Title: HUMAN ENDOGENOUS RETROVIRUS PEPTIDES, ANTIBODIES TO THE PEPTIDES, AND METHODS OF USE THEREOF

Abstract: The present disclosure provides anti-HERV-K antibodies, and compositions comprising the antibodies. An antibody to HERV-K is useful in various therapeutic and diagnostic applications, which are also provided. The present disclosure also provides HERV-K peptides, as well as compositions comprising the peptides. HERV-K peptides of the present disclosure are useful in therapeutic applications, and for generating antibodies.
HUMAN ENDOGENOUS RETROVIRUS PEPTIDES, ANTIBODIES TO THE PEPTIDES, 
AND METHODS OF USE THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 61/550,177, filed October 21, 2011, which application is incorporated herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with government support under Grant No. AI087474-01 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

[0003] Human endogenous retrovirus (HERV) sequences make up 8.29% of the draft human genome. Their prevalence has resulted from the accumulation of past retroviral infectious agents that have entered the germline and established a truce with the host cell. Biologically active HERVs include members of the HERV-K superfamily.

Literature


SUMMARY

[0005] The present disclosure provides anti-HERV-K antibodies, and compositions comprising the antibodies. An antibody to HERV-K is useful in various therapeutic and diagnostic applications, which are also provided. The present disclosure also provides HERV-K peptides, as well as compositions comprising the peptides. HERV-K peptides of the present disclosure are useful in therapeutic applications, and for generating antibodies.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] Figures 1A and 1B depict mapping of HERV-K envelope polypeptide.

[0007] Figures 2A-B depict titration of the anti-HERV-k envelope humoral response. The % of positive patients is based on a signal at least higher than two times the background. Symbols used include BD: Below detection; Positives: Patients with positive HIV serology; HD: Healthy Donors; HIV+: Patients positive for HIV-1 infection without treatment. EC: Elite Controllers; VNC: Viremic Non Controllers; HAART: Infected patients under highly active anti-retroviral therapy
Figures 3A-D depict anti-HERV-K envelope antibody detection. A,C: Detection of anti-SU antibodies by ELISA using 1/200 sera dilution. OD are normalized with serum from a high responder and a standard curve. The STDEV intra experiment is less than 7%. B,D: Detection of anti-TM antibodies by ELISA using 1/400 sera dilution. OD are normalized with an anti-TM antibody and a standard curve. The STDEV intra experiment is less than 4%. A and B: Mann and Whitney test. C and D: Kruskal-Wallis and Dunn's Multiple Comparison Test. HD: Healthy Donors; Patients positive for HIV-1 infection without treatment. EC: Elite Controllers; VNC: Viremic Non Controllers. Statistic abv: ns: p>0.05; *: 0.01<p<0.05; **: 0.001<p<0.01; ***:p<0.001.

Figures 4A-D depict anti-transmembrane response and HIV-1 activity.

Figures 5A-C depict HERV-K gag mapping.

Figure 6 depicts humoral response against Capsid in HIV-1 infected patients and HD.

Figures 7A-F depict isotypic composition of the anti-HERV-K responses.

Figures 8A and 8B depict the relationship between HERV-K humoral and cellular responses.

Figure 9 depicts the dynamics of IgG anti-HERV-K Env humoral response during HIV-1 acquisition.

Figure 10 depicts the dynamics of IgM anti-HERV-K Env humoral response during HIV-1 acquisition.

Figure 11 depicts the effect of HAART on anti-HERV-K Env humoral response.

Figure 12 depicts the total IgG and anti-TM responses in HIV-1 infected patients and HD.

Figure 13 depicts the humoral response on consecutive peptides from TM sequences.

Figures 14A-D the sequence conservation between SU-56 and TM-137 and viruses. Figure 14A depicts the SU epitope sequence (SEQ ID NO:896) of K101, K102, K104, K107, K108, K109, K113, and K115; and the SU-epitope sequence of K103 (SEQ ID NO:1111). Figure 14A depicts the TM-epitope sequence of K101, K102, K103, K107, K108, K109, K113, and K115 (SEQ ID NO:664); and the TM-epitope sequence of K104 (SEQ ID NO:1112). Figure 14B depicts SU-56 (SEQ ID NO:603); TAT (SEQ ID NO:1113); TM136 (SEQ ID NO:1114); POL (SEQ ID NO:1115); and PolyProtein (SEQ ID NO:1117). Figure 14D depicts SEQ ID NO:1.

Figures 15A-C depict the binding of HA-137 to naturally expressed HERV-K proteins and specific peptides.

Figure 16 depicts immunofluorescence. PFA-fixed non-permeabilized MCF-7 and T47-D cells were stained with either the mouse monoclonal anti-TM (HERM-1811-5), HA-137 B-cell clone supernatant or a serum from a VNC previously isolated as negative for SU-Ab and highly positive for TM-Ab.

Figures 17A-C depict mapping of the epitope recognized by HA-137 and the humoral response in HD and HIV+ cohorts.
Figures 18A and 18B provide HA-137 VH and VL nucleotide and amino acid sequences.

DEFINITIONS

The terms "antibodies" and "immunoglobulin" include antibodies or immunoglobulins of any isotype, fragments of antibodies which retain specific binding to antigen, including, but not limited to, Fab, Fv, scFv, and Fd fragments, chimeric antibodies, humanized antibodies, single-chain antibodies, and fusion proteins comprising an antigen-binding portion of an antibody and a non-antibody protein. The antibodies may be detectably labeled, *e.g.*, with a radioisotope, an enzyme which generates a detectable product, a fluorescent protein, and the like. The antibodies may be further conjugated to other moieties, such as members of specific binding pairs, *e.g.*, biotin (member of biotin-avidin specific binding pair), and the like. The antibodies may also be bound to a solid support, including, but not limited to, polystyrene plates or beads, and the like. Also encompassed by the term are Fab', Fv, F(ab')₂, and other antibody fragments that retain specific binding to antigen, and monoclonal antibodies. An antibody may be monovalent or bivalent.

"Antibody fragments" comprise a portion of an intact antibody, for example, the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')₂, and Fv fragments; diabodies; linear antibodies (Zapata et al., Protein Eng. 8(10): 1057-1062 (1995)); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments. Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. Pepsin treatment yields an F(ab')₂ fragment that has two antigen combining sites and is still capable of cross-linking antigen.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V₅H-V₅L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The "Fab" fragment also contains the constant domain of the light chain and the first constant domain (CH₁) of the heavy chain. Fab fragments differ from Fab' fragments by the addition of a few residues at the carboxyl terminus of the heavy chain CH₂ domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')₂ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.
[0028] The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgGl, IgG2, IgG3, IgG4, IgA, and IgA2.

[0029] "Single-chain Fv" or "sFv" antibody fragments comprise the $V_H$ and $V_L$ domains of antibody, wherein these domains are present in a single polypeptide chain. In some embodiments, the Fv polypeptide further comprises a polypeptide linker between the $V_H$ and $V_L$ domains, which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994).

[0030] The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain ($V_H$) connected to a light-chain variable domain ($V_L$) in the same polypeptide chain ($V_H$-$V_L$). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993).

[0031] As used herein, the term "affinity" refers to the equilibrium constant for the reversible binding of two agents; "affinity" can be expressed as a dissociation constant (Kd). Affinity can be at least 1-fold greater, at least 2-fold greater, at least 3-fold greater, at least 4-fold greater, at least 5-fold greater, at least 6-fold greater, at least 7-fold greater, at least 8-fold greater, at least 9-fold greater, at least 10-fold greater, at least 20-fold greater, at least 30-fold greater, at least 40-fold greater, at least 50-fold greater, at least 60-fold greater, at least 70-fold greater, at least 80-fold greater, at least 90-fold greater, at least 100-fold greater, or at least 1000-fold greater, or more, than the affinity of an antibody for unrelated amino acid sequences. Affinity of an antibody to a target protein can be, for example, from about 100 nanomolar (nM) to about 0.1 nM, from about 100 nM to about 1 picomolar (pM), or from about 100 nM to about 1 femtomolar (fM) or more. As used herein, the term "avidity" refers to the resistance of a complex of two or more agents to dissociation after dilution. The terms "immunoreactive" and "preferentially binds" are used interchangeably herein with respect to antibodies and/or antigen-binding fragments.

[0032] The term "binding" refers to a direct association between two molecules, due to, for example, covalent, electrostatic, hydrophobic, and ionic and/or hydrogen-bond interactions, including interactions such as salt bridges and water bridges. A subject anti-HERV-K antibody binds specifically to an epitope within a HERV-K polypeptide. Non-specific binding would refer to
binding with an affinity of less than about $10^{-7}$ M, e.g., binding with an affinity of $10^{-6}$ M, $10^{-5}$ M, $10^{-4}$ M, etc.

As used herein, the term "CDR" or "complementarity determining region" is intended to mean the non-contiguous antigen combining sites found within the variable region of both heavy and light chain polypeptides. These particular regions have been described by Kabat et al., J. Biol. Chem. 252:6609-6616 (1977); Kabat et al., U.S. Dept. of Health and Human Services, "Sequences of proteins of immunological interest" (1991); by Chothia et al., J. Mol. Biol. 196:901-917 (1987); MacCallum et al., J. Mol. Biol. 262:732-745 (1996); and in "Antibody Engineering" (Springer Lab Manuals), Roland Kontermann and Stefan Duebel (2001), Chapter 21: "Protein sequence analysis and structure analysis of antibody variable domains" by Andrew Martin, pages 422-442, where the definitions include overlapping or subsets of amino acid residues when compared against each other. Nevertheless, application of any of these definitions to refer to a CDR of an antibody or grafted antibodies or variants thereof is intended to be within the scope of the term as defined and used herein. The amino acid residues which encompass the CDRs as defined by the above cited Kabat, Chothia, and MacCallum references are set forth below in Table 1 as a comparison.

**Table 1: CDR Definitions**

<table>
<thead>
<tr>
<th></th>
<th>Kabat&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Chothia&lt;sup&gt;2&lt;/sup&gt;</th>
<th>MacCallum&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{H}$ CDR1</td>
<td>31-35</td>
<td>26-32</td>
<td>30-35</td>
</tr>
<tr>
<td>$V_{H}$ CDR2</td>
<td>50-65</td>
<td>53-55</td>
<td>47-58</td>
</tr>
<tr>
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<td>95-102</td>
<td>96-101</td>
<td>93-101</td>
</tr>
<tr>
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<td>24-34</td>
<td>26-32</td>
<td>30-36</td>
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<td>$V_{L}$ CDR2</td>
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<td>50-52</td>
<td>46-55</td>
</tr>
<tr>
<td>$V_{L}$ CDR3</td>
<td>89-97</td>
<td>91-96</td>
<td>89-96</td>
</tr>
</tbody>
</table>

<sup>1</sup> Residue numbering follows the nomenclature of Kabat et al., supra

<sup>2</sup> Residue numbering follows the nomenclature of Chothia et al., supra

<sup>3</sup> Residue numbering follows the nomenclature of MacCallum et al., supra

As used herein, the term "framework" when used in reference to an antibody variable region is intended to mean all amino acid residues outside the CDR regions within the variable region of an antibody. A variable region framework is generally a discontinuous amino acid sequence between about 100-120 amino acids in length but is intended to reference only those amino acids outside of the CDRs. As used herein, the term "framework region" is intended to mean each domain of the framework that is separated by the CDRs.

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts.

"Monoclonal antibodies" include hybrid and recombinant antibodies (e.g. "humanized" antibodies) regardless of species of origin or immunoglobulin class or subclass designation, as well
as antibody fragments (e.g., Fab, F(ab')₂, and Fv), so long as they are capable of binding specifically to a target antigen as described herein. Cabilly, et al., U.S. Pat. No. 4,816,567; Mage & Lamoyi, in Monoclonal Antibody Production Techniques and Applications, pp.79-97 (Marcel Dekker, Inc., New York, 1987).

Thus, the modifier "monoclonal" indicates the character of the antibody as being obtained from such a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, a monoclonal antibody can be made using the hybridoma method first described by Kohler & Milstein, Nature 256:495 (1975), or may be made by recombinant DNA methods. Cabilly, et al., U.S. Pat. No. 4,816,567.

An "isolated" antibody is one that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In some embodiments, the antibody will be purified (1) to greater than 90%, greater than 95%, or greater than 98%, by weight of antibody as determined by the Lowry method, for example, more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) under reducing or nonreducing conditions using Coomassie blue or silver stain. Isolated antibody includes the antibody in situ within recombinant cells since at least one component of the antibody's natural environment will not be present. In some instances, isolated antibody will be prepared by at least one purification step.

As used herein, the terms "treatment," "treating," and the like, refer to obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease. "Treatment," as used herein, covers any treatment of a disease in a mammal, particularly in a human, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; and (c) relieving the disease, i.e., causing regression of the disease.

The terms "co-administration" and "in combination with" include the administration of two or more therapeutic agents either simultaneously, concurrently or sequentially within no specific time limits. In one embodiment, the agents are present in the cell or in the subject's body at the same time or exert their biological or therapeutic effect at the same time. In one embodiment, the therapeutic agents are in the same composition or unit dosage form. In other embodiments, the therapeutic agents are in separate compositions or unit dosage forms. In certain embodiments, a first agent can be administered prior to (e.g., minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks,
4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapeutic agent.

The terms "individual," "subject," "host," and "patient," used interchangeably herein, refer to a mammal, including, but not limited to, murines (rats, mice), non-human primates, humans, canines, felines, ungulates (e.g., equines, bovines, ovines, porcines, caprines), etc.

A "therapeutically effective amount" or "efficacious amount" refers to the amount of a subject anti-HERV-K antibody that, when administered to a mammal or other subject for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the anti-HERV-K antibody, the disease and its severity and the age, weight, etc., of the subject to be treated.

A "biological sample" encompasses a variety of sample types obtained from an individual and can be used in a diagnostic or monitoring assay. The definition encompasses blood and other liquid samples of biological origin, solid tissue samples such as a biopsy specimen or tissue cultures or cells derived therefrom and the progeny thereof. The definition also includes samples that have been manipulated in any way after their procurement, such as by treatment with reagents, solubilization, or enrichment for certain components, such as polynucleotides. The term "biological sample" encompasses a clinical sample, and also includes cells in culture, cell supernatants, cell lysates, cells, serum, plasma, biological fluid, and tissue samples. "Biological sample" includes cells; biological fluids such as cerebrospinal fluid, semen, saliva, and the like; bile; bone marrow; skin (e.g., skin biopsy); and antibodies obtained from an individual.

The terms "polypeptide," "peptide," and "protein," used interchangeably herein, refer to a polymeric form of amino acids of any length, which can include coded and non-coded amino acids, chemically or biochemically modified or derivatized amino acids, and polypeptides having modified peptide backbones. The term includes fusion proteins, including, but not limited to, fusion proteins with a heterologous amino acid sequence, fusions with heterologous and homologous leader sequences, with or without N-terminal methionine residues; immunologically tagged proteins; and the like. NH₂ refers to the free amino group present at the amino terminus of a polypeptide. COOH refers to the free carboxyl group present at the carboxyl terminus of a polypeptide. In keeping with standard polypeptide nomenclature, J. Biol. Chem., 243 (1969), 3552-59 is used.

As used herein, the terms "label" and "detectable label" refer to a molecule capable of detection, including, but not limited to, radioactive isotopes, fluorescers, chemiluminescers, chromophores, enzymes, enzyme substrates, enzyme cofactors, enzyme inhibitors, chromophores, dyes, metal ions, metal sols, ligands (e.g., biotin, avidin, streptavidin or haptens), intercalating dyes and the like. The term "fluorescer" refers to a substance or a portion thereof which is capable of exhibiting fluorescence in the detectable range.
As used herein the term "isolated" is meant to describe a polynucleotide, a polypeptide, or a cell that is in an environment different from that in which the polynucleotide, the polypeptide, or the cell naturally occurs. An isolated genetically modified host cell may be present in a mixed population of genetically modified host cells. An isolated polypeptide will in some embodiments be synthetic. "Synthetic polypeptides" are assembled from amino acids, and are chemically synthesized in vitro, e.g., cell-free chemical synthesis, using procedures known to those skilled in the art. An isolated polypeptide will in some embodiments be purified.

By "purified" is meant a compound of interest (e.g., a polypeptide) has been separated from components that accompany it in nature. "Purified" can also be used to refer to a compound of interest (e.g., a polypeptide) separated from components that can accompany it during manufacture (e.g., in chemical synthesis). In some embodiments, a compound (e.g., a polypeptide) is substantially pure when it is at least 50% to 60%, by weight, free from organic molecules with which it is naturally associated or with which it is associated during manufacture. In some embodiments, the preparation is at least 75%, at least 90%, at least 95%, or at least 99%, by weight, of the compound of interest. Thus, e.g., a subject polypeptide that is "purified" is present in a composition where the polypeptide is present in an amount of at least 75%, at least 90%, at least 95%, or at least 99%, by weight, of the composition. A substantially pure compound can be obtained, for example, by extraction from a natural source (e.g., bacteria), by chemically synthesizing a compound, or by a combination of purification and chemical modification. A substantially pure compound can also be obtained by, for example, enriching a sample having a compound that binds an antibody of interest. Purity can be measured by any appropriate method, e.g., chromatography, mass spectroscopy, high performance liquid chromatography analysis, etc.

The term "heterologous," as used herein in the context of a HERV-K polypeptide, where a HERV-K polypeptide fusion protein comprises a HERV-K polypeptide and a heterologous polypeptide, refers to a polypeptide that is other than a HERV-K polypeptide, e.g., a polypeptide that is not normally associated with a HERV-K polypeptide. For example, a heterologous polypeptide bears no significant amino acid sequence identity to the HERV-K immunogenic polypeptide, e.g., the heterologous polypeptide has less than about 50%, less than about 40%, less than about 30%, or less than about 20% amino acid sequence identity to the HERV-K immunogenic polypeptide.

An "antigen" is a term that is well understood in the art, and includes any substance that may be specifically bound by an antigen-binding site of an antibody molecule or a T cell receptor. An "immunogen" is an antigen that is capable of initiating lymphocyte activation resulting in an antigen-specific immune response.

By "epitope" is meant a site on an antigen to which specific B cells and/or T cells respond. The term is also used interchangeably with "antigenic determinant" or "antigenic determinant site." B cell epitope sites on proteins, polysaccharides, or other biopolymers may be composed of moieties
from different parts of the macromolecule that have been brought together by folding. Epitopes of this kind are referred to as conformational or discontinuous epitopes, since the site is composed of segments of the polymer that are discontinuous in the linear sequence but are continuous in the folded conformation(s). Epitopes that are composed of single segments of biopolymers or other molecules are termed continuous or linear epitopes. Antibodies that recognize the same epitope can be identified in a simple immunoassay showing the ability of one antibody to block the binding of another antibody to a target antigen.

The terms "subject," "individual," "host," and "patient" are used interchangeably herein to refer to a mammal, including, but not limited to, murines (rats, mice), felines, non-human primates (e.g., simians), humans, canines, ungulates, etc.

As used herein, the term "correlates," or "correlates with," and like terms, refers to a statistical association between instances of two events, where events include numbers, data sets, and the like. For example, when the events involve numbers, a positive correlation (also referred to herein as a "direct correlation") means that as one increases, the other increases as well. A negative correlation (also referred to herein as an "inverse correlation") means that as one increases, the other decreases.

The term "substantially similar" as used in the context of nucleic acid or amino acid sequence identity refers to two or more sequences which have at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100% sequence identity.

As used herein "% sequence identity" is determined using the EMBOSS Pairwise Alignment Algorithms tool available from The European Bioinformatics Institute (EMBL-EBI), which is part of the European Molecular Biology Laboratory (EMBL). This tool is accessible at the website located by placing "www." in front of "ebi.ac.uk/Tools/emboss/align/". This tool utilizes the Needleman-Wunsch global alignment algorithm (Needleman, S. B. and Wunsch, C. D. (1970) J. Mol. Biol. 48, 443-453; Kruskal, J. B. (1983) An overview of sequence comparison In D. Sankoff and J. B. Kruskal, (ed.), Time warps, string edits and macromolecules: the theory and practice of sequence comparison, pp. 1-44 Addison Wesley. Default settings are utilized which include Gap Open: 10.0 and Gap Extend 0.5. The default matrix "Blosum62" is utilized for amino acid sequences and the default matrix "DNAfull" is utilized for nucleic acid sequences.

The term "conservative substitution" is used in reference to proteins or peptides to reflect amino acid substitutions that do not substantially alter the activity (specificity or binding affinity) of the molecule. Conservative amino acid substitutions can involve substituting one amino acid for another amino acid with similar chemical properties (e.g. charge or hydrophobicity). The following six groups each contain amino acids that are typical conservative substitutions for one another: 1) Alanine (A), Serine (S), Threonine (T); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N),
Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); and 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W).

[0056] Before the present invention is further described, it is to be understood that this invention is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0057] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

[0058] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

[0059] It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an anti-HERV-K antibody" includes a plurality of such antibodies and reference to "the HERV-K peptide" includes reference to one or more HERV-K peptides and equivalents thereof known to those skilled in the art, and so forth. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely," "only" and the like in connection with the recitation of claim elements, or use of a "negative" limitation.

[0060] It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination. All combinations of the embodiments pertaining to the invention are specifically embraced by the present invention and are disclosed herein just as if each and every combination was individually and explicitly disclosed. In addition, all sub-combinations of the various embodiments and elements
thereof are also specifically embraced by the present invention and are disclosed herein just as if each and every such sub-combination was individually and explicitly disclosed herein.

[0061] The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

**DETAILED DESCRIPTION**

[0062] The present disclosure provides anti-HERV-K antibodies, and compositions comprising the antibodies. An antibody to HERV-K is useful in various therapeutic and diagnostic applications, which are also provided. The present disclosure also provides HERV-K peptides, as well as compositions comprising the peptides. HERV-K peptides of the present disclosure are useful in therapeutic applications, and for generating antibodies.

**ANTI-HERV-K ANTIBODIES**

[0063] The present disclosure provides antibodies specific for a HERV-K peptide, as well as compositions comprising a subject antibody.

[0064] A subject antibody specifically binds a HERV-K polypeptide. In some embodiments, an epitope (e.g., a linear epitope or a conformational epitope) of a HERV-K polypeptide can be formed by a polypeptide having at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from about 50 amino acids (aa) to about 100 aa, from about 100 aa to about 173, of amino acids 25-173 of SEQ ID NO: 2.

[0065] AVAGVALHSSVQSVPNFWQKNSTRWNSQSSIDQKLANQLRQTVIWMGD RLMSLEHRFQLQCDWNTSDFCITPQYNESEHHWDVMRHLQGREDNLTDISKLKEQIFE ASKAHNLSVLPGTEAIALGAGLNLNPVTWVTIGSTTTINLILILVCLFC (SEQ ID NO: 2).

[0066] In some embodiments, an epitope (e.g., a linear epitope or a conformational epitope) of a HERV-K polypeptide can be formed by a polypeptide having at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from about 50 amino acids (aa) to about 100 aa, from about 100 aa to about 200 aa, from about 200 aa to about 300 aa, from 300 aa to about 373 aa, of amino acids 25-373 of SEQ ID NO: 3.

[0067] VVSLPMPAGAAAANYTWAYYPFPPLLRAVTWMDNPPIEYVYVNDSVWVPGPIDDC RAPKPEEGGMINISIYRYPICLGRAPGCLMPAVQNWLVEVPVSPICRFYHMVSGLSLR PRVYNLQDFSYSRRKFRPKGKCPKEIpKESKNTELVWEECVANAVLQNNFGETIDW APRGQFYHNCSSGTQTSCPSAQVSPAVIDSLTSLDHKHKHLKLQSYPWEPWEGKISTPRPK IVSPVSGPEPHPELWRTLHSHIIIWGNQDTRLETrDRKFYTIDLNSSLTVPQLSCVKVPPYML
In some embodiments, an epitope (e.g., a linear epitope or a conformational epitope) of a HERV-K polypeptide can be formed by a polypeptide having at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100%, amino acid sequence identity to a contiguous stretch of from about 50 amino acids (aa) to about 100 aa, from about 100 aa to about 200 aa, from about 200 aa to about 300 aa, from about 300 aa to about 400 aa, from about 400 aa to about 500 aa, from about 500 aa to about 600 aa, from about 600 aa to 672 aa, of amino acids 25-672 of SEQ ID NO:3.

In some embodiments, a subject anti-HERV-K antibody recognizes an epitope within a HERV-K envelope transmembrane protein (SEQ ID NO:2). In some embodiments, a subject anti-HERV-K antibody recognizes an epitope within a HERV-K surface unit protein (SEQ ID NO:3). In some embodiments, a subject anti-HERV-K antibody recognizes an epitope within a HERV-K capsid protein (SEQ ID NO:4).

In some cases, a subject anti-HERV-K antibody binds an epitope (e.g., a linear or a conformational epitope) formed by a peptide comprising an amino acid sequence having at least about 95% amino acid sequence identity to any one of SEQ ID NOs:5-557, and 603-1 110:

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TLETRDRKPFYTI (SEQ ID NO: 1028);
LETTRDRKPFYTIDLN (SEQ ID NO: 1029);
ETRDRKPFYTIDLN (SEQ ID NO: 1030);
TRDRKPFYTI (SEQ ID NO: 1031);
RDRKPFYTIDLNSSL (SEQ ID NO: 1032);
DRKPFYTI (SEQ ID NO: 1033);
RKPFTIDNLNS (SEQ ID NO: 1034);
KFYTIDLNSSLTL (SEQ ID NO: 1035);
PFYTIDLNSSLTP (SEQ ID NO: 1036);
FYTI (SEQ ID NO: 1037);
YTI (SEQ ID NO: 1038);
TIDLNS (SEQ ID NO: 1039);
IDLNS (SEQ ID NO: 1040);
DLNS (SEQ ID NO: 1041);
LN (SEQ ID NO: 1042);
NSSL (SEQ ID NO: 1043);
SSLVPL (SEQ ID NO: 1044);
SLVPL (SEQ ID NO: 1045);
LVP (SEQ ID NO: 1046);
TVPL (SEQ ID NO: 1047);
VPL (SEQ ID NO: 1048);
PLQSCV (SEQ ID NO: 1049);
LQSCV (SEQ ID NO: 1050);
QSCV (SEQ ID NO: 1051);
SCV (SEQ ID NO: 1052);
CV (SEQ ID NO: 1053);
VK (SEQ ID NO: 1054);
K (SEQ ID NO: 1055);
P (SEQ ID NO: 1056);
PYMLVVGNIVIKPDS (SEQ ID NO: 1057);
YMLVVGNIVIKPDSQ (SEQ ID NO: 1058);
MLVVGNIVIKPDSQT (SEQ ID NO: 1059);
LVVGNIVIKPDSQTIT (SEQ ID NO: 1060);
VVGNIVIKPDSQTITC (SEQ ID NO: 1061);
VGNIVIKPDSQTITCEN (SEQ ID NO: 1062);
GNIVKPDSQTITCENC (SEQ ID NO: 1063);
NIIVKPDSQTITCENC (SEQ ID NO: 1064);
IVIKPDSQTITCENC (SEQ ID NO: 1065);
VIKPDSQTITCENC (SEQ ID NO: 1066);
IKPDSQTITCENCRL (SEQ ID NO: 1067);
KPDSQTITCENCRLL (SEQ ID NO: 1068);
PDSQTITCENCRLLT (SEQ ID NO: 1069);
DSQITTENCRLLTC (SEQ ID NO: 1070);
SQITTENCRLLTCI (SEQ ID NO: 1071);
QTITTENCRLLTCID (SEQ ID NO: 1072);
TITCENCRLLTCIDS (SEQ ID NO: 1073);
ITCENCRLLTCIDST (SEQ ID NO: 1074);
TCENCRLLTCIDSTF (SEQ ID NO: 1075);
CENCRLLTCIDSTFN (SEQ ID NO: 1076);
ENCRLLTCIDSTFNW (SEQ ID NO: 1077);
NCRLLTCIDSTFNWQ (SEQ ID NO: 1078);
CRLLTCIDSTFNWQH (SEQ ID NO: 1079);
RLLTCIDSTFNWQHR (SEQ ID NO: 1080);
LLLCIDSTFNWQHRIL (SEQ ID NO: 1081);
LTCIDSTFNWQHRIL (SEQ ID NO: 1082);
TCIDSTFNWQHRIL (SEQ ID NO: 1083);
CIDSTFNWQHRILLV (SEQ ID NO: 1084);
IDSTFNWQHRILLVR (SEQ ID NO: 1085);
DSTFNWQHRILLVRA (SEQ ID NO: 1086);
STFNWQHRILLVRA (SEQ ID NO: 1087);
TFNWQHRILLVRAE (SEQ ID NO: 1088);
FNWQHRILLVRAEG (SEQ ID NO: 1089);
NWQHRILLVRAEGV (SEQ ID NO: 1090);
WQHRILLVRAEGVW (SEQ ID NO: 1091);
QHRILLVRAEGVWI (SEQ ID NO: 1092);
HRILLVRAEGVWIP (SEQ ID NO: 1093);
RILLVRAREGVWIPV (SEQ ID NO: 1094);  
ILLVRAREGVWIPVS (SEQ ID NO: 1095);  
LLVRAREGVWIPVSM (SEQ ID NO: 1096);  
LVRAREGVWIPVSMD (SEQ ID NO: 1097);  
VRAREGVWIPVSMDRP (SEQ ID NO: 1098);  
RAREGVWIPVSMDRP (SEQ ID NO: 1099);  
AREGVWIPVSMDRPW (SEQ ID NO: 1100);  
REGVWIPVSMDRPWE (SEQ ID NO: 1101);  
EGVWIPVSMDRPWEA (SEQ ID NO: 1102);  
GVWIPVSMDRPWEAS (SEQ ID NO: 1103);  
VWIPVSMDRPWEASP (SEQ ID NO: 1104);  
WIPVSMDRPWEASPS (SEQ ID NO: 1105);  
IPVSMDRPWEASPSV (SEQ ID NO: 1106);  
PVSMRDWEASPSVH (SEQ ID NO: 1107);  
VSMRDWEASPSVH (SEQ ID NO: 1108);  
SMRDWEASPSVHIL (SEQ ID NO: 1109);  
MDRPWEASPSVHILT (SEQ ID NO: 1110).

**Affinity**  

[0072] A subject antibody exhibits high affinity binding to HERV-K. For example, a subject antibody binds to a HERV-K envelope transmembrane protein, a HERV-K envelope surface unit protein, or a HERV-K capsid protein with an affinity of at least about $10^{-7}$ M, at least about $10^{-9}$ M, at least about $10^{-10}$ M, at least about $10^{-11}$ M, or at least about $10^{-12}$ M, or greater than $10^{-12}$ M. A subject antibody binds to an epitope present on a HERV-K envelope transmembrane polypeptide, a HERV-K envelope surface unit polypeptide, or a HERV-K capsid polypeptide with an affinity of from about $10^{-7}$ M to about $10^{-8}$ M, from about $10^{-8}$ M to about $10^{-9}$ M, from about $10^{-9}$ M to about $10^{-10}$ M, from about $10^{-10}$ M to about $10^{-11}$ M, or from about $10^{-11}$ M to about $10^{-12}$ M, or greater than $10^{-12}$ M.

[0073] In some embodiments, a subject anti-HERV-K antibody does not substantially cross-react with a polypeptide other than a HERV-K polypeptide.

**Antibody structure**  

[0074] The term "antibody" refers to a protein comprising one or more (e.g., one or two) heavy chain variable regions (VH) and/or one or more (e.g., one or two) light chain variable regions (VL), or subfragments thereof capable of binding an epitope. The VH and VL regions can be further subdivided into regions of hypervariability, termed "complementarity determining regions (CDR)", interspersed with regions that are more conserved, termed "framework regions (FR)". The extent of the FR and CDRs has been precisely defined (see, Kabat, et al. (1991) Sequences of Proteins of
Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Chothia et al. (1987) J. Mol. Biol. 196: 901-917. A VH can comprise three CDRs and four FRs arranged from N-terminus to C-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. Similarly, a VL can comprise three CDRs and four FRs arranged from N-terminus to C-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.

The VH or VL chain of an antibody can further include all or part of a heavy or light chain constant region, to thereby form a heavy or light immunoglobulin chain, respectively. In one embodiment, the antibody is a tetramer of two heavy and two light chains, wherein the heavy and light chains are interconnected by, for example, disulfide bonds. The heavy chain constant region is comprised of three domains, CHI, CH2 and CH3. The light chain constant region is comprised of one domain, CL. The variable regions of the heavy and light chains comprise binding regions that interact with antigen. The constant regions of the antibodies typically mediate the binding of the antibody to host tissues and factors, including various cells of the immune system and the first component of the complement system. The term "antibody" includes intact immunoglobulins of types IgA, IgG, IgE, IgD, IgM and subtypes thereof. In some embodiments, a subject antibody is an IgG isotype.

As used herein the term "immunoglobulin" refers to a protein consisting of one or more polypeptides substantially encoded by immunoglobulin genes. The recognized human immunoglobulin genes include the kappa, lambda, alpha (IgAl and IgA2), gamma (IgGl, IgG2, IgG3, IgG4), delta, epsilon and mu constant region genes; and numerous immunoglobulin variable region genes. Full-length immunoglobulin light chains (about 25 kD or 214 amino acids) are encoded by a variable region gene at the N-terminus (about 110 amino acids) and a kappa or lambda constant region at the C-terminus. Full-length immunoglobulin heavy chains (about 50 kD or 446 amino acids) are encoded by a variable region gene at the N-terminus (about 116 amino acids) and one of the other aforementioned constant region genes at the C-terminus, e.g. gamma (encoding about 330 amino acids). In some embodiments, a subject antibody comprises full-length immunoglobulin heavy chain and a full-length immunoglobulin light chain.

In some embodiments, a subject antibody does not comprise a full-length immunoglobulin heavy chain and a full-length immunoglobulin light chain, and instead comprises antigen-binding fragments of a full-length immunoglobulin heavy chain and a full-length immunoglobulin light chain. In some embodiments, the antigen-binding fragments are contained on separate polypeptide chains; in other embodiments, the antigen-binding fragments are contained within a single polypeptide chain. The term "antigen-binding fragment" refers to one or more fragments of a full-length antibody that are capable of specifically binding to a HERV-K polypeptide, as described above. Examples of binding fragments include (i) a Fab fragment (a monovalent fragment consisting of the VL, VH, CL and CHI domains; (ii) a F(ab')2 fragment (a bivalent fragment comprising two
Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment (consisting of the VH and CHI domains); (iv) a Fv fragment (consisting of the VH and VL domains of a single arm of an antibody); (v) a dAb fragment (consisting of the VH domain); (vi) an isolated CDR; (vii) a single chain Fv (scFv) (consisting of the VH and VL domains of a single arm of an antibody) joined by a synthetic linker using recombinant means such that the VH and VL domains pair to form a monovalent molecule; (viii) diabodies (consisting of two scFvs in which the VH and VL domains are joined such that they do not pair to form a monovalent molecule; the VH of each one of the scFv pairs with the VL domain of the other scFv to form a bivalent molecule); (ix) bi-specific antibodies (consisting of at least two antigen binding regions, each region binding a different epitope). In some embodiments, a subject antibody fragment is a Fab fragment. In some embodiments, a subject antibody fragment is a single-chain antibody (scFv).

