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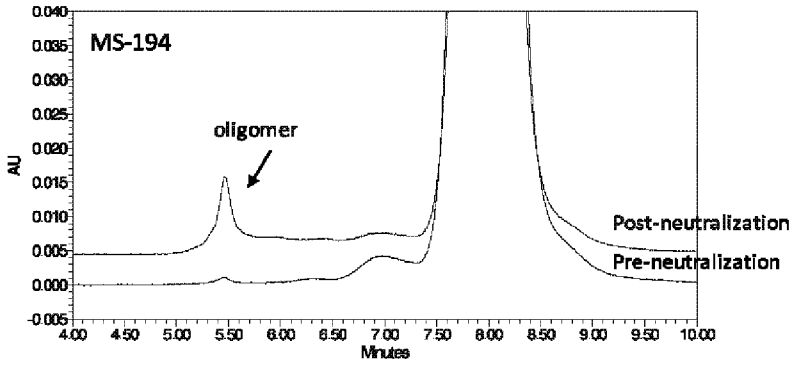

FIG. 1A

(57) Abstract: The present disclosure provides optimized broadly-neutralizing anti-HIV antibodies, having modified light chain variable regions and/or heavy chain variable regions leading to improved biophysical characteristics. The present disclosure also provides methods for producing these anti-HIV antibodies and methods of use thereof.

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ANTI-HIV ANTIBODY 10-1074 VARIANTS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. §119(e) to U.S. Provisional Patent Application No. 62/731,356, filed September 14, 2018. The foregoing application is incorporated by reference herein in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

This invention was made with government support under Grant No. P01 AI081677 awarded the NIH. The government has certain rights in the invention.

FIELD OF THE INVENTION

This invention relates generally to broad and potent antibodies against Human Immunodeficiency Virus ("HIV") and more specifically to anti-HIV antibody 10-1074 variants and the use thereof.

BACKGROUND OF THE INVENTION

HIV causes acquired immunodeficiency syndrome (AIDS), a condition in humans characterized by clinical features including wasting syndromes, central nervous system degeneration and profound immunosuppression that results in life-threatening opportunistic infections and malignancies. Since its discovery in 1981, HIV type 1 (HIV-1) has led to the death of at least 25 million people worldwide. It is predicted that 20-60 million people will become infected over the next two decades even if there is a 2.5% annual decrease in HIV infections. There is a need for therapeutic agents and methods for treatment or inhibition of HIV infection.

Some HIV infected individuals show broadly neutralizing IgG antibodies in their serum. Yet, little is known regarding the specificity and activity of these antibodies, despite their potential importance in designing effective vaccines. In animal models, passive transfer of neutralizing antibodies can contribute to protection against virus challenge. Neutralizing antibody responses also can be developed in HIV-infected individuals, but the detailed composition of the serologic response is yet to be fully uncovered.

SUMMARY OF INVENTION

The present disclosure relates to a new category of broadly-neutralizing anti-HIV antibodies, having modified light chain variable regions and/or heavy chain variable regions leading to improved biophysical characteristics, as well as methods of production and methods of use thereof.

Accordingly, in a first aspect, the present disclosure provides an isolated anti-HIV antibody, or antigen-binding portion thereof, including a light chain variable region having a light chain amino acid sequence that is at least 75% identical to a polypeptide sequence selected from the group consisting of the light chain variable regions of SEQ ID NOs: 3-13, 22, 24-28, 35-39, 43-45, and 47. The isolated anti-HIV antibody, or antigen-binding portion thereof includes one or more light chain substitutions at one or more residues located within or outside the light chain variable region. The one or more residues are selected from the group consisting of LmdV:Y2, LmdV:R7, LmdV:P9, LmdV:E17, LmdV:H46, LmdV:P81.1, LmdV:I81.3, LmdV:N82, LmdV:R88, LmdV:D110, and LmdV:A142.

In another aspect, the present disclosure provides an isolated anti-HIV antibody, or antigen-binding portion thereof, including a heavy chain variable region having a heavy chain amino acid sequence that is at least 75% identical to a polypeptide sequence selected from the group consisting of the heavy chain variable regions of SEQ ID NOs: 61-94. The isolated anti-HIV antibody, or antigen-binding portion thereof includes one or more heavy chain substitutions at one or more residues located within or outside of the heavy chain variable region. The one or more residues are selected from the group consisting of HV:D29, HV:S47, HV:N75, HV:V79, HV:R82, HV:L89, HV:T108, and HV:K141.

In another aspect, the present disclosure provides an isolated anti-HIV antibody, or antigen-binding portion thereof, including a light chain variable region having a light chain amino acid sequence that is at least 75% identical to a polypeptide sequence selected from the group consisting of the light chain variable regions of SEQ ID NOs: 3-13, 22, 24-28, 35-39, 43-45, and 47. The isolated anti-HIV antibody, or antigen-binding portion thereof includes one or more light chain substitutions at one or more residues selected from the group consisting of LmdV:Y2, LmdV:R7, LmdV:P9, LmdV:E17, LmdV:H46, LmdV:P81.1, LmdV:I81.3, LmdV:N82, LmdV:R88, LmdV:D110, and LmdV:A142. The anti-HIV antibody, or antigen-binding portion thereof, further includes a heavy chain variable region having a heavy chain amino acid sequence is at least 75% identical to a polypeptide sequence selected from the group consisting of the heavy chain variable regions of SEQ ID NOs: 61-94. The isolated anti-HIV antibody, or antigen-binding portion thereof includes one or more heavy chain substitutions at one or more residues selected from the group consisting of HV:D29, HV:S47, HV:N75, HV:V79, HV:R82, HV:L89, HV:T108, and HV:K141.

In some embodiments, the isolated anti-HIV antibody, or antigen-binding portion thereof includes the one or more light chain substitutions selected from the group consisting of LmdV:Y2P, LmdV:R7P, LmdV:P9S, LmdV:E17Q, LmdV:H46Q, LmdV:P81.1N,

LmdV:I81.3S, LmdV:N82G, LmdV:R88T, LmdV:D110E, and LmdV:A142G or conservative substitutions thereof (*i.e.*, LmdV:P9C, LmdV:P9T, LmdV:E17N, LmdV:H46N, LmdV:P81.1Q, LmdV:R88C, LmdV:R88S).

In some embodiments, the isolated anti-HIV antibody, or antigen-binding portion thereof includes the one or more heavy chain substitutions selected from the group consisting of HV:D29G, HV:S47P, HV:N75Q, HV:V79T, HV:R82V, HV:L89F, HV:T108R, and HV:K141Q or conservative substitutions thereof (*i.e.*, HV:L89W, HV:L89Y, HV:T108H, HV:T108K, HV:K141N).

In some embodiments, the isolated anti-HIV antibody, or antigen-binding portion thereof, includes the one or more light chain substitutions selected from the group consisting of LmdV:Y2P, LmdV:R7P, LmdV:P9S, LmdV:E17Q, LmdV:H46Q, LmdV:P81.1N, LmdV:I81.3S, LmdV:N82G, LmdV:R88T, LmdV:D110E, and LmdV:A142G or conservative substitutions thereof (*i.e.*, LmdV:P9C, LmdV:P9T, LmdV:E17N, LmdV:H46N, LmdV:P81.1Q, LmdV:R88C, LmdV:R88S) and the one or more heavy chain substitutions selected from the group consisting of HV:D29G, HV:S47P, HV:N75Q, HV:V79T, HV:R82V, HV:L89F, HV:T108R, and HV:K141Q or conservative substitutions thereof (*i.e.*, HV:L89W, HV:L89Y, HV:T108H, HV:T108K, HV:K141N).

In some embodiments, the light chain amino acid sequence is at least 75% identical to the light chain variable region of SEQ ID NO.: 3 and includes a LmdV:Y2P substitution or a conservative substitution of proline at LmdV:Y2.

In some embodiments, the heavy chain amino acid sequence is at least 75% identical to to the heavy chain variable region of SEQ ID NO.: 63 and includes an HV:V79T substitution or a conservative substitution of threonine at HV:V79.

In some embodiments, the heavy chain amino acid sequence is at least 75% identical to to the heavy chain variable region of SEQ ID NO.: 64 and includes an HV:R82V substitution or a conservative substitution of valine at HV:R82.

In some embodiments, the heavy chain amino acid sequence is at least 75% identical to to the heavy chain variable region of SEQ ID NO.: 65 and includes an HV:L89F substitution or a conservative substitution of phenylalanine of HV:L89.

In some embodiments, the heavy chain amino acid sequence is at least 75% identical to to the heavy chain variable region of SEQ ID NO.: 66 and includes an HV:T108R substitution or a conservative substitution of arginine at HV:T108.

In some embodiments, the light chain amino acid sequence is at least 75% identical to the light chain variable region of SEQ ID NO.: 22 and includes a LmdV:Y2P substitution or a

conservative substitution of proline at LmdV:Y2, and the heavy chain amino acid sequence is at least 75% identical to the heavy chain variable region of SEQ ID NO.: 69 and includes an HV:R82V substitution or a conservative substitution of valine at HV:R82, and an HV:T108R substitution or a conservative substitution of arginine at HV:T108.

In some embodiments, the heavy chain amino acid sequence is at least 75% identical to the heavy chain variable region of SEQ ID NO.: 70 and includes an HV:V79T substitution or a conservative substitutions of threonine at HV:V79, an HV:L89F substitution or a conservative substitution of phenylalanine at HV:L89, and an HV:T108R substitution or a conservative substitution of arginine at HV:T108.

In some embodiments, the light chain amino acid sequence is at least 75% identical to the light chain variable region of SEQ ID NO.: 24 and comprises a LmdV:Y2P substitution or a conservative substitution of proline at LmdV:Y2, and the heavy chain amino acid sequence is at least 75% identical to the heavy chain variable region of SEQ SEQ ID NO.: 71 and includes an HV:V79T substitution or a conservative substitution of threonine at HV:V79, an HV:L89F substitution or a conservative substitution of phenylalanine at HV:L89, and an HV:T108R substitution or a conservative substitution of arginine at HV:T108.

In some embodiments, the isolated anti-HIV antibody, or antigen-binding portion thereof includes SEQ NO.: 3. In some embodiments, the isolated anti-HIV antibody, or antigen-binding portion thereof includes SEQ NO.: 63, 64, 65, 66, or 70. In some embodiments, the light chain variable region includes the light chain variable region of SEQ NO.: 22 and the heavy chain variable region includes the heavy chain variable region of SEQ No.: 69. In some embodiments, the light chain variable region includes the light chain variable region of SEQ NO.: 24 and the heavy chain variable region includes the heavy chain variable region of SEQ No.: 71.

In another aspect, the present disclosure also provides a pharmaceutical composition having the above-presented anti-HIV antibody or antigen-binding portion and a pharmaceutically acceptable carrier or excipient. In some embodiments, the pharmaceutical composition further includes a second therapeutic agent. In some embodiments, the second therapeutic agent is an anti-HIV-1 broadly neutralizing antibody, such as 3BNC117.

In another aspect, the present disclosure additionally provides a nucleic acid, or a codon-optimized nucleic acid, encoding the above-presented anti-HIV antibody or antigen-binding portion thereof. Also provided is a vector or vector system having at least one above-presented nucleic acid and a cell having at least one above-presented nucleic acid.

In another aspect, the present disclosure provides a method of making recombinant anti-HIV antibody, or antigen-binding portion thereof. The method includes, among others, obtaining the cultured cell mentioned above, culturing the cell in a medium under conditions permitting expression of a polypeptide encoded by the vector and assembling of an antibody or fragment thereof, and purifying the antibody or fragment from the cultured cell or the medium of the cell.

In another aspect, the present disclosure provides a method of preventing or treating an HIV infection or an HIV-related disease. The method includes, among others, identifying a patient in need of such prevention or treatment, and administering to said patient a first therapeutic agent having a therapeutically effective amount of at least one above presented anti-HIV antibody of or an antigen-binding portion thereof. The method can further include administering a second therapeutic agent. The second therapeutic agent can be administered before, concurrently with or after the administration of the anti-HIV antibody or antigen-binding portion thereof. In some embodiments, the second therapeutic agent is an anti-HIV-1 broadly neutralizing antibody, such as 3BNC117.

In another aspect, the present disclosure further provides a kit having a pharmaceutically acceptable dose unit of a pharmaceutically effective amount of at least one isolated anti-HIV antibody presented above or antigen-binding portion thereof. The kit can further include a pharmaceutically acceptable dose unit of a pharmaceutically effective amount of an anti-HIV agent. The two pharmaceutically acceptable dose units can optionally take the form of a single pharmaceutically acceptable dose unit. An exemplary anti-HIV agent can be selected from the group consisting of a non-nucleoside reverse transcriptase inhibitor, a protease inhibitor, an entry or fusion inhibitor, and an integrase inhibitor. In some embodiments, the anti-HIV agent is an anti-HIV broadly neutralizing antibody, such as 3BNC117.

The foregoing summary is not intended to define every aspect of the disclosure, and additional aspects are described in other sections, such as the following detailed description. The entire document is intended to be related as a unified disclosure, and it should be understood that all combinations of features described herein are contemplated, even if the combination of features are not found together in the same sentence, or paragraph, or section of this document. Other features and advantages of the invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the disclosure, are given by way of illustration only, because various changes and modifications within the

spirit and scope of the disclosure will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGs. 1A and **1B** (collectively "**FIG. 1**") show the characterization of anti-HIV antibody 10-1074 variants MS-194 (**FIG. 1A**) and MS-203 (**FIG. 1B**) by high-performance size exclusion chromatography ("HP-SEC") before and after viral neutralization. Peaks in the HP-SEC profiles corresponding to the oligomeric species formed during viral inactivation are indicated by arrows.

FIG. 2 shows quantification of the degree of aggregation represented by the level of high molecular weight ("HMW") and oligomeric species following each of the purification steps for the 10-1074 antibody variants MS-194, MS-200, MS-201, and MS-203.

FIG. 3 shows the level of HMW during incubation at 40°C for up to 13 weeks for the 10-1074 antibody variants MS-194, MS-200, MS-201, and MS-203.

FIG. 4 shows the level of sub-visible particle formation during 6 weeks and 13 weeks for the 10-1074 antibody variants MS-194, MS-200, MS-201, and MS-203.

FIGs. 5A, **5B**, and **5C** (collectively "**FIG. 5**") show delayed viral rebound with 3BNC117 and 10–1074 combination therapy during analytical treatment interruption (ATI). **FIG. 5A** shows the study design of the Phase 1b clinical trial in which a combination of 3BNC117 and 10–1074, two potent monoclonal anti-HIV-1 broadly neutralizing antibodies that target independent sites on the HIV-1 envelope spike, was administered during ATI. Red and blue triangles represent 3BNC117 and 10–1074 infusions, respectively. **FIG. 5B** shows plasma HIV-1 RNA levels (black; left y-axis) and bNAb serum concentrations (3BNC117, red; 10–1074, blue; right y-axis) in the 9 bNAb-sensitive participants (left) and the 2 participants with pre-existing resistance against one of the antibodies (right). Red and blue triangles indicate 3BNC117 and 10–1074 infusions, respectively. Serum antibody concentrations were determined by TZM-bl assay. Grey shaded areas indicate time on ART. Lower limit of detection of HIV-1 RNA was 20 copies/ml. **FIG. 5C** shows Kaplan-Meier plots summarizing time to viral rebound for the participants with HIV-1 RNA < 20 copies/ml 2 weeks before and at the start of ATI (n=11, left), for the participants sensitive to both antibodies (n=9, center), and for the participants that showed pre-existing resistance to one of the antibodies (n=2, right). Y-axis indicates percentage of participants that maintain viral suppression. X-axis indicates weeks after start of ATI. Participants receiving the combination of 3BNC117 + 10–1074 are indicated by the blue line. Dotted red lines indicate a cohort of individuals receiving 3BNC117

alone during ATI (n=13) and dotted black lines indicate a cohort of participants who underwent ATI without intervention (n=52).

FIGs. 6A, **6B**, **6C, 6D**, **6E**, and **6F** (collectively "**FIG. 6**") show demographics, $CD4^+$ T cells during study period in participants and pharamacokinetics of 3BNC117 and 10–1074. **FIG. 6A** is a table showing baseline participant demographics. *NNRTI - Non-nucleoside reverse transcriptase inhibitor. **FIG. 6B** shows absolute $CD4^+$ T cell counts and percentage of $CD4^+$ T cells among $CD3^+$ T cells at screening (n=15), day 0 (n=15), at the time of viral rebound (n=13) and at the end of the study are shown (n=15) (see also Supplementary Table 2). The last available time point after resuppression was used as end of the study time point for the participants that reinitiated ART. Red lines indicate mean, and error bars indicate standard deviation. *P* values were obtained using a two-tailed paired t-test comparing $CD4^+$ T cell counts between day 0 and the time of viral rebound. **FIGs. 6C** and **6D** show 3BNC117 (red) and 10–1074 (blue) levels in serum (n=15) as determined by TZM-bl assay (**FIG. 6C**) and ELISA (**FIG. 6D**). Curves indicate mean serum antibody concentrations and error bars represent standard deviation. Red and blue triangles indicate 3BNC117 and 10–1074 infusions, respectively. In the TZM-bl assay, lower limits of detection were 0.46 μg/ml and 0.01 μg/ml for 3BNC117 and 10–1074, respectively (**FIG. 6C**). In the ELISA, lower limits of detection were 0.78 μg/ml and 0.41 μg/ml, respectively (**FIG. 6D**). In cases where participants only received 2 infusions due to early viral rebound (9245, 9249 and 9253), only antibody concentrations up to the second infusion were included. The half-life of each bNAb is indicated in days. **FIGs. 6E** and **6F** show half-lives of both antibodies as measured by TZM-bl assay (**FIG. 6E**) and ELISA (**FIG. 6F**). Each dot represents a single participant. The half-lives of both antibodies from the 15 participants enrolled in the study are represented. Black lines indicate the mean value and standard deviation (n=15). *P* values were obtained using a two-tailed unpaired t-test comparing the two antibodies.

FIGs. 7A, **7B**, and **7C** (collectively "**FIG. 7**") show amino acid variants at 10–1074 contact sites and bNAb sensitivity of reactivated latent and rebound viruses. **FIG. 7A** is a set of charts showing Env contact sites of 10–1074 at the G(D/N)IR motif (positions 324–327, according to HXB2 numbering) and the glycan at the potential *N*-linked glycosylation site at position 332 (NxS/T motif at positions 332–334). The diagram shows the 7 bNAb-sensitive participants that rebounded before week 30 (left) and the 2 individuals with preexisting resistance to one of the 2 antibodies (right). LR indicates latent reservoir viruses isolated by Q^2VOA, and RB indicates rebound viruses isolated by SGA (plasma) or viral outgrowth (PBMCs). Each amino acid is represented by a color, and the frequency of each amino acid is

indicated by the height of the rectangle. Shaded rectangles indicate the lack of variation between latent reservoir virus and rebound virus at the indicated position. Full-color rectangles represent amino acid residues with changes in distribution between reservoir and rebound viruses. **FIGs. 7B** and **7C** are dot plots indicating IC80 (μg/ml) of 3BNC117 (**FIG. 7B**, left panel) and 10–1074 (**FIG. 7C**, right panel) against latent and rebound viruses determined by TZM-bl neutralization assay. Q^2VOA-derived latent viruses from week -2 and week 12 are shown as black and grey circles, respectively. For outgrowth culture-derived rebound viruses, the highest IC80 determined is shown as red circle. For 9246, 9252, 9245 and 9251 viruses could not be obtained from rebound outgrowth cultures and pseudoviruses were made from *env* sequences from Q^2VOA and plasma SGA.

FIG. 8 shows a comparison of the circulating latent reservoir and rebound viruses. Maximum likelihood phylogenetic trees of full-length *env* sequences of viruses isolated from Q^2VOA, rebound plasma SGA, and rebound PBMC outgrowth cultures from 3 out of 7 participants (9242, 9243 and 9252) that rebounded before week 30. Open and closed black rectangles indicate Q^2VOA-derived viruses from week -2 and week 12, respectively. Viruses obtained at the time of rebound are indicated by red rectangles (plasma SGA) and red stars (rebound PBMC outgrowth cultures). Asterisks indicate nodes with significant bootstrap values (bootstrap support $\geq$ 70%). Boxes indicate IC80s (μg/ml) of 3BNC117 and 10–1074 against representative viruses throughout the phylogenetic tree and clones, when possible. Asterisks in boxes indicate IC100 values of > 50 μg/ml.

FIGs. 9A and **9B** (collectively "**FIG. 9**") show distribution of the circulating latent reservoir and rebound viruses. **FIG. 9A** is a set of Venn diagrams showing sequence identity between *env* sequences obtained from Q^2VOA at week -2 (blue) and week 12 (grey), and plasma SGA or rebound PBMC outgrowth culture at the time of viral rebound (red). Area of overlap is proportional to the number of identical sequences. Number of sequences obtained is indicated. **FIG. 9B** shows infectious units per million (IUPM) $CD4^+$ T cells at weeks -2 and 12 as determined by Q^2VOA. Participants with IUPMs higher and lower than 0.1 are shown on the top and bottom, respectively. The 2 time points were not statistically different ($P = 0.078$ (paired t-test)).

DETAILED DESCRIPTION OF THE INVENTION

This disclosure is based, at least in part, on an unexpected discovery of a new category of broadly neutralizing antibodies (bNAbs) against HIV that can recognize carbohydrate-dependent epitopes, including complex-type *N*-glycan, on gp120.

Antibodies are essential for the success of most vaccines, and antibodies against HIV appear to be the only correlate of protection in the recent RV144 anti-HIV vaccine trial. Some HIV-1 infected patients develop broadly neutralizing serologic activity against the gp160 viral spike 2-4 years after infection, but these antibodies do not generally protect infected humans because autologous viruses escape through mutation. Nevertheless, broadly neutralizing activity puts selective pressure on the virus and passive transfer of broadly neutralizing antibodies (bNAbs) to macaques protects against SHIV infection. It has therefore been proposed that vaccines that elicit such antibodies may be protective against HIV infection in humans.

The development of single cell antibody cloning techniques revealed that bNAbs target several different epitopes on the HIV-1 gp160 spike. The most potent HIV-1 bNAbs recognize the CD4 binding site (CD4bs) (Science 333(6049):1633-1637; Nature 477(7365):466-470; Science 334(6060):1289-1293) and carbohydrate-dependent epitopes associated with the variable loops (Nature 477(7365):466-470; Science 326(5950):285-289; Science 334(6059):1097-1103; Nature 480(7377):336-343), including the V1/V2 (PG9/PG16) (Science 326(5950):285-289) and V3 loops (PGTs) (Nature 477(7365):466-470). Less is known about carbohydrate-dependent epitopes because the antibodies studied to date are either unique examples or members of small clonal families.

To better understand the neutralizing antibody response to HIV-1 and the epitope targeted by PGT antibodies, members of a large clonal family dominating the gp160-specific IgG memory response from the clade A-infected patient who produced PGT121 have been isolated. The isolation of PGT121 is described in greater details in PCT/US13/65696. PGT121 antibodies can be divided into two groups, a PGT121-like and a 10-1074-like group, according to sequence, binding affinity, neutralizing activity and recognition of carbohydrates and the V3 loop. 10-1074 and related family members exhibit unusual potent neutralization, including broad reactivity against newly-transmitted viruses. Unlike previously-characterized carbohydrate-dependent bNAbs, PGT121 binds to complex-type, rather than high-mannose, *N*-glycans in glycan microarray experiments. The 10-1074 group exhibits remarkable potency and breadth despite not binding detectably to protein-free glycans. Crystal structures of un-liganded PGT121, 10-1074, and their germline precursor reveal that differential carbohydrate recognition maps to a cleft between CDRH2 and CDRH3, which was occupied by a complex-type N-glycan in a separate PGT121 structure. Swapping glycan contact residues between PGT121 and 10-1074 confirmed the importance of these residues in neutralizing activities.

Because the biophysical stability of monoclonal antibodies is an important determinant of their usefulness and commercial value, this disclosure presents the processes to optimize biophysical characteristics of the 10-1074 broadly neutralizing antibody. For example, a series of substitutions were carried out to identify potentially destabilizing residues in the Fv region of the 10-1074 broadly neutralizing antibody. These residues may, by themselves or in combination, lead to instability at low pH, increase susceptibility to chemical degradation, or lead to aggregation during production or long-term storage. Based on this analysis, a series of variants are designed for maintaining potency while optimizing desired characteristics using combinatorial residue replacement techniques. The optimization process is divided into different stages with the first being identification of single residues in the framework region which are potentially responsible for destabilization. Specifically, anti-HIV 10-1074 antibody variants (shown in **Tables 2-7** and **9**) were produced by transient expression, each containing a single residue modification of the identified amino acids. The variants were characterized for retention of neutralization activity and for desired biophysical characteristics as shown in **Tables 8-16**. Five distinct amino acid residues, LmdV:Y2, HV:V79, HV:R82, HV:L89, and HV:T108, were identified that showed an increase in desirable biophysical characteristics and did not impact neutralization. The residues were used to produce a library of variants (shown in **Tables 2-7** and **12**) encompassing all possible combinations of the five amino acids. The variants were again produced by transient expression, and the purified combinatorial variants were analyzed for retention of neutralization activity and desired biophysical characteristics. From the combinatorial library three variants, MS-200, MS-201, and MS-202 were identified for more in-depth analysis including expression, purification, and storage stability to identify combinatorial variants with optimized characteristics which included increased thermal stability, increased resistance to chemical unfolding, increased solubility, and increased resistance to aggregation during storage.

Isolated Anti-HIV Antibodies, Pharmaceutical Compositions, and Kits

Accordingly, in one aspect, this disclosure provides an isolated anti-HIV antibody, or antigen-binding portion thereof, including a light chain variable region having a light chain amino acid sequence that is at least 75% (*i.e.*, 80%, 85%, 90%, 95%, 97%, 98%, 99%) identical to a polypeptide sequence selected from the group consisting of the light chain variable regions of SEQ ID NOs: 3-13, 22, 24-28, 35-39, 43-45, and 47 (**Table 2**). The isolated anti-HIV antibody, or antigen-binding portion thereof may include one or more light chain substitutions at one or more residues located within or outside the light chain variable region. The residues for substitution are can be one or more of LmdV:Y2, LmdV:R7, LmdV:P9, LmdV:E17,

LmdV:H46, LmdV:P81.1, LmdV:I81.3, LmdV:N82, LmdV:R88, LmdV:D110, and LmdV:A142.

Also provided is an isolated anti-HIV antibody, or antigen-binding portion thereof, including a heavy chain variable region having a heavy chain amino acid sequence that is at least 75% (*i.e.*, 80%, 85%, 90%, 95%, 97%, 98%, 99%) identical to a polypeptide sequence selected from the group consisting of the heavy chain variable regions of SEQ ID NOs: 61-94 (**Table 3**). The isolated anti-HIV antibody, or antigen-binding portion thereof includes one or more heavy chain substitutions at one or more residues located within or outside of the heavy chain variable region. The residues for substitution can be one or more of HV:D29, HV:S47, HV:N75, HV:V79, HV:R82, HV:L89, HV:T108, and HV:K141.

In another aspect, the present disclosure provides an isolated anti-HIV antibody, or antigen-binding portion thereof, including a light chain variable region having a light chain amino acid sequence that is at least 75% (*i.e.*, 80%, 85%, 90%, 95%, 97%, 98%, 99%) identical to a polypeptide sequence selected from the group consisting of the light chain variable regions of SEQ ID NOs: 3-13, 22, 24-28, 35-39, 43-45, and 47 (**Table 2**). The isolated anti-HIV antibody, or antigen-binding portion thereof includes one or more light chain substitutions at one or more residues of LmdV:Y2, LmdV:R7, LmdV:P9, LmdV:E17, LmdV:H46, LmdV:P81.1, LmdV:I81.3, LmdV:N82, LmdV:R88, LmdV:D110, and LmdV:A142. The anti-HIV antibody, or antigen-binding portion thereof, further includes a heavy chain variable region having a heavy chain amino acid sequence is at least 75% (*i.e.*, 80%, 85%, 90%, 95%, 97%, 98%, 99%) identical to a polypeptide sequence selected from the group consisting of the heavy chain variable regions of SEQ ID NOs: 61-94 (**Table 3**). The isolated anti-HIV antibody, or antigen-binding portion thereof includes one or more heavy chain substitutions at one or more residues of HV:D29, HV:S47, HV:N75, HV:V79, HV:R82, HV:L89, HV:T108, and HV:K141.

In some embodiments, the isolated anti-HIV antibody, or antigen-binding portion thereof includes the one or more light chain substitutions of LmdV:Y2P, LmdV:R7P, LmdV:P9S, LmdV:E17Q, LmdV:H46Q, LmdV:P81.1N, LmdV:I81.3S, LmdV:N82G, LmdV:R88T, LmdV:D110E, and LmdV:A142G or conservative substitutions thereof (*i.e.*, LmdV:P9C, LmdV:P9T, LmdV:E17N, LmdV:H46N, LmdV:P81.1Q, LmdV:R88C, LmdV:R88S).

In some embodiments, the isolated anti-HIV antibody, or antigen-binding portion thereof includes the one or more heavy chain substitutions of HV:D29G, HV:S47P, HV:N75Q,

HV:V79T, HV:R82V, HV:L89F, HV:T108R, and HV:K141Q or conservative substitutions thereof (*i.e.*, HV:L89W, HV:L89Y, HV:T108H, HV:T108K, HV:K141N).

In some embodiments, the isolated anti-HIV antibody, or antigen-binding portion thereof, includes the one or more light chain substitutions of LmdV:Y2P, LmdV:R7P, LmdV:P9S, LmdV:E17Q, LmdV:H46Q, LmdV:P81.1N, LmdV:I81.3S, LmdV:N82G, LmdV:R88T, LmdV:D110E, and LmdV:A142G or conservative substitutions thereof (*i.e.*, LmdV:P9C, LmdV:P9T, LmdV:E17N, LmdV:H46N, LmdV:P81.1Q, LmdV:R88C, LmdV:R88S) and the one or more heavy chain substitutions of HV:D29G, HV:S47P, HV:N75Q, HV:V79T, HV:R82V, HV:L89F, HV:T108R, and HV:K141Q or conservative substitutions thereof (*i.e.*, HV:L89W, HV:L89Y, HV:T108H, HV:T108K, HV:K141N).

In some embodiments, the light chain amino acid sequence is at least 75% (*i.e.*, 80%, 85%, 90%, 95%, 97%, 98%, 99%) identical to the light chain variable region of SEQ ID NO.: 3 and includes a LmdV:Y2P substitution or a conservative substitution of proline at LmdV:Y2.

In some embodiments, the heavy chain amino acid sequence is at least 75% (*i.e.*, 80%, 85%, 90%, 95%, 97%, 98%, 99%) identical to to the heavy chain variable region of SEQ ID NO.: 63 and includes an HV:V79T substitution or a conservative substitution of threonine at HV:V79.

In some embodiments, the heavy chain amino acid sequence is at least 75% (*i.e.*, 80%, 85%, 90%, 95%, 97%, 98%, 99%) identical to to the heavy chain variable region of SEQ ID NO.: 64 and includes an HV:R82V substitution or a conservative substitution of valine at HV:R82.

In some embodiments, the heavy chain amino acid sequence is at least 75% (*i.e.*, 80%, 85%, 90%, 95%, 97%, 98%, 99%) identical to to the heavy chain variable region of SEQ ID NO.: 65 and includes an HV:L89F substitution or a conservative substitution of phenylalanine of HV:L89.

In some embodiments, the heavy chain amino acid sequence is at least 75% (*i.e.*, 80%, 85%, 90%, 95%, 97%, 98%, 99%) identical to to the heavy chain variable region of SEQ ID NO.: 66 and includes an HV:T108R substitution or a conservative substitution of arginine at HV:T108.

In some embodiments, the light chain amino acid sequence is at least 75% (*i.e.*, 80%, 85%, 90%, 95%, 97%, 98%, 99%) identical to the light chain variable region of SEQ ID NO.: 22 and includes a LmdV:Y2P substitution or a conservative substitution of proline at LmdV:Y2, and the heavy chain amino acid sequence is at least 75% (*i.e.*, 80%, 85%, 90%, 95%, 97%, 98%, 99%) identical to the heavy chain variable region of SEQ ID NO.: 69 and

includes an HV:R82V substitution or a conservative substitution of valine at HV:R82, and an HV:T108R substitution or a conservative substitution of arginine at HV:T108.

In some embodiments, the heavy chain amino acid sequence is at least 75% (*i.e.*, 80%, 85%, 90%, 95%, 97%, 98%, 99%) identical to the heavy chain variable region of SEQ ID NO.: 70 and includes an HV:V79T substitution or a conservative substitutions of threonine at HV:V79, an HV:L89F substitution or a conservative substitution of phenylalanine at HV:L89, and an HV:T108R substitution or a conservative substitution of arginine at HV:T108.

In some embodiments, the light chain amino acid sequence is at least 75% (*i.e.*, 80%, 85%, 90%, 95%, 97%, 98%, 99%) identical to the light chain variable region of SEQ ID NO.: 24 and comprises a LmdV:Y2P substitution or a conservative substitution of proline at LmdV:Y2, and the heavy chain amino acid sequence is at least 75% (*i.e.*, 80%, 85%, 90%, 95%, 97%, 98%, 99%) identical to the heavy chain variable region of SEQ SEQ ID NO.: 71 and includes an HV:V79T substitution or a conservative substitution of threonine at HV:V79, an HV:L89F substitution or a conservative substitution of phenylalanine at HV:L89, and an HV:T108R substitution or a conservative substitution of arginine at HV:T108.

In some embodiments, the isolated anti-HIV antibody, or antigen-binding portion thereof includes SEQ NO.: 3. In some embodiments, the isolated anti-HIV antibody, or antigen-binding portion thereof includes SEQ NO.: 63, 64, 65, 66, or 70. In some embodiments, the light chain variable region includes the light chain variable region of SEQ NO.: 22 and the heavy chain variable region includes the heavy chain variable region of SEQ No.: 69. In some embodiments, the light chain variable region includes the light chain variable region of SEQ NO.: 24 and the heavy chain variable region includes the heavy chain variable region of SEQ No.: 71.

Variable domain residue positions are numbered according to the AHo (Honegger, A., & Plückthun, A. (2001). Journal of Molecular Biology, 309(3), 657–70.) structure-based numbering system. An exemplary residue numbering of variable domains of MS-194 is shown in **Table 1**. The abbreviations used in **Table 1** are described as follows. "Ldr" refers leader sequence (*e.g.*, AKA signal sequence or signal peptide). "Mat. Linear" refers to the linear number of the mature form of protein chains. "LmdV" refers variable regions in light chains which are of the lambda type.

The term "antibody" (Ab) as used herein includes monoclonal antibodies, polyclonal antibodies, multispecific antibodies (for example, bispecific antibodies and polyreactive antibodies), and antibody fragments. Thus, the term "antibody" as used in any context within this specification is meant to include, but not be limited to, any specific binding member,

immunoglobulin class and/or isotype (*e.g.*, IgG1, IgG2, IgG3, IgG4, IgM, IgA, IgD, IgE and IgM); and biologically relevant fragment or specific binding member thereof, including but not limited to Fab, F(ab')2, Fv, and scFv (single chain or related entity). It is understood in the art that an antibody is a glycoprotein having at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, or an antigen-binding portion thereof. A heavy chain is comprised of a heavy chain variable region (VH) and a heavy chain constant region (CH1, CH2, and CH3). A light chain is comprised of a light chain variable region (VL) and a light chain constant region (CL). The variable regions of both the heavy and light chains comprise framework regions (FWR) and complementarity determining regions (CDR). The four FWR regions are relatively conserved while CDR regions (CDR1, CDR2, and CDR3) represent hypervariable regions and are arranged from NH2 terminus to the COOH terminus as follows: FWR1, CDR1, FWR2, CDR2, FWR3, CDR3, and FWR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen while, depending on the isotype, the constant region(s) may mediate the binding of the immunoglobulin to host tissues or factors.

Also included in the definition of "antibody" as used herein are chimeric antibodies, humanized antibodies, and recombinant antibodies, human antibodies generated from a transgenic non-human animal, as well as antibodies selected from libraries using enrichment technologies available to the artisan.

The term "variable" refers to the fact that certain segments of the variable (V) domains differ extensively in sequence among antibodies. The V domain mediates antigen-binding and defines specificity of a particular antibody for its particular antigen. However, the variability is not evenly distributed across the amino acid span of the variable regions. Instead, the V regions consist of relatively invariant stretches called framework regions (FRs) of 15-30 amino acids separated by shorter regions of extreme variability called "hypervariable regions" that may be 9-12 amino acids long. The variable regions of native heavy and light chains each comprise four FRs, largely adopting a beta-sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the beta-sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies (see, for example, Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)).

The term "hypervariable region" as used herein refers to the amino acid residues of an antibody that are responsible for antigen binding. The hypervariable region generally comprises amino acid residues from a "complementarity determining region" ("CDR").

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. The term "polyclonal antibody" refers to preparations that include different antibodies directed against different determinants ("epitopes").

The monoclonal antibodies herein include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with, or homologous to, corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with, or homologous to, corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (see, for example, U.S. Pat. No. 4,816,567; and Morrison *et al.*, Proc. Natl. Acad. Sci. USA, 81:6851-6855 (1984)). The described invention provides variable region antigen-binding sequences derived from human antibodies. Accordingly, chimeric antibodies of primary interest herein include antibodies having one or more human antigen-binding sequences (for example, CDRs) and containing one or more sequences derived from a non-human antibody, for example, an FR or C region sequence. In addition, chimeric antibodies included herein are those comprising a human variable region antigen-binding sequence of one antibody class or subclass and another sequence, for example, FR or C region sequence, derived from another antibody class or subclass.

A "humanized antibody" generally is considered to be a human antibody that has one or more amino acid residues introduced into it from a source that is non-human. These non-human amino acid residues often are referred to as "import" residues, which typically are taken from an "import" variable region. Humanization may be performed following the method of Winter and co-workers (see, for example, Jones *et al.*, Nature, 321:522-525 (1986); Reichmann *et al.*, Nature, 332:323-327 (1988); Verhoeyen *et al.*, Science, 239:1534-1536 (1988)), by substituting import hypervariable region sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (see, for example, U.S. Pat. No. 4,816,567), where substantially less than an intact human variable region has been substituted by the corresponding sequence from a non-human species.

An "antibody fragment" comprises a portion of an intact antibody, such as the antigen-binding or variable region of the intact antibody. Examples of antibody fragments include, but are not limited to, Fab, Fab', F(ab')2, and Fv fragments; diabodies; linear antibodies (see, for example, U.S. Pat. No. 5,641,870; Zapata *et al.*, Protein Eng. 8(10): 1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

"Fv" is the minimum antibody fragment that contains a complete antigen-recognition and antigen-binding site. This fragment contains a dimer of one heavy- and one light-chain variable region domain in tight, non-covalent association. From the folding of these two domains emanate six hypervariable regions (three loops each from the H and L chain) that contribute the amino acid residues for antigen-binding and confer antigen-binding specificity to the antibody. However, even a single variable region (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

"Single-chain Fv" ("sFv" or "scFv") are antibody fragments that comprise the VH and VL antibody domains connected into a single polypeptide chain. The sFv polypeptide can further comprise a polypeptide linker between the VH and VL domains that enables the sFv to form the desired structure for antigen binding. For a review of sFv, see, for example, Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994); Borrebaeck 1995, infra.

The term "diabodies" refers to small antibody fragments prepared by constructing sFv fragments with short linkers (about 5-10 residues) between the VH and VL domains such that inter-chain but not the intra-chain pairing of the V domains is achieved, resulting in a bivalent fragment, *i.e.*, fragment having two antigen-binding sites. Bispecific diabodies are heterodimers of two "crossover" sFv fragments in which the VH and VL domains of the two antibodies are present on different polypeptide chains. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger *et al.*, Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993).

Domain antibodies (dAbs), which can be produced in fully human form, are the smallest known antigen-binding fragments of antibodies, ranging from about 11 kDa to about 15 kDa. DAbs are the robust variable regions of the heavy and light chains of immunoglobulins (VH and VL, respectively). They are highly expressed in microbial cell culture, show favorable biophysical properties including, for example, but not limited to, solubility and temperature stability, and are well suited to selection and affinity maturation by *in vitro* selection systems such as, for example, phage display. DAbs are bioactive as monomers and, owing to their

small size and inherent stability, can be formatted into larger molecules to create drugs with prolonged serum half-lives or other pharmacological activities. Examples of this technology have been described in, for example, WO9425591 for antibodies derived from Camelidae heavy chain Ig, as well in US20030130496 describing the isolation of single domain fully human antibodies from phage libraries.

Fv and sFv are the only species with intact combining sites that are devoid of constant regions. Thus, they are suitable for reduced nonspecific binding during *in vivo* use. sFv fusion proteins can be constructed to yield fusion of an effector protein at either the amino or the carboxy terminus of an sFv. *See*, for example, Antibody Engineering, ed. Borrebaeck, supra. The antibody fragment also can be a "linear antibody," for example, as described in U.S. Pat. No. 5,641,870 for example. Such linear antibody fragments can be monospecific or bispecific.

In certain embodiments, antibodies of the described invention are bispecific or multi-specific. Bispecific antibodies are antibodies that have binding specificities for at least two different epitopes. Exemplary bispecific antibodies can bind to two different epitopes of a single antigen. Other such antibodies can combine a first antigen-binding site with a binding site for a second antigen. Alternatively, an anti-HIV arm can be combined with an arm that binds to a triggering molecule on a leukocyte, such as a T-cell receptor molecule (for example, CD3), or Fc receptors for IgG (Fc gamma R), such as Fc gamma RI (CD64), Fc gamma RII (CD32) and Fc gamma RIII (CD16), so as to focus and localize cellular defense mechanisms to the infected cell. Bispecific antibodies also can be used to localize cytotoxic agents to infected cells. Bispecific antibodies can be prepared as full-length antibodies or antibody fragments (for example, F(ab')2 bispecific antibodies). For example, WO 96/16673 describes a bispecific anti-ErbB2/anti-Fc gamma RIII antibody and U.S. Pat. No. 5,837,234 discloses a bispecific anti-ErbB2/anti-Fc gamma RI antibody. For example, a bispecific anti-ErbB2/Fc alpha antibody is reported in WO98/02463; U.S. Pat. No. 5,821,337 teaches a bispecific anti-ErbB2/anti-CD3 antibody. See also, for example, Mouquet *et al.*, Polyreactivity Increases The Apparent Affinity Of Anti-HIV Antibodies By Heteroligation. Nature. 467, 591-5 (2010), and Mouquet *et al.*, Enhanced HIV-1 neutralization by antibody heteroligation" Proc Natl Acad Sci U S A. 2012 Jan 17;109(3):875-80.

