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(54) Title: METHODS FOR AFFINITY MATURATION-BASED ANTIBODY OPTIMIZATION

(57) Abstract: Provided herein is a rational method of affinity maturation to evolve the activity of an antibody or portion thereof based on the structure/affinity or activity relationship of an antibody. The resulting affinity matured antibodies exhibit improved or optimized binding affinity for a target antigen.

METHODS FOR AFFINITY MATURATION-BASED ANTIBODY OPTIMIZATION

RELATED APPLICATIONS

Benefit of priority is claimed to U.S. Provisional Application Serial No. 61/280,618, entitled "Methods for Affinity Maturation-Based Antibody Optimization," filed November 04, 2009, and to U.S. Provisional Application Serial No. 61/395,670, entitled "Methods for Affinity Maturation-Based Antibody Optimization, Antibody Conversion and Antibodies," filed May 13, 2010. Where permitted, the subject matter of the above-noted applications are incorporated by reference in its entirety.

This application also is related to International PCT Application No. PCT/US2009/063299, entitled "Combinatorial Antibody Libraries and Uses Thereof," filed November 04, 2009, which claims priority to U.S. Provisional Application No. 61/198,764 filed November 7, 2008 and to U.S. Provisional Application No. 61/211,204 filed March 25, 2009, each entitled "Combinatorial Antibody Libraries and Uses Thereof." This application also is related to International PCT Application No. PCT/US09/63303, entitled Anti-DLL4 Antibodies and Uses Thereof, which also claims priority to each of U.S. Provisional Application Nos. 61/198,764 and 61/211,204.

The subject matter of each of the above-noted applications is incorporated by reference in its entirety.

Incorporation by reference of Sequence Listing provided on compact discs

An electronic version of the Sequence Listing is filed herewith, the contents of which are incorporated by reference in their entirety. The electronic file is 2.66 megabytes in size, and titled 702seqPC1.txt.

FIELD OF THE INVENTION

Provided herein is a rational method of affinity maturation to evolve the activity of an antibody or portion thereof based on the structure/affinity or activity relationship of an antibody. The resulting affinity matured antibodies exhibit improved or optimized binding affinity for a target antigen.

BACKGROUND

Numerous therapeutic and diagnostic monoclonal antibodies (MAbs) are used in the clinical setting to treat and diagnose human diseases, for example, cancer and autoimmune diseases. For example, exemplary therapeutic antibodies include Rituxan (Rituximab), Herceptin (Trastuzumab), Avastin (Bevacizumab) and Remicade (Infliximab). In designing antibody therapeutics, it is desirable to create antibodies, for example, antibodies that modulate a functional activity of a target, and/or improved antibodies such as antibodies with higher specificity and/or affinity and/or and antibodies that are more bioavailable, or stable or

soluble in particular cellular or tissue environments. It is among the objects herein to provide methods for optimizing and improving the binding affiniites of antibodies and for selecting antibodies with desired affinities.

SUMMARY

Provided herein are methods of affinity maturation of antibodies or fragments thereof based on structure/activity relationship (SAR). The methods result in the optimization of antibodies to have increased and improved activity (e.g. binding specificity or affinity) for a target antigen compared to the starting antibody that is affinity matured.

Provided herein is a method of affinity maturation of a first antibody or portion thereof for a target antigen. In the method, a related antibody or portion thereof is identified that exhibits a reduced activity for the target antigen than the corresponding form of a first antibody, whereby the related antibody or portion thereof contains a related variable heavy chain or a related variable light chain that is either 1) one in which the corresponding variable heavy chain or variable light chain of the related antibody exhibits at least 75% amino acid sequence identity to the variable heavy chain or variable light chain of the first antibody but does not exhibit 100% sequence identity therewith; or 2) one in which at least one of the V_H, D_H and J_H germline segments of the nucleic acid molecule encoding the variable heavy chain of the related antibody is identical to one of the V_H, D_H and J_H germline segments of the nucleic acid molecule encoding the variable heavy chain of the first antibody and/or at least one of the V_κ and J_κ or at least one of the V_λ and J_λ germline segments of the nucleic acid molecule encoding the variable light chain is identical to one of the V_κ and J_κ or V_λ and J_λ germline segments of the nucleic acid molecule encoding the variable light chain of the first antibody. Further, in the method, the amino acid sequence of the variable heavy chain or variable light chain of the first antibody is compared to the amino acid sequence of the corresponding related variable heavy chain or variable light chain of the related antibody. Following comparison, a target region within the variable heavy chain or variable light chain of a first antibody is identified, whereby a target region is a region in the first antibody that exhibits at least one amino acid difference compared to the same region in the related antibody. After identifying a target region, a plurality of modified antibodies are produced each containing a variable heavy chain and a variable light chain, or a portion thereof, where at least one of the variable heavy chain or variable light chain is modified in its target region by replacement of a single amino acid residue, such that the target region in each of the plurality of antibodies contains replacement of an amino acid to a different amino acid compared to the first antibody. The resulting plurality of mutated antibodies are screened for an activity to the target antigen. Modified antibodies that exhibit increased activity for the

target antigen compared to the first antibody. In one example of the method, the plurality of modified antibodies are produced by producing a plurality of nucleic acid molecules that encode modified forms of a variable heavy chain or a variable light chain of the first antibody, wherein the nucleic acid molecules contain one codon encoding an amino acid in the target region that encodes a different amino acid from the unmodified variable heavy or variable light chain, such that each nucleic acid molecule of the plurality encodes a variable heavy chain or variable light chain that is modified in its target region by replacement of a single amino acid residue.

In the method provided herein, the target region in the first antibody exhibits 1, 2, 3, 4, 5, 6 7, 8, 9 or 10 amino acid differences compared to the corresponding region in the related antibody. Further, in the method, the first antibody can be compared to 1, 2, 3, 4, or 5 related antibodies. In the method herein, the target region is selected from among a CDR1, CDR2, CDR3, FR1, FR2, FR3 and FR4. For example, the target region is a CDR1, CDR2 or CDR3.

In the method provided herein, an activity that is assessed can be binding, signal transduction, differentiation, alteration of gene expression, cellular proliferation, apoptosis, chemotaxis, cytotoxicity, cancer cell invasion, endothelial cell proliferation or tube formation. In one example, the activity is binding and binding is assessed by an immunoassay, whole cell panning or surface plasmon resonance (SPR). For example, binding can be assessed by immunoassay such as by a radioimmunoassay, enzyme linked immunosorbent assay (ELISA) or electrochemiluminescence assay. In particular, binding is assessed using an electrochemiluminescence assay such as meso scale discovery (MSD).

In the method herein, the first antibody that is affinity matured binds to the target antigen with a binding affinity that is at or about 10^{-4} M, 10^{-5} M, 10^{-6} M, 10^{-7} M, 10^{-8} M, or lower, when the antibody is in a Fab form.

In one example, the affinity maturation method provided herein involves comparison to a related antibody or portion thereof that exhibits 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5% or less activity than the corresponding form of the first antibody. For example, the related antibody can exhibit the same or similar level of activity to the target antigen compared to a negative control. In another example, the related antibody exhibits a binding affinity that is less than the binding affinity of the first antibody, whereby the binding affinity is at or about 10^{-4} M, 10^{-5} M, 10^{-6} M, 10^{-7} M, 10^{-8} M or lower in its Fab form.

In one example of the method provided herein, a target region is identified within the variable heavy chain of the first antibody, and the method is performed therefrom. In another example of a method provided herein, a target region is identified within the variable light

chain of the first antibody, the method is performed therefrom. In a further example of the method herein, a target region is identified within the variable heavy chain of the first antibody and steps the method is performed therefrom; and separately and independently a target region is identified within the variable light chain of the first antibody, and the method is performed therefrom.

In one aspect of the method herein, a related antibody that contains the related corresponding variable heavy chain is different than a related antibody that contains the related corresponding variable light chain. In another aspect of the method herein, a related antibody that contains the related corresponding variable heavy chain is the same as a related antibody that contains the related corresponding variable light chain.

In one example of the method herein, the variable heavy chain or variable light chain of the first antibody exhibits 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity with the corresponding related variable heavy chain or variable light chain of the related antibody. In particular, the variable heavy chain or variable light chain of the first antibody exhibits at least 95% sequence identity with the corresponding related variable heavy chain or variable light chain of the related antibody.

In another example, the related antibody contains a related variable heavy chain or variable light chain that is one in which at least one of the V_H, D_H and J_H germline segments of the nucleic acid molecule encoding the variable heavy chain of the first antibody is identical to one of the V_H, D_H and J_H germline segments of the nucleic acid molecule encoding the variable heavy chain of the related antibody; and/or at least one of the V_κ and J_κ or at least one of the V_λ and J_λ germline segments of the nucleic acid molecule encoding the variable light chain of the first antibody is identical to one of the V_κ and J_κ or V_λ and J_λ germline segments of the nucleic acid molecule encoding the variable light chain of the related antibody. For example, the related antibody contains a related variable heavy chain or variable light that is one in which at least one of the V_H, D_H and J_H germline segments of the nucleic acid molecule encoding the variable heavy chain of the first antibody is from the same gene family as one of the V_H, D_H and J_H germline segments of the nucleic acid molecule encoding the variable heavy chain of the related antibody; and/or at least one of the V_κ and J_κ or at least one of the V_λ and J_λ germline segments of the nucleic acid molecule encoding the variable light chain of the first antibody is from the same gene family as one of the V_κ and J_κ or V_λ and J_λ germline segments of the nucleic acid molecule encoding the variable light chain of the related antibody. In such examples, the variable heavy chain or variable light chain of the first antibody exhibits 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%,

97%, 98% or 99% sequence identity with the corresponding related variable heavy chain or variable light chain of the related antibody.

In the method herein, the first antibody is identified by screening a combinatorial antibody library, where the combinatorial antibody library is produced by combining a V_H, a D_H and a J_H human germline segment or portion thereof in frame to generate a sequence of a nucleic acid molecule encoding a VH chain or a portion thereof; and combining a V_κ and a J_κ human germline segment or portion thereof, or a V_λ and a J_λ germline segment or portion thereof in frame to generate a sequence of a nucleic acid molecule encoding a VL chain or a portion thereof. In the steps of combining, each of the portions of the V_H, D_H, J_H, V_κ, J_κ, V_λ or J_λ are sufficient to produce an antibody or portion thereof containing a VH or VL or portion thereof that forms a sufficient antigen binding site. The steps of combining are repeated a plurality of times to generate sequences of a plurality of different nucleic acid molecules. The nucleic acid molecules are synthesized to produce two libraries. The first library contains nucleic acid molecules encoding a VH chain or a portion thereof; and the second library contains nucleic acid molecules encoding a VL chain or a portion thereof. The nucleic acid molecules from the first and second library are introduced into a cell, which is repeated a plurality of times to produce a library of cells, wherein each cell contains nucleic acid molecules encoding a different combination of VH and VL from every other cell in the library of cells. Finally, in the method of generating a combinatorial library, the cells are grown to express the antibodies or portions thereof in each cell, thereby producing a plurality of antibodies or portion thereof, wherein each antibody or portion thereof in the library comprises a different combination of a VH and a VL chain or a sufficient portion thereof to form an antigen binding site from all other antibodies or portions thereof in the library. To identify a first antibody, the library is screened by contacting an antibody or portion thereof in the library with a target protein, assessing binding of the antibody or portion thereof with the target protein and/or whether the antibody or portion thereof modulates a functional activity of the target protein; and identifying an antibody or portion thereof that exhibits an activity for the target protein, wherein the identified antibody or portion thereof is a first antibody. Similarly, a related antibody also can be identified by screening such a combinatorial antibody library for the target antigen to identify a related antibody that exhibits reduced activity for the target antigen compared to the first antibody.

The combinatorial library that is screened can be an addressable library. In an addressable library, the synthesized nucleic acid sequences are individually addressed, thereby generating a first addressed nucleic acid library and a second addressed nucleic acid

library. The cells also are addressed such that each locus contains a cell that contains nucleic acid molecules encoding a different combination of a VH and a VL from every other cell in the addressed library of cells. Finally, the plurality of antibodies or portions thereof are addressed, such that the antibodies or portions thereof at each locus in the library are the same antibody and are different from those at each and every other locus; and the identity of the antibody or portion thereof is known by its address. The addressable library can be arranged in a spatial array, wherein each individual locus of the array corresponds to a different antibody member. The spatial array can be a multiwell plate. In another example, the antibodies in the addressable library can be attached to a solid support that is a filter, chip, slide, bead or cellulose, and the different antibody members are immobilized to the surface thereof.

In the affinity maturation method herein, the target antigen is a polypeptide, carbohydrate, lipid, nucleic acid or a small molecule. The target antigen can expressed on the surface of a virus, bacteria, tumor or other cell, or is a recombinant protein or peptide. In one example, the target antigen is a protein that is a target for therapeutic intervention. For example, the target antigen is involved in cell proliferation and differentiation, cell migration, apoptosis or angiogenesis. Exemplary of target antigens include, but are not limited to, a VEGFR-1, VEGFR-2, VEGFR-3 (vascular endothelial growth factor receptors 1, 2, and 3), a epidermal growth factor receptor (EGFR), ErbB-2, ErbB-3, IGF-R1, C-Met (also known as hepatocyte growth factor receptor; HGFR), DLL4, DDR1 (discoidin domain receptor), KIT (receptor for c-kit), FGFR1, FGFR2, FGFR4 (fibroblast growth factor receptors 1, 2, and 4), RON (recepteur d'origine nantais; also known as macrophage stimulating 1 receptor), TEK (endothelial-specific receptor tyrosine kinase), TIE (tyrosine kinase with immunoglobulin and epidermal growth factor homology domains receptor), CSF1R (colony stimulating factor 1 receptor), PDGFRB (platelet-derived growth factor receptor B), EPHA1, EPHA2, EPHB1 (erythropoietin-producing hepatocellular receptor A1, A2 and B1), TNF-R1, TNF-R2, HVEM, LT-βR, CD20, CD3, CD25, NOTCH, G-CSF-R, GM-CSF-R, EPO-R., a cadherin, an integrin, CD52, CD44, VEGF-A, VEGF-B, VEGF-C, VEGF-D, PIGF, EGF, HGF, TNF-α, LIGHT, BTLA, lymphotoxin (LT), IgE, G-CSF, GM-CSF and EPO.

In the affinity maturation method provided herein, a subset of the amino acid residues in the target region are modified by amino acid replacement. In one example, only the amino acid residues that differ between the first antibody and related antibody in the target region are modified by amino acid replacement. In another example, only the amino acid residues that are the same between the first antibody and the related antibody in the target region are modified by amino acid replacement. In some instances in the method provided herein, all of

the amino acids residues in the target region are modified by amino acid replacement. For amino acid that is modified, the amino acid replacement can be to all 19 other amino acid residues, or a restricted subset thereof.

In the method provided herein, that antibody is mutated by PCR mutagenesis, cassette mutagenesis, site-directed mutagenesis, random point mutagenesis, mutagenesis using uracil containing templates, oligonucleotide-directed mutagenesis, phosphorothioate-modified DNA mutagenesis, mutagenesis using gapped duplex DNA, point mismatch repair, mutagenesis using repair-deficient host strains, restriction-selection and restriction-purification, deletion mutagenesis, mutagenesis by total gene synthesis, and double-strand break repair. The antibody can be mutated by NNK, NNS, NNN, NNY or NNR mutagenesis.

In one aspect of the method, scanning mutagenesis of the target region is performed to further elucidate amino acid residues to mutagenenize. In such a method, scanning mutagenesis is performed on the first antibody by producing a plurality of modified antibodies comprising a variable heavy chain and a variable light chain, or a portion thereof, where at least one of the variable heavy chain or variable light chain is one that is modified by replacement of a single amino acid residue with another amino acid residue in the target region, whereby each of the plurality of antibodies contains replacement of an amino acid in the target region compared to the first antibody. Each of the plurality of modified antibodies are screened for an activity to the target antigen. A second antibody is selected from among the modified antibodies that exhibits retained or increased activity for the target antigen compared to the first antibody not containing the amino acid replacement, whereby the second antibody is used in place of the first antibody in the affinity maturation method herein above. In such an example, the plurality of modified antibodies can be produced by producing a plurality of nucleic acid molecules that encode modified forms of a variable heavy chain or a variable light chain of the first antibody containing the target region, wherein the nucleic acid molecules contain one codon that encodes an amino acid in the target region compared to the corresponding codon of the unmodified variable heavy or variable light chain that does not encode the neutral amino acid, whereby each nucleic acid molecule of the plurality encodes a variable heavy chain or variable light chain that is modified by replacement of a single amino acid residue to a neutral amino acid residue in the target region.

Further, in a method where scanning mutagenesis is performed on a target region, a second antibody can be selected that exhibits an activity that is at least or about 75%, 80%, 85%, 90%, 95%, 100%, 105%, 110%, 115%, 120%, 130%, 140%, 150%, 200% or more of the activity of the corresponding form of the first antibody. After selecting the antibody that exhibits retained or increased activity, the amino acid residue position that is modified in the

second antibody to contain a scanned acid compared to the first antibody not containing the amino acid replacement can be determined.

In examples of the affinity maturation method herein where scanning mutagenesis is employed, the scanned amino acid can be alanine, threonine, proline or glycine. For example, the scanned amino acid is alanine. The scanned amino acid also can be a non-natural amino acid.

Further, when performing scanning mutagenesis in the methods herein, a subset of the amino acid residues in the target region are modified by amino acid replacement to a scanned amino acid. In one example, only the amino acid residues that differ between the first antibody and related antibody in the target region are modified by amino acid replacement to a scanned amino acid. In another example, only the amino acid residues that are the same between the first antibody and the related antibody in the target region are modified by amino acid replacement to a scanned amino acid. In an additional example, all of the amino acids in the target region are modified by amino acid replacement to a neutral amino acid.

In the affinity maturation methods herein, the selected modified antibody exhibits 2-fold, 5-fold, 10-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold, 600-fold, 700-fold, 800-fold, 900-fold, 1000-fold, 2000-fold, 3000-fold, 4000-fold, 5000-fold, 10000-fold or more improved activity for the target antigen compared to the first antibody. For example, the modified antibody exhibits a binding affinity that is greater than the binding affinity of the first antibody and is or is about 1×10^{-9} M, 2×10^{-9} M, 3×10^{-9} M, 4×10^{-9} M, 5×10^{-9} M, 6×10^{-9} M, 7×10^{-9} M, 8×10^{-9} M, 9×10^{-9} M, 1×10^{-10} M, 2×10^{-10} M, 3×10^{-10} M, 4×10^{-10} M, 5×10^{-10} M, 6×10^{-10} M, 7×10^{-10} M, 8×10^{-10} M, 9×10^{-10} M or less.

In the methods herein, the amino acid modifications that are altered in the modified antibody compared to the first antibody not containing the amino acid replacements can be determined. Further, the method of affinity maturation provided herein can be repeated iteratively where a modified antibody is selected and is used as the first for subsequent affinity maturation thereof. In addition, in the methods herein, one or more amino acid replacements in the target region of one or more variable heavy chains or one or more variable light chains of selected modified antibodies are combined to generate a further modified antibody, whereby the further modified antibodies are screened for an activity to the target antigen to identify a further modified antibody that exhibits an increased activity for the target antigen compared to the first antibody and to the selected modified antibodies.

In the affinity maturation methods herein, the method can be performed on the variable heavy chain of the first antibody and first modified antibodies selected each

containing an amino acid replacement in the target region. Then, independent and separately, the method can be performed on the variable light chain of the first antibody and a second modified antibodies each containing an amino acid replacement in the target region can be selected. The variable heavy chain of a first modified antibody can be combined with the variable light chain of a second modified antibody to generate a plurality of different third modified antibodies each comprising an amino acid replacement in the target region of the variable heavy chain and variable light chain. Such third antibodies can be screened for an activity to the target antigen, and further modified antibodies that exhibit an increased activity for the target antigen compared to the first and second modified antibodies can be selected.

Further, in any of the methods herein, other regions of the antibody can be optimized. For example, after selecting a modified antibody, another different region within the variable heavy chain or variable light chain of the first modified antibody can be selected for further mutagenesis. In such an example, a plurality of nucleic acid molecules that encode modified forms of the variable heavy chain or variable light chain of the first modified antibody can be produced , wherein the nucleic acid molecules contain one codon encoding an amino acid in the selected region that encodes a different amino acid from the first modified variable heavy or variable light chain, whereby each nucleic acid molecule of the plurality encodes a variable heavy chain or variable light chain that is modified in the selected region by replacement of a single amino acid residue. A plurality of further modified antibodies then are produced each containg a variable heavy chain and a variable light chain, or a portion thereof, wherein at least one of the variable heavy chain or variable light chain is modified, whereby the selected region in each of the plurality of antibodies contains replacement of an amino acid to a different amino acid compared to the first modified antibody. The further modified antibodies are screen for activity for the target antigen those further modified antibodies that exhibit increased activity for the target antigen compared to the first modified antibody are selected. In such examples, the different region that is modified can be a CDR1, CDR2, CDR3, FR1, FR2, FR3 or FR4.

In any of the affinity maturation methods herein, any of the antibodoes can include an antibody or portion thereof. Such antibodies can be a Fab, Fab', $F(ab')_2$, single-chain Fv (scFv), Fv, dsFv, diabody, Fd and Fd' fragments, Fab fragments, Fd fragments, scFv fragments, and scFab fragments.

Provided herein is a method of affinity maturation based on scanning mutagenesis. In the method, scanning mutagenesis of a first antibody is performed by producing a plurality of nucleic acid molecules that encode modified forms of a variable heavy chain or a variable light chain of a first antibody, wherein the nucleic acid molecules contain one codon that

encodes another amino acid compared to the corresponding codon of the unmodified variable heavy or variable light chain that does not encode the other amino acid, whereby each nucleic acid molecule of the plurality encodes a variable heavy chain or variable light chain that is modified by replacement of a single amino acid residue to another amino acid such that every position across the full-length of the encoded variable heavy or light chain is replaced or every position in a selected region of the encoded variable heavy or variable light chain is replaced, whereby each replacement is to the same amino acid residue. A plurality of modified antibodies are then produced each containing a variable heavy chain and a variable light chain, or a portion thereof, whereby each of the plurality of antibodies contains replacement of an amino acid position with another amino acid compared to the first antibody. The plurality of modified antibodies are screened for an activity to the target antigen. A second antibody is selected from among the modified antibodies that exhibits retained or increased activity for the target antigen compared to the first antibody not containing the amino acid replacement. Further mutagenesis of the second antibody is performed by producing a plurality of nucleic acid molecules that encode modified forms of a variable heavy chain or a variable light chain of the second antibody, wherein the nucleic acid molecules contain one codon encoding an amino acid at the scanned amino acid position that encodes a different amino acid than the scanned amino acid in the second antibody, whereby each nucleic acid molecule of the plurality encodes a variable heavy chain or variable light chain that is modified at the scanned amino acid position by a single amino acid residue. A plurality of further modified antibodies are produced each containing a variable heavy chain and a variable light chain, or a portion thereof whereby the scanned amino acid position contains replacement to a different amino acid compared to the second antibody. The further modified antibodies are screened for an activity to the target antigen. From among the further modified antibodies, a third antibody is selected that exhibits increased activity for the target antigen compared to the first antibody or compared to the second antibody.

In one example of the scanning affinity maturation method provided herein, every position in a region of the encoded variable heavy or variable light chain is replaced. The selected region can be a complementary determining region in the variable heavy chain or variable light chain selected that is a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3.

In the method herein, a second antibody containing a scanning mutation is selected that exhibits retained or increased binding compared to the first antibody. Generally, the second antibody that is selected exhibits an activity that is at least or about 75%, 80%, 85%,

90%, 95%, 100%, 105%, 110%, 115%, 120%, 130%, 140%, 150%, 200% or more of the activity of the corresponding form of the first antibody.

In the affinity maturation method provided herein, the amino acid residue position that is modified in the second antibody to contain a scanned amino acid compared to the first antibody not containing the amino acid replacement can be determined.

In the scanning methods of affinity maturation provided herein, the scanning amino acid residue can be an alaninie, threonine, proline and glycine. For example, the amino acid is an alanine. In other examples, the scanning amino acid is a non-natural amino acid. In the methods herein, each of the plurality of nucleic acid molecules encodes a variable heavy chain or variable light chain that is modified by replacement of a single amino acid residue to the same scanned amino acid. In the method, the scanned amino acid position is modified by amino acid replacement to all other amino acid residues, or to a restricted subset thereof.

In the scanning methods of affinity maturation provided herein, once a second antibody is selected, further modification of the antibody is effected. In the method, modification does not include amino acid replacement to the scanned amino acid or to the original amino acid at that position in the first antibody. The further modification of the second antibody can be effected by a method that is PCR mutagenesis, cassette mutagenesis, site-directed mutagenesis, random point mutagenesis, mutagenesis using uracil containing templates, oligonucleotide-directed mutagenesis, phosphorothioate-modified DNA mutagenesis, mutagenesis using gapped duplex DNA, point mismatch repair, mutagenesis using repair-deficient host strains, restriction-selection and restriction-purification, deletion mutagenesis, mutagenesis by total gene synthesis, and double-strand break repair. In one example, further mutations are made by NNK, NNS, NNN, NNY or NNR mutagenesis.

In the scanning methods of affinity maturation provided herein, the activity that is assessed is binding, signal transduction, differentiation, alteration of gene expression, cellular proliferation, apoptosis, chemotaxis, cytotoxicity, cancer cell invasion, endothelial cell proliferation and tube formation. For example, where the activity is binding, binding is assessed by immunoassay, whole cell panning and surface plasmon resonance (SPR). The immunoassay can be a radioimmunoassay, enzyme linked immunosorbent assay (ELISA) or electrochemiluminescence assay. For example, the electrochemiluminescence assay can be meso scale discovery (MSD).

In the scanning methods of affinity maturation provided herein, the target antigen is a polypeptide, carbohydrate, lipid, nucleic acid or a small molecule. The target antigen can be expressed on the surface of a virus, bacteria, tumor or other cell, or is a recombinant protein or peptide. The target antigen can a protein that is a target for therapeutic intervention. For

example, the target antigen is involved in cell proliferation and differentiation, cell migration, apoptosis or angiogenesis. Exemplary target antigen include a VEGFR-1, VEGFR-2, VEGFR-3 (vascular endothelial growth factor receptors 1, 2, and 3), a epidermal growth factor receptor (EGFR), ErbB-2, ErbB-3, IGF-R1, C-Met (also known as hepatocyte growth factor receptor; HGFR), DLL4, DDR1 (discoidin domain receptor), KIT (receptor for c-kit), FGFR1, FGFR2, FGFR4 (fibroblast growth factor receptors 1, 2, and 4), RON (recepteur d'origine nantais; also known as macrophage stimulating 1 receptor), TEK (endothelial-specific receptor tyrosine kinase), TIE (tyrosine kinase with immunoglobulin and epidermal growth factor homology domains receptor), CSF1R (colony stimulating factor 1 receptor), PDGFRB (platelet-derived growth factor receptor B), EPHA1, EPHA2, EPHB1 (erythropoietin-producing hepatocellular receptor A1, A2 and B1), TNF-R1, TNF-R2, HVEM, LT-βR, CD20, CD3, CD25, NOTCH, G-CSF-R, GM-CSF-R, EPO-R., a cadherin, an integrin, CD52, CD44, VEGF-A, VEGF-B, VEGF-C, VEGF-D, PIGF, EGF, HGF, TNF-α, LIGHT, BTLA, lymphotoxin (LT), IgE, G-CSF, GM-CSF and EPO.

In the scanning methods herein, the third antibody exhibits 2-fold, 5-fold, 10-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold, 600-fold, 700-fold, 800-fold, 900-fold, 1000-fold, 2000-fold, 3000-fold, 4000-fold, 5000-fold, 10000-fold or more improved activity for the target antigen compared to the first antibody or the second antibody. For example, where the first antibody binds to the target antigen with a binding affinity that is at or about 10^{-4} M, 10^{-5} M, 10^{-6} M, 10^{-7} M, 10^{-8} M, or lower, when the antibody is in a Fab form, the further optimized antibodies, such as the selected third antibody, are those that are optimized to have an improved binding affinity compared to the first antibody. For example, the third antibody exhibits a binding affinity that is greater than the binding affinity of the first antibody and is or is about 1 x 10^{-9} M, 2 x 10^{-9} M, 3 x 10^{-9} M, 4 x 10^{-9} M, 5 x 10^{-9} M, 6 x 10^{-9} M, 7 x 10^{-9} M, 8 x 10^{-9} M, 9 x 10^{-9} M, 1 x 10^{-10} M, 2 x 10^{-10} M, 3 x 10^{-10} M, 4 x 10^{-10} M, 5 x 10^{-10} M, 6 x 10^{-10} M, 7 x 10^{-10} M, 8 x 10^{-10} M, 9 x 10^{-10} M or less.

In one aspect of the method, scanning mutagenesis is performed within the variable heavy chain of the first antibody, and the method performed therefrom. In another aspect, scanning mutagenesis is performed within the variable light chain of the first antibody, and steps of the method are performed therefrom. In an additional aspect of the method, scanning mutagenesis is performed within the variable heavy chain of the first antibody and steps of the method performed therefrom; and separately and independently scanning mutagenesis is performed within the variable light chain of the first antibody, and steps of the method are performed therefrom.

In the method herein, further optimization can be achieved. The method can include determining the amino acid modifications that are altered in the third antibody compared to the first antibody not containing the amino acid replacements. Combination mutants can be generated. Also provided in the method herein, is a method that is repeated iteratively, wherein the third antibody identified in that is selected and used as the first antibody for subsequent maturation thereof, whereby the amino acid residue that is modified is not further modified in subsequent iterations of the method. In another example of optimization, one or more amino acid replacement in one or more variable heavy chains or one or more variable light chains of selected third antibodies are combined to generate a further modified antibody, whereby the further modified antibodies are screened for an activity to the target antigen to identify a further modified antibody that exhibits an increased activity for the target antigen compared to the first antibody, second antibody and to the selected third antibodies. For example, the steps of the method can be performed on the variable heavy chain of the first antibody and third antibodies selected each containing an amino acid replacement in the variable heavy chain compared to the corresponding variable heavy chain of the first antibody. Independently and separately, the steps of the method are performed on the variable light chain of the first antibody and different third modified antibodies are selected each containing an amino replacement in the variable light chain compared to the corresponding variable light chain of the first antibody. The variable heavy chain of a third antibody can be combined with the variable light chain of a different third antibody to generate a plurality of different further modified antibodies each containing an amino acid replacement of the variable heavy chain and variable light chain compared to the corresponding variable heavy chain and variable light chain of the first antibody. The further modified antibodies can be screened for activity (e.g. binding) to the target antigen; and those fourth antibodies that exhibit an increased activity for the target antigen compared to the first antibody, second antibody, and third antibodies are selected.

In another example, after selecting a third antibody another different region within the variable heavy chain or variable light chain of the third antibody is selected for further mutagenesis. In such a method, a plurality of nucleic acid molecules are produced that encode modified forms of the variable heavy chain or variable light chain of the third antibody, wherein the nucleic acids molecules contain one codon encoding an amino acid in the selected region that encodes a different amino acid from the first modified variable heavy or variable light chain, whereby each nucleic acid molecule of the plurality encodes a variable heavy chain or variable light chain that is modified in the selected region by replacement of a single amino acid residue. Then, a plurality of further modified antibodies are produced each

containing a variable heavy chain and a variable light chain, or a portion thereof, whereby the selected region in each of the plurality of antibodies contains replacement of an amino acid to a different amino acid compared to the third antibody. The further modified antibodies are screened for an activity (e.g. binding) to the target antigen and those further modified antibodies that exhibit increased activity for the target antigen compared to the third antibody are selected. In such an example, the different region that is subject to further mutagenesis can be a CDR1, CDR2, CDR3, FR1, FR2, FR3 and FR4.

In any of the methods herein, the antibody can be an antibody or fragment thereof containing a variable heavy chain and a variable light chain, or a portion thereof. For example, the antibody can be a full-length antibody or a fragment thereof that is a Fab, Fab', $F(ab')_2$, single-chain Fv (scFv), Fv, dsFv, diabody, Fd and Fd' fragments, Fab fragments, Fd fragments, scFv fragments, and scFab fragments.

Also provided herein is a method of antibody conversion, whereby, following mutageneis of a first or reference antibody having a known activity, an antibody is selected that exhibits an activity that is changed or inverted compared to the activity of the first or reference antibody for the same target antigen. In one example of the method, an activity of an antibody is converted from an antagonist to an activator. In the method, a first antibody or fragment thereof that is an antagonist antibody is selected, whereby the antibody inhibits a functional activity associated with its target antigen. A plurality of modified antibodies is produced each containing a variable heavy chain and a variable light chain, or a portion thereof sufficient to bind antigen, where at least one of the variable heavy chain or variable light chain is modified such that it contains at least one amino acid modification compared to the first antibody. For example, amino acid modification is replacement of at least a single amino acid residue, such that each of the plurality of antibodies contains replacement of an amino acid(s) to a different amino acid(s) compared to the first antibody. In one example of the method, the plurality of modified antibodies are produced by producing a plurality of nucleic acid molecules that encode modified forms of a variable heavy chain or a variable light chain of the first antibody, wherein the nucleic acid molecules contain at least one codon that encodes a different amino acid from the unmodified variable heavy or variable light chain, such that each nucleic acid molecule of the plurality encodes a variable heavy chain or variable light chain that is modified by replacement of a single amino acid residue. Following mutagenesis, the plurality of modified antibodies are each screened for an activity to the target antigen. Antibodies are selected or identified that result in an increase in a functional activity associated with the target antigen compared to activity in the presence of the first antibody, thereby converting the first antibody to an activator.

In some examples of the method of converting an antagonist antibody to an activator, before the antibodies are screened for a functional activity the plurality of antibodies are each assessed for binding affinity for the target antigen. Antibodies that exhibit a binding affinity that is greater then the corresponding form of the first antibody for the target antigen are identified or selected. Then, that subset of antibodies are further screened for a functional activity to identify or select those that have a converted activator activity.

In another example of the method of antibody conversion, an activity of an antibody is converted from an activator to an antagonist. In the method, a first antibody or fragment thereof that is an activator antibody is selected, whereby the antibody increases a functional activity associated with its target antigen. A plurality of modified antibodies is produced each containing a variable heavy chain and a variable light chain, or a portion thereof sufficient to bind antigen, where at least one of the variable heavy chain or variable light chain is modified such that it contains at least one amino acid modification compared to the first antibody. For example, amino acid modification is replacement of at least a single amino acid residue, such that each of the plurality of antibodies contains replacement of an amino acid(s) to a different amino acid(s) compared to the first antibody. In one example of the method, the plurality of modified antibodies are produced by producing a plurality of nucleic acid molecules that encode modified forms of a variable heavy chain or a variable light chain of the first antibody, wherein the nucleic acid molecules contain at least one codon that encodes a different amino acid from the unmodified variable heavy or variable light chain, such that each nucleic acid molecule of the plurality encodes a variable heavy chain or variable light chain that is modified by replacement of a single amino acid residue. Following mutagenesis, the plurality of modified antibodies are each screened for an activity to the target antigen. Antibodies are selected or identified that result in a decrease in a functional activity associated with the target antigen compared to activity in the presence of the first antibody, thereby converting the first antibody to an antagonist.

In some examples of the method of converting an activator antibody to an antagonist, before the antibodies are screened for a functional activity the plurality of antibodies are each assessed for binding affinity for the target antigen. Antibodies that exhibit a binding affinity that is lower then the corresponding form of the first antibody for the target antigen are identified or selected. Then, that subset of antibodies are further screened for a functional activity to identify or select those that have a converted antagonist activity.

In each of the conversion methods above, the target antigen is a VEGFR-1, VEGFR-2, VEGFR-3 (vascular endothelial growth factor receptors 1, 2, and 3), a epidermal growth factor receptor (EGFR), ErbB-2, ErbB-b3, IGF-R1, C-Met (also known as hepatocyte growth factor receptor; HGFR), DLL4, DDR1 (discoidin domain receptor), KIT (receptor for c-kit), FGFR1, FGFR2, FGFR4 (fibroblast growth factor receptors 1, 2, and 4), RON (recepteur d'origine nantais; also known as macrophage stimulating 1 receptor), TEK (endothelial-specific receptor tyrosine kinase), TIE (tyrosine kinase with immunoglobulin and epidermal growth factor homology domains receptor), CSF1R (colony stimulating factor 1 receptor), PDGFRB (platelet-derived growth factor receptor B), EPHA1, EPHA2, EPHB1 (erythropoietin-producing hepatocellular receptor A1, A2 and B1), TNF-R1, TNF-R2, HVEM, LT-βR, CD20, CD3, CD25, NOTCH, G-CSF-R, GM-CSF-R or EPO-R.

Provided herein is an anti-DLL4 antibody multimer that has a binding affinity for DLL4 that is 10^{-8} M or lower binding affinity as measured by surface plasmon resonance (SPR) as a monomeric Ig fragment and that is an activator of DLL4 activity. For example, the binding affinity is between 10^{-6} M to 10^{-8} M. The antibody multimer can be, for example, a full-length antibody, a $F(ab')_2$ or a scFv dimer. In some examples, that antibody multimer is a full-length antibody that contains a constant region from a constant region of IgG1, IgG2, IgG3, IgA or IgM. For example, the constant region is an IgG1 constant region, or modified form thereof.

In one example, the antibody multimer contains a heavy chain CDR1 (CDRH1) set forth in SEQ ID NO:2908, a heavy chain CDR2 (CDRH2) set forth in SEQ ID NO:2909, a heavy chain CDR3 (CDRH3) set forth in SEQ ID NO: 2910, a light chain CDR1 (CDRL1) set forth in SEQ ID NO:2911, a light chain CDR2 (CDRL2) set forth in SEQ ID NO:2912, and a light chain CDR3 (CDRL3) set forth in SEQ ID NO:2913; or contains a sequences of amino acids that exhibits at least 70% sequence identity to any of SEQ ID NOS: 2908-2913, whereby the antibody binds to DLL4 and is an activator of DLL4 activity. For example, the antibody multimer contains a heavy chain having a variable region set forth in SEQ ID NO: 88 and a light chain comprising a variable region set forth in SEQ ID NO:107.

In another example, the antibody multimer contains a a heavy chain CDR1 (CDRH1) set forth in SEQ ID NO:2914, a heavy chain CDR2 (CDRH2) set forth in SEQ ID NO:2915, a heavy chain CDR3 (CDRH3) set forth in SEQ ID NO: 2916, a light chain CDR1 (CDRL1) set forth in SEQ ID NO:2917, a light chain CDR2 (CDRL2) set forth in SEQ ID NO:2918, and a light chain CDR3 (CDRL3) set forth in SEQ ID NO:2919; or contains a sequences of amino acids that exhibits at least 70% sequence identity to any of SEQ ID NOS: 2914-2919, whereby the antibody binds to DLL4 and is an activator of DLL4 activity. For example, the

antibody multimer contains a heavy chain having a variable region set forth in SEQ ID NO: 89 and a light chain comprising a variable region set forth in SEQ ID NO:108.

In examples of antibody multimers provided herein, the the heavy chain can contain an IgG1 constant region (e.g. set forth in SEQ ID NO: 2922) a light chain constant region, lambda or kappa (e.g. set forth in SEQ ID NO: 2923 or 2924).

Provided herein is a method of treating aberrant angiogenesis associated with an angiogenic disease or condition by administering any of the antibody multimers provided herein to a subject, whereby the activity of a DLL4 receptor is increased. For example, the DLL4 receptor is Notch-1 or Notch-4. The angiogenic disease or condition can be a cancer, diabetic retinopathies and other diabetic complications, inflammatory diseases, endometriosis and age-related macular degeneration.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: Figure 1 is a flow chart that illustrates the method of structure-affinity/activity relationship (SAR) based affinity maturation.

Figure 2: Amino acid alignments of "Hit" Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01. Figure 2A shows the alignment of the variable heavy chain of "Hit" Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 (SEQ ID NOS:88 and 107) with the variable heavy chain of "non-Hit" Fab VH1-46_IGHD6-13*01_IGHJ4*01 & L6_IGKJ1*01 (SEQ ID NOS:93 and 107). **Figure 2B** shows the alignment of the variable light chain of "Hit" Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 (SEQ ID NOS:88 and 107) with the variable light chains of "non-Hit" Fabs VH1-46_IGHD6-6*01_IGHJ1*01 & A27_IGKJ1*01 (SEQ ID NOS:8 and 110), VH1-46_IGHD6-6*01_IGHJ1*01 & L25_IGKJ1*01 (SEQ ID NOS:88 and 120) and VH1-46_IGHD6-6*01_IGHJ1*01 & L2_IGKJ1*01 (SEQ ID NOS:88 and 112). The regions of variation are highlighted in grey. The amino acid sequence of the "Hit" Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 is shown in bold.

Figure 3: Amino acid alignment of the variable heavy chain of "Hit" Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01. Figure 3 shows the alignment of the variable heavy chain of "Hit" Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 (SEQ ID NOS:89 and 108) with the variable heavy chain of "non-Hit" Fab VH5-51_IGHD6-25*01_IGHJ4*01 & V3-4_IGLJ1*01 (SEQ ID NOS:106 and 108). The regions of variation are highlighted in grey. The amino acid sequence of the "Hit" Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 is shown in bold.

Figure 4: Amino acid alignments of germline swapped variable heavy chains. Figure 4A shows the alignment of the variable heavy chain of "Hit" Fab VH1-46_IGHD6-

6*01_IGHJ1*01 & L6_IGKJ1*01 (SEQ ID NOS:88 and 107) with the variable heavy chains of J segment germline swapped Fabs VH1-46_IGHD6-6*01_IGHJ2*01 & L6_IGKJ1*01 (SEQ ID NOS:585 and 107), VH1-46_IGHD6-6*01_IGHJ4*01 & L6_IGKJ1*01 (SEQ ID NOS:586 and 107) and VH1-46_IGHD6-6*01_IGHJ5*01 & L6_IGKJ1*01 (SEQ ID NOS:587 and 107). **Figure 4B** shows the alignment of the variable heavy chain of "Hit" Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 (SEQ ID NOS:89 and 108) with the variable heavy chains of J segment germline swapped Fabs VH5-51_IGHD5-18*01>3_IGHJ1*01 & V3-4_IGLJ1*01 (SEQ ID NOS:588 and 108), VH5-51_IGHD5-18*01>3_IGHJ3*01 & V3-4_IGLJ4*01 (SEQ ID NOS:589 and 108) and VH5-51_IGHD5-18*01>3_IGHJ5*01 & V3-4_IGLJ4*01 (SEQ ID NOS:590 and 108). **Figure 4C** shows the alignment of the variable heavy chain of "Hit" Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 (SEQ ID NOS:89 and 108) with the variable heavy chains of D segment germline swapped Fabs VH5-51_IGHD5-12*01_IGHJ4*01 & V3-4_IGLJ1*01 (SEQ ID NOS:591 and 108) and VH5-51_IGHD5-24*01_IGHJ4*01 & V3-4_IGLJ1*01 (SEQ ID NOS:592 and 108). The regions of variation are highlighted in grey. The amino acid sequence of the "Hit" Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 is shown in bold.

Figure 5: Amino acid alignment of the variable heavy chain of "Hit" Fab VH3-23_IGHD2-21*01>3_IGHJ6*01 & V2-13_IGLJ2*01. **Figure 5** shows the alignment of the variable heavy chain of "Hit" Fab VH3-23_IGHD2-21*01>3_IGHJ6*01 & V2-13_IGLJ2*01 (SEQ ID NOS:1729 and 594) with the variable heavy chains of related "Hit" Fabs VH3-23_IGHD2-2*01>3_IGHJ6*01 & V2-13_IGLJ2*01 (SEQ ID NOS:1723 and 594), VH3-23_IGHD2-8*01>3_IGHJ6*01 & V2-13_IGLJ2*01 (SEQ ID NOS:1725 and 594) and VH3-23_IGHD2-15*01>3_IGHJ6*01 & V2-13_IGLJ2*01 (SEQ ID NOS:1727 and 594). The regions of variation are highlighted in grey. The amino acid sequence of the "Hit" Fab VH3-23_IGHD2-21*01>3_IGHJ6*01 & V2-13_IGLJ2*01 is shown in bold.

DETAILED DESCRIPTION

Outline

a. Selection of a First Antibody for Affinity Maturation
i. Immunization and Hybridoma Screening
ii. Screening Assays for Identification of a "Hit"
1) Display Libraries
2) Phage Display Libraries
3) Addressable Libraries
b. Identification of a Related Antibody
c. Comparison of the amino acid sequences of the First Antibody and Related Antibodies
d. Mutagenesis of an Identified Region
2. SAR by Scanning Mutagenesis
3. Further Optimization
a. Complementarity Determining Regions
b. Framework Regions
c. Germline Swapping
D. Method of Antibody Conversion
1. Choosing the Starting or Reference Antibody
2. Mutagenesis
3. Selecting for a Converted Antibody
a. Binding
b. Functional Activity
E. Assays
1. Binding Assays
2. Functional Activity
a. Differentiation
b. Alteration of Gene Expression
c. Cytotoxicity Assay
3. In Vivo Assays
F. Methods of Production of Antibodies
1. Vectors
2. Cells and Expression System
a. Prokaryotic Expression
b. Yeast
c. Insects
d. Mammalian cells
e. Plants
3. Purification
G. Anti-DLL4 Activator/Modulator Antibodies and Uses Thereof
1. DLL4
a. Structure
b. Expression
c. Function
2. Activator/Modulator Anti-DLL4 Multimer Antibodies
Exemplary Antibodies
3. Modifications
a. Modifications to Reduce Immunogenicity
b. Glycosylation
c. Fc Modifications
d. PEGylation
4. Compositions, Formulations, Administration and Articles of Manufacture/Kits
a. Compositions and Formulations

A. DEFINITIONS

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the invention(s) belong. All patents, patent applications, published applications and publications, Genbank sequences, databases, websites and other published materials referred to throughout the entire disclosure herein, unless noted otherwise, are incorporated by reference in their entirety. In the event that there are a plurality of definitions for terms herein, those in this section prevail. Where reference is made to a URL or other such identifier or address, it understood that such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet. Reference thereto evidences the availability and public dissemination of such information.

As used herein, an antibody refers to immunoglobulins and immunoglobulin portions, whether natural or partially or wholly synthetic, such as recombinantly, produced, including any portion thereof containing at least a portion of the variable region of the immunoglobulin molecule that is sufficient to form an antigen binding site. Hence, an antibody or portion thereof includes any protein having a binding domain that is homologous or substantially homologous to an immunoglobulin antigen binding site. For example, an antibody refers to an antibody that contains two heavy chains (which can be denoted H and H') and two light chains (which can be denoted L and L'), where each heavy chain can be a full-length immunoglobulin heavy chain or a portion thereof sufficient to form an antigen binding site (e.g. heavy chains include, but are not limited to, VH, chains VH-CH1 chains and VH-CH1-CH2-CH3 chains), and each light chain can be a full-length light chain or a portion thereof sufficient to form an antigen binding site (e.g. light chains include, but are not limited to, VL chains and VL-CL chains). Each heavy chain (H and H') pairs with one light chain (L and L', respectively). Typically, antibodies minimally include all or at least a portion of the variable heavy (VH) chain and/or the variable light (VL) chain. The antibody also can include all or a portion of the constant region.

For purposes herein, the term antibody includes full-length antibodies and portions thereof including antibody fragments, such as, but not limited to, Fab, Fab', $F(ab')_2$, single-chain Fvs (scFv), Fv, dsFv, diabody, Fd and Fd' fragments Fab fragments, Fd fragments and scFv fragments. Other known fragments include, but are not limited to, scFab fragments

(Hust *et al.*, *BMC Biotechnology* (2007), 7:14). Antibodies include members of any immunoglobulin class, including IgG, IgM, IgA, IgD and IgE.

As used herein, a full-length antibody is an antibody having two full-length heavy chains (e.g. VH-CH1-CH2-CH3 or VH-CH1-CH2-CH3- CH4) and two full-length light chains (VL-CL) and hinge regions, such as human antibodies produced by antibody secreting B cells and antibodies with the same domains that are produced synthetically.

As used herein, antibody fragment or antibody portion with reference to a "portion thereof" or "fragment thereof" of an antibody refers to any portion of a full-length antibody that is less than full length but contains at least a portion of the variable region of the antibody sufficient to form an antigen binding site (e.g. one or more CDRs) and thus retains the a binding specificity and/or an activity of the full-length antibody; antibody fragments include antibody derivatives produced by enzymatic treatment of full-length antibodies, as well as synthetically, e.g. recombinantly produced derivatives. Examples of antibody fragments include, but are not limited to, Fab, Fab', $F(ab')_2$, single-chain Fvs (scFv), Fv, dsFv, diabody, Fd and Fd' fragments (see, for example, *Methods in Molecular Biology*, Vol 207: *Recombinant Antibodies for Cancer Therapy Methods and Protocols* (2003); Chapter 1; p 3-25, Kipriyanov). The fragment can include multiple chains linked together, such as by disulfide bridges and/or by peptide linkers. An antibody fragment generally contains at least about 50 amino acids and typically at least 200 amino acids.

Hence, reference to an "antibody or portion thereof that is sufficient to form an antigen binding site" means that the antibody or portion thereof contains at least 1 or 2, typically 3, 4, 5 or all 6 CDRs of the VH and VL sufficient to retain at least a portion of the binding specificity of the corresponding full-length antibody containing all 6 CDRs. Generally, a sufficient antigen binding site at least requires CDR3 of the heavy chain (CDRH3). It typically futher requires the CDR3 of the light chain (CDRL3). As described herein, one of skill in the art knows and can identify the CDRs based on kabat or Chothia numbering (see e.g., Kabat, E.A. *et al.* (1991) *Sequences of Proteins of Immunological Interest*, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242, and Chothia, C. *et al.* (1987) *J. Mol. Biol.* 196:901-917). For example, based on Kabat numbering, CDR-LI corresponds to residues L24-L34; CDR-L2 corresponds to residues L50-L56; CDR-L3 corresponds to residues L89-L97; CDR-H1 corresponds to residues H31 – H35, 35a or 35b depending on the length; CDR-H2 corresponds to residues H50-H65; and CDR-H3 corresponds to residues H95-H102.

As used herein, "antigen-binding site" refers to the interface formed by one or more complementary determining regions (CDRs; also called hypervariable region). Each antigen

binding site contains three CDRs from the heavy chain variable region and three CDRs from the light chain variable region. An antibody molecule typically has two antigen combining sites, each containing portions of a heavy chain variable region and portions of a light chain variable region. The antigen combining sites can contain other portions of the variable region domains in addition to the CDRs.

As used herein, an Fv antibody fragment is composed of one variable heavy domain (VH) and one variable light (VL) domain linked by noncovalent interactions.

As used herein, a dsFv refers to an Fv with an engineered intermolecular disulfide bond, which stabilizes the VH-VL pair.

As used herein, an Fd fragment is a fragment of an antibody containing a variable domain (VH) and one constant region domain (CH1) of an antibody heavy chain.

As used herein, "Fab fragment" is an antibody fragment that contains the portion of the full-length antibody that results from digestion of a full-length immunoglobulin with papain, or a fragment having the same structure that is produced synthetically, e.g. recombinantly. A Fab fragment contains a light chain (containing a VL and CL portion) and another chain containing a variable domain of a heavy chain (VH) and one constant region domain portion of the heavy chain (CH1); it can be recombinantly produced.

As used herein, a $F(ab')_2$ fragment is an antibody fragment that results from digestion of an immunoglobulin with pepsin at pH 4.0-4.5, or a synthetically, e.g. recombinantly, produced antibody having the same structure. The F(ab')2 fragment contains two Fab fragments but where each heavy chain portion contains an additional few amino acids, including cysteine residues that form disulfide linkages joining the two fragments; it can be recombinantly produced.

A Fab' fragment is a fragment containing one half (one heavy chain and one light chain) of the F(ab')2 fragment.

As used herein, an Fd' fragment is a fragment of an antibody containing one heavy chain portion of a F(ab')2 fragment.

As used herein, an Fv' fragment is a fragment containing only the V_H and V_L domains of an antibody molecule.

As used herein, a scFv fragment refers to an antibody fragment that contains a variable light chain (VL) and variable heavy chain (VH), covalently connected by a polypeptide linker in any order. The linker is of a length such that the two variable domains are bridged without substantial interference. Exemplary linkers are $(Gly\text{-}Ser)_n$ residues with some Glu or Lys residues dispersed throughout to increase solubility.

As used herein, diabodies are dimeric scFv; diabodies typically have shorter peptide linkers than scFvs, and they preferentially dimerize.

As used herein, hsFv refers to antibody fragments in which the constant domains normally present in a Fab fragment have been substituted with a heterodimeric coiled-coil domain (see, e.g., Arndt *et al.* (2001) *J Mol Biol.* 7:312:221-228).

