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(54) Title: HIV-1 IMMUNOGENS AND BROADLY NEUTRALIZING HIV-1 ANTIBODIES

(57) Abstract: The present invention relates, in general, to HIV-1 and, in particular, to broadly neutralizing anti-HIV-1 antibodies (and fragments thereof) and to methods of using same to inhibit HIV-1 infection in a subject (e.g., a human). The invention further relates to compositions comprising such antibodies (or fragments). The invention also relates to methods of using the antibodies (and fragments thereof) as templates for vaccine design. The invention further relates to HIV-1 immunogens and to methods of using such immunogens to induce the production of broadly neutralizing HIV-1 antibodies in a subject (e.g., a human).



HIV-1 IMMUNOGENS AND BROADLY NEUTRALIZING HIV-1 ANTIBODIES

[1] This application claims the benefit of U.S. Application Ser No. 61/883,561 filed September 27, 2013 the entire content of which application is herein incorporated by reference.

[2] This invention was made with government support under Grants AI1067854 and AI100645 awarded by the National Institutes of Health. The government has certain rights in the invention.

TECHNICAL FIELD

[3] The present invention relates, in general, to HIV-1 and, in particular, to broadly neutralizing anti-HIV-1 antibodies (and fragments thereof) and to methods of using same to inhibit HIV-1 infection in a subject (e.g., a human). The invention further relates to compositions comprising such antibodies (or fragments). The invention also relates to methods of using the antibodies (and fragments thereof) as templates for vaccine design. The invention further relates to HIV-1 immunogens and to methods of using such immunogens to induce the production of broadly neutralizing HIV-1 antibodies in a subject (e.g., a human).

BACKGROUND

[4] Induction of HIV-1 envelope (Env) broadly neutralizing antibodies (BnAbs) is a key goal of HIV-1 vaccine development. BnAbs can target conserved regions that include conformational glycans, the gp41 membrane proximal region, the V1/V2 region, glycans-associated C3/V3 on gp120, and the CD4 binding site (CD4bs) (Walker et al, Science 326:285-289 (2009), Walker et al, Nature 477:466-470 (2011), Burton et al, Science 337:183-186 (2012), Kwong and Mascola, Immunity 37:412-425 (2012), Wu et al, Science 329:856-861 (2010), Wu et al, Science 333:1593-1602 (2011), Zhou et al, Science 329:811-817 (2010), Sattentau and McMichael, F1000 Biol. Rep. 2:60 (2010), Stamatatos, Curr. Opin. Immunol. 24:316-323 (2012)). Most mature BnAbs have one or more unusual features (long heavy chain third complementarity determining regions [HCDR3s], polyreactivity for non-HIV-1 antigens, and high levels of somatic mutation) suggesting substantial barriers to their elicitation (Kwong and Mascola, Immunity 37:412-425 (2012), Haynes et al, Science 308:1906-1908 (2005), Haynes et al, Nat. Biotechnol. 30:423-433 (2012), Mouquet and Nussenzweig, Cell Mol. Life Sci. 69:1435-1445

(2012), Scheid et al, *Nature* 458:636-640 (2009)). In particular, CD4bs BnAbs have extremely high levels of somatic mutation suggesting complex or prolonged maturation pathways (Kwong and Mascola, *Immunity* 37:412-425 (2012), Wu et al, *Science* 329:856-861 (2010), Wu et al, *Science* 333:1593-1602 (2011), Zhou et al, *Science* 329:811-817 (2010)). Moreover, it has been difficult to find Envs that bind with high affinity to BnAb germline or unmutated common ancestors (UCAs), a trait that would be desirable for candidate immunogens for induction of BnAbs (Zhou et al, *Science* 329:811-817 (2010), Chen et al, *AIDS Res. Human Retrovirol.* 23:11 (2008), Dimitroff, *MAbs* 2:347-356 (2010), Ma et al, *PLoS Pathog.* 7:e1002200 (2011), Pancera et al, *J. Virol.* 84:8098-8110 (2010), Xiao et al, *Biochem. Biophys. Res. Commun.* 390:404-409 (2009)). Whereas it has been found that Envs bind to UCAs of BnAbs targeting gp41 membrane proximal region (Ma et al, *PLoS Pathog.* 7:e1002200 (2011), Alam et al, *J. Virol.* 85:11725-11731 (2011)), and to UCAs of some V1/V2 BnAb (Bonsignori et al, *J. Virol.* 85:9998-10009 (2011)), to date, heterologous Envs have not been identified that bind the UCAs of CD4bs BnAb lineages (Zhou et al, *Science* 329:811-817 (2010), Xiao et al, *Biochem. Biophys. Res. Commun.* 390:404-409 (2009), Mouquet et al, *Nature* 467:591-595 (2010), Scheid et al, *Science* 333:1633-1637 (2011), Hoot et al, *PLoS Pathog.* 9:e1003106 (2013)), although Envs that bind CD4bs BnAb UCAs should exist (Hoot et al, *PLoS Pathog.* 9:e1003106 (2013)).

[5] Eighty percent of heterosexual HIV-1 infections are established by one transmitted/founder (T/F) virus (Keele et al, *Proc. Natl. Acad. Sci. USA* 105:7552-7557 (2008)). The initial neutralizing antibody response to this virus arises approximately 3 months after transmission and is strain-specific (Richman et al, *Proc. Natl. Acad. Sci. USA* 100:4144-4149 (2003), Corti et al, *PLoS One* 5:e8805 (2010)). This antibody response to the T/F virus drives viral escape, such that virus mutants become resistant to neutralization by autologous plasma (Richman et al, *Proc. Natl. Acad. Sci. USA* 100:4144-4149 (2003), Corti et al, *PLoS One* 5:e8805 (2010)). This antibody-virus race leads to poor or restricted specificities of neutralizing antibodies in ~80% of patients; however in ~20% of patients, evolved variants of the T/F virus induce antibodies with considerable neutralization breadth, e.g. BnAbs (Walker et al, *Nature* 477:466-470 (2011), Bonsignori et al, *J. Virol.* 85:9998-10009 (2011), Corti et al, *PLoS One* 5:e8805 (2010), Gray et al, *J. Virol.* 85:4828-4840 (2011), Klein et al, *J. Exp. Med.* 209:1469-1479 (2012), Lynch et al, *J. Virol.* 86:7588-7595 (2012), Moore et al, *Curr. Opin. HIV AIDS*

4:358-363 (2009), Moore et al, J. Virol. 85:3128-3141 (2011), Tomaras et al, J. Virol. 85:11502-11519 (2011)).

[6] There are a number of potential molecular routes by which antibodies to HIV-1 may evolve and, indeed, types of antibodies with different neutralizing specificities may follow different routes (Wu et al, Science 333:1593-1602 (2011), Haynes et al, Nat. Biotechnol. 30:423-433 (2012), Dimitroff, MAbs 2:347-356 (2010), Liao et al, J. Exp. Med. 208:2237-2249 (2011)). Because the initial autologous neutralizing antibody response is specific for the T/F virus (Moore et al, Curr. Opin. HIV AIDS 4:358-363 (2009)), some T/F Envs might be predisposed to binding the germline or unmutated common ancestor (UCA) of the observed BnAb in those rare patients that make BnAbs. Thus, although neutralizing breadth generally is not observed until chronic infection, a precise understanding of the interplay between virus evolution and maturing BnAb lineages in early infection may provide insight into events that ultimately lead to BnAb development. BnAbs studied to date have only been isolated from individuals who were sampled during chronic infection (Walker et al, Science 326:285-289 (2009), Burton et al, Science 337:183-186 (2012), Kwong and Mascola, Immunity 37:412-425 (2012), Wu et al, Science 329:856-861 (2010), Wu et al, Science 333:1593-1602 (2011), Zhou et al, Science 329:811-817 (2010), Bonsignori et al, J. Virol. 85:9998-10009 (2011), Corti et al, PLoS One 5:e8805 (2010), Klein et al, J. Exp. Med. 209:1469-1479 (2012)). Thus, the evolutionary trajectories of virus and antibody from the time of virus transmission through the development of broad neutralization remain unknown.

[7] Vaccine strategies have been proposed that begin by targeting unmutated common ancestors (UCAs), the putative naïve B cell receptors of BnAbs, with relevant Env immunogens to trigger antibody lineages with potential ultimately to develop breadth (Wu et al, Science 333:1593-1602 (2011), Haynes et al, Nat. Biotechnol. 30:423-433 (2012), Scheid et al, Nature 458:636-640 (2009), Chen et al, AIDS Res. Human Retrovirol. 23:11 (2008), Dimitroff, MAbs 2:347-356 (2010), Ma et al, PLoS Pathog. 7:e1002200 (2011), Xiao et al, Biochem. Biophys. Res. Commun. 390:404-409 (2009), Alam et al, J. Virol. 85:11725-11731 (2011), Mouquet et al, Nature 467:591-595 (2010)). This would be followed by vaccination with Envs specifically selected to stimulate somatic mutation pathways that give rise to BnAbs. Both aspects of this strategy have proved challenging due to lack of knowledge of specific Envs capable of interacting with UCAs and early intermediate (I) antibodies of BnAbs.

[8] The present invention results, at least in part, from studies that resulted in the isolation of antibody DH175 from an African patient, CH0694, who was followed from early acute HIV-1 infection phase to over 4 years post-transmission. During this period CH0694 developed plasma HIV-1 neutralization breadth. Isolation of this antibody makes it possible to study virus/antibody co-evolution.

SUMMARY OF THE INVENTION

[9] The invention is directed towards selection of envelopes and recombinant bnAbs from individual CH0694.

[10] In general, the present invention relates to HIV-1. More specifically, the invention relates to broadly neutralizing anti-HIV-1 antibodies (and fragments thereof) and to methods of using same to inhibit HIV-1 infection in a subject (e.g., a human). The invention further relates to compositions comprising such antibodies (or fragments). The invention also relates to methods of using the antibodies (and fragments thereof) as templates for vaccine design. The invention further relates to HIV-1 immunogens and to methods of using such immunogens to induce the production of broadly neutralizing HIV-1 antibodies in a subject (e.g., a human).

[11] In certain aspects the invention provides HIV-1 envelope protein as set forth in Figure 26, or immunogenic subunit thereof. In certain aspects the envelope proteins are recombinant.

[12] In certain aspects the invention provides immunogenic compositions comprising an HIV-1 envelope protein as set forth in Figure 26, or immunogenic subunit thereof, and a carrier. In certain embodiments, the compositions comprise a nucleic acid encoding the HIV-1 envelope protein of Figure 26, or any of the variants described therein. In non-limiting embodiments, the compositions comprise the gp120 subunit or gp140 subunit of an HIV-1 envelope protein from a sequence set forth in Figure 26. In certain embodiments the gp120 protein is gp120deltaN design as described herein. In certain embodiments, the compositions further comprise an adjuvant.

[13] In certain aspects the invention provides a construct comprising a nucleotide sequence encoding an HIV-1 envelope protein, as set forth in Figure 26 or immunogenic subunit thereof, wherein said nucleotide sequence is present in a vector. In certain embodiments the vector is any suitable vector, for example but not limited to a viral vector or mycobacterial vector. In certain

embodiments, the vector is an adenoviral vector or a pox virus vector. The invention also provide immunogenic compositions comprising the construct described herein and a carrier.

[14] In certain aspects the invention provides methods of inducing an immune response comprising administering to a mammal in need thereof the composition of claim 1 or 5 in an amount sufficient to effect the induction. In certain embodiments of the methods the composition is administered by injection, intrarectally or vaginally. In certain embodiments, the subject is a human.

[15] In certain embodiments of the methods and compositions of the invention, the composition comprises CH694TF HIV-1 envelope, which can be administered as a prime.

[16] In certain embodiments of the methods and compositions of the invention the composition comprises a selection of CH694 envelopes, which can be administered as a boost. The envelopes described herein can be grouped in various selections such that the antigenic diversity of the CH0694 envelopes is represented in the immunization methods—swarm immunization. Non-limiting embodiments of various swarms selected from a group of one hundred and one CH0694 envelopes are described herein. The invention contemplates other combinations of CH0694 envelopes as described herein such that the antigenic diversity of the HIV-1 envelope responsible for the induction of the DH175 lineage is represented.

[17] In certain aspects the invention provides an isolated antibody having the binding specificity DH175, or antigen binding subunit thereof. The antibody is recombinantly produced. In certain embodiments, the antibody comprises the any one of VH and VL CDRs as set forth in Figure 27. In certain embodiments, the antibody comprises all of the VH and VL CDRs as set forth in Figure 27. In certain embodiments, the antibody comprises a heavy or light chain amino acid sequence set forth in Figure 27. In certain embodiments, the antibody is DH175.

[18] In certain aspects the invention provides methods of preventing or treating HIV-1 comprising administering to a subject in need thereof the antibody of the invention, or a subunit thereof in an amount sufficient to effect said prevention or treatment.

[19] Objects and advantages of the present invention will be clear from the description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

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

[21] Figure 1. Profile of HIV-1 infection in CHAVI 703010694 (CH0694) over four years of clinical follow-up, as viral load (red), CD4+ T cell count (blue), heterologous neutralization potency (black lines), and breadth (pink). Vertical lines depict samples from which half-genome sequencing was available. Neutralization results are from 16 viruses (6535.3, QH0692.42, SC422661.8, PVO.4, AC10.0.29, RHPA4259.7, Du156.12, Du172.17, Du422.1, ZM197M.PB7, ZM214M.PL15, CAP45.2.00.G3, Q23.17, Q842.d12, Q259.d2.17, Q769.d22).

[22] Figure 2. Within-host evolution from a single transmitted/founder virus. The 3-prime half-genome nucleotide sequences as both tree (right) and pixel plot (left). Sequence variation is rendered as a phylogeny paired with a pixel plot. In the pixel plot, only sites that differ from the T/F are shown in blue for mutations or grey for indels. Sequences (rows) follow the ordering of leaves in the tree. Numbering is provided for HXB2 nucleotide sites (bottom) and the CH0694 alignment (top). Grey boxes highlight Env landmarks (V1-V5). The tree was obtained by PhyML 3 with GTR+ Γ 4+I. Leaf colors depict when each sequence was sampled. A genomic map is aligned below the pixel plot.

[23] Figure 3. Dynamics of variant frequencies in 53 early polymorphic Env sites. Sites are ordered by when T/F form (dashed lines) becomes less common than a variant form. In the legend below each plot, variants are ordered by their total frequency over time. All plots are scaled as in the top-left panel. The alignment position is followed by a slash, and the TF amino acids, HXB2 position, most selected amino acid. Figure 8 continues with 53 additional sites, that were added as they might be of interest and show sites that have an amino acid that at at least one time point has a mutation that becomes more frequent than the TF. Sites in the V3-glycan epitope, the V2-glycan epitope, and CD4 contacts, are noted.

[24] Figure 4. Sequence logos depict selected variant frequencies with letter heights. Outlined letters depict the transmitted/founder sequence and filled letters depict mutations. For clarity, only weeks 5-101 are depicted; all 26 samples are shown in Figure 7. Sites are ordered by the same criterion as in Figure 2 and Table 1. Colors indicate amino-acid charge (blue for negative, red for positive). Indels (gaps) appear as blank white space.

[25] Figure 5. Variant frequencies hierarchically clustered by the “complete” hierarchical method, with the addition of indel variants. For clarity, only variants with over 50% frequency are depicted, and linked V2 insertion sites 167/-140S, 168/-140T, 169/-140S, 170/-140I are excluded. Neutralization data were normalized and scaled from 0 (black, no neutralization) to 1 (white, highest neutralization). Pink rectangles indicate missing data.

[26] Figure 6. Diversity of 100 selected isolates (red names) represents within-host diversity. Paired Env tree (right) and pixel plots of Env (left) and selected sites (center). Thin horizontal lines indicate the selected isolates. In the pixel plots, red sites show non-synonymous substitutions in the Env translation, blue sites nucleotide changes, and grey sites indels. In the center panel, sites indicated by red lettering indicate the 12 sites added to the initial 48, thought to contact V2 or V3 epitopes, or the CD4 binding site. Grey are indels, and whole codons are depicted in the columns – the thicker orange stripe indicates that the amino acid has changed, and the thin red/purple indicates the base(s) that change within the codon. For clarity, only 720 Env sequences are depicted, which do not contain stops or incomplete codons, and which do not match the T/F Env. This tree is a pruned version of the tree obtained from PhyML with all Env sequences and HIVw+Γ4+I.

[27] Figure 7. Sequence logos depict variant frequencies with letter heights. Here sites are ordered by when the T/F form becomes less common than a new variant. Colors indicate amino-acid charge (blue for negative, red for positive). Indels (gaps) appear as grey boxes.

[28] Figure 8. Dynamics of variant frequencies in 53 polymorphic Env sites that emerge later. This figure continues from the 53 earlier polymorphic sites in Figure 3. Sites are ordered by when T/F form (dashed lines) becomes less common than a variant form. In the legend below each plot, variants are ordered by their total frequency over time. All plots are scaled as in the top-left panel.

[29] Figure 9. Longitudinal CH0694 Neutralization Potency and Breadth

[30] Figure 10 shows plasma neutralization fingerprinting of CH694 individual. Plasma antibody mapping studies identified: N332-sensitive plasma antibodies ; N160-sensitive plasma antibodies; CD4bs RSC3-binding plasma antibodies. Gp120 Env-deplete-able plasma neutralizing activity (consensus C Env).

[31] Figure 11 shows that 22,800 IgG+ memory B cells were isolated from peripheral blood (week 192 post-transmission) and cultured at limiting dilution. Cell culture supernatants were

screened for consensus C neutralization; differential binding of 1086C and 63521 V1/V2 proteins vs their N156Q/N160Q mutants, and RSC3 protein binding

[32] Figure 12 shows a summary of some of the characteristics of DH175: Primary Culture supernatant neutralized 82% of Consensus C pseudovirus infectivity in Tzm-bl assay; Frequency of ConC neutralizing ab: $1/22800 = 0.004\%$.

[33] Figure 13A and 13B show DH175 ability to neutralize CH0694 T/F virus and capture infectious virions.

[34] Figure 14A and 14B show DH175 Binding to CH0694 T/F gp120 and gp140 Env

[35] Figure 15 shows DH175 Heterologous Neutralization Profile. DH175 is a broadly neutralizing antibody that neutralizes certain tier-2 viruses from multiple clades.

[36] Figure 16 shows DH175 Neutralization Fingerprinting.

[37] Figure 17 shows Effect of N332A Mutation on DH175 Neutralizing Activity-- The effect of N332A on DH175 neutralizing activity was strain-specific.

[38] Figure 18 shows that DH175 uses a VH4-34 Gene Segment. VH4-34 is recognized by the anti-idiotypic antibody 9G4, which defines a subpopulation of autoreactive antibodies overrepresented in SLE subjects.

[39] Figure 19 shows that DH175 Binds to Anti-Idiotypic 9G4 Ab.

[40] Figure 20A and B shows DH175 Autoreactivity.

[41] Figure 21 shows DH175 cross reactivity with human proteins.

[42] Figure 22 shows that DH175 binds to Man9 glycans.

[43] Figure 23 shows the effect of mutations of other N residues and glycosylation sites on DH175 neutralization: effect of N234A and T236A mutations.

[44] Figure 24 shows the effect of mutations of other N residues and glycosylation sites on DH175 neutralization: effect of N234A, N276A and T278A.

[45] Figure 25 shows the effect of mutations of other N residues and glycosylation sites on DH175 neutralization: effect of N295 and N160.

[46] Figure 26 Amino acids sequences of a selection of Envelopes from CH0694 as gp160s. (SEQ ID NOs: _____ to _____ in order of appearance). The amino acids between “can” and “vpv” (both designated with the small letters in the listing) are deleted in the designs of gp120deltaN proteins.

[47] Figure 27A and 27B show nucleic acid (Fig. 27A, CDRs are underlined) and amino acid (Fig. 27B, CDRs are highlighted) VH and VL sequences of DH175. SEQ ID NOs: ____, ____, ____, and ____ (in order of appearance).

[48] Figure 28. Selected envelopes from CH0694. Week 005.20.3 is referred to as T/F.

DETAILED DESCRIPTION OF THE INVENTION

[49] The present invention results, at least in part, from studies that resulted in the isolation of antibody DH175 from an African patient, CH0694, who was followed from the early acute HIV-1 infection phase to over 4 years post transmission. During this period, CH0694 developed plasma HIV-1 neutralization breadth. The invention relates the Env gene sequences shown in the sequence listing and the encoded amino acid sequences (Figure 26), the use thereof as immunogens. The envelopes to be used as immunogens in accordance with the invention can be, for example, expressed as full gp140, gp145 with transmembrane portions, gp120s, gp120 resurfaced core proteins, gp120 outer domain constructs, or other minimal gp120 constructs with portions of the DH175 contacts. The invention also relates to the DH175 antibody, fragments thereof, and to methods of using same as detailed below.

[50] The envelopes to be used as immunogens in accordance with the invention can be expressed as full gp140, gp145 with transmembrane portions, gp120s, gp120 resurfaced core proteins, gp120 outer domain constructs, or other minimal gp120 constructs with portions of the DH175 contacts.

[51] In accordance with the invention, immunization regimens can include sequential immunizations of Env constructs selected from those encoded by the sequences described herein, or can involve prime and boosts of combinations of Envs, or the administration of “swarms” of such sequences. Immunogenic fragments/subunits can also be used as can encoding nucleic acid sequences. Alternatively, the transmitted founder virus Env constructs can be used as primes, followed by a boost with the transmitted founder Env and sequential additions of Envs from progressively later times after transmission in patient CH0694. Further, repetitive immunization can be effected with “swarms” of CH0694 Envs (for example, including various combinations of the nucleic acid sequences in Fig.10 and encoded proteins) ranging from, for example, 2 to 40 Envs. (See Example 3.)

[52] In one embodiment, the present invention relates to a method of activating an appropriate naïve B cell response in a subject (e.g., a human) by administering the CH0694 T/F Env or Env subunits that can include the gp145 with a transmembrane portion, gp41 and gp120, an uncleaved gp140, a cleaved gp140, a gp120, a gp120 subunit such as a resurfaced core (Wu X, Science 329:856-61 (2010)), an outerdomain, or a minimum epitope expressing only the contact points of DH175 with Env (the minimal epitope to avoid dominant Env non-neutralizing epitopes), followed by boosting with representatives of subsequently evolved CH0694 Env variants (e.g., see Fig. 26) either given in combination to mimic the high diversity observed *in vivo* during affinity maturation, or in series, using vaccine immunogens specifically selected to trigger the appropriate maturation pathway by high affinity binding to UCA and antibody intermediates (Haynes et al, Nat. Biotechnol. 30:423-433 (2012)). DNA, RNA, protein or vectored immunogens can be used alone or in combination. In one embodiment of the invention, transmitted founder virus envelope is administered to the subject (e.g., human) as the priming envelope and then one or more of the sequential envelopes disclosed herein is administered as a boost in an amount and under conditions such that BnAbs are produced in the subject (e.g., human). By way of non-limiting examples, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 or more envelopes, e.g. one hundred envelopes (or subunits thereof) can be used with one prime and multiple boosts.

[53] The invention provides various methods to choose a subset of viral variants, including but not limited to envelopes, to investigate the role of antigenic diversity in serial samples. In other aspects, the invention provides compositions comprising viral variants, for example but not limited to envelopes, selected based on various criteria as described herein to be used as immunogens.

[54] In other aspects, the invention provides immunization strategies using the selections of immunogens to induce cross-reactive neutralizing antibodies. In certain aspects, the immunization strategies as described herein are referred to as “swarm” immunizations to reflect that multiple envelopes are used to induce immune responses. The multiple envelopes in a swarm could be combined in various immunization protocols of priming and boosting.

[55] Sequences/Clones

[56] Described herein are nucleic and amino acids sequences of HIV-1 envelopes. In certain embodiments, the described HIV-1 envelope sequences are gp160s. In certain embodiments, the

described HIV-1 envelope sequences are gp120s. Other sequences, for example but not limited to gp140s, both cleaved and uncleaved, gp150s, gp41s, which are readily derived from the nucleic acid and amino acid gp160 sequences as shown in the sequence listing. In certain embodiments the nucleic acid sequences are codon optimized for optimal expression in a host cell, for example a mammalian cell, a rBCG cell or any other suitable expression system.

[57] In certain embodiments, the envelope design in accordance with the present invention involves deletion of residues (e.g., 5-11, 5, 6, 7, 8, 9, 10, or 11 amino acids) at the N-terminus. For delta N-terminal design, amino acid residues ranging from 4 residues or even fewer to 14 residues or even more are deleted. These residues are between the maturation (signal peptide, usually ending with CX, X can be any amino acid) and "VPVXXXX...". In the case of CH0694w101.20.20gp120 delta design, as an example, fourteen amino acids were deleted (bold underlined):

MRARGIQRNYQHWWTWGILGFWMLMICNAG**GLEQQORWTVYYG**VPVWKEAKTTL
FCASDAKAYEKE (rest of envelope sequence is indicated as "...").

[58] In certain embodiments, the invention relates generally to an immunogen, gp160, gp120 or gp140, without an N-terminal Herpes Simplex gD tag substituted for amino acids of the N-terminus of gp120, with an HIV leader sequence (or other leader sequence), and without the original about 4 to about 25, for example 11, 14 amino acids of the N-terminus of the envelope (e.g. gp120). See WO2013/006688, e.g. at pages 10-12, the contents of which publication is hereby incorporated by reference in its entirety.

[59] The general strategy of deletion of N-terminal amino acids of envelopes results in proteins, for example gp120s, expressed in mammalian cells that are primarily monomeric, as opposed to dimeric, and, therefore, solves the production and scalability problem of commercial gp120 Env vaccine production. In other embodiments, the amino acid deletions at the N-terminus result in increased immunogenicity of the envelopes.

[60] In certain embodiments, the invention provides envelope sequences, amino acid sequences and the corresponding nucleic acids, and in which the V3 loop is substituted with the following V3 loop sequence TRPNNNTRKSIRIGPGQTFY ATGDIIGNIRQAH. This substitution of the V3 loop reduced product cleavage and improves protein yield during recombinant protein production in CHO cells.

[61] In certain aspects, the invention provides composition and methods which use a selection of sequential CH0694 Envs, as gp120s, gp 140s cleaved and uncleaved and gp160s, as proteins, DNAs, RNAs, or any combination thereof, administered as primes and boosts to elicit immune response. Sequential CH0694 Envs as proteins would be co-administered with nucleic acid vectors containing Envs to amplify antibody induction.

[62] In certain embodiments the invention provides immunogens and compositions which include immunogens as trimers. In certain embodiments, the immunogens include a trimerization domain which is not derived from the HIV-1 envelope.

[63] In certain aspects the invention provides compositions and methods of Env genetic immunization either alone or with Env proteins to recreate the swarms of evolved viruses that have led to bnAb induction. Nucleotide-based vaccines offer a flexible vector format to immunize against virtually any protein antigen. Currently, two types of genetic vaccination are available for testing—DNAs and mRNAs.

[64] In certain aspects the invention contemplates using immunogenic compositions wherein immunogens are delivered as DNA. See Graham BS, Enama ME, Nason MC, Gordon IJ, Peel SA, et al. (2013) DNA Vaccine Delivered by a Needle-Free Injection Device Improves Potency of Priming for Antibody and CD8+ T-Cell Responses after rAd5 Boost in a Randomized Clinical Trial. PLoS ONE 8(4): e59340, page 9. Various technologies for delivery of nucleic acids, as DNA and/or RNA, so as to elicit immune response, both T-cell and humoral responses, are known in the art and are under developments. In certain embodiments, DNA can be delivered as naked DNA. In certain embodiments, DNA is formulated for delivery by a gene gun. In certain embodiments, DNA is administered by electroporation, or by a needle-free injection technologies, for example but not limited to Biojector® device. In certain embodiments, the DNA is inserted in vectors. The DNA is delivered using a suitable vector for expression in mammalian cells. In certain embodiments the nucleic acids encoding the envelopes are optimized for expression. In certain embodiments DNA is optimized, e.g. codon optimized, for expression. In certain embodiments the nucleic acids are optimized for expression in vectors and/or in mammalian cells. In non-limiting embodiments these are bacterially derived vectors, adenovirus based vectors, rAdenovirus (Barouch DH, et al. Nature Med. 16: 319-23, 2010), recombinant mycobacteria (i.e., rBCG or M smegmatis) (Yu, JS et al. Clinical Vaccine Immunol. 14: 886-093,2007; ibid 13: 1204-11,2006), and recombinant vaccinia type of vectors (Santra S.

Nature Med. 16: 324-8, 2010), for example but not limited to ALVAC, replicating (Kibler KV et al., PLoS One 6: e25674, 2011 nov 9.) and non-replicating (Perreau M et al. J. virology 85: 9854-62, 2011) NYVAC, modified vaccinia Ankara (MVA)), adeno-associated virus, Venezuelan equine encephalitis (VEE) replicons, Herpes Simplex Virus vectors, and other suitable vectors.

[65] In certain aspects the invention contemplates using immunogenic compositions wherein immunogens are delivered as DNA or RNA in suitable formulations. Various technologies which contemplate using DNA or RNA, or may use complexes of nucleic acid molecules and other entities to be used in immunization. In certain embodiments, DNA or RNA is administered as nanoparticles consisting of low dose antigen-encoding DNA formulated with a block copolymer (amphiphilic block copolymer 704). See Cany et al., Journal of Hepatology 2011 vol. 54 j 115–121; Arnaoty et al., Chapter 17 in Yves Bigot (ed.), Mobile Genetic Elements: Protocols and Genomic Applications, Methods in Molecular Biology, vol. 859, pp293-305 (2012); Arnaoty et al. (2013) Mol Genet Genomics. 2013 Aug;288(7-8):347-63. Nanocarrier technologies called Nanotaxi® for immunogenic macromolecules (DNA, RNA, Protein) delivery are under development. See www.incellart.com/en/research-and-development/technologies.html.

[66] In certain aspects the invention contemplates using immunogenic compositions wherein immunogens are delivered as recombinant proteins. Various methods for production and purification of recombinant proteins suitable for use in immunization are known in the art.

[67] The immunogenic envelopes can also be administered as a protein boost in combination with a variety of nucleic acid envelope primes (e.g., HIV -1 Envs delivered as DNA expressed in viral or bacterial vectors).

[68] Dosing of proteins and nucleic acids can be readily determined by a skilled artisan. A single dose of nucleic acid can range from a few nanograms (ng) to a few micrograms (µg) or milligram of a single immunogenic nucleic acid. Recombinant protein dose can range from a few µg micrograms to a few hundred micrograms, or milligrams of a single immunogenic polypeptide.

[69] Administration: The compositions can be formulated with appropriate carriers using known techniques to yield compositions suitable for various routes of administration. In certain

embodiments the compositions are delivered via intramuscular (IM), via subcutaneous, via intravenous, via nasal, via mucosal routes.

[70] The compositions can be formulated with appropriate carriers and adjuvants using techniques to yield compositions suitable for immunization. The compositions can include an adjuvant, such as, for example but not limited to, alum, poly IC, MF-59 or other squalene-based adjuvant, ASOIB, or other liposomal based adjuvant suitable for protein or nucleic acid immunization. In certain embodiments, TLR agonists are used as adjuvants. In some embodiments, the TLR agonist is a TLR4 agonist, such as but not limited to GLA/SE. In other embodiment, adjuvants which break immune tolerance are included in the immunogenic compositions. In some embodiments the adjuvant is TLR7 or a TLR7/8 agonist, or a TLR-9 agonist, or a combination thereof. See PCT/US2013/029164.

[71] The present invention includes the specific envelope proteins disclosed herein (e.g., those encoded by the sequences in Fig. 26) and nucleic acids comprising nucleotide sequences encoding same. Examples include the nucleic acid sequences shown in Fig. 26 and referred to in Fig. 28 and the encoded amino acid sequences. The envelope proteins (and subunits) can be expressed, for example, in 293T cells, 293F cells or CHO cells (Liao et al, Virology 353:268-82 (2006)). As indicated above, the envelope proteins can be expressed, for example, as gp120 or gp140 proteins and portions of the envelope proteins can be used as immunogens such as the resurfaced core protein design (RSC) (Wu et al, Science 329:856-861 (2010)); another possible design is an outer domain design (Lynch et al, J. Virol. 86:7588-95 (2012)). The invention includes immunogenic fragments/subunits of the envelope sequences disclosed herein, including fragments at least 6, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 220, 240, 260, 280 300, 320 or more amino acids in length, as well as nucleic acids comprising nucleotide sequences encoding such fragments and vectors containing same.