Methods for making bispecific antibodies are known in the art. Traditional production of full-length bispecific antibodies is based on the co-expression of two immunoglobulin heavy chain-light chain pairs, where the two chains have different specificities (see, for example, Millstein *et al.*, Nature, 305:537-539 (1983)). Similar procedures are disclosed in, for example, WO 93/08829, Traunecker *et al.*, EMBO J., 10:3655-3659 (1991) and see also Mouquet *et al.*,

Enhanced HIV-1 neutralization by antibody heteroligation" Proc Natl Acad Sci U S A. 2012 Jan 17;109(3):875-80.

Alternatively, antibody variable regions with the desired binding specificities (antibody-antigen combining sites) are fused to immunoglobulin constant domain sequences. The fusion is with an Ig heavy chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. According to some embodiments, the first heavy-chain constant region (CH1) containing the site necessary for light chain bonding, is present in at least one of the fusions. DNAs encoding the immunoglobulin heavy chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors and are co-transfected into a suitable host cell. This provides for greater flexibility in adjusting the mutual proportions of the three polypeptide fragments in embodiments when unequal ratios of the three polypeptide chains used in the construction provide the optimum yield of the desired bispecific antibody. It is, however, possible to insert the coding sequences for two or all three polypeptide chains into a single expression vector when the expression of at least two polypeptide chains in equal ratios results in high yields or when the ratios have no significant effect on the yield of the desired chain combination.

Techniques for generating bispecific antibodies from antibody fragments also have been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. For example, Brennan *et al.*, Science, 229: 81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate F(ab')2 fragments. These fragments are reduced in the presence of the dithiol complexing agent, sodium arsenite, to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated then are converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives then is reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Other modifications of the antibody are contemplated herein. For example, the antibody can be linked to one of a variety of nonproteinaceous polymers, for example, polyethylene glycol, polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol and polypropylene glycol. The antibody also can be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization (for example, hydroxymethyl cellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively), in colloidal drug delivery systems (for example, liposomes,

albumin microspheres, microemulsions, nanoparticles and nanocapsules), or in macroemulsions. Such techniques are disclosed in, for example, Remington's Pharmaceutical Sciences, 16th edition, Oslo, A., Ed., (1980).

Typically, the antibodies of the described invention are produced recombinantly, using vectors and methods available in the art. Human antibodies also can be generated by *in vitro* activated B cells (see, for example, U.S. Pat. Nos. 5,567,610 and 5,229,275). General methods in molecular genetics and genetic engineering useful in the present disclosure are described in the current editions of Molecular Cloning: A Laboratory Manual (Sambrook, *et al.*, 1989, Cold Spring Harbor Laboratory Press), Gene Expression Technology (Methods in Enzymology, Vol. 185, edited by D. Goeddel, 1991. Academic Press, San Diego, CA), "Guide to Protein Purification" in Methods in Enzymology (M.P. Deutscher, ed., (1990) Academic Press, Inc.); PCR Protocols: A Guide to Methods and Applications (Innis *et al.* 1990. Academic Press, San Diego, CA), Culture of Animal Cells: A Manual of Basic Technique, 2nd Ed. (R.I. Freshney. 1987. Liss, Inc. New York, NY), and Gene Transfer and Expression Protocols, pp. 109-128, ed. E.J. Murray, The Humana Press Inc., Clifton, N.J.). Reagents, cloning vectors, and kits for genetic manipulation are available from commercial vendors such as BioRad, Stratagene, Invitrogen, ClonTech and Sigma-Aldrich Co.

Human antibodies also can be produced in transgenic animals (for example, mice) that are capable of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. For example, it has been described that the homozygous deletion of the antibody heavy-chain joining region (JH) gene in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array into such germ-line mutant mice results in the production of human antibodies upon antigen challenge. See, for example, Jakobovits *et al.*, Proc. Natl. Acad. Sci. USA, 90:2551 (1993); Jakobovits *et al.*, Nature, 362:255-258 (1993); Bruggemann *et al.*, Year in Immuno., 7:33 (1993); U.S. Pat. Nos. 5,545,806, 5,569,825, 5,591,669 (all of GenPharm); U.S. Pat. No. 5,545,807; and WO 97/17852. Such animals can be genetically engineered to produce human antibodies comprising a polypeptide of the described invention.

Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies (see, for example, Morimoto *et al.*, Journal of Biochemical and Biophysical Methods 24:107-117 (1992); and Brennan *et al.*, Science, 229:81 (1985)). However, these fragments can now be produced directly by recombinant host cells. Fab, Fv and ScFv antibody fragments can all be

expressed in and secreted from E. coli, thus allowing the facile production of large amounts of these fragments. Fab'-SH fragments can be directly recovered from E. coli and chemically coupled to form F(ab')2 fragments (see, for example, Carter *et al.*, Bio/Technology 10:163-167 (1992)). According to another approach, F(ab')2 fragments can be isolated directly from recombinant host cell culture. Fab and F(ab')2 fragment with increased *in vivo* half-life comprising a salvage receptor binding epitope residues are described in U.S. Pat. No. 5,869,046. Other techniques for the production of antibody fragments will be apparent to the skilled practitioner.

Other techniques that are known in the art for the selection of antibody fragments from libraries using enrichment technologies, including but not limited to phage display, ribosome display (Hanes and Pluckthun, 1997, *Proc. Nat. Acad. Sci.* 94: 4937-4942), bacterial display (Georgiou, *et al.*, 1997, *Nature Biotechnology* 15: 29-34) and/or yeast display (Kieke, *et al.*, 1997, *Protein Engineering* 10: 1303-1310) may be utilized as alternatives to previously discussed technologies to select single chain antibodies. Single-chain antibodies are selected from a library of single chain antibodies produced directly utilizing filamentous phage technology. Phage display technology is known in the art (*e.g.*, see technology from Cambridge Antibody Technology (CAT)) as disclosed in U.S. Patent Nos. 5,565,332; 5,733,743; 5,871,907; 5,872,215; 5,885,793; 5,962,255; 6,140,471; 6,225,447; 6,291650; 6,492,160; 6,521,404; 6,544,731; 6,555,313; 6,582,915; 6,593, 081, as well as other U.S. family members, or applications which rely on priority filing GB 9206318, filed 24 May 1992; see also Vaughn, *et al.* 1996, *Nature Biotechnology* 14: 309-314). Single chain antibodies may also be designed and constructed using available recombinant DNA technology, such as a DNA amplification method (*e.g.*, PCR), or possibly by using a respective hybridoma cDNA as a template.

Variant antibodies also are included within the scope of the invention. Thus, variants of the sequences recited in the application also are included within the scope of the invention. Further variants of the antibody sequences having improved affinity can be obtained using methods known in the art and are included within the scope of the invention. For example, amino acid substitutions can be used to obtain antibodies with further improved affinity. Alternatively, codon optimization of the nucleotide sequence can be used to improve the efficiency of translation in expression systems for the production of the antibody.

Such variant antibody sequences will share 70% or more (*i.e.*, 75%, 80%, 85%, 90%, 95%, 97%, 98%, 99% or greater) sequence identity with the sequences disclosed in the application. Such sequence identity is calculated with regard to the full length of the reference

sequence (*i.e.*, the sequence recited in the application). Percentage identity, as referred to herein, is as determined using BLAST version 2.1.3 using the default parameters specified by the NCBI (the National Center for Biotechnology Information) [Blosum 62 matrix; gap open penalty=11 and gap extension penalty=1]. For example, peptide sequences provided by this disclosure include at least about 5, 10, 15, 20, 30, 40, 50, 75, 100, 150, or more contiguous peptides of one or more of the sequences disclosed herein as well as all intermediate lengths therebetween. As used herein, the term "intermediate lengths" is meant to describe any length between the quoted values, such as 7, 8, 9, 10, 11, 12,13, 14, 15, 16, 17, 18, 19, etc.; 21, 22, 23, etc.; 30, 31, 32, etc.; 50, 51, 52, 53, etc.; 100, 101, 102, 103, etc.; 150, 151, 152, 153, etc.

The present disclosure provides for antibodies, either alone or in combination with other antibodies, such as, but not limited to, VRC01, anti-V3 loop, CD4bs, and CD4i antibodies as well as PG9/PG16-like antibodies, that have broad neutralizing activity in serum.

According to another embodiment, the present disclosure provides methods for the preparation and administration of an HIV antibody composition that is suitable for administration to a human or non-human primate patient having HIV infection, or at risk of HIV infection, in an amount and according to a schedule sufficient to induce a protective immune response against HIV, or reduction of the HIV virus, in a human.

According to another embodiment, the present disclosure provides a vaccine comprising at least one antibody of the disclosure and a pharmaceutically acceptable carrier. According to one embodiment, the vaccine is a vaccine comprising at least one antibody described herein and a pharmaceutically acceptable carrier. The vaccine can include a plurality of the antibodies having the characteristics described herein in any combination and can further include antibodies neutralizing to HIV as are known in the art.

It is to be understood that compositions can be a single or a combination of antibodies disclosed herein, which can be the same or different, in order to prophylactically or therapeutically treat the progression of various subtypes of HIV infection after vaccination. Such combinations can be selected according to the desired immunity. When an antibody is administered to an animal or a human, it can be combined with one or more pharmaceutically acceptable carriers, excipients or adjuvants as are known to one of ordinary skilled in the art. The composition can further include broadly neutralizing antibodies known in the art, including but not limited to, VRC01, b12, anti-V3 loop, CD4bs, and CD4i antibodies as well as PG9/PG16-like antibodies.

Further, with respect to determining the effective level in a patient for treatment of HIV, in particular, suitable animal models are available and have been widely implemented for

evaluating the *in vivo* efficacy against HIV of various gene therapy protocols (Sarver *et al.* (1993b), supra). These models include mice, monkeys, and cats. Even though these animals are not naturally susceptible to HIV disease, chimeric mice models (for example, SCID, bg/nu/xid, NOD/SCID, SCID-hu, immunocompetent SCID-hu, bone marrow-ablated BALB/c) reconstituted with human peripheral blood mononuclear cells (PBMCs), lymph nodes, fetal liver/thymus or other tissues can be infected with lentiviral vector or HIV, and employed as models for HIV pathogenesis. Similarly, the simian immune deficiency virus (SIV)/monkey model can be employed, as can the feline immune deficiency virus (FIV)/cat model. The pharmaceutical composition can contain other pharmaceuticals, in conjunction with a vector according to the invention, when used to therapeutically treat AIDS. These other pharmaceuticals can be used in their traditional fashion (*i.e.*, as agents to treat HIV infection).

According to another embodiment, the present disclosure provides an antibody-based pharmaceutical composition comprising an effective amount of an isolated HIV antibody, or an affinity matured version, which provides a prophylactic or therapeutic treatment choice to reduce infection of the HIV virus. The pharmaceutical composition may further include a second therapeutic agent. In some embodiments, the second therapeutic agent can be an anti-HIV-1 broadly neutralizing antibody. The anti-HIV-1 broadly neutralizing antibody can be one of 10-259, 10-303, 10-410, 10-847, 10-996, 10-1121, 10-1130, 10-1146, 10-1341, 10-1369, 10-1074GM, GL, 10E8, 12A12, 12A21, 2F5, 2G12, 35022, 3BC176, 3BNC117, 3BNC55, 3BNC60, 3BNC62, 447-52D, 4E10, 5H/I1-BMV-D5, 8ANC195, b12, CAP256-VRC26.01, CAP256-VRC26.02, CAP256-VRC26.03, CAP256-VRC26.04, CAP256-VRC26.05, CAP256-VRC26.06, CAP256-VRC26.07, CAP256-VRC26.08, CAP256-VRC26.09, CAP256-VRC26.10, CAP256-VRC26.11, CAP256-VRC26.12, CH01, CH02, CH03, CH04, CH103, HGN194, HJ16, HK20, M66.6, NIH45-46, PCDN-33A, PCDN-33B, PCDN-38A, PG9, PG16, PGDM1400, PGDM1401, PGDM1402, PGDM1403, PGDM1404, PGDM1405, PGDM1406, PGDM1407, PGDM1408, PGDM1409, PGDM1410, PGDM1411, PGDM1412, PGT121, PGT122, PGT123, PGT125, PGT126, PGT127, PGT128, PGT130, PGT131, PGT135, PGT136, PGT137, PGT141, PGT142, PGT143, PGT145, PGT151, PGT152, VRC-CH30, VRC-CH31, VRC-CH32, VRC-CH33, VRC-CH34, VRC-PG04, VRC-CH04b, VRC-PG20, VRC01, VRC02, VRC03, VRC07, VRC23, and Z13. In some embodiments, the anti-HIV-1 broadly neutralizing antibody is 3BNC117. 3BNC117 is a next-generation bNAb that targets the CD4 binding site on HIV envelope gp160. It is a recombinant human IgG1 kappa monoclonal antibody cloned from an HIV-infected viremic controller. A long-acting version of 3BNC117 is known as 3BNC117-LS. 3BNC117 was described in US patent US9,783,594.

The antibody-based pharmaceutical composition of the present disclosure may be formulated by any number of strategies known in the art (*e.g.*, *see* McGoff and Scher, 2000, Solution Formulation of Proteins/Peptides: In McNally, E.J., ed. Protein Formulation and Delivery. New York, NY: Marcel Dekker; pp. 139-158; Akers and Defilippis, 2000, Peptides and Proteins as Parenteral Solutions. In: Pharmaceutical Formulation Development of Peptides and Proteins. Philadelphia, PA: Talyor and Francis; pp. 145-177; Akers *et al.*, 2002, Pharm. Biotechnol. 14:47-127). A pharmaceutically acceptable composition suitable for patient administration will contain an effective amount of the antibody in a formulation which both retains biological activity while also promoting maximal stability during storage within an acceptable temperature range. The pharmaceutical compositions can also include, depending on the formulation desired, pharmaceutically acceptable diluents, pharmaceutically acceptable carriers and/or pharmaceutically acceptable excipients, or any such vehicle commonly used to formulate pharmaceutical compositions for animal or human administration. The diluent is selected so as not to affect the biological activity of the combination. Examples of such diluents are distilled water, physiological phosphate-buffered saline, Ringer's solutions, dextrose solution, and Hank's solution. The amount of an excipient that is useful in the pharmaceutical composition or formulation of this disclosure is an amount that serves to uniformly distribute the antibody throughout the composition so that it can be uniformly dispersed when it is to be delivered to a subject in need thereof. It may serve to dilute the antibody to a concentration which provides the desired beneficial palliative or curative results while at the same time minimizing any adverse side effects that might occur from too high a concentration. It may also have a preservative effect. Thus, for the antibody having high physiological activity, more of the excipient will be employed. On the other hand, for any active ingredient(s) that exhibit a lower physiological activity, a lesser quantity of the excipient will be employed.

The above-described antibodies and antibody compositions or vaccine compositions, comprising at least one or a combination of the antibodies described herein, can be administered for the prophylactic and therapeutic treatment of HIV viral infection.

The present disclosure also relates to isolated polypeptides comprising the novel amino acid sequences of the light chain regions and heavy chain variable regions, listed in **Tables 2-3**. In other related embodiments, this disclosure provides polypeptide variants having the amino acid sequences of the light chain regions and heavy chain variable regions of the HIV antibodies that share at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%, or greater sequence identity compared to a polypeptide sequence, listed in **Tables 2-3**, as determined using the methods described herein (*i.e.*, BLAST analysis using standard

parameters). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by taking into amino acid similarity and the like. In other related embodiments, this disclosure provides polypeptide variants having the amino acid sequences of the light chain regions and heavy chain variable regions of the HIV antibodies that share at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%, or greater sequence identity compared to a polypeptide sequence, listed in **Tables 2-3**, and having the amino acid sequences of the CDR regions identical or substantially identical to those listed in **Table 4** or to the amino acid sequences of the CDR regions of the unmodified 10-1074-LS antibody (or MS-193). In other related embodiments, this disclosure provides polypeptide variants having the amino acid sequences of the light chain regions and heavy chain variable regions of the HIV antibodies that share at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%, or greater sequence identity compared to a polypeptide sequence, listed in **Tables 2-3**, and having the amino acid sequences of the CDR regions identical or substantially identical to those listed in **Table 4** or to the amino acid sequences of the CDR regions of the unmodified 10-1074-LS antibody (or MS-193), such that polypeptide variants retain 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%, or greater binding affinity to the HIV virus. The term "substantially identical" refers to the identity of a sequence to another sequence greater than about 85%.

The term "polypeptide" is used in its conventional meaning, *i.e.*, as a sequence of amino acids. The polypeptides are not limited to a specific length of the product. Peptides, oligopeptides, and proteins are included within the definition of polypeptide, and such terms can be used interchangeably herein unless specifically indicated otherwise. This term also includes post-expression modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations and the like, as well as other modifications known in the art, both naturally occurring and non-naturally occurring. A polypeptide can be an entire protein or a subsequence thereof. Particular polypeptides of interest in the context of this disclosure are amino acid subsequences comprising CDRs, VH, and VL, being capable of binding an antigen or HIV-infected cell.

A polypeptide "variant," as the term is used herein, is a polypeptide that typically differs from a polypeptide specifically disclosed herein in one or more substitutions, deletions, additions and/or insertions. Such variants can be naturally occurring or can be synthetically generated, for example, by modifying one or more of the above polypeptide sequences of the disclosure and evaluating one or more biological activities of the polypeptide as described herein and/or using any of some techniques well known in the art.

For example, certain amino acids can be substituted for other amino acids in a protein structure without appreciable loss of its ability to bind other polypeptides (for example, antigens) or cells. Since it is the binding capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, accordingly, its underlying DNA coding sequence, whereby a protein with like properties is obtained. It is thus contemplated that various changes can be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences that encode said peptides without appreciable loss of their biological utility or activity.

Variant antibody sequences include those wherein conservative substitutions have been introduced by modification of polynucleotides encoding polypeptides of the invention. Amino acids can be classified according to physical properties and contribution to secondary and tertiary protein structure. A "conservative substitution" is recognized in the art as a substitution of one amino acid for another amino acid that has similar properties. Exemplary conservative substitutions are set out below:

CONSERVATIVE SUBSTITUTION I	
Side chain characteristic	Amino acid
Aliphatic	
Non-polar	G A P I L V
Polar - uncharged	C S T M N Q
Polar - charged	D E K R
Aromatic	H F W Y
Other	N Q D E

Alternatively, conservative amino acids can be grouped as described in Lehninger, [Biochemistry, Second Edition; Worth Publishers, Inc. NY, N.Y. (1975), pp. 71-77] as set out below:

CONSERVATIVE SUBSTITUTION II	
Side chain characteristic	Amino acid
Non-polar (hydrophobic)	
A. Aliphatic:	A L I V P
B. Aromatic:	F W
C. Sulfur-containing:	M

D. Borderline:	G
Uncharged-polar	
A. Hydroxyl:	S T Y
B. Amides:	N Q
C. Sulfhydryl:	C
D. Borderline:	G
Positively Charged (Basic):	K R H
Negatively Charged (Acidic):	D E

As still another alternative, exemplary conservative substitutions are set out below:

CONSERVATIVE SUBSTITUTIONS III	
Original residue	Exemplary substitution
Ala (A)	Val, Leu, Ile
Arg (R)	Lys, Gln, Asn
Asn (N)	Gln, His, Lys, Arg
Asp (D)	Glu
Cys (C)	Ser
Gln (Q)	Asn
Glu (E)	Asp
His (H)	Asn, Gln, Lys, Arg
Ile (I)	Leu, Val, Met, Ala, Phe,
Leu (L)	Ile, Val, Met, Ala, Phe
Lys (K)	Arg, Gln, Asn
Met (M)	Leu, Phe, Ile
Phe (F)	Leu, Val, Ile, Ala
Pro (P)	Gly
Ser (S)	Thr
Thr (T)	Ser
Trp (W)	Tyr

Tyr (Y)	Trp, Phe, Thr, Ser
Val (V)	Ile, Leu, Met, Phe, Ala

A conservative substitution of an existing substitution refers to a conservative substitution of the substituting residue. For example, a conservative substitution of LmdV:Y2P refers to a conservative substitution (*i.e.*, glycine (G)) of proline (P) at position LmdV:Y2. In another example, a conservative substitution of HV:V79T refers to a conservative substitution (*i.e.*, serine (S), cysteine (C)) of threonine (T) at position HV:V79.

"Homology" or "sequence identity" refers to the percentage of residues in the polynucleotide or polypeptide sequence variant that are identical to the non-variant sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent homology. In particular embodiments, polynucleotide and polypeptide variants have at least about 70%, at least about 75%, at least about 80%, at least about 90%, at least about 95%, at least about 98%, or at least about 99% polynucleotide or polypeptide homology with a polynucleotide or polypeptide described herein.

Such variant polypeptide sequences will share 70% or more (*i.e.* 80%, 85%, 90%, 95%, 97%, 98%, 99% or more) sequence identity with the sequences recited in the application. In additional embodiments, the described invention provides polypeptide fragments comprising various lengths of contiguous stretches of amino acid sequences disclosed herein. For example, peptide sequences provided by this disclosure include at least about 5, 10, 15, 20, 30, 40, 50, 75, 100, 150, or more contiguous peptides of one or more of the sequences disclosed herein as well as all intermediate lengths therebetween.

The disclosure also includes nucleic acid sequences encoding part or all of the light and heavy chains of the described inventive antibodies, and fragments thereof. Due to the redundancy of the genetic code, variants of these sequences will exist that encode the same amino acid sequences.

The present disclosure also includes isolated nucleic acid sequences encoding the polypeptides for the light and heavy chains of the HIV antibodies listed in **Tables 2-3**. In other related embodiments, the described invention provides polynucleotide variants that encode the peptide sequences of the heavy and light chains of the HIV antibodies listed in **Tables 5-6**. These polynucleotide variants have at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%, or greater, sequence identity compared to a polynucleotide sequence of this disclosure, as determined

using the methods described herein (*i.e.*, BLAST analysis using standard parameters). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning, and the like.

The terms "nucleic acid" and "polynucleotide" are used interchangeably herein to refer to single-stranded or double-stranded RNA, DNA, or mixed polymers. Polynucleotides can include genomic sequences, extra-genomic and plasmid sequences, and smaller engineered gene segments that express, or can be adapted to express polypeptides.

An "isolated nucleic acid" is a nucleic acid that is substantially separated from other genome DNA sequences as well as proteins or complexes such as ribosomes and polymerases, which naturally accompany a native sequence. The term encompasses a nucleic acid sequence that has been removed from its naturally occurring environment and includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems. A substantially pure nucleic acid includes isolated forms of the nucleic acid. Accordingly, this refers to the nucleic acid as originally isolated and does not exclude genes or sequences later added to the isolated nucleic acid by the hand of man.

A polynucleotide "variant," as the term is used herein, is a polynucleotide that typically differs from a polynucleotide specifically disclosed herein in one or more substitutions, deletions, additions and/or insertions. Such variants can be naturally occurring or can be synthetically generated, for example, by modifying one or more of the polynucleotide sequences of the disclosure and evaluating one or more biological activities of the encoded polypeptide as described herein and/or using any of some techniques well known in the art.

Modifications can be made in the structure of the polynucleotides of the described invention and still obtain a functional molecule that encodes a variant or derivative polypeptide with desirable characteristics. When it is desired to alter the amino acid sequence of a polypeptide to create an equivalent or even an improved, variant or portion of a polypeptide of the invention, one skilled in the art typically will change one or more of the codons of the encoding DNA sequence.

Typically, polynucleotide variants contain one or more substitutions, additions, deletions and/or insertions, such that the immunogenic binding properties of the polypeptide encoded by the variant polynucleotide is not substantially diminished relative to a polypeptide encoded by a polynucleotide sequence specifically set forth herein.

In additional embodiments, the described invention provides polynucleotide fragments comprising various lengths of contiguous stretches of sequence identical to or complementary

to one or more of the sequences disclosed herein. For example, polynucleotides are provided by this disclosure that comprise at least about 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides of one or more of the sequences disclosed herein as well as all intermediate lengths therebetween and encompass any length between the quoted values, such as 16, 17, 18, 19, etc.; 21, 22, 23, etc.; 30, 31, 32, etc.; 50, 51, 52, 53, etc.; 100, 101, 102, 103, etc.; 150, 151, 152, 153, etc.; and including all integers through 200-500; 500-1,000.

In another embodiment of the invention, polynucleotide compositions are provided that are capable of hybridizing under moderate to high stringency conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this disclosure with other polynucleotides include prewashing in a solution of 5x SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50-60° C., 5x SSC, overnight; followed by washing twice at 65° C for 20 minutes with each of 2x, 0.5x, and 0.2x SSC containing 0.1% SDS. One skilled in the art will understand that the stringency of hybridization can be readily manipulated, such as by altering the salt content of the hybridization solution and/or the temperature at which the hybridization is performed. For example, in another embodiment, suitable highly stringent hybridization conditions include those described above, with the exception that the temperature of hybridization is increased, for example, to 60-65 °C or 65-70 °C.

In some embodiments, the polypeptide encoded by the polynucleotide variant or fragment has the same binding specificity (*i.e.*, specifically or preferentially binds to the same epitope or HIV strain) as the polypeptide encoded by the native polynucleotide. In some embodiments, the described polynucleotides, polynucleotide variants, fragments, and hybridizing sequences, encode polypeptides that have a level of binding activity of at least about 50%, at least about 70%, and at least about 90% of that for a polypeptide sequence specifically set forth herein.

The polynucleotides of the described invention, or fragments thereof, regardless of the length of the coding sequence itself, can be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length can vary considerably. A nucleic acid fragment of almost any length is employed. For example, illustrative polynucleotide segments with total lengths of about 10000, about 5000, about 3000, about

2000, about 1000, about 500, about 200, about 100, about 50 base pairs in length, and the like, (including all intermediate lengths) are included in many implementations of this invention.

Further included within the scope of the invention are vectors such as expression vectors, comprising a nucleic acid sequence according to the invention. Cells transformed with such vectors also are included within the scope of the invention.

The present disclosure also provides vectors and host cells comprising a nucleic acid of the invention, as well as recombinant techniques for the production of a polypeptide of the invention. Vectors of the invention include those capable of replication in any type of cell or organism, including, for example, plasmids, phage, cosmids, and minichromosomes. In some embodiments, vectors comprising a polynucleotide of the described invention are vectors suitable for propagation or replication of the polynucleotide, or vectors suitable for expressing a polypeptide of the described invention. Such vectors are known in the art and commercially available.

"Vector" includes shuttle and expression vectors. Typically, the plasmid construct also will include an origin of replication (for example, the ColE1 origin of replication) and a selectable marker (for example, ampicillin or tetracycline resistance), for replication and selection, respectively, of the plasmids in bacteria. An "expression vector" refers to a vector that contains the necessary control sequences or regulatory elements for expression of the antibodies including antibody fragment of the invention, in bacterial or eukaryotic cells.

As used herein, the term "cell" can be any cell, including, but not limited to, that of a eukaryotic, multicellular species (for example, as opposed to a unicellular yeast cell), such as, but not limited to, a mammalian cell or a human cell. A cell can be present as a single entity or can be part of a larger collection of cells. Such a "larger collection of cells" can comprise, for example, a cell culture (either mixed or pure), a tissue (for example, endothelial, epithelial, mucosa or other tissue), an organ (for example, lung, liver, muscle and other organs), an organ system (for example, circulatory system, respiratory system, gastrointestinal system, urinary system, nervous system, integumentary system or other organ system), or an organism (*e.g.*, a bird, mammal, or the like).

Polynucleotides of the invention may be synthesized, in whole or in parts that are then combined, and inserted into a vector using routine molecular and cell biology techniques, including, for example, subcloning the polynucleotide into a linearized vector using appropriate restriction sites and restriction enzymes. Polynucleotides of the described invention are amplified by polymerase chain reaction using oligonucleotide primers complementary to each strand of the polynucleotide. These primers also include restriction enzyme cleavage sites to

facilitate subcloning into a vector. The replicable vector components generally include but are not limited to, one or more of the following: a signal sequence, an origin of replication, and one or more marker or selectable genes.

In order to express a polypeptide of the invention, the nucleotide sequences encoding the polypeptide, or functional equivalents, may be inserted into an appropriate expression vector, *i.e.*, a vector that contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods well known to those skilled in the art may be used to construct expression vectors containing sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Such techniques are described, for example, in Sambrook, J. *et al.* (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. *et al.* (1989) Current Protocols in Molecular Biology, John Wiley & Sons, New York. N.Y.

The present disclosure also provides kits useful in performing diagnostic and prognostic assays using the antibodies, polypeptides and nucleic acids of the present invention. Kits of the present invention include a suitable container comprising an HIV antibody, a polypeptide or a nucleic acid of the invention in either labeled or unlabeled form. In addition, when the antibody, polypeptide or nucleic acid is supplied in a labeled form suitable for an indirect binding assay, the kit further includes reagents for performing the appropriate indirect assay. For example, the kit may include one or more suitable containers including enzyme substrates or derivatizing agents, depending on the nature of the label. Control samples and/or instructions may also be included. The present disclosure also provides kits for detecting the presence of the HIV antibodies or the nucleotide sequence of the HIV antibody of the present disclosure in a biological sample by PCR or mass spectrometry.

In some embodiments, the kit includes a pharmaceutically acceptable dose unit of a pharmaceutically effective amount of at least one isolated anti-HIV antibody described herein or antigen-binding portion thereof. The kit can further include a pharmaceutically acceptable dose unit of a pharmaceutically effective amount of an anti-HIV agent. The two pharmaceutically acceptable dose units can optionally take the form of a single pharmaceutically acceptable dose unit. An exemplary anti-HIV agent can be selected from the group consisting of a non-nucleoside reverse transcriptase inhibitor, a protease inhibitor, an entry or fusion inhibitor, and an integrase inhibitor. In some embodiments, the anti-HIV agent is an anti-HIV broadly neutralizing antibody, such as 3BNC117.

"Label" as used herein refers to a detectable compound or composition that is conjugated directly or indirectly to the antibody so as to generate a "labeled" antibody. A label can also be conjugated to a polypeptide and/or a nucleic acid sequence disclosed herein. The label can be detectable by itself (for example, radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, can catalyze chemical alteration of a substrate compound or composition that is detectable. Antibodies and polypeptides of the described invention also can be modified to include an epitope tag or label, for example, for use in purification or diagnostic applications. Suitable detection means include the use of labels such as, but not limited to, radionucleotides, enzymes, coenzymes, fluorescers, chemiluminescers, chromogens, enzyme substrates or co-factors, enzyme inhibitors, prosthetic group complexes, free radicals, particles, dyes, and the like.

According to another embodiment, the present disclosure provides diagnostic methods. Diagnostic methods generally involve contacting a biological sample obtained from a patient, such as, for example, blood, serum, saliva, urine, sputum, a cell swab sample, or a tissue biopsy, with an HIV antibody and determining whether the antibody preferentially binds to the sample as compared to a control sample or predetermined cut-off value, thereby indicating the presence of the HIV virus.

According to another embodiment, the present disclosure provides methods to detect the presence of the HIV antibodies of the present disclosure in a biological sample from a patient. Detection methods generally involve obtaining a biological sample from a patient, such as, for example, blood, serum, saliva, urine, sputum, a cell swab sample, or a tissue biopsy and isolating HIV antibodies or fragments thereof, or the nucleic acids that encode an HIV antibody, and assaying for the presence of an HIV antibody in the biological sample. Also, the present disclosure provides methods to detect the nucleotide sequence of an HIV antibody in a cell. The nucleotide sequence of an HIV antibody may also be detected using the primers disclosed herein. The presence of the HIV antibody in a biological sample from a patient may be determined by utilizing known recombinant techniques and/or the use of a mass spectrometer.

In another embodiment, the present disclosure provides a method for detecting an HIV antibody comprising a heavy chain comprising a highly conserved consensus sequence and a light chain comprising a highly conserved consensus sequence in a biological sample, comprising obtaining an immunoglobulin-containing biological sample from a mammalian subject, isolating an HIV antibody from said sample, and identifying the highly conserved consensus sequences of the heavy chain and the light chain. The biological sample may be

blood, serum, saliva, urine, sputum, a cell swab sample, or a tissue biopsy. The amino acid sequences may be determined by methods known in the art including, for example, PCR and mass spectrometry.

The term "assessing" includes any form of measurement, and includes determining if an element is present or not. The terms "determining," "measuring," "evaluating," "assessing" and "assaying" are used interchangeably and include quantitative and qualitative determinations. Assessing may be relative or absolute. "Assessing the presence of" includes determining the amount of something present, and/or determining whether it is present or absent. As used herein, the terms "determining," "measuring," and "assessing," and "assaying" are used interchangeably and include both quantitative and qualitative determinations.

Method of Reducing Viral Replication

Methods for reducing an increase in HIV virus titer, virus replication, virus proliferation or an amount of an HIV viral protein in a subject are further provided. According to another aspect, a method includes administering to the subject an amount of an HIV antibody effective to reduce an increase in HIV titer, virus replication or an amount of an HIV protein of one or more HIV strains or isolates in the subject.

According to another embodiment, the present disclosure provides a method of reducing viral replication or spread of HIV infection to additional host cells or tissues comprising contacting a mammalian cell with the antibody, or a portion thereof, which binds to an antigenic epitope on gp120.

Method of Treatment

According to another embodiment, the present disclosure provides a method for treating a mammal infected with a virus infection, such as, for example, HIV, comprising administering to said mammal a pharmaceutical composition comprising the HIV antibodies disclosed herein. According to one embodiment, the method for treating a mammal infected with HIV comprises administering to said mammal a pharmaceutical composition that comprises an antibody of the present disclosure, or a fragment thereof. The compositions of the disclosure can include more than one antibody having the characteristics disclosed (for example, a plurality or pool of antibodies). It also can include other HIV neutralizing antibodies as are known in the art, for example, but not limited to, 10-259, 10-303, 10-410, 10-847, 10-996, 10-1121, 10-1130, 10-1146, 10-1341, 10-1369, 10-1074GM, GL, 10E8, 12A12, 12A21, 2F5, 2G12, 35022, 3BC176, 3BNC117, 3BNC55, 3BNC60, 3BNC62, 447-52D, 4E10, 5H/I1-BMV-D5, 8ANC195, b12, CAP256-VRC26.01, CAP256-VRC26.02, CAP256-VRC26.03, CAP256-VRC26.04, CAP256-VRC26.05, CAP256-VRC26.06, CAP256-VRC26.07, CAP256-VRC26.08,

CAP256-VRC26.09, CAP256-VRC26.10, CAP256-VRC26.11, CAP256-VRC26.12, CH01, CH02, CH03, CH04, CH103, HGN194, HJ16, HK20, M66.6, NIH45-46, PCDN-33A, PCDN-33B, PCDN-38A, PG9, PG16, PGDM1400, PGDM1401, PGDM1402, PGDM1403, PGDM1404, PGDM1405, PGDM1406, PGDM1407, PGDM1408, PGDM1409, PGDM1410, PGDM1411, PGDM1412, PGT121, PGT122, PGT123, PGT125, PGT126, PGT127, PGT128, PGT130, PGT131, PGT135, PGT136, PGT137, PGT141, PGT142, PGT143, PGT145, PGT151, PGT152, VRC-CH30, VRC-CH31, VRC-CH32, VRC-CH33, VRC-CH34, VRC-PG04, VRC-CH04b, VRC-PG20, VRC01, VRC02, VRC03, VRC07, VRC23, and Z13.

The method can further include administering a second therapeutic agent, such as a therapeutically effective amount of the second therapeutic agent. The second therapeutic agent can be administered before, concurrently with or after the administration of the anti-HIV antibody or antigen-binding portion thereof. In some embodiments, the second therapeutic agent is an anti-HIV-1 broadly neutralizing antibody. Examples of anti-HIV-1 broadly neutralizing antibodies are provided above. In some embodiments, the anti-HIV-1 broadly neutralizing antibody is 3BNC117.

Passive immunization has proven to be an effective and safe strategy for the prevention and treatment of viral diseases. (See, for example, Keller *et al.*, Clin. Microbiol. Rev. 13:602-14 (2000); Casadevall, Nat. Biotechnol. 20:114 (2002); Shibata *et al.*, Nat. Med. 5:204-10 (1999); and Igarashi *et al.*, Nat. Med. 5:211-16 (1999). Passive immunization using human monoclonal antibodies provides an immediate treatment strategy for emergency prophylaxis and treatment of HIV.

Subjects at risk for HIV-related diseases or disorders include patients who have come into contact with an infected person or who have been exposed to HIV in some other way. Administration of a prophylactic agent can occur prior to the manifestation of symptoms characteristic of HIV-related disease or disorder, such that a disease or disorder is prevented or, alternatively, delayed in its progression.

For *in vivo* treatment of human and non-human patients, the patient is administered or provided a pharmaceutical formulation including an HIV antibody of this disclosure. When used for *in vivo* therapy, the antibodies of this disclosure are administered to the patient in therapeutically effective amounts (*i.e.*, amounts that eliminate or reduce the patient's viral burden). The antibodies are administered to a human patient, in accord with known methods, such as intravenous administration, for example, as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerobrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes. The antibodies can be

administered parenterally, when possible, at the target cell site, or intravenously. In some embodiments, the antibody is administered by an intravenous or subcutaneous administration. Therapeutic compositions of the disclosure may be administered to a patient or subject systemically, parenterally, or locally. The above parameters for assessing successful treatment and improvement in the disease are readily measurable by routine procedures familiar to a physician.

For parenteral administration, the antibodies may be formulated in a unit dosage injectable form (solution, suspension, emulsion) in association with a pharmaceutically acceptable, parenteral vehicle. Examples of such vehicles include, but are not limited, water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Nonaqueous vehicles include, but are not limited to, fixed oils and ethyl oleate. Liposomes can be used as carriers. The vehicle may contain minor amounts of additives such as substances that enhance isotonicity and chemical stability, such as, for example, buffers and preservatives. The antibodies can be formulated in such vehicles at concentrations of about 1 mg/ml to 150 mg/ml.

The dose and dosage regimen depends upon a variety of factors readily determined by a physician, such as the nature of the infection, for example, its therapeutic index, the patient, and the patient's history. Generally, a therapeutically effective amount of an antibody is administered to a patient. In some embodiments, the amount of antibody administered is in the range of about 0.1 mg/kg to about 50 mg/kg of patient body weight. Depending on the type and severity of the infection, about 0.1 mg/kg to about 50 mg/kg body weight (for example, about 0.1-15 mg/kg/dose) of antibody is an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. The progress of this therapy is readily monitored by conventional methods and assays and based on criteria known to the physician or other persons of skill in the art. The above parameters for assessing successful treatment and improvement in the disease are readily measurable by routine procedures familiar to a physician.

Other therapeutic regimens may be combined with the administration of the HIV antibody of the present disclosure. The combined administration includes co-administration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities. Such combined therapy can result in a synergistic therapeutic effect. The above parameters for assessing successful treatment and improvement in the disease are readily measurable by routine procedures familiar to a physician.

The terms "treating" or "treatment" or "alleviation" are used interchangeably and refer to both therapeutic treatment and prophylactic or preventative measures; wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented. A subject or mammal is successfully "treated" for an infection if, after receiving a therapeutic amount of an antibody according to the methods of the present disclosure, the patient shows observable and/or measurable reduction in or absence of one or more of the following: reduction in the number of infected cells or absence of the infected cells; reduction in the percent of total cells that are infected; and/or relief to some extent, one or more of the symptoms associated with the specific infection; reduced morbidity and mortality, and improvement in quality of life issues. The above parameters for assessing successful treatment and improvement in the disease are readily measurable by routine procedures familiar to a physician.

The term "effective amount," "effective dose," or "effective dosage" is defined as an amount sufficient to achieve or at least partially achieve a desired effect. A "therapeutically effective amount" or "therapeutically effective dosage" of a drug or therapeutic agent is any amount of the drug that, when used alone or in combination with another therapeutic agent, promotes disease regression evidenced by a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. A "prophylactically effective amount" or a "prophylactically effective dosage" of a drug is an amount of the drug that, when administered alone or in combination with another therapeutic agent to a subject at risk of developing a disease or of suffering a recurrence of disease, inhibits the development or recurrence of the disease. The ability of a therapeutic or prophylactic agent to promote disease regression or inhibit the development or recurrence of the disease can be evaluated using a variety of methods known to the skilled practitioner, such as in human subjects during clinical trials, in animal model systems predictive of efficacy in humans, or by assaying the activity of the agent in *in vitro* assays.

Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

"Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers that are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include, but not limited to,

buffers such as phosphate, citrate, acetate and other organic acids; antioxidants including, but not limited to, ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as, but not limited to, serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as, but not limited to, polyvinylpyrrolidone; amino acids such as, but not limited to, glycine, glutamine, asparagine, arginine, proline or lysine; monosaccharides, disaccharides, and other carbohydrates including, but not limited to, glucose, mannose, or dextrins; chelating agents such as, but not limited to, EDTA; sugar alcohols such as, but not limited to, mannitol, sorbitol, sucrose or trehalose; salt-forming counterions such as, but not limited to, sodium; and/or nonionic surfactants such as, but not limited to, TWEEN.; polyethylene glycol (PEG), poloxamers, *i.e.* Pluronic F-68 and polysorbates, *i.e.* polysorbate 20 or polysorbate 80

DEFINITIONS

To aid in understanding the detailed description of the compositions and methods according to the disclosure, a few express definitions are provided to facilitate an unambiguous disclosure of the various aspects of the disclosure. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

The term "recombinant" when made in reference to a nucleic acid molecule refers to a nucleic acid molecule which is comprised of segments of nucleic acid joined together by means of molecular biological techniques. The term "recombinant," when made in reference to a protein or a polypeptide, refers to a protein molecule which is expressed using a recombinant nucleic acid molecule.

The term "operably linked" refers to a functional linkage between a nucleic acid expression control sequence (such as a promoter, or array of transcription factor binding sites) and a second nucleic acid sequence, wherein the expression control sequence directs transcription of the nucleic acid corresponding to the second sequence.

As used herein, the term "*in vitro*" refers to events that occur in an artificial environment, *e.g.*, in a test tube or reaction vessel, in cell culture, etc., rather than within a multi-cellular organism.

As used herein, the term "*in vivo*" refers to events that occur within a multi-cellular organism such as a non-human animal.

The terms "prevent," "preventing," "prevention," "prophylactic treatment" and the like refer to reducing the probability of developing a disorder or condition in a subject, who does not have, but is at risk of or susceptible to developing a disorder or condition.

As used herein, "administering" refers to the physical introduction of a composition comprising a therapeutic agent to a subject, using any of the various methods and delivery systems known to those skilled in the art. Routes of administration described herein include intravenous, intraperitoneal, intramuscular, subcutaneous, spinal or other parenteral routes of administration, for example by injection or infusion. The phrase "parenteral administration" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intraperitoneal, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion, as well as *in vivo* electroporation. Alternatively, a composition described herein can be administered via a non-parenteral route, such as a topical, epidermal or mucosal route of administration, for example, intranasally, orally, vaginally, rectally, sublingually or topically. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

The term "agent" is used herein to denote a chemical compound, a mixture of chemical compounds, a biological macromolecule (such as a nucleic acid, an antibody, a protein or portion thereof, *e.g.,* a peptide), or an extract made from biological materials such as bacteria, plants, fungi, or animal (particularly mammalian) cells or tissues. The activity of such agents may render it suitable as a "therapeutic agent," which is a biologically, physiologically, or pharmacologically active substance (or substances) that acts locally or systemically in a subject.