As used herein, an "antibody multimer" refers to an antibody containing at least two or more antigen-binding sites. Antibody multimers include dimers, trimer, tetramers pentamers, and higher ordered oligomers. Formation of an antibody as a multimer can be achieved based on the knowledge of one of skill in the art. For ezample, multimeric forms include antibody oligomers that form via a multimerization domain that coordinates or facilitates the intereaction of at least two polypeptides or a covalent bond.

As used herein, a multimerization domain refers to a sequence of amino acids that promotes stable interaction of a polypeptide molecule with one or more additional polypeptide molecules, each containing a complementary multimerization domain, which can be the same or a different multimerization domain to form a stable multimer with the first domain. Generally, a polypeptide is joined directly or indirectly to the multimerization domain. Exemplary multimerization domains include the immunoglobulin sequences or portions thereof, leucine zippers, hydrophobic regions, hydrophilic regions, and compatible protein-protein interaction domains. The multimerization domain, for example, can be an immunoglobulin constant region or domain, such as, for example, the constant domain or portions thereof from IgG, including IgG1, IgG2, IgG3 or IgG4 subtypes, IgA, IgE, IgD and IgM and modified forms thereof.

As used herein, a "monospecific" is an antibody that contains two or more antigen-binding sites, where each antigen-binding site immunospecifically binds to the same epitope.

As used herein, a "multispecific" antibody is an antibody that contains two or more antigen-binding sites, where at least two of the antigen-binding sites immunospecifically bind to different epitopes.

As used herein, a "bispecific" antibody is a multispecific antibody that contains two or more antigen-binding sites and can immunospecifically bind to two different epitopes. A "trispecific" antibody is a multispecific antibody that contains three or more antigen-binding sites and can immunospecifically bind to three different epitopes, a "tetraspecific" antibody is a multispecific antibody that contains four or more antigen-binding sites and can immunospecifically bind to four different epitopes, and so on.

As used herein, reference to a "monomeric Ig fragment" refers to an antibody portion that contains only one antigen-binding site. For example, a monomeric Ig fragment includes, for example, a Fab, Fv or a scFv.

As used herein, a polypeptide domain is a part of a polypeptide (a sequence of three or more, generally 5 or 7 or more amino acids) that is a structurally and/or functionally distinguishable or definable. Exemplary of a polypeptide domain is a part of the polypeptide that can form an independently folded structure within a polypeptide made up of one or more structural motifs (e.g. combinations of alpha helices and/or beta strands connected by loop regions) and/or that is recognized by a particular functional activity, such as enzymatic activity or antigen binding. A polypeptide can have one, typically more than one, distinct domains. For example, the polypeptide can have one or more structural domains and one or more functional domains. A single polypeptide domain can be distinguished based on structure and function. A domain can encompass a contiguous linear sequence of amino acids. Alternatively, a domain can encompass a plurality of non-contiguous amino acid portions, which are non-contiguous along the linear sequence of amino acids of the polypeptide. Typically, a polypeptide contains a plurality of domains. For example, each heavy chain and each light chain of an antibody molecule contains a plurality of immunoglobulin (Ig) domains, each about 110 amino acids in length.

As used herein, an Ig domain is a domain, recognized as such by those in the art, that is distinguished by a structure, called the Immunoglobulin (Ig) fold, which contains two beta-pleated sheets, each containing anti-parallel beta strands of amino acids connected by loops. The two beta sheets in the Ig fold are sandwiched together by hydrophobic interactions and a conserved intra-chain disulfide bond. Individual immunoglobulin domains within an antibody chain further can be distinguished based on function. For example, a light chain contains one variable region domain (VL) and one constant region domain (CL), while a heavy chain contains one variable region domain (VH) and three or four constant region domains (CH). Each VL, CL, VH, and CH domain is an example of an immunoglobulin domain.

As used herein, a "variable domain" with reference to an antibody is a specific Ig domain of an antibody heavy or light chain that contains a sequence of amino acids that varies among different antibodies. Each light chain and each heavy chain has one variable region domain (VL, and, VH). The variable domains provide antigen specificity, and thus are responsible for antigen recognition. Each variable region contains CDRs that are part of the antigen binding site domain and framework regions (FRs).

As used herein, reference to a variable heavy (VH) chain or a variable light (VL) chain (also termed VH domain or VL domain) refers to the polypeptide chains that make up the variable domain of an antibody.

As used herein, a "region" of an antibody refers to a domain of an antibody or a portion of a domain is associated with a particular function or structure. In an antibody, regions of an antibody include the complementarity-determining region, the framework region, and/or the constant region. Generally, for purposes herein, a region of an antibody is a complementarity determining region CDR1, CDR2 and/or CDR3 of the variable light chain or variable heavy chain (CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, or CDRH3), or is a framework region FR1, FR2 or FR3 of the variable light chain or variable heavy chain.

As used herein, "hypervariable region," "HV," "complementarity-determining region" and "CDR" and "antibody CDR" are used interchangeably to refer to one of a plurality of portions within each variable region that together form an antigen binding site of an antibody. Each variable region domain contains three CDRs, named CDR1, CDR2, and CDR3. The three CDRs are non-contiguous along the linear amino acid sequence, but are proximate in the folded polypeptide. The CDRs are located within the loops that join the parallel strands of the beta sheets of the variable domain.

As used herein, framework regions (FRs) are the regions within the antibody variable region domains that are located within the beta sheets; the FR regions are comparatively more conserved, in terms of their amino acid sequences, than the hypervariable regions.

As used herein, a constant region domain is a domain in an antibody heavy or light chain that contains a sequence of amino acids that is comparatively more conserved among antibodies than the variable region domain. Each light chain has a single light chain constant region (CL) domain and each heavy chain contains one or more heavy chain constant region (CH) domains, which include, CH1, CH2, CH3 and CH4. Full-length IgA, IgD and IgG isotypes contain CH1, CH2 CH3 and a hinge region, while IgE and IgM contain CH1, CH2 CH3 and CH4. CH1 and CL domains extend the Fab arm of the antibody molecule, thus contributing to the interaction with antigen and rotation of the antibody arms. Antibody constant regions can serve effector functions, such as, but not limited to, clearance of antigens, pathogens and toxins to which the antibody specifically binds, e.g. through interactions with various cells, biomolecules and tissues.

As used herein, humanized antibodies refer to antibodies that are modified to include "human" sequences of amino acids so that administration to a human does not provoke an immune response. Methods for preparation of such antibodies are known. For example, the

antibody in which the amino acid composition of the non-variable regions can be based on human antibodies. Computer programs have been designed to identify such regions.

As used herein, "antibody conversion" refers to a process in which the functionl activity of an antibody or fragment thereof for a target antigen or substrate is changed, typically by mutation of one or more amino acid residues, to have an inverse functional activity of the starting or reference antibody. For example, if the starting or reference antibody exhibits antagonist activity for a target antigen, antibody coversion changes the antibody to an agonist or activator/modulator activity. In another example, if the starting or reference antibody exhibits activator/modulator activity for a target antigen, antibody conversion changes the antibody to an antagonist activity.

As used herein, "affinity maturation" refers to a process in which an antibody is evolved from a reference antibody (also referred to herein as a template or parent antibody), typically by mutation of one or more amino acid residues, to have increased activity for a target antigen than a corresponding form of the reference antibody has for the same target antigen. Hence, the evolved antibody is optimized compared to the reference or template antibody.

As used herein, reference to an affinity matured antibody refers to an antibody that has an increased activity for a target antigen relative to a reference antibody. For example, the affinity matured antibody exhibits increased binding to the target antigen compared to the reference or parent antibody. Typically, the affinity matured antibody binds to the same epitope as the reference antibody.

As used herein, an optimized antibody refers to an antibody, or portion thereof, that has an increased activity for a target protein or antigen compared to a reference antibody, for example, improved binding affinity for a target protein and/or an improved functional activity. Typically, the antibody is optimized by virtue of one or more amino acid modifications (amino acid deletion, replacement or insertion) compared to a parent antibody not containing the one or more amino acid modifications. Generally, an activity, for example binding affinity, is increased by at or about 1.5-fold to 1000-fold, generally at least or about 2-fold to 100-fold, for example at or about 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 20-fold, 30-fold, 40-fold, 50-fold, 60-fold, 70-fold, 80-fold, 90-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold, 600-fold, 700-fold, 800-fold, 900-fold, 1000-fold or more compared to an activity of the parent antibody (e.g. germline antibody Hit not containing the modification(s)).

As used herein, "structure affinity/activity relationship" (SAR) refers to the relationship between structure (e.g. sequence) and function of a molecule, whereby the

activity of an antibody can be correlated to it sequence. Thus, knowledge of the SAR elucidates a region of a sequence, including particular amino acid residues, that contribute to the activity of an antibody. Methods of determining SAR are described herein.

As used herein, activity towards a target protein or target antigen refers to binding specificity or binding affinity and/or modulation of a functional activity of a target protein, or other measurements that reflects the activity of an antibody or portion thereof towards a target protein. Activitity of an antibody can be measured using a binding or affinity based assay, such as an ELISA, electrochemiluminescence assay (e.g. Meso Scale Discovery), or surface plasmon resonance, or can measured using a cell based assay as described herein.

As used herein, "functional activity" refer to activities of a polypeptide (e.g. target protein) or portion thereof associated with a full-length (complete) protein. Functional activities include, but are not limited to, biological activity, catalytic or enzymatic activity, antigenicity (ability to bind to or compete with a polypeptide for binding to an anti-polypeptide antibody), immunogenicity, ability to form multimers, the ability to specifically bind to a receptor or ligand for the polypeptide and signaling and downstream effector functions. For purposes herein, modulation (i.e. activation or inhibition) of a functional activity of a polypeptide by an antibody or portion thereof herein means that a functional activity of the polypeptide is changed or altered in the presence of the antibody compared to the absence of the antibody or portion thereof.

As used herein, binding activity refer to characteristics of a molecule, e.g. a polypeptide, relating to whether or not, and how, it binds one or more binding partners. Binding activities include ability to bind the binding partner(s), the affinity with which it binds to the binding partner (e.g. high affinity), the avidity with which it binds to the binding partner, the strength of the bond with the binding partner and specificity for binding with the binding partner.

As used herein, "affinity" or "binding affinity" refers to the strength with which an antibody molecule or portion thereof binds to an epitope on a target protein or antigen. Affinity is often measured by equilibrium association constant (K_A) or equilibrium dissociation constant (K_D). Low-affinity antibody-antigen interaction is weak, and the molecules tend to dissociate rapidly, while high affinity antibody-antigen binding is strong and the molecules remain bound for a longer amount of time. Generally, affinity of an antibody to a target protein is with an equilibrium association constant (K_A) of greater than or equal to about $10^6 M^{-1}$, greater than or equal to about $10^7 M^{-1}$, greater than or equal to about $10^8 M^{-1}$, or greater than or equal to about $10^9 M^{-1}$, $10^{10} M^{-1}$, $10^{11} M^{-1}$ or $10^{12} M^{-1}$. Antibodies also can be characterized by an equilibrium dissociation constant (K_D) 10^{-4} M, 10^{-6} M to 10^{-7} M, or

10^{-8} M, 10^{-10}M, 10^{-11}M or 10^{-12}M or lower dissociation constant. It is understood that a lower dissociation constant means that the antibody is characterized by a higher binding affinity. Generally, antibodies having a nanomolar or sub-nanomolar dissociaton constant are deemed to be high affinity antibodies. Such affinities can be readily determined using conventional techniques, such as by equilibrium dialysis; by using the BIAcore 2000 instrument, using general procedures outlined by the manufacturer; by radioimmunoassay using radiolabeled target antigen; or by another method known to the skilled artisan. The affinity data can be analyzed, for example, by the method of Scatchard *et al.*, Ann N.Y. Acad. ScL, 51:660 (1949).

As used herein, "specifically bind" or "immunospecifically bind" with respect to an antibody or antigen-binding fragment thereof are used interchangeably herein and refer to the ability of the antibody or antigen-binding fragment to form one or more noncovalent bonds with a cognate antigen, by noncovalent interactions between the antibody combining site(s) of the antibody and the antigen (e.g. human DLL4). Typically, an antibody that immunospecifically binds (or that specifically binds) to an antigen is one that binds to the antigen with an affinity constant Ka of about or $1\times10^{7}M^{-1}$ or $1x\ 10^{8}M^{-1}$or greater (or a dissociation constant (K_d) of $1x\ 10^{-7}$M or 1×10^{-8}M or less). Affinity constants can be determined by standard kinetic methodology for antibody reactions, for example, immunoassays, surface plasmon resonance (SPR) (Rich and Myszka (2000) *Curr. Opin. Biotechnol* 11:54; Englebienne (1998) *Analyst.* 123:1599), isothermal titration calorimetry (ITC) or other kinetic interaction assays known in the art (see, *e.g.*, Paul, ed., Fundamental Immunology, 2nd ed., Raven Press, New York, pages 332-336 (1989); see also U.S. Pat. No. 7,229,619 for a description of exemplary SPR and ITC methods for calculating the binding affinity of anti-RSV antibodies). Instrumentation and methods for real time detection and monitoring of binding rates are known and are commercially available (*e.g.*, BiaCore 2000, Biacore AB, Upsala, Sweden and GE Healthcare Life Sciences; Malmqvist (2000) *Biochem. Soc. Trans.* 27:335).

As used herein, the term "bind selectively" or "selectively binds," in reference to a polypeptide or an antibody provided herein, means that the polypeptide or antibody binds with a selected epitope without substantially binding to another epitope. Typically, an antibody or fragment thereof that selectively binds to a selected epitope specifically binds to the epitope, such as with an affinity constant Ka of about or $1\times10^{7}M^{-1}$ or $1\ x\ 10^{8}M^{-1}$or greater.

As used herein, "epitope" refers to the localized region on the surface of an antigen or protein that is recognized by an antibody. Peptide epitopes include those that are continuous

epitopes or discontinuous epitopes. An epitope is generally determined by the three dimensional structure of a protein as opposed to the linear amino acid sequence.

As used herein, "binds to the same epitope" with reference to two or more antibodies means that the antibodies compete for binding to an antigen and bind to the same, overlapping or encompassing continuous or discontinuous segments of amino acids. Those of skill in the art understand that the phrase "binds to the same epitope" does not necessarily mean that the antibodies bind to exactly the same amino acids. The precise amino acids to which the antibodies bind can differ. For example, a first antibody can bind to a segment of amino acids that is completely encompassed by the segment of amino acids bound by a second antibody. In another example, a first antibody binds one or more segments of amino acids that significantly overlap the one or more segments bound by the second antibody. For the purposes herein, such antibodies are considered to "bind to the same epitope."

Antibody competition assays can be used to determine whether an antibody "binds to the same epitope" as another antibody. Such assays are well known on the art. Typically, competition of 70 % or more, such as 70%, 71%, 72%, 73%, 74%, 75%, 80%, 85%, 90%, 95% or more, of an antibody known to interact with the epitope by a second antibody under conditions in which the second antibody is in excess and the first saturates all sites, is indicative that the antibodies "bind to the same epitope." To assess the level of competition between two antibodies, for example, radioimmunoassays or assays using other labels for the antibodies, can be used. For example, a DLL4 antigen can be incubated with a a saturating amount of a first anti-DLL4 antibody or antigen-binding fragment thereof conjugated to a labeled compound (e.g., ^{3}H, ^{125}I, biotin, or rubidium) in the presence the same amount of a second unlabeled anti-DLL4 antibody. The amount of labeled antibody that is bound to the antigen in the presence of the unlabeled blocking antibody is then assessed and compared to binding in the absence of the unlabeled blocking antibody. Competition is determined by the percentage change in binding signals in the presence of the unlabeled blocking antibody compared to the absence of the blocking antibody. Thus, if there is a 70 % inhibition of binding of the labeled antibody in the presence of the blocking antibody compared to binding in the absence of the blocking antibody, then there is competition between the two antibodies of 70 %. Thus, reference to competition between a first and second antibody of 70 % or more, such as 70 %, 71 %, 72 %, 73 %, 74 %, 75 %, 80 %, 85 %, 90 %, 95 % or more, means that the first antibody inhibits binding of the second antibody (or *vice versa*) to the antigen by 70 %, 71 %, 72 %, 73 %, 74 %, 75 %, 80 %, 85 %, 90 %, 95 % or more (compared to binding of the antigen by the second antibody in the absence of the first antibody). Thus, inhibition of binding of a first antibody to an antigen by a second antibody of 70 %, 71 %, 72 %, 73 %, 74

%, 75 %, 80 %, 85 %, 90 %, 95 % or more indicates that the two antibodies bind to the same epitope.

As used herein, the term "surface plasmon resonance" refers to an optical phenomenon that allows for the analysis of real-time interactions by detection of alterations in protein concentrations within a biosensor matrix, for example, using the BiaCore system (GE Healthcare Life Sciences).

As used herein, a "bispecific" antibody is a multispecific antibody that contains two or more antigen-binding sites and can immunospecifically bind to two different epitopes. A "trispecific" antibody is a multispecific antibody that contains three or more antigen-binding sites and can immunospecifically bind to three different epitopes, a "tetraspecific" antibody is a multispecific antibody that contains four or more antigen-binding sites and can immunospecifically bind to four different epitopes, and so on.

As used herein, "epitope mapping" is the process of identification of the molecular determinants for antibody-antigen recognition.

As used herein, a "target protein" or "target antigen" refers to candidate proteins or peptides that are specifically recognized by an antibody or portion thereof and/or whose activity is modulated by an antibody or protion thereof. A target protein includes any peptide or protein that contains an epitope for antibody recognition. Target proteins include proteins involved in the etiology of a disease or disorder by virtue of expression or activity. Exemplary target proteins are described herein.

As used herein, a "Hit" refers to an antibody or portion thereof generated, identified, recognized or selected as having an activity for a target antigen. For example, a "Hit" can be identified in a screening assay. Generally, a "Hit" is identified based on its binding activity or affinity for the target antigen. For purposes herein, a "Hit" is generally recognized to be an antibody or portion thereof that has a binding affinity for a target antigen that is at least about or is 10^{-5} M, 10^{-6} M, 10^{-7} M, 10^{-8} M, or lower. For purposes herein, a Hit typically is a first antibody or a reference or parent antibody that is further optimized using affinity maturation methods herein. Thus, the terms "Hit", first antibody, reference antibody or parent antibody are used interchangeably herein.

As used herein, a "modified antibody" refers to an antibody, or portion thereof, that contains one ore more amino acid modifications compared to a a parent or reference antibody. An amino acid modification includes an amino acid deletion, replacement (or substitution), or addition. A modified antibody can contain 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more amino acid modifications. Typically, an amino acid modification is an amino acid replacement. Generally, the amino acid modifications are present in a region or

target region of an antibody, but also can be present in other regions of the antibody or portion thereof.

As used herein, a "related antibody" is an antibody that exhibits structural and functional similarity to a corresponding form of a reference antibody (e.g. a Hit antibody or first antibody), but that does not exhibit the same activity or structure (e.g. sequence) as the reference antibody. For example, a related antibody is one that exhibits sequence simiarlity but is not identical to the reference antibody, and exhibits reduced activity or less activity than the activity of a reference antibody towards a target protein or antigen, such as reduced binding affinity. For purposes herein, an antibody is a related antibody if 1) it exhibits sequence similarity to a reference antibody such that it contains a variable heavy chain and/or a variable light chain that exhibits at least 75% amino acid sequence identity to the corresponding variable heavy chain or variable light chain of the first antibody, where the related antibody (variable heavy chain and variable light chain) does not exhibit 100% sequence identity to the reference antibody; and 2) it exhibits reduced activity compared to a corresponding form of the reference antibody. The sequence similiarity or sequence identity can be In another example, an antibody is a related antibody if 1) it exhibits sequence similarity to a reference antibody such that at least one of the V_H, D_H and J_H germline segments of the nucleic acid molecule encoding the variable heavy chain of the related antibody is identical to one of the V_H, D_H and J_H germline segments of the nucleic acid molecule encoding the variable heavy chain of the first antibody and/or at lcast one of the V_κ and J_κ or at least one of the V_λ and J_λ germline segments of the nucleic acid molecule encoding the variable light chain is identical to one of the V_κ and J_κ or V_λ and J_λ germline segments of the nucleic acid molecule encoding the variable light chain of the first antibody; and 2) it exhibits reduced activity compared to a corresponding form of the reference antibody.

As used herein "reduced activity" or "less activity" for a target antigen means that an antibody, or portion thereof, exhibits an activity towards a target antigen (e.g. binding or other functional activity) that is not as high or of the same degree as the activity of a reference antibody for the same target antigen. It is understood that in comparing an activity to a reference antibody, the activity is compared to the corresponding form of the antibody using the same assay to assess activity under the same or similar conditions. Hence, the requisite level of activity between and among two or more antibodies is compared under similar parameters or conditions. For purposes herein, an antibody that has a "reduced activity" or "less activity" for a target antigen generally exhibits 80% or lower the activity towards a target antigen as a reference antibody, such as 5% to 80% of the activity, for example, at or

about 80%, 75%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5% or lower the activity towards a target antigen as a reference antibody.

As used herein, a "related variable heavy chain" or a "related variable light chain" is one that exhibits sequence identity to the corresponding variable heavy chain and/or variable light chain of a reference antibody, but that is not identical (e.g. does not exhibit 100% sequence identity) to the corresponding variable heavy chain and/or variable light chain of a reference antibody. Generally, a related variable heavy chain or a variable light chain is one that exhibits at least 60% sequence identity to the corresponding chain of the reference antibody, generally at least 75% sequence identity. For example, a related variable heavy chain or a variable light chain is one that exhibits 60% to 99% sequence identity, for example, at or about 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the corresponding chain of the reference antibody. For example, a related antibody includes an antibody in which at least one of the V_H, D_H and J_H germline segments of the nucleic acid molecule encoding the variable heavy chain of the related antibody is identical to one of the V_H, D_H and J_H germline segments of the nucleic acid molecule encoding the variable heavy chain of the first antibody and/or at least one of the V_κ and J_κ or at least one of the V_λ and J_λ germline segments of the nucleic acid molecule encoding the variable light chain is identical to one of the V_κ and J_κ or V_λ and J_λ germline segments of the nucleic acid molecule encoding the variable light chain of the first antibody. Generally, a related variable heavy chain and/or variable light chain of an antibody exhibits at least 75% amino acid sequence identity to the corresponding variable heavy chain or variable light of a reference antibody.

As used herein, a form of an antibody refers to a particular structure of an antibody. Antibodies herein include full length antibodies and portions thereof, such as, for example, a Fab fragment or other antibody fragment. Thus, a Fab is a particular form of an antibody.

As used herein, reference to a "corresponding form" of an antibody means that when comparing a property or activity of two antibodies, the property is compared using the same form of the antibody. For example, if its stated that an antibody has less activity compared to the activity of the corresponding form of a first antibody, that means that a particular form, such as a Fab of that antibody, has less activity compared to the Fab form of the first antibody.

As used herein, "sequence diversity" or "sequence similarity" refers to a representation of nucleic acid sequence similarity and is determined using sequence alignments, diversity scores, and/or sequence clustering. Any two sequences can be aligned by laying the sequences side-by-side and analyzing differences within nucleotides at every

position along the length of the sequences. Sequence alignment can be assessed *in silico* using Basic Local Alignment Search Tool (BLAST), an NCBI tool for comparing nucleic acid and/or protein sequences. The use of BLAST for sequence alignment is well known to one of skill in the art. The Blast search algorithm compares two sequences and calculates the statistical significance of each match (a Blast score). Sequences that are most similar to each other will have a high Blast score, whereas sequences that are most varied will have a low Blast score.

As used herein, Basic Local Alignment Search Tool (BLAST) is a search algorithm developed by Altschul *et al.* (1990) to separately search protein or DNA databases, for example, based on sequence identity. For example, blastn is a program that compares a nucleotide query sequence against a nucleotide sequence database (e.g. GenBank). BlastP is a program that compares an amino acid query sequence against a protein sequence database.

As used herein, a "target region" refers to a region of a variable heavy chain or variable light chain of an antibody (e.g. a Hit antibody) or portion thereof that exhibits at least one amino acid differences compared to the corresponding region of related antibody or antibodies. Thus, a target region includes one or more of a CDR1, CDR2, CDR3, FR1, FR2, FR3 or FR4 of the variable heavy chain or variable light chain of a an antibody that contains at least one amino acid difference compared to the corresponding region of a related antibody. Generally, a target region is a region of an antibody that is associated with the structure/activity relationship (SAR) of the antibody. Thus, for purposes of practice of the method herein, a target region is one that is targeted for further mutagenesis. As described herein, it is within the level of one of skill in the art to identify such regions and to determine if amino acid differences exist. One of skill in the art knows and can identify a region in an antibody, for example a CDR or FR, based on Kabat or Chothia numbering (see e.g., Kabat, E.A. *et al.* (1991) *Sequences of Proteins of Immunological Interest*, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242, and Chothia, C. *et al.* (1987) *J. Mol. Biol.* 196:901-917).

As used herein, "saturation mutagenesis" refers to the process of systematically generating a plurality of mutants by replacing at least one amino acid residue of a protein sequence to all or a subset of the remaining amino acid residues or to effect replacement of a number of amino acid residues (within or across the full length of the protein or within or across a region of a protein) each to all or a subset of the remaining amino acid residues. Saturation mutagenesis can be full or partial.

As used herein, "full saturation mutagenesis" refers to the process of systematically generating a plurality of mutants by replacing an amino acid residue in a protein sequence

with the other 19 other naturally-occuring amino acids. A single amino acid residue in a protein sequence can be subject to mutagenesis. Alternatively, all or a subset of amino acid residues across the full length sequence of a protein or a region of the protein sequence (e.g. target region) can be subjected to full saturation mutagenesis.

As used herein, "partial saturation mutagenesis" refers to the process of systematically generating a plurality of mutant sequences by replacing an amino acid residue in a protein sequence to a subset of the other 19 other naturally-occurring amino acids. A single amino acid residue in a protein sequence can be subject to mutagenesis. Alternatively, all or a subset of amino acid residues across the full length sequence of a protein or a region of the protein sequence (e.g. target region) can be subjected to partial saturation mutagenesis.

As used herein, "scanning mutagenesis" refers to the process of systematically replacing all or a subset of amino acids in a protein or in a region of a protein (e.g. target region) with a selected amino acid, typically alanine, glycine or serine, as long as each residue is replaced with the same residue. Typically, the replacing amino acid is an alanine.

As used herein, reference to an antibody that is an "Up mutant" or an antibody that "exhibits retained or increased activity", refers to an antibody subjected to scanning mutagenesis whose activity when containing a single amino acid mutation to a scanned amino acid is retained or increased compared to the parent antibody not containined the scanned amino acid mutation. The antibody that retains an activity to a target antigen can exhibit some increase or decrease in binding, but generally exhibits the same binding as the first antibody not containing the scanned mutation, for example, exhibits at least 75% of the binding activity, such as 75% to 120% of the binding, for example, 75 %, 80 %, 85 %, 90 %, 95 %, 100 %, 105 %, 110 % or 115 % of the binding. An antibody that exhibits increased activity to a target antigen generally exhibits greater than 115% of the activity, such as greater than 115 %, 120 %, 130 %, 140 %, 150 %, 200 % or more activity than the first antibody not containing the mutation.

As used herein "iterative" with respect to performing the steps of the method means that the method is repeated a plurality of times, such as 2, 3, 4, 5 or more times, until a modified "Hit" is identified whose activity is optimized or improved compared to prior iterations.

As used herein, an "intermediate" with reference to an antibody or portion thereof refers to an antibody that is derived from or evolved from a reference antibody, template or parent antibody, for example, by the process of affinity maturation, but that is itself further evolved. For example, once a modified Hit is selected in the affinity maturation method herein, it can itself be used as a template in order to further evolve or optimize the antibody.

Hence, the modified Hit is an intermediate antibody in order to identify or select a further modified Hit.

As used herein, an "antibody library" refers to a collection of antibody members or portions thereof, for example, 2 or more, typically 5 or more, and typically 10 or more, such as, for example, at or about 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 1000, 10^4, 10^5, 10^6, 10^7, 10^8, 10^9, 10^{10}, 10^{11}, 10^{12}, 10^{13}, 10^{14} or more of such molecules. In some examples, the members of the collection are analogous to each other in that members within a collection are varied compared to a target or template antibody. An antibody library, however, encompasses a collection of any antibody members, or portions thereof. Thus, it is not necessary that each member within the collection is varied compared to a template member. Generally, collections contain different members (i.e. based on sequence), although in some cases collections of antibodies can contain some members that are the same. Typically, collections contain at least 10^4 or about 10^4, 10^5 or about 10^5, 10^6 or about 10^6, at least 10^8 or about 10^8, at least 10^9 or about 10^9, at least 10^{10} or about 10^{10}, or more different antibody members. Thus, the collections typically have a diversity of at least 10^4 or about 10^4, 10^5 or about 10^5, 10^6 or about 10^6, at least 10^8 or about 10^8, at least 10^9 or about 10^9, at least 10^{10} or about 10^{10}, at least 10^{11} or about 10^{11}, at least 10^{12} or about 10^{12}, at least 10^{13} or about 10^{13}, at least 10^{14} or about 10^{14}, or more. Thus, an antibody library having a diversity of 10^7 means that it contains 10^7 different members.

As used herein, "diversity" with respect to members in a collection or library refers to the number of unique members in a collection. Hence, diversity refers to the number of different amino acid sequences or nucleic acid sequences, respectively, among the analogous polypeptide members of that collection. For example, a collection of polynucleotides having a diversity of 10^4 contains 10^4 different nucleic acid sequences among the analogous polynucleotide members. In one example, the provided collections of polynucleotides and/or polypeptides have diversities of at least at or about 10^2, 10^3, 10^4, 10^5, 10^6, 10^7, 10^8, 10^9, 10^{10} or more.

As used herein, "a diversity ratio" refers to a ratio of the number of different members in the library over the number of total members of the library. Thus, a library with a larger diversity ratio than another library contains more different members per total members, and thus more diversity per total members. The provided libraries include libraries having high diversity ratios, such as diversity ratios approaching 1, such as, for example, at or about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 0.91, 0.92, 0.93, 0.94, 0.95. 0.96, 0.97, 0.98, or 0.99.

As used herein, "combinatorial library" refers to collections of compounds formed by reacting different combinations of interchangeable chemical "building blocks" to produce a

collection of compounds based on permutations of the building blocks. For an antibody combinatorial library, the building blocks are the component V, D and J regions (or modified forms thereof) from which antibodies are formed. For purposes herein, the terms "library" or "collection" are used interchangeably.

As used herein, a combinatorial antibody library is a collection of antibodies (or portions thereof, such as Fabs), where the antibodies are encoded by nucleic acid molecules produced by the combination of V, D and J gene segments, particularly human V, D and J germline segments. The combinatorial libraries herein typically contain at least 50 different antibody (or antibody portions or fragment) members, typically at least or about 50 to 10^{10} or more different members, generally at least or about 10^2 to 10^6 or more different members, for example, at least or about 50, 100, 500, 10^3, 1 x 10^3, 2 x 10^3, 3 x 10^3, 4x 10^3, 5 x 10^3, 6 x 10^3, 7 x 10^3, 8 x 10^3, 9 x 10^3, 1 x 10^4, 2 x 10^4, 3 x 10^4, 4x 10^4, 5 x 10^4, 6 x 10^4, 7 x 10^4, 8 x 10^4, 9 x 10^4, 1 x 10^5, 2 x 10^5, 3 x 10^5, 4x 10^5, 5 x 10^5, 6 x 10^5, 7 x 10^5, 8 x 10^5, 9 x 10^5, 10^6, 10^7, 10^8, 10^9, 10^{10}, or more different members. The resulting libraries or collections of antibodies or portions thereof, can be screened for binding to a target protein or modulation of a functional activity.

As used herein, a human combinatorial antibody library is a collection of antibodies or portions thereof, whereby each member contains a VL and VH chains or a sufficient portion thereof to form an antigen binding site encoded by nucleic acid containing human germline segments produced as described in U.S. Provisional Application Nos. 61/198,764 and 61/211,204, incorporated by reference herein.

As used herein, a locus in a library refers to a location or position, that can contain a member or members of library. The position does not have to be a physical position. For example, if the collection is provided as an array on a solid support, the support contains loci that can or do present members of the array.

As used herein, an address refers to a unique identifier for each locus in a collection whereby an addressed member (e.g. an antibody) can be identified. An addressed moiety is one that can be identified by virtue of its locus or location. Addressing can be effected by position on a surface, such as a well of a microplate. For example, an address for a protein in a microwell plate that is F9 means that the protein is located in row F, column 9 of the microwell plate. Addressing also can be effected by other identifiers, such as a tag encoded with a bar code or other symbology, a chemical tag, an electronic, such RF tag, a color-coded tag or other such identifier.

As used herein, an array refers to a collection of elements, such as antibodies, containing three or more members.

As used herein, a "spatial array" is an array where members are separated or occupy a distinct space in an array. Hence, spatial arrays are a type of addressable array. Examples of spatial arrays include microtiter plates where each well of a plate is an address in the array. Spacial arrays include any arrangement wherein a plurality of different molecules, e.g, polypeptides, are held, presented, positioned, situated, or supported. Arrays can include microtiter plates, such as 48-well, 96-well, 144-well, 192-well, 240-well, 288-well, 336-well, 384-well, 432-well, 480-well, 576-well, 672-well, 768-well, 864-well, 960-well, 1056-well, 1152-well, 1248-well, 1344-well, 1440-well, or 1536-well plates, tubes, slides, chips, flasks, or any other suitable laboratory apparatus. Furthermore, arrays can also include a plurality of sub-arrays. A plurality of sub-arrays encompasses an array where more than one arrangement is used to position the polypeptides. For example, multiple 96-well plates can constitute a plurality of sub-arrays and a single array.

As used herein, an addressable library is a collection of molecules such as nucleic acid molecules or protein agents, such as antibodies, in which each member of the collection is identifiable by virtue of its address.

As used herein, an addressable array is one in which the members of the array are identifiable by their address, the position in a spatial array, such as a well of a microtiter plate, or on a solid phase support, or by virtue of an identifiable or detectable label, such as by color, fluorescence, electronic signal (i.e. RF, microwave or other frequency that does not substantially alter the interaction of the molecules of interest), bar code or other symbology, chemical or other such label. Hence, in general the members of the array are located at identifiable loci on the surface of a solid phase or directly or indirectly linked to or otherwise associated with the identifiable label, such as affixed to a microsphere or other particulate support (herein referred to as beads) and suspended in solution or spread out on a surface.

As used herein, "an addressable antibody library" or "an addressable combinatorial antibody library" refers to a collection of antibodies in which member antibodies are identifiable and all antibodies with the same identifier, such as position in a spatial array or on a solid support, or a chemical or RF tag, bind to the same antigen, and generally are substantially the same in amino acid sequence. For purposes herein, reference to an "addressable arrayed combinatorial antibody library" means that the antibody members are addressed in an array.

As used herein, a support (also referred to as a matrix support, a matrix, an insoluble support or solid support) refers to any solid or semisolid or insoluble support to which a molecule of interest, typically a biological molecule, organic molecule or biospecific ligand is linked or contacted. Such materials include any materials that are used as affinity matrices or

supports for chemical and biological molecule syntheses and analyses, such as, but are not limited to: polystyrene, polycarbonate, polypropylene, nylon, glass, dextran, chitin, sand, pumice, agarose, polysaccharides, dendrimers, buckyballs, polyacrylamide, silicon, rubber, and other materials used as supports for solid phase syntheses, affinity separations and purifications, hybridization reactions, immunoassays and other such applications. The matrix herein can be particulate or can be in the form of a continuous surface, such as a microtiter dish or well, a glass slide, a silicon chip, a nitrocellulose sheet, nylon mesh, or other such materials. When particulate, typically the particles have at least one dimension in the 5-10 mm range or smaller. Such particles, referred collectively herein as "beads", are often, but not necessarily, spherical. Such reference, however, does not constrain the geometry of the matrix, which can be any shape, including random shapes, needles, fibers, and elongated. Roughly spherical "beads", particularly microspheres that can be used in the liquid phase, also are contemplated. The "beads" can include additional components, such as magnetic or paramagnetic particles (see, e.g., Dynabeads® (Dynal, Oslo, Norway)) for separation using magnets, as long as the additional components do not interfere with the methods and analyses herein.

As used herein, matrix or support particles refers to matrix materials that are in the form of discrete particles. The particles have any shape and dimensions, but typically have at least one dimension that is 100 mm or less, 50 mm or less, 10 mm or less, 1 mm or less, 100 μm or less, 50 μm or less and typically have a size that is 100 mm^3 or less, 50 mm^3 or less, 10 mm^3 or less, and 1 mm^3 or less, 100 μm^3 or less and can be on the order of cubic microns. Such particles are collectively called "beads."

As used herein, germline gene segments refer to immunoglobulin (Ig) variable (V), diversity (D) and junction (J) or constant (C) genes from the germline that encode immunoglobulin heavy or light (kappa and lambda) chains. There are multiple V, D, J and C gene segments in the germline, but gene rearrangement results in only one segment of each occurring in each functional rearranged gene. For example, a functionally rearranged heavy chain contains one V, one D and one J and a functionally rearranged light chain gene contains one V and one J. Hence, these gene segments are carried in the germ cells but cannot be transcribed and translated into heavy and light chains until they are arranged into functional genes. During B-cell differentiation in the bone marrow, these gene segments are randomly shuffled by a dynamic genetic system capable of generating more than 10^{10} specificities.

For purposes herein, heavy chain germline segments are designated as V_H, D_H and J_H, and compilation thereof results in a nucleic acid encoding a VH chain. Light chain germline segments are designated as V_L or J_L, and include kappa and lambda light chains (V_κ and J_κ; V_λ

and J_{λ}) and compilation thereof results in a nucleic acid encoding a VL chain. It is understood that a light chain chain is either a kappa or lambda light chain, but does not include a kappa/lambda combination by virtue of compilation of a V_{κ} and J_{λ}.

Reference to a variable germline segment herein refers to V, D and J groups, subgroups, genes or alleles thereof. Gene segment sequences are accessible from known database (e.g., National Center for Biotechnology Information (NCBI), the international ImMunoGeneTics information system® (IMGT), the Kabat database and the Tomlinson's VBase database (Lefranc (2003) *Nucleic Acids Res.*, 31:307-310; Martin *et al.*, Bioinformatics Tools for Antibody Engineering in Handbook of Therapeutic Antibodies, Wiley-VCH (2007), pp. 104-107).

As used herein, a "group" with reference to a germline segment refers to a core coding region from an immunoglobulin, i.e. a variable (V) gene, diversity (D) gene, joining (J) gene or constant (C) gene encoding a heavy or light chain. Exemplary of germline segment groups include V_H, D_H, J_H, V_{κ}, J_{κ}, V_{λ} and J_{λ}.

As used herein, a "subgroup" with reference to a germline segment refers to a set of sequences that are defined by nucleotide sequence similarity or identity. Generally, a subgroup is a set of genes that belong to the same group [V, D, J or C], in a given species, and that share at least 75% identity at the nucleotide level. Subgroups are classified based on IMGT nomenclature (imgt.cines.fr; see e.g., Lefranc *et al.* (2008) Briefings in Bioinformatics, 9:263-275). Generally, a subgroup represent a multigene family.

As used herein, an allele of a gene refer to germline sequences that have sequence polymorphism due to one or more nucleotide differences in the coding region compared to a reference gene sequence (e.g. substitutions, insertions or deletions). Thus, IG sequences that belong to the same subgroup can be highly similar in their coding sequence, but nonetheless exhibit high polymorphism. Subgroup alleles are classified based on IMGT nomenclature with an asterisk(*) followed by a two figure number.

As used herein, a "family" with reference to a germline segment refers to sets of germline segment sequences that are defined by amino acid sequence similarity or identity. Generally, a germline family includes all alleles of a gene.

As used herein, inverted sequence with reference to nucleotides of a germline segment means that the gene segment has a sequence of nucleotides that is the reverse complement of a reference sequence of nucleotides.

As used herein, "compilation," "compile," "combine," "combination," "rearrange," "rearrangement," or other similar terms or grammatical variations thereof refers to the process by which germline segments are ordered or assembled into nucleic acid sequences

representing genes. For example, in the combinatorial method, variable heavy chain germline segments are assembled such that the V_H segment is 5' to the D_H segment which is 5' to the J_H segment, thereby resulting in a nucleic acid sequence encoding a VH chain. Variable light chain germline segments are assembled such that the V_L segment is 5' to the J_L segment, thereby resulting in a nucleic acid sequence encoding a VL chain. A constant gene segment or segments also can be assembled onto the 3' end of a nucleic acid encoding a VH or VL chain.

As used herein, "linked," or "linkage" or other grammatical variations thereof with reference to germline segments refers to the joining of germline segments. Linkage can be direct or indirect. Germline segments can be linked directly without additional nucleotides between segments, or additional nucleotides can be added to render the entire segment in-frame, or nucleotides can be deleted to render the resulting segment in-frame. In the method of generating a combinatorial antibody library, it is understood that the choice of linker nucleotides is made such that the resulting nucleic acid molecule is in-frame and encodes a functional and productive antibody.

As used herein, "in-frame" or "linked in-frame" with reference to linkage of human germline segments means that there are insertions and/or deletions in the nucleotide germline segments at the joined junctions to render the resulting nucleic acid molecule in-frame with the 5' start codon (ATG), thereby producing a "productive" or functional full-length polypeptide. The choice of nucleotides inserted or deleted from germline segments, particularly at joints joining various VD, DJ and VJ segments, is in accord with the rules provided in the method herein for V(D)J joint generation described in detail in U.S. Provisional Application Nos. 61/198,764 and 61/211,204. For example, germline segments are assembled such that the V_H segment is 5' to the D_H segment which is 5' to the J_H segment. At the junction joining the V_H and the D_H and at the junction joining the D_H and J_H segments, nucleotides can be inserted or deleted from the individual V_H, D_H or J_H segments, such that the resulting nucleic acid molecule containing the joined VDJ segments are in-frame with the 5' start codon (ATG).

As used herein, a "functional antibody" or "productive antibody" with reference to a nucleic acid encoding an antibody or portion thereof refers to an antibody or portion thereof, such as Fab, that is encoded by the nucleic acid molecule produced by the combinatorial method. In a functional or productive antibody, the V(D)J germline segments are compiled (i.e. rearranged) such that the encoded antibody or portion thereof is not truncated and/or the amino acid sequence is not out of frame. This means that the nucleic acid molecule does not

contain internal stop codons that result in the protein translation machinery terminating protein assembly prematurely.

As used herein, corresponding with reference to corresponding residues, for example "amino acid residues corresponding to", refers to residues compared among or between two polypeptides that are related sequences (e.g. allelic variants, genes of the same family, species variants). One of skill in the art can readily identify residues that correspond between or among polypeptides. For example, by aligning two sequences, one of skill in the art can identify corresponding residues, using conserved and identical amino acids as guides. One of skill in the art can manually align a sequence or can use any of the numerous alignment programs available (for example, BLAST). Hence, an amino acid residues or positions that correspond to each other are those residues that are determined to correspond to one another based on sequence and/or structural alignments with a specified reference polypeptide.

As used herein, "screening" refers to identification or selection of an antibody or portion thereof from a plurality of antibodies, such as a collection or library of antibodies and/or portions thereof, based on determination of the activity or property of an antibody or portion thereof. Screening can be performed in any of a variety of ways, including, for example, by assays assessing direct binding (e.g. binding affinity) of the antibody to a target protein or by functional assays assessing modulation of an activity of a target protein.

As used herein the term assessing is intended to include quantitative and qualitative determination in the sense of obtaining an absolute value for the binding of an antibody or portion thereof with a target protein and/or modulation of an activity of a target protein by an antibody or portion thereof, and also of obtaining an index, ratio, percentage, visual or other value indicative of the level of the binding or activity. Assessment can be direct or indirect. For example, binding can be determined by directly labeling of an antibody or portion thereof with a detectable label and/or by using a secondary antibody that itself is labeled. In addition, functional activities can be determined using any of a variety of assays known to one of skill in the art, for example, proliferation, cytotoxicity and others as described herein, and comparing the activity of the target protein in the presence versus the absence of an antibody or portion thereof.

As used herein, "modulate" or "modulation" and other various grammatical forms thereof with reference to the effect of an antibody or portion thereof on the functional activity of a target protein refers to increased activity such as induction or potentiation of activity, as well as inhibition of one or more activities of the target protein. Hence, modulation can include an increase in the activity (i.e., up-regulation or agonist activity) a decrease in activity (i.e., down-regulation or inhibition) or any other alteration in an activity (such as a

change in periodicity, frequency, duration, kinetics or other parameter) . Modulation can be context dependent and typically modulation is compared to a designated state, for example, the wildtype protein, the protein in a constitutive state, or the protein as expressed in a designated cell type or condition. The functional activity of a target protein by an antibody or portion thereof can be modulated by 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more compared to the activity of the target protein in the abasence of the antibody or portion thereof.

As used herein, Delta-like 4 (DLL4) refers to a protein that is a ligand for Notch receptors 1 and 4. DLL4 includes any DLL4 polypeptide, including but not limited to, a recombinantly produced polypeptide, a sythentically produced polypeptide, a native DLL4 polypeptide, and a DLL4 polypeptide extracted from cells or tissues, including endothelial cells. DLL4 also includes related polypeptides from different species including, but not limited to animals of human and non-human origin. Human DLL4 includes DLL4, allelic variant isoforms, synthetic molecules from nucleic acids, protein isolated from human tissue and cells, and modified forms thereof. An exemplary DLL4 includes human DLL4 having a sequence of amino acids set forth in SEQ ID NO:2904 and encoded by a sequence of nucleotides set forth in SEQ ID NO:2905. For purposes herein, reference to DLL4 is typically with reference to human DLL4, unless stated otherwise.

As used herein, an "activator", such as an "agonist" or "activator/modulator," refers to an antibody or portion thereof that modulates signal transduction or other functional activity of a receptor by potentiating, inducing or otherwise enhancing the signal transduction activity or other functional activity of a receptor. An activator, such as an agonists or activator/modulator, can modulate or increase signal transduction or other functional activity when used alone or can alter signal transduction or other functional activity in the presence of the natural ligand of the receptor or other receptor stimulator to enhance signaling by the receptor compared to the ligand alone. An activator includes an agonist or activator/modulator.

As used herein, an "agonist" refers to an antibody or portion thereof that mimics the activity of an endogenous ligand, and can replace the endogenous ligand.

As used herein, a "modulator/activator" refers to an antibody or portion thereof that binds an allosteric site of a target substrate and alters, such as increases, the activation of a receptor by its ligand.

As used herein, an "allosteric site" is a site on the target substrate that is not the site conferring ligand/receptor interaction, but that when bound by an antibody or a portion thereof alters the activity of the target substrate.

As used herein, "antagonist" refers to an antibody or portion thereof that modulates signal transduction or other functional activity of a receptor by blocking or decreasing the signal transduction activity or other functional activity of a receptor.

As used herein, off-rate (k_{off}) is the rate at which an antibody dissociates from its antigen.

As used herein, on-rate (k_{on}) is the rate at which an antibody binds antigen.

As used herein, "half-life" ($t_{1/2}$) or "dissociation half-life" refers to the time in which half of the initially present protein-ligand or substrate-antibody complexes have disassociated. It is designated as $Ln(2)/k_{off}$.

As used herein, reference to an "antibody or portion thereof that is sufficient to form an antigen binding site" means that the antibody or portion thereof contains at least 1 or 2, typically 3, 4, 5 or all 6 CDRs of the VH and VL sufficient to retain at least a portion of the binding specificity of the corresponding full-length antibody containing all 6 CDRs. Generally, a sufficient antigen binding site at least requires CDR3 of the heavy chain (CDRH3). It typically futher requires the CDR3 of the light chain (CDRL3). As described herein, one of skill in the art knows and can identify the CDRs based on Kabat or Chothia numbering (see e.g., Kabat, E.A. *et al.* (1991) *Sequences of Proteins of Immunological Interest*, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242, and Chothia, C. *et al.* (1987) *J. Mol. Biol.* 196:901-917). For example, based on Kabat numbering, CDR-LI corresponds to residues L24-L34; CDR-L2 corresponds to residues L50-L56; CDR-L3 corresponds to residues L89-L97; CDR-H1 corresponds to residues H31 – H35, 35a or 35b depending on the length; CDR-H2 corresponds to residues H50-H65; and CDR-H3 corresponds to residues H95-H102.

As used herein, a label is a detectable marker that can be attached or linked directly or indirectly to a molecule or associated therewith. The detection method can be any method known in the art.

As used herein, a human protein is one encoded by a nucleic acid molecule, such as DNA, present in the genome of a human, including all allelic variants and conservative variations thereof. A variant or modification of a protein is a human protein if the modification is based on the wildtype or prominent sequence of a human protein.

As used herein, "naturally occurring amino acids" refer to the 20 L-amino acids that occur in polypeptides. The residues are those 20 α-amino acids found in nature which are incorporated into protein by the specific recognition of the charged tRNA molecule with its cognate mRNA codon in humans.

As used herein, non-naturally occurring amino acids refer to amino acids that are not genetically encoded. For example, a non-natural amino acid is an organic compound that has a structure similar to a natural amino acid but has been modified structurally to mimic the structure and reactivity of a natural amino acid. Non-naturally occurring amino acids thus include, for example, amino acids or analogs of amino acids other than the 20 naturally-occurring amino acids and include, but are not limited to, the D-isostereomers of amino acids. Exemplary non-natural amino acids are known to those of skill in the art.

As used herein, nucleic acids include DNA, RNA and analogs thereof, including peptide nucleic acids (PNA) and mixtures thereof. Nucleic acids can be single or double-stranded. When referring to probes or primers, which are optionally labeled, such as with a detectable label, such as a fluorescent or radiolabel, single-stranded molecules are contemplated. Such molecules are typically of a length such that their target is statistically unique or of low copy number (typically less than 5, generally less than 3) for probing or priming a library. Generally a probe or primer contains at least 14, 16 or 30 contiguous nucleotides of sequence complementary to or identical to a gene of interest. Probes and primers can be 10, 20, 30, 50, 100 or more nucleic acids long.

As used herein, a peptide refers to a polypeptide that is from 2 to 40 amino acids in length.

As used herein, the amino acids which occur in the various sequences of amino acids provided herein are identified according to their known, three-letter or one-letter abbreviations (Table 1). The nucleotides which occur in the various nucleic acid fragments are designated with the standard single-letter designations used routinely in the art.

As used herein, an "amino acid" is an organic compound containing an amino group and a carboxylic acid group. A polypeptide contains two or more amino acids. For purposes herein, amino acids include the twenty naturally-occurring amino acids, non-natural amino acids and amino acid analogs (i.e., amino acids wherein the α-carbon has a side chain).

As used herein, "amino acid residue" refers to an amino acid formed upon chemical digestion (hydrolysis) of a polypeptide at its peptide linkages. The amino acid residues described herein are presumed to be in the "L" isomeric form. Residues in the "D" isomeric form, which are so designated, can be substituted for any L-amino acid residue as long as the desired functional property is retained by the polypeptide. NH_2 refers to the free amino group present at the amino terminus of a polypeptide. COOH refers to the free carboxy group present at the carboxyl terminus of a polypeptide. In keeping with standard polypeptide nomenclature described in *J. Biol. Chem.*, 243: 3557-3559 (1968), and adopted 37 C.F.R. §§ 1.821-1.822, abbreviations for amino acid residues are shown in Table 1:

Table 1 – Table of Correspondence

SYMBOL		
1-Letter	**3-Letter**	**AMINO ACID**
Y	Tyr	Tyrosine
G	Gly	Glycine
F	Phe	Phenylalanine
M	Met	Methionine
A	Ala	Alanine
S	Ser	Serine
I	Ile	Isoleucine
L	Leu	Leucine
T	Thr	Threonine
V	Val	Valine
P	Pro	Proline
K	Lys	Lysine
H	His	Histidine
Q	Gln	Glutamine
E	Glu	Glutamic acid
Z	Glx	Glu and/or Gln
W	Trp	Tryptophan
R	Arg	Arginine
D	Asp	Aspartic acid
N	Asn	Asparagine
B	Asx	Asn and/or Asp
C	Cys	Cysteine
X	Xaa	Unknown or other

It should be noted that all amino acid residue sequences represented herein by formulae have a left to right orientation in the conventional direction of amino-terminus to carboxyl-terminus. In addition, the phrase "amino acid residue" is broadly defined to include the amino acids listed in the Table of Correspondence (Table 1) and modified and unusual amino acids, such as those referred to in 37 C.F.R. §§ 1.821-1.822, and incorporated herein by reference. Furthermore, it should be noted that a dash at the beginning or end of an amino acid residue sequence indicates a peptide bond to a further sequence of one or more amino acid residues, to an amino-terminal group such as NH_2 or to a carboxyl-terminal group such as COOH. The abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (see, (1972) *Biochem.* 11:1726). Each naturally occurring L-amino acid is identified by the standard three letter code (or single letter code) or the standard three letter code (or single letter code) with the prefix "L-"; the prefix "D-" indicates that the stereoisomeric form of the amino acid is D.