[72] In other embodiments, the invention provides variants of the sequences encoded by the sequences in Fig. 26, including variants that comprise a mutation which repairs a trypsin cleavage site, thereby preventing protein clipping during Env protein production in a cell line, e.g., a CHO cell line.

[73] The envelopes (immunogens) can be formulated with appropriate carriers using standard techniques to yield compositions suitable for administration. The compositions can include an

adjuvant, such as, for example, alum, poly IC, MF-59 or other squalene-based adjuvant, ASO1B or other liposomal based adjuvant suitable for protein immunization.

[74] As indicated above, nucleic acid sequences (e.g., DNA sequences) encoding the immunogens can also be administered to a subject (e.g., a human) under conditions such that the immunogen is expressed *in vivo* and BnAbs are produced. The DNA can be present as an insert in a vector, such as a rAdenoviral (Barouch, et al. Nature Med. 16: 319-23 (2010), recombinant mycobacterial (i.e., BCG or *M smegmatis*) (Yu et al. Clinical Vaccine Immunol. 14: 886-093 (2007); *ibid* 13: 1204-11 (2006), or recombinant vaccinia type of vector (Santra S. Nature Med. 16: 324-8 (2010)).

[75] Immunogens of the invention, and nucleic acids (e.g., DNAs) encoding same, are suitable for use in generating an immune response (e.g., BnAbs) in a patient (e.g., a human patient) to HIV-1. The mode of administration of the immunogen, or encoding sequence, can vary with the particular immunogen, the patient and the effect sought, similarly, the dose administered. Typically, the administration route is intramuscular or subcutaneous injection (intravenous and intraperitoneal can also be used). Additionally, the formulations can be administered via the intranasal route, or intrarectally or vaginally as a suppository-like vehicle. Optimum dosing regimens can be readily determined by one skilled in the art. The immunogens (and nucleic acids encoding same) are suitable for use prophylactically, however, their administration to infected individuals may reduce viral load.

[76] The present invention further relates to the DH175 antibody, and fragments thereof (e.g., antigen-binding fragments), and to methods of using same to inhibit HIV-1 infection in a subject (e.g., a human). The invention also relates to nucleic acids comprising nucleotide sequences encoding DH175 and fragments thereof.

[77] Recently, a method of making HIV vaccine immunogens based on their ability to bind to early members of a BnAb clonal lineage was proposed (US Prov. Appln. 61/542,469, filed October 3, 2011). This method is termed B cell lineage immunogen design (Haynes et al. Nature Biotech. 30: 423-433 (2012)). This method is based on the use of clonal lineage antibody members as templates for design of HIV envelope proteins that bind well to lineage members. This method is based on the use of clonal lineage antibody members as templates for design of HIV envelope proteins that bind well to lineage members. This method is based on the principle that those antigens that bind best to naïve BnAb B cell receptors (the unmutated ancestors of

mature BnAbs) will be the best immunogens for driving such a clonal lineage. Thus, mature antibodies are isolated, their intermediate ancestor and unmutated ancestor precursors inferred, and the clonal lineage tree reconstructed by Bayesian probability statistics and maximum likelihood analysis, and then the tree antibodies are made by recombinant techniques (Haynes et al, Nature Biotech. 30:423-433 (2012)). Then, by screening Envs, or by solving antibody and Env structures and then rational design of Envs that optimally bind to clonal tree members, immunogens are designed and produced for vaccination studies (Haynes et al, Nature Biotech. 30:423-433 (2012)).

[78] Exemplary antibodies of the invention for therapeutic use include those comprising variable heavy (VH) and light (VL) chain amino acid sequences selected from those shown in Example 1. In accordance with the methods of the present invention, either the intact antibody or a fragment thereof can be used. Either single chain Fv, bispecific antibody for T cell engagement, and chimeric antigen receptors can be used (Chow et al, Adv. Exp. Biol. Med. 746:121-41 (2012)). That is, for example, intact antibody, a Fab fragment, a diabody, or a bispecific whole antibody can be used to inhibit HIV-1 infection in a subject (e.g., a human). A bispecific F(ab)₂ can also be used with one arm a targeting molecule like CD3 to deliver it to T cells and the other arm the arm of the native antibody (Chow et al, Adv. Exp. Biol. Med. 746:121-41 (2012)). Toxins that can be bound to the antibodies or antibody fragments described herein include unbound antibody, radioisotopes, biological toxins, boronated dendrimers, and immunoliposomes (Chow et al, Adv. Exp. Biol. Med. 746:121-41, 2012)). Toxins can be conjugated to the antibody or antibody fragment using methods well known in the art (Chow et al, Adv. Exp. Biol. Med. 746:121-41 (2012)). The invention also includes variants of the antibodies (and fragments) disclosed herein, including variants that retain the ability to bind to recombinant Env protein, and methods of using same to, for example, reduce HIV-1 infection risk. Combinations of the antibodies, or fragments thereof, disclosed herein can also be used in the methods of the invention.

[79] The antibodies, and fragments thereof, described above can be formulated as a composition (e.g., a pharmaceutical composition). Suitable compositions can comprise the BnAb (or antibody fragment) dissolved or dispersed in a pharmaceutically acceptable carrier (e.g., an aqueous medium). The compositions can be sterile and can be in an injectable form (e.g., a form suitable for intravenous injection). The antibodies (and fragments thereof) can also be

formulated as a composition appropriate for topical administration to the skin or mucosa. Such compositions can take the form of liquids, ointments, creams, gels and pastes. The antibodies (and fragments thereof) can also be formulated as a composition appropriate for intranasal administration. The antibodies (and fragments thereof) can be formulated so as to be administered as a post-coital douche or with a condom. Standard formulation techniques can be used in preparing suitable compositions.

[80] The BnAbs (and fragments thereof) described herein have utility, for example, in settings including the following:

i) in the setting of anticipated known exposure to HIV-1 infection, the antibodies described herein (or fragments thereof) can be administered prophylactically (e.g., IV, topically or intranasally) as a microbiocide,

ii) in the setting of known or suspected exposure, such as occurs in the setting of rape victims, or commercial sex workers, or in any homosexual or heterosexual transmission without condom protection, the antibodies described herein (or fragments thereof) can be administered as post-exposure prophylaxis, e.g., IV or topically, and

iii) in the setting of Acute HIV infection (AHI), the antibodies described herein (or fragments thereof) can be administered as a treatment for AHI to control the initial viral load or for the elimination of virus-infected CD4 T cells.

[81] Suitable dose ranges can depend on the antibody (or fragment) and on the nature of the formulation and route of administration. Optimum doses can be determined by one skilled in the art without undue experimentation. Doses of antibodies in the range of 1-50 mg/kg can be used.

[82] In accordance with the invention, the BnAbs (or antibody fragments) described herein can be administered prior to contact of the subject or the subject's immune system/cells with HIV-1 or within about 48 hours of such contact. Administration within this time frame can maximize inhibition of infection of vulnerable cells of the subject with HIV-1.

[83] Antibodies of the invention and fragments thereof can be produced recombinantly using nucleic acids comprising nucleotide sequences encoding VH and VL sequences selected from those shown in Example 1.

[84] Certain aspects of the invention can be described in greater detail in the non-limiting Examples that follows. (See also Provisional Appln. 61/613,222, filed March 20, 2012, Provisional Application No. 61/700,234, filed September 12, 2012, Provisional Application

No. 61/700,252, filed September 12, 2012, Provisional Application No. 61/708,466, filed October 1, 2012, Provisional Application No. 61/764,421, filed February 13, 2013, Provisional Application No. 61/542,469, filed October 3, 2011, Provisional Application No. 61/708,413, filed October 1, 2012, Provisional Application No. 61/708,503, filed October 1, 2012, Provisional Application No. 61/806,717, filed March 29, 2013, U.S. Application No. 13/314,712, filed December 8, 2011, PCT/US2012/000442, filed October 3, 2012, PCT/US2013/00210, filed September 12, 2013 and PCT/US2013/059515, filed September 12, 2013, the entire contents of each of which are incorporated herein by reference.)

[85] This application includes a sequence listing filed electronically concurrently herewith.

EXAMPLE 1

[86] This example (Figures 9-21) shows isolation of broadly neutralizing antibody DH175 from a Malawian chronically HIV-1 infected subject with plasma neutralization breadth.

[87] CH0694 is an African female followed in the CHAVI001 protocol from the early acute HIV-1 infection phase to over 4 years post-transmission. During this period, CH0694 developed plasma HIV-1 neutralization breadth. This subject was selected for virus/antibody co-evolution studies.

[88] The goal was to isolate broadly neutralizing antibodies (i.e., consensus C neutralization) from memory B cells using the memory B cell culture system for antibody/virus co-evolution studies. Cell culture supernatants were screened for consensus C neutralization, differential binding of 1086C and 63521 V1/V2 tags vs N156Q/N160Q mutants and RSC3 protein binding.

[89] DH175 is a broadly neutralizing antibody that neutralizes selected tier-2 viruses from multiple clades. DH175 does not appear to recapitulate the observed CH0694 serum neutralization breadth in the Tzm-bl assay.

[90] DH175 does not bind to: i) RSC3, ii) linear peptides from Consensus A, B, C, D and M, CRF1 and CRF2; and AE.A244, AE.TH023, B.MN, C.1086, C.TV1 and C.ZM651 HIV-1 strains, iii) Con6, 92TH023, A.9004SS, BaL gp120 Envs and A1.con.env01; B.con.env03, conS, VRC A, VRC B and VRC C gp140 Envs, or iv) B.MN gp41. The DH175 epitope is likely gp120 conformational.

[91] DH175 does not bind to: Linear peptides from Consensus A, B, C, D and M, CRF1 and CRF2; and AE.A244, AE.TH023, B.MN, C.1086, C.TV1 and C.ZM651 HIV-1 strains; Con6,

92TH023, A.9004SS, BaL gp120 Envs and A1.con.env01; B.con.env03, conS, VRC A, VRC B and VRC C gp140 Envs; B.MN gp41; RSC3. DH175 bound weakly to consensus C gp120 and binding was abrogated by N332A. DH175 epitope is likely gp120 conformational and the current hypothesis is that it is a PGT-like antibody

[92] DH175 neutralizes consensus C (primary culture conC neutralization = 82%). DH175 binds to consensus C gp120 (end-point titer = 25 µg/ml). DH175 binding to consensus C gp120 was abrogated by the N332A mutation in the gp120 Env.

[93] DH175 does not require N332 to neutralize. Provisional neutralization fingerprinting indicates that DH175 clusters more closely to PGT antibodies than to other known BnAb specificities but it is relatively distal from other PGT antibodies. Figures 22-25 show that DH175 binds to Man9 (Figure 22), and that antibody binding depends on the presence of glycans at positions N332 and N234.

[94] DH175 is a 9G4+ antibody. 9G4+ antibodies were originally identified to be SLE-induced autoreactive antibodies in SLE subjects (faulty GC censorship of autoreactive B cells). They are intrinsically autoreactive against N-acetylactosamine moieties, also cross-react with glycolipids including LPS and gangliosides. 9G4+ plasma antibodies have been identified in chronically HIV-1 infected subjects and found to correlate with HIV-1 plasma neutralization breadth.

[95] The sequences of the heavy and light chain (V(D)J rearrangement) of antibody DH175 from the CHAVI subject CH0694 are shown in Figure 27 (CDRs underlined and bolded).

[96] In summary, using the memory B cell culture system, antibody DH175 was isolated from a chronically HIV-1 infected broad neutralizer. With the isolation of autologous virus quasi-species across multiple time points, and the definition of the viral evolution and sites of immune pressure, DH175 will allow the study of virus/antibody co-evolution in a second broad neutralizer.

[97] DH175 is a polyreactive neutralizing antibody that recognizes a conformational HIV-1 epitope. DH175 cross-reacts with lectins. Neutralization fingerprinting provisionally positions DH175 more closely to PGT-like BnAbs than to other known BnAb specificities.

[98] DH175 is a 9G4+ antibody, a common autoreactive idiootype associated with SLE. DH175 may have been generated from the same pool of B cells that also generate autoreactive antibodies during SLE.

[99] Unlike traditional antibody affinity maturation for non-HIV-1 antigens where affinity maturation is associated with loss of polyreactivity, observations suggest that HIV-1 neutralization breadth is frequently associated with the acquisition of autoreactivity.

[100] The DH175 epitope will be further mapped by making mutations using the 694 T/F virus. Clonally related antibodies will be isolated as well as new bnAbs from CH694 from multiple time points (memory B cell cultures, antigen-specific sorts and Illumina pyrosequencing). The contribution of DH175 and DH175 clonally-related antibodies to autologous viral escape will be evaluated.

EXAMPLE 2

[101] From over 1000 half-genome SGA (single genome amplification) sequences in CH0694, identification of at most 100 is sought for pseudovirus construction, for subsequent use in neutralization assays, and 12 for infectious molecular clones. These will be prioritized by genetic analyses that suggest the sets would be representative of evolving forms, and have the potential to yield insight about virus coevolution with adaptive immunity for the intermediate-ancestor vaccine-design strategy.

[102] Choosing 100 representative sequences from 1103 sequences over 26 time-points might be done at random, with roughly 4 sequences per time-point. To the extent that sequence diversity approximates shape-space diversity, and often it reflects immune selection, it is anticipated that it would be advantageous to more systematically define an informative set for baseline analysis. A simple alternative to random selection would select both the most representative and most evolved sequences per time-point, with preference for any monotypic sequences, and include representatives from multiple clades where they persist (post-week 101, henceforth designated “w101”, where the lineages diversification begins to resolve into distinct clades that are maintained over time). By testing both the average and leading sequences per time-point, this would enable characterizing the progression of antibody neutralization to understand development of neutralization potency in autologous sera.

[103] A still more elaborate alternative favors sequences that contain mutations away from the T/F form that eventually reach high prevalence (“fixation”). Such sites reveal diverse dynamics: varied rates of spread, reversion to the T/F form, and stable persistence of multiple variants at a site. Insertions and deletions further complicate this approach. Up to w101, a partially stable progression of mutations can be seen, as described below. Thus, another alternative is to isolate

the first instances of such mutations, even when rare, to evaluate whether partial neutralization resistance is conferred in the earliest forms, as a new addition to accumulating changes relative to the T/F.

[104] Not all mutations occur in isolation, and are sampled with the cumulative progressive mutations that occur together *in vivo*. After wk101, understanding the progression of escape is complicated by the emergence of distinct clades marking diverse viral lineages.

[105] Finally, a third point of interest is to attempt to include variants in epitope regions for antibody specificities that are evident in the immune sera (e.g., V2-glycan (PG9-like) and V3 glycan (PGT-like) antibodies.

[106] 35 sequences with deletions over 30 nt long, which are presumably not viable, were excluded. Identified were escaping Env sites with over 95% non-T/F form in at least one time-point (Table 1.) A five-site linked insertion into V2 is treated as one variant. The 95% threshold was used just to sift out the single sites that ranked the highest in terms of potential for positive selection in the whole of Env; certainly other sites may be relevant to antibody escape that are missed by this criterion.

[107] Frequencies of T/F, dominant, and other escape forms per site over time were computed. Amino acid frequencies over time were plotted to summarize the diverse dynamics across sites (Figs. 3 & 8). There are many ways for a T/F amino acid to be lost: complete change to another amino acid (eg Fig. 3, 722/ D616N, row1 col2), serial substitutions (eg Fig. 3, 330/ D280H V3, row1 col3), and complex replacements with multiple variants (eg Fig. 3, 229/ E185K, row3 col3). Variant frequencies per time-point were clustered with hierarchical clustering, to identify positions that vary and the relative progression of these variants. A heatmap depicts the clusters (Fig. 5). A larger graph tracking all variant amino acids at each position is included in Figs. 7 and 8.

[108] Pixel plots paired with trees were used to review the distribution of polymorphisms per sample. Trees were inferred with PhyML version 3 with the HIVw substitution model.

[109] **Distinct Epochs pre wk101** (Greek letters correspond to clusters in Figure 5.) The number of clusters varies with a threshold distance. Lacking some objectively defined cutoff, the focus was on cluster patterns that were amenable to interpretation.

[110] Variant nomenclature is as follows: AIn position/ (slash) TF_AA, HXB2 site, Esc_AA.

[111] Here,

bold indicates simplest 0->1 constant frequency “turnover” replacements,
underline indicates presence of multiple non-T/F forms to at least 50%,
italics indicate a site that *reverts* to the T/F form, and
 *asterisks indicate sites with dominant amino acids or indels change in time.

α : Seven sites change within the first year

1. **722/D616N**
2. 330/D280H* (this is replaced by D280N at w101).
3. 53/A50T (appears very early, fades in prevalence w122-w194, then returns).
4. 550/K460E (yields at w122)
5. 950/G835E
6. 236/D189N*, which adds a tandem PNG site, i.e. NNSS.
7. 519/N442S*

β : Seven sites change between w041 and w064:

8. **525/D448N**, which adds a PNG site
9. **663/R557K**
10. **483/D411N**
11. **284/K234N**
12. 343/G293E
13. **755/K648E**
14. **624/M518V**

γ : Nine sites change at w064-w101, and tend to persist:

15. **619/A513V**
16. **724/S618T**
17. 469/G399E
18. **325/K275E**
19. **773/R665K**
20. 330/D280N*
21. 854/I746V

- 22. 886/I778L
- 23. 185/Y151K

δ: Six sites change by w101 but do not persist, either reverting to T/F or replaced by another mutation. Here, sampling will be shifted to the sequences nearest consensus and most divergent within a time-point.

[112] Considerably more diversity evolves after w122 (ε-η), yielding greater complexity in the phylogeny that persists through the end of the sampling period. Rather than single escapes emerging sequentially, diverse new variants appear together in the same sample. Contributions to this complexity include length polymorphisms from indels, greater intervals between sampling, and recombination. Some 16 mutations emerge slowly (a few having first been present but rare very early), until they prevail after w165. Another 5 mutations never become abundant but contribute to diversity in these chronic samples.

[113] Changing the criterion to include variants that reach less than 50% frequency preserves the overall clustering pattern, and adds more rare variants to late-emerging cluster η.

[114] Table 2 lists 100 candidate isolates for pseudoviruses without stop codons or incomplete codons, which represent the within-host virus diversity. The overall 3-prime half-genome nucleotide-sequence phylogeny (Fig. 2) resembles the tree obtained from only the Env translation (Fig. 6). One third of these variants represent variants sampled within the first two years of infection. If autologous neutralization and virus escape follow the ladder-like progression of emerging variants, this would provide confirmation that they are produced serially by escape from immune selection.

[115] The remaining variants represent a series of bifurcations on the phylogeny. Fig. 6 shows that the variants depicted in Fig. 3 based on the 95% loss of are accumulating through this set, and the changes among these sites are well represented by the Envs suggested for experimental testing. It is unclear what drives the bifurcating lineages, and why there seem to be two or more dominant clades on this part of the tree for any given sample timepoint. One possibility is that a division of the virus population into escape variants subpopulations recognized by antibody lineages with different specificities. Recombination may also contribute to structuring the tree this way.

[116] Several of the PG9-like V2 glycan and PGT V3 glycan epitope and signature positions are among the set highlighted in Fig. 3. Another 12 sites were included that showed some polymorphisms but not 95% displacement of the TF virus, in these and CD4 binding-site contact regions. These sites are depicted in Figures 6, 7, and 8. They do not emerge until very late in the study sampling period, presumably to their association with expanding heterologous neutralization breadth in mature antibodies.

[117] Mutations that occur in the LTR of particular interest (in view of interest in CTL activity. Expression levels and IFN sensitivity). (See Example 4)

Table 1. CH0694 variants at sites with less than 5% T/F frequency in at least one sample.

Rank	Variant	Aln pos	HXB22 pos	T/F aa	Esc aa	non-T/F ¹
1	722/D616N	722	616	D	N	94.3
2	330/D280N	330	280	D	N	93.7
3	525/D448N	525	448	D	N	86.5
4	663/R557K	663	557	R	K	86.4
5	550/K460E	550	460	K	E	85.6
6	950/G835E	950	835	G	E	83.8
7	483/D411N	483	411	D	N	82.0
8	284/K234N	284	234	K	N	81.9
9	53/A50T	53	50	A	T	81.0
10	624/M518V	624	518	M	V	79.7
11	755/K648E	755	648	K	E	79.2
12	236/D189N	236	189	D	N	78.9
13	343/G293E	343	293	G	E	78.9
14	229/E185-	229	185	E	-	77.2
15	568/T465-	568	465	T	-	76.3
16	619/A513V	619	513	A	V	72.9
17	751/D644E	751	644	D	E	72.3
18	387/E336A	387	336	E	A	71.8
19	724/S618T	724	618	S	T	71.5
20	773/R665K	773	665	R	K	70.4
21	469/G399E	469	399	G	E	69.8
22	325/K275E	325	275	K	E	69.4
23	185/Y151K	185	151	Y	K	68.2
24	519/N442S	519	442	N	S	67.5
25	854/I746V	854	746	I	V	65.8
26	449/Y396D	449	396	Y	D	65.7
27	485/T413N	485	413	T	N	64.5
28	886/I778L	886	778	I	L	64.1
29	552/E462G	552	462	E	G	62.6
30	175/S145F	175	145	S	F	62.2
31	34/K33Q	34	33	K	Q	61.6
32	142/-134T	142	134	-	T	56.5
33	138/K131T	138	131	K	T	55.5
34	397/R346K	397	346	R	K	55.3
35	31/V30G	31	30	V	G	53.8
36	3/V3A	3	3	V	A	50.4
37	157/N135-	157	135	N	-	50.3
38	156/-134S	156	134	-	S	50.0
39	413/I360R	413	360	I	R	48.9
40	143/-134A	143	134	-	A	47.6
41	747/G640D	747	640	G	D	47.3
42 ²	166/-140N	166	140	-	N	46.0
47	165/-140N	165	140	-	N	45.9

48	135/E130N	135	130	E	N	45.5
49	621/L515M	621	515	L	M	43.5
50	331/T281A	331	281	T	A	31.9
51	369/A319T	369	319	A	T	31.0
52	604/E500K	604	500	E	K	28.3

¹ Cumulative percentage of non-T/F variants over sampling period, used for ranking.

² Not shown: linked V1 insertion sites 167/-140S, 168/-140T, 169/-140S, 170/-140I.

Table 2. Isolate candidates for pseudovirus construction & autologous Nab assay.¹

- n=18 from before roughly 6-months post-infection, capturing the earliest emergent forms with substitutions that rapidly replaced the T/F virus:
 - w005: 20.3, 20.14
 - w006: 10.3, 10.6
 - w007: 15.1, 15.48
 - w009: 15.4, 15.32
 - w013: 30.2, 30.16
 - w017: 4.30, 6.2, 6.19, 6.20
 - w020: 6.10, 6.55
 - w028: 10.2, 10.48
- n=15 from 6 to 24 months post-infection:
 - w041: 40.72, 40.82
 - w053: 70.32, 70.38, 70.43
 - w064: 10.1, 10.4, 10.25
 - w101: 10.5, 20.6, 20.20, 20.30, 20.45, 20.48, 30.7
- n=37 from years 2 through 3:
 - w122: 4.11, 4.20, 4.21, 4.3, 5.61, 5.79, 10.84, 10.90, 81.26
 - w124: 6.9, 6.15, 6.16, 6.20, 6.29, 6.37
 - w126: 20.35, 20.41, 20.43, 20.51
 - w130: 3.3, 3.4, 10.21, 10.36, 10.63
 - w134: 10.7, 20.58, 20.60, 20.65, 20.75
 - w138: 10.18, 10.47, 10.50, 10.57
 - w146: 3.2, 3.7, 15.41, 15.53
- n=30 from after year 3:
 - w165: 10.14, 10.21, 10.30, 10.32, 10.37, 10.40, 10.43, 10.47
 - w194: 5.11, 5.12, 5.31, 5.39, 5.41
 - w215: 30.11, 30.21, 30.35, 30.36, 30.40, 30.60, 30.65
 - w221: 30.23, 40.51, 40.63
 - w223: 5.13, 5.24, 5.25, 5.61, 5.62, 5.69, 10.82

¹ Env sequences containing premature stops or incomplete codons were not considered.

EXAMPLE 3

[118] Provided herein are non-limiting examples of combinations of antigens derived from CH694 envelope sequences for a swarm immunization. The selection includes priming with a virus which binds to the UCA, for example a T/F virus or another early virus envelope.

[119] Non-limiting embodiments of envelopes selected for swarm vaccination are shown as the selections described below. A skilled artisan would appreciate that a vaccination protocol can include a sequential immunization starting with the “prime” envelope(s) and followed by sequential boosts, which include individual envelopes or combination of envelopes. In another vaccination protocol, the sequential immunization starts with the “prime” envelope(s) and is followed with boosts of cumulative prime and/or boost envelopes. In certain embodiments, there is some variance in the immunization regimen; in some embodiments, the selection of HIV-1 envelopes may be grouped in various combinations of primes and boosts, either as nucleic acids, proteins, or combinations thereof.

[120] In certain embodiments the immunization includes a prime administered as DNA, and MVA boosts. See Goepfert, et al. 2014; “Specificity and 6-Month Durability of Immune Responses Induced by DNA and Recombinant Modified Vaccinia Ankara Vaccines Expressing HIV-1 Virus-Like Particles” J Infect Dis. 2014 Feb 9. [Epub ahead of print].

[121] Immunization protocols contemplated by the invention include envelopes sequences as described herein including but not limited to nucleic acids and/or amino acid sequences of gp160s, gp150s, cleaved and uncleaved gp140s, gp120s, gp41s, N-terminal deletion variants as described herein, cleavage resistant variants as described herein, or codon optimized sequences thereof. A skilled artisan can readily modify the gp160 and gp120 sequences described herein to obtain these envelope variants. The swarm immunization protocols can be administered in any subject, for example monkeys, mice, guinea pigs, or human subjects.

[122] In non-limiting embodiments, the immunization includes a nucleic acid is administered as DNA, for example in a modified vaccinia vector (MVA). In non-limiting embodiments, the nucleic acids encode gp160 envelopes. In other embodiments, the nucleic acids encode gp120 envelopes. In other embodiments, the boost comprises a recombinant gp120 envelope. The vaccination protocols include envelopes formulated in a suitable carrier and/or adjuvant, for example but not limited to alum or GLA/SE. In certain embodiments the immunizations include

a prime, as a nucleic acid or a recombinant protein, followed by a boost, as a nucleic acid or a recombinant protein. A skilled artisan can readily determine the number of boosts and intervals between boosts. In certain embodiments, the immunization methods can include agents which modulate host immune tolerance responses.

[123] As indicated above, the invention includes the use of "swarm" vaccines as DNA constructs. Envs selected for reagent design as described in Example 2 also represent a rational and representative down-selection for "swarm design" for vaccination, to mimic consequences of evolution in CH0694 for generation of antibodies with greater breadth. It is contemplated that earlier forms of the antibodies in the lineage select for resistant forms of the virus, and that exposure to the resistant forms enables the antibody lineage to evolve to tolerate the resistant mutation. For example, 10-20, or more DNA encoded Envs can be included in a single vaccination.

[124] In the down-selection, the amino acids where the transmitted founder (TF) amino acid becomes less than 5% of the population at at least 1 time point were selected; generally these mutations go to fixation, or at least the loss of the TF form becomes fixed, although sometimes it is replaced by several different amino acids with differing frequencies over time. These sites are prime candidates for contributing to immune escape, as they are likely to be under very strong positive selective pressure. In addition to these sites, also attended to were mutations thought to impact V2-glycan antibodies (PG-9 like) and V3-glycan antibodies (PGT-like) through signature analysis, as well as CD4 contact sites, tracking mutations in these positions in Env, even if the mutations that accrue never fully replaced the TF viruses.

[125] All of these mutations accrue sequentially throughout the time period the serum antibodies are gaining potency and breadth, and a hundred Envs isolates were selected that capture their acquisition (Fig. 6).

[126] Prior to week 101 in subject CH0694, the sequential emergence of the mutations away from the TF can be seen, and these mutations can be tracked through the phylogeny, but between weeks 64 and week 101 the virus begins to really diverge (Fig. 2). It is only after this initial divergence that neutralizing breadth begins to become apparent in the subject CH0694's sera (very like CH0505). There is a natural building of diversity prior to the beginning of breadth, and an expansion of the diversity as breadth increases.

[127] Swarms of these representative variants can be used in vaccines delivered sequentially, to mimic natural infection in CH0694, with a feasible number of variants included in a swarm. For example: start with the T/F alone, then following up with 5 serial vaccinations, each including 20 variants from the 100 representative forms (e.g., start with the 20 earliest or closest to T/F and the ancestral root of the phylogeny, and then sequentially include later times points and sequences that have evolved further from the T/F, as the vaccination series progresses). An advantage of this strategy is that each variant remains relatively close to a variant the vaccinated individual has seen before, so it is expected that the epitope modifications gradually introduced would not be so drastic as to completely abolish antibody binding but could provide gradual accumulation of differences in different parts of the epitope, allowing antibodies to evolve to develop high affinities to the gradually altered epitopes forms.

[128] An example of the foregoing strategy is set forth below (see Example 2 and Figures 26 for sequence and designation details):

Swarm 1		Swarm 2		Swarm3		Swarm 4	
week 5	20.3 (prime)	week 41	40.72	Week 122	10.84	week 134	10.7
	20.13		40.82		10.9		20.58
	20.14	week 53	70.32		81.26		20.60
week 6	10.3		70.38	week 124	6.9		20.65
	10.6		70.43		6.15		20.75
week 7	15.48	week 64	10.1		6.16	week 138	10.18
	15.1		10.4		6.20		10.47
week 9	15.4		10.25		6.29		10.50
	15.32	week 101	10.5		6.37		10.57
week 13	30.2		20.6	week 126	20.35	week 146	3.2
	30.16		20.20		20.41		3.7
week 17	6.2		20.30		20.43		15.41
	6.19		20.45		20.51		15.53
	6.20		20.48	week 130	3.3	week 165	10.14
	4.30		30.7		3.4		10.21
week 20	6.10	week 122	4.11		10.21		10.30
	6.55		4.20		10.36		10.32
week 28	10.2		4.21		10.63		10.37
	10.48		4.3				10.40
			5.61				10.43
			5.79				10.47

[129] Table 2 in Example 1 provides another non-limiting embodiment of selection of CH0694 envelopes for swarm immunization. In a non-limiting embodiment, the prime is CH0694 T/F.

[130] Below is a non-limiting example of a selection of groups of envelopes for sequential immunization protocol using a swarm of CH694 envelopes.

[131] Group 1: TF -> week 009, very limited diversification that precedes autologous neutralization

[132] Group 2: Autologous neutralization -> beginning of breadth steady slow diversification w013 – w101

[133] Group 3: Modest heterologous neutralization, consistent new level of diversity w122-146

[134] Group 4: Increase in viral diversity, increase in breadth w165-w223.

[135] In certain embodiments, CMV-Env DNA synthesized.