In some embodiments, a subject antibody is a recombinant or modified antibody, e.g., a chimeric, humanized, deimmunized or an in vitro generated antibody. The term "recombinant" or "modified" antibody as used herein is intended to include all antibodies that are prepared, expressed, created, or isolated by recombinant means, such as (i) antibodies expressed using a recombinant expression vector transfected into a host cell; (ii) antibodies isolated from a recombinant, combinatorial antibody library; (iii) antibodies isolated from an animal (e.g. a mouse) that is transgenic for human immunoglobulin genes; or (iv) antibodies prepared, expressed, created, or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant antibodies include humanized, CDR grafted, chimeric, deimmunized, and in vitro generated antibodies; and can optionally include constant regions derived from human germline immunoglobulin sequences.

Exemplary VH and VL CDR amino acid sequences are also depicted in Figures 18A and 18B.

In some embodiments, a subject antibody competes for binding to a HERV-K envelope transmembrane peptide with an antibody that comprises:

(i) a VfCDR1 comprising an amino acid sequence of SEQ ID NO:573;
(ii) a VfCDR2 comprising an amino acid sequence of SEQ ID NO:574;
(iii) a VfCDR3 comprising an amino acid sequence of SEQ ID NO:575;
(iv) a VfCDR1 comprising an amino acid sequence of SEQ ID NO:576;
(v) a VfCDR2 comprising an amino acid sequence of SEQ ID NO:577; and
(vi) a VfCDR3 comprising an amino acid sequence of SEQ ID NO:578.
(iii) a V<sub>L</sub>CDR3 comprising an amino acid sequence of SEQ ID NO:575;
(iv) a V<sub>H</sub>CDR1 comprising an amino acid sequence of SEQ ID NO:576;
(v) a V<sub>H</sub>CDR2 comprising an amino acid sequence of SEQ ID NO:577; and
(vi) a V<sub>H</sub>CDR3 comprising an amino acid sequence of SEQ ID NO:578.

In some embodiments, a subject antibody comprises: a variable domain comprising: a) a heavy chain variable domain comprising: i. a CDR1 region that is identical in amino acid sequence to the heavy chain CDR1 region of the anti-HERV-K antibody designated HA-137; ii. a CDR2 region that is identical in amino acid sequence to the heavy chain CDR2 region of the HA-137 antibody; and iii. a CDR3 region that is identical in amino acid sequence to the heavy chain CDR3 region of the HA-137 antibody; and b) a light chain variable domain comprising: i. a CDR1 region that is identical in amino acid sequence to the light chain CDR1 region of the HA-137 antibody; ii. a CDR2 region that is identical in amino acid sequence to the light chain CDR2 region of the HA-137 antibody; and iii. a CDR3 region that is identical in amino acid sequence to the light chain CDR3 region of the HA-137 antibody wherein the antibody specifically binds a HERV-K polypeptide.

In certain embodiments, an antibody comprising: a) a variable domain comprising: i. a CDR1 region that is identical in amino acid sequence to the heavy chain CDR1 region of a HA-137 antibody; ii. a CDR2 region that is identical in amino acid sequence to the heavy chain CDR2 region of the HA-137 antibody; and iii. a CDR3 region that is identical in amino acid sequence to the heavy chain CDR3 region of the HA-137 antibody; and b) a light chain variable domain comprising: i. a CDR1 region that is identical in amino acid sequence to the light chain CDR1 region of the HA-137 antibody; ii. a CDR2 region that is identical in amino acid sequence to the light chain CDR2 region of the HA-137 antibody; and iii. a CDR3 region that is identical in amino acid sequence to the light chain CDR3 region of the HA-137 antibody; or b) a variant of the variable domain of part a) that is otherwise identical to the variable domain of part a) except for a number of (e.g., 1, 2, 3, 4, 5, 6, 7 or 8) amino acid substitutions in the CDR regions, where the antibody specifically binds a HERV-K polypeptide.

In some embodiments, a subject anti-HERV-K antibody comprises: a) a light chain region comprising: i) one, two, or three complementarity determining regions (CDRs) from the HA-137 light chain variable region sequence; and ii) a light chain framework region, e.g., a framework region from a human immunoglobulin light chain; and b) a heavy chain region comprising: i) one, two, or three CDRs from the HA-137 heavy chain variable region sequence; and ii) a heavy chain framework region, e.g., a framework region from a human immunoglobulin heavy chain.

A subject antibody can comprise a heavy chain variable region comprising an amino acid sequence that is 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the sequence depicted in Figure 18B and set forth in SEQ ID NO:580. A subject antibody can comprise a heavy chain variable region comprising one, two, or three of the heavy
chain complementarity determining regions (CDRs) having an amino acid sequence selected from one or more of SEQ ID NOs: 576, 577, and 578.

[0098] In some embodiments, a subject antibody comprises a heavy chain variable region comprising one, two, or three of the heavy chain CDRs having an amino acid sequence selected from one or more of SEQ ID NOs: 576, 577, and 578; and FR regions that are human sequences (e.g., encoded by human heavy chain FR-encoding sequences). For example, in some embodiments, a subject antibody comprises a heavy chain variable region that comprises, in order from N-terminus to C-terminus: a human heavy chain FR1; a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 576; a human heavy chain FR2; a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 577; a human heavy chain FR3; a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 578; and a human heavy chain FR4.

[0099] A subject antibody can comprise a light chain variable region comprising an amino acid sequence that is 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the sequence depicted in Figure 18A and set forth in SEQ ID NO: 579. A subject antibody can comprise a light chain variable region comprising one, two, or three of the light chain CDRs having the amino acid sequence set forth in SEQ ID NOs: 573, 574, and 575.

[00100] In some embodiments, a subject antibody comprises a light chain variable region comprising one, two, or three of the light chain CDRs having a polypeptide sequence selected from one or more of SEQ ID NOs: 573, 574, and 575; and FR regions that are human sequences (e.g., encoded by human light chain FR-encoding sequences). For example, in some embodiments, a subject antibody comprises a light chain variable region that comprises, in order from N-terminus to C-terminus: a human light chain FR1; a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 573; a human light chain FR2; a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 574; a human light chain FR3; a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 575; and a human light chain FR4.

[00101] In some embodiments, a subject antibody comprises HA-137 heavy chain CDRs and HA-137 light chain CDRs in a single polypeptide chain, e.g., in some embodiments, a subject antibody is a scFv. In some embodiments, a subject antibody comprises, in order from N-terminus to C-terminus: a first amino acid sequence of from about 5 amino acids to about 25 amino acids in length; a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 576; a second amino acid sequence of from about 5 amino acids to about 25 amino acids in length; a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 577; a third amino acid sequence of from about 5 amino acids to about 25 amino acids in length; a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 578; a fourth amino acid sequence of from about 5 amino acids to about 25 amino acids in length; a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 573; a fifth amino acid sequence of from about 5 amino acids to about 25 amino acids in length; a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 574 a sixth amino acid sequence of
from about 5 amino acids to about 25 amino acids in length; a CDR3 comprising the amino acid sequence set forth in SEQ ID NO:575; and a seventh amino acid sequence of from about 5 amino acids to about 25 amino acids in length.

[00102] Linkers suitable for use a subject antibody include "flexible linkers". If present, the linker molecules are generally of sufficient length to permit some flexible movement between linked regions. The linker molecules are generally about 6-50 atoms long. The linker molecules may also be, for example, aryl acetylene, ethylene glycol oligomers containing 2-10 monomer units, diamines, diacids, amino acids, or combinations thereof. Other linker molecules which can bind to polypeptides may be used in light of this disclosure.

[00103] Suitable linkers can be readily selected and can be of any of a suitable of different lengths, such as from 1 amino acid (e.g., Gly) to 20 amino acids, from 2 amino acids to 15 amino acids, from 3 amino acids to 12 amino acids, including 4 amino acids to 10 amino acids, 5 amino acids to 9 amino acids, 6 amino acids to 8 amino acids, or 7 amino acids to 8 amino acids, and may be 1, 2, 3, 4, 5, 6, or 7 amino acids.

[00104] Exemplary flexible linkers include glycine polymers (G), glycine-serine polymers (including, for example, (GS)n, GSGS, (SEQ ID NO:581) and GGGSG, (SEQ ID NO:582), where n is an integer of at least one), glycine-alanine polymers, alanine-serine polymers, and other flexible linkers known in the art. Glycine and glycine-serine polymers are of interest since both of these amino acids are relatively unstructured, and therefore may serve as a neutral tether between components. Glycine polymers are of particular interest since glycine accesses significantly more phi-psi space than even alanine, and is much less restricted than residues with longer side chains (see Scheraga, Rev. Computational Chem. 11173-142 (1992)). Exemplary flexible linkers include, but are not limited GGSG (SEQ ID NO:583), GGSG (SEQ ID NO:584), GSGSG (SEQ ID NO:585), GSGGG (SEQ ID NO:586), GGGSG (SEQ ID NO:587), GSSSG (SEQ ID NO:588), and the like. The ordinarily skilled artisan will recognize that design of a peptide conjugated to any elements described above can include linkers that are all or partially flexible, such that the linker can include a flexible linker as well as one or more portions that confer less flexible structure.

[00105] It will be appreciated that the affinity of a subject antibody can be altered using any suitable method known in the art. The present disclosure therefore also provides variants of an anti-HERV-K antibody that have increased affinity for HERV-K. Such variants can be obtained by a number of affinity maturation protocols including mutating the CDRs (Yang et al., J. Mol. Biol., 254, 392-403, 1995), chain shuffling (Marks et al., Bio/Technology, 10, 779-783, 1992), use of mutator strains of E. coli (Low et al., J. Mol. Biol., 250, 359-368, 1996), DNA shuffling (Patten et al., Curr. Opin. Biotechnol., 8, 724-733, 1997), phage display (Thompson et al., J. Mol. Biol., 256, 77-88, 1996) and sexual PCR (Cramer et al., Nature, 391, 288-291, 1998). Vaughan et al (Nature Biotechnology, 16, 535-539, 1998) discusses various methods of affinity maturation, any of which methods can be used to increase affinity of an anti-HERV-K antibody. For example, display techniques, chain shuffling
techniques, site-directed mutagenesis methods, or other methods, can be used to increase antibody affinity; see, e.g., U.S. Patent Publication No. 2011/0200615, which describes various methods for affinity maturation of antibodies.

A subject anti-HERV-K antibody can be a (scFv')2 homodimer, a (scFv)_2, a Fab, a (Fab')_2, or other antibody form. Other antibody forms include, e.g., V_{nH}/nanobodies, UniBodies, and affibodies; see, e.g., U.S. Patent Publication No. 2011/0200615.


UniBodies are generated by an antibody technology that produces a stable, smaller antibody format with an anticipated longer therapeutic window than certain small antibody formats. UniBodies may be produced from IgG4 antibodies by eliminating the hinge region of the antibody. Unlike the full size IgG4 antibody, the half molecule fragment is very stable and is termed a UniBody. Halving the IgG4 molecule left only one area on the UniBody that can bind to a target. Methods of producing UniBodies are described in detail in PCT Publication WO2007/059782; and Kolfschoten et al. (2007) Science 317: 1554-1557.

Affibody molecules are class of affinity proteins based on a 58-amino acid residue protein domain, derived from one of the IgG-binding domains of staphylococcal protein A. This three helix bundle domain has been used as a scaffold for the construction of combinatorial phagemid libraries, from which affibody variants that target the desired molecules can be selected using phage display technology (see, e.g., Nord et al. (1997) Nat. Biotechnol. 15: 772-777; Ronmark et al. (2002) Eur. J. Biochem., 269: 2647-2655). Details of affibodies and methods of production are known to those of skill (see, e.g., U.S. Pat. No. 5,831,012).

In some embodiments, e.g., where an antibody is of non-human origin, a subject antibody is "humanized." The term "humanized antibody" refers to an antibody comprising at least one chain comprising variable region framework residues substantially from a human antibody chain (referred to as the acceptor immunoglobulin or antibody) and at least one CDR substantially from a mouse antibody, (referred to as the donor immunoglobulin or antibody). See, Queen et al., Proc. Natl. Acad. Sci. USA 86:10029 10033 (1989), U.S. Pat. No. 5,530,101, U.S. Pat. No. 5,585,089, U.S. Pat. No. 5,693,761, WO 90/07861, and U.S. Pat. No. 5,225,539. The constant region(s), if present, can also be substantially or entirely from a human immunoglobulin. In some embodiments, a subject
antibody comprises one or more HA-137 CDRs and one or more FR regions from a human antibody. Methods of making humanized antibodies are known in the art. See, e.g., U.S. Patent No. 7,256,273.

[00111] Having identified the complementarity determining regions of the murine donor immunoglobulin and appropriate human acceptor immunoglobulins, the next step is to determine which, if any, residues from these components should be substituted to optimize the properties of the resulting humanized antibody. In general, substitution of human amino acid residues with murine should be minimized, because introduction of murine residues increases the risk of the antibody eliciting a human-anti-mouse-antibody (HAMA) response in humans. Art-recognized methods of determining immune response can be performed to monitor a HAMA response in a particular patient or during clinical trials. Patients administered humanized antibodies can be given an immunogenicity assessment at the beginning and throughout the administration of said therapy. The HAMA response is measured, for example, by detecting antibodies to the humanized therapeutic reagent, in serum samples from the patient using a method known to one in the art, including surface plasmon resonance technology (BIACORE) and/or solid-phase ELISA analysis. In many embodiments, a subject humanized antibody does not substantially elicit a HAMA response in a human subject.

[00112] Certain amino acids from the human variable region framework residues are selected for substitution based on their possible influence on CDR conformation and/or binding to antigen. The unnatural juxtaposition of murine CDR regions with human variable framework region can result in unnatural conformational restraints, which, unless corrected by substitution of certain amino acid residues, lead to loss of binding affinity.

[00113] The selection of amino acid residues for substitution can be determined, in part, by computer modeling. Computer hardware and software for producing three-dimensional images of immunoglobulin molecules are known in the art. In general, molecular models are produced starting from solved structures for immunoglobulin chains or domains thereof. The chains to be modeled are compared for amino acid sequence similarity with chains or domains of solved three-dimensional structures, and the chains or domains showing the greatest sequence similarity is/are selected as starting points for construction of the molecular model. Chains or domains sharing at least 50% sequence identity are selected for modeling, and preferably those sharing at least 60%, 70%, 80%, or 90% sequence identity, or more than 90% identity (e.g., 95% identity, 98% identity, or 99% identity) are selected for modeling. The solved starting structures are modified to allow for differences between the actual amino acids in the immunoglobulin chains or domains being modeled, and those in the starting structure. The modified structures are then assembled into a composite immunoglobulin. Finally, the model is refined by energy minimization and by verifying that all atoms are within appropriate distances from one another and that bond lengths and angles are within chemically acceptable limits.
CDR and framework regions are as defined by Kabat, Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md., 1987 and 1991); or as defined by Martin in "Antibody Engineering" (Springer Lab Manuals), Roland Kontermann and Stefan Duebel (2001), Chapter 21: "Protein sequence analysis and structure analysis of antibody variable domains" by Andrew Martin, pages 422-442. An alternative structural definition has been proposed by Chothia et al., J. Mol. Biol. 196:901 (1987); Nature 342:878 (1989); and J. Mol. Biol. 186:651 (1989) (collectively referred to as "Chothia"). When framework residues, as defined by Kabat, supra, constitute structural loop residues as defined by Chothia, supra, or Martin, supra, the amino acids present in the mouse antibody may be selected for substitution into the humanized antibody. Residues which are "adjacent to a CDR region" include amino acid residues in positions immediately adjacent to one or more of the CDRs in the primary sequence of the humanized immunoglobulin chain, for example, in positions immediately adjacent to a CDR as defined by Kabat, or a CDR as defined by Chothia (See e.g., Chothia and Lesk JMB 196:901 (1987)), or a CDR as defined by Martin, supra. These amino acids are particularly likely to interact with the amino acids in the CDRs and, if chosen from the acceptor, to distort the donor CDRs and reduce affinity. Moreover, the adjacent amino acids may interact directly with the antigen (Amit et al., Science, 233:747 (1986)) and selecting these amino acids from the donor may be desirable to keep all the antigen contacts that provide affinity in the original antibody.

In some embodiments, a subject antibody comprises scFv multimers. For example, in some embodiments, a subject antibody is an scFv dimer (e.g., comprises two tandem scFv (scFv$_2$)), an scFv trimer (e.g., comprises three tandem scFv (scFv$_3$)), an scFv tetramer (e.g., comprises four tandem scFv (scFv$_4$)), or is a multimer of more than four scFv (e.g., in tandem). The scFv monomers can be linked in tandem via linkers of from about 2 amino acids to about 10 amino acids in length, e.g., 2 aa, 3 aa, 4 aa, 5 aa, 6 aa, 7 aa, 8 aa, 9 aa, or 10 aa in length. Suitable linkers include, e.g., (Gly)$_x$, where $x$ is an integer from 2 to 10. Other suitable linkers are those discussed above. In some embodiments, each of the scFv monomers in a subject scFv multimer is humanized, as described above.

In some embodiments, a subject antibody comprises a constant region of an immunoglobulin (e.g., an Fc region). The Fc region, if present, can be a human Fc region. If constant regions are present, the antibody can contain both light chain and heavy chain constant regions. Suitable heavy chain constant region include CH1, hinge, CH2, CH3, and CH4 regions. The antibodies described herein include antibodies having all types of constant regions, including IgM, IgG, IgD, IgA and IgE, and any isotype, including IgGl, IgG2, IgG3 and IgG4. An example of a suitable heavy chain Fc region is a human isotype IgGl Fc. Light chain constant regions can be lambda or kappa. A subject antibody (e.g., a subject humanized antibody) can comprise sequences from more than one class or isotype. Antibodies can be expressed as tetramers containing two light
and two heavy chains, as separate heavy chains, light chains, as Fab, Fab', F(ab')2, and Fv, or as single chain antibodies in which heavy and light chain variable domains are linked through a spacer.

In some embodiments, a subject antibody comprises a free thiol (-SH) group at the carboxyl terminus, where the free thiol group can be used to attach the antibody to a second polypeptide (e.g., another antibody, including a subject antibody), a scaffold, a carrier, etc.

**Non-naturally occurring amino acids**

In some embodiments, a subject antibody comprises one or more non-naturally occurring (e.g., non-encoded) amino acids. In some embodiments, the non-naturally encoded amino acid comprises a carbonyl group, an acetyl group, an aminooxy group, a hydrazine group, a hydrazide group, a semicarbazide group, an azide group, or an alkyne group. See, e.g., U.S. Patent No. 7,632,924 for suitable non-naturally occurring amino acids. Inclusion of a non-naturally occurring amino acid can provide for linkage to a polymer, a second polypeptide, a scaffold, etc. For example, a subject antibody linked to a water-soluble polymer can be made by reacting a water-soluble polymer (e.g., PEG) that comprises a carbonyl group to the subject antibody that comprises a non-naturally encoded amino acid that comprises an aminooxy, hydrazine, hydrazide or semicarbazide group. As another example, a subject antibody linked to a water-soluble polymer can be made by reacting a subject antibody that comprises an alkyne-containing amino acid with a water-soluble polymer (e.g., PEG) that comprises an azide moiety; in some embodiments, the azide or alkyne group is linked to the PEG molecule through an amide linkage. A "non-naturally encoded amino acid" refers to an amino acid that is not one of the 20 common amino acids or pyrolysine or selenocysteine. Other terms that may be used synonymously with the term "non-naturally encoded amino acid" are "non-natural amino acid," "unnatural amino acid," "non-naturally-occurring amino acid," and variously hyphenated and non-hyphenated versions thereof. The term "non-naturally encoded amino acid" also includes, but is not limited to, amino acids that occur by modification (e.g. post-translational modifications) of a naturally encoded amino acid (including but not limited to, the 20 common amino acids or pyrolysine and selenocysteine) but are not themselves naturally incorporated into a growing polypeptide chain by the translation complex. Examples of such non-naturally-occurring amino acids include, but are not limited to, N-acetylgulosaminyl-L-serine, N-acetylgulosaminyl-L-threonine, and O-phosphotyrosine.

**Modifications**

In some embodiments, a subject antibody is linked (e.g., covalently linked) to a polymer (e.g., a polymer other than a polypeptide). Suitable polymers include, e.g., biocompatible polymers, and water-soluble biocompatible polymers. Suitable polymers include synthetic polymers and naturally-occurring polymers. Suitable polymers include, e.g., substituted or unsubstituted straight or branched chain polyalkylene, polyalkylene or polyoxyalkylene polymers or branched or unbranched polysaccharides, e.g. a homo- or hetero-polysaccharide. Suitable polymers include, e.g., ethylene vinyl alcohol copolymer (commonly known by the generic name EVOH or by the trade
name EVAL; polybutylmethacrylate; poly(hydroxyvalerate); poly(L-lactic acid); polycaprolactone; poly(lactide-co-glycolide); poly(hydroxybutyrate); poly(hydroxybutyrate-co-valerate); polydioxanone; polyorthoester; polyanhydride; poly(glycolic acid); poly(D.L-lactic acid); poly(glycolic acid-co-trimethylene carbonate); polyphosphoester; polyphosphoester urethane; poly(amino acids); cyanoacrylates; poly(trimethylene carbonate); poly(iminocarbonate); copoly(ether-esters) (e.g., poly(ethylene oxide)-poly(lactic acid) (PEO/PLA) co-polymers); polyalkylene oxalates; polyphosphazenes; biomolecules, such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid; polyurethanes; silicones; polyesters; polyolefins; polyisobutylene and ethylene-alphaolefin copolymers; acrylic polymers and copolymers; vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile; polyvinyl ketones; polyvinyl aromatics, such as polystyrene; polyvinyl esters, such as polyvinyl acetate; copolymers of vinyl monomers with each other and olefins, such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers; polyamides, such as Nylon 66 and polycaprolactam; alkyd resins; polycarbonates; polyoxymethylene's; polyimides; polyethers; epoxy resins; polyurethanes; rayon; rayon-triacetate; cellulose; cellulose acetate; cellulose butyrate; cellulose acetate butyrate; cellophane; cellulose nitrate; cellulose propionate; cellulose ethers; amorphous Teflon; poly(ethylene glycol); and carboxymethyl cellulose.

[00120] Suitable synthetic polymers include unsubstituted and substituted straight or branched chain poly(ethylene glycol), poly(propylene glycol) poly(vinylalcohol), and derivatives thereof, e.g., substituted poly(ethylene glycol) such as methoxypoly(ethylene glycol), and derivatives thereof. Suitable naturally-occurring polymers include, e.g., albumin, amylose, dextran, glycogen, and derivatives thereof.

[00121] Suitable polymers can have an average molecular weight in a range of from 500 Da to 50000 Da, e.g., from 500 Da to 40000 Da, or from 25000 to 40000 Da. For example, in some embodiments, where a subject antibody comprises a poly(ethylene glycol) (PEG) or methoxypoly(ethylene glycol) polymer, the PEG or methoxypoly(ethylene glycol) polymer can have a molecular weight in a range of from about 0.5 kiloDaltons (kDa) to 1 kDa, from about 1 kDa to 5 kDa, from 5 kDa to 10 kDa, from 10 kDa to 25 kDa, from 25 kDa to 40 kDa, or from 40 kDa to 60 kDa.

[00122] As noted above, in some embodiments, a subject antibody is covalently linked to a PEG polymer. In some embodiments, a subject scFv multimer is covalently linked to a PEG polymer. See, e.g., Albrecht et al. (2006) J. Immunol. Methods 310:100. Methods and reagents suitable for PEGylation of a protein are well known in the art and may be found in, e.g., U.S. Pat. No. 5,849,860. PEG suitable for conjugation to a protein is generally soluble in water at room temperature, and has the general formula R(0-CH₂CH₂)ₙO-R, where R is hydrogen or a protective
group such as an alkyl or an alkanol group, and where n is an integer from 1 to 1000. Where R is a protective group, it generally has from 1 to 8 carbons.

[00123] The PEG conjugated to the subject antibody can be linear. The PEG conjugated to the subject protein may also be branched. Branched PEG derivatives such as those described in U.S. Pat. No. 5,643,575, "star-PEG's" and multi-armed PEG's such as those described in Shearwater Polymers, Inc. catalog "Polyethylene Glycol Derivatives 1997-1998." Star PEGs are described in the art including, e.g., in U.S. Patent No. 6,046,305.

[00124] A subject antibody can be glycosylated, e.g., comprise a covalently linked carbohydrate or polysaccharide moiety. Glycosylation of antibodies is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-acetylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxlysine may also be used.

[00125] Addition of glycosylation sites to an antibody is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tripeptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the sequence of the original antibody (for O-linked glycosylation sites). Similarly, removal of glycosylation sites can be accomplished by amino acid alteration within the native glycosylation sites of an antibody.

[00126] A subject antibody will in some embodiments comprise a "radiopaque" label, e.g. a label that can be easily visualized using for example x-rays. Radiopaque materials are well known to those of skill in the art. The most common radiopaque materials include iodide, bromide or barium salts. Other radiopaque materials are also known and include, but are not limited to organic bismuth derivatives (see, e.g., U.S. Pat. No. 5,939,045), radiopaque multiurethanes (see U.S. Pat. No. 5,346,981), organobismuth composites (see, e.g., U.S. Pat. No. 5,256,334), radiopaque barium multimer complexes (see, e.g., U.S. Pat. No. 4,866,132), and the like.

[00127] A subject antibody can be covalently linked to a second moiety (e.g., a lipid, a polypeptide other than a subject antibody, a synthetic polymer, a carbohydrate, and the like) using for example, glutaraldehyde, a homobiunional cross-linker, or a heterobifunctional cross-linker. Glutaraldehyde cross-links polypeptides via their amino moieties. Homobiunional cross-linkers (e.g., a homobiunional imidoester, a homobiunional N-hydroxysuccinimidyl (NHS) ester, or a homobiunional sulfhydryl reactive cross-linker) contain two or more identical reactive moieties and can be used in a one step reaction procedure in which the cross-linker is added to a solution containing a mixture of the polypeptides to be linked. Homobiunional NHS ester and imi...
cross-link amine containing polypeptides. In a mild alkaline pH, imido esters react only with primary amines to form imidoamides, and overall charge of the cross-linked polypeptides is not affected. Homobifunctional sulhydryl reactive cross-linkers includes bismaleimidhexane (BMH), 1,5-difluoro-2,4-dinitrobenzene (DFDNB), and 1,4-di-(3',2'-pyridyldithio) propinoamido butane (DPDPB).

[00128] Heterobifunctional cross-linkers have two or more different reactive moieties (e.g., amine reactive moiety and a sulhydryl-reactive moiety) and are cross-linked with one of the polypeptides via the amine or sulhydryl reactive moiety, then reacted with the other polypeptide via the non-reacted moiety. Multiple heterobifunctional haloacetyl cross-linkers are available, as are pyridyl disulfide cross-linkers. Carbodiimides are a classic example of heterobifunctional cross-linking reagents for coupling carboxyls to amines, which results in an amide bond.

[00129] In some embodiments, a subject antibody is modified to include a carbohydrate moiety, where the carbohydrate moiety can be covalently linked to the antibody. In some embodiments, a subject antibody is modified to include a lipid moiety, where the lipid moiety can be covalently linked to the antibody. Suitable lipid moieties include, e.g., an N-fatty acyl group such as N-lauroyl, N-oleoyl, etc.; a fatty amine such as dodecyl amine, oleoyl amine, etc.; a C3-C16 long-chain aliphatic lipid; and the like. See, e.g., U.S. Pat. No. 6,638,513. In some embodiments, a subject antibody is incorporated into a liposome.

**Solid supports**

[00130] A subject antibody can be immobilized on a solid support. Suitable supports are well known in the art and comprise, inter alia, commercially available column materials, polystyrene beads, latex beads, magnetic beads, colloid metal particles, glass and/or silicon chips and surfaces, nitrocellulose strips, nylon membranes, sheets, duracyes, wells of reaction trays (e.g., multi-well plates), plastic tubes, etc. A solid support can comprise any of a variety of substances, including, e.g., glass, polystyrene, polyvinyl chloride, polypropylene, polyethylene, polycarbonate, dextran, nylon, amylose, natural and modified celluloses, polyacrylamides, agaroses, and magnetite. Suitable methods for immobilizing a subject antibody onto a solid support are well known and include, but are not limited to ionic, hydrophobic, covalent interactions and the like. Solid supports can be soluble or insoluble, e.g., in aqueous solution. In some embodiments, a suitable solid support is generally insoluble in an aqueous solution.

**Labels**

[00131] A subject antibody will in some embodiments comprise a detectable label. Suitable detectable labels include any composition detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Suitable include, but are not limited to, magnetic beads (e.g. Dynabeads™), fluorescent dyes (e.g., fluorescein isothiocyanate, texas red, rhodamine, a green fluorescent protein, a red fluorescent protein, a yellow fluorescent protein, and the like), radiolabels (e.g., ³H, ¹²⁵I, ³⁵S, ¹⁴C, or ³²P), enzymes (e.g., horse radish peroxidase, alkaline
phosphatase, luciferase, and others commonly used in an enzyme-linked immunosorbent assay (ELISA), and colorimetric labels such as colloidal gold or colored glass or plastic (e.g. polystyrene, polypropylene, latex, etc.) beads.

[00132] In some embodiments, a subject antibody comprises a contrast agent or a radioisotope, where the contrast agent or radioisotope is one that is suitable for use in imaging, e.g., imaging procedures carried out on humans. Non-limiting examples of labels include radioisotope such as ¹²³I (iodine), ¹⁸F (fluorine), ⁹⁹Tc (technetium), ¹¹¹In (indium), and ⁶⁷Ga (gallium), and contrast agent such as gadolinium (Gd), dysprosium, and iron. Radioactive Gd isotopes (¹⁵³Gd) also are available and suitable for imaging procedures in non-human mammals. A subject antibody can be labeled using standard techniques. For example, a subject antibody can be iodinated using chloramine T or 1,3,4,6-tetrachloro-3a,6a-dephenylglycouril. For fluorination, fluorine is added to a subject antibody during the synthesis by a fluoride ion displacement reaction. See, Muller-Gartner, H., TIB Tech., 16:122-130 (1998) and Saji, H., Crit. Rev. Ther. Drug Carrier Syst., 16(2):209-244 (1999) for a review of synthesis of proteins with such radioisotopes. A subject antibody can also be labeled with a contrast agent through standard techniques. For example, a subject antibody can be labeled with Gd by conjugating low molecular Gd chelates such as Gd diethylene triamine pentaacetic acid (GdDTPA) or Gd tetraazacyclododecanetetraacetic (GdDOTA) to the antibody. See, Caravan et al., Chem. Rev. 99:2293-2352 (1999) and Lauffer et al., J. Magn. Reson. Imaging, 3:11-16 (1985). A subject antibody can be labeled with Gd by, for example, conjugating polylysine-Gd chelates to the antibody. See, for example, Curtet et al., Invest. Radiol., 33(10):752-761 (1998). Alternatively, a subject antibody can be labeled with Gd by incubating paramagnetic polymerized liposomes that include Gd chelator lipid with avidin and biotinylated antibody. See, for example, Sipkins et al., Nature Med., 4:623-626 (1998).

[00133] Suitable fluorescent proteins that can be linked to a subject antibody include, but are not limited to, a green fluorescent protein from Aequoria victoria or a mutant or derivative thereof, e.g., as described in U.S. Patent No. 6,066,476; 6,020,192; 5,985,577; 5,976,796; 5,968,750; 5,968,738; 5,958,713; 5,919,445; 5,874,304; e.g., Enhanced GFP, many such GFP which are available commercially, e.g., from Clontech, Inc.; a red fluorescent protein; a yellow fluorescent protein; any of a variety of fluorescent and colored proteins from Anthozoan species, as described in, e.g., Matz et al. (1999) Nature Biotechnol. 17:969-973; and the like.

**Fusion partners**

[00134] A subject antibody will in some embodiments be linked to (e.g., covalently or non-covalently linked) a fusion partner, e.g., a ligand; an epitope tag; a peptide; a protein other than an antibody; and the like. Suitable fusion partners include peptides and polypeptides that confer enhanced stability in vivo (e.g., enhanced serum half-life); provide ease of purification, e.g., (His)₅, e.g., 6His, and the like; provide for secretion of the fusion protein from a cell; provide an epitope tag, e.g., glutathione-S-transferase (GST), hemagglutinin (HA); e.g., CYPYDVPDYA; SEQ ID
NO:589), FLAG (e.g., DYKDDDDK; SEQ ID NO:590), c-myc (e.g., CEQKLISEEDL; SEQ ID NO:591), and the like; provide a detectable signal, e.g., an enzyme that generates a detectable product (e.g., β-galactosidase, luciferase), or a protein that is itself detectable, e.g., a green fluorescent protein, a red fluorescent protein, a yellow fluorescent protein, etc.; provides for multimerization, e.g., a multimerization domain such as an Fc portion of an immunoglobulin; and the like.

[00135] The fusion may also include an affinity domain, including peptide sequences that can interact with a binding partner, e.g., such as one immobilized on a solid support, useful for identification or purification. Consecutive single amino acids, such as histidine, when fused to a protein, can be used for one-step purification of the fusion protein by high affinity binding to a resin column, such as nickel sepharose. Exemplary affinity domains include His5 (HHHHH) (SEQ ID NO:592), HisX6 (HHHHHH) (SEQ ID NO:593), C-myc (EQKLISEEDL) (SEQ ID NO:594), Flag (DYKDDDDK) (SEQ ID NO:595), StrepTag (WSHPQFEK) (SEQ ID NO:596), hemagglutinin, e.g., HA Tag (YPYDVPDYA; SEQ ID NO:597), glutathione-S-transferase (GST), thioredoxin, cellulose binding domain, RYIRS (SEQ ID NO:598), Phe-His-His-Thr (SEQ ID NO:599), chitin binding domain, S-peptide, T7 peptide, SH2 domain, C-end RNA tag, WEAAAREACCRECCARA (SEQ ID NO:600), metal binding domains, e.g., zinc binding domains or calcium binding domains such as those from calcium-binding proteins, e.g., calmodulin, troponin C, calcineurin B, myosin light chain, recoverin, S-modulin, visinin, VILIP, neurocalcin, hippocalcin, frequenin, caltractin, calpain large-subunit, S100 proteins, parvalbumin, calbindin D9K, calbindin D28K, and calretinin, inteins, biotin, streptavidin, MyoD, leucine zipper sequences, and maltose binding protein.

