produced according to the method described in the Material and Methods section.

[0460] The physical and functional titers of this batch were determined according to the methods described in the introduction of this section and the following values were obtained:

- 20
- Physical titer: 3.10E+10 p24 LP/mL
 - Functional titer on TMZ-1b: 3.44E+06 TU/mL

[0461] Following this characterization, T cells were transduced with this VLP batch according to the method described in the introduction of this section. T cells were then

analyzed by FACS to determine the percentage of CD3+ cells transduced by Ex#1 VLP that are GFP+ (see **Figure 2**).

[0462] The percentage of CD4+ GFP+ cells is 5.31%.

[0463] In conclusion, VLP pseudotyped with GP160 LAI (SEQ ID NO: 51) only
5 transduce a small percentage of CD3+ cells with a strong tropism towards CD4+ rather than CD8+ T cells.

Example 3:

Materials and Methods

10 [0464] See Example 1.

Results

[0465] A batch of VLPs pseudotyped with gp160 SIV Mac251 (SEQ ID NO: 52) was produced according to the method described in the Material and Methods section.

[0466] The physical and functional titers of this batch were determined according to the
15 methods described in the introduction of this section and the following values were obtained:

- Physical titer: 2.55E+11 p24 LP/mL
- Functional titer on TMZ-1b: 2.60E+06 TU/mL

[0467] Following this characterization, T cells were transduced with this VLP batch
20 according to the method described in the Material and Methods section. T cells were then analyzed by FACS to determine the percentage of CD3+ cells transduced by Ex#1 VLP that are GFP+ (see **Figure 3**).

[0468] The percentage of CD4+ GFP+ cells is 4.31%.

[0469] In conclusion, VLP pseudotyped with this GP160 mutant (SEQ ID NO: 52) only transduce a small percentage of CD3+ cells with a strong tropism towards CD4+ rather than CD8+ T cells.

5 Example 4:

Materials and Methods

[0470] See Example 1.

Results

[0471] A batch of VLPs pseudotyped with GP160 mutated (GP160 TM1) (SEQ ID NO:
10 5) was produced according to the method described in the Material and Methods section.

[0472] The physical and functional titers of this batch were determined according to the methods described in the Material and Methods section and the following values were obtained:

- Physical titer: 1.57E+11 p24 LP/mL
- 15 - Functional titer on TMZ-1b: 1.43E+07 TU/mL

[0473] The percentage of CD4+ GFP+ cells is 20.6% (see **Figure 4**).

[0474] In conclusion, VLP pseudotyped with GP160 TM1 (SEQ ID NO: 5) transduce more efficiently CD3+ cells with a strong tropism towards CD4+ rather than CD8+ T cells.

20 [0475] Following this characterization, NALM-6 cells were transduced with this VLP batch according to the method described in the Material and Methods section. NALM-6 cells were then analyzed by FACS to determine the percentage of GFP+ cells.

[0476] The percentage of GFP positive cells is 0.05% (see **Figure 5**).

[0477] In conclusion, VLP pseudotyped with GP160 TM1 of SEQ ID NO: 5 do not transduce NALM-6 cells.

[0478] Thus, Examples 1 to 4 show that VLP pseudotyped with a mutant of GP160 with a modified cytoplasmic tail enable increased transduction of CD4+ cells, but not GP160
5 wild type nor other GP160 mutant that do not have a modified cytoplasmic tail.

Example 5:

Materials and Methods

[0479] See Example 1.

[0480] In the present disclosure, certain sequences were generated and are disclosed with
10 an identifier as shown in Table 5.

[0481] Table 5: Identifier / sequence number comparison.

Identifier	SEQ ID NO:
F04	61
F06	5
F24	57
F25	58
F26	60
F27	50
F28	59
F29	70
F30	51
F35	78
F45	4
F46	62
F47	79
F48	79
F49	62
F50	64
F51	80
F52	66
F54	82
F56	83
F57	63

F58	80
F59	66
F61	82
F63	83
F64	84
F65	85
F66	94
F67	75
F68	68
F69	69
F71	71
F72	72
F73	73
F74	74
F75	76
F76	77
F80	67
F81	81
F82	65
F84	86
F85	87

Results

[0482] As seen on **Figure 6**, various VLP pseudotyped with mutated cytoplasmic tail (corresponding to TM1 in the figure; black bins) yield an increased transduction, as indicated by GFP expression, compared to their wild-type (WT; white bins) counterpart.