[136] Group 1: Prime: T/F (w005.20.3) or another week 005 sequence that has the amino acid sequence of the TF virus.

n=18 from before roughly 6-months post-infection, capturing the earliest emergent forms with substitutions that rapidly replaced the T/F virus:

w005: 20.13, 20.14

w006: 10.3, 10.6

w007: 15.1, 15.48

w009: 15.4, 15.32

[137] Group 2:

w013: 30.2, 30.16

w017: 4.30, 6.2, 6.19, 6.20

w020: 6.10, 6.55

w028: 10.2, 10.48

w041: 40.72, 40.82

w053: 70.32, 70.38, 70.43

w064: 10.1, 10.4, 10.25

w101: 10.5, 20.6, 20.20, 20.30, 20.45, 20.48, 30.7

[138] Group 3:

n=37 from years 2 through 3:

w122: 4.11, 4.20, 4.21, 4.3, 5.61, 5.79, 10.84, 10.90, 81.26

w124: 6.9, 6.15, 6.16, 6.20, 6.29, 6.37

w126: 20.35, 20.41, 20.43, 20.51

w130: 3.3, 3.4, 10.21, 10.36, 10.63

w134: 10.7, 20.58, 20.60, 20.65, 20.75

w138: 10.18, 10.47, 10.50, 10.57

w146: 3.2, 3.7, 15.41, 15.53

[139] Group 4:

n=30 from after year 3:

w165: 10.14, 10.21, 10.30, 10.32, 10.37, 10.40, 10.43, 10.47

w194: 5.11, 5.12, 5.31, 5.39, 5.41

w215: 30.11, 30.21, 30.35, 30.36, 30.40, 30.60, 30.65

w221: 30.23, 40.51, 40.63

w223: 5.13, 5.24, 5.25, 5.61, 5.62, 5.69, 10.82

[140] In another non-limiting example, CH694 T/F envelope as a prime, and a selection of 100 envelopes from CH694 (plasma with PGT like and V1V2 bnAbs) could be divided in four groups for sequential immunization as follows:

[141] Group 1. 100 CH694 Envs as DNAs and as proteins divided into 4 sequential immunogens. Envs in DNAs are gp120s and in proteins as gp120s. This study is to recreate as best and practically as possible the evolution of viruses over time of BnAb development in this person for PGT and V1V2 Bnab inductions.

[142] Part 1- 25 envs as DNAs electroporated in the thigh, and 25 Envs as proteins IM contralateral thigh as a prime

[143] Part 2- 25 next envs as DNAs electroporated in the thigh and 25 next Envs as proteins IM in contralateral thigh as first boost

[144] Part 3- 25 next envs as DNAs electroporated in the thigh and 25 next Envs as proteins IM in contralateral thigh as first boost

[145] Part 4 25 next envs as DNAs electroporated in the thigh and 25 next eN Envs vs as proteins IM in contralateral thigh as first boost

[146] Group 2. 100 CH649 Envs as DNAs and as proteins (test the effect of having gp41 in the immunogen and effect of quality and quantity of abs by having gp41 in vaccine.

[147] Immunization 1- immunize prime with Transmitted founder Env gp160 as DNA and protein as gp140C

[148] Immunization 2 (next boost) IM Immunize with 3 variants from Part 1 above in addition to TF as DNA gp160 and protein as gp140C

[149] Immunization 3 (next boost) IM Immunize with 3 variants from Part 2 above in addition to TF as DNA gp160 and protein as gp140C

[150] Immunization 4 (next boost) IM Immunize with 3 variants from Part 3 above in addition to TF as DNA gp160 and protein as gp140C

[151] Immunization 5 (next boost) IM Immunize with 3 variants from Part 4 above in addition to TF as DNA gp160 and protein as gp140C

[152] Adjuvant could be IDRI GLA (TLR4), quil A and liposome adjuvant (similar to ASO1B).

Example 4

[153] LTR mutations: There are 4 positions that have a 95% loss of the T/F based at least one time point in subject 0694. These 4 are surrounded by additional mutations that come and go, as we often see with CTL escape, but 4 these represent the most dramatic changes over time within such local clusters of mutations.

[154] They are readily visible in the two accompanying CTL figures.

Alignment Position: HXB2 Position: 0694 T/F LTR position
Global frequency, database

115 T->A	A 115	115
A: 63.92% (163) T: 35.29% (90) G: 0.78% (2)		

380 C->T	T 357	360
T: 98.89% (268) other: 1.11% (3)		

484 G->A->T	T 440	441
T: 99.65% (288) G: 0.35% (1)		

548 G->A	A 504	505
A: 71.15% (254) G: 24.93% (89) other: 3.92% (14)		

[155] In each case they evolve towards the global consensus, the transmitted founder form at position 380 and 384 are both very rare in the data, the 115 and 548 less common but not that rare. Only 115 1 overlaps with the Nef reading from, shown in blue below. It would be

interesting to compare a TF without these mutations, and one with only these mutations as an IMC to see if they impact expression... The first natural strain to arise that carries all 4 might also be of interest, it is w101.10.6. (Its reading frames are intact, see the end of the file.)

```

0694TFe      TGGAAGGGTTAATTTACTCCAAGAAAAGGCAAGAGATCCTTGATTGTGGGTCTATCACA   60
w101.10.6    -----
0694TFe      CACAAGGCTTCTTCCTGATTGGCAAACTACACACCGGGACCAGGGGTGAGATTTCAC   120
w101.10.6    -----A-----
0694TFe      TGACCTTTGGATGGTGCTTCAAGCTAGTGCCAGTCAGCCCAGAGGAAGTAGAAGAGGCCA   180
w101.10.6    -----
0694TFe      ATAAAGGAGAAAACAACTGTCTACTGCACCCTGGGAGCCTGCATGGAATGGAGGATGAAC   240
w101.10.6    -----
0694TFe      ACAGAGAAGTATTAAGATGGAAGTTTGACAGTCAACTAGCACGCAGACACCTGGCCCGCG   300
w101.10.6    -----
0694TFe      AACAAACATCCGGAGTATTACAAAGACTGCTGACACAGAAGGGACTTTCCGCTGGGACTTC   360
w101.10.6    -----T-----
0694TFe      CCACTAGGGGCGTTCCAGGGGAGTGGTCTGGGCGGGACTTGGGAGTGGCCAGCCCTCAGA   420
w101.10.6    -----
0694TFe      TGCTGCATATAAGCAGCTGCGTTTCGCCTGTACTGGGTCTCTCTAGGTAGACCAGATCTG   480
w101.10.6    -----T-----
0694TFe      AGCCTGGGAGCTCTCTGGCTATCTGGGGAACCCACTGCT   519
w101.10.6    -----A----- 519

```

If you wanted to study if these mutations might impact CTL escape in the LTR, as George has been studying, you could use the following for peptide design:

115

AAACTACACACCGGGACCAGGGGTGAGATTTCCTACTGACCTTTGGATGGTGCTTCAAGCTA
 AAACTACACACCGGGACCAGGGGTGAGATATCTACTGACCTTTGGATGGTGCTTCAAGCTA

115 RF1:

K T T H R D Q G S D F H *
 K T T H R D Q G S D I H *

115 RF2: silent substitution – so NOT CTL selection in this frame

K L H T G T R G Q I S T D L W M V L Q A
 K L H T G T R G Q I S T D L W M V L Q A

115 RF3: This is in Nef and in the LTR both:

Q N Y T P G P G V R F P L T F G W C F K L
 Q N Y T P G P G V R Y P L T F G W C F K L

357

TGACACAGAAGGGACTTTCCGCTGGGACTTCCCACTAGGGGCGTTCCAGGGGAGTGGTCTG
 TGACACAGAAGGGACTTTCCGCTGGGACTTCCCACTAGGGGCGTTCCAGGGGAGTGGTCTG

357 RF1: silent substitution – so NOT CTL selection in this frame

D T E G T F R W D F P L G A F Q G S G L
 D T E G T F R W D F P L G A F Q G S G L

357 RF2:

L T Q K G L S A G T S H *

L T Q K G L S A G T F H *

357 RF3:

* H R R D F P L G L P T R G V P G E W S G
* H R R D F P L G L S T R G V P G E W S G

440:

AGCCCTCAGATGCTGCATATAAGCAGCTGCGTTTCGCCTGTACTGGGTCTCTCTAGGTAGAC
AGCCCTCAGATGCTGCATATAAGCAGCTGCGTTTCGCCTGTACTGGGTCTCTCTAGGTAGAC

440 RF1:

* A A A F R L Y W V S L G R
* A A A F R L Y W V S L G R

440 RF2:

Q P S D A A Y K Q L R F A C T G S L *
Q P S D A A Y K Q L L F A C T G S L *

440 RF3:

S P Q M L H I S S C V S P V L G L S R *
S P Q M L H I S S C F S P V L G L S R *

504:

GATCTGAGCCTGGGAGCTCTCTGGCTATCTGGGAACCCACTGCT
GATCTGAGCCTGGGAGCTCTCTGGCTATCTAGGGAACCCACTGCT

504 RF1:

D L S L G A L W L S G E P T A
D L S L G A L W L S R E P T A

504 RF2: silent substitution – so NOT CTL selection in this frame

* A W E L S G Y L G N P L
* A W E L S G Y L G N P L

504 RF3: early stop codon introduced:

R S E P G S S L A I W G T H C
R S E P G S S L A I *

115 Rev Comp: Overlapping with Nef ORF

CTAGCTTGAAGCACCATCCAAAGGTCAGTGGAAATCTGACCCCTGGTCCCGGTGTGTAGTTTT
CTAGCTTGAAGCACCATCCAAAGGTCAGTGGATATCTGACCCCTGGTCCCGGTGTGTAGTTTT

115 Rev Comp RF1:

* S T I Q R S V E I *
* S T I Q R S V D I *

115 Rev Comp RF2:

* L E A P S K G Q W K S D P W S R C V V L
* L E A P S K G Q W I S D P W S R C V V L

115 Rev Comp RF3:

T S L K H H P K V S G Y L T P G P G V *
T S L K H H P K V S G N L T P G P G V *

357 Rev Comp

CCAGACCACTCCCCTGGAACGCCCTAGTGGGAAGTCCCAGCGGAAAGTCCCTTCTGTGTCAG
CCAGACCACTCCCCTGGAACGCCCTAGTGGAAAGTCCCAGCGGAAAGTCCCTTCTGTGTCAG

357 Rev Comp RF1:

* W E V P A E S P F C V S
* W K V P A E S P F C V S

357 Rev Comp RF2: silent substitution – so NOT CTL selection in this frame

P R P L P W N A P S G K S Q R K V P S V S
P R P L P W N A P S G K S Q R K V P S V S

357 Rev Comp RF3:

P D H S P G T P L V G S P S G K S L L C Q
P D H S P G T P L V E S P S G K S L L C Q

440 Rev Comp

GGTCTACCTAGAGAGACCCAGTACAGGCGAAA**C**GCAGCTGCTTATATGCAGCATCTGAGGGCT
 GGTCTACCTAGAGAGACCCAGTACAGGCGAAA**A**GCAGCTGCTTATATGCAGCATCTGAGGGCT

440 Rev Comp RF1:

* _ R _ D _ P _ V _ Q _ A _ K _ **R** _ S _ C _ L _ Y _ A _ A _ S _ E _ G _
 * _ R _ D _ P _ V _ Q _ A _ K _ **S** _ S _ C _ L _ Y _ A _ A _ S _ E _ G _

440 Rev Comp RF2:

_ G _ L _ P _ R _ E _ T _ Q _ Y _ R _ R _ **N** _ A _ A _ A _ Y _ M _ Q _ H _ L _ R _ A _
 _ G _ L _ P _ R _ E _ T _ Q _ Y _ R _ R _ **K** _ A _ A _ A _ Y _ M _ Q _ H _ L _ R _ A _

440 Rev Comp RF3:

_ V _ Y _ L _ E _ R _ P _ S _ T _ G _ E _ **T** _ Q _ L _ L _ I _ C _ S _ I _ *
 _ V _ Y _ L _ E _ R _ P _ S _ T _ G _ E _ **K** _ Q _ L _ L _ I _ C _ S _ I _ *

504 Rev Comp

AGCAGTGGGTTCCCCAGATAGCCAGAGAGCTCCCAGGCTCAGATCTG
 AGCAGTGGGTTCCCTAGATAGCCAGAGAGCTCCCAGGCTCAGATCTG

504 Rev Comp RF1: too short

_ S _ G _ F _ P _ **R** _ *
 _ S _ G _ F _ P _ **R** _ *

504 Rev Comp RF2:

_ A _ V _ G _ S _ **P** _ D _ S _ Q _ R _ A _ P _ R _ L _ R _ S _ G _
 _ A _ V _ G _ S _ **L** _ D _ S _ Q _ R _ A _ P _ R _ L _ R _ S _ G _

504 Rev Comp RF3

_ Q _ W _ V _ P _ **Q** _ I _ A _ R _ E _ L _ P _ G _ S _ D _ L _ V _
 _ Q _ W _ V _ P _ *

[156] If you wanted to test if the 4 mutations that are most strongly selected in the LTR are CTL susceptible, you would need to test the 18 peptides on the left. This fully scans the regions bounding these mutations in each of the 6 reading frames, including the reverse complement. All peptides bounding these sites that: i) don't run into a stop codon, and ii) where the change that goes to fixation is not silent in that frame are included. Some are short because they run up against a stop codon.

115 RF1:	KTTHRDQGSDFH	KTTHRDQGSDIH
115 RF3*:	NYTPGPGVR F PLTFGWCFK	NYTPGPGVRYPLTFGWCFK
357 RF2:	LTQKGLSAGT S H	LTQKGLSAGT F H
357 RF3:	HRRDFPLGL P TRGVPGEWS	HRRDFPLGL S TRGVPGEWS
440 RF2:	QPSDAAYKQ L RFACTGSL	QPSDAAYKQ L LFACTGSL
440 RF3:	PQMLHISSC V SPVLGLSR	PQMLHISSC F SPVLGLSR
504 RF1:	DLSLGALWLS G EPTA	DLSLGALWLS R EPTA
504 RF3:	RSEPGSSLA I WGTHC	RSEPGSSLA I **
115-RC-RF1:	STIQRS V EI	STIQRS V DI
115-RC-RF2:	LEAPSKGQ W KSDPWRCVV	LEAPSKGQ W ISDPWRCVV
115-RC-RF3:	LKHHPKVSG Y LTPGPGV	LKHHPKVSG N LTPGPGV
357-RC-RF1:	W EVPAESPFCVS	W KVPAESPFCVS
357-RC-RF3:	DHSPGTPLV G SPSGKSLLC	DHSPGTPLV E SPSGKSLLC
440-RC-RF1:	RDPVQAK R SCLYAASEG	RDPVQAK S SCLYAASEG
440-RC-RF2:	LPRETQYRR N AAAYMQHLR	LPRETQYRR K AAAYMQHLR
440-RC-RF3:	YLERPSTGET T QLLICSI	YLERPSTGE K QLLICSI

504-RC-RF2:	AVGSPDSQRAPRLRSG	AVGSLDSQRAPRLRSG
504-RF-3:	QWVPQIARELPGSDLV	**

*This is in Nef and in the LTR both

** introduces a stop codon.

[157] The HLA for this individual is:

A*30:01

A*74:01/02/03/09

B*42:02

B*15:10

Cw*17:01/02/03/04

Cw*03:04/06/09/19/23/24/26/32/37/44/46/48/54/57/63/64/72/73/74/77/78

[158] IEDB predict a number of possible HLA binding peptides within these fragments; it is not sure what to think about epitope prediction and processing in such cases, so it would be best just to check them for T-cell activity.

[159] CH0694.3.w101.10.6-env has many differences relative to the TF virus, as do all w102 Env, but it has all 4 changes of interest in the LTR and no others within the LTR, so could be an interesting virus for comparing phenotypes.

>CH0694.3.w101.10.6-env

```

MRVRGIPRN-YQHWWTWGILGFWMMLMICNAG-EQ--RWVTVYYGVPVWKE
AKTTLFCASDAKAYEKEAHNVWATHACVPTDPSPQELV-LENVTFENFMW
KNDMVEQMHEDIISLWDQSL-KPCVKLTPLCVTLECTKANFT-----
-----NSTSS-----NNSTYS---NNTM-K-EEMKNCSFNATTEI
RDKQ-KKMYAL-FYKLDIVPL-----KEDKNNSNNSNKYILINCNTST
IAQACPKISFDPIPIHYCAPAGYAILKCNNKTFNGTGPCSNVSTVQCTHG
IKPVVSTQLLNGSLAEEEEIIIRSENLTDNKTIIIVHLNESVEIKCTRPG
NNTRQ--SVRIGPGQTFYATGDIIGDIRQAHCNISEGKWNATLLKVRE-K
LAEHF-PNKTI-RFNSSAGGDLEITHTTFICGGEFFYCNTSGLFNRTYYA
N-----ANETAK--YVN---STNGN-----ITLQCRIKQF
INMWQRVGRAMYAPPIAGSITCRSNITGLL-----LTRDGG-----E

```

NGT-----ETFRPGGDMRDNRSELYKYKVVEIKPL-GI
 APTEAK-RRVVEREK-RAVGLGAVLLGFLGAAGSTMGAASITLTVQARQL
 LSGIVQQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDQQLLG
 LWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMTWMQW-DREVSNYTDIIY
 ELLEESQ-NQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGL
 IGLRIVFAILSLVNRVRQGYSPSLQTLIPNQRPDRPGGIEEEEGGEKDR
 GRSVRLVSGFLALAWDDLRSCLFSYHRLRDLLLILARAVELLGHSILRS
 LQRGWEVLKYLGNLVQYWGLELKKS AISLLDTIAIAVAEGTDRIIE----
 F-CRAIYNIPTRI-RRGFEEALQ*

>CH0694.3.w101.10.6-env.not-TF

.....P.....G-.Q.....
 ..T.....
T.....
-S.....Y.....K.....
K.....NNSN.....
N.....
E...N.....E.K.....
G.....
R.....
 N.....A.E.....N.N.....
S.....N.....E
 .G.....-.....
V...V.....
K.....
N.T.....D...
 E...E.....K.....

 ...V.....L.....

.....----

F.....

>CH0694.3.w101.10.6-nef

MGNKWSK---GWPTIRERMRQTDPAAEVGAASQDLDRRGALTTSNTAQ

TNAACAWLEAQEEEGEVGFVPRPQVPLRPMTFKAAFDLSFFLKEKGGLEG

LIYSKKRQEILDLWVYHTQGFFPDWQNYTPGPGVRYPLTFGWCFKLVPVS

PEEVEEANKGENNCLLHPGSLHGMEDEHREVLRWKFDSQLARRHLAREQH

PEYYKDC*

>CH0694.3.w101.10.6-nef.not-TF

.....I.....D.....

.....E.....R.....F...F.....

.....Y.....

.....

>CH0694.3.w101.10.6-pol

PIWKGPALLWKGEAVVIQDNSDIKVVPRR-KAKIIRDYKGQMGADCV

AGRQDEDQ

>CH0694.3.w101.10.6-pol.not-TF

.....

.....

>CH0694.3.w101.10.6-rev

MAGRSGSDAALLQAVRTIKILYQSNPYPKPEGTRQARRNRRRRWRKRQR

QIRALSERILSTCLGRPTPEVPFQLPPIERLAINSSSGTSGTQHSQEP

AEGVGSP*VSGKPCAVLGSGTKKE

>CH0694.3.w101.10.6-rev.not-TF

.....T.....

..RA.....S.....

.....

>CH0694.3.w101.10.6-tat

MDPVDPNLEPWNHPPGSPNTACNKCCKRCCYHCSVCFLTGLGISYGRK
KRRQRRSSPPSSEDHQNPLSKQPLSQTRGDPTGPEESKKKVEKKTEADPC

A*

>CH0694.3.w101.10.6-tat.not-TF

.....K.....S.....
.....C
..

>CH0694.3.w101.10.6-vif

MENKWQGLIVWQVDRMRIRTWNSLVKHHMYVSKKTTGWFYRHHYESRHRP
VSSEVHIPIGDARLVIITYWGLQTGERDWHLGNGVSIWRLRRYSTQVDP
GLADQLIHMYFDCFADSAIRRAILGEIVSPRCEYPAGHNQVGSLLQYLAL
TALIKPK-KRKPPLPSVRK-LVEDRWKPKQKTRGRRGNHTMNGH*

>CH0694.3.w101.10.6-vif.not-TF

.....
.....I.....N.....
.....E.....
.....R.....

>CH0694.3.w101.10.6-vpr

MEQAPEDQGPQREPYNEWALELLEELKQEAVRHFPWPWLHGLGQYIYETY
GDTWTGVEAIIRVLQQLLFH-FRIGCRHSRIGILRQRRARNGSSRS*

>CH0694.3.w101.10.6-vpr.not-TF

.....
.....R.....

>CH0694.3.w101.10.6-vpu

HEMIDFLARVDYRLGVGALIVALILAIIVWTIAYLEYRKVVRQRKIDWLI
ERIRERAEDSGNESEGDTEE-LSTLVDMGHLRLLDVNDL*

>CH0694.3.w101.10.6-vpu.not-TF

....D.....V.R.....

.....

WHAT IS CLAIMED IS:

1. A composition comprising an HIV-1 envelope protein as set forth in Figure 26, or immunogenic subunit thereof, and a carrier.
2. A composition comprising a nucleic acid encoding the envelope protein of claim 1.
3. The composition according to claim 1 wherein said composition comprises the gp120 subunit or gp140 subunit of an HIV-1 envelope protein from a sequence set forth in Figure 26.
4. The composition according to claim 1 wherein said composition further comprises an adjuvant.
5. A nucleotide sequence encoding an HIV-1 envelope protein, as set forth in Figure 26 or immunogenic subunit thereof, wherein said nucleotide sequence is present in a vector.
6. The nucleotide sequence of claim 5 wherein the vector is a viral vector or mycobacterial vector.
7. A composition comprising the nucleotide sequence according to claim 5 and an adjuvant.
8. A method of inducing an immune response comprising administering to a mammal in need thereof the composition of claim 1 or 5 in an amount sufficient to effect the induction.
9. The method according to claim 8 wherein said mammal is a human.
10. The method of claim 8, wherein the composition comprises CH694TF HIV-1 envelope or a nucleotide sequence encoding the same administered as a prime.
11. The method of claim 8, wherein the composition comprises a selection of CH694 envelopes of Figure 26 or nucleic acids sequences encoding the same administered as a boost.
12. An isolated antibody having the binding specificity DH175, or antigen binding subunit thereof.

13. The antibody according to claim 12 wherein said antibody, or said subunit thereof, comprises the CDRs as set forth in Figure 27.
14. The antibody according to claim 12 wherein said antibody, or said subunit thereof, comprises a heavy or light chain amino acid sequence set forth in Figure 27.
15. The antibody according to claim 12 wherein said antibody is DH175.
16. A method of preventing or treating HIV-1 comprising administering to a subject in need thereof said antibody, or said subunit thereof, according to claim 12 in an amount sufficient to treat or prevent HIV-1 infection.
17. The method according to claim 16 wherein said subject is a human.

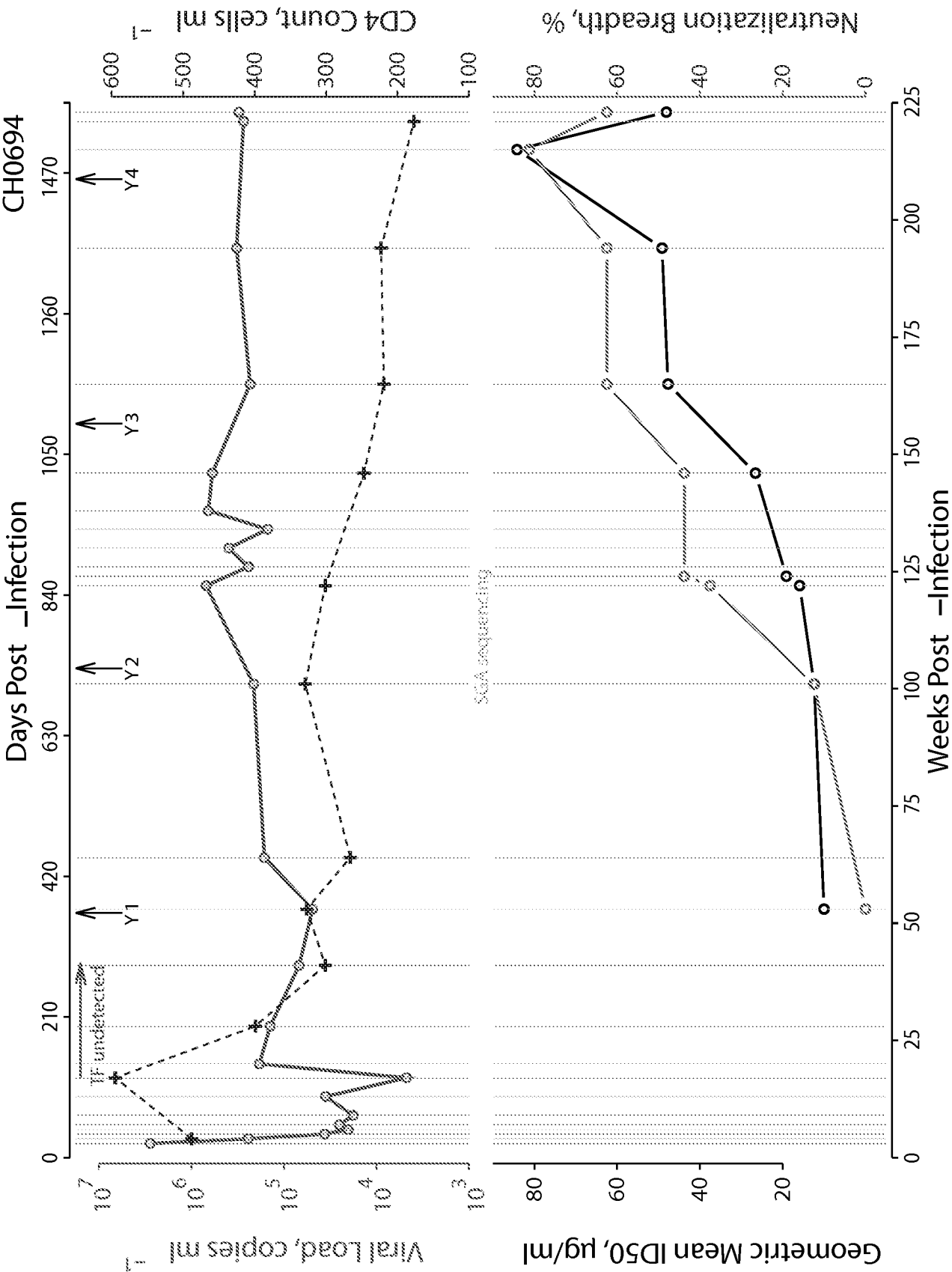
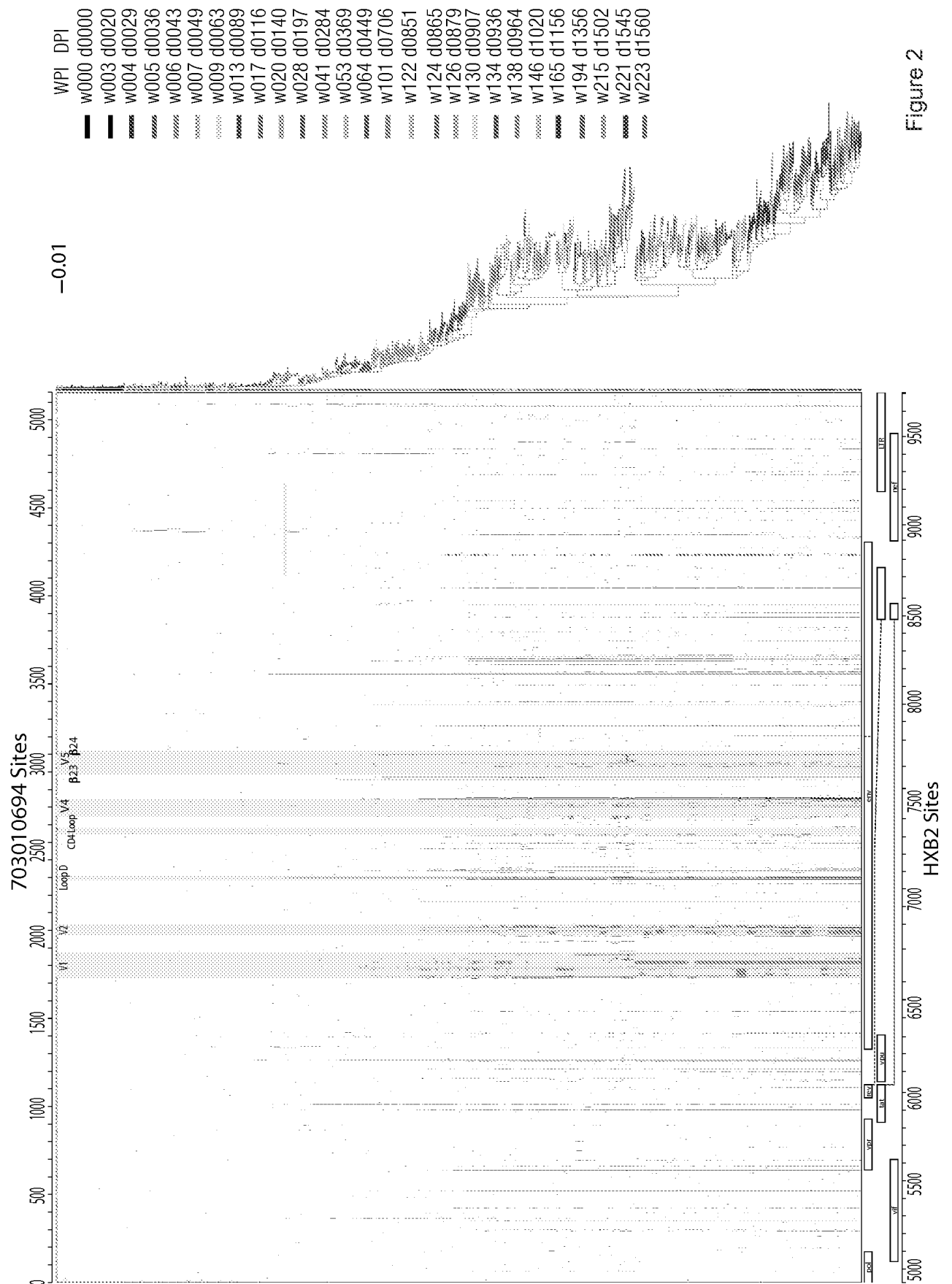


Figure 1



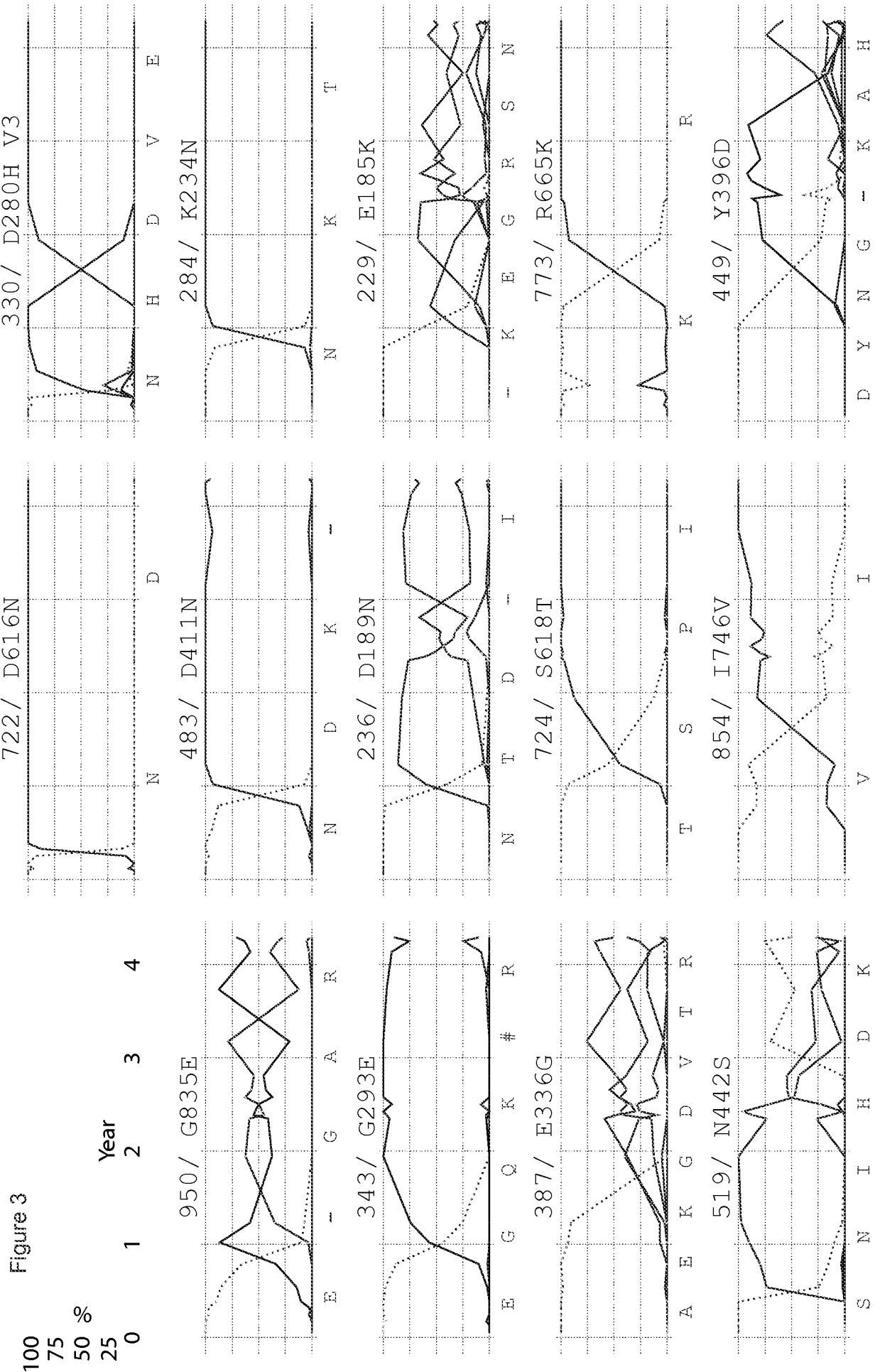


Figure 3 Cont.