Preparation of an anti-HERV-K antibody

[00136] Using the information provided herein, and the general knowledge in the art, HERV-K binding antibodies of the present disclosure are prepared using standard techniques well known to those of skill in the art.

[00137] A subject antibody can be produced by any known method, e.g., conventional synthetic methods for protein synthesis; recombinant DNA methods; etc.

[00138] Where a subject antibody is a single chain polypeptide, it can be synthesized using standard chemical peptide synthesis techniques. Where a polypeptide is chemically synthesized, the synthesis may proceed via liquid-phase or solid-phase. Solid phase polypeptide synthesis (SPPS), in which the C-terminal amino acid of the sequence is attached to an insoluble support followed by sequential addition of the remaining amino acids in the sequence, is an example of a suitable method for the chemical synthesis of a subject antibody. Various forms of SPPS, such as Fmoc and Boc, are available for synthesizing a subject antibody. Techniques for solid phase synthesis are described by Barany and Merrifield, Solid-Phase Peptide Synthesis; pp. 3-284 in The Peptides: Analysis, Synthesis, Biology. Vol. 2 : Special Methods in Peptide Synthesis, Part A., Merrifield, et al. J. Am. Chem. Soc, 85: 2149-2156 (1963); Stewart et al., Solid Phase Peptide Synthesis, 2nd ed. Pierce
Chem. Co., Rockford, 111. (1984); and Ganesan A. 2006 Mini Rev. Med Chem. 6:3-10 and Camarero JA et al. 2005 Protein Pept Lett. 12:723-8. Briefly, small insoluble, porous beads are treated with functional units on which peptide chains are built. After repeated cycling of coupling/deprotection, the free N-terminal amine of a solid-phase attached is coupled to a single N-protected amino acid unit. This unit is then deprotected, revealing a new N-terminal amine to which a further amino acid may be attached. The peptide remains immobilized on the solid-phase and undergoes a filtration process before being cleaved off.

[00139] Standard recombinant methods can be used for production of a subject antibody. For example, nucleic acids encoding light and heavy chain variable regions, optionally linked to constant regions, are inserted into expression vectors. The light and heavy chains can be cloned in the same or different expression vectors. The DNA segments encoding immunoglobulin chains are operably linked to control sequences in the expression vector(s) that ensure the expression of immunoglobulin polypeptides. Expression control sequences include, but are not limited to, promoters (e.g., naturally-associated or heterologous promoters), signal sequences, enhancer elements, and transcription termination sequences. The expression control sequences can be eukaryotic promoter systems in vectors capable of transforming or transfecting eukaryotic host cells (e.g., COS or CHO cells). Once the vector has been incorporated into the appropriate host, the host is maintained under conditions suitable for high level expression of the nucleotide sequences, and the collection and purification of the antibodies.

[00140] Because of the degeneracy of the code, a variety of nucleic acid sequences can encode each immunoglobulin amino acid sequence. The desired nucleic acid sequences can be produced by de novo solid-phase DNA synthesis or by polymerase chain reaction (PCR) mutagenesis of an earlier prepared variant of the desired polynucleotide. Oligonucleotide-mediated mutagenesis is an example of a suitable method for preparing substitution, deletion and insertion variants of target polypeptide DNA. See Adelman et al., DNA 2:183 (1983). Briefly, the target polypeptide DNA is altered by hybridizing an oligonucleotide encoding the desired mutation to a single-stranded DNA template. After hybridization, a DNA polymerase is used to synthesize an entire second complementary strand of the template that incorporates the oligonucleotide primer, and encodes the selected alteration in the target polypeptide DNA.

[00141] Suitable expression vectors are typically replicable in the host organisms either as episomes or as an integral part of the host chromosomal DNA. Commonly, expression vectors contain selection markers (e.g., ampicillin-resistance, hygromycin-resistance, tetracycline resistance, kanamycin resistance or neomycin resistance) to permit detection of those cells transformed with the desired DNA sequences.

[00142] *Escherichia coli* is an example of a prokaryotic host cell that can be used for cloning a subject antibody-encoding polynucleotide. Other microbial hosts suitable for use include bacilli, such as *Bacillus subtilis*, and other enterobacteriaceae, such as Salmonella, Serratia, and various...
Pseudomonas species. In these prokaryotic hosts, one can also make expression vectors, which will typically contain expression control sequences compatible with the host cell (e.g., an origin of replication). In addition, any number of a variety of well-known promoters will be present, such as the lactose promoter system, a tryptophan (trp) promoter system, a beta-lactamase promoter system, or a promoter system from phage lambda. The promoters will typically control expression, optionally with an operator sequence, and have ribosome binding site sequences and the like, for initiating and completing transcription and translation.

Other microbes, such as yeast, are also useful for expression. Saccharomyces (e.g., S. cerevisiae) and Pichia are examples of suitable yeast host cells, with suitable vectors having expression control sequences (e.g., promoters), an origin of replication, termination sequences and the like as desired. Typical promoters include 3-phosphoglycerate kinase and other glycolytic enzymes. Inducible yeast promoters include, among others, promoters from alcohol dehydrogenase, isocytochrome C, and enzymes responsible for maltose and galactose utilization.

In addition to microorganisms, mammalian cells (e.g., mammalian cells grown in *in vitro* cell culture) can also be used to express and produce the polypeptides of the present invention (e.g., polynucleotides encoding immunoglobulins or fragments thereof). See Winnacker, From Genes to Clones, VCH Publishers, N.Y., N.Y. (1987). Suitable mammalian host cells include CHO cell lines, various Cos cell lines, HeLa cells, myeloma cell lines, and transformed B-cells or hybridomas. Expression vectors for these cells can include expression control sequences, such as an origin of replication, a promoter, and an enhancer (Queen et al., Immunol. Rev. 89:49 (1986)), and necessary processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites, and transcriptional terminator sequences. Examples of suitable expression control sequences are promoters derived from immunoglobulin genes, SV40, adenovirus, bovine papilloma virus, cytomegalovirus and the like. See Co et al., J. Immunol. 148:1149 (1992).

Once synthesized (either chemically or recombinantly), the whole antibodies, their dimers, individual light and heavy chains, or other forms of a subject antibody (e.g., scFv, etc.) can be purified according to standard procedures of the art, including ammonium sulfate precipitation, affinity columns, column chromatography, high performance liquid chromatography (HPLC) purification, gel electrophoresis, and the like (see generally Scopes, Protein Purification (Springer-Verlag, N.Y., (1982))). A subject antibody can be substantially pure, e.g., at least about 80% to 85% pure, at least about 85% to 90% pure, at least about 90% to 95% pure, or 98% to 99%, or more, pure, e.g., free from contaminants such as cell debris, macromolecules other than a subject antibody, etc.

**Compositions**

The present disclosure provides a composition comprising a subject antibody. A subject antibody composition can comprise, in addition to a subject antibody, one or more of: a salt, e.g., NaCl, MgCl₂, KCl, MgSO₄, etc.; a buffering agent, e.g., a Tris buffer, N-(2-
Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES), 2-(N-Morpholino)ethanesulfonic acid (MES), 2-(N-Morpholino)ethanesulfonic acid sodium salt (MES), 3-(N-Morpholino)propanesulfonic acid (MOPS), N-tris[Hydroxymethyl]methyl-3-aminopropansulfonic acid (TAPS), etc.; a solubilizing agent; a detergent, e.g., a non-ionic detergent such as Tween-20, etc.; a protease inhibitor; glycerol; and the like.

**NUCLEIC ACIDS**

[00147] The present disclosure provides nucleic acids comprising nucleotide sequences encoding a subject antibody. A nucleotide sequence encoding a subject antibody can be operably linked to one or more regulatory elements, such as a promoter and enhancer, that allow expression of the nucleotide sequence in the intended target cells (e.g., a cell that is genetically modified to synthesize the encoded antibody).

[00148] Suitable promoter and enhancer elements are known in the art. For expression in a bacterial cell, suitable promoters include, but are not limited to, lac, lacZ, T3, T7, gpt, lambda P and trc. For expression in a eukaryotic cell, suitable promoters include, but are not limited to, light and/or heavy chain immunoglobulin gene promoter and enhancer elements; cytomegalovirus immediate early promoter; herpes simplex virus thymidine kinase promoter; early and late SV40 promoters; promoter present in long terminal repeats from a retrovirus; mouse metallothionein-I promoter; and various art-known tissue specific promoters.

[00149] In some embodiments, e.g., for expression in a yeast cell, a suitable promoter is a constitutive promoter such as an ADH1 promoter, a PGK1 promoter, an ENO promoter, a PYK1 promoter and the like; or a regulatable promoter such as a GAL1 promoter, a GAL10 promoter, an ADH2 promoter, a PH05 promoter, a CUP1 promoter, a GAL7 promoter, a MET25 promoter, a MET3 promoter, a CYC1 promoter, a HIS3 promoter, an ADH1 promoter, a PGK promoter, a GAPDH promoter, an ADC1 promoter, a TRP1 promoter, a URA3 promoter, a LEU2 promoter, an ENO promoter, a TP1 promoter, and AOX1 (e.g., for use in *Pichia*). Selection of the appropriate vector and promoter is well within the level of ordinary skill in the art.

[00150] Suitable promoters for use in prokaryotic host cells include, but are not limited to, a bacteriophage T7 RNA polymerase promoter; a trp promoter; a lac operon promoter; a hybrid promoter, e.g., a lac/tac hybrid promoter, a tac/trc hybrid promoter, a trp/lac promoter, a T7/lac promoter; a trc promoter; a tac promoter, and the like; an araBAD promoter; *in vivo* regulated promoters, such as an *ssag* promoter or a related promoter [see, e.g., U.S. Patent Publication No. 20040131637], *apagC* promoter (Pulkkinen and Miller, *J. Bacteriol.*, 1991: 173(1): 86-93; Alpuce-Aranda et al., PNAS, 1992; 89(21): 10079-83), a nirB promoter (Harborne et al. (1992) *Mol. Micro*., 6:2805-2813), and the like [see, e.g., Dunstan et al. (1999) *Infect. Immun*. 67:5133-5141; McKelvie et al. (2004) *Vaccine* 22:3243-3255; and Chatfield et al. (1992) *Biotechnol* 10:888-892); a sigma70 promoter, e.g., a consensus sigma70 promoter (see, e.g., GenBank Accession Nos. AX798980, AX798961, and AX798183); a stationary phase promoter, e.g., a *dps* promoter, an *spv
promoter, and the like; a promoter derived from the pathogenicity island SPI-2 (see, e.g., WO96/17951); an actA promoter (see, e.g., Shetron-Rama et al. (2002) Infect. Immun. 70:1087-1096); an rpsM promoter (see, e.g., Valdivia and Falkow (1996). Mol. Microbiol. 22:367); a tet promoter (see, e.g., Hillen, W. and Wisssmann, A. (1989) In Saenger, W. and Heinemann, U. (eds), *Topics in Molecular and Structural Biology, Protein-Nucleic Acid Interaction.* Macmillan, London, UK, Vol. 10, pp. 143-162); an SP6 promoter (see, e.g., Melton et al. (1984) Nucl. Acids Res. 12:7035); and the like. Suitable strong promoters for use in prokaryotes such as *Escherichia coli* include, but are not limited to Trc, Tac, T5, T7, and pLambdA. Non-limiting examples of operators for use in bacterial host cells include a lactose promoter operator (LacI repressor protein changes conformation when contacted with lactose, thereby preventing the LacI repressor protein from binding to the operator), a tryptophan promoter operator (when complexed with tryptophan, TrpR repressor protein has a conformation that binds the operator; in the absence of tryptophan, the TrpR repressor protein has a conformation that does not bind to the operator), and a tac promoter operator (see, for example, deBoer et al. (1983) Proc. Natl. Acad. Sci. U.S.A. 80:21-25).

[00151] A nucleotide sequence encoding a subject antibody can be present in an expression vector and/or a cloning vector. Where a subject antibody comprises two separate polypeptides, nucleotide sequences encoding the two polypeptides can be cloned in the same or separate vectors. An expression vector can include a selectable marker, an origin of replication, and other features that provide for replication and/or maintenance of the vector.

[00152] Large numbers of suitable vectors and promoters are known to those of skill in the art; many are commercially available for generating a subject recombinant constructs. The following vectors are provided by way of example. Bacterial: pBs, phagescript, PsiX174, pBluescript SK, pBs KS, pNH8a, pNH16a, pNH18a, pNH46a (Stratagene, La Jolla, Calif., USA); pTrc99A, pKK223-3, pKK233-3, pDR540, and pRIT5 (Pharmacia, Uppsala, Sweden). Eukaryotic: pWlneo, pSV2cat, pOG44, PXR1, pSG (Stratagene) pSVK3, pBPV, pMSG and pSVL (Pharmacia).

[00153] Expression vectors generally have convenient restriction sites located near the promoter sequence to provide for the insertion of nucleic acid sequences encoding heterologous proteins. A selectable marker operative in the expression host may be present. Suitable expression vectors include, but are not limited to, viral vectors (e.g. viral vectors based on vaccinia virus; poliovirus; adenovirus (see, e.g., Li et al., Invest Opthalmol Vis Sci 35:2543 2549, 1994; Borras et al., Gene Ther 6:515 524, 1999; Li and Davidson, PNAS 92:7700 7704, 1995; Sakamoto et al., H Gene Ther 5:1088 1097, 1999; WO 94/12649, WO 93/03769; WO 93/19191; WO 94/28938; WO 95/11984 and WO 95/00655); adeno-associated virus (see, e.g., Ali et al., Hum Gene Ther 9:81 86, 1998, Flannery et al., PNAS 94:6916 6921, 1997; Bennett et al., Invest Opthalmol Vis Sci 38:2857 2863, 1997; Jomary et al., Gene Ther 4:683 690, 1997, Rolling et al., Hum Gene Ther 10:641 648, 1999; Ali et al., Hum Mol Genet 5:591 594, 1996; Srivastava in WO 93/09239, Samulski et al., J. Vir. (1989) 63:3822-3828; Mendelson et al., Virol. (1988) 166:154-165; and Flotte et al., PNAS (1993)
90:10613-10617); SV40; herpes simplex virus; human immunodeficiency virus (see, e.g., Miyoshi et al., PNAS 94:10319-23, 1997; Takahashi et al., J Virol 73:7812-7816, 1999); a retroviral vector (e.g., Murine Leukemia Virus, spleen necrosis virus, and vectors derived from retroviruses such as Rous Sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, human immunodeficiency virus, myeloproliferative sarcoma virus, and mammatory tumor virus); and the like.

[00154] As noted above, a subject nucleic acid comprises a nucleotide sequence encoding a subject antibody. A subject nucleic acid can comprise a nucleotide sequence encoding heavy- and light-chain anti-HERV-K CDRs. In some embodiments, a subject nucleic acid comprises a nucleotide sequence encoding heavy- and light-chain HA-137 CDRs, where the CDR-encoding sequences are interspersed with FR-encoding nucleotide sequences. In some embodiments, the FR-encoding nucleotide sequences are human FR-encoding nucleotide sequences.

CELLS

[00155] The present disclosure provides isolated genetically modified host cells (e.g., in vitro cells) that are genetically modified with a subject nucleic acid. In some embodiments, a subject isolated genetically modified host cell can produce a subject antibody.

[00156] Suitable host cells include eukaryotic host cells, such as a mammalian cell, an insect host cell, a yeast cell; and prokaryotic cells, such as a bacterial cell. Introduction of a subject nucleic acid into the host cell can be effected, for example by calcium phosphate precipitation, DEAE dextran mediated transfection, liposome-mediated transfection, electroporation, or other known method.

[00157] Suitable mammalian cells include primary cells and immortalized cell lines. Suitable mammalian cell lines include human cell lines, non-human primate cell lines, rodent (e.g., mouse, rat) cell lines, and the like. Suitable mammalian cell lines include, but are not limited to, HeLa cells (e.g., American Type Culture Collection (ATCC) No. CCL-2), CHO cells (e.g., ATCC Nos. CRL9618, CCL61, CRL9096), 293 cells (e.g., ATCC No. CRL-1573), Vero cells, NIH 3T3 cells (e.g., ATCC No. CRL-1658), Huh-7 cells, BHK cells (e.g., ATCC No. CCL10), PC12 cells (ATCC No. CRL1721), COS cells, COS-7 cells (ATCC No. CRL1651), RATl cells, mouse L cells (ATCC No. CCL.3), human embryonic kidney (HEK) cells (ATCC No. CRL1573), HLHepG2 cells, and the like.

[00158] Suitable yeast cells include, but are not limited to, Pichia pastoris, Pichia fimlandica, Pichia trehalophila, Pichia koclamae, Pichia membraaefaciens, Pichia opuntiae, Pichia therma tolerans, Pichia salictaria, Pichia guercum, Pichia piiperi, Pichia stiptis, Pichia methanolica, Pichia sp., Saccharomyces cerevisiae, Saccharomyces sp., Hansenula polymorpha, Kluyveromyces sp., Kluyveromyces lactis, Candida albicans, Aspergillus nidulans, Aspergillus niger, Aspergillus oryzae, Trichoderma reesei, Chrysosporium lucknowense, Fusarium sp., Fusarium gramineum, Fusarium venenatum, Neurospora crassa, Chlamydomonas reinhardtii, and the like.

[00159] Suitable prokaryotic cells include, but are not limited to, any of a variety of laboratory strains of Escherichia coli, Lactobacillus sp., Salmonella sp., Shigella sp., and the like. See, e.g.,
Carrier et al. (1992) *J. Immunol.* 148:1176-1181; U.S. Patent No. 6,447,784; and Sizemore et al. (1995) *Science* 270:299-302. Examples of Salmonella strains which can be employed include, but are not limited to, *Salmonella typhi* and *S. typhimurium*. Suitable Shigella strains include, but are not limited to, *Shigella flexneri*, *Shigella sonnei*, and *Shigella disenteriae*. Typically, the laboratory strain is one that is non-pathogenic. Non-limiting examples of other suitable bacteria include, but are not limited to, *Bacillus subtilis*, *Pseudomonas putida*, *Pseudomonas aeruginosa*, *Pseudomonas mevalonii*, *Rhodobacter sphaeroides*, *Rhodobacter capsulatus*, *Rhodospirillum rubrum*, *Rhodococcus* sp., and the like. In some embodiments, the host cell is *Escherichia coli*.

**COMPOSITIONS**

[00160] The present disclosure provides compositions, including pharmaceutical compositions, comprising a subject antibody. In general, a formulation comprises an effective amount of a subject antibody. In the context of treatment of an immunodeficiency virus infection, an "effective amount" of a subject antibody means a dosage sufficient to produce a desired result, e.g., reduction in viral load, reduction in adverse symptoms of an immunodeficiency virus infection, etc.

[00161] A subject antibody can be incorporated into a variety of formulations for therapeutic administration. More particularly, a subject antibody can be formulated into pharmaceutical compositions by combination with appropriate, pharmaceutically acceptable carriers or diluents, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants and aerosols.

[00162] In pharmaceutical dosage forms, a subject antibody can be administered in the form of their pharmaceutically acceptable salts, or they may also be used alone or in appropriate association, as well as in combination, with other pharmaceutically active compounds. The following methods and excipients are merely exemplary and are in no way limiting.

[00163] For oral preparations, a subject antibody can be used alone or in combination with appropriate additives to make tablets, powders, granules or capsules, for example, with conventional additives, such as lactose, mannitol, corn starch or potato starch; with binders, such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators, such as corn starch, potato starch or sodium carboxymethylcellulose; with lubricants, such as talc or magnesium stearate; and if desired, with diluents, buffering agents, moistening agents, preservatives and flavoring agents.

[00164] A subject antibody can be formulated into preparations for injection by dissolving, suspending or emulsifying them in an aqueous or nonaqueous solvent, such as vegetable or other similar oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives.

[00165] Pharmaceutical compositions comprising a subject antibody are prepared by mixing the antibody having the desired degree of purity with optional pharmaceutically acceptable carriers,
excipients, stabilizers, surfactants, buffers and/or tonicity agents. Acceptable carriers, excipients and/or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid, glutathione, cysteine, methionine and citric acid; preservatives (such as ethanol, benzyl alcohol, phenol, m-cresol, p-chlor-m-cresol, methyl or propyl parabens, benzalkonium chloride, or combinations thereof); amino acids such as arginine, glycine, ornithine, lysine, histidine, glutamic acid, aspartic acid, isoleucine, leucine, alanine, phenylalanine, tyrosine, tryptophan, methionine, serine, proline and combinations thereof; monosaccharides, disaccharides and other carbohydrates; low molecular weight (less than about 10 residues) polypeptides; proteins, such as gelatin or serum albumin; chelating agents such as EDTA; sugars such as trehalose, sucrose, lactose, glucose, mannose, maltose, galactose, fructose, sorbose, raffinose, glucosamine, N-methylglucosamine, galactosamine, and neuraminic acid; and/or non-ionic surfactants such as Tween, Brij Pluronics, Triton-X, or polyethylene glycol (PEG).

[00166] The pharmaceutical composition may be in a liquid form, a lyophilized form or a liquid form reconstituted from a lyophilized form, wherein the lyophilized preparation is to be reconstituted with a sterile solution prior to administration. The standard procedure for reconstituting a lyophilized composition is to add back a volume of pure water (typically equivalent to the volume removed during lyophilization); however solutions comprising antibacterial agents may be used for the production of pharmaceutical compositions for parenteral administration; see also Chen (1992) Drug Dev Ind Pharm 18, 1311-54.

[00167] Exemplary antibody concentrations in a subject pharmaceutical composition can range from about 1 mg/mL to about 200 mg/mL or from about 50 mg/mL to about 200 mg/mL, or from about 150 mg/mL to about 200 mg/mL.

[00168] An aqueous formulation of the antibody may be prepared in a pH-buffered solution, e.g., at pH ranging from about 4.0 to about 7.0, or from about 5.0 to about 6.0, or alternatively about 5.5. Examples of buffers that are suitable for a pH within this range include phosphate-, histidine-, citrate-, succinate-, acetate-buffers and other organic acid buffers. The buffer concentration can be from about 1 mM to about 100 mM, or from about 5 mM to about 50 mM, depending, e.g., on the buffer and the desired tonicity of the formulation.

[00169] A tonicity agent may be included in the antibody formulation to modulate the tonicity of the formulation. Exemplary tonicity agents include sodium chloride, potassium chloride, glycerin and any component from the group of amino acids, sugars as well as combinations thereof. In some embodiments, the aqueous formulation is isotonic, although hypertonic or hypotonic solutions may be suitable. The term "isotonic" denotes a solution having the same tonicity as some other solution with which it is compared, such as physiological salt solution or serum. Tonicity agents may be used in an amount of about 5 mM to about 350 mM, e.g., in an amount of 100 mM to 350 mM.
A surfactant may also be added to the antibody formulation to reduce aggregation of the formulated antibody and/or minimize the formation of particulates in the formulation and/or reduce adsorption. Exemplary surfactants include polyoxyethylene sorbitan fatty acid esters (Tween), polyoxyethylene alkyl ethers (Brij), alkylphenolpolyoxyethylene ethers (Triton-X), polyoxyethylene-polyoxypropylene copolymer (Poloxamer, Pluronic), and sodium dodecyl sulfate (SDS). Examples of suitable polyoxyethylene sorbitan-fatty acid esters are polysorbate 20, (sold under the trademark Tween 20™) and polysorbate 80 (sold under the trademark Tween 80™). Examples of suitable polyethylene-polypropylene copolymers are those sold under the names Pluronic® F68 or Poloxamer 188™. Examples of suitable Polyoxyethylene alkyl ethers are those sold under the trademark Brij™. Exemplary concentrations of surfactant may range from about 0.001% to about 1% w/v.

A lyoprotectant may also be added in order to protect the labile active ingredient (e.g. a protein) against destabilizing conditions during the lyophilization process. For example, known lyoprotectants include sugars (including glucose and sucrose); polyols (including mannitol, sorbitol and glycerol); and amino acids (including alanine, glycine and glutamic acid). Lyoprotectants can be included in an amount of about 10 mM to 500 mM.

In some embodiments, a subject formulation includes a subject antibody, and one or more of the above-identified agents (e.g., a surfactant, a buffer, a stabilizer, a toxicity agent) and is essentially free of one or more preservatives, such as ethanol, benzyl alcohol, phenol, m-cresol, p-chlor-m-cresol, methyl or propyl parabens, benzalkonium chloride, and combinations thereof. In other embodiments, a preservative is included in the formulation, e.g., at concentrations ranging from about 0.001 to about 2% (w/v).

For example, a subject formulation can be a liquid or lyophilized formulation suitable for parenteral administration, and can comprise: about 1 mg/mL to about 200 mg/mL of a subject antibody; about 0.001% to about 1% of at least one surfactant; about 1 mM to about 100 mM of a buffer; optionally about 10 mM to about 500 mM of a stabilizer; and about 5 mM to about 305 mM of a toxicity agent; and has a pH of about 4.0 to about 7.0.

As another example, a subject parenteral formulation is a liquid or lyophilized formulation comprising: about 1 mg/mL to about 200 mg/mL of a subject antibody; 0.04% Tween 20 w/v; 20 mM L-histidine; and 250 mM Sucrose; and has a pH of 5.5.

As another example, a subject parenteral formulation comprises a lyophilized formulation comprising: 1) 15 mg/mL of a subject antibody; 0.04% Tween 20 w/v; 20 mM L-histidine; and 250 mM sucrose; and has a pH of 5.5; or 2) 75 mg/mL of a subject antibody; 0.04% Tween 20 w/v; 20 mM L-histidine; and 250 mM sucrose; and has a pH of 5.5; or 3) 75 mg/mL of a subject antibody; 0.02% Tween 20 w/v; 20 mM L-histidine; and 250 mM Sucrose; and has a pH of 5.5; or 4) 75 mg/mL of a subject antibody; 0.04% Tween 20 w/v; 20 mM L-histidine; and 250 mM trehalose; and
has a pH of 5.5; or 6) 75 mg/mL of a subject antibody; 0.02% Tween 20 w/v; 20 mM L-histidine; and 250 mM trehalose; and has a pH of 5.5.

As another example, a subject parenteral formulation is a liquid formulation comprising: 1) 7.5 mg/mL of a subject antibody; 0.022% Tween 20 w/v; 120 mM L-histidine; and 250 125 mM sucrose; and has a pH of 5.5; or 2) 37.5 mg/mL of a subject antibody; 0.02% Tween 20 w/v; 10 mM L-histidine; and 125 mM sucrose; and has a pH of 5.5; or 3) 37.5 mg/mL of a subject antibody; 0.01% Tween 20 w/v; 10 mM L-histidine; and 125 mM sucrose; and has a pH of 5.5; or 4) 37.5 mg/mL of a subject antibody; 0.02% Tween 20 w/v; 10 mM L-histidine; 125 mM trehalose; and has a pH of 5.5; or 5) 37.5 mg/mL of a subject antibody; 0.01% Tween 20 w/v; 10 mM L-histidine; and 125 mM trehalose; and has a pH of 5.5; or 6) 5 mg/mL of a subject antibody; 0.02% Tween 20 w/v; 20 mM L-histidine; and 250 mM trehalose; and has a pH of 5.5; or 7) 75 mg/mL of a subject antibody; 0.02% Tween 20 w/v; 20 mM L-histidine; and 250 mM mannitol; and has a pH of 5.5; or 8) 75 mg/mL of a subject antibody; 0.02% Tween 20 w/v; 20 mM L histidine; and 140 mM sodium chloride; and has a pH of 5.5; or 9) 150 mg/mL of a subject antibody; 0.02% Tween 20 w/v; 20 mM L-histidine; and 250 mM trehalose; and has a pH of 5.5; or 10) 150 mg/mL of a subject antibody; 0.02% Tween 20 w/v; 20 mM L-histidine; and 250 mM mannitol; and has a pH of 5.5; or 11) 150 mg/mL of a subject antibody; 0.02% Tween 20 w/v; 20 mM L-histidine; and 140 mM sodium chloride; and has a pH of 5.5; or 12) 10 mg/mL of a subject antibody; 0.01% Tween 20 w/v; 20 mM L-histidine; and 40 mM sodium chloride; and has a pH of 5.5.

A subject antibody can be utilized in aerosol formulation to be administered via inhalation. A subject antibody can be formulated into pressurized acceptable propellants such as dichlorodifluoromethane, propane, nitrogen and the like.

Furthermore, a subject antibody can be made into suppositories by mixing with a variety of bases such as emulsifying bases or water-soluble bases. A subject antibody can be administered rectally via a suppository. The suppository can include vehicles such as cocoa butter, carbowaxes and polyethylene glycols, which melt at body temperature, yet are solidified at room temperature.

Unit dosage forms for oral or rectal administration such as syrups, elixirs, and suspensions may be provided wherein each dosage unit, for example, teaspoonful, tablespoonful, tablet or suppository, contains a predetermined amount of the composition containing one or more inhibitors. Similarly, unit dosage forms for injection or intravenous administration may comprise a subject antibody in a composition as a solution in sterile water, normal saline or another pharmaceutically acceptable carrier.

The term "unit dosage form," as used herein, refers to physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined quantity of compounds of the present invention calculated in an amount sufficient to produce the desired effect in association with a pharmaceutically acceptable diluent, carrier or vehicle. The specifications for a
subject antibody may depend on the particular antibody employed and the effect to be achieved, and
the pharmacodynamics associated with each antibody in the host.

[00181] Other modes of administration will also find use. For instance, a subject antibody can be
formulated in suppositories and, in some cases, aerosol and intranasal compositions. For
suppositories, the vehicle composition will include traditional binders and carriers such as,
polyalkylene glycols, or triglycerides. Such suppositories may be formed from mixtures containing
the active ingredient in the range of about 0.5% to about 10% (w/w), e.g., about 1% to about 2%.

[00182] Intranasal formulations will usually include vehicles that neither cause irritation to the nasal
mucosa nor significantly disturb ciliary function. Diluents such as water, aqueous saline or other
known substances can be employed. The nasal formulations may also contain preservatives such as,
but not limited to, chlorobutanol and benzalkonium chloride. A surfactant may be present to enhance
absorption of the subject proteins by the nasal mucosa.

[00183] A subject antibody can be administered as an injectable formulation. Typically, injectable
compositions are prepared as liquid solutions or suspensions; solid forms suitable for solution in, or
suspension in, liquid vehicles prior to injection may also be prepared. The preparation may also be
emulsified or the antibody encapsulated in liposome vehicles.

[00184] Suitable excipient vehicles are, for example, water, saline, dextrose, glycerol, ethanol, or the
like, and combinations thereof. In addition, if desired, the vehicle may contain minor amounts of
auxiliary substances such as wetting or emulsifying agents or pH buffering agents. Actual methods
of preparing such dosage forms are known, or will be apparent, to those skilled in the art. See, e.g.,
Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 17th
dition, 1985. The composition or formulation to be administered will, in any event, contain a
quantity of a subject antibody adequate to achieve the desired state in the subject being treated.

[00185] The pharmaceutically acceptable excipients, such as vehicles, adjuvants, carriers or diluents,
are readily available to the public. Moreover, pharmaceutically acceptable auxiliary substances, such
as pH adjusting and buffering agents, tonicity adjusting agents, stabilizers, wetting agents and the
like, are readily available to the public.

[00186] In some embodiments, a subject antibody is formulated in a controlled release formulation.
Sustained-release preparations may be prepared using methods well known in the art. Suitable
examples of sustained-release preparations include semipermeable matrices of solid hydrophobic
polymers containing the antibody in which the matrices are in the form of shaped articles, e.g. films
or microcapsules. Examples of sustained-release matrices include polysters, copolymers of L-
glutamic acid and ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, hydrogels, polylactides,
degradable lactic acid-glycolic acid copolymers and poly-D(-)-3-hydroxybutyric acid. Possible loss
of biological activity and possible changes in immunogenicity of antibodies comprised in sustained-
release preparations may be prevented by using appropriate additives, by controlling moisture
content and by developing specific polymer matrix compositions.
Controlled release within the scope of this invention can be taken to mean any one of a number of extended release dosage forms. The following terms may be considered to be substantially equivalent to controlled release, for the purposes of the present disclosure: continuous release, controlled release, delayed release, depot, gradual release, long-term release, programmed release, prolonged release, proportionate release, protracted release, repository, retard, slow release, spaced release, sustained release, time coat, timed release, delayed action, extended action, layered-time action, long acting, prolonged action, repeated action, slowing acting, sustained action, sustained-action medications, and extended release. Further discussions of these terms may be found in Lesczek Krowczynski, "Extended-Release Dosage Forms," 1987 (CRC Press, Inc.).

The various controlled release technologies cover a very broad spectrum of drug dosage forms. Controlled release technologies include, but are not limited to physical systems and chemical systems. Physical systems include, but are not limited to, reservoir systems with rate-controlling membranes, such as microencapsulation, macroencapsulation, and membrane systems; reservoir systems without rate-controlling membranes, such as hollow fibers, ultra microporous cellulose triacetate, and porous polymeric substrates and foams; monolithic systems, including those systems physically dissolved in non-porous, polymeric, or elastomeric matrices (e.g., nonerodible, erodible, environmental agent ingestion, and degradable), and materials physically dispersed in non-porous, polymeric, or elastomeric matrices (e.g., nonerodible, erodible, environmental agent ingestion, and degradable); laminated structures, including reservoir layers chemically similar or dissimilar to outer control layers; and other physical methods, such as osmotic pumps, or adsorption onto ion-exchange resins.

Chemical systems include, but are not limited to, chemical erosion of polymer matrices (e.g., heterogeneous, or homogeneous erosion), or biological erosion of a polymer matrix (e.g., heterogeneous, or homogeneous). Additional discussion of categories of systems for controlled release may be found in Agis F. Kydonieus, Controlled Release Technologies: Methods, Theory and Applications, 1980 (CRC Press, Inc.).

There are a number of controlled release drug formulations that are developed for oral administration. These include, but are not limited to, osmotic pressure-controlled gastrointestinal delivery systems; hydrodynamic pressure-controlled gastrointestinal delivery systems; membrane permeation-controlled gastrointestinal delivery systems, which include microporous membrane permeation-controlled gastrointestinal delivery devices; gastric fluid-resistant intestine targeted controlled-release gastrointestinal delivery devices; gel diffusion-controlled gastrointestinal delivery systems; and ion-exchange-controlled gastrointestinal delivery systems, which include cationic and anionic drugs. Additional information regarding controlled release drug delivery systems may be found in Yie W. Chien, Novel Drug Delivery Systems, 1992 (Marcel Dekker, Inc.). Some of these formulations will now be discussed in more detail.
UTILITY

[00192] A subject anti-HERV-K antibody is useful in various treatment, diagnostic, and monitoring applications, which are also provided.