5 The list of GP160 sequences used in **Figure 6** is presented in Table 6.

[0483] Table 6: GP160 mutants used in Figure 6

GP160 protein	Wild-Type (WT)	Mutated cytoplasmic tail (TM1)
J1Hx(197)	F74 (SEQ ID NO: 74)	F76 (SEQ ID NO: 77)
92US077-T8	F59 (SEQ ID NO: 66)	F80 (SEQ ID NO: 67)
92UG046-T8	F57 (SEQ ID NO: 63)	F82 (SEQ ID NO: 65)
gp160 HXB2	F45 (SEQ ID NO: 4)	F06 (SEQ ID NO: 5)

[0484] The data thus indicates that the VLP pseudotyped with a GP160 with a mutated cytoplasmic tail (SEQ ID NO: 5, 65, 67, 76 and 77) yield better transduction efficiency compared to their WT counterparts (SEQ ID NO: 4, 63, 66, 94 and 74, respectively) as

well as compared to HXB2 WT.

[0485] Further, **Figure 7** shows a comparison between the GP160 mutants. The mutants F28 (SEQ ID NO: 59), F80 (SEQ ID NO: 67), F82 (SEQ ID NO: 65), and F04 (SEQ ID NO: 61) show improved transduction compared to mutant F06 (SEQ ID NO: 5).

- 5 [0486] Finally, **Figure 8** shows the phylogenetic tree and sequence comparison of the tested variants.

CLAIMS

1. A pseudotyped viral-like particle (VLP) or viral vector that selectively targets CD4-positive cells, wherein said VLP or viral vector comprises a modified envelope protein comprising:
 - 5 - a mutant glycoprotein 41 (GP41) comprising an amino acid sequence having at least one mutation compared to the amino acid sequence of sequence of **SEQ ID NO: 1**, wherein said at least one mutation is localized on the cytoplasmic domain of the mutant glycoprotein 41 (GP41), and
 - a glycoprotein 120 (GP120) comprising an amino acid sequence having at least
10 70% sequence identity with **SEQ ID NO: 3**,wherein the envelope protein does not comprise an amino acid sequence as set forth in **SEQ ID NO: 95**.
2. The pseudotyped VLP or viral vector according to claim 1, wherein said mutant
15 GP41 comprises an amino acid sequence having at least 70% sequence identity with an amino acid sequence selected from the group consisting of **SEQ ID NO: 2, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, and SEQ ID NO: 26**.
3. The pseudotyped VLP or viral vector according to claim 1 or 2, wherein said mutant
20 glycoprotein 41 (GP41) comprises an amino acid sequence having at least 70% sequence identity with an amino acid sequence selected from the group comprising **SEQ ID NO: 2, SEQ ID NO: 6, and SEQ ID NO: 9**.
4. The pseudotyped VLP or viral vector according to claim 3, wherein said mutant
25 glycoprotein 41 (GP41) comprises an amino acid sequence having at least 70% sequence identity with **SEQ ID NO: 2**, preferably said mutant glycoprotein 41 (GP41) has the amino acid sequence of **SEQ ID NO: 2**.