The terms "therapeutic agent," "therapeutic capable agent," or "treatment agent" are used interchangeably and refer to a molecule or compound that confers some beneficial effect upon administration to a subject. The beneficial effect includes enablement of diagnostic determinations; amelioration of a disease, symptom, disorder, or pathological condition; reducing or preventing the onset of a disease, symptom, disorder or condition; and generally counteracting a disease, symptom, disorder or pathological condition.

"Combination" therapy, as used herein, unless otherwise clear from the context, is meant to encompass administration of two or more therapeutic agents in a coordinated fashion, and includes, but is not limited to, concurrent dosing. Specifically, combination therapy encompasses both co-administration (*e.g.,* administration of a co-formulation or simultaneous administration of separate therapeutic compositions) and serial or sequential administration, provided that administration of one therapeutic agent is conditioned in some way on

administration of another therapeutic agent. For example, one therapeutic agent may be administered only after a different therapeutic agent has been administered and allowed to act for a prescribed period of time. See, *e.g.*, Kohrt *et al.* (2011) *Blood* 117:2423.

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

It is noted here that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

The terms "including," "comprising," "containing," or "having" and variations thereof are meant to encompass the items listed thereafter and equivalents thereof as well as additional subject matter unless otherwise noted.

The phrases "in one embodiment," "in various embodiments," "in some embodiments," and the like are used repeatedly. Such phrases do not necessarily refer to the same embodiment, but they may unless the context dictates otherwise.

The terms "and/or" or "/" means any one of the items, any combination of the items, or all of the items with which this term is associated.

The word "substantially" does not exclude "completely," *e.g.*, a composition which is "substantially free" from Y may be completely free from Y. Where necessary, the word "substantially" may be omitted from the definition of the invention.

As used herein, the term "approximately" or "about," as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In some embodiments, the term "approximately" or "about" refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value). Unless indicated otherwise herein, the term "about" is intended to include values, *e.g.,* weight percents, proximate to the recited range that are equivalent in terms of the functionality of the individual ingredient, the composition, or the embodiment.

As used herein, the term "each," when used in reference to a collection of items, is intended to identify an individual item in the collection but does not necessarily refer to every item in the collection. Exceptions can occur if explicit disclosure or context clearly dictates otherwise.

The use of any and all examples, or exemplary language (*e.g.*, "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

All methods described herein are performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. In regard to any of the methods provided, the steps of the method may occur simultaneously or sequentially. When the steps of the method occur sequentially, the steps may occur in any order, unless noted otherwise.

In cases in which a method comprises a combination of steps, each and every combination or sub-combination of the steps is encompassed within the scope of the disclosure, unless otherwise noted herein.

Each publication, patent application, patent, and other reference cited herein is incorporated by reference in its entirety to the extent that it is not inconsistent with the present disclosure. Publications disclosed herein are provided solely for their disclosure prior to the filing date of the present invention. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates, which may need to be independently confirmed.

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims.

EXAMPLES

EXAMPLE 1

Identification and characterization of the variants of the 10-1074 broadly neutralizing antibody—Round 1

The first round variants, including MS-203, MS-204, MS-205, MS-206, MS-207, MS-208, MS-209, MS-210, MS-211, MS-212, MS-213, MS-214, MS-215, MS-216, MS-217, MS-218, MS-219, MS-220, and MS-224, as shown in **Table 9**, were produced using transient

expression in HEK293 cells and purified by protein A chromatography. The characterization methods used to analyze the variants are listed in **Table 8**, including size exclusion chromatography (SEC), differential scanning fluorimetry (DSF), low pH stability, and relative solubility assay (RSA). The antibodies were buffer exchanged into phosphate-buffered saline and used for analysis. Assays used for analysis of the first round variants included SEC to quantify monomer and high molecular weight species following purification, DSF to characterize stability of the CH2 and Fab domains during thermal ramping, and retention of neutralization capacity.

The monomer content of the variants ranged from a low of 60.8% to a high of 96.3%. The monomer content of the unmodified 10-1074-LS (or MS-194) was 91.5% with the remainder of material for all variants being high molecular weight species (HMW). Variants with less than 10% HMW were considered for the second round combinatorial variants. In addition to SEC analysis, differential scanning fluorimetry was used to define molecules with increased thermodynamic stability. For the 10-1074-LS (or MS-194) parental molecule, only a single Tm was measured indicating that the CH2 and Fab domains unfolded at the same temperature. Similar results were observed for some of the variants. A few, though, also showed the presence of both a Tm1 and a second melting transition termed Tm2, because modifications that help to stabilize the Fab domain were made in the Fv domain of the antibodies, resulting in the increased thermal transition. Antibodies that did not show a consistent Tm2 for both replicates of the DSF analysis were not considered for Round 2 combinations.

Neutralization activity was also measured to ensure retention of activity of the bnAb variants. Results are shown in **Table 10** for neutralization against six pseudoviruses of HIV (*e.g.*, Du156.12, WITO4160.33, CNE17, CNE30, CAAN5342.A2, Du172.17), which are representative of the broader set of viruses against which 10-1074 is active. Antibodies with more than a 3-fold increase in the IC50 or IC80 value for a particular pseudovirus were considered inactive and discarded from further consideration. As evidenced by the data, only one variant, MS-208, lost neutralization activity and was not selected for further development.

The final set of amino acids for further development was based on the combination of amount purified, percent high molecular weight, increase in thermodynamic stability by DSF, and retention of neutralization activity. An example of the reasoning for the selection of residues for combinatorial analysis is described in **Table 11**. Five amino acid residues selected for further development are MS-203 (LmdV: Y2P), MS-216 (HV: V79T), MS-217 (HV: R82V), MS-218 (HV: L89F) and MS-219 (HV: T108R).

EXAMPLE 2

Identification and characterization of the variants of the 10-1074 broadly neutralizing antibody—Round 2

The second round combinatorial variants were designed based on the first round variants as described in the prior section. The combinatorial variants tested in the second round of optimization are shown in **Table 12** and consist of ten double combinations, ten triple combinations, five quadruples and one quintuple combination consisting of all five amino acid modifications. These variants include MS-200, MS-201, MS-202, MS-225, MS-226, MS-227, MS-228, MS-229, MS-230, MS-231, MS-232, MS-233, MS-234, MS-235, MS-236, MS-237, MS-238, MS-239, MS-240, MS-241, MS-242, MS-243, MS-244, and MS-245. The combinatorial variants were produced using transient expression in HEK293 cells and purified by protein A chromatography. The antibodies were buffer exchanged into phosphate-buffered saline before being used for analysis. Assays used for analysis of the second round variants included SEC to quantify monomer and high molecular weight species following purification, differential scanning fluorimetry to characterize stability of the CH2 and Fab domains during thermal ramping, chemical unfolding, low pH stability, solubility, and retention of neutralization capacity.

Results of the initial screening consisting of SEC analysis for dimer and oligomer content and DSF for increased thermodynamic stability are shown in **Table 13**. For example, MS-200 has lower HMW than the control variant MS-194. MS-200 also has a Tm1=70.15 °C and a Tm2=74.62 °C, suggesting it has improved thermal stability. Separation of the HMW species into dimer and oligomer species, with HMW species eluting earlier than dimer, provides a more refined view of the data. The data show that the dimer content was relatively unchanged from 10-1074-LS (or MS-194), while the oligomer content of the variants both increased up to 2-fold for a few variants and decreased up to approximately 7-fold for others. The variants were also characterized by DSF to identify those with increased thermodynamic stability as evidenced by the presence of distinct Tm2 unfolding temperatures.

To better differentiate the variants by DSF, an alternative analysis of the data was devised which took advantage of the change between Tm1 and Tm2 and the area under the thermal unfolding curves. As indicated by the data in **Table 14** termed DSF Shoulder Score, the variants may have similar Tm2 values, but different shoulder score values with the increased values indicative of greater stability. For example, the DSF Shoulder Score values for MS-200, MS-201, and MS-202 are 16.12, 29.39, and 22.49, respectively, which are significantly larger than the Shoulder Score value, 7.65, of the control antibody variant MS-

194, suggesting the variants MS-200, MS-201, and MS-203 are more stable than the control antibody variant MS-194. Thermodynamic stability was also assessed by chemical unfolding which asses the intrinsic resistance of the native state against unfolding as measured by the mid-point of the denaturation curve. The higher the value, the greater the stability. Together with the DSF shoulder score, a much finer differentiation of the intrinsic thermodynamic stability of the antibodies was obtained. In addition to the intrinsic stability, the resistance to aggregation during low pH incubation, neutralization, and solubility of the variants was also analyzed. While the parental 10-1074-LS (or MS-194) aggregated with up to 40% HMW formation, some variants showed only 2-3% HMW formation. Solubility was also increased for some variants, with up to a 42% increase in solubility over the parental molecule.

The neutralization capacity of a subset of the combinatorial variants was also examined to ensure no loss in neutralization occurred. As shown in **Table 15**, a reduced set of variants were tested against a representative set of 12 pseudoviruses, including SC422661.8, WITO4160.33, CAAN5342.A2, DU156.12, DU172.17, CNE17, CNE30, CNE53, 235-47, X1193_c1, X1254_c3, and 3301.v1.c24. Variants with a Tm2 were selected for the testing. Of the variants that were tested they all retained neutralization activity against the set of pseudoviruses examined.

The final set of variants for in-depth biophysical analysis was defined based on the biophysical attributes since the reduced set of antibodies defined in **Table 15** all retained neutralization activity. The specific reasons for exclusion of bnAbs from the set for in-depth analysis are described in **Table 16**, and the final set is shown below.

	ORIGINAL NAME	LIGHT CHAIN MODIFICATIONS	HEAVY CHAIN MODIFICATIONS
MS-200	10-1074_ROUND2_XTEND.015	LMDV:Y2P	HV:R82V, HV:T108R
MS-201	10-1074_ROUND2_XTEND.019		HV:V79T, HV:L89F, HV:T108R
MS-202	10-1074_ROUND2_XTEND.023	LMDV:Y2P	HV:V79T, HV:L89F, HV:T108R

In-Depth Analysis of The Final Variant Set

The final optimized variant was based on the final variant set defined above. Analysis performed was downstream purification (**FIGS. 1-2**), accelerated stability (**FIGS. 3-4**). For the downstream purification analysis and accelerated stability, molecules were produced using transient expression in a CHO-S cell line.

The results from the in-depth analysis indicate that MS-202 was the best performing molecule of the optimized variants. While both MS-200, MS-201, and MS-202 have similar rates of dimer formation at 40°C, MS-202 shows better resistance to sub-visible particle formation over a 13 week period.

Production of Antibodies

Antibody materials were cloned and produced as previously described (Durocher, Y., Perret, S., & Kamen, A. (2002). *Nucleic Acids Research*, *30*(2), E9). bNAbs antibody materials were generated from transient expression of two suspension cell lines, Human Embryonic Kidney 293 (HEK293) and Chinese Hamster Ovary (CHO). The pTT5 mammalian expression vectors containing either a light chain (LC) or heavy chain(HC) coding region were co-transfected into HEK293 cells at a viable cell density (VCD) of 1* 10^6 cells/mL using polyethyleneimine (PEI) (Durocher, Perret, & Kamen, 2002) then two-fold diluted with pre-warmed medium to 1/5 shake flask volume. Expression duration was 5-7 days at 37°C, 5% CO_2, and 85% humidity at a shaking speed of 130 RPM with an orbit of 19 mm. The ExpiCHO-S™ "max titer" method was followed essentially as described by ThermoFisher (catalog number A29133, document part number A29518). The pcDNA3.4 expression vectors containing either LC or HC coding regions were co-transfected into CHO-S cells at a VCD of 6*10^6 using expifectamine. The expression duration was 12 days at 32°C, 5% CO_2, and 85% humidity at a shaking speed of 130 RPM with an orbit of 19 mm. All clarified supernatants were produced by pelleting the cells at 3000 g for 20 minutes followed by 0.22 µm filtration. Antibodies were purified from the clarified supernatants using Mab Select SuRe protein A resin. A sodium phosphate, sodium chloride buffer system with an arginine wash and an acetate pH 3.5 elution was utilized. Protein A elutions were neutralized with tris and buffer exchanged into 20 mM sodium phosphate, 150 mM NaCl, pH 7.4.

Neutralization Assays

Virus neutralization was evaluated using a luciferase-based assay in TZM.bl cells (J Virol 79(16):10108-10125). The HIV-1 pseudoviruses tested contained mostly tier-2 and tier-3 viruses (Journal of Virology 84(3):1439-1452). High-mannose-only pseudoviruses were produced in wild-type cells treated with 25 µM kifunensine (Enzo Life Sciences) or in HEK 293S GnTI$^{-/-}$ cells. Non-linear regression analysis was used to calculate concentrations at which half-maximal inhibition was observed (IC_{50} values). Neutralization activities were also evaluated with a previously characterized PBMC-based assay using infection with primary HIV-1 variants (n=95) isolated from clade B-infected donors with known seroconversion dates

either between 1985 and 1989 ("historical seroconverters", n=14) or between 2003 and 2006 ("contemporary seroconverters", n=21) (Journal of Virology 85(14):7236-7245; Nat Med 16(9):995-997). Neutralization activity for each antibody was calculated using GraphPad Prism software (v5.0b) as the area under the best-fit curve, which fits the proportion of viruses neutralized over IC_{50} values ranging from 0.001 to 50 µg/ml.

HP-SEC

High-Performance Size Exclusion Chromatography ("HP-SEC") separates proteins based on differences in their hydrodynamic volumes. Molecules with larger hydrodynamic protein volumes elute earlier than molecules with smaller volumes. Undiluted samples were loaded onto a Waters XBridge Protein BEH SEC 200A column (3.5 µm, 7.8 x 300 mm), separated isocratically with a 100 mM sodium phosphate, 250 mM sodium chloride, pH 6.8 running buffer, and the eluent was monitored by UV absorbance at 280 nm. Purity was determined by calculating the percentage of each separated component as compared to the total integrated area.

DSF

The DSF technique consists of measuring the fluorescence intensity of a hydrophobic probe at gradually increasing temperatures to determine the transition temperature and exposure of the hydrophobic regions of a protein. The measurements from this technique, reported as transition temperatures, correlate well with data obtained from differential scanning calorimetry (DSC). DSF is a high throughput technique that is used to estimate a protein's relative thermodynamic stability and by ranking the results, can be used as a tool to select candidates with more favorable stability properties. Thermal transition temperature(s) by DSF were measured according to the method previously described (Feng H, *et al.* J Pharm Sci, 2010; 99:4, 1707-1720). The analysis was carried out in PBS buffer (20 mM sodium phosphate and 150 mM sodium chloride pH 7.1) at a final protein concentration of 0.15 mg/mL and a final Sypro Orange concentration of 3X. Protein and Sypro Orange were mixed at a 1:1 volumetric ratio in a 96 well PCR plate and analyzed using a Roche Light Cycler 480 instrument equipped with Thermal Shift Analysis Software. Thermal curves were generated by heating the samples from 20-95 °C at a ramp rate of 4.4 °C/s and 10 acquisitions per °C, at Ex = 465nm Em = 580nm. Transition temperatures and shoulder scores were determined using the first derivative of the melting curve.

Low pH Stability

The pH of protein samples at 1 mg/mL in 20 mM PBS was lowered to approximately pH 3.3 using 2 M acetic acid. After a 30 minute incubation, samples were neutralized to approximately pH 5 using 2 M Tris base. Samples were measured for high molecular weight species using the SE-HPLC method and measured in duplicate. As a control, protein samples had PBS added that was the same volume of the 2 M acetic acid and 2 M Tris base and measured for high molecular weight species.

Relative Solubility

Solubility was assessed according to the method previously described (Vishal M. Toprani, Sangeeta B. Joshi, Lisa A. Kueltzo, Richard M. Schwartz, C. Russell Middaugh, David B. Volkin). A micro-polyethylene glycol precipitation assay as a relative solubility screening tool for monoclonal antibody design and formulation development (J. Pharm. Sci 2016; 105:8: 2319-2327). Analysis was done in PBS buffer (20 mM sodium phosphate and 150 mM sodium chloride pH 7.1) and a final PEG 10,000 concentration of 7.9%. Protein at 1 mg/mL was diluted into the PEG solution at a 1:4 ratio and incubated at room temperature overnight in a 96 well 0.22 μm filter plate. After PEG incubation, samples are passed through the filter by centrifugation and the remaining soluble protein is measured by a protein A titer assay.

Chemical Unfolding

Thirty-two guanidine hydrochloride (GND) concentrations in PBS ranging from 0 to 6 M GND were prepared using a liquid handling robot. Then, the protein samples at 1 mg/mL in 20 mM PBS were transferred to each GND concentration to achieve a final protein concentration of 0.05 mg/mL. After a 24 hr incubation, the samples were measured on a SpectraMax M5 plate reader (excitation: 280 nm, emission: 300-450 nm). The measured fluorescence intensity at 373nm was corrected for scattering and stray light by subtraction of a small amount of the summed intensity measured between 300 and 320 nm (used as a surrogate for signal due to scattering) and then ratioed to the total intensity measured between 320 and 440 nm to correct for total intensity fluctuations. Then, the chemical unfolding curve was generated by graphing each corrected intensity against the GND concentration. The inflection point of the curve was calculated and reported for each protein sample from this curve. Samples were completed in triplicate.

Sub-visible Particle Analysis

Sub-visible particles were measured using a Flowcam 8100 benchtop microflow imaging system equipped with an 80 µm flow cell and a 10X magnification lens and controlled by the Visual Spreadsheet software. Samples were equilibrated to room temperature and gently swirled to mix thoroughly. Single readings of 100 µl per sample were collected, and total particle concentration above 2 µm was recorded.

EXAMPLE 3

Characterization for the formation of oligomeric species and HMW of the 10-1074 variants during viral inactivation and the purification steps

FIG. 1 shows the characterization of anti-HIV antibody 10-1074 variants MS-194 (**FIG. 1A**) and MS-203 (**FIG. 1B**) by high-performance size exclusion chromatography ("HP-SEC") before and after viral neutralization. Peaks in the HP-SEC profiles corresponding to the oligomeric species formed during viral inactivation are indicated by arrows. **FIG. 2** shows quantification of the degree of aggregation represented by the level of high molecular weight ("HMW") and oligomeric species following each of the purification steps for the 10-1074 antibody variants MS-194, MS-200, MS-201, and MS-203.

Molecules MS-194, MS-200, MS-201, and MS-203, were produced using the ExpiCHO-S™ "max titer" method essentially as described by ThermoFisher (catalog number A29133, document part number A29518). The pcDNA3.4 expression vectors containing either light chain or heavy chain coding regions were co-transfected into CHO-S cells at a VCD of 6*10^6 using expifectamine. The expression duration was 12 days at 32°C, 5% CO_2, and 85% humidity at a shaking speed of 130 RPM with an orbit of 19mm. All clarified supernatants were produced by pelleting the cells at 3000g for 20 minutes followed by 0.22 µm filtration.

Antibodies were purified from the clarified supernatants using MabSelect SuRe protein A resin. Equilibrated with a Tris and sodium chloride buffer. Following loading of the column, the column was washed with a Tris buffer containing 0.5M sodium chloride. Bound mAb was eluted with a 0.1 M acetate buffer at pH 3.6 and neutralized. The stability of each molecule during viral inactivation was ascertained by titrating the eluate to pH 3.5, followed by incubating for 1 hour followed by neutralization with Tris buffer. The remainder of the Protein A elutions were also neutralized with a tris buffer system immediately following elution. Further purification was achieved by loading the neutralized eluent onto a Fractogel SO_3^- cation-exchange resin (EMD Millipore Corporation) and eluting with a sodium chloride

gradient. The peak containing the mAb was collected, concentrated to 20 mg/mL, and buffer exchanged into 10 mM acetate, 9% sucrose, pH 5.2.

The percent high molecular weight and oligomer were determined for each sample using HP-SEC analysis as previously described. As shown in **FIGS. 1A** and **1B** and quantified in **FIG. 2** the MS-194 antibody shows a significant increase in oligomer during the low pH viral inactivation while molecules MS-200, MS-201, and MS-203 showed no increase in HMW or oligomer content during the viral inactivation process.

EXAMPLE 4

Characterization of stability of the 10-1074 variants

FIG. 3 shows the level of HMW during incubation at 40°C for up to 13 weeks for the 10-1074 antibody variants MS-194, MS-200, MS-201, and MS-203. The figure shows a similar rate of dimer formation during incubation at 40°C for up to 13 weeks. **FIG. 4** shows the level of sub-visible particle formation during 6 weeks and 13 weeks for the 10-1074 antibody variants MS-194, MS-200, MS-201, and MS-203. The figure shows that antibodies MS-200, MS-201 and MS-203 particulated to a much smaller degree than MS-194. After 6 weeks, MS-194 showed 6X more particles than MS-200, MS-201, and MS-203, while after 13 weeks MS-200 and MS-203 had approximately 2X less than MS-194 and MS-203 showed 4X less particle formation.

Monoclonal antibodies MS-194, MS-200, MS-201 and MS-203 purified by cation-exchange chromatography and buffer exchanged as previously described were buffer exchanged into 20 mM acetate, 9% sucrose and concentrated to 100 mg/mL at a final pH of 5.2. A 500 µL aliquot of each sample was placed in a 4 mL Type I glass vial, sealed with a rubber stopper and aluminum crimp seal. The samples were incubated for up to 13 weeks at 40°C. Samples were removed at the indicated time points and the vials resealed and placed back in the incubator. The % HMW was determined using HP-SEC and sub-visible particles determined using the FlowCam instrument as described above.

EXAMPLE 5

Combination therapy with anti-HIV-1 antibodies

Although anti-HIV-1 antibodies constitute a potential alternative to ART5, treatment of viremic individuals with a single antibody also results in emergence of resistant viral variants ((Caskey, M. *et al.* Nature 522, 487–491 (2015); Caskey, M. *et al.* Nat. Med. 23, 185–191 (2017); Lynch, R. M. *et al.* Sci. Transl. Med. 7, 319ra206 (2015)). Moreover, combinations of first-generation anti-HIV-1 broadly neutralizing antibodies (bNAbs) had little measurable

effect on the infection. This disclosure presents the results from a phase 1b clinical trial (NCT02825797) in which a combination of 3BNC117 and 10–1074, two potent monoclonal anti-HIV-1 broadly neutralizing antibodies that target independent sites on the HIV-1 envelope spike, was administered during analytical treatment interruption (ATI) (Mendoza *et al.*, Nature. 2018 September; 561(7724): 479–484; Bar-On *et al.*, Nature Medicine 24:1701–1707 (2018)). Participants received three infusions of 30 mg/kg of each antibody at 0, 3, and 6 weeks. Infusions of the two antibodies were generally well tolerated. The nine enrolled individuals with antibody-sensitive latent viral reservoirs maintained suppression for 15 to > 30 weeks (median = 21 weeks). In the four individuals with dual antibody-sensitive viruses, immunotherapy resulted in an average reduction in HIV-1 viral load of 2.05 $\log_{10}$ copies per ml that remained significantly reduced for three months following the first of up to three infusions. In addition, none developed viruses resistant to both antibodies. It was concluded that the combination of anti-HIV-1 monoclonal antibodies 3BNC117 and 10–1074 could maintain long-term suppression in the absence of ART in individuals with antibody-sensitive viral reservoirs.

Study Design

An open-label phase 1b study was conducted in HIV-1-infected participants who were virologically suppressed on antiretroviral therapy (ART) (http://www.clinicaltrials.gov; NCT02825797; EudraCT: 2016-002803-25) (Mendoza *et al.*, Nature. 2018 September; 561(7724): 479–484; Bar-On *et al.*, Nature Medicine 24:1701–1707 (2018)). Study participants were enrolled sequentially according to eligibility criteria. Participants received 3BNC117 and 10–1074 intravenously at a dose of 30 mg/kg body weight of each antibody, at weeks 0, 3, and 6, unless viral rebound occurred. ART was discontinued 2 days after the first infusion of antibodies (day 2). Plasma HIV-1 viral RNA levels were monitored weekly and ART was resumed if viral load increased to ≥ 200 copies/ml or $CD4^+$ T cell counts decreased to < 350 cells/pl in two consecutive measurements. Time of viral rebound was determined by the first viral load > 200 copies/ml. Study participants were followed for 30 weeks after the first infusion. Safety data are reported until the end of study follow-up. All participants provided written informed consent before participation in the study, and the study was conducted in accordance with Good Clinical Practice (GCP). The protocol was approved by the Federal Drug Administration (FDA) in the USA, the Paul-Ehrlich-Institute in Germany, and the Institutional Review Boards (IRBs) at the Rockefeller University and the University of Cologne.

Study Participants

Study participants were recruited at the Rockefeller University Hospital, New York, USA, and the University Hospital Cologne, Cologne, Germany. Eligible participants were adults aged 18–65 years, HIV-1-infected, on ART for a minimum of 24 months, with plasma HIV-1 RNA levels of < 50 copies/ml for at least 18 months (one viral blip of > 50 but < 500 copies/ml during this 18-month period was allowed), plasma HIV-1 RNA levels < 20 copies/ml at the screening visit, and a current $CD4^+$ T cell count > 500 cells/pl. In addition, participants were pre-screened for sensitivity of latent proviruses against 3BNC117 and 10– 1074 by bulk PBMC viral outgrowth culture as described below. Sensitivity was defined as an IC50 < 2 pg/ml for both 3BNC117 and 10–1074 against outgrowth virus. Participants on an NNRTI-based ART regimen were switched to an integrase inhibitor-based regimen (dolutegravir plus tenofovir disoproxil fumarate/emtricitabine) 4 weeks before treatment interruption due to the prolonged half-life of NNRTIs. Exclusion criteria included reported $CD4^+$ T cell nadir of < 200 cells/pl, concomitant hepatitis B or C infection, previous receipt of monoclonal antibodies of any kind, clinically relevant physical findings, medical conditions or laboratory abnormalities, and pregnancy or lactation.

Study Procedures

3BNC117 and 10–1074 were administered intravenously at a dose level of 30 mg/kg (Mendoza *et al.*, Nature. 2018 September; 561(7724): 479–484; Bar-On *et al.*, Nature Medicine 24:1701–1707 (2018)). The appropriate stock volume of 3BNC117 and 10–1074 was calculated according to body weight and diluted in sterile normal saline to a total volume of 250 ml per antibody. Monoclonal antibody infusions were administered sequentially and intravenously over 60 minutes. Study participants were observed at the Rockefeller University Hospital or the University Hospital Cologne for one hour after the last antibody infusion. Participants returned for weekly follow-up visits during the ATI period for safety assessments, which included physical examination and measurements of clinical laboratory parameters such as hematology, chemistries, urinalysis, and pregnancy tests (for women). Plasma HIV-1 RNA levels were monitored weekly during the ATI period, and $CD4^+$ T cell counts were measured every 1 to 2 weeks. After ART was re-initiated, participants returned for follow up every 2 weeks until viral re-suppression was achieved, and every 8 weeks thereafter. Study investigators evaluated and graded adverse events according to the DAIDS AE Grading Table (version 2.0, November 2014) and determined causality. Leukapheresis was performed at the Rockefeller University Hospital or at the University Hospital Cologne at week -2 and week 12. Blood samples were collected before and at multiple times after 3BNC117 and 10–1074

infusions. Samples were processed within 4 h of collection, and serum and plasma samples were stored at –80°C. Peripheral blood mononuclear cells (PBMCs) were isolated by density gradient centrifugation. The absolute number of PBMCs was determined by an automated cell counter (Vi-Cell XR; Beckman Coulter) or manually, and cells were cryopreserved in fetal bovine serum plus 10% DMSO.

Plasma HIV-1 RNA Levels

HIV-1 RNA levels in plasma were measured at the time of screening, at week -2, day 0 (before infusion), weekly during ATI, and every two weeks to every eight weeks after viral rebound had occurred. HIV-1 RNA levels were determined using the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Assay (version 2.0) or the Roche COBAS HIV-1 quantitative nucleic acid test (COBAS 6800), which quantitate HIV-1 RNA over a range of 2×10^1 to 1×10^7 copies/ml. These assays were performed at LabCorp or at the University Hospital Cologne.

$CD4^+$ T cells

$CD4^+$ T-cell counts were determined by a clinical flow cytometry assay, performed at LabCorp or at the University Hospital Cologne, at screening, week 0 (before infusion), weeks 2, 3, 5, 6, 8, 10, and weekly thereafter, while participants remained off ART.

Determination of Baseline Neutralizing Antibody Activity

Purified IgG (Protein G Sepharose 4 Fast Flow, GE Life Sciences) obtained before antibody infusions was tested against a panel of 12 HIV-1 pseudoviruses as described previously (Schoofs T *et al.* Science 352, 997–1001 (2016)).

Measurement of 3BNC117 and 10–1074 Serum Levels

Blood samples were collected before, at the end of each 3BNC117 infusion and at the end of each 10–1074 infusion at weeks 0, 3, and 6, and weekly during the ATI period, up to week 30. Serum levels of 3BNC117 and 10–1074 were determined by a TZM-bl assay and by ELISA from samples obtained before and after each antibody infusion, and approximately every three weeks during follow up as well as at the time of viral rebound.

3BNC117 and 10–1074 serum concentrations were measured by a validated sandwich ELISA. High bind polystyrene plates were coated with 4 µg/ml of an anti-idiotypic antibody specifically recognizing 3BNC117 (anti-ID 1F1-2E3 mAb) or 2µg/ml of an anti-idiotypic antibody specifically recognizing 10–1074 (anti-ID 3A1–4E11 mAb), and incubated overnight at 2–8°C. After washing, plates were blocked with 5% Milk Blotto (w/v), 5% NGS (v/v), and 0.05% Tween 20 (v/v) in PBS. Serum samples, QCs and standards were added (1:50 minimum dilution in 5% Milk Blotto (w/v), 5% NGS (v/v), and 0.05% Tween 20 (v/v) in PBS) and

incubated at room temperature. 3BNC117 or 10–1074 were detected using a horseradish peroxidase (HRP)-conjugated mouse anti-human IgG kappa-chain-specific antibody (Abcam) for 3BNC117 or an HRP-conjugated goat antihuman IgG Fc-specific antibody for 10–1074 (Jackson ImmunoResearch) and the HRP substrate tetra-methylbenzidine. 3BNC117 and 10–1074 concentrations were then calculated from a standard curve of 3BNC117 or 10–1074 run on the same plate using a 5-PL curve-fitting algorithm (Softmax Pro, v5.4.5). Standard curves and positive controls were created from the drug product lots of 3BNC117 and 10–1074 used in the clinical study. The capture anti-idiotypic mAbs were produced using a stable hybridoma cell line (Duke Protein Production Facility). The lower limit of quantitation for the 3BNC117 ELISA is 0.78 μg/ml and for the 10–1074 ELISA is 0.41 μg/ml. The lower limit of detection was determined to be 0.51 μg/ml and 0.14 μg/ml in HIV-1 seropositive serum for the 3BNC117 and 10–1074 ELISA, respectively. For values that were detectable (*i.e.*, positive for mAb) but were below the lower limit of quantitation, values are reported as < 0.78 μg/ml and < 0.41 μg/ml for 3BNC117 and 10–1074 ELISA, respectively. If day 0 baseline samples had measurable levels of antibody by the respective assays, the background measured antibody level was subtracted from subsequent results. In addition, samples with antibody levels measured to be within 3-fold from background were excluded from the analysis of PK parameters.

Serum concentrations of active 3BNC117 and 10–1074 were also measured using a validated luciferase-based neutralization assay in TZM-bl cells as previously described (Sarzotti-Kelsoe M *et al.* J Immunol Methods 409, 131–146 (2014)). Briefly, serum samples were tested using a primary 1:20 dilution with a 5-fold titration series against HIV-1 Env pseudoviruses Q769.d22 and X2088_c9, which are highly sensitive to neutralization by 3BNC117 and 10–1074, respectively, while fully resistant against the other administered antibody. In the case of the post-infusion time points of 10–1074, instances where serum ID50 titers against X2088_c9 were > 100,000, serum samples were also tested against a less sensitive strain, Du422. To generate standard curves, 3BNC117 and 10–1074 clinical drug products were included in every assay set-up using a primary concentration of 10 μg/ml with a 5-fold titration series. Serum concentrations of 3BNC117 and 10–1074 for each sample were calculated as follows: serum ID50 titer (dilution) × 3BNC117 $_{IC50}$ or 10–1074 IC50 titer (μg/ml) = serum concentration of 3BNC117 or 10–1074 (μg/ml). Env pseudoviruses were produced using an ART-resistant backbone vector that reduces background inhibitory activity of antiretroviral drugs if present in the serum sample (SG3ΔEnv/K101P.Q148H.Y181C). Virus pseudotyped with the envelope protein of murine leukemia virus (MuLV) was utilized as a negative control.

Antibody concentrations were calculated using the serum ID80 titer and monoclonal antibody IC80 if non-specific activity against MuLV was detected (ID50 > 20; 9246, week 30; 9248, baseline, d0, wk 18). All assays were performed in a laboratory meeting GCLP standards.

Pre-Screening Bulk PBMC Culture

To test HIV-1 viral strains for sensitivity to 3BNC117 and 10–1074, bulk viral outgrowth cultures were performed by co-culturing isolated $CD4^+$ T cells with MOLT-4/CCR-5 cells or $CD8^+$ T cell-depleted donor lymphoblasts. PBMCs for pre-screening were obtained up to 72 weeks (range 54 – 505 days) before enrollment under separate protocols approved by the IRBs of The Rockefeller University and the University of Cologne. Sensitivity was determined by TZM-bl neutralization assay as described below. Culture supernatants with IC50 < 2 μg/ml were deemed sensitive.

Quantitative and Qualitative Viral Outgrowth Assay (Q^2VOA)

The quantitative and qualitative viral outgrowth assay (Q^2VOA) was performed using isolated PBMCs from leukapheresis at week –2 and week 12 as previously described (Lorenzi JC *et al.* PNAS 113, E7908– E7916 (2016)). Briefly, isolated $CD4^+$ T cells were activated with 1 μg/ml phytohemagglutinin (Life Technologies) and 100 U/ml IL-2 (Peprotech) and co-cultured with 1×10^6 irradiated PBMCs from a healthy donor in 24-well plates. A total of $6 \times 10^7 – 6.2 \times 10^8$ cells were assayed for each individual at each of the 2 time points. After 24 hours, PHA was removed and 0.1×10^6 MOLT-4/CCR5 cells were added to each well. Cultures were maintained for 2 weeks, splitting by half the MOLT- 4/CCR5 cells 7 days after the initiation of the culture and every other day after that. Positive wells were detected by measuring p24 by ELISA. The frequency of latently infected cells was calculated through the infectious units per million (IUPM) algorithm developed by the Siliciano lab (http://silicianolab.johnshopkins.edu).

Rebound Outgrowth Cultures

$CD4^+$ T cells isolated from PBMCs from the rebound time points were cultured at limiting dilution exactly as described for Q^2VOA. $CD4^+$ T cells were activated with T cell activation beads (Miltenyi) at a concentration of 0.5×10^6 beads per 10^6 $CD4^+$ T cells and 20 U/ml of IL-2. Rebound outgrowth was performed using PBMCS from the highest viral load sample (usually the repeat measurement ≥ 200 copies/ml). Viruses whose sequences matched the SGA *env* sequences, and therefore were identical to those present in plasma, as opposed to potentially reactivated PBMC-derived latent reservoir viruses, were selected to test for neutralization.

Viral Sensitivity Testing

Supernatants from p24-positive bulk PBMC cultures, rebound PBMC outgrowth cultures and Q^2VOA wells were tested for sensitivity to 3BNC117 and 10–1074 by TZM-bl neutralization assay as previously described (Sarzotti-Kelsoe M *et al.* J Immunol Methods 409, 131–146 (2014)).

Sequencing

HIV-1 RNA extraction and single genome amplification were performed as previously described (Salazar-Gonzalez JF *et al.* J Virol 82, 3952– 3970 (2008)). In brief, HIV-1 RNA was extracted from plasma samples or Q^2VOA-derived virus supernatants using the MinElute Virus Spin kit (Qiagen) followed by first strand cDNA synthesis using SuperScript III reverse transcriptase (Invitrogen). cDNA synthesis for plasma-derived HIV-1 RNA was performed using the antisense primer envB3out Fidelity Platinum Taq (Invitrogen) and run at 94°C for 2 min; 35 cycles of 94°C for 15 s, 55°C for 30 s, and 68°C for 4 min; and 68°C for 15 min. Second round PCR was performed with 1 µl of first PCR product as template and High Fidelity Platinum Taq at 94 °C for 2 min; 45 cycles of 94°C for 15 s, 55°C for 30 s, and 68°C for 4 min; and 68°C for 15 min. cDNA synthesis for Q^2VOA-derived HIV-1 RNA was performed using the antisense primer R3B6R

Study Outcomes

Combination bNab Infusion is Well Tolerated

To evaluate the effects of the combination of 3BNC117 and 10–1074 on maintaining HIV-1 suppression during ATI, a Phase 1b clinical trial was conducted (**FIG. 5A**) (Mendoza *et al.*, Nature. 2018 September; 561(7724): 479–484). HIV-1-infected individuals on ART were pre-screened for 3BNC117 and 10–1074 sensitivity of bulk outgrowth culture-derived viruses using the TZM-bl neutralization assay. Consistent with previous results, 64% and 71% of the outgrowth viruses were sensitive to 3BNC117 and 10–1074, respectively, and 48% were sensitive to both (IC50 $\leq$ 2µg/ml).

Study eligibility criteria included ongoing ART for at least 24 months with plasma HIV-1 RNA levels of < 50 copies/ml for at least 18 months (with one blip < 500 copies/ml allowed) and < 20 copies/ml at screening, as well as $CD4^+$ T cell counts > 500 cells/µl. Enrolled participants received 3 infusions of 30 mg/kg each of 3BNC117 + 10–1074 at 3-week intervals beginning 2 days before treatment interruption (**FIG. 5A**). Individuals whose regimens contained non-nucleoside reverse transcriptase inhibitors were switched to an integrase inhibitor-based regimen 4 weeks before discontinuing ART (**FIG. 6A**). Viral load and $CD4^+$ T cell counts were monitored every 1–2 weeks. ART was reinitiated, and antibody infusions were

discontinued if viremia of > 200 copies/ml was confirmed. Time of viral rebound was defined as the first of two consecutive viral loads > 200 copies/ml. Fifteen individuals were enrolled, but four of them showed viral loads of > 20 copies/ml two weeks before or at the time of the first bNAb infusion, and they were excluded from efficacy analyses.

Antibody infusions were generally safe and well-tolerated with no reported serious adverse events or antibody-related adverse events except for mild fatigue in two participants. The mean $CD4^+$ T cell count was 685 and 559 cells/μl at the time of first antibody infusion and at rebound, respectively (**FIG. 6B**). Re-initiation of ART after viral rebound resulted in resuppression of viremia. It was concluded that combination therapy with 3BNC117 + 10–1074 is generally safe and well-tolerated.

Combination bNAbs Maintain Viral Suppression

For the 11 individuals who had complete viral suppression (HIV-1 RNA < 20 copies/ml) during the screening period and at day 0, combination antibody therapy was associated with maintenance of viral suppression for 5 to > 30 weeks (**FIGs. 5B** and **5C**) (Mendoza *et al.*, Nature. 2018 September; 561(7724): 479–484). The median time to rebound was 21 weeks compared to 2.3 weeks for historical controls who participated in non-interventional ATI studies and 6–10 weeks for monotherapy with 3BNC117 (**FIG. 5C**). Altogether, 9 of the 11 participants maintained viral suppression for over 15 weeks, while 2 rebounded at weeks 5 and 7 (**FIGs. 5B** and **5C**).

Quantitative and qualitative viral outgrowth assays (Q^2VOA) were used to retrospectively analyze the replication-competent latent viral reservoir in all individuals. Phylogenetic analysis showed that the trial participants were infected with epidemiologically distinct clade B viruses. Q^2VOA analysis revealed that the pre-infusion latent reservoir in the two individuals rebounding early, 9245 and 9251, harbored 10–1074- or 3BNC117-resistant viruses, respectively (**FIG. 7**). Therefore, these two individuals were effectively subjected to antibody monotherapy because there was pre-existing resistance in the reservoir to one of the two bNAbs. Consistent with this idea, the delay in rebound in these two participants was within the range anticipated for antibody monotherapy (**FIG. 5C**). In addition, all four of the individuals excluded from the analysis due to incomplete viral suppression showed pre-existing resistance or viruses that were not fully neutralized by one or both of the antibodies and these individuals rebounded before week 12.

To examine the viruses arising in the early rebounding individuals, single genome analysis (SGA) on rebound plasma was performed. Pseudoviruses constructed from plasma SGA were tested for bNAb sensitivity in the TZM-b1 assay. In addition to the pre-existing

sequences associated with resistance in the 10–1074 target site (N332T + S334N, **FIG. 7A**), rebound viruses in 9245 also carried an extended V5 loop and potential *N*-linked glycosylation sites that could interfere with 3BNC117 binding. Conversely, genetic features associated with resistance to 3BNC117 were found in the pre-infusion reservoir of 9251 and were accompanied by mutations in the 10–1074 target site in the rebounding viruses (S334N, **FIG. 7A**). For both individuals, resistance of rebound viruses to both antibodies was confirmed by the TZM-bl neutralization assay (**FIGs. 7B** and **7C**). Thus, bulk outgrowth cultures used for screening failed to detect pre-existing resistance in the reservoir of 2 of the 11 individuals studied. This result is not surprising given that bulk cultures are dominated by a limited number of rapidly growing viral species which may not be representative of the diversity in the latent reservoir.

Similarly, participant 91C33, who failed to respond to antibody infusions, had preexisting circulating viruses that were resistant to both antibodies (Bar-On *et al.*, Nature Medicine 24:1701–1707 (2018)). These viruses carried mutations in 3BNC117 contact sites (N280S and A281H) and in 10-1074 contact sites (N332T and S334N). Two individuals, 91C35 and 9341, responded to antibody therapy with a decrease in viremia of -1.58 and -1.32 $\log_{10}$ copies per ml but HIV-1 RNA levels returned to baseline within 3 and 4 weeks, respectively. 91C35 was found to have pre-infusion circulating viruses with reduced sensitivity to 3BNC117, and carried a CD4 contact residue mutation (A281T) that was associated with viral escape from 3BNC11720. Pre-infusion viruses derived from bulk CD4+ T cell outgrowth cultures of 9341 showed a 10-1074 IC80 that was 1.3 $\log_{10}$ higher than the geometric mean IC80 of all other enrolled viremic individuals. In both of these cases, rebounding viruses were resistant to both antibodies and carried mutations resulting in the loss of the potential *N*-linked glycosylation site at position 332 that is critical for 10-1074 binding. In addition, rebound viruses from 91C35 and 9341 contained G471E and N276D mutations, respectively, that are associated with increased resistance to 3BNC117. These mutations were not found in the pre-infusion circulating viruses described above or in the additional 113 pre-infusion *env* sequences that were analyzed from these two participants. Thus, 91C35 and 9341 were infected with viruses with reduced sensitivity to one of the two antibodies and resemble individuals that received antibody monotherapy, both in the magnitude of the drop in viremia and time required to return to baseline viremia. It was concluded that the bulk outgrowth cultures used for initial screening failed to detect partial or complete preexisting resistance against one or both of the antibodies in three of the seven individuals studied.