As used herein, an isokinetic mixture is one in which the molar ratios of amino acids has been adjusted based on their reported reaction rates (see, e.g., Ostresh *et al.*, (1994) *Biopolymers* 34:1681).

As used herein, modification is in reference to modification of a sequence of amino acids of a polypeptide or a sequence of nucleotides in a nucleic acid molecule and includes deletions, insertions, and replacements of amino acids and nucleotides, respectively. Methods of modifying a polypeptide are routine to those of skill in the art, such as by using recombinant DNA methodologies.

As used herein, suitable conservative substitutions of amino acids are known to those of skill in this art and can be made generally without altering the biological activity of the resulting molecule. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (see, e.g., Watson *et al.* Molecular Biology of the Gene, 4th Edition, 1987, The Benjamin/Cummings Pub. co., p.224). Such substitutions can be made in accordance with those set forth in TABLE 2 as follows:

TABLE 2

Original residue	Exemplary conservative substitution
Ala (A)	Gly; Ser
Arg (R)	Lys
Asn (N)	Gln; His
Cys (C)	Ser
Gln (Q)	Asn
Glu (E)	Asp
Gly (G)	Ala; Pro
His (H)	Asn; Gln
Ile (I)	Leu; Val
Leu (L)	Ile; Val
Lys (K)	Arg; Gln; Glu
Met (M)	Leu; Tyr; Ile
Phe (F)	Met; Leu; Tyr
Ser (S)	Thr
Thr (T)	Ser
Trp (W)	Tyr
Tyr (Y)	Trp; Phe
Val (V)	Ile; Leu

Other substitutions also are permissible and can be determined empirically or in accord with known conservative substitutions.

As used herein, a DNA construct is a single or double stranded, linear or circular DNA molecule that contains segments of DNA combined and juxtaposed in a manner not found in nature. DNA constructs exist as a result of human manipulation, and include clones and other copies of manipulated molecules.

As used herein, a DNA segment is a portion of a larger DNA molecule having specified attributes. For example, a DNA segment encoding a specified polypeptide is a portion of a longer DNA molecule, such as a plasmid or plasmid fragment, which, when read from the 5' to 3' direction, encodes the sequence of amino acids of the specified polypeptide.

As used herein, the term "nucleic acid" refers to single-stranded and/or double-stranded polynucleotides such as deoxyribonucleic acid (DNA), and ribonucleic acid (RNA) as well as analogs or derivatives of either RNA or DNA. Also included in the term "nucleic acid" are analogs of nucleic acids such as peptide nucleic acid (PNA), phosphorothioate DNA, and other such analogs and derivatives or combinations thereof. Nucleic acid can refer to polynucleotides such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). The term also includes, as equivalents, derivatives, variants and analogs of either RNA or DNA made from nucleotide analogs, single (sense or antisense) and double-stranded polynucleotides. Deoxyribonucleotides include deoxyadenosine, deoxycytidine, deoxyguanosine and deoxythymidine. For RNA, the uracil base is uridine.

As used herein, "nucleic acid molecule encoding" refers to a nucleic acid molecule which directs the expression of a specific protein or peptide. The nucleic acid sequences include both the DNA strand sequence that is transcribed into RNA and the RNA sequence that is translated into protein or peptide. The nucleic acid molecule includes both the full length nucleic acid sequences as well as non-full length sequences derived from the full length mature polypeptide, such as for example a full length polypeptide lacking a precursor sequence. For purposes herein, a nucleic acid sequence also includes the degenerate codons of the native sequence or sequences which can be introduced to provide codon preference in a specific host.

As used herein, the term "polynucleotide" refers to an oligomer or polymer containing at least two linked nucleotides or nucleotide derivatives, including a deoxyribonucleic acid (DNA), a ribonucleic acid (RNA), and a DNA or RNA derivative containing, for example, a nucleotide analog or a "backbone" bond other than a phosphodiester bond, for example, a phosphotriester bond, a phosphoramidate bond, a phophorothioate bond, a thioester bond, or a peptide bond (peptide nucleic acid). The term "oligonucleotide" also is used herein essentially synonymously with "polynucleotide," although those in the art recognize that oligonucleotides, for example, PCR primers, generally are less than about fifty to one hundred nucleotides in length.

Polynucleotides can include nucleotide analogs, including, for example, mass modified nucleotides, which allow for mass differentiation of polynucleotides; nucleotides containing a detectable label such as a fluorescent, radioactive, luminescent or

chemiluminescent label, which allow for detection of a polynucleotide; or nucleotides containing a reactive group such as biotin or a thiol group, which facilitates immobilization of a polynucleotide to a solid support. A polynucleotide also can contain one or more backbone bonds that are selectively cleavable, for example, chemically, enzymatically or photolytically. For example, a polynucleotide can include one or more deoxyribonucleotides, followed by one or more ribonucleotides, which can be followed by one or more deoxyribonucleotides, such a sequence being cleavable at the ribonucleotide sequence by base hydrolysis. A polynucleotide also can contain one or more bonds that are relatively resistant to cleavage, for example, a chimeric oligonucleotide primer, which can include nucleotides linked by peptide nucleic acid bonds and at least one nucleotide at the 3' end, which is linked by a phosphodiester bond or other suitable bond, and is capable of being extended by a polymerase. Peptide nucleic acid sequences can be prepared using well-known methods (see, for example, Weiler *et al.* Nucleic acids Res. 25: 2792-2799 (1997)).

As used herein, "similarity" between two proteins or nucleic acids refers to the relatedness between the sequence of amino acids of the proteins or the nucleotide sequences of the nucleic acids. Similarity can be based on the degree of identity and/or homology of sequences of residues and the residues contained therein. Methods for assessing the degree of similarity between proteins or nucleic acids are known to those of skill in the art. For example, in one method of assessing sequence similarity, two amino acid or nucleotide sequences are aligned in a manner that yields a maximal level of identity between the sequences. "Identity" refers to the extent to which the amino acid or nucleotide sequences are invariant. Alignment of amino acid sequences, and to some extent nucleotide sequences, also can take into account conservative differences and/or frequent substitutions in amino acids (or nucleotides). Conservative differences are those that preserve the physico-chemical properties of the residues involved. Alignments can be global (alignment of the compared sequences over the entire length of the sequences and including all residues) or local (the alignment of a portion of the sequences that includes only the most similar region or regions).

"Identity" per se has an art-recognized meaning and can be calculated using published techniques. (See, e.g.: *Computational Molecular Biology*, Lesk, A.M., ed., Oxford University Press, New York, 1988; *Biocomputing: Informatics and Genome Projects*, Smith, D.W., ed., Academic Press, New York, 1993; *Computer Analysis of Sequence Data*, Part I, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; *Sequence Analysis in Molecular Biology*, von Heinje, G., Academic Press, 1987; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991). While there exists a number of methods to measure identity between two polynucleotide or polypeptides, the

term "identity" is well known to skilled artisans (Carillo, H. & Lipton, D., *SIAM J Applied Math 48*:1073 (1988)).

As used herein, homologous (with respect to nucleic acid and/or amino acid sequences) means about greater than or equal to 25% sequence homology, typically greater than or equal to 25%, 40%, 50%, 60%, 70%, 80%, 85%, 90% or 95% sequence homology; the precise percentage can be specified if necessary. For purposes herein the terms "homology" and "identity" are often used interchangeably, unless otherwise indicated. In general, for determination of the percentage homology or identity, sequences are aligned so that the highest order match is obtained (see, e.g.: *Computational Molecular Biology*, Lesk, A.M., ed., Oxford University Press, New York, 1988; *Biocomputing: Informatics and Genome Projects*, Smith, D.W., ed., Academic Press, New York, 1993; *Computer Analysis of Sequence Data, Part I*, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; *Sequence Analysis in Molecular Biology*, von Heinje, G., Academic Press, 1987; and *Sequence Analysis Primer*, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; Carillo *et al.* (1988) *SIAM J Applied Math 48*:1073). By sequence homology, the number of conserved amino acids is determined by standard alignment algorithms programs, and can be used with default gap penalties established by each supplier. Substantially homologous nucleic acid molecules hybridize typically at moderate stringency or at high stringency all along the length of the nucleic acid of interest. Also contemplated are nucleic acid molecules that contain degenerate codons in place of codons in the hybridizing nucleic acid molecule.

Whether any two molecules have nucleotide sequences or amino acid sequences that are at least 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% "identical" or "homologous" can be determined using known computer algorithms such as the "FASTA" program, using for example, the default parameters as in Pearson *et al.* (1988) *Proc. Natl. Acad. Sci. USA 85*:2444 (other programs include the GCG program package (Devereux, J., *et al., Nucleic Acids Research 12(I)*:387 (1984)), BLASTP, BLASTN, FASTA (Atschul, S.F., *et al., J Molec Biol 215*:403 (1990)); Guide to Huge Computers, Martin J. Bishop, ed., Academic Press, San Diego, 1994, and Carillo *et al.* (1988) *SIAM J Applied Math 48*:1073). For example, the BLAST function of the National Center for Biotechnology Information database can be used to determine identity. Other commercially or publicly available programs include, DNAStar "MegAlign" program (Madison, WI) and the University of Wisconsin Genetics Computer Group (UWG) "Gap" program (Madison WI). Percent homology or identity of proteins and/or nucleic acid molecules can be determined, for example, by comparing sequence information using a GAP computer program (e.g.,

Needleman *et al.* (1970) *J. Mol. Biol.* 48:443, as revised by Smith and Waterman ((1981) *Adv. Appl. Math.* 2:482). Briefly, the GAP program defines similarity as the number of aligned symbols (i.e., nucleotides or amino acids), which are similar, divided by the total number of symbols in the shorter of the two sequences. Default parameters for the GAP program can include: (1) a unary comparison matrix (containing a value of 1 for identities and 0 for non-identities) and the weighted comparison matrix of Gribskov *et al.* (1986) *Nucl. Acids Res.* 14:6745, as described by Schwartz and Dayhoff, eds., *ATLAS OF PROTEIN SEQUENCE AND STRUCTURE*, National Biomedical Research Foundation, pp. 353-358 (1979); (2) a penalty of 3.0 for each gap and an additional 0.10 penalty for each symbol in each gap; and (3) no penalty for end gaps.

Therefore, as used herein, the term "identity" or "homology" represents a comparison between a test and a reference polypeptide or polynucleotide. As used herein, the term at least "90% identical to" refers to percent identities from 90 to 99.99 relative to the reference nucleic acid or amino acid sequence of the polypeptide. Identity at a level of 90% or more is indicative of the fact that, assuming for exemplification purposes a test and reference polypeptide length of 100 amino acids are compared. No more than 10% (i.e., 10 out of 100) of the amino acids in the test polypeptide differs from that of the reference polypeptide. Similar comparisons can be made between test and reference polynucleotides. Such differences can be represented as point mutations randomly distributed over the entire length of a polypeptide or they can be clustered in one or more locations of varying length up to the maximum allowable, e.g. 10/100 amino acid difference (approximately 90% identity). Differences are defined as nucleic acid or amino acid substitutions, insertions or deletions. At the level of homologies or identities above about 85-90%, the result should be independent of the program and gap parameters set; such high levels of identity can be assessed readily, often by manual alignment without relying on software.

As used herein, an aligned sequence refers to the use of homology (similarity and/or identity) to align corresponding positions in a sequence of nucleotides or amino acids. Typically, two or more sequences that are related by 50% or more identity are aligned. An aligned set of sequences refers to 2 or more sequences that are aligned at corresponding positions and can include aligning sequences derived from RNAs, such as ESTs and other cDNAs, aligned with genomic DNA sequence.

As used herein, “primer" refers to a nucleic acid molecule that can act as a point of initiation of template-directed DNA synthesis under appropriate conditions (e.g., in the presence of four different nucleoside triphosphates and a polymerization agent , such as DNA polymerase, RNA polymerase or reverse transcriptase) in an appropriate buffer and at a

suitable temperature. It will be appreciated that a certain nucleic acid molecules can serve as a "probe" and as a "primer." A primer, however, has a 3' hydroxyl group for extension. A primer can be used in a variety of methods, including, for example, polymerase chain reaction (PCR), reverse-transcriptase (RT)-PCR, RNA PCR, LCR, multiplex PCR, panhandle PCR, capture PCR, expression PCR, 3' and 5' RACE, in situ PCR, ligation-mediated PCR and other amplification protocols.

As used herein, "primer pair" refers to a set of primers that includes a 5' (upstream) primer that hybridizes with the 5' end of a sequence to be amplified (e.g. by PCR) and a 3' (downstream) primer that hybridizes with the complement of the 3' end of the sequence to be amplified.

As used herein, "specifically hybridizes" refers to annealing, by complementary base-pairing, of a nucleic acid molecule (e.g. an oligonucleotide) to a target nucleic acid molecule. Those of skill in the art are familiar with *in vitro* and *in vivo* parameters that affect specific hybridization, such as length and composition of the particular molecule. Parameters particularly relevant to *in vitro* hybridization further include annealing and washing temperature, buffer composition and salt concentration. Exemplary washing conditions for removing non-specifically bound nucleic acid molecules at high stringency are 0.1 x SSPE, 0.1% SDS, 65°C, and at medium stringency are 0.2 x SSPE, 0.1% SDS, 50°C. Equivalent stringency conditions are known in the art. The skilled person can readily adjust these parameters to achieve specific hybridization of a nucleic acid molecule to a target nucleic acid molecule appropriate for a particular application.

As used herein, substantially identical to a product means sufficiently similar so that the property of interest is sufficiently unchanged so that the substantially identical product can be used in place of the product.

As used herein, it also is understood that the terms "substantially identical" or "similar" varies with the context as understood by those skilled in the relevant art.

As used herein, an allelic variant or allelic variation references any of two or more alternative forms of a gene occupying the same chromosomal locus. Allelic variation arises naturally through mutation, and can result in phenotypic polymorphism within populations. Gene mutations can be silent (no change in the encoded polypeptide) or can encode polypeptides having altered amino acid sequence. The term "allelic variant" also is used herein to denote a protein encoded by an allelic variant of a gene. Typically the reference form of the gene encodes a wildtype form and/or predominant form of a polypeptide from a population or single reference member of a species. Typically, allelic variants, which include variants between and among species typically have at least 80%, 90% or greater amino acid

identity with a wildtype and/or predominant form from the same species; the degree of identity depends upon the gene and whether comparison is interspecies or intraspecies. Generally, intraspecies allelic variants have at least about 80%, 85%, 90% or 95% identity or greater with a wildtype and/or predominant form, including 96%, 97%, 98%, 99% or greater identity with a wildtype and/or predominant form of a polypeptide. Reference to an allelic variant herein generally refers to variations n proteins among members of the same species.

As used herein, "allele," which is used interchangeably herein with "allelic variant" refers to alternative forms of a gene or portions thereof. Alleles occupy the same locus or position on homologous chromosomes. When a subject has two identical alleles of a gene, the subject is said to be homozygous for that gene or allele. When a subject has two different alleles of a gene, the subject is said to be heterozygous for the gene. Alleles of a specific gene can differ from each other in a single nucleotide or several nucleotides, and can include substitutions, deletions and insertions of nucleotides. An allele of a gene also can be a form of a gene containing a mutation.

As used herein, species variants refer to variants in polypeptides among different species, including different mammalian species, such as mouse and human.

As used herein, a splice variant refers to a variant produced by differential processing of a primary transcript of genomic DNA that results in more than one type of mRNA.

As used herein, the term promoter means a portion of a gene containing DNA sequences that provide for the binding of RNA polymerase and initiation of transcription. Promoter sequences are commonly, but not always, found in the 5' non-coding region of genes.

As used herein, isolated or purified polypeptide or protein or biologically-active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue from which the protein is derived, or substantially free from chemical precursors or other chemicals when chemically synthesized. Preparations can be determined to be substantially free if they appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography (TLC), gel electrophoresis and high performance liquid chromatography (HPLC), used by those of skill in the art to assess such purity, or sufficiently pure such that further purification does not detectably alter the physical and chemical properties, such as enzymatic and biological activities, of the substance. Methods for purification of the compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound, however, can be a mixture of stereoisomers. In such instances, further purification might increase the specific activity of the compound.

The term substantially free of cellular material includes preparations of proteins in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly-produced. In one embodiment, the term substantially free of cellular material includes preparations of protease proteins having less that about 30% (by dry weight) of non-protease proteins (also referred to herein as a contaminating protein), generally less than about 20% of non-protease proteins or 10% of non-protease proteins or less that about 5% of non-protease proteins. When the protease protein or active portion thereof is recombinantly produced, it also is substantially free of culture medium, i.e., culture medium represents less than about or at 20%, 10% or 5% of the volume of the protease protein preparation.

As used herein, the term substantially free of chemical precursors or other chemicals includes preparations of protease proteins in which the protein is separated from chemical precursors or other chemicals that are involved in the synthesis of the protein. The term includes preparations of protease proteins having less than about 30% (by dry weight) 20%, 10%, 5% or less of chemical precursors or non-protease chemicals or components.

As used herein, synthetic, with reference to, for example, a synthetic nucleic acid molecule or a synthetic gene or a synthetic peptide refers to a nucleic acid molecule or polypeptide molecule that is produced by recombinant methods and/or by chemical synthesis methods.

As used herein, production by recombinant means by using recombinant DNA methods means the use of the well known methods of molecular biology for expressing proteins encoded by cloned DNA.

As used herein, vector (or plasmid) refers to discrete elements that are used to introduce a heterologous nucleic acid into cells for either expression or replication thereof. The vectors typically remain episomal, but can be designed to effect integration of a gene or portion thereof into a chromosome of the genome. Also contemplated are vectors that are artificial chromosomes, such as yeast artificial chromosomes and mammalian artificial chromosomes. Selection and use of such vehicles are well known to those of skill in the art.

As used herein, an expression vector includes vectors capable of expressing DNA that is operatively linked with regulatory sequences, such as promoter regions, that are capable of effecting expression of such DNA fragments. Such additional segments can include promoter and terminator sequences, and optionally can include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, and the like. Expression vectors are generally derived from plasmid or viral DNA, or can contain elements of both. Thus, an expression vector refers to a recombinant DNA or RNA construct, such as a

plasmid, a phage, recombinant virus or other vector that, upon introduction into an appropriate host cell, results in expression of the cloned DNA. Appropriate expression vectors are well known to those of skill in the art and include those that are replicable in eukaryotic cells and/or prokaryotic cells and those that remain episomal or those which integrate into the host cell genome.

As used herein, vector also includes "virus vectors" or "viral vectors." Viral vectors are engineered viruses that are operatively linked to exogenous genes to transfer (as vehicles or shuttles) the exogenous genes into cells.

As used herein, operably or operatively linked when referring to DNA segments means that the segments are arranged so that they function in concert for their intended purposes, e.g., transcription initiates in the promoter and proceeds through the coding segment to the terminator.

As used herein, biological sample refers to any sample obtained from a living or viral source and includes any cell type or tissue of a subject from which nucleic acid or protein or other macromolecule can be obtained. Biological samples include, but are not limited to, body fluids, such as blood, plasma, serum, cerebrospinal fluid, synovial fluid, urine and sweat, tissue and organ samples from animals and plants. Also included are soil and water samples and other environmental samples, viruses, bacteria, fungi, algae, protozoa and components thereof. Hence bacterial and viral and other contamination of food products and environments can be assessed. The methods herein are practiced using biological samples and in some embodiments, such as for profiling, also can be used for testing any sample.

As used herein, macromolecule refers to any molecule having a molecular weight from the hundreds up to the millions. Macromolecules include peptides, proteins, nucleotides, nucleic acids, and other such molecules that are generally synthesized by biological organisms, but can be prepared synthetically or using recombinant molecular biology methods.

As used herein, a composition refers to any mixture. It can be a solution, a suspension, liquid, powder, a paste, aqueous, non-aqueous or any combination thereof.

As used herein, a combination refers to any association between or among two or more items. The combination can be two or more separate items, such as two compositions or two collections, can be a mixture thereof, such as a single mixture of the two or more items, or any variation thereof.

As used herein, kit refers to a packaged combination, optionally including instructions and/or reagents for their use.

As used herein, a pharmaceutical effect or therapeutic effect refers to an effect observed upon administration of an agent intended for treatment of a disease or disorder or for amelioration of the symptoms thereof.

As used herein, "disease or disorder" refers to a pathological condition in an organism resulting from cause or condition including, but not limited to, infections, acquired conditions, genetic conditions, and characterized by identifiable symptoms. Diseases and disorders of interest herein are those involving a specific target protein including those mediated by a target protein and those in which a target protein plays a role in the etiology or pathology. Exemplary target proteins and associated diseases and disorders are described elsewhere herein.

As used herein, angiogenic diseases (or angiogenesis-related diseases) are diseases in which the balance of angiogenesis is altered or the timing thereof is altered. Angiogenic diseases include those in which an alteration of angiogenesis, such as undesirable vascularization, occurs. Such diseases include, but are not limited to cell proliferative disorders, including cancers, diabetic retinopathies and other diabetic complications, inflammatory diseases, endometriosis, age-related macular degeneration and other diseases in which excessive vascularization is part of the disease process, including those known in the art or noted elsewhere herein.

As used herein, "treating" a subject with a disease or condition means that the subject's symptoms are partially or totally alleviated, or remain static following treatment. Hence treatment encompasses prophylaxis, therapy and/or cure. Prophylaxis refers to prevention of a potential disease and/or a prevention of worsening of symptoms or progression of a disease. Treatment also encompasses any pharmaceutical use of a modified interferon and compositions provided herein.

As used herein, a therapeutic agent, therapeutic regimen, radioprotectant, or chemotherapeutic mean conventional drugs and drug therapies, including vaccines, which are known to those skilled in the art. Radiotherapeutic agents are well known in the art.

As used herein, treatment means any manner in which the symptoms of a condition, disorder or disease or other indication, are ameliorated or otherwise beneficially altered.

As used herein therapeutic effect means an effect resulting from treatment of a subject that alters, typically improves or ameliorates the symptoms of a disease or condition or that cures a disease or condition. A therapeutically effective amount refers to the amount of a composition, molecule or compound which results in a therapeutic effect following administration to a subject.

As used herein, the term "subject" refers to an animal, including a mammal, such as a human being.

As used herein, a patient refers to a human subject.

As used herein, amelioration of the symptoms of a particular disease or disorder by a treatment, such as by administration of a pharmaceutical composition or other therapeutic, refers to any lessening, whether permanent or temporary, lasting or transient, of the symptoms that can be attributed to or associated with administration of the composition or therapeutic.

As used herein, prevention or prophylaxis refers to methods in which the risk of developing disease or condition is reduced.

As used herein, an effective amount is the quantity of a therapeutic agent necessary for preventing, curing, ameliorating, arresting or partially arresting a symptom of a disease or disorder.

As used herein, administration refers to any method in which an antibody or protion thereof is contacted with its target protein. Adminstration can be effected *in vivo* or *ex vivo* or *in vitro*. For example, for *ex vivo* administration a body fluid, such as blood, is removed from a subject and contacted outside the body with the antibody or portion thereof. For *in vivo* administration, the antibody or portion thereof can be introduced into the body, such as by local, topical, systemic and/or other route of introduction. *In vitro* administration encompasses methods, such as cell culture methods.

As used herein, unit dose form refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art.

As used herein, a single dosage formulation refers to a formulation for direct administration.

As used herein, an "article of manufacture" is a product that is made and sold. As used throughout this application, the term is intended to encompass compiled germline antibodies or antibodies obtained therefrom contained in articles of packaging.

As used herein, fluid refers to any composition that can flow. Fluids thus encompass compositions that are in the form of semi-solids, pastes, solutions, aqueous mixtures, gels, lotions, creams and other such compositions.

As used herein, animal includes any animal, such as, but are not limited to primates including humans, gorillas and monkeys; rodents, such as mice and rats; fowl, such as chickens; ruminants, such as goats, cows, deer, sheep; mammals, such as pigs and other animals. Non-human animals exclude humans as the contemplated animal. The germline segments, and resulting antibodies, provided herein are from any source, animal, plant,

prokaryotic and fungal. Most germline segments, and resulting antibodies, are of animal origin, including mammalian origin.

As used herein, a control refers to a sample that is substantially identical to the test sample, except that it is not treated with a test parameter, or, if it is a sample plasma sample, it can be from a normal volunteer not affected with the condition of interest. A control also can be an internal control.

As used herein, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to compound, comprising "an extracellular domain" includes compounds with one or a plurality of extracellular domains.

As used herein, ranges and amounts can be expressed as "about" a particular value or range. About also includes the exact amount. Hence "about 5 bases" means "about 5 bases" and also "5 bases."

As used herein, "optional" or "optionally" means that the subsequently described event or circumstance does or does not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not. For example, an optionally substituted group means that the group is unsubstituted or is substituted.

As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (see, (1972) Biochem. 11:1726).

B. OVERVIEW OF METHODS

Provided herein are methods of selecting antibodies with desired affinities and activities. The methods include affinity maturation and antibody conversion methods. The methods can be used to engineer antibodies to thereby identify or select antibodies that are antagonist antibodies, partial antagonist antibodies, agonist antibodies and/or activator/modulator antibodies. The ability to "tune" a particular pathway as opposed to completely inhibiting it would be an advantage for protein therapeutics. For example, pharmacologically, the ability to turn a pathway "on" or "off" by a high affinity interaction, might be less desirable than modulation of a pathway through "rheostat" based therapeutics. In other examples, an antibody with a high affinity is desired.

The resulting affinity-based or activity-based antibodies generated by practice of the methods can be used for any application or purpose as desired, including for example, in a variety of *in vitro* and *in vivo* applications by virtue of their specificity for one or more target proteins. Because of their diversity, specificity and effector functions, antibodies are

attractive candidates for protein-based therapeutics. Accordingly, the methods provided herein for generating antibodies with desired affinities, specificities and/or activities permits their use as therapeutic antibodies. For example, the antibodies can be used in methods of treatment and other uses for treating a disease or disorder which is associated with expression or activation of a particular target protein, for which the antibody can modulate.

1. Antibody Polypeptides

In the methods provided herein, mutagenesis is typically performed on the variable region of the antibody. Accordingly, the parent antibody selected for affinity conversion or affinity maturation using the methods provided herein typically minimally include all or a portion of a variable heavy chain (VH) and/or a variable light (VL) chain so long as the antibody contains a sufficient antibody binding site. It is understood, however, that any antibody used or obtained by practice of the methods can be generated to include all or a portion of the constant heavy chain (e.g. one or more CH domains such as CH1, CH2, CH3 and CH4 and/or a constant light chain (CL)). Hence, the antibodies subjected to affinity conversion or affinity maturation herein include those that are full-length antibodies, and also include fragments or portions thereof including, for example, Fab, Fab', $F(ab')_2$, single-chain Fvs (scFv), Fv, dsFv, diabody, Fd and Fd' fragments, Fab fragments, scFv fragments, and scFab fragments. For example, antibodies affinity converted or affinity matured herein include Fabs.

A skilled artisan understands the structure, sequence and function of antibodies. A general description of the structure, sequence and function of antibodies is provided below.

a. Antibody Structure and Function

Antibodies are produced naturally by B cells in membrane-bound and secreted forms. In addition to naturally produced antibodies, antibodies also include synthetically, i.e. recombinantly, produced antibodies, such as antibody fragments. Antibodies specifically recognize and bind antigen epitopes through cognate interactions. Antibody binding to cognate antigens can initiate multiple effector functions, which cause neutralization and clearance of toxins, pathogens and other infectious agents. Diversity in antibody specificity arises naturally due to recombination events during B cell development. Through these events, various combinations of multiple antibody V, D and J gene segments, which encode variable regions of antibody molecules, are joined with constant region genes to generate a natural antibody repertoire with large numbers of diverse antibodies. A human antibody repertoire contains more than 10^{10} different antigen specificities and thus theoretically can specifically recognize any foreign antigen.

A full-length antibody contains four polypeptide chains, two identical heavy (H) chains (each usually containing about 440 amino acids) and two identical light (L) chains (each containing about 220 amino acids). The light chains exist in two distinct forms called kappa (κ) and lambda (λ). Each chain is organized into a series of domains organized as immunoglobulin (Ig) domains, including variable (V) and constant (C) region domains. Light chains have two domains, corresponding to the C region (CL) and the V region (VL). Heavy chains have four domains, the V region (VH) and three or four domains in the C region (CH1, CH2 , CH3 and CH4), and, in some cases, hinge region. The four chains (two heavy and two light) are held together by a combination of covalent (disulfide) and non-covalent bonds.

Antibodies include those that are full-lengths and those that are fragments thereof, namely Fab, Fab', $F(ab')_2$, single-chain Fvs (scFv), Fv, dsFv, diabody, Fd and Fd' fragments. The fragments include those that are in single-chain or dimeric form. The Fv fragment, which contains only the VH and VL domain, is the smallest immunoglobulin fragment that retains the whole antigen-binding site (see, for example, *Methods in Molecular Biology*, Vol 207: *Recombinant Antibodies for Cancer Therapy Methods and Protocols* (2003); Chapter 1; p 3-25, Kipriyanov). Stabilization of Fv are achieved by direct linkage of the VH and VL chains, such as for example, by linkage with peptides (to generate single-chain Fvs (scFv)), disulfide bridges or knob-into-hole mutations. Fab fragments, in contrast, are stable because of the presence of the CH1 and CL domains that hold together the variable chains. Fd antibodies, which contain only the VH domain, lack a complete antigen-binding site and can be insoluble.

In folded antibody polypeptides, binding specificity is conferred by antigen binding site domains, which contain portions of heavy and/or light chain variable region domains. Other domains on the antibody molecule serve effector functions by participating in events such as signal transduction and interaction with other cells, polypeptides and biomolecules. These effector functions cause neutralization and/or clearance of the infecting agent recognized by the antibody.

b. Antibody Sequence and Specificity

The variable region of the heavy and light chains are encoded by multiple germline gene segments separated by non-coding regions, or introns, and often are present on different chromosomes. During B cell differentiation germline DNA is rearranged whereby one D_H and one J_H gene segment of the heavy chain locus are recombined, which is followed by the joining of one V_H gene segment forming a rearranged VDJ gene that encodes a VH chain. The rearrangement occurs only on a single heavy chain allele by the process of allelic exclusion. Allelic exclusion is regulated by in-frame or "productive" recombination of the

VDJ segments, which occurs in only about one-third of VDJ recombinations of the variable heavy chain. When such productive recombination events first occur in a cell, this results in production of a μ heavy chain that gets expressed on the surface of a pre- B cell and transmits a signal to shut off further heavy chain recombination, thereby preventing expression of the allelic heavy chain locus. The surface-expressed μ heavy chain also acts to activate the kappa (κ) locus for rearrangement. The lambda (λ) locus is only activated for rearrangement if the κ recombination is unproductive on both loci. The light chain rearrangement events are similar to heavy chain, except that only the V_L and J_L segments are recombined. Before primary transcription of each, the corresponding constant chain gene is added. Subsequent transcription and RNA splicing leads to mRNA that is translated into an intact light chain or heavy chain.

The variable regions of antibodies confer antigen binding and specificity due to recombination events of individual germline V, D and J segments, whereby the resulting recombined nucleic acid sequences encoding the variable region domains differ among antibodies and confer antigen-specificity to a particular antibody. The variation, however, is limited to three complementarity determining regions (CDR1, CDR2, and CDR3) found within the N-terminal domain of the heavy (H) and (L) chain variable regions. The CDRs are interspersed with regions that are more conserved, termed "framework regions" (FR). The extent of the framework region and CDRs has been precisely defined (see e.g., Kabat, E.A. *et al.* (1991) *Sequences of Proteins of Immunological Interest*, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242, and Chothia, C. *et al.* (1987) *J. Mol. Biol.* 196:901-917). Each VH and VL is typically composed of three CDRs and four FRs arranged from the amino terminus to carboxy terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. Sequence variability among VL and VH domains is generally limited to the CDRs, which are the regions that form the antigen binding site. For example, for the heavy chain, generally, V_H genes encode the N-terminal three framework regions, the first two complete CDRs and the first part of the third CDR; the D_H gene encodes the central portion of the third CDR, and the J_H gene encodes the last part of the third CDR and the fourth framework region. For the light chain, the V_L genes encode the first CDR and second CDR. The third CDR (CDRL3) is formed by the joining of the V_L and J_L gene segments. Hence, CDRs 1 and 2 are exclusively encoded by germline V gene segment sequences. The VH and VL chain CDR3s form the center of the Ag-binding site, while CDRs 1 and 2 form the outside boundaries; the FRs support the scaffold by orienting the H and L CDRs. On average, an antigen binding site typically requires that at least four of the CDRs make contact with the antigen's epitope, with CDR3 of both the heavy and light chain being

the most variable and contributing the most specificity to antigen binding (see e.g., Janis Kuby, Immunology, Third Edition, New York, W.H. Freeman and Company, 1998, pp. 115-118). CDRH3, which includes all of the D gene segment, is the most diverse component of the Ab-binding site, and typically plays a critical role in defining the specificity of the Ab. In addition to sequence variation, there is variation in the length of the CDRs between the heavy and light chains.

The constant regions, on the other hand, are encoded by sequences that are more conserved among antibodies. These domains confer functional properties to antibodies, for example, the ability to interact with cells of the immune system and serum proteins in order to cause clearance of infectious agents. Different classes of antibodies, for example IgM, IgD, IgG, IgE and IgA, have different constant regions, allowing them to serve distinct effector functions.

These natural recombination events of V, D, and J, can provide nearly $2x10^7$ different antibodies with both high affinity and specificity. Additional diversity is introduced by nucleotide insertions and deletions in the joining segments and also by somatic hypermutation of V regions. The result is that there are approximately 10^{10} antibodies present in an individual with differing antigen specificities.

2. Methods of Identifying Antibodies

Antibodies can be identified that have a binding specificity and/or activity against a target protein or antigen by any method known to one of skill in the art. For example, antibodies can be generated against a target antigen by conventional immunization methods resulting in the generation of hybridoma cells secreting the antibody (see e.g. Kohler et al. (1975) Nature, 256:495; Goding, Monoclonal Antibodies: Principles and Practice, pp. 59-103 (Macademic Press, 1986), Kozbor, J. Immunol., (1984) 133:3001; Brodeur et al., Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987). In another method, antibodies specific for a target antigen are identified by screening antibody libraries for the desired binding or activity. Antibody libraries can be provided as "one-pot" libraries containing a diverse population of antibody members, for example, as display libraries such as phage display libraries. In such libraries, the identity of each member of the library is typically unknown preceding sequencing of a positive clone with a desired binding activity.

In other examples, antibody libraries include addressable combinatorial antibody libraries as described in U.S. Provisional Application Nos. 61/198,764 and 61/211,204, and published International PCT Appl. No. WO2010054007, incorporated by reference herein. In the addressable libaries, the nucleic acid molecules encoding each VH chain and/or VL

chain are individually synthesized, using standard DNA synthesis techniques, in an addressable format, whereby the identity of the nucleic acid sequence of each VH chain and/or VL chain in each locus is known. VH chains and VL chains are then paired, also in an addressable format, such that the identity of each member of the library is known based on its locus or "address". The addressable combinatorial antibody libraries can be screened for binding or activity against a target protein to identify antibodies or portions thereof that bind to a target protein and/or modulate an activity of a target protein. By virtue of the fact that these libraries are arrayed, the identity of each individual member in the collection is known during screening, thereby allowing facile comparison of "Hit" antibody.

3. Existing Methods of Optimizing Antibodies

Typically, the antibodies generated and/or identified by any of the above methods are of moderate affinity (e.g. Kd^{-1} of about 10^6 to 10^7 M^{-1}). As discussed herein, existing methods of antibody discovery and engineering seek high-affinity antagonist antibodies. Thus, methods of affinity maturation to optimize and improve the binding affinity are employed to further optimize the antibody. An affinity matured antibody generally is one that contains one or more amino acid alterations that result in improvement of an activity, such as antigen binding affinity. Known method for affinity maturing and antibody include, for example, generating and screening antibody libraries using the previously identified antibody as a template by introducing mutations at random *in vitro* by using error-prone PCR (Zhou et al., *Nucleic Acids Research* (1991) 19(21):6052; and US2004/0110294); randomly mutating one or more CDRs or FRs (see e.g., WO 96/07754; Barbas et al. (1994) *Proc. Natl. Acad. Sci.*, 91:3809-3813; Cumbers et al. (2002) *Nat. Biotechnol.*, 20:1129-1134; Hawkins et al. (1992) *J. Mol. Biol.*, 226:889-896; Jackson et al., (1995) *J. Immunol.*, 154:3310-3319; Wu et al. (1998) *Proc. Natl. Acad. Sci.*, 95: 6037-6042; McCall et al. (1999) *Molecular Immunology*, 36:433-445); oligonucleotide directed mutagenesis (Rosok et al., *The Journal of Immunology*, (1998) 160:2353-2359); codon cassette mutagenesis (Kegler-Ebo et al., *Nucleic Acids Research,* (1994) 22(9):1593-1599); degenerate primer PCR, including two-step PCR and overlap PCR (U.S. Patent Nos. 5,545,142, 6,248,516, and 7,189,841; Higuchi et al., *Nucleic Acids Research* (1988); 16(15):7351-7367; and Dubreuil et al., *The Journal of Biological Chemistry* (2005) 280(26):24880-24887); domain shuffling by recombining the VH or VL domains selected by phage display with repertoires of naturally occurring V domain variants obtained from unimmunized donors and screening for higher affinity in several rounds of chain reshuffling as described in Marks *et al.*, *Biotechnology,* 10: 779-783 (1992).

Each of the available approaches for optimizing antibodieshas limitations. First, the approaches fail to recognize that antibodies with low affinity are candidate therapeutics acting

as agonists, partial agonist/antagonists or activator/modulators. Where generating a high affinity antibody is desired, for example to generate an antagonist antibody, the existing affinity maturation approaches also are limited. For example, many available approaches carry the risk of introducing unwanted mutations (e.g. mutations at undesired positions) and/or biases against selection of particular mutants. Limitations in library size and completeness exist, since it is unfeasible to generate all possible combinations of mutants. Additionally, competition must be avoided to prevent abundant low-affinity variants from excluding rarer high-affinity variants. In addition, many of the affinity matured antibodies are produced either by VH and VL domain shuffling or by random mutagenesis of CDR and/or framework residues. These methods, however, require some type of displayed selection because of the vast number of clones to be evaluated. Finally, very high affinity antibodies are difficult to isolate by panning, since the elution conditions required to break a very strong antibody-antigen interaction are generally harsh enough (e.g., low pH, high salt) to denature the phage particle sufficiently to render it non-infective.

The methods provided herein overcome some or all of these limitations.

C. METHOD FOR AFFINITY MATURATION OF ANTIBODIES

Provided herein is a rational method for affinity maturation of an antibody to improve its activity towards a target antigen based on the structure/activity relationship (SAR) of the antibody that is being affinity matured. The SAR can be used to identify a region or regions or particular amino acid residues in the antibody that are important for its activity (e.g. binding to a target antigen). For example, in the method, knowledge of the structure (e.g. sequence) of a "Hit" or parent antibody to be affinity matured is correlated to an activity (e.g. binding) for a target antigen. Such knowledge can be used to elucidate the region and/or amino acid residues that are involved in the activity toward the target antigen. The region(s) or amino acid residues are targeted for further mutagenesis. Thus, the SAR information provides guidance for further optimization by providing rational identification of region(s) of the antibody polypeptides to be mutagenized. The resulting mutant antibodies can be screened to identify those antibodies that are optimized compared to the starting or reference antibody.

In the methods provided herein, affinity maturation of a "Hit" or parent antibody is based on its structure-affinity/activity-relationship. Thus, the method is a rational and targeted mutagenesis approach with much smaller libraries guided by SARs to identify regions and residues that modulate activity.

The SAR of an antibody can be determined by various approaches. For example, SAR can be determined by comparing the sequence of an antibody that has a desired activity

for a target antigen to a related antibody that has reduced activity for the same target antigen to identify those amino acid residues that differ between the antibodies. The region of the antibody that exhibits amino acid differences is identified as a structure that is important in the activity of the antibody, and is targeted for further mutagenesis.

In particular, the SAR can be quickly elucidated using a spatially addressed combinatorial antibody library as described in U.S. Provisional Application No. 61/198,764 and U.S. Provisional Application No. 61/211,204; and in published International PCT Appl. No. WO2010054007. In the spatially addressed format, activities and binding affinities can be correlated to structure (e.g. sequence) coincident with a screening assay, since the sequences of addressed members are known a priori. In the spatially addressed format, the binding affinities of the hit versus nearby non-hit antibody can be compared in sequence space because their sequence identities are known a priori. Comparisons of sequence can be made between "Hits" and related antibodies that have less activity or no activity in the same assay. Such comparisons can reveal SARs and identify important regions or amino acid residues involved in the activity of the antibody. For example, such comparisons can reveal SARs of important CDRs and potentially important residues within the CDRs for binding the target. SAR also can be determined using other methods that identify regions of an antibody or amino acid residues therein that contribute to the activity of an antibody. For example, mutagenesis methods, for example, scanning mutagenesis, can be used to determine SAR.

The rational approach described herein facilitates identifying SARs that aid in the optimization of preliminary hits, mimicking the approach used in small molecule medicinal chemistry. This has advantages over existing methods of affinity maturation. Currently many of the *in vitro* affinity matured antibodies are produced either by VH and VL domain shuffling or by random mutagenesis of CDR and/or framework residues. Many of these methods, however, require some type of displayed selection because of the vast number of clones to be evaluated. In the method herein, a more rational and targeted mutagenesis approach is employed, using much smaller libraries guided by SARs and scanning mutagenesis to identify regions and residues that modulate affinity. True SARs can be identified because active hits can be compared with related, but less active or inactive antibodies present in the library. In addition, the methods herein can be practiced to avoid generating simultaneous mutations to circumvent exponential expansion of the library size. For example, for a given CDR or target region, one the best substitution is identified in each of the mutated positions, the mutations can be combined in a new antibody in order to generate further improvement in activity. In one example, binding affinity is increased. The

increase in affinity, measured as a decrease in K_d, can be achieved through either an increase in association rate (k_{on}), a reduction in dissociation rate (k_{off}), or both.

In one aspect of the method, residues to mutagenize in the "Hit" antibody are identified by comparison of the amino acid sequence of the variable heavy or light chain of the "Hit" antibody with a respective variable heavy or light chain of a related antibody that exhibits reduced activity for the target antigen compared to the Hit antibody that is being affinity matured. In some examples, the related antibody is a non-Hit antibody that exhibits significantly less activity towards the target antigen than the Hit antibody, such as less than 80% of the activity, generally less than 50% of the activity, for example 5% to 50% of the activity, such as 50%, 40%, 30%, 20%, 10%, 5% or less the activity. For example, a no-Hit antibody can be one that exhibits no detectable activity or shows only negligible activity towards the target antigen. In practicing the method, a requisite level of relatedness between the "Hit" and a related antibody is required in order to permit rational analysis of the contributing regions to activity. This structure-affinity/activity relationship analysis between the "Hit" antibody and related antibodies reveals target regions of the antibody polypeptide that are important for activity.

In another aspect of the method provided herein, scanning mutagenesis can be used to reveal more explicit information about the structure/activity relationship of an antibody. In such a method, scanning mutagenesis is generally employed to identify residues to further mutate. Hence, scanning mutagenesis can be employed as the means to determine SAR. Alternatively or optionally, scanning mutagenesis can be used to in combination with the comparison method above. In such an example, once a target region is identified that is involved with an activity, scanning mutagenesis is used to further elucidate the role of individual amino acid residues in an activity in order to rationally select amino acid residues for mutagenesis. As discussed in detail below, in the scanning mutagenesis method herein only those scanned mutant residues that do not negatively impact the activity of the antibody (e.g. either preserve or increase an activity to the target antigen) are subjected to further mutagenesis by further mutating the scanned residue individually to other amino acids.

Once the SAR is determined, a target region containing residues important for activity are revealed in the variable heavy chain and/or variable light chain of an antibody. Once a target region is identified for either the variable heavy chain or light chain, mutagenesis of amino acid residues within the region is employed and mutants are screened for an activity towards the target antigen. In the methods herein, the mutagenized antibodies can be individually generated, such as by DNA synthesis or by recombinant DNA techniques, expressed, and assayed for their activity for a target antigen. By individually mutating each

antibody, for example using cassette mutagenesis, simultaneous mutations can be avoided to avoid exponential expansion of the library. In addition, unwanted mutations can be avoided. In other examples, if desired, mutations can be effected by other mutagenesis approaches, for example by using various doping strategies, and the identity of the mutant identified upon screening and sequencing. Affinity maturation can be performed separately and independently on the variable heavy chain and variable light chain of a reference Hit antibody. The resulting affinity matured variable heavy and light chains can then be paired for further optimization of the antibody.

The affinity maturation method provided herein can be performed iteratively to further optimize binding affinity. For example, further optimization can be performed by mutagenesis and iterative screening of additional regions of the antibody polypeptide. At each step of the method, the affinity matured antibody can be tested for an activity (e.g. binding) to the target antigen. Antibodies are identified that have improved activity for the target antigen compared to the parent antibody or any intermediate antibody therefrom. Also, once the best substitutions in a region of an antibody are identified for improving an activity towards a target antigen, they can be combined to create a new antibody to further improve and optimize the antibodies activity. Such combination mutants can provide an additive improvement. Accordingly, the method of affinity maturation herein permits a rational optimization of antibody binding affinity.

1. Comparision of Structure and Activity

Provided herein is a method of affinity maturation based on the SAR of a Hit antibody by comparison of its structure and activity to a related antibody. In practicing the method, the amino acid sequence of the heavy chain and/or light chain of a "Hit" antibody is compared to the corresponding sequence of a related antibody that exhibits reduced or less activity for the target antigen compared to the "Hit" antibody. As discussed below, for purposes of practice of the method herein, the related antibody is sufficiently related in sequence to the "Hit" antibody in order to limit regions of the primary sequences that exhibit amino acid differences between the "Hit" and related antibody when compared (e.g. by sequence alignment). Thus, the method permits identification of a region of the "Hit" antibody that is involved in an activity to the target antigen. For example, alignment of the primary sequence (e.g. variable heavy chain and/or variable light chain) of the "Hit" and related antibody can identify one or more regions where amino acid differences exist between the "Hit" and the related antibody. The region(s) can be one or more of CDR1, CDR2 or CDR3 and/or can be amino acid residues within the framework regions of the antibody (e.g. FR1, FR2, FR3 or FR4). A region of the antibody that exhibits at least one amino acid

difference compared to the corresponding region in the related antibody is a target region targeted for further mutagenesis.

In the method, mutagenesis to any other amino acid or to a subset of amino acids is performed on amino acid residues within the identified target region. For example, some or up to all amino acid residues of the selected region in the heavy chain and/or light chain of the "Hit" antibody are mutated, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more amino acid residues. Each amino acid residue selected for mutagenesis can be mutated to all 19 other amino acid residues, or to a restricted subset thereof. The resulting mutant antibodies are screened for activity to the target antigen as compared to the starting "Hit" antibody. As discussed below, in some examples, prior to mutagenesis of individual amino acid residues, scanning-mutagenesis of all or select amino acid residues within the target region region can be used to identify particular residues for mutagenesis. The subset of identifed residues are then subjected to mutagenesis to improve or optimize an activity towards the target antigen.

Typically, the method is performed on the variable heavy chain and/or variable light chain of the antibody. Typically, affinity maturation is separately performed for one or both of the heavy and/or light chain(s) of the "Hit" antibody independently of the other. The heavy and light chains can be affinity matured independently such as sequentially in any order. Alternatively, the heavy and light chain are subjected to affinity maturation in parallel. Mutant DNA molecules encoding the variable heavy chain and/or variable light chain are designed, generated by mutagenesis and cloned. In some examples, the modified variable heavy and light chains can be synthetically generated or generated by other recombinant means. Various combinations of heavy and light chains can be paired to generate libraries of variant antibodies. The resulting antibodies or fragments thereof are tested for an activity to the target antigen. Antibodies exhibiting an optimized or improved binding affinity as compared to the starting "Hit" antibody are selected.

Iterative screening can be performed to further optimize an activity to the target antigen. For example, mutations that increase an activity to the target antigen within a variable heavy or light chain can be combined, thereby creating an antibody that has an improved activity as compared to the starting "Hit" antibody and/or intermediate single mutant antibodies. Also, pairing of an affinity matured heavy chain with an affinity matured light chain can further optimize and improve the activity of resulting antibodies produced by practice of the method. Further, mutagenesis, e.g. scanning mutagenesis or full or partial saturation mutagenesis, of amino acid residues in one or more additional regions of the

variable heavy or light chain can be performed to identify further mutations that further optimize an activity to the target antigen.

At any step in the method, the affinity matured antibodies can be further evaluated for activity. Any activity can be assessed, such as any exemplified in Section E herein. In one example, binding is assessed. Any method known to one of skill in the art can be used to measure the binding or binding affinity of an antibody. In one example, binding affinity is determined using surface Plasmon resonance (SPR). In another example, binding affinity is determined by dose response using ELISA. The resulting antibodies also can be tested for a functional activity as discussed elsewhere herein.

The resulting affinity matured antibodies are selected to have improved and/or optimized activity towards a target antigen compared to the parent "Hit" antibody. By practice of the method, the activity of an antibody for a target antigen can be improved at least 1.5-fold, generally at least 2-fold, for example at least 2-fold to 10000-fold, such as at least 2-fold, 5-fold, 10-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold, 600-fold, 700-fold, 800-fold, 900-fold, 1000-fold, 2000-fold, 3000-fold, 4000-fold, 5000-fold, 10000-fold or more. For example, the affinity matured antibodies generated by practice of the method can have a binding affinity for a target antigen that is improved, for example, that is or is about 1 1 x 10^{-9} M to 1 x 10^{-11}M, generally 5 x 10^{-9} M to 5 x 10^{-10} M, such as at or about 1 x 10^{-9} M, 2 x 10^{-9} M, 3 x 10^{-9} M, 4 x 10^{-9} M, 5 x 10^{-9} M, 6 x 10^{-9} M, 7 x 10^{-9} M, 8 x 10^{-9} M, 9 x 10^{-9} M, 1 x 10^{-10} M, 2 x 10^{-10} M, 3 x 10^{-10} M, 4 x 10^{-10} M, 5 x 10^{-10} M, 6 x 10^{-10} M, 7 x 10^{-10} M, 8 x 10^{-10} M, 9 x 10^{-10} M or less.

A summary of the steps of the method is set forth in Figure 1. A detailed description of each step of the method is provided below. It is understood that the steps of the affinity maturation method provided herein are the same whether the method is performed on the variable heavy chain or variable light chain sequence of an antibody. Hence, for purposes herein, the description below applies to practice of the method on either one or both of the heavy and light chain sequences, unless explicitly stated otherwise. As discussed elsewhere herein, typically, affinity maturation is performed for one or both of the heavy and/or light chain(s) of the antibody independently of the other. If desired, an affinity matured heavy chain can be paired with an affinity matured light chain to further optimize or improve activity of the antibody.

a. Selection of a First Antibody For Affinity Maturation

The antibody chosen to be affinity matured is any antibody that is known in the art or identified as having an activity for a target antigen or antigens. For example, the antibody can be a "Hit" antibody, such as one identified in a screening assay. Generally, the antibody is an

antibody that exhibits an activity for a target antigen such that it not ideal for use as a therapeutic because its affinity is not sufficiently high or such that improvement of its activity is achievable or desirable. For example, an antibody chosen for affinity maturation typically has a binding affinity for the target antigen that is at or about 10^{-5} M to 10^{-8} M, for example that is at or about 10^{-5} M, 10^{-6} M, 10^{-7} M, 10^{-8} M, or lower. Generally, an antibody selected for affinity maturation specifically binds to the target antigen. Assays to assess activity of an antibody for a target antigen are known in the art. Exemplary assays are provided in Section E.

Thus, the first antibody is an antibody that is known to have an activity to a target antigen. The target antigen can be a polypeptide, carbohydrate, lipid, nucleic acid or a small molecule (e.g. neurotransmitter). The antibody can exhibit activity for the antigen expressed on the surface of a virus, bacterial, tumor or other cell, or exhibits an activity (e.g. binding) for the purified antigen. Typically, the target antigen is a purified protein or peptide, including, for example, a recombinant protein.