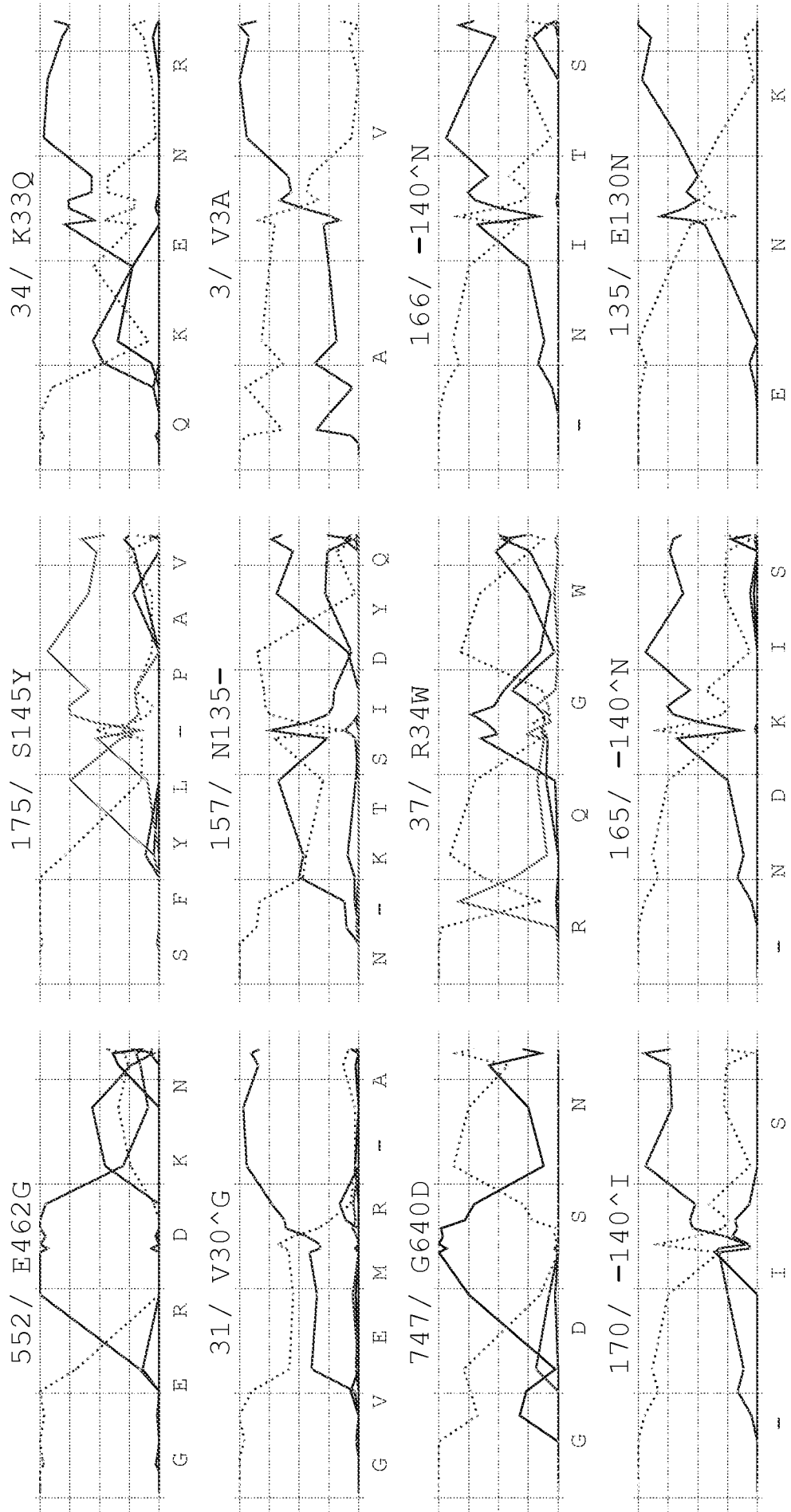


Figure 3 Cont.

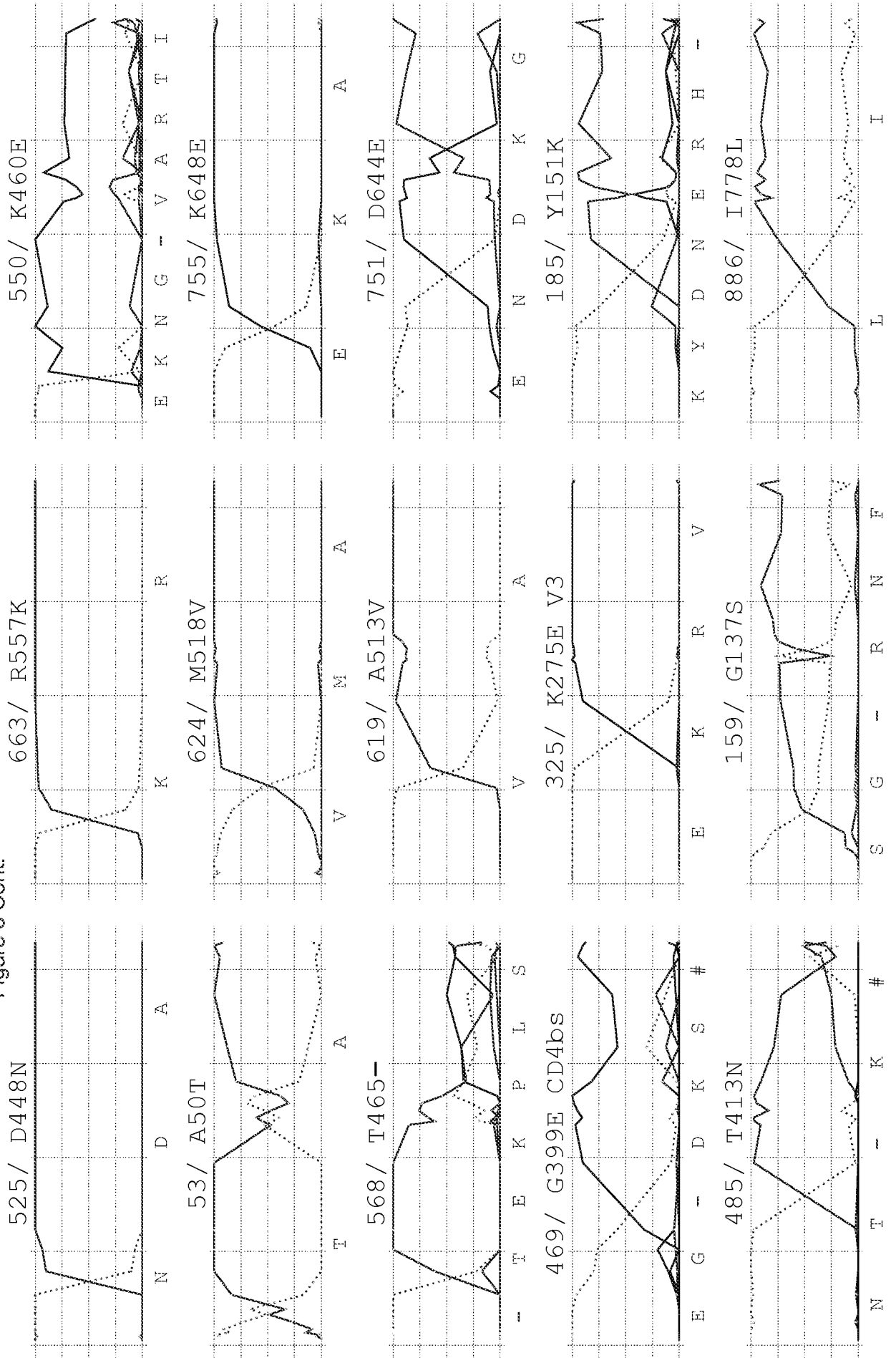
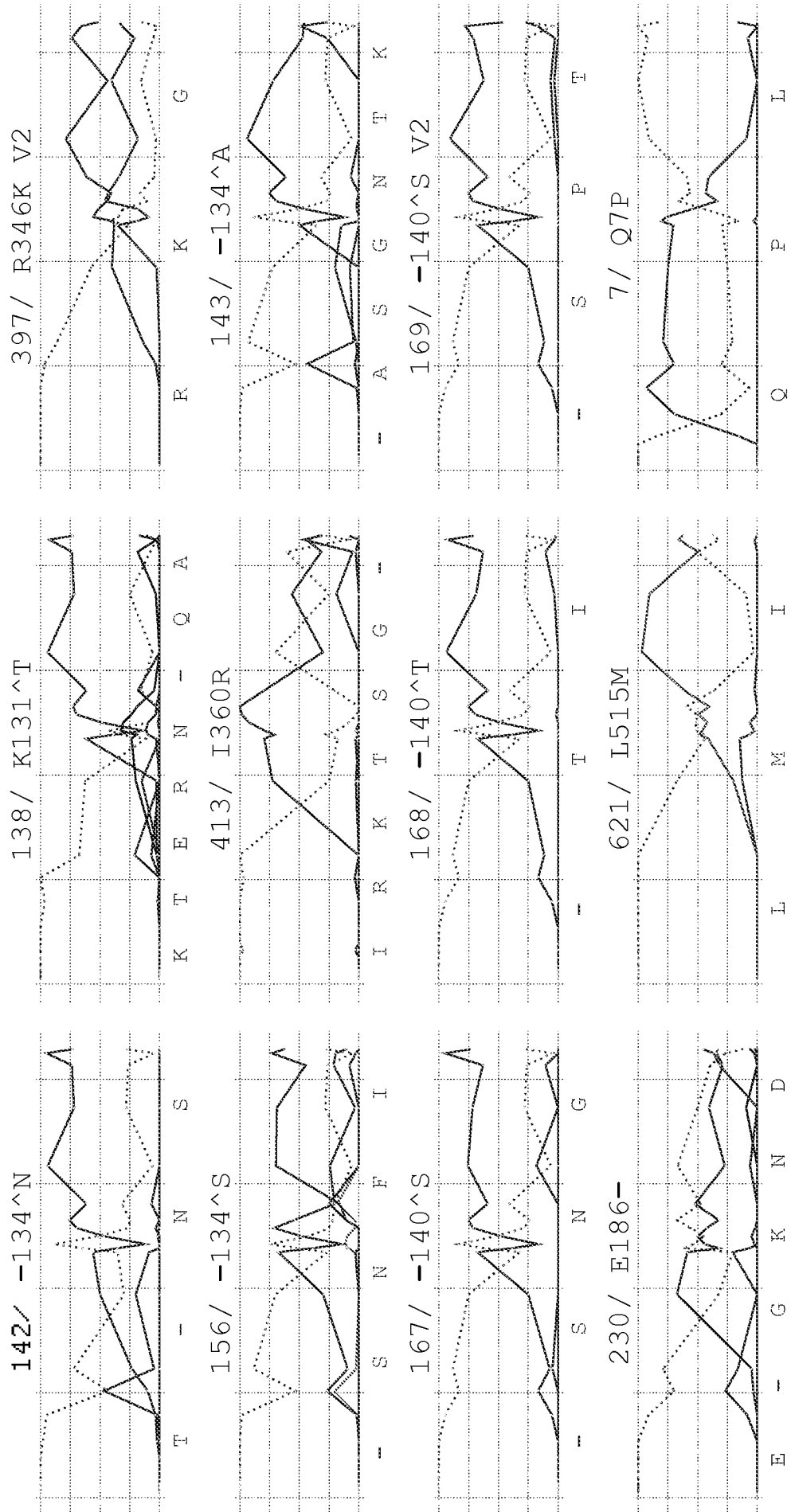


Figure 3 Cont.



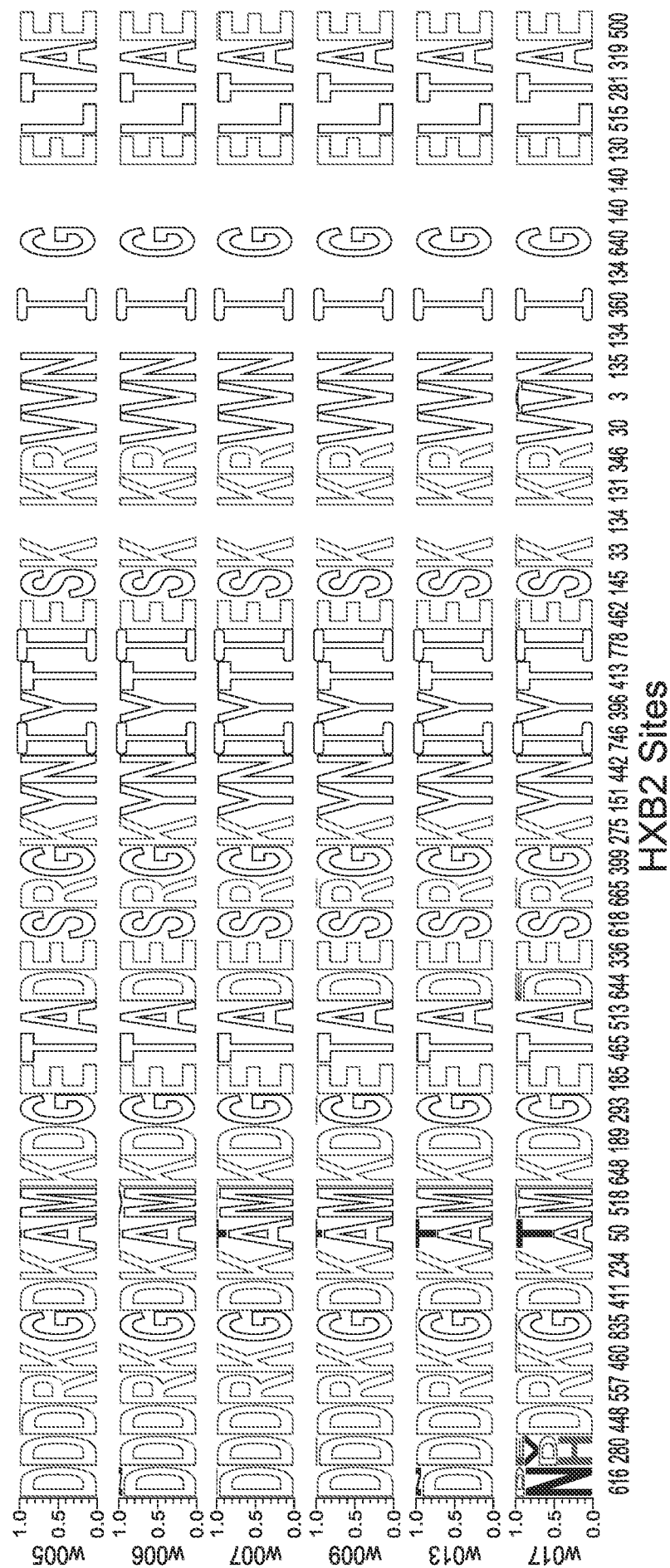


Figure 4

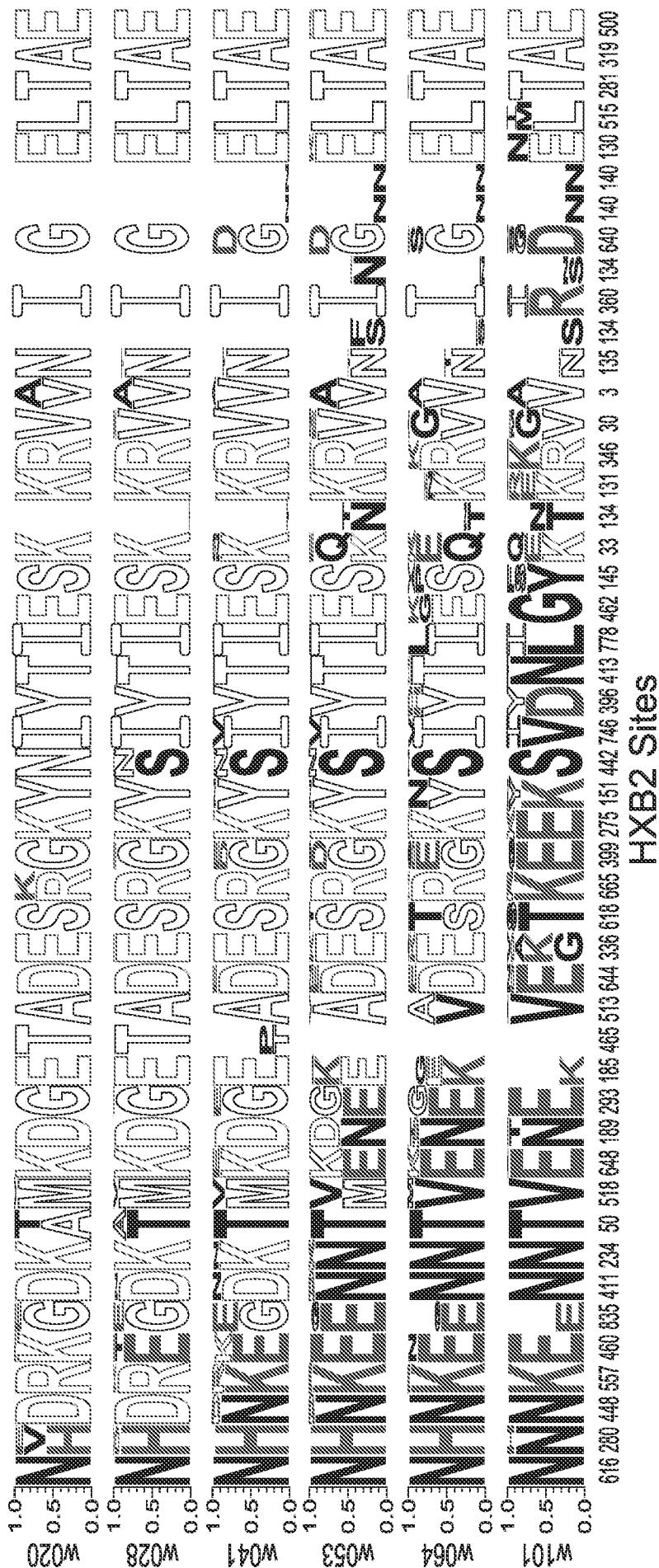


Figure 4 Cont.

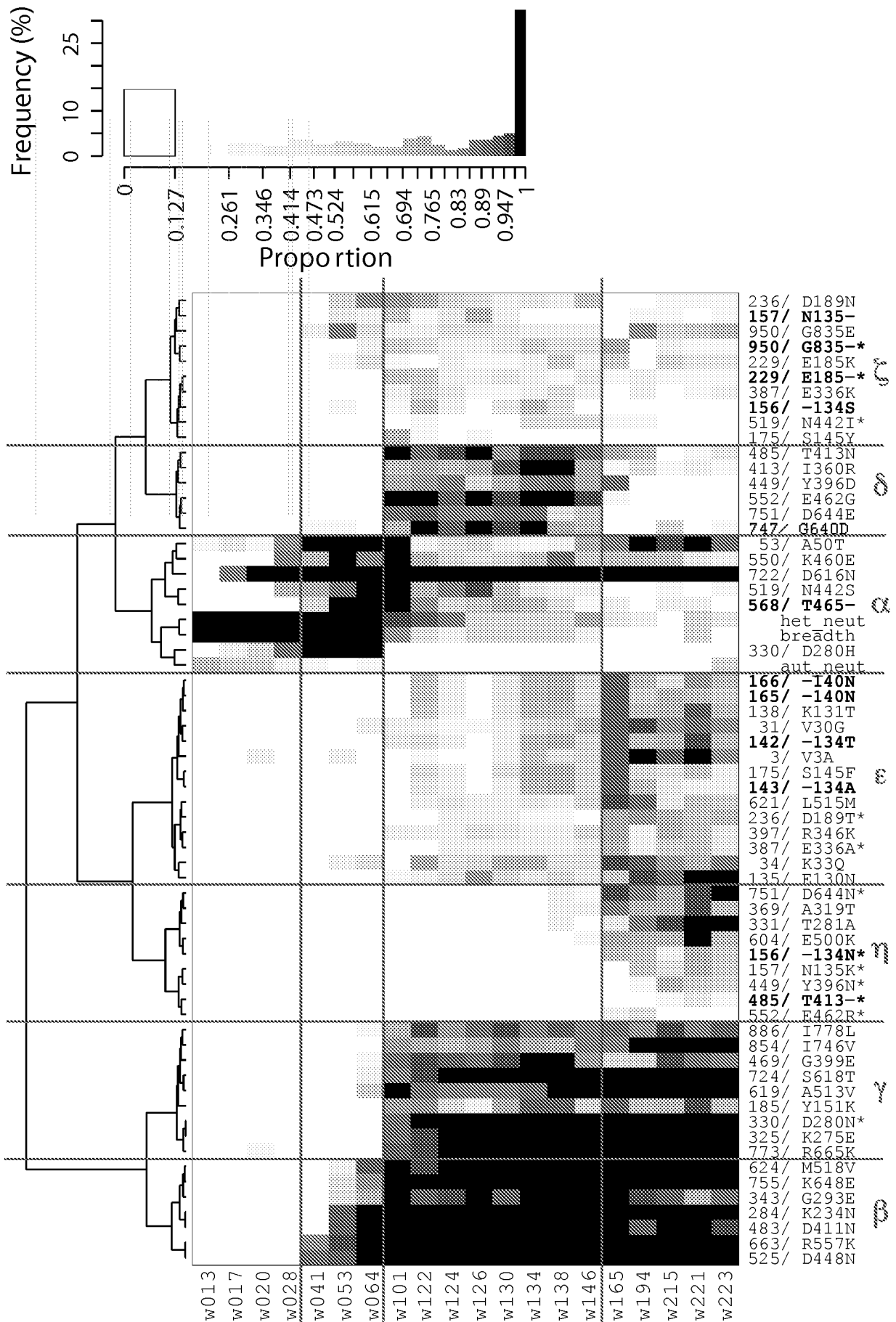
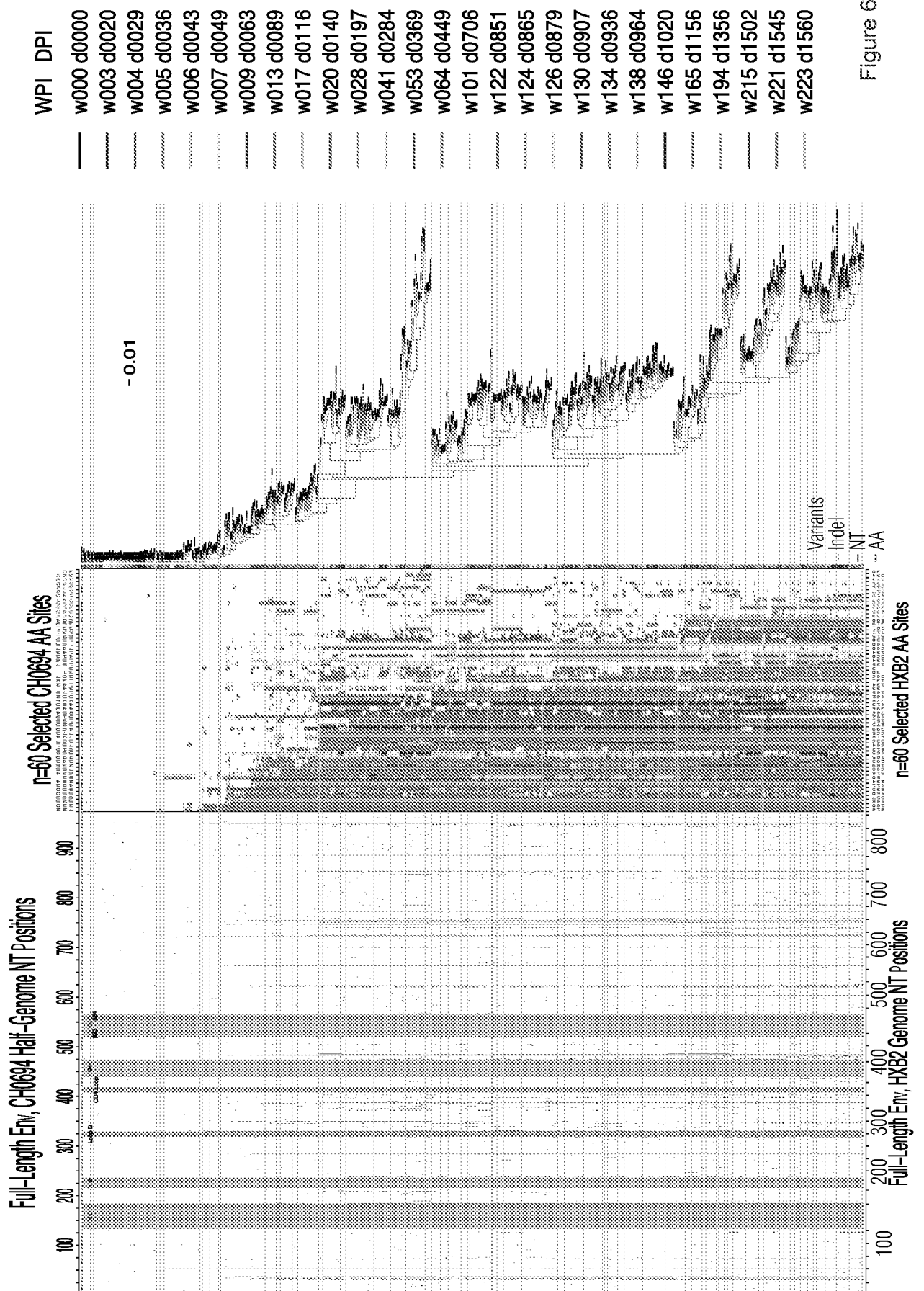


Figure 5





w028	1.0	NH	DR	EG	DK	TM	KG	ET	AD	ES	RK	YS	YT	IES	K	KRV	NI	G	EL	NT	AE	NQ	ET	GR	DG	YS	A
	0.5																										
	1.0																										
w041	1.0	NH	KE	GD	K	TM	KG	ET	AD	ES	RK	YS	YT	IES	K	KRV	NI	G	EL	NT	AE	NQ	ET	GR	DG	YS	A
	0.5																										
	1.0																										
w053	1.0	NH	KE	EN	NT	ME	NE	KE	AD	ES	RK	YS	YT	IES	K	KRV	NI	G	EL	NT	AE	NQ	ET	GR	DG	YS	A
	0.5																										
	1.0																										
w064	1.0	NH	KE	EN	NT	VE	NE	KE	AD	ES	RK	YS	YT	IES	K	KRV	NI	G	EL	NT	AE	NQ	ET	GR	DG	YS	A
	0.5																										
	1.0																										
w101	1.0	NN	KE	EN	NT	VE	NE	KE	SV	DL	GY	RT	KS	VR	DR	AD	EN	NT	AE	NQ	ET	GR	DG	YS	A		
	0.5																										
	1.0																										
w122	1.0	NN	KE	EN	NA	VE	NE	KE	SV	DL	GF	QT	TS	VS	NR	AD	NN	NT	AE	NQ	ET	GR	DG	YS	A		
	0.5																										
	1.0																										
w124	1.0	NN	KE	EN	NA	VE	NE	KE	SV	DL	GS	QT	TS	VS	NR	AD	NN	NT	AE	NQ	ET	GR	DG	YS	A		
	0.5																										
	1.0																										
w126	1.0	NN	KE	EN	NA	VE	NE	KE	SV	DL	GS	QT	TS	VS	NR	AD	NN	NT	AE	NQ	ET	GR	DG	YS	A		
	0.5																										
	1.0																										
w130	1.0	NN	KE	EN	NA	VE	NE	KE	SV	DL	GF	QT	TS	VS	NR	AD	NN	NT	AE	NQ	ET	GR	DG	YS	A		
	0.5																										
	1.0																										

Figure 7 Cont.

w134	1.0	0.5	1.0	NNNKE	NNNA	VE	KE	IV	ER	TK	EE	K	IV	DN	LG	FQ	TT	GG	NS	RA	DN	MT	AT	AE	NN	ET	GR	DG	YS	A	
w138	1.0	0.5	1.0	NNNKE	NNNA	VE	KE	IV	ER	TK	EE	K	IV	DN	LG	FQ	TT	GG	NS	RA	DN	MT	AT	AE	NN	ET	GR	DG	YS	A	
w146	1.0	0.5	1.0	NNNKE	NNNT	VE	KE	IV	ER	TK	EE	K	IV	DN	LG	FQ	TT	GG	NS	RA	DN	MT	AT	AE	NN	ET	GR	DG	YS	A	
w165	1.0	0.5	1.0	NNNKE	NNNT	VE	TE	KE	VN	AT	KE	K	V	DN	LG	FQ	TT	GG	NI	AG	NN	MT	AT	TK	NN	RE	TS	GR	DG	YS	A
w194	1.0	0.5	1.0	NNNKE	NNNT	VE	TE	KE	VN	AT	KE	K	V	DN	LG	FQ	TT	GG	NI	AG	NN	MT	AT	TK	NN	RE	TS	GR	DG	YS	A
w215	1.0	0.5	1.0	NNNKE	NNNT	VE	TE	KE	VN	AT	KE	K	V	DN	LG	FQ	TT	GG	NI	AG	NN	MT	AT	TK	NN	RE	TS	GR	DG	YS	A
w221	1.0	0.5	1.0	NNNKE	NNNT	VE	TE	KE	VN	AT	KE	K	V	DN	LG	FQ	TT	GG	NI	AG	NN	MT	AT	TK	NN	RE	TS	GR	DG	YS	A
w223	1.0	0.5	1.0	NNNKE	NNNT	VE	TE	KE	VN	AT	KE	K	V	DN	LG	FQ	TT	GG	NI	AG	NN	MT	AT	TK	NN	RE	TS	GR	DG	YS	A

722

330

525

663

550

950

483

284

53

624

236

343

229

568

619

751

387

724

773

469

325

185

519

854

449

485

886

552

175

142

138

397

31

3

157

156

413

143

747

135

621

831

331

369

604

546

345

355

386

347

545

378

372

840

209

385

30

Figure 7 Cont.