Treatment methods - immunodeficiency virus infection

[00193] A subject antibody is useful in methods of treating an immunodeficiency virus infection. The present disclosure thus provides treating an immunodeficiency virus infection in an individual, the methods generally involving administering to an individual who has an immunodeficiency virus infection, or who is at greater risk that the general population of becoming infected with an immunodeficiency virus, an effective amount of a subject anti-HERV-K antibody.

[00194] In some embodiments, an "effective amount" of a subject anti-HERV-K antibody is an amount that, when administered to an individual in one or more doses, in monotherapy or in combination therapy, is effective to reduce immunodeficiency virus load in the individual by at least about 10%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or greater than 80%, compared to the immunodeficiency virus load in the individual in the absence of treatment with the agent.

[00195] In some embodiments, an "effective amount" of a subject anti-HERV-K antibody is an amount that, when administered to an individual in one or more doses, in monotherapy or in combination therapy, is effective to reduce the latent reservoir of immunodeficiency virus in the individual by at least about 10%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or greater than 80%, compared to the latent reservoir of immunodeficiency virus in the individual in the absence of treatment with the agent.

[00196] In some embodiments, an "effective amount" of a subject anti-HERV-K antibody is an amount that, when administered to an individual in one or more doses, in monotherapy or in combination therapy, is effective to reduce cell-to-cell spread of immunodeficiency virus in the individual by at least about 10%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or greater than 80%, compared to the level of cell-to-cell spread of immunodeficiency virus in the individual in the absence of treatment with the agent.

[00197] Any of a variety of methods can be used to determine whether a treatment method is effective. For example, methods of determining whether a subject method (e.g., a subject anti-HERV-K antibody) is effective in reducing immunodeficiency virus (e.g., HIV) viral load, and/or treating an immunodeficiency virus (e.g., HIV) infection, are any known test for indicia of immunodeficiency virus (e.g., HIV) infection, including, but not limited to, measuring viral load, e.g., by measuring the amount of immunodeficiency virus (e.g., HIV) in a biological sample, e.g., using a polymerase chain reaction (PCR) with primers specific for an immunodeficiency virus (e.g.,
HIV) polynucleotide sequence; detecting and/or measuring a polypeptide encoded by an
immunodeficiency virus (e.g., HIV), e.g., p24, gp120, reverse transcriptase, using, e.g., an
immunological assay such as an enzyme-linked immunosorbent assay (ELISA) with an antibody
specific for the polypeptide; and measuring the CD4+ T cell count in the individual.

Formulations

A subject anti-HERV-K antibody is administered to an individual in need thereof in a
formulation with a pharmaceutically acceptable excipient(s). A wide variety of pharmaceutically
acceptable excipients is known in the art and need not be discussed in detail herein.
Pharmaceutically acceptable excipients have been amply described in a variety of publications,
including, for example, A. Gennaro (2000) "Remington: The Science and Practice of Pharmacy",
20th edition, Lippincott, Williams, & Wilkins; Pharmaceutical Dosage Forms and Drug Delivery
Systems (1999) H. C. Ansel et al., eds 7th ed., Lippincott, Williams, & Wilkins; and Handbook of
the purposes of the following description of formulations, "active agent" includes an active agent as
described above, and optionally one or more additional therapeutic agent.

In a subject method, a subject anti-HERV-K antibody may be administered to the host using
any route of administration that results in the desired degree of: 1) reduction of immunodeficiency
virus load; or 2) reduction of latent immunodeficiency virus reservoir. Thus, a subject anti-HERV-K
antibody can be incorporated into a variety of formulations for therapeutic administration. For
example, a subject anti-HERV-K antibody can be formulated into pharmaceutical compositions by
combination with appropriate, pharmaceutically acceptable carriers or diluents, and may be
formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules,
powders, granules, ointments, solutions, suppositories, injections, inhalants and aerosols. In an
exemplary embodiment, a subject anti-HERV-K antibody is formulated as a gel, as a solution, or in
some other form suitable for intravaginal administration. In a further exemplary embodiment, an
active agent is formulated as a gel, as a solution, or in some other form suitable for rectal (e.g.,
intrarectal) administration.

In pharmaceutical dosage forms, a subject anti-HERV-K antibody may be administered in
the form of its pharmaceutically acceptable salts, or it may also be used alone or in appropriate
association, as well as in combination, with other pharmaceutically active compounds. The
following methods and excipients are merely exemplary and are in no way limiting.

In some embodiments, a subject anti-HERV-K antibody is formulated in an aqueous buffer.
Suitable aqueous buffers include, but are not limited to, acetate, succinate, citrate, and phosphate
buffers varying in strengths from about 5 mM to about 100 mM. In some embodiments, the aqueous
buffer includes reagents that provide for an isotonic solution. Such reagents include, but are not
limited to, sodium chloride; and sugars e.g., mannitol, dextrose, sucrose, and the like. In some
embodiments, the aqueous buffer further includes a non-ionic surfactant such as polysorbate 20 or
80. Optionally the formulations may further include a preservative. Suitable preservatives include, but are not limited to, a benzyl alcohol, phenol, chlorobutanol, benzalkonium chloride, and the like. In many cases, the formulation is stored at about 4°C. Formulations may also be lyophilized, in which case they generally include cryoprotectants such as sucrose, trehalose, lactose, maltose, mannitol, and the like. Lyophilized formulations can be stored over extended periods of time, even at ambient temperatures.

For oral preparations, a subject anti-HERV-K antibody can be used alone or in combination with appropriate additives to make tablets, powders, granules or capsules, for example, with conventional additives, such as lactose, mannitol, corn starch or potato starch; with binders, such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators, such as corn starch, potato starch or sodium carboxymethylcellulose; with lubricants, such as talc or magnesium stearate; and if desired, with diluents, buffering agents, moistening agents, preservatives and flavoring agents.

A subject anti-HERV-K antibody can be formulated into preparations for injection by dissolving, suspending or emulsifying them in an aqueous or nonaqueous solvent, such as vegetable or other similar oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives.

A subject anti-HERV-K antibody can be utilized in aerosol formulation to be administered via inhalation. An active agent can be formulated into pressurized acceptable propellants such as dichlorodifluoromethane, propane, nitrogen and the like.

Furthermore, a subject anti-HERV-K antibody can be made into suppositories by mixing with a variety of bases such as emulsifying bases or water-soluble bases. A subject anti-HERV-K antibody can be administered rectally via a suppository. The suppository can include vehicles such as cocoa butter, carbowaxes and polyethylene glycols, which melt at body temperature, yet are solidified at room temperature.

Unit dosage forms for oral or rectal administration such as syrups, elixirs, and suspensions may be provided wherein each dosage unit, for example, teaspoonful, tablespoonful, tablet or suppository, contains a predetermined amount of the composition containing one or more active agents. Similarly, unit dosage forms for injection or intravenous administration may comprise the subject anti-HERV-K antibody(ies) in a composition as a solution in sterile water, normal saline or another pharmaceutically acceptable carrier.

Unit dosage forms for intravaginal or intrarectal administration such as syrups, elixirs, gels, and suspensions may be provided wherein each dosage unit, for example, teaspoonful, tablespoonful, tablet, unit gel volume, or suppository, contains a predetermined amount of the composition containing one or more antibodies.
The term "unit dosage form," as used herein, refers to physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined quantity of a subject anti-HERV-K antibody, calculated in an amount sufficient to produce the desired effect in association with a pharmaceutically acceptable diluent, carrier or vehicle. The specifications for a given antibody will depend in part on the particular compound employed and the effect to be achieved, and the pharmacodynamics associated with each compound in the host.

Other modes of administration will also find use with the subject invention. For instance, a subject anti-HERV-K antibody can be formulated in suppositories and, in some cases, aerosol and intranasal compositions. For suppositories, the vehicle composition will include traditional binders and carriers such as, polyalkylene glycols, or triglycerides. Such suppositories may be formed from mixtures containing the active ingredient in the range of about 0.5% to about 10% (w/w), e.g. about 1% to about 2%.

A subject anti-HERV-K antibody can be administered in an injectable formulation. Typically, injectable compositions are prepared as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection may also be prepared. The preparation may also be emulsified or the active ingredient encapsulated in liposome vehicles.

A subject anti-HERV-K antibody will in some embodiments be formulated for vaginal delivery. A subject formulation for intravaginal administration comprises a subject anti-HERV-K antibody formulated as an intravaginal bioadhesive tablet, intravaginal bioadhesive microparticle, intravaginal cream, intravaginal lotion, intravaginal foam, intravaginal ointment, intravaginal paste, intravaginal solution, or intravaginal gel.

A subject anti-HERV-K antibody will in some embodiments be formulated for rectal delivery. A subject formulation for intrarectal administration comprises a subject anti-HERV-K antibody formulated as an intrarectal bioadhesive tablet, intrarectal bioadhesive microparticle, intrarectal cream, intrarectal lotion, intrarectal foam, intrarectal ointment, intrarectal paste, intrarectal solution, or intrarectal gel.

A subject formulation comprising a subject anti-HERV-K antibody includes one or more of an excipient (e.g., sucrose, starch, mannitol, sorbitol, lactose, glucose, cellulose, talc, calcium phosphate or calcium carbonate), a binder (e.g., cellulose, methylcellulose, hydroxyethylcellulose, polypropylyrrolidone, polyvinylpyrrolidone, gelatin, gum arabic, poly(ethylene glycol), sucrose or starch), a disintegrator (e.g., starch, carboxymethylcellulose, hydroxypropyl starch, low substituted hydroxypropylcellulose, sodium bicarbonate, calcium phosphate or calcium citrate), a lubricant (e.g., magnesium stearate, light anhydrous silicic acid, talc or sodium lauryl sulfate), a flavoring agent (e.g., citric acid, menthol, glycine or orange powder), a preservative (e.g., sodium benzoate, sodium bisulfite, methylparaben or propylparaben), a stabilizer (e.g., citric acid, sodium citrate or acetic acid), a suspending agent (e.g., methylcellulose, polyvinylpyrrolidone or aluminum stearate),
a dispersing agent (e.g., hydroxypropylmethylcellulose), a diluent (e.g., water), and base wax (e.g.,
cocoa butter, white petrolatum or polyethylene glycol).

Tablets comprising a subject anti-HERV-K antibody may be coated with a suitable film-
forming agent, e.g., hydroxypropylmethyl cellulose, hydroxypropyl cellulose or ethyl cellulose, to
which a suitable excipient may optionally be added, e.g., a softener such as glycerol, propylene
glycol, diethylphthalate, or glycerol triacetate; a filler such as sucrose, sorbitol, xylitol, glucose, or
lactose; a colorant such as titanium hydroxide; and the like.

Suitable excipient vehicles are, for example, water, saline, dextrose, glycerol, ethanol, or the
like, and combinations thereof. In addition, if desired, the vehicle may contain minor amounts of
auxiliary substances such as wetting or emulsifying agents or pH buffering agents. Actual methods
of preparing such dosage forms are known, or will be apparent, to those skilled in the art. See, e.g.,
The composition or formulation to be administered will, in any event, contain a quantity of the agent
adequate to achieve the desired state in the subject being treated.

The pharmaceutically acceptable excipients, such as vehicles, adjuvants, carriers or diluents,
are readily available to the public. Moreover, pharmaceutically acceptable auxiliary substances, such
as pH adjusting and buffering agents, tonicity adjusting agents, stabilizers, wetting agents and the
like, are readily available to the public.

dosages

Although the dosage used will vary depending on the clinical goals to be achieved, a
suitable dosage range of a subject anti-HERV-K antibody is one which provides up to about 1 mg to
about 1000 mg, e.g., from about 1 mg to about 25 mg, from about 25 mg to about 50 mg, from about
50 mg to about 100 mg, from about 100 mg to about 200 mg, from about 200 mg to about 250 mg,
from about 250 mg to about 500 mg, or from about 500 mg to about 1000 mg of an active agent can
be administered in a single dose.

Those of skill will readily appreciate that dose levels can vary as a function of the specific
antibody, the severity of the symptoms and the susceptibility of the subject to side effects. Preferred
dosages for a given antibody are readily determinable by those of skill in the art by a variety of
means.

In some embodiments, a single dose of a subject anti-HERV-K antibody is administered. In
other embodiments, multiple doses of an active agent are administered. Where multiple doses are
administered over a period of time, an active agent is administered twice daily (qid), daily (qd),
every other day (qod), every third day, three times per week (tiw), or twice per week (biw) over a
period of time. For example, an active agent is administered qid, qd, qod, tiw, or biw over a period
of from one day to about 2 years or more. For example, a subject anti-HERV-K antibody is
administered at any of the aforementioned frequencies for one week, two weeks, one month, two
months, six months, one year, or two years, or more, depending on various factors.
Where two different antibodies are administered, a first antibody and a second antibody can be administered in separate formulations. A first antibody and a second antibody can be administered substantially simultaneously, or within about 30 minutes, about 1 hour, about 2 hours, about 4 hours, about 8 hours, about 16 hours, about 24 hours, about 36 hours, about 72 hours, about 4 days, about 7 days, or about 2 weeks of one another.

Where two different active agents (e.g., an anti-HERV-K antibody ("a first active agent"); and a second agent that treats an immunodeficiency virus infection) are administered, a first active agent and a second active agent can be administered in separate formulations. A first active agent and a second active agent can be administered substantially simultaneously, or within about 30 minutes, about 1 hour, about 2 hours, about 4 hours, about 8 hours, about 16 hours, about 24 hours, about 36 hours, about 72 hours, about 4 days, about 7 days, or about 2 weeks of one another.

Routes of Administration

A subject anti-HERV-K antibody is administered to an individual using any available method and route suitable for drug delivery, including *in vivo* and *ex vivo* methods, as well as systemic and localized routes of administration.

Conventional and pharmaceutically acceptable routes of administration include intranasal, intramuscular, intratracheal, transdermal, subcutaneous, intradermal, topical application, intravenous, vaginal, nasal, and other parenteral routes of administration. In some embodiments, a subject anti-HERV-K antibody is administered via an intravaginal route of administration. In other embodiments, an active agent is administered via an intrarectal route of administration. Routes of administration may be combined, if desired, or adjusted depending upon the agent and/or the desired effect. The composition can be administered in a single dose or in multiple doses.

A subject anti-HERV-K antibody can be administered to a host using any available conventional methods and routes suitable for delivery of conventional drugs, including systemic or localized routes. In general, routes of administration contemplated by the invention include, but are not necessarily limited to, enteral, parenteral, or inhalational routes.

Parenteral routes of administration other than inhalation administration include, but are not necessarily limited to, topical, vaginal, transdermal, subcutaneous, intramuscular, and intravenous routes, i.e., any route of administration other than through the alimentary canal. Parenteral administration can be carried to effect systemic or local delivery of the agent. Where systemic delivery is desired, administration typically involves invasive or systemically absorbed topical or mucosal administration of pharmaceutical preparations.

A subject anti-HERV-K antibody can also be delivered to the subject by enteral administration. Enteral routes of administration include, but are not necessarily limited to, oral and rectal (e.g., using a suppository) delivery.

By treatment is meant at least an amelioration of the symptoms associated with the pathological condition afflicting the host, where amelioration is used in a broad sense to refer to at
least a reduction in the magnitude of a parameter, e.g. symptom, associated with the pathological condition being treated, such as the number of viral particles per unit blood. As such, treatment also includes situations where the pathological condition, or at least symptoms associated therewith, are completely inhibited, e.g. prevented from happening, or stopped, e.g. terminated, such that the host no longer suffers from the pathological condition, or at least the symptoms that characterize the pathological condition.

A variety of hosts (wherein the term "host" is used interchangeably herein with the terms "subject" and "patient") are treatable according to the subject methods. Generally such hosts are "mammals" or "mammalian," where these terms are used broadly to describe organisms which are within the class mammalia, and primates (e.g., humans, chimpanzees, and monkeys), that are susceptible to immunodeficiency virus (e.g., HIV) infection. For example, the host can be a human.

Kits, Containers, Devices, Delivery Systems

Kits with unit doses of a subject anti-HERV-K antibody, e.g. in oral, vaginal, rectal, transdermal, or injectable doses (e.g., for intramuscular, intravenous, or subcutaneous injection), are provided. In such kits, in addition to the containers containing the unit doses will be an informational package insert describing the use and attendant benefits of the antibody in treating an immunodeficiency virus (e.g., an HIV) infection. Suitable active agents and unit doses are those described herein above.

In many embodiments, a subject kit will further include instructions for practicing the subject methods or means for obtaining the same (e.g., a website URL directing the user to a webpage or manuscript that provides the instructions), where these instructions are typically printed on a substrate, which substrate may be one or more of: a package insert, the packaging, formulation containers, and the like.

In some embodiments, a subject kit includes one or more components or features that increase patient compliance, e.g., a component or system to aid the patient in remembering to take the active agent at the appropriate time or interval. Such components include, but are not limited to, a calendaring system to aid the patient in remembering to take the active agent at the appropriate time or interval.

The present disclosure provides a delivery system comprising a subject anti-HERV-K antibody. In some embodiments, the delivery system is a delivery system that provides for injection of a formulation comprising an active agent subcutaneously, intravenously, or intramuscularly. In other embodiments, the delivery system is a vaginal or rectal delivery system.

In some embodiments, an active agent is packaged for oral administration. The present disclosure provides a packaging unit comprising daily dosage units of an active agent. For example, the packaging unit is in some embodiments a conventional blister pack or any other form that includes tablets, pills, and the like. The blister pack will contain the appropriate number of unit dosage forms, in a sealed blister pack with a cardboard, paperboard, foil, or plastic backing, and
enclosed in a suitable cover. Each blister container may be numbered or otherwise labeled, e.g.,
starting with day 1.

[00234] In some embodiments, a subject delivery system comprises an injection device. Exemplary,
non-limiting drug delivery devices include injections devices, such as pen injectors, and
needle/syringe devices. In some embodiments, the present disclosure provides an injection delivery
device that is pre-loaded with a formulation comprising an effective amount of a subject anti-
HERV-K antibody. For example, a subject delivery device comprises an injection device pre-loaded
with a single dose of a subject anti-HERV-K antibody. A subject injection device can be re-usable
or disposable.

[00235] Pen injectors are well known in the art. Exemplary devices which can be adapted for use in
the present methods are any of a variety of pen injectors from Becton Dickinson, e.g., BD™ Pen,
BD™ Pen II, BD™ Auto-Injector; a pen injector from Innoject, Inc.; any of the medication delivery
pen devices discussed in U.S. Pat. Nos. 5,728,074, 6,096,010, 6,146,361, 6,248,095, 6,277,099, and
6,221,053; and the like. The medication delivery pen can be disposable, or reusable and refillable.

[00236] The present invention provides a delivery system for vaginal or rectal delivery of a subject
anti-HERV-K antibody to the vagina or rectum of an individual. The delivery system comprises a
device for insertion into the vagina or rectum. In some embodiments, the delivery system comprises
an applicator for delivery of a formulation into the vagina or rectum; and a container that contains a
formulation comprising a subject anti-HERV-K antibody. In these embodiments, the container (e.g.,
a tube) is adapted for delivering a formulation into the applicator. In other embodiments, the
delivery system comprises a device that is inserted into the vagina or rectum, which device includes
a subject anti-HERV-K antibody. For example, the device is coated with, impregnated with, or
otherwise contains a formulation comprising a subject anti-HERV-K antibody.

[00237] In some embodiments, the vaginal or rectal delivery system is a tampon or tampon-like
device that comprises a subject formulation. Drug delivery tampons are known in the art, and any
such tampon can be used in conjunction with a subject drug delivery system. Drug delivery tampons
are described in, e.g., U.S. Pat. No. 6,086,909. If a tampon or tampon-like device is used, there are
numerous methods by which an active agent can be incorporated into the device. For example, the
active agent can be incorporated into a gel-like bioadhesive reservoir in the tip of the device.
Alternatively, the active agent can be in the form of a powdered material positioned at the tip of the
tampon. The active agent can also be absorbed into fibers at the tip of the tampon, for example, by
dissolving the drug in a pharmaceutically acceptable carrier and absorbing the drug solution into the
tampon fibers. The active agent can also be dissolved in a coating material which is applied to the
tip of the tampon. Alternatively, the active agent can be incorporated into an insertable suppository
which is placed in association with the tip of the tampon.

[00238] In other embodiments, the drug delivery device is a vaginal or rectal ring. Vaginal or rectal
rings usually consist of an inert elastomer ring coated by another layer of elastomer containing an
active agent (e.g., a subject anti-HERV-K antibody) to be delivered. The rings can be easily inserted, left in place for the desired period of time (e.g., up to 7 days), then removed by the user. The ring can optionally include a third, outer, rate-controlling elastomer layer which contains no drug. Optionally, the third ring can contain a second drug for a dual release ring. The drug can be incorporated into polyethylene glycol throughout the silicone elastomer ring to act as a reservoir for drug to be delivered.

[00239] In other embodiments, a subject vaginal or rectal delivery system is a vaginal or rectal sponge. The active agent is incorporated into a silicone matrix which is coated onto a cylindrical drug-free polyurethane sponge, as described in the literature.

[00240] Pessaries, tablets, and suppositories are other examples of drug delivery systems which can be used in the present invention. These systems have been described extensively in the literature.

[00241] Bioadhesive microparticles constitute still another drug delivery system suitable for use in the present invention. This system is a multi-phase liquid or semi-solid preparation which does not seep from the vagina or rectum as do many suppository formulations. The substances cling to the wall of the vagina or rectum and release the drug over a period of time. Many of these systems were designed for nasal use but can be used in the vagina or rectum as well (e.g. U.S. Pat. No. 4,756,907). The system may comprise microspheres with an active agent; and a surfactant for enhancing uptake of the drug. The microparticles have a diameter of 10-100 µm and can be prepared from starch, gelatin, albumin, collagen, or dextran.

[00242] Another system is a container comprising a subject formulation (e.g., a tube) that is adapted for use with an applicator. The active agent is incorporated into creams, lotions, foams, paste, ointments, and gels which can be applied to the vagina or rectum using an applicator. Processes for preparing pharmaceuticals in cream, lotion, foam, paste, ointment and gel formats can be found throughout the literature. An example of a suitable system is a standard fragrance free lotion formulation containing glycerol, ceramides, mineral oil, petrolatum, parabens, fragrance and water such as the product sold under the trademark JERGENSTM (Andrew Jergens Co., Cincinnati, Ohio). Suitable nontoxic pharmaceutically acceptable systems for use in the compositions of the present invention will be apparent to those skilled in the art of pharmaceutical formulations and examples are described in Remington's Pharmaceutical Sciences, 19th Edition, A. R. Gennaro, ed., 1995. The choice of suitable carriers will depend on the exact nature of the particular vaginal or rectal dosage form desired, e.g., whether the active ingredient(s) is/are to be formulated into a cream, lotion, foam, ointment, paste, solution, or gel, as well as on the identity of the active ingredient(s). Other suitable delivery devices are those described in U.S. Pat. No. 6,476,079.

Combination therapy

[00243] In some embodiments, a subject anti-HERV-K antibody is administered to an individual in need thereof in combination therapy with one or more additional therapeutic agents. Suitable additional therapeutic agents include agents that inhibit one or more functions of an
immunodeficiency virus; agents that treat or ameliorate a symptom of an immunodeficiency virus infection; agents that treat an infection that occurs secondary to an immunodeficiency virus infection; and the like.

[00244] Therapeutic agents include, e.g., beta-lactam antibiotics, tetracyclines, chloramphenicol, neomycin, gramicidin, bacitracin, sulfonamides, nitrofurazone, nalidixic acid, cortisone, hydrocortisone, betamethasone, dexamethasone, fluocortolone, prednisolone, triamcinolone, indomethacin, sulindac, acyclovir, amantadine, rimantadine, recombinant soluble CD4 (rsCD4), anti-receptor antibodies (e.g., for rhinoviruses), nevirapine, cidofovir (Vistide™), trisodium phosphonoformate (Foscarnet™), famcyclovir, pencyclovir, valacyclovir, nuleic acid/replication inhibitors, interferon, zidovudine (AZT, Retrovir™), didanosine (dideoxinosine, ddl, Videx™), stavudine (d4T, Zerit™), zalcitabine (dideoxycytosine, ddC, Hivid™), nevirapine (Viramune™), lamivudine (Epivir™, 3TC), protease inhibitors, saquinavir (Invirase™, Fortovase™), ritonavir (Norvir™), nelfinavir (Viracept™), efavirenz (Sustiva™), abacavir (Ziagen™), amprenavir (Agenerase™) indinavir (Crixivan™), ganciclovir, AzDU, delavirdine (Rescriptor™), kaletra, trizivir, rifampin, clathriomycin, erythropoietin, colony stimulating factors (G-CSF and GM-CSF), non-nucleoside reverse transcriptase inhibitors, nucleoside inhibitors, adriamycin, fluorouracil, methotrexate, aspiraginase and combinations thereof. Anti-HIV agents are those in the preceding list that specifically target a function of one or more HIV proteins.

[00245] In some embodiments, subject anti-HERV-K antibody is administered in combination therapy with two or more anti-HIV agents. For example, a subject anti-HERV-K antibody can be administered in combination therapy with one, two, or three nucleoside reverse transcriptase inhibitors (e.g., Combidiv, Epivir, Hivid, Retrovir, Videx, Zerit, Ziagen, etc.). A subject anti-HERV-K antibody can be administered in combination therapy with one or two non-nucleoside reverse transcriptase inhibitors (e.g., Rescriptor, Sustiva, Viramune, etc.). A subject anti-HERV-K antibody can be administered in combination therapy with one or two protease inhibitors (e.g., Agenerase, Crixivan, Fortovase, Invirase, Kaletra, Norvir, Viracept, etc.). A subject anti-HERV-K antibody can be administered in combination therapy with a protease inhibitor and a nucleoside reverse transcriptase inhibitor. A subject anti-HERV-K antibody can be administered in combination therapy with a protease inhibitor, a nucleoside reverse transcriptase inhibitor, and a non-nucleoside reverse transcriptase inhibitor. A subject anti-HERV-K antibody can be administered in combination therapy with a protease inhibitor and a non-nucleoside reverse transcriptase inhibitor. Other combinations of an active agent (e.g., a subject anti-HERV-K antibody) with one or more of a protease inhibitor, a nucleoside reverse transcriptase inhibitor, and a non-nucleoside reverse transcriptase inhibitor are contemplated.

[00246] In some embodiments, a subject treatment method involves administering: a) subject anti-HERV-K antibody; and b) an agent that inhibits an immunodeficiency virus function selected from viral replication, viral protease activity, viral reverse transcriptase activity, viral entry into a cell,
viral integrase activity, viral Rev activity, viral Tat activity, viral Nef activity, viral Vpr activity, viral Vpu activity, and viral Vif activity.

In some embodiments, a subject treatment method involves administering: a) subject anti-HERV-K antibody; and b) an HIV inhibitor, where suitable HIV inhibitors include, but are not limited to, one or more nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (Pis), fusion inhibitors, integrase inhibitors, chemokine receptor (e.g., CXCR4, CCR5) inhibitors, and hydroxyurea.

Nucleoside reverse transcriptase inhibitors include, but are not limited to, abacavir (ABC; ZIAGEN™), didanosine (dideoxyinosine (ddl); VIDEX™), lamivudine (3TC; EPIVIR™), stavudine (d4T; ZERIT™, ZERIT XR™), zalcitabine (dideoxyctydine (ddC); HVID™), zidovudine (ZDV, formerly known as azidothymidine (AZT); RETROVIR™), abacavir, zidovudine, and lamivudine (TRIZIVIR™), zidovudine and lamivudine (COMBIVIR™), and emtricitabine (EMTRIVA™). Nucleotide reverse transcriptase inhibitors include tenofovir disoproxil fumarate (VIRED™). Non-nucleoside reverse transcriptase inhibitors for HIV include, but are not limited to, nevirapine (VIRAMUNE™), delavirdine mesylate (RESPICRIPTOR™), and efavirenz (SUSTIVA™).

Protease inhibitors (Pis) for treating HIV infection include amprenavir (AGENERASE™), saquinavir mesylate (FORTOVASE™, INVIRASE™), ritonavir (NORVIR™), indinavir sulfate (CRIXIVAN™), nelfinavir mesylate (VIRACEPT™), lopinavir and ritonavir (KALETRA™), atazanavir (REYATAZ™), and fosamprenavir (LEXIVA™).

Fusion inhibitors prevent fusion between the virus and the cell from occurring, and therefore, prevent HIV infection and multiplication. Fusion inhibitors include, but are not limited to, enfuvirtide (FUZEON™), Lalezari et al., New England J. Med., 348:2175-2185 (2003); and maraviroc (SELZENTRY™, Pfizer).

An integrase inhibitor blocks the action of integrase, preventing HIV-1 genetic material from integrating into the host DNA, and thereby stopping viral replication. Integrase inhibitors include, but are not limited to, raltegravir (ISENTRESS™, Merck); and elvitegravir (GS 9137, Gilead Sciences).

Maturation inhibitors include, e.g., bevirimat (3β-(3-carboxy-3-methyl -butanoyloxy) lup-20(29)-en-28-oic acid); and Vivecon (MPC9055).

In some embodiments, a subject treatment method involves administering: a) subject anti-HERV-K antibody; and b) one or more of: (1) an HIV protease inhibitor selected from amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, PPL-100, DG35, and AG 1859; (2) an HIV non-nucleoside inhibitor of reverse transcriptase selected from capravirine, emivirine, delavirdine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961,
DPC-963, MIV-150, and TMC-120, TMC-278 (rilpivirene), efavirenz, BILR 355 BS, VRX 840773, UK-453061, and RDEA806; (3) an HIV nucleoside inhibitor of reverse transcriptase selected from zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitabine (AVX754), and fozalvudine (Lexiva; [(2 R,35)-l-[N-(2-methylpropyl)(4-arninobenzene)sulfonamido]-l-phenylbutan-2-yl]carbamate) in an amount of 133 mg twice daily; vi) fosamprenavir (Lexiva; [(2 R,35)-l-[N-(2-methylpropyl)(4-arninobenzene)sulfonamido]-l-phenylbutan-2-yl]carbamoyl)butyl l-N-teri-butyl-4-(pyridin-3-ylmethyl)piperazine-2-carboxamide) in an amount of 800 mg three times daily; iv) saquinavir (Invirase; 2S)-N-[(25,3R)-4-[(35)-3-(teri-butylcarbamoyl)-decahydroisoquinolin-2-yl]-3-hydroxy-l-phenylbutan-2-yl]-2-(quinolin-2-ylformamido)butanediamide) in an amount of 1,000 mg twice daily; v) lopinavir and ritonavir (Kala; where lopinavir is 2S)-N-[(25,45,55)-5-[2-(2,6-dimethylphenoxy)acetamido]-4-hydroxy-1,6-diphenylhexan-2-yl]-3-methyl-2-(2-oxo-l,3-diazinan-1-yl)butanamide; and ritonavir is 1,3-thiazol-5-ylmethyl N-[(25,35,55)-3-hydroxy-5-[(25)-3-methyl-2-[[methyl([2-(propan-2-yl)-l,3-thiazol-4-yl]methyl )carbamoyl]amino]butanamido]-1,6-diphenylhexan-2-yl]carbamate) in an amount of 133 mg twice daily; vi) fosamprenavir (Lexiva;([(2R,35)-l-[N-(2-methylpropyl)](4-}

[00254] For example, in some embodiments, a subject treatment method involves administering: a) a subject anti-HERV-K antibody; and b) one or more of: i) amprenavir (Agenerase; (35)-oxolan-3-yl 1-N-[(25,3R)-3-hydroxy-4,-N-(2-methylpropyl)(4-arninobenzene)sulfonamido]-l-phenylbutan-2-yl]carbamate) in an amount of 600 mg or 1200 mg twice daily; ii) tipranavir (Aptivus; N-3-{(1R)-1-[(2R)-6-hydroxy-4-oxo-2-(2-phenylethyl)-2-propyl-3,4-dihydro-2 H-pyran-5-yl]propyl[phenyl]-5-(trifluoromethyl)pyridine-2-sulfonamide) in an amount of 500 mg twice daily; iii) idinavir (Crixivan; (25)-1-[(25,4R)-4-benzyl-2-hydroxy-4-[(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl]butyl l-N-teri-butyl-4-(pyridin-3-ylmethyl)piperazine-2-carboxamide) in an amount of 800 mg three times daily; iv) saquinavir (Invirase; 2S)-N-[(25,3R)-4-[(35)-3-(teri-butylcarbamoyl)-decahydroisoquinolin-2-yl]-3-hydroxy-l-phenylbutan-2-yl]-2-(quinolin-2-ylformamido)butanediamide) in an amount of 1,000 mg twice daily; v) lopinavir and ritonavir (Kala; where lopinavir is 2S)-N-[(25,45,55)-5-[2-(2,6-dimethylphenoxy)acetamido]-4-hydroxy-1,6-diphenylhexan-2-yl]-3-methyl-2-(2-oxo-l,3-diazinan-1-yl)butanamide; and ritonavir is 1,3-thiazol-5-ylmethyl N-[(25,35,55)-3-hydroxy-5-[(25)-3-methyl-2-[[methyl([2-(propan-2-yl)-l,3-thiazol-4-yl]methyl )carbamoyl]amino]butanamido]-1,6-diphenylhexan-2-yl]carbamate) in an amount of 133 mg twice daily; vi) fosamprenavir (Lexiva;([(2R,35)-l-[N-(2-methylpropyl)](4-
aminobenzene)sulfonamido]-3-[(35)-oxolan-3-yloxy]carbonyl]amino)-4-phenylbutan-2-
yl]oxy}phosphonic acid) in an amount of 700 mg or 1400 mg twice daily; vii) ritonavir (Norvir) in an amount of 600 mg twice daily; viii) nelfinavir (Viracept; (3\$4a,\$8a\$)-N-teri-butyl-2-[(2R,3R)-2-
decahydroisoquinoline-3-carboxamide) in an amount of 750 mg three times daily or in an amount of 1250 mg twice daily; ix) Fuzeon (Acetyl-\mbox{-}TYSLIHSLIEESQNQ
QueneleLDKWSLWNF-amide; SEQ ID NO:601) in an amount of 90 mg twice daily; x) Combivir in an amount of 150 mg lamivudine (3TC; 2',3'-dideoxy-3'-thiacytidine) and 300 mg zidovudine (AZT; azidothymidine) twice daily; xi) emtricitabine (Emtriva; 4-amino-5-fluoro-1-
[(2R,55)-2-(hydroxymethyl]-1,3-oxathiolan-5-yl]-1,2-dihydropirimidin-2-one) in an amount of 200 mg once daily; xii) Epzicom in an amount of 600 mg abacavir (ABV; [(15,4R)-4-\mbox{-}[2-amino-6-(
cyclopropylamino)-9H-purin-9-yl]cyclopent-2-en-1-yl]methanol) and 300 mg 3TC once daily; xiii) zidovudine (Retrovir; AZT or azidothymidine) in an amount of 200 mg three times daily; xiv) Trizivir in an amount of 150 mg 3TC and 300 mg ABV and 300 mg AZT twice daily; xv) Truvada in an amount of 200 mg emtricitabine and 300 mg tenofovir (\mbox{-}[{(2R)-1-(6-amino-9 H-purin-9-
yl)propan-2-yl]oxy}methyl]phosphonic acid) once daily; xvi) didanosine (Videx; 2',3'-
dideoxyinosine) in an amount of 400 mg once daily; xvii) tenofovir (Viread) in an amount of 300 mg once daily; xviii) abacavir (Ziagen) in an amount of 300 mg twice daily; xix) atazanavir (Reyataz; methyl N-\mbox{-}[\mbox{(15)-1-\mbox{-}\mbox{[25,35]-3-hydroxy-4-\mbox{-}[(25)-2-\mbox{-}[\mbox{methoxy]carbonyl]amino]-3,3-
dimethyl-N']. \mbox{-}[4-(pyridin-2-yl]phenyl] methyl Jbutaneyhydrizado]-1-phenylbutan-2-yl[carbamoyl]-
2,2-dimethylpropyl] carbamate) in an amount of 300 mg once daily or 400 mg once daily; xx) lamivudine (Epivir) in an amount of 150 mg twice daily; xxi) stavudine (Zerit; 2',3'-dideohydro-2',3'-
dideoxythymidine) in an amount of 40 mg twice daily; xxii) delavirdine (Recriptor; N-\mbox{-}[2-\mbox{-}[\mbox{4-[\mbox{3-(
propan-2-ylamino)pyridin-2-yl]piperazin-1-yl}carbonyl]-1 H-indol-5-yl]methanesulphonamide) in an amount of 400 mg three times daily; xxiii) efavirenz (Sustiva; (45)-6-chloro-4-(2-
cyclopropylethynyl)-4-(trifluoromethyl)-2,4-dihydro-1 H-3,1-benzoaxazin-2-one) in an amount of 600 mg once daily; xxiv) nevirapine (Viramune; 1l-cyclopropyl-4-methyl-5,1l-dihydro-6 H-
dipyrido[3,2-&2',3',e][1,4]diazepin-6-one) in an amount of 200 mg twice daily; xxv) bevirmimat; and
xxvi) Vivecon.