The four remaining individuals showed no detectable pre-existing resistant viruses in circulation and experienced significantly suppressed viremia until day 94 after the first

antibody infusion with an average maximum drop in viral load of -2.05 log_{10} copies per ml (Bar-On *et al.*, Nature Medicine 24:1701–1707 (2018)). The individual in this group with the highest initial viral load (97,800 copies per ml; patient 9343) was the first to rebound at eight weeks. The two individuals with the lowest initial viral loads, 91C22 and 9342 (750 and 2,550 copies per ml, respectively), demonstrated suppression to near or below the limit of detection for 12 and 16 weeks, respectively. Finally, viremia in participant 91C34 was reduced for a period of 12 weeks, however it never dropped below 810 copies per ml. Despite the persistent viremia, no resistance against both antibodies developed in this individual for as long as bNAb serum levels were above 10 μg/ml. In three of the four initially sensitive individuals, rebound viremia was associated with the appearance of viruses that were resistant to 10-1074, but these individuals remained sensitive to 3BNC117. This is consistent with the relatively shorter half-life of 3BNC117, which means that participants were effectively exposed to 10-1074 monotherapy at the end of the observation period. In accordance with the increased resistance to 10-1074, rebound viruses carried mutations in 10-1074 contact sites. By contrast, there was no accumulation of de novo mutations in 3BNC117 contact sites. 91C22, the participant with the lowest initial viral load, only returned to baseline viremia after both antibodies were below the limit of detection, and rebound viruses remained sensitive to both antibodies. Overall none of the four participants that were initially sensitive to the two antibodies developed de novo resistance to 3BNC117 over a cumulative observation period of over one year (56 weeks), despite the residual viremia observed in three of these participants and frequent recombination events between circulating viruses.

The median time to rebound in the 7 individuals that had no detectable resistant viruses in the pre-infusion latent reservoir, and rebounded during the study period, was also 21 weeks and different from 6–10 weeks for monotherapy with 3BNC117 (**FIG. 5C**) (Mendoza *et al.*, Nature. 2018 September; 561(7724): 479–484). In these participants, viral suppression was maintained for 15 to 26 weeks after ART discontinuation. The two remaining participants (9254 and 9255) completed the study follow-up at 30 weeks without experiencing rebound. Notably, viral rebound never occurred when the concentration of both administered antibodies was above 10 μg/ml. The average 3BNC117 serum concentration (determined by TZM-bl assay) at the time of rebound in sensitive individuals that rebounded during study follow-up was 1.9 μg/ml (**FIG. 5B**). In contrast, the average serum concentration of 10–1074 at rebound was 14.8 μg/ml (**FIG. 5B**). The difference in the antibody concentrations at the time of rebound is consistent with the longer half-life of 10–1074 which resulted in a period of 10–1074

monotherapy (**FIG. 5B**). Finally, these 9 individuals showed little or no preexisting neutralizing antibodies against a diagnostic panel of viruses before bNAb infusion.

Rebound and Latent Viruses

To examine the relationship between rebound viruses and the circulating latent reservoir, *env* sequences obtained from plasma rebound viruses were compared by SGA with sequences obtained by Q^2VOA from both pre-infusion and week 12 samples. In addition, sensitivity of rebound outgrowth viruses and/or pseudoviruses to 3BNC117 and 10–1074 was measured by the TZM-bl neutralization assay (**FIGs. 7B** and **7C**). A total of 154 viral *env* sequences obtained by plasma SGA were analyzed and compared to 408 sequences obtained from the latent reservoir by Q^2VOA. Although rebound and reservoir viruses clustered together for each individual, no identical sequences between the two compartments in any of the individuals studied were found (**FIGs. 8** and **9A**). The difference could be accounted for by distinct requirements for HIV-1 reactivation *in vitro* and *in vivo*, compartmentalization of reservoir viruses, HIV-1 mutation during the course of the trial, and/or by viral recombination in some individuals. Whether or not bNAb therapy influences selection for recombination events remains to be determined.

Similar to 3BNC117 monotherapy, the vast majority of rebounding viruses clustered within low diversity lineages consistent with expansion of 1–2 recrudescent viruses (**FIG. 8**). In contrast, rebound viruses are consistently polyclonal during ATI in the absence of antibody therapy. Thus, the antibodies restrict the outgrowth of latent viruses *in vivo*.

The emerging viruses in 6 of the 7 individuals that rebounded when the mean 3BNC117 and 10–1074 concentrations were 1.9 and 14.8 μg/ml, respectively, carried resistance-associated mutations in the 10–1074 target site (**FIGs. 5B** and **8A**). Consistent with the sequence data, these rebound viruses were generally resistant to 10–1074 by the TZM-bl neutralization assay but remained sensitive to 3BNC117 (**FIGs. 7B** and **7C**). The level of sensitivity to 3BNC117 in these emerging viruses was similar to that found in the reservoir viruses in each of the individuals (**FIG. 7B**). One individual, 9244, showed rebound viruses that remained sensitive to both antibodies in TZM-bl neutralization assays. Rebound occurred when 3BNC117 and 10–1074 concentrations in serum of this individual were undetectable and 11.6 μg/ml, respectively (**FIG. 5B**). The sensitivity of the plasma rebound viruses was similar to that of latent pre-infusion and week 12 viruses obtained in viral outgrowth cultures (**FIGs. 7B** and **7C**). Therefore, this individual did not develop resistance to either of the antibodies despite prolonged exposure to both. In conclusion, none of the 9 individuals with pre-infusion

reservoirs containing viruses that were sensitive to both antibodies developed double resistance during the observation period.

The Latent Reservoir

To determine whether there were changes in the circulating reservoir during the observation period, the results of Q^2VOA assays performed at entry and 12 weeks after the start of ATI for 8 of the 9 individuals that remained suppressed for at least 12 weeks were compared (**FIG. 9**). Similar to previous reports, 63% of all viruses obtained by Q^2VOA belonged to expanded clones. Comparison of the *env* sequences of the viruses that emerged in outgrowth cultures revealed that 60% of the sequences could be found at both time points. However, there were numerous examples of clones that appeared or disappeared between the time points, and some of these changes were significant. To determine the number of infectious units per million (IUPM, http://silicianolab.johnshopkins.edu/), $6.0 \times 10^7 - 6.2 \times 10^8$ $CD4^+$ T cells were assayed by Q^2VOA for each time point for each individual (**FIG. 9B**). The difference between the 2 time points was never greater than 6.5-fold for any individual, and the 2 time points were not statistically different ($P = 0.078$). Moreover, time to rebound was not directly correlated with IUPM. Additional time points would be required to calculate the half-life of the reservoir in individuals receiving immunotherapy.

Discussion

First generation anti-HIV-1 bNAbs were generally ineffective in suppressing viremia in animal models and humans leading to the conclusion that this approach should not be pursued. bNAb monotherapy with 3BNC117 or VRC01 was not enough to maintain control during ATI in HIV-1-infected humans. In contrast, the combination of 3BNC117 and 10–1074 was sufficient to maintain viral suppression in sensitive individuals when the concentration of both antibodies remains above a certain level in serum, for example, above 10 μg/ml. Rebound occurred when 3BNC117 levels dropped below 10 μg/ml effectively leading to 10–1074 monotherapy, from which nearly all individuals rapidly escaped by mutations in the 10–1074 contact site. The observation that 9 individuals infected with distinct viruses were unable to develop double resistant viruses over a median 21 week period suggests that viral replication was severely limited by this antibody combination.

In human studies, monotherapy with 3BNC117 is associated with enhanced humoral immunity and accelerated clearance of HIV-1-infected cells. In addition, when administered early to SHIVAD8-infected macaques, combined 3BNC117 + 10–1074 immunotherapy induced host $CD8^+$ T cell responses that contributed to the control of viremia in nearly 50% of the animals. However, virus-specific $CD8^+$ T cells responsible for control of viremia in these

macaques were not detected in the circulation, and their contribution to viral suppression was only documented after $CD8^+$ T cell depletion. In most controller macaques, complete viral suppression was only established after rebound viremia that followed antibody clearance.

Two individuals in this study remained suppressed for over 30 weeks after ATI, 9254 and 9255. Neither one had detectable levels of ART in the blood or carried the B*27 and B*57 HLA alleles that are most frequently associated with elite control (Walker BD & Yu XG. Nat Rev Immunol 13, 487–498 (2013)). The first, 9254, reports starting ART within 4–5 months after probable exposure to the virus with an initial viral load of 860,000 copies/ml. Despite relatively early therapy and excellent virological control for 21 years on therapy, this individual had an IUPM of 0.68 by Q^2VOA at the 12-week time point. The second individual, 9255, showed several viral blips that were spontaneously controlled beginning 15 weeks after ATI when antibody levels were waning. This individual was infected for at least 7 months before starting ART with an initial viral load of 85,800 copies/ml and had an IUPM of 1.4 at the 12-week time point. A small fraction of individuals on ART show spontaneous prolonged virologic control after ART was discontinued, and this number appears to increase when ART treatment was initiated during the acute phase of infection.

A significant fraction of the circulating latent reservoir is composed of expanded clones of infected T cells. These T cell clones appear to be dynamic in that the specific contribution of individual clones of circulating latently infected $CD4^+$ T cells to the reservoir of individuals receiving ART fluctuates over time. Individuals that maintain viral suppression by antibody therapy appear to show similar fluctuations in reservoir clones that do not appear to be associated with antibody sensitivity. Whether the apparent differences observed in the reservoir during immunotherapy lead to changes in the reservoir half-life cannot be determined from the available data and will require reservoir assessments in additional individuals at multiple time points over an extended observation period.

Individuals harboring viruses sensitive to 3BNC117 and 10–1074 maintained viral suppression during ATI for a median of almost 4 months after the final antibody administration. In macaques, the therapeutic efficacy of anti-HIV-1 antibodies is directly related to their half-life, which can be extended by mutations that enhance Fc domain interactions with the neonatal Fc receptor. The mutations can increase the half-life of antibodies in humans by 2-4-fold. The data suggest that a single administration of combinations of bNAbs with extended half-lives could maintain suppression for 6–12 months in individuals harboring sensitive viruses.

Table 1: Residue numbering of anti-HIV antibody 10-1074 variant MS-194

MS-194_LC				MS-194_HC			
Residue	Linear #	Mat. Linear #	ASN #	Residue	Linear #	Mat. Linear #	ASN #
M	1		Ldr:-19	M	1		Ldr:-19
G	2		Ldr:-18	G	2		Ldr:-18
W	3		Ldr:-17	W	3		Ldr:-17
S	4		Ldr:-16	S	4		Ldr:-16
C	5		Ldr:-15	C	5		Ldr:-15
I	6		Ldr:-14	I	6		Ldr:-14
I	7		Ldr:-13	I	7		Ldr:-13
L	8		Ldr:-12	L	8		Ldr:-12
F	9		Ldr:-11	F	9		Ldr:-11
L	10		Ldr:-10	L	10		Ldr:-10
V	11		Ldr:-9	V	11		Ldr:-9
A	12		Ldr:-8	A	12		Ldr:-8
T	13		Ldr:-7	T	13		Ldr:-7
A	14		Ldr:-6	A	14		Ldr:-6
T	15		Ldr:-5	T	15		Ldr:-5
G	16		Ldr:-4	G	16		Ldr:-4
V	17		Ldr:-3	V	17		Ldr:-3
H	18		Ldr:-2	H	18		Ldr:-2
S	19		Ldr:-1	S	19		Ldr:-1
S	20	1	LmdV:1	Q	20	1	HV:1
Y	21	2	LmdV:2	V	21	2	HV:2
V	22	3	LmdV:3	Q	22	3	HV:3
-	22.1	3.1	LmdV:4	L	23	4	HV:4
-	22.2	3.2	LmdV:5	Q	24	5	HV:5
-	22.3	3.3	LmdV:6	E	25	6	HV:6
R	23	4	LmdV:7	S	26	7	HV:7
-	23.1	4.1	LmdV:8	-	26.1	7.1	HV:8
P	24	5	LmdV:9	G	27	8	HV:9
-	24.1	5.1	LmdV:10	P	28	9	HV:10
L	25	6	LmdV:11	G	29	10	HV:11
S	26	7	LmdV:12	L	30	11	HV:12
V	27	8	LmdV:13	V	31	12	HV:13
A	28	9	LmdV:14	K	32	13	HV:14
L	29	10	LmdV:15	P	33	14	HV:15
G	30	11	LmdV:16	S	34	15	HV:16
E	31	12	LmdV:17	E	35	16	HV:17

T	32	13	LmdV:18	T	36	17	HV:18
A	33	14	LmdV:19	L	37	18	HV:19
R	34	15	LmdV:20	S	38	19	HV:20
I	35	16	LmdV:21	V	39	20	HV:21
S	36	17	LmdV:22	T	40	21	HV:22
C	37	18	LmdV:23	C	41	22	HV:23
G	38	19	LmdV:24	S	42	23	HV:24
R	39	20	LmdV:25	V	43	24	HV:25
Q	40	21	LmdV:26	S	44	25	HV:26
-	40.1	21.1	LmdV:27	G	45	26	HV:27
-	40.2	21.2	LmdV:28	-	45.1	26.1	HV:28
-	40.3	21.3	LmdV:29	D	46	27	HV:29
A	41	22	LmdV:30	S	47	28	HV:30
L	42	23	LmdV:31	M	48	29	HV:31
G	43	24	LmdV:32	N	49	30	HV:32
S	44	25	LmdV:33	N	50	31	HV:33
-	44.1	25.1	LmdV:34	-	50.1	31.1	HV:34
-	44.2	25.2	LmdV:35	-	50.2	31.2	HV:35
-	44.3	25.3	LmdV:36	-	50.3	31.3	HV:36
-	44.4	25.4	LmdV:37	-	50.4	31.4	HV:37
-	44.5	25.5	LmdV:38	-	50.5	31.5	HV:38
R	45	26	LmdV:39	Y	51	32	HV:39
A	46	27	LmdV:40	Y	52	33	HV:40
V	47	28	LmdV:41	W	53	34	HV:41
Q	48	29	LmdV:42	T	54	35	HV:42
W	49	30	LmdV:43	W	55	36	HV:43
Y	50	31	LmdV:44	I	56	37	HV:44
Q	51	32	LmdV:45	R	57	38	HV:45
H	52	33	LmdV:46	Q	58	39	HV:46
R	53	34	LmdV:47	S	59	40	HV:47
P	54	35	LmdV:48	P	60	41	HV:48
G	55	36	LmdV:49	G	61	42	HV:49
Q	56	37	LmdV:50	K	62	43	HV:50
A	57	38	LmdV:51	G	63	44	HV:51
P	58	39	LmdV:52	L	64	45	HV:52
I	59	40	LmdV:53	E	65	46	HV:53
L	60	41	LmdV:54	W	66	47	HV:54
L	61	42	LmdV:55	I	67	48	HV:55
I	62	43	LmdV:56	G	68	49	HV:56
Y	63	44	LmdV:57	Y	69	50	HV:57
N	64	45	LmdV:58	I	70	51	HV:58
-	64.1	45.1	LmdV:59	S	71	52	HV:59

-	64.2	45.2	LmdV:60	D	72	53	HV:60
-	64.3	45.3	LmdV:61	-	72.1	53.1	HV:61
-	64.4	45.4	LmdV:62	-	72.2	53.2	HV:62
-	64.5	45.5	LmdV:63	-	72.3	53.3	HV:63
-	64.6	45.6	LmdV:64	-	72.4	53.4	HV:64
-	64.7	45.7	LmdV:65	R	73	54	HV:65
-	64.8	45.8	LmdV:66	E	74	55	HV:66
N	65	46	LmdV:67	S	75	56	HV:67
Q	66	47	LmdV:68	A	76	57	HV:68
D	67	48	LmdV:69	T	77	58	HV:69
R	68	49	LmdV:70	Y	78	59	HV:70
P	69	50	LmdV:71	N	79	60	HV:71
S	70	51	LmdV:72	P	80	61	HV:72
G	71	52	LmdV:73	S	81	62	HV:73
I	72	53	LmdV:74	L	82	63	HV:74
P	73	54	LmdV:75	N	83	64	HV:75
E	74	55	LmdV:76	S	84	65	HV:76
R	75	56	LmdV:77	R	85	66	HV:77
F	76	57	LmdV:78	V	86	67	HV:78
S	77	58	LmdV:79	V	87	68	HV:79
G	78	59	LmdV:80	I	88	69	HV:80
T	79	60	LmdV:81	S	89	70	HV:81
P	80	61	LmdV:81.1	R	90	71	HV:82
D	81	62	LmdV:81.2	D	91	72	HV:83
I	82	63	LmdV:81.3	T	92	73	HV:84
N	83	64	LmdV:82	S	93	74	HV:85
F	84	65	LmdV:83	K	94	75	HV:86
G	85	66	LmdV:84	N	95	76	HV:87
-	85.1	66.1	LmdV:85	Q	96	77	HV:88
-	85.2	66.2	LmdV:86	L	97	78	HV:89
T	86	67	LmdV:87	S	98	79	HV:90
R	87	68	LmdV:88	L	99	80	HV:91
A	88	69	LmdV:89	K	100	81	HV:92
T	89	70	LmdV:90	L	101	82	HV:93
L	90	71	LmdV:91	N	102	83	HV:94
T	91	72	LmdV:92	S	103	84	HV:95
I	92	73	LmdV:93	V	104	85	HV:96
S	93	74	LmdV:94	T	105	86	HV:97
G	94	75	LmdV:95	P	106	87	HV:98
V	95	76	LmdV:96	A	107	88	HV:99
E	96	77	LmdV:97	D	108	89	HV:100
A	97	78	LmdV:98	T	109	90	HV:101

G	98	79	LmdV:99	A	110	91	HV:102
D	99	80	LmdV:100	V	111	92	HV:103
E	100	81	LmdV:101	Y	112	93	HV:104
A	101	82	LmdV:102	Y	113	94	HV:105
D	102	83	LmdV:103	C	114	95	HV:106
Y	103	84	LmdV:104	A	115	96	HV:107
Y	104	85	LmdV:105	T	116	97	HV:108
C	105	86	LmdV:106	A	117	98	HV:109
H	106	87	LmdV:107	R	118	99	HV:110
M	107	88	LmdV:108	R	119	100	HV:111
W	108	89	LmdV:109	G	120	101	HV:112
D	109	90	LmdV:110	Q	121	102	HV:113
S	110	91	LmdV:111	R	122	103	HV:114
R	111	92	LmdV:112	I	123	104	HV:115
-	111.1	92.1	LmdV:113	Y	124	105	HV:116
-	111.2	92.2	LmdV:114	G	125	106	HV:117
-	111.3	92.3	LmdV:115	V	126	107	HV:118
-	111.4	92.4	LmdV:116	V	127	108	HV:119
-	111.5	92.5	LmdV:117	-	127.1	108.1	HV:120
-	111.6	92.6	LmdV:118	-	127.2	108.2	HV:121
-	111.7	92.7	LmdV:119	-	127.3	108.3	HV:122
-	111.8	92.8	LmdV:120	-	127.4	108.4	HV:123
-	111.9	92.9	LmdV:121	-	127.5	108.5	HV:124
-	111.10	92.10	LmdV:122	-	127.6	108.6	HV:125
-	111.11	92.11	LmdV:123	S	128	109	HV:126
-	111.12	92.12	LmdV:124	F	129	110	HV:127
-	111.13	92.13	LmdV:125	G	130	111	HV:128
-	111.14	92.14	LmdV:126	E	131	112	HV:129
-	111.15	92.15	LmdV:127	F	132	113	HV:130
-	111.16	92.16	LmdV:128	F	133	114	HV:131
-	111.17	92.17	LmdV:129	Y	134	115	HV:132
-	111.18	92.18	LmdV:130	Y	135	116	HV:133
-	111.19	92.19	LmdV:131	Y	136	117	HV:134
-	111.20	92.20	LmdV:132	S	137	118	HV:135
S	112	93	LmdV:133	M	138	119	HV:136
G	113	94	LmdV:134	D	139	120	HV:137
F	114	95	LmdV:135	V	140	121	HV:138
S	115	96	LmdV:136	W	141	122	HV:139
W	116	97	LmdV:137	G	142	123	HV:140
S	117	98	LmdV:138	K	143	124	HV:141
F	118	99	LmdV:139	G	144	125	HV:142
G	119	100	LmdV:140	T	145	126	HV:143

G	120	101	LmdV:141	T	146	127	HV:144
A	121	102	LmdV:142	V	147	128	HV:145
T	122	103	LmdV:143	T	148	129	HV:146
R	123	104	LmdV:144	V	149	130	HV:147
L	124	105	LmdV:145	S	150	131	HV:148
T	125	106	LmdV:146	S	151	132	HV:149
V	126	107	LmdV:147	-	151.1	132.1	HCnst-Ig:1
L	127	108	LmdV:148	-	151.2	132.2	HCnst-Ig:2
G	128	109	LmdV:149	A	152	133	HCnst-Ig:3
Q	129	110	LmdCnst-Ig:1	S	153	134	HCnst-Ig:4
P	130	111	LmdCnst-Ig:2	T	154	135	HCnst-Ig:5
K	131	112	LmdCnst-Ig:3	K	155	136	HCnst-Ig:6
A	132	113	LmdCnst-Ig:4	G	156	137	HCnst-Ig:7
A	133	114	LmdCnst-Ig:5	P	157	138	HCnst-Ig:8
P	134	115	LmdCnst-Ig:6	S	158	139	HCnst-Ig:9
S	135	116	LmdCnst-Ig:7	V	159	140	HCnst-Ig:10
V	136	117	LmdCnst-Ig:8	F	160	141	HCnst-Ig:11
T	137	118	LmdCnst-Ig:9	P	161	142	HCnst-Ig:12
L	138	119	LmdCnst-Ig:10	L	162	143	HCnst-Ig:13
F	139	120	LmdCnst-Ig:11	A	163	144	HCnst-Ig:14
P	140	121	LmdCnst-Ig:12	P	164	145	HCnst-Ig:15
P	141	122	LmdCnst-Ig:13	-	164.1	145.1	HCnst-Ig:16
S	142	123	LmdCnst-Ig:14	S	165	146	HCnst-Ig:17
S	143	124	LmdCnst-Ig:15	-	165.1	146.1	HCnst-Ig:18
E	144	125	LmdCnst-Ig:16	S	166	147	HCnst-Ig:19
-	144.1	125.1	LmdCnst-Ig:17	K	167	148	HCnst-Ig:20
-	144.2	125.2	LmdCnst-Ig:18	S	168	149	HCnst-Ig:21
E	145	126	LmdCnst-Ig:19	T	169	150	HCnst-Ig:22
L	146	127	LmdCnst-Ig:20	S	170	151	HCnst-Ig:23
-	146.1	127.1	LmdCnst-Ig:21	G	171	152	HCnst-Ig:24
-	146.2	127.2	LmdCnst-Ig:22	G	172	153	HCnst-Ig:25
Q	147	128	LmdCnst-Ig:23	T	173	154	HCnst-Ig:26
A	148	129	LmdCnst-Ig:24	A	174	155	HCnst-Ig:27
N	149	130	LmdCnst-Ig:25	A	175	156	HCnst-Ig:28
K	150	131	LmdCnst-Ig:26	L	176	157	HCnst-Ig:29
A	151	132	LmdCnst-Ig:27	G	177	158	HCnst-Ig:30
T	152	133	LmdCnst-Ig:28	C	178	159	HCnst-Ig:31
L	153	134	LmdCnst-Ig:29	L	179	160	HCnst-Ig:32
V	154	135	LmdCnst-Ig:30	V	180	161	HCnst-Ig:33
C	155	136	LmdCnst-Ig:31	K	181	162	HCnst-Ig:34
L	156	137	LmdCnst-Ig:32	D	182	163	HCnst-Ig:35
I	157	138	LmdCnst-Ig:33	Y	183	164	HCnst-Ig:36

S	158	139	LmdCnst-Ig:34	F	184	165	HCnst-Ig:37
D	159	140	LmdCnst-Ig:35	P	185	166	HCnst-Ig:38
F	160	141	LmdCnst-Ig:36	-	185.1	166.1	HCnst-Ig:39
Y	161	142	LmdCnst-Ig:37	-	185.2	166.2	HCnst-Ig:40
P	162	143	LmdCnst-Ig:38	E	186	167	HCnst-Ig:41
-	162.1	143.1	LmdCnst-Ig:39	P	187	168	HCnst-Ig:42
-	162.2	143.2	LmdCnst-Ig:40	V	188	169	HCnst-Ig:43
G	163	144	LmdCnst-Ig:41	T	189	170	HCnst-Ig:44
A	164	145	LmdCnst-Ig:42	V	190	171	HCnst-Ig:45
V	165	146	LmdCnst-Ig:43	S	191	172	HCnst-Ig:46
T	166	147	LmdCnst-Ig:44	W	192	173	HCnst-Ig:47
V	167	148	LmdCnst-Ig:45	-	192.1	173.1	HCnst-Ig:48
A	168	149	LmdCnst-Ig:46	N	193	174	HCnst-Ig:49
W	169	150	LmdCnst-Ig:47	S	194	175	HCnst-Ig:50
-	169.1	150.1	LmdCnst-Ig:48	G	195	176	HCnst-Ig:51
K	170	151	LmdCnst-Ig:49	A	196	177	HCnst-Ig:52
A	171	152	LmdCnst-Ig:50	L	197	178	HCnst-Ig:53
D	172	153	LmdCnst-Ig:51	T	198	179	HCnst-Ig:54
S	173	154	LmdCnst-Ig:52	S	199	180	HCnst-Ig:55
S	174	155	LmdCnst-Ig:53	G	200	181	HCnst-Ig:56
P	175	156	LmdCnst-Ig:54	V	201	182	HCnst-Ig:57
V	176	157	LmdCnst-Ig:55	H	202	183	HCnst-Ig:58
K	177	158	LmdCnst-Ig:56	T	203	184	HCnst-Ig:59
A	178	159	LmdCnst-Ig:57	-	203.1	184.1	HCnst-Ig:60
G	179	160	LmdCnst-Ig:58	-	203.2	184.2	HCnst-Ig:61
V	180	161	LmdCnst-Ig:59	F	204	185	HCnst-Ig:62
E	181	162	LmdCnst-Ig:60	P	205	186	HCnst-Ig:63
T	182	163	LmdCnst-Ig:61	A	206	187	HCnst-Ig:64
T	183	164	LmdCnst-Ig:62	V	207	188	HCnst-Ig:65
T	184	165	LmdCnst-Ig:63	L	208	189	HCnst-Ig:66
P	185	166	LmdCnst-Ig:64	Q	209	190	HCnst-Ig:67
S	186	167	LmdCnst-Ig:65	-	209.1	190.1	HCnst-Ig:68
K	187	168	LmdCnst-Ig:66	-	209.2	190.2	HCnst-Ig:69
Q	188	169	LmdCnst-Ig:67	-	209.3	190.3	HCnst-Ig:70
-	188.1	169.1	LmdCnst-Ig:68	-	209.4	190.4	HCnst-Ig:71
-	188.2	169.2	LmdCnst-Ig:69	-	209.5	190.5	HCnst-Ig:72
-	188.3	169.3	LmdCnst-Ig:70	S	210	191	HCnst-Ig:73
-	188.4	169.4	LmdCnst-Ig:71	S	211	192	HCnst-Ig:74
-	188.5	169.5	LmdCnst-Ig:72	G	212	193	HCnst-Ig:75
S	189	170	LmdCnst-Ig:73	L	213	194	HCnst-Ig:76
N	190	171	LmdCnst-Ig:74	Y	214	195	HCnst-Ig:77
N	191	172	LmdCnst-Ig:75	S	215	196	HCnst-Ig:78

K	192	173	LmdCnst-Ig:76	L	216	197	HCnst-Ig:79
Y	193	174	LmdCnst-Ig:77	S	217	198	HCnst-Ig:80
A	194	175	LmdCnst-Ig:78	S	218	199	HCnst-Ig:81
A	195	176	LmdCnst-Ig:79	V	219	200	HCnst-Ig:82
S	196	177	LmdCnst-Ig:80	V	220	201	HCnst-Ig:83
S	197	178	LmdCnst-Ig:81	T	221	202	HCnst-Ig:84
Y	198	179	LmdCnst-Ig:82	V	222	203	HCnst-Ig:85
L	199	180	LmdCnst-Ig:83	P	223	204	HCnst-Ig:86
S	200	181	LmdCnst-Ig:84	S	224	205	HCnst-Ig:87
L	201	182	LmdCnst-Ig:85	S	225	206	HCnst-Ig:88
T	202	183	LmdCnst-Ig:86	S	226	207	HCnst-Ig:89
P	203	184	LmdCnst-Ig:87	L	227	208	HCnst-Ig:90
E	204	185	LmdCnst-Ig:88	-	227.1	208.1	HCnst-Ig:91
Q	205	186	LmdCnst-Ig:89	G	228	209	HCnst-Ig:92
W	206	187	LmdCnst-Ig:90	T	229	210	HCnst-Ig:93
-	206.1	187.1	LmdCnst-Ig:91	Q	230	211	HCnst-Ig:94
K	207	188	LmdCnst-Ig:92	T	231	212	HCnst-Ig:95
S	208	189	LmdCnst-Ig:93	-	231.1	212.1	HCnst-Ig:96
H	209	190	LmdCnst-Ig:94	-	231.2	212.2	HCnst-Ig:97
R	210	191	LmdCnst-Ig:95	-	231.3	212.3	HCnst-Ig:98
S	211	192	LmdCnst-Ig:96	Y	232	213	HCnst-Ig:99
-	211.1	192.1	LmdCnst-Ig:97	I	233	214	HCnst-Ig:100
-	211.2	192.2	LmdCnst-Ig:98	C	234	215	HCnst-Ig:101
Y	212	193	LmdCnst-Ig:99	N	235	216	HCnst-Ig:102
S	213	194	LmdCnst-Ig:100	V	236	217	HCnst-Ig:103
C	214	195	LmdCnst-Ig:101	N	237	218	HCnst-Ig:104
Q	215	196	LmdCnst-Ig:102	H	238	219	HCnst-Ig:105
V	216	197	LmdCnst-Ig:103	K	239	220	HCnst-Ig:106
T	217	198	LmdCnst-Ig:104	P	240	221	HCnst-Ig:107
H	218	199	LmdCnst-Ig:105	S	241	222	HCnst-Ig:108
E	219	200	LmdCnst-Ig:106	N	242	223	HCnst-Ig:109
G	220	201	LmdCnst-Ig:107	-	242.1	223.1	HCnst-Ig:110
S	221	202	LmdCnst-Ig:108	-	242.2	223.2	HCnst-Ig:111
T	222	203	LmdCnst-Ig:109	T	243	224	HCnst-Ig:112
-	222.1	203.1	LmdCnst-Ig:110	K	244	225	HCnst-Ig:113
-	222.2	203.2	LmdCnst-Ig:111	V	245	226	HCnst-Ig:114
V	223	204	LmdCnst-Ig:112	D	246	227	HCnst-Ig:115
E	224	205	LmdCnst-Ig:113	K	247	228	HCnst-Ig:116
K	225	206	LmdCnst-Ig:114	-	247.1	228.1	HCnst-Ig:117
T	226	207	LmdCnst-Ig:115	K	248	229	HCnst-Ig:118
V	227	208	LmdCnst-Ig:116	V	249	230	HCnst-Ig:119
-	227.1	208.1	LmdCnst-Ig:117	-	249.1	230.1	HCnst-Ig:120

A	228	209	LmdCnst-Ig:118	-	249.2	230.2	HCnst-Ig:121
P	229	210	LmdCnst-Ig:119	-	249.3	230.3	HCnst-Ig:122
T	230	211	LmdCnst-Ig:120	-	249.4	230.4	HCnst-Ig:123
E	231	212	LmdCnst-Ig:121	-	249.5	230.5	Hinge:1
C	232	213	LmdCnst-Ig:122	-	249.6	230.6	Hinge:2
S	233	214	LmdCnst-Ig:123	-	249.7	230.7	Hinge:3
				-	249.8	230.8	Hinge:4
				-	249.9	230.9	Hinge:5
				-	249.10	230.10	Hinge:6
				-	249.11	230.11	Hinge:7
				-	249.12	230.12	Hinge:8
				-	249.13	230.13	Hinge:9
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				-	249.50	230.50	Hinge:46
				-	249.51	230.51	Hinge:47
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				-	249.98	230.98	Hinge:94
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				P	251	232	Hinge:97
				K	252	233	Hinge:98
				S	253	234	Hinge:99
				-	253.1	234.1	Hinge:100
				-	253.2	234.2	Hinge:101
				-	253.3	234.3	Hinge:102
				-	253.4	234.4	Hinge:103
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				-	253.6	234.6	Hinge:105
				-	253.7	234.7	Hinge:106
				C	254	235	Hinge:107
				D	255	236	Hinge:108
				K	256	237	Hinge:109
				T	257	238	Hinge:110
				H	258	239	Hinge:111
				T	259	240	Hinge:112
				C	260	241	Hinge:113
				P	261	242	Hinge:114
				P	262	243	Hinge:115
				C	263	244	Hinge:116
				P	264	245	Hinge:117
				A	265	246	Hinge:118
				P	266	247	Hinge:119
				E	267	248	Hinge:120
				L	268	249	Hinge:121
				L	269	250	Hinge:122

				G	270	251	Hinge:123
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				-	270.2	251.2	Fc-N:2
				-	270.3	251.3	Fc-N:3
				-	270.4	251.4	Fc-N:4
				G	271	252	Fc-N:5
				P	272	253	Fc-N:6
				S	273	254	Fc-N:7
				V	274	255	Fc-N:8
				F	275	256	Fc-N:9
				L	276	257	Fc-N:10
				F	277	258	Fc-N:11
				P	278	259	Fc-N:12
				P	279	260	Fc-N:13
				-	279.1	260.1	Fc-N:14
				K	280	261	Fc-N:15
				P	281	262	Fc-N:16
				K	282	263	Fc-N:17
				-	282.1	263.1	Fc-N:18
				D	283	264	Fc-N:19
				T	284	265	Fc-N:20
				L	285	266	Fc-N:21
				M	286	267	Fc-N:22
				I	287	268	Fc-N:23
				S	288	269	Fc-N:24
				R	289	270	Fc-N:25
				T	290	271	Fc-N:26
				P	291	272	Fc-N:27
				E	292	273	Fc-N:28
				V	293	274	Fc-N:29
				T	294	275	Fc-N:30
				C	295	276	Fc-N:31
				V	296	277	Fc-N:32
				V	297	278	Fc-N:33
				V	298	279	Fc-N:34
				D	299	280	Fc-N:35
				V	300	281	Fc-N:36
				S	301	282	Fc-N:37
				H	302	283	Fc-N:38
				E	303	284	Fc-N:39
				D	304	285	Fc-N:40
				P	305	286	Fc-N:41

				E	306	287	Fc-N:42
				V	307	288	Fc-N:43
				K	308	289	Fc-N:44
				F	309	290	Fc-N:45
				N	310	291	Fc-N:46
				W	311	292	Fc-N:47
				-	311.1	292.1	Fc-N:48
				Y	312	293	Fc-N:49
				V	313	294	Fc-N:50
				D	314	295	Fc-N:51
				G	315	296	Fc-N:52
				V	316	297	Fc-N:53
				E	317	298	Fc-N:54
				-	317.1	298.1	Fc-N:55
				-	317.2	298.2	Fc-N:56
				V	318	299	Fc-N:57
				H	319	300	Fc-N:58
				N	320	301	Fc-N:59
				A	321	302	Fc-N:60
				K	322	303	Fc-N:61
				T	323	304	Fc-N:62
				K	324	305	Fc-N:63
				P	325	306	Fc-N:64
				R	326	307	Fc-N:65
				E	327	308	Fc-N:66
				E	328	309	Fc-N:67
				Q	329	310	Fc-N:68
				-	329.1	310.1	Fc-N:69
				-	329.2	310.2	Fc-N:70
				-	329.3	310.3	Fc-N:71
				-	329.4	310.4	Fc-N:72
				Y	330	311	Fc-N:73
				N	331	312	Fc-N:74
				S	332	313	Fc-N:75
				T	333	314	Fc-N:76
				Y	334	315	Fc-N:77
				R	335	316	Fc-N:78
				V	336	317	Fc-N:79
				V	337	318	Fc-N:80
				S	338	319	Fc-N:81
				V	339	320	Fc-N:82
				L	340	321	Fc-N:83

				T	341	322	Fc-N:84
				V	342	323	Fc-N:85
				L	343	324	Fc-N:86
				H	344	325	Fc-N:87
				Q	345	326	Fc-N:88
				D	346	327	Fc-N:89
				W	347	328	Fc-N:90
				-	347.1	328.1	Fc-N:91
				L	348	329	Fc-N:92
				N	349	330	Fc-N:93
				G	350	331	Fc-N:94
				K	351	332	Fc-N:95
				E	352	333	Fc-N:96
				-	352.1	333.1	Fc-N:97
				-	352.2	333.2	Fc-N:98
				Y	353	334	Fc-N:99
				K	354	335	Fc-N:100
				C	355	336	Fc-N:101
				K	356	337	Fc-N:102
				V	357	338	Fc-N:103
				S	358	339	Fc-N:104
				N	359	340	Fc-N:105
				K	360	341	Fc-N:106
				A	361	342	Fc-N:107
				L	362	343	Fc-N:108
				P	363	344	Fc-N:109
				-	363.1	344.1	Fc-N:110
				-	363.2	344.2	Fc-N:111
				A	364	345	Fc-N:112
				P	365	346	Fc-N:113
				I	366	347	Fc-N:114
				E	367	348	Fc-N:115
				K	368	349	Fc-N:116
				T	369	350	Fc-N:117
				I	370	351	Fc-N:118
				S	371	352	Fc-N:119
				K	372	353	Fc-N:120
				A	373	354	Fc-N:121
				K	374	355	Fc-N:122
				G	375	356	Fc-N:123
				-	375.1	356.1	Fc-C:1
				Q	376	357	Fc-C:2

				P	377	358	Fc-C:3
				R	378	359	Fc-C:4
				E	379	360	Fc-C:5
				P	380	361	Fc-C:6
				Q	381	362	Fc-C:7
				V	382	363	Fc-C:8
				Y	383	364	Fc-C:9
				T	384	365	Fc-C:10
				L	385	366	Fc-C:11
				P	386	367	Fc-C:12
				P	387	368	Fc-C:13
				-	387.1	368.1	Fc-C:14
				S	388	369	Fc-C:15
				R	389	370	Fc-C:16
				D	390	371	Fc-C:17
				-	390.1	371.1	Fc-C:18
				E	391	372	Fc-C:19
				L	392	373	Fc-C:20
				-	392.1	373.1	Fc-C:21
				-	392.2	373.2	Fc-C:22
				T	393	374	Fc-C:23
				K	394	375	Fc-C:24
				N	395	376	Fc-C:25
				Q	396	377	Fc-C:26
				V	397	378	Fc-C:27
				S	398	379	Fc-C:28
				L	399	380	Fc-C:29
				T	400	381	Fc-C:30
				C	401	382	Fc-C:31
				L	402	383	Fc-C:32
				V	403	384	Fc-C:33
				K	404	385	Fc-C:34
				G	405	386	Fc-C:35
				F	406	387	Fc-C:36
				Y	407	388	Fc-C:37
				P	408	389	Fc-C:38
				-	408.1	389.1	Fc-C:39
				-	408.2	389.2	Fc-C:40
				S	409	390	Fc-C:41
				D	410	391	Fc-C:42
				I	411	392	Fc-C:43
				A	412	393	Fc-C:44

				V	413	394	Fc-C:45
				E	414	395	Fc-C:46
				W	415	396	Fc-C:47
				-	415.1	396.1	Fc-C:48
				E	416	397	Fc-C:49
				S	417	398	Fc-C:50
				N	418	399	Fc-C:51
				G	419	400	Fc-C:52
				Q	420	401	Fc-C:53
				P	421	402	Fc-C:54
				-	421.1	402.1	Fc-C:55
				-	421.2	402.2	Fc-C:56
				E	422	403	Fc-C:57
				N	423	404	Fc-C:58
				N	424	405	Fc-C:59
				Y	425	406	Fc-C:60
				K	426	407	Fc-C:61
				T	427	408	Fc-C:62
				T	428	409	Fc-C:63
				P	429	410	Fc-C:64
				P	430	411	Fc-C:65
				V	431	412	Fc-C:66
				L	432	413	Fc-C:67
				D	433	414	Fc-C:68
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				-	433.3	414.3	Fc-C:71
				-	433.4	414.4	Fc-C:72
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				G	436	417	Fc-C:75
				S	437	418	Fc-C:76
				F	438	419	Fc-C:77
				F	439	420	Fc-C:78
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				K	443	424	Fc-C:82
				L	444	425	Fc-C:83
				T	445	426	Fc-C:84
				V	446	427	Fc-C:85
				D	447	428	Fc-C:86

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				S	449	430	Fc-C:88
				R	450	431	Fc-C:89
				W	451	432	Fc-C:90
				-	451.1	432.1	Fc-C:91
				Q	452	433	Fc-C:92
				Q	453	434	Fc-C:93
				G	454	435	Fc-C:94
				N	455	436	Fc-C:95
				V	456	437	Fc-C:96
				-	456.1	437.1	Fc-C:97
				-	456.2	437.2	Fc-C:98
				F	457	438	Fc-C:99
				S	458	439	Fc-C:100
				C	459	440	Fc-C:101
				S	460	441	Fc-C:102
				V	461	442	Fc-C:103
				L	462	443	Fc-C:104
				H	463	444	Fc-C:105
				E	464	445	Fc-C:106
				A	465	446	Fc-C:107
				L	466	447	Fc-C:108
				H	467	448	Fc-C:109
				-	467.1	448.1	Fc-C:110
				-	467.2	448.2	Fc-C:111
				S	468	449	Fc-C:112
				H	469	450	Fc-C:113
				Y	470	451	Fc-C:114
				T	471	452	Fc-C:115
				-	471.1	452.1	Fc-C:116
				Q	472	453	Fc-C:117
				K	473	454	Fc-C:118
				S	474	455	Fc-C:119
				L	475	456	Fc-C:120
				S	476	457	Fc-C:121
				L	477	458	Fc-C:122
				S	478	459	Fc-C:123
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				G	480	461	HCnst-Po:2
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				-	481.1	462.1	HCnst-Po:4
				-	481.2	462.2	HCnst-Po:5