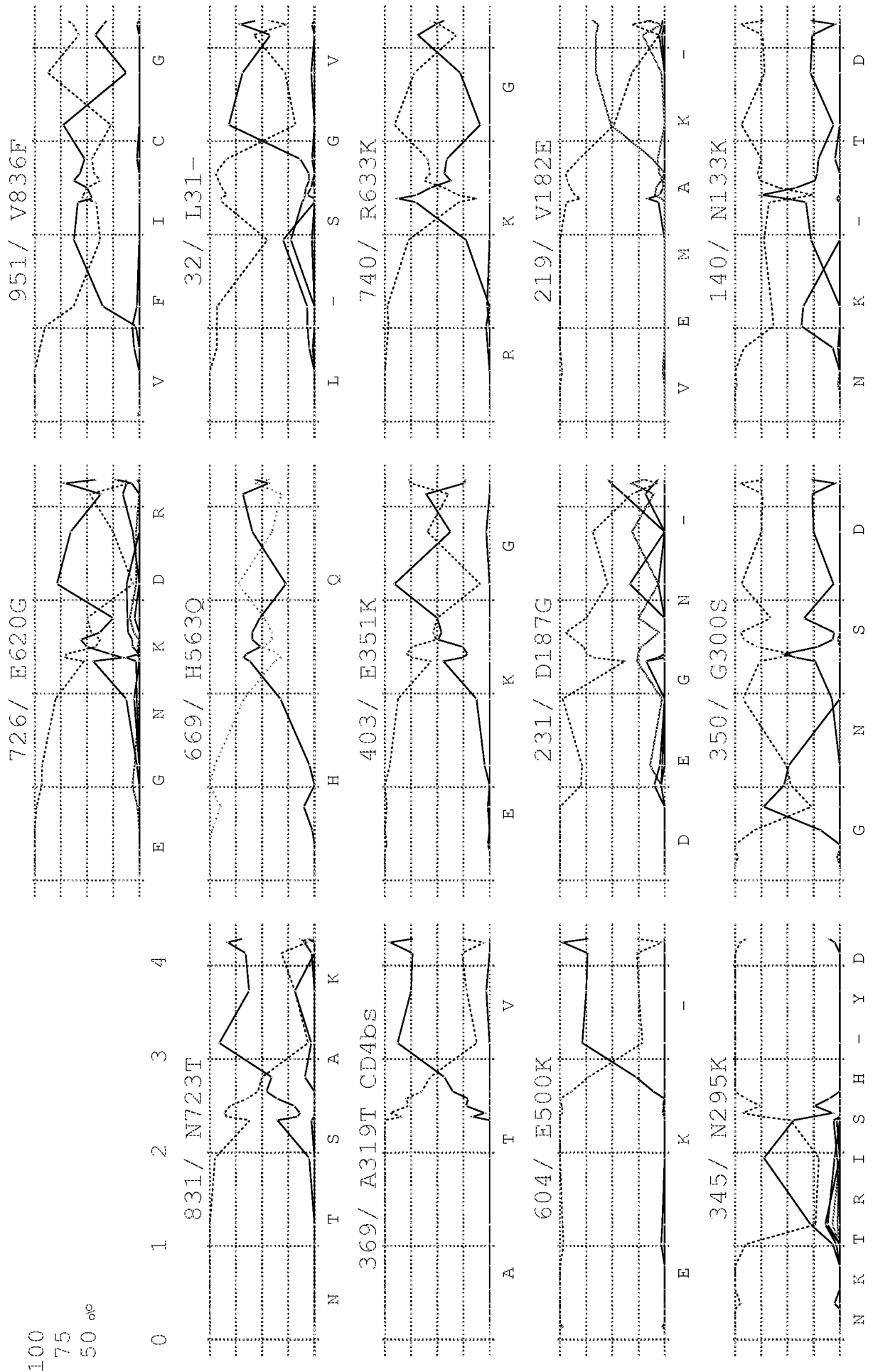


Figure 8

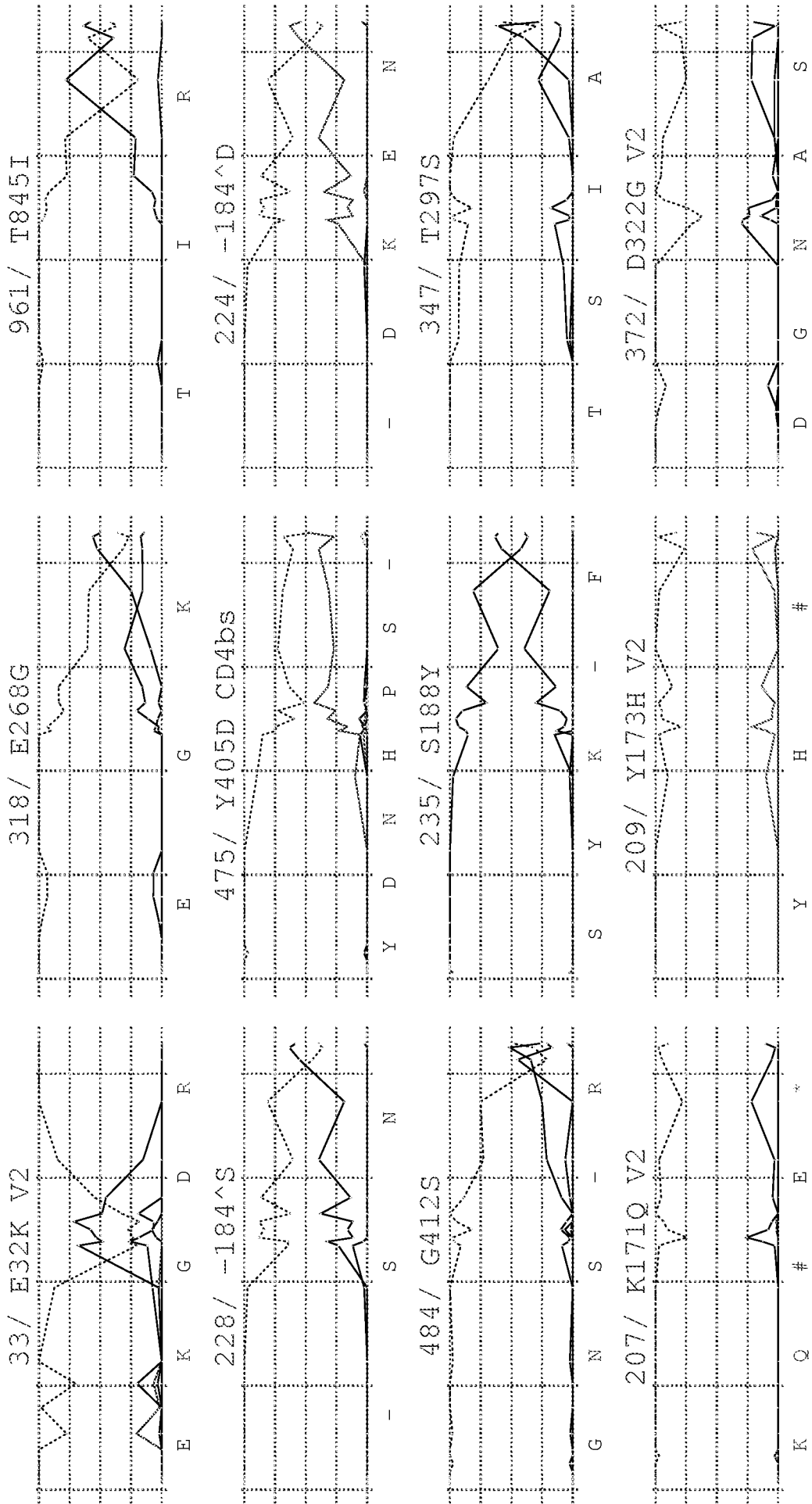


Figure 8 Cont.

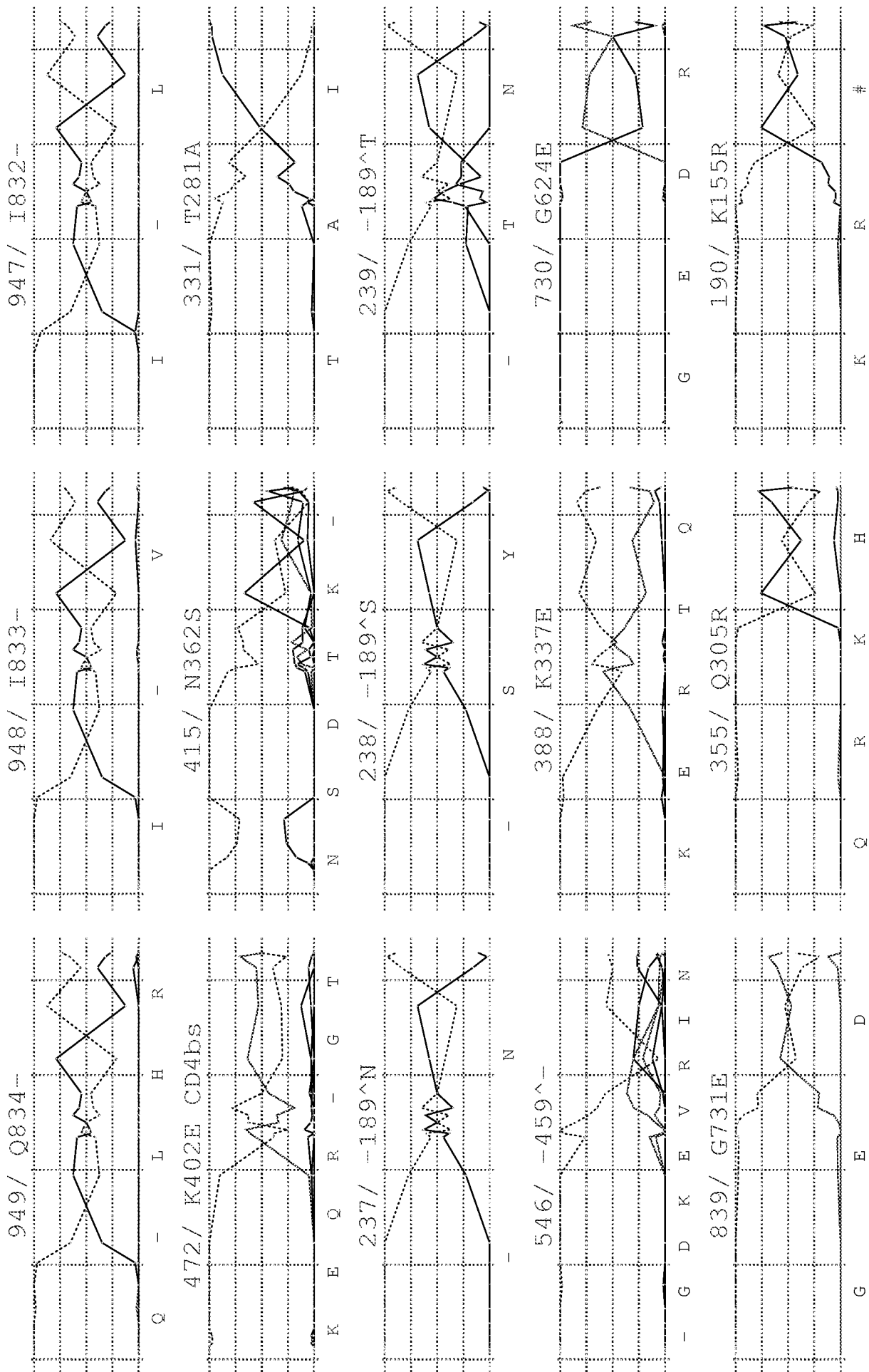


Figure 8 Cont.

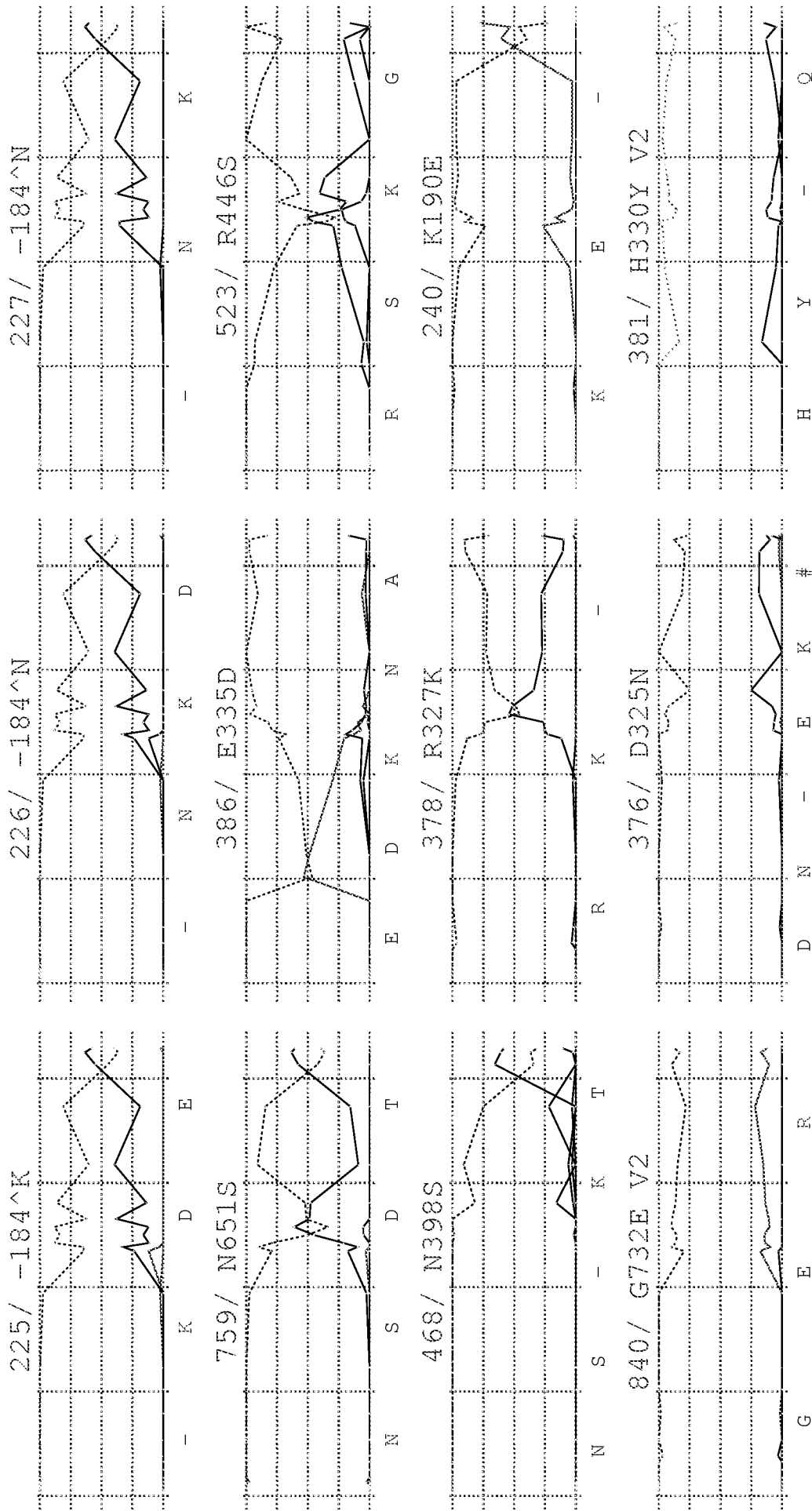


Figure 8 Cont.

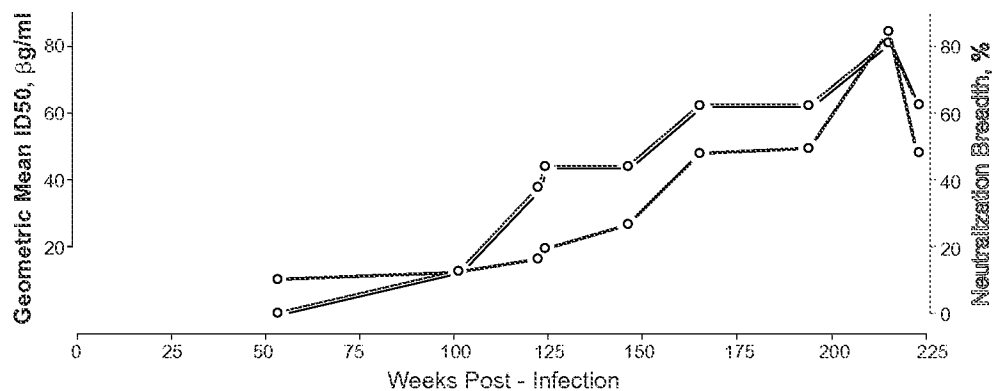


Figure 9

CHAVIID	Neut breadth (%)	Average potency	VRC01-like	b12-like	CD4-like	HJ16-like	8ANC195-like	PG9-like	PCT128-like	2G12-like	2F5-like	10E8-like
694	81%	145	0.09	0.08	0.05				0.52	0.26		

Figure 10

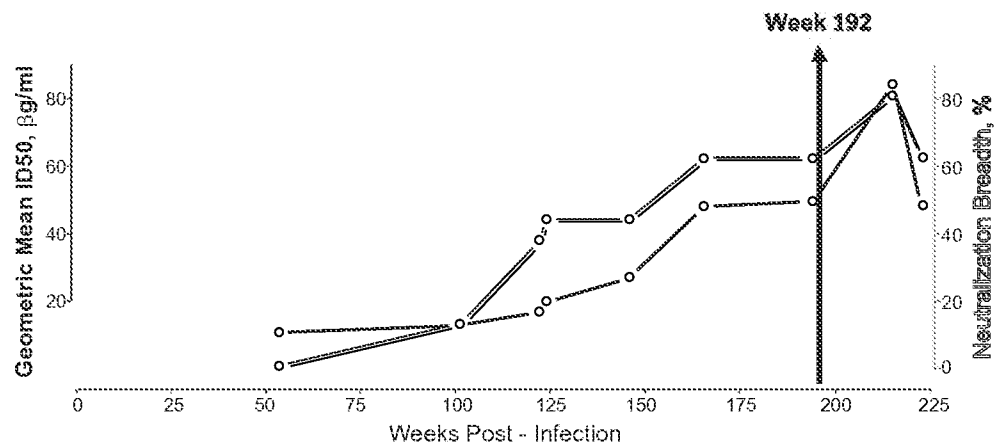


Figure 11

VH	D	JH	Mut. Freq.	HCDR3 length (AA)	HCDR3	Isotype	VL	JL	Mut. Freq.	LCDR3 length (AA)
4-34	2-IR2	6	14%	21	CVRGGALRWVGPWDPARHGLDVW	IgG1	K1-17	2	6%	9

- 9-nucleotide insertion in HCDR2 (gcaagtGGTGTGAACgcc)

High levels of somatic mutations, long HCDR3 and presence of indels characterize poly-/auto-reactive antibodies and are also commonly found among broadly HIV-1 neutralizing antibodies.

Figure 12

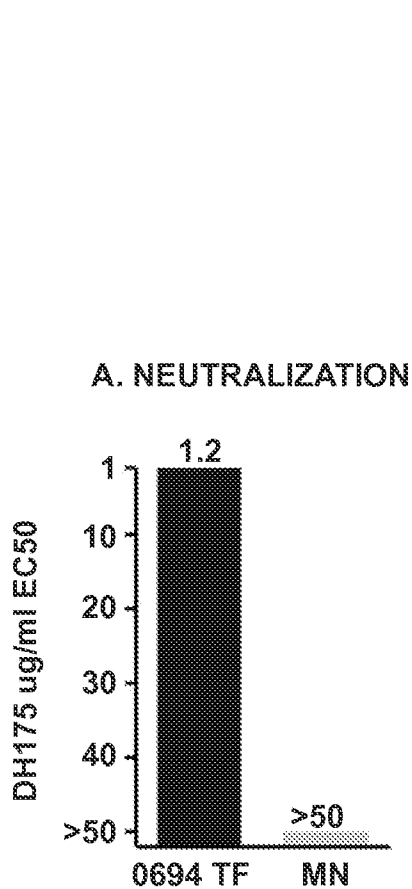


Figure 13A

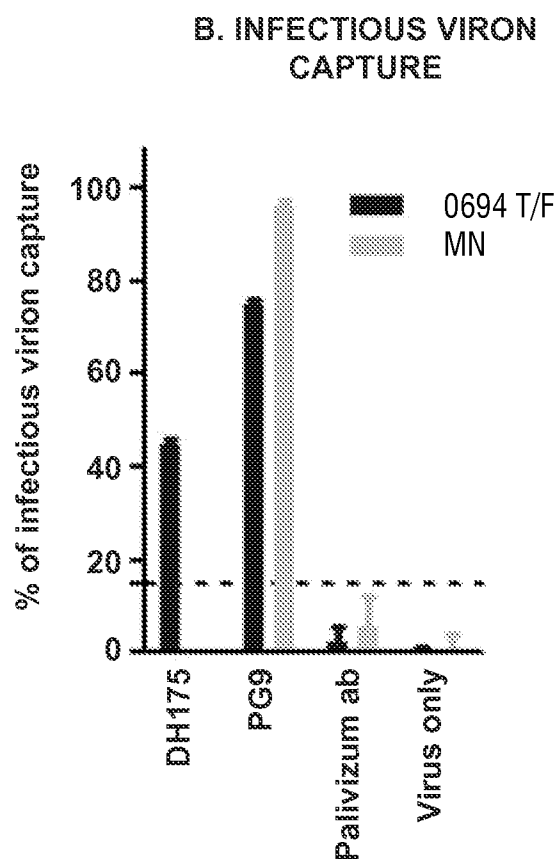


Figure 13B

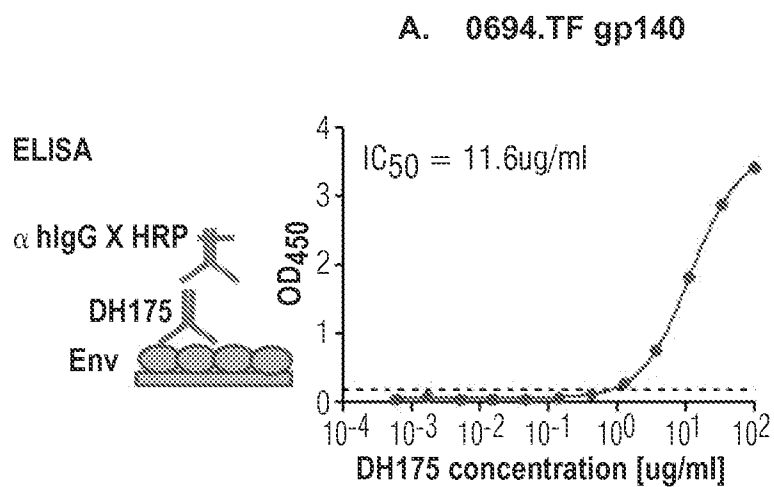


Figure 14A

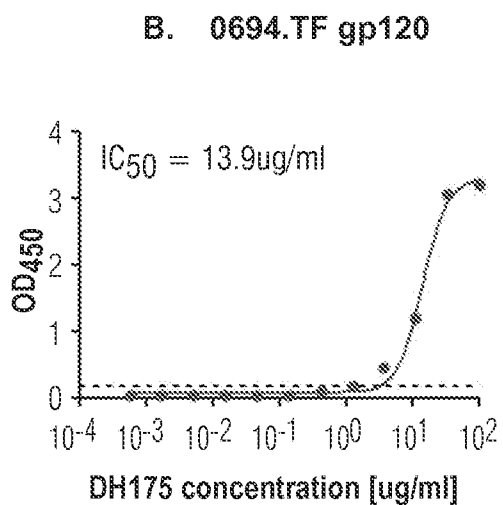


Figure 14B

TIER-1				Non-HIV			
iC ₅₀ values				iC ₅₀ values			
Sample	MN	>50	>50	Sample	SVA-MLV	>50	>50
	BaL	>50	>50		SIVmac	251.30	
	BG1168	>50	0.000				
	SF162	>50					
	MW965	>50					
Clade B			Clade C				

TIER-2

Sample	Clade A										Clade B										IC ₅₀ values		
	KER2008.12	KER2018.11	Q23.17	Q168.a2	Q769.h5	Q842.d12	398.F1	RW020.2	UG037.8	6101.10	7165.18	Bal.01	BG1168.01	BL01	CAANS342.A2	JR.FL	JR.CSF	PVO.4	THRO4156.18	TRJO4551.58		TRQ.11	YU2
DH176	> 50	> 50	0.677	> 50	> 50	28.3	0.590	> 50	> 50	> 50	> 50	> 50	> 50	> 50	> 50	4.994	> 50	> 50	> 50	1.49	0.652	> 50	> 50

Sample	IC ₅₀ values																									
	Clade C												Clade D		Clade G	CRF AC		CRF BC								
DH475	< 50	< 50	1.69	> 50	Du156.12	Du172.17	Du422.01	X2278	Ce703010217	SO18.18	25710	TV1.29	TZA125.17	ZA012.29	ZM55.28a	ZM106.9	ZM109F.PB4	ZM176.66	57128.vrc15	X1632	246-F3	BJOX	CNE8	Ce1176	CH119	> 50

Figure 15

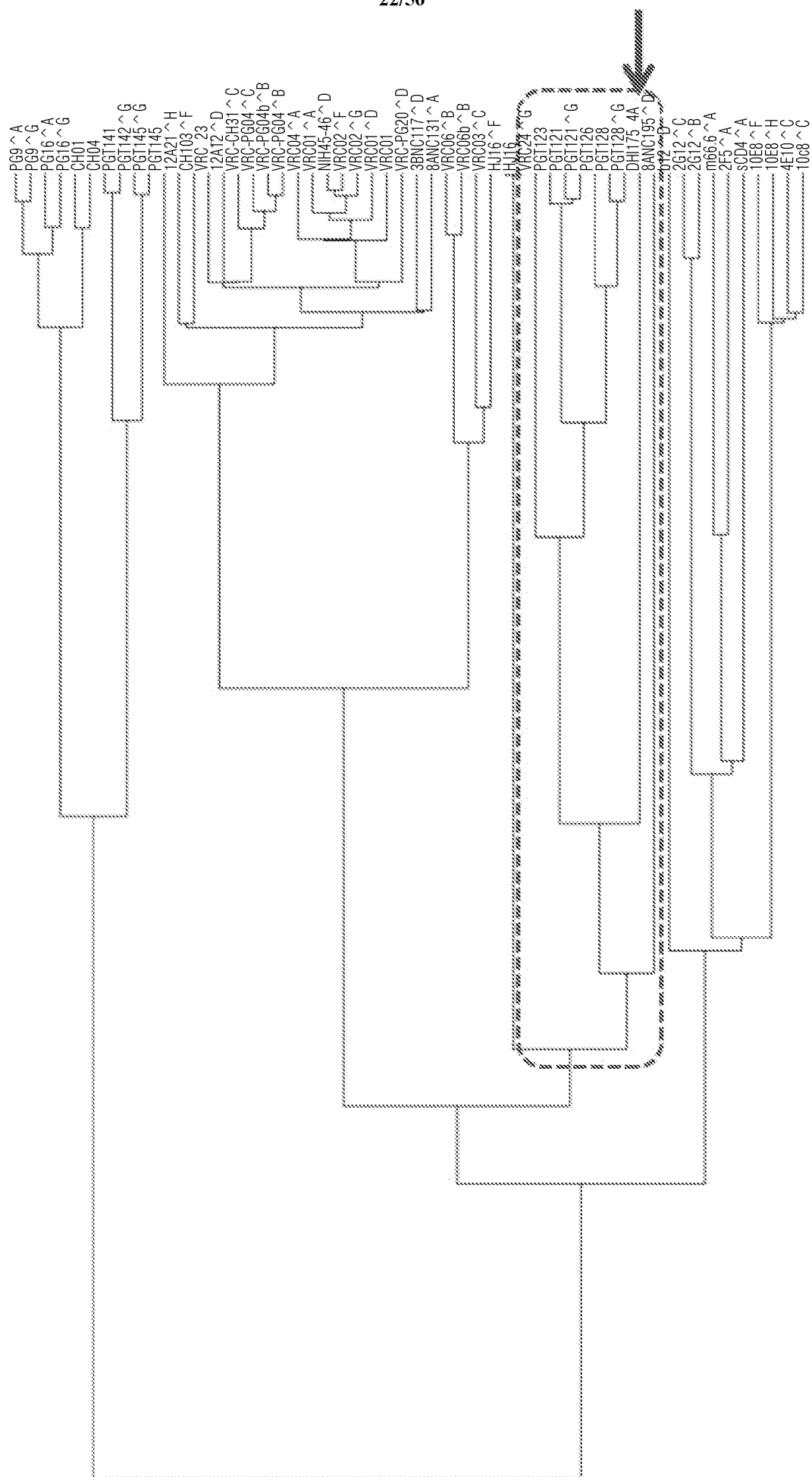


Figure 16

Strain	IC ₅₀ (ug/ml)	
	WT	N332A
RHPA	>50	>50
PVO	24	>50
TRO.11	0.5	0.7
AC10	22	7.3

Figure 17

VH	D	H	Mut. Freq.	HCDR3 length (AA)	HCDR3	Isotype	VL	JL	Mut. Freq.	LCDR3 length (AA)
4-34	IR2	6	14%	21	CVRGGALRWVGPWDPARHGLDVW	IgG1	K1-17	2	6%	9