**Subjects suitable for treatment - immunodeficiency virus infection**

[00255] The methods of the present disclosure are suitable for treating individuals who have an
immunodeficiency virus infection, e.g., who have been diagnosed as having an immunodeficiency
virus infection.

[00256] The methods of the present disclosure are suitable for treating individuals who have an HIV
infection (e.g., who have been diagnosed as having an HIV infection), and individuals who are at
risk of contracting an HIV infection. Such individuals include, but are not limited to, individuals
with healthy, intact immune systems, but who are at risk for becoming HIV infected ("at-risk"
individuals). At-risk individuals include, but are not limited to, individuals who have a greater likelihood than the general population of becoming HIV infected. Individuals at risk for becoming HIV infected include, but are not limited to, individuals at risk for HIV infection due to sexual activity with HIV-infected individuals. Individuals suitable for treatment include individuals infected with, or at risk of becoming infected with, HIV-1 and/or HIV-2 and/or HIV-3, or any variant thereof. For example, individuals who are suitable for treatment include highly exposed uninfected individuals.

[00257] In some cases, the individual is one who has an HIV infection, who has been treated with conventional anti-HIV drug(s) for the HIV infection, and who has developed resistance to the drug(s) (e.g., the HIV in the individual has become resistant to the drug(s) used to treat the HIV infection). In some cases, the individual is one who has an HIV infection, who has been treated with conventional anti-HIV drug(s) for the HIV infection, and who has failed to respond to such treatment.

[00258] In some cases, the individual is one who has only recently become exposed, for the first time, to HIV. A subject anti-HERV-K antibody can be administered to such an individual prophylactically, e.g., to reduce infection of the individual's cells with the HIV; to reduce cell-to-cell spread of the HIV; etc.

[00259] Individuals who are suitable for treatment according to a method of the present disclosure include individuals who are at greater risk than the general population of becoming infected with HIV, where such individuals include, e.g., individuals who engage in sexual activity with HIV-infected individuals; intravenous drug users; and the like.

[00260] Individuals who are suitable for treatment according to a method of the present disclosure include individuals exposed to HIV as an occupational hazard (e.g., medical personnel); and infants born to HIV-infected women.

Detection methods - immunodeficiency virus infection

[00261] A subject anti-HERV-K antibody can be used in various detection methods, for use in, e.g., monitoring the progression of an immunodeficiency virus infection; monitoring patient response to treatment for an immunodeficiency virus infection, etc.

[00262] The present disclosure provides methods of detecting a HERV-K polypeptide in a biological sample obtained from an individual. The methods generally involve: a) contacting the biological sample with a subject anti-HERV-K antibody; and b) detecting binding, if any, of the antibody to an epitope present in the sample. In some instances, the antibody comprises a detectable label. In some instances, the antibody is immobilized on an insoluble support.

[00263] The level of HERV-K polypeptide detected in the biological sample can provide an indication of the stage, degree, or severity of an immunodeficiency virus infection. The level of HERV-K polypeptide detected in the biological sample can provide an indication of the individual's response to treatment for an immunodeficiency virus infection.
IMMUNOGENIC PEPTIDES

[00264] The present disclosure provides isolated immunogenic peptides corresponding to a fragment of a HERV-K envelope transmembrane (TM) protein, a HERV-K envelope surface unit (SU) protein, or a HERV-K capsid protein. A subject isolated immunogenic HERV-K peptide finds use in, e.g., generating immunogenic compositions (e.g., for enhancing an immune response in an individual to a HERV-K peptide); and for generating anti-HERV-K antibodies.

[00265] In some embodiments, a subject isolated HERV-K polypeptide comprises a fragment of a HERV-K envelope protein comprising from about 9, 10, 11, 12, 13-15, 15-17, 17-20, from 20 to 25, from 25 to 50, from 50 to 75, from 75 to 100, from 100 to 150, from 150 to 200, from 200 to 250, from 250 to 300, from 300 to 350, or from 350 to 400 or from 400 to 450, or from 450 to 500, or from 500 to 550, or from 550 to 600, or from 600 to 650, or from 650 to 700, from 700 to 707, or more, contiguous amino acids of an amino acid sequence having at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100% amino acid sequence identity to the amino acid sequence of a HERV-K envelope protein.

[00266] In some embodiments, a subject isolated HERV-K polypeptide comprises a fragment of a HERV-K envelope transmembrane protein comprising from about 9, 10, 11, 12, 13-15, 15-17, 17-20, from 20 to 25, from 25 to 50, from 50 to 75, from 75 to 100, from 100 to 150, from 150 to 173, or more, contiguous amino acids of an amino acid sequence having at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100% amino acid sequence identity to the amino acid sequence of a HERV-K envelope transmembrane protein.

[00267] In some embodiments, a subject isolated HERV-K polypeptide comprises a fragment of a HERV-K envelope surface unit protein comprising from about 9, 10, 11, 12, 13-15, 15-17, 17-20, from 20 to 25, from 25 to 50, from 50 to 75, from 75 to 100, from 100 to 150, from 150 to 200, from 200 to 250, from 250 to 300, from 300 to 350, or from 350 to 373, or more, contiguous amino acids of an amino acid sequence having at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100% amino acid sequence identity to the amino acid sequence of a HERV-K envelope surface unit protein.

[00268] In some embodiments, a subject isolated HERV-K polypeptide comprises a fragment of a HERV-K capsid protein comprising from about 9, 10, 11, 12, 13-15, 15-17, 17-20, from 20 to 25, from 25 to 50, from 50 to 75, from 75 to 100, from 100 to 150, from 150 to 200, from 200 to 250, from 250 to 300, from 300 to 350, or from 350 to 400 or from 400 to 450, or from 450 to 500, or from 500 to 550, or from 550 to 600, or from 600 to 650, or from 650 to 672, or more, contiguous amino acids of an amino acid sequence having at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%,
95%, at least about 98%, at least about 99%, or 100% amino acid sequence identity to the amino acid sequence of a HERV-K capsid protein.

[00269] A subject immunogenic HERV-K polypeptide can be from 9 amino acids in length up to the length of a naturally-occurring HERV-K polypeptide, e.g., a HERV-K polypeptide can be 9 amino acids (aa), 10 aa, 11 aa, 12-15 aa, 15-20 aa, 20-25 aa, 25-30 aa, 30-40 aa, 40-50 aa, 50-100 aa, or longer than 100 amino acids, e.g., 100 aa to 150 aa, 150 aa to 200 aa.

[00270] Exemplary, non-limiting examples of HERV-K encoded polypeptides are found in GenBank Accession Nos. AAD51797 (HERV-K Gag-Pro-Pol); AAD51798 (HERV-K env protein); Q69384; Q7LD19.3; etc.

[00271] In some embodiments, a subject isolated HERV-K polypeptide comprises a polypeptide comprising from about 9, 10, 11, 12, 13-15, 15-17, 17-20, from 20 to 25, from 25 to 50, from 50 to 75, from 75 to 100, from 100 to 150, from 150 to 200, from 200 to 250, from 250 to 300, from 300 to 350, from 350 to 400, from 400 to 450, from 450 to 500, from 500 to 550, from 550 to 600, from 600 to 650, from 650 to 700, from 700 to 707, or more contiguous amino acids of a HERV-K polypeptide having at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO:1:

MASNPSEMQRKAPPRRRHRNRAPLTHKMNKMTSEQMLPSTKKAEPPTWAQLKKTQLATKYLENTKVTQPESMLLAAIMIVSMVSLPMAGAAANYTYWAYVPFPPLIRAVTWMDNPIEYVYVNDVWVPGPIDDRCAPKPEEEGMMINISIGYRPICLGRAPGCLMPAVQNLVEVPTVPICRFTYHVMVSGMLRPVRVNYLQDQS3RSLKFRPKGKPCPKPEIKPSKNTEVLVWEECVANSAVILQNNEGFTIDWAPRGQFYHNCSSGQTQCSAPQAQVSPAVDSLTDLESKKHKKQSFYFPWEWGEKISTPRPKIVSPVSGPEHPELWRLTVASHHHRSWGNQTLQERDRKPYFIDLNLSSLTVPLQCVKPPYMVLVGNNIVKPDQITITCENCRLTICDSTFNWQHRILLVRAREGVIWIPVSMDRPWEASPSVHILTEVLKVLNRSKRFIFTLIAVIMGLIAVTATAAVAGVALHSSVQSVNFVNDWQKNSTRLWNSQSSIDQKLQINDLRQTIVMGMGDRLMLSEHRQFLQCDWNTSDFCITPQIYNESEHHWDMVRRHLQGREDNLTDLISKLKEQIFEASKAHNLVPGTEIAGVADGLANLNVPVTWKTIGSTTIINLILLVCLLLVCRCTQQQRRDSDHRERAMMTMAVLSKRGGNGSKRDQIVTVSV (SEQ ID NO: 1)

[00272] In some embodiments, a subject isolated HERV-K polypeptide comprises a polypeptide comprising from about 9, 10, 11, 12, 13-15, 15-17, 17-20, from 20 to 25, from 25 to 50, from 50 to 75, from 75 to 100, from 100 to 150, from 150 to 173 contiguous amino acids of an amino acid sequence having at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at
least about 99%, or 100% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO:2:

```
AVAGVALHSSVQSVNFVDQWKNSTRLWNSQDQQIDQLANQINDLRQTVIWMGD
RLMSLEHRFQFDWNTSDFCITIPQYNESEHHDMVRRHLQGREDNLTLDISKLK
EQIFEASKAHLNLVPGETEIAAGVADGLANLNPVTWVKTIGSTTIINLILILVCLFCL
```

(SEQ ID NO: 2)

[00273] In some embodiments, a subject isolated HERV-K polypeptide comprises a polypeptide comprising from about 9, 10, 11, 12, 13-15, 15-17, 17-20, from 20 to 25, from 25 to 50, from 50 to 75, from 75 to 100, from 100 to 150, from 150 to 200, from 200 to 250, from 250 to 300, from 300 to 350, or from 350 to 373 contiguous amino acids of an amino acid sequence having at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, or 100% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO:3:

```
VVSLPMPAGAAAAANYTWAYYPFPPLIRAVTWMNPIEYYVYNDSVWVPGPIIDDR
PAKEEEGMMINISIGYRYPPICLUAPGCLMPAQQNLVEVTVPSPICRFYHMVS
GMSLRPRVNYLQDFSYQRSLKFPRKGKPCPEKESKNTEVLWEECVANSAVIL
QNNEFGLIIDWAPRGGQFYHNCQGQGTSCPSAQVSPAVDSDLTSLDHKHKHKLQSF
YPWEWEGKGSTPRPKIVSPYGPEHLWRLTVASHHIWSGNTLTDRTKPFY
TIDLNSSLTVPLQSCPKKYMLVNGNIVKPDSTITCENCRLLTCDSTFNWHRILL
VRAREGVVIPVSMDRPWEASPSVHIL (SEQ ID NO: 3)
```

[00274] In some embodiments, a subject isolated HERV-K polypeptide comprises a polypeptide comprising from about 9, 10, 11, 12, 13-15, 15-17, 17-20, from 20 to 25, from 25 to 50, from 50 to 75, from 75 to 100, from 100 to 150, from 150 to 200, from 200 to 250, from 250 to 300, from 300 to 350, from 350 to 400, from 400 to 450, from 450 to 500, from 500 to 550, from 550 to 600, from 600 to 650, from 650 to 672 contiguous amino acids of an amino acid sequence having at least about 50%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or 100% amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO:4:

```
MGQTKSKIKSKYASYLSFIKILLKRGGVSTKNLILFLQIQIEQFCPWPEQGTLDLK
DWKRIGKELKQAQRKGNIIPLTVWVDWAIAALEPQTEEDSVSVSDAPGSCIIDC
NENTRKKSQKETEGLICHVEYAEVPMAQSTQNVNDYLQGEVIYPETKLKLEGKPS
VGPSESKPRGTSPLPAQGVPVTQLPKQKVKENKTQPPVAYQYWPPAEIQYPREPPES
QYGYGPMPAPQGRAPYPQPPTRRNPLTAPRSQGSKLHEI1DKSKEGTDTEAWQF
VTLEPMPPGEGAEQEGPTEARYKFSIKKLKDMKEGKQVGPNPSYMTRLLDSI
AHGHRILPYWDEILAKSSLSPSQFLQLFQFLKTWWIDVGQEOQVRRNAAANPPVNIADQL
LGIGQNWSTISQQALMQEAIEVRAICLRAWEKIQDPSFNTVRQSGKEYP
DFVARLQDVFAQKSIADEKARKVIVELMAYENANPECQSAIKPLKGKVPGSDVISE
```

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In some embodiments, a subject isolated HERV-K polypeptide comprises one or more of the following amino acid sequences:

- AVAGVALHSS (SEQ ID NO:5)
- VAGVALHSSV (SEQ ID NO:6)
- AGVALHSSVQ (SEQ ID NO:7)
- GVALHSSVQS (SEQ ID NO:8)
- VALHSSVQSV (SEQ ID NO:9)
- ALHSSVQSVN (SEQ ID NO:10)
- LHSSVQSVNF (SEQ ID NO:11)
- HSSVQSVNFD (SEQ ID NO:12)
- SSVQSVNFV (SEQ ID NO:13)
- SVQSVNFVND (SEQ ID NO:14)
- VQSVNFVNDW (SEQ ID NO:15)
- QSVNFVNDWQ (SEQ ID NO:16)
- SVNFDWQK (SEQ ID NO:17)
- VNFNWDQKN (SEQ ID NO:18)
- NFVNDWQKN (SEQ ID NO:19)
- FVNDWQKNST (SEQ ID NO:20)
- VNDWQKNSTR (SEQ ID NO:21)
- NDWQKNSTR (SEQ ID NO:22)
- DWQKNSTR (SEQ ID NO:23)
- WQKNSTR (SEQ ID NO:24)
- QKNSTR (SEQ ID NO:25)
- KNSTRWNSQ (SEQ ID NO:26)
- NSTRLWNSQ (SEQ ID NO:27)
- STRLWNSQS (SEQ ID NO:28)
- TRLWNSQSS (SEQ ID NO:29)
- RLWNSQSS (SEQ ID NO:30)
- LWNSQSSIDQ (SEQ ID NO:31)
- WNSQSSIDQK (SEQ ID NO:32)
- NSQSSIDQKL (SEQ ID NO:33)
- SQSSIDQKL (SEQ ID NO:34)
- QSSIDQKL (SEQ ID NO:35)
SSIDQKLANQ (SEQ ID NO:36)
SIDQKLANQI (SEQ ID NO:37)
IDQKLANQIN (SEQ ID NO:38)
DQKLANQIND (SEQ ID NO:39)
QKLANQINDL (SEQ ID NO:40)
KLANQINDLR (SEQ ID NO:41)
LANQINDLRQ (SEQ ID NO:42)
ANQINDLRQT (SEQ ID NO:43)
NQINDLRQTV (SEQ ID NO:44)
QINDLRQTVI (SEQ ID NO:45)
INDLRQTVIW (SEQ ID NO:46)
NDLRQTVIWM (SEQ ID NO:47)
DLRQTVIWMG (SEQ ID NO:48)
LRQTVIWMGD (SEQ ID NO:49)
RQTVIWMGDR (SEQ ID NO:50)
QTVIWMGDRL (SEQ ID NO:51)
TVIWMGDRLM (SEQ ID NO:52)
VIWMGDRLMS (SEQ ID NO:53)
IWIMGDRLMS (SEQ ID NO:54)
WIMGDRLMSLE (SEQ ID NO:55)
MGDRLMSLEH (SEQ ID NO:56)
GDRLMSLEHR (SEQ ID NO:57)
DRLMSLEHRF (SEQ ID NO:58)
RLMSLEHRFQ (SEQ ID NO:59)
LMSLEHRFQL (SEQ ID NO:60)
MSLEHRFQLQ (SEQ ID NO:61)
SLEHRFQLQC (SEQ ID NO:62)
LEHRFQLQCD (SEQ ID NO:63)
EHRFQLQCDW (SEQ ID NO:64)
HRFQLQCDWN (SEQ ID NO:65)
RFQLQCDWNT (SEQ ID NO:66)
FQLQCDWNTS (SEQ ID NO:67)
QLQCDWNTSD (SEQ ID NO:68)
LQCDWNTSDF (SEQ ID NO:69)
QCDWNTSDFC (SEQ ID NO:70)
CDWNTSDFCI (SEQ ID NO:71)
DWNTSDFCIT (SEQ ID NO:72)
WNTSDFCITP  (SEQ ID NO:73)
NTSDFCITPQ  (SEQ ID NO:74)
TSDFCITPQI  (SEQ ID NO:75)
SDFCITPQIY  (SEQ ID NO:76)
DFCITPQIYN  (SEQ ID NO:77)
FCITPQIYNE  (SEQ ID NO:78)
CITPQIYNES  (SEQ ID NO:79)
ITPQIYNESE  (SEQ ID NO:80)
TPQIYNESEH (SEQ ID NO:81)
PQIYNESEHH (SEQ ID NO:82)
QIYNESEHHW (SEQ ID NO:83)
IYNESEHHWD (SEQ ID NO:84)
YNESSEHHMD (SEQ ID NO:85)
NESEHHWDMV (SEQ ID NO:86)
ESEHHWDMVR (SEQ ID NO:87)
SEHHWDMVRR (SEQ ID NO:88)
EHWHDMVRRH (SEQ ID NO:89)
HHWHDMVRRHL (SEQ ID NO:90)
HWDMVRRHQL (SEQ ID NO:91)
WDVMVRRHQLG (SEQ ID NO:92)
DMVRRHQLGR (SEQ ID NO:93)
MVRRHQLGREQ (SEQ ID NO:94)
VRRHLQGRED (SEQ ID NO:95)
RRHLQGREDN (SEQ ID NO:96)
RHLQGREDNL (SEQ ID NO:97)
HLQGREDNLT (SEQ ID NO:98)
LQGREDNLT (SEQ ID NO:99)
QGREDNLTLD (SEQ ID NO:100)
GREDNLTLDI (SEQ ID NO:101)
REDNLTLDI (SEQ ID NO:102)
EDNLTLDISK (SEQ ID NO:103)
DNLTLISKL (SEQ ID NO:104)
NLTLISKLK (SEQ ID NO:105)
LTLDISKLKE (SEQ ID NO:106)
TLDISKLKEQ (SEQ ID NO:107)
LDISKLKEQI (SEQ ID NO:108)
DISKLKEQIF (SEQ ID NO:109)
ISKLKEQIFE (SEQ ID NO: 110)
SKLKEQIFEA (SEQ ID NO: 111)
KLKEQIFEAS (SEQ ID NO: 112)
LKEQIFEASK (SEQ ID NO: 113)
KEQIFEASKA (SEQ ID NO: 114)
EQIFEASKAH (SEQ ID NO: 115)
QIFEASKAHL (SEQ ID NO: 116)
IFEASKAHLN (SEQ ID NO: 117)
FEASKAHLNL (SEQ ID NO: 118)
EASKAHLNLV (SEQ ID NO: 119)
ASKAHLNLVP (SEQ ID NO: 120)
SKAHLNLVPG (SEQ ID NO: 121)
KAHLNLVPGT (SEQ ID NO: 122)
AHLNLVPGTE (SEQ ID NO: 123)
HLNLVPGTEA (SEQ ID NO: 124)
LNVPGTEAI (SEQ ID NO: 125)
NLVPGTEAIA (SEQ ID NO: 126)
LVPGTEAIAG (SEQ ID NO: 127)
VPGTEAIAGV (SEQ ID NO: 128)
PGTEAIAGVA (SEQ ID NO: 129)
GTEAIAGVAD (SEQ ID NO: 130)
TEAIAGVADG (SEQ ID NO: 131)
EAIAGVADGL (SEQ ID NO: 132)
AIAGVADGLA (SEQ ID NO: 133)
IAGVADGLAN (SEQ ID NO: 134)
AGVADGLANL (SEQ ID NO: 135)
GVADGLANLN (SEQ ID NO: 136)
VADGLANLN (SEQ ID NO: 137)
ADVLANLN (SEQ ID NO: 138)
GVADGLANLP (SEQ ID NO: 139)
GLANLPVTW (SEQ ID NO: 140)
LANLPVTWV (SEQ ID NO: 141)
ANLPVTWVK (SEQ ID NO: 142)
NLNPVTWVK (SEQ ID NO: 143)
LNVTWVKTI (SEQ ID NO: 144)
NPVTWKTI (SEQ ID NO: 145)
PVTWKTI (SEQ ID NO: 146)
VTWVKTIGST (SEQ ID NO: 147)
TWVKTIGSTT (SEQ ID NO: 148)
WVKTIGSTTI (SEQ ID NO: 149)
VKTIGSTTI (SEQ ID NO: 150)
KTIGSTTIIN (SEQ ID NO: 151)
TIGSTTIINL (SEQ ID NO: 152)
IGSTTIINLI (SEQ ID NO: 153)
GSTTIINLIL (SEQ ID NO: 154)
STTIINLILI (SEQ ID NO: 155)
TTIINLILIL (SEQ ID NO: 156)
TIINLILILV (SEQ ID NO: 157)
IINLILILVC (SEQ ID NO: 158)
INLILILVCL (SEQ ID NO: 159)
NLILILVCLF (SEQ ID NO: 160)
LILILVCLFC (SEQ ID NO: 161)
ILILVCLFL (SEQ ID NO: 162)
VVSLPMPAGA (SEQ ID NO: 163)
VSLPMPAGAA (SEQ ID NO: 164)
SLPMPAGAAA (SEQ ID NO: 165)
LPMPAGAAAA (SEQ ID NO: 166)
PMPAGAAAAN (SEQ ID NO: 167)
MPAGAAAAANY (SEQ ID NO: 168)
PAGAAAAANYT (SEQ ID NO: 169)
AGAAAAANYTY (SEQ ID NO: 170)
GAAAAANYTYW (SEQ ID NO: 171)
AAAANYTYWA (SEQ ID NO: 172)
AAAAANYTYWAY (SEQ ID NO: 173)
AANYTYWAYV (SEQ ID NO: 174)
ANYTYWAYVP (SEQ ID NO: 175)
NYTYWAYVPF (SEQ ID NO: 176)
YTYWAYVPPF (SEQ ID NO: 177)
TYWAYVPPFP (SEQ ID NO: 178)
WAYVPPFPPL (SEQ ID NO: 179)
WAYVPPFPPLI (SEQ ID NO: 180)
AYVPPFPPLIR (SEQ ID NO: 181)
YVPPFPPLIRA (SEQ ID NO: 182)
VFPFPPLIRAV (SEQ ID NO: 183)
PFPLIRAVT (SEQ ID NO: 184)
FPPLIRAVTW (SEQ ID NO: 185)
PPLIRAVTWMD (SEQ ID NO: 186)
PLIRAVTWMDN (SEQ ID NO: 187)
LIRAVTWM (SEQ ID NO: 188)
IRAVTWMDNP (SEQ ID NO: 189)
RAVTWMDNPI (SEQ ID NO: 190)
AVTWMNDNPIE (SEQ ID NO: 191)
VTWMDNPIEV (SEQ ID NO: 192)
TWMDNPIE (SEQ ID NO: 193)
WMDNPIEYV (SEQ ID NO: 194)
MDNPIEYV (SEQ ID NO: 195)
DNPIEYVNV (SEQ ID NO: 196)
NPIEYVVNS (SEQ ID NO: 197)
PIEYVNDSV (SEQ ID NO: 198)
IEYVNVND (SEQ ID NO: 199)
EVYVVNVWW (SEQ ID NO: 200)
VVYVNVWWVP (SEQ ID NO: 201)
YVNVWVPG (SEQ ID NO: 202)
VNDSVWVPD (SEQ ID NO: 203)
NSVWVPGP (SEQ ID NO: 204)
DSVWVVPID (SEQ ID NO: 205)
SVWVPGP ID (SEQ ID NO: 206)
VWVVPIDDP (SEQ ID NO: 207)
WVPIDDDRC (SEQ ID NO: 208)
VPGIDDRC (SEQ ID NO: 209)
PGPIDDDCP (SEQ ID NO: 210)
GPIDDDCP (SEQ ID NO: 211)
PDDPCPAKP (SEQ ID NO: 212)
PDDDCPAKPE (SEQ ID NO: 213)
DDCPAKPEE (SEQ ID NO: 214)
DRCAPPEEE (SEQ ID NO: 215)
RPCAPEEE (SEQ ID NO: 216)
CPKPEEEGM (SEQ ID NO: 217)
PAKPEEEGM (SEQ ID NO: 218)
AKPEEEGMM (SEQ ID NO: 219)
KPEEEGMM (SEQ ID NO: 220)
PEEEGMMINI (SEQ ID NO:221)
EEEGMMINIS (SEQ ID NO:222)
EEGMMINISI (SEQ ID NO:223)
EGMMINISIG (SEQ ID NO:224)
GMMINISIGY (SEQ ID NO:225)
MMINISIGYR (SEQ ID NO:226)
MINISIGRY (SEQ ID NO:227)
INISIGRYYP (SEQ ID NO:228)
NISIGRYYP (SEQ ID NO:229)
ISIGRYPPPI (SEQ ID NO:230)
SIGRYPPPIC (SEQ ID NO:231)
IGRYPPICL (SEQ ID NO:232)
GYRYPICLGR (SEQ ID NO:233)
YRYPICLGR (SEQ ID NO:234)
RYPICLGRA (SEQ ID NO:235)
YPICLGRAP (SEQ ID NO:236)
PPICLGRAPG (SEQ ID NO:237)
PICLGRAPGC (SEQ ID NO:238)
ICLGRAPGCL (SEQ ID NO:239)
CLGRAPGCLM (SEQ ID NO:240)
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TVSPICRFYHMVS (SEQ ID NO: 856)
VSPICRFYHMVS (SEQ ID NO: 857)
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PICRFTYHMVSGMSL (SEQ ID NO:859)
ICRFTYHMVSGMSLR (SEQ ID NO:860)
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FG TIIDW APRGQFYH (SEQ ID NO: 930)
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TQTQSCP  (SEQ ID NO:949)
QTQSCP  (SEQ ID NO:950)
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SCP  (SEQ ID NO:952)
CP  (SEQ ID NO:953)
P  (SEQ ID NO:954)
S  (SEQ ID NO:955)
A  (SEQ ID NO:956)
Q  (SEQ ID NO:957)
V  (SEQ ID NO:958)
D  (SEQ ID NO:959)
L  (SEQ ID NO:960)
S  (SEQ ID NO:961)
T  (SEQ ID NO:962)
E  (SEQ ID NO:963)
D  (SEQ ID NO:964)
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Q  (SEQ ID NO:968)
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QSFYPWEWG (SEQ ID NO:977)
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FYPWEWG (SEQ ID NO:979)
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WG (SEQ ID NO:984)
G (SEQ ID NO:985)
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G (SEQ ID NO:987)
E (SEQ ID NO:988)
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SCVKPPYMLVVGNI  (SEQ ID NO: 1052)
CVKPPYMLVVGNI  (SEQ ID NO: 1053)
VKPPYMLVVGNI  (SEQ ID NO: 1054)
KPPYMLVVGNI  (SEQ ID NO: 1055)
PPYMLVVGNI  (SEQ ID NO: 1056)
PYMLVVGNI  (SEQ ID NO: 1057)
YMLVVGNI  (SEQ ID NO: 1058)
MLVVGNI  (SEQ ID NO: 1059)
LVVVGNI  (SEQ ID NO: 1060)
VVVVGNI  (SEQ ID NO: 1061)
VVVGVNI  (SEQ ID NO: 1062)
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NIVKPDQTTITCENC  (SEQ ID NO: 1064)
IVKPDQTTITCENC  (SEQ ID NO: 1065)
VIFPDQTTITCENCNR  (SEQ ID NO: 1066)
IKPDQTTITCENCRL  (SEQ ID NO: 1067)
KPDSQTTITCENCRL  (SEQ ID NO: 1068)
PDSQTTITCENCRL  (SEQ ID NO: 1069)
DSQTTITCENCRL  (SEQ ID NO: 1070)
SQTITCENCRL  (SEQ ID NO: 1071)
QTITCENCRL  (SEQ ID NO: 1072)
TITCENCRL  (SEQ ID NO: 1073)
ITCENCRL  (SEQ ID NO: 1074)
TCENCRL  (SEQ ID NO: 1075)
CENCRL  (SEQ ID NO: 1076)
ENCRL  (SEQ ID NO: 1077)
NCRLL  (SEQ ID NO: 1078)
CRLL  (SEQ ID NO: 1079)
In certain embodiments, one or more of the above peptides specified by SEQ ID NO:5-557, or 603-1110 is specifically excluded.

**Fusion proteins**

In some embodiments, a subject immunogenic peptide is a fusion protein, e.g., a HERV-K fusion protein comprises a HERV-K polypeptide covalently linked to a heterologous protein, where
the heterologous protein is also referred to as a "fusion partner." In some embodiments, the fusion partner is attached to the N-terminus of the HERV-K peptide, e.g., NH$_2$-fusion partner- HERV-K-COOH. In other embodiments, the fusion partner is attached to the C-terminus of the HERV-K protein, e.g., NH$_2$-HERV-K-fusion partner-COOH. In other embodiments, the fusion partner is internal to the HERV-K protein, e.g., NHHHERV-K*-FP-CHERV-COONH*, where FP is a fusion partner, and HERV-Ki and HERV-K$_2$ are N-terminal and C-terminal regions, respectively, of HERV-K.

Suitable fusion partners include, but are not limited to, immunological tags such as epitope tags, including, but not limited to, hemagglutinin (e.g., CYPYDVPDYA; SEQ ID NO:558), FLAG (e.g., DYKDDDDK; SEQ ID NO:559), c-myc (EQKLISEEDL; SEQ ID NO:560), and the like; proteins that provide for a detectable signal, including, but not limited to, fluorescent proteins, enzymes (e.g., β-galactosidase, luciferase, horse radish peroxidase, alkaline phosphatase, etc.), and the like; polypeptides that facilitate purification or isolation of the fusion protein, e.g., metal ion binding polypeptides such as 6His tags, glutathione-S-transferase, and the like; polypeptides that provide for subcellular localization; and polypeptides that provide for secretion from a cell. Fusion partners that provide for a detectable signal are also referred to as "reporters." In some embodiments, a fusion partner is an immunomodulatory polypeptide other than a HERV-K polypeptide, e.g., an antigen, a cytokine, etc.

Suitable fusion partners also include a Protein Transduction Domain (PTD). "Protein Transduction Domain" or PTD refers to a polypeptide, polynucleotide, carbohydrate, or organic or inorganic compound that facilitates traversing a lipid bilayer, micelle, cell membrane, organelle membrane, or vesicle membrane. A PTD attached to another molecule facilitates the molecule traversing a membrane, for example going from extracellular space to intracellular space, or cytosol to within an organelle. In some embodiments, a PTD is covalently linked to the amino terminus of a polypeptide. In some embodiments, a PTD is covalently linked to the carboxyl terminus of a polypeptide.