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				-	481.107	462.107	HCnst-Po:110
				-	481.108	462.108	HCnst-Po:111
				-	481.109	462.109	HCnst-Po:112
				-	481.110	462.110	HCnst-Po:113
				-	481.111	462.111	HCnst-Po:114
				-	481.112	462.112	HCnst-Po:115
				-	481.113	462.113	HCnst-Po:116
				-	481.114	462.114	HCnst-Po:117
				-	481.115	462.115	HCnst-Po:118
				-	481.116	462.116	HCnst-Po:119
				-	481.117	462.117	HCnst-Po:120
				-	481.118	462.118	HCnst-Po:121
				-	481.119	462.119	HCnst-Po:122
				-	481.120	462.120	HCnst-Po:123

Table 2: Amino acid sequences of light chain variable regions (hightlighted in bold) of the 10-1074 antibody variants

SEQ ID NO.	SEQUENCE	OTHER INFORMATION
SEQ ID NO: 1	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-193_LC
SEQ ID NO: 2	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-194_LC
SEQ ID NO: 3	MGWSCIILFLVATATGVHSSPVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIYN** **NQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLTV LGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-203_LC
SEQ ID NO: 4	MGWSCIILFLVATATGVHSSYVPPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIYN** **NQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLTV LGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-204_LC

SEQ ID NO: 5	MGWSCIILFLVATATGVHSSYVRSLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-205_LC
SEQ ID NO: 6	MGWSCIILFLVATATGVHSSYVRPLSVALGQTARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-206_LC
SEQ ID NO: 7	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQQRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-207_LC
SEQ ID NO: 8	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTNDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-208_LC
SEQ ID NO: 9	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDSNFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-209_LC

SEQ ID NO: 10	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDIGFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-210_LC
SEQ ID NO: 11	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTTATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-211_LC
SEQ ID NO: 12	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWESRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-212_LC
SEQ ID NO: 13	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGGTRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-213_LC
SEQ ID NO: 14	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-214_LC

SEQ ID NO: 15	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-215_LC
SEQ ID NO: 16	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-216_LC
SEQ ID NO: 17	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-217_LC
SEQ ID NO: 18	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-218_LC
SEQ ID NO: 19	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-219_LC

SEQ ID NO: 20	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-220_LC
SEQ ID NO: 21	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-224_LC
SEQ ID NO: 22	MGWSCIILFLVATATGVHSSPVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIYN** **NQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLTV LGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-200_LC
SEQ ID NO: 23	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-201_LC
SEQ ID NO: 24	MGWSCIILFLVATATGVHSSPVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIYN** **NQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLTV LGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-202_LC

SEQ ID NO: 25	MGWSCIILFLVATATGVHSSPVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIYN** **NQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLTV LGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-225_LC
SEQ ID NO: 26	MGWSCIILFLVATATGVHSSPVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIYN** **NQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLTV LGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-226_LC
SEQ ID NO: 27	MGWSCIILFLVATATGVHSSPVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIYN** **NQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLTV LGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-227_LC
SEQ ID NO: 28	MGWSCIILFLVATATGVHSSPVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIYN** **NQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLTV LGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-228_LC
SEQ ID NO: 29	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-229_LC

SEQ ID NO: 30	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-230_LC
SEQ ID NO: 31	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-231_LC
SEQ ID NO: 32	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-232_LC
SEQ ID NO: 33	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-233_LC
SEQ ID NO: 34	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-234_LC

SEQ ID NO: 35	MGWSCIILFLVATATGVHSSPVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIYN** **NQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLTV LGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-235_LC
SEQ ID NO: 36	MGWSCIILFLVATATGVHSSPVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIYN** **NQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLTV LGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-236_LC
SEQ ID NO: 37	MGWSCIILFLVATATGVHSSPVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIYN** **NQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLTV LGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-237_LC
SEQ ID NO: 38	MGWSCIILFLVATATGVHSSPVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIYN** **NQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLTV LGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-238_LC
SEQ ID NO: 39	MGWSCIILFLVATATGVHSSPVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIYN** **NQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLTV LGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-239_LC

SEQ ID NO: 40	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-240_LC
SEQ ID NO: 41	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-241_LC
SEQ ID NO: 42	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-242_LC
SEQ ID NO: 43	MGWSCIILFLVATATGVHSSPVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIYN** **NQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLTV LGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-243_LC
SEQ ID NO: 44	MGWSCIILFLVATATGVHSSPVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIYN** **NQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLTV LGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-244_LC

SEQ ID NO: 45	MGWSCIILFLVATATGVHSSPVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIYN** **NQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLTV LGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-245_LC
SEQ ID NO: 46	MGWSCIILFLVATATGVHSSYVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIY** **NNQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLT VLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSN NKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-246_LC
SEQ ID NO: 47	MGWSCIILFLVATATGVHSSPVRPLSVALGETARISC**GRQALGSRAVQWYQHRPGQAPILLIYN** **NQDRPSGIPERFSGTPDINFGTRATLTISGVEAGDEADYYCHMWDSRSGFSWS**FGGATRLTV LGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNN KYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	MS-247_LC

Table 3: Amino acid sequences of heavy chain variable regions (highlighted in bold) of the 10-1074 antibody variants

SEQ ID NO.	SEQUENCE	OTHER INFORMATION
SEQ ID NO: 48	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISRDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALHNHYTQKSLSLSPGK	MS-193_HC
SEQ ID NO: 49	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISRDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-194_HC
SEQ ID NO: 50	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISRDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF**	MS-203_HC

	GEFFYYYSMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS	
	GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP	
	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE	
	EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT	
	KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC	
	SVLHEALHSHYTQKSLSLSPGK	
SEQ ID	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE**	MS-204_HC
NO: 51	**WIGYISDRESATYNPSLNSRVVISRDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF**	
	GEFFYYYSMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS	
	GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP	
	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE	
	EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT	
	KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC	
	SVLHEALHSHYTQKSLSLSPGK	
SEQ ID	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE**	MS-205_HC
NO: 52	**WIGYISDRESATYNPSLNSRVVISRDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF**	
	GEFFYYYSMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS	
	GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP	
	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE	
	EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT	

	KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	
SEQ ID NO: 53	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISRDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-206_HC
SEQ ID NO: 54	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISRDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-207_HC
SEQ ID NO: 55	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISRDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS	MS-208_HC

	GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-209_HC
SEQ ID NO: 56	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISRDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-210_HC
SEQ ID NO: 57	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISRDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	

SEQ ID NO: 58	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISRDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-211_HC
SEQ ID NO: 59	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISRDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-212_HC
SEQ ID NO: 60	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISRDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE	MS-213_HC

	EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	
SEQ ID NO: 61	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGGSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISRDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-214_HC
SEQ ID NO: 62	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQPPGKGLE** **WIGYISDRESATYNPSLNSRVVISRDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-215_HC
SEQ ID NO: 63	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVTISRDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF**	MS-216_HC

	GEFFYYYSMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS	
	GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP	
	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE	
	EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT	
	KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC	
	SVLHEALHSHYTQKSLSLSPGK	
SEQ ID NO: 64	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE**	MS-217_HC
	WIGYISDRESATYNPSLNSRVVISVDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF	
	GEFFYYYSMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS	
	GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP	
	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE	
	EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT	
	KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC	
	SVLHEALHSHYTQKSLSLSPGK	
SEQ ID NO: 65	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE**	MS-218_HC
	WIGYISDRESATYNPSLNSRVVISRDTSKNQFSLKLNSVTPADTAVYYCATARRGQRIYGVVSF	
	GEFFYYYSMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS	
	GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP	
	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE	
	EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT	

	KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	
SEQ ID NO: 66	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISRDTSKNQLSLKLNSVTPADTAVYYCARARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-219_HC
SEQ ID NO: 67	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISRDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-220_HC
SEQ ID NO: 68	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLQSRVVISRDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF**	MS-224_HC

	GEFFYYYSMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS	
	GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP	
	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE	
	EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT	
	KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC	
	SVLHEALHSHYTQKSLSLSPGK	
SEQ ID	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE**	MS-200_HC
NO: 69	**WIGYISDRESATYNPSLNSRVVISVDTSKNQLSLKLNSVTPADTAVYYCARRRGQRIYGVVSF**	
	GEFFYYYSMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS	
	GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP	
	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE	
	EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT	
	KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC	
	SVLHEALHSHYTQKSLSLSPGK	
SEQ ID	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE**	MS-201_HC
NO: 70	**WIGYISDRESATYNPSLNSRVTISRDTSKNQFSLKLNSVTPADTAVYYCARRRGQRIYGVVSF**	
	GEFFYYYSMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS	
	GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP	
	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE	
	EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT	

	KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	
SEQ ID NO: 71	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVTISRDTSKNQFSLKLNSVTPADTAVYYCARARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-202_HC
SEQ ID NO: 72	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVTISRDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-225_HC
SEQ ID NO: 73	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISVDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS	MS-226_HC

	GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-227_HC
SEQ ID NO: 74	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISRDTSKNQFSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	
		MS-228_HC
SEQ ID NO: 75	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISRDTSKNQLSLKLNSVTPADTAVYYCARARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	

SEQ ID NO: 76	MS-229_HC
MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE**	
WIGYISDRESATYNPSLNSRVTISVDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF	
GEFFYYYSMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS	
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP	
PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE	
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT	
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC	
SVLHEALHSHYTQKSLSLSPGK	
SEQ ID NO: 77	MS-230_HC
MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE**	
WIGYISDRESATYNPSLNSRVTISRDTSKNQFSLKLNSVTPADTAVYYCATARRGQRIYGVVSF	
GEFFYYYSMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS	
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP	
PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE	
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT	
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC	
SVLHEALHSHYTQKSLSLSPGK	
SEQ ID NO: 78	MS-231_HC
MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE**	
WIGYISDRESATYNPSLNSRVTISRDTSKNQLSLKLNSVTPADTAVYYCARARRGQRIYGVVSF	
GEFFYYYSMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS	
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP	
PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE	

	EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	
SEQ ID NO: 79	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISVDTSKNQFSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-232_HC
SEQ ID NO: 80	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISVDTSKNQLSLKLNSVTPADTAVYYCARARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-233_HC

SEQ ID NO: 81	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISRDTSKNQFSLKLNSVTPADTAVYYCARARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-234_HC
SEQ ID NO: 82	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVTISVDTSKNQLSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-235_HC
SEQ ID NO: 83	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVTISRDTSKNQFSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE	MS-236_HC

	EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	
SEQ ID NO: 84	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVTISRDTSKNQLSLKLNSVTPADTAVYYCARARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-237_HC
SEQ ID NO: 85	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISVDTSKNQFSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-238_HC
SEQ ID NO: 86	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISRDTSKNQFSLKLNSVTPADTAVYYCARARRGQRIYGVVSF**	MS-239_HC

	GEFFYYYSMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS	
	GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP	
	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE	
	EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT	
	KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC	
	SVLHEALHSHYTQKSLSLSPGK	
SEQ ID NO: 87	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE**	MS-240_HC
	WIGYISDRESATYNPSLNSRVTISVDTSKNQFSLKLNSVTPADTAVYYCATARRGQRIYGVVSF	
	GEFFYYYSMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS	
	GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP	
	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE	
	EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT	
	KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC	
	SVLHEALHSHYTQKSLSLSPGK	
SEQ ID NO: 88	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE**	MS-241_HC
	WIGYISDRESATYNPSLNSRVTISVDTSKNQLSLKLNSVTPADTAVYYCARARRGQRIYGVVSF	
	GEFFYYYSMDVWGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS	
	GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP	
	PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE	
	EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT	

	KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	
SEQ ID NO: 89	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISVDTSKNQFSLKLNSVTPADTAVYYCARARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-242_HC
SEQ ID NO: 90	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVTISVDTSKNQFSLKLNSVTPADTAVYYCATARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-243_HC
SEQ ID NO: 91	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVTISVDTSKNQLSLKLNSVTPADTAVYYCARARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS	MS-244_HC

	GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-245_HC
SEQ ID NO: 92	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVVISVDTSKNQFSLKLNSVTPADTAVYYCARARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-246_HC
SEQ ID NO: 93	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVTISVDTSKNQFSLKLNSVTPADTAVYYCARARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT	

	KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	
SEQ ID NO: 94	MGWSCIILFLVATATGVHSQVQLQESGPGLVKPSETLSVTCSVSGDSM**NNYYWTWIRQSPGKGLE** **WIGYISDRESATYNPSLNSRVTISVDTSKNQFSLKLNSVTPADTAVYYCARARRGQRIYGVVSF** **GEFFYYYSMDV**WGKGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCP PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVLHEALHSHYTQKSLSLSPGK	MS-247_HC

Table 4: Amino acid sequences of CDR regions of the 10-1074 antibody variants

SEQ ID NO.	SEQUENCE	OTHER INFORMATION
SEQ ID NO: 95	GRQALGSRAVQ	MS-193_LC CDR1
SEQ ID NO: 96	NNQDRPS	MS-193_LC CDR2
SEQ ID NO: 97	HMWDSRSGFSWS	MS-193_LC CDR3
SEQ ID NO: 98	NNYYWT	MS-193_HC CDR1
SEQ ID NO: 99	YISDRESATYNPSLNS	MS-193_HC CDR2
SEQ ID NO: 100	ARRGQRIYGVVSFGEFFYYYSMDV	MS-193_HC CDR3
SEQ ID NO: 101	GRQALGSRAVQ	MS-194_LC CDR1
SEQ ID NO: 102	NNQDRPS	MS-194_LC CDR2
SEQ ID NO: 103	HMWDSRSGFSWS	MS-194_LC CDR3
SEQ ID NO: 104	NNYYWT	MS-194_HC CDR1
SEQ ID NO: 105	YISDRESATYNPSLNS	MS-194_HC CDR2
SEQ ID NO: 106	ARRGQRIYGVVSFGEFFYYYSMDV	MS-194_HC CDR3
SEQ ID NO: 107	GRQALGSRAVQ	MS-203_LC CDR1
SEQ ID NO: 108	NNQDRPS	MS-203_LC CDR2
SEQ ID NO: 109	HMWDSRSGFSWS	MS-203_LC CDR3
SEQ ID NO: 110	NNYYWT	MS-203_HC CDR1
SEQ ID NO: 111	YISDRESATYNPSLNS	MS-203_HC CDR2
SEQ ID NO: 112	ARRGQRIYGVVSFGEFFYYYSMDV	MS-203_HC CDR3
SEQ ID NO: 113	GRQALGSRAVQ	MS-204_LC CDR1
SEQ ID NO: 114	NNQDRPS	MS-204_LC CDR2
SEQ ID NO: 115	HMWDSRSGFSWS	MS-204_LC CDR3
SEQ ID NO: 116	NNYYWT	MS-204_HC CDR1
SEQ ID NO: 117	YISDRESATYNPSLNS	MS-204_HC CDR2
SEQ ID NO: 118	ARRGQRIYGVVSFGEFFYYYSMDV	MS-204_HC CDR3
SEQ ID NO: 119	GRQALGSRAVQ	MS-205_LC CDR1
SEQ ID NO: 120	NNQDRPS	MS-205_LC CDR2
SEQ ID NO: 121	HMWDSRSGFSWS	MS-205_LC CDR3
SEQ ID NO: 122	NNYYWT	MS-205_HC CDR1
SEQ ID NO: 123	YISDRESATYNPSLNS	MS-205_HC CDR2
SEQ ID NO: 124	ARRGQRIYGVVSFGEFFYYYSMDV	MS-205_HC CDR3

SEQ ID NO: 125	GRQALGSRAVQ	MS-206_LC CDR1
SEQ ID NO: 126	NNQDRPS	MS-206_LC CDR2
SEQ ID NO: 127	HMWDSRSGFSWS	MS-206_LC CDR3
SEQ ID NO: 128	NNYYWT	MS-206_HC CDR1
SEQ ID NO: 129	YISDRESATYNPSLNS	MS-206_HC CDR2
SEQ ID NO: 130	ARRGQRIYGVVSFGEFFYYYSMDV	MS-206_HC CDR3
SEQ ID NO: 131	GRQALGSRAVQ	MS-207_LC CDR1
SEQ ID NO: 132	NNQDRPS	MS-207_LC CDR2
SEQ ID NO: 133	HMWDSRSGFSWS	MS-207_LC CDR3
SEQ ID NO: 134	NNYYWT	MS-207_HC CDR1
SEQ ID NO: 135	YISDRESATYNPSLNS	MS-207_HC CDR2
SEQ ID NO: 136	ARRGQRIYGVVSFGEFFYYYSMDV	MS-207_HC CDR3
SEQ ID NO: 137	GRQALGSRAVQ	MS-208_LC CDR1
SEQ ID NO: 138	NNQDRPS	MS-208_LC CDR2
SEQ ID NO: 139	HMWDSRSGFSWS	MS-208_LC CDR3
SEQ ID NO: 140	NNYYWT	MS-208_HC CDR1
SEQ ID NO: 141	YISDRESATYNPSLNS	MS-208_HC CDR2
SEQ ID NO: 142	ARRGQRIYGVVSFGEFFYYYSMDV	MS-208_HC CDR3
SEQ ID NO: 143	GRQALGSRAVQ	MS-209_LC CDR1
SEQ ID NO: 144	NNQDRPS	MS-209_LC CDR2
SEQ ID NO: 145	HMWDSRSGFSWS	MS-209_LC CDR3
SEQ ID NO: 146	NNYYWT	MS-209_HC CDR1
SEQ ID NO: 147	YISDRESATYNPSLNS	MS-209_HC CDR2
SEQ ID NO: 148	ARRGQRIYGVVSFGEFFYYYSMDV	MS-209_HC CDR3
SEQ ID NO: 149	GRQALGSRAVQ	MS-210_LC CDR1
SEQ ID NO: 150	NNQDRPS	MS-210_LC CDR2
SEQ ID NO: 151	HMWDSRSGFSWS	MS-210_LC CDR3
SEQ ID NO: 152	NNYYWT	MS-210_HC CDR1
SEQ ID NO: 153	YISDRESATYNPSLNS	MS-210_HC CDR2
SEQ ID NO: 154	ARRGQRIYGVVSFGEFFYYYSMDV	MS-210_HC CDR3
SEQ ID NO: 155	GRQALGSRAVQ	MS-211_LC CDR1
SEQ ID NO: 156	NNQDRPS	MS-211_LC CDR2

SEQ ID NO: 157	HMWDSRSGFSWS	MS-211_LC CDR3
SEQ ID NO: 158	NNYYWT	MS-211_HC CDR1
SEQ ID NO: 159	YISDRESATYNPSLNS	MS-211_HC CDR2
SEQ ID NO: 160	ARRGQRIYGVVSFGEFFYYYSMDV	MS-211_HC CDR3
SEQ ID NO: 161	GRQALGSRAVQ	MS-212_LC CDR1
SEQ ID NO: 162	NNQDRPS	MS-212_LC CDR2
SEQ ID NO: 163	HMWESRSGFSWS	MS-212_LC CDR3
SEQ ID NO: 164	NNYYWT	MS-212_HC CDR1
SEQ ID NO: 165	YISDRESATYNPSLNS	MS-212_HC CDR2
SEQ ID NO: 166	ARRGQRIYGVVSFGEFFYYYSMDV	MS-212_HC CDR3
SEQ ID NO: 167	GRQALGSRAVQ	MS-213_LC CDR1
SEQ ID NO: 168	NNQDRPS	MS-213_LC CDR2
SEQ ID NO: 169	HMWDSRSGFSWS	MS-213_LC CDR3
SEQ ID NO: 170	NNYYWT	MS-213_HC CDR1
SEQ ID NO: 171	YISDRESATYNPSLNS	MS-213_HC CDR2
SEQ ID NO: 172	ARRGQRIYGVVSFGEFFYYYSMDV	MS-213_HC CDR3
SEQ ID NO: 173	GRQALGSRAVQ	MS-214_LC CDR1
SEQ ID NO: 174	NNQDRPS	MS-214_LC CDR2
SEQ ID NO: 175	HMWDSRSGFSWS	MS-214_LC CDR3
SEQ ID NO: 176	NNYYWT	MS-214_HC CDR1
SEQ ID NO: 177	YISDRESATYNPSLNS	MS-214_HC CDR2
SEQ ID NO: 178	ARRGQRIYGVVSFGEFFYYYSMDV	MS-214_HC CDR3
SEQ ID NO: 179	GRQALGSRAVQ	MS-215_LC CDR1
SEQ ID NO: 180	NNQDRPS	MS-215_LC CDR2
SEQ ID NO: 181	HMWDSRSGFSWS	MS-215_LC CDR3
SEQ ID NO: 182	NNYYWT	MS-215_HC CDR1
SEQ ID NO: 183	YISDRESATYNPSLNS	MS-215_HC CDR2
SEQ ID NO: 184	ARRGQRIYGVVSFGEFFYYYSMDV	MS-215_HC CDR3
SEQ ID NO: 185	GRQALGSRAVQ	MS-216_LC CDR1
SEQ ID NO: 186	NNQDRPS	MS-216_LC CDR2
SEQ ID NO: 187	HMWDSRSGFSWS	MS-216_LC CDR3
SEQ ID NO: 188	NNYYWT	MS-216_HC CDR1

SEQ ID NO: 189	YISDRESATYNPSLNS	MS-216_HC CDR2
SEQ ID NO: 190	ARRGQRIYGVVSFGEFFYYYSMDV	MS-216_HC CDR3
SEQ ID NO: 191	GRQALGSRAVQ	MS-217_LC CDR1
SEQ ID NO: 192	NNQDRPS	MS-217_LC CDR2
SEQ ID NO: 193	HMWDSRSGFSWS	MS-217_LC CDR3
SEQ ID NO: 194	NNYYWT	MS-217_HC CDR1
SEQ ID NO: 195	YISDRESATYNPSLNS	MS-217_HC CDR2
SEQ ID NO: 196	ARRGQRIYGVVSFGEFFYYYSMDV	MS-217_HC CDR3
SEQ ID NO: 197	GRQALGSRAVQ	MS-218_LC CDR1
SEQ ID NO: 198	NNQDRPS	MS-218_LC CDR2
SEQ ID NO: 199	HMWDSRSGFSWS	MS-218_LC CDR3
SEQ ID NO: 200	NNYYWT	MS-218_HC CDR1
SEQ ID NO: 201	YISDRESATYNPSLNS	MS-218_HC CDR2
SEQ ID NO: 202	ARRGQRIYGVVSFGEFFYYYSMDV	MS-218_HC CDR3
SEQ ID NO: 203	GRQALGSRAVQ	MS-219_LC CDR1
SEQ ID NO: 204	NNQDRPS	MS-219_LC CDR2
SEQ ID NO: 205	HMWDSRSGFSWS	MS-219_LC CDR3
SEQ ID NO: 206	NNYYWT	MS-219_HC CDR1
SEQ ID NO: 207	YISDRESATYNPSLNS	MS-219_HC CDR2
SEQ ID NO: 208	ARRGQRIYGVVSFGEFFYYYSMDV	MS-219_HC CDR3
SEQ ID NO: 209	GRQALGSRAVQ	MS-220_LC CDR1
SEQ ID NO: 210	NNQDRPS	MS-220_LC CDR2
SEQ ID NO: 211	HMWDSRSGFSWS	MS-220_LC CDR3
SEQ ID NO: 212	NNYYWT	MS-220_HC CDR1
SEQ ID NO: 213	YISDRESATYNPSLNS	MS-220_HC CDR2
SEQ ID NO: 214	ARRGQRIYGVVSFGEFFYYYSMDV	MS-220_HC CDR3
SEQ ID NO: 215	GRQALGSRAVQ	MS-224_LC CDR1
SEQ ID NO: 216	NNQDRPS	MS-224_LC CDR2
SEQ ID NO: 217	HMWDSRSGFSWS	MS-224_LC CDR3
SEQ ID NO: 218	NNYYWT	MS-224_HC CDR1
SEQ ID NO: 219	YISDRESATYNPSLQS	MS-224_HC CDR2
SEQ ID NO: 220	ARRGQRIYGVVSFGEFFYYYSMDV	MS-224_HC CDR3

SEQ ID NO: 221	GRQALGSRAVQ	MS-200_LC CDR1
SEQ ID NO: 222	NNQDRPS	MS-200_LC CDR2
SEQ ID NO: 223	HMWDSRSGFSWS	MS-200_LC CDR3
SEQ ID NO: 224	NNYYWT	MS-200_HC CDR1
SEQ ID NO: 225	YISDRESATYNPSLNS	MS-200_HC CDR2
SEQ ID NO: 226	ARRGQRIYGVVSFGEFFYYYSMDV	MS-200_HC CDR3
SEQ ID NO: 227	GRQALGSRAVQ	MS-201_LC CDR1
SEQ ID NO: 228	NNQDRPS	MS-201_LC CDR2
SEQ ID NO: 229	HMWDSRSGFSWS	MS-201_LC CDR3
SEQ ID NO: 230	NNYYWT	MS-201_HC CDR1
SEQ ID NO: 231	YISDRESATYNPSLNS	MS-201_HC CDR2
SEQ ID NO: 232	ARRGQRIYGVVSFGEFFYYYSMDV	MS-201_HC CDR3
SEQ ID NO: 233	GRQALGSRAVQ	MS-202_LC CDR1
SEQ ID NO: 234	NNQDRPS	MS-202_LC CDR2
SEQ ID NO: 235	HMWDSRSGFSWS	MS-202_LC CDR3
SEQ ID NO: 236	NNYYWT	MS-202_HC CDR1
SEQ ID NO: 237	YISDRESATYNPSLNS	MS-202_HC CDR2
SEQ ID NO: 238	ARRGQRIYGVVSFGEFFYYYSMDV	MS-202_HC CDR3
SEQ ID NO: 239	GRQALGSRAVQ	MS-225_LC CDR1
SEQ ID NO: 240	NNQDRPS	MS-225_LC CDR2
SEQ ID NO: 241	HMWDSRSGFSWS	MS-225_LC CDR3
SEQ ID NO: 242	NNYYWT	MS-225_HC CDR1
SEQ ID NO: 243	YISDRESATYNPSLNS	MS-225_HC CDR2
SEQ ID NO: 244	ARRGQRIYGVVSFGEFFYYYSMDV	MS-225_HC CDR3
SEQ ID NO: 245	GRQALGSRAVQ	MS-226_LC CDR1
SEQ ID NO: 246	NNQDRPS	MS-226_LC CDR2
SEQ ID NO: 247	HMWDSRSGFSWS	MS-226_LC CDR3
SEQ ID NO: 248	NNYYWT	MS-226_HC CDR1
SEQ ID NO: 249	YISDRESATYNPSLNS	MS-226_HC CDR2
SEQ ID NO: 250	ARRGQRIYGVVSFGEFFYYYSMDV	MS-226_HC CDR3
SEQ ID NO: 251	GRQALGSRAVQ	MS-227_LC CDR1
SEQ ID NO: 252	NNQDRPS	MS-227_LC CDR2

SEQ ID NO: 253	HMWDSRSGFSWS	MS-227_LC CDR3
SEQ ID NO: 254	NNYYWT	MS-227_HC CDR1
SEQ ID NO: 255	YISDRESATYNPSLNS	MS-227_HC CDR2
SEQ ID NO: 256	ARRGQRIYGVVSFGEFFYYYSMDV	MS-227_HC CDR3
SEQ ID NO: 257	GRQALGSRAVQ	MS-228_LC CDR1
SEQ ID NO: 258	NNQDRPS	MS-228_LC CDR2
SEQ ID NO: 259	HMWDSRSGFSWS	MS-228_LC CDR3
SEQ ID NO: 260	NNYYWT	MS-228_HC CDR1
SEQ ID NO: 261	YISDRESATYNPSLNS	MS-228_HC CDR2
SEQ ID NO: 262	ARRGQRIYGVVSFGEFFYYYSMDV	MS-228_HC CDR3
SEQ ID NO: 263	GRQALGSRAVQ	MS-229_LC CDR1
SEQ ID NO: 264	NNQDRPS	MS-229_LC CDR2
SEQ ID NO: 265	HMWDSRSGFSWS	MS-229_LC CDR3
SEQ ID NO: 266	NNYYWT	MS-229_HC CDR1
SEQ ID NO: 267	YISDRESATYNPSLNS	MS-229_HC CDR2
SEQ ID NO: 268	ARRGQRIYGVVSFGEFFYYYSMDV	MS-229_HC CDR3
SEQ ID NO: 269	GRQALGSRAVQ	MS-230_LC CDR1
SEQ ID NO: 270	NNQDRPS	MS-230_LC CDR2
SEQ ID NO: 271	HMWDSRSGFSWS	MS-230_LC CDR3
SEQ ID NO: 272	NNYYWT	MS-230_HC CDR1
SEQ ID NO: 273	YISDRESATYNPSLNS	MS-230_HC CDR2
SEQ ID NO: 274	ARRGQRIYGVVSFGEFFYYYSMDV	MS-230_HC CDR3
SEQ ID NO: 275	GRQALGSRAVQ	MS-231_LC CDR1
SEQ ID NO: 276	NNQDRPS	MS-231_LC CDR2
SEQ ID NO: 277	HMWDSRSGFSWS	MS-231_LC CDR3
SEQ ID NO: 278	NNYYWT	MS-231_HC CDR1
SEQ ID NO: 279	YISDRESATYNPSLNS	MS-231_HC CDR2
SEQ ID NO: 280	ARRGQRIYGVVSFGEFFYYYSMDV	MS-231_HC CDR3
SEQ ID NO: 281	GRQALGSRAVQ	MS-232_LC CDR1
SEQ ID NO: 282	NNQDRPS	MS-232_LC CDR2
SEQ ID NO: 283	HMWDSRSGFSWS	MS-232_LC CDR3
SEQ ID NO: 284	NNYYWT	MS-232_HC CDR1

SEQ ID NO: 285	YISDRESATYNPSLNS	MS-232_HC CDR2
SEQ ID NO: 286	ARRGQRIYGVVSFGEFFYYYSMDV	MS-232_HC CDR3
SEQ ID NO: 287	GRQALGSRAVQ	MS-233_LC CDR1
SEQ ID NO: 288	NNQDRPS	MS-233_LC CDR2
SEQ ID NO: 289	HMWDSRSGFSWS	MS-233_LC CDR3
SEQ ID NO: 290	NNYYWT	MS-233_HC CDR1
SEQ ID NO: 291	YISDRESATYNPSLNS	MS-233_HC CDR2
SEQ ID NO: 292	ARRGQRIYGVVSFGEFFYYYSMDV	MS-233_HC CDR3
SEQ ID NO: 293	GRQALGSRAVQ	MS-234_LC CDR1
SEQ ID NO: 294	NNQDRPS	MS-234_LC CDR2
SEQ ID NO: 295	HMWDSRSGFSWS	MS-234_LC CDR3
SEQ ID NO: 296	NNYYWT	MS-234_HC CDR1
SEQ ID NO: 297	YISDRESATYNPSLNS	MS-234_HC CDR2
SEQ ID NO: 298	ARRGQRIYGVVSFGEFFYYYSMDV	MS-234_HC CDR3
SEQ ID NO: 299	GRQALGSRAVQ	MS-235_LC CDR1
SEQ ID NO: 300	NNQDRPS	MS-235_LC CDR2
SEQ ID NO: 301	HMWDSRSGFSWS	MS-235_LC CDR3
SEQ ID NO: 302	NNYYWT	MS-235_HC CDR1
SEQ ID NO: 303	YISDRESATYNPSLNS	MS-235_HC CDR2
SEQ ID NO: 304	ARRGQRIYGVVSFGEFFYYYSMDV	MS-235_HC CDR3
SEQ ID NO: 305	GRQALGSRAVQ	MS-236_LC CDR1
SEQ ID NO: 306	NNQDRPS	MS-236_LC CDR2
SEQ ID NO: 307	HMWDSRSGFSWS	MS-236_LC CDR3
SEQ ID NO: 308	NNYYWT	MS-236_HC CDR1
SEQ ID NO: 309	YISDRESATYNPSLNS	MS-236_HC CDR2
SEQ ID NO: 310	ARRGQRIYGVVSFGEFFYYYSMDV	MS-236_HC CDR3
SEQ ID NO: 311	GRQALGSRAVQ	MS-237_LC CDR1
SEQ ID NO: 312	NNQDRPS	MS-237_LC CDR2
SEQ ID NO: 313	HMWDSRSGFSWS	MS-237_LC CDR3
SEQ ID NO: 314	NNYYWT	MS-237_HC CDR1
SEQ ID NO: 315	YISDRESATYNPSLNS	MS-237_HC CDR2
SEQ ID NO: 316	ARRGQRIYGVVSFGEFFYYYSMDV	MS-237_HC CDR3

SEQ ID NO: 317	GRQALGSRAVQ	MS-238_LC CDR1
SEQ ID NO: 318	NNQDRPS	MS-238_LC CDR2
SEQ ID NO: 319	HMWDSRSGFSWS	MS-238_LC CDR3
SEQ ID NO: 320	NNYYWT	MS-238_HC CDR1
SEQ ID NO: 321	YISDRESATYNPSLNS	MS-238_HC CDR2
SEQ ID NO: 322	ARRGQRIYGVVSFGEFFYYYSMDV	MS-238_HC CDR3
SEQ ID NO: 323	GRQALGSRAVQ	MS-239_LC CDR1
SEQ ID NO: 324	NNQDRPS	MS-239_LC CDR2
SEQ ID NO: 325	HMWDSRSGFSWS	MS-239_LC CDR3
SEQ ID NO: 326	NNYYWT	MS-239_HC CDR1
SEQ ID NO: 327	YISDRESATYNPSLNS	MS-239_HC CDR2
SEQ ID NO: 328	ARRGQRIYGVVSFGEFFYYYSMDV	MS-239_HC CDR3
SEQ ID NO: 329	GRQALGSRAVQ	MS-240_LC CDR1
SEQ ID NO: 330	NNQDRPS	MS-240_LC CDR2
SEQ ID NO: 331	HMWDSRSGFSWS	MS-240_LC CDR3
SEQ ID NO: 332	NNYYWT	MS-240_HC CDR1
SEQ ID NO: 333	YISDRESATYNPSLNS	MS-240_HC CDR2
SEQ ID NO: 334	ARRGQRIYGVVSFGEFFYYYSMDV	MS-240_HC CDR3
SEQ ID NO: 335	GRQALGSRAVQ	MS-241_LC CDR1
SEQ ID NO: 336	NNQDRPS	MS-241_LC CDR2
SEQ ID NO: 337	HMWDSRSGFSWS	MS-241_LC CDR3
SEQ ID NO: 338	NNYYWT	MS-241_HC CDR1
SEQ ID NO: 339	YISDRESATYNPSLNS	MS-241_HC CDR2
SEQ ID NO: 340	ARRGQRIYGVVSFGEFFYYYSMDV	MS-241_HC CDR3
SEQ ID NO: 341	GRQALGSRAVQ	MS-242_LC CDR1
SEQ ID NO: 342	NNQDRPS	MS-242_LC CDR2
SEQ ID NO: 343	HMWDSRSGFSWS	MS-242_LC CDR3
SEQ ID NO: 344	NNYYWT	MS-242_HC CDR1
SEQ ID NO: 345	YISDRESATYNPSLNS	MS-242_HC CDR2
SEQ ID NO: 346	ARRGQRIYGVVSFGEFFYYYSMDV	MS-242_HC CDR3
SEQ ID NO: 347	GRQALGSRAVQ	MS-243_LC CDR1
SEQ ID NO: 348	NNQDRPS	MS-243_LC CDR2

SEQ ID NO: 349	HMWDSRSGFSWS	MS-243_LC CDR3
SEQ ID NO: 350	NNYYWT	MS-243_HC CDR1
SEQ ID NO: 351	YISDRESATYNPSLNS	MS-243_HC CDR2
SEQ ID NO: 352	ARRGQRIYGVVSFGEFFYYYSMDV	MS-243_HC CDR3
SEQ ID NO: 353	GRQALGSRAVQ	MS-244_LC CDR1
SEQ ID NO: 354	NNQDRPS	MS-244_LC CDR2
SEQ ID NO: 355	HMWDSRSGFSWS	MS-244_LC CDR3
SEQ ID NO: 356	NNYYWT	MS-244_HC CDR1
SEQ ID NO: 357	YISDRESATYNPSLNS	MS-244_HC CDR2
SEQ ID NO: 358	ARRGQRIYGVVSFGEFFYYYSMDV	MS-244_HC CDR3
SEQ ID NO: 359	GRQALGSRAVQ	MS-245_LC CDR1
SEQ ID NO: 360	NNQDRPS	MS-245_LC CDR2
SEQ ID NO: 361	HMWDSRSGFSWS	MS-245_LC CDR3
SEQ ID NO: 362	NNYYWT	MS-245_HC CDR1
SEQ ID NO: 363	YISDRESATYNPSLNS	MS-245_HC CDR2
SEQ ID NO: 364	ARRGQRIYGVVSFGEFFYYYSMDV	MS-245_HC CDR3
SEQ ID NO: 365	GRQALGSRAVQ	MS-246_LC CDR1
SEQ ID NO: 366	NNQDRPS	MS-246_LC CDR2
SEQ ID NO: 367	HMWDSRSGFSWS	MS-246_LC CDR3
SEQ ID NO: 368	NNYYWT	MS-246_HC CDR1
SEQ ID NO: 369	YISDRESATYNPSLNS	MS-246_HC CDR2
SEQ ID NO: 370	ARRGQRIYGVVSFGEFFYYYSMDV	MS-246_HC CDR3
SEQ ID NO: 371	GRQALGSRAVQ	MS-247_LC CDR1
SEQ ID NO: 372	NNQDRPS	MS-247_LC CDR2
SEQ ID NO: 373	HMWDSRSGFSWS	MS-247_LC CDR3
SEQ ID NO: 374	NNYYWT	MS-247_HC CDR1
SEQ ID NO: 375	YISDRESATYNPSLNS	MS-247_HC CDR2
SEQ ID NO: 376	ARRGQRIYGVVSFGEFFYYYSMDV	MS-247_HC CDR3

Table 5: Nucleic acid sequences of light chain variable regions of the 10-1074 antibody variants

SEQ ID NO.	SEQUENCE	OTHER INFORMATION
SEQ ID NO: 377	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-193_LC
SEQ ID NO: 378	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC	MS-194_LC

	GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-203_LC
SEQ ID NO: 379	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCCCT GTGCGCCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACCGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	
SEQ ID NO: 380	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCCACCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTTA	MS-204_LC

	TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT	
	TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT	
	GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC	
	GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT	
	CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT	
	GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA	
	CAAAGCAACAACAAGTACGGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC	
	CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC	
	CCTACAGAATGTTCA	
SEQ ID NO: 381	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT	MS-205_LC
	GTGCGCAGCCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT	
	TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA	
	TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT	
	TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT	
	GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC	
	GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT	
	CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT	
	GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA	
	CAAAGCAACAACAAGTACGGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC	
	CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC	
	CCTACAGAATGTTCA	

SEQ ID NO: 382	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGCCCTGGGGCAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-206_LC
SEQ ID NO: 383	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACAGAGGCCAGGCCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGAGTGGAGACCACCACACCCTCCAAA	MS-207_LC

	CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-208_LC
SEQ ID NO: 384	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCAATGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGTCGAAGCCGGCGGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	
SEQ ID NO: 385	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATTCCAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGTCGAAGCCGGCGGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC	MS-209_LC

	GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-210_LC
SEQ ID NO: 386	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTGGCTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	
SEQ ID NO: 387	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCCTATATTGCTCATTTA	MS-211_LC

	TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT	
	TGGGACCACCGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT	
	GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC	
	GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT	
	CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT	
	GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA	
	CAAAGCAACAACAAGTACGGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC	
	CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC	
	CCTACAGAATGTTCA	
SEQ ID	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT	MS-212_LC
NO: 388	GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT	
	TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA	
	TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT	
	TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT	
	GTCACATGTGGGAGAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC	
	GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT	
	CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT	
	GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA	
	CAAAGCAACAACAAGTACGGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC	
	CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC	
	CCTACAGAATGTTCA	

SEQ ID NO: 389	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGGAACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-213_LC
SEQ ID NO: 390	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGAGTGGAGACCACCACACCCTCCAAA	MS-214_LC

	CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-215_LC
SEQ ID NO: 391	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	
SEQ ID NO: 392	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGGATGAAGCCGACTATTACT	MS-216_LC

	GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-217_LC
SEQ ID NO: 393	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	
SEQ ID NO: 394	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT	MS-218_LC

	TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCAGGCCCCTATATTGCTCATTTA	
	TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT	
	TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT	
	GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC	
	GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT	
	CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT	
	GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA	
	CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC	
	CCACAGAAGCTACAGCTGCCAGGTCACCGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC	
	CCTACAGAATGTTCA	
SEQ ID NO: 395	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT	MS-219_LC
	GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT	
	TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA	
	TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT	
	TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT	
	GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC	
	GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT	
	CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT	
	GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA	
	CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC	

	CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	
SEQ ID NO: 396	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGTCGAAGCCGGGGCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-220_LC
SEQ ID NO: 397	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC	MS-224_LC

	GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-200_LC
SEQ ID NO: 398	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCCCT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACCGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	
SEQ ID NO: 399	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA	MS-201_LC

	TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT	
	TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT	
	GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC	
	GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT	
	CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT	
	GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA	
	CAAAGCAACAACAAGTACGGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC	
	CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC	
	CCTACAGAATGTTCA	
SEQ ID NO: 400	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCCCT	MS-202_LC
	GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT	
	TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA	
	TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT	
	TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT	
	GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC	
	GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT	
	CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT	
	GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA	
	CAAAGCAACAACAAGTACGGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC	
	CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC	
	CCTACAGAATGTTCA	

SEQ ID NO: 401	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCCCT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-225_LC
SEQ ID NO: 402	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCCCT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGAGTGGAGACCACCACACCCTCCAAA	MS-226_LC

	CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-227_LC
SEQ ID NO: 403	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCCCT GTGCGCCCGCTGTCAGTGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGTCGAAGCCGGAGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	
SEQ ID NO: 404	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCCCT GTGCGCCCGCTGTCAGTGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGTCGAAGCCGGAGGATGAAGCCGACTATTACT	MS-228_LC

	GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-229_LC
SEQ ID NO: 405	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	
SEQ ID NO: 406	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT	MS-230_LC

	TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCAGGCCCCTATATTGCTCATTTA	
	TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT	
	TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT	
	GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC	
	GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT	
	CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT	
	GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA	
	CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC	
	CCACAGAAGCTACAGCTGCCAGGTCACCGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC	
	CCTACAGAATGTTCA	
SEQ ID NO: 407	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT	MS-231_LC
	GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT	
	TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA	
	TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT	
	TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT	
	GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC	
	GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT	
	CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT	
	GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA	
	CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC	

	CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-232_LC
SEQ ID NO: 408	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-233_LC
SEQ ID NO: 409	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT	

	CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-234_LC
SEQ ID NO: 410	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCCGCTGTCAGTGGCCCTGGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	
SEQ ID NO: 411	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCCCT GTGCGCCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT	MS-235_LC

TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACCGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-236_LC
SEQ ID NO: 412	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCCCT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACCGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	

SEQ ID NO: 413	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCCCT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-237_LC
SEQ ID NO: 414	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCCCT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGAGTGGAGACCACCACACCCTCCAAA	MS-238_LC

	CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-239_LC
SEQ ID NO: 415	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCCCT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	
SEQ ID NO: 416	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGGATGAAGCCGACTATTACT	MS-240_LC

	GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-241_LC
SEQ ID NO: 417	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-242_LC

	TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCAGGCCCCTATATTGCTCATTTA	
	TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT	
	TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT	
	GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC	
	GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT	
	CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT	
	GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA	
	CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC	
	CCACAGAAGCTACAGCTGCCAGGTCACCGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC	
	CCTACAGAATGTTCA	
SEQ ID NO: 419	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCCCT	MS-243_LC
	GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT	
	TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA	
	TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT	
	TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT	
	GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC	
	GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT	
	CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT	
	GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA	
	CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC	

	CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-244_LC
SEQ ID NO: 420	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCCCT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	
SEQ ID NO: 421	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCCCT GTGCGCCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT	MS-245_LC

	CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	MS-246_LC
SEQ ID NO: 422	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCTAT GTGCGCCCGCTGTCAGTGGCCCTGGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	
SEQ ID NO: 423	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGGCCACAGCAACCGGTGTACATTCTTCCCCT GTGCGCCCGCTGTCAGTGGCCCTGGGGGGAGACGGCCAGGATTTCCTGTGGACGACAGGCCCT TGGAAGTAGAGCTGTTCAGTGGTATCAACATAGGCCAGGCCAGGCCCCTATATTGCTCATTTA TAATAATCAAGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGGCACCCCTGATATTAATTT	MS-247_LC

TGGGACCAGGGCCACCCTGACCATCAGCGGGGGTCGAAGCCGGGGATGAAGCCGACTATTACT GTCACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTGACC GTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTT CAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGT GGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCCTCCAAA CAAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTC CCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA	

Table 6: Nucleic acid sequences of heavy chain variable regions of the 10-1074 antibody variants

SEQ ID NO.	SEQUENCE	OTHER INFORMATION
SEQ ID NO: 424	ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACACTCGCAGGTGC AGCTGCAGGAGTCGGGCCCAGGACTGGTGAAACCTTCGGAGACCCTGTCCGTCACCTGCAGTG TCTCTGGAGATTCCATGAATAATTACTACTGGACTTGGATCCGGCAGTCCCCCGGAAAGGGAC TGGAGTGGATAGGCTATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGTC GAGTCGTCATATCACGAGACACGTCGAAAAACCAATTGTCCCTAAAATTAAACTCCGTCACCC CTGCGGACACCGGCCGTCTATTACTGTGCGACAGCGCGCCGAGGACAGAGGATTTATGGAGTGG TTTCCTTTGGAGAGTTCTTCTACTACTCCATGGACGTCTGGGGCAAGGGACCACGGTCAC CGTCTCCTCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACC TCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCGGTGACGGTG TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGT CTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGC GTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGT GGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGG TCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCT CCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA	MS-193_HC

	GAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTG	
	ACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG	
	CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTAC	
	AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGAT	
	GCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA	
SEQ ID NO: 425	ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACACTCGCAGGTGC	MS-194_HC
	AGCTGCAGGAGTCGGGCCCAGGACTGGTGAAACCTTCGGAGACCCTGTCCGTCACCTGCAGTG	
	TCTCTGGAGATTCCATGAATAATTACTACTGGACTTGGATCCGGCAGTCCCCCGGAAAGGGAC	
	TGGAGTGGATAGGCTATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGTC	
	GAGTCGTCATATCACGAGACACGTCGAAAAACCAATTGTCCCTAAAATTAAACTCCGTCACCC	
	CTGCGGACACGGCCGTCTATTACTGTGCGACAGCGCGCCGAGGACAGAGGATTTATGGAGTGG	
	TTTCCTTTGGAGAGTTCTTCTACTACTCCATGGACGTCTGGGGCAAGGGGACCACGGTCAC	
	CGTCTCCTCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACC	
	TCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCGGTGACGGTG	
	TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA	
	GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC	
	ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC	
	TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGT	
	CTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGC	
	GTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGT	
	GGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACCGTACCGTGTGG	

	TCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCT	
	CCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA	
	GAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTG	
	ACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG	
	CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTAC	
	AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGCTG	
	CATGAGGCTCTGCACTCCCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA	
SEQ ID NO: 426	ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACACTCGCAGGTGC	MS-203_HC
	AGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCGTCACCTGCAGTG	
	TCTCTGGAGATTCCATGAATAATTACTACTGGATCCGGCAGTCCCCCGGAAAGGGAC	
	TGGAGTGGATAGGCTATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGTC	
	GAGTCGTCATATCACGAGACACGTCGAAAAACCAATTGTCCCTAAAATTAAACTCCGTCACCC	
	CTGCGGACACGGCCGTCTATTACTGTGCGACAGCGCGCCGAGGACAGAGGATTTATGGAGTGG	
	TTTCCTTTGGAGAGTTCTTCTACTACTCCATGGACGTCTGGGGCAAGGGGACCACGGTCAC	
	CGTCTCCTCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACC	
	TCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCGGTGACGGTG	
	TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA	
	GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC	
	ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC	
	TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGT	
	CTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGC	

	GTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGT	
	GGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGG	
	TCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCT	
	CCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA	
	GAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTG	
	ACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG	
	CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTAC	
	AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGCTG	
	CATGAGGCTCTGCACTCCCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA	
SEQ ID NO: 427	ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACACTCGCAGGTGC	MS-204_HC
	AGCTGCAGGAGTCGGGCCCAGGACTGGTGAAACCTTCGGAGACCCTGTCCGTCACCTGCAGTG	
	TCTCTGGAGATTCCATGAATAATTACTACTGGACTTGGATCCGGCAGTCCCCCGGAAAGGGAC	
	TGGAGTGGATAGGCTATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGTC	
	GAGTCGTCATATCACGAGACACCGTCGAAAAACCAATTGTCCCTAAAATTAAACTCCGTCACCC	
	CTGCGGACACGGCCGTCTATTACTGTGCGACAGCGCGCCGAGGACAGAGGATTTATGGAGTGG	
	TTTCCTTTGGAGAGTTCTTCTACTACTCCATGGACGTCTGGGGCAAGGGGACCACGGTCAC	
	CGTCTCCTCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACC	
	TCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCGGTGACGGTG	
	TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA	
	GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC	
	ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC	

	TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGT	
	CTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGC	
	GTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGT	
	GGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGG	
	TCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCT	
	CCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA	
	GAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTG	
	ACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG	
	CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTAC	
	AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGCTG	
	CATGAGGCTCTGCACTCCCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA	
SEQ ID NO: 428	ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACACTCGCAGGTGC	MS-205_HC
	AGCTGCAGGAGTCGGGCCCAGGACTGGTGAAACCTTCGGAGACCCTGTCCGTCACCTGCAGTG	
	TCTCTGGAGATTCCATGAATAATTACTACTGGACTTGGATCCGGCAGTCCCCCGGAAAGGGAC	
	TGGAGTGGATAGGCTATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGTC	
	GAGTCGTCATATCACGAGACACGTCGAAAAACCAATTGTCCCTAAAATTAAACTCCGTCACCC	
	CTGCGGACACGGCCGTCTATTACTGTGCGACAGCGCGCCGAGGACAGAGGATTTATGGAGTGG	
	TTTCCTTTGGAGAGTTCTTCTACTACTCCATGGACGTCTGGGGCAAGGGGACCACGGTCAC	
	CGTCTCCTCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACC	
	TCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCGGTGACGGTG	
	TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA	

	GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC	
	ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC	
	TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGT	
	CTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGC	
	GTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGT	
	GGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGG	
	TCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCT	
	CCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA	
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	CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTAC
	AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGCTG
	CATGAGGCTCTGCACTCCCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA
SEQ ID NO: 462	ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACACTCGCAGGTGC AGCTGCAGGAGTCGGGCCCAGGACTGGTGAAACCTTCGGAGACCCTGTCCGTCACCTGCAGTG TCTCTGGAGATTCCATGAATAATTACTACTGGATCCGGCAGTCCCCCGGAAAGGGAC
	MS-239_HC

	TGGAGTGGATAGGCTATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGTC
	GAGTCGTCATATCACGAGACACGTCGAAAAAACCAATTTTCCCTAAAATTAAACTCCGTCACCC
	CTGCGGACACCGGCCGTCTATTACTGTGCGCGCGCCGCCGAGGACAGAGGATTTATGGAGTGG
	TTTCCTTTGGAGAGTTCTTCTACTACTCCATGGACGTCTGGGGCAAGGGGACCACGGTCAC
	CGTCTCCTCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACC
	TCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCGGTGACGGTG
	TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA
	GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC
	ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC
	TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGT
	CTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGC
	GTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGT
	GGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGG
	TCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCT
	CCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA
	GAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTG
	ACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG
	CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTAC
	AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGCTG
	CATGAGGCTCTGCACTCCCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

SEQ ID NO: 463	MS-240_HC
ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACACTCGCAGGTGC	
AGCTGCAGGAGTCGGGCCCAGGACTGGTGAAACCTTCGGAGACCCTGTCCGTCACCTGCAGTG	
TCTCTGGAGATTCCATGAATAATTACTACTGGATCCGGCAGTCCCCCGGAAAGGGAC	
TGGAGTGGATAGGCTATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGTC	
GAGTCACCATATCAGTTGACACGTCGAAAAACCAATTTTCCCTAAAATTAAACTCCGTCACCC	
CTGCGGACACGGCCGTCTATTACTGTGCGACAGCGCGCCGAGGACAGAGGATTTATGGAGTGG	
TTTCCTTTGGAGAGTTCTTCTACTACTCCATGGACGTCTGGGGCAAGGGGACCACGGTCAC	
CGTCTCCTCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACC	
TCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCGGTGACGGTG	
TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA	
GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC	
ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC	
TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGT	
CTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGC	
GTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGT	
GGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGG	
TCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCT	
CCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA	
GAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTG	
ACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG	
CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTAC	

	AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGCTG CATGAGGCTCTGCACTCCCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA	MS-241_HC
SEQ ID NO: 464	ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACACTCGCAGGTGC AGCTGCAGGAGTCGGGCCCAGGACTGGTGAAACCTTCGGAGACCCTGTCCGTCACCTGCAGTG TCTCTGGAGATTCCATGAATAATTACTACTGGATCCGGCAGTCCCCCGGAAAGGGAC TGGAGTGGATAGGCTATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGTC GAGTCACCATATCAGTTGACACGTCGAAAAACCAATTGTCCCTAAAATTAAACTCCGTCACCC CTGCGGACACGGCCGTCTATTACTGTGCGCGCGCCGCCGAGGACAGAGGATTTATGGAGTGG TTTCCTTTGGAGAGTTCTTCTACTACTCCATGGACGTCTGGGGCAAGGGGACCACGGTCAC CGTCTCCTCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACC TCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCGGTGACGGTG TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGT CTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGC GTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGT GGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGG TCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCT CCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA GAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTG	

	ACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG
	CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTAC
	AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGCTG
	CATGAGGCTCTGCACTCCCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA
SEQ ID NO: 465	ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACACTCGCAGGTGC
	AGCTGCAGGAGTCGGGCCCAGGACTGGTGAAACCTTCGGAGACCCTGTCCGTCACCTGCAGTG
	TCTCTGGAGATTCCATGAATAATTACTACTGGATCCGGCAGTCCCCCGGAAAGGGAC
	TGGAGTGGATAGGCTATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGTC
	GAGTCGTCATATCAGTTGACACGTCGAAAAACCAATTTTCCCTAAAATTAAACTCCGTCACCC
	CTGCGGACACCGGCCGTCTATTACTGTGCGCGCGCCGCCGAGGACAGAGGATTTATGGAGTGG
	TTTCCTTTGGAGAGTTCTTCTACTACTCCATGGACGTCTGGGGCAAGGGGACCACGGTCAC
	CGTCTCCTCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACC
	TCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCGGTGACGGTG
	TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA
	GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC
	ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC
	TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGT
	CTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCCTGAGGTCACATGC
	GTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGT
	GGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGG
	TCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCT

CCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA	
GAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTG	
ACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG	
CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTAC	
AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGCTG	
CATGAGGCTCTGCACTCCCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA	
SEQ ID NO: 466	MS-243_HC
ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACACTCGCAGGTGC	
AGCTGCAGGAGTCGGGCCCAGGACTGGTGAAACCTTCGGAGACCCTGTCCGTCACCTGCAGTG	
TCTCTGGAGATTCCATGAATAATTACTACTGGACTTGGATCCGGCAGTCCCCCGGAAAGGGAC	
TGGAGTGGATAGGCTATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGTC	
GAGTCACCATATCAGTTGACACGTCGAAAAACCAATTTTCCCTAAAATTAAACTCCGTCACCC	
CTGCGGACACGGCCGTCTATTACTGTGCGACAGCGCGCCGAGGACAGAGGATTTATGGAGTGG	
TTTCCTTTGGAGAGTTCTTCTACTACTACTCCATGGACGTCTGGGGCAAGGGGACCACGGTCAC	
CGTCTCCTCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACC	
TCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCGGTGACGGTG	
TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA	
GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC	
ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC	
TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGT	
CTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGC	
GTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGT	

	GGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGG	
	TCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCT	
	CCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA	
	GAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTG	
	ACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG	
	CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTAC	
	AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGCTG	
	CATGAGGCTCTGCACTCCCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA	
SEQ ID NO: 467	ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACACTCGCAGGTGC	MS-244_HC
	AGCTGCAGGAGTCGGGCCCAGGACTGGTGAAACCTTCGGAGACCCTGTCCGTCACCTGCAGTG	
	TCTCTGGAGATTCCATGAATAATTACTACTGGACTTGGATCCGGCAGTCCCCCGGAAAGGGAC	
	TGGAGTGGATAGGCTATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGTC	
	GAGTCACCATATCAGTTGACACGTCGAAAAACCAATTGTCCCTAAAATTAAACTCCGTCACCC	
	CTGCGGACACGGCCGTCTATTACTGTGCGCGCGCCGCGAGGACAGAGGATTTATGGAGTGG	
	TTTCCTTTGGAGAGTTCTTCTACTACTCCATGGACGTCTGGGGCAAGGGGACCACGGTCAC	
	CGTCTCCTCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACC	
	TCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCGGTGACGGTG	
	TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA	
	GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC	
	ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC	
	TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGGACCGTCAGT	

CTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGC	
GTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGT	
GGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGG	
TCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCT	
CCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA	
GAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTG	
ACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG	
CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTAC	
AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGCTG	
CATGAGGCTCTGCACTCCCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA	
ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACACTCGCAGGTGC	MS-245_HC
AGCTGCAGGAGTCGGGCCCAGGACTGGTGAAACCTTCGGAGACCCTGTCCGTCACCTGCAGTG	
TCTCTGGAGATTCCATGAATAATTACTACTGGACTTGGATCCGGCAGTCCCCCGGAAAGGGAC	
TGGAGTGGATAGGCTATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGTC	
GAGTCGTCATATCAGTTGACACGTCGAAAAACCAATTTTCCCTAAAATTAAACTCCGTCACCC	
CTGCGGACACGGCCGTCTATTACTGTGCGCGCGCCGCGCCGAGGACAGAGGATTTATGGAGTGG	
TTTCCTTTGGAGAGTTCTTCTACTACTCCATGGACGTCTGGGGCAAGGGGACCACGGTCAC	
CGTCTCCTCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACC	
TCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCGGTGACGGTG	
TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA	
GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC	

	ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC	
	TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGT	
	CTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGC	
	GTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGT	
	GGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGG	
	TCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCT	
	CCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA	
	GAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTG	
	ACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG	
	CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTAC	
	AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGCTG	
	CATGAGGCTCTGCACTCCCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA	
SEQ ID NO: 469	ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACACTCGCAGGTGC	MS-246_HC
	AGCTGCAGGAGTCGGGCCCAGGACTGGTGAAACCTTCGGAGACCCTGTCCGTCACCTGCAGTG	
	TCTCTGGAGATTCCATGAATAATTACTACTGGACTTGGATCCGGCAGTCCCCCGGAAAGGGAC	
	TGGAGTGGATAGGCTATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGTC	
	GAGTCACCATATCAGTTGACACGTCGAAAAAACCAATTTTCCCTAAAATTAAACTCCGTCACCC	
	CTGCGGACACGGCCGTCTATTACTGTGCGCGCCGCCGAGGACAGAGGATTTATGGAGTGG	
	TTTCCTTTGGAGAGTTCTTCTACTACTCCATGGACGTCTGGGGCAAGGGGACCACGGTCAC	
	CGTCTCCTCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACC	
	TCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCGGTGACGGTG	

	TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA	
	GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC	
	ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC	
	TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGT	
	CTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGC	
	GTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGT	
	GGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGG	
	TCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCT	
	CCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA	
	GAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTG	
	ACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG	
	CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTAC	
	AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGCTG	
	CATGAGGCTCTGCACTCCCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA	
SEQ ID NO: 470	ATGGGATGGTCATGTATCATCCTTTTTCTAGTAGCAACTGCAACCGGTGTACACTCGCAGGTGC	MS-247_HC
	AGCTGCAGGAGTCGGGCCCAGGACTGGTGAAACCTTCGGAGACCCTGTCCGTCACCTGCAGTG	
	TCTCTGGAGATTCCATGAATAATTACTACTGGATCTTGGATCCGGCAGTCCCCCGGAAAGGGAC	
	TGGAGTGGATAGGCTATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGTC	
	GAGTCACCATATCAGTTGACACGTCGAAAAACCAATTTTCCCTAAAATTAAACTCCGTCACCC	
	CTGCGGACACGGCCGTCTATTACTGTGCGCGCCGCCGAGGACAGAGGATTTATGGAGTGG	
	TTTCCTTTGGAGAGTTCTTCTACTACTCCATGGACGTCTGGGGCAAGGGGACCACGGTCAC	

	CGTCTCCTCAGCTAGCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACC
	TCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAGCCGGTGACGGTG
	TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCCTACAGTCCTCA
	GGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC
	ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATC
	TTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGT
	CTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGC
	GTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGT
	GGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGG
	TCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCT
	CCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA
	GAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTG
	ACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG
	CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTAC
	AGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGCTG
	CATGAGGCTCTGCACTCCCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

Table 7: Nucleic acid sequences of CDR regions of the 10-1074 antibody variants

SEQ ID NO.	SEQUENCE	OTHER INFORMATION
SEQ ID NO: 471	ATGGGATGGAGCTGTATCATCCTGTTCCTCGTGG CCACAGCAACCGGTGTACATTCTTCCTATGTGCG CCCGCTGTCAGTGGCCCTGGGGGAGACGGCCAG GATTTCCTGTGGACGACAGGCCCTTGGAAGTAGA GCTGTTCAGTGGTATCAACATAGGCCAGGCCAGG CCCCTATATTGCTCATTTATAATAATCAAGACCG GCCCTCAGGGATCCCTGAGCGATTCTCTGGCACC CCTGATATTAATTTTGGGACCAGGGCCACCCTGA CCATCAGCGGGGTCGAAGCCGGGGATGAAGCCG ACTATTACTGTCACATGTGGGATAGTAGAAGTGG CTTCAGTTGGTCTTTCGGCGGGGCGACCAGGCTG ACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGG TCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAA GCCAACAAGGCCACACTGGTGTGTCTCATAAGTG ACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAA GGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGA GACCACCACACCCTCCAAACAAAGCAACAACAA GTACGCGGCCAGCAGCTATCTGAGCCTGACGCCT GAGCAGTGGAAGTCCCACAGAAGCTACAGCTGC CAGGTCACGCATGAAGGGAGCACCGTGGAGAAG ACAGTGGCCCCTACAGAATGTTCA	MS-193_LC
SEQ ID NO: 472	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-193_LC CDR1
SEQ ID NO: 473	AATAATCAAGACCGGCCCTCA	MS-193_LC CDR2
SEQ ID NO: 474	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-193_LC CDR3
SEQ ID NO: 475	AATAATTACTACTGGACT	MS-193_HC CDR1

SEQ ID NO: 476	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-193_HC CDR2
SEQ ID NO: 477	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-193_HC CDR3
SEQ ID NO: 478	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-194_LC CDR1
SEQ ID NO: 479	AATAATCAAGACCGGCCCTCA	MS-194_LC CDR2
SEQ ID NO: 480	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-194_LC CDR3
SEQ ID NO: 481	AATAATTACTACTGGACT	MS-194_HC CDR1
SEQ ID NO: 482	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-194_HC CDR2
SEQ ID NO: 483	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-194_HC CDR3
SEQ ID NO: 484	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-203_LC CDR1
SEQ ID NO: 485	AATAATCAAGACCGGCCCTCA	MS-203_LC CDR2
SEQ ID NO: 486	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-203_LC CDR3
SEQ ID NO: 487	AATAATTACTACTGGACT	MS-203_HC CDR1
SEQ ID NO: 488	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-203_HC CDR2
SEQ ID NO: 489	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-203_HC CDR3
SEQ ID NO: 490	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-204_LC CDR1

SEQ ID NO: 491	AATAATCAAGACCGGCCCTCA	MS-204_LC CDR2
SEQ ID NO: 492	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-204_LC CDR3
SEQ ID NO: 493	AATAATTACTACTGGACT	MS-204_HC CDR1
SEQ ID NO: 494	TATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGT	MS-204_HC CDR2
SEQ ID NO: 495	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTTCCTTTGGAGAGTTCTTCTACTACTACTCCATGGACGTC	MS-204_HC CDR3
SEQ ID NO: 496	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-205_LC CDR1
SEQ ID NO: 497	AATAATCAAGACCGGCCCTCA	MS-205_LC CDR2
SEQ ID NO: 498	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-205_LC CDR3
SEQ ID NO: 499	AATAATTACTACTGGACT	MS-205_HC CDR1
SEQ ID NO: 500	TATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGT	MS-205_HC CDR2
SEQ ID NO: 501	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTTCCTTTGGAGAGTTCTTCTACTACTACTCCATGGACGTC	MS-205_HC CDR3
SEQ ID NO: 502	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-206_LC CDR1
SEQ ID NO: 503	AATAATCAAGACCGGCCCTCA	MS-206_LC CDR2
SEQ ID NO: 504	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-206_LC CDR3
SEQ ID NO: 505	AATAATTACTACTGGACT	MS-206_HC CDR1

SEQ ID NO: 506	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-206_HC CDR2
SEQ ID NO: 507	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-206_HC CDR3
SEQ ID NO: 508	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-207_LC CDR1
SEQ ID NO: 509	AATAATCAAGACCGGCCCTCA	MS-207_LC CDR2
SEQ ID NO: 510	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-207_LC CDR3
SEQ ID NO: 511	AATAATTACTACTGGACT	MS-207_HC CDR1
SEQ ID NO: 512	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-207_HC CDR2
SEQ ID NO: 513	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-207_HC CDR3
SEQ ID NO: 514	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-208_LC CDR1
SEQ ID NO: 515	AATAATCAAGACCGGCCCTCA	MS-208_LC CDR2
SEQ ID NO: 516	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-208_LC CDR3
SEQ ID NO: 517	AATAATTACTACTGGACT	MS-208_HC CDR1
SEQ ID NO: 518	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-208_HC CDR2
SEQ ID NO: 519	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-208_HC CDR3
SEQ ID NO: 520	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-209_LC CDR1

SEQ ID NO: 521	AATAATCAAGACCGGCCCTCA	MS-209_LC CDR2
SEQ ID NO: 522	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-209_LC CDR3
SEQ ID NO: 523	AATAATTACTACTGGACT	MS-209_HC CDR1
SEQ ID NO: 524	TATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGT	MS-209_HC CDR2
SEQ ID NO: 525	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTTCCTTTGGAGAGTTCTTCTACTACTACTCCATGGACGTC	MS-209_HC CDR3
SEQ ID NO: 526	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-210_LC CDR1
SEQ ID NO: 527	AATAATCAAGACCGGCCCTCA	MS-210_LC CDR2
SEQ ID NO: 528	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-210_LC CDR3
SEQ ID NO: 529	AATAATTACTACTGGACT	MS-210_HC CDR1
SEQ ID NO: 530	TATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGT	MS-210_HC CDR2
SEQ ID NO: 531	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTTCCTTTGGAGAGTTCTTCTACTACTACTCCATGGACGTC	MS-210_HC CDR3
SEQ ID NO: 532	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-211_LC CDR1
SEQ ID NO: 533	AATAATCAAGACCGGCCCTCA	MS-211_LC CDR2
SEQ ID NO: 534	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-211_LC CDR3
SEQ ID NO: 535	AATAATTACTACTGGACT	MS-211_HC CDR1

SEQ ID NO: 536	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-211_HC CDR2
SEQ ID NO: 537	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-211_HC CDR3
SEQ ID NO: 538	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-212_LC CDR1
SEQ ID NO: 539	AATAATCAAGACCGGCCCTCA	MS-212_LC CDR2
SEQ ID NO: 540	CACATGTGGGAGAGTAGAAGTGGCTTCAGTTGGT CT	MS-212_LC CDR3
SEQ ID NO: 541	AATAATTACTACTGGACT	MS-212_HC CDR1
SEQ ID NO: 542	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-212_HC CDR2
SEQ ID NO: 543	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-212_HC CDR3
SEQ ID NO: 544	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-213_LC CDR1
SEQ ID NO: 545	AATAATCAAGACCGGCCCTCA	MS-213_LC CDR2
SEQ ID NO: 546	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-213_LC CDR3
SEQ ID NO: 547	AATAATTACTACTGGACT	MS-213_HC CDR1
SEQ ID NO: 548	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-213_HC CDR2
SEQ ID NO: 549	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-213_HC CDR3
SEQ ID NO: 550	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-214_LC CDR1

SEQ ID NO: 551	AATAATCAAGACCGGCCCTCA	MS-214_LC CDR2
SEQ ID NO: 552	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-214_LC CDR3
SEQ ID NO: 553	AATAATTACTACTGGACT	MS-214_HC CDR1
SEQ ID NO: 554	TATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGT	MS-214_HC CDR2
SEQ ID NO: 555	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTTCCTTTGGAGAGTTCTTCTACTACTACTCCATGGACGTC	MS-214_HC CDR3
SEQ ID NO: 556	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-215_LC CDR1
SEQ ID NO: 557	AATAATCAAGACCGGCCCTCA	MS-215_LC CDR2
SEQ ID NO: 558	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-215_LC CDR3
SEQ ID NO: 559	AATAATTACTACTGGACT	MS-215_HC CDR1
SEQ ID NO: 560	TATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGT	MS-215_HC CDR2
SEQ ID NO: 561	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTTCCTTTGGAGAGTTCTTCTACTACTACTCCATGGACGTC	MS-215_HC CDR3
SEQ ID NO: 562	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-216_LC CDR1
SEQ ID NO: 563	AATAATCAAGACCGGCCCTCA	MS-216_LC CDR2
SEQ ID NO: 564	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-216_LC CDR3
SEQ ID NO: 565	AATAATTACTACTGGACT	MS-216_HC CDR1

SEQ ID NO: 566	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-216_HC CDR2
SEQ ID NO: 567	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-216_HC CDR3
SEQ ID NO: 568	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-217_LC CDR1
SEQ ID NO: 569	AATAATCAAGACCGGCCCTCA	MS-217_LC CDR2
SEQ ID NO: 570	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-217_LC CDR3
SEQ ID NO: 571	AATAATTACTACTGGACT	MS-217_HC CDR1
SEQ ID NO: 572	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-217_HC CDR2
SEQ ID NO: 573	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-217_HC CDR3
SEQ ID NO: 574	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-218_LC CDR1
SEQ ID NO: 575	AATAATCAAGACCGGCCCTCA	MS-218_LC CDR2
SEQ ID NO: 576	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-218_LC CDR3
SEQ ID NO: 577	AATAATTACTACTGGACT	MS-218_HC CDR1
SEQ ID NO: 578	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-218_HC CDR2
SEQ ID NO: 579	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-218_HC CDR3
SEQ ID NO: 580	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-219_LC CDR1

SEQ ID NO: 581	AATAATCAAGACCGGCCCTCA	MS-219_LC CDR2
SEQ ID NO: 582	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-219_LC CDR3
SEQ ID NO: 583	AATAATTACTACTGGACT	MS-219_HC CDR1
SEQ ID NO: 584	TATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGT	MS-219_HC CDR2
SEQ ID NO: 585	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTTCCTTTGGAGAGTTCTTCTACTACTACTCCATGGACGTC	MS-219_HC CDR3
SEQ ID NO: 586	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-220_LC CDR1
SEQ ID NO: 587	AATAATCAAGACCGGCCCTCA	MS-220_LC CDR2
SEQ ID NO: 588	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-220_LC CDR3
SEQ ID NO: 589	AATAATTACTACTGGACT	MS-220_HC CDR1
SEQ ID NO: 590	TATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGT	MS-220_HC CDR2
SEQ ID NO: 591	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTTCCTTTGGAGAGTTCTTCTACTACTACTCCATGGACGTC	MS-220_HC CDR3
SEQ ID NO: 592	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-224_LC CDR1
SEQ ID NO: 593	AATAATCAAGACCGGCCCTCA	MS-224_LC CDR2
SEQ ID NO: 594	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-224_LC CDR3
SEQ ID NO: 595	AATAATTACTACTGGACT	MS-224_HC CDR1

SEQ ID NO: 596	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCCAAAGT	MS-224_HC CDR2
SEQ ID NO: 597	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-224_HC CDR3
SEQ ID NO: 598	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-200_LC CDR1
SEQ ID NO: 599	AATAATCAAGACCGGCCCTCA	MS-200_LC CDR2
SEQ ID NO: 600	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-200_LC CDR3
SEQ ID NO: 601	AATAATTACTACTGGACT	MS-200_HC CDR1
SEQ ID NO: 602	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-200_HC CDR2
SEQ ID NO: 603	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-200_HC CDR3
SEQ ID NO: 604	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-201_LC CDR1
SEQ ID NO: 605	AATAATCAAGACCGGCCCTCA	MS-201_LC CDR2
SEQ ID NO: 606	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-201_LC CDR3
SEQ ID NO: 607	AATAATTACTACTGGACT	MS-201_HC CDR1
SEQ ID NO: 608	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-201_HC CDR2
SEQ ID NO: 609	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-201_HC CDR3
SEQ ID NO: 610	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-202_LC CDR1

SEQ ID NO: 611	AATAATCAAGACCGGCCCTCA	MS-202_LC CDR2
SEQ ID NO: 612	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-202_LC CDR3
SEQ ID NO: 613	AATAATTACTACTGGACT	MS-202_HC CDR1
SEQ ID NO: 614	TATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGT	MS-202_HC CDR2
SEQ ID NO: 615	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTTCCTTTGGAGAGTTCTTCTACTACTACTCCATGGACGTC	MS-202_HC CDR3
SEQ ID NO: 616	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-225_LC CDR1
SEQ ID NO: 617	AATAATCAAGACCGGCCCTCA	MS-225_LC CDR2
SEQ ID NO: 618	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-225_LC CDR3
SEQ ID NO: 619	AATAATTACTACTGGACT	MS-225_HC CDR1
SEQ ID NO: 620	TATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGT	MS-225_HC CDR2
SEQ ID NO: 621	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTTCCTTTGGAGAGTTCTTCTACTACTACTCCATGGACGTC	MS-225_HC CDR3
SEQ ID NO: 622	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-226_LC CDR1
SEQ ID NO: 623	AATAATCAAGACCGGCCCTCA	MS-226_LC CDR2
SEQ ID NO: 624	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-226_LC CDR3
SEQ ID NO: 625	AATAATTACTACTGGACT	MS-226_HC CDR1

SEQ ID NO: 626	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-226_HC CDR2
SEQ ID NO: 627	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-226_HC CDR3
SEQ ID NO: 628	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-227_LC CDR1
SEQ ID NO: 629	AATAATCAAGACCGGCCCTCA	MS-227_LC CDR2
SEQ ID NO: 630	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-227_LC CDR3
SEQ ID NO: 631	AATAATTACTACTGGACT	MS-227_HC CDR1
SEQ ID NO: 632	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-227_HC CDR2
SEQ ID NO: 633	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-227_HC CDR3
SEQ ID NO: 634	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-228_LC CDR1
SEQ ID NO: 635	AATAATCAAGACCGGCCCTCA	MS-228_LC CDR2
SEQ ID NO: 636	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-228_LC CDR3
SEQ ID NO: 637	AATAATTACTACTGGACT	MS-228_HC CDR1
SEQ ID NO: 638	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-228_HC CDR2
SEQ ID NO: 639	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-228_HC CDR3
SEQ ID NO: 640	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-229_LC CDR1

SEQ ID NO: 641	AATAATCAAGACCGGCCCTCA	MS-229_LC CDR2
SEQ ID NO: 642	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-229_LC CDR3
SEQ ID NO: 643	AATAATTACTACTGGACT	MS-229_HC CDR1
SEQ ID NO: 644	TATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGT	MS-229_HC CDR2
SEQ ID NO: 645	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTTCCTTTGGAGAGTTCTTCTACTACTACTCCATGGACGTC	MS-229_HC CDR3
SEQ ID NO: 646	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-230_LC CDR1
SEQ ID NO: 647	AATAATCAAGACCGGCCCTCA	MS-230_LC CDR2
SEQ ID NO: 648	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-230_LC CDR3
SEQ ID NO: 649	AATAATTACTACTGGACT	MS-230_HC CDR1
SEQ ID NO: 650	TATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGT	MS-230_HC CDR2
SEQ ID NO: 651	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTTCCTTTGGAGAGTTCTTCTACTACTACTCCATGGACGTC	MS-230_HC CDR3
SEQ ID NO: 652	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-231_LC CDR1
SEQ ID NO: 653	AATAATCAAGACCGGCCCTCA	MS-231_LC CDR2
SEQ ID NO: 654	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-231_LC CDR3
SEQ ID NO: 655	AATAATTACTACTGGACT	MS-231_HC CDR1

SEQ ID NO: 656	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-231_HC CDR2
SEQ ID NO: 657	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-231_HC CDR3
SEQ ID NO: 658	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-232_LC CDR1
SEQ ID NO: 659	AATAATCAAGACCGGCCCTCA	MS-232_LC CDR2
SEQ ID NO: 660	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-232_LC CDR3
SEQ ID NO: 661	AATAATTACTACTGGACT	MS-232_HC CDR1
SEQ ID NO: 662	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-232_HC CDR2
SEQ ID NO: 663	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-232_HC CDR3
SEQ ID NO: 664	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-233_LC CDR1
SEQ ID NO: 665	AATAATCAAGACCGGCCCTCA	MS-233_LC CDR2
SEQ ID NO: 666	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-233_LC CDR3
SEQ ID NO: 667	AATAATTACTACTGGACT	MS-233_HC CDR1
SEQ ID NO: 668	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-233_HC CDR2
SEQ ID NO: 669	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-233_HC CDR3
SEQ ID NO: 670	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-234_LC CDR1

SEQ ID NO: 671	AATAATCAAGACCGGCCCTCA	MS-234_LC CDR2
SEQ ID NO: 672	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-234_LC CDR3
SEQ ID NO: 673	AATAATTACTACTGGACT	MS-234_HC CDR1
SEQ ID NO: 674	TATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGT	MS-234_HC CDR2
SEQ ID NO: 675	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTTCCTTTGGAGAGTTCTTCTACTACTACTCCATGGACGTC	MS-234_HC CDR3
SEQ ID NO: 676	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-235_LC CDR1
SEQ ID NO: 677	AATAATCAAGACCGGCCCTCA	MS-235_LC CDR2
SEQ ID NO: 678	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-235_LC CDR3
SEQ ID NO: 679	AATAATTACTACTGGACT	MS-235_HC CDR1
SEQ ID NO: 680	TATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGT	MS-235_HC CDR2
SEQ ID NO: 681	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTTCCTTTGGAGAGTTCTTCTACTACTACTCCATGGACGTC	MS-235_HC CDR3
SEQ ID NO: 682	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-236_LC CDR1
SEQ ID NO: 683	AATAATCAAGACCGGCCCTCA	MS-236_LC CDR2
SEQ ID NO: 684	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-236_LC CDR3
SEQ ID NO: 685	AATAATTACTACTGGACT	MS-236_HC CDR1

SEQ ID NO: 686	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-236_HC CDR2
SEQ ID NO: 687	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-236_HC CDR3
SEQ ID NO: 688	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-237_LC CDR1
SEQ ID NO: 689	AATAATCAAGACCGGCCCTCA	MS-237_LC CDR2
SEQ ID NO: 690	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-237_LC CDR3
SEQ ID NO: 691	AATAATTACTACTGGACT	MS-237_HC CDR1
SEQ ID NO: 692	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-237_HC CDR2
SEQ ID NO: 693	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-237_HC CDR3
SEQ ID NO: 694	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-238_LC CDR1
SEQ ID NO: 695	AATAATCAAGACCGGCCCTCA	MS-238_LC CDR2
SEQ ID NO: 696	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-238_LC CDR3
SEQ ID NO: 697	AATAATTACTACTGGACT	MS-238_HC CDR1
SEQ ID NO: 698	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-238_HC CDR2
SEQ ID NO: 699	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-238_HC CDR3
SEQ ID NO: 700	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-239_LC CDR1

SEQ ID NO: 701	AATAATCAAGACCGGCCCTCA	MS-239_LC CDR2
SEQ ID NO: 702	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-239_LC CDR3
SEQ ID NO: 703	AATAATTACTACTGGACT	MS-239_HC CDR1
SEQ ID NO: 704	TATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGT	MS-239_HC CDR2
SEQ ID NO: 705	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTTCCTTTGGAGAGTTCTTCTACTACTACTCCATGGACGTC	MS-239_HC CDR3
SEQ ID NO: 706	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-240_LC CDR1
SEQ ID NO: 707	AATAATCAAGACCGGCCCTCA	MS-240_LC CDR2
SEQ ID NO: 708	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-240_LC CDR3
SEQ ID NO: 709	AATAATTACTACTGGACT	MS-240_HC CDR1
SEQ ID NO: 710	TATATCTCTGACAGAGAATCAGCGACTTACAACCCCTCCCTCAATAGT	MS-240_HC CDR2
SEQ ID NO: 711	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTTCCTTTGGAGAGTTCTTCTACTACTACTCCATGGACGTC	MS-240_HC CDR3
SEQ ID NO: 712	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-241_LC CDR1
SEQ ID NO: 713	AATAATCAAGACCGGCCCTCA	MS-241_LC CDR2
SEQ ID NO: 714	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGTCT	MS-241_LC CDR3
SEQ ID NO: 715	AATAATTACTACTGGACT	MS-241_HC CDR1

SEQ ID NO: 716	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-241_HC CDR2
SEQ ID NO: 717	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-241_HC CDR3
SEQ ID NO: 718	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-242_LC CDR1
SEQ ID NO: 719	AATAATCAAGACCGGCCCTCA	MS-242_LC CDR2
SEQ ID NO: 720	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-242_LC CDR3
SEQ ID NO: 721	AATAATTACTACTGGACT	MS-242_HC CDR1
SEQ ID NO: 722	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-242_HC CDR2
SEQ ID NO: 723	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-242_HC CDR3
SEQ ID NO: 724	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-243_LC CDR1
SEQ ID NO: 725	AATAATCAAGACCGGCCCTCA	MS-243_LC CDR2
SEQ ID NO: 726	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-243_LC CDR3
SEQ ID NO: 727	AATAATTACTACTGGACT	MS-243_HC CDR1
SEQ ID NO: 728	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-243_HC CDR2
SEQ ID NO: 729	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-243_HC CDR3
SEQ ID NO: 730	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-244_LC CDR1

SEQ ID NO: 731	AATAATCAAGACCGGCCCTCA	MS-244_LC CDR2
SEQ ID NO: 732	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-244_LC CDR3
SEQ ID NO: 733	AATAATTACTACTGGACT	MS-244_HC CDR1
SEQ ID NO: 734	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-244_HC CDR2
SEQ ID NO: 735	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-244_HC CDR3
SEQ ID NO: 736	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-245_LC CDR1
SEQ ID NO: 737	AATAATCAAGACCGGCCCTCA	MS-245_LC CDR2
SEQ ID NO: 738	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-245_LC CDR3
SEQ ID NO: 739	AATAATTACTACTGGACT	MS-245_HC CDR1
SEQ ID NO: 740	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-245_HC CDR2
SEQ ID NO: 741	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-245_HC CDR3
SEQ ID NO: 742	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-246_LC CDR1
SEQ ID NO: 743	AATAATCAAGACCGGCCCTCA	MS-246_LC CDR2
SEQ ID NO: 744	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-246_LC CDR3
SEQ ID NO: 745	AATAATTACTACTGGACT	MS-246_HC CDR1

SEQ ID NO: 746	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-246_HC CDR2
SEQ ID NO: 747	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-246_HC CDR3
SEQ ID NO: 748	GGACGACAGGCCCTTGGAAGTAGAGCTGTTCAG	MS-247_LC CDR1
SEQ ID NO: 749	AATAATCAAGACCGGCCCTCA	MS-247_LC CDR2
SEQ ID NO: 750	CACATGTGGGATAGTAGAAGTGGCTTCAGTTGGT CT	MS-247_LC CDR3
SEQ ID NO: 751	AATAATTACTACTGGACT	MS-247_HC CDR1
SEQ ID NO: 752	TATATCTCTGACAGAGAATCAGCGACTTACAACC CCTCCCTCAATAGT	MS-247_HC CDR2
SEQ ID NO: 753	GCGCGCCGAGGACAGAGGATTTATGGAGTGGTTT CCTTTGGAGAGTTCTTCTACTACTACTCCATGGAC GTC	MS-247_HC CDR3

Table 8: Methods for characterizing anti-HIV antibody 10-1074 variants

Method Name	Discard limits	Priority molecules
Titer (with caveat that transient titer is not correlative with stable titer)	Discard molecules with significant reduction in titer	Variants with significant increase in titer over parental
Purification Yield	Discard molecules with a significant decrease in yield as compared to the titer	Variants with yield close to 100% based on the titer
Neutralization	Discard molecules with greater than 3-fold reduction in neutralization potency for any given virus	Variants with no decrease in potency
Size Exclusion Chromatography (SEC)	Dimer and higher order aggregates less than 10%. Priority for molecules with lower values.	Molecules with less than 5% dimer and higher order aggregates
Differential Scanning Fluorimetry (DSF)	Discard molecules with loss of Tm2	Molecules with increased or additional Tm
Chemical Unfolding by Guanidine-HCl	Discard molecules with inflection point of unfolding less than parental molecule	Molecules with inflection point of unfolding greater than parental molecule
Relative Solubility Analysis (RSA)	Discard molecules with decreased solubility	Molecules with increased relative solubility given priority
Low pH Stability	Discard molecules with greater than 5% increase in aggregation following low pH incubation	No change in aggregation level following low pH incubation