Generally, the target antigen is a protein that is a target for a therapeutic intervention. Exemplary target antigens include, but are not limited to, targets involved in cell proliferation and differentiation, cell migration, apoptosis and angiogenesis. Such targets include, but are not limited to, growth factors, cytokines, lymphocytic antigens, other cellular activators and receptors thereof. Exemplary of such targets include, membrane bound receptors, such as cell surface receptors, including, but are not limited to, a VEGFR-1, VEGFR-2, VEGFR-3 (vascular endothelial growth factor receptors 1, 2, and 3), a epidermal growth factor receptor (EGFR), ErbB-2, ErbB-b3, IGF-R1, C-Met (also known as hepatocyte growth factor receptor; HGFR), DLL4, DDR1 (discoidin domain receptor), KIT (receptor for c-kit), FGFR1, FGFR2, FGFR4 (fibroblast growth factor receptors 1, 2, and 4), RON (recepteur d'origine nantais; also known as macrophage stimulating 1 receptor), TEK (endothelial-specific receptor tyrosine kinase), TIE (tyrosine kinase with immunoglobulin and epidermal growth factor homology domains receptor), CSF1R (colony stimulating factor 1 receptor), PDGFRB (platelet-derived growth factor receptor B), EPHA1, EPHA2, EPHB1 (erythropoietin-producing hepatocellular receptor A1, A2 and B1), TNF-R1, TNF-R2, HVEM, LT-βR, CD20, CD3, CD25, NOTCH, G-CSF-R, GM-CSF-R and EPO-R. Other targets include membrane-bound proteins such as selected from among a cadherin, integrin, CD52 or CD44. Exemplary ligands that can be targets of the screening methods herein, include, but are not limited to, VEGF-A, VEGF-B, VEGF-C, VEGF-D, PIGF, EGF, HGF, TNF-α, LIGHT, BTLA, lymphotoxin (LT), IgE, G-CSF, GM-CSF and EPO. In some examples, the "Hit" antibody can bind to one or more antigens. For example, as exemplified in Example 1, "Hit"

antibodies have been identified that binds to only one target antigen, e.g., DLL4, or that bind to two or more different target antigens, e.g., P-cadherin and erythropoietin (EPO).

In practicing the method provided herein, typically only the variable heavy chain and/or variable light chain of the antibody is affinity matured. Thus, the antibody that is chosen typically contains a variable heavy chain and a variable light chain, or portion thereof sufficient to form an antigen binding site. It is understood, however, that the antibody also can include all or a portion of the constant heavy chain (e.g. one or more CH domains, such as CH1, CH2, CH3 and CH4, and/or a constant light chain (CL)). Hence, the antibody can include those that are full-length antibodies, and also include fragments or portions thereof including, for example, Fab, Fab', $F(ab')_2$, single-chain Fvs (scFv), Fv, dsFv, diabody, Fd and Fd' fragments, Fab fragments, scFv fragments, and scFab fragments. For example, affinity maturation of antibodies exemplified in the examples herein are Fabs. It is understood that once the antibody is affinity matured as provided herein, the resulting antibody can be produced as a full-length antibody or a fragment thereof, such as a Fab, Fab', $F(ab')_2$, single-chain Fvs (scFv), Fv, dsFv, diabody, Fd and Fd' fragments, Fab fragments, scFv fragments, and scFab fragments. Further, the constant region of any isotype can be used in the generation of full or partial antibody fragments, including IgG, IgM, IgA, IgD and IgE constant regions. Such constant regions can be obtained from any human or animal species. It is understood that activities and binding affinities can differ depending on the structure of an antibody. For example, generally a bivalent antibody, for example a bivalent $F(ab')_2$ fragment or full-length IgG, has a better binding affinity then a monovalent Fab antibody. As a result, where a Fab has a specified binding affinity for a particular target, it is excepted that the binding affinity is even greater for a full-length IgG that is bivalent. Thus, comparison of binding affinities between a first antibody and an affinity matured antibody are typically made between antibodies that have the same structure, e.g. Fab compared to Fab.

An antibody for affinity maturation can include an existing antibody known to one of skill in the art. In other examples, an antibody is generated or identified empirically depending on a desired target. For example, an antibody can be generated using conventional immunization and hybridoma screening methods. In other examples, an antibody is identified by any of a variety of screening methods known to one of skill in the art.

i. Immunization and Hybridoma Screening

Antibodies specific for a target antigen can be made using the hybridoma method first described by Kohler et al. (1975) *Nature*, 256:495, or made by recombinant DNA methods (U.S. Patent No. 4,816,567).

In the hybridoma method, a mouse or other appropriate host animal, such as a hamster, is immunized to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Antibodies to a target antigen can be raised in animals by multiple subcutaneous (sc) or intraperitoneal (ip) injections of protein antigen and an adjuvant. Two weeks later, animals are boosted. 7 to 14 days later animals are bled and the serum is assayed for antibody titer specific for the target antigen. Animals are boosted until titers plateau.

Alternatively, lymphocytes can be immunized *in vitro*. Lymphocytes then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, pp. 59-103 (Academic Press, 1986)).

The hybridoma cells that are prepared are seeded and grown in a suitable culture medium that contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

Myeloma cells include those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. Among myeloma cell lines are murine myeloma lines, such as those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, CA, USA, and SP-2 or X63-Ag8-653 cells available from the American Type Culture Collection (ATCC), Rockville, Md., USA. Human myeloma and mouse-human heterocyeloma cells lines also have been described for the production of human monoclonal antibodies (Kozbor, (1984) *J. Immunol.*, 133:3001; and Brodeur et al., Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)).

Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the target antigen. The binding specificity of monoclonal antibodies produced by hybridoma cells can be determined by any method known to one of skill in the art (e.g. as described in Section E.1), for example, by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoadsorbent assay (ELISA). The binding affinity also can be determined, for example, using Scatchard analysis.

After hybridoma cells are identified that produce antibodies of the desired specificity, affinity, and/or activity, the clones can be subcloned by limiting dilution procedures and

grown by standard methods (Goding, Monoclonal Antibodies: Principles and Practice, pp. 59-103 (Academic Press, 1986)). Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells can be grown *in vivo* as ascites tumors in an animal.

The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

DNA-encoding the hybridoma-derived monoclonal antibody can be readily isolated and sequenced using conventional procedures. For example, sequencing can be effected using oligonucleotide primers designed to specifically amplify the heavy and light chain coding regions of interest from the hybridoma. Once isolated, the DNA can be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein to obtain the synthesis of the desired monoclonal antibodies in the recombinant host cells.

ii. Screening Assays for Identification of a "Hit"

Antibodies that are affinity matured by the method herein can be identified by using combinatorial libraries to screen for synthetic antibody clones with the desired activity or activities. Antibodies with a desired activity can be selected as "Hits." Such "Hit" antibodies can be further affinity matured to optimize the activity.

1) Display Libraries

Typical of screening methods are high throughput screening of antibody libraries. For example, antibody libraries are screened using a display technique, such that there is a physical link between the individual molecules of the library (phenotype) and the genetic information encoding them (genotype). These methods include, but are not limited to, cell display, including bacterial display, yeast display and mammalian display, phage display (Smith, G. P. (1985) *Science* 228:1315-1317), mRNA display, ribosome display and DNA display. Using display techniques, the identity of each of the individual antibodies is unknown prior to screening, but the phenotype-genotype link allows for facile identification of selected antibodies. Prior to practice of the method herein, the sequence of a "Hit" antibody is determined.

Typically, in the libraries, nucleic acids encoding antibody gene fragments are obtained from immune cells harvested from humans or animals. If a library biased in favor of an antigen-specific antibody is desired, the subject is immunized with the target antigen to

generate an antibody response, and spleen cells and/or circulating B cells or other peripheral blood lymphocytes (PBLs) are recovered for library construction. Additional enrichment for antigen-specific antibody reactive cell populations can be obtained using a suitable screening procedure to isolate B cells expressing antigen-specific membrane bound antibody, e.g. by cell separation with antigen affinity chromatography or adsorption of cells to fluorochrome-labeled antigen followed by fluorescence-activated cell sorting (FACs).

Alternatively, the use of spleen cells and/or B cells or other PBLs from an unimmunized donor provides a better representation of the possible antibody repertoire, and also permits the construction of an antibody library using any animal (human or non-human) species in which the target antigen is not antigenic. For libraries incorporating *in vitro* antibody gene construction, stem cells are harvested from the subject to provide nucleic acids encoding unrearranged antibody gene segments. The immune cells of interest can be obtained from a variety of animal species, such as human, mouse, rat, lagomorpha, lupine, canine, feline, porcine, bovine, equine, and avian species.

Nucleic acid encoding antibody variable gene segments (including VH and VL segments) can be recovered from the cells of interest and amplified. In the case of rearranged VH and VL gene libraries, the desired DNA can be obtained by isolating genomic DNA or mRNA from lymphocytes followed by polymerase chain reaction (PCR) with primers matching the 5' and 3' ends of rearranged VH and VL genes as described in Orlandi *et al.*, (1989) *Proc. Natl. Acad. Sci. (USA)*, 86:3833-3837, thereby making diverse V gene repertoires for expression. The V genes can be amplified from cDNA and genomic DNA, with back primers at the 5' end of the exon encoding the mature V-domain and forward primers based within the J-segment as described in Orlandi *et al.*, (1989) and in Ward *et al.*, (1989) *Nature*, 341:544-546. For amplifying from cDNA, however, back primers can also be based in the leader exon as described in Jones *et al.*, (1991) *Biotechnology*, 9:88-89, and forward primers within the constant region as described in Sastry *et al.*, (1989) *Proc. Natl. Acad. Sci. (USA)*, 86:5728-5732. To maximize complementarity, degeneracy can be incorporated in the primers as described in Orlandi *et al.* (1989) or Sastry *et al.* (1989). The library diversity can be maximized by using PCR primers targeted to each V-gene family in order to amplify all available VH and VL arrangements present in the immune cell nucleic acid sample, e.g. as described in the method of Marks *et al.*, (1991) *J. Mol. Biol.*, 222:581-597, or as described in the method of Orum *et al.*, (1993) *Nucleic Acids Res.*, 21:4491-4498. For cloning of the amplified DNA into expression vectors, rare restriction sites can be introduced within the PCR primer as a tag at one end as described in Orlandi *et al.* (1989), or

by further PCR amplification with a tagged primer as described in Clackson *et al.*, (1991) *Nature*, 352:624-628.

In another example of generating an antibody library, repertoires of synthetically rearranged V genes can be derived *in vitro* from V gene segments. Most of the human VH-gene segments have been cloned and sequenced (see e.g. Tomlinson *et al.*, (1992) *J. Mol. Biol.*, 227:776-798), and mapped (see e.g. Matsuda *et al.*, (1993) *Nature Genet.*, 3:988-94). These segments can be used to generate diverse VH gene repertoires with PCR primers encoding H3 loops of diverse sequence and length as described in Hoogenboom and Winter (1992) *J. Mol. Biol.*, 227:381-388. VH repertoires also can be made with all of the sequence diversity focused in a long H3 loop of a single length as described in Barbas *et al.*, (1992) *Proc. Natl. Acad. Sci. USA*, 89:4457-4461. Human Vκ and Vλ segments have been cloned and sequenced (see e.g. Williams and Winter (1993) *Eur. J. Immunol.*, 23:1456-1461) and can be used to make synthetic light chain repertoires. Synthetic V gene repertoires, based on a range of VH and VL folds, and L3 and H3 lengths, encode antibodies of considerable structural diversity. Following amplification of V-gene encoding DNAs, germline V-gene segments can be rearranged *in vitro* according to the methods of Hoogenboom and Winter (1992) *J. Mol. Biol.*, 227:381-388.

Repertoires of antibody fragments can be constructed by combining VH and VL gene repertoires together in several ways. Each repertoire can be created in different vectors, and the vectors recombined *in vitro* (see e.g. Hogrefe *et al.*, (1993) *Gene*, 128:119-126), or in vivo by combinatorial infection, for example, using the lox P system (Waterhouse *et al.*, (1993) *Nucl. Acids Res.*, 21:2265-2266). The *in vivo* recombination approach exploits the two-chain nature of Fab fragments to overcome the limit on library size imposed by *E. coli* transformation efficiency. Alternatively, the repertoires can be cloned sequentially into the same vector (see e.g. Barbas *et al.*, (1991) *Proc. Natl. Acad. Sci. USA*, 88:7978-7982), or assembled together by PCR and then cloned (see e.g. Clackson *et al.*, (1991) *Nature*, 352:624-628). PCR assembly can also be used to join VH and VL DNAs with DNA encoding a flexible peptide spacer to form single chain Fv (scFv) repertoires. In another technique, "in cell PCR assembly" can be used to combine VH and VL genes within lymphocytes by PCR and then clone repertoires of linked genes (see e.g. Embleton (1992) *Nucl. Acids Res.*, 20:3831-3837).

In typical display libraries, the repertoire of VH and VL chains are constructed as one-pot libraries, such that the sequence of each member of the library is not known. Accordingly, sequencing is required following identification of a "Hit" antibody in order to obtain any knowledge of the SAR relationship as required for practice of the method herein.

Thus, as above for hybridoma-generated antibodies, DNA-encoding antibody clones identified from a display library can be readily isolated and sequenced using conventional procedures. For example, sequencing can be effected using oligonucleotide primers designed to specifically amplify the heavy and light chain coding regions of interest from a DNA template, e.g. phage DNA template.

Exemplary of such antibody libraries that can be used for screening are those described in any of the following: European Patent Application Nos. EP0368684 and EP89311731; International Published Patent Application Nos. WO92/001047, WO 02/38756, WO 97/08320, WO 2005/023993, WO 07/137616 and WO 2007/054816; United States Patent Nos. US 6,593,081 and US 6,989,250; United States Published Patent Application Nos. US 2002/0102613, US 2003/153038, US 2003/0022240, US 2005/0119455, US 2005/0079574 and US 2006/0234302; and Orlandi *et al.* (1989) *Proc Natl. Acad. Sci. U.S.A.,* 86:3833-3837; Ward *et al.* (1989) *Nature*, 341:544-546; Huse *et al.* (1989) *Science,* 246:1275-1281; Burton *et al.* (1991) *Proc. Natl. Acad. Sci., U.S.A.*, 88:10134-10137; Marks *et al.* (1991) *J Mol Biol*, 222:581-591; Hoogenboom *et al.* (1991) *J Mol Biol*, 227:381-388; Nissim *et al.* (1994) *EMBO J*, 13:692-698; Barbas *et al.* (1992) *Proc. Natl. Acad. Sci., U.S.A.*, 89:4457-4461; Akamatsu *et al.* (1993) *J. Immunol.*, 151:4651-1659; Griffiths *et al.* (1994) *EMBO J,* 13:3245-3260; Fellouse (2004) PNAS, 101:12467-12472; Persson *et al.* (2006) J. Mol. Biol. 357:607-620; Knappik *et al.* (2000) J. Mol. Biol. 296:57-86; Rothe *et al.* (2008) J. Mol. Biol. 376:1182-1200; Mondon *et al.* (2008) *Frontiers in Bioscience*, 13:1117-1129; and Behar, I. (2007) *Expert Opin. Biol. Ther.*, 7:763-779.

2) Phage Display Libraries

For example, natural or synthetic antibodies are selected by screening phage libraries containing phage that display various fragments of antibody variable region (Fv) fused to phage coat protein. Variable domains can be displayed functionally on phage, either as single-chain Fv (scFv) fragments, in which VH and VL are covalently linked through a short, flexible peptide, or as Fab fragments, in which they are each fused to a constant domain and interact non-covalently, as described in Winter *et al.*, (1994) *Ann. Rev. Immunol.*, 12:433-455. Such phage libraries are panned by affinity chromatography against the desired antigen. Clones expressing Fv fragments capable of binding to the desired antigen are bound to the antigen and thus separated from the non-binding clones in the library. The binding clones are then eluted from the antigen, and can be further enriched by additional cycles of antigen binding/elution. Any antibody can be obtained by designing a suitable antigen screening procedure to select for the phage clone of interest followed by construction of a full length antibody clone using the Fv sequences from the phage clone of interest and suitable constant

region (Fc) sequences described in Kabat *et al.*, Sequences of Proteins of Immunological Interest, Fifth Edition, NIH Publication 91-3242, Bethesda Md. (1991), vols. 1-3.

Repertoires of VH and VL genes can be separately cloned by polymerase chain reaction (PCR) and recombined randomly in phage libraries, which can then be searched for antigen-binding clones as described in Winter *et al.*, *Ann. Rev. Immunol.*, 12: 433-455 (1994). Libraries from immunized sources provide high-affinity antibodies to the immunogen without the requirement of constructing hybridomas. Alternatively, the naive repertoire can be cloned to provide a single source of human antibodies to a wide range of non-self and also self antigens without any immunization as described by Griffiths *et al.*, *EMBO J.* 12: 725-734 (1993). Finally, naive libraries can also be made synthetically by cloning the unrearranged V-gene segments from stem cells, and using PCR primers containing random sequence to encode the highly variable CDR3 regions and to accomplish rearrangement *in vitro* as described by Hoogenboom and Winter, *J. Mol. Biol.*, 227: 381-388 (1992).

VH and VL repertoires are cloned separately, one into a phagemid and the other into a phage vector. The two libraries are then combined by phage infection of phagemid-containing bacteria so that each cell contains a different combination and the library size is limited only by the number of cells present (about 10^{12} clones). Both vectors contain *in vivo* recombination signals so that the VH and VL genes are recombined onto a single replicon and are co-packaged into phage virions. The libraries can provide a large number of diverse antibodies of good affinity (Kd^{-1} of about 10^{-8} M).

Filamentous phage is used to display antibody fragments by fusion to a coat protein, for example, the minor coat protein pIII. The antibody fragments can be displayed as single chain Fv fragments, in which VH and VL domains are connected on the same polypeptide chain by a flexible polypeptide spacer, e.g. as described by Marks *et al.*, *J. Mol. Biol.*, 222: 581-597 (1991), or as Fab fragments, in which one chain is fused to pIII and the other is secreted into the bacterial host cell periplasm where assembly of a Fab-coat protein structure which becomes displayed on the phage surface by displacing some of the wild type coat proteins, e.g. as described in Hoogenboom *et al.*, *Nucl. Acids Res.*, 19: 4133-4137 (1991).

3) Addressable Libraries

Another method of identifying antibodies, or fragments thereof, that have a desired specificity and/or activity for a target protein includes addressable combinatorial antibody libraries as described in U.S. Provisional Application Nos. 61/198,764 and 61/211,204, and in International published PCT Appl. No. WO2010054007, incorporated by reference herein. These include, for example, spatially addressed combinatorial antibody libraries. An advantage of addressable combinatorial libraries compared to display libraries is that each

loci represents a different library member whose identity is known by virtue of its address. In such libraries, each individual member of the library is individually generated, and thus the sequence of each member is known. Display of the members of the library can be achieved on any desired format, which permits screening the members not only for binding but also for function. The "Hits" can be quickly identified, including by sequence, coincident with the screening results. Sequencing is not required to obtain structural information about an identified antibody since the sequence of an identified "Hit" is known *a priori*. Accordingly, affinity maturation of a "Hit" antibody can be performed immediately after screening and identification of a "Hit" antibody.

Addressable combinatorial antibody libraries contain antibodies with variable heavy chain and variable light chains composed of recombined human germline segments. Antibody combinatorial diversity in the library exists from recombination of individual V, D and J segments that make up the variable heavy chains and of individual V (V_κ or V_λ) and J (J_κ or J_λ) segments that make up the variable light chains. Additional combinatorial diversity derives from the pairing of different variable heavy chains and variable light chains.

The nucleic acid molecules encoding each VH chain and/or VL chain are individually synthesized, using standard DNA synthesis techniques, in an addressable format, whereby the identity of the nucleic acid sequence of each VH chain and/or VL chain in each locus is known. VH chains and VL chains are then paired, also in an addressable format, such that the identity of each member of the library is known based on its locus or "address". The addressable combinatorial antibody libraries can be screened for binding or activity against a target protein to identify antibodies or portions thereof that bind to a target protein and/or modulate an activity of a target protein. By virtue of the fact that these libaries are arrayed, the identity of each individual member in the collection is known during screening, thereby allowing facile comparison of "Hit" and related "non-Hit" antibodies.

U.S. Provisional Appl. Nos. 61/198,764 and 61/211,204, and published International PCT Appl. No. WO2010054007, incorporated by reference herein, provide a method of generating a combinatorial antibody library where the identity of every antibody is known at the time of screening by virtue of the combinatorial generation of antibody members. In the combinatorial addressable libraries, variable heavy (VH) and variable light (VL) chain members of the libraries are generated, recombinantly or synthetically by DNA synthesis, from known germline antibody sequences or modified sequences thereof. Antibody combinatorial diversity in the library exists from recombination of individual V, D and J segments that make up the variable heavy chains and of individual V (V_κ or V_λ) and J (J_κ or

J_λ) segments that make up the variable light chains. Additional combinatorial diversity derives from the pairing of different variable heavy chains and variable light chains.

Each VL chain of the antibodies in the library is encoded by a nucleic acid molecule that contains a V_κ and a J_κ human germline segment or degenerate codons thereof, or a V_λ and a J_λ human germline segment or degenerate codons thereof, whereby the segments are linked in-frame. The germline segments are joined such that the V_L segment is 5' of the J_L segment. Each VH chain of the antibodies in the library is encoded by a nucleic acid molecule that contains a V_H, D_H and a J_H germline segment, whereby the segments are linked in-frame. The germline segments are joined such that the V_H segment is 5' of the D_H segment, which is 5' of the J_H segment.

The recombination is effected so that each gene segment is in-frame, such that resulting recombined nucleic acid molecules encodes a functional VH or VL polypeptide. For example, recombined segments are joined such that the recombined full length nucleic acid is in frame with the 5' start codon (ATG), thereby allowing expression of a full length polypeptide. Any combination of a V(D)J can be made, and junctions modified accordingly in order to generate a compiled V(D)J sequence that is in-frame, while preserving reading frames of each segment. The choice of junction modification is a function of the combination of V(D)J that will be joined, and the proper reading frame of each gene segment. In some examples, the nucleic acid molecule encoding a VH chain and/or a VL chain are further modified to remove stop codons and/or restriction enzyme sites so that the resulting encoded polypeptide is in-frame and functional.

A nucleic acid that encodes a variable heavy chain or a variable light chain is generated as follows. In the first step, individual germline segments (V_H, D_H and J_H for a heavy chain or V_κ and a J_κ, or V_λ and J_λ for a light chain) are selected for recombination. The germline segments can be human germline segments, or dgenerate sequences thereof, or alternatively the germline segments can be modified. For example, the D_H segment of a variable heavy chain can be translated in any open reading frame, or alternatively, the D_H segment can be the reverse complement of a D_H germline segment. Once selected, the germline segments are joined such that the recombined full length nucleic acid is in frame with the 5' start codon (ATG), thereby allowing expression of a full length polypeptide. Any combination of a V(D)J can be made, and junctions modified accordingly in order to generate a compiled V(D)J sequence that is in-frame, while preserving reading frames of each segment. The V segment is always reading frame 1. The reading frame of the J segment is selected so the correct amino acids are encoded. The D segment can be in any reading frame,

but typically, the reading frame is chosen such that the resulting amino acids are predominately hydrophobic. As necessary, nucleic acid modifications are made at the junctions between the gene segments such that each segment is in the desired reading frame. For example, at the V-D junction, one or more nucleotides can be deleted from the 5' end of the D, one or more nucleotides can be deleted from the 3' end of the V or one or more nucleotides can be inserted between the V and D (e.g. a nucleotide can be added to the 3' end of the V). Once the junctions are formed, the sequence is modified to remove any stop codons by substitution of nucleotides, such that stop codon TAA is replaced by codon TAT; stop codon TAG is replaced by codon TAT, and stop codon TGA is replaced by codon TCA. Finally, the nucleic acid can be further modified to, for example, remove unwanted restriction sites, splicing donor or acceptor sites, or other nucleotide sequences potentially detrimental to efficient translation. Modifications of the nucleic acid sequences include replacements or substitutions, insertions, or deletions of nucleotides, or any combination thereof.

The nucleic acid molecules encoding each VH chain and/or VL chain are individually synthesized, using standard DNA synthesis techniques, in an addressable format, whereby the identity of the nucleic acid sequence of each VH chain and/or VL chain in each locus is known.

VH chains and VL chains are then paired, also in an addressable format, such that the identity of each member of the library is known based on its locus or "address". For example, resulting members of the library are produced by co-expression of nucleic acid molecules encoding the recombined variable region genes together, such that when expressed, a combinatorial antibody member is generated minimally containing a VH and VL chain, or portions thereof. In some examples of the methods, the nucleic acid molecule encoding the VH and VL chain can be expressed as a single nucleic acid molecule, whereby the genes encoding the heavy and light chain are joined by a linker. In another example of the methods, the nucleic acid molecules encoding the VH and VL chain can be separately provided for expression together. Thus, upon expression from the recombined nucleic acid molecules, each different member of the library represents a germline encoded antibody, whereby diversity is achieved by combinatorial diversity of V(D)J segments and pairing diversity of heavy and light chains.

The antibodies within the combinatorial addressable germline antibody libraries contain all or a portion of the variable heavy chain (VH) and variable light chain (VL), as long as the resulting antibody is sufficient to form an antigen binding site. Typically, the combinatorial addressable germline antibodies are Fabs. Exemplary nucleic acids encoding variable heavy chains and light chains are set forth in Table 3 below. A library of antibodies

can be generated upon co-expression of a nucleic acid molecule encoding the VH chain and a nucleic acid encoding the VL chain to generate a combinatorial library containing a plurality of different members. An exemplary paired nucleic acid library is set forth in Table 4 below, where each row sets forth a different loci of the library. The combinatorial addressable antibody library can be screened to identify a "Hit" antibody against any target antigen. Related non-Hit antibodies that do not bind the target antigen also can be readily identified, since the identity by sequence structure of each "Hit" or "non-Hit" are immediately known coincident with the binding results.

Table 3: Exemplary Variable Heavy Chains and Light Chains

Heavy Chain		
Number	Name	SEQ ID NO.
1	gnl|Fabrus|VH1-18_IGHD1-26*01_IGHJ2*01	1828
2	gnl|Fabrus|VH1-18_IGHD2-21*01_IGHJ2*01	1829
3	gnl|Fabrus|VH1-18_IGHD3-16*01_IGHJ6*01	1830
4	gnl|Fabrus|VH1-18_IGHD3-22*01_IGHJ4*01	1831
5	gnl|Fabrus|VH1-18_IGHD4-23*01_IGHJ1*01	1832
6	gnl|Fabrus|VH1-18_IGHD5-12*01_IGHJ4*01	1833
7	gnl|Fabrus|VH1-18_IGHD6-6*01_IGHJ1*01	1834
8	gnl|Fabrus|VH1-2_IGHD1-1*01_IGHJ3*01	1835
9	gnl|Fabrus|VH1-24_IGHD1-7*01_IGHJ4*01	1836
10	gnl|Fabrus|VH1-24_IGHD2-15*01_IGHJ2*01	1837
11	gnl|Fabrus|VH1-24_IGHD3-10*01_IGHJ4*01	1838
12	gnl|Fabrus|VH1-24_IGHD3-16*01_IGHJ4*01	1839
13	gnl|Fabrus|VH1-24_IGHD4-23*01_IGHJ2*01	1840
14	gnl|Fabrus|VH1-24_IGHD5-12*01_IGHJ4*01	1841
15	gnl|Fabrus|VH1-24_IGHD5-18*01_IGHJ6*01	1842
16	gnl|Fabrus|VH1-24_IGHD6-19*01_IGHJ4*01	1843
17	gnl|Fabrus|VH1-3_IGHD2-15*01_IGHJ2*01	1844
18	gnl|Fabrus|VH1-3_IGHD2-2*01_IGHJ5*01	1845
19	gnl|Fabrus|VH1-3_IGHD3-9*01_IGHJ6*01	1846
20	gnl|Fabrus|VH1-3_IGHD4-23*01_IGHJ4*01	101
21	gnl|Fabrus|VH1-3_IGHD5-18*01_IGHJ4*01	1847
22	gnl|Fabrus|VH1-3_IGHD6-6*01_IGHJ1*01	1848
23	gnl|Fabrus|VH1-3_IGHD7-27*01_IGHJ4*01	1849
24	gnl|Fabrus|VH1-45_IGHD1-26*01_IGHJ4*01	1850
25	gnl|Fabrus|VH1-45_IGHD2-15*01_IGHJ6*01	1851
26	gnl|Fabrus|VH1-45_IGHD2-8*01_IGHJ3*01	1852
27	gnl|Fabrus|VH1-45_IGHD3-10*01_IGHJ4*01	1853
28	gnl|Fabrus|VH1-45_IGHD3-16*01_IGHJ2*01	1854
29	gnl|Fabrus|VH1-45_IGHD4-23*01_IGHJ4*01	1855
30	gnl|Fabrus|VH1-45_IGHD5-24*01_IGHJ4*01	1856
31	gnl|Fabrus|VH1-45_IGHD6-19*01_IGHJ4*01	1857
32	gnl|Fabrus|VH1-45_IGHD7-27*01_IGHJ6*01	1858
33	gnl|Fabrus|VH1-46_IGHD1-26*01_IGHJ4*01	1859
34	gnl|Fabrus|VH1-46_IGHD2-15*01_IGHJ2*01	99
35	gnl|Fabrus|VH1-46_IGHD3-10*01_IGHJ4*01	92
36	gnl|Fabrus|VH1-46_IGHD4-17*01_IGHJ4*01	1860
37	gnl|Fabrus|VH1-46_IGHD5-18*01_IGHJ4*01	1861

38	gnl|Fabrus|VH1-46_IGHD6-13*01_IGHJ4*01	93
39	gnl|Fabrus|VH1-46_IGHD6-6*01_IGHJ1*01	88
40	gnl|Fabrus|VH1-46_IGHD7-27*01_IGHJ2*01	97
41	gnl|Fabrus|VH1-58_IGHD1-26*01_IGHJ4*01	1862
42	gnl|Fabrus|VH1-58_IGHD2-15*01_IGHJ2*01	1863
43	gnl|Fabrus|VH1-58_IGHD3-10*01_IGHJ6*01	1864
44	gnl|Fabrus|VH1-58_IGHD4-17*01_IGHJ4*01	1865
45	gnl|Fabrus|VH1-58_IGHD5-18*01_IGHJ4*01	1866
46	gnl|Fabrus|VH1-58_IGHD6-6*01_IGHJ1*01	1867
47	gnl|Fabrus|VH1-58_IGHD7-27*01_IGHJ5*01	1868
48	gnl|Fabrus|VH1-69_IGHD1-1*01_IGHJ6*01	98
49	gnl|Fabrus|VH1-69_IGHD1-14*01_IGHJ4*01	1869
50	gnl|Fabrus|VH1-69_IGHD2-2*01_IGHJ4*01	1870
51	gnl|Fabrus|VH1-69_IGHD2-8*01_IGHJ6*01	1871
52	gnl|Fabrus|VH1-69_IGHD3-16*01_IGHJ4*01	1872
53	gnl|Fabrus|VH1-69_IGHD3-3*01_IGHJ4*01	1873
54	gnl|Fabrus|VH1-69_IGHD3-9*01_IGHJ6*01	1874
55	gnl|Fabrus|VH1-69_IGHD4-17*01_IGHJ4*01	1875
56	gnl|Fabrus|VH1-69_IGHD5-12*01_IGHJ4*01	1876
57	gnl|Fabrus|VH1-69_IGHD5-24*01_IGHJ6*01	1877
58	gnl|Fabrus|VH1-69_IGHD6-19*01_IGHJ4*01	1878
59	gnl|Fabrus|VH1-69_IGHD6-6*01_IGHJ1*01	1879
60	gnl|Fabrus|VH1-69_IGHD7-27*01_IGHJ4*01	1880
61	gnl|Fabrus|VH1-8_IGHD1-26*01_IGHJ4*01	1881
62	gnl|Fabrus|VH1-8_IGHD2-15*01_IGHJ6*01	1882
63	gnl|Fabrus|VH1-8_IGHD2-2*01_IGHJ6*01	102
64	gnl|Fabrus|VH1-8_IGHD3-10*01_IGHJ4*01	1883
65	gnl|Fabrus|VH1-8_IGHD4-17*01_IGHJ4*01	1884
66	gnl|Fabrus|VH1-8_IGHD5-5*01_IGHJ4*01	1885
67	gnl|Fabrus|VH1-8_IGHD7-27*01_IGHJ4*01	1886
68	gnl|Fabrus|VH2-26_IGHD1-20*01_IGHJ4*01	1887
69	gnl|Fabrus|VH2-26_IGHD2-15*01_IGHJ2*01	1888
70	gnl|Fabrus|VH2-26_IGHD2-2*01_IGHJ4*01	1889
71	gnl|Fabrus|VH2-26_IGHD3-10*01_IGHJ4*01	1890
72	gnl|Fabrus|VH2-26_IGHD3-9*01_IGHJ6*01	1891
73	gnl|Fabrus|VH2-26_IGHD4-11*01_IGHJ4*01	1892
74	gnl|Fabrus|VH2-26_IGHD5-12*01_IGHJ4*01	1893
75	gnl|Fabrus|VH2-26_IGHD5-18*01_IGHJ4*01	1894
76	gnl|Fabrus|VH2-26_IGHD6-13*01_IGHJ4*01	1895
77	gnl|Fabrus|VH2-26_IGHD7-27*01_IGHJ4*01	1896
78	gnl|Fabrus|VH2-26_IGHD7-27*01_IGHJ4*01	1897
79	gnl|Fabrus|VH2-5_IGHD1-1*01_IGHJ5*01	1898
80	gnl|Fabrus|VH2-5_IGHD2-15*01_IGHJ6*01	1899
81	gnl|Fabrus|VH2-5_IGHD3-16*01_IGHJ4*01	1900
82	gnl|Fabrus|VH2-5_IGHD3-9*01_IGHJ6*01	1901
83	gnl|Fabrus|VH2-5_IGHD5-12*01_IGHJ4*01	1902
84	gnl|Fabrus|VH2-5_IGHD6-13*01_IGHJ4*01	1903
85	gnl|Fabrus|VH2-5_IGHD7-27*01_IGHJ2*01	96
86	gnl|Fabrus|VH2-70_IGHD1-1*01_IGHJ2*01	1904
87	gnl|Fabrus|VH2-70_IGHD2-15*01_IGHJ2*01	1905
88	gnl|Fabrus|VH2-70_IGHD3-22*01_IGHJ4*01	1906
89	gnl|Fabrus|VH2-70_IGHD3-9*01_IGHJ6*01	1907
90	gnl|Fabrus|VH2-70_IGHD5-12*01_IGHJ4*01	1908
91	gnl|Fabrus|VH2-70_IGHD7-27*01_IGHJ2*01	1909
92	gnl|Fabrus|VH3-11_IGHD1-26*01_IGHJ4*01	1910

93	gnl|Fabrus|VH3-11_IGHD2-2*01_IGHJ6*01	1911
94	gnl|Fabrus|VH3-11_IGHD3-16*01_IGHJ4*01	1912
95	gnl|Fabrus|VH3-11_IGHD3-9*01_IGHJ6*01	1913
96	gnl|Fabrus|VH3-11_IGHD4-23*01_IGHJ5*01	1914
97	gnl|Fabrus|VH3-11_IGHD5-18*01_IGHJ4*01	1915
98	gnl|Fabrus|VH3-11_IGHD6-19*01_IGHJ6*01	1916
99	gnl|Fabrus|VH3-11_IGHD6-6*01_IGHJ1*01	1917
100	gnl|Fabrus|VH3-11_IGHD7-27*01_IGHJ4*01	1918
101	gnl|Fabrus|VH3-13_IGHD1-26*01_IGHJ4*01	1919
102	gnl|Fabrus|VH3-13_IGHD2-8*01_IGHJ5*01	1920
103	gnl|Fabrus|VH3-13_IGHD3-3*01_IGHJ1*01	1921
104	gnl|Fabrus|VH3-13_IGHD3-9*01_IGHJ6*01	1922
105	gnl|Fabrus|VH3-13_IGHD4-23*01_IGHJ5*01	1923
106	gnl|Fabrus|VH3-13_IGHD5-5*01_IGHJ4*01	1924
107	gnl|Fabrus|VH3-13_IGHD6-6*01_IGHJ1*01	1925
108	gnl|Fabrus|VH3-13_IGHD7-27*01_IGHJ5*01	1926
109	gnl|Fabrus|VH3-15_IGHD1-26*01_IGHJ4*01	1927
110	gnl|Fabrus|VH3-15_IGHD2-15*01_IGHJ2*01	1928
111	gnl|Fabrus|VH3-15_IGHD2-15*01_IGHJ6*01	1929
112	gnl|Fabrus|VH3-15_IGHD3-10*01_IGHJ4*01	1930
113	gnl|Fabrus|VH3-15_IGHD3-9*01_IGHJ2*01	1931
114	gnl|Fabrus|VH3-15_IGHD5-12*01_IGHJ4*01	1932
115	gnl|Fabrus|VH3-15_IGHD6-6*01_IGHJ1*01	1933
116	gnl|Fabrus|VH3-16_IGHD1-1*01_IGHJ1*01	1934
117	gnl|Fabrus|VH3-16_IGHD1-7*01_IGHJ6*01	1935
118	gnl|Fabrus|VH3-16_IGHD2-15*01_IGHJ2*01	1936
119	gnl|Fabrus|VH3-16_IGHD2-2*01_IGHJ2*01	1937
120	gnl|Fabrus|VH3-16_IGHD3-10*01_IGHJ4*01	1938
121	gnl|Fabrus|VH3-16_IGHD4-4*01_IGHJ2*01	1939
122	gnl|Fabrus|VH3-16_IGHD5-24*01_IGHJ4*01	1940
123	gnl|Fabrus|VH3-16_IGHD6-13*01_IGHJ4*01	1941
124	gnl|Fabrus|VH3-16_IGHD7-27*01_IGHJ2*01	1942
125	gnl|Fabrus|VH3-20_IGHD1-14*01_IGHJ4*01	1943
126	gnl|Fabrus|VH3-20_IGHD2-15*01_IGHJ2*01	1944
127	gnl|Fabrus|VH3-20_IGHD2-8*01_IGHJ4*01	1945
128	gnl|Fabrus|VH3-20_IGHD3-10*01_IGHJ4*01	1946
129	gnl|Fabrus|VH3-20_IGHD3-9*01_IGHJ6*01	1947
130	gnl|Fabrus|VH3-20_IGHD4-23*01_IGHJ4*01	1948
131	gnl|Fabrus|VH3-20_IGHD5-12*01_IGHJ4*01	1949
132	gnl|Fabrus|VH3-20_IGHD6-13*01_IGHJ4*01	1950
133	gnl|Fabrus|VH3-20_IGHD7-27*01_IGHJ2*01	1951
134	gnl|Fabrus|VH3-21_IGHD1-26*01_IGHJ4*01	1952
135	gnl|Fabrus|VH3-21_IGHD2-2*01_IGHJ5*01	1953
136	gnl|Fabrus|VH3-21_IGHD3-22*01_IGHJ4*01	1954
137	gnl|Fabrus|VH3-21_IGHD4-23*01_IGHJ5*01	1955
138	gnl|Fabrus|VH3-21_IGHD5-24*01_IGHJ5*01	1956
139	gnl|Fabrus|VH3-21_IGHD6-19*01_IGHJ1*01	1957
140	gnl|Fabrus|VH3-21_IGHD7-27*01_IGHJ4*01	1958
141	gnl|Fabrus|VH3-23_IGHD1-1*01_IGHJ1*01	1959
142	gnl|Fabrus|VH3-23_IGHD1-1*01_IGHJ4*01	1960
143	gnl|Fabrus|VH3-23_IGHD1-20*01_IGHJ3*01	1961
144	gnl|Fabrus|VH3-23_IGHD1-26*01_IGHJ4*01	1962
145	gnl|Fabrus|VH3-23_IGHD2-15*01_IGHJ4*01	1963
146	gnl|Fabrus|VH3-23_IGHD2-21*01_IGHJ1*01	1964
147	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	1965

148	gnl|Fabrus|VH3-23_IGHD3-16*01_IGHJ4*01	1966
149	gnl|Fabrus|VH3-23_IGHD3-22*01_IGHJ4*01	1967
150	gnl|Fabrus|VH3-23_IGHD3-3*01_IGHJ5*01	1968
151	gnl|Fabrus|VH3-23_IGHD4-11*01_IGHJ4*01	1969
152	gnl|Fabrus|VH3-23_IGHD4-23*01_IGHJ2*01	1970
153	gnl|Fabrus|VH3-23_IGHD5-12*01_IGHJ4*01	1971
154	gnl|Fabrus|VH3-23_IGHD5-24*01_IGHJ1*01	1972
155	gnl|Fabrus|VH3-23_IGHD5-5*01_IGHJ4*01	1973
156	gnl|Fabrus|VH3-23_IGHD6-13*01_IGHJ4*01	1974
157	gnl|Fabrus|VH3-23_IGHD6-25*01_IGHJ2*01	1975
158	gnl|Fabrus|VH3-23_IGHD6-6*01_IGHJ1*01	1976
159	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ4*01	1977
160	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ6*01	1978
161	gnl|Fabrus|VH3-30_IGHD1-1*01_IGHJ6*01	1979
162	gnl|Fabrus|VH3-30_IGHD1-26*01_IGHJ1*01	1980
163	gnl|Fabrus|VH3-30_IGHD1-26*01_IGHJ4*01	1981
164	gnl|Fabrus|VH3-30_IGHD2-15*01_IGHJ2*01	1982
165	gnl|Fabrus|VH3-30_IGHD2-2*01_IGHJ6*01	1983
166	gnl|Fabrus|VH3-30_IGHD3-10*01_IGHJ1*01	1984
167	gnl|Fabrus|VH3-30_IGHD3-16*01_IGHJ6*01	1985
168	gnl|Fabrus|VH3-30_IGHD4-17*01_IGHJ4*01	1986
169	gnl|Fabrus|VH3-30_IGHD5-12*01_IGHJ4*01	1987
170	gnl|Fabrus|VH3-30_IGHD5-18*01_IGHJ1*01	1988
171	gnl|Fabrus|VH3-30_IGHD6-13*01_IGHJ4*01	1989
172	gnl|Fabrus|VH3-30_IGHD6-6*01_IGHJ1*01	1990
173	gnl|Fabrus|VH3-35_IGHD1-1*01_IGHJ2*01	1991
174	gnl|Fabrus|VH3-35_IGHD1-20*01_IGHJ6*01	1992
175	gnl|Fabrus|VH3-35_IGHD2-15*01_IGHJ2*01	1993
176	gnl|Fabrus|VH3-35_IGHD2-21*01_IGHJ6*01	1994
177	gnl|Fabrus|VH3-35_IGHD3-10*01_IGHJ4*01	1995
178	gnl|Fabrus|VH3-35_IGHD3-9*01_IGHJ6*01	1996
179	gnl|Fabrus|VH3-35_IGHD5-12*01_IGHJ4*01	1997
180	gnl|Fabrus|VH3-35_IGHD6-13*01_IGHJ4*01	1998
181	gnl|Fabrus|VH3-35_IGHD7-27*01_IGHJ1*01	1999
182	gnl|Fabrus|VH3-38_IGHD1-14*01_IGHJ5*01	2000
183	gnl|Fabrus|VH3-38_IGHD1-20*01_IGHJ6*01	2001
184	gnl|Fabrus|VH3-38_IGHD2-15*01_IGHJ6*01	2002
185	gnl|Fabrus|VH3-38_IGHD2-2*01_IGHJ1*01	2003
186	gnl|Fabrus|VH3-38_IGHD3-10*01_IGHJ4*01	2004
187	gnl|Fabrus|VH3-38_IGHD3-16*01_IGHJ1*01	2005
188	gnl|Fabrus|VH3-38_IGHD4-17*01_IGHJ2*01	2006
189	gnl|Fabrus|VH3-38_IGHD5-24*01_IGHJ3*01	2007
190	gnl|Fabrus|VH3-38_IGHD6-6*01_IGHJ1*01	2008
191	gnl|Fabrus|VH3-38_IGHD7-27*01_IGHJ6*01	2009
192	gnl|Fabrus|VH3-43_IGHD1-26*01_IGHJ5*01	2010
193	gnl|Fabrus|VH3-43_IGHD1-7*01_IGHJ6*01	2011
194	gnl|Fabrus|VH3-43_IGHD2-2*01_IGHJ3*01	2012
195	gnl|Fabrus|VH3-43_IGHD2-21*01_IGHJ6*01	2013
196	gnl|Fabrus|VH3-43_IGHD3-16*01_IGHJ6*01	2014
197	gnl|Fabrus|VH3-43_IGHD3-22*01_IGHJ4*01	2015
198	gnl|Fabrus|VH3-43_IGHD4-23*01_IGHJ3*01	2016
199	gnl|Fabrus|VH3-43_IGHD5-18*01_IGHJ5*01	2017
200	gnl|Fabrus|VH3-43_IGHD6-13*01_IGHJ4*01	2018
201	gnl|Fabrus|VH3-43_IGHD7-27*01_IGHJ1*01	2019
202	gnl|Fabrus|VH3-48_IGHD6-6*01_IGHJ1*01	2020

203	gnl|Fabrus|VH3-49_IGHD1-26*01_IGHJ4*01	2021
204	gnl|Fabrus|VH3-49_IGHD1-7*01_IGHJ6*01	2022
205	gnl|Fabrus|VH3-49_IGHD2-2*01_IGHJ6*01	2023
206	gnl|Fabrus|VH3-49_IGHD2-8*01_IGHJ4*01	2024
207	gnl|Fabrus|VH3-49_IGHD3-22*01_IGHJ4*01	2025
208	gnl|Fabrus|VH3-49_IGHD3-9*01_IGHJ6*01	2026
209	gnl|Fabrus|VH3-49_IGHD5-18*01_IGHJ4*01	2027
210	gnl|Fabrus|VH3-49_IGHD6-13*01_IGHJ4*01	2028
211	gnl|Fabrus|VH3-49_IGHD7-27*01_IGHJ1*01	2029
212	gnl|Fabrus|VH3-53_IGHD1-14*01_IGHJ6*01	2030
213	gnl|Fabrus|VH3-53_IGHD1-7*01_IGHJ1*01	2031
214	gnl|Fabrus|VH3-53_IGHD2-2*01_IGHJ2*01	2032
215	gnl|Fabrus|VH3-53_IGHD3-22*01_IGHJ3*01	2033
216	gnl|Fabrus|VH3-53_IGHD4-23*01_IGHJ1*01	2034
217	gnl|Fabrus|VH3-53_IGHD5-5*01_IGHJ4*01	2035
218	gnl|Fabrus|VH3-53_IGHD6-13*01_IGHJ3*01	2036
219	gnl|Fabrus|VH3-53_IGHD7-27*01_IGHJ4*01	2037
220	gnl|Fabrus|VH3-64_IGHD1-26*01_IGHJ4*01	2038
221	gnl|Fabrus|VH3-64_IGHD1-7*01_IGHJ6*01	2039
222	gnl|Fabrus|VH3-64_IGHD2-2*01_IGHJ5*01	2040
223	gnl|Fabrus|VH3-64_IGHD3-3*01_IGHJ4*01	2041
224	gnl|Fabrus|VH3-64_IGHD4-17*01_IGHJ4*01	2042
225	gnl|Fabrus|VH3-64_IGHD5-12*01_IGHJ4*01	2043
226	gnl|Fabrus|VH3-64_IGHD6-19*01_IGHJ1*01	2044
227	gnl|Fabrus|VH3-64_IGHD7-27*01_IGHJ4*01	2045
228	gnl|Fabrus|VH3-66_IGHD6-6*01_IGHJ1*01	2046
229	gnl|Fabrus|VH3-7_IGHD1-20*01_IGHJ3*01	2047
230	gnl|Fabrus|VH3-7_IGHD1-7*01_IGHJ6*01	2048
231	gnl|Fabrus|VH3-7_IGHD2-21*01_IGHJ5*01	2049
232	gnl|Fabrus|VH3-7_IGHD2-8*01_IGHJ6*01	2050
233	gnl|Fabrus|VH3-7_IGHD3-22*01_IGHJ3*01	2051
234	gnl|Fabrus|VH3-7_IGHD3-9*01_IGHJ6*01	2052
235	gnl|Fabrus|VH3-7_IGHD4-17*01_IGHJ4*01	2053
236	gnl|Fabrus|VH3-7_IGHD5-12*01_IGHJ4*01	2054
237	gnl|Fabrus|VH3-7_IGHD5-24*01_IGHJ4*01	2055
238	gnl|Fabrus|VH3-7_IGHD6-19*01_IGHJ6*01	2056
239	gnl|Fabrus|VH3-7_IGHD6-6*01_IGHJ1*01	2057
240	gnl|Fabrus|VH3-7_IGHD7-27*01_IGHJ2*01	2058
241	gnl|Fabrus|VH3-72_IGHD1-1*01_IGHJ4*01	2059
242	gnl|Fabrus|VH3-72_IGHD2-15*01_IGHJ1*01	2060
243	gnl|Fabrus|VH3-72_IGHD3-22*01_IGHJ4*01	2061
244	gnl|Fabrus|VH3-72_IGHD3-9*01_IGHJ6*01	2062
245	gnl|Fabrus|VH3-72_IGHD4-23*01_IGHJ2*01	2063
246	gnl|Fabrus|VH3-72_IGHD5-18*01_IGHJ4*01	2064
247	gnl|Fabrus|VH3-72_IGHD5-24*01_IGHJ6*01	2065
248	gnl|Fabrus|VH3-72_IGHD6-6*01_IGHJ1*01	2066
249	gnl|Fabrus|VH3-72_IGHD7-27*01_IGHJ2*01	2067
250	gnl|Fabrus|VH3-73_IGHD1-1*01_IGHJ5*01	2068
251	gnl|Fabrus|VH3-73_IGHD2-8*01_IGHJ2*01	2069
252	gnl|Fabrus|VH3-73_IGHD3-22*01_IGHJ4*01	2070
253	gnl|Fabrus|VH3-73_IGHD3-9*01_IGHJ6*01	2071
254	gnl|Fabrus|VH3-73_IGHD4-11*01_IGHJ6*01	2072
255	gnl|Fabrus|VH3-73_IGHD4-23*01_IGHJ5*01	2073
256	gnl|Fabrus|VH3-73_IGHD5-12*01_IGHJ4*01	2074
257	gnl|Fabrus|VH3-73_IGHD6-19*01_IGHJ1*01	2075

258	gnl|Fabrus|VH3-73_IGHD7-27*01_IGHJ5*01	2076
259	gnl|Fabrus|VH3-74_IGHD1-1*01_IGHJ6*01	2077
260	gnl|Fabrus|VH3-74_IGHD1-26*01_IGHJ4*01	2078
261	gnl|Fabrus|VH3-74_IGHD2-2*01_IGHJ5*01	2079
262	gnl|Fabrus|VH3-74_IGHD3-22*01_IGHJ5*01	2080
263	gnl|Fabrus|VH3-74_IGHD4-17*01_IGHJ1*01	2081
264	gnl|Fabrus|VH3-74_IGHD5-12*01_IGHJ4*01	2082
265	gnl|Fabrus|VH3-74_IGHD6-6*01_IGHJ1*01	2083
266	gnl|Fabrus|VH3-74_IGHD7-27*01_IGHJ4*01	2084
267	gnl|Fabrus|VH3-9_IGHD1-1*01_IGHJ6*01	2085
268	gnl|Fabrus|VH3-9_IGHD1-7*01_IGHJ5*01	2086
269	gnl|Fabrus|VH3-9_IGHD2-2*01_IGHJ4*01	2087
270	gnl|Fabrus|VH3-9_IGHD3-16*01_IGHJ6*01	2088
271	gnl|Fabrus|VH3-9_IGHD3-22*01_IGHJ4*01	2089
272	gnl|Fabrus|VH3-9_IGHD4-11*01_IGHJ4*01	2090
273	gnl|Fabrus|VH3-9_IGHD5-24*01_IGHJ1*01	2091
274	gnl|Fabrus|VH3-9_IGHD6-13*01_IGHJ4*01	2092
275	gnl|Fabrus|VH3-9_IGHD6-25*01_IGHJ6*01	2093
276	gnl|Fabrus|VH3-9_IGHD7-27*01_IGHJ2*01	2094
277	gnl|Fabrus|VH4-28_IGHD1-20*01_IGHJ1*01	2095
278	gnl|Fabrus|VH4-28_IGHD1-7*01_IGHJ6*01	2096
279	gnl|Fabrus|VH4-28_IGHD2-15*01_IGHJ6*01	2097
280	gnl|Fabrus|VH4-28_IGHD3-16*01_IGHJ2*01	2098
281	gnl|Fabrus|VH4-28_IGHD3-9*01_IGHJ6*01	2099
282	gnl|Fabrus|VH4-28_IGHD4-4*01_IGHJ4*01	2100
283	gnl|Fabrus|VH4-28_IGHD5-5*01_IGHJ1*01	2101
284	gnl|Fabrus|VH4-28_IGHD6-13*01_IGHJ4*01	2102
285	gnl|Fabrus|VH4-28_IGHD7-27*01_IGHJ1*01	94
286	gnl|Fabrus|VH4-31_IGHD1-26*01_IGHJ2*01	91
287	gnl|Fabrus|VH4-31_IGHD2-15*01_IGHJ2*01	103
288	gnl|Fabrus|VH4-31_IGHD2-2*01_IGHJ6*01	2103
289	gnl|Fabrus|VH4-31_IGHD3-10*01_IGHJ4*01	2104
290	gnl|Fabrus|VH4-31_IGHD3-9*01_IGHJ6*01	2105
291	gnl|Fabrus|VH4-31_IGHD4-17*01_IGHJ5*01	2106
292	gnl|Fabrus|VH4-31_IGHD5-12*01_IGHJ4*01	2107
293	gnl|Fabrus|VH4-31_IGHD6-13*01_IGHJ4*01	2108
294	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	2109
295	gnl|Fabrus|VH4-31_IGHD7-27*01_IGHJ5*01	95
296	gnl|Fabrus|VH4-34_IGHD1-7*01_IGHJ4*01	2110
297	gnl|Fabrus|VH4-34_IGHD2-2*01_IGHJ4*01	2111
298	gnl|Fabrus|VH4-34_IGHD3-16*01_IGHJ4*01	2112
299	gnl|Fabrus|VH4-34_IGHD3-22*01_IGHJ6*01	2113
300	gnl|Fabrus|VH4-34_IGHD4-17*01_IGHJ4*01	2114
301	gnl|Fabrus|VH4-34_IGHD5-12*01_IGHJ4*01	2115
302	gnl|Fabrus|VH4-34_IGHD6-13*01_IGHJ4*01	2116
303	gnl|Fabrus|VH4-34_IGHD6-25*01_IGHJ6*01	2117
304	gnl|Fabrus|VH4-34_IGHD6-6*01_IGHJ6*01	2118
305	gnl|Fabrus|VH4-34_IGHD7-27*01_IGHJ4*01	100
306	gnl|Fabrus|VH4-39_IGHD1-14*01_IGHJ1*01	2119
307	gnl|Fabrus|VH4-39_IGHD1-20*01_IGHJ6*01	2120
308	gnl|Fabrus|VH4-39_IGHD2-21*01_IGHJ3*01	2121
309	gnl|Fabrus|VH4-39_IGHD3-10*01_IGHJ4*01	2122
310	gnl|Fabrus|VH4-39_IGHD3-16*01_IGHJ2*01	2123
311	gnl|Fabrus|VH4-39_IGHD3-9*01_IGHJ6*01	2124
312	gnl|Fabrus|VH4-39_IGHD4-23*01_IGHJ2*01	2125