Figure 18

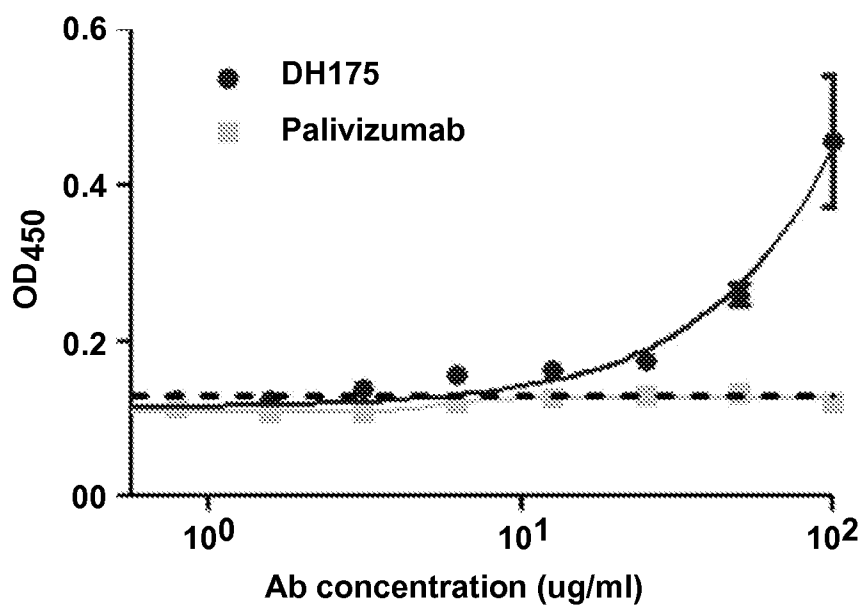


Figure 19

A. AtheNA assay

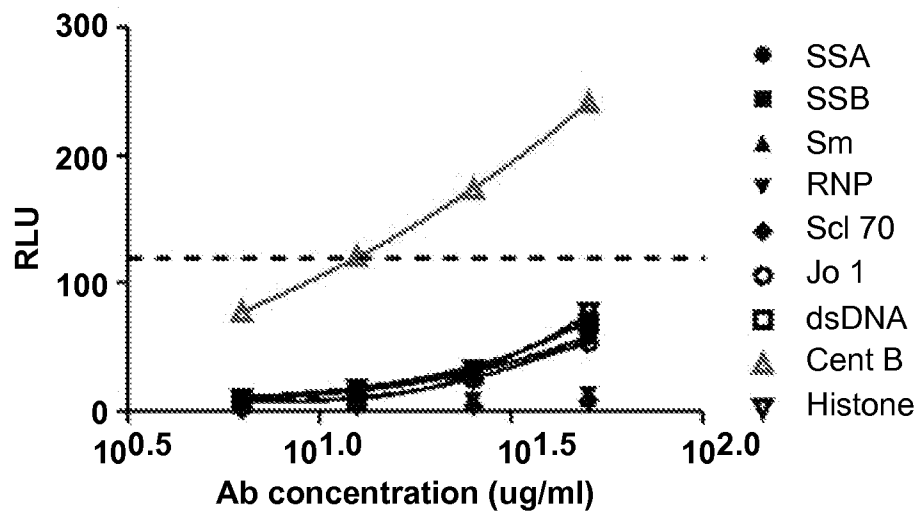


Figure 20A

B. Cardiolipin binding

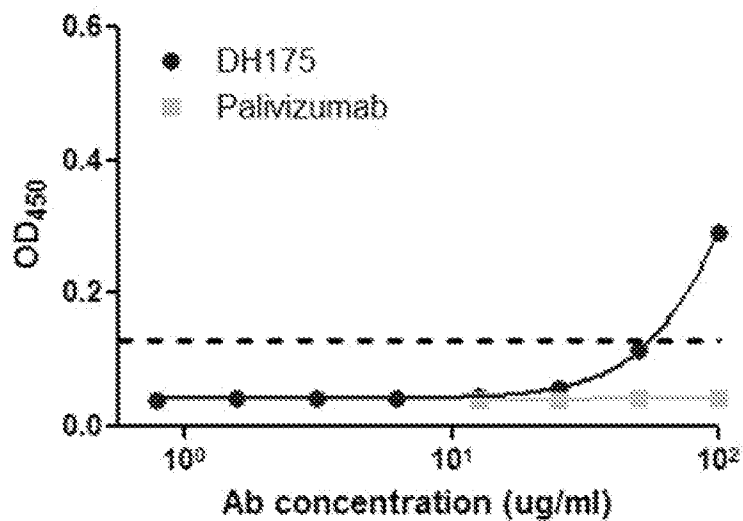


Figure 20B

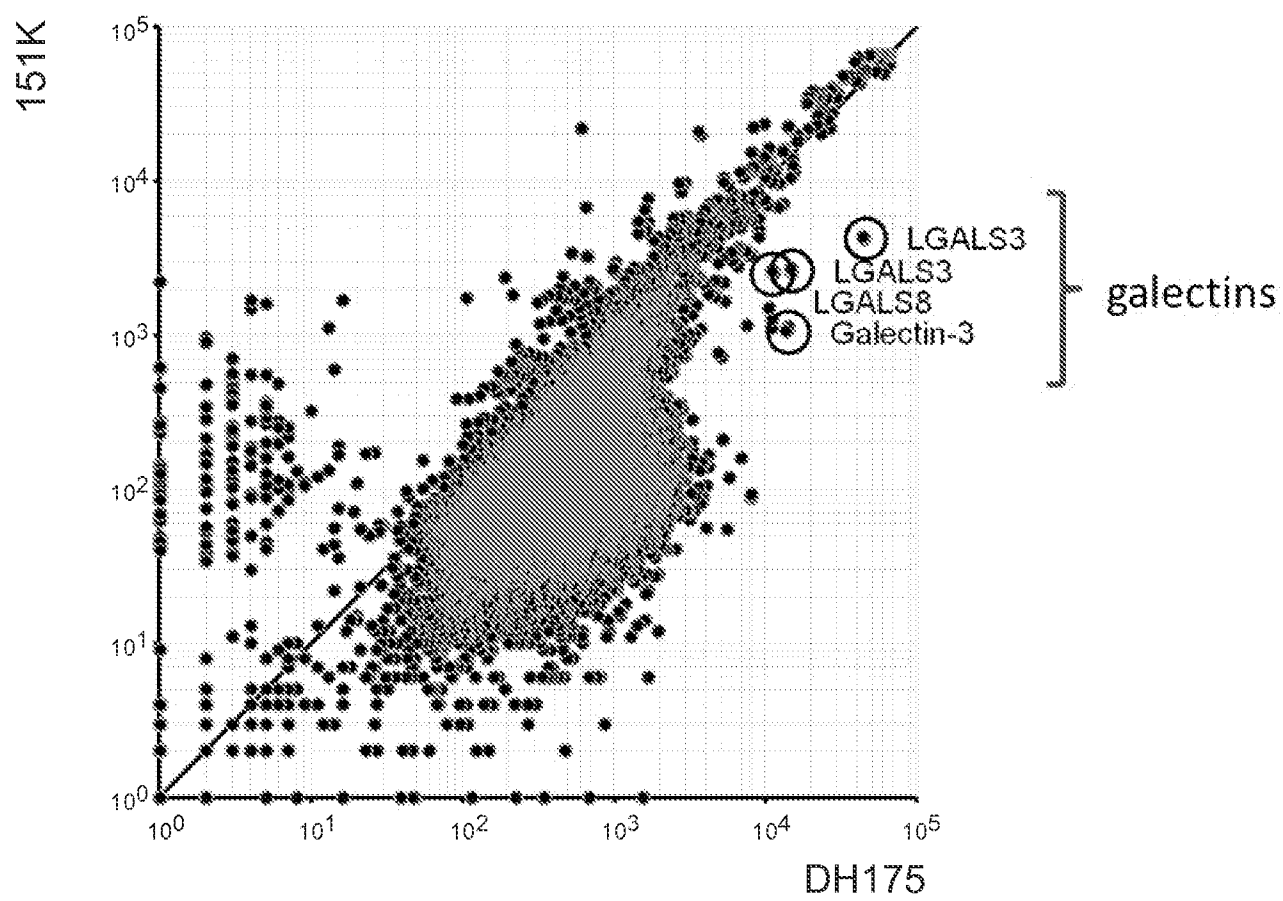


Figure 21

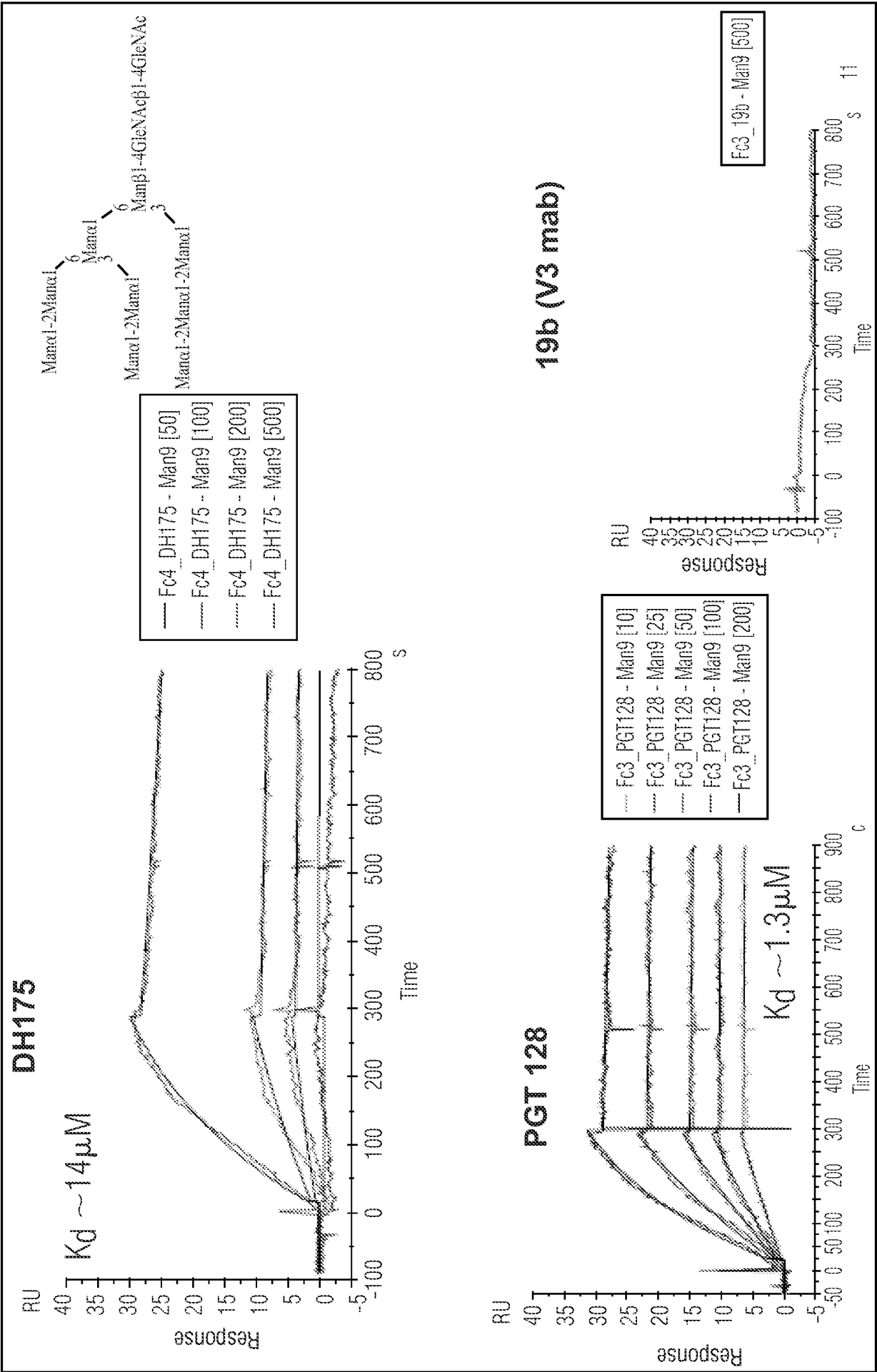


Figure 22

	ConC	ConC N234A	ConC T236A	PVO	PVO N234A	TRO	TRO N234Q
DH175	0.17 0.23 0.10	18.87 6.43 7.10	0.14 0.19 0.07	25.9	41.1	0.6	0.7
0694 plasma* (week 192)	1478 3255	438 820	1907 3144	255	112	1578	1740
8ANC195	25.3 27.1 29.4	51.3 91.9 >100.0	>100 >100 >100	0.17	>50	0.28	12.3
PGT128	0.005 0.01	0.09 0.22	0.01 0.01	0.02	0.02	0.06	0.04
PG9	0.01	0.01	0.01	nd	nd	nd	nd

* ID50 (1/dilution)

Figure 23

	TRO	TRO T278A	BG505	BG505 N234A	BG505 T278A
DH175	1.73	1.93	1.38	0.92	2.9
BANC195	0.18	>50	0.076	>50	>50

Lei Chen, John Mascolo

	TRO	TRO T278A	TRO N276A
DH175	0.51	1.21	1.07
VRC01	0.15	0.81	>10
HJ16	0.07	>10	>10

Figure 24

	0694.TF	0694.TF N295A	conC	conC V295N	conC N160A	Q23.17	Q23.17 N160K
DH175	0.89	0.96	0.37	0.50	0.53	0.13	0.11
0694 plasma* (week 192)	3373	2809	1327	1625	276	464	990
2G12	0.50	>50	>50	1.61	nd	nd	nd
PGT128	0.005	0.04	0.01	0.01	nd	nd	nd
PG9	nd	nd	<0.005	nd	>10	0.01	>10

* ID50 (1/dilution)

Figure 25

Figure 26

>CH694TF

MRVRGIQRNYQHWWTWGILGFWMMLIcnaVLEKRWVTVYYGvpvWKEAKATLFCASDAKAYEKEAHNVWATHACVPTDPS
 PQELVLENTVENFNMWKNDMVEQMHEDIISLWDQSLKPCVKLTPLCVTLECTKANFNNGTSSNNSTSSNNNTMYEEMKNCS
 FNATTEIRDKQKKMYALFYKLDIVPLEEDKNNSDKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCNKTKFKG
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>CH694w005.20.13

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>CH694w006.10.3

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 FNATTEIRDKQKKMYALFYKLDIVPLEEDKNNSDKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCNKTKFKG
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 QHLLQLTVWGIKQLQARVLAIERYLKDDQQLLGLWGCSGKLICTTTVPWNSSWSKSLLEEIWGNMTWMQWDREVSNTGI
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>CH694w006.10.6

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Figure 26 Cont.

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>CH694w007.15.1

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 PNQRGPDRPGGIEEEGGEKDRGRSIRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLIARAVELLGHSILRSLQRGWVFLK
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>CH694w007.15.48

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 FNATTEIRDKQKKMYALFYKLDIVPLEEDKNNSDKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCNKTFKG
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 PNQRGPDRPGGIEEEGGEKDRGRSIRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLIARAVELLGHSILRSLQRGWVFLK
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>CH694w009.15.32

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 TGPCSNVSTVQCTHGIKPVVSTQLLNGLSLAEIIIIRSKNLTDDTKTIIVHLNESVGINCTRPGNNTRQSVRIGPGQTF
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>CH694w009.15.4

MVRVGIQRNYQHWWTWGILGFWMMLIcnaVLEKRWVTVYYGvpvWKEAKATLFCASDAKAYEKEAHNVWATHACVPTDPS
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 FNATTEIRDKQKKMYALFYKLDIVPLEEDKNNSDKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCNKTFKG
 TGPCSNVSTVQCTHGIKPVVSTQLLNGLSLAEIIIIRSKNLTDDTKTIIVHLNESVGINCTRPGNNTRQSVRIGPGQTF
 YATGDIIGDIRQAHNCNISEEKWNATLLKVREKLAEHFPNKTIIFNSSAGGDLEITHTFTICGGEFFYCNTSGLFNRTYYA
 NGTAKYVNSTDGTITLQCRKQFINMWQRVGRAMYAPPIAGNITCRSDITGLLLTRDGGKNETTETFRPGGGDMRDNRWS
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Figure 26 Cont.

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>CH694w013.30.16

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FNATTEIRDKQKKMYALFYKLDIVPLEEDKNNSDKYILINCNTSTIAQACPKISFDPPIPIHYCAPAGYAILKCNKTKFG
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PNQRGPDRPGGIEEEGGEKDRGRSIRLVSGFLALAWDDLRSICLFSYHRLRDLIIIIVRAVELLGHSILRSLQRGWEVLK
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>CH694w013.30.2

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ELYKVKVVEIKPLGIAPTEAKRRVverekrAAGLGAMLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQSNNLRAIEA
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>CH694w017.4.30

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>CH694w017.6.19

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YATGDIIGDIRQAHNCNISEEKWNATLLKVREKLAEHFPNKTIIFNSAAGGDLEITHTTFICGGEFFYCNTSGLFNRTYYA
NGTAKYVNSTDGTITLQCRKQFINMWQVRGRAMYAPPIAGNITCRSDITGLLLTRDGGKNETTETFRPGGGDMRDNWRS
ELYKVKVVEIKPLGIAPTEAKRRVverekrAAGLGAMLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQSNNLRAIEA
QHLLQLTVWGIKQLQARVLAIERYLKDDQQLLGLWGCSGKLICTTTVPWNSSWSNKSLEEIWGNMTWMQWDREVSNYTGI
IYDLLEKSQNQQEKNEQDLLALDRWNSLWNWFDITNLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPLSLQTLI
PNQRGPDRPGGIEEEGGEKDRGRSIRLVSGFLALAWDDLRSICLFSYHRLRDLIIIIVRAVELLGHSILRSLQRGWEVLK
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>CH694w017.6.2

Figure 26 Cont.

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 FNATTEIRDKQKKMYALFYKLDIVPLEEDKNNNDKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCNKTKFG
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>CH694w017.6.20

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>CH694w020.6.10

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>CH694w020.6.55

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>CH694w028.10.2

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 FNTTTEIRDKQKKMYALFYKLDIVPLEEDKNNNDKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCNKTKFG
 TGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEEIIIRSKNLTDHKTIIIVHLNESVGINCTRPGNNTRQSVRIGPGQTF
 YATGDIIGDIRQAHNCNISEEKWNATLLKVREKLAEHFPNKTIIIFNSSAGGDLEITHTFTICGGEFFYCNTSGLFNRTYYA
 NGTAKYVNSTDGTITLQCRKQFINMWQVRGRAMYAPPIAGNITCRSDITGLLLTRDGGKNETTETFRPGGGDMRDNWS

Figure 26 Cont.

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>CH694w028.10.48

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QHMLQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKSLEEIWGNMTWMQWDREVSNTYGI
IYDLLEKSQNOQEKNEQDLLALDRWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPLSLQTLI
PNQRGPDRPGGIEEEGGEKDRGRSIRLVSGFLALAWDDLRLSLCLFSYHRLRDLLLI IARAVELLGHSILRSLQRGWEVLK
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>CH694w041.40.72

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FNATTEIRDKQKKMYALFYKLDIVPLEEDKNNSDKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCNKTFKG
TGPCSNVSTVQCTHGIKPVVSTQLLNGLSLAEEEEIIIRSKNLTDHTKTIIVHLNESVGINCTRPSNNTRQSVRIGPGQTF
YATGDIIGDIRQAHCNISEEKWNATLLKVREKLAEHFPNKTIIFNSSAGGDLEITHTFTICGGEFFYCNTSGLFNRTYYA
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YDLLEKSQNOQEKNEQDLLALDRWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPLSLQTLIP
NQRGPDRPGGIEEEGGEKDRGRSIRLVSGFLALAWDDLRLSLCLFSYHRLRDLLLI IARAVELLGHSILRSLQRGWEVLKY
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>CH694w041.40.82

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NQRGPDRPGGIEEEGGEKDRGRSIRLVSGFLALAWDDLRLSLCLFSYHRLRDLLLI IARAVELLGHSILRSLQRGWEVLKY
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>CH694w053.70.32

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LQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKSLEEIWGNMTWMQWDREVSNTYGIYEL
LEKSQNOQEKNEQDLLALDRWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPLSLQTLIPNQR
GPDRPGGIEEEGGEKDRGRSIRLVSGFLTLAWDDLRLSLCLFSYHRLRDLLLI IARAVELLGHSILRSLQRGWEVLKYLG
LVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEIIQEVCAIYNIPTIRRGFEAALQ*

>CH694w053.70.38

Figure 26 Cont.

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 NNTMYEEMKNCSFNATTEIRDKQKKMYALFYKLDIVPLEEDKNNSNKYILINCNTSTIAQACPKISFDPIPIHYCAPAGY
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 QQSNNLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKSLEEIWGNMTWMQ
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 GYSPLSLQTLIPNQRPDRPGGIEEEGGEKDRGRSIRLVSGFLALAWDDLRSCLFSYHRLRDLLLIARAVELLGHSIL
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>CH694w053.70.43

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 GDIIGDIRQAHCDISEEKWNATLLKVREKLAEHFPNKTIIFNSSAGGDLEITHTTFICGGEFFYCNTSGLFNRTYYANGT
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 YKVVEIKPLGIAPTEAKRRVverekrAAGLGAMLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQSNNLKAIEAQHLL
 LQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKSLEEIWGNMTWMQWDREVSNYTGIIYDL
 LEESQNOQEKNEQDLLALDRWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPLSLQTLIPNQ
 RGPDRPGGIEEEGGEKDRGRSIRLVSGFLALAWDDLRSCLFSYHRLRDLLLIARAVELLGHSILRSLQRGWEVLKYLGN
 LVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEIIQEVCAIYNIPTIRRGFEAALQ*

>CH694w064.10.1

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 ATTEIRDKQKKMYALFYKLDIVPLKEDKNNSNKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCNKTFNGTG
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 TGDIIGDIRQAYCNISEEKWNATLLKVREKLAEHFPNKTIIFNSSAGGDLEITHTTFICGGEFFYCNTSGLFNRTYYANG
 TAKYVNSTNGTITLQCRIKQFINMWQRVGRAMYAPPIAGSITCRSNITGLLLTRDGGNETETFRPGGGDMRDNRSELY
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 RGPDRPGGIEEEGGEKDRGRSIRLVSGFLALAWDDLRSCLFSYHRLRDLLLIARAVELLGHSILRSLQRGWEVLKYLGN
 NLVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEIFCRAIYNIPTIRRGFEAALQ*

>CH694w064.10.25

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 NCSFNATTEIRDKQKKMYALFYKLDIVPLEKDKNNNSNKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCNKTF
 FNGTGPCSNVSTVQCTHGKIPVVSTQLLNGSLAEEEEIIIRSKNLT DHTKTIIVHLNESVEIKCTRPSNNTRQSVRIGPG
 QTFYATGDIIGDIRQAHCNISDEKWNATLLKVREKLAEHFPNKTIIFNSSAGGDLEITHTTFICGGEFFYCNTSGLFNRT
 YYANGTAKYVNSTNGTITLQCRIKQFINMWQRVGRAMYAPPIAGSITCRSNITGLLLTRDGGNETETFRPGGGDMRDNR
 RSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGLGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQSNNLKAIE
 AQHLLQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKSLEEIWGNMTWMQWDREVSNYT
 GIIYDLLEESQNOQEKNEQDLLALDRWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPLSLQTL
 LIPNQRPDRPGGIEEEGGEKDRGRSIRLVSGFLALAWDDLRSCLFSYHRLRDLLLIARAVELLGHSILRSLQRGWEVL
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>CH694w064.10.4

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 FNATTEIRDKQKKMYALFYKLDIVPLKEDKNNSNKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCNKTFNG
 TGPCSNVSTVQCTHGKIPVVSTQLLNGSLAEEEEIIIRSKNLT DHTKTIIVHLNESVEITCTRPNNTRQSVRIGPGQTF
 YATGDIIGDIRQAHCNISDEKWNATLLKVREKLAEHFPNKTIIFNSSAGGDLEITHTTFICGGEFFYCNTSGLFNSTYYV
 NGTAKYVNSTNGTITLQCRIKQFINMWQRVGRAMYAPPIAGSITCRSNITGLLLTRDGGNETETFRPGGGDMRDNRSE

Figure 26 Cont.

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YDLLEESQNQQEKNEQDLLALDRWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPLSLQTLIP
NQRGPDRPGGIEEGGEKDRGRSIRLVSGFLALAWDDLRSLCLFSYHRLRDLILLIARAVELLGHSILRSLQRGWEVLKY
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>CH694w101.10.5

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EMKNCSFNATTEIRDKQKKMYALFYKLDIVPLKEDENNSNKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCN
NKTfNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEEEEIIIRSENLTNDTKTIIVHLNESVEINCTRPNNTRQSVRI
GPGQTFYATGDIIGDIRQAYCNISDKKWNATLLKVREKLAEHFPNKTIRFNSSAGGDLEITHTTFICGGEFFYCNTSGLF
NRTYDANETAKYVNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGSITCRSNITGLLLTRDGGENGTEFRPGGGDMR
DNWRSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGLGA VLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQSNLL
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NYTGIIYELLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPLS
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>CH694w101.20.20

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QSVRI GPGQTFYATGDIIGDIRQAHCNISEGKWNATLLKVREKLAEHFPNKTIRFNSSAGGDLEITHTTFICGGEFFYC
NTSGLFNRTYDANDVNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGSITCRSNITGLLLTRDGGENGTEFRPGGGD
MRDNWRSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGLGA VLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQSN
LLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMTWMQWDRE
VSNYTDIIYELLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSP
LSLQTLIPNQRGPDRPGGIEEGGEKDRGRSVRLVSGFLALAWDDLRSLCLFSYHRLRDLILLIARAVELLGHSILRSLQ
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>CH694w101.20.30

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LQTLIPNQRGPDRPGGIEEGGEKDRGRSVRLVSGFLALAWDDLRSLCLFSYHRLRDLILLIARAVELLGHSILRSLQ
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>CH694w101.20.45

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GDIIGDIRQAHCNISEGKWNATLLKVREKLAEHFPNKTIRFNSSAGGDLEITHTTFICGGEFFYCNTSGLFNRTYDANET
AKDVNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGSITCRSNITGLLLTRDGGENGTEFRPGGGDMRDNRSELYK
YKVVEIKPLGIAPTEAKRRVverekrAVGMGA VLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQSNLLKAIEAQHLL
LQLTVWGIKQLQARVLAIERYLKDDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMTWMQWDREVSNYTDIIYEL
LEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPLSLQTLIPNQR
GPDRPGGIEEGGEKDRGRSVRLVSGFLALAWDDLRSLCLFSYHRLRDLILLIARAVELLGHSILRSLQRGWEVLKYLGN
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>CH694w101.20.48

Figure 26 Cont.

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LQLTVWGIKQLQARVLAIERYLKDDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMTWMQWDKEVSNYTDIIYEL
LEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPSLQTLIPNQR
GPDPRGGIEEEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLARAVELLGHNIILRSIQRGWEVLKYLGN
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>CH694w101.20.6

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DANETAKYVNSTNGNITLQCRIKQFINMWQVRVGRAMYAPPIAGSITCRSNITGLLLTRDGGENGTEFRPGGGDMRDNR
SELYKYKVVEIKPLGIAPTEAKRRVverekrAVGLGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQSNLLKAIE
AQHLLQLTVWGIKQLQARVLAIERYLKDDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMTWMQWDREVSNTS
IIYELLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPSLQTL
IPNQRGPDPRGGIEEEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLARAVELLGHSILRSIQRGWEVL
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>CH694w101.30.7

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>CH694w122.10.84

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PQELVLENTENFNMWKNMVEQMHEDIISLWDQSLKPCVKLTPLCVTLNCTEAKFNGTSSNNSTFSNNTMKEEMKNCSE
NATTEIRDKQKKMYALFYKLDIVPLDKNNSTNSTKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCNKTFNG
TGPCSNVSTVQCTHGIKPVVSTQLLLLNGSLAEEEEIIIRSENLTDNAKTIIVHLNESVEINCTRPGNNTQSVRIGPGQTF
YATGDIIGDIKQAHCNISEAKWNATLLKVKEKLAEHFPNKTIIRFKSSAGGDLEITHTFTICGGEFFYCNTSGLFNRTYDV
NETAKYDNSTNGNITLQCRIKQFINMWQVRVGRAMYAPPIAGSITCRSNITGLLLTRDGGENGTEFRPGGGDMRDNRSE
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HHLLQLTVWGIKQLQARVLAIERYLKDDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMTWMQWDKEVSNYTDII
YELLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPSLQTLIP
NQRGPDPRGGIEEEEGGEKDRSRSIRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLARAVELLGHSILRSIQRGWEVLKY
LGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEIIQEVCAIYNIPTIRRGFEAALQ*

>CH694w122.10.90

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MKEEMKNCSEFNATTEIRDKQKKMYALFYKLDIVPLDKNNSNKNNSNKYILINCNTSTIAQACPKISFDPIPIHYCAPAG
YAILRCNNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLLLNGSLAEEEEIIIRSENLTDNKTIIIVHLNESVEINCTRPNN
TRQSVRIGPGQTFYATGNIIGDIRQAHCNISEGKWNATLLKVKEKLAKHFPNKTIIFNSAAGGDLEITHTFTICGGEFF
CNTSGLFNRTYANTDYANETAKNVNSTNGNITLQCRIKQFINMWQVRVGRAMYAPPIAGSITCSSNITGLLLTRDGEENG

Figure 26 Cont.

TETFRPGGGDMRDNRSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGLGAVLLGFLGAAGSTMGAASITLTVQARQL
LSGIVQQQSNLLKAI EAQQHLLQLTVWGIKQLQARVLAIERYLKDDQQLGLWGCSGKLICTTTVPWNSSWSNKTIGEIWG
NMTWMQWDREVSNYTDI IYELLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSL
VNRVRQGYSPLSLQTLIPTQRGPDRPGEIEEEGGEKDRGRSVRLVSGFLALAWDDLRSLCLFSYHRLRDLILLSLARAVEL
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>CH694w122.4.11

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FNRTYDANETAKDVNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGSITCRSNTIGLLLTRDGGDGGENGTEFRPGG
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SNLLKAI EAQQHLLQLTVWGIKQLQARVLAIERYLKDDQQLGLWGCSGKLICTTTVPWNSSWSNKTIGEIWGNMTWMQWD
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SPLSLQTLIPNQRGPDRPGGIEEEGGEKDRGRSVRLVSGFLALAWDDLRSLCLFSYHRLRDLILLILARAVELLGHSILRS
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>CH694w122.4.20

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YAILRCNNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLLNGLSLAEIIIIRSENLTDNKTIIIVHLNESVEIKCTRPGNN
TRQSVRIGPGQTFYATGDIIGDIRQAHCNISEKEWNATLLKVGEKLAKHFNPNTIRFNPSAGGDLEITHTTFICGGEFFY
CNTSGLFNRTYDANETAKYGNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGIITCRSNTIGLLLTRDGEENGTEFR
PGGGDMRDNRSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGIGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIV
QQQSNLLKAI EAQQHLLQLTVWGIKQLQARVLAIERYLKDDQQLGLWGCSGKLICTTTVPWNSSWSNKTIGEIWGNMTWM
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QGYSPLSLQTLIPNQRGPDRPGGIEEEGGEKDRGRSVRLVSGFLALAWDDLRSLCLFSYHRLRDLILLILARAVELLGHSI
LRSLQRGWEVLKYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEFCRAIYNIPTIRRGFEAALQ*

>CH694w122.4.21

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NGTGPCSNVSTVQCTHGIKPVVSTQLLLNGLSLAEIIIIRSENLTDNKTIIIVHLNESVEINCTRPGNNTRQSVRIGPGQ
TFYATGDIIGDIKQAHCNISEAKWNATLLKVKGKLAHFNPNTIIFNSSAGGDLEITHTTFICGGEFFYCNTSGLFNRTY
DANGTAEYVNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGSITCKSNITIGLLLTRDGGKDGTPETFRPGGGDMRDNW
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DI IYELLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPLSLQ
TLIPNQRGPDRPGGIEEEGGEKDRSRSIRLVSGFLALAWDDLRSLCLFSYHRLRDLILLILARAVELLGHSILRSLQRGWEV
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>CH694w122.4.3

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FNATTEIRDKQKQMYALFYIILDIVPLGEEKNNSTNSTKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCNKTF
NGTGPCSNVSTVQCTHGIKPVVSTQLLLNGLSLAEIIIIRSENLTDNKTIIIVHLNESVEINCTRPGNNTRQSVRIGPGQ
TFYATGDIIGDIKQAHCNISEAKWNATLLKVKEKLAHFNPNTIIFNSSAGGDLEITHTTFICGGEFFYCNTSGLFNRTY
DANETAQYVNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGSITCKSNITIGLLLTRDGGEDGTSETFRPGGGDMRDNW
RSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQSNLLKAI
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DI IYELLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPLSLQ
TLIPNQRGPDRPGGIEEEGGEKDRGRSVRLVSGFLALAWDDLRSLCLFSYHRLRDLILLILARAVELLGHSILRSLQRGWEV
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>CH694w122.5.61

Figure 26 Cont.

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 MKEEMKNCSEFNATTEIRDKQKKMYALFYKLDIVPLDKNNSNNKNSNXYILINCNTSTIAQACPKISFDPIPIHYCAPAG
 YAILRCNNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEEEEIIIRSENLTNDNTKTIIVHLNESVEIKCTRPGNN
 TRQSVRIGPGQTFYATGDIIGDIRQAHCNISEKEWNATLLKVGEKLAKHFPNKTIRFNSSAGGDLEITHTFTICGGEFFY
 CNTSGLFNRTYDANETAAYVNSTNGNITLQCRIKQFINMWQRVGRAMYAPPIAGSITCRSNITGLLLTRDGGENGTTETFR
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 VQQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQLLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMTW
 MQWDKEVSNYTDIIYELLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIFAILSLVNRV
 RQGYSPLSLQTLIPNQRGPDRPGGIEEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHS
 ILRLSLQRGWEVLKYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEFCRAIYNIPTRIRRGFEAALQ*

>CH694w122.5.79

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 MKEEMKNCSEFNATTEIRDKQKKMYALFYKLDVQLEKNNSNXYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKC
 NNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEEEEIIIRSENLTNDNTKTIIVHLNESVEINCTRPNNNTRQSVR
 IGPGQTFYATGDIIGDIRQAHCNISEGKWNATLLKVREKLAEHFPNKTIRFNSSAGGDLEITHTFTICGGEFFYCNTSGL
 FNRTYDANETAAYVNSTNGNITLQCRIKQFINMWQRVGRAMYAPPIAGIITCRSNITGLLLTRDGGDGGENGTTETFRPGG
 GDMRDNRSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGLGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQ
 SNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQLLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMTWMQWD
 REVSNYTDIIYELLEESQSQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIIGGLIGLRIVFAILSLVNRVRQGY
 SPLSLQTLIPTQRGPDRPGEIEEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHSILRS
 LQRGWEVLKYLGNLVQYWGLELKKSAISLIDTIAIAVAEGTDRIIEFCRAIYNIPTRIRRGFEAALQ*

>CH694w122.81.26

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 NATTEIRDKQKKMYALFYKLDIVPLKEDKNNSNNSNEYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCNKTF
 NGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEEEEIIIRSENLTNDNTKTIIVHLNESVEINCTRPNNNTRQSVRIGPGQ
 TFYATGNIIGDIRQAHCNISEGKWNATLLKVREKLAEHFPNKTIRFDSSAGGDLEITHTFTICGGEFFYCNTSGLFNRTY
 YANANETAAYVNSTNGNITLQCRIKQFINMWQRVGRAMYAPPIAGSITCSSNITGLLLTRDGEENGTTETFRPGGGDMRDN
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>CH694w124.6.15

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 MKEEMRNCSEFNATTEIRDKQKKMYALFYKLDIVPLKEDKNNSNNSNXYILINCNTSTIAQACPKISFDPIPIHYCAPAGY
 AILKCNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEEEEIIIRSENLTNDNAKTIIVHLNKSVEIKCTRPGNN
 RQSVRIGPGQTFYATGDIIGDIRQAHCNISEKEWNATLLKVGEKLAKHFPNKTIRFNSSAGGDLEITHTFTICGGEFFYC
 NTSGLFNRTYDANETAKYGNSTNGNITLQCRIKQFINMWQRVGRAMYAPPIAGIITCRSNITGLLLTRDGGENGTTETFRP
 GGGDMRDNRSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGLGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQ
 QQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQLLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMTWMQ
 WDKEVSNYTDIIYELLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQ
 GYSPLSLQTLIPNQRGPDRPGGIEEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHSIL
 RSLQRGWEVLKYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEIIQEVCRAIYNIPTRIRRGFEAALQ*

>CH694w124.6.16

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 NCSEFNATTEIRDKQKKMHAFYRLDIVPLDKNNSNXYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCNKTFN
 GTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEEEEIIIRSENLTNDNTKTIIVHLNESVEINCTRPNNNTRQSVRIGPGQ
 FYATGDIIGDIRQAHCNISEAKWNATLLKVGEKLAKHFPNKTIFSSAGGDLEITHTFTICGGEFFYCNTSGLFNRTYY
 ANANETAAYVNSTNGNITLQCRIKQFINMWQRVGRAMYAPPIAGSITCSSNITGLLLTRDGEENGTTETFRPGGGDMRDN

Figure 26 Cont.