Exemplary polypeptide PTD include, but are not limited to, a minimal undecapeptide protein transduction domain (corresponding to residues 47-57 of HIV-1 Tat comprising YGRKKRRQRRR; SEQ ID NO:561); a polyarginine sequence comprising a number of arginines sufficient to direct entry into a cell (e.g., 3, 4, 5, 6, 7, 8, 9, 10, or 10-50 arginines); a VP22 domain (Zender et al. (2002) Cancer Gene Ther. 9(6):489-96); an Drosophila Antennapedia protein transduction domain (Noguchi et al. (2003) Diabetes 52(7): 1732-1737); a truncated human calcitonin peptide (Trehin et al. (2004) Pharm. Research 21:1248-1256); polylysine (Wender et al. (2000) Proc. Natl Acad. Sci. USA 97:13003-13008); RRQRRTSKLMKR (SEQ ID NO:562); Transportan GWTLSAGYLLGKINLKALAALKKIL (SEQ ID NO:563); KALAWEAKLAKALAKHLAKALAKALKCEA (SEQ ID NO:564); and RQIKIWFQNRMKWKK (SEQ ID NO:565). Exemplary PTDs include but are not limited to,
YGRKKRRQRRR (SEQ ID NO:566), RKKRRQRRR (SEQ ID NO:567); an arginine homopolymer of from 3 arginine residues to 50 arginine residues; Exemplary PTD domain amino acid sequences include, but are not limited to, any of the following: YGRKKRRQRRR (SEQ ID NO:568); RKKRRQRRR (SEQ ID NO:569); YARAAARQARA (SEQ ID NO:570); THRLPRRRRRR (SEQ ID NO:571); and GGRRARRRRRR (SEQ ID NO:572).

**Multimerized HERV-K polypeptides**

In some embodiments, a subject immunogenic HERV-K polypeptide is multimerized, e.g., two or more HERV-K polypeptides are linked in tandem. Multimers include dimers, trimers, tetramers, pentamers, etc. Monomeric HERV-K polypeptides are linked to one another directly or via a linker. Thus, in some embodiments, a subject HERV-K polypeptide has the formula (Xi-(Y)n-4iX2-(Y)n-4i)k, where Xi and X2 are HERV-K polypeptides, Y is a linker, and n is an integer from 1 to about 10 (e.g., n = 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10). Where a linker is used, Y is one or more amino acids, or other linking groups. Xi and X2 can be the same or different, e.g., can have the same amino acid sequence, or can differ from one another in amino acid sequence. Thus, e.g., a subject HERV-K polypeptide can have the formula X1-(Y)n-4iX2, e.g., where the HERV-K polypeptide is a dimer. As another example, a subject HERV-K polypeptide can have the formula X1-(Y)n-4iX2-(Y)n-4iX3, e.g., where the HERV-K polypeptide is a trimer.

For example, in some embodiments, a subject an immunogenic peptide is a multimer of the formula (Xi-(Y)n-4iX2-(Y)n-4i)k, wherein X1 and X2 are HERV-K polypeptides, Y is a linker, and n is an integer from 1 to about 10, where the HERV-K polypeptides each comprise an amino acid sequence having at least about 95% amino acid sequence identity to a contiguous stretch of from about 6 amino acids to about 60 amino acids of a HERV-K envelope transmembrane protein, a HERV-K envelope surface unit protein, or a HERV-K capsid protein. In some of these embodiments, the immunogenic peptide has a length of from about 20 amino acids to about 150 amino acids. In some cases, the immunogenic peptide is a multimer of HERV-K peptides, where each of the HERV-K peptides independently comprises an amino acid sequence having at least about 95% amino acid sequence identity to any one of SEQ ID NOs:5-557, or 603-1110. In some cases, the immunogenic peptide is a multimer of HERV-K peptides, where each of the HERV-K peptides independently comprises an amino acid sequence set forth in any one of SEQ ID NOs: 5-557, or 603-1110.

Where Y is a spacer peptide, it is generally of a flexible nature, although other chemical linkages are not excluded. Currently, it is contemplated that the most useful linker sequences will generally be peptides of between about 2 and about 40 amino acids in length, e.g., from about 2 amino acids to about 10 amino acids, from about 10 amino acids to about 20 amino acids, or from about 6 amino acids to about 25 amino acids in length. These linkers are generally produced by using synthetic, linker-encoding oligonucleotides to couple the proteins. Peptide linkers with a degree of flexibility will generally be used. The linking peptides may have virtually any amino acid
sequence, bearing in mind that the preferred linkers will have a sequence that results in a generally flexible peptide. The use of small amino acids, such as glycine and alanine, are of use in creating a flexible peptide. Exemplary peptide linkers include (Gly)$_{2-4_0}$, (Ser)$_{2-4_0}$, and (Ala)$_{2-4_0}$. The creation of such sequences is routine to those of skill in the art. A variety of different linkers are commercially available and are considered suitable for use according to the present disclosure. However, any flexible linker generally between about 2 amino acids and about 40 amino acids, e.g., from about 6 amino acids to about 10 amino acids in length may be used. Linkers may have virtually any sequence that results in a generally flexible peptide.

[00284] Linkages for homo- or hetero-polymers or for coupling to carriers can be provided in a variety of ways. For example, cysteine residues can be added at both the amino- and carboxyl-termini, where the peptides are covalently bonded via controlled oxidation of the cysteine residues. Also useful are a large number of heterobifunctional agents which generate a disulfide link at one functional group end and a peptide link at the other, including N-succidimidyl-3-(2-pyridylidithio) propionate (SPDP). This reagent creates a disulfide linkage between itself and a cysteine residue in one protein and an amide linkage through the amino on a lysine or other free amino group in the other. A variety of such disulfide/amide forming agents are known. See, for example, Immun. Rev. 62:185 (1982). Other bifunctional coupling agents form a thioether rather than a disulfide linkage. Many of these thioether forming agents are commercially available and include reactive esters of 6-maleimidocaproic acid, 2 bromoacetic acid, 2-iodoacetic acid, 4-(N-maleimido-methyl) cyclohexane-1-carboxylic acid and the like. The carboxyl groups can be activated by combining them with succinimide or 1-hydroxy-2-nitro-4-sulfonic acid, sodium salt. A particularly preferred coupling agent is succinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC). Of course, it will be understood that linkage should not substantially interfere with either of the linked groups to function for its intended use, e.g., as an immunogen.

Carriers

[00285] In some embodiments, a subject immunogenic HERV-K polypeptide is linked to a carrier. The term "linked," as used herein interchangeably with the term "coupled," refers to proximately associated, e.g., the HERV-K polypeptide and the carrier are in close spatial proximity. In some embodiments, the linkage is a covalent linkage. In other embodiments, the linkage is a non-covalent linkage. In some embodiments, the HERV-K polypeptide is linked directly to the carrier. In other embodiments, the HERV-K polypeptide is linked indirectly, e.g., via a linker molecule.

[00286] Examples of suitable carriers include large, slowly metabolized macromolecules such as: proteins; polysaccharides, such as sepharose, agarose, cellulose, cellulose beads and the like; polymeric amino acids such as polyglutamic acid, polylysine, and the like; amino acid copolymers; inactivated virus particles; inactivated bacterial toxins such as toxoid from diptheria, tetanus, cholera, leukotoxin molecules; liposomes; inactivated bacteria; dendritic cells; and the like. Carriers are described in further detail below.
Suitable carriers are well known in the art, and include, e.g., thyroglobulin, albumins such as human serum albumin, tetanus toxoid; Diphtheria toxoid; polyamino acids such as poly(D-lysine:D-glutamic acid); VP6 polypeptides of rotaviruses; influenza virus hemagglutinin, influenza virus nucleoprotein; hepatitis B virus core protein, hepatitis B virus surface antigen; purified protein derivative (PPD) of tuberculin from Mycobacterium tuberculosis; inactivated Pseudomonas aeruginosa exotoxin A (toxin A); Keyhole Limpet Hemocyanin (KLH); filamentous hemagglutinin (FHA) of Bordetella pertussis; T helper cell (Th) epitopes of tetanus toxoid (TT) and Bacillus Calmette-Guerin (BCG) cell wall; recombinant 10 kDa, 19 kDa and 30-32 kDa proteins from M. leprae or from M. tuberculosis, or any combination of these proteins; and the like. See, e.g., U.S. Patent No. 6,447,778 for a discussion of carriers methods of conjugating peptides to carriers. Pseudomonas aeruginosa exotoxin A (toxin A) has been used effectively as a carrier in conjugate vaccines. Pseudomonas aeruginosa exotoxin A may be purified from the supernatant of fermentor-grown cultures of Pseudomonas aeruginosa PA 103. Toxin A has been classified as a superantigen based upon results in animals. Toxin A can be completely and irreversibly detoxified by covalent coupling to adipic acid dihydrazide (ADH), a 4 carbon spacer molecule. This step destroys the ADPR-transferase activity of the toxin molecule, hence rendering it nontoxic. The non-reacted hydrazide group can be used to covalently couple a polypeptide to toxin A. Toxin A may also be coupled to a polypeptide using a carbodiimide reagent.


The methods by which a subject polypeptide is conjugated with a carrier include disulfide linkages through a C terminal peptide cysteine linkage, coupling with glutaraldehyde solution for two hours, coupling with tyrosine, or coupling with water soluble carbodiimide.

In some embodiments, a subject immunogenic HERV-K polypeptide is lipidated. Lipidation increases a cytotoxic T cell (CTL) response to the peptide that is linked to the lipid. The lipid residue, such as palmitic acid or the like, is attached to the amino terminus of the peptide. The lipid can be attached directly to the peptide, or, indirectly via a linkage, such as a Ser-Ser, Gly, Gly-Gly, Ser linkage or the like. As another example, E. coli lipoprotein, such as tripalmitoyl-S-glycerlycysteinyl-seryl-serine (P₃ CSS), can be used to prime specific CTL when covalently attached to the peptide. See, Deres et al., Nature 342:561-564 (1989). A HERV-K polypeptide can be conjugated with uncharged fatty acid residues of different chain lengths and degrees of unsaturation, ranging from acetic to stearic acid as well as to negatively charged succinyl residues via the appropriate carboxylic acid anhydrides. See, e.g., U.S. Patent No. 6,419,931.

A subject immunogenic HERV-K polypeptide may be conjugated directly or indirectly, e.g., via a linker molecule, to a carrier. A wide variety of linker molecules are known in the art and can be used in the conjugates. The linkage from the peptide to the carrier may be through a peptide reactive side chain, or the N- or C-terminus of the peptide. A linker may be an organic, inorganic, or
semi-organic molecule, and may be a polymer of an organic molecule, an inorganic molecule, or a co-polymer comprising both inorganic and organic molecules.

If present, the linker molecules are generally of sufficient length to permit the HERV-K polypeptide and a linked carrier to allow some flexible movement between the HERV-K polypeptide and the carrier. The linker molecules are generally about 6-50 atoms long. The linker molecules may also be, for example, aryl acetylene, ethylene glycol oligomers containing 2-10 monomer units, diamines, diacids, amino acids, or combinations thereof. Other linker molecules which can bind to polypeptides may be used in light of this disclosure.

**Compositions**

The present disclosure provides compositions comprising a subject immunogenic HERV-K polypeptide. Compositions comprising a HERV-K polypeptide can include one or more of: a salt, e.g., NaCl, MgCl₂, KCl, MgSO₄, etc.; a buffering agent, e.g., a Tris buffer, N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES), 2-(N-Morpholino)ethanesulfonic acid (MES), 2-(N-Morpholino)ethanesulfonic acid sodium salt (MES), 3-(N-Morpholino)propanesulfonic acid (MOPS), N-tris[Hydroxymethyl]methyl-3-aminopropanesulfonic acid (TAPS), etc.; a solubilizing agent; a detergent, e.g., a non-ionic detergent such as Tween-20, etc.; a protease inhibitor; and the like. In some embodiments, as described in more detail below, a subject HERV-K composition is an immunogenic composition. In other embodiments, as described in more detail below, a subject HERV-K composition is a pharmaceutical composition, e.g., a composition comprising a HERV-K polypeptide and a pharmaceutically acceptable excipient.

In some embodiments, a subject composition comprises a single type (or “species”) of HERV-K polypeptide, e.g., in some embodiments, the HERV-K polypeptides in a subject composition all comprise substantially the same amino acid sequence. In other embodiments, a subject immunogenic composition comprises two or more different HERV-K polypeptides, e.g., the composition comprises a population of HERV-K polypeptides, the member of which population can differ in amino acid sequence. A subject composition can comprise from two to about 20 different HERV-K polypeptides, e.g., a subject composition can comprise two, three, four, five, six, seven, eight, nine, ten, 11-15, or 15-20 different HERV-K polypeptides, each having an amino acid that differs from the amino acid sequences of the other HERV-K polypeptides. For example, in some embodiments, a subject composition comprises a first HERV-K polypeptide having a first amino acid sequence; and at least a second HERV-K polypeptide having a second amino acid sequence, where the second amino acid sequence differs from the first amino acid sequence. As another example, in some embodiments, a subject composition comprises a first HERV-K polypeptide having a first amino acid sequence; second HERV-K polypeptide having a second amino acid sequence, where the second amino acid sequence differs from the first amino acid sequence; and at least a third HERV-K polypeptide having a third amino acid sequence, where the third amino acid
sequence differs from both the first and the second amino acid sequences. In other embodiments, a subject composition comprises a multimerized HERV-K polypeptide, as described above.

Production of HERV-K polypeptides

A subject HERV-K polypeptide can be produced in a number of ways, including, e.g., by chemical synthesis, where the HERV-K polypeptide is a "synthetic" polypeptide; by isolation and purification from a naturally-occurring source; and by recombinant means, where the HERV-K polypeptide is a "recombinant" polypeptide. Recombinant means for producing a HERV-K polypeptide are well known in the art, and involve genetically modifying a host cell with a polynucleotide comprising a nucleotide sequence encoding a HERV-K polypeptide, culturing the host cell in vitro under conditions and for a suitable time such that the HERV-K polypeptide is produced by the genetically modified cell, and isolating the HERV-K polypeptide produced by the genetically modified cell.

IMMUNOGENIC COMPOSITIONS

The present disclosure provides an immunogenic composition comprising a HERV-K polypeptide corresponding to a fragment of a HERV-K envelope transmembrane protein, a HERV-K envelope surface unit protein, or a HERV-K capsid protein.

A subject immunogenic composition comprising a subject HERV-K polypeptide can be formulated in a number of ways, as described in more detail below. In some embodiments, a subject immunogenic composition comprises single species of HERV-K polypeptide, e.g., the immunogenic composition comprises a population of HERV-K polypeptides, substantially all of which have the same amino acid sequence. In other embodiments, a subject immunogenic composition comprises two or more different HERV-K polypeptides, e.g., the immunogenic composition comprises a population of HERV-K polypeptides, the member of which population can differ in amino acid sequence. A subject immunogenic composition can comprise from two to about 20 different HERV-K polypeptides, e.g., a subject immunogenic composition can comprise 2, 3, 4, 5, 6, 7, 8, 9, 10, 11-15, or 15-20 different HERV-K polypeptides, each having an amino acid that differs from the amino acid sequences of the other HERV-K polypeptides. For example, in some embodiments, a subject immunogenic composition comprises a first HERV-K polypeptide having a first amino acid sequence; and at least a second HERV-K polypeptide having a second amino acid sequence, where the second amino acid sequence differs from the first amino acid sequence. As another example, in some embodiments, a subject immunogenic composition comprises a first HERV-K polypeptide having a first amino acid sequence; second HERV-K polypeptide having a second amino acid sequence, where the second amino acid sequence differs from the first amino acid sequence; and at least a third HERV-K polypeptide having a third amino acid sequence, where the third amino acid sequence differs from both the first and the second amino acid sequences. In other embodiments, a subject immunogenic composition comprises a multimerized HERV-K polypeptide, as described above.
Adjuvants

[00299] A subject immunogenic composition can include, in addition to a HERV-K peptide as described above, an adjuvant. Examples of known suitable adjuvants that can be used in humans include, but are not necessarily limited to, alum, aluminum phosphate, aluminum hydroxide, MF59 (4.3% w/v squalene, 0.5% w/v Tween 80, 0.5% w/v Span 85), CpG-containing nucleic acid (where the cytosine is unmethylated), QS21, MPL, 3DMPL, extracts from Aquilla, ISCOMS, LT/CT mutants, poly(D,L-lactide-co-glycolide) (PLG) microparticles, Quil A, interleukins, and the like. For non-human animals (e.g. for veterinary applications; for experimental non-human animals), one can use Freund's, N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acetyl-nor-muramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1’-2’-dialmitoyl-sn-glycero-3-hydroxyphosphoryloxy)-ethylamine (CGP 19835A, referred to as MTP-PE), and RIBI, which contains three components extracted from bacteria, monophosphoryl lipid A, trehalose dimycolate and cell wall skeleton (MPL+TDM+CWS) in a 2% squalene/Tween 80 emulsion. The effectiveness of an adjuvant may be determined by measuring the amount of antibodies directed against the immunogenic antigen.

[00300] Further exemplary adjuvants to enhance effectiveness of the composition include, but are not limited to: (1) oil-in-water emulsion formulations (with or without other specific immunostimulating agents such as muramyl peptides (see below) or bacterial cell wall components), such as for example (a) MF59™ (WO 90/14837; Chapter 10 in Vaccine design: the subunit and adjuvant approach, eds. Powell & Newman, Plenum Press 1995), containing 5% Squalene, 0.5% Tween 80 (polyoxyethylene sorbitan mono-oleate), and 0.5% Span 85 (sorbitan trioleate) (optionally containing muramyl tri-peptide covalently linked to dipalmitoyl phosphatidylethanolamine (MTP-PE)) formulated into submicron particles using a microfluidizer, (b) SAF, containing 10% Squalane, 0.4% Tween 80, 5% pluronic-blocked polymer L121, and thr-MDP either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion, and (c) RIBI™ adjuvant system (RAS), (Ribi Immunochem, Hamilton, MT) containing 2% Squalene, 0.2% Tween 80, and one or more bacterial cell wall components such as monophosphoryl lipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), e.g., MPL + CWS (DETOX™); (2) saponin adjuvants, such as QS21 or STIMULON™ (Cambridge Bioscience, Worcester, MA) may be used or particles generated therefrom such as ISCOMs (immunostimulating complexes), which ISCOMS may be devoid of additional detergent e.g. WO00/07621; (3) Complete Freund's Adjuvant (CFA) and Incomplete Freund's Adjuvant (IFA); (4) cytokines, such as interleukins (e.g. IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12 (WO99/44636), etc.), interferons (e.g. gamma interferon), macrophage colony stimulating factor (M-CSF), tumor necrosis factor (TNF), etc.; (5) monophosphoryl lipid A (MPL) or 3-O-deacylated MPL (3dMPL) e.g. GB-2220221, EP-A-0689454, optionally in the substantial absence of alum when used with pneumococcal saccharides e.g. WO00/56358; (6) combinations of 3dMPL with, for example, QS21 and/oil-in-water emulsions e.g. EP-A-0835318,
EP-A-0735898, EP-A-0761231; (7) oligonucleotides comprising CpG motifs (see, e.g., Krieg Vaccine 2000, 19, 618-622; Roman et al., Nat. Med., 1997, 3, 849-854; WO98/18810, WO98/40100, WO98/55495, WO98/37919 and WO98/52581) e.g. containing at least one CG dinucleotide, where the cytosine is unmethylated; (8) a polyoxyethylene ether or a polyoxyethylene ester e.g. W099/52549; (9) a polyoxyethylene sorbitan ester surfactant in combination with an octoxynol (WO01/21207) or a polyoxyethylene alkyl ether or ester surfactant in combination with at least one additional non-ionic surfactant such as an octoxynol (WO01/21152); (10) a saponin and an immunostimulatory oligonucleotide (e.g. a CpG oligonucleotide) (WO00/62800); (11) an immunostimulant and a particle of metal salt e.g. WO00/23105; (12) a saponin and an oil-in-water emulsion e.g. W099/11241; (13) a saponin (e.g. QS21) + 3dMPL + IM2 (optionally + a sterol) e.g. W098/57659; (14) other substances that act as immunostimulating agents to enhance the efficacy of the composition. Muramyl peptides include N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-25 acetyl-normuramyl-L-alanyl-D-isoglutamine (nor-MDP), N-acetylmuramyl-L-alanyl-D-isoglutarninyl-L-alanine-2-(l'-2'-dipalmitoyl-i-ε-glycero-3-hydroxyphosphoryloxy)-ethylamine (MTP-PE), etc.

[00301] The immunogenic compositions may be combined with a conventional pharmaceutically acceptable excipient, such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium, carbonate, and the like. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity adjusting agents and the like, for example, sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate and the like. The concentration of antigen in these formulations can vary widely, and will be selected primarily based on fluid volumes, viscosities, body weight and the like in accordance with the particular mode of administration selected and the patient's needs. The resulting compositions may be in the form of a solution, suspension, tablet, pill, capsule, powder, gel, cream, lotion, ointment, aerosol or the like.

[00302] The protein concentration of a subject immunogenic in the pharmaceutical formulations can vary widely, i.e. from less than about 0.1% usually at or at least about 2% to as much as 20% to 50% or more by weight, and will be selected primarily by fluid volumes, viscosities, etc., in accordance with the particular mode of administration selected.

[00303] In some embodiments, a HERV-K polypeptide is formulated with one or more lipids. For example, liposomes of various sizes can be made. Small liposomes or vesicles formed are unilamellar and have a size in the range of about 20 to 400 nanometers and can be produced by subjecting multi-lamellar vesicles to ultrasound, by extrusion under pressure through membranes having pores of defined size, or by high pressure homogenization. Larger unilamellar liposomes having a size in the range of about 0.1 to 1 μm in diameter can be obtained when the lipid is solubilized in an organic solvent or a detergent and the solubilized agent is removed by evaporation.
or dialysis, respectively. The fusion of smaller unilamellar liposomes by methods requiring particular lipids or stringent dehydration-hydration conditions can yield unilamellar vessels as large as or larger than cells.

Liposomes may comprise one or more cationic lipids, e.g., DDAB, dimethyldioctadecyl ammonium bromide; N-[l-(2,3-Dioleyloxy)propyl]-N,N,N-trimethylammonium methylsulfate; 1,2-diacyl-3-trimethylammonium-propanes, (including but not limited to, dioleoyl (DOTAP), dimyristoyl, dipalmitoyl, disearoyl); 1,2-diacyl-3-dimethylammonium- propanes, (including but not limited to, dioleoyl, dimyristoyl, dipalmitoyl, disearoyl) DOTMA, N-[l-[2,3-bis(oleoyloxy)]propyl]-N,N,N-trimethylammonium chloride; DOGS, dioctadecylamidoglycylspermine; DC-cholesterol, 3β-[N-(N',N'-dimethylaminoethane)carbamoyl]cholesterol; DOSPA, 2,3-dioleoyloxy-N-[2(sperminecarboxamido)-ethyl]-N,N-dimethyl-1-propanaminium trifluoroacetate; 1,2-diacyl-sn-glycero-3-ethylphosphocholines, (including but not limited to dioleoyl (DOEPC), dilauroyl, dimyristoyl, dipalmitoyl, palmitoyloleoyl); β-alanyl cholesterol; CTAB, cetyl trimethyl ammonium bromide; diC14-amidine, N-t-butyl-N′-tetradecyl-3-tetradecylaminopropionamidine; 14Dea2, 0,0′-ditetradecanoyl-N-(trimethylammonioacetyl) diethanolamine chloride; DOSPER, 1,3-dioleoyloxy-2-(6-carboxy-spermyl)-propylamide; N,N,N′-tetramethyl-N,N′-bis(2-hydroxyethyl)-2,3-dioleoyloxy-1,4-butanedi ammonium iodide; l-[2-acyloxyethyl]2-alkyl (alkenyl)-3-(2-hydroxyethyl)imidazolium chloride derivatives such as l-[2-(9(Z)-octadecenyloxy)ethyl]-2-(8(Z)-heptadecenyl-3-(2-hydroxyethyl)imidazolium chloride (DOTIM), l-[2-(hexadecanoyloxy)ethyl]-2-pentadecyl-3-(2-hydroxyethyl)imidazolium chloride (DPTIM); l-[2-tetradecanoyloxy]ethyl]-2-tridecyl-3-(2-hydroxyethyl)imidazolium chloride (DMTIM) - as described in Solodin et al. (1995) Biochem. 43:13537-13544; 2,3-dialklyoxypropyl quaternary ammonium compound derivates, containing a hydroxyalkyl moiety on the quaternary amine, such as 1,2-dioleoyl-3-dimethyl- hydroxyethyl ammonium bromide (DORI); 1,2-dioleoyloxypropyl-3-dimethyl-hydroxyethyl ammonium bromide (DORIE); 1,2-dioleoyloxypropyl-3-dimethyl-hydroxypropammonium bromide (DORIE-HP); 1,2-dioleoyloxypropyl-3-dimethyl-hydroxybutyl ammonium bromide (DORIE-HB); 1,2-dioleoyloxypropyl-3-dimethyl- hydroxypentyl ammonium bromide (DORIE-HPe); 1,2-dimyristoxypropyl-3-dimethyl-hydroxylethyl ammonium bromide (DMRlE); 1,2-dipalmitoxypropyl-3-dimethyl-hydroxyethyl ammonium bromide (DPRIE); 1,2-disteryoxypropyl-3-dimethyl-hydroxyethyl ammonium bromide (DSRIE) - as described, e.g., in Feigner et al. (1994) J. Biol. Chem. 269:2550-2561. Many of the above-mentioned lipids are available commercially from, e.g., Avanti Polar Lipids, Inc.; Sigma Chemical Co.; Molecular Probes, Inc.; Northern Lipids, Inc.; Roche Molecular Biochemicals; and Promega Corp.

Liposomes may comprise cationic lipids alone, or in admixture with other lipids, particularly neutral lipids such as: cholesterol; 1,2-diacyl-sn-glycero-3-phosphoethanolamines,
(including but not limited to dioleoyl (DOPE), 1,2-diacyl-sn-glycero-3-phosphocholines; natural egg yolk phosphatidyl choline (PC), and the like; synthetic mono- and diacyl phosphocholines (e.g., monoacilyl phosphatidyl choline (MOPC)) and phosphoethanolamines. Asymmetric fatty acids, both synthetic and natural, and mixed formulations, for the above diacyl derivatives may also be included.

[00306] Other suitable liposome compositions include dimyristoylphosphatidylcholine (DMPC) and cholesterol. Such liposomes are described in, e.g., U.S. Patent No. 5,916,588. Additional suitable liposomal compositions, and methods of preparing same, are known in the art, and are described in various publications, including, e.g., U.S. Patent Nos. 4,241,046 and 6,355,267.

**HERV-K POLYNUCLEOTIDES**

[00307] The present disclosure provides HERV-K polynucleotides, and compositions, including immunogenic compositions, comprising the HERV-K polynucleotides. A subject HERV-K polynucleotide comprises a nucleotide sequence encoding a subject HERV-K polypeptide.

[00308] A subject HERV-K polynucleotide can be used to produce a subject HERV-K polypeptide. Methods of producing a HERV-K polypeptide are described above.

[00309] An immunogenic composition comprising a subject HERV-K polynucleotide can be used to induce an immune response in an individual. When administered to an individual in need thereof, the polynucleotide (the "HERV-K polynucleotide") comprising a nucleotide sequence encoding a HERV-K polypeptide is taken up by a cell, e.g., an antigen-presenting cell, the encoded HERV-K polypeptide is produced in the cell, and the HERV-K polypeptide is processed into epitope-displaying polypeptide fragments ("epitope fragments") that are then displayed on the surface of the cell in association with an MHC molecule. The encoded HERV-K polypeptide stimulates or enhances a B cell response to the epitope(s) displayed on the cell surface. Where the HERV-K epitopes are also present on an immunodeficiency virus-infected cell, a B cell response to the immunodeficiency virus-infected cell also occurs.

**Expression vectors and delivery vehicles**

[00310] In some embodiments, a HERV-K polynucleotide is an expression vector. The expression vector will provide a transcriptional and translational initiation region, which may be inducible or constitutive, where the coding region is operably linked under the transcriptional control of the transcriptional initiation region, and a transcriptional and translational termination region.

[00311] Expression vectors generally have convenient restriction sites located near the promoter sequence to provide for the insertion of nucleic acid sequences encoding heterologous proteins. A selectable marker operative in the expression host may be present. Suitable expression vectors include, but are not limited to, viral vectors (e.g. viral vectors based on vaccinia virus; poliovirus; adenovirus (see, e.g., Li et al., Invest Ophthmol Vis Sci 35:2543 2549, 1994; Borras et al., Gene Ther 6:515 524, 1999; Li and Davidson, PNAS 92:7700 7704, 1995; Sakamoto et al., H Gene Ther 5:1088 1097, 1999; WO 94/12649, WO 93/03769; WO 93/19191; WO 94/28938; WO 95/11984 and
WO 95/00655); adeno-associated virus (see, e.g., Ali et al., Hum Gene Ther 9:81 86, 1998, Flannery et al., PNAS 94:6916 6921, 1997; Bennett et al., Invest Ophthmol Vis Sci 38:2857 2863, 1997; Jomary et al., Gene Ther 4:683 690, 1997, Rolling et al., Hum Gene Ther 10:641 648, 1999; Ali et al., Hum Mol Genet 5:591 594, 1996; Srivastava in WO 93/09239, Samulski et al., J. Vir. (1989) 63:3822-3828; Mendelson et al., Virol. (1988) 166:154-165; and Flotte et al., PNAS (1993) 90:10613-10617); SV40; herpes simplex virus; human immunodeficiency virus (see, e.g., Miyoshi et al., PNAS 94:10319 23, 1997; Takahashi et al., J Virol 73:7812 7816, 1999); a retroviral vector (e.g., Murine Leukemia Virus, spleen necrosis virus, and vectors derived from retroviruses such as Rous Sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, human immunodeficiency virus, myeloproliferative sarcoma virus, and mammary tumor virus); and the like. Numerous suitable expression vectors are known to those of skill in the art, and many are commercially available. The following vectors are provided by way of example; for eukaryotic host cells: pXT1, pSG5 (Stratagene), pSVK3, pBPV, pMSG, and pSVLSV40 (Pharmacia). However, any other vector may be used so long as it is compatible with the host cell. Depending on the host/vector system utilized, any of a number of suitable transcription and translation control elements, including constitutive and inducible promoters, transcription enhancer elements, transcription terminators, etc. may be used in the expression vector (see e.g., Bitter et al. (1987) Methods in Enzymology, 153:516-544). Non-limiting examples of suitable eukaryotic promoters (promoters functional in a eukaryotic cell) include CMV immediate early, HSV thymidine kinase, early and late SV40, LTRs from retrovirus, and mouse metallothionein-I. Selection of the appropriate vector and promoter is well within the level of ordinary skill in the art. The expression vector may also contain a ribosome binding site for translation initiation and a transcription terminator. The expression vector may also include appropriate sequences for amplifying expression. A subject recombinant vector will in some embodiments include one or more selectable markers. In addition, the expression vectors will in many embodiments contain one or more selectable marker genes to provide a phenotypic trait for selection of transformed host cells such as dihydrofolate reductase or neomycin resistance for eukaryotic cell culture. Other gene delivery vehicles and methods may be employed, including polycationic condensed DNA linked or unlinked to killed adenovirus alone, for example Curiel (1992) Hum. Gene Ther. 3:147-154; ligand linked DNA, for example see Wu (1989) J. Biol. Chem. 264:16985-16987; eukaryotic cell delivery vehicles cells; deposition of photopolymerized hydrogel materials; hand-held gene transfer particle gun, as described in U.S. Patent No. 5,149,655; ionizing radiation as described in U.S. Patent No. 5,206,152 and in WO 92/11033; nucleic charge neutralization or fusion with cell membranes. Additional approaches are described in Philip (1994) Mol. Cell Biol. 14:2411-2418, and in Woffendin (1994) Proc. Natl. Acad. Sci. 91:1581-1585.
Naked DNA may also be employed. Exemplary naked DNA introduction methods are described in WO 90/1092 and U.S. Patent No. 5,580,859. Uptake efficiency may be improved using biodegradable latex beads. DNA coated latex beads are efficiently transported into cells after endocytosis initiation by the beads. The method may be improved further by treatment of the beads to increase hydrophobicity and thereby facilitate disruption of the endosome and release of the DNA into the cytoplasm. Liposomes that can act as gene delivery vehicles are described in U.S. Patent No. 5,422,120, PCT Nos. WO 95/13796, WO 94/23697, and WO 91/14445, and EP No. 524,968.

Liposome or lipid nucleic acid delivery vehicles can also be used. Liposome complexes for gene delivery are described in, e.g., U.S. Patent No. 7,001,614. For example, liposomes comprising DOTAP and at least one cholesterol and/or cholesterol-derivative, present in a molar ratio range of 2.0 mM to 10 mM provide an effective delivery system, e.g., where the molar ratio of DOTAP to cholesterol is 1:1 to 3:1. The cationic lipid N-[(2,3-dioleoyloxy)propyl]-L-lysinamide (LADOP) can be used in a composition for delivering a HERV-K polynucleotide, where LADOP-containing liposomes are described in, e.g., U.S. Patent No. 7,067,697. Liposome formulations comprising amphiphatic lipids having a polar headgroup and aliphatic components capable of promoting transfection are suitable for use and are described in, e.g., U.S. Patent No. 6,433,017.

Further non-viral delivery suitable for use includes mechanical delivery systems such as the approach described in Woffendin et al. (1994) Proc. Natl Acad. Sci. USA 91:11581-11585. Moreover, the coding sequence and the product of expression of such can be delivered through deposition of photopolymerized hydrogel materials. Other conventional methods for gene delivery that can be used for delivery of the coding sequence include, for example, use of hand-held gene transfer particle gun, as described in U.S. Patent No. 5,149,655; use of ionizing radiation for activating transferred gene, as described in U.S. Patent No. 5,206,152 and PCT No. WO 92/11033.

**TREATMENT METHODS**

A subject HERV-K peptide is useful in methods for inducing, eliciting, or enhancing a B cell immune response to an immunodeficiency virus-infected cell, e.g., an HIV-infected cell, in an individual in need thereof. The methods generally involve administering an effective amount of a subject immunogenic composition to the individual.

1) reduction in viral load;
2) increase in the number of immunodeficiency virus-specific B cells;
3) increase in the number of B cells secreting antibody that binds to an immunodeficiency virus-infected cell;
4) increase in the level of immunodeficiency virus-specific antibody;
5) increase in the level of HERV-K-specific antibody; and
6) increase in the CD4+ T cell count.
In some embodiments, an "effective amount" of a subject immunogenic composition is an amount that, when administered to an individual in one or more doses, reduces viral load (e.g., immunodeficiency virus load) in the individual by at least about 5%, at least about 10%, at least about 20%, at least about 25%, at least about 50%, at least about 75%, at least about 85%, or at least about 90%, compared to the viral load in the individual before treatment with the immunogenic composition.

In some embodiments, an "effective amount" of a subject immunogenic composition is an amount that, when administered to an individual in one or more doses, results in an increase in B cell levels and function(s) in the individual. For example, an "effective amount" of a subject immunogenic composition can be an amount that, when administered to an individual in one or more doses, results in an increase in the number of immunodeficiency virus-specific B cells in the individual. In some embodiments, an "effective amount" of a subject immunogenic composition is an amount that, when administered to an individual in one or more doses, results in an increase of at least about 25%, at least about 50%, at least about 100% or 2-fold, at least about 5-fold, at least about 10-fold, at least about 10^2-fold, at least about 10^3-fold, or more, in the number of immunodeficiency virus-specific B cells, compared to the number of immunodeficiency virus-specific B cells in the individual before treatment with the immunogenic composition.