313	gnl|Fabrus|VH4-39_IGHD5-12*01_IGHJ4*01	2126
314	gnl|Fabrus|VH4-39_IGHD6-6*01_IGHJ1*01	2127
315	gnl|Fabrus|VH4-4_IGHD1-20*01_IGHJ3*01	2128
316	gnl|Fabrus|VH4-4_IGHD2-8*01_IGHJ4*01	2129
317	gnl|Fabrus|VH4-4_IGHD3-22*01_IGHJ2*01	2130
318	gnl|Fabrus|VH4-4_IGHD4-23*01_IGHJ4*01	2131
319	gnl|Fabrus|VH4-4_IGHD5-12*01_IGHJ5*01	2132
320	gnl|Fabrus|VH4-4_IGHD6-6*01_IGHJ4*01	2133
321	gnl|Fabrus|VH4-4_IGHD7-27*01_IGHJ6*01	2134
322	gnl|Fabrus|VH4-59_IGHD6-25*01_IGHJ3*01	2135
323	gnl|Fabrus|VH5-51_IGHD1-14*01_IGHJ4*01	2136
324	gnl|Fabrus|VH5-51_IGHD1-26*01_IGHJ6*01	2137
325	gnl|Fabrus|VH5-51_IGHD2-8*01_IGHJ4*01	2138
326	gnl|Fabrus|VH5-51_IGHD3-10*01_IGHJ6*01	2139
327	gnl|Fabrus|VH5-51_IGHD3-3*01_IGHJ4*01	2140
328	gnl|Fabrus|VH5-51_IGHD4-17*01_IGHJ4*01	2141
329	gnl|Fabrus|VH5-51_IGHD5-18*01>3_IGHJ4*01	89
330	gnl|Fabrus|VH5-51_IGHD5-18*01>1_IGHJ4*01	2142
331	gnl|Fabrus|VH5-51_IGHD6-25*01_IGHJ4*01	106
332	gnl|Fabrus|VH5-51_IGHD7-27*01_IGHJ4*01	2143
333	gnl|Fabrus|VH6-1_IGHD1-1*01_IGHJ4*01	2144
334	gnl|Fabrus|VH6-1_IGHD1-20*01_IGHJ6*01	2145
335	gnl|Fabrus|VH6-1_IGHD2-15*01_IGHJ4*01	2146
336	gnl|Fabrus|VH6-1_IGHD2-21*01_IGHJ6*01	2147
337	gnl|Fabrus|VH6-1_IGHD3-16*01_IGHJ5*01	2148
338	gnl|Fabrus|VH6-1_IGHD3-3*01_IGHJ4*01	90
339	gnl|Fabrus|VH6-1_IGHD4-11*01_IGHJ6*01	2149
340	gnl|Fabrus|VH6-1_IGHD4-23*01_IGHJ4*01	2150
341	gnl|Fabrus|VH6-1_IGHD5-5*01_IGHJ4*01	2151
342	gnl|Fabrus|VH6-1_IGHD6-13*01_IGHJ4*01	2152
343	gnl|Fabrus|VH6-1_IGHD6-25*01_IGHJ6*01	2153
344	gnl|Fabrus|VH6-1_IGHD7-27*01_IGHJ4*01	2154
345	gnl|Fabrus|VH7-81_IGHD1-14*01_IGHJ4*01	2155
346	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ2*01	2156
347	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ6*01	2157
348	gnl|Fabrus|VH7-81_IGHD3-16*01_IGHJ6*01	2158
349	gnl|Fabrus|VH7-81_IGHD4-23*01_IGHJ1*01	2159
350	gnl|Fabrus|VH7-81_IGHD5-12*01_IGHJ6*01	2160
351	gnl|Fabrus|VH7-81_IGHD6-25*01_IGHJ4*01	2161
352	gnl|Fabrus|VH7-81_IGHD7-27*01_IGHJ4*01	2162
353	gi|Fabrus|VH3-23_IGHD1-1*01>1_IGHJ1*01	2211
355	gi|Fabrus|VH3-23_IGHD1-1*01>2_IGHJ1*01	2212
356	gi|Fabrus|VH3-23_IGHD1-1*01>3_IGHJ1*01	2213
357	gi|Fabrus|VH3-23_IGHD1-7*01>1_IGHJ1*01	2214
358	gi|Fabrus|VH3-23_IGHD1-7*01>3_IGHJ1*01	2215
359	gi|Fabrus|VH3-23_IGHD1-14*01>1_IGHJ1*01	2216
360	gi|Fabrus|VH3-23_IGHD1-14*01>3_IGHJ1*01	2217
361	gi|Fabrus|VH3-23_IGHD1-20*01>1_IGHJ1*01	2218
362	gi|Fabrus|VH3-23_IGHD1-20*01>3_IGHJ1*01	2219
363	gi|Fabrus|VH3-23_IGHD1-26*01>1_IGHJ1*01	2220
364	gi|Fabrus|VH3-23_IGHD1-26*01>3_IGHJ1*01	2221
365	gi|Fabrus|VH3-23_IGHD2-2*01>2_IGHJ1*01	2222
366	gi|Fabrus|VH3-23_IGHD2-2*01>3_IGHJ1*01	2223
367	gi|Fabrus|VH3-23_IGHD2-8*01>2_IGHJ1*01	2224
368	gi|Fabrus|VH3-23_IGHD2-8*01>3_IGHJ1*01	2225

369	gi|Fabrus|VH3-23_IGHD2-15*01>2_IGHJ1*01	2226
370	gi|Fabrus|VH3-23_IGHD2-15*01>3_IGHJ1*01	2227
371	gi|Fabrus|VH3-23_IGHD2-21*01>2_IGHJ1*01	2228
372	gi|Fabrus|VH3-23_IGHD2-21*01>3_IGHJ1*01	2229
373	gi|Fabrus|VH3-23_IGHD3-3*01>1_IGHJ1*01	2230
374	gi|Fabrus|VH3-23_IGHD3-3*01>2_IGHJ1*01	2231
375	gi|Fabrus|VH3-23_IGHD3-3*01>3_IGHJ1*01	2232
376	gi|Fabrus|VH3-23_IGHD3-9*01>2_IGHJ1*01	2233
377	gi|Fabrus|VH3-23_IGHD3-10*01>2_IGHJ1*01	2234
378	gi|Fabrus|VH3-23_IGHD3-10*01>3_IGHJ1*01	2235
379	gi|Fabrus|VH3-23_IGHD3-16*01>2_IGHJ1*01	2236
380	gi|Fabrus|VH3-23_IGHD3-16*01>3_IGHJ1*01	2237
381	gi|Fabrus|VH3-23_IGHD3-22*01>2_IGHJ1*01	2238
382	gi|Fabrus|VH3-23_IGHD3-22*01>3_IGHJ1*01	2239
383	gi|Fabrus|VH3-23_IGHD4-4*01(1)>2_IGHJ1*01	2240
384	gi|Fabrus|VH3-23_IGHD4-4*01(1)>3_IGHJ1*01	2241
385	gi|Fabrus|VH3-23_IGHD4-11*01(1)>2_IGHJ1*01	2242
386	gi|Fabrus|VH3-23_IGHD4-11*01(1)>3_IGHJ1*01	2243
387	gi|Fabrus|VH3-23_IGHD4-17*01>2_IGHJ1*01	2244
388	gi|Fabrus|VH3-23_IGHD4-17*01>3_IGHJ1*01	2245
389	gi|Fabrus|VH3-23_IGHD4-23*01>2_IGHJ1*01	2246
390	gi|Fabrus|VH3-23_IGHD4-23*01>3_IGHJ1*01	2247
391	gi|Fabrus|VH3-23_IGHD5-5*01(2)>1_IGHJ1*01	2248
392	gi|Fabrus|VH3-23_IGHD5-5*01(2)>2_IGHJ1*01	2249
393	gi|Fabrus|VH3-23_IGHD5-5*01(2)>3_IGHJ1*01	2250
394	gi|Fabrus|VH3-23_IGHD5-12*01>1_IGHJ1*01	2251
395	gi|Fabrus|VH3-23_IGHD5-12*01>3_IGHJ1*01	2252
396	gi|Fabrus|VH3-23_IGHD5-18*01(2)>1_IGHJ1*01	2253
397	gi|Fabrus|VH3-23_IGHD5-18*01(2)>2_IGHJ1*01	2254
398	gi|Fabrus|VH3-23_IGHD5-18*01(2)>3_IGHJ1*01	2255
399	gi|Fabrus|VH3-23_IGHD5-24*01>1_IGHJ1*01	2256
400	gi|Fabrus|VH3-23_IGHD5-24*01>3_IGHJ1*01	2257
401	gi|Fabrus|VH3-23_IGHD6-6*01>1_IGHJ1*01	2258
402	gi|Fabrus|VH3-23_IGHD6-6*01>2_IGHJ1*01	2259
403	gi|Fabrus|VH3-23_IGHD6-13*01>1_IGHJ1*01	2260
404	gi|Fabrus|VH3-23_IGHD6-13*01>2_IGHJ1*01	2261
405	gi|Fabrus|VH3-23_IGHD6-19*01>1_IGHJ1*01	2262
406	gi|Fabrus|VH3-23_IGHD6-19*01>2_IGHJ1*01	2263
407	gi|Fabrus|VH3-23_IGHD6-25*01>1_IGHJ1*01	2264
408	gi|Fabrus|VH3-23_IGHD6-25*01>2_IGHJ1*01	2265
409	gi|Fabrus|VH3-23_IGHD7-27*01>1_IGHJ1*01	2266
410	gi|Fabrus|VH3-23_IGHD7-27*01>3_IGHJ1*01	2267
411	gi|Fabrus|VH3-23_IGHD1-1*01>1'_IGHJ1*01	2268
412	gi|Fabrus|VH3-23_IGHD1-1*01>2'_IGHJ1*01	2269
413	gi|Fabrus|VH3-23_IGHD1-1*01>3'_IGHJ1*01	2270
414	gi|Fabrus|VH3-23_IGHD1-7*01>1'_IGHJ1*01	2271
415	gi|Fabrus|VH3-23_IGHD1-7*01>3'_IGHJ1*01	2272
416	gi|Fabrus|VH3-23_IGHD1-14*01>1'_IGHJ1*01	2273
417	gi|Fabrus|VH3-23_IGHD1-14*01>2'_IGHJ1*01	2274
418	gi|Fabrus|VH3-23_IGHD1-14*01>3'_IGHJ1*01	2275
419	gi|Fabrus|VH3-23_IGHD1-20*01>1'_IGHJ1*01	2276
420	gi|Fabrus|VH3-23_IGHD1-20*01>2'_IGHJ1*01	2277
421	gi|Fabrus|VH3-23_IGHD1-20*01>3'_IGHJ1*01	2278
422	gi|Fabrus|VH3-23_IGHD1-26*01>1'_IGHJ1*01	2279
423	gi|Fabrus|VH3-23_IGHD1-26*01>3'_IGHJ1*01	2280

424	gi|Fabrus|VH3-23_IGHD2-2*01>1'_IGHJ1*01	2281
425	gi|Fabrus|VH3-23_IGHD2-2*01>3'_IGHJ1*01	2282
426	gi|Fabrus|VH3-23_IGHD2-8*01>1'_IGHJ1*01	2283
427	gi|Fabrus|VH3-23_IGHD2-15*01>1'_IGHJ1*01	2284
428	gi|Fabrus|VH3-23_IGHD2-15*01>3'_IGHJ1*01	2285
429	gi|Fabrus|VH3-23_IGHD2-21*01>1'_IGHJ1*01	2286
430	gi|Fabrus|VH3-23_IGHD2-21*01>3'_IGHJ1*01	2287
431	gi|Fabrus|VH3-23_IGHD3-3*01>1'_IGHJ1*01	2288
432	gi|Fabrus|VH3-23_IGHD3-3*01>3'_IGHJ1*01	2289
433	gi|Fabrus|VH3-23_IGHD3-9*01>1'_IGHJ1*01	2290
434	gi|Fabrus|VH3-23_IGHD3-9*01>3'_IGHJ1*01	2291
435	gi|Fabrus|VH3-23_IGHD3-10*01>1'_IGHJ1*01	2292
436	gi|Fabrus|VH3-23_IGHD3-10*01>3'_IGHJ1*01	2293
437	gi|Fabrus|VH3-23_IGHD3-16*01>1'_IGHJ1*01	2294
438	gi|Fabrus|VH3-23_IGHD3-16*01>3'_IGHJ1*01	2295
439	gi|Fabrus|VH3-23_IGHD3-22*01>1'_IGHJ1*01	2296
440	gi|Fabrus|VH3-23_IGHD4-4*01(1)>1'_IGHJ1*01	2297
441	gi|Fabrus|VH3-23_IGHD4-4*01(1)>3'_IGHJ1*01	2298
442	gi|Fabrus|VH3-23_IGHD4-11*01(1)>1'_IGHJ1*01	2299
443	gi|Fabrus|VH3-23_IGHD4-11*01(1)>3'_IGHJ1*01	2300
444	gi|Fabrus|VH3-23_IGHD4-17*01>1'_IGHJ1*01	2301
445	gi|Fabrus|VH3-23_IGHD4-17*01>3'_IGHJ1*01	2302
446	gi|Fabrus|VH3-23_IGHD4-23*01>1'_IGHJ1*01	2303
447	gi|Fabrus|VH3-23_IGHD4-23*01>3'_IGHJ1*01	2304
448	gi|Fabrus|VH3-23_IGHD5-5*01(2)>1'_IGHJ1*01	2305
449	gi|Fabrus|VH3-23_IGHD5-5*01(2)>3'_IGHJ1*01	2306
450	gi|Fabrus|VH3-23_IGHD5-12*01>1'_IGHJ1*01	2307
451	gi|Fabrus|VH3-23_IGHD5-12*01>3'_IGHJ1*01	2308
452	gi|Fabrus|VH3-23_IGHD5-18*01(2)>1'_IGHJ1*01	2309
453	gi|Fabrus|VH3-23_IGHD5-18*01(2)>3'_IGHJ1*01	2310
454	gi|Fabrus|VH3-23_IGHD5-24*01>1'_IGHJ1*01	2311
455	gi|Fabrus|VH3-23_IGHD5-24*01>3'_IGHJ1*01	2312
456	gi|Fabrus|VH3-23_IGHD6-6*01>1'_IGHJ1*01	2313
457	gi|Fabrus|VH3-23_IGHD6-6*01>2'_IGHJ1*01	2314
458	gi|Fabrus|VH3-23_IGHD6-6*01>3'_IGHJ1*01	2315
459	gi|Fabrus|VH3-23_IGHD6-13*01>1'_IGHJ1*01	2316
460	gi|Fabrus|VH3-23_IGHD6-13*01>2'_IGHJ1*01	2317
461	gi|Fabrus|VH3-23_IGHD6-13*01>3'_IGHJ1*01	2318
462	gi|Fabrus|VH3-23_IGHD6-19*01>1'_IGHJ1*01	2319
463	gi|Fabrus|VH3-23_IGHD6-19*01>2'_IGHJ1*01	2320
464	gi|Fabrus|VH3-23_IGHD6-19*01>3'_IGHJ1*01	2321
465	gi|Fabrus|VH3-23_IGHD6-25*01>1'_IGHJ1*01	2322
466	gi|Fabrus|VH3-23_IGHD6-25*01>3'_IGHJ1*01	2323
467	gi|Fabrus|VH3-23_IGHD7-27*01>1'_IGHJ1*01	2324
468	gi|Fabrus|VH3-23_IGHD7-27*01>2'_IGHJ1*01	2325
469	gi|Fabrus|VH3-23_IGHD1-1*01>1_IGHJ2*01	2326
470	gi|Fabrus|VH3-23_IGHD1-1*01>2_IGHJ2*01	2327
471	gi|Fabrus|VH3-23_IGHD1-1*01>3_IGHJ2*01	2328
472	gi|Fabrus|VH3-23_IGHD1-7*01>1_IGHJ2*01	2329
473	gi|Fabrus|VH3-23_IGHD1-7*01>3_IGHJ2*01	2330
474	gi|Fabrus|VH3-23_IGHD1-14*01>1_IGHJ2*01	2331
475	gi|Fabrus|VH3-23_IGHD1-14*01>3_IGHJ2*01	2332
476	gi|Fabrus|VH3-23_IGHD1-20*01>1_IGHJ2*01	2333
477	gi|Fabrus|VH3-23_IGHD1-20*01>3_IGHJ2*01	2334
478	gi|Fabrus|VH3-23_IGHD1-26*01>1_IGHJ2*01	2335

479	gi|Fabrus|VH3-23_IGHD1-26*01>3_IGHJ2*01	2336
480	gi|Fabrus|VH3-23_IGHD2-2*01>2_IGHJ2*01	2337
481	gi|Fabrus|VH3-23_IGHD2-2*01>3_IGHJ2*01	2338
482	gi|Fabrus|VH3-23_IGHD2-8*01>2_IGHJ2*01	2339
483	gi|Fabrus|VH3-23_IGHD2-8*01>3_IGHJ2*01	2340
484	gi|Fabrus|VH3-23_IGHD2-15*01>2_IGHJ2*01	2341
485	gi|Fabrus|VH3-23_IGHD2-15*01>3_IGHJ2*01	2342
486	gi|Fabrus|VH3-23_IGHD2-21*01>2_IGHJ2*01	2343
487	gi|Fabrus|VH3-23_IGHD2-21*01>3_IGHJ2*01	2344
488	gi|Fabrus|VH3-23_IGHD3-3*01>1_IGHJ2*01	2345
489	gi|Fabrus|VH3-23_IGHD3-3*01>2_IGHJ2*01	2346
490	gi|Fabrus|VH3-23_IGHD3-3*01>3_IGHJ2*01	2347
491	gi|Fabrus|VH3-23_IGHD3-9*01>2_IGHJ2*01	2348
492	gi|Fabrus|VH3-23_IGHD3-10*01>2_IGHJ2*01	2349
493	gi|Fabrus|VH3-23_IGHD3-10*01>3_IGHJ2*01	2350
494	gi|Fabrus|VH3-23_IGHD3-16*01>2_IGHJ2*01	2351
495	gi|Fabrus|VH3-23_IGHD3-16*01>3_IGHJ2*01	2352
496	gi|Fabrus|VH3-23_IGHD3-22*01>2_IGHJ2*01	2353
497	gi|Fabrus|VH3-23_IGHD3-22*01>3_IGHJ2*01	2354
498	gi|Fabrus|VH3-23_IGHD4-4*01(1)>2_IGHJ2*01	2355
499	gi|Fabrus|VH3-23_IGHD4-4*01(1)>3_IGHJ2*01	2356
500	gi|Fabrus|VH3-23_IGHD4-11*01(1)>2_IGHJ2*01	2357
501	gi|Fabrus|VH3-23_IGHD4-11*01(1)>3_IGHJ2*01	2358
502	gi|Fabrus|VH3-23_IGHD4-17*01>2_IGHJ2*01	2359
503	gi|Fabrus|VH3-23_IGHD4-17*01>3_IGHJ2*01	2360
504	gi|Fabrus|VH3-23_IGHD4-23*01>2_IGHJ2*01	2361
505	gi|Fabrus|VH3-23_IGHD4-23*01>3_IGHJ2*01	2362
506	gi|Fabrus|VH3-23_IGHD5-5*01(2)>1_IGHJ2*01	2363
507	gi|Fabrus|VH3-23_IGHD5-5*01(2)>2_IGHJ2*01	2364
508	gi|Fabrus|VH3-23_IGHD5-5*01(2)>3_IGHJ2*01	2365
509	gi|Fabrus|VH3-23_IGHD5-12*01>1_IGHJ2*01	2366
510	gi|Fabrus|VH3-23_IGHD5-12*01>3_IGHJ2*01	2367
511	gi|Fabrus|VH3-23_IGHD5-18*01(2)>1_IGHJ2*01	2368
512	gi|Fabrus|VH3-23_IGHD5-18*01(2)>2_IGHJ2*01	2369
513	gi|Fabrus|VH3-23_IGHD5-18*01(2)>3_IGHJ2*01	2370
514	gi|Fabrus|VH3-23_IGHD5-24*01>1_IGHJ2*01	2371
515	gi|Fabrus|VH3-23_IGHD5-24*01>3_IGHJ2*01	2372
516	gi|Fabrus|VH3-23_IGHD6-6*01>1_IGHJ2*01	2373
517	gi|Fabrus|VH3-23_IGHD6-6*01>2_IGHJ2*01	2374
518	gi|Fabrus|VH3-23_IGHD6-13*01>1_IGHJ2*01	2375
519	gi|Fabrus|VH3-23_IGHD6-13*01>2_IGHJ2*01	2376
520	gi|Fabrus|VH3-23_IGHD6-19*01>1_IGHJ2*01	2377
521	gi|Fabrus|VH3-23_IGHD6-19*01>2_IGHJ2*01	2378
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523	gi|Fabrus|VH3-23_IGHD6-25*01>2_IGHJ2*01	2380
524	gi|Fabrus|VH3-23_IGHD7-27*01>1_IGHJ2*01	2381
525	gi|Fabrus|VH3-23_IGHD7-27*01>3_IGHJ2*01	2382
526	gi|Fabrus|VH3-23_IGHD1-1*01>1'_IGHJ2*01	2383
527	gi|Fabrus|VH3-23_IGHD1-1*01>2'_IGHJ2*01	2384
528	gi|Fabrus|VH3-23_IGHD1-1*01>3'_IGHJ2*01	2385
529	gi|Fabrus|VH3-23_IGHD1-7*01>1'_IGHJ2*01	2386
530	gi|Fabrus|VH3-23_IGHD1-7*01>3'_IGHJ2*01	2387
531	gi|Fabrus|VH3-23_IGHD1-14*01>1'_IGHJ2*01	2388
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533	gi|Fabrus|VH3-23_IGHD1-14*01>3'_IGHJ2*01	2390

534	gi|Fabrus|VH3-23_IGHD1-20*01>1'_IGHJ2*01	2391
535	gi|Fabrus|VH3-23_IGHD1-20*01>2'_IGHJ2*01	2392
536	gi|Fabrus|VH3-23_IGHD1-20*01>3'_IGHJ2*01	2393
537	gi|Fabrus|VH3-23_IGHD1-26*01>1'_IGHJ2*01	2394
538	gi|Fabrus|VH3-23_IGHD1-26*01>3'_IGHJ2*01	2395
539	gi|Fabrus|VH3-23_IGHD2-2*01>1'_IGHJ2*01	2396
540	gi|Fabrus|VH3-23_IGHD2-2*01>3'_IGHJ2*01	2397
541	gi|Fabrus|VH3-23_IGHD2-8*01>1'_IGHJ2*01	2398
542	gi|Fabrus|VH3-23_IGHD2-15*01>1'_IGHJ2*01	2399
543	gi|Fabrus|VH3-23_IGHD2-15*01>3'_IGHJ2*01	2400
544	gi|Fabrus|VH3-23_IGHD2-21*01>1'_IGHJ2*01	2401
545	gi|Fabrus|VH3-23_IGHD2-21*01>3'_IGHJ2*01	2402
546	gi|Fabrus|VH3-23_IGHD3-3*01>1'_IGHJ2*01	2403
547	gi|Fabrus|VH3-23_IGHD3-3*01>3'_IGHJ2*01	2404
548	gi|Fabrus|VH3-23_IGHD3-9*01>1'_IGHJ2*01	2405
549	gi|Fabrus|VH3-23_IGHD3-9*01>3'_IGHJ2*01	2406
550	gi|Fabrus|VH3-23_IGHD3-10*01>1'_IGHJ2*01	2407
551	gi|Fabrus|VH3-23_IGHD3-10*01>3'_IGHJ2*01	2408
552	gi|Fabrus|VH3-23_IGHD3-16*01>1'_IGHJ2*01	2409
553	gi|Fabrus|VH3-23_IGHD3-16*01>3'_IGHJ2*01	2410
554	gi|Fabrus|VH3-23_IGHD3-22*01>1'_IGHJ2*01	2411
555	gi|Fabrus|VH3-23_IGHD4-4*01(1)>1'_IGHJ2*01	2412
556	gi|Fabrus|VH3-23_IGHD4-4*01(1)>3'_IGHJ2*01	2413
557	gi|Fabrus|VH3-23_IGHD4-11*01(1)>1'_IGHJ2*01	2414
558	gi|Fabrus|VH3-23_IGHD4-11*01(1)>3'_IGHJ2*01	2415
559	gi|Fabrus|VH3-23_IGHD4-17*01>1'_IGHJ2*01	2416
560	gi|Fabrus|VH3-23_IGHD4-17*01>3'_IGHJ2*01	2417
561	gi|Fabrus|VH3-23_IGHD4-23*01>1'_IGHJ2*01	2418
562	gi|Fabrus|VH3-23_IGHD4-23*01>3'_IGHJ2*01	2419
563	gi|Fabrus|VH3-23_IGHD5-5*01(2)>1'_IGHJ2*01	2420
564	gi|Fabrus|VH3-23_IGHD5-5*01(2)>3'_IGHJ2*01	2421
565	gi|Fabrus|VH3-23_IGHD5-12*01>1'_IGHJ2*01	2422
566	gi|Fabrus|VH3-23_IGHD5-12*01>3'_IGHJ2*01	2423
567	gi|Fabrus|VH3-23_IGHD5-18*01(2)>1'_IGHJ2*01	2424
568	gi|Fabrus|VH3-23_IGHD5-18*01(2)>3'_IGHJ2*01	2425
569	gi|Fabrus|VH3-23_IGHD5-24*01>1'_IGHJ2*01	2426
570	gi|Fabrus|VH3-23_IGHD5-24*01>3'_IGHJ2*01	2427
571	gi|Fabrus|VH3-23_IGHD6-6*01>1'_IGHJ2*01	2428
572	gi|Fabrus|VH3-23_IGHD6-6*01>2'_IGHJ2*01	2429
573	gi|Fabrus|VH3-23_IGHD6-6*01>3'_IGHJ2*01	2430
574	gi|Fabrus|VH3-23_IGHD6-13*01>1'_IGHJ2*01	2431
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576	gi|Fabrus|VH3-23_IGHD6-13*01>3'_IGHJ2*01	2433
577	gi|Fabrus|VH3-23_IGHD6-19*01>1'_IGHJ2*01	2434
578	gi|Fabrus|VH3-23_IGHD6-19*01>2'_IGHJ2*01	2435
579	gi|Fabrus|VH3-23_IGHD6-19*01>3'_IGHJ2*01	2436
580	gi|Fabrus|VH3-23_IGHD6-25*01>1'_IGHJ2*01	2437
581	gi|Fabrus|VH3-23_IGHD6-25*01>3'_IGHJ2*01	2438
582	gi|Fabrus|VH3-23_IGHD7-27*01>1'_IGHJ2*01	2439
583	gi|Fabrus|VH3-23_IGHD7-27*01>2'_IGHJ2*01	2440
584	gi|Fabrus|VH3-23_IGHD1-1*01>1_IGHJ3*01	2441
585	gi|Fabrus|VH3-23_IGHD1-1*01>2_IGHJ3*01	2442
586	gi|Fabrus|VH3-23_IGHD1-1*01>3_IGHJ3*01	2443
587	gi|Fabrus|VH3-23_IGHD1-7*01>1_IGHJ3*01	2444
588	gi|Fabrus|VH3-23_IGHD1-7*01>3_IGHJ3*01	2445

589	gi|Fabrus|VH3-23_IGHD1-14*01>1_IGHJ3*01	2446
590	gi|Fabrus|VH3-23_IGHD1-14*01>3_IGHJ3*01	2447
591	gi|Fabrus|VH3-23_IGHD1-20*01>1_IGHJ3*01	2448
592	gi|Fabrus|VH3-23_IGHD1-20*01>3_IGHJ3*01	2449
593	gi|Fabrus|VH3-23_IGHD1-26*01>1_IGHJ3*01	2450
594	gi|Fabrus|VH3-23_IGHD1-26*01>3_IGHJ3*01	2451
595	gi|Fabrus|VH3-23_IGHD2-2*01>2_IGHJ3*01	2452
596	gi|Fabrus|VH3-23_IGHD2-2*01>3_IGHJ3*01	2453
597	gi|Fabrus|VH3-23_IGHD2-8*01>2_IGHJ3*01	2454
598	gi|Fabrus|VH3-23_IGHD2-8*01>3_IGHJ3*01	2455
599	gi|Fabrus|VH3-23_IGHD2-15*01>2_IGHJ3*01	2456
600	gi|Fabrus|VH3-23_IGHD2-15*01>3_IGHJ3*01	2457
601	gi|Fabrus|VH3-23_IGHD2-21*01>2_IGHJ3*01	2458
602	gi|Fabrus|VH3-23_IGHD2-21*01>3_IGHJ3*01	2459
603	gi|Fabrus|VH3-23_IGHD3-3*01>1_IGHJ3*01	2460
604	gi|Fabrus|VH3-23_IGHD3-3*01>2_IGHJ3*01	2461
605	gi|Fabrus|VH3-23_IGHD3-3*01>3_IGHJ3*01	2462
606	gi|Fabrus|VH3-23_IGHD3-9*01>2_IGHJ3*01	2463
607	gi|Fabrus|VH3-23_IGHD3-10*01>2_IGHJ3*01	2464
608	gi|Fabrus|VH3-23_IGHD3-10*01>3_IGHJ3*01	2465
609	gi|Fabrus|VH3-23_IGHD3-16*01>2_IGHJ3*01	2466
610	gi|Fabrus|VH3-23_IGHD3-16*01>3_IGHJ3*01	2467
611	gi|Fabrus|VH3-23_IGHD3-22*01>2_IGHJ3*01	2468
612	gi|Fabrus|VH3-23_IGHD3-22*01>3_IGHJ3*01	2469
613	gi|Fabrus|VH3-23_IGHD4-4*01(1)>2_IGHJ3*01	2470
614	gi|Fabrus|VH3-23_IGHD4-4*01(1)>3_IGHJ3*01	2471
615	gi|Fabrus|VH3-23_IGHD4-11*01(1)>2_IGHJ3*01	2472
616	gi|Fabrus|VH3-23_IGHD4-11*01(1)>3_IGHJ3*01	2473
617	gi|Fabrus|VH3-23_IGHD4-17*01>2_IGHJ3*01	2474
618	gi|Fabrus|VH3-23_IGHD4-17*01>3_IGHJ3*01	2475
619	gi|Fabrus|VH3-23_IGHD4-23*01>2_IGHJ3*01	2476
620	gi|Fabrus|VH3-23_IGHD4-23*01>3_IGHJ3*01	2477
621	gi|Fabrus|VH3-23_IGHD5-5*01(2)>1_IGHJ3*01	2478
622	gi|Fabrus|VH3-23_IGHD5-5*01(2)>2_IGHJ3*01	2479
623	gi|Fabrus|VH3-23_IGHD5-5*01(2)>3_IGHJ3*01	2480
624	gi|Fabrus|VH3-23_IGHD5-12*01>1_IGHJ3*01	2481
625	gi|Fabrus|VH3-23_IGHD5-12*01>3_IGHJ3*01	2482
626	gi|Fabrus|VH3-23_IGHD5-18*01(2)>1_IGHJ3*01	2483
627	gi|Fabrus|VH3-23_IGHD5-18*01(2)>2_IGHJ3*01	2484
628	gi|Fabrus|VH3-23_IGHD5-18*01(2)>3_IGHJ3*01	2485
629	gi|Fabrus|VH3-23_IGHD5-24*01>1_IGHJ3*01	2486
630	gi|Fabrus|VH3-23_IGHD5-24*01>3_IGHJ3*01	2487
631	gi|Fabrus|VH3-23_IGHD6-6*01>1_IGHJ3*01	2488
632	gi|Fabrus|VH3-23_IGHD6-6*01>2_IGHJ3*01	2489
633	gi|Fabrus|VH3-23_IGHD6-13*01>1_IGHJ3*01	2490
634	gi|Fabrus|VH3-23_IGHD6-13*01>2_IGHJ3*01	2491
635	gi|Fabrus|VH3-23_IGHD6-19*01>1_IGHJ3*01	2492
636	gi|Fabrus|VH3-23_IGHD6-19*01>2_IGHJ3*01	2493
637	gi|Fabrus|VH3-23_IGHD6-25*01>1_IGHJ3*01	2494
638	gi|Fabrus|VH3-23_IGHD6-25*01>2_IGHJ3*01	2495
639	gi|Fabrus|VH3-23_IGHD7-27*01>1_IGHJ3*01	2496
640	gi|Fabrus|VH3-23_IGHD7-27*01>3_IGHJ3*01	2497
641	gi|Fabrus|VH3-23_IGHD1-1*01>1'_IGHJ3*01	2498
642	gi|Fabrus|VH3-23_IGHD1-1*01>2'_IGHJ3*01	2499
643	gi|Fabrus|VH3-23_IGHD1-1*01>3'_IGHJ3*01	2500

644	gi|Fabrus|VH3-23_IGHD1-7*01>1'_IGHJ3*01	2501
645	gi|Fabrus|VH3-23_IGHD1-7*01>3'_IGHJ3*01	2502
646	gi|Fabrus|VH3-23_IGHD1-14*01>1'_IGHJ3*01	2503
647	gi|Fabrus|VH3-23_IGHD1-14*01>2'_IGHJ3*01	2504
648	gi|Fabrus|VH3-23_IGHD1-14*01>3'_IGHJ3*01	2505
649	gi|Fabrus|VH3-23_IGHD1-20*01>1'_IGHJ3*01	2506
650	gi|Fabrus|VH3-23_IGHD1-20*01>2'_IGHJ3*01	2507
651	gi|Fabrus|VH3-23_IGHD1-20*01>3'_IGHJ3*01	2508
652	gi|Fabrus|VH3-23_IGHD1-26*01>1'_IGHJ3*01	2509
653	gi|Fabrus|VH3-23_IGHD1-26*01>3'_IGHJ3*01	2510
654	gi|Fabrus|VH3-23_IGHD2-2*01>1'_IGHJ3*01	2511
655	gi|Fabrus|VH3-23_IGHD2-2*01>3'_IGHJ3*01	2512
656	gi|Fabrus|VH3-23_IGHD2-8*01>1'_IGHJ3*01	2513
657	gi|Fabrus|VH3-23_IGHD2-15*01>1'_IGHJ3*01	2514
658	gi|Fabrus|VH3-23_IGHD2-15*01>3'_IGHJ3*01	2515
659	gi|Fabrus|VH3-23_IGHD2-21*01>1'_IGHJ3*01	2516
660	gi|Fabrus|VH3-23_IGHD2-21*01>3'_IGHJ3*01	2517
661	gi|Fabrus|VH3-23_IGHD3-3*01>1'_IGHJ3*01	2518
662	gi|Fabrus|VH3-23_IGHD3-3*01>3'_IGHJ3*01	2519
663	gi|Fabrus|VH3-23_IGHD3-9*01>1'_IGHJ3*01	2520
664	gi|Fabrus|VH3-23_IGHD3-9*01>3'_IGHJ3*01	2521
665	gi|Fabrus|VH3-23_IGHD3-10*01>1'_IGHJ3*01	105
666	gi|Fabrus|VH3-23_IGHD3-10*01>3'_IGHJ3*01	2522
667	gi|Fabrus|VH3-23_IGHD3-16*01>1'_IGHJ3*01	2523
668	gi|Fabrus|VH3-23_IGHD3-16*01>3'_IGHJ3*01	2524
669	gi|Fabrus|VH3-23_IGHD3-22*01>1'_IGHJ3*01	2525
670	gi|Fabrus|VH3-23_IGHD4-4*01(1)>1'_IGHJ3*01	2526
671	gi|Fabrus|VH3-23_IGHD4-4*01(1)>3'_IGHJ3*01	2527
672	gi|Fabrus|VH3-23_IGHD4-11*01(1)>1'_IGHJ3*01	2528
673	gi|Fabrus|VH3-23_IGHD4-11*01(1)>3'_IGHJ3*01	2529
674	gi|Fabrus|VH3-23_IGHD4-17*01>1'_IGHJ3*01	2530
675	gi|Fabrus|VH3-23_IGHD4-17*01>3'_IGHJ3*01	2531
676	gi|Fabrus|VH3-23_IGHD4-23*01>1'_IGHJ3*01	2532
677	gi|Fabrus|VH3-23_IGHD4-23*01>3'_IGHJ3*01	2533
678	gi|Fabrus|VH3-23_IGHD5-5*01(2)>1'_IGHJ3*01	2534
679	gi|Fabrus|VH3-23_IGHD5-5*01(2)>3'_IGHJ3*01	2535
680	gi|Fabrus|VH3-23_IGHD5-12*01>1'_IGHJ3*01	2536
681	gi|Fabrus|VH3-23_IGHD5-12*01>3'_IGHJ3*01	2537
682	gi|Fabrus|VH3-23_IGHD5-18*01(2)>1'_IGHJ3*01	2538
683	gi|Fabrus|VH3-23_IGHD5-18*01(2)>3'_IGHJ3*01	2539
684	gi|Fabrus|VH3-23_IGHD5-24*01>1'_IGHJ3*01	2540
685	gi|Fabrus|VH3-23_IGHD5-24*01>3'_IGHJ3*01	2541
686	gi|Fabrus|VH3-23_IGHD6-6*01>1'_IGHJ3*01	2542
687	gi|Fabrus|VH3-23_IGHD6-6*01>2'_IGHJ3*01	2543
688	gi|Fabrus|VH3-23_IGHD6-6*01>3'_IGHJ3*01	2544
689	gi|Fabrus|VH3-23_IGHD6-13*01>1'_IGHJ3*01	2545
690	gi|Fabrus|VH3-23_IGHD6-13*01>2'_IGHJ3*01	2546
691	gi|Fabrus|VH3-23_IGHD6-13*01>3'_IGHJ3*01	2547
692	gi|Fabrus|VH3-23_IGHD6-19*01>1'_IGHJ3*01	2548
693	gi|Fabrus|VH3-23_IGHD6-19*01>2'_IGHJ3*01	2549
694	gi|Fabrus|VH3-23_IGHD6-19*01>3'_IGHJ3*01	2550
695	gi|Fabrus|VH3-23_IGHD6-25*01>1'_IGHJ3*01	2551
696	gi|Fabrus|VH3-23_IGHD6-25*01>3'_IGHJ3*01	2552
697	gi|Fabrus|VH3-23_IGHD7-27*01>1'_IGHJ3*01	2553
698	gi|Fabrus|VH3-23_IGHD7-27*01>2'_IGHJ3*01	2554

699	gi|Fabrus|VH3-23_IGHD1-1*01>1_IGHJ4*01	2555
700	gi|Fabrus|VH3-23_IGHD1-1*01>2_IGHJ4*01	2556
701	gi|Fabrus|VH3-23_IGHD1-1*01>3_IGHJ4*01	2557
702	gi|Fabrus|VH3-23_IGHD1-7*01>1_IGHJ4*01	2558
703	gi|Fabrus|VH3-23_IGHD1-7*01>3_IGHJ4*01	2559
704	gi|Fabrus|VH3-23_IGHD1-14*01>1_IGHJ4*01	2560
705	gi|Fabrus|VH3-23_IGHD1-14*01>3_IGHJ4*01	2561
706	gi|Fabrus|VH3-23_IGHD1-20*01>1_IGHJ4*01	2562
707	gi|Fabrus|VH3-23_IGHD1-20*01>3_IGHJ4*01	2563
708	gi|Fabrus|VH3-23_IGHD1-26*01>1_IGHJ4*01	2564
709	gi|Fabrus|VH3-23_IGHD1-26*01>3_IGHJ4*01	2565
710	gi|Fabrus|VH3-23_IGHD2-2*01>2_IGHJ4*01	2566
711	gi|Fabrus|VH3-23_IGHD2-2*01>3_IGHJ4*01	2567
712	gi|Fabrus|VH3-23_IGHD2-8*01>2_IGHJ4*01	2568
713	gi|Fabrus|VH3-23_IGHD2-8*01>3_IGHJ4*01	2569
714	gi|Fabrus|VH3-23_IGHD2-15*01>2_IGHJ4*01	2570
715	gi|Fabrus|VH3-23_IGHD2-15*01>3_IGHJ4*01	2571
716	gi|Fabrus|VH3-23_IGHD2-21*01>2_IGHJ4*01	2572
717	gi|Fabrus|VH3-23_IGHD2-21*01>3_IGHJ4*01	2573
718	gi|Fabrus|VH3-23_IGHD3-3*01>1_IGHJ4*01	2574
719	gi|Fabrus|VH3-23_IGHD3-3*01>2_IGHJ4*01	2575
720	gi|Fabrus|VH3-23_IGHD3-3*01>3_IGHJ4*01	2576
721	gi|Fabrus|VH3-23_IGHD3-9*01>2_IGHJ4*01	2577
722	gi|Fabrus|VH3-23_IGHD3-10*01>2_IGHJ4*01	2578
723	gi|Fabrus|VH3-23_IGHD3-10*01>3_IGHJ4*01	2579
724	gi|Fabrus|VH3-23_IGHD3-16*01>2_IGHJ4*01	2580
725	gi|Fabrus|VH3-23_IGHD3-16*01>3_IGHJ4*01	2581
726	gi|Fabrus|VH3-23_IGHD3-22*01>2_IGHJ4*01	2582
727	gi|Fabrus|VH3-23_IGHD3-22*01>3_IGHJ4*01	2583
728	gi|Fabrus|VH3-23_IGHD4-4*01(1)>2_IGHJ4*01	2584
729	gi|Fabrus|VH3-23_IGHD4-4*01(1)>3_IGHJ4*01	2585
730	gi|Fabrus|VH3-23_IGHD4-11*01(1)>2_IGHJ4*01	2586
731	gi|Fabrus|VH3-23_IGHD4-11*01(1)>3_IGHJ4*01	2587
732	gi|Fabrus|VH3-23_IGHD4-17*01>2_IGHJ4*01	2588
733	gi|Fabrus|VH3-23_IGHD4-17*01>3_IGHJ4*01	2589
734	gi|Fabrus|VH3-23_IGHD4-23*01>2_IGHJ4*01	2590
735	gi|Fabrus|VH3-23_IGHD4-23*01>3_IGHJ4*01	2591
736	gi|Fabrus|VH3-23_IGHD5-5*01(2)>1_IGHJ4*01	2592
737	gi|Fabrus|VH3-23_IGHD5-5*01(2)>2_IGHJ4*01	2593
738	gi|Fabrus|VH3-23_IGHD5-5*01(2)>3_IGHJ4*01	2594
739	gi|Fabrus|VH3-23_IGHD5-12*01>1_IGHJ4*01	2595
740	gi|Fabrus|VH3-23_IGHD5-12*01>3_IGHJ4*01	2596
741	gi|Fabrus|VH3-23_IGHD5-18*01(2)>1_IGHJ4*01	2597
742	gi|Fabrus|VH3-23_IGHD5-18*01(2)>2_IGHJ4*01	2598
743	gi|Fabrus|VH3-23_IGHD5-18*01(2)>3_IGHJ4*01	2599
744	gi|Fabrus|VH3-23_IGHD5-24*01>1_IGHJ4*01	2600
745	gi|Fabrus|VH3-23_IGHD5-24*01>3_IGHJ4*01	2601
746	gi|Fabrus|VH3-23_IGHD6-6*01>1_IGHJ4*01	2602
747	gi|Fabrus|VH3-23_IGHD6-6*01>2_IGHJ4*01	2603
748	gi|Fabrus|VH3-23_IGHD6-13*01>1_IGHJ4*01	2604
749	gi|Fabrus|VH3-23_IGHD6-13*01>2_IGHJ4*01	2605
750	gi|Fabrus|VH3-23_IGHD6-19*01>1_IGHJ4*01	2606
751	gi|Fabrus|VH3-23_IGHD6-19*01>2_IGHJ4*01	2607
752	gi|Fabrus|VH3-23_IGHD6-25*01>1_IGHJ4*01	2608
753	gi|Fabrus|VH3-23_IGHD6-25*01>2_IGHJ4*01	2609

754	gi|Fabrus|VH3-23_IGHD7-27*01>1_IGHJ4*01	2610
755	gi|Fabrus|VH3-23_IGHD7-27*01>3_IGHJ4*01	2611
756	gi|Fabrus|VH3-23_IGHD1-1*01>1'_IGHJ4*01	2612
757	gi|Fabrus|VH3-23_IGHD1-1*01>2'_IGHJ4*01	2613
758	gi|Fabrus|VH3-23_IGHD1-1*01>3'_IGHJ4*01	2614
759	gi|Fabrus|VH3-23_IGHD1-7*01>1'_IGHJ4*01	2615
760	gi|Fabrus|VH3-23_IGHD1-7*01>3'_IGHJ4*01	2616
761	gi|Fabrus|VH3-23_IGHD1-14*01>1'_IGHJ4*01	2617
762	gi|Fabrus|VH3-23_IGHD1-14*01>2'_IGHJ4*01	2618
763	gi|Fabrus|VH3-23_IGHD1-14*01>3'_IGHJ4*01	2619
764	gi|Fabrus|VH3-23_IGHD1-20*01>1'_IGHJ4*01	2620
765	gi|Fabrus|VH3-23_IGHD1-20*01>2'_IGHJ4*01	2621
766	gi|Fabrus|VH3-23_IGHD1-20*01>3'_IGHJ4*01	2622
767	gi|Fabrus|VH3-23_IGHD1-26*01>1'_IGHJ4*01	2623
768	gi|Fabrus|VH3-23_IGHD1-26*01>3'_IGHJ4*01	2624
769	gi|Fabrus|VH3-23_IGHD2-2*01>1'_IGHJ4*01	2625
770	gi|Fabrus|VH3-23_IGHD2-2*01>3'_IGHJ4*01	2626
771	gi|Fabrus|VH3-23_IGHD2-8*01>1'_IGHJ4*01	2627
772	gi|Fabrus|VH3-23_IGHD2-15*01>1'_IGHJ4*01	2628
773	gi|Fabrus|VH3-23_IGHD2-15*01>3'_IGHJ4*01	2629
774	gi|Fabrus|VH3-23_IGHD2-21*01>1'_IGHJ4*01	2630
775	gi|Fabrus|VH3-23_IGHD2-21*01>3'_IGHJ4*01	2631
776	gi|Fabrus|VH3-23_IGHD3-3*01>1'_IGHJ4*01	2632
777	gi|Fabrus|VH3-23_IGHD3-3*01>3'_IGHJ4*01	2633
778	gi|Fabrus|VH3-23_IGHD3-9*01>1'_IGHJ4*01	2634
779	gi|Fabrus|VH3-23_IGHD3-9*01>3'_IGHJ4*01	2635
780	gi|Fabrus|VH3-23_IGHD3-10*01>1'_IGHJ4*01	2636
781	gi|Fabrus|VH3-23_IGHD3-10*01>3'_IGHJ4*01	2637
782	gi|Fabrus|VH3-23_IGHD3-16*01>1'_IGHJ4*01	2638
783	gi|Fabrus|VH3-23_IGHD3-16*01>3'_IGHJ4*01	2639
784	gi|Fabrus|VH3-23_IGHD3-22*01>1'_IGHJ4*01	2640
785	gi|Fabrus|VH3-23_IGHD4-4*01(1)>1'_IGHJ4*01	2641
786	gi|Fabrus|VH3-23_IGHD4-4*01(1)>3'_IGHJ4*01	2642
787	gi|Fabrus|VH3-23_IGHD4-11*01(1)>1'_IGHJ4*01	2643
788	gi|Fabrus|VH3-23_IGHD4-11*01(1)>3'_IGHJ4*01	2644
789	gi|Fabrus|VH3-23_IGHD4-17*01>1'_IGHJ4*01	2645
790	gi|Fabrus|VH3-23_IGHD4-17*01>3'_IGHJ4*01	2646
791	gi|Fabrus|VH3-23_IGHD4-23*01>1'_IGHJ4*01	2647
792	gi|Fabrus|VH3-23_IGHD4-23*01>3'_IGHJ4*01	2648
793	gi|Fabrus|VH3-23_IGHD5-5*01(2)>1'_IGHJ4*01	2649
794	gi|Fabrus|VH3-23_IGHD5-5*01(2)>3'_IGHJ4*01	2650
795	gi|Fabrus|VH3-23_IGHD5-12*01>1'_IGHJ4*01	2651
796	gi|Fabrus|VH3-23_IGHD5-12*01>3'_IGHJ4*01	2652
797	gi|Fabrus|VH3-23_IGHD5-18*01(2)>1'_IGHJ4*01	2653
798	gi|Fabrus|VH3-23_IGHD5-18*01(2)>3'_IGHJ4*01	2654
799	gi|Fabrus|VH3-23_IGHD5-24*01>1'_IGHJ4*01	2655
800	gi|Fabrus|VH3-23_IGHD5-24*01>3'_IGHJ4*01	2656
801	gi|Fabrus|VH3-23_IGHD6-6*01>1'_IGHJ4*01	2657
802	gi|Fabrus|VH3-23_IGHD6-6*01>2'_IGHJ4*01	2658
803	gi|Fabrus|VH3-23_IGHD6-6*01>3'_IGHJ4*01	2659
804	gi|Fabrus|VH3-23_IGHD6-13*01>1'_IGHJ4*01	2660
805	gi|Fabrus|VH3-23_IGHD6-13*01>2'_IGHJ4*01	2661
806	gi|Fabrus|VH3-23_IGHD6-13*01>3'_IGHJ4*01	2662
807	gi|Fabrus|VH3-23_IGHD6-19*01>1'_IGHJ4*01	2663
808	gi|Fabrus|VH3-23_IGHD6-19*01>2'_IGHJ4*01	2664