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DIIYELLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPLSLQTL
LIPNQRGPDRPGGIEEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHSILRSLQRGWEV
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>CH694w124.6.20

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IVQQQSNLLKAI EAQHLLQLTVWGIKQLQARVLAIERYLKDDQLLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMT
WMQWDKEVSNYTDIIYELLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNR
VRQGYSPLSLQTLIPNQRGPDRPGGIEEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGH
SILRSLQRGWEVLKYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEIIQEVCRAIYNIPTRIRRGFEAALQ*

>CH694w124.6.29

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NATTEIRDKQKKMYALFYKLDIVPLDKNNSKEDKNNTKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCNK
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GQTFYATGNIIGDIRQAHCNISKKEWSATLLKVREKLAEHFPNKTIRFNSSAGGDLEITHTFTICGGEFFYCNTSGLFN
TYDANETAKDVNSTNGNITLQCRKQFINMWQVRGRAMYAPPIAGSITCSSNITGLLLTRDGGENGTEETETFRPGGDMR
DNRSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGLGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQSNLL
KAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQLLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMTWMQWDKEVS
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>CH694w124.6.37

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RQGYSPLSLQTLIPNQRGPDRPGGIEEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHS
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>CH694w124.6.9

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NCSEFNATTEIRDKQKKMYTLFYKLDVVQLEKNNSNKNKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCNKTFN
GTGPCSNVSTVQCTHGKIPVSTQLLNGSLAEEEEIIIRSENLTDNKTIIIVHLNESVEINCTRPNNNTRQSVRIGPGQT
FYATGDIIGDIRQAHCNISEAKWNATLLKVKEKLAEHFPNKTIIIFNSSAGGDLEITHTFTICGGEFFYCNTSGLFNRTYD
ANETAHEYVNSTNGNITLQCRKQFINMWQVRGRAMYAPPIAGSITCSSNITGLLLTRDGGKDGTPETFRPGGDMRDNR
SELYKYKVVEIKPLGIAPTEAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQSNLLKAI
AQHLLQLTVWGIKQLQARVLAIERYLKDDQLLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMTWMQWDKEVSNYTD
IIYELLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPLSLQTL
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>CH694w126.20.35

Figure 26 Cont.

MRARGIQRNYQHWWTWGILGFWMMLIcnaGLKQQWVTVYYGvpvWKEAKATLFCASDAKAYEKEAHNVWATHACVPTDPS
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 NKTFTNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEKEIIIRSENLTNDNTKTIIVHLNESVEINCTRPGNNTQSVRI
 GPGQTFYATGDIIGDIRQAYCNISEKEWNATLLKVGEKLAKHFPNKTIRFNPSAGGDLEITHTFICGGEFFYCNTSGLF
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 KAIEAQHLLQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKTIGEIWGNMTWMQWDREVS
 NYTDIIYELLEESQSQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIGGLIGLRIVFAILSLVNRVRQGYSPLS
 LQTLIPTQRGPDPRPGEIEEGGEKDRGRSVRLVSGFLALAWDDLRSLCLFSYHRLRDLILLILARAVELLGHSILRSLQRG
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>CH694w126.20.41

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 NATTEIRDKQKKMYALFYKLDIVPLDKNNSTNSTKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCNKTFNG
 TGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEKEIIIRSENLTNDNAKTIIVHLNESVEINCTRPGNNTQSVRIGPGQTF
 YATGDIIGDIKQAHNCNISEAKWNATLLKVKENLAEHFPNKTIRFKSSAGGDLEITHTFICGGEFFYCNTSGLFNRTYHA
 NYHANETAKDVNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGSITCRSNITGLLLTRDGGENGTEFRPGGDMRD
 NWRSELYKYKVVEIKPLGIAPTEAKRRVverekAAGLGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQSNLLK
 AIEAQHLLQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKTIGEIWGNMTWMQWDREVS
 YTDIIYELLEESQSQQEKNEQDLLALDKWNSLWSWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPLS
 QTLIPTQRGPDPRPGGIEEGGEKDRGRSIRLVSGFLALAWDDLRSLCLFSYHRLRDLILLILARAVELLGHSILRSLQRGW
 EVLKYLGNLVQYWGLELKKSAISLDDTIAIAVAEGTDRIIEFCRAIYNIPTIRRGFEAALQ*

>CH694w126.20.43

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 PQELVLENTENFNMWKNDMVEQMHEDIISLWDQSLKPCVKLTPLCVTLNCTTANFTASNNSTSSNNSTSSNNSTFSNNT
 MKEEMKNCFSNATTEIRDKQKKMYALFYKLDIVPLEKDENNSTKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAIL
 KCNNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEKEIIIRSENLTNDNTKTIIVHLNESVEIKCARPGNNTRQS
 VRIGPGQTFYATGDIIGDIRQAYCNISEGKWNATLLKVKEKLAHFPNKTIRFNSSAGGDLEITHTFICGGEFFYCNTS
 GLFNRTYDANETAKYVNSTNSTITLQCRIKQFINMWQVRGRAMYAPPIAGSITCKSNITGLLLTRDGAENGTEFRPGGG
 DMRDNWRSELYKYKVVEIKPLGIAPTEAKRRVverekAVGMGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQS
 NLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMTWMQWDK
 EVSNYTDIIYELLEESQNQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSP
 LSLQTLIPTQRGPDPRPGGIEEGGEKDRGRSVRLVSGFLALAWDDLRSLCLFSYHRLRDLILLILARAVELLGHSILRSL
 QRGWEVLKYLGNLVQYWGRELKKSAISLDDTIAIAVAEGTDRIIEIIEVCRAIYNIPTIRRGFEAALQ*

>CH694w126.20.51

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 NATTEIRDKQKQMYALFYTLTDIEPLGEEKNNSTNSTKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCNKTF
 NGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEKEIIIRSENLTNDNTKTIIVHLNESVEINCTRPGNNTQSVRIGPGQ
 TFYATGNIIIGDIRQAYCNISSKEWNTLLKVREKLAHFPNKTIRFNPSAGGDLEITHTFICGGEFFYCNTSGLFNRTY
 DANETAAYVNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGSITCKSNITGLLLTRDGGKDGTTETFRPGGDMRDW
 RSELYKYKVVEIKPLGIAPTEAKRRVverekAVGLGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQSNLLKAI
 EAQQHLLQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMTWMQWDKEVSNY
 TDIIYELLEESQNQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPSLQ
 TLIPNQRGPDRPGGIEEGGEKDRGRSVRLVSGFLALAWDDLRSLCLFSYHRLRDLILLILARAVELLGHSILRSLQRGW
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>CH694w130.10.21

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 KEEMRNCFSNATTEIRDKQKKMYALFYKLDIVPLKEDKNNSTNSTKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYA
 ILKCNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEKEIIIRSENLTNDNTKTIIVHLNESVEINCTRPGNNT
 QSVRIGPGQTFYTTGDIIGDIRQAHNCNISEGKWNATLLKVRKKLAHFPNKTIRFNSSAGGDLEITHTFICGGEFFYC
 NTSGLFNRTYANANETAAYVNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGIITCRSNITGLLLTRDGGDGGENGTE

Figure 26 Cont.

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RVRQGYSPLSLQTLIPNQRGPDRPGGIEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLG
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>CH694w130.10.36

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YATGDIIGDIKQAHNCNISEAKWNATLLKVKEKLAHEFPNRTIRFKSSAGGDLEITHTFTICGGEFFYCNTSGLFNRTYDA
NETAKDVNSTNGNITLQCRKQFINMWQVRGRAMYAPPIAGSITCSSNITGLLLTRDGGENGTEETETFRPGGDMRDNR
SELYKYKVVEIKPLGIAPTEAKRRVverekrAVGLGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQSNLLKAI
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IIYNLLEESQNQQEKNEQDLLALDKWNSLWNWFDITNLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPLSLQTL
IPNQRGPDRPGGIEEGGERDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHSILRSLQRGWEVL
KYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEFCRAIYNIPTIRRGFEAALQ*

>CH694w130.10.63

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MKEEMKNCSEFNATTEIRDKQKKMYALFYKLDIVPLDKNNSTKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCN
NKTFTNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEKEIIIRSENLTDNKTIIIVHLNESVEIKCTRPNNTRQSVRI
GPGQTFYATGNIIGDIRQAHNCNISEKEWNATLLKVGEKLAHEFPNKTIRFNSSAGGDLEITHTFTICGGEFFYCNTSGLF
NRTYDANETAKYGNSTNGNITLQCRKQFINMWQVRGRAMYAPPIAGIITCRSNITGLLLTRDGGENNTEETETFRPGGDM
RDNRSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGLGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQSNL
LKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQLLGLWGCSGKLICTTTVPWNSSWSNKTLEGIWGNMTWMQWDREV
SNYTDIIYELLEESQSQEKNEQDLLALDKWNSLWNWFDITNLWYIKIFIMIIGGLIGLRIVFAILSLVNRVRQGYSP
LSLQTLIPNQRGPDRPGGIEEGGERDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHSILRSLQ
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>CH694w130.3.3

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VRIGPGQTFYATGDIIGDIRQAYCNISEGKNATLLKVKEKLAHEFPNKTIRFNSSAGGDLEITHTFTICGGEFFYCNTS
GLFNNGTYDANETAKYVNSTNSTITLQCRKQFINMWQVRGRAMYAPPIAGSITCKSNITGLLLTRDGAENGTEETFRPGG
DMRDNRSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQS
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SPLSLQTLIPNQRGPDRPGGIEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHSILRSL
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>CH694w130.3.4

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TFYATGNIIGDIRQAHNCNISKWENATLLKVKEKLAHEFPNKTIRFDSSAGGDLEITHTFTICGGEFFYCNTSGLFNNGTY
DANETAKDVNSTNRTITLQCRKQFINMWQVRGRAMYAPPIAGSITCKSNITGLLLTRDGGEDGTSETFRPGGDMRDNR
SELYKYKVVEIKPLGIAPTEAKRRVverekrAVGLGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQSNLLKAI
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TLIPNQRGPDRPGGIEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHSILRSLQK
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>CH694w134.10.7

Figure 26 Cont.

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 NATTEIRDKQKKMYALFYKLDIVPLDKNNSKEDKNNTKYILINCNTSTIAQACPKISFDPPIPIHYCAPAGYAILKCNK
 TFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEEIIIRSENLTDNKTIIIVHLNESVEINCTRPGNNTRQSVRIGP
 GQTFYATGDIIGDIKQAHNCNISEAKWNATLLKVKEKLAHFHPNKTIRFNSSAGGDLEITHTTFICGGEFFYCNTSGLFNR
 TYDANETAKDVNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGSITCSSNITGLLLTRDGGENGTEETETFRPGGGDMR
 DNWRSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGLGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQSNLL
 KAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQLLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMTWMQWDKEVS
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 LQTLIPNQRGPDRPGGIEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHSILRSLQRG
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>CH694w134.20.58

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 NATTEIRDKQKKMYALFYKLDIVPLDKNNSKEDKNNTKYILINCNTSTIAQACPKISFDPPIPIHYCAPAGYAILKCNK
 TFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEEIIIRSENLTDNKTIIIVHLNESVEINCTRPGNNTRQSVRIGP
 GQTFYATGDIIGDIKQAHNCNISEAKWNATLLKVKEKLAHFHPNKTIRFDSSAGGDLEITHTTFICGGEFFYCNTSGLFNR
 TYDANETAKDVNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGSITCSSNITGLLLTRDGGENGTEETETFRPGGGDMR
 DNWRSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGLGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQSNLL
 KAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQLLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMTWMQWDKEVS
 NYTDI IYNLLEESQSQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPLS
 LQTLIPNQRGPDRPGGIEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHSILRSLQRG
 WEVLKYLGNLVQYWGLELKRSASISLLDTIAIAVAEGTDRIIEIIQEVCAIYNIPTRIRRGFEAALQ*

>CH694w134.20.60

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 AILKCNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEEIIIRSENLTDNKTIIIVHLNESVEINCTRPGNNTR
 RQSVRIGPGQTFYATGDIIGDIKQAHNCNISEKEWNATLLKVGEKLAHFHPNKTIRFNPSAGGDLEITHTTFICGGEFFYC
 NTSGLFNRITYDANETAKYGNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGIITCRSNIITGLLLTRDGEENGTEETFRP
 GGGDMRDNRSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQ
 QQSNNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQLLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMTWMQ
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 GYSPLSLQTLIPTQRGPDRPGGIEEGGEKDRGRSIRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHSIL
 RSLQRGWEVLKYLGNLVQYWGLELKKSASISLLDTIAIAVAEGTDRIIEFCRAIYNIPTRVRRGFEAALQ*

>CH694w134.20.65

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 RQSVRIGPGQTFYATGDIIGDIKQAHNCNISEKEWNATLLKVGEKLAHFHPNKTIRFNPSAGGDLEITHTTFICGGEFFYC
 NTSGLFNRITYDANETAKYGNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGIITCRSNIITGLLLTRDGEENGTEETFRP
 GGGDMRDNRSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQ
 QQSNNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQLLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMTWMQ
 WDREVSNYTDI IYELLEESQSQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQ
 GYSPLSLQTLIPTQRGPDRPGGIEEGGEKDRGRSIRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHSIL
 RSLQRGWEVLKYLGNLVQYWGLELKKSASISLLDTIAIAVAEGTDRIIEFCRAIYNIPTRVRRGFEAALQ*

>CH694w134.20.75

MRARGIQRNYQHWWTWGILGFWMLMlcnaVEKRWVTVYYGvpvWKEAKATLFCASDAKAYEKEAHNVWATHACVPTDPS
 QELVLENTENFNMWKNMVEQMHEDIISLWDQSLKPCVKLTPLCVTLECTTANFTASNNSTSSNNSTSIINNSTFSNNTM
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 IILKCNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEEIIIRSENLTDNKTIIIVHLNESVEINCTRPGNNTR
 QSVRIGPGQTFYATGDIIGNIRQAHNCNISEAKWNATLLKVGEKLAHFHPNKTIRFNPSAGGDLEITHTTFICGGEFFYC
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Figure 26 Cont.

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 QWDREVSNYTDIIYELLEESQSQQEKNEQDALLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVR
 QGYSPLSLQTLIPNQRGPDRPEGIEEEGGEKDRGRSVRLVSGFLALAWDDLRSLCLFSYHRLRDLILLILARAVELLGHSI
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>CH694w138.10.18

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 NTSGLFNRITYDANETAKYGNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGIITCRSNITGLLLTRDGAENGTEFRP
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 GYSPLSLQTLIPNQRGPDRPGGIEEEGGEKDRGRSVRLVSGFLALAWDDLRSLCLFSYHRLRDLILLILARAVELLGHSIL
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>CH694w138.10.47

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 NTSGLFNRITYDANETAKDVNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGSITCRSNITGLLLTRDGGDGGENGTEFR
 RPPGGMRDNWRSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASITLTVQARQLLSGI
 VQQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLEIWNMTW
 MQWDREVSNYTGIIYNLLEESQSQQEKNEQDALLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRV
 RQGYSPLSLQTLIPTQRGPDRPGGIEEEGGEKDRGRSIRLVSGFLALAWDDLRSLCLFSYHRLRDLILLILARAVELLGHS
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>CH694w138.10.50

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 VEINCTRPGNNTRQSVRIGPGQTFYTTGDIIGDIRQAHCNISEKEWNATLLKVGEKLAHFHPNKTIRFNSSAGGDLEITT
 HTFICGGEFFCYCNTSSLFNRITYDANETAEYVNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGIITCRSNITGLLLTR
 DGGDGGENGTEFRPGGGMRDNWRSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASI
 TLTVQARQLLSGIVQQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQQLLGLWGCSGKLICTTTVPWNSSWS
 NKTLEIWNMTWMQWDREVSNYTGIIYNLLEESQSQQEKNEQDALLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGL
 RIVFAILSLVNRVRQGYSPLSLQTLIPTQRGPDRPEGIEEEGGEKDRGRSVRLVSGFLALAWDDLRSLCLFSYHRLRDL
 LILARAVELLGHSILRLSLQRGWEVLKYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEFCRAIYNIPTRIRRGFE
 AALQ*

>CH694w138.10.57

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 PPIPIHYCAPAGYAILKCNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEEEEIIIRSENLTDNKTIIIVHLNES
 VEINCTRPGNNTRQSVRIGPGQTFYTTGDIIGDIRQAHCNISEKEWNATLLKVGEKLAHFHPNKTIRFNPSAGGDLEITT
 HTFICGGEFFCYCNTSGLFNRITYDANETAKYGNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGIITCRSNITGLLLTR
 DGGDGGENGTEFRPGGGMRDNWRSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASI
 TLTVQARQLLSGIVQQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQQLLGLWGCSGKLICTTTVPWNSSWS
 NKTLEIWNMTWMQWDREVSNYTGIIYNLLEESQSQQEKNEQDALLALDKWNSLWNWFDITNWLWYIKIFIMIIGGLIGL
 RIVFAILSLVNRVRQGYSPLSLQTLIPTQRGPDRPEGIEEEGGEKDRGRSIRLVSGFLALAWDDLRSLCLFSYHRLRDL
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Figure 26 Cont.

LILARAVELLGHSILRSLQRGWEVLKYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRVIEFCRAIYNIPTRIRRGFE
AALQ*

>CH694w146.15.41

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TFYATGDIIGDIKQAHNCISEAKWNATLLKVKEKLAEHFPNKTIIIFNSSAGGDLEITHTFTICGGEFFYCNTSGLFEYVN
STNGNITLQCRKQFINMWQVRGRAMYAPPIAGSITCSSNITGLLLTRDGGGNGTEETFRPGGGMDRDNWRSELYKYKV
EIKPLGVAPTEAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQSNLLKAIEAQHLLQLT
VWGIKQLQARVLAIERYLKDDQQLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMTWMQWDKEVSNYTDIIYELLEES
QNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPSLQTLIPNQRGPDR
PGGIEEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHSILRSLQRGWEVLKYLGNLVQY
WGLELKKSAISLLDTIAIAVAEGTDRIIECCRAIYNIPTRIRRGFEAALQ*

>CH694w146.15.53

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NSTSINNSTFSNNTMREEMKNCSFNATTEIRDKQKKMYALFYKLDIVSLKEDKNNSNNSNKYILINCNTSTIAQACPKIS
FDPPIPIHYCAPAGYAILKCNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNLGSLAEEEEIIIRSENLTDNKTIIIVHLN
ESVEINCTRPNNTRQSVRIGPGQTFYTTGDIIGDIRQAHNCISEKEWNATLLKVGEKLAHFPNKTIRFNPSAGGDLEI
THTFTICGGEFFYCNTSGLFNRTYDANETATYGNSTNGNITLQCRKQFINMWQVRGRAMYAPPIAGIITCRSNITGLLL
TRDGGDGGENGTEETFRPGGGMDRDNWRSELYKYKVVEIKPLGIAPTAKARRVverekrAVGMGAVLLGFLGAAGSTMG
AASITLTVQARQLLSGIVQQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQQLGLWGCSGKLICTTTVPWN
SSWSNKTLEEIWGNMTWMQWDREVSNTGIIYNLLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIIGG
LIGLRIVFAILSLVNRVRQGYSPSLQTLIPTQRGPDREPGIEEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRL
RDLILLIARAVELLGHSILRSLQRGWEVLKYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRVIEFCRAIYNIPTRIR
RGFEAALQ*

>CH694w146.3.2

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YAILKCNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNLGSLAEEEEIIIRSENLTDNKTIIIVHLNESVEINCTRPNN
TRRSVRIGPGQTFYTTGDIIGDIRQAHNCISEAKWNATLLKVKEKLAHFPNKTIIIFSSAGGDLEITHTFTICGGEFFY
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TFRPGGGMDRDNWRSELYKYKVVEIKPLGIAPTAKARRVverekrAVGLGAVLLGFLGAAGSTMGAASITLTVQARQLLS
GIVQQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQQLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNM
TWMQWDREVSNTGIIYNLLEESQSQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIIGGLIGLRIVFAILSLV
NRVRQGYSPSLQTLIPTQRGPDREPGIEEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLIARAVELLG
HSILRSLQRGWEVLKYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRVIEFCRAIYNIPTRIRRGFEAALQ*

>CH694w146.3.7

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TSINNSTFSNNTMKEEMKNCSFNATTEIRDKQKKMYALFYKLDIVSLKEDKNNSNNSNKYILINCNTSTIAQACPKISFD
PIPIHYCAPAGYAILKCNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNLGSLAEEEEIIIRSENLTDNKTIIIVHLNES
VEINCTRPNNTRQSVRIGPGQTFYTTGDIIGDIRQAHNCISEAKWNATLLKVKEKLAEHFPNKTIRFTSSAGGDLEITT
HTFTICGGEFFYCNTSGLFNRTYDVNETAEYVNSVNSTNNITLQCRKQFINMWQVRGRAMYAPPIAGIITCRSNITGLLL
TRDGGDGGENGTEETFRPGGGMDRDNWRSELYKYKVVEIKPLGIAPTAKARRVverekrAVGMGAVLLGFLGAAGSTMGA
SITLTVQARQLLSGIVQQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQQLGLWGCSGKLICTTTVPWNSS
WSNKTLEEIWGNMTWMQWDREVSNTGIIYNLLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLI
GLRIVFAILSLVNRVRQGYSPSLQTLIPNQRGPDRPGGIEEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLR
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FEAALQ*

>CH694w165.10.14

Figure 26 Cont.

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 KEEMKNCSFNATTEIRDKQKKMYALFYKLDIEPLDKNNSTNSTKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAIL
 KCNNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEEEEIIIRSENLTDNAKTIIVHLNESVEINCTRPGNNTRRS
 VRIGPGQTFYTTGDIIGDIRQAHCNISEAKWNATLLKVKEKLAKHFPNKTIIFTSSAGGDLEITHTFTICGGEFFYCNTS
 GLFNRTYDVNETTEYVNSVNSTNNITLQCRIKQFINMWQVRGRAMYAPPIAGNITCRSNIITGLLLTRDGGGENRTETFRP
 GGGDMRDNRSELYKYKVVEIKPLGIAPTAKARRVvrekRAVGMGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQ
 QQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLDIWNMTWMQ
 WDREVSNYTGIIYNLLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSVNVRVQ
 GYSPLSLQTLIPTQRPDRPEGIEEGGEKDRGRSVRLVSGFLALAWDDLRSCLFSYHRLRDLILLILARAVELLGHSIL
 RSLQRGWEVLKYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEFCRAIYNIPTRIRRGFEAALQ*

>CH694w165.10.21

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 MKEEMKNCSFNATTEIRDKQKKMYALFYKLDIEPLDKNNSTNSTKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAI
 LKCNNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEEEEIIIRSENLTDNAKTIIVHLNESVEINCTRPGNNTRQ
 SVRIGPGQTFYTTGDIIGDIKQAHCNISEKEWNATLLKVGEKLAKHFPNKKIRFNPSAGGDLEITHTFTICGGEFFYCNT
 SGLFNRTYDVNETAEYGNSTNSNITLQCRIKQFINMWQVRGRAMYAPPIAGIITCRSNIITGLLLTRDGGGENGTETFRPG
 GGGDMRDNRSELYKYKVVEIKPLGIAPTEAKARRVvrekRAVGMGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQ
 QSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLDIWNMTWMQW
 DREVSNYTGIIYNLLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSVNVRVQ
 YSPLSLQTLIPTQRPDRPGGIEEGGEKDRGRSIRLVSGFLALAWDDLRSCLFSYHRLRDLILLILARAVELLGHSILR
 SLQRGWEVLKYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEVCRAIYNIPTRIRRGFEAALQ*

>CH694w165.10.30

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 QELVLENTENFNMWKNMVEQMHEDIISLWDQSLKPCVKLTPLCVTLNCTTANFTANNNSTSSNNSTPINNSTFSNNMT
 KEEMKNCSFNATTEIRDKQKKMYALFYKLDIEPLDKNNSTNSTKYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAIL
 KCNNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEEEEIIIRSENLTDNKTIIVHLNESVEINCTRPGNNTRQS
 VRIGPGQTFYTTGDIIGDIKQAHCNISEKEWNATLLKVGEKLAKHFPNKTIRFNPSAGGDLEITHTFTICGGEFFYCNTS
 GLFNRTYDAKETAEYGNSTNGNITIQCRIKQFINMWQVRGRAMYAPPIAGIITCRSNIITGLLLTRDGGKENGTEETFRPG
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 QSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLDIWNMTWMQW
 DREVSNYTGIIYNLLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSVNVRVQ
 YSPLSLQTLIPTQRPDRPGGIEEGGEKDRGRSVRLVSGFLALAWDDLRSCLFSYHRLRDLILLILARAVELLGHSILR
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>CH694w165.10.32

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 YAILKCNNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEKEIIIRSENLTDNKTIIVHLNESVEINCTRPGNN
 TRRSVRIGPGQTFYTTGDIIGDIRQAHCNISEAKWNATLLKVKEKLAKHFPNKTIIFTSSAGGDLEITHTFTICGGEFFY
 CNTSGLFNRTYDANGTAEYGNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGNITCRSNIITGLLLTRDGGDGENRTE
 ETFRPGGGDMRDNRSELYKYKVVEIKPLGIAPTAKARRVvrekRAVGMGAVLLGFLGAAGSTMGAASITLTVQARQLL
 SGIVQQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLDIWN
 MTWMQWDREVSNYTGIIYNLLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSV
 NVRVQGYSPSLQTLIPTQRPDRPEGIEEGGEKDRGRSVRLVSGFLALAWDDLRSCLFSYHRLRDLILLILARAVELL
 GHSILRSLQRGWEVLKYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEFCRAIYNIPTRIRRGFEAALQ*

>CH694w165.10.37

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 QELVLENTENFNMWKNMVEQMHEDIISLWDQSLKPCVKLTPLCVTLNCTTANFTANNNSTSSNNSTPINNSTFSNNMT
 KEEMRNCNCSFNATTEIRDKQKKMYALFYKLDIVPLDKNNNSNRNNTKYILINCNTSTIAQACPKISFDPIPIHYCAPAGY
 AILKCNNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEEEEIIIRSENLTDNKTIIVHLNESVEINCTRPGNN
 TRRSVRIGPGQTFYTTGDIIGDIRQAHCNISEAKWNATLLKVKEKLAKHFPNKTIIFTSSAGGDLEITHTFTICGGEFFY
 CNTSGLFNRTYNANETAQYGNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGNITCRSNIITGLLLTRDGGKEKETETET

Figure 26 Cont.

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WMQWDREVSNYTGIIYNLLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNR
VRQGYSPSLQTLIPTQRGPDRPGGIEEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLARAVELLGH
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>CH694w165.10.40

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PGNNTRRSVRIGPGQTFYTTGDIIGDIRQAHNCNISEAKWNATLLKVKEKLAKHFPNKTIIFSSSAGGDLEITHTFICGG
EFFYCNTSGLFNRTYDVNETAEYVNSVNSTNNITLQCRIKQFINMWQVRGRAMYAPPIAGNITCRSNITGLLLTRDGGGE
NRTETFRPGGGMDRDNWRSELYKYKVVEIKPLGIAPTKAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASITLTVQAR
QLLSGIVQQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQLLGLWGCSGKLICTTTVPWNSSWSNKTIGE
WENMTWMQWDREVSNYTGIIYNLLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAIL
SLVNRVRQGYSPSLQTLIPTQRGPDRPEGIEEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLARAV
ELLGHSILRSLQRGWEVLKYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRVIEFCRAIYNIPTRIRRGFEAALQ*

>CH694w165.10.43

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FYATGNIIGDIKQAHNCNISEAKWNATLLKVKEKLAEHFPNKTIIRFNPSAGGDLEITHTFICGGEFFYCNTSGLFNRTYD
ANETAKDVNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGSITCRSNITGLLLTRDGGGNGTEETFRPGGGMDRDNWR
SELYKYKVVEIKPLGIAPTEAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQSNLLKAIE
AQHLLQLTVWGIKQLQARVLAIERYLKDDQLLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMTWMQWDKEVSNTD
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>CH694w165.10.47

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>CH694w194.5.11

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APAGYAILKCNKTFNGTGPCSNVSTVQCTHGKIPVSTQLLLNGLSLAEKEIIIRSENLTDNAKTIIVHLNESVEINCIR
PGNNTRRSVRIGPGQTFYTTGDIIGDIRQAHNCNISEAKWNATLLKVGEKLAEHFPNKTIIRFDSSAGGDLEITHTFICGG
EFFYCNTSGLFNRTYGANETAKDVNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGNITCRSNITGLLLTRDGGGENR
TEETFRPGGGMDRDNWRSELYKYKVVEIKPLGIAPTKAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASITLTVQARQ
LLSGIVQQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQLLGLWGCSGKLICTTTVPWNSSWSNKTIGEIW
ENMTWMQWDREVSNYTGIIYNLLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILS
LVNRVRQGYSPSLQTLIPTQRGPDRPEGIEEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLARAVE
LLGHSILRSLQRGWEVLKYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEIIQEVCAIYNIPTRIRRGFEAALQ

*

Figure 26 Cont.