In some embodiments, an "effective amount" of a subject immunogenic composition is an amount that, when administered to an individual in one or more doses, results in an increase in B cell levels and function(s) in the individual. For example, an "effective amount" of a subject immunogenic composition can be an amount that, when administered to an individual in one or more doses, results in an increase in the number of B cells secreting antibody that binds to an immunodeficiency virus-infected cell in the individual. In some embodiments, an "effective amount" of a subject immunogenic composition is an amount that, when administered to an individual in one or more doses, results in an increase of at least about 25%, at least about 50%, at least about 100% or 2-fold, at least about 5-fold, at least about 10-fold, at least about 10^2-fold, at least about 10^3-fold, or more, in the number of B cells secreting antibody that binds to an immunodeficiency virus-infected cell, compared to the number of B cells secreting antibody that binds to an immunodeficiency virus-infected cell in the individual before treatment with the immunogenic composition.

In some embodiments, an "effective amount" of a subject immunogenic composition is an amount that, when administered to an individual in one or more doses, results in an increase in antibody levels in the individual. For example, an "effective amount" of a subject immunogenic composition can be an amount that, when administered to an individual in one or more doses, results in an increase in the level of immunodeficiency virus-specific antibody in the individual. In some embodiments, an "effective amount" of a subject immunogenic composition is an amount that, when administered to an individual in one or more doses, results in an increase of at least about 25%, at
least about 50%, at least about 100% or 2-fold, at least about 5-fold, at least about 10-fold, at least about 10^{2}-fold, at least about 10^{3}-fold, or more, in the level of immunodeficiency virus-specific antibody, compared to the level of immunodeficiency virus-specific antibody in the individual before treatment with the immunogenic composition.

In some embodiments, an "effective amount" of a subject immunogenic composition is an amount that, when administered to an individual in one or more doses, results in an increase in antibody levels in the individual. For example, an "effective amount" of a subject immunogenic composition can be an amount that, when administered to an individual in one or more doses, results in an increase in the level of HERV-K-specific antibody in the individual. In some embodiments, an "effective amount" of a subject immunogenic composition is an amount that, when administered to an individual in one or more doses, results in an increase of at least about 25%, at least about 50%, at least about 100% or 2-fold, at least about 5-fold, at least about 10-fold, at least about 10^{2}-fold, at least about 10^{3}-fold, or more, in the level of HERV-K-specific antibody, compared to the level of HERV-K-specific antibody in the individual before treatment with the immunogenic composition.

In some embodiments, an "effective amount" of a subject immunogenic composition is an amount that, when administered to an individual in one or more doses, results in an increase in the number of CD4^{+} T cells in the individual. In some embodiments, an "effective amount" of a subject immunogenic composition is an amount that, when administered to an individual in one or more doses, results in an increase of at least about 25%, at least about 50%, at least about 100% or 2-fold, at least about 5-fold, at least about 10-fold, at least about 10^{2}-fold, at least about 10^{3}-fold, or more, in the number of CD4^{+} T cells, compared to the number of CD4^{+} T cells in the individual before treatment with the immunogenic composition.

In some embodiments, e.g., where the immunogenic composition is administered to a naive individual (i.e., an individual not infected with an immunodeficiency virus such as HIV), an "effective amount" of a subject immunogenic composition is an amount that, when administered to an individual in one or more doses, reduces the likelihood that the individual, if later infected with an immunodeficiency virus such as HIV, would develop disease symptoms from the immunodeficiency virus infection. In some embodiments, e.g., where the immunogenic composition is administered to a naive individual (i.e., an individual not infected with a lentivirus such as HIV), an "effective amount" of a subject immunogenic composition is an amount that, when administered to an individual in one or more doses, increases the likelihood that the individual, if later infected with an immunodeficiency virus such as HIV, would limit and/or clear the immunodeficiency virus infection.

Formulations

A HERV-K polypeptide, as described above, can be formulated in any of a variety of ways for administration to an individual in need thereof. The present disclosure provides pharmaceutical
formulations comprising a HERV-K polypeptide. Immunogenic compositions comprising a HERV-K polypeptide are described above. Additional formulations are described below.

[00335] A subject formulation comprising a HERV-K polypeptide generally includes one or more of an excipient (e.g., sucrose, starch, mannitol, sorbitol, lactose, glucose, cellulose, talc, calcium phosphate or calcium carbonate), a binder (e.g., cellulose, methylcellulose, hydroxymethylcellulose, polypropylpyrrolidone, polyvinylpyrrolidone, gelatin, gum arabic, polyethylene glycol, sucrose or starch), a disintegrator (e.g., starch, carboxymethylcellulose, hydroxypropylstarch, low substituted hydroxypropylcellulose, sodium bicarbonate, calcium phosphate or calcium citrate), a lubricant (e.g., magnesium stearate, light anhydrous silicic acid, talc or sodium lauryl sulfate), a flavoring agent (e.g., citric acid, menthol, glycine or orange powder), a preservative (e.g., sodium benzoate, sodium bisulfite, methylparaben or propylparaben), a stabilizer (e.g., citric acid, sodium citrate or acetic acid), a suspending agent (e.g., methylcellulose, polyvinylpyrrolidone or aluminum stearate), a dispersing agent (e.g., hydroxypropylmethylcellulose), a diluent (e.g., water), and base wax (e.g., cocoa butter, white petrolatum or polyethylene glycol).

[00336] Tablets comprising an active agent (e.g., an anti-HERV-K antibody) may be coated with a suitable film-forming agent, e.g., hydroxypropylmethyl cellulose, hydroxypropyl cellulose or ethyl cellulose, to which a suitable excipient may optionally be added, e.g., a softener such as glycerol, propylene glycol, diethylphthalate, or glycerol triacetate; a filler such as sucrose, sorbitol, xylitol, glucose, or lactose; a colorant such as titanium hydroxide; and the like.

[00337] Suitable excipient vehicles are, for example, water, saline, dextrose, glycerol, ethanol, or the like, and combinations thereof. In addition, if desired, the vehicle may contain minor amounts of auxiliary substances such as wetting or emulsifying agents or pH buffering agents. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in the art. See, e.g., Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 17th edition, 1985. The composition or formulation to be administered will, in any event, contain a quantity of the agent adequate to achieve the desired state in the subject being treated. The pharmaceutically acceptable excipients, such as vehicles, adjuvants, carriers or diluents, are readily available to the public. Moreover, pharmaceutically acceptable auxiliary substances, such as pH adjusting and buffering agents, tonicity adjusting agents, stabilizers, wetting agents and the like, are readily available to the public.

[00338] In some embodiments, e.g., for use in inducing or enhancing an immune response to an immunodeficiency virus, a HERV-K polypeptide is formulated for vaginal delivery. A subject formulation for intravaginal administration is formulated as an intravaginal bioadhesive tablet, intravaginal bioadhesive microparticle, intravaginal cream, intravaginal lotion, intravaginal foam, intravaginal ointment, intravaginal paste, intravaginal solution, or intravaginal gel.
Dosages

[00339] The appropriate dosage of a HERV-K polypeptide that, when administered in one or multiple doses, has the desired effect (e.g., increases a B cell immune response; increases an immune response to HIV-1; etc.), will vary, depending on various factors, but will generally be in the range of from about 1 µg to about 100 mg, e.g., from about 1 µg to about 5 µg, from about 5 µg to about 10 µg, from about 10 µg to about 25 µg, from about 25 µg to about 50 µg, from about 50 µg to about 100 µg, from about 100 µg to about 500 µg, from about 500 µg to about 1 mg, from about 1 mg to about 10 mg, from about 10 mg to about 50 mg, or from about 50 mg to about 100 mg, administered in one dose or divided into multiple doses.

[00340] In some embodiments, the amount of HERV-K polypeptide per dose is determined on a per body weight basis. For example, in some embodiments, a HERV-K polypeptide is administered in an amount of from about 0.5 mg/kg to about 100 mg/kg, e.g., from about 0.5 mg/kg to about 1 mg/kg, from about 1 mg/kg to about 2 mg/kg, from about 2 mg/kg to about 3 mg/kg, from about 3 mg/kg to about 5 mg/kg, from about 5 mg/kg to about 7 mg/kg, from about 7 mg/kg to about 10 mg/kg, from about 10 mg/kg to about 15 mg/kg, from about 15 mg/kg to about 20 mg/kg, from about 20 mg/kg to about 25 mg/kg, from about 25 mg/kg to about 30 mg/kg, from about 30 mg/kg to about 40 mg/kg, from about 40 mg/kg to about 50 mg/kg per dose, from about 50 mg/kg to about 60 mg/kg, from about 60 mg/kg to about 70 mg/kg, from about 70 mg/kg to about 80 mg/kg, from about 80 mg/kg to about 90 mg/kg, or from about 90 mg/kg to about 100 mg/kg, or more than about 100 mg/kg.

[00341] Those of skill will readily appreciate that dose levels can vary as a function of the specific compound, the severity of the symptoms and the susceptibility of the subject to side effects. Preferred dosages for a given compound are readily determinable by those of skill in the art by a variety of means.

[00342] In some embodiments, multiple doses of a HERV-K polypeptide are administered. The frequency of administration of a HERV-K polypeptide can vary depending on any of a variety of factors, e.g., severity of the symptoms, etc. For example, in some embodiments, a HERV-K polypeptide is administered once per month, twice per month, three times per month, every other week (qow), once per week (qw), twice per week (biw), three times per week (tiw), four times per week, five times per week, six times per week, every other day (qod), daily (qd), twice a day (qid), or three times a day (tid).

[00343] The duration of administration of a HERV-K polypeptide, e.g., the period of time over which a HERV-K polypeptide is administered, can vary, depending on any of a variety of factors, e.g., patient response, etc. For example, a HERV-K polypeptide can be administered over a period of time ranging from about one day to about one week, from about two weeks to about four weeks, from about one month to about two months, from about two months to about four months, from about four months to about six months, from about six months to about eight months, from about
eight months to about 1 year, from about 1 year to about 2 years, or from about 2 years to about 4 years, or more.

**Routes of Administration**

[00344] Conventional and pharmaceutically acceptable routes of administration include intranasal, intramuscular, intratracheal, intratumoral, transdermal, subcutaneous, intradermal, topical application, intravenous, vaginal, nasal, and other parenteral routes of administration. Suitable routes of administration also include oral and rectal routes. Routes of administration may be combined, if desired, or adjusted depending upon the agent and/or the desired effect. The composition can be administered in a single dose or in multiple doses.

[00345] A subject HERV-K composition can be administered to a host using any available conventional methods and routes suitable for delivery of conventional drugs, including systemic or localized routes. In general, routes of administration contemplated by the invention include, but are not necessarily limited to, enteral, parenteral, or inhalational routes.

[00346] Parenteral routes of administration other than inhalation administration include, but are not necessarily limited to, topical, vaginal, transdermal, subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intrastemal, intratumoral, peritumoral, and intravenous routes, i.e., any route of administration other than through the alimentary canal. Parenteral administration can be carried to effect systemic or local delivery of the agent. Where systemic delivery is desired, administration typically involves invasive or systemically absorbed topical or mucosal administration of pharmaceutical preparations.

[00347] A subject HERV-K composition can also be delivered to the subject by enteral administration. Enteral routes of administration include, but are not necessarily limited to, oral and rectal (e.g., using a suppository) delivery.

[00348] A subject HERV-K composition can be delivered to mucosal tissue, e.g., to vaginal tissue, to rectal tissue, etc.

**Combinations**

[00349] In some embodiments, a subject immunogenic composition is administered to an individual in need thereof in combination therapy with one or more additional therapeutic agents. Suitable additional therapeutic agents include agents that inhibit one or more functions of an immunodeficiency virus; agents that treat orameliorate a symptom of an immunodeficiency virus infection; agents that treat an infection that occurs secondary to an immunodeficiency virus infection; and the like.

[00350] Therapeutic agents include, e.g., beta-lactam antibiotics, tetracyclines, chloramphenicol, neomycin, gramicidin, bacitracin, sulfonamides, nitrofurazone, nalidixic acid, cortisone, hydrocortisone, betamethasone, dexamethasone, fluocortolone, prednisolone, triamcinolone, indomethacin, sulindac, acyclovir, amantadine, rimantadine, recombinant soluble CD4 (rsCD4), anti-receptor antibodies (e.g., for rhinoviruses), nevirapine, cidofovir (Vistide™), trisodium
phosphonoformate (Foscarnet™), famcyclovir, pencyclovir, valacyclovir, nucleic acid/replication inhibitors, interferon, zidovudine (AZT, Retrovir™), didanosine (dideoxyinosine, ddl, Videx™), stavudine (d4T, Zerit™), zalcitabine (dideoxycytosine, ddC, Hivid™), nevirapine (Viramune™), lamivudine (Epivir™, 3TC), protease inhibitors, saquinavir (Invirase™, Fortovase™), ritonavir (Norvir™), nelfinavir (Viracept™), efavirenz (Sustiva™), abacavir (Ziagen™), amiprenavir (Agenerase™) indinavir (Crixivan™), ganciclovir, AzDU, delavirdine (Rescriptor™), kaletra, trizivir, rifampin, clathiromycin, erythromycin, colony stimulating factors (G-CSF and GM-CSF), non-nucleoside reverse transcriptase inhibitors, nucleoside inhibitors, adriamycin, fluorouracil, methotrexate, asparaginase and combinations thereof. Anti-HIV agents are those in the preceding list that specifically target a function of one or more HIV proteins.

In some embodiments, subject HERV-K peptide is administered in combination therapy with two or more anti-HIV agents. For example, a subject HERV-K peptide can be administered in combination therapy with one, two, or three nucleoside reverse transcriptase inhibitors (e.g., Combivir, Epivir, Hivid, Retrovir, Videx, Zerit, Ziagen, etc.). A subject HERV-K peptide can be administered in combination therapy with one or two non-nucleoside reverse transcriptase inhibitors (e.g., Rescriptor, Sustiva, Viramune, etc.). A subject HERV-K peptide can be administered in combination therapy with one or two protease inhibitors (e.g., Agenerase, Crixivan, Fortovase, Invirase, Kaletra, Norvir, Viracept, etc.). A subject HERV-K peptide can be administered in combination therapy with a protease inhibitor and a nucleoside reverse transcriptase inhibitor. A subject HERV-K peptide can be administered in combination therapy with a protease inhibitor, a nucleoside reverse transcriptase inhibitor, and a non-nucleoside reverse transcriptase inhibitor. A subject HERV-K peptide can be administered in combination therapy with a protease inhibitor and a non-nucleoside reverse transcriptase inhibitor. Other combinations of an active agent (e.g., a subject HERV-K peptide) with one or more of a protease inhibitor, a nucleoside reverse transcriptase inhibitor, and a non-nucleoside reverse transcriptase inhibitor are contemplated.

In some embodiments, a subject treatment method involves administering: a) subject HERV-K peptide; and b) an agent that inhibits an immunodeficiency virus function selected from viral replication, viral protease activity, viral reverse transcriptase activity, viral entry into a cell, viral integrase activity, viral Rev activity, viral Tat activity, viral Nef activity, viral Vpr activity, viral Vpu activity, and viral Vif activity.

In some embodiments, a subject treatment method involves administering: a) subject HERV-K peptide; and b) an HIV inhibitor, where suitable HIV inhibitors include, but are not limited to, one or more nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (Pis), fusion inhibitors, integrase inhibitors, chemokine receptor (e.g., CXCR4, CCR5) inhibitors, and hydroxyurea.

Nucleoside reverse transcriptase inhibitors include, but are not limited to, abacavir (ABC; ZIAGEN™), didanosine (dideoxyinosine (ddl); VIDEX™), lamivudine (3TC; EPIVIR™),
stavudine (d4T; ZERIT™, ZERIT XR™), zalcitabine (dideoxycytidine (ddC); HIVID™),
zidovudine (ZDV, formerly known as azidothymidine (AZT); RETROVIR™), abacavir, zidovudine, and
lamivudine (TRIZIVIR™), zidovudine and lamivudine (COMBIVIR™), and emtricitabine
(EMTRIVA™). Nucleotide reverse transcriptase inhibitors include tenofovir disoproxil fumarate
(VIREAD™). Non-nucleoside reverse transcriptase inhibitors for HIV include, but are not limited to,
nevirapine (VIRAMUNE™), delavirdine mesylate (RESCRIPTOR™), and efavirenz
(SUSTIVA™).

Protease inhibitors (Pis) for treating HIV infection include amprenavir (AGENERASE™),
saquinavir mesylate (FORTOVASE™, IN VIRASE™), ritonavir (NORVIR™), indinavir sulfate
(CRIXIVAN™), nelfinavir mesylate (VIRACEPT™), lopinavir and ritonavir (KALETRA™),
atazanavir (REYATAZ™), and fosamprenavir (LEXIVA™).

Fusion inhibitors prevent fusion between the virus and the cell from occurring, and therefore,
prevent HIV infection and multiplication. Fusion inhibitors include, but are not limited to,
enfuvirtide (FUZEON™), Lalezari et al., New England J. Med., 348:2175-2185 (2003); and
maraviroc (SELZENTRY™, Pfizer).

An integrase inhibitor blocks the action of integrase, preventing HIV-1 genetic material
from integrating into the host DNA, and thereby stopping viral replication. Integrase inhibitors
include, but are not limited to, raltegravir (ISENTRESS™, Merck); and elvitegravir
(GS 9137, Gilead Sciences).

Maturation inhibitors include, e.g., bevirimat (3β-(3-carboxy-3-methyl -butanoyloxy) lup-
20(29)-en-28-oic acid); and Vivecon (MPC9055).

In some embodiments, a subject treatment method involves administering: a) subject
HERV-K peptide; and b) one or more of: (1) an HIV protease inhibitor selected from amprenavir,
atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir,
breakanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423,
RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, PPL-100, DG35, and AG 1859;
(2) an HIV non-nucleoside inhibitor of reverse transcriptase selected from capravirine, emivirine,
delavirdine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961,
DPC-963, MIV-150, and TMC-120, TMC-278 (rilpivirine), efavirenz, BILR 355 BS, VRX 840773,
UK-453061, and RDEA806; (3) an HIV nucleoside inhibitor of reverse transcriptase selected from
zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amoxovir,
elvucitabine, alovudine, MIV-210, racivir, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil,
apricitibine (AVX754), amoxovir, KP-1461, and fosalvudine tidoxil (formerly HDP 99.0003); (4)
an HIV nucleotide inhibitor of reverse transcriptase selected from tenofovir and adefovir; (5) an HIV
integrase inhibitor selected from curcumin, derivatives of curcumin, chlortic acid, derivatives of
chlicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic
acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid

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phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, and L-870810, MK-0518 (raltegravir), BMS-538158, GSK364735C, BMS-707035, MK-2048, and BA 011; (6) a gp41 inhibitor selected from enfuvirtide, sifuvirtide, FB006M, and TRI-1144; (7) a CXCR4 inhibitor, such as AMD-070; (8) an entry inhibitor, such as SP01A; (9) a gp120 inhibitor, such as BMS-488043 and/or BlockAide/CR; (10) a G6PD and NADH-oxidase inhibitor, such as immunitin; (11) a CCR5 inhibitors selected from the group consisting of aplaviroc, vicriviroc, maraviroc, PRO-140, INCB 15050, PF-232798 (Pfizer), and CCR5 mAb004; (12) another drug for treating HIV selected from BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevirimat), Ampligen, HRG214, Cytolin, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS119, ALG 889, and PA-1050040 (PA-040); (13) any combinations or mixtures of the above.

For example, in some embodiments, a subject treatment method involves administering: a) a subject HERV-K peptide; and b) one or more of: i) amprenavir (Agenerase; (35)-oxolan-3-yl N-[(25,3R)-3-hydroxy-4/-N-(2-methylpropyl)(4-aminobenzene)sulfamido]l-phenylbutan-2-yl]carbamate) in an amount of 600 mg or 1200 mg twice daily; ii) tipranavir (Aptivus; N-[(3-[(1R)-1-[(2R)-6-hydroxy-4-oxo-2-(2-phenylethyl)-2-propyl-3,4-dihydro-2 H-pyran-5-yl]propyl][phenyl]-5-(trifluoromethy)pyridine-2-sulfonamide) in an amount of 500 mg twice daily; iii) idinavir (Crixivan; (25)-1-[(25,4R)-4-benzyl-2-hydroxy-4-[(1S,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl]butyl]-N-teri-butyl-4-(pyridin-3-ylmethyl)piperazine-2-carboxamide) in an amount of 800 mg three times daily; iv) saquinavir (Invirase; (25)-N-[(25,3R)-4-[(35)-3-(teri-butylcarbamoayl)-decahydroisoquinolin-2-yl]-3-hydroxy-l-phenylbutan-2-yl]-2-(quinolin-2-yl)formamido)butanediamide) in an amount of 1,000 mg twice daily; v) lopinavir and ritonavir (Kalera; where lopinavir is 2S)-N-[(25,45,55)-5-2-(2,6-dimethylphenoxy)acetamido]-4-hydroxy-1,6-diphenylhexan-2-yl]-3-methyl-2-(2-oxo-1,3-diazinan-1-yl)butanamide; and ritonavir is 1,3-thiazol-5-ylmethyl N-[(25,35,55)-3-hydroxy-5-[(25)-3-methyl-2-[(methyl-[(2-[propan-2-yl]-l,3-thiazol-4-yl]methyl)]carbamoyl]amino Jbutanamido]-1,6-diphenylhexan-2-yl] carbamate) in an amount of 133 mg twice daily; vi) fosamprenavir (Lexiva; [2R,3S]-2-(2-methylpropyl)(4-aminobenzene)sulfamido)-3-[(35-oxolan-3-yl)oxy]carbonyl]amino)-4-phenylbutan-2-yl][oxy]phosphonic acid) in an amount of 700 mg or 1400 mg twice daily); vii) ritonavir (Norvir) in an amount of 600 mg twice daily; viii) nelfinavir (Viracept; (3S,4aS,8aS)-N-teri-butyl-2-[(2R,3R)-2-hydroxy-3-[(3-hydroxy-2-methylphenyl)formamido] -4-(phenylsulfanyl)butyl]-decahydroisoquinoline-3-carboxamide) in an amount of 750 mg three times daily or in an amount of 1250 mg twice daily; ix) Fuzeon (Acetyl-YTLSLIHELIESQNQ QEKNEQELLEDKWSLWNNWF-amide; SEQ ID NO:558) in an amount of 90 mg twice daily; x) Combivir in an amount of 150 mg lamivudine (3TC; 2',3'-dideoxy-3'-thiacytidine) and 300 mg zidovudine (AZT; azidothymidine) twice daily; xi) emtricitabine (Emtriva; 4-amino-5-fluoro-l-
[(2R,55)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one) in an amount of 200 mg once daily; xii) Epzicon in an amount of 600 mg abacavir (ABV; [(15,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]cyclopent-2-en-1-yl]methanol) and 300 mg 3TC once daily; xiii) zidovudine (Retrovir; AZT or azidothymidine) in an amount of 200 mg three times daily; xiv) Trizivir in an amount of 150 mg 3TC and 300 mg ABV and 300 mg AZT twice daily; xv) Truvada in an amount of 200 mg emtricitabine and 300 mg tenofovir (4-[[2(R)-1-(6-amino-9H-purin-9-yl)propan-2-yl]oxy]methyl)phosphonic acid) once daily; xvi) didanosine (Videx; 2',3'-dideoxyinosine) in an amount of 400 mg once daily; xvii) tenofovir (Viread) in an amount of 300 mg once daily; xviii) abacavir (Ziagen) in an amount of 300 mg twice daily; xix) atazanavir (Reyataz; methyl N-[(15)-1-[(25,35)-3-hydroxy-4-[(25)-2-[(methoxycarbonyl)amino]-3,3-dimethyl-N'-[[4-(pyridin-2-yl)phenyl]methyl]butane-2-yl]carbamoyl]-2,2-dimethylpropyl]carbamate) in an amount of 300 mg once daily or 400 mg once daily; xx) lamivudine (Epivir) in an amount of 150 mg twice daily; xxi) stavudine (Zerit; 2',3'-didehydro-2',3'-dideoxythymidine) in an amount of 40 mg twice daily; xxii) delavirdine (Rescriptor; N-[2-[(4-[3-(propan-2-ylamino)pyridin-2-yl]piperazin-1-yl]carbonyl]-1H-indol-5-yl]methanesulfonamide) in an amount of 400 mg three times daily; xxiii) efavirenz (Sustiva; (4S)-6-chloro-4-[(2-cyclopropylethynyl)-4-(trifluoromethyl)]-2,4-dihydro-1H-3,1-benzoxazin-2-one) in an amount of 600 mg once daily; xxiv) nevirapine (Viramune; 1H-cyclopropyl-4-methyl-5,5-dihydro-6H-dipyrido[3,2-\&:2',3'-e][1,4]diazepin-6-one) in an amount of 200 mg twice daily); xxv) bevirimat; and xxvi) Vivecon.

**EXAMPLES**

[00361] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Celsius, and pressure is at or near atmospheric. Standard abbreviations may be used, e.g., bp, base pair(s); kb, kilobase(s); pi, picoliter(s); s or sec, second(s); min, minute(s); h or hr, hour(s); aa, amino acid(s); kb, kilobase(s); bp, base pair(s); nt, nucleotide(s); i.m., intramuscular(lly); i.p., intraperitoneal(ly); s.c, subcutaneous(ly); and the like.
Example 1: HERV-K env has two linear epitopes eliciting humoral response.

MATERIALS AND METHODS

Study populations

Samples of peripheral blood mononuclear cells (PBMCs) were selected from participants in two different San Francisco-based HIV-1-infected cohorts: Options (n=1) and SCOPE (n=120). Samples from HIV-1-negative controls were obtained from Blood Centers of the Pacific (n=80). The study was approved by the local institutional review boards (University of California San Francisco Committee on Human Research) and individuals gave written informed consent. Studies were performed on cryopreserved PBMCs and sera.

PBMC and sera samples were obtained from the following categories of chronically HIV-1-infected individuals: 40 elite controllers (EC: naive for treatment, undetectable viral load for two years, CD4>350); 40 highly active antiretroviral therapy (HAART: Viremic suppressed with undetectable viral load for at least two years, CD4>350), and 40 untreated virologic non-controllers (naive for treatment, viral load >2000 copies/mL).

ELISA

For the mapping, 15mer polypeptides were first prepared and purified by JPT Peptide Technologies for the whole protein mapping. Peptides that gave a positive signal were then produced by two other companies (New England Peptide and Gene Script) to confirm the results.

For the cross-sectional and longitudinal study, 96 microtiter wells plate (Nunc-Immuno Plate MaxiSorp Surface) were coated for 1 hour at 37°C with peptides (Gene Script) corresponding to TM (HRFQLQCDWNTSDFC; SEQ ID NO:665), SU (RPKGPCKPKEIPKES; SEQ ID NO: 892) and gp120 V3loop (Zwart, et al. (1992) AIDS Res Hum Retroviruses 8:1897-1908) (KSIHIGPGRAYFTTG; SEQ ID NO:1111) at 10µg/ml in PBS or over-night at 4°C with recombinant capsid (Pfizer) at 5µg/ml in PBS. Plates were then washed 3 times with 200 µE of PBS/0.05%-Tween 20 and blocked with 100 µE of blocking buffer (phosphate-buffered saline (PBS)/2.5%-bovine serum albumin (BSA)) at room temperature (RT). The samples were diluted in blocking buffer and incubated 2h at RT in duplicates. Plates were then washed 3 times with 200 µE of PBS/0.05%-Tween 20. The appropriate horse radish peroxidase (HRP)-conjugated secondary antibody (anti-IgG, -IgGl , -IgG2, -IgG3, -IgG4, IgM and IgA) was diluted at 1:1000 in blocking buffer and incubated at RT for 1 hour. Plates were then washed 6 times with 200 µE of PBS/0.05%-Tween 20 and incubated for 10 minutes with 100 µE of TMB (Invitrogen). Addition of 50 µE 2M H2SO4 stopped the reaction. The plates were read at 450nm and 690 nm for the background on a plate reader. Background from 690nm uncoated wells and PBS-BSA as negative controls were subtracted from the mean absorbance of the coated wells.

Western Blot

MCF-7 and T47-D breast cancer cells were lysed in the presence of anti-protease cocktail (Sigma) in n-Dodecyl β-D maltoside (Sigma) diluted at 0.1mg/ml according the manufacture
protocol in dH₂O/0.05M-TRIS HCl/0.15M-NaCl lysis buffer. Prior to loading, the samples were mixed with Laemmli buffer 2x and boiled at 95°C for 5 minutes. Approximately, 25 µg of total proteins were loaded (assayed with BCA Proteins assay kit). Polyvinylidene difluoride (PVDF) membranes were blocked 1h at RT in PBS/0.05%-Tween 20/10%-non-fat dry milk and incubated with mouse monoclonal anti-HERV-K TM (HERM-1811-5) or anti-HERV-K SU (HERM-1821-5) primary antibodies (Austral Biologicals) in PBS/0.05%-Tween 20/5%-non-fat dry milk at 1/1000 or with HA-137 supernatant in PBS/0.05%-Tween 20/10%-non-fat dry milk over-night at 4°C. Membranes were then washed for 3 washes in PBS/0.1%-PBS) and incubated with an HRP-conjugated anti-mouse or anti-human IgG (Abeam) 2 hours at room temperature. After 6 washes, the membranes were incubated with ECL-plus (GE Healthcare) and exposed at different time points on Kodak® Biomax™ MR film.

B-cell immortalization

PBMCs were isolated by standard Ficoll-Hypaque density gradient centrifugation on fresh blood samples and 10⁷ mononuclear cells were incubated in 2.5 ml complete R10 into a 50-ml conical tube in the presence of 2.5 ml of B95-8 Epstein-Barr virus (EBV) suspension obtained from UCSF cell facility 2h in in a 37°C water bath. 5ml of R10 was the added, with cyclosporin A (Sigma) at a final concentration 1µg/ml. The 10-ml of cell suspension was transferred to a 25-cm² tissue culture flask and incubated for 3 weeks in a humidified 37°C C, 5% CO₂ incubator. After 3 weeks, the cells formed macroscopic clumps. By phase-contrast microscopy, many cells appeared large, clear, often hairy, and tended to form tight clumps of varying size. All these features indicated the occurrence of B cell immortalization by EBV. At the step, a first limit dilution could be performed to isolate the best secreting clone. After immortalization, the cells can be maintained in long-term culture. A quantification of the antibodies is made by ELISA each month to follow the production rate.

B-cell SPOT

Adapted from the protocol described in Crotty, et al. (2003) J Immunol 171 :4969-4973. Briefly, ELISpot plates were activated with 70% ethanol and washed 2 times with PBS. Peptides were coated according the ELISA protocol. The plates were then washed 3 times with PBS, blocked 2 hours in RPMI/1%-BSA. Serial dilution of the immortalized B-cells was incubated overnight in a humidified 37°C C, 5% CO₂ incubator. Plates are then washed 4 times in PBS and 4 times in PBS/0.05%-Tween 20 and incubated with an alkaline phosphatase-conjugated anti-human IgG (Jackson ImmunoResearch) diluted in PBS/1 %-fetal calf serum (FCS)/0.05%-Tween 20 at 1:1000 for 2 hours at RT. Plates were then washed 4 times with PBS/0.05%-Tween 20, 4 times in PBS and 3 times with dH₂O. 100 µL of BCIP/NTB were added for 10 minutes and the plates rinsed with dH₂O to stop the reaction. The plates were then left in the dark for drying.
**Immunofluorescence**

MCF-7 and T47D were cultured on L-polylysin (Sigma) treated coverslip (Fischerbrand) on day prior the immunofluorescence (IF). Cells were rinsed twice in PBS and fixed in PBS/4%-PFA (Electron Microscopy Sciences) 30 minutes at RT, washed twice with PBS and blocked 15 minutes in PBS/0.5%-BSA. Cells were incubated with anti-HERV-K TM (HERM-1811-5, Austral Biologicals) at 1:50 dilution, serum at 1:50 dilution or HA-137 supernatant in a humidified dark room at 37°C for 1 hour and then washed 5 times with PBS. Then, the cells were incubated with either an Alexa-647 anti-mouse IgG (Invitrogen) or a DyLight-649 anti-human IgG (Abeam) in a humidified dark room at 37°C for 1 hour and then washed 5 times with PBS. DNA was then stained with 4',6-diamidino-2-phenylindole (DAPI) (1/5000) for 5 minute at RT and the cells are washed 5 times in PBS and 1 time with dH₂O. Coverslips were next mounted with PermaFluor (Thermo Electron Corporation) on microscope slides (Fisherbrand) and dried in the dark.

**RESULTS**

The whole envelope of the human endogenous retrovirus HERV-K was mapped using a set of manufactured 15mer peptides. One hundred seventy four (174) 15mer peptides (overlapping by 11 amino acids) covering the three envelope proteins, signal peptide, surface unit and transmembrane protein, were used to map the humoral response of 4 individual HIV-1 infected patients and 2 healthy donors (HD) in a peptide-based ELISA assay. Two sequences came-up: one on the surface unit protein and one on the transmembrane protein of HERV-K env (Figure 1A). Herve et al. ((2002) Clin. Exp. Immunol. 128:75) have previously shown a humoral response against a sequence from HERV-K-10 presenting 60% sequence identity (GKTCPKEIPKSKNT; SEQ ID NO:602) with the peptide used for the surface unit (SU-56: RPKGKPCPKESKnte, SEQ ID NO:603). Herve showed that about 20% healthy donors have anti-HERV-K10 antibodies in the serum at a 1/50 dilution. Interestingly, a similar result was found in HD with 15% of positivity at a 1/200 titer (Figure 2A).

The sequence corresponding to the peptide TM-137 (MSLEHRFQLOQCDWNTSDFC; SEQ ID NO:604) on the transmembrane protein seems to be an entirely new HERV-K B-cell epitope. The result of the peptide-based ELISA was confirmed with the corresponding recombinant protein and peptide from two other companies (NEP and Genscript). Six patients were selected from a cohort of chronically HIV-1 infected patients (Figure 1B). This assay shows the antibodies that recognize the peptide of the two epitopes can also recognize the corresponding recombinant protein and do not cross-react with each other.

HIV-1 infection modifies the level of anti-HERV-K Env SU and TM.