809	gi|Fabrus|VH3-23_IGHD6-19*01>3'_IGHJ4*01	2665
810	gi|Fabrus|VH3-23_IGHD6-25*01>1'_IGHJ4*01	2666
811	gi|Fabrus|VH3-23_IGHD6-25*01>3'_IGHJ4*01	2667
812	gi|Fabrus|VH3-23_IGHD7-27*01>1'_IGHJ4*01	2668
813	gi|Fabrus|VH3-23_IGHD7-27*01>2'_IGHJ4*01	2669
814	gi|Fabrus|VH3-23_IGHD1-1*01>1_IGHJ5*01	2670
815	gi|Fabrus|VH3-23_IGHD1-1*01>2_IGHJ5*01	2671
816	gi|Fabrus|VH3-23_IGHD1-1*01>3_IGHJ5*01	2672
817	gi|Fabrus|VH3-23_IGHD1-7*01>1_IGHJ5*01	2673
818	gi|Fabrus|VH3-23_IGHD1-7*01>3_IGHJ5*01	2674
819	gi|Fabrus|VH3-23_IGHD1-14*01>1_IGHJ5*01	2675
820	gi|Fabrus|VH3-23_IGHD1-14*01>3_IGHJ5*01	2676
821	gi|Fabrus|VH3-23_IGHD1-20*01>1_IGHJ5*01	2677
822	gi|Fabrus|VH3-23_IGHD1-20*01>3_IGHJ5*01	2678
823	gi|Fabrus|VH3-23_IGHD1-26*01>1_IGHJ5*01	2679
824	gi|Fabrus|VH3-23_IGHD1-26*01>3_IGHJ5*01	2680
825	gi|Fabrus|VH3-23_IGHD2-2*01>2_IGHJ5*01	2681
826	gi|Fabrus|VH3-23_IGHD2-2*01>3_IGHJ5*01	2682
827	gi|Fabrus|VH3-23_IGHD2-8*01>2_IGHJ5*01	2683
828	gi|Fabrus|VH3-23_IGHD2-8*01>3_IGHJ5*01	2684
829	gi|Fabrus|VH3-23_IGHD2-15*01>2_IGHJ5*01	2685
830	gi|Fabrus|VH3-23_IGHD2-15*01>3_IGHJ5*01	2686
831	gi|Fabrus|VH3-23_IGHD2-21*01>2_IGHJ5*01	2687
832	gi|Fabrus|VH3-23_IGHD2-21*01>3_IGHJ5*01	2688
833	gi|Fabrus|VH3-23_IGHD3-3*01>1_IGHJ5*01	2689
834	gi|Fabrus|VH3-23_IGHD3-3*01>2_IGHJ5*01	2690
835	gi|Fabrus|VH3-23_IGHD3-3*01>3_IGHJ5*01	2691
836	gi|Fabrus|VH3-23_IGHD3-9*01>2_IGHJ5*01	2692
837	gi|Fabrus|VH3-23_IGHD3-10*01>2_IGHJ5*01	2693
838	gi|Fabrus|VH3-23_IGHD3-10*01>3_IGHJ5*01	2694
839	gi|Fabrus|VH3-23_IGHD3-16*01>2_IGHJ5*01	2695
840	gi|Fabrus|VH3-23_IGHD3-16*01>3_IGHJ5*01	2696
841	gi|Fabrus|VH3-23_IGHD3-22*01>2_IGHJ5*01	2697
842	gi|Fabrus|VH3-23_IGHD3-22*01>3_IGHJ5*01	2698
843	gi|Fabrus|VH3-23_IGHD4-4*01(1)>2_IGHJ5*01	2699
844	gi|Fabrus|VH3-23_IGHD4-4*01(1)>3_IGHJ5*01	2700
845	gi|Fabrus|VH3-23_IGHD4-11*01(1)>2_IGHJ5*01	2701
846	gi|Fabrus|VH3-23_IGHD4-11*01(1)>3_IGHJ5*01	2702
847	gi|Fabrus|VH3-23_IGHD4-17*01>2_IGHJ5*01	2703
848	gi|Fabrus|VH3-23_IGHD4-17*01>3_IGHJ5*01	2704
849	gi|Fabrus|VH3-23_IGHD4-23*01>2_IGHJ5*01	2705
850	gi|Fabrus|VH3-23_IGHD4-23*01>3_IGHJ5*01	2706
851	gi|Fabrus|VH3-23_IGHD5-5*01(2)>1_IGHJ5*01	2707
852	gi|Fabrus|VH3-23_IGHD5-5*01(2)>2_IGHJ5*01	2708
853	gi|Fabrus|VH3-23_IGHD5-5*01(2)>3_IGHJ5*01	2709
854	gi|Fabrus|VH3-23_IGHD5-12*01>1_IGHJ5*01	2710
855	gi|Fabrus|VH3-23_IGHD5-12*01>3_IGHJ5*01	2711
856	gi|Fabrus|VH3-23_IGHD5-18*01(2)>1_IGHJ5*01	2712
857	gi|Fabrus|VH3-23_IGHD5-18*01(2)>2_IGHJ5*01	2713
858	gi|Fabrus|VH3-23_IGHD5-18*01(2)>3_IGHJ5*01	2714
859	gi|Fabrus|VH3-23_IGHD5-24*01>1_IGHJ5*01	2715
860	gi|Fabrus|VH3-23_IGHD5-24*01>3_IGHJ5*01	2716
861	gi|Fabrus|VH3-23_IGHD6-6*01>1_IGHJ5*01	2717
862	gi|Fabrus|VH3-23_IGHD6-6*01>2_IGHJ5*01	2718
863	gi|Fabrus|VH3-23_IGHD6-13*01>1_IGHJ5*01	2719

864	gi|Fabrus|VH3-23_IGHD6-13*01>2_IGHJ5*01	2720
865	gi|Fabrus|VH3-23_IGHD6-19*01>1_IGHJ5*01	2721
866	gi|Fabrus|VH3-23_IGHD6-19*01>2_IGHJ5*01	2722
867	gi|Fabrus|VH3-23_IGHD6-25*01>1_IGHJ5*01	2723
868	gi|Fabrus|VH3-23_IGHD6-25*01>2_IGHJ5*01	2724
869	gi|Fabrus|VH3-23_IGHD7-27*01>1_IGHJ5*01	2725
870	gi|Fabrus|VH3-23_IGHD7-27*01>3_IGHJ5*01	2726
871	gi|Fabrus|VH3-23_IGHD1-1*01>1'_IGHJ5*01	2727
872	gi|Fabrus|VH3-23_IGHD1-1*01>2'_IGHJ5*01	2728
873	gi|Fabrus|VH3-23_IGHD1-1*01>3'_IGHJ5*01	2729
874	gi|Fabrus|VH3-23_IGHD1-7*01>1'_IGHJ5*01	2730
875	gi|Fabrus|VH3-23_IGHD1-7*01>3'_IGHJ5*01	2731
876	gi|Fabrus|VH3-23_IGHD1-14*01>1'_IGHJ5*01	2732
877	gi|Fabrus|VH3-23_IGHD1-14*01>2'_IGHJ5*01	2733
878	gi|Fabrus|VH3-23_IGHD1-14*01>3'_IGHJ5*01	2734
879	gi|Fabrus|VH3-23_IGHD1-20*01>1'_IGHJ5*01	2735
880	gi|Fabrus|VH3-23_IGHD1-20*01>2'_IGHJ5*01	2736
881	gi|Fabrus|VH3-23_IGHD1-20*01>3'_IGHJ5*01	2737
882	gi|Fabrus|VH3-23_IGHD1-26*01>1'_IGHJ5*01	2738
883	gi|Fabrus|VH3-23_IGHD1-26*01>3'_IGHJ5*01	2739
884	gi|Fabrus|VH3-23_IGHD2-2*01>1'_IGHJ5*01	2740
885	gi|Fabrus|VH3-23_IGHD2-2*01>3'_IGHJ5*01	2741
886	gi|Fabrus|VH3-23_IGHD2-8*01>1'_IGHJ5*01	2742
887	gi|Fabrus|VH3-23_IGHD2-15*01>1'_IGHJ5*01	2743
888	gi|Fabrus|VH3-23_IGHD2-15*01>3'_IGHJ5*01	2744
889	gi|Fabrus|VH3-23_IGHD2-21*01>1'_IGHJ5*01	2745
890	gi|Fabrus|VH3-23_IGHD2-21*01>3'_IGHJ5*01	2746
891	gi|Fabrus|VH3-23_IGHD3-3*01>1'_IGHJ5*01	2747
892	gi|Fabrus|VH3-23_IGHD3-3*01>3'_IGHJ5*01	2748
893	gi|Fabrus|VH3-23_IGHD3-9*01>1'_IGHJ5*01	2749
894	gi|Fabrus|VH3-23_IGHD3-9*01>3'_IGHJ5*01	2750
895	gi|Fabrus|VH3-23_IGHD3-10*01>1'_IGHJ5*01	2751
896	gi|Fabrus|VH3-23_IGHD3-10*01>3'_IGHJ5*01	2752
897	gi|Fabrus|VH3-23_IGHD3-16*01>1'_IGHJ5*01	2753
898	gi|Fabrus|VH3-23_IGHD3-16*01>3'_IGHJ5*01	2754
899	gi|Fabrus|VH3-23_IGHD3-22*01>1'_IGHJ5*01	2755
900	gi|Fabrus|VH3-23_IGHD4-4*01(1)>1'_IGHJ5*01	2756
901	gi|Fabrus|VH3-23_IGHD4-4*01(1)>3'_IGHJ5*01	2757
902	gi|Fabrus|VH3-23_IGHD4-11*01(1)>1'_IGHJ5*01	2758
903	gi|Fabrus|VH3-23_IGHD4-11*01(1)>3'_IGHJ5*01	2759
904	gi|Fabrus|VH3-23_IGHD4-17*01>1'_IGHJ5*01	2760
905	gi|Fabrus|VH3-23_IGHD4-17*01>3'_IGHJ5*01	2761
906	gi|Fabrus|VH3-23_IGHD4-23*01>1'_IGHJ5*01	2762
907	gi|Fabrus|VH3-23_IGHD4-23*01>3'_IGHJ5*01	2763
908	gi|Fabrus|VH3-23_IGHD5-5*01(2)>1'_IGHJ5*01	2764
909	gi|Fabrus|VH3-23_IGHD5-5*01(2)>3'_IGHJ5*01	2765
910	gi|Fabrus|VH3-23_IGHD5-12*01>1'_IGHJ5*01	2766
911	gi|Fabrus|VH3-23_IGHD5-12*01>3'_IGHJ5*01	2767
912	gi|Fabrus|VH3-23_IGHD5-18*01(2)>1'_IGHJ5*01	2768
913	gi|Fabrus|VH3-23_IGHD5-18*01(2)>3'_IGHJ5*01	2769
914	gi|Fabrus|VH3-23_IGHD5-24*01>1'_IGHJ5*01	2770
915	gi|Fabrus|VH3-23_IGHD5-24*01>3'_IGHJ5*01	2771
916	gi|Fabrus|VH3-23_IGHD6-6*01>1'_IGHJ5*01	2772
917	gi|Fabrus|VH3-23_IGHD6-6*01>2'_IGHJ5*01	2773
918	gi|Fabrus|VH3-23_IGHD6-6*01>3'_IGHJ5*01	2774

919	gi|Fabrus|VH3-23_IGHD6-13*01>1'_IGHJ5*01	2775
920	gi|Fabrus|VH3-23_IGHD6-13*01>2'_IGHJ5*01	2776
921	gi|Fabrus|VH3-23_IGHD6-13*01>3'_IGHJ5*01	2777
922	gi|Fabrus|VH3-23_IGHD6-19*01>1'_IGHJ5*01	2778
923	gi|Fabrus|VH3-23_IGHD6-19*01>2'_IGHJ5*01	2779
924	gi|Fabrus|VH3-23_IGHD6-19*01>3'_IGHJ5*01	2780
925	gi|Fabrus|VH3-23_IGHD6-25*01>1'_IGHJ5*01	2781
926	gi|Fabrus|VH3-23_IGHD6-25*01>3'_IGHJ5*01	2782
927	gi|Fabrus|VH3-23_IGHD7-27*01>1'_IGHJ5*01	2783
928	gi|Fabrus|VH3-23_IGHD7-27*01>2'_IGHJ5*01	2784
929	gi|Fabrus|VH3-23_IGHD1-1*01>1_IGHJ6*01	2785
930	gi|Fabrus|VH3-23_IGHD1-1*01>2_IGHJ6*01	2786
931	gi|Fabrus|VH3-23_IGHD1-1*01>3_IGHJ6*01	2787
932	gi|Fabrus|VH3-23_IGHD1-7*01>1_IGHJ6*01	2788
933	gi|Fabrus|VH3-23_IGHD1-7*01>3_IGHJ6*01	2789
934	gi|Fabrus|VH3-23_IGHD1-14*01>1_IGHJ6*01	2790
935	gi|Fabrus|VH3-23_IGHD1-14*01>3_IGHJ6*01	2791
936	gi|Fabrus|VH3-23_IGHD1-20*01>1_IGHJ6*01	2792
937	gi|Fabrus|VH3-23_IGHD1-20*01>3_IGHJ6*01	2793
938	gi|Fabrus|VH3-23_IGHD1-26*01>1_IGHJ6*01	2794
939	gi|Fabrus|VH3-23_IGHD1-26*01>3_IGHJ6*01	2795
940	gi|Fabrus|VH3-23_IGHD2-2*01>2_IGHJ6*01	2796
941	gi|Fabrus|VH3-23_IGHD2-2*01>3_IGHJ6*01	2797
942	gi|Fabrus|VH3-23_IGHD2-8*01>2_IGHJ6*01	2798
943	gi|Fabrus|VH3-23_IGHD2-8*01>3_IGHJ6*01	2799
944	gi|Fabrus|VH3-23_IGHD2-15*01>2_IGHJ6*01	2800
945	gi|Fabrus|VH3-23_IGHD2-15*01>3_IGHJ6*01	2801
946	gi|Fabrus|VH3-23_IGHD2-21*01>2_IGHJ6*01	2802
947	gi|Fabrus|VH3-23_IGHD2-21*01>3_IGHJ6*01	2803
948	gi|Fabrus|VH3-23_IGHD3-3*01>1_IGHJ6*01	2804
949	gi|Fabrus|VH3-23_IGHD3-3*01>2_IGHJ6*01	2805
950	gi|Fabrus|VH3-23_IGHD3-3*01>3_IGHJ6*01	2806
951	gi|Fabrus|VH3-23_IGHD3-9*01>2_IGHJ6*01	2807
952	gi|Fabrus|VH3-23_IGHD3-10*01>2_IGHJ6*01	2808
953	gi|Fabrus|VH3-23_IGHD3-10*01>3_IGHJ6*01	104
954	gi|Fabrus|VH3-23_IGHD3-16*01>2_IGHJ6*01	2809
955	gi|Fabrus|VH3-23_IGHD3-16*01>3_IGHJ6*01	2810
956	gi|Fabrus|VH3-23_IGHD3-22*01>2_IGHJ6*01	2811
957	gi|Fabrus|VH3-23_IGHD3-22*01>3_IGHJ6*01	2812
958	gi|Fabrus|VH3-23_IGHD4-4*01(1)>2_IGHJ6*01	2813
959	gi|Fabrus|VH3-23_IGHD4-4*01(1)>3_IGHJ6*01	2814
960	gi|Fabrus|VH3-23_IGHD4-11*01(1)>2_IGHJ6*01	2815
961	gi|Fabrus|VH3-23_IGHD4-11*01(1)>3_IGHJ6*01	2816
962	gi|Fabrus|VH3-23_IGHD4-17*01>2_IGHJ6*01	2817
963	gi|Fabrus|VH3-23_IGHD4-17*01>3_IGHJ6*01	2818
964	gi|Fabrus|VH3-23_IGHD4-23*01>2_IGHJ6*01	2819
965	gi|Fabrus|VH3-23_IGHD4-23*01>3_IGHJ6*01	2820
966	gi|Fabrus|VH3-23_IGHD5-5*01(2)>1_IGHJ6*01	2821
967	gi|Fabrus|VH3-23_IGHD5-5*01(2)>2_IGHJ6*01	2822
968	gi|Fabrus|VH3-23_IGHD5-5*01(2)>3_IGHJ6*01	2823
969	gi|Fabrus|VH3-23_IGHD5-12*01>1_IGHJ6*01	2824
970	gi|Fabrus|VH3-23_IGHD5-12*01>3_IGHJ6*01	2825
971	gi|Fabrus|VH3-23_IGHD5-18*01(2)>1_IGHJ6*01	2826
972	gi|Fabrus|VH3-23_IGHD5-18*01(2)>2_IGHJ6*01	2827
973	gi|Fabrus|VH3-23_IGHD5-18*01(2)>3_IGHJ6*01	2828

974	gi|Fabrus|VH3-23_IGHD5-24*01>1_IGHJ6*01	2829
975	gi|Fabrus|VH3-23_IGHD5-24*01>3_IGHJ6*01	2830
976	gi|Fabrus|VH3-23_IGHD6-6*01>1_IGHJ6*01	2831
977	gi|Fabrus|VH3-23_IGHD6-6*01>2_IGHJ6*01	2832
978	gi|Fabrus|VH3-23_IGHD6-13*01>1_IGHJ6*01	2833
979	gi|Fabrus|VH3-23_IGHD6-13*01>2_IGHJ6*01	2834
980	gi|Fabrus|VH3-23_IGHD6-19*01>1_IGHJ6*01	2835
981	gi|Fabrus|VH3-23_IGHD6-19*01>2_IGHJ6*01	2836
982	gi|Fabrus|VH3-23_IGHD6-25*01>1_IGHJ6*01	2837
983	gi|Fabrus|VH3-23_IGHD6-25*01>2_IGHJ6*01	2838
984	gi|Fabrus|VH3-23_IGHD7-27*01>1_IGHJ6*01	2839
985	gi|Fabrus|VH3-23_IGHD7-27*01>3_IGHJ6*01	2840
986	gi|Fabrus|VH3-23_IGHD1-1*01>1'_IGHJ6*01	2841
987	gi|Fabrus|VH3-23_IGHD1-1*01>2'_IGHJ6*01	2842
988	gi|Fabrus|VH3-23_IGHD1-1*01>3'_IGHJ6*01	2843
989	gi|Fabrus|VH3-23_IGHD1-7*01>1'_IGHJ6*01	2844
990	gi|Fabrus|VH3-23_IGHD1-7*01>3'_IGHJ6*01	2845
991	gi|Fabrus|VH3-23_IGHD1-14*01>1'_IGHJ6*01	2846
992	gi|Fabrus|VH3-23_IGHD1-14*01>2'_IGHJ6*01	2847
993	gi|Fabrus|VH3-23_IGHD1-14*01>3'_IGHJ6*01	2848
994	gi|Fabrus|VH3-23_IGHD1-20*01>1'_IGHJ6*01	2849
995	gi|Fabrus|VH3-23_IGHD1-20*01>2'_IGHJ6*01	2850
996	gi|Fabrus|VH3-23_IGHD1-20*01>3'_IGHJ6*01	2851
997	gi|Fabrus|VH3-23_IGHD1-26*01>1'_IGHJ6*01	2852
998	gi|Fabrus|VH3-23_IGHD1-26*01>3'_IGHJ6*01	2853
999	gi|Fabrus|VH3-23_IGHD2-2*01>1'_IGHJ6*01	2854
1000	gi|Fabrus|VH3-23_IGHD2-2*01>3'_IGHJ6*01	2855
1001	gi|Fabrus|VH3-23_IGHD2-8*01>1'_IGHJ6*01	2856
1002	gi|Fabrus|VH3-23_IGHD2-15*01>1'_IGHJ6*01	2857
1003	gi|Fabrus|VH3-23_IGHD2-15*01>3'_IGHJ6*01	2858
1004	gi|Fabrus|VH3-23_IGHD2-21*01>1'_IGHJ6*01	2859
1005	gi|Fabrus|VH3-23_IGHD2-21*01>3'_IGHJ6*01	2860
1006	gi|Fabrus|VH3-23_IGHD3-3*01>1'_IGHJ6*01	2861
1007	gi|Fabrus|VH3-23_IGHD3-3*01>3'_IGHJ6*01	2862
1008	gi|Fabrus|VH3-23_IGHD3-9*01>1'_IGHJ6*01	2863
1009	gi|Fabrus|VH3-23_IGHD3-9*01>3'_IGHJ6*01	2864
1010	gi|Fabrus|VH3-23_IGHD3-10*01>1'_IGHJ6*01	2865
1011	gi|Fabrus|VH3-23_IGHD3-10*01>3'_IGHJ6*01	2866
1012	gi|Fabrus|VH3-23_IGHD3-16*01>1'_IGHJ6*01	2867
1013	gi|Fabrus|VH3-23_IGHD3-16*01>3'_IGHJ6*01	2868
1014	gi|Fabrus|VH3-23_IGHD3-22*01>1'_IGHJ6*01	2869
1015	gi|Fabrus|VH3-23_IGHD4-4*01(1)>1'_IGHJ6*01	2870
1016	gi|Fabrus|VH3-23_IGHD4-4*01(1)>3'_IGHJ6*01	2871
1017	gi|Fabrus|VH3-23_IGHD4-11*01(1)>1'_IGHJ6*01	2872
1018	gi|Fabrus|VH3-23_IGHD4-11*01(1)>3'_IGHJ6*01	2873
1019	gi|Fabrus|VH3-23_IGHD4-17*01>1'_IGHJ6*01	2874
1020	gi|Fabrus|VH3-23_IGHD4-17*01>3'_IGHJ6*01	2875
1021	gi|Fabrus|VH3-23_IGHD4-23*01>1'_IGHJ6*01	2876
1022	gi|Fabrus|VH3-23_IGHD4-23*01>3'_IGHJ6*01	2877
1023	gi|Fabrus|VH3-23_IGHD5-5*01(2)>1'_IGHJ6*01	2878
1024	gi|Fabrus|VH3-23_IGHD5-5*01(2)>3'_IGHJ6*01	2879
1025	gi|Fabrus|VH3-23_IGHD5-12*01>1'_IGHJ6*01	2880
1026	gi|Fabrus|VH3-23_IGHD5-12*01>3'_IGHJ6*01	2881
1027	gi|Fabrus|VH3-23_IGHD5-18*01(2)>1'_IGHJ6*01	2882
1028	gi|Fabrus|VH3-23_IGHD5-18*01(2)>3'_IGHJ6*01	2883

1029	gi|Fabrus|VH3-23_IGHD5-24*01>1'_IGHJ6*01	2884
1030	gi|Fabrus|VH3-23_IGHD5-24*01>3'_IGHJ6*01	2885
1031	gi|Fabrus|VH3-23_IGHD6-6*01>1'_IGHJ6*01	2886
1032	gi|Fabrus|VH3-23_IGHD6-6*01>2'_IGHJ6*01	2887
1033	gi|Fabrus|VH3-23_IGHD6-6*01>3'_IGHJ6*01	2888
1034	gi|Fabrus|VH3-23_IGHD6-13*01>1'_IGHJ6*01	2889
1035	gi|Fabrus|VH3-23_IGHD6-13*01>2'_IGHJ6*01	2890
1036	gi|Fabrus|VH3-23_IGHD6-13*01>3'_IGHJ6*01	2891
1037	gi|Fabrus|VH3-23_IGHD6-19*01>1'_IGHJ6*01	2892
1038	gi|Fabrus|VH3-23_IGHD6-19*01>2'_IGHJ6*01	2893
1039	gi|Fabrus|VH3-23_IGHD6-19*01>3'_IGHJ6*01	2894
1040	gi|Fabrus|VH3-23_IGHD6-25*01>1'_IGHJ6*01	2895
1041	gi|Fabrus|VH3-23_IGHD6-25*01>3'_IGHJ6*01	2896
1042	gi|Fabrus|VH3-23_IGHD7-27*01>1'_IGHJ6*01	2897
1043	gi|Fabrus|VH3-23_IGHD7-27*01>2'_IGHJ6*01	2898
Light Chains		
Number	Name	SEQ ID NO
1	gnl|Fabrus|A14_IGKJ1*01	2163
2	gnl|Fabrus|A17_IGKJ1*01	113
3	gnl|Fabrus|A2_IGKJ1*01	2164
4	gnl|Fabrus|A20_IGKJ1*01	2165
5	gnl|Fabrus|A23_IGKJ1*01	2166
6	gnl|Fabrus|A26_IGKJ1*01	2167
7	gnl|Fabrus|A27_IGKJ1*01	110
8	gnl|Fabrus|A27_IGKJ3*01	2168
9	gnl|Fabrus|A30_IGKJ1*01	2169
10	gnl|Fabrus|B2_IGKJ1*01	2170
11	gnl|Fabrus|B2_IGKJ3*01	2171
12	gnl|Fabrus|B3_IGKJ1*01	111
14	gnl|Fabrus|L11_IGKJ1*01	2173
15	gnl|Fabrus|L12_IGKJ1*01	115
16	gnl|Fabrus|L14_IGKJ1*01	2174
17	gnl|Fabrus|L2_IGKJ1*01	112
18	gnl|Fabrus|L22_IGKJ3*01	2175
19	gnl|Fabrus|L23_IGKJ1*01	2176
20	gnl|Fabrus|L25_IGKJ1*01	120
21	gnl|Fabrus|L25_IGKJ3*01	2177
22	gnl|Fabrus|L4/18a_IGKJ1*01	2178
23	gnl|Fabrus|L5_IGKJ1*01	114
24	gnl|Fabrus|L6_IGKJ1*01	107
25	gnl|Fabrus|L8_IGKJ1*01	2179
26	gnl|Fabrus|L9_IGKJ2*01	2180
27	gnl|Fabrus|O1_IGKJ1*01	116
28	gnl|Fabrus|O12_IGKJ1*01	119
29	gnl|Fabrus|O18_IGKJ1*01	2181
31	gnl|Fabrus|V1-11_IGLJ2*01	2183
32	gnl|Fabrus|V1-13_IGLJ5*01	2184
33	gnl|Fabrus|V1-16_IGLJ6*01	2185
34	gnl|Fabrus|V1-18_IGLJ2*01	2186
35	gnl|Fabrus|V1-2_IGLJ7*01	2187
36	gnl|Fabrus|V1-20_IGLJ6*01	2188
37	gnl|Fabrus|V1-3_IGLJ1*01	2189
38	gnl|Fabrus|V1-4_IGLJ4*01	117
39	gnl|Fabrus|V1-5_IGLJ2*01	2190
40	gnl|Fabrus|V1-7_IGLJ1*01	2191

41	gnl|Fabrus|V1-9_IGLJ6*01	2192
42	gnl|Fabrus|V2-1_IGLJ6*01	2193
43	gnl|Fabrus|V2-11_IGLJ7*01	2194
44	gnl|Fabrus|V2-13_IGLJ2*01	2195
45	gnl|Fabrus|V2-14_IGLJ4*01	2196
46	gnl|Fabrus|V2-15_IGLJ7*01	2197
47	gnl|Fabrus|V2-17_IGLJ2*01	2198
48	gnl|Fabrus|V2-19_IGLJ4*01	2199
49	gnl|Fabrus|V2-6_IGLJ4*01	2200
50	gnl|Fabrus|V2-7_IGLJ2*01	2201
51	gnl|Fabrus|V2-7_IGLJ7*01	2202
52	gnl|Fabrus|V2-8_IGLJ6*01	2203
53	gnl|Fabrus|V3-2_IGLJ4*01	2204
54	gnl|Fabrus|V3-3_IGLJ7*01	2205
55	gnl|Fabrus|V3-4_IGLJ1*01	108
56	gnl|Fabrus|V4-1_IGLJ4*01	2206
57	gnl|Fabrus|V4-2_IGLJ4*01	2207
58	gnl|Fabrus|V4-3_IGLJ4*01	109
59	gnl|Fabrus|V4-4_IGLJ5*01	2208
60	gnl|Fabrus|V4-6_IGLJ4*01	118
61	gnl|Fabrus|V5-4_IGLJ2*01	2209
62	gnl|Fabrus|V5-6_IGLJ1*01	2210

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1	gnl|Fabrus|VH3-23_IGHD1-1*01_IGHJ4*01	863	gnl|Fabrus|O12_IGKJ1*01	1101
2	gnl|Fabrus|VH3-23_IGHD2-15*01_IGHJ4*01	866	gnl|Fabrus|O12_IGKJ1*01	1101
3	gnl|Fabrus|VH3-23_IGHD3-22*01_IGHJ4*01	870	gnl|Fabrus|O12_IGKJ1*01	1101
4	gnl|Fabrus|VH3-23_IGHD4-11*01_IGHJ4*01	872	gnl|Fabrus|O12_IGKJ1*01	1101
5	gnl|Fabrus|VH3-23_IGHD5-12*01_IGHJ4*01	874	gnl|Fabrus|O12_IGKJ1*01	1101
6	gnl|Fabrus|VH3-23_IGHD5-5*01_IGHJ4*01	876	gnl|Fabrus|O12_IGKJ1*01	1101
7	gnl|Fabrus|VH3-23_IGHD6-13*01_IGHJ4*01	877	gnl|Fabrus|O12_IGKJ1*01	1101
8	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ4*01	880	gnl|Fabrus|O12_IGKJ1*01	1101
9	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ6*01	881	gnl|Fabrus|O12_IGKJ1*01	1101
10	gnl|Fabrus|VH1-69_IGHD1-14*01_IGHJ4*01	770	gnl|Fabrus|O12_IGKJ1*01	1101
11	gnl|Fabrus|VH1-69_IGHD2-2*01_IGHJ4*01	771	gnl|Fabrus|O12_IGKJ1*01	1101
12	gnl|Fabrus|VH1-69_IGHD2-8*01_IGHJ6*01	772	gnl|Fabrus|O12_IGKJ1*01	1101
13	gnl|Fabrus|VH1-69_IGHD3-16*01_IGHJ4*01	773	gnl|Fabrus|O12_IGKJ1*01	1101
14	gnl|Fabrus|VH1-69_IGHD3-3*01_IGHJ4*01	774	gnl|Fabrus|O12_IGKJ1*01	1101
15	gnl|Fabrus|VH1-69_IGHD4-17*01_IGHJ4*01	776	gnl|Fabrus|O12_IGKJ1*01	1101
16	gnl|Fabrus|VH1-69_IGHD5-12*01_IGHJ4*01	777	gnl|Fabrus|O12_IGKJ1*01	1101
17	gnl|Fabrus|VH1-69_IGHD6-19*01_IGHJ4*01	779	gnl|Fabrus|O12_IGKJ1*01	1101
18	gnl|Fabrus|VH1-69_IGHD7-27*01_IGHJ4*01	781	gnl|Fabrus|O12_IGKJ1*01	1101
19	gnl|Fabrus|VH4-34_IGHD1-7*01_IGHJ4*01	1017	gnl|Fabrus|O12_IGKJ1*01	1101
20	gnl|Fabrus|VH4-34_IGHD2-2*01_IGHJ4*01	1018	gnl|Fabrus|O12_IGKJ1*01	1101
21	gnl|Fabrus|VH4-34_IGHD3-16*01_IGHJ4*01	1019	gnl|Fabrus|O12_IGKJ1*01	1101

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
22	gnl|Fabrus|VH4-34_IGHD4-17*01_IGHJ4*01	1021	gnl|Fabrus|O12_IGKJ1*01	1101
23	gnl|Fabrus|VH4-34_IGHD5-12*01_IGHJ4*01	1022	gnl|Fabrus|O12_IGKJ1*01	1101
24	gnl|Fabrus|VH4-34_IGHD6-13*01_IGHJ4*01	1023	gnl|Fabrus|O12_IGKJ1*01	1101
25	gnl|Fabrus|VH4-34_IGHD6-25*01_IGHJ6*01	1024	gnl|Fabrus|O12_IGKJ1*01	1101
26	gnl|Fabrus|VH4-34_IGHD7-27*01_IGHJ4*01	1026	gnl|Fabrus|O12_IGKJ1*01	1101
27	gnl|Fabrus|VH2-26_IGHD1-20*01_IGHJ4*01	789	gnl|Fabrus|O12_IGKJ1*01	1101
28	gnl|Fabrus|VH2-26_IGHD2-2*01_IGHJ4*01	791	gnl|Fabrus|O12_IGKJ1*01	1101
29	gnl|Fabrus|VH2-26_IGHD3-10*01_IGHJ4*01	792	gnl|Fabrus|O12_IGKJ1*01	1101
30	gnl|Fabrus|VH2-26_IGHD4-11*01_IGHJ4*01	794	gnl|Fabrus|O12_IGKJ1*01	1101
31	gnl|Fabrus|VH2-26_IGHD5-18*01_IGHJ4*01	796	gnl|Fabrus|O12_IGKJ1*01	1101
32	gnl|Fabrus|VH2-26_IGHD6-13*01_IGHJ4*01	797	gnl|Fabrus|O12_IGKJ1*01	1101
33	gnl|Fabrus|VH2-26_IGHD7-27*01_IGHJ4*01	798	gnl|Fabrus|O12_IGKJ1*01	1101
34	gnl|Fabrus|VH5-51_IGHD1-14*01_IGHJ4*01	1044	gnl|Fabrus|O12_IGKJ1*01	1101
35	gnl|Fabrus|VH5-51_IGHD2-8*01_IGHJ4*01	1046	gnl|Fabrus|O12_IGKJ1*01	1101
36	gnl|Fabrus|VH5-51_IGHD3-3*01_IGHJ4*01	1048	gnl|Fabrus|O12_IGKJ1*01	1101
37	gnl|Fabrus|VH5-51_IGHD4-17*01_IGHJ4*01	1049	gnl|Fabrus|O12_IGKJ1*01	1101
38	gnl|Fabrus|VH5-51_IGHD5-18*01>3_IGHJ4*01	1050	gnl|Fabrus|O12_IGKJ1*01	1101
39	gnl|Fabrus|VH5-51_IGHD5-18*01>1_IGHJ4*01	1051	gnl|Fabrus|O12_IGKJ1*01	1101
40	gnl|Fabrus|VH5-51_IGHD6-25*01_IGHJ4*01	1052	gnl|Fabrus|O12_IGKJ1*01	1101
41	gnl|Fabrus|VH5-51_IGHD7-27*01_IGHJ4*01	1053	gnl|Fabrus|O12_IGKJ1*01	1101
42	gnl|Fabrus|VH6-1_IGHD1-1*01_IGHJ4*01	1054	gnl|Fabrus|O12_IGKJ1*01	1101
43	gnl|Fabrus|VH6-1_IGHD2-15*01_IGHJ4*01	1056	gnl|Fabrus|O12_IGKJ1*01	1101
44	gnl|Fabrus|VH6-1_IGHD3-3*01_IGHJ4*01	1059	gnl|Fabrus|O12_IGKJ1*01	1101
45	gnl|Fabrus|VH6-1_IGHD4-23*01_IGHJ4*01	1061	gnl|Fabrus|O12_IGKJ1*01	1101
46	gnl|Fabrus|VH6-1_IGHD4-11*01_IGHJ6*01	1060	gnl|Fabrus|O12_IGKJ1*01	1101
47	gnl|Fabrus|VH6-1_IGHD5-5*01_IGHJ4*01	1062	gnl|Fabrus|O12_IGKJ1*01	1101
48	gnl|Fabrus|VH6-1_IGHD6-13*01_IGHJ4*01	1063	gnl|Fabrus|O12_IGKJ1*01	1101
49	gnl|Fabrus|VH6-1_IGHD6-25*01_IGHJ6*01	1064	gnl|Fabrus|O12_IGKJ1*01	1101
50	gnl|Fabrus|VH6-1_IGHD7-27*01_IGHJ4*01	1065	gnl|Fabrus|O12_IGKJ1*01	1101
51	gnl|Fabrus|VH4-59_IGHD6-25*01_IGHJ3*01	1043	gnl|Fabrus|O12_IGKJ1*01	1101
52	gnl|Fabrus|VH3-48_IGHD6-6*01_IGHJ1*01	923	gnl|Fabrus|O12_IGKJ1*01	1101
53	gnl|Fabrus|VH3-30_IGHD6-6*01_IGHJ1*01	893	gnl|Fabrus|O12_IGKJ1*01	1101
54	gnl|Fabrus|VH3-66_IGHD6-6*01_IGHJ1*01	949	gnl|Fabrus|O12_IGKJ1*01	1101
55	gnl|Fabrus|VH3-53_IGHD5-5*01_IGHJ4*01	938	gnl|Fabrus|O12_IGKJ1*01	1101
56	gnl|Fabrus|VH2-5_IGHD5-12*01_IGHJ4*01	804	gnl|Fabrus|O12_IGKJ1*01	1101
57	gnl|Fabrus|VH2-70_IGHD5-12*01_IGHJ4*01	811	gnl|Fabrus|O12_IGKJ1*01	1101
58	gnl|Fabrus|VH3-15_IGHD5-12*01_IGHJ4*01	835	gnl|Fabrus|O12_IGKJ1*01	1101
59	gnl|Fabrus|VH3-15_IGHD3-10*01_IGHJ4*01	833	gnl|Fabrus|O12_IGKJ1*01	1101
60	gnl|Fabrus|VH3-49_IGHD5-18*01_IGHJ4*01	930	gnl|Fabrus|O12_IGKJ1*01	1101
61	gnl|Fabrus|VH3-49_IGHD6-13*01_IGHJ4*01	931	gnl|Fabrus|O12_IGKJ1*01	1101
62	gnl|Fabrus|VH3-72_IGHD5-18*01_IGHJ4*01	967	gnl|Fabrus|O12_IGKJ1*01	1101

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
63	gnl|Fabrus|VH3-72_IGHD6-6*01_IGHJ1*01	969	gnl|Fabrus|O12_IGKJ1*01	1101
64	gnl|Fabrus|VH3-73_IGHD5-12*01_IGHJ4*01	977	gnl|Fabrus|O12_IGKJ1*01	1101
65	gnl|Fabrus|VH3-73_IGHD4-23*01_IGHJ5*01	976	gnl|Fabrus|O12_IGKJ1*01	1101
66	gnl|Fabrus|VH3-43_IGHD3-22*01_IGHJ4*01	918	gnl|Fabrus|O12_IGKJ1*01	1101
67	gnl|Fabrus|VH3-43_IGHD6-13*01_IGHJ4*01	921	gnl|Fabrus|O12_IGKJ1*01	1101
68	gnl|Fabrus|VH3-9_IGHD3-22*01_IGHJ4*01	992	gnl|Fabrus|O12_IGKJ1*01	1101
69	gnl|Fabrus|VH3-9_IGHD1-7*01_IGHJ5*01	989	gnl|Fabrus|O12_IGKJ1*01	1101
70	gnl|Fabrus|VH3-9_IGHD6-13*01_IGHJ4*01	995	gnl|Fabrus|O12_IGKJ1*01	1101
71	gnl|Fabrus|VH4-39_IGHD3-10*01_IGHJ4*01	1030	gnl|Fabrus|O12_IGKJ1*01	1101
72	gnl|Fabrus|VH4-39_IGHD5-12*01_IGHJ4*01	1034	gnl|Fabrus|O12_IGKJ1*01	1101
73	gnl|Fabrus|VH1-18_IGHD6-6*01_IGHJ1*01	728	gnl|Fabrus|O12_IGKJ1*01	1101
74	gnl|Fabrus|VH1-24_IGHD5-12*01_IGHJ4*01	735	gnl|Fabrus|O12_IGKJ1*01	1101
75	gnl|Fabrus|VH1-2_IGHD1-1*01_IGHJ3*01	729	gnl|Fabrus|O12_IGKJ1*01	1101
76	gnl|Fabrus|VH1-3_IGHD6-6*01_IGHJ1*01	743	gnl|Fabrus|O12_IGKJ1*01	1101
77	gnl|Fabrus|VH1-45_IGHD3-10*01_IGHJ4*01	748	gnl|Fabrus|O12_IGKJ1*01	1101
78	gnl|Fabrus|VH1-46_IGHD1-26*01_IGHJ4*01	754	gnl|Fabrus|O12_IGKJ1*01	1101
79	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ6*01	1068	gnl|Fabrus|O12_IGKJ1*01	1101
80	gnl|Fabrus|VH2-70_IGHD3-9*01_IGHJ6*01	810	gnl|Fabrus|O12_IGKJ1*01	1101
81	gnl|Fabrus|VH1-58_IGHD3-10*01_IGHJ6*01	764	gnl|Fabrus|O12_IGKJ1*01	1101
82	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ2*01	1067	gnl|Fabrus|O12_IGKJ1*01	1101
83	gnl|Fabrus|VH4-28_IGHD3-9*01_IGHJ6*01	1002	gnl|Fabrus|O12_IGKJ1*01	1101
84	gnl|Fabrus|VH4-31_IGHD2-15*01_IGHJ2*01	1008	gnl|Fabrus|O12_IGKJ1*01	1101
85	gnl|Fabrus|VH2-5_IGHD3-9*01_IGHJ6*01	803	gnl|Fabrus|O12_IGKJ1*01	1101
86	gnl|Fabrus|VH1-8_IGHD2-15*01_IGHJ6*01	783	gnl|Fabrus|O12_IGKJ1*01	1101
87	gnl|Fabrus|VH2-70_IGHD2-15*01_IGHJ2*01	808	gnl|Fabrus|O12_IGKJ1*01	1101
88	gnl|Fabrus|VH3-38_IGHD3-10*01_IGHJ4*01	907	gnl|Fabrus|O12_IGKJ1*01	1101
89	gnl|Fabrus|VH3-16_IGHD1-7*01_IGHJ6*01	838	gnl|Fabrus|O12_IGKJ1*01	1101
90	gnl|Fabrus|VH3-73_IGHD3-9*01_IGHJ6*01	974	gnl|Fabrus|O12_IGKJ1*01	1101
91	gnl|Fabrus|VH3-11_IGHD3-9*01_IGHJ6*01	816	gnl|Fabrus|O12_IGKJ1*01	1101
92	gnl|Fabrus|VH3-11_IGHD6-6*01_IGHJ1*01	820	gnl|Fabrus|O12_IGKJ1*01	1101
93	gnl|Fabrus|VH3-20_IGHD5-12*01_IGHJ4*01	852	gnl|Fabrus|O12_IGKJ1*01	1101
94	gnl|Fabrus|VH3-16_IGHD2-15*01_IGHJ2*01	839	gnl|Fabrus|O12_IGKJ1*01	1101
95	gnl|Fabrus|VH3-7_IGHD6-6*01_IGHJ1*01	960	gnl|Fabrus|O12_IGKJ1*01	1101
96	gnl|Fabrus|VH3-16_IGHD6-13*01_IGHJ4*01	844	gnl|Fabrus|O12_IGKJ1*01	1101
97	gnl|Fabrus|VH3-23_IGHD1-1*01_IGHJ4*01	863	gnl|Fabrus|O18_IGKJ1*01	1102
98	gnl|Fabrus|VH3-23_IGHD2-15*01_IGHJ4*01	866	gnl|Fabrus|O18_IGKJ1*01	1102
99	gnl|Fabrus|VH3-23_IGHD3-22*01_IGHJ4*01	870	gnl|Fabrus|O18_IGKJ1*01	1102
100	gnl|Fabrus|VH3-23_IGHD4-11*01_IGHJ4*01	872	gnl|Fabrus|O18_IGKJ1*01	1102
101	gnl|Fabrus|VH3-23_IGHD5-12*01_IGHJ4*01	874	gnl|Fabrus|O18_IGKJ1*01	1102
102	gnl|Fabrus|VH3-23_IGHD5-5*01_IGHJ4*01	876	gnl|Fabrus|O18_IGKJ1*01	1102
103	gnl|Fabrus|VH3-23_IGHD6-13*01_IGHJ4*01	877	gnl|Fabrus|O18_IGKJ1*01	1102
104	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ4*01	880	gnl|Fabrus|O18_IGKJ1*01	1102

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
105	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ6*01	881	gnl|Fabrus|O18_IGKJ1*01	1102
106	gnl|Fabrus|VH1-69_IGHD1-14*01_IGHJ4*01	770	gnl|Fabrus|O18_IGKJ1*01	1102
107	gnl|Fabrus|VH1-69_IGHD2-2*01_IGHJ4*01	771	gnl|Fabrus|O18_IGKJ1*01	1102
108	gnl|Fabrus|VH1-69_IGHD2-8*01_IGHJ6*01	772	gnl|Fabrus|O18_IGKJ1*01	1102
109	gnl|Fabrus|VH1-69_IGHD3-16*01_IGHJ4*01	773	gnl|Fabrus|O18_IGKJ1*01	1102
110	gnl|Fabrus|VH1-69_IGHD3-3*01_IGHJ4*01	774	gnl|Fabrus|O18_IGKJ1*01	1102
111	gnl|Fabrus|VH1-69_IGHD4-17*01_IGHJ4*01	776	gnl|Fabrus|O18_IGKJ1*01	1102
112	gnl|Fabrus|VH1-69_IGHD5-12*01_IGHJ4*01	777	gnl|Fabrus|O18_IGKJ1*01	1102
113	gnl|Fabrus|VH1-69_IGHD6-19*01_IGHJ4*01	779	gnl|Fabrus|O18_IGKJ1*01	1102
114	gnl|Fabrus|VH1-69_IGHD7-27*01_IGHJ4*01	781	gnl|Fabrus|O18_IGKJ1*01	1102
115	gnl|Fabrus|VH4-34_IGHD1-7*01_IGHJ4*01	1017	gnl|Fabrus|O18_IGKJ1*01	1102
116	gnl|Fabrus|VH4-34_IGHD2-2*01_IGHJ4*01	1018	gnl|Fabrus|O18_IGKJ1*01	1102
117	gnl|Fabrus|VH4-34_IGHD3-16*01_IGHJ4*01	1019	gnl|Fabrus|O18_IGKJ1*01	1102
118	gnl|Fabrus|VH4-34_IGHD4-17*01_IGHJ4*01	1021	gnl|Fabrus|O18_IGKJ1*01	1102
119	gnl|Fabrus|VH4-34_IGHD5-12*01_IGHJ4*01	1022	gnl|Fabrus|O18_IGKJ1*01	1102
120	gnl|Fabrus|VH4-34_IGHD6-13*01_IGHJ4*01	1023	gnl|Fabrus|O18_IGKJ1*01	1102
121	gnl|Fabrus|VH4-34_IGHD6-25*01_IGHJ6*01	1024	gnl|Fabrus|O18_IGKJ1*01	1102
122	gnl|Fabrus|VH4-34_IGHD7-27*01_IGHJ4*01	1026	gnl|Fabrus|O18_IGKJ1*01	1102
123	gnl|Fabrus|VH2-26_IGHD1-20*01_IGHJ4*01	789	gnl|Fabrus|O18_IGKJ1*01	1102
124	gnl|Fabrus|VH2-26_IGHD2-2*01_IGHJ4*01	791	gnl|Fabrus|O18_IGKJ1*01	1102
125	gnl|Fabrus|VH2-26_IGHD3-10*01_IGHJ4*01	792	gnl|Fabrus|O18_IGKJ1*01	1102
126	gnl|Fabrus|VH2-26_IGHD4-11*01_IGHJ4*01	794	gnl|Fabrus|O18_IGKJ1*01	1102
127	gnl|Fabrus|VH2-26_IGHD5-18*01_IGHJ4*01	796	gnl|Fabrus|O18_IGKJ1*01	1102
128	gnl|Fabrus|VH2-26_IGHD6-13*01_IGHJ4*01	797	gnl|Fabrus|O18_IGKJ1*01	1102
129	gnl|Fabrus|VH2-26_IGHD7-27*01_IGHJ4*01	798	gnl|Fabrus|O18_IGKJ1*01	1102
130	gnl|Fabrus|VH5-51_IGHD1-14*01_IGHJ4*01	1044	gnl|Fabrus|O18_IGKJ1*01	1102
131	gnl|Fabrus|VH5-51_IGHD2-8*01_IGHJ4*01	1046	gnl|Fabrus|O18_IGKJ1*01	1102
132	gnl|Fabrus|VH5-51_IGHD3-3*01_IGHJ4*01	1048	gnl|Fabrus|O18_IGKJ1*01	1102
133	gnl|Fabrus|VH5-51_IGHD4-17*01_IGHJ4*01	1049	gnl|Fabrus|O18_IGKJ1*01	1102
134	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1050	gnl|Fabrus|O18_IGKJ1*01	1102
135	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1051	gnl|Fabrus|O18_IGKJ1*01	1102
136	gnl|Fabrus|VH5-51_IGHD6-25*01_IGHJ4*01	1052	gnl|Fabrus|O18_IGKJ1*01	1102
137	gnl|Fabrus|VH5-51_IGHD7-27*01_IGHJ4*01	1053	gnl|Fabrus|O18_IGKJ1*01	1102
138	gnl|Fabrus|VH6-1_IGHD1-1*01_IGHJ4*01	1054	gnl|Fabrus|O18_IGKJ1*01	1102
139	gnl|Fabrus|VH6-1_IGHD2-15*01_IGHJ4*01	1056	gnl|Fabrus|O18_IGKJ1*01	1102
140	gnl|Fabrus|VH6-1_IGHD3-3*01_IGHJ4*01	1059	gnl|Fabrus|O18_IGKJ1*01	1102
141	gnl|Fabrus|VH6-1_IGHD4-23*01_IGHJ4*01	1061	gnl|Fabrus|O18_IGKJ1*01	1102
142	gnl|Fabrus|VH6-1_IGHD4-11*01_IGHJ6*01	1060	gnl|Fabrus|O18_IGKJ1*01	1102
143	gnl|Fabrus|VH6-1_IGHD5-5*01_IGHJ4*01	1062	gnl|Fabrus|O18_IGKJ1*01	1102
144	gnl|Fabrus|VH6-1_IGHD6-13*01_IGHJ4*01	1063	gnl|Fabrus|O18_IGKJ1*01	1102
145	gnl|Fabrus|VH6-1_IGHD6-25*01_IGHJ6*01	1064	gnl|Fabrus|O18_IGKJ1*01	1102
146	gnl|Fabrus|VH6-1_IGHD7-27*01_IGHJ4*01	1065	gnl|Fabrus|O18_IGKJ1*01	1102

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
147	gnl|Fabrus|VH4-59_IGHD6-25*01_IGHJ3*01	1043	gnl|Fabrus|O18_IGKJ1*01	1102
148	gnl|Fabrus|VH3-48_IGHD6-6*01_IGHJ1*01	923	gnl|Fabrus|O18_IGKJ1*01	1102
149	gnl|Fabrus|VH3-30_IGHD6-6*01_IGHJ1*01	893	gnl|Fabrus|O18_IGKJ1*01	1102
150	gnl|Fabrus|VH3-66_IGHD6-6*01_IGHJ1*01	949	gnl|Fabrus|O18_IGKJ1*01	1102
151	gnl|Fabrus|VH3-53_IGHD5-5*01_IGHJ4*01	938	gnl|Fabrus|O18_IGKJ1*01	1102
152	gnl|Fabrus|VH2-5_IGHD5-12*01_IGHJ4*01	804	gnl|Fabrus|O18_IGKJ1*01	1102
153	gnl|Fabrus|VH2-70_IGHD5-12*01_IGHJ4*01	811	gnl|Fabrus|O18_IGKJ1*01	1102
154	gnl|Fabrus|VH3-15_IGHD5-12*01_IGHJ4*01	835	gnl|Fabrus|O18_IGKJ1*01	1102
155	gnl|Fabrus|VH3-15_IGHD3-10*01_IGHJ4*01	833	gnl|Fabrus|O18_IGKJ1*01	1102
156	gnl|Fabrus|VH3-49_IGHD5-18*01_IGHJ4*01	930	gnl|Fabrus|O18_IGKJ1*01	1102
157	gnl|Fabrus|VH3-49_IGHD6-13*01_IGHJ4*01	931	gnl|Fabrus|O18_IGKJ1*01	1102
158	gnl|Fabrus|VH3-72_IGHD5-18*01_IGHJ4*01	967	gnl|Fabrus|O18_IGKJ1*01	1102
159	gnl|Fabrus|VH3-72_IGHD6-6*01_IGHJ1*01	969	gnl|Fabrus|O18_IGKJ1*01	1102
160	gnl|Fabrus|VH3-73_IGHD5-12*01_IGHJ4*01	977	gnl|Fabrus|O18_IGKJ1*01	1102
161	gnl|Fabrus|VH3-73_IGHD4-23*01_IGHJ5*01	976	gnl|Fabrus|O18_IGKJ1*01	1102
162	gnl|Fabrus|VH3-43_IGHD3-22*01_IGHJ4*01	918	gnl|Fabrus|O18_IGKJ1*01	1102
163	gnl|Fabrus|VH3-43_IGHD6-13*01_IGHJ4*01	921	gnl|Fabrus|O18_IGKJ1*01	1102
164	gnl|Fabrus|VH3-9_IGHD3-22*01_IGHJ4*01	992	gnl|Fabrus|O18_IGKJ1*01	1102
165	gnl|Fabrus|VH3-9_IGHD1-7*01_IGHJ5*01	989	gnl|Fabrus|O18_IGKJ1*01	1102
166	gnl|Fabrus|VH3-9_IGHD6-13*01_IGHJ4*01	995	gnl|Fabrus|O18_IGKJ1*01	1102
167	gnl|Fabrus|VH4-39_IGHD3-10*01_IGHJ4*01	1030	gnl|Fabrus|O18_IGKJ1*01	1102
168	gnl|Fabrus|VH4-39_IGHD5-12*01_IGHJ4*01	1034	gnl|Fabrus|O18_IGKJ1*01	1102
169	gnl|Fabrus|VH1-18_IGHD6-6*01_IGHJ1*01	728	gnl|Fabrus|O18_IGKJ1*01	1102
170	gnl|Fabrus|VH1-24_IGHD5-12*01_IGHJ4*01	735	gnl|Fabrus|O18_IGKJ1*01	1102
171	gnl|Fabrus|VH1-2_IGHD1-1*01_IGHJ3*01	729	gnl|Fabrus|O18_IGKJ1*01	1102
172	gnl|Fabrus|VH1-3_IGHD6-6*01_IGHJ1*01	743	gnl|Fabrus|O18_IGKJ1*01	1102
173	gnl|Fabrus|VH1-45_IGHD3-10*01_IGHJ4*01	748	gnl|Fabrus|O18_IGKJ1*01	1102
174	gnl|Fabrus|VH1-46_IGHD1-26*01_IGHJ4*01	754	gnl|Fabrus|O18_IGKJ1*01	1102
175	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ6*01	1068	gnl|Fabrus|O18_IGKJ1*01	1102
176	gnl|Fabrus|VH2-70_IGHD3-9*01_IGHJ6*01	810	gnl|Fabrus|O18_IGKJ1*01	1102
177	gnl|Fabrus|VH1-58_IGHD3-10*01_IGHJ6*01	764	gnl|Fabrus|O18_IGKJ1*01	1102
178	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ2*01	1067	gnl|Fabrus|O18_IGKJ1*01	1102
179	gnl|Fabrus|VH4-28_IGHD3-9*01_IGHJ6*01	1002	gnl|Fabrus|O18_IGKJ1*01	1102
180	gnl|Fabrus|VH4-31_IGHD2-15*01_IGHJ2*01	1008	gnl|Fabrus|O18_IGKJ1*01	1102
181	gnl|Fabrus|VH2-5_IGHD3-9*01_IGHJ6*01	803	gnl|Fabrus|O18_IGKJ1*01	1102
182	gnl|Fabrus|VH1-8_IGHD2-15*01_IGHJ6*01	783	gnl|Fabrus|O18_IGKJ1*01	1102
183	gnl|Fabrus|VH2-70_IGHD2-15*01_IGHJ2*01	808	gnl|Fabrus|O18_IGKJ1*01	1102
184	gnl|Fabrus|VH3-38_IGHD3-10*01_IGHJ4*01	907	gnl|Fabrus|O18_IGKJ1*01	1102
185	gnl|Fabrus|VH3-16_IGHD1-7*01_IGHJ6*01	838	gnl|Fabrus|O18_IGKJ1*01	1102
186	gnl|Fabrus|VH3-73_IGHD3-9*01_IGHJ6*01	974	gnl|Fabrus|O18_IGKJ1*01	1102
187	gnl|Fabrus|VH3-11_IGHD3-9*01_IGHJ6*01	816	gnl|Fabrus|O18_IGKJ1*01	1102
188	gnl|Fabrus|VH3-11_IGHD6-6*01_IGHJ1*01	820	gnl|Fabrus|O18_IGKJ1*01	1102