5. The pseudotyped VLP or viral vector according to any one of claims **1** to **4**, wherein said envelope protein comprises an amino acid sequence having at least 70% sequence identity with an amino acid sequence selected from the group comprising **SEQ ID NO: 5**, **SEQ ID NO: 13**, and **SEQ ID NO: 16**.
- 5 6. The pseudotyped VLP or viral vector according to claim **5**, wherein said envelope protein has an amino acid sequence having at least 70% sequence identity with **SEQ ID NO: 5**, preferably said envelope protein has the amino acid sequence of **SEQ ID NO: 5**.
7. The pseudotyped VLP or viral vector according to any one of claims **1** to **6**, wherein
10 said glycoprotein 120 (GP120) comprises an amino acid sequence selected from the group comprising **SEQ ID NO: 3**, **SEQ ID NO: 36**, **SEQ ID NO: 37**, **SEQ ID NO: 38**, and **SEQ ID NO: 39**.
8. A pseudotyped viral-like particle (VLP) or viral vector that selectively targets CD4-
15 positive cells, wherein said viral VLP or viral vector comprises a modified envelope protein having an amino acid sequence selected from the group consisting of **SEQ ID NO: 5**, **SEQ ID NO: 13**, **SEQ ID NO: 14**, **SEQ ID NO: 15**, **SEQ ID NO: 16**, **SEQ ID NO: 17**, **SEQ ID NO: 18**, **SEQ ID NO: 19**, **SEQ ID NO: 27**, **SEQ ID NO: 28**, **SEQ ID NO: 29**, **SEQ ID NO: 30**, **SEQ ID NO: 31**, **SEQ ID NO: 32**, **SEQ ID NO: 33**, **SEQ ID NO: 59**, **SEQ ID NO: 61**, **SEQ ID NO: 65**, **SEQ ID NO: 67**, **SEQ ID NO: 70**, **SEQ ID NO: 71**, **SEQ ID NO: 75**, **SEQ ID NO: 76**, **SEQ ID NO: 77**, **SEQ ID NO: 81**, and **SEQ ID NO: 87**.
20
9. The pseudotyped VLP or viral vector according to claim **8**, wherein said envelope protein has an amino acid sequence selected from the group consisting of **SEQ ID NO: 5**, **SEQ ID NO: 59**, **SEQ ID NO: 61**, **SEQ ID NO: 65**, **SEQ ID NO: 67**,
25 **SEQ ID NO: 76**, and **SEQ ID NO: 77**.
10. The pseudotyped VLP or viral vector according to claim **9**, wherein said envelope protein has the amino acid sequence of **SEQ ID NO: 59**.

11. The pseudotyped VLP or viral vector according to any one of claims **1** to **10**, wherein the amino acid sequence of said envelope protein is not **SEQ ID NO: 4**.
12. The pseudotyped VLP or viral vector according to any one of claims **1** to **11**, wherein said VLP or viral vector is a retroviral VLP or retroviral vector.
- 5 13. The pseudotyped VLP or viral vector according to any one of claims **1** to **12**, further comprising at least one nucleic acid molecule of interest or polypeptide of interest, preferably wherein said at least one nucleic acid molecule of interest encodes at least one polypeptide of interest.
- 10 14. The pseudotyped VLP or viral vector according to claim **13**, wherein said nucleic acid molecule of interest encodes a gene editor.
15. The pseudotyped VLP or viral vector according to claim **13**, wherein said nucleic acid molecule of interest encodes a chimeric antigen receptor (CAR).
16. The pseudotyped VLP or viral vector according to any one of claims **1** to **15**, wherein said CD4-positive cells are CD4-positive immune cells.
- 15 17. The pseudotyped VLP or viral vector according to any one of claims **1** to **16**, wherein said CD4-positive cells are CD4-positive T cells.
18. A pharmaceutical composition comprising the pseudotyped VLP or viral vector according to any one of claims **1** to **17**, and at least one pharmaceutically acceptable excipient or carrier.
- 20 19. The pseudotyped VLP or viral vector according to any one of claims **1** to **17**, or the pharmaceutical composition according to claim **18**, for use as a medicament.
20. The pseudotyped VLP or viral vector according to any one of claims **1** to **17**, or the pharmaceutical composition according to claim **18**, for use for treating cancer or an autoimmune disease in a subject in need thereof.
- 25 21. A nucleic acid encoding the pseudotyped VLP or viral vector according to any one of claims **1** to **17**.

- 22.** A method of transducing a cell or a population of cells comprising contacting said cell or population of cells with the pseudotyped VLP or viral vector according to any one of claims **1** to **17**, or the nucleic acid according to claim **21**.
- 23.** The method according to claim **22**, wherein said method is an *in vitro* method.
- 5 **24.** A cell or a population of cells transduced by the pseudotyped VLP or viral vector according to any one of claims **1** to **17**, or the nucleic acid according to claim **21**.
- 25.** Use of the pseudotyped VLP or viral vector according to any one of claims **1** to **17**, or the pharmaceutical composition according to claim **18**, for the manufacture of a medicament for treating cancer.
- 10 **26.** A method of treating and/or preventing cancer in a subject in need thereof, comprising administering to said subject a therapeutically effective dose of the pseudotyped VLP or viral vector according to any one of claims **1** to **17**, or the pharmaceutical composition according to claim **18**.