>CH694w194.5.12

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 KEEMRNC SFNATTEIRDKQKKMYALFYKLDIEPLKEDKNNSTNSTKYILINCNTSTIAQACPKISFDPPIHYCAPAGYA
 ILKCNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEGEIIIRSENLTDNAKTIIVHLNESVEINCRPGNNTR
 RSVRIGPGQTFYTTGDIIGDIRQAHCNISEAKWNATLLKVGEKLAEHFPNKTIREFDSSAGGDLEITHTTFICGGEFFYCN
 TSGLFNRTYGANETAKDVNNTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGNITCRSNITGLLLTRDGGGENRTEETFR
 PGGGDMRDNRSELYKYKVVEIKPLGIAPTKAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIV
 QQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLEIWEINMTWM
 QWDREVSNTGIIYNLLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVR
 QGYSPLSLQTLIPTQRGPDREGEIEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHSI
 LRLSLQRGWEVLKYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEIIQEVCAIYNIPIRIRRGFEAALQ*

>CH694w194.5.31

MRARGIQRNYQHWWIWGILGFWMMLIcnaGLEQGWVTVYYGvpvWKEAKTTLFCASDAKAYEKEAHNVWATHACVPTDPSP
 PQELVLENTENFNMWKNMVEQMHEDIISLWDQSLKPCVKLTPLCVTLNCTKAKFNGTSSNNSNPMDEEMKNC SFNAT
 TEIRDKKKQMYALFYTLTDIEPLGEEKNNSTNSTKYVLINCNTSTIAQACPKISFDPPIHYCAPAGYAILKCNKTFNGT
 GPCSNVSTVQCTHGIKPVVSTQLLNGSLAEEEEIIIRSENLTDNAKTIIVHLNESVEINCRPNMNTROSVRIGPGQTFY
 ATGGIIGDIRQAHCNINEGKWNATLLKVRKKLAEHFPNKTIKFDSAGGDLEITHTTFICGGEFFYCNSTSGLEFYDNSTN
 GNITLQCRIKQFINMWQVRGRAMYAPPIAGSITCSSNITGLLLTRDGGNGTEETFRPGGGDMRDNRSELYKYKVVEIKP
 LGIAPTEAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQSNLLKAIEAQHLLQLTVWGI
 KQLQARVLAIERYLKDDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLEIWEINMTWMQWDKEVSNTDIIYELLESQNQQ
 EKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPLSLQTLIPNQRGPDREPGGI
 EEEGERDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHSILRLSLQRGWEVLKYLGNLVQYWGLE
 LKKSAISLLDTIAIAVAEGTDRIIEIIQEVCAIYNIPIRIRRGFEAALQ*

>CH694w194.5.39

MRARGIQRNYQHWWTWGILGFWMMLIcnaGEQRWVTVYYGvpvWKEAKTTLFCASDAKAYEKEAHNVWATHACVPTDPSP
 QELVLENTENFNMWKNMVEQMHEDIISLWDQSLKPCVKLTPLCVTLNCTTANFTANKNSTSSNNSTTINNSTFSNNTM
 KEEMRNC SFNATTEIRDKQKKMYALFYKLDIEPLDKNNSTNSTKYILINCNTSTIAQACPKISFDPPIHYCAPAGYAIL
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 GGDMRDNRSELYKYKVVEIKPLGIAPTKAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQ
 QSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLEIWEINMTWMQW
 DREVSNTGIIYNLLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQG
 YSPLSLQTLIPTQRGPDREGEIEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHSILR
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>CH694w194.5.41

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 KEEMRNC SFNATTEIRDKQKKMYALFYKLDIEPLKEDKNNSTNSTKYILINCNTSTIAQACPKISFDPPIHYCAPAGYA
 ILKCNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEEEEIIIRSENLTDNAKTIIVHLNESVEINCRPGNNTR
 QSVRIGPGQTFYTTGDIIGDIKQAHCNISEKEWNATLLKVGEKLAKHFPNKKIRFNPSAGGDLEITHTTFICGGEFFYCN
 TSGLFNRTYNANETAEGNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGIITCRSNITGLLLTRDGGGENETEPETFR
 PGGGDMRDNRSELYKYKVVEIKPLGIAPTKAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIV
 QQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLEIWEINMTWM
 QWDREVSNTGIIYNLLEESQNQQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSVVNRVR
 QGYSPLSLQTLIPTQRGPDREGEIEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHSI
 LRLSLQRGWEVLKYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEIIQEVCAIYNIPIRIRRGFEAALQ*

>CH694w215.30.11

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 QELVLENTENFNMWKNMVEQMHEDIISLWDQSLKPCVKLTPLCVTLNCTTANFTANKNSTTINNSTSSNNSTPINNST
 FSNNTMKEEMRNC SFNATTEIRDKQKKMYALFYKLDIEPLDKNNKSGGKNNYTEYILINCNTSTIAQACPKISFDPPIHY
 YCAPAGYAILKCNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEGEIIIRSENLTDNAKTIIVHLNESVEMNC
 SRPGNNTRRSVRIGPGQTFYTTGDIIGDIRQAHCNISEAKWNATLLKVGEKLAEHFPNKTIREFNSSAGGDLEITHTTFNC

Figure 26 Cont.

GGEFFYCNTSGLFNRTYNASETAEYVNSGNSTNNITLQCRIKQFINMWQRVGRAMYAPPIAGNITCRSNITGLLLTRDGG
KENNETEETFRPGGDMRDNRSELYKYKVVEIKPLGIAPTAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASITLT
VQARQLLSGIVQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKT
LGEIWENMTWMQWDREVSNYTGIIYNLLEESQSQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIV
FAILSLVNRVRQGYSPSLQTLIPTQRGPDREGEIEEGGKDRGRSVRLVSGFLALAWDDLRSCLFSYHRLRDLILL
ARAVELLGRSILRSLQRGWEVLKYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEIIQEVCAIYNIPIRIRRGF
EAALQ*

>CH694w215.30.21

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MKEEMRNCSEFNATTEIRDKQKKMYALFYKLDIEPLDKNNSKGGKNNYTEYILINCNTSTIAQACPKISFDPIPIHYCAPA
GYAILKCNKTFNGTGPCSNVSTVQCTHGKIPVVSTQLLLNGSLAEKEIIIRSENLTDNAKTIIVHLNESVEINCTRPGN
NTRQSVRIGPGQAFYTTGDIIGDIKQAHNCISEKEWNATLLKVGEKLAKHFPNKTIFKPSAGGDLEITHTFTICGGEFF
YCNTSGLFNKTYNASETAKDVNSTNGNITLQCRIRQFINMWQRVGRAMYAPPIAGIITCRSNITGLLLTRDGGGGGENRT
DGTEETFRPGGDMRDNRSELYKYKVVEIKPLGIAPTAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASITLTVQA
RQLLSGIVQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLINE
IWENMTWMQWDREVSNYTGIIYNLLEESQSQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAI
LSVVNRVRQGYSPSLQTLIPTQRGPDREGEIEEGGKDRGRSVRLVSGFLALAWDDLRSCLFSYHRLRDLILLILARA
VELLGHHSILRSLQRGWEVLKYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEIIQEVCAIYNIPIRIRRGFEAA
LQ*

>CH694w215.30.35

MRARGIQRNYQHWWTWGILGFWMMLIcnaVEKQWVTVYYGvpvWKEAKTTLFCASDAKAYEKEAHNVWATHACVPTDPS
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LGNNMTKEEMKNCSEFNATTEIRDKQKKMYALFYKLDIEPLDKNNSREGKNNYTEYILINCNTSTIAQACPKISFDPIPIH
YCAPAGYAILKCNKTFNGTGPCSNVSTVQCTHGKIPVVSTQLLLNGSLAEKEIIIRSENLTDNAKTIIVHLNESVEINC
SRPGNNTRRSVRIGPGQTFYTTGDIIGDIRQAHNCISEAKWNATLLKVGKKLAKHFPNKTIFDSSAGGDLEITHTFTIC
GGEFFYCNTSGLFNNGTYGANETAKDVNSTNGNITLQCRIKQFINMWQRVGRAMYAPPIAGNITCRSNITGLLLTRDGGEG
EENRTKETFRPGGDMRDNRSELYKYKVVEIKPLGIAPTAKRRVverekrAVGLGAVLFGFLGAAGSTMGAASITLTV
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AILSLVNRVRQGYSPSLQTLIPTQRGPDREGEIEEGGKDRGRSVRLVSGFLALAWDDLRSCLFSYHRLRDLILLILARA
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LQ*

>CH694w215.30.36

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NATTEIRDKQKKMHALFYRLDIMPLDKNNSNEYILINCNTSTIAQACPKISFDPIPIHYCAPAGYAILKCNKTFNGTG
CSNVSTVQCTHGKIPVVSTQLLLNGSLAEKEIIIRSENLTDNAKTIIVHLNESVEINCTRPNNTRQSVRIGPGQTFYAT
GGIIGNIRQAYCNINEGKWNATLLKVKEKLAKHFPNKTIFSSSAGGDLEITHTFTICGGEFFYCNTSGLFNRTYNASET
AKDVNSTNSTITLQCRIKQFINMWQRVGRAMYAPPIAGSITCSSNITGLLLTRDGGKENETEETFRETEFRPGGDMRD
NRSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGLGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQSNLLKA
IEAQHLLQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLEEIWGNMTWMQWDKEVS
TDIIYNLLEESQSQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGYSPSLQ
TLIPNQRGPDRPGGIEEGGERDRGRSVRLVSGFLALAWDDLRSCLFSYHRLRDLILLILARAVELLGHHSILRSLQ
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>CH694w215.30.40

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TFSPNNMTKEEMRNCSEFNATTEIRDKQKKMYALFYKLDIEPLKEDENNSTNSTKYILINCNTSTIAQACPKISFDPIPIH
YCAPAGYAILKCNKTFNGTGPCSNVSTVQCTHGKIPVVSTQLLLNGSLAEKEIIIRSENLTDNAKTIIVHLNESVEIN
RPGNNTRRSVRIGPGQTFYTTGDIIGDIRQAHNCISEAKWNATLLKVGGKLAHFPNKTIRFDSSAGGDLEITHTFTIC
GGEFFYCNTSGLFNNGTYGANETAKDVNSTNGNITLQCRIKQFINMWQRVGRAMYAPPIAGNITCGSNITGLLLTRDGGGE
KNRTETFRPGGDMRDNRSELYKYKVVEIKPLGIAPTAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASITLTVQA
RQLLSGIVQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLEK

Figure 26 Cont.

IWGNMTWMQWDKEVSNYTDIIYKLLSESONQQETNEQDILLALDKWNSLWNWFDITNWLWYIRIFIMIVGGLIGLRIVFAI
LSLVNRVRQGYSPSLQTLIPTQRGPDREGEIEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARA
VELLGHSLRLSLQRGWEVLKYLGLVQYWGLELKKSAISLLDTIAIAVAEGTDRVIEFCRAIYNIPTIRIRRGFEAALQ*

>CH694w215.30.60

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YAILKCNNTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGLSLAEGEIIIRSENLTDNAKTIIVHLNESVEINCTRPGNN
TRQSVRIGPGQTFYTTGDIIGDIKQAHCNISEKEWNATLLKVRKKLAEHFPNKTIISFKPSAGGDLEITHTFTICGGEFFY
CNTSGLFNRTYNASETAKDVNSTNGNITLQCRKQFINMWQVRGRAMYAPPIAGIITCRSNITGLLLTRDGAENDTETFR
PGGDMRDNRSELYKYKVVEIKPLGIAPTKAKRRVVDREKRAVGLGAVLLGLGAAGSTMGAASITLTVQARQLLSGIV
QQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLEIWIENMTWM
QWDREVSNYTGIIYNLLEESQSQEKNEQDILLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVR
QGYSPSLQTLIPTQRGPDREGEIEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHSL
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>CH694w215.30.65

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TFSNNTMKEEMRNCSFNATTEIRDKQKKMYALFYKLDIEPLDKNNSKGGKNNTYIILINCNTSTIAQACPKISFDPIPI
HYCAPAGYAILKCNNTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGLSLAEGEIIIRSENLTDNAKTIIVHLNESVEIN
CSRPGNNTRRSVRIGPGQTFYTTGDIIGDIRQAHCNISEAKWNATLLKVKELAKHFPNKTIIFSSSAGGDLEITHTFTI
CGGEFFYCNTSGLFNRTFNRTYEVNETAEYVNGVNSTNNITLQCRKQFINMWQVRGRAMYAPPIAGNITCRSNITGLLL
TRDGAENDTETFRPGGDMRDNRSELYKYKVVEIKPLGIAPTKAKRRVverekrAVGMGAVLLGLGAAGSTMGAASIT
LTVQARQLLSGIVQQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSN
KTLEKIWGNMTWMQWDKEVSNYTDIIYKLLSESONQQETNEQDILLALDKWNSLWNWFDITNWLWYIRIFIMIVGGLIGLR
IAFAILSVVNRVRQGYSPSLQTLIPTQRGPDREGEIEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILL
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ALQ*

>CH694w221.30.23

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RRSVRIGPGQTFYTTGDIIGDIRQAHCNISEAKWNATLLKVKELAKHFPNKTIIFSSSAGGDLEITHTFTICGGEFFYC
NTSGLFNRTYNASETAEYVNRVNSTNNITLQCRKQFINMWQVRGRAMYAPPIAGNITCRSNITGLLLTRDGGVNNETTE
ETFRPGGDMRDNRSELYKYKVVEIKPLGIAPTKAKRRVverekrAVGMGAVFLGLGAAGSTMGAASITLTVQARQLL
SGIVQQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLEIWIEN
MTWMQWDREVSNYTGIIYNLLEESQSQEKNEQDILLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIFAFAILSVV
NRVRQGYSPSLQTLIPAQRGPDRPGEIEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELL
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>CH694w221.40.51

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GPGQTFYTTGDIIGDIRQAHCNISEAKWNATLLKVKELAKHFPNKTIKFTSSAGGDLEITHTFTICGGEFLYCNTSGLF
NRTYKVNETAEDNSVNSTNNITLQCRKQFINMWQVRGRAMYAPPIAGNITCRSNITGLLLTRDGGKNGTETETEETFRP
GGGDMRDNRSELYKYKVVEIKPLGIAPTKAKRRVverekrAVGMGAVFLGLGAAGSTMGAASITLTVQARQLLSGIVQ
QQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLEIWIENMTWMQ
WDKEVSNYTGIIYNLLEESQSQEKNEQDILLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFTILSLVNRVRQ
GYSPLSLQTLIPTQRGPDREGEIEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHSL
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>CH694w221.40.63

Figure 26 Cont.

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 KEEMKNCSFNATTEIRDKQKKMYALFYKLDIEPLDKNNSKGGKNNYTEYILINCNTSTIAQACPKISFDPPIPIHYCAPAG
 YAILKCNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEGEIIIRSENLTDNAKTIIVHLNESVEINCSRPGNN
 TRRSVRIGPGQTFYTTGDIIGDIRQAHCNISEAKWNATLLKVKEKLAEHFPNKTIKFTSSAGGDLEITHTTFNCGGEFFY
 CNTSGLFNRTYNASETAEYVNRVNSTNNITLQCRIKQFINMWQVRGRAMYAPPIAGNITCRSNITGLLLTRDGAENDTET
 FRPGGDMRDNRSELYKYKVVEIKPLGIAPTAKARRVverekrAVGLGAVLLGFLGAAGSTMGAASITLTVQARQLLSG
 IVQQQSNLLKAI EAQQLLQLTWVGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKT LGQIWENMT
 WMQWDREVSNYTGIIYNLLEESQSQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIFAILSLVNR
 VRQGSPLSLQTLIPTQRPDRPEGIEEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGH
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>CH694w223.10.82

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 YCAPAGYAILKCNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEGEIIIRSENLTDNAKTIIVHLNESVQINC
 SRPGNNTRRSVRIGPGQTFYTTGDIIGDIRQAHCNISEAKWNATLLKVGGKLAEHFPNKTIRFDSSAGGDLEITHTTFIC
 GGEFFYCNTSGLFNRTYGANETAKDVNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGNITCRSNITGLLLTRDGGVN
 ETKTETFRPGGDMRDNRSELYKYKVVEIKPLGIAPTAKARRVverekrAVGMGAVLLGFLGAAGSTMGAASITLTVQA
 RQLLSGIVQQQSNLLKAI EAQQLLQLTWVGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKT LKE
 IWENMTWMQWDREVSNYTGIIYNLLEESQSQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMVVGGLIGLRIVFAI
 LSLVNRVRQGSPLSLQTLIPTQRPDRPEGIEEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARA
 VELLGHSILRSLQRGWEVLKYLGNLVQYWGLELKKSAISLLDAIAIAVAEGTDRVIEFCRAIYNIPTIRIRRGFEAALQ*

>CH694w223.5.13

MRVRGIPRNYQHWWTWSILGFWMMLIcnaGLEQQWVTVYYGvpvWKEAKTTLFCASDAKAYEKEAHNVWATHACVPTDPSP
 PQELVLENTENFNMWKNMVEQMHEDIISLWDQSLKPCVKLTPLCVTLNCTKAKFNSTSSNNISISSNNPVEEEMKNCSF
 NATTEIRDKQKQMYALFYTLTDIEPLGEEKNNSTNYTKYILINCNTSTIAQACPKISFDPPIPIHYCAPAGYAILKCNKTF
 NGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEGEIIIRSENLTDNAKTIIVHLNESVEINCTRPNNNRQSVRIGPGQ
 TFYATGGIIGKIRQAHCNINERKWNATLLKVKGKLAEHFPNKTIKFNPSAGGDLEITHTTFNCGGEFFYCDTSGLFNRTY
 NASETAKDVNSTNSTITLQCRIKQFINMWQVRGRAMYAPPIAGSITCSSNITGLLLTRDGEKNRTEETFRPGGDMRDNW
 RSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQQQSNLLKAI
 EAQQLLQLTWVGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKT LKEIWGNMTWMQWDREVSNYT
 DIIYNLLEESQSQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQGSPLSLQTL
 LIPTQRPDRPGGIEEEGERDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHSILRSLQRGWEV
 LKYLGNLVHYWGLELKKSAISLLDTIAIAVAEGTDRIIEIIQEVCAIYNIPTIRIRRGFEAALQ*

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MRARGIQRNYQHWWTWGILGFWMMLIcnaGEQQWVTVYYGvpvWKEAKTTLFCASDAKAYEKEAHNVWATHACVPTDPSP
 QELVLENTENFNMWKNMVEQMHEDIISLWDQSLKPCVKLTPLCVTLNCTTANFTANKNSTSSNNSTPINNSTFSNNMT
 KEEMRNCFSFNATTEIRDKQKKMYALFYKLDIVQLEKNNSNKYILINCNTSTIAQACPKISFDPPIPIHYCAPAGYAILKCN
 NKTTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEIIIIRSENLTDNAKTIIVHLNESVQINCSRPGNNTRRSVRI
 GPGQTFYTTGDIIGDIRQAHCNISEAKWNATLLKVKEKLAEHFPNKTIKFTSSAGGDLEITHTTFICGGEFLYCNSTGLF
 NRTYKVNETAEYDNSVNSTNNITLQCRIKQFINMWQVRGRAMYAPPIAGNITCRSNITGLLLTRDGGENNKT KTEETFRP
 GGGDMRDNRSELYKYKVVEIKPLGIAPTAKARRVverekrAVGMGAVLLGFLGAAGSTMGAASITLTVQARQLLSGIVQ
 QQSNLLKAI EAQQLLQLTWVGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKT LGQIWENMTWMQ
 WDREVSNYTGIIYNLLEESQSQEKNEQDLLALDKWNSLWNWFDITNWLWYIKIFIMIVGGLIGLRIVFAILSLVNRVRQ
 GYSPLSLQTLIPTQRPDRPEGIEEEGGEKDRGRSVRLVSGFLALAWDDLRLSLCLFSYHRLRDLILLILARAVELLGHSIL
 RSLQRGWEVLKYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEIIQEVCAIYNIPTIRIRRGFEAALQ*

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MRARGIQRNYQHWWTWGILGFWMMLIcnaGEQQWVTVYYGvpvWKEAKTTLFCASDAKAYEKEAHNVWATHACVPTDPSP
 QELVLENTENFNMWKNMVEQMHEDIISLWDQSLKPCVKLTPLCVTLNCTTANFTANKNSTSSNNSTPINNSTFSNNMT
 KEEMRNCFSFNATTEIRDKQKKMYALFYKLDIEPLDKNNSKGGKNNYTEYILINCNTSTIAQACPKISFDPPIPIHYCAPAG
 YAILKCNKTFNGTGPCSNVSTVQCTHGIKPVVSTQLLNGSLAEIIIIRSENLTDNAKTIIVHLNESVEINCTRPNN
 TRQSVRIGPGQTFYTTGDIIGDIKQAHCNISEKEWNATLLKVRKKLAEHFPNKTISFKPSAGGDLEITHTTFICGGEFFY
 CNTSGLFNRTYNASETAKDVNSTNGNITLQCRIKQFINMWQVRGRAMYAPPIAGIITCRSNITGLLLTRDGGKNETQTET

Figure 26 Cont.

FRPGGGDMRDNRSELYKYKVVEIKPLGIAPTKAKRRVverekrAVGMGAVLLGFLGAAGSTMGAASITLTVQARQLLSG
IVQQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKTIGEIWENMT
WMQWDREVSNYTGIIYNLLEESQNQQEKNEQDLLALDKWNSLWNWFDITNLWYIKIFIMIVGGGLIGLRIAFAILSVVNR
VRQGYSPSLQTLIPAQRGPDRPGGIEEGGEKDRGRSVRLVSGFLALAWDDLRSLCLFSYHRLRDLILLIARAVELLGH
SILRSLQRGWEVLKYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEIIQEVCAIYNIPIRIRRGFEAALQ*

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MRARGIQRNYQHWWTWGILGFWMMLIcnaGLEQGWTVYYGvpvWKEAKTTLFCASDAKAYEKEAHNVWATHACVPTDPS
PQELVLENTENFNMWKNDMVEQMHEDIISLWDQSLKPCVKLTPLCVTLNCTTANFTGNKNSTSSNNSTSIDNSTLGNNT
MKEEMKNCSEFNATTEIRDKQKKMYALFYKLDIEPLDKNNSKGGKNNYTEYILINCNTSTIAQACPKISFDPIPIHYCAPA
GYAILKCNKTFNGTGPCSNVSTVQCTHGKIPVSTQLLNGLSLAEGETIIRSENLTDNAKTIIVHLNESVEINCSRPGN
NTRRSVRIGPGQTFYTTGDIIGDIRQAHCNISEAKWNATLLKVKEKLAKHFPNKTIIFNSSAGGDLEITHTTFICGGEFL
YCNTSGLFNRTYNASETAEYVNRVNSTNNITLQCRIKQFINMWQRVGRAMYAPPIAGNITCRSNITGLLLTRDGGKENG
ETEETFRPGGGDMRDNRSELYKYKVVEIKPLGIAPTKAKRRVverekrAVGMGAVFLGFLGAAGSTMGAASITLTVQAR
QLLSGIVQQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKTIGE
IWENMTWMQWDKEVSNYTGIIYNLLEESQSQQEKNEQDLLALDKWNSLWNWFDITNLWYIKIFIMIVGGGLIGLRIVFAI
SLVNRVRQGYSPSLQTLIPTQRGPDRPEGIEEGGEKDRGRSVRLVSGFLALAWDDLRSLCLFSYHRLRDLILLIARAV
ELLGHSILRSLQRGWEVLKYLGSVLQYWGLELKKSAISLLDTIAIAVAEGTDRIIEIIQEVCAIYNIPIRIRRGFEAAL
Q*

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MRARGIQRNYQHWWTWGILGFWMMLIcnaGEQRWTVYYGvpvWKEAKTTLFCASDAKAYEKEAHNVWATHACVPTDPS
QELVLENTENFNMWKNDMVEQMHEDIISLWDQSLKPCVKMTPLCVTLNCTTANFTGNKNSTSINNSTSIDNSTLGNNTM
KEEMKNCSEFNATTEIRDKQKKMYALFYKLDIEPLDKNNSKGGKNNYTEYILINCNTSTIAQACPKISFDPIPIHYCAPA
YAILKCNKTFNGTGPCSNVSTVQCTHGKIPVSTQLLNGLSLAEGETIIRSENLTDNAKTIIVHLNESVQINCSRPGNN
TRRSVRIGPGQTFYTTGDIIGDIRQAHCNISEKRWATLLKVKEKLAEHFPNKTIKFTSSAGGDLEITHTTFICGGEFFY
CNTSGLFNRTYNASETSEYVNVNSTKNITLQCRIKQFINMWQRVGRAMYAPPIAGNITCRSNITGLLLTRDGAENDTET
FRPGGGDMRDNRSELYKYKVVEIKPLGIAPTKAKRRVverekrAVGLGAVLFGFLGAAGSTMGAASITLTVQARQLLSG
IVQQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKTIGEWEKMT
WMQWDKEVSNYTGIIYNLLEESQSQQEKNEQDLLALDKWNSLWNWFDITNLWYIKIFIMIVGGGLIGLRIVFAIISLVNR
VRQGYSPSLQTLIPTQRGPDRPEGIEEGGEKDRGRSVRLVSGFLALAWDDLRSLCLFSYHRLRDLILLIARAVELLGH
SILRSLQRGWEVLKYLGNLVQYWGLELKKSAISLLDTIAIAVAEGTDRIIEIIQAVCAIYNIPTRIRRGFEAALQ*

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MRARGIQRNYQHWWTWGILGFWMMLIcnaRLEQGWTVYYGvpvWKEAKTTLFCASDAKAYEKEAHNVWATHACVPTDPS
PQELVLENTENFNMWKNDMVEQMHEDIISLWDQSLKPCVKMTPLCVTLNCTTANFTGNKNSTSSNNSTPINNSTFSNNT
MKEEMRNCSEFNATTEIRDKQKKMYALFYKLDIEPLDKNNSKGGKNNYTEYILINCNTSTIAQACPKISFDPIPIHYCAPA
GYAILKCNKTFNGTGPCSNVSTVQCTHGKIPVSTQLLNGLSLAEETIIRSENLTDNAKTIIVHLNESVEINCTRPGN
NTRQSVRIGPGQAFYTTGDIIGDIKQAHCNISEKEWNATLLKVGEKLAKHFPNKTIKFKPSAGGDLEITHTTFICGGEFF
YCNTSGLFNKTYNASETAKDVNSTNGNITLQCRIKQFINMWQRVGRAMYAPPIAGIITCRSNITGLLLTRDGAENDTET
RPGGGDMRDNRSELYKYKVVEIKPLGIAPTEAKRRVverekrAVGLGAVLLGFLGAAGSTMGAASITLTVQARQLLSGI
VQQQSNLLKAIEAQHLLQLTVWGIKQLQARVLAIERYLKDQQLLGLWGCSGKLICTTTVPWNSSWSNKTLEKIWENMTW
MQWDREVSNYTGIIYNLLEESQNQQEKNEQDLLALDKWNSLWNWFDITNLWYIKIFIMIVGGGLIGLRIVFAIISLVNRV
RQGYSPSLQTLIPTQRGPDRPEGIEEGGEKDRGRSVRLVSGFLALAWDDLRSLCLFSYHRLRDLILLIARAVELLGHS
ILRNLQRGWEVLKYLGSVLQYWGLELKKSAISLLDTIAIAVAEGTDRIIEIIQEVCAIYNIPIRIRRGFEAALQ*

Figure 26 Cont.

DH175HC|CH002113

CAGGTGCAGCTGCAGGAGTCGGGGCGCAGGACTGTTGAAGCCTTCGGAGACCCTGTCCCTCA**GGTGTCTACGG**
TCAGTCTATCAGTTATCAATACTGGCACTGGATTTCGCCAGGGCCCCAGGGAAGGGGCTGGAGTGGATAGG**GTG**
GATCATACTGCAAGTGGTGTGAACGCCGACTACAAGTGGCCCCCTCAAGAGACGACTCTCCCTGTCATTGGACACGTC
 GAAGAATCAATTTTCCCTGAAGATGACGTCTGTGACCGCCGCGGACACGGGTGTATATT**GTGAGAGGGGGCG**
CCCTTCGCTGGGTTGGGCCCTTGGGACCCGCTCGCCACGGGCTCGACGTCTGGGGCCAAGGGACCACTGTCACAGTC
 TCCTCA

DH175LC|CK001512

GACATCCAGATGACCCAGTCTCCAGCCTCCCTGTCTGCATCTGTGGGAGACAGAGTCACCATCACTTGCCGGGCAAGT
CAGGACGTTGGAGATGATTTAGGCTGGTTTCAACACAAACCAGGGAAAGTCCCTAAGCGCCTGATCTT**GGTGGCTC**
CAGTTTGAAAGTGGGGTCCCGCCAAGATTCAGCGGCAGTGGAGGTGGGACAGAATTCCTCTAACAATCAGCAGCC
 TGCAGGCTGAAGATTTTGCAACTTATTACTGT**ATGCAGTATCATTCTTTACCGCACACTTTTGGCCAGGGGGGGCCACCT**
 GGAGATCAACC

Figure 27A

DH175 heavy chain amino acid sequence

	
	10 20 30 40 50
DH175	QVQLQESGAG LLKPSETLSL TCAVYGQSIG YQYWHWIRQA PGKGLEWIGR
	
	60 70 80 90 CVR 100
DH175	VDHTASGVNA DYKWPLKRRL SLSLDTSKNQ FSLKMTSVTA ADTGVVY
	
	110 120 130
DH175	GGALRWVGPW DPARHGLDVW GQGTTVTVSS

DH175 light chain amino acid sequence

	
	10 20 30 40 G 50
DH175	DIQMTQSPAS LSASVGDRVIT ITCRASQDVG DDLGWFAQHP GKVPKRLIF
	
	60 70 80 90 GQ 100
DH175	ASSLQSGVPP RFGSGGGTE FTLTISSLQA EDFATYYCMQ YHSLPHTF
	
DH175	GAHLEIN

Legend: CDR1 CDR2 CDR3

Figure 27B

Figure 28

1		20.3
2	week 5	20.13
3		20.14
4		10.3
5	week 6	10.6
6		15.48
7	week 7	15.1
8		15.4
9	week 9	15.32
10		30.2
11	week 13	30.16
12		6.2
13		6.19
14	week 17	6.20
15		4.30
16		6.10
17	week 20	6.55
18		10.2
19	week 28	10.48
20		40.72
21	week 41	40.82
22		70.32
23	week 53	70.38
24		70.43
25		10.1
26	week 64	10.4
27		10.25
28	week 101	10.5

Figure 28 Cont.

29		20.6
30		20.20
31		20.30
32		20.45
33		20.48
34		30.7
35		4.11
36		4.20
37		4.21
38		4.3
39	week 122	5.61
40		5.79
41		10.84
42		10.9
43		81.26
44		6.9
45		6.15
46		6.16
47	week 124	6.20
48		6.29
49		6.37
50		20.35
51		20.41
52	week 126	20.43
53		20.51
54	week 130	3.3
55		3.4
56		10.21
57		10.36

Figure 28 Cont.

55/56

58		10.63
59		10.7
60		20.58
61	week 134	20.60
62		20.65
63		20.75
64		10.18
65	week 138	10.47
66		10.50
67		10.57
68		3.2
69	week 146	3.7
70		15.41
71		15.53
72		10.14
73		10.21
74		10.30
75	week 165	10.32
76		10.37
77		10.40
78		10.43
79		10.47
80		5.11
81		5.12
82	week 194	5.31
83		5.39
84		5.41
85	week 215	30.11
86		30.21

Figure 28 Cont.

87		30.35
88		30.36
89		30.40
90		30.60
91		30.65
92		30.23
93	week 221	40.51
94		40.63
95		5.13
96		5.24
97		5.25
98	week 223	5.61
99		5.62
100		5.69
101		10.82

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/057955**A. CLASSIFICATION OF SUBJECT MATTER****C07K 14/16(2006.01)i, C12N 15/49(2006.01)i, C12N 15/63(2006.01)i, A61K 35/76(2006.01)i**

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07K 14/16; C07K 16/10; A61K 39/21; A61K 45/06; A61P 31/18; A61K 39/42; A61K 38/21; C12N 15/49; C12N 15/63; A61K 35/76

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal) & Keywords: broadly neutralizing HIV-1 Antibody, DP175, gp120 epitope

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2013-0251726 A1 (MASCOLA et al.) 26 September 2013 See abstract; claims 1-13; and paragraphs [0041]-[0042].	12, 15
A	US 2012-0282264 A1 (MASCOLA et al.) 08 November 2012 See abstract; and claims 1-7.	12, 15
A	US 2007-0292390 A1 (DIMITROV et al.) 20 December 2007 See the whole document.	12, 15
A	SCHEID et al., 'Broad diversity of neutralizing antibodies isolated from memory B cells in HIV-infected individuals' Nature, Vol.458, No.7238, pp.636-640 (2009) See the whole document.	12, 15
A	US 2008-0279879 A1 (ZOLLA-PAZNER) 13 November 2008 See the whole document.	12, 15



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

07 January 2015 (07.01.2015)

Date of mailing of the international search report

08 January 2015 (08.01.2015)

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/057955

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.: 8-11, 16-17
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 8-11 and 16-17 pertain to methods for treatment of the human body by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv), to search.
2. ☒ Claims Nos.: 1-11, 13-14
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:
Claims 1-11 and 13-14 are contrary to PCT Rule 6.2(a), because they rely on unnecessary reference to the drawings.
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:

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 an additional fees, this Authority did not invite payment of any 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.:

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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2014/057955

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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