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
189	gnl|Fabrus|VH3-20_IGHD5-12*01_IGHJ4*01	852	gnl|Fabrus|O18_IGKJ1*01	1102
190	gnl|Fabrus|VH3-16_IGHD2-15*01_IGHJ2*01	839	gnl|Fabrus|O18_IGKJ1*01	1102
191	gnl|Fabrus|VH3-7_IGHD6-6*01_IGHJ1*01	960	gnl|Fabrus|O18_IGKJ1*01	1102
192	gnl|Fabrus|VH3-16_IGHD6-13*01_IGHJ4*01	844	gnl|Fabrus|O18_IGKJ1*01	1102
193	gnl|Fabrus|VH3-23_IGHD1-1*01_IGHJ4*01	863	gnl|Fabrus|A20_IGKJ1*01	1077
194	gnl|Fabrus|VH3-23_IGHD2-15*01_IGHJ4*01	866	gnl|Fabrus|A20_IGKJ1*01	1077
195	gnl|Fabrus|VH3-23_IGHD3-22*01_IGHJ4*01	870	gnl|Fabrus|A20_IGKJ1*01	1077
196	gnl|Fabrus|VH3-23_IGHD4-11*01_IGHJ4*01	872	gnl|Fabrus|A20_IGKJ1*01	1077
197	gnl|Fabrus|VH3-23_IGHD5-12*01_IGHJ4*01	874	gnl|Fabrus|A20_IGKJ1*01	1077
198	gnl|Fabrus|VH3-23_IGHD5-5*01_IGHJ4*01	876	gnl|Fabrus|A20_IGKJ1*01	1077
199	gnl|Fabrus|VH3-23_IGHD6-13*01_IGHJ4*01	877	gnl|Fabrus|A20_IGKJ1*01	1077
200	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ4*01	880	gnl|Fabrus|A20_IGKJ1*01	1077
201	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ6*01	881	gnl|Fabrus|A20_IGKJ1*01	1077
202	gnl|Fabrus|VH1-69_IGHD1-14*01_IGHJ4*01	770	gnl|Fabrus|A20_IGKJ1*01	1077
203	gnl|Fabrus|VH1-69_IGHD2-2*01_IGHJ4*01	771	gnl|Fabrus|A20_IGKJ1*01	1077
204	gnl|Fabrus|VH1-69_IGHD2-8*01_IGHJ6*01	772	gnl|Fabrus|A20_IGKJ1*01	1077
205	gnl|Fabrus|VH1-69_IGHD3-16*01_IGHJ4*01	773	gnl|Fabrus|A20_IGKJ1*01	1077
206	gnl|Fabrus|VH1-69_IGHD3-3*01_IGHJ4*01	774	gnl|Fabrus|A20_IGKJ1*01	1077
207	gnl|Fabrus|VH1-69_IGHD4-17*01_IGHJ4*01	776	gnl|Fabrus|A20_IGKJ1*01	1077
208	gnl|Fabrus|VH1-69_IGHD5-12*01_IGHJ4*01	777	gnl|Fabrus|A20_IGKJ1*01	1077
209	gnl|Fabrus|VH1-69_IGHD6-19*01_IGHJ4*01	779	gnl|Fabrus|A20_IGKJ1*01	1077
210	gnl|Fabrus|VH1-69_IGHD7-27*01_IGHJ4*01	781	gnl|Fabrus|A20_IGKJ1*01	1077
211	gnl|Fabrus|VH4-34_IGHD1-7*01_IGHJ4*01	1017	gnl|Fabrus|A20_IGKJ1*01	1077
212	gnl|Fabrus|VH4-34_IGHD2-2*01_IGHJ4*01	1018	gnl|Fabrus|A20_IGKJ1*01	1077
213	gnl|Fabrus|VH4-34_IGHD3-16*01_IGHJ4*01	1019	gnl|Fabrus|A20_IGKJ1*01	1077
214	gnl|Fabrus|VH4-34_IGHD4-17*01_IGHJ4*01	1021	gnl|Fabrus|A20_IGKJ1*01	1077
215	gnl|Fabrus|VH4-34_IGHD5-12*01_IGHJ4*01	1022	gnl|Fabrus|A20_IGKJ1*01	1077
216	gnl|Fabrus|VH4-34_IGHD6-13*01_IGHJ4*01	1023	gnl|Fabrus|A20_IGKJ1*01	1077
217	gnl|Fabrus|VH4-34_IGHD6-25*01_IGHJ6*01	1024	gnl|Fabrus|A20_IGKJ1*01	1077
218	gnl|Fabrus|VH4-34_IGHD7-27*01_IGHJ4*01	1026	gnl|Fabrus|A20_IGKJ1*01	1077
219	gnl|Fabrus|VH2-26_IGHD1-20*01_IGHJ4*01	789	gnl|Fabrus|A20_IGKJ1*01	1077
220	gnl|Fabrus|VH2-26_IGHD2-2*01_IGHJ4*01	791	gnl|Fabrus|A20_IGKJ1*01	1077
221	gnl|Fabrus|VH2-26_IGHD3-10*01_IGHJ4*01	792	gnl|Fabrus|A20_IGKJ1*01	1077
222	gnl|Fabrus|VH2-26_IGHD4-11*01_IGHJ4*01	794	gnl|Fabrus|A20_IGKJ1*01	1077
223	gnl|Fabrus|VH2-26_IGHD5-18*01_IGHJ4*01	796	gnl|Fabrus|A20_IGKJ1*01	1077
224	gnl|Fabrus|VH2-26_IGHD6-13*01_IGHJ4*01	797	gnl|Fabrus|A20_IGKJ1*01	1077
225	gnl|Fabrus|VH2-26_IGHD7-27*01_IGHJ4*01	798	gnl|Fabrus|A20_IGKJ1*01	1077
226	gnl|Fabrus|VH5-51_IGHD1-14*01_IGHJ4*01	1044	gnl|Fabrus|A20_IGKJ1*01	1077
227	gnl|Fabrus|VH5-51_IGHD2-8*01_IGHJ4*01	1046	gnl|Fabrus|A20_IGKJ1*01	1077
228	gnl|Fabrus|VH5-51_IGHD3-3*01_IGHJ4*01	1048	gnl|Fabrus|A20_IGKJ1*01	1077
229	gnl|Fabrus|VH5-51_IGHD4-17*01_IGHJ4*01	1049	gnl|Fabrus|A20_IGKJ1*01	1077
230	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1050	gnl|Fabrus|A20_IGKJ1*01	1077

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
231	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1051	gnl|Fabrus|A20_IGKJ1*01	1077
232	gnl|Fabrus|VH5-51_IGHD6-25*01_IGHJ4*01	1052	gnl|Fabrus|A20_IGKJ1*01	1077
233	gnl|Fabrus|VH5-51_IGHD7-27*01_IGHJ4*01	1053	gnl|Fabrus|A20_IGKJ1*01	1077
234	gnl|Fabrus|VH6-1_IGHD1-1*01_IGHJ4*01	1054	gnl|Fabrus|A20_IGKJ1*01	1077
235	gnl|Fabrus|VH6-1_IGHD2-15*01_IGHJ4*01	1056	gnl|Fabrus|A20_IGKJ1*01	1077
236	gnl|Fabrus|VH6-1_IGHD3-3*01_IGHJ4*01	1059	gnl|Fabrus|A20_IGKJ1*01	1077
237	gnl|Fabrus|VH6-1_IGHD4-23*01_IGHJ4*01	1061	gnl|Fabrus|A20_IGKJ1*01	1077
238	gnl|Fabrus|VH6-1_IGHD4-11*01_IGHJ6*01	1060	gnl|Fabrus|A20_IGKJ1*01	1077
239	gnl|Fabrus|VH6-1_IGHD5-5*01_IGHJ4*01	1062	gnl|Fabrus|A20_IGKJ1*01	1077
240	gnl|Fabrus|VH6-1_IGHD6-13*01_IGHJ4*01	1063	gnl|Fabrus|A20_IGKJ1*01	1077
241	gnl|Fabrus|VH6-1_IGHD6-25*01_IGHJ6*01	1064	gnl|Fabrus|A20_IGKJ1*01	1077
242	gnl|Fabrus|VH6-1_IGHD7-27*01_IGHJ4*01	1065	gnl|Fabrus|A20_IGKJ1*01	1077
243	gnl|Fabrus|VH4-59_IGHD6-25*01_IGHJ3*01	1043	gnl|Fabrus|A20_IGKJ1*01	1077
244	gnl|Fabrus|VH3-48_IGHD6-6*01_IGHJ1*01	923	gnl|Fabrus|A20_IGKJ1*01	1077
245	gnl|Fabrus|VH3-30_IGHD6-6*01_IGHJ1*01	893	gnl|Fabrus|A20_IGKJ1*01	1077
246	gnl|Fabrus|VH3-66_IGHD6-6*01_IGHJ1*01	949	gnl|Fabrus|A20_IGKJ1*01	1077
247	gnl|Fabrus|VH3-53_IGHD5-5*01_IGHJ4*01	938	gnl|Fabrus|A20_IGKJ1*01	1077
248	gnl|Fabrus|VH2-5_IGHD5-12*01_IGHJ4*01	804	gnl|Fabrus|A20_IGKJ1*01	1077
249	gnl|Fabrus|VH2-70_IGHD5-12*01_IGHJ4*01	811	gnl|Fabrus|A20_IGKJ1*01	1077
250	gnl|Fabrus|VH3-15_IGHD5-12*01_IGHJ4*01	835	gnl|Fabrus|A20_IGKJ1*01	1077
251	gnl|Fabrus|VH3-15_IGHD3-10*01_IGHJ4*01	833	gnl|Fabrus|A20_IGKJ1*01	1077
252	gnl|Fabrus|VH3-49_IGHD5-18*01_IGHJ4*01	930	gnl|Fabrus|A20_IGKJ1*01	1077
253	gnl|Fabrus|VH3-49_IGHD6-13*01_IGHJ4*01	931	gnl|Fabrus|A20_IGKJ1*01	1077
254	gnl|Fabrus|VH3-72_IGHD5-18*01_IGHJ4*01	967	gnl|Fabrus|A20_IGKJ1*01	1077
255	gnl|Fabrus|VH3-72_IGHD6-6*01_IGHJ1*01	969	gnl|Fabrus|A20_IGKJ1*01	1077
256	gnl|Fabrus|VH3-73_IGHD5-12*01_IGHJ4*01	977	gnl|Fabrus|A20_IGKJ1*01	1077
257	gnl|Fabrus|VH3-73_IGHD4-23*01_IGHJ5*01	976	gnl|Fabrus|A20_IGKJ1*01	1077
258	gnl|Fabrus|VH3-43_IGHD3-22*01_IGHJ4*01	918	gnl|Fabrus|A20_IGKJ1*01	1077
259	gnl|Fabrus|VH3-43_IGHD6-13*01_IGHJ4*01	921	gnl|Fabrus|A20_IGKJ1*01	1077
260	gnl|Fabrus|VH3-9_IGHD3-22*01_IGHJ4*01	992	gnl|Fabrus|A20_IGKJ1*01	1077
261	gnl|Fabrus|VH3-9_IGHD1-7*01_IGHJ5*01	989	gnl|Fabrus|A20_IGKJ1*01	1077
262	gnl|Fabrus|VH3-9_IGHD6-13*01_IGHJ4*01	995	gnl|Fabrus|A20_IGKJ1*01	1077
263	gnl|Fabrus|VH4-39_IGHD3-10*01_IGHJ4*01	1030	gnl|Fabrus|A20_IGKJ1*01	1077
264	gnl|Fabrus|VH4-39_IGHD5-12*01_IGHJ4*01	1034	gnl|Fabrus|A20_IGKJ1*01	1077
265	gnl|Fabrus|VH1-18_IGHD6-6*01_IGHJ1*01	728	gnl|Fabrus|A20_IGKJ1*01	1077
266	gnl|Fabrus|VH1-24_IGHD5-12*01_IGHJ4*01	735	gnl|Fabrus|A20_IGKJ1*01	1077
267	gnl|Fabrus|VH1-2_IGHD1-1*01_IGHJ3*01	729	gnl|Fabrus|A20_IGKJ1*01	1077
268	gnl|Fabrus|VH1-3_IGHD6-6*01_IGHJ1*01	743	gnl|Fabrus|A20_IGKJ1*01	1077
269	gnl|Fabrus|VH1-45_IGHD3-10*01_IGHJ4*01	748	gnl|Fabrus|A20_IGKJ1*01	1077
270	gnl|Fabrus|VH1-46_IGHD1-26*01_IGHJ4*01	754	gnl|Fabrus|A20_IGKJ1*01	1077
271	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ6*01	1068	gnl|Fabrus|A20_IGKJ1*01	1077
272	gnl|Fabrus|VH2-70_IGHD3-9*01_IGHJ6*01	810	gnl|Fabrus|A20_IGKJ1*01	1077

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
273	gnl|Fabrus|VH1-58_IGHD3-10*01_IGHJ6*01	764	gnl|Fabrus|A20_IGKJ1*01	1077
274	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ2*01	1067	gnl|Fabrus|A20_IGKJ1*01	1077
275	gnl|Fabrus|VH4-28_IGHD3-9*01_IGHJ6*01	1002	gnl|Fabrus|A20_IGKJ1*01	1077
276	gnl|Fabrus|VH4-31_IGHD2-15*01_IGHJ2*01	1008	gnl|Fabrus|A20_IGKJ1*01	1077
277	gnl|Fabrus|VH2-5_IGHD3-9*01_IGHJ6*01	803	gnl|Fabrus|A20_IGKJ1*01	1077
278	gnl|Fabrus|VH1-8_IGHD2-15*01_IGHJ6*01	783	gnl|Fabrus|A20_IGKJ1*01	1077
279	gnl|Fabrus|VH2-70_IGHD2-15*01_IGHJ2*01	808	gnl|Fabrus|A20_IGKJ1*01	1077
280	gnl|Fabrus|VH3-38_IGHD3-10*01_IGHJ4*01	907	gnl|Fabrus|A20_IGKJ1*01	1077
281	gnl|Fabrus|VH3-16_IGHD1-7*01_IGHJ6*01	838	gnl|Fabrus|A20_IGKJ1*01	1077
282	gnl|Fabrus|VH3-73_IGHD3-9*01_IGHJ6*01	974	gnl|Fabrus|A20_IGKJ1*01	1077
283	gnl|Fabrus|VH3-11_IGHD3-9*01_IGHJ6*01	816	gnl|Fabrus|A20_IGKJ1*01	1077
284	gnl|Fabrus|VH3-11_IGHD6-6*01_IGHJ1*01	820	gnl|Fabrus|A20_IGKJ1*01	1077
285	gnl|Fabrus|VH3-20_IGHD5-12*01_IGHJ4*01	852	gnl|Fabrus|A20_IGKJ1*01	1077
286	gnl|Fabrus|VH3-16_IGHD2-15*01_IGHJ2*01	839	gnl|Fabrus|A20_IGKJ1*01	1077
287	gnl|Fabrus|VH3-7_IGHD6-6*01_IGHJ1*01	960	gnl|Fabrus|A20_IGKJ1*01	1077
288	gnl|Fabrus|VH3-16_IGHD6-13*01_IGHJ4*01	844	gnl|Fabrus|A20_IGKJ1*01	1077
289	gnl|Fabrus|VH3-23_IGHD1-1*01_IGHJ4*01	863	gnl|Fabrus|A30_IGKJ1*01	1082
290	gnl|Fabrus|VH3-23_IGHD2-15*01_IGHJ4*01	866	gnl|Fabrus|A30_IGKJ1*01	1082
291	gnl|Fabrus|VH3-23_IGHD3-22*01_IGHJ4*01	870	gnl|Fabrus|A30_IGKJ1*01	1082
292	gnl|Fabrus|VH3-23_IGHD4-11*01_IGHJ4*01	872	gnl|Fabrus|A30_IGKJ1*01	1082
293	gnl|Fabrus|VH3-23_IGHD5-12*01_IGHJ4*01	874	gnl|Fabrus|A30_IGKJ1*01	1082
294	gnl|Fabrus|VH3-23_IGHD5-5*01_IGHJ4*01	876	gnl|Fabrus|A30_IGKJ1*01	1082
295	gnl|Fabrus|VH3-23_IGHD6-13*01_IGHJ4*01	877	gnl|Fabrus|A30_IGKJ1*01	1082
296	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ4*01	880	gnl|Fabrus|A30_IGKJ1*01	1082
297	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ6*01	881	gnl|Fabrus|A30_IGKJ1*01	1082
298	gnl|Fabrus|VH1-69_IGHD1-14*01_IGHJ4*01	770	gnl|Fabrus|A30_IGKJ1*01	1082
299	gnl|Fabrus|VH1-69_IGHD2-2*01_IGHJ4*01	771	gnl|Fabrus|A30_IGKJ1*01	1082
300	gnl|Fabrus|VH1-69_IGHD2-8*01_IGHJ6*01	772	gnl|Fabrus|A30_IGKJ1*01	1082
301	gnl|Fabrus|VH1-69_IGHD3-16*01_IGHJ4*01	773	gnl|Fabrus|A30_IGKJ1*01	1082
302	gnl|Fabrus|VH1-69_IGHD3-3*01_IGHJ4*01	774	gnl|Fabrus|A30_IGKJ1*01	1082
303	gnl|Fabrus|VH1-69_IGHD4-17*01_IGHJ4*01	776	gnl|Fabrus|A30_IGKJ1*01	1082
304	gnl|Fabrus|VH1-69_IGHD5-12*01_IGHJ4*01	777	gnl|Fabrus|A30_IGKJ1*01	1082
305	gnl|Fabrus|VH1-69_IGHD6-19*01_IGHJ4*01	779	gnl|Fabrus|A30_IGKJ1*01	1082
306	gnl|Fabrus|VH1-69_IGHD7-27*01_IGHJ4*01	781	gnl|Fabrus|A30_IGKJ1*01	1082
307	gnl|Fabrus|VH4-34_IGHD1-7*01_IGHJ4*01	1017	gnl|Fabrus|A30_IGKJ1*01	1082
308	gnl|Fabrus|VH4-34_IGHD2-2*01_IGHJ4*01	1018	gnl|Fabrus|A30_IGKJ1*01	1082
309	gnl|Fabrus|VH4-34_IGHD3-16*01_IGHJ4*01	1019	gnl|Fabrus|A30_IGKJ1*01	1082
310	gnl|Fabrus|VH4-34_IGHD4-17*01_IGHJ4*01	1021	gnl|Fabrus|A30_IGKJ1*01	1082
311	gnl|Fabrus|VH4-34_IGHD5-12*01_IGHJ4*01	1022	gnl|Fabrus|A30_IGKJ1*01	1082
312	gnl|Fabrus|VH4-34_IGHD6-13*01_IGHJ4*01	1023	gnl|Fabrus|A30_IGKJ1*01	1082
313	gnl|Fabrus|VH4-34_IGHD6-25*01_IGHJ6*01	1024	gnl|Fabrus|A30_IGKJ1*01	1082
314	gnl|Fabrus|VH4-34_IGHD7-27*01_IGHJ4*01	1026	gnl|Fabrus|A30_IGKJ1*01	1082

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
315	gnl|Fabrus|VH2-26_IGHD1-20*01_IGHJ4*01	789	gnl|Fabrus|A30_IGKJ1*01	1082
316	gnl|Fabrus|VH2-26_IGHD2-2*01_IGHJ4*01	791	gnl|Fabrus|A30_IGKJ1*01	1082
317	gnl|Fabrus|VH2-26_IGHD3-10*01_IGHJ4*01	792	gnl|Fabrus|A30_IGKJ1*01	1082
318	gnl|Fabrus|VH2-26_IGHD4-11*01_IGHJ4*01	794	gnl|Fabrus|A30_IGKJ1*01	1082
319	gnl|Fabrus|VH2-26_IGHD5-18*01_IGHJ4*01	796	gnl|Fabrus|A30_IGKJ1*01	1082
320	gnl|Fabrus|VH2-26_IGHD6-13*01_IGHJ4*01	797	gnl|Fabrus|A30_IGKJ1*01	1082
321	gnl|Fabrus|VH2-26_IGHD7-27*01_IGHJ4*01	798	gnl|Fabrus|A30_IGKJ1*01	1082
322	gnl|Fabrus|VH5-51_IGHD1-14*01_IGHJ4*01	1044	gnl|Fabrus|A30_IGKJ1*01	1082
323	gnl|Fabrus|VH5-51_IGHD2-8*01_IGHJ4*01	1046	gnl|Fabrus|A30_IGKJ1*01	1082
324	gnl|Fabrus|VH5-51_IGHD3-3*01_IGHJ4*01	1048	gnl|Fabrus|A30_IGKJ1*01	1082
325	gnl|Fabrus|VH5-51_IGHD4-17*01_IGHJ4*01	1049	gnl|Fabrus|A30_IGKJ1*01	1082
326	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1050	gnl|Fabrus|A30_IGKJ1*01	1082
327	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1051	gnl|Fabrus|A30_IGKJ1*01	1082
328	gnl|Fabrus|VH5-51_IGHD6-25*01_IGHJ4*01	1052	gnl|Fabrus|A30_IGKJ1*01	1082
329	gnl|Fabrus|VH5-51_IGHD7-27*01_IGHJ4*01	1053	gnl|Fabrus|A30_IGKJ1*01	1082
330	gnl|Fabrus|VH6-1_IGHD1-1*01_IGHJ4*01	1054	gnl|Fabrus|A30_IGKJ1*01	1082
331	gnl|Fabrus|VH6-1_IGHD2-15*01_IGHJ4*01	1056	gnl|Fabrus|A30_IGKJ1*01	1082
332	gnl|Fabrus|VH6-1_IGHD3-3*01_IGHJ4*01	1059	gnl|Fabrus|A30_IGKJ1*01	1082
333	gnl|Fabrus|VH6-1_IGHD4-23*01_IGHJ4*01	1061	gnl|Fabrus|A30_IGKJ1*01	1082
334	gnl|Fabrus|VH6-1_IGHD4-11*01_IGHJ6*01	1060	gnl|Fabrus|A30_IGKJ1*01	1082
335	gnl|Fabrus|VH6-1_IGHD5-5*01_IGHJ4*01	1062	gnl|Fabrus|A30_IGKJ1*01	1082
336	gnl|Fabrus|VH6-1_IGHD6-13*01_IGHJ4*01	1063	gnl|Fabrus|A30_IGKJ1*01	1082
337	gnl|Fabrus|VH6-1_IGHD6-25*01_IGHJ6*01	1064	gnl|Fabrus|A30_IGKJ1*01	1082
338	gnl|Fabrus|VH6-1_IGHD7-27*01_IGHJ4*01	1065	gnl|Fabrus|A30_IGKJ1*01	1082
339	gnl|Fabrus|VH4-59_IGHD6-25*01_IGHJ3*01	1043	gnl|Fabrus|A30_IGKJ1*01	1082
340	gnl|Fabrus|VH3-48_IGHD6-6*01_IGHJ1*01	923	gnl|Fabrus|A30_IGKJ1*01	1082
341	gnl|Fabrus|VH3-30_IGHD6-6*01_IGHJ1*01	893	gnl|Fabrus|A30_IGKJ1*01	1082
342	gnl|Fabrus|VH3-66_IGHD6-6*01_IGHJ1*01	949	gnl|Fabrus|A30_IGKJ1*01	1082
343	gnl|Fabrus|VH3-53_IGHD5-5*01_IGHJ4*01	938	gnl|Fabrus|A30_IGKJ1*01	1082
344	gnl|Fabrus|VH2-5_IGHD5-12*01_IGHJ4*01	804	gnl|Fabrus|A30_IGKJ1*01	1082
345	gnl|Fabrus|VH2-70_IGHD5-12*01_IGHJ4*01	811	gnl|Fabrus|A30_IGKJ1*01	1082
346	gnl|Fabrus|VH3-15_IGHD5-12*01_IGHJ4*01	835	gnl|Fabrus|A30_IGKJ1*01	1082
347	gnl|Fabrus|VH3-15_IGHD3-10*01_IGHJ4*01	833	gnl|Fabrus|A30_IGKJ1*01	1082
348	gnl|Fabrus|VH3-49_IGHD5-18*01_IGHJ4*01	930	gnl|Fabrus|A30_IGKJ1*01	1082
349	gnl|Fabrus|VH3-49_IGHD6-13*01_IGHJ4*01	931	gnl|Fabrus|A30_IGKJ1*01	1082
350	gnl|Fabrus|VH3-72_IGHD5-18*01_IGHJ4*01	967	gnl|Fabrus|A30_IGKJ1*01	1082
351	gnl|Fabrus|VH3-72_IGHD6-6*01_IGHJ1*01	969	gnl|Fabrus|A30_IGKJ1*01	1082
352	gnl|Fabrus|VH3-73_IGHD5-12*01_IGHJ4*01	977	gnl|Fabrus|A30_IGKJ1*01	1082
353	gnl|Fabrus|VH3-73_IGHD4-23*01_IGHJ5*01	976	gnl|Fabrus|A30_IGKJ1*01	1082
354	gnl|Fabrus|VH3-43_IGHD3-22*01_IGHJ4*01	918	gnl|Fabrus|A30_IGKJ1*01	1082
355	gnl|Fabrus|VH3-43_IGHD6-13*01_IGHJ4*01	921	gnl|Fabrus|A30_IGKJ1*01	1082
356	gnl|Fabrus|VH3-9_IGHD3-22*01_IGHJ4*01	992	gnl|Fabrus|A30_IGKJ1*01	1082

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
357	gnl|Fabrus|VH3-9_IGHD1-7*01_IGHJ5*01	989	gnl|Fabrus|A30_IGKJ1*01	1082
358	gnl|Fabrus|VH3-9_IGHD6-13*01_IGHJ4*01	995	gnl|Fabrus|A30_IGKJ1*01	1082
359	gnl|Fabrus|VH4-39_IGHD3-10*01_IGHJ4*01	1030	gnl|Fabrus|A30_IGKJ1*01	1082
360	gnl|Fabrus|VH4-39_IGHD5-12*01_IGHJ4*01	1034	gnl|Fabrus|A30_IGKJ1*01	1082
361	gnl|Fabrus|VH1-18_IGHD6-6*01_IGHJ1*01	728	gnl|Fabrus|A30_IGKJ1*01	1082
362	gnl|Fabrus|VH1-24_IGHD5-12*01_IGHJ4*01	735	gnl|Fabrus|A30_IGKJ1*01	1082
363	gnl|Fabrus|VH1-2_IGHD1-1*01_IGHJ3*01	729	gnl|Fabrus|A30_IGKJ1*01	1082
364	gnl|Fabrus|VH1-3_IGHD6-6*01_IGHJ1*01	743	gnl|Fabrus|A30_IGKJ1*01	1082
365	gnl|Fabrus|VH1-45_IGHD3-10*01_IGHJ4*01	748	gnl|Fabrus|A30_IGKJ1*01	1082
366	gnl|Fabrus|VH1-46_IGHD1-26*01_IGHJ4*01	754	gnl|Fabrus|A30_IGKJ1*01	1082
367	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ6*01	1068	gnl|Fabrus|A30_IGKJ1*01	1082
368	gnl|Fabrus|VH2-70_IGHD3-9*01_IGHJ6*01	810	gnl|Fabrus|A30_IGKJ1*01	1082
369	gnl|Fabrus|VH1-58_IGHD3-10*01_IGHJ6*01	764	gnl|Fabrus|A30_IGKJ1*01	1082
370	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ2*01	1067	gnl|Fabrus|A30_IGKJ1*01	1082
371	gnl|Fabrus|VH4-28_IGHD3-9*01_IGHJ6*01	1002	gnl|Fabrus|A30_IGKJ1*01	1082
372	gnl|Fabrus|VH4-31_IGHD2-15*01_IGHJ2*01	1008	gnl|Fabrus|A30_IGKJ1*01	1082
373	gnl|Fabrus|VH2-5_IGHD3-9*01_IGHJ6*01	803	gnl|Fabrus|A30_IGKJ1*01	1082
374	gnl|Fabrus|VH1-8_IGHD2-15*01_IGHJ6*01	783	gnl|Fabrus|A30_IGKJ1*01	1082
375	gnl|Fabrus|VH2-70_IGHD2-15*01_IGHJ2*01	808	gnl|Fabrus|A30_IGKJ1*01	1082
376	gnl|Fabrus|VH3-38_IGHD3-10*01_IGHJ4*01	907	gnl|Fabrus|A30_IGKJ1*01	1082
377	gnl|Fabrus|VH3-16_IGHD1-7*01_IGHJ6*01	838	gnl|Fabrus|A30_IGKJ1*01	1082
378	gnl|Fabrus|VH3-73_IGHD3-9*01_IGHJ6*01	974	gnl|Fabrus|A30_IGKJ1*01	1082
379	gnl|Fabrus|VH3-11_IGHD3-9*01_IGHJ6*01	816	gnl|Fabrus|A30_IGKJ1*01	1082
380	gnl|Fabrus|VH3-11_IGHD6-6*01_IGHJ1*01	820	gnl|Fabrus|A30_IGKJ1*01	1082
381	gnl|Fabrus|VH3-20_IGHD5-12*01_IGHJ4*01	852	gnl|Fabrus|A30_IGKJ1*01	1082
382	gnl|Fabrus|VH3-16_IGHD2-15*01_IGHJ2*01	839	gnl|Fabrus|A30_IGKJ1*01	1082
383	gnl|Fabrus|VH3-7_IGHD6-6*01_IGHJ1*01	960	gnl|Fabrus|A30_IGKJ1*01	1082
384	gnl|Fabrus|VH3-16_IGHD6-13*01_IGHJ4*01	844	gnl|Fabrus|A30_IGKJ1*01	1082
385	gnl|Fabrus|VH3-23_IGHD1-1*01_IGHJ4*01	863	gnl|Fabrus|L4/18a_IGKJ1*01	1095
386	gnl|Fabrus|VH3-23_IGHD2-15*01_IGHJ4*01	866	gnl|Fabrus|L4/18a_IGKJ1*01	1095
387	gnl|Fabrus|VH3-23_IGHD3-22*01_IGHJ4*01	870	gnl|Fabrus|L4/18a_IGKJ1*01	1095
388	gnl|Fabrus|VH3-23_IGHD4-11*01_IGHJ4*01	872	gnl|Fabrus|L4/18a_IGKJ1*01	1095
389	gnl|Fabrus|VH3-23_IGHD5-12*01_IGHJ4*01	874	gnl|Fabrus|L4/18a_IGKJ1*01	1095
390	gnl|Fabrus|VH3-23_IGHD5-5*01_IGHJ4*01	876	gnl|Fabrus|L4/18a_IGKJ1*01	1095
391	gnl|Fabrus|VH3-23_IGHD6-13*01_IGHJ4*01	877	gnl|Fabrus|L4/18a_IGKJ1*01	1095
392	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ4*01	880	gnl|Fabrus|L4/18a_IGKJ1*01	1095
393	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ6*01	881	gnl|Fabrus|L4/18a_IGKJ1*01	1095
394	gnl|Fabrus|VH1-69_IGHD1-14*01_IGHJ4*01	770	gnl|Fabrus|L4/18a_IGKJ1*01	1095
395	gnl|Fabrus|VH1-69_IGHD2-2*01_IGHJ4*01	771	gnl|Fabrus|L4/18a_IGKJ1*01	1095
396	gnl|Fabrus|VH1-69_IGHD2-8*01_IGHJ6*01	772	gnl|Fabrus|L4/18a_IGKJ1*01	1095
397	gnl|Fabrus|VH1-69_IGHD3-16*01_IGHJ4*01	773	gnl|Fabrus|L4/18a_IGKJ1*01	1095
398	gnl|Fabrus|VH1-69_IGHD3-3*01_IGHJ4*01	774	gnl|Fabrus|L4/18a_IGKJ1*01	1095

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
399	gnl|Fabrus|VH1-69_IGHD4-17*01_IGHJ4*01	776	gnl|Fabrus|L4/18a_IGKJ1*01	1095
400	gnl|Fabrus|VH1-69_IGHD5-12*01_IGHJ4*01	777	gnl|Fabrus|L4/18a_IGKJ1*01	1095
401	gnl|Fabrus|VH1-69_IGHD6-19*01_IGHJ4*01	779	gnl|Fabrus|L4/18a_IGKJ1*01	1095
402	gnl|Fabrus|VH1-69_IGHD7-27*01_IGHJ4*01	781	gnl|Fabrus|L4/18a_IGKJ1*01	1095
403	gnl|Fabrus|VH4-34_IGHD1-7*01_IGHJ4*01	1017	gnl|Fabrus|L4/18a_IGKJ1*01	1095
404	gnl|Fabrus|VH4-34_IGHD2-2*01_IGHJ4*01	1018	gnl|Fabrus|L4/18a_IGKJ1*01	1095
405	gnl|Fabrus|VH4-34_IGHD3-16*01_IGHJ4*01	1019	gnl|Fabrus|L4/18a_IGKJ1*01	1095
406	gnl|Fabrus|VH4-34_IGHD4-17*01_IGHJ4*01	1021	gnl|Fabrus|L4/18a_IGKJ1*01	1095
407	gnl|Fabrus|VH4-34_IGHD5-12*01_IGHJ4*01	1022	gnl|Fabrus|L4/18a_IGKJ1*01	1095
408	gnl|Fabrus|VH4-34_IGHD6-13*01_IGHJ4*01	1023	gnl|Fabrus|L4/18a_IGKJ1*01	1095
409	gnl|Fabrus|VH4-34_IGHD6-25*01_IGHJ6*01	1024	gnl|Fabrus|L4/18a_IGKJ1*01	1095
410	gnl|Fabrus|VH4-34_IGHD7-27*01_IGHJ4*01	1026	gnl|Fabrus|L4/18a_IGKJ1*01	1095
411	gnl|Fabrus|VH2-26_IGHD1-20*01_IGHJ4*01	789	gnl|Fabrus|L4/18a_IGKJ1*01	1095
412	gnl|Fabrus|VH2-26_IGHD2-2*01_IGHJ4*01	791	gnl|Fabrus|L4/18a_IGKJ1*01	1095
413	gnl|Fabrus|VH2-26_IGHD3-10*01_IGHJ4*01	792	gnl|Fabrus|L4/18a_IGKJ1*01	1095
414	gnl|Fabrus|VH2-26_IGHD4-11*01_IGHJ4*01	794	gnl|Fabrus|L4/18a_IGKJ1*01	1095
415	gnl|Fabrus|VH2-26_IGHD5-18*01_IGHJ4*01	796	gnl|Fabrus|L4/18a_IGKJ1*01	1095
416	gnl|Fabrus|VH2-26_IGHD6-13*01_IGHJ4*01	797	gnl|Fabrus|L4/18a_IGKJ1*01	1095
417	gnl|Fabrus|VH2-26_IGHD7-27*01_IGHJ4*01	798	gnl|Fabrus|L4/18a_IGKJ1*01	1095
418	gnl|Fabrus|VH5-51_IGHD1-14*01_IGHJ4*01	1044	gnl|Fabrus|L4/18a_IGKJ1*01	1095
419	gnl|Fabrus|VH5-51_IGHD2-8*01_IGHJ4*01	1046	gnl|Fabrus|L4/18a_IGKJ1*01	1095
420	gnl|Fabrus|VH5-51_IGHD3-3*01_IGHJ4*01	1048	gnl|Fabrus|L4/18a_IGKJ1*01	1095
421	gnl|Fabrus|VH5-51_IGHD4-17*01_IGHJ4*01	1049	gnl|Fabrus|L4/18a_IGKJ1*01	1095
422	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1050	gnl|Fabrus|L4/18a_IGKJ1*01	1095
423	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1051	gnl|Fabrus|L4/18a_IGKJ1*01	1095
424	gnl|Fabrus|VH5-51_IGHD6-25*01_IGHJ4*01	1052	gnl|Fabrus|L4/18a_IGKJ1*01	1095
425	gnl|Fabrus|VH5-51_IGHD7-27*01_IGHJ4*01	1053	gnl|Fabrus|L4/18a_IGKJ1*01	1095
426	gnl|Fabrus|VH6-1_IGHD1-1*01_IGHJ4*01	1054	gnl|Fabrus|L4/18a_IGKJ1*01	1095
427	gnl|Fabrus|VH6-1_IGHD2-15*01_IGHJ4*01	1056	gnl|Fabrus|L4/18a_IGKJ1*01	1095
428	gnl|Fabrus|VH6-1_IGHD3-3*01_IGHJ4*01	1059	gnl|Fabrus|L4/18a_IGKJ1*01	1095
429	gnl|Fabrus|VH6-1_IGHD4-23*01_IGHJ4*01	1061	gnl|Fabrus|L4/18a_IGKJ1*01	1095
430	gnl|Fabrus|VH6-1_IGHD4-11*01_IGHJ6*01	1060	gnl|Fabrus|L4/18a_IGKJ1*01	1095
431	gnl|Fabrus|VH6-1_IGHD5-5*01_IGHJ4*01	1062	gnl|Fabrus|L4/18a_IGKJ1*01	1095
432	gnl|Fabrus|VH6-1_IGHD6-13*01_IGHJ4*01	1063	gnl|Fabrus|L4/18a_IGKJ1*01	1095
433	gnl|Fabrus|VH6-1_IGHD6-25*01_IGHJ6*01	1064	gnl|Fabrus|L4/18a_IGKJ1*01	1095
434	gnl|Fabrus|VH6-1_IGHD7-27*01_IGHJ4*01	1065	gnl|Fabrus|L4/18a_IGKJ1*01	1095
435	gnl|Fabrus|VH4-59_IGHD6-25*01_IGHJ3*01	1043	gnl|Fabrus|L4/18a_IGKJ1*01	1095
436	gnl|Fabrus|VH3-48_IGHD6-6*01_IGHJ1*01	923	gnl|Fabrus|L4/18a_IGKJ1*01	1095
437	gnl|Fabrus|VH3-30_IGHD6-6*01_IGHJ1*01	893	gnl|Fabrus|L4/18a_IGKJ1*01	1095
438	gnl|Fabrus|VH3-66_IGHD6-6*01_IGHJ1*01	949	gnl|Fabrus|L4/18a_IGKJ1*01	1095
439	gnl|Fabrus|VH3-53_IGHD5-5*01_IGHJ4*01	938	gnl|Fabrus|L4/18a_IGKJ1*01	1095
440	gnl|Fabrus|VH2-5_IGHD5-12*01_IGHJ4*01	804	gnl|Fabrus|L4/18a_IGKJ1*01	1095

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
441	gnl|Fabrus|VH2-70_IGHD5-12*01_IGHJ4*01	811	gnl|Fabrus|L4/18a_IGKJ1*01	1095
442	gnl|Fabrus|VH3-15_IGHD5-12*01_IGHJ4*01	835	gnl|Fabrus|L4/18a_IGKJ1*01	1095
443	gnl|Fabrus|VH3-15_IGHD3-10*01_IGHJ4*01	833	gnl|Fabrus|L4/18a_IGKJ1*01	1095
444	gnl|Fabrus|VH3-49_IGHD5-18*01_IGHJ4*01	930	gnl|Fabrus|L4/18a_IGKJ1*01	1095
445	gnl|Fabrus|VH3-49_IGHD6-13*01_IGHJ4*01	931	gnl|Fabrus|L4/18a_IGKJ1*01	1095
446	gnl|Fabrus|VH3-72_IGHD5-18*01_IGHJ4*01	967	gnl|Fabrus|L4/18a_IGKJ1*01	1095
447	gnl|Fabrus|VH3-72_IGHD6-6*01_IGHJ1*01	969	gnl|Fabrus|L4/18a_IGKJ1*01	1095
448	gnl|Fabrus|VH3-73_IGHD5-12*01_IGHJ4*01	977	gnl|Fabrus|L4/18a_IGKJ1*01	1095
449	gnl|Fabrus|VH3-73_IGHD4-23*01_IGHJ5*01	976	gnl|Fabrus|L4/18a_IGKJ1*01	1095
450	gnl|Fabrus|VH3-43_IGHD3-22*01_IGHJ4*01	918	gnl|Fabrus|L4/18a_IGKJ1*01	1095
451	gnl|Fabrus|VH3-43_IGHD6-13*01_IGHJ4*01	921	gnl|Fabrus|L4/18a_IGKJ1*01	1095
452	gnl|Fabrus|VH3-9_IGHD3-22*01_IGHJ4*01	992	gnl|Fabrus|L4/18a_IGKJ1*01	1095
453	gnl|Fabrus|VH3-9_IGHD1-7*01_IGHJ5*01	989	gnl|Fabrus|L4/18a_IGKJ1*01	1095
454	gnl|Fabrus|VH3-9_IGHD6-13*01_IGHJ4*01	995	gnl|Fabrus|L4/18a_IGKJ1*01	1095
455	gnl|Fabrus|VH4-39_IGHD3-10*01_IGHJ4*01	1030	gnl|Fabrus|L4/18a_IGKJ1*01	1095
456	gnl|Fabrus|VH4-39_IGHD5-12*01_IGHJ4*01	1034	gnl|Fabrus|L4/18a_IGKJ1*01	1095
457	gnl|Fabrus|VH1-18_IGHD6-6*01_IGHJ1*01	728	gnl|Fabrus|L4/18a_IGKJ1*01	1095
458	gnl|Fabrus|VH1-24_IGHD5-12*01_IGHJ4*01	735	gnl|Fabrus|L4/18a_IGKJ1*01	1095
459	gnl|Fabrus|VH1-2_IGHD1-1*01_IGHJ3*01	729	gnl|Fabrus|L4/18a_IGKJ1*01	1095
460	gnl|Fabrus|VH1-3_IGHD6-6*01_IGHJ1*01	743	gnl|Fabrus|L4/18a_IGKJ1*01	1095
461	gnl|Fabrus|VH1-45_IGHD3-10*01_IGHJ4*01	748	gnl|Fabrus|L4/18a_IGKJ1*01	1095
462	gnl|Fabrus|VH1-46_IGHD1-26*01_IGHJ4*01	754	gnl|Fabrus|L4/18a_IGKJ1*01	1095
463	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ6*01	1068	gnl|Fabrus|L4/18a_IGKJ1*01	1095
464	gnl|Fabrus|VH2-70_IGHD3-9*01_IGHJ6*01	810	gnl|Fabrus|L4/18a_IGKJ1*01	1095
465	gnl|Fabrus|VH1-58_IGHD3-10*01_IGHJ6*01	764	gnl|Fabrus|L4/18a_IGKJ1*01	1095
466	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ2*01	1067	gnl|Fabrus|L4/18a_IGKJ1*01	1095
467	gnl|Fabrus|VH4-28_IGHD3-9*01_IGHJ6*01	1002	gnl|Fabrus|L4/18a_IGKJ1*01	1095
468	gnl|Fabrus|VH4-31_IGHD2-15*01_IGHJ2*01	1008	gnl|Fabrus|L4/18a_IGKJ1*01	1095
469	gnl|Fabrus|VH2-5_IGHD3-9*01_IGHJ6*01	803	gnl|Fabrus|L4/18a_IGKJ1*01	1095
470	gnl|Fabrus|VH1-8_IGHD2-15*01_IGHJ6*01	783	gnl|Fabrus|L4/18a_IGKJ1*01	1095
471	gnl|Fabrus|VH2-70_IGHD2-15*01_IGHJ2*01	808	gnl|Fabrus|L4/18a_IGKJ1*01	1095
472	gnl|Fabrus|VH3-38_IGHD3-10*01_IGHJ4*01	907	gnl|Fabrus|L4/18a_IGKJ1*01	1095
473	gnl|Fabrus|VH3-16_IGHD1-7*01_IGHJ6*01	838	gnl|Fabrus|L4/18a_IGKJ1*01	1095
474	gnl|Fabrus|VH3-73_IGHD3-9*01_IGHJ6*01	974	gnl|Fabrus|L4/18a_IGKJ1*01	1095
475	gnl|Fabrus|VH3-11_IGHD3-9*01_IGHJ6*01	816	gnl|Fabrus|L4/18a_IGKJ1*01	1095
476	gnl|Fabrus|VH3-11_IGHD6-6*01_IGHJ1*01	820	gnl|Fabrus|L4/18a_IGKJ1*01	1095
477	gnl|Fabrus|VH3-20_IGHD5-12*01_IGHJ4*01	852	gnl|Fabrus|L4/18a_IGKJ1*01	1095
478	gnl|Fabrus|VH3-16_IGHD2-15*01_IGHJ2*01	839	gnl|Fabrus|L4/18a_IGKJ1*01	1095
479	gnl|Fabrus|VH3-7_IGHD6-6*01_IGHJ1*01	960	gnl|Fabrus|L4/18a_IGKJ1*01	1095
480	gnl|Fabrus|VH3-16_IGHD6-13*01_IGHJ4*01	844	gnl|Fabrus|L4/18a_IGKJ1*01	1095
481	gnl|Fabrus|VH3-23_IGHD1-1*01_IGHJ4*01	863	gnl|Fabrus|L5_IGKJ1*01	1096
482	gnl|Fabrus|VH3-23_IGHD2-15*01_IGHJ4*01	866	gnl|Fabrus|L5_IGKJ1*01	1096

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
483	gnl|Fabrus|VH3-23_IGHD3-22*01_IGHJ4*01	870	gnl|Fabrus|L5_IGKJ1*01	1096
484	gnl|Fabrus|VH3-23_IGHD4-11*01_IGHJ4*01	872	gnl|Fabrus|L5_IGKJ1*01	1096
485	gnl|Fabrus|VH3-23_IGHD5-12*01_IGHJ4*01	874	gnl|Fabrus|L5_IGKJ1*01	1096
486	gnl|Fabrus|VH3-23_IGHD5-5*01_IGHJ4*01	876	gnl|Fabrus|L5_IGKJ1*01	1096
487	gnl|Fabrus|VH3-23_IGHD6-13*01_IGHJ4*01	877	gnl|Fabrus|L5_IGKJ1*01	1096
488	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ4*01	880	gnl|Fabrus|L5_IGKJ1*01	1096
489	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ6*01	881	gnl|Fabrus|L5_IGKJ1*01	1096
490	gnl|Fabrus|VH1-69_IGHD1-14*01_IGHJ4*01	770	gnl|Fabrus|L5_IGKJ1*01	1096
491	gnl|Fabrus|VH1-69_IGHD2-2*01_IGHJ4*01	771	gnl|Fabrus|L5_IGKJ1*01	1096
492	gnl|Fabrus|VH1-69_IGHD2-8*01_IGHJ6*01	772	gnl|Fabrus|L5_IGKJ1*01	1096
493	gnl|Fabrus|VH1-69_IGHD3-16*01_IGHJ4*01	773	gnl|Fabrus|L5_IGKJ1*01	1096
494	gnl|Fabrus|VH1-69_IGHD3-3*01_IGHJ4*01	774	gnl|Fabrus|L5_IGKJ1*01	1096
495	gnl|Fabrus|VH1-69_IGHD4-17*01_IGHJ4*01	776	gnl|Fabrus|L5_IGKJ1*01	1096
496	gnl|Fabrus|VH1-69_IGHD5-12*01_IGHJ4*01	777	gnl|Fabrus|L5_IGKJ1*01	1096
497	gnl|Fabrus|VH1-69_IGHD6-19*01_IGHJ4*01	779	gnl|Fabrus|L5_IGKJ1*01	1096
498	gnl|Fabrus|VH1-69_IGHD7-27*01_IGHJ4*01	781	gnl|Fabrus|L5_IGKJ1*01	1096
499	gnl|Fabrus|VH4-34_IGHD1-7*01_IGHJ4*01	1017	gnl|Fabrus|L5_IGKJ1*01	1096
500	gnl|Fabrus|VH4-34_IGHD2-2*01_IGHJ4*01	1018	gnl|Fabrus|L5_IGKJ1*01	1096
501	gnl|Fabrus|VH4-34_IGHD3-16*01_IGHJ4*01	1019	gnl|Fabrus|L5_IGKJ1*01	1096
502	gnl|Fabrus|VH4-34_IGHD4-17*01_IGHJ4*01	1021	gnl|Fabrus|L5_IGKJ1*01	1096
503	gnl|Fabrus|VH4-34_IGHD5-12*01_IGHJ4*01	1022	gnl|Fabrus|L5_IGKJ1*01	1096
504	gnl|Fabrus|VH4-34_IGHD6-13*01_IGHJ4*01	1023	gnl|Fabrus|L5_IGKJ1*01	1096
505	gnl|Fabrus|VH4-34_IGHD6-25*01_IGHJ6*01	1024	gnl|Fabrus|L5_IGKJ1*01	1096
506	gnl|Fabrus|VH4-34_IGHD7-27*01_IGHJ4*01	1026	gnl|Fabrus|L5_IGKJ1*01	1096
507	gnl|Fabrus|VH2-26_IGHD1-20*01_IGHJ4*01	789	gnl|Fabrus|L5_IGKJ1*01	1096
508	gnl|Fabrus|VH2-26_IGHD2-2*01_IGHJ4*01	791	gnl|Fabrus|L5_IGKJ1*01	1096
509	gnl|Fabrus|VH2-26_IGHD3-10*01_IGHJ4*01	792	gnl|Fabrus|L5_IGKJ1*01	1096
510	gnl|Fabrus|VH2-26_IGHD4-11*01_IGHJ4*01	794	gnl|Fabrus|L5_IGKJ1*01	1096
511	gnl|Fabrus|VH2-26_IGHD5-18*01_IGHJ4*01	796	gnl|Fabrus|L5_IGKJ1*01	1096
512	gnl|Fabrus|VH2-26_IGHD6-13*01_IGHJ4*01	797	gnl|Fabrus|L5_IGKJ1*01	1096
513	gnl|Fabrus|VH2-26_IGHD7-27*01_IGHJ4*01	798	gnl|Fabrus|L5_IGKJ1*01	1096
514	gnl|Fabrus|VH5-51_IGHD1-14*01_IGHJ4*01	1044	gnl|Fabrus|L5_IGKJ1*01	1096
515	gnl|Fabrus|VH5-51_IGHD2-8*01_IGHJ4*01	1046	gnl|Fabrus|L5_IGKJ1*01	1096
516	gnl|Fabrus|VH5-51_IGHD3-3*01_IGHJ4*01	1048	gnl|Fabrus|L5_IGKJ1*01	1096
517	gnl|Fabrus|VH5-51_IGHD4-17*01_IGHJ4*01	1049	gnl|Fabrus|L5_IGKJ1*01	1096
518	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1050	gnl|Fabrus|L5_IGKJ1*01	1096
519	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1051	gnl|Fabrus|L5_IGKJ1*01	1096
520	gnl|Fabrus|VH5-51_IGHD6-25*01_IGHJ4*01	1052	gnl|Fabrus|L5_IGKJ1*01	1096
521	gnl|Fabrus|VH5-51_IGHD7-27*01_IGHJ4*01	1053	gnl|Fabrus|L5_IGKJ1*01	1096
522	gnl|Fabrus|VH6-1_IGHD1-1*01_IGHJ4*01	1054	gnl|Fabrus|L5_IGKJ1*01	1096
523	gnl|Fabrus|VH6-1_IGHD2-15*01_IGHJ4*01	1056	gnl|Fabrus|L5_IGKJ1*01	1096
524	gnl|Fabrus|VH6-1_IGHD3-3*01_IGHJ4*01	1059	gnl|Fabrus|L5_IGKJ1*01	1096