Table 9: Molecule sets and biophysical analysis of 10-1074 antibody variants (Round 1)

Molecule Set	LC	IgG1 HC	Amount Purified (mg)	SEC (% Monomer)	SEC (% HMW)	DSF Tm1, °C (rep 1)	DSF Tm2, °C (rep 1)	DSF Tm1, °C (rep 2)	DSF Tm2, °C (rep 2)
MS-194			1.20	91.52	8.48	69.8		70.0	
MS-203	LmdV:Y2P		0.60	95.24	4.76	69.3	81.6	69.3	81.1
MS-204	LmdV:R7P		0.87	65.98	34.02	69.9		70.1	
MS-205	LmdV:P9S		1.25	71.66	28.34	70.1		70.2	
MS-206	LmdV:E17Q		1.25	91.35	8.65	70.0		70.0	
MS-207	LmdV:H46Q		0.87	65.30	34.70	69.8	80.8	69.9	
MS-208	LmdV:P81.1N		0.24	88.68	11.32	68.8	81.3	69.0	
MS-209	LmdV:I81.3S		1.27	60.79	39.21	70.0	81.3	70.1	80.1
MS-210	LmdV:N82G		0.28	88.24	11.76	70.1	81.7	70.3	81.3
MS-211	LmdV:R88T		0.22	83.11	16.89	66.9		67.1	
MS-212	LmdV:D110E		0.25	82.78	17.22	68.5		68.6	
MS-213	LmdV:A142G		0.44	90.48	9.52	68.1		68.2	
MS-214		HV:D29G	2.01	94.00	6.00	69.9		69.9	
MS-215		HV:S47P	2.68	92.88	7.12	70.0		70.1	
MS-216		HV:V79T	1.48	94.67	5.33	69.8	81.8	69.9	80.1
MS-217		HV:R82V	1.31	94.21	5.79	69.8	80.9	69.9	80.1
MS-218		HV:L89F	0.68	96.33	3.67	70.0	80.9	70.1	81.3
MS-219		HV:T108R	2.24	91.93	8.07	70.3	75.4	70.3	76.0

MS-220		HV:K141Q	2.87	94.56	5.44	69.9		69.9	
MS-224		HV:N75Q	0.05			70.2		69.9	80.8

Table 10: Molecule sets and neutralization analysis against 10-1074 sensitive virus panel in TZM.bl cells (Round 1)

	Du156.12		WITO4160.33		CNE17		CNE30		CAAN5342.A2		Du172.17	
Molecule Set	IC50	IC80	IC50	IC80	IC50	IC80	IC50	IC80	IC50	IC80	IC50	IC80
Control	0.010	0.030	0.168	1.173	1.201	6.067	0.164	0.605	0.009	0.029	0.110	0.391
MS-203	0.008	0.025	0.205	0.979	1.291	4.519	0.193	0.546	0.009	0.024	0.084	0.295
MS-204	0.014	0.040	0.236	1.664	1.211	5.895	0.270	0.902	0.017	0.048	0.092	0.334
MS-205	0.012	0.035	0.162	0.922	1.237	4.411	0.249	0.824	0.011	0.029	0.098	0.329
MS-206	0.010	0.035	0.161	1.142	0.986	3.484	0.225	0.614	0.009	0.024	0.095	0.272
MS-207	0.010	0.036	0.252	0.840	1.285	5.873	0.240	0.836	0.026	0.115	0.211	0.875
MS-208	0.007	0.036	0.699	5.174	3.569	17.98	0.206	1.018	0.016	0.047	0.231	0.816
MS-209	0.007	0.025	0.276	1.833	1.155	5.751	0.174	0.618	0.009	0.029	0.088	0.303
MS-210	0.005	0.013	0.091	0.594	0.598	2.834	0.097	0.340	0.003	0.013	0.044	0.156
MS-211	0.008	0.028	0.237	1.514	1.151	4.240	0.205	0.744	0.010	0.025	0.092	0.309
MS-212	0.009	0.041	0.304	1.938	1.395	6.928	0.242	1.130	0.007	0.031	0.113	0.399
MS-213	0.007	0.028	0.183	1.271	0.955	5.049	0.141	0.689	0.011	0.033	0.119	0.315
MS-214	0.005	0.018	0.221	1.553	0.987	4.567	0.185	0.630	0.009	0.024	0.090	0.238
MS-215	0.007	0.023	0.157	1.118	1.174	5.438	0.224	0.760	0.011	0.031	0.095	0.305
MS-216	0.007	0.020	0.132	0.887	1.116	4.999	0.194	0.517	0.009	0.032	0.084	0.277
MS-217	0.010	0.037	0.260	1.678	1.159	5.397	0.216	0.743	0.010	0.038	0.075	0.275
MS-218	0.005	0.018	0.142	1.016	0.815	4.195	0.156	0.557	0.010	0.027	0.091	0.312
MS-219	0.006	0.020	0.308	1.349	0.966	3.559	0.176	0.609	0.007	0.022	0.104	0.278

MS-220	0.009	0.027	0.215	1.023	1.242	4.415	0.193	0.528	0.009	0.027	0.099	0.335
MS-224	0.005	0.022	0.269	1.219	1.147	4.026	0.162	0.564	0.009	0.032	0.096	0.329

Table 11: Reasons for including or excluding variants based on neutralization activity and biophysical analysis (Round1)

Molecule Set	Reason for inclusion/exclusion in Round 2
MS-203	Include: presence of Tm2 by DSF, HMW <10%
MS-204	Exclude: Lack of Tm2
MS-205	Exclude: Lack of Tm2
MS-206	Exclude: Lack of Tm2
MS-207	Exclude: Lack of Tm2
MS-208	Exclude: Lack of Tm2; Reduced neutralization activity
MS-209	Exclude: SEC shows HMW of 39.2%
MS-210	Exclude: Low production titer
MS-211	Exclude: Lack of Tm2
MS-212	Exclude: Lack of Tm2
MS-213	Exclude: Lack of Tm2
MS-214	Exclude: Lack of Tm2
MS-215	Exclude: Lack of Tm2
MS-216	Include: presence of Tm2 by DSF, HMW <10%
MS-217	Include: presence of Tm2 by DSF, HMW <10%
MS-218	Include: presence of Tm2 by DSF, HMW <10%
MS-219	Include: presence of Tm2 by DSF, HMW <10%
MS-220	Exclude: Lack of Tm2
MS-224	Exclude: Low production titer

Table 12: Molecule sets of anti-HIV antibody 10-1074 variants (Round 2)

Molecule Set	LC	IgG1 HC
MS-194		
MS-225	LmdV:Y2P	HV:V79T
MS-226	LmdV:Y2P	HV:R82V
MS-227	LmdV:Y2P	HV:L89F
MS-228	LmdV:Y2P	HV:T108R
MS-229		HV:V79T, HV:R82V
MS-230		HV:V79T, HV:L89F
MS-231		HV:V79T, HV:T108R
MS-232		HV:R82V, HV:L89F
MS-233		HV:R82V, HV:T108R
MS-234		HV:L89F, HV:T108R
MS-235	LmdV:Y2P	HV:V79T, HV:R82V
MS-236	LmdV:Y2P	HV:V79T, HV:L89F
MS-237	LmdV:Y2P	HV:V79T, HV:T108R
MS-238	LmdV:Y2P	HV:R82V, HV:L89F
MS-200	LmdV:Y2P	HV:R82V, HV:T108R
MS-239	LmdV:Y2P	HV:L89F, HV:T108R
MS-240		HV:V79T, HV:R82V, HV:L89F
MS-241		HV:V79T, HV:R82V, HV:T108R
MS-201		HV:V79T, HV:L89F, HV:T108R

MS-242		HV:R82V, HV:L89F, HV:T108R
MS-243	LmdV:Y2P	HV:V79T, HV:R82V, HV:L89F
MS-244	LmdV:Y2P	HV:V79T, HV:R82V, HV:T108R
MS-202	LmdV:Y7P	HV:V79T, HV:L89F, HV:T108R
MS-245	LmdV:Y2P	HV:R82V, HV:L89F, HV:T108R
MS-246		HV:V79T, HV:R82V, HV:L89F, HV:T108R
MS-247	LmdV:Y2P	HV:V79T, HV:R82V, HV:L89F, HV:T108R

Table 13: Molecule sets and biophysical analysis of 10-1074 antibody variants (Round 2)

Molecule Set	SEC (% monomer)	SEC (% dimer)	SEC (% Oligomer)	DSF Tm1 °C (Avg. n=2)	DSF Tm1 (Std Dev)	DSF Tm2 °C (Avg. n=2)	DSF Tm2 (Std Dev)
MS-194	92.40	3.72	3.89	70.00	0.01		
MS-225	89.07	3.12	7.81	69.44	0.05		
MS-226	93.49	3.51	3.00	69.52	0.03		
MS-227	90.18	3.10	6.72	69.76	0.07		
MS-228	95.37	3.59	1.04	70.48	0.02	74.50	0.00
MS-229	93.39	4.03	2.58	70.04	0.05		
MS-230	94.00	3.42	2.58	70.25	0.05		
MS-231	95.35	3.87	0.79	70.41	0.02	74.50	0.03
MS-232	94.62	3.52	1.86	70.07	0.03		
MS-233	95.45	3.94	0.61	70.30	0.00	76.69	0.15
MS-234	96.70	2.94	0.36	70.40	0.06	76.85	0.11
MS-235	92.77	3.46	3.77	69.74	0.05		
MS-236	93.06	3.78	3.16	69.92	0.10		
MS-237	94.61	4.03	1.36	70.47	0.02	74.50	0.00
MS-238	91.73	3.94	4.33	69.36	0.01		
MS-200	94.64	4.56	0.80	70.15	0.01	74.62	0.33
MS-239	95.99	3.35	0.66	70.28	0.01	75.42	0.09
MS-240	94.87	3.61	1.52	69.99	0.01		
MS-241	94.36	4.93	0.71	70.11	0.02	76.41	0.04
MS-201	94.58	4.68	0.73	70.28	0.04	76.69	0.01

MS-242	94.82	4.52	0.66	70.25	0.02	77.30	0.03
MS-243	91.81	4.51	3.67	69.57	0.06		
MS-244	93.97	5.04	0.99	70.17	0.02	74.70	0.18
MS-202	93.88	5.04	1.08	70.42	0.00	75.43	0.15
MS-245	93.40	5.61	0.99	70.36	0.02	76.15	0.04
MS-246	94.88	4.59	0.53	70.19	0.05	77.13	0.09
MS-247	94.37	4.88	0.75	69.44	0.05		

Table 14: Additional biophysical characterization for the combination variants (Round 2)

Molecule Set	Shoulder Score (Avg. n=2)	(Std Dev)	Inflection Pt of Unfolding (Avg n=3)	Std Dev	pH 3.3 HMW% (Avg n=2)	Std Dev	PEG solubility (avg. n=2)	Std Dev
MS-194	7.65	0.17	2.44	0.01	39.76	0.19	0.14	0.02
MS-225	7.22	0.97	2.37	0.03	40.43	14.01	0.18	0.02
MS-226	7.72	0.16	2.49	0.04	14.33	6.02	0.19	0.01
MS-227	8.12	0.61	2.53	0.03	28.13	14.86	0.18	0.02
MS-228	16.25	0.55	2.64	0.02	9.10	6.29	0.17	0.02
MS-229	9.03	0.98	2.60	0.01	9.77	2.43	0.19	0.02
MS-230	10.03	0.39	2.62	0.05	12.14	2.04	0.18	0.02
MS-231	20.80	0.22	2.63	0.02	3.35	0.16	0.14	0.02
MS-232	9.70	0.25	2.65	0.06	8.67	1.77	0.19	0.01
MS-233	20.00	0.23	2.98	0.03	2.48	0.03	0.17	0.02
MS-234	28.36	2.18	2.97	0.19	2.61	0.51	0.15	0.02
MS-235	7.79	0.22	2.60	0.03	13.92	1.48	0.19	0.01
MS-236	8.32	0.07	2.53	0.00	22.13	6.12	0.19	0.02
MS-237	16.01	0.05	2.65	0.05	4.58	0.49	0.15	0.03
MS-238	8.21	0.56	2.57	0.01	31.37	25.30	0.20	0.01
MS-200	16.12	0.42	2.93	0.04	2.93	0.01	0.19	0.02
MS-239	22.28	0.72	2.98	0.04	3.19	0.49	0.18	0.02
MS-240	9.98	0.18	2.71	0.03	9.63	4.33	0.19	0.02
MS-241	21.39	0.09	2.98	0.06	3.12	0.06	0.17	0.03
MS-201	29.39	0.45	3.15	0.03	2.21	0.06	0.17	0.02
MS-242	23.85	0.29	2.89	0.14	2.49	0.06	0.19	0.02
MS-243	7.62	0.22	2.57	0.03	9.86	1.38	0.18	0.01

MS-244	16.12	0.51	2.90	0.08	3.25	0.16	0.18	0.02
MS-202	22.49	1.53	3.08	0.09	3.64	0.09	0.17	0.02
MS-245	18.77	0.55	3.06	0.07	3.29	0.30	0.18	0.02
MS-246	22.39	0.97	3.29	0.03	2.32	0.23	0.17	0.03
MS-247	7.22	0.97	2.91	0.07	3.14	0.24	0.19	0.02

Table 15: Neutralization analysis of selected variants in Round 2 in TZM.bl cells. Loss of potency are values > 3-fold of control value

	SC422661.8		WITO4160.33		CAAN5342.A2		DU156.12		DU172.17		CNE17	
Molecule Set	IC50	IC80	IC50	IC80	IC50	IC80	IC50	IC80	IC50	IC80	IC50	IC80
Control	0.045	0.157	0.205	1.439	0.005	0.019	0.008	0.034	0.055	0.156	1.34	4.574
MS-228	0.03	0.114	0.097	0.71	0.002	0.01	0.003	0.017	0.036	0.134	0.928	3.21
MS-231	0.032	0.092	0.092	0.646	0.001	0.012	0.003	0.017	0.034	0.125	0.796	2.719
MS-233	0.037	0.128	0.172	0.789	0.005	0.015	0.004	0.02	0.033	0.124	0.625	3.085
MS-234	0.04	0.136	0.22	0.932	0.003	0.011	0.004	0.017	0.058	0.232	0.734	2.646
MS-237	0.028	0.126	0.113	0.744	0.004	0.016	0.004	0.019	0.037	0.117	0.792	3.673
MS-200	0.036	0.156	0.13	0.794	0.005	0.02	0.007	0.028	0.037	0.152	0.922	3.21
MS-239	0.033	0.114	0.199	0.951	0.003	0.012	0.005	0.017	0.03	0.125	0.63	2.887
MS-241	0.034	0.106	0.229	0.999	0.004	0.014	0.008	0.02	0.038	0.137	0.81	2.939
MS-201	0.027	0.104	0.177	1.153	0.002	0.011	0.005	0.016	0.028	0.102	0.782	2.62
MS-242	0.04	0.116	0.145	0.889	0.003	0.012	0.006	0.021	0.034	0.161	0.762	3.331
MS-244	0.041	0.123	0.172	1.169	0.005	0.017	0.003	0.017	0.045	0.167	0.694	3.637
MS-202	0.028	0.135	0.185	0.708	0.003	0.011	0.004	0.021	0.028	0.104	0.825	2.903
MS-245	0.029	0.102	0.132	0.774	0.002	0.012	0.006	0.022	0.038	0.139	0.991	4.443
MS-246	0.037	0.128	0.145	0.82	0.004	0.017	0.006	0.025	0.039	0.146	0.907	3.175
MS-247	0.034	0.151	0.107	0.611	0.003	0.014	0.009	0.032	0.03	0.149	0.642	3.141

Table 15-continued

	CNE30		CNE53		235-47		X1193_c1		X1254_c3		3301.v1.c24	
Molecule Set	IC50	IC80	IC50	IC80	IC50	IC80	IC50	IC80	IC50	IC80	IC50	IC80
Control	0.258	0.709	0.017	0.049	0.029	0.116	0.04	0.139	0.055	0.154	0.008	0.021
MS-228	0.215	0.595	0.007	0.028	0.019	0.086	0.03	0.13	0.039	0.117	0.003	0.013
MS-231	0.184	0.517	0.007	0.025	0.016	0.078	0.028	0.12	0.035	0.116	0.002	0.012
MS-233	0.186	0.649	0.006	0.023	0.03	0.113	0.03	0.133	0.041	0.129	0.003	0.016
MS-234	0.184	0.5	0.008	0.037	0.019	0.077	0.031	0.142	0.03	0.122	0.003	0.014
MS-237	0.17	0.46	0.005	0.027	0.022	0.086	0.042	0.146	0.035	0.101	0.002	0.014
MS-200	0.17	0.583	0.007	0.027	0.022	0.085	0.059	0.177	0.047	0.133	0.005	0.019
MS-239	0.175	0.588	0.004	0.02	0.023	0.088	0.03	0.182	0.036	0.102	0.002	0.011
MS-241	0.181	0.498	0.006	0.023	0.028	0.08	0.042	0.155	0.034	0.119	0.003	0.01
MS-201	0.173	0.471	0.003	0.025	0.011	0.067	0.033	0.154	0.037	0.1	0.003	0.008
MS-242	0.197	0.535	0.004	0.023	0.028	0.092	0.042	0.185	0.031	0.107	0.003	0.009
MS-244	0.18	0.639	0.001	0.014	0.032	0.113	0.041	0.184	0.027	0.108	0.001	0.005
MS-202	0.16	0.568	0.005	0.021	0.022	0.084	0.037	0.139	0.028	0.117	0.005	0.018
MS-245	0.156	0.553	0.004	0.019	0.028	0.1	0.049	0.172	0.04	0.137	0.006	0.019
MS-246	0.204	0.557	0.002	0.021	0.037	0.128	0.046	0.199	0.047	0.164	0.007	0.021
MS-247	0.197	0.554	0.005	0.027	0.036	0.126	0.043	0.203	0.029	0.113	0.008	0.023

Table 16: Reasons for excluding combinatorial variants based on biophysical analysis (Round 2)

Molecule Set	Reasons for exclusion of molecules from further in-depth analysis
MS-225	Excluded: Lack of Tm2, Aggregation at 65°C, Lower chemical unfolding stability, aggregation at pH 3.3 > 5%
MS-226	Excluded: Lack of Tm2, Aggregation at 65°C, Lower chemical unfolding stability, aggregation at pH 3.3 > 5%
MS-227	Excluded: Lack of Tm2, Aggregation at 65°C, Lower chemical unfolding stability, aggregation at pH 3.3 > 5%
MS-228	Excluded: Lower chemical unfolding stability, aggregation at pH 3.3 > 5%
MS-229	Excluded: Lack of Tm2, Aggregation at 65°C, Lower chemical unfolding stability, aggregation at pH 3.3 > 5%
MS-230	Excluded: Lack of Tm2, Aggregation at 65°C, Lower chemical unfolding stability, aggregation at pH 3.3 > 5%
MS-231	Excluded: Aggregation at 65°C, Lower chemical unfolding stability
MS-232	Excluded: Lack of Tm2, Aggregation at 65°C, Lower chemical unfolding stability, aggregation at pH 3.3 > 5%
MS-233	Excluded: Aggregation at 65°C
MS-234	Excluded: Low titer
MS-235	Excluded: Lack of Tm2, Aggregation at 65°C, Lower chemical unfolding stability, aggregation at pH 3.3 > 5%
MS-236	Excluded: Lack of Tm2, Aggregation at 65°C, Lower chemical unfolding stability, aggregation at pH 3.3 > 5%
MS-237	Excluded: Lower chemical unfolding stability
MS-238	Excluded: Lack of Tm2, Aggregation at 65°C, Lower chemical unfolding stability, aggregation at pH 3.3 > 5%

MS-200	Include
MS-239	Excluded: Low Titer
MS-240	Excluded: Lack of Tm2, Aggregation at 65°C, Lower chemical unfolding stability, aggregation at pH 3.3 > 5%
MS-241	Excluded: Similar to 19, but slightly less stability to chemical unfolding
MS-201	Include
MS-242	Exclude: Decreased chemical unfolding stability compared to 19
MS-243	Excluded: Lack of Tm2, Aggregation at 65°C, Lower chemical unfolding stability, aggregation at pH 3.3 > 5%
MS-244	Excluded: Aggregation at 65°C
MS-202	Include
MS-245	Exclude: No improvement over variants 15, 19, or 23
MS-246	Excluded: Low titer (less than parental)
MS-247	Excluded: Low titer (less than parental)

The foregoing examples and description of the preferred embodiments should be taken as illustrating, rather than as limiting the present invention as defined by the claims. As will be readily appreciated, numerous variations and combinations of the features set forth above can be utilized without departing from the present invention as set forth in the claims. Such variations are not regarded as a departure from the scope of the invention, and all such variations are intended to be included within the scope of the following claims. All references cited herein are incorporated herein in their entireties.

CLAIMS

What is claimed is:

1. An isolated anti-HIV antibody, or antigen-binding portion thereof, comprising a light chain variable region having a light chain amino acid sequence that is at least 75% identical to a polypeptide sequence selected from the group consisting of the light chain variable regions of SEQ ID NOs: 3-13, 22, 24-28, 35-39, 43-45, and 47, wherein the isolated anti-HIV antibody, or antigen-binding portion thereof comprises one or more light chain substitutions at one or more residues selected from the group consisting of LmdV:Y2, LmdV:R7, LmdV:P9, LmdV:E17, LmdV:H46, LmdV:P81.1, LmdV:I81.3, LmdV:N82, LmdV:R88, LmdV:D110, and LmdV:A142.

2. An isolated anti-HIV antibody, or antigen-binding portion thereof, comprising a heavy chain variable region having a heavy chain amino acid sequence that is at least 75% identical to a polypeptide sequence selected from the group consisting of the heavy chain variable regions of SEQ ID NOs: 61-94, wherein the isolated anti-HIV antibody, or antigen-binding portion thereof comprises one or more heavy chain substitutions at one or more residues selected from the group consisting of HV:D29, HV:S47, HV:N75, HV:V79, HV:R82, HV:L89, HV:T108, and HV:K141.

3. The isolated anti-HIV antibody, or antigen-binding portion thereof, of claim 1, further comprising a heavy chain variable region having an heavy chain amino acid sequence that is at least 75% identical to a polypeptide sequence selected from the group consisting of the heavy chain variable regions of SEQ ID NOs: 61-94, wherein the isolated anti-HIV antibody, or antigen-binding portion thereof comprises one or more heavy chain substitutions at one or more residues selected from the group consisting of HV:D29, HV:S47, HV:N75, HV:V79, HV:R82, HV:L89, HV:T108, and HV:K141.

4. The isolated anti-HIV antibody, or antigen-binding portion thereof, of claim 1, comprising the one or more light chain substitutions selected from the group consisting of LmdV:Y2P, LmdV:R7P, LmdV:P9S, LmdV:E17Q, LmdV:H46Q, LmdV:P81.1N, LmdV:I81.3S, LmdV:N82G, LmdV:R88T, LmdV:D110E, and LmdV:A142G or conservative substitutions thereof.

5. The isolated anti-HIV antibody, or antigen-binding portion thereof, of claim 2, comprising the one or more heavy chain substitutions selected from the group consisting of HV:D29G, HV:S47P, HV:N75Q, HV:V79T, HV:R82V, HV:L89F, HV:T108R, and HV:K141Q or conservative substitutions thereof.

6. The isolated anti-HIV antibody, or antigen-binding portion thereof, of claim 3, comprising the one or more light chain substitutions selected from the group consisting of LmdV:Y2P, LmdV:R7P, LmdV:P9S, LmdV:E17Q, LmdV:H46Q, LmdV:P81.1N, LmdV:I81.3S, LmdV:N82G, LmdV:R88T, LmdV:D110E, and LmdV:A142G or conservative substitutions thereof and the one or more heavy chain substitutions selected from the group consisting of HV:D29G, HV:S47P, HV:N75Q, HV:V79T, HV:R82V, HV:L89F, HV:T108R, and HV:K141Q or conservative substitutions thereof.

7. The isolated anti-HIV antibody, or antigen-binding portion thereof, of claim 1, wherein the light chain amino acid sequence is at least 75% identical to the light chain variable region of SEQ ID NO.: 3 and comprises a LmdV:Y2P substitution or a conservative substitution of proline at LmdV:Y2.

8. The isolated anti-HIV antibody, or antigen-binding portion thereof, of claim 2, wherein the heavy chain amino acid sequence is at least 75% identical to the heavy chain variable region of SEQ ID NO.: 63 and comprises an HV:V79T substitution or a conservative substitution of threonine at HV:V79.

9. The isolated anti-HIV antibody, or antigen-binding portion thereof, of claim 2, wherein the heavy chain amino acid sequence is at least 75% identical to the heavy chain variable region of SEQ ID NO.: 64 and comprises an HV:R82V substitution or a conservative substitution of valine at HV:R82.

10. The isolated anti-HIV antibody, or antigen-binding portion thereof, of claim 2, wherein the heavy chain amino acid sequence is at least 75% identical to the heavy chain variable region of SEQ ID NO.: 65 and comprises an HV:L89F substitution or a conservative substitution of phenylalanine of HV:L89.

11. The isolated anti-HIV antibody, or antigen-binding portion thereof, of claim 2, wherein the heavy chain amino acid sequence is at least 75% identical to the heavy chain variable region of SEQ ID NO.: 66 and comprises an HV:T108R substitution or a conservative substitution of arginine at HV:T108.

12. The isolated anti-HIV antibody, or antigen-binding portion thereof, of claim 3, wherein the light chain amino acid sequence is at least 75% identical to the light chain variable region of SEQ ID NO.: 22 and comprises a LmdV:Y2P substitution or a conservative substitution of proline at LmdV:Y2, and wherein the heavy chain amino acid sequence is at least 75% identical to the heavy chain variable region of SEQ ID NO.: 69 and comprises:

an HV:R82V substitution or a conservative substitution of valine at HV:R82,

and an HV:T108R substitution or a conservative substitution of arginine at HV:T108.

13. The isolated anti-HIV antibody, or antigen-binding portion thereof, of claim 3, wherein the heavy chain amino acid sequence is at least 75% identical to the heavy chain variable region of SEQ ID NO.: 70 and comprises:

an HV:V79T substitution or a conservative substitution of threonine at HV:V79,

an HV:L89F substitution or a conservative substitution of phenylalanine at HV:L89, and

an HV:T108R substitution or a conservative substitution of arginine at HV:T108.

14. The isolated anti-HIV antibody, or antigen-binding portion thereof, of claim 3, wherein the light chain amino acid sequence is at least 75% identical to the light chain variable region of SEQ ID NO.: 24 and comprises a LmdV:Y2P substitution or a conservative substitution of proline at LmdV:Y2, and wherein the heavy chain amino acid sequence is at least 75% identical to the heavy chain variable region of SEQ ID NO.: 71 and comprises:

an HV:V79T substitution or a conservative substitution of threonine at HV:V79,

an HV:L89F substitution or a conservative substitution of phenylalanine at HV:L89, and

an HV:T108R substitution or a conservative substitution of arginine at HV:T108.

15. The isolated anti-HIV antibody, or antigen-binding portion thereof, of claim 1, comprising SEQ NO.: 3.

16. The isolated anti-HIV antibody, or antigen-binding portion thereof, of claim 2, comprising SEQ NO.: 63, 64, 65, 66, or 70.

17. The isolated anti-HIV antibody, or antigen-binding portion thereof, of claim 3, wherein the light chain variable region comprises the light variable region of SEQ NO.: 22 and the heavy chain variable region comprises the heavy variable region of SEQ No.: 69.

18. The isolated anti-HIV antibody, or antigen-binding portion thereof, of claim 3, wherein the light chain variable region comprises the light variable region of SEQ NO.: 24 and the heavy chain variable region comprises the heavy variable region of SEQ No.: 71.

19. A pharmaceutical composition comprising the isolated anti-HIV antibody, or antigen-binding portion thereof, of any one of claims 1-18, and a pharmaceutically acceptable carrier or excipient.

20. The pharmaceutical composition further comprising a second therapeutic agent.

21. A nucleic acid, or a codon-optimized nucleic acid, encoding the isolated anti-HIV antibody, or antigen-binding portion thereof, of any one of claims 1-18.

22. A vector or vector system comprising at least one nucleic acid of any one of claim 21.

23. A cell comprising the nucleic acid of claim 21.

24. A method of making recombinant anti-HIV antibody, or antigen-binding portion thereof, comprising:

a. obtaining the cell of claim 23;

b. culturing the cell in a medium under conditions permitting expression of a polypeptide encoded by the vector and assembling of an antibody or fragment thereof; and

c. purifying the antibody or fragment from the cultured cell or the medium of the cell.

25. A method of preventing or treating an HIV infection or an HIV-related disease comprising the steps of :

a. identifying a patient in need of such prevention or treatment, and

b. administering to said patient a first therapeutic agent comprising a therapeutically effective amount of at least one anti-HIV antibody of any one of claims 1-18, or antigen-binding portion thereof.

26. The method of claim 25, further comprising administering a second therapeutic agent.

27. The method of claim 26, wherein the second therapeutic agent is administered before, concurrently with or after the administration of the anti-HIV antibody or antigen-binding portion thereof.

28. The method of claim 24 or 25 and the pharmaceutical composition of claim 20, wherein the second therapeutic agent is an anti-HIV-1 broadly neutralizing antibody (bNAb).

29. The method of claim 26, wherein the anti-HIV-1 broadly neutralizing antibody is 3BNC117.

30. A kit comprising a pharmaceutically acceptable dose unit of a pharmaceutically effective amount of at least one isolated anti-HIV antibody according to any one of claims 1-18, or antigen-binding portion thereof.

31. The kit of claim 30 further comprising a pharmaceutically acceptable dose unit of a pharmaceutically effective amount of an anti-HIV agent, wherein the two pharmaceutically acceptable dose units can optionally take the form of a single pharmaceutically acceptable dose unit.

32. The kit of claim 31, wherein the anti-HIV agent is one selected from the group consisting of a non-nucleoside reverse transcriptase inhibitor, a protease inhibitor, an entry or fusion inhibitor, and an integrase inhibitor.

33. The kit of claim 31, wherein the anti-HIV agent is an anti-HIV broadly neutralizing antibody.

34. The kit of claim 33, wherein the anti-HIV broadly neutralizing antibody is 3BNC117.

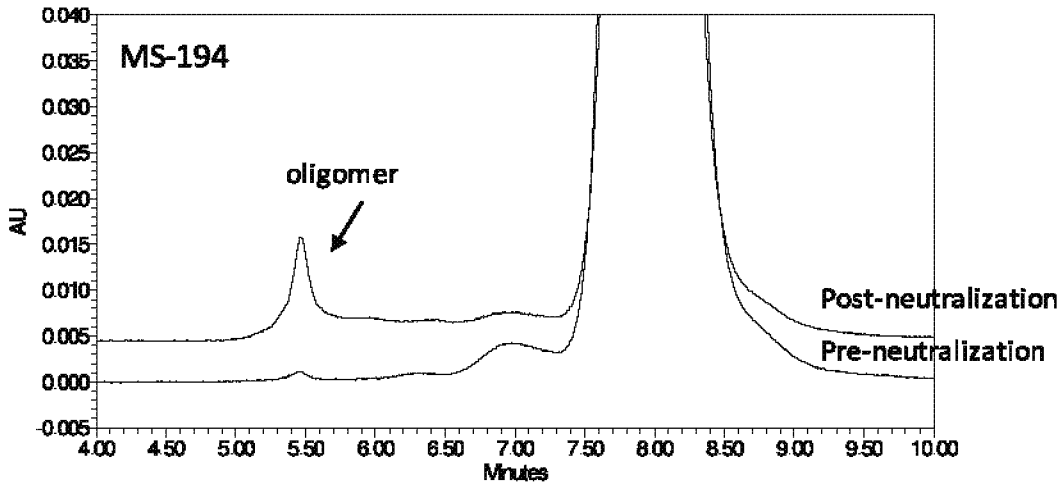
MS-194
oligomer
Post-neutralization
Pre-neutralization
AU
Minutes
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0.000
-0.005
4.00
4.50
5.00
5.50
6.00
6.50
7.00
7.50
8.00
8.50
9.00
9.50
10.00

FIG. 1A

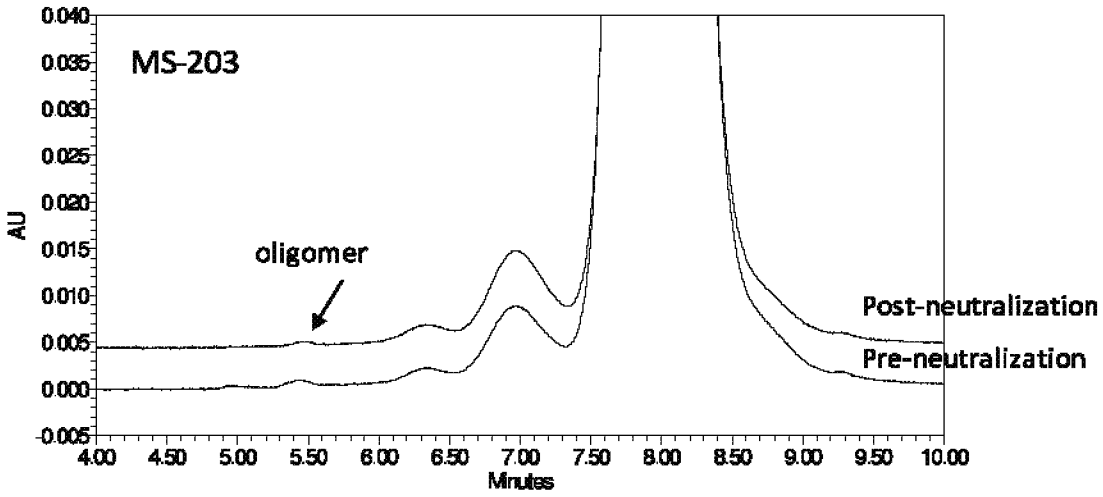
MS-203
oligomer
Post-neutralization
Pre-neutralization
AU
Minutes
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0.000
-0.005
4.00
4.50
5.00
5.50
6.00
6.50
7.00
7.50
8.00
8.50
9.00
9.50
10.00

FIG. 1B

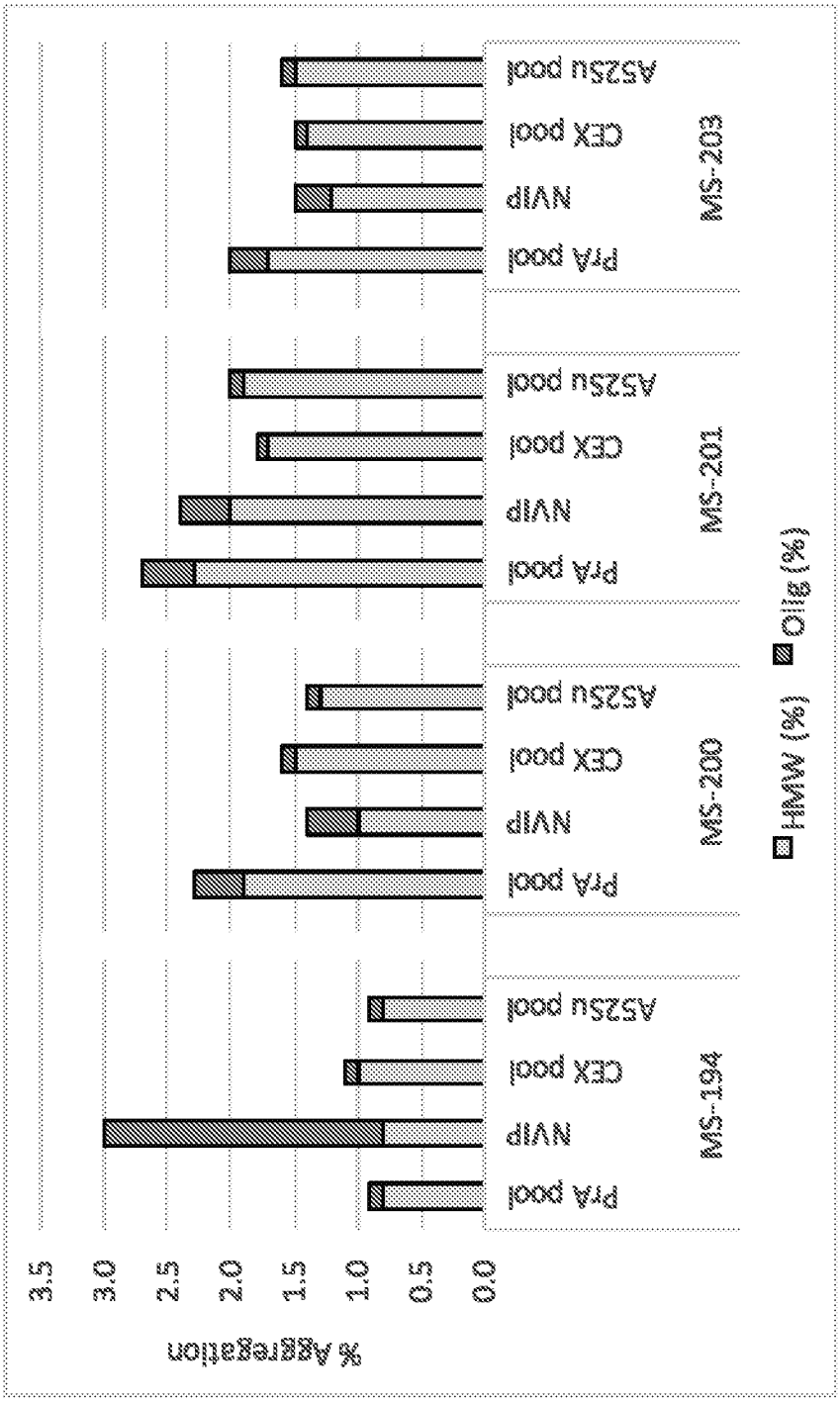
% Aggregation
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
HMW (%)
Olig (%)
MS-194
MS-200
MS-201
MS-203
PrA pool
NVIP
CEX pool
AS25u pool

FIG. 2

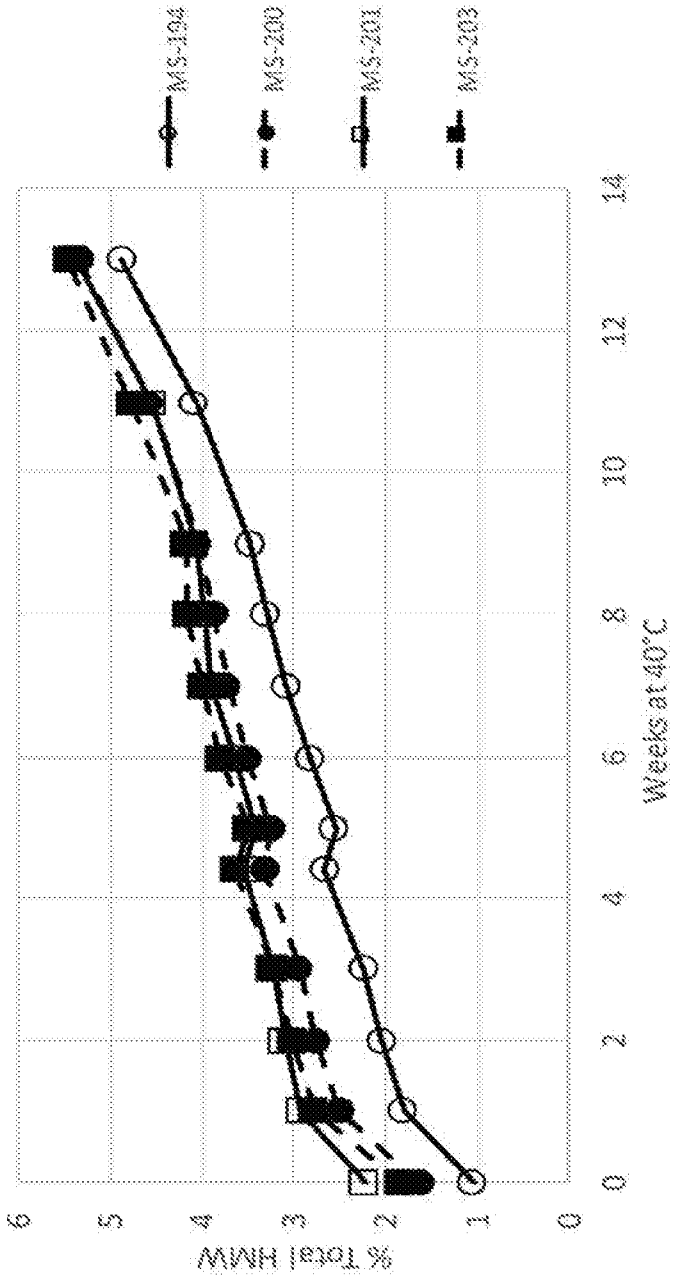
MS-194
MS-200
MS-201
MS-203
% Total HMW
Weeks at 40°C
0
1
2
3
4
5
6
0
2
4
6
8
10
12
14