Humoral responses were screened in a larger cohort of healthy donors (n=40), and chronically HIV-1 infected patients (HIV+) (n=80), in a cross-sectional study (Figure 2A-B). The anti-TM response was more frequent in both HD and HIV+ 65% and 89.5% respectively, compared to 15% and 11.75% for the anti-SU response. We showed also that the percentage of anti-HERV-K
response patients varies dependent upon HIV-1 infection compared to HD, with a decrease in percentage for the anti-SU response, and an increase in anti-TM. This indicates that the titer of anti-SU antibody (SU-Ab) is lower in infected individuals, while the anti-TM antibody (TM-Ab) titer is increased.

The two responses were titrated. Serial dilution of the sera used in the ELISA shows that the HIV+ cohort had a slightly lower SU-Ab titer, with a maximum of 1/400 compared to the HD, but a dramatic increase of TM-Ab titer, up to 1/3200. The HIV+ cohorts show a slight but significant decrease of the anti-SU at the 1/200 titer (p=0.0028) and a clear increase of the TM-Ab level at 1/400 (p<0.0001) (Figure 3A-B). Furthermore, the study of the two responses within each patient shows two distinct responses and suggests a divergence of these two responses consistent with the different evolution of these responses upon HIV-1 infection (Figure 4A). The anti-TM response is increased in viremic non-controllers and is correlated with HIV-1 viremia.

To assess the question if these responses are linked with the HIV-1 viremia, the HIV+ cohort was divided into groups segregated by clinical status. The 80 untreated patients in the cohort are divided into groups composed of 40 elite controllers (EC), without detectable viral load, and 40 viremic non-controllers (VNC) with a high viral load between $10^4$ and $10^6$ copies per ml of blood. VNC did not have a significant difference in the amplitude of the anti-SU response compared to EC (Figure 3C). However, they had a significantly higher response against TM compared to the EC and HD and EC had a higher response compared to the HD (Figure 3D).

These two responses were compared with the viral load and the CD4 count. A strong correlation was found between the anti-TM response and the viral load for the VNC group (p<0.001), and an inverse correlation was found between the anti-TM response and the CD4 count for the 80 HIV+ patients (Figure 4B-D). No correlation was found in the HD cohort or for the anti-SU response. The low level of SU-Ab in all the groups may explain the absence of difference in the amplitude of the anti-SU response between VNC and EC and the absence of a significant correlation in this cross-sectional study with the viral load or the CD4 count. A correlation was found between the anti-TM response and the response against a HIV-1 gp120 peptide used as an internal control for the ELISAs (Figure 4D). Furthermore, even without detectable viral load in the elite controllers, they made antibodies against this epitope. The presence of this humoral response could be explained either by a latent replication (below the detection threshold of the assays) or the presence of a memory B cell response in this group. This suggests that these antibodies may have a functional role in the control of viremia, helping the EC to maintain an undetectable viral replication, or could be used as a biomarker for latent virus.

These results show a distinctive modification of the humoral response against the HERV-K-trans-membrane protein and the surface unit protein during HIV-1 infection.
Mapping of the humoral response against HERV-K gag.

The mapping of the linear epitopes on gag was assessed by a pepscan using a peptide-based ELISA and 16 sera from 8 HIV+ patients, 5 highly exposed-uninfected (HUE) and 3 HD. The average of the responses from the 16 sera shows a 6 potentials immunogenic epitopes in HERV-K gag (Figure 5A). HERV-K gag p24, the HERV-K capsid, seems to have two immunogenic domains (Figure 5B). The humoral response against the epitopes 19, 103 and 137 to induce a higher response in the HIV-1 infected patients whereas the response against the epitopes 85 and 157 seem to be the same between HIV-1 infection and HD, and the one against the epitope 58 seems to be reduced during infection (Figure 5C).

The anti-HERV-K capsid response is increased in elite controllers.

As previously shown, the HERV-K capsid has the most immunogenic domains. The recombinant protein was used to start a first screen on the 80 HIV+ patients and 40 HD used for the anti-HERV-K Env cross sectional study. The comparison of the humoral response against the recombinant capsid between the HIV-1 infected patients and the healthy donors did not show any significant (Figure 6A). Elite controllers had an increase in titer (Figure 6B).

Anti-TM and anti-Capsid have a similar IgG composition but differs concerning IgA and IgM.

The study of the isotypic composition of the anti-TM response in VNC and anti-capsid response in EC shows that these two responses are mainly composed of IgG1 isotype. However, anti-TM IgG2 are also found at a lower level (Figure 7A-B). More interestingly, no difference was found between VNC and EC for the anti-TM IgM, while a higher IgA response against the transmembrane protein was found in VNC, suggesting that the reactivation or the protein modification of HERV-K occurred in the mucosal during gut permeabilization (Figure 7C-D). A comparison of the anti-TM and the anti-capsid HERV-K response in the HIV+ cohort showed an increase in the level of IgA and IgM specific for HERV-K-TM compared to the specific response against HERV-K capsid (Figure 7E-F).

The humoral response against HK-TM is inversely correlated with the T-cell response against gag, while the anti-capsid responses correlate with the T-cell response.

The humoral response against HERV-K TM and HERV-K Capsid was compared with the HERV-K specific T-cell response. Patients who have previously been shown to have a strong HERV-K specific T-cell response against gag (SenGupta et al. (2011) J. Virol. 85:6977-85) belong to the elite controller group. A comparison of their T-cell response with the humoral response against HK shows an inverse correlation with the anti-TM response and a positive trend with the anti-capsid response, reinforcing the hypothesis of a protective effect of a global anti-HK gag immune response (Figure 8A-B).

Induction of anti-HERV-K antibodies after HIV-1 infection.

These results suggest a specific induction of the anti-TM responses and a down-regulation of the anti-SU response by HIV-1 in vivo. To assess this, a longitudinal study of HERV-K specific
antibody responses was performed in a HIV-1 patient before and after seroconversion. A 38 year old (yo) gay white male enrolled as a highly exposed uninfected man in the OPTIONS cohort, on 10 December 2010, and had an undetectable HIV viral load. Twelve days later (22 Dec, 2010), he returned to clinic and was found to have a VL=2,113. The patient reported potential exposure due to unprotected receptive anal intercourse. He reported two episodes suggestive of acute retroviral syndrome, with onset dates of 01 Nov (five symptoms) and 26 December (ten symptoms).

The study of the kinetics of the humoral responses against HK Env (SU and TM) HK capsid and HIV-gpl20 (Figure 9) shows the appearance of anti-gp120 (red) after the second time point while the viremia (”) is already detectable one month. The response against TM137 (green), already present before infection is increased with viremia but decreases between the two last time points. It was also observed that when the anti-SU56 (blue) was low, the response disappeared completely in relation to the anti-TM137. The kinetics of the level of CD4 reinforces the inverse correlation between anti-TM and the CD4 T cell count observed in the cross sectional study. The different kinetics between the two last time points for these three humoral responses allowed exclusion of any cross-reaction between the anti-HERV-K and the anti-HIV-1 humoral response. The decay of the viremia from February 2011 is explained by an antiretroviral therapy (Atripla). These results suggest strongly two opposite effects of HIV-1 on the SU and TM immunogenicity and their antibody responses. Furthermore, they add credence to the correlation between the anti-TM response and HIV-1 viremia.

The study of the anti-IgM response directed against HK SU (blue), TM (green) and Capsid (red) showed no reactivation of the humoral response for capsid, but two distinct peaks for the IgM anti-TM and IgM anti-SU responses. Interestingly, the peak of IgM against TM (plain line) occurs in the same time (day40) as the peak of the corresponding IgG response (dashed line), suggesting a reactivation of a memory response, or a de novo humoral response against TM. Furthermore, the IgM anti-SU peak appeared before the IgG anti-SU pick (day75 and day105) suggesting the absence or a weak memory B-cell response against SU prior the infection and explaining the very low level of SU before and after infection (Figure 8B). The two IgM peaks do not appear at the same time. The IgM anti-SU peak occurred when the patient received ART, reinforcing the hypothesis that HAART inhibits the HIV-1 inhibitory effect on the SU response. Furthermore, the IgM anti-SU peak appeared before the IgG anti-SU peak suggesting the absence or a weak memory B-cell response against SU prior to infection, and explaining the low level of anti-SU before and after infection (Figure 9). These results suggest strongly that HIV-1 affects the immunogenicity of the SU, TM and Capsid differently. The peaks of IgM reinforce the hypothesis of a transcriptional reactivation and protein production, but the different kinetics reinforce a post-transcriptional modification of the two envelope proteins.
HAART inhibits the HIV-1 effect on anti-HK env humoral response

The longitudinal study highlighted the question of what effect highly active anti-retroviral treatment (HAART) had on the anti-HK env antibody response. To assess this, the two humoral responses between HIV-1 infected patients who have been treated (n=80) or not (n=40) were compared in a cross sectional study. This study showed an increased in anti-SU antibodies in the treated group and an inhibition of the anti-TM response, confirming the results observed in the longitudinal study (Figure 10A-B). Furthermore, the study of the global IgG response in these patients showed that the total IgG level was decreased in the treated patients, reinforcing the observation of an inhibition of the SU response in the infected/non-treated group compared to the HAART group. A similar level of IgG was found between EC and VNC. These two groups showed a higher tlgG level than those on HAART or HD. These two last groups did not show any significant difference (Figure 10A). These results reinforce the difference of anti-TM level between EC and VNC. To rule out an artifact, the SU and TM response was compared with the total IgG. No correlation was found between the anti-SU and the total IgG (tlgG).

These data show a specific interaction of HIV-1 with the immunogenicity of the SU and TM, gag and capsid, and their antibody responses.

Sequence identity between the peptides 56 and 137 with the other HERV-K families and viruses

A blast query of the two sequences 56 and 137 shows that these two sequences are highly conserved among the majority of the different HERV-K families, including the most active, HK-1 15 and HK1 13 (Figure 14A). It is interesting that SU-56 showed a weak homology with HIV-TAT (5aa) (Figure 14B). The fact that the anti-SU response was not increased during HIV-1 infection, but inhibited, suggests that the assay is specific for anti-HK SU. TM-137 shows a significant homology with the polyprotein of HCV. As almost 50% of the patients tested in the cross-sectional study are HCV+, the HIV+ cohort was discriminated regarding their HCV status. The two groups, HCV+ and HCV-, showed a very similar pattern of anti-TM response, suggesting there is no cross-reaction between anti-HERV-K TM and anti-HCV antibodies in the assay used (Figure 14C).

Example 2: Characterization of a fully human IgG anti-TM antibody isolated from an infected patient.

MATERIALS AND METHODS

Study populations

Samples of peripheral blood mononuclear cells (PBMCs) were selected from participants in two different San Francisco-based HIV-1-infected cohorts: Options (n=1) and SCOPE (n=120). Samples from HIV-1-negative controls were obtained from the Blood Centers of the Pacific (n=80). The study was approved by the local institutional review boards (University of California San Francisco Committee on Human Research) and individuals gave written informed consent. Studies were performed on cryopreserved PBMCs and sera.
PBMC and sera samples were obtained from the following categories of chronically HIV-1-infected individuals: 40 elite controllers (EC; naive for treatment, undetectable viral load for two years, CD4>350); 40 highly active antiretroviral therapy (HAART: Viremic suppressed with undetectable viral load for at least two years, CD4>350), and 40 untreated virologic non-controllers (naive for treatment, viral load >2000 copies/mL).

ELISA

For the mapping, 15mer polypeptides were first prepared and purified by JPT Peptide Technologies for the whole protein mapping. Peptides that gave a positive signal were then produced by two other companies (New England Peptide and Gene Script) to confirm the results.

For the cross-sectional and longitudinal study, 96 microtiter wells plate (Nunc-Immuno Plate MaxiSorp Surface) were coated for 1 hour at 37°C with peptides (Gene Script) corresponding to TM (HRFQLQCDWNTSDFC; SEQ ID NO:665), SU (RPKGKPCPKIEPKES; SEQ ID NO:892) and gpl20 V3loop (Zwart, et al. (1992). AIDS Res Hum Retroviruses 8:1897-1908) (KSHIGHPGRAFYTTG; SEQ ID NO:1111) at 10μg/μl in PBS or over-night at 4°C with recombinant capsid at 5μg/ml in PBS. Plates were then washed 3 times with 200μl of PBS/0.05%-Tween 20 and blocked with 100μl of blocking buffer (PBS/2.5%-BSA) at room temperature (RT). The samples were diluted in blocking buffer and incubated 2h at RT in duplicates. Plates were then washed 3 times with 200μl of PBS/0.05%-Tween 20. The appropriate HRP-conjugated secondary antibody (anti-IgG, -IgG1, -IgG2, -IgG3, -IgG4, IgM and IgA) was diluted at 1:1000 in blocking buffer and incubated at RT for 1 hour. Plates were then washed 6 times with 200μl of PBS/0.05%-Tween 20 and incubated for 10 minutes with 100μl of TMB (Invitrogen). Addition of 50μl H2S04 2M stopped the reaction. The plates were read at 450nm and 690 nm for the background on a plate reader. Background from 690nm uncoated wells and PBS-BSA as negative controls were subtracted from the mean absorbance of the coated wells.

Western Blot

MCF-7 and T47-D breast cancer cells were lysed in presence of anti-protease cocktail (Sigma) in n-Dodecyl β-D maltoside (Sigma) diluted at 0.1mg/ml according the manufacture protocol in dH2O/0.05M-TRIS HCl/0. 15M-NaCl lysis buffer. Prior to loading, the samples were mixed with Laemmli buffer 2x and boiled at 95°C for 5 minutes. Approximately, 25μg of total proteins were loaded (assayed with BCA Proteins assay kit). PVDF membranes were blocked 1h at RT in PBS/0.05%-Tween 20/10%-non-fat dry milk and incubated with mouse monoclonal anti-HERV-K TM and anti-HERV-K SU primary antibodies, respectively HERM-1 811-5 and HERM-1821-5 (Austral Biologicals) in PBS/0.05%-Tween 20/5%-non-fat dry milk at 1/1000 or with HA-137 supernatant in PBS/0.05%-TWEEN 20/10%-non-fat dry milk over-night at 4°C. Membranes were then washed for 3 washes in PBS/0. 1%-PBS) and incubated with an HRP-conjugated anti-mouse or anti-human IgG (Abeam) 2 hours at room temperature. After 6 washes, the membranes were
incubated with ECL-plus (GE Healthcare) and exposed at different time points on Kodak®
Biomax™ MR film.

B-cell immortalization

Adapted from the protocol described in Tosato, G., and J. I. Cohen. 2007. Generation of
Epstein-Barr Virus (EBV)-immortalized B cell lines. Curr Protoc Immunol Chapter 7:Unit 7.22.
PBMCs were isolated by standard Ficoll-Hypaque density gradient centrifugation on fresh blood
samples and 10^7 mononuclear cells were incubated in 2.5 ml complete R10 into a 50-ml conical tube
in the presence of 2.5 ml of B95-8 EBV suspension obtained from UCSF cell facility 2h in in a 37°
C water bath. 5ml of R10 was then added, with cyclosporin A (Sigma) at a final concentration
1µg/ml. The 10-ml of cell suspension was transferred to a 25-cm² tissue culture flask and incubated
for 3 weeks in a humidified 37° C, 5% CO₂ incubator. After 3 weeks, the cells formed macroscopic
clumps. By phase-contrast microscopy, many cells appeared large, clear, often hairy, and tend to
form tight clumps of varying size. All these features indicated the occurrence of B cell
immortalization by EBV. After immortalization, the cells can be maintained in long-term culture. A
quantification of the antibodies was made by ELISA each month to follow the production rate.

B-cell SPOT

Adapted from the protocol described in Crotty et al. (2003) J Immunol 171:4969-4973.
Briefly, ELISPOT plates were activated with 70% ethanol and washed 2 times with PBS. Peptides
were coated according the ELISA protocol. The plates were then washed 3 times with PBS, blocked
2 hours in RPMI/1%-BSA. Serial dilution of the immortalized B-cells was incubated overnight in a
humidified 37° C, 5% CO₂ incubator. Plates were then washed 4 times in PBS and 4 times in
PBS/0.05%-Tween 20 and incubated with an alkaline phosphatase-conjugated anti-human IgG
(Jackson Immunoresearch) diluted in PBS/1%-FCS/0.05%-Tween 20 at 1:1000 for 2 hours at RT.
Plates were then washed 4 times with PBS/0.05%-Tween 20, 4 times in PBS and 3 times with dH₂O.
100µE of BCIP/NTB were added for 10 minutes and the plates rinsed with dH₂O to stop the
reaction. The plates were then left in the dark for drying.

Immunofluorescence

MCF-7 and T47D were cultured on L-polylysine (Sigma) treated coverslip (Fisher) on the
day prior the IF. Cells were rinsed twice in PBS and fixed in PBS/4%-PFA (Electron Microscopy
Sciences) 30 minutes at RT, washed twice with PBS and blocked 15 minutes in PBS/0.5%-BSA.
Cells were incubated with anti-HERV-K TM (HERM-1811-5, Austral Biologicals) at 1:50 dilution,
serum at 1:50 dilution or HA-137 supernatant in a humidified dark room at 37°C for 1 hour and then
washed 5 times with PBS. Then, the cells were incubated with either an Alexa-647 anti-mouse IgG
(Invitrogen) or a DyLight-649 anti-human IgG (Abeam) in a humidified dark room at 37°C for 1
hour and then washed 5 times with PBS. DNA was then stained with DAPI (1/5000) for 5 minute at
RT and the cells were washed 5 times in PBS and 1 time with dH₂O. Coverslips were next mounted
with PermaFluor (Thermo Electron Corporation) on microscope slides (Fischerbrand) and dried in
the dark.

RESULTS

Peripheral blood mononuclear cells (PBMC) from two HIV-1 infected elite controllers were
immortalized with Epstein-Barr virus (EBV). After 2 months of culture, one clone (HA-137) was
isolated using serial dilution and peptide-based ELISA. The mapping of the anti-TM humoral
response showed that the higher signal obtained with ELISA was with the consecutive peptides 136
and 137 and a decrease of the signal with the two peptides 135 and 138 (Figure 13). The selection of
the B-cell clone was done with the peptide 137 (HRFQLQCDWNTSDFC; SEQ ID NO:665). It was
confirmed that these cells secrete HA-137 by ELISA, western blot, B-cell spot and
immunofluorescence (Figure 15A-C). The breast cancer MCF-7 and T47-D cell lines were used as
positive controls for western blot. Both express SU, but only T47-D expresses TM. The exact linear
epitope was mapped using a set of 13 15mer peptides corresponding to the original TM-137
sequence on which one amino acid has been mutated (Figure 17B). The results show that HA-137
recognizes a sequence centered on an asparagine (N). The serum from patients with a strong
response against TM by peptide-based ELISA, SC-94 (VNC) and HD-SU (healthy donor) both
negative for SU-Ab, were also tested. Interestingly, they showed the same specificity, suggesting the
absence of variation or mutation of the response. Five sera corresponding to the 5 time points from
the sero-converted patients were also tested in a longitudinal study with the same results (Figure
17C). The stability was confirmed. The asparagine is known to be glycosylated; the glycosylation
of the gp36 leads it to reach the membrane and induce an immune response (Hanke et al. (2009) J.
Virol. 83:12790). Furthermore, the TM-137 epitope comprises the cys-cys loop (Kammerer et al

Example 3: Treatment of HIV-infected individual with an anti-HERV-K antibody

An anti-HA-137 antibody is formulated with saline. The anti-HA-137 antibody is
administered to an HIV-infected individual at a loading dose of from about 3 mg/kg to about 6
mg/kg (e.g., from about 3 mg/kg to about 4 mg/kg, from about 4 mg/kg to about 5 mg/kg, or from
about 5 mg/kg to about 6 mg/kg); and is administered once per week at a lower dose (e.g., about 1
mg/kg to about 3 mg/kg). The anti-HA-137 antibody is administered subcutaneously,
intramuscularly, or intravenously. Viral load is monitored weekly.

While the present invention has been described with reference to the specific embodiments
thereof, it should be understood by those skilled in the art that various changes may be made and
equivalents may be substituted without departing from the true spirit and scope of the invention. In
addition, many modifications may be made to adapt a particular situation, material, composition of
matter, process, process step or steps, to the objective, spirit and scope of the present invention. All
such modifications are intended to be within the scope of the claims appended hereto.
 CLAIMS

What is claimed is:

1. An antibody that specifically binds an epitope in a HERV-K polypeptide, wherein
the antibody competes for binding to a HERV-K polypeptide with an antibody that comprises:
   (i) a V\textsubscript{L}CDR1 comprising an amino acid sequence of SEQ ID NO:573;
   (ii) a V\textsubscript{L}CDR2 comprising an amino acid sequence of SEQ ID NO:574;
   (iii) a V\textsubscript{L}CDR3 comprising an amino acid sequence of SEQ ID NO:575;
   (iv) a V\textsubscript{H}CDR1 comprising an amino acid sequence of SEQ ID NO:576;
   (v) a V\textsubscript{H}CDR2 comprising an amino acid sequence of SEQ ID NO:577; and
   (vi) a V\textsubscript{H}CDR3 comprising an amino acid sequence of SEQ ID NO:578.

2. The antibody of claim 1, wherein the light chain variable region and the heavy chain variable region are present in separate polypeptides.

3. The antibody of claim 1, wherein the light chain variable region and the heavy chain variable region are present in a single polypeptide.

4. The antibody of claim 1, wherein the antibody binds the epitope with an affinity of from about 10\textsuperscript{7} M\textsuperscript{-1} to about 10\textsuperscript{12} M\textsuperscript{-1}.

5. The antibody of claim 1, wherein the heavy chain region is of the isotype IgGl, IgG2, IgG3, or IgG4.

6. The antibody of claim 1, wherein the antibody comprises a detectable label.

7. The antibody of claim 1, wherein the antibody is a Fv, scFv, Fab, F(ab')2, or Fab'.

8. The antibody of claim 1, wherein the antibody comprises a covalently linked non-peptide synthetic polymer.

9. The antibody of claim 8, wherein the synthetic polymer is poly(ethylene glycol) polymer.

10. The antibody of claim 1, wherein the antibody comprises a covalently linked lipid or fatty acid moiety.
11. The antibody of claim 1, wherein the antibody comprises a covalently linked polysaccharide or carbohydrate moiety.

12. The antibody of claim 1, wherein the antibody comprises a contrast agent.

13. The antibody of claim 1, wherein the antibody comprises an affinity domain.

14. The antibody of claim 1, wherein the antibody is immobilized on a solid support.

15. The antibody of claim 1, wherein the antibody is a single chain Fv (scFv) antibody.

16. The antibody of claim 17, wherein the scFv is multimerized.

17. The antibody of claim 1, wherein the antibody comprises a polyamine modification.

18. The antibody of claim 1, wherein the antibody is a humanized antibody.

19. A recombinant expression vector comprising a nucleotide sequence encoding the antibody of claim 1, wherein the nucleotide sequence is operably linked to a transcriptional control element that is active in a eukaryotic cell.

20. A genetically modified host cell comprising the recombinant vector of claim 19.

21. A pharmaceutical composition comprising:
   a) the antibody of claim 1; and
   b) a pharmaceutically acceptable carrier.

22. The pharmaceutical composition of claim 21, wherein the antibody is encapsulated in a liposome.

23. A method of detecting a HERV-K polypeptide in a biological sample obtained from an individual, the method comprising:
   a) contacting the biological sample with the antibody of claim 1; and
   b) detecting binding, if any, of the antibody to an epitope present in the sample.

24. The method of claim 23, wherein the level of the HERV-K polypeptide in the biological sample provides an indication of the stage of an immunodeficiency virus infection.
25. The method of claim 23, wherein the level of the HERV-K polypeptide in the biological sample provides an indication of the individual's response to treatment for an immunodeficiency virus infection.

26. An immunogenic composition comprising:
   a) an immunogenic peptide, wherein the immunogenic peptide is a multimer of the formula \((X_1-Y-o_{-4o-X_2-Y-o_{-4o}})_n\), wherein \(X_1\) and \(X_2\) are HERV-K polypeptides, \(Y\) is a linker, and \(n\) is an integer from 1 to about 10,
      wherein the HERV-K polypeptides each comprise an amino acid sequence having at least about 95% amino acid sequence identity to a contiguous stretch of from about 6 amino acids to about 60 amino acids of a HERV-K envelope transmembrane protein, a HERV-K envelope surface unit protein, or a HERV-K capsid protein; and
   b) a pharmaceutically acceptable carrier.

27. The immunogenic composition of claim 26, wherein the immunogenic peptide has a length of from about 20 amino acids to about 150 amino acids.

28. The immunogenic composition of claim 26, wherein \(X_1\) and \(X_2\) each independently comprises an amino acid sequence having at least about 95% amino acid sequence identity to any one of SEQ ID NOs:5-557 and 603-1 110.

29. The immunogenic composition of claim 26, wherein \(X_1\) and \(X_2\) each independently comprises an amino acid sequence set forth in any one of SEQ ID NOs: 5-557 and 603-1 110.

30. The immunogenic composition of claim 26, further comprising an adjuvant.

31. The immunogenic composition of claim 26, wherein the composition, when administered to an individual, is capable of inducing a B lymphocyte response to a cell infected with an immunodeficiency virus.

32. The immunogenic composition of claim 26, wherein the immunogenic polypeptide comprises at least one non-naturally occurring amino acid.

33. An immunogenic composition comprising:
   a) at least two different immunogenic HERV-K polypeptides, wherein each of the at least two different HERV-K polypeptides comprises an amino acid sequence having at least about 95% amino acid sequence identity to any one of SEQ ID NOs:5-557 and 603-1 110; and
b) a pharmaceutically acceptable excipient.

34. The immunogenic composition of claim 33, wherein the composition, when administered to an individual, is capable of inducing a B lymphocyte response to a cell infected with an immunodeficiency virus.

35. The immunogenic composition of claim 33, further comprising an adjuvant.

36. The immunogenic composition of claim 33, wherein at least one of the immunogenic HERV-K polypeptides comprises at least one non-naturally occurring amino acid.
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**FIG. 2**

A. Anti-SU response
B. Anti-TM response
FIG. 12
FIG. 13
### Conservation with all HERV-K family

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### TM-epitope sequence

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**FIG. 14A**
Conservation with HIV HCV
SU -56: RPKGKPCPKEI>PKESK<NT
TAT: QPRGDPTGPKESKKVERETE
TM136: GDRLMSLEHRFQLQCDWNTSDFC
POL: GIDKAQDHEKHYHSNWRAMASDFN
TM136: GDRLMSLEHRFQLQCDWNTSDFC
PolyProtein: LEHRFQAACNW

FIG. 14B

No correlation between anti-TM response and HCV status

FIG. 14C
HA-137 VL sequences

**VL CDRs**
CDR1: QGISSW (SEQ ID NO:573)
CDR2: AAS (SEQ ID NO:574)
CDR3: QQANSFPLT (SEQ ID NO:575)

**VL nucleotide sequence**
AGATGTGAGCTCCAGATGACCCAGTCTCCATCTTCTTGGTCTCATTGAGACAGACAGTCAC
CATCACTTTGTCGGGCAGTCAAGGTTGATTAGCAGCTGGTITAGGCTTATCAGCAGAAACCAGGGA
AAGCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAAGAGGGGTCCCATCAGGTTACGC
GGCACTGGATCTGGAGAGATGTTCACTCTCATACTACAGACGCTGCAGCTGAGATTGTTGCAAC
TTACTATGTCAACAAGCATAACAGTTTCCCTCCTCACTTTGCGGGAGGGACCAAGGTGAGATCA
AAGCAACTGTGCTGCACCATCTGCTCTTCTCTCTCCTCCGCCATTCTGATGAGCAGCTGTTGGAAAATCGGA
ACTGCTCTGTTTGTTGTGCCTGCTGATATAACCTCTATCCAGAGAGGGCAGAAGATAGCTATTGAAAGGGT
GAGATAACGCCCCTCTAACTCGGTAACCTCCAGAGAGTGCTCAAGCAGCAAGAINCAAGGACAGCA
CCTACACGCTCAAGCAGGCAAAGCTAGCAGAAACACAAAACCTCTACGCC
CTGCGAAGTCAACCATTACGGGCTGAGTTCGCAGGCCGTCCACAAAGACCTGCAACAGGGGAGAGTGTTAG
G (SEQ ID NO:581)

**VL amino acid sequence**
RCGLTMTPQSPSSVSAVGDRVTITCRASQGISSWLAWYQQPKGAPKLIYAASSLQRGSVPSTFKSGS
GSGLDFTTLTISSLQEDFATYYCQANSFPLTFGGKTVKIERTVAAPSVFIFPPSDEQLKSTASVV
CLNNFYPREAKVQKWVDAQLQGSNQSVTEQDSKDSTYSLSSSLTSKADYEHKLYACEVTH
QGLSSPVKSFNRGEC (SEQ ID NO:579)

**FIG. 18A**
HA-137 VH sequences

**VH CDRs**

CDR1: GFTFGDY (SEQ ID NO:576)

CDR2: ISSNGNKR (SEQ ID NO:577)

CDR3: ASSARTGYKGDYLDH (SEQ ID NO:578)

**VH nucleotide sequence**

GT CCTGCTCGAGGGTGAAGTTCAGGCAGGGAGGCTTGGTCAACCTGGGAGGTCCGAGACTCTGCTTTTCAGAACATGA
ACTCT CCTGTAAGCCTCGTTCTGCTATTACTACATGAGTTGAGTCCGAGGCCGACTGCTATAT
AAGGGTGGGACTATTGGACACTGGGAGGGCCAGGGAACCCAGGCAGGTCTCTCTAGCTCCAC
CAAGGGCCATCGGGTCCCTCGGAGGCAGCTACCTATTCGGGCAACAGGCGCTGCGGCTGCTTGGTGACTCAGGCGCCTGA
CCAGGCGGAGCGACACCTCCGGGTGCTCTACGTCCTCAGACTCTCCCTCACAGCGGCTGCTGG

**VH aa sequence**

VLLEVQLQESGGGLVKPPGSLRSLSCVASEGFTFGDDYMSWIRQAPKGKLEYISYISSNGNRRYYSV
RGRFTISRDNARNLSNFLQMSLGAEDTAVYCASSARTGYYGWDYLDHWCGQGTQVSVSSASTK
GPSVFPLAPCSRSTYSTGGTAALGCLVKDFEPFVTVSWNSGALTSGVHTFPALQSSRLESLSVTV
PSSSL (SEQ ID NO:580)

**FIG. 18B**
INTERNATIONAL SEARCH REPORT

International application No. PCT/US 12/60772

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) ... W. Young
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No.

Form PCT/ISA/2 1 0 (second sheet) (July 2009)

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): A61K 39/42, A61K 39/12, C07K 16/08 (2012.01)

USPC - 424/1 59.1, 424/204.1 , 530/388.35

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>A</td>
<td>US 2008/00197977 A1 (WANG-JOHANNING) 24 January 2008 (24.01.2008); para [0148], claim 10</td>
<td>1-25</td>
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<tr>
<td>A</td>
<td>US 2007/0280945 A1 (STEVENS et al.) 06 December 2007 (06.12.2007); para [0023], [0024], SEQ ID NO: 29 and 159</td>
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<tr>
<td>A</td>
<td>US 2003/0207349 A1 (BAKER et al.) 06 November 2003 (06.11.2003); SEQ ID NO: 550</td>
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* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

Further documents are listed in the continuation of Box C.

Date of the actual completion of the international search 07 February 2013 (07.02.2013)

Date of mailing of the international search report 26 FEB 2013

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Authorized officer: Lee W. Young
PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

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## INTERNATIONAL SEARCH REPORT

### Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. □ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. □ Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. □ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

This International Searching Authority found multiple inventions in this international application, as follows: This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

**Group I** Claims 1-25, drawn to an antibody that binds to an epitope in a HERV-K polypeptide

**Group II** Claims 26-36, drawn to an immunogenic composition comprising two HERV-K polypeptides, wherein the HERV-K polypeptides have identity to any one of SEQ ID NOs:5-557 and 603-1110. If Applicant elects to have this group searched, Applicant must specify the specific HERV-K polypeptide sequence to be searched. Each unique HERV-K polypeptide sequence constitutes an inventive concept.

—please see continuaton on extra sheet—

1. □ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. □ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. □ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-25

### Remark on Protest

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

Form PCT/ISA/2 10 (continuation of first sheet (2)) (July 2009)
INTERNATIONAL SEARCH REPORT

Continuation of Box No III Observations where unity of invention is lacking

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

The shared technical feature of the inventions listed as Groups I and II is HERV-K polypeptide. This shared technical feature fails to provide a contribution over the prior art, as evidenced by US 2008/0019979 A1 to Wang-Johanning. Wang-Johanning discloses an antibody that specifically binds an epitope in a HERV-K polypeptide (para [0014]) - The present disclosure also provides HERV-K env protein-specific antibodies; and related methods of using these materials to detect the presence of HERV-K env proteins or nucleic acids.”). In the absence of a contribution over the prior art, the shared technical feature is not a shared special technical feature.

The shared technical feature of the inventions listed as Group II is an immunogenic composition comprising: a) at least two different immunogenic HERV-K polypeptides, and b) a pharmaceutically acceptable excipient. This shared technical feature fails to provide a contribution over Wang-Johanning. Wang-Johanning teaches an immunogenic composition (para [0189]-[0190] - “vaccine”); para [0195]-[0196] - “HERV-K env protein may serve as a tumor-associated antigen which can be used to elicit T cell and B cell responses”); comprising: a) at least two different immunogenic HERV-K polypeptides (para [0190] - “one or more of the polypeptides”); and b) a pharmaceutically acceptable excipient (para [0187]). In the absence of a contribution over the prior art, the shared technical feature is not a shared special technical feature.

A further special technical feature of each of the inventions listed as Group II is the specific HERV-K polypeptides recited therein. HERV-K polypeptides comprising an amino acid sequence having at least about 95% amino acid sequence identity to anyone of SEQ ID NOs:557 and 603-1 110 are known in the art, as evidenced by US 2003/0194704 A1 to Penn et al., which teaches a sequence with 100% amino acid sequence identity to SEQ ID NO:5 (claim 45; SEQ ID NO: 33720 amino acids 12 to 21 exhibit 100% identity to SEQ ID NO:5). Furthermore, significant structural similarities cannot readily be ascertained among the HERV-K polypeptides. Without significant structural similarities, the polypeptides do not have a shared special technical feature. In the absence of a shared special technical feature, the inventions lack unity with one another.

Further, the special technical feature of the inventions listed as Group I is an antibody. This special technical feature is not shared by the inventions of Group II. The special technical feature of the inventions listed as Group II is an immunogenic composition comprising the HERV-K polypeptide. This special technical feature is not shared by the inventions of Group I.

Therefore, the inventions of Groups I and II lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.