FIG. 3

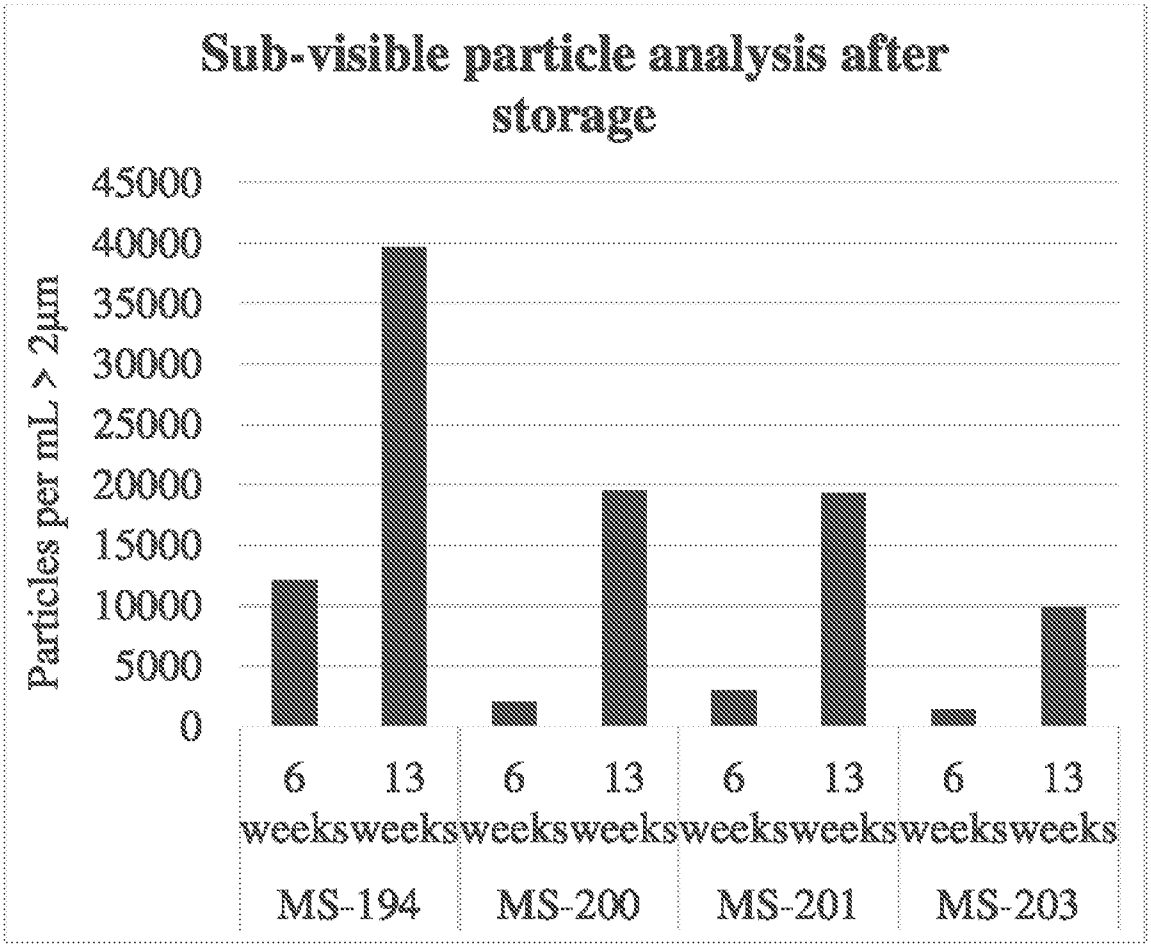
Sub-visible particle analysis after storage
Particles per mL > 2µm
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
6 weeks
13 weeks
6 weeks
13 weeks
6 weeks
13 weeks
6 weeks
13 weeks
MS-194
MS-200
MS-201
MS-203

FIG. 4

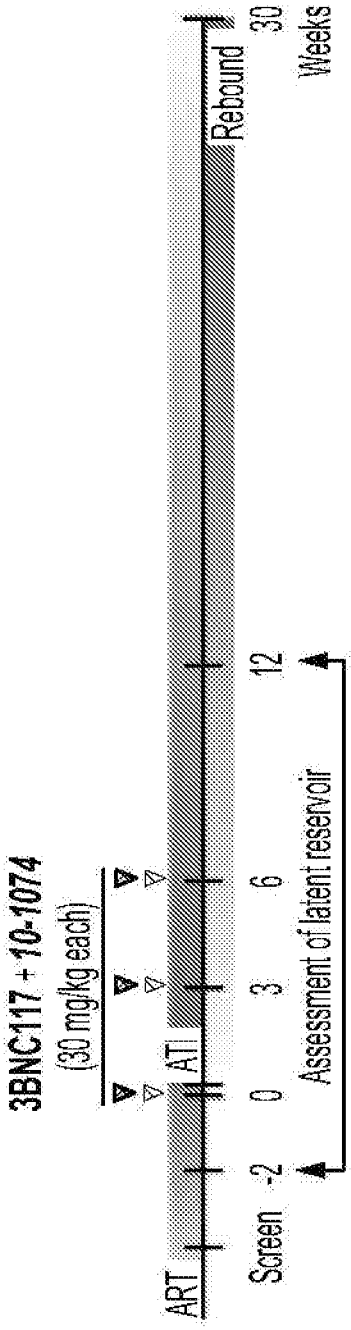
3BNC117 + 10-1074
(30 mg/kg each)
ART
ATI
Rebound
Screen
-2
0
3
6
12
30
Weeks
Assessment of latent reservoir

FIG. 5A

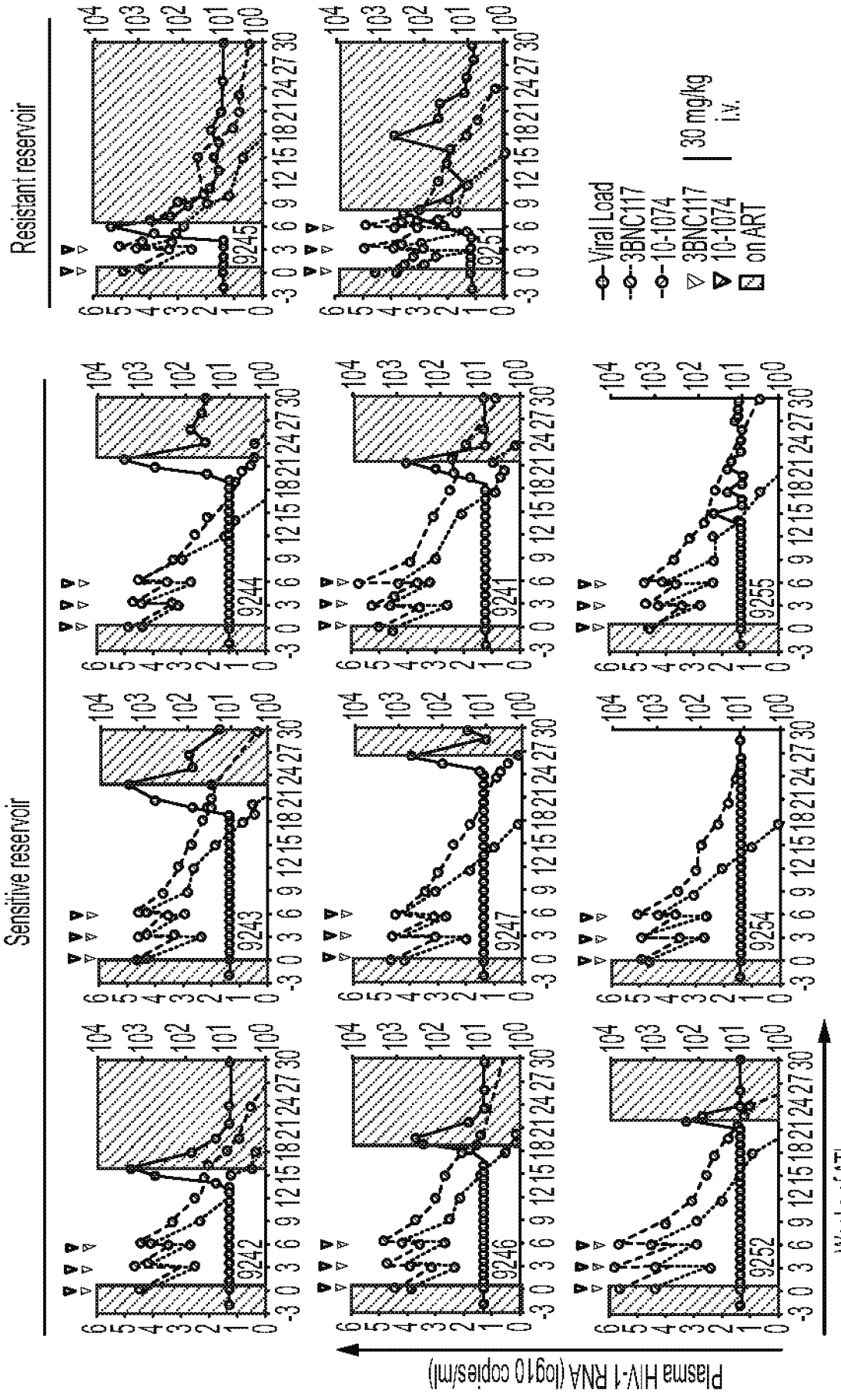
bNAb serum levels (µg/ml)
Resistant reservoir
Sensitive reservoir
Viral Load
3BNC117
10-1074
3BNC117
10-1074
on ART
30 mg/kg
i.v.
Plasma HIV-1 RNA (log10 copies/ml)
Weeks of ATI
9242
9243
9244
9245
9246
9247
9241
9251
9252
9254
9255

FIG. 5B

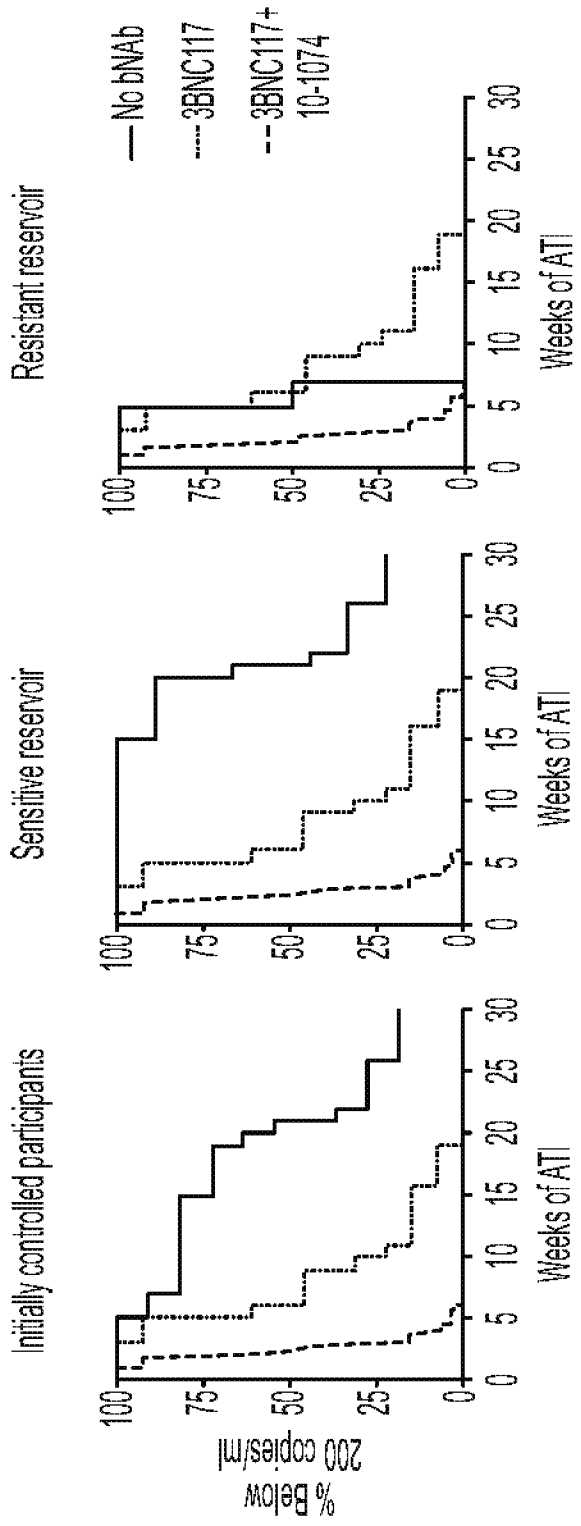
Initially controlled participants
Sensitive reservoir
Resistant reservoir
% Below 200 copies/ml
100
75
50
25
0
0 5 10 15 20 25 30
Weeks of ATI
No bNAb
3BNC117
3BNC117+ 10-1074

FIG. 5C

Baseline characteristics of participants (*n*=15)	
Male sex - *n* (%)	14(93%)
Age - Median years (range)	40 (22-55)
Race or ethnicity - *n* (%)	
White non-Hispanic	6 (40.0%)
Black non-Hispanic	4 (26.7%)
Hispanic, regardless of race	4 (26.7%)
Multiple, non-Hispanic	1 (6.7%)
Years since HIV-1 diagnosis - Median (range)	6 (3-23)
HIV-1 RNA level prior to ATI - *n* (%)	
< 20 copies/ml (screen)	15 (100%)
< 20 copies/ml (week-2 and day 0)	11 (73%)
CD4+ T-cell count - Median cells/µl (range)	
Day 0	730 (515-1,360)
Reported nadir	450 (270- 1,000)
Years on ART - Median (range)	
First ART	5 (2-21)
Uninterrupted ART	5 (2-21)
ART regimen at screening - *n* (%)	
Integrase inhibitor-based	10 (66.7%)
NNRTI*-based	3 (20.0%)
Protease inhibitor-based	2 (13.3%)

FIG. 6A

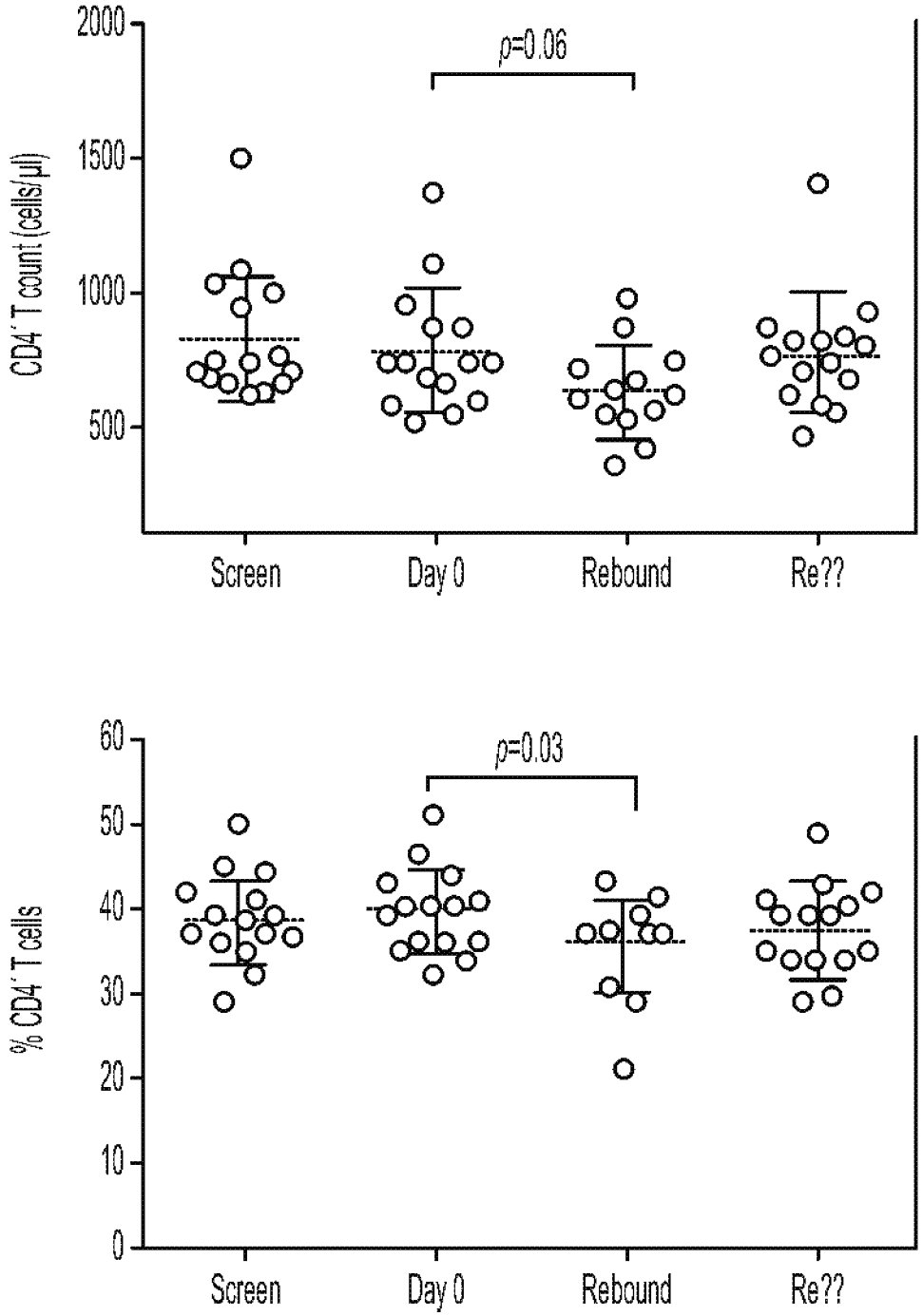
2000
1500
1000
500
CD4+ T count (cells/µl)
p=0.06
Screen
Day 0
Rebound
Re??
60
50
40
30
20
10
0
% CD4+ T cells
p=0.03
Screen
Day 0
Rebound
Re??

FIG. 6B

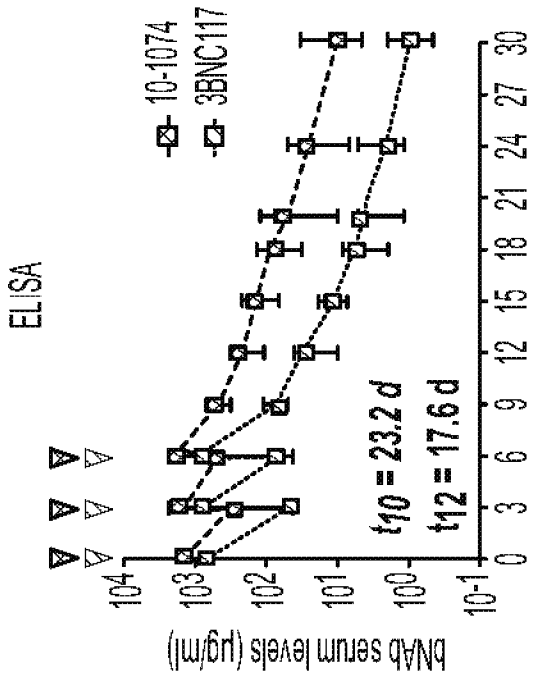

FIG. 6D

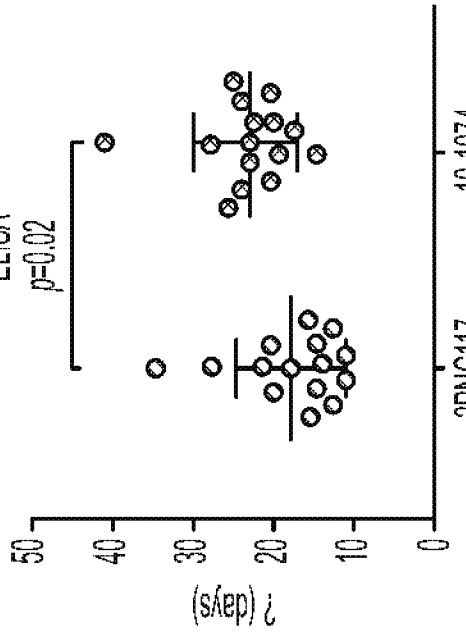

FIG. 6F

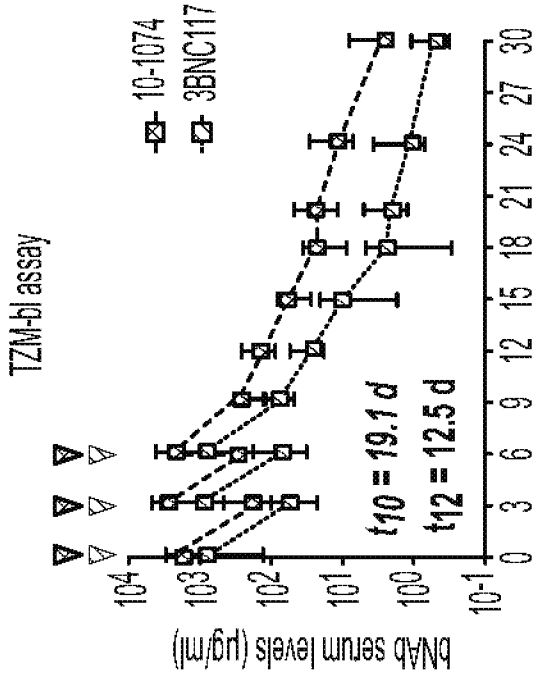

FIG. 6C

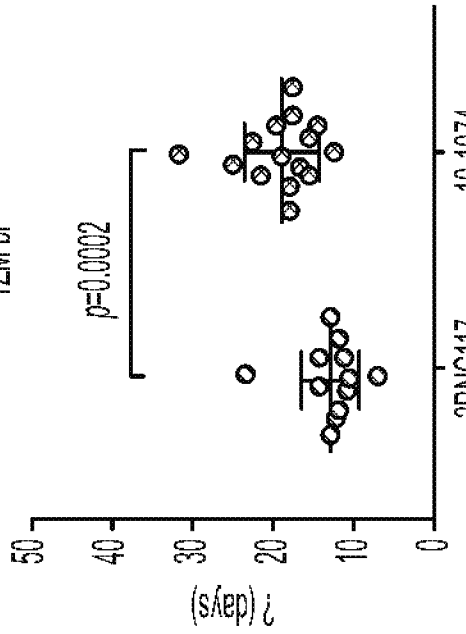

FIG. 6E

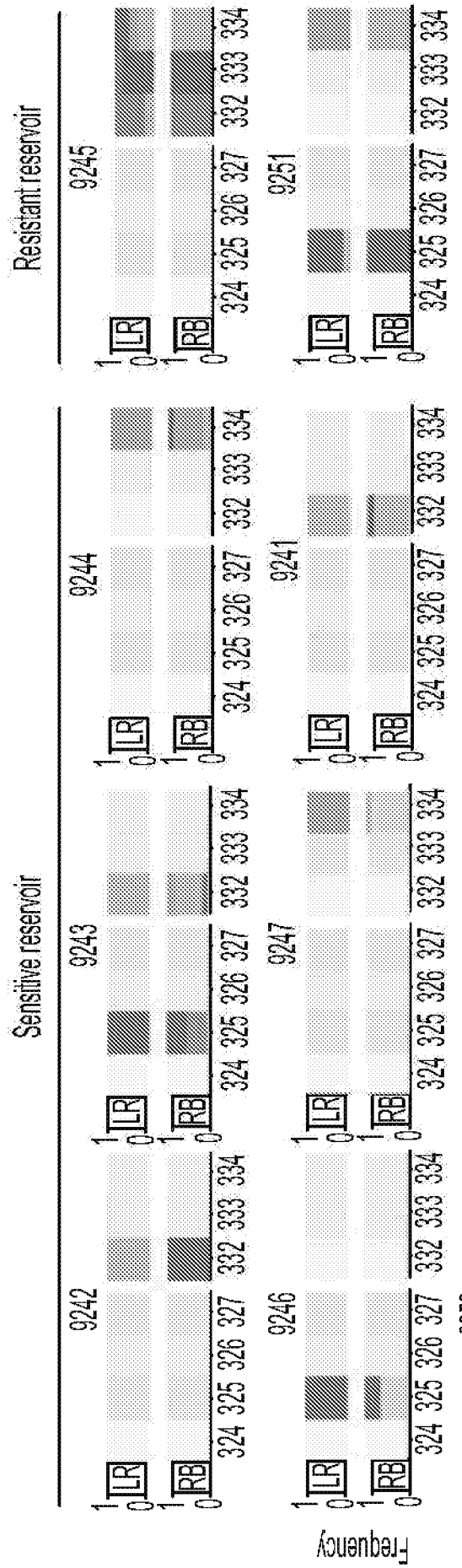
Sensitive reservoir
Resistant reservoir
9242
9243
9244
9245
9246
9247
9241
9251
9252
LR
RB
324 325 326 327 332 333 334
Frequency
10-1074 contact sites
G D N R N X S T
shading
no variation
variable
amino acid
D E C M R K S T F Y
N Q G I L V A W H P

FIG. 7A

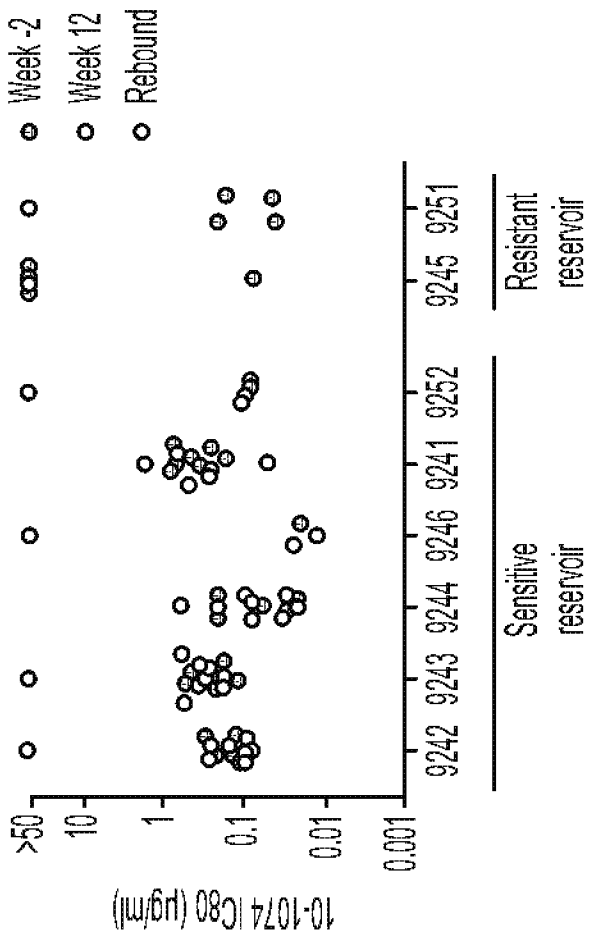
Week -2
Week 12
Rebound
10-1074 IC80 (µg/ml)
>50
10
1
0.1
0.01
0.001
9242 9243 9244 9246 9241 9252 9245 9251
Sensitive reservoir
Resistant reservoir

FIG. 7C

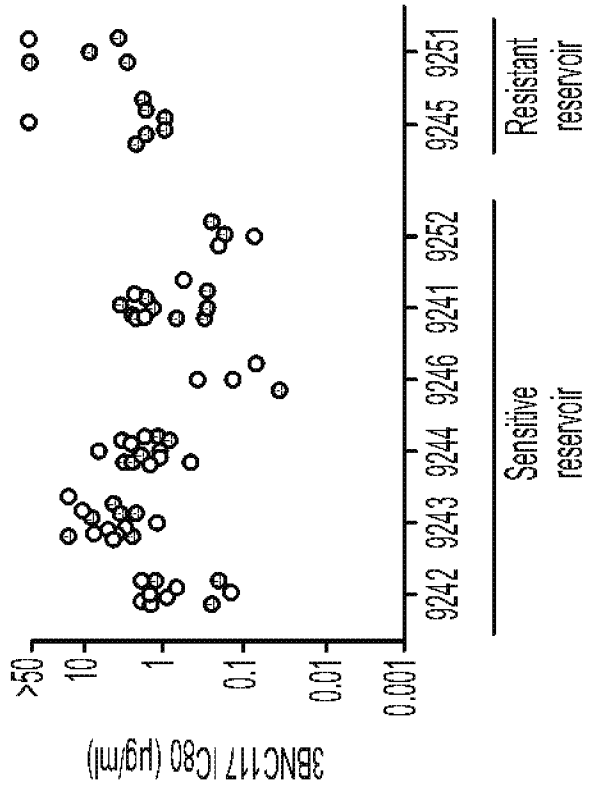
3BNC117 IC80 (µg/ml)
>50
10
1
0.1
0.01
0.001
9242 9243 9244 9246 9241 9252 9245 9251
Sensitive reservoir
Resistant reservoir

FIG. 7B

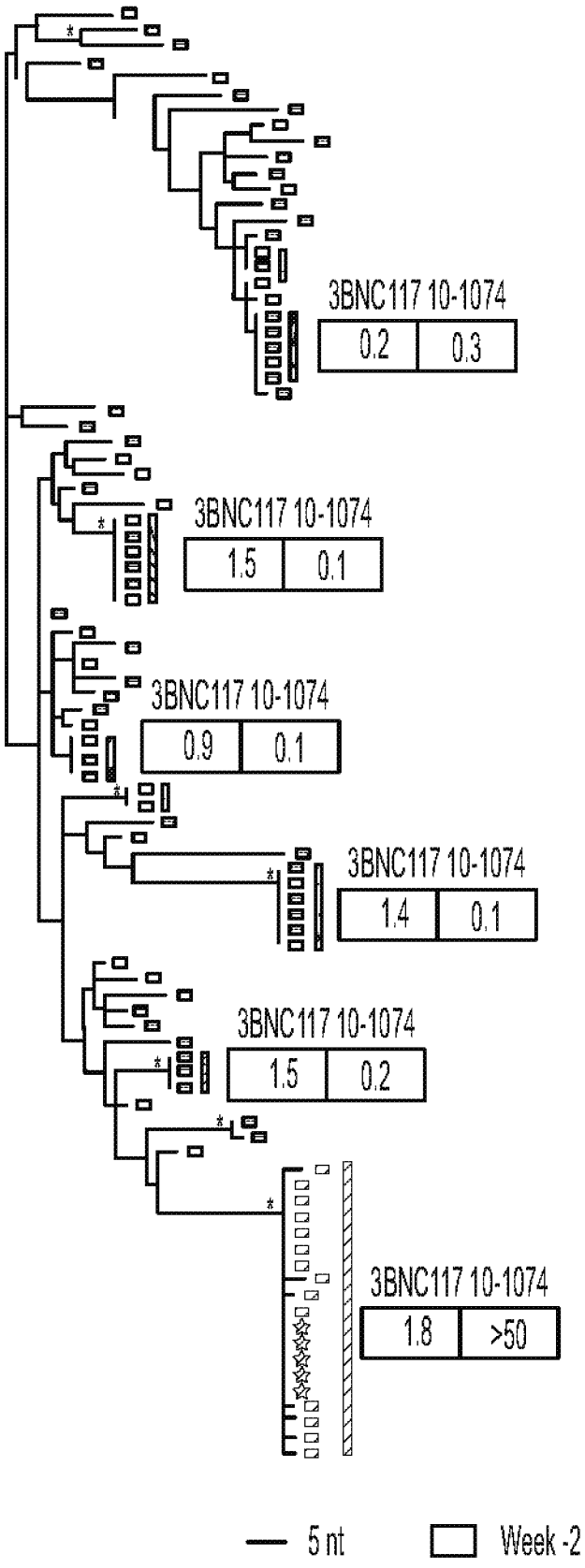
3BNC117 10-1074
0.2
0.3
3BNC117 10-1074
1.5
0.1
3BNC117 10-1074
0.9
0.1
3BNC117 10-1074
1.4
0.1
3BNC117 10-1074
1.5
0.2
3BNC117 10-1074
1.8
>50
5 nt
Week -2

FIG. 8

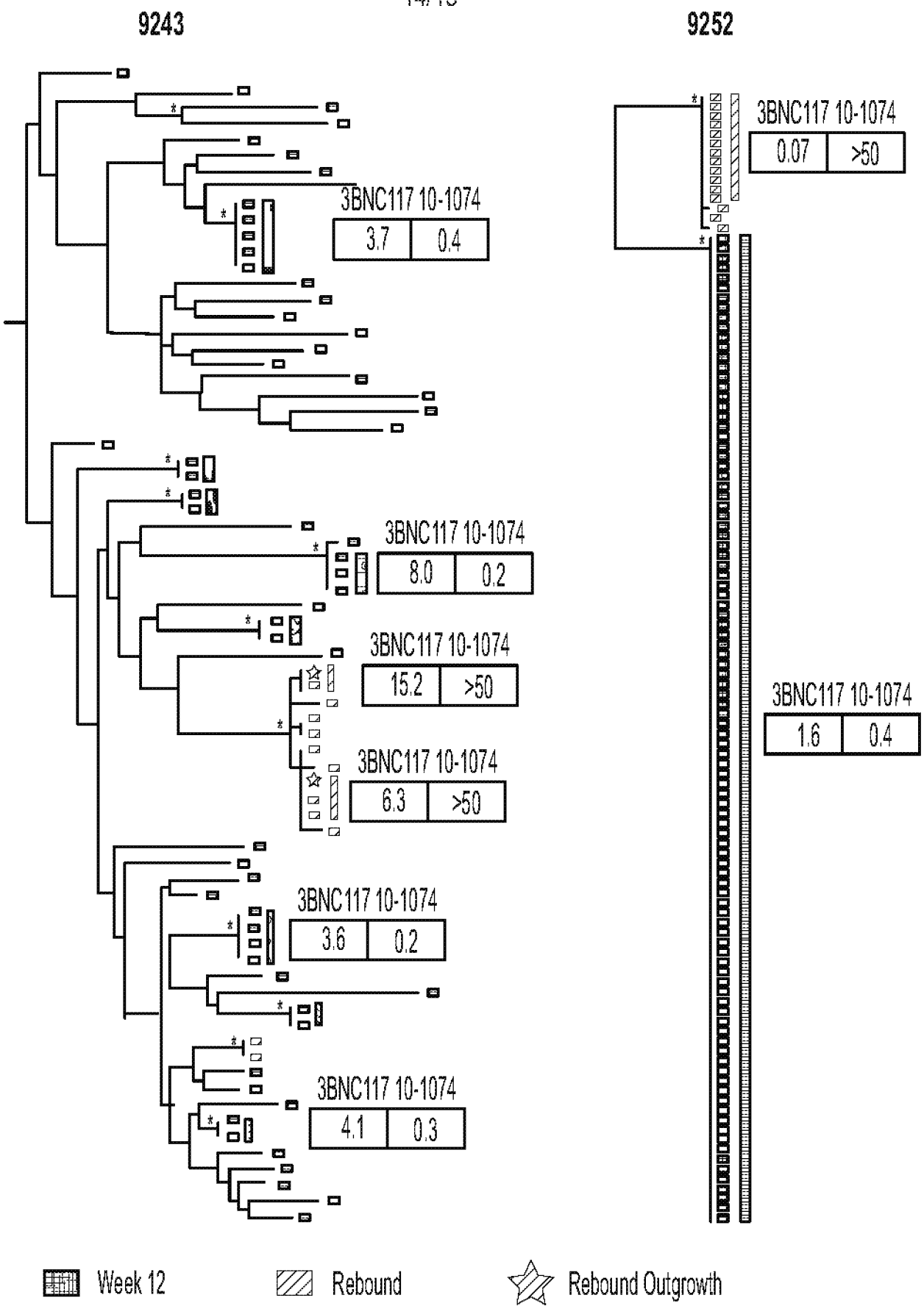

FIG. 8
CONTINUED

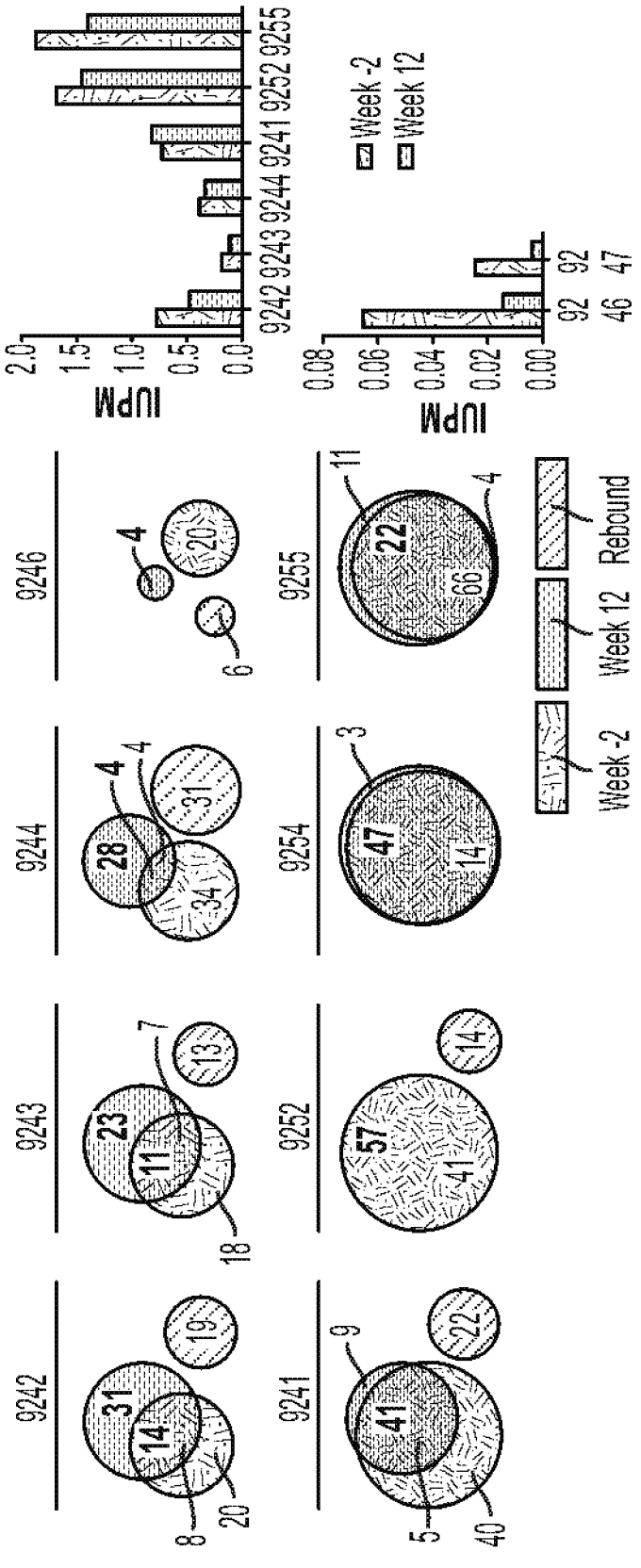
IUPM
2.0
1.5
1.0
0.5
0.0
9242 9243 9244 9241 9252 9255
Week -2
Week 12
IUPM
0.08
0.06
0.04
0.02
0.00
92 92
46 47
9246
9244
9243
9242
9255
9254
9252
9241
Week -2
Week 12
Rebound

FIG. 9B

FIG. 9A

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/050823

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/42; C07K 16/10; C12P 21/08 (2020.01)

CPC - A61K 39/42; C07K 16/1045; C12N 5/163; C12N 5/166; C12P 21/02 (2020.01)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

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

USPC - 424/148.1; 435/70.21; 530/388.35 (keyword delimited)

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	KERWIN et al. "Framework Mutations of the 10-1074 bnAb Increase Conformational Stability, Manufacturability, and Stability While Preserving Full Neutralization Activity," Journal of Pharmaceutical Sciences, 23 July 2019 (23.07.2019), Pgs. 1-14. entire document	1-7, 19-27, 30-33
A	US 2018/0230203 A1 (CALIFORNIA INSTITUTE OF TECHNOLOGY et al) 16 August 2018 (16.08.2018) entire document	1-7, 19-27, 30-33
A	KLEIN et al. "Somatic mutations of the immunoglobulin framework are generally required for broad and potent HIV-1 neutralization," Cell, 28 March 2013 (28.03.2013), Vol. 153, No. 1, Pgs. 126-138. entire document	1-7, 19-27, 30-33
A	WO 2014/063059 A1 (THE ROCKEFELLER UNIVERSITY) 24 April 2014 (24.04.2014) entire document	1-7, 19-27, 30-33
A	MOUQUET et al. "Complex-type N-glycan recognition by potent broadly neutralizing HIV antibodies," Proc. Natl. Acad. Sci. U.S.A, 30 October 2012 (30.10.2012), Vol. 109, Iss. 47, Pgs. 3268-3277. entire document	1-7, 19-27, 30-33

☐ 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	Date of mailing of the international search report
07 January 2020	30 JAN 2020
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/050823

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

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☒ forming part of the international application as filed:

      ☒ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

SEQ ID NOs: 1-10 and 61-70 were searched.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/050823

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

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

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

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

3. ☒ Claims Nos.: 28
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:
See extra sheet(s).

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

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

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

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-7, 19-27, and 30-33 to the extent that they read on an anti-HIV antibody of SEQ ID NOs:3 and 61.

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.

Continued from Box No. III Observations where unity of invention is lacking

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

Group I+: claims 1-27 and 29-34 are drawn to anti-HIV antibodies.

The first invention of Group I+ is restricted to an anti-HIV antibody comprising a heavy chain variable region wherein in the heavy chain variable region is selected to be SEQ ID NO:61; and a light chain variable region, wherein the light chain variable region is selected to be SEQ ID NO:3. It is believed that claims 1-7, 19-27, and 30-33 read on this first named invention and thus these claims will be searched without fee to the extent that they read on an anti-HIV antibody of SEQ ID NOs:3 and 61.

Applicant is invited to elect additional anti-HIV antibodies, each with specific SEQ ID NO for each heavy chain variable region and light chain variable region, to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be an anti-HIV antibody comprising a heavy chain variable region wherein in the heavy chain variable region is selected to be SEQ ID NO:62; and a light chain variable region, wherein the light chain variable region is selected to be SEQ ID NO:4. Additional anti-HIV antibodies will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

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

The Groups I+ formulas do not share a significant structural element responsible for binding an HIV antigen, requiring the selection of alternatives for the amino acid sequences of each light and heavy chain variable regions, where "...[the] light chain variable region having a light chain amino acid sequence that is at least 75% identical to a polypeptide sequence selected from the group consisting of the light chain variable regions of SEQ ID NOs: 3-13, 22, 24-28, 35-39, 43-45, and 47" and "...[the] heavy chain variable region having a heavy chain amino acid sequence that is at least 75% identical to a polypeptide sequence selected from the group consisting of the heavy chain variable regions of SEQ ID NOs: 61-94".

Additionally, even if Groups I+ were considered to share the technical features of an isolated anti-HIV antibody, or antigen-binding portion thereof, comprising a light chain variable region having a light chain amino acid sequence polypeptide sequence selected from the group consisting of the light chain variable regions, wherein the isolated anti-HIV antibody, or antigen-binding portion thereof comprises one or more light chain substitutions at one or more residues; an isolated anti-HIV antibody, or antigen-binding portion thereof, comprising a heavy chain variable region having a heavy chain amino acid sequence polypeptide sequence selected from the group consisting of the heavy chain variable region, wherein the isolated anti-HIV antibody, or antigen-binding portion thereof comprises one or more heavy chain substitutions at one or more residues; these shared technical features do not represent a contribution over the prior art.

Specifically, US 2018/0230203 A1 to California Institute of Technology et al. discloses an isolated anti-HIV antibody, or antigen-binding portion thereof (embodiments of the present invention are directed to compositions and methods for anti-HIV (anti-CD4 binding site) broadly neutralizing antibodies, Abstract; a composition includes an isolated anti-CD4 binding site, Para. [0007]), comprising a light chain variable region having a light chain amino acid sequence polypeptide sequence selected from the group consisting of the light chain variable regions (antibody having a... light chain... the light chain including a substitution of tyrosine at position 28 of the light chain for serine, Para. [0008]), wherein the isolated anti-HIV antibody, or antigen-binding portion thereof comprises one or more light chain substitutions at one or more residues (antibody having a... light chain... the light chain including a substitution of tyrosine at position 28 of the light chain for serine, Para. [0008]); an isolated anti-HIV antibody, or antigen-binding portion thereof (embodiments of the present invention are directed to compositions and methods for anti-HIV (anti-CD4 binding site) broadly neutralizing antibodies, Abstract; a composition includes an isolated anti-CD4 binding site, Para. [0007]), comprising a heavy chain variable region having a heavy chain amino acid sequence polypeptide sequence selected from the group consisting of the heavy chain variable region, wherein the isolated anti-HIV antibody, or antigen-binding portion thereof comprises one or more heavy chain substitutions at one or more residues (antibody having a heavy chain... the heavy chain including a first substitution at a position equivalent to Phe43 of a CD4 receptor protein, Para. [0007]).

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