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
525	gnl|Fabrus|VH6-1_IGHD4-23*01_IGHJ4*01	1061	gnl|Fabrus|L5_IGKJ1*01	1096
526	gnl|Fabrus|VH6-1_IGHD4-11*01_IGHJ6*01	1060	gnl|Fabrus|L5_IGKJ1*01	1096
527	gnl|Fabrus|VH6-1_IGHD5-5*01_IGHJ4*01	1062	gnl|Fabrus|L5_IGKJ1*01	1096
528	gnl|Fabrus|VH6-1_IGHD6-13*01_IGHJ4*01	1063	gnl|Fabrus|L5_IGKJ1*01	1096
529	gnl|Fabrus|VH6-1_IGHD6-25*01_IGHJ6*01	1064	gnl|Fabrus|L5_IGKJ1*01	1096
530	gnl|Fabrus|VH6-1_IGHD7-27*01_IGHJ4*01	1065	gnl|Fabrus|L5_IGKJ1*01	1096
531	gnl|Fabrus|VH4-59_IGHD6-25*01_IGHJ3*01	1043	gnl|Fabrus|L5_IGKJ1*01	1096
532	gnl|Fabrus|VH3-48_IGHD6-6*01_IGHJ1*01	923	gnl|Fabrus|L5_IGKJ1*01	1096
533	gnl|Fabrus|VH3-30_IGHD6-6*01_IGHJ1*01	893	gnl|Fabrus|L5_IGKJ1*01	1096
534	gnl|Fabrus|VH3-66_IGHD6-6*01_IGHJ1*01	949	gnl|Fabrus|L5_IGKJ1*01	1096
535	gnl|Fabrus|VH3-53_IGHD5-5*01_IGHJ4*01	938	gnl|Fabrus|L5_IGKJ1*01	1096
536	gnl|Fabrus|VH2-5_IGHD5-12*01_IGHJ4*01	804	gnl|Fabrus|L5_IGKJ1*01	1096
537	gnl|Fabrus|VH2-70_IGHD5-12*01_IGHJ4*01	811	gnl|Fabrus|L5_IGKJ1*01	1096
538	gnl|Fabrus|VH3-15_IGHD5-12*01_IGHJ4*01	835	gnl|Fabrus|L5_IGKJ1*01	1096
539	gnl|Fabrus|VH3-15_IGHD3-10*01_IGHJ4*01	833	gnl|Fabrus|L5_IGKJ1*01	1096
540	gnl|Fabrus|VH3-49_IGHD5-18*01_IGHJ4*01	930	gnl|Fabrus|L5_IGKJ1*01	1096
541	gnl|Fabrus|VH3-49_IGHD6-13*01_IGHJ4*01	931	gnl|Fabrus|L5_IGKJ1*01	1096
542	gnl|Fabrus|VH3-72_IGHD5-18*01_IGHJ4*01	967	gnl|Fabrus|L5_IGKJ1*01	1096
543	gnl|Fabrus|VH3-72_IGHD6-6*01_IGHJ1*01	969	gnl|Fabrus|L5_IGKJ1*01	1096
544	gnl|Fabrus|VH3-73_IGHD5-12*01_IGHJ4*01	977	gnl|Fabrus|L5_IGKJ1*01	1096
545	gnl|Fabrus|VH3-73_IGHD4-23*01_IGHJ5*01	976	gnl|Fabrus|L5_IGKJ1*01	1096
546	gnl|Fabrus|VH3-43_IGHD3-22*01_IGHJ4*01	918	gnl|Fabrus|L5_IGKJ1*01	1096
547	gnl|Fabrus|VH3-43_IGHD6-13*01_IGHJ4*01	921	gnl|Fabrus|L5_IGKJ1*01	1096
548	gnl|Fabrus|VH3-9_IGHD3-22*01_IGHJ4*01	992	gnl|Fabrus|L5_IGKJ1*01	1096
549	gnl|Fabrus|VH3-9_IGHD1-7*01_IGHJ5*01	989	gnl|Fabrus|L5_IGKJ1*01	1096
550	gnl|Fabrus|VH3-9_IGHD6-13*01_IGHJ4*01	995	gnl|Fabrus|L5_IGKJ1*01	1096
551	gnl|Fabrus|VH4-39_IGHD3-10*01_IGHJ4*01	1030	gnl|Fabrus|L5_IGKJ1*01	1096
552	gnl|Fabrus|VH4-39_IGHD5-12*01_IGHJ4*01	1034	gnl|Fabrus|L5_IGKJ1*01	1096
553	gnl|Fabrus|VH1-18_IGHD6-6*01_IGHJ1*01	728	gnl|Fabrus|L5_IGKJ1*01	1096
554	gnl|Fabrus|VH1-24_IGHD5-12*01_IGHJ4*01	735	gnl|Fabrus|L5_IGKJ1*01	1096
555	gnl|Fabrus|VH1-2_IGHD1-1*01_IGHJ3*01	729	gnl|Fabrus|L5_IGKJ1*01	1096
556	gnl|Fabrus|VH1-3_IGHD6-6*01_IGHJ1*01	743	gnl|Fabrus|L5_IGKJ1*01	1096
557	gnl|Fabrus|VH1-45_IGHD3-10*01_IGHJ4*01	748	gnl|Fabrus|L5_IGKJ1*01	1096
558	gnl|Fabrus|VH1-46_IGHD1-26*01_IGHJ4*01	754	gnl|Fabrus|L5_IGKJ1*01	1096
559	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ6*01	1068	gnl|Fabrus|L5_IGKJ1*01	1096
560	gnl|Fabrus|VH2-70_IGHD3-9*01_IGHJ6*01	810	gnl|Fabrus|L5_IGKJ1*01	1096
561	gnl|Fabrus|VH1-58_IGHD3-10*01_IGHJ6*01	764	gnl|Fabrus|L5_IGKJ1*01	1096
562	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ2*01	1067	gnl|Fabrus|L5_IGKJ1*01	1096
563	gnl|Fabrus|VH4-28_IGHD3-9*01_IGHJ6*01	1002	gnl|Fabrus|L5_IGKJ1*01	1096
564	gnl|Fabrus|VH4-31_IGHD2-15*01_IGHJ2*01	1008	gnl|Fabrus|L5_IGKJ1*01	1096
565	gnl|Fabrus|VH2-5_IGHD3-9*01_IGHJ6*01	803	gnl|Fabrus|L5_IGKJ1*01	1096
566	gnl|Fabrus|VH1-8_IGHD2-15*01_IGHJ6*01	783	gnl|Fabrus|L5_IGKJ1*01	1096

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
567	gnl|Fabrus|VH2-70_IGHD2-15*01_IGHJ2*01	808	gnl|Fabrus|L5_IGKJ1*01	1096
568	gnl|Fabrus|VH3-38_IGHD3-10*01_IGHJ4*01	907	gnl|Fabrus|L5_IGKJ1*01	1096
569	gnl|Fabrus|VH3-16_IGHD1-7*01_IGHJ6*01	838	gnl|Fabrus|L5_IGKJ1*01	1096
570	gnl|Fabrus|VH3-73_IGHD3-9*01_IGHJ6*01	974	gnl|Fabrus|L5_IGKJ1*01	1096
571	gnl|Fabrus|VH3-11_IGHD3-9*01_IGHJ6*01	816	gnl|Fabrus|L5_IGKJ1*01	1096
572	gnl|Fabrus|VH3-11_IGHD6-6*01_IGHJ1*01	820	gnl|Fabrus|L5_IGKJ1*01	1096
573	gnl|Fabrus|VH3-20_IGHD5-12*01_IGHJ4*01	852	gnl|Fabrus|L5_IGKJ1*01	1096
574	gnl|Fabrus|VH3-16_IGHD2-15*01_IGHJ2*01	839	gnl|Fabrus|L5_IGKJ1*01	1096
575	gnl|Fabrus|VH3-7_IGHD6-6*01_IGHJ1*01	960	gnl|Fabrus|L5_IGKJ1*01	1096
576	gnl|Fabrus|VH3-16_IGHD6-13*01_IGHJ4*01	844	gnl|Fabrus|L5_IGKJ1*01	1096
577	gnl|Fabrus|VH3-23_IGHD1-1*01_IGHJ4*01	863	gnl|Fabrus|L8_IGKJ1*01	1098
578	gnl|Fabrus|VH3-23_IGHD2-15*01_IGHJ4*01	866	gnl|Fabrus|L8_IGKJ1*01	1098
579	gnl|Fabrus|VH3-23_IGHD3-22*01_IGHJ4*01	870	gnl|Fabrus|L8_IGKJ1*01	1098
580	gnl|Fabrus|VH3-23_IGHD4-11*01_IGHJ4*01	872	gnl|Fabrus|L8_IGKJ1*01	1098
581	gnl|Fabrus|VH3-23_IGHD5-12*01_IGHJ4*01	874	gnl|Fabrus|L8_IGKJ1*01	1098
582	gnl|Fabrus|VH3-23_IGHD5-5*01_IGHJ4*01	876	gnl|Fabrus|L8_IGKJ1*01	1098
583	gnl|Fabrus|VH3-23_IGHD6-13*01_IGHJ4*01	877	gnl|Fabrus|L8_IGKJ1*01	1098
584	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ4*01	880	gnl|Fabrus|L8_IGKJ1*01	1098
585	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ6*01	881	gnl|Fabrus|L8_IGKJ1*01	1098
586	gnl|Fabrus|VH1-69_IGHD1-14*01_IGHJ4*01	770	gnl|Fabrus|L8_IGKJ1*01	1098
587	gnl|Fabrus|VH1-69_IGHD2-2*01_IGHJ4*01	771	gnl|Fabrus|L8_IGKJ1*01	1098
588	gnl|Fabrus|VH1-69_IGHD2-8*01_IGHJ6*01	772	gnl|Fabrus|L8_IGKJ1*01	1098
589	gnl|Fabrus|VH1-69_IGHD3-16*01_IGHJ4*01	773	gnl|Fabrus|L8_IGKJ1*01	1098
590	gnl|Fabrus|VH1-69_IGHD3-3*01_IGHJ4*01	774	gnl|Fabrus|L8_IGKJ1*01	1098
591	gnl|Fabrus|VH1-69_IGHD4-17*01_IGHJ4*01	776	gnl|Fabrus|L8_IGKJ1*01	1098
592	gnl|Fabrus|VH1-69_IGHD5-12*01_IGHJ4*01	777	gnl|Fabrus|L8_IGKJ1*01	1098
593	gnl|Fabrus|VH1-69_IGHD6-19*01_IGHJ4*01	779	gnl|Fabrus|L8_IGKJ1*01	1098
594	gnl|Fabrus|VH1-69_IGHD7-27*01_IGHJ4*01	781	gnl|Fabrus|L8_IGKJ1*01	1098
595	gnl|Fabrus|VH4-34_IGHD1-7*01_IGHJ4*01	1017	gnl|Fabrus|L8_IGKJ1*01	1098
596	gnl|Fabrus|VH4-34_IGHD2-2*01_IGHJ4*01	1018	gnl|Fabrus|L8_IGKJ1*01	1098
597	gnl|Fabrus|VH4-34_IGHD3-16*01_IGHJ4*01	1019	gnl|Fabrus|L8_IGKJ1*01	1098
598	gnl|Fabrus|VH4-34_IGHD4-17*01_IGHJ4*01	1021	gnl|Fabrus|L8_IGKJ1*01	1098
599	gnl|Fabrus|VH4-34_IGHD5-12*01_IGHJ4*01	1022	gnl|Fabrus|L8_IGKJ1*01	1098
600	gnl|Fabrus|VH4-34_IGHD6-13*01_IGHJ4*01	1023	gnl|Fabrus|L8_IGKJ1*01	1098
601	gnl|Fabrus|VH4-34_IGHD6-25*01_IGHJ6*01	1024	gnl|Fabrus|L8_IGKJ1*01	1098
602	gnl|Fabrus|VH4-34_IGHD7-27*01_IGHJ4*01	1026	gnl|Fabrus|L8_IGKJ1*01	1098
603	gnl|Fabrus|VH2-26_IGHD1-20*01_IGHJ4*01	789	gnl|Fabrus|L8_IGKJ1*01	1098
604	gnl|Fabrus|VH2-26_IGHD2-2*01_IGHJ4*01	791	gnl|Fabrus|L8_IGKJ1*01	1098
605	gnl|Fabrus|VH2-26_IGHD3-10*01_IGHJ4*01	792	gnl|Fabrus|L8_IGKJ1*01	1098
606	gnl|Fabrus|VH2-26_IGHD4-11*01_IGHJ4*01	794	gnl|Fabrus|L8_IGKJ1*01	1098
607	gnl|Fabrus|VH2-26_IGHD5-18*01_IGHJ4*01	796	gnl|Fabrus|L8_IGKJ1*01	1098
608	gnl|Fabrus|VH2-26_IGHD6-13*01_IGHJ4*01	797	gnl|Fabrus|L8_IGKJ1*01	1098

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
609	gnl|Fabrus|VH2-26_IGHD7-27*01_IGHJ4*01	798	gnl|Fabrus|L8_IGKJ1*01	1098
610	gnl|Fabrus|VH5-51_IGHD1-14*01_IGHJ4*01	1044	gnl|Fabrus|L8_IGKJ1*01	1098
611	gnl|Fabrus|VH5-51_IGHD2-8*01_IGHJ4*01	1046	gnl|Fabrus|L8_IGKJ1*01	1098
612	gnl|Fabrus|VH5-51_IGHD3-3*01_IGHJ4*01	1048	gnl|Fabrus|L8_IGKJ1*01	1098
613	gnl|Fabrus|VH5-51_IGHD4-17*01_IGHJ4*01	1049	gnl|Fabrus|L8_IGKJ1*01	1098
614	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1050	gnl|Fabrus|L8_IGKJ1*01	1098
615	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1051	gnl|Fabrus|L8_IGKJ1*01	1098
616	gnl|Fabrus|VH5-51_IGHD6-25*01_IGHJ4*01	1052	gnl|Fabrus|L8_IGKJ1*01	1098
617	gnl|Fabrus|VH5-51_IGHD7-27*01_IGHJ4*01	1053	gnl|Fabrus|L8_IGKJ1*01	1098
618	gnl|Fabrus|VH6-1_IGHD1-1*01_IGHJ4*01	1054	gnl|Fabrus|L8_IGKJ1*01	1098
619	gnl|Fabrus|VH6-1_IGHD2-15*01_IGHJ4*01	1056	gnl|Fabrus|L8_IGKJ1*01	1098
620	gnl|Fabrus|VH6-1_IGHD3-3*01_IGHJ4*01	1059	gnl|Fabrus|L8_IGKJ1*01	1098
621	gnl|Fabrus|VH6-1_IGHD4-23*01_IGHJ4*01	1061	gnl|Fabrus|L8_IGKJ1*01	1098
622	gnl|Fabrus|VH6-1_IGHD4-11*01_IGHJ6*01	1060	gnl|Fabrus|L8_IGKJ1*01	1098
623	gnl|Fabrus|VH6-1_IGHD5-5*01_IGHJ4*01	1062	gnl|Fabrus|L8_IGKJ1*01	1098
624	gnl|Fabrus|VH6-1_IGHD6-13*01_IGHJ4*01	1063	gnl|Fabrus|L8_IGKJ1*01	1098
625	gnl|Fabrus|VH6-1_IGHD6-25*01_IGHJ6*01	1064	gnl|Fabrus|L8_IGKJ1*01	1098
626	gnl|Fabrus|VH6-1_IGHD7-27*01_IGHJ4*01	1065	gnl|Fabrus|L8_IGKJ1*01	1098
627	gnl|Fabrus|VH4-59_IGHD6-25*01_IGHJ3*01	1043	gnl|Fabrus|L8_IGKJ1*01	1098
628	gnl|Fabrus|VH3-48_IGHD6-6*01_IGHJ1*01	923	gnl|Fabrus|L8_IGKJ1*01	1098
629	gnl|Fabrus|VH3-30_IGHD6-6*01_IGHJ1*01	893	gnl|Fabrus|L8_IGKJ1*01	1098
630	gnl|Fabrus|VH3-66_IGHD6-6*01_IGHJ1*01	949	gnl|Fabrus|L8_IGKJ1*01	1098
631	gnl|Fabrus|VH3-53_IGHD5-5*01_IGHJ4*01	938	gnl|Fabrus|L8_IGKJ1*01	1098
632	gnl|Fabrus|VH2-5_IGHD5-12*01_IGHJ4*01	804	gnl|Fabrus|L8_IGKJ1*01	1098
633	gnl|Fabrus|VH2-70_IGHD5-12*01_IGHJ4*01	811	gnl|Fabrus|L8_IGKJ1*01	1098
634	gnl|Fabrus|VH3-15_IGHD5-12*01_IGHJ4*01	835	gnl|Fabrus|L8_IGKJ1*01	1098
635	gnl|Fabrus|VH3-15_IGHD3-10*01_IGHJ4*01	833	gnl|Fabrus|L8_IGKJ1*01	1098
636	gnl|Fabrus|VH3-49_IGHD5-18*01_IGHJ4*01	930	gnl|Fabrus|L8_IGKJ1*01	1098
637	gnl|Fabrus|VH3-49_IGHD6-13*01_IGHJ4*01	931	gnl|Fabrus|L8_IGKJ1*01	1098
638	gnl|Fabrus|VH3-72_IGHD5-18*01_IGHJ4*01	967	gnl|Fabrus|L8_IGKJ1*01	1098
639	gnl|Fabrus|VH3-72_IGHD6-6*01_IGHJ1*01	969	gnl|Fabrus|L8_IGKJ1*01	1098
640	gnl|Fabrus|VH3-73_IGHD5-12*01_IGHJ4*01	977	gnl|Fabrus|L8_IGKJ1*01	1098
641	gnl|Fabrus|VH3-73_IGHD4-23*01_IGHJ5*01	976	gnl|Fabrus|L8_IGKJ1*01	1098
642	gnl|Fabrus|VH3-43_IGHD3-22*01_IGHJ4*01	918	gnl|Fabrus|L8_IGKJ1*01	1098
643	gnl|Fabrus|VH3-43_IGHD6-13*01_IGHJ4*01	921	gnl|Fabrus|L8_IGKJ1*01	1098
644	gnl|Fabrus|VH3-9_IGHD3-22*01_IGHJ4*01	992	gnl|Fabrus|L8_IGKJ1*01	1098
645	gnl|Fabrus|VH3-9_IGHD1-7*01_IGHJ5*01	989	gnl|Fabrus|L8_IGKJ1*01	1098
646	gnl|Fabrus|VH3-9_IGHD6-13*01_IGHJ4*01	995	gnl|Fabrus|L8_IGKJ1*01	1098
647	gnl|Fabrus|VH4-39_IGHD3-10*01_IGHJ4*01	1030	gnl|Fabrus|L8_IGKJ1*01	1098
648	gnl|Fabrus|VH4-39_IGHD5-12*01_IGHJ4*01	1034	gnl|Fabrus|L8_IGKJ1*01	1098
649	gnl|Fabrus|VH1-18_IGHD6-6*01_IGHJ1*01	728	gnl|Fabrus|L8_IGKJ1*01	1098
650	gnl|Fabrus|VH1-24_IGHD5-12*01_IGHJ4*01	735	gnl|Fabrus|L8_IGKJ1*01	1098

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
651	gnl|Fabrus|VH1-2_IGHD1-1*01_IGHJ3*01	729	gnl|Fabrus|L8_IGKJ1*01	1098
652	gnl|Fabrus|VH1-3_IGHD6-6*01_IGHJ1*01	743	gnl|Fabrus|L8_IGKJ1*01	1098
653	gnl|Fabrus|VH1-45_IGHD3-10*01_IGHJ4*01	748	gnl|Fabrus|L8_IGKJ1*01	1098
654	gnl|Fabrus|VH1-46_IGHD1-26*01_IGHJ4*01	754	gnl|Fabrus|L8_IGKJ1*01	1098
655	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ6*01	1068	gnl|Fabrus|L8_IGKJ1*01	1098
656	gnl|Fabrus|VH2-70_IGHD3-9*01_IGHJ6*01	810	gnl|Fabrus|L8_IGKJ1*01	1098
657	gnl|Fabrus|VH1-58_IGHD3-10*01_IGHJ6*01	764	gnl|Fabrus|L8_IGKJ1*01	1098
658	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ2*01	1067	gnl|Fabrus|L8_IGKJ1*01	1098
659	gnl|Fabrus|VH4-28_IGHD3-9*01_IGHJ6*01	1002	gnl|Fabrus|L8_IGKJ1*01	1098
660	gnl|Fabrus|VH4-31_IGHD2-15*01_IGHJ2*01	1008	gnl|Fabrus|L8_IGKJ1*01	1098
661	gnl|Fabrus|VH2-5_IGHD3-9*01_IGHJ6*01	803	gnl|Fabrus|L8_IGKJ1*01	1098
662	gnl|Fabrus|VH1-8_IGHD2-15*01_IGHJ6*01	783	gnl|Fabrus|L8_IGKJ1*01	1098
663	gnl|Fabrus|VH2-70_IGHD2-15*01_IGHJ2*01	808	gnl|Fabrus|L8_IGKJ1*01	1098
664	gnl|Fabrus|VH3-38_IGHD3-10*01_IGHJ4*01	907	gnl|Fabrus|L8_IGKJ1*01	1098
665	gnl|Fabrus|VH3-16_IGHD1-7*01_IGHJ6*01	838	gnl|Fabrus|L8_IGKJ1*01	1098
666	gnl|Fabrus|VH3-73_IGHD3-9*01_IGHJ6*01	974	gnl|Fabrus|L8_IGKJ1*01	1098
667	gnl|Fabrus|VH3-11_IGHD3-9*01_IGHJ6*01	816	gnl|Fabrus|L8_IGKJ1*01	1098
668	gnl|Fabrus|VH3-11_IGHD6-6*01_IGHJ1*01	820	gnl|Fabrus|L8_IGKJ1*01	1098
669	gnl|Fabrus|VH3-20_IGHD5-12*01_IGHJ4*01	852	gnl|Fabrus|L8_IGKJ1*01	1098
670	gnl|Fabrus|VH3-16_IGHD2-15*01_IGHJ2*01	839	gnl|Fabrus|L8_IGKJ1*01	1098
671	gnl|Fabrus|VH3-7_IGHD6-6*01_IGHJ1*01	960	gnl|Fabrus|L8_IGKJ1*01	1098
672	gnl|Fabrus|VH3-16_IGHD6-13*01_IGHJ4*01	844	gnl|Fabrus|L8_IGKJ1*01	1098
673	gnl|Fabrus|VH3-23_IGHD1-1*01_IGHJ4*01	863	gnl|Fabrus|L11_IGKJ1*01	1087
674	gnl|Fabrus|VH3-23_IGHD2-15*01_IGHJ4*01	866	gnl|Fabrus|L11_IGKJ1*01	1087
675	gnl|Fabrus|VH3-23_IGHD3-22*01_IGHJ4*01	870	gnl|Fabrus|L11_IGKJ1*01	1087
676	gnl|Fabrus|VH3-23_IGHD4-11*01_IGHJ4*01	872	gnl|Fabrus|L11_IGKJ1*01	1087
677	gnl|Fabrus|VH3-23_IGHD5-12*01_IGHJ4*01	874	gnl|Fabrus|L11_IGKJ1*01	1087
678	gnl|Fabrus|VH3-23_IGHD5-5*01_IGHJ4*01	876	gnl|Fabrus|L11_IGKJ1*01	1087
679	gnl|Fabrus|VH3-23_IGHD6-13*01_IGHJ4*01	877	gnl|Fabrus|L11_IGKJ1*01	1087
680	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ4*01	880	gnl|Fabrus|L11_IGKJ1*01	1087
681	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ6*01	881	gnl|Fabrus|L11_IGKJ1*01	1087
682	gnl|Fabrus|VH1-69_IGHD1-14*01_IGHJ4*01	770	gnl|Fabrus|L11_IGKJ1*01	1087
683	gnl|Fabrus|VH1-69_IGHD2-2*01_IGHJ4*01	771	gnl|Fabrus|L11_IGKJ1*01	1087
684	gnl|Fabrus|VH1-69_IGHD2-8*01_IGHJ6*01	772	gnl|Fabrus|L11_IGKJ1*01	1087
685	gnl|Fabrus|VH1-69_IGHD3-16*01_IGHJ4*01	773	gnl|Fabrus|L11_IGKJ1*01	1087
686	gnl|Fabrus|VH1-69_IGHD3-3*01_IGHJ4*01	774	gnl|Fabrus|L11_IGKJ1*01	1087
687	gnl|Fabrus|VH1-69_IGHD4-17*01_IGHJ4*01	776	gnl|Fabrus|L11_IGKJ1*01	1087
688	gnl|Fabrus|VH1-69_IGHD5-12*01_IGHJ4*01	777	gnl|Fabrus|L11_IGKJ1*01	1087
689	gnl|Fabrus|VH1-69_IGHD6-19*01_IGHJ4*01	779	gnl|Fabrus|L11_IGKJ1*01	1087
690	gnl|Fabrus|VH1-69_IGHD7-27*01_IGHJ4*01	781	gnl|Fabrus|L11_IGKJ1*01	1087
691	gnl|Fabrus|VH4-34_IGHD1-7*01_IGHJ4*01	1017	gnl|Fabrus|L11_IGKJ1*01	1087
692	gnl|Fabrus|VH4-34_IGHD2-2*01_IGHJ4*01	1018	gnl|Fabrus|L11_IGKJ1*01	1087

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
693	gnl|Fabrus|VH4-34_IGHD3-16*01_IGHJ4*01	1019	gnl|Fabrus|L11_IGKJ1*01	1087
694	gnl|Fabrus|VH4-34_IGHD4-17*01_IGHJ4*01	1021	gnl|Fabrus|L11_IGKJ1*01	1087
695	gnl|Fabrus|VH4-34_IGHD5-12*01_IGHJ4*01	1022	gnl|Fabrus|L11_IGKJ1*01	1087
696	gnl|Fabrus|VH4-34_IGHD6-13*01_IGHJ4*01	1023	gnl|Fabrus|L11_IGKJ1*01	1087
697	gnl|Fabrus|VH4-34_IGHD6-25*01_IGHJ6*01	1024	gnl|Fabrus|L11_IGKJ1*01	1087
698	gnl|Fabrus|VH4-34_IGHD7-27*01_IGHJ4*01	1026	gnl|Fabrus|L11_IGKJ1*01	1087
699	gnl|Fabrus|VH2-26_IGHD1-20*01_IGHJ4*01	789	gnl|Fabrus|L11_IGKJ1*01	1087
700	gnl|Fabrus|VH2-26_IGHD2-2*01_IGHJ4*01	791	gnl|Fabrus|L11_IGKJ1*01	1087
701	gnl|Fabrus|VH2-26_IGHD3-10*01_IGHJ4*01	792	gnl|Fabrus|L11_IGKJ1*01	1087
702	gnl|Fabrus|VH2-26_IGHD4-11*01_IGHJ4*01	794	gnl|Fabrus|L11_IGKJ1*01	1087
703	gnl|Fabrus|VH2-26_IGHD5-18*01_IGHJ4*01	796	gnl|Fabrus|L11_IGKJ1*01	1087
704	gnl|Fabrus|VH2-26_IGHD6-13*01_IGHJ4*01	797	gnl|Fabrus|L11_IGKJ1*01	1087
705	gnl|Fabrus|VH2-26_IGHD7-27*01_IGHJ4*01	798	gnl|Fabrus|L11_IGKJ1*01	1087
706	gnl|Fabrus|VH5-51_IGHD1-14*01_IGHJ4*01	1044	gnl|Fabrus|L11_IGKJ1*01	1087
707	gnl|Fabrus|VH5-51_IGHD2-8*01_IGHJ4*01	1046	gnl|Fabrus|L11_IGKJ1*01	1087
708	gnl|Fabrus|VH5-51_IGHD3-3*01_IGHJ4*01	1048	gnl|Fabrus|L11_IGKJ1*01	1087
709	gnl|Fabrus|VH5-51_IGHD4-17*01_IGHJ4*01	1049	gnl|Fabrus|L11_IGKJ1*01	1087
710	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1050	gnl|Fabrus|L11_IGKJ1*01	1087
711	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1051	gnl|Fabrus|L11_IGKJ1*01	1087
712	gnl|Fabrus|VH5-51_IGHD6-25*01_IGHJ4*01	1052	gnl|Fabrus|L11_IGKJ1*01	1087
713	gnl|Fabrus|VH5-51_IGHD7-27*01_IGHJ4*01	1053	gnl|Fabrus|L11_IGKJ1*01	1087
714	gnl|Fabrus|VH6-1_IGHD1-1*01_IGHJ4*01	1054	gnl|Fabrus|L11_IGKJ1*01	1087
715	gnl|Fabrus|VH6-1_IGHD2-15*01_IGHJ4*01	1056	gnl|Fabrus|L11_IGKJ1*01	1087
716	gnl|Fabrus|VH6-1_IGHD3-3*01_IGHJ4*01	1059	gnl|Fabrus|L11_IGKJ1*01	1087
717	gnl|Fabrus|VH6-1_IGHD4-23*01_IGHJ4*01	1061	gnl|Fabrus|L11_IGKJ1*01	1087
718	gnl|Fabrus|VH6-1_IGHD4-11*01_IGHJ6*01	1060	gnl|Fabrus|L11_IGKJ1*01	1087
719	gnl|Fabrus|VH6-1_IGHD5-5*01_IGHJ4*01	1062	gnl|Fabrus|L11_IGKJ1*01	1087
720	gnl|Fabrus|VH6-1_IGHD6-13*01_IGHJ4*01	1063	gnl|Fabrus|L11_IGKJ1*01	1087
721	gnl|Fabrus|VH6-1_IGHD6-25*01_IGHJ6*01	1064	gnl|Fabrus|L11_IGKJ1*01	1087
722	gnl|Fabrus|VH6-1_IGHD7-27*01_IGHJ4*01	1065	gnl|Fabrus|L11_IGKJ1*01	1087
723	gnl|Fabrus|VH4-59_IGHD6-25*01_IGHJ3*01	1043	gnl|Fabrus|L11_IGKJ1*01	1087
724	gnl|Fabrus|VH3-48_IGHD6-6*01_IGHJ1*01	923	gnl|Fabrus|L11_IGKJ1*01	1087
725	gnl|Fabrus|VH3-30_IGHD6-6*01_IGHJ1*01	893	gnl|Fabrus|L11_IGKJ1*01	1087
726	gnl|Fabrus|VH3-66_IGHD6-6*01_IGHJ1*01	949	gnl|Fabrus|L11_IGKJ1*01	1087
727	gnl|Fabrus|VH3-53_IGHD5-5*01_IGHJ4*01	938	gnl|Fabrus|L11_IGKJ1*01	1087
728	gnl|Fabrus|VH2-5_IGHD5-12*01_IGHJ4*01	804	gnl|Fabrus|L11_IGKJ1*01	1087
729	gnl|Fabrus|VH2-70_IGHD5-12*01_IGHJ4*01	811	gnl|Fabrus|L11_IGKJ1*01	1087
730	gnl|Fabrus|VH3-15_IGHD5-12*01_IGHJ4*01	835	gnl|Fabrus|L11_IGKJ1*01	1087
731	gnl|Fabrus|VH3-15_IGHD3-10*01_IGHJ4*01	833	gnl|Fabrus|L11_IGKJ1*01	1087
732	gnl|Fabrus|VH3-49_IGHD5-18*01_IGHJ4*01	930	gnl|Fabrus|L11_IGKJ1*01	1087
733	gnl|Fabrus|VH3-49_IGHD6-13*01_IGHJ4*01	931	gnl|Fabrus|L11_IGKJ1*01	1087
734	gnl|Fabrus|VH3-72_IGHD5-18*01_IGHJ4*01	967	gnl|Fabrus|L11_IGKJ1*01	1087

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
735	gnl|Fabrus|VH3-72_IGHD6-6*01_IGHJ1*01	969	gnl|Fabrus|L11_IGKJ1*01	1087
736	gnl|Fabrus|VH3-73_IGHD5-12*01_IGHJ4*01	977	gnl|Fabrus|L11_IGKJ1*01	1087
737	gnl|Fabrus|VH3-73_IGHD4-23*01_IGHJ5*01	976	gnl|Fabrus|L11_IGKJ1*01	1087
738	gnl|Fabrus|VH3-43_IGHD3-22*01_IGHJ4*01	918	gnl|Fabrus|L11_IGKJ1*01	1087
739	gnl|Fabrus|VH3-43_IGHD6-13*01_IGHJ4*01	921	gnl|Fabrus|L11_IGKJ1*01	1087
740	gnl|Fabrus|VH3-9_IGHD3-22*01_IGHJ4*01	992	gnl|Fabrus|L11_IGKJ1*01	1087
741	gnl|Fabrus|VH3-9_IGHD1-7*01_IGHJ5*01	989	gnl|Fabrus|L11_IGKJ1*01	1087
742	gnl|Fabrus|VH3-9_IGHD6-13*01_IGHJ4*01	995	gnl|Fabrus|L11_IGKJ1*01	1087
743	gnl|Fabrus|VH4-39_IGHD3-10*01_IGHJ4*01	1030	gnl|Fabrus|L11_IGKJ1*01	1087
744	gnl|Fabrus|VH4-39_IGHD5-12*01_IGHJ4*01	1034	gnl|Fabrus|L11_IGKJ1*01	1087
745	gnl|Fabrus|VH1-18_IGHD6-6*01_IGHJ1*01	728	gnl|Fabrus|L11_IGKJ1*01	1087
746	gnl|Fabrus|VH1-24_IGHD5-12*01_IGHJ4*01	735	gnl|Fabrus|L11_IGKJ1*01	1087
747	gnl|Fabrus|VH1-2_IGHD1-1*01_IGHJ3*01	729	gnl|Fabrus|L11_IGKJ1*01	1087
748	gnl|Fabrus|VH1-3_IGHD6-6*01_IGHJ1*01	743	gnl|Fabrus|L11_IGKJ1*01	1087
749	gnl|Fabrus|VH1-45_IGHD3-10*01_IGHJ4*01	748	gnl|Fabrus|L11_IGKJ1*01	1087
750	gnl|Fabrus|VH1-46_IGHD1-26*01_IGHJ4*01	754	gnl|Fabrus|L11_IGKJ1*01	1087
751	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ6*01	1068	gnl|Fabrus|L11_IGKJ1*01	1087
752	gnl|Fabrus|VH2-70_IGHD3-9*01_IGHJ6*01	810	gnl|Fabrus|L11_IGKJ1*01	1087
753	gnl|Fabrus|VH1-58_IGHD3-10*01_IGHJ6*01	764	gnl|Fabrus|L11_IGKJ1*01	1087
754	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ2*01	1067	gnl|Fabrus|L11_IGKJ1*01	1087
755	gnl|Fabrus|VH4-28_IGHD3-9*01_IGHJ6*01	1002	gnl|Fabrus|L11_IGKJ1*01	1087
756	gnl|Fabrus|VH4-31_IGHD2-15*01_IGHJ2*01	1008	gnl|Fabrus|L11_IGKJ1*01	1087
757	gnl|Fabrus|VH2-5_IGHD3-9*01_IGHJ6*01	803	gnl|Fabrus|L11_IGKJ1*01	1087
758	gnl|Fabrus|VH1-8_IGHD2-15*01_IGHJ6*01	783	gnl|Fabrus|L11_IGKJ1*01	1087
759	gnl|Fabrus|VH2-70_IGHD2-15*01_IGHJ2*01	808	gnl|Fabrus|L11_IGKJ1*01	1087
760	gnl|Fabrus|VH3-38_IGHD3-10*01_IGHJ4*01	907	gnl|Fabrus|L11_IGKJ1*01	1087
761	gnl|Fabrus|VH3-16_IGHD1-7*01_IGHJ6*01	838	gnl|Fabrus|L11_IGKJ1*01	1087
762	gnl|Fabrus|VH3-73_IGHD3-9*01_IGHJ6*01	974	gnl|Fabrus|L11_IGKJ1*01	1087
763	gnl|Fabrus|VH3-11_IGHD3-9*01_IGHJ6*01	816	gnl|Fabrus|L11_IGKJ1*01	1087
764	gnl|Fabrus|VH3-11_IGHD6-6*01_IGHJ1*01	820	gnl|Fabrus|L11_IGKJ1*01	1087
765	gnl|Fabrus|VH3-20_IGHD5-12*01_IGHJ4*01	852	gnl|Fabrus|L11_IGKJ1*01	1087
766	gnl|Fabrus|VH3-16_IGHD2-15*01_IGHJ2*01	839	gnl|Fabrus|L11_IGKJ1*01	1087
767	gnl|Fabrus|VH3-7_IGHD6-6*01_IGHJ1*01	960	gnl|Fabrus|L11_IGKJ1*01	1087
768	gnl|Fabrus|VH3-16_IGHD6-13*01_IGHJ4*01	844	gnl|Fabrus|L11_IGKJ1*01	1087
769	gnl|Fabrus|VH3-23_IGHD1-1*01_IGHJ4*01	863	gnl|Fabrus|L12_IGKJ1*01	1088
770	gnl|Fabrus|VH3-23_IGHD2-15*01_IGHJ4*01	866	gnl|Fabrus|L12_IGKJ1*01	1088
771	gnl|Fabrus|VH3-23_IGHD3-22*01_IGHJ4*01	870	gnl|Fabrus|L12_IGKJ1*01	1088
772	gnl|Fabrus|VH3-23_IGHD4-11*01_IGHJ4*01	872	gnl|Fabrus|L12_IGKJ1*01	1088
773	gnl|Fabrus|VH3-23_IGHD5-12*01_IGHJ4*01	874	gnl|Fabrus|L12_IGKJ1*01	1088
774	gnl|Fabrus|VH3-23_IGHD5-5*01_IGHJ4*01	876	gnl|Fabrus|L12_IGKJ1*01	1088
775	gnl|Fabrus|VH3-23_IGHD6-13*01_IGHJ4*01	877	gnl|Fabrus|L12_IGKJ1*01	1088
776	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ4*01	880	gnl|Fabrus|L12_IGKJ1*01	1088

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
777	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ6*01	881	gnl|Fabrus|L12_IGKJ1*01	1088
778	gnl|Fabrus|VH1-69_IGHD1-14*01_IGHJ4*01	770	gnl|Fabrus|L12_IGKJ1*01	1088
779	gnl|Fabrus|VH1-69_IGHD2-2*01_IGHJ4*01	771	gnl|Fabrus|L12_IGKJ1*01	1088
780	gnl|Fabrus|VH1-69_IGHD2-8*01_IGHJ6*01	772	gnl|Fabrus|L12_IGKJ1*01	1088
781	gnl|Fabrus|VH1-69_IGHD3-16*01_IGHJ4*01	773	gnl|Fabrus|L12_IGKJ1*01	1088
782	gnl|Fabrus|VH1-69_IGHD3-3*01_IGHJ4*01	774	gnl|Fabrus|L12_IGKJ1*01	1088
783	gnl|Fabrus|VH1-69_IGHD4-17*01_IGHJ4*01	776	gnl|Fabrus|L12_IGKJ1*01	1088
784	gnl|Fabrus|VH1-69_IGHD5-12*01_IGHJ4*01	777	gnl|Fabrus|L12_IGKJ1*01	1088
785	gnl|Fabrus|VH1-69_IGHD6-19*01_IGHJ4*01	779	gnl|Fabrus|L12_IGKJ1*01	1088
786	gnl|Fabrus|VH1-69_IGHD7-27*01_IGHJ4*01	781	gnl|Fabrus|L12_IGKJ1*01	1088
787	gnl|Fabrus|VH4-34_IGHD1-7*01_IGHJ4*01	1017	gnl|Fabrus|L12_IGKJ1*01	1088
788	gnl|Fabrus|VH4-34_IGHD2-2*01_IGHJ4*01	1018	gnl|Fabrus|L12_IGKJ1*01	1088
789	gnl|Fabrus|VH4-34_IGHD3-16*01_IGHJ4*01	1019	gnl|Fabrus|L12_IGKJ1*01	1088
790	gnl|Fabrus|VH4-34_IGHD4-17*01_IGHJ4*01	1021	gnl|Fabrus|L12_IGKJ1*01	1088
791	gnl|Fabrus|VH4-34_IGHD5-12*01_IGHJ4*01	1022	gnl|Fabrus|L12_IGKJ1*01	1088
792	gnl|Fabrus|VH4-34_IGHD6-13*01_IGHJ4*01	1023	gnl|Fabrus|L12_IGKJ1*01	1088
793	gnl|Fabrus|VH4-34_IGHD6-25*01_IGHJ6*01	1024	gnl|Fabrus|L12_IGKJ1*01	1088
794	gnl|Fabrus|VH4-34_IGHD7-27*01_IGHJ4*01	1026	gnl|Fabrus|L12_IGKJ1*01	1088
795	gnl|Fabrus|VH2-26_IGHD1-20*01_IGHJ4*01	789	gnl|Fabrus|L12_IGKJ1*01	1088
796	gnl|Fabrus|VH2-26_IGHD2-2*01_IGHJ4*01	791	gnl|Fabrus|L12_IGKJ1*01	1088
797	gnl|Fabrus|VH2-26_IGHD3-10*01_IGHJ4*01	792	gnl|Fabrus|L12_IGKJ1*01	1088
798	gnl|Fabrus|VH2-26_IGHD4-11*01_IGHJ4*01	794	gnl|Fabrus|L12_IGKJ1*01	1088
799	gnl|Fabrus|VH2-26_IGHD5-18*01_IGHJ4*01	796	gnl|Fabrus|L12_IGKJ1*01	1088
800	gnl|Fabrus|VH2-26_IGHD6-13*01_IGHJ4*01	797	gnl|Fabrus|L12_IGKJ1*01	1088
801	gnl|Fabrus|VH2-26_IGHD7-27*01_IGHJ4*01	798	gnl|Fabrus|L12_IGKJ1*01	1088
802	gnl|Fabrus|VH5-51_IGHD1-14*01_IGHJ4*01	1044	gnl|Fabrus|L12_IGKJ1*01	1088
803	gnl|Fabrus|VH5-51_IGHD2-8*01_IGHJ4*01	1046	gnl|Fabrus|L12_IGKJ1*01	1088
804	gnl|Fabrus|VH5-51_IGHD3-3*01_IGHJ4*01	1048	gnl|Fabrus|L12_IGKJ1*01	1088
805	gnl|Fabrus|VH5-51_IGHD4-17*01_IGHJ4*01	1049	gnl|Fabrus|L12_IGKJ1*01	1088
806	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1050	gnl|Fabrus|L12_IGKJ1*01	1088
807	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1051	gnl|Fabrus|L12_IGKJ1*01	1088
808	gnl|Fabrus|VH5-51_IGHD6-25*01_IGHJ4*01	1052	gnl|Fabrus|L12_IGKJ1*01	1088
809	gnl|Fabrus|VH5-51_IGHD7-27*01_IGHJ4*01	1053	gnl|Fabrus|L12_IGKJ1*01	1088
810	gnl|Fabrus|VH6-1_IGHD1-1*01_IGHJ4*01	1054	gnl|Fabrus|L12_IGKJ1*01	1088
811	gnl|Fabrus|VH6-1_IGHD2-15*01_IGHJ4*01	1056	gnl|Fabrus|L12_IGKJ1*01	1088
812	gnl|Fabrus|VH6-1_IGHD3-3*01_IGHJ4*01	1059	gnl|Fabrus|L12_IGKJ1*01	1088
813	gnl|Fabrus|VH6-1_IGHD4-23*01_IGHJ4*01	1061	gnl|Fabrus|L12_IGKJ1*01	1088
814	gnl|Fabrus|VH6-1_IGHD4-11*01_IGHJ6*01	1060	gnl|Fabrus|L12_IGKJ1*01	1088
815	gnl|Fabrus|VH6-1_IGHD5-5*01_IGHJ4*01	1062	gnl|Fabrus|L12_IGKJ1*01	1088
816	gnl|Fabrus|VH6-1_IGHD6-13*01_IGHJ4*01	1063	gnl|Fabrus|L12_IGKJ1*01	1088
817	gnl|Fabrus|VH6-1_IGHD6-25*01_IGHJ6*01	1064	gnl|Fabrus|L12_IGKJ1*01	1088
818	gnl|Fabrus|VH6-1_IGHD7-27*01_IGHJ4*01	1065	gnl|Fabrus|L12_IGKJ1*01	1088

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
819	gnl|Fabrus|VH4-59_IGHD6-25*01_IGHJ3*01	1043	gnl|Fabrus|L12_IGKJ1*01	1088
820	gnl|Fabrus|VH3-48_IGHD6-6*01_IGHJ1*01	923	gnl|Fabrus|L12_IGKJ1*01	1088
821	gnl|Fabrus|VH3-30_IGHD6-6*01_IGHJ1*01	893	gnl|Fabrus|L12_IGKJ1*01	1088
822	gnl|Fabrus|VH3-66_IGHD6-6*01_IGHJ1*01	949	gnl|Fabrus|L12_IGKJ1*01	1088
823	gnl|Fabrus|VH3-53_IGHD5-5*01_IGHJ4*01	938	gnl|Fabrus|L12_IGKJ1*01	1088
824	gnl|Fabrus|VH2-5_IGHD5-12*01_IGHJ4*01	804	gnl|Fabrus|L12_IGKJ1*01	1088
825	gnl|Fabrus|VH2-70_IGHD5-12*01_IGHJ4*01	811	gnl|Fabrus|L12_IGKJ1*01	1088
826	gnl|Fabrus|VH3-15_IGHD5-12*01_IGHJ4*01	835	gnl|Fabrus|L12_IGKJ1*01	1088
827	gnl|Fabrus|VH3-15_IGHD3-10*01_IGHJ4*01	833	gnl|Fabrus|L12_IGKJ1*01	1088
828	gnl|Fabrus|VH3-49_IGHD5-18*01_IGHJ4*01	930	gnl|Fabrus|L12_IGKJ1*01	1088
829	gnl|Fabrus|VH3-49_IGHD6-13*01_IGHJ4*01	931	gnl|Fabrus|L12_IGKJ1*01	1088
830	gnl|Fabrus|VH3-72_IGHD5-18*01_IGHJ4*01	967	gnl|Fabrus|L12_IGKJ1*01	1088
831	gnl|Fabrus|VH3-72_IGHD6-6*01_IGHJ1*01	969	gnl|Fabrus|L12_IGKJ1*01	1088
832	gnl|Fabrus|VH3-73_IGHD5-12*01_IGHJ4*01	977	gnl|Fabrus|L12_IGKJ1*01	1088
833	gnl|Fabrus|VH3-73_IGHD4-23*01_IGHJ5*01	976	gnl|Fabrus|L12_IGKJ1*01	1088
834	gnl|Fabrus|VH3-43_IGHD3-22*01_IGHJ4*01	918	gnl|Fabrus|L12_IGKJ1*01	1088
835	gnl|Fabrus|VH3-43_IGHD6-13*01_IGHJ4*01	921	gnl|Fabrus|L12_IGKJ1*01	1088
836	gnl|Fabrus|VH3-9_IGHD3-22*01_IGHJ4*01	992	gnl|Fabrus|L12_IGKJ1*01	1088
837	gnl|Fabrus|VH3-9_IGHD1-7*01_IGHJ5*01	989	gnl|Fabrus|L12_IGKJ1*01	1088
838	gnl|Fabrus|VH3-9_IGHD6-13*01_IGHJ4*01	995	gnl|Fabrus|L12_IGKJ1*01	1088
839	gnl|Fabrus|VH4-39_IGHD3-10*01_IGHJ4*01	1030	gnl|Fabrus|L12_IGKJ1*01	1088
840	gnl|Fabrus|VH4-39_IGHD5-12*01_IGHJ4*01	1034	gnl|Fabrus|L12_IGKJ1*01	1088
841	gnl|Fabrus|VH1-18_IGHD6-6*01_IGHJ1*01	728	gnl|Fabrus|L12_IGKJ1*01	1088
842	gnl|Fabrus|VH1-24_IGHD5-12*01_IGHJ4*01	735	gnl|Fabrus|L12_IGKJ1*01	1088
843	gnl|Fabrus|VH1-2_IGHD1-1*01_IGHJ3*01	729	gnl|Fabrus|L12_IGKJ1*01	1088
844	gnl|Fabrus|VH1-3_IGHD6-6*01_IGHJ1*01	743	gnl|Fabrus|L12_IGKJ1*01	1088
845	gnl|Fabrus|VH1-45_IGHD3-10*01_IGHJ4*01	748	gnl|Fabrus|L12_IGKJ1*01	1088
846	gnl|Fabrus|VH1-46_IGHD1-26*01_IGHJ4*01	754	gnl|Fabrus|L12_IGKJ1*01	1088
847	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ6*01	1068	gnl|Fabrus|L12_IGKJ1*01	1088
848	gnl|Fabrus|VH2-70_IGHD3-9*01_IGHJ6*01	810	gnl|Fabrus|L12_IGKJ1*01	1088
849	gnl|Fabrus|VH1-58_IGHD3-10*01_IGHJ6*01	764	gnl|Fabrus|L12_IGKJ1*01	1088
850	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ2*01	1067	gnl|Fabrus|L12_IGKJ1*01	1088
851	gnl|Fabrus|VH4-28_IGHD3-9*01_IGHJ6*01	1002	gnl|Fabrus|L12_IGKJ1*01	1088
852	gnl|Fabrus|VH4-31_IGHD2-15*01_IGHJ2*01	1008	gnl|Fabrus|L12_IGKJ1*01	1088
853	gnl|Fabrus|VH2-5_IGHD3-9*01_IGHJ6*01	803	gnl|Fabrus|L12_IGKJ1*01	1088
854	gnl|Fabrus|VH1-8_IGHD2-15*01_IGHJ6*01	783	gnl|Fabrus|L12_IGKJ1*01	1088
855	gnl|Fabrus|VH2-70_IGHD2-15*01_IGHJ2*01	808	gnl|Fabrus|L12_IGKJ1*01	1088
856	gnl|Fabrus|VH3-38_IGHD3-10*01_IGHJ4*01	907	gnl|Fabrus|L12_IGKJ1*01	1088
857	gnl|Fabrus|VH3-16_IGHD1-7*01_IGHJ6*01	838	gnl|Fabrus|L12_IGKJ1*01	1088
858	gnl|Fabrus|VH3-73_IGHD3-9*01_IGHJ6*01	974	gnl|Fabrus|L12_IGKJ1*01	1088
859	gnl|Fabrus|VH3-11_IGHD3-9*01_IGHJ6*01	816	gnl|Fabrus|L12_IGKJ1*01	1088
860	gnl|Fabrus|VH3-11_IGHD6-6*01_IGHJ1*01	820	gnl|Fabrus|L12_IGKJ1*01	1088

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
861	gnl|Fabrus|VH3-20_IGHD5-12*01_IGHJ4*01	852	gnl|Fabrus|L12_IGKJ1*01	1088
862	gnl|Fabrus|VH3-16_IGHD2-15*01_IGHJ2*01	839	gnl|Fabrus|L12_IGKJ1*01	1088
863	gnl|Fabrus|VH3-7_IGHD6-6*01_IGHJ1*01	960	gnl|Fabrus|L12_IGKJ1*01	1088
864	gnl|Fabrus|VH3-16_IGHD6-13*01_IGHJ4*01	844	gnl|Fabrus|L12_IGKJ1*01	1088
865	gnl|Fabrus|VH3-23_IGHD1-1*01_IGHJ4*01	863	gnl|Fabrus|O1_IGKJ1*01	1100
866	gnl|Fabrus|VH3-23_IGHD2-15*01_IGHJ4*01	866	gnl|Fabrus|O1_IGKJ1*01	1100
867	gnl|Fabrus|VH3-23_IGHD3-22*01_IGHJ4*01	870	gnl|Fabrus|O1_IGKJ1*01	1100
868	gnl|Fabrus|VH3-23_IGHD4-11*01_IGHJ4*01	872	gnl|Fabrus|O1_IGKJ1*01	1100
869	gnl|Fabrus|VH3-23_IGHD5-12*01_IGHJ4*01	874	gnl|Fabrus|O1_IGKJ1*01	1100
870	gnl|Fabrus|VH3-23_IGHD5-5*01_IGHJ4*01	876	gnl|Fabrus|O1_IGKJ1*01	1100
871	gnl|Fabrus|VH3-23_IGHD6-13*01_IGHJ4*01	877	gnl|Fabrus|O1_IGKJ1*01	1100
872	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ4*01	880	gnl|Fabrus|O1_IGKJ1*01	1100
873	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ6*01	881	gnl|Fabrus|O1_IGKJ1*01	1100
874	gnl|Fabrus|VH1-69_IGHD1-14*01_IGHJ4*01	770	gnl|Fabrus|O1_IGKJ1*01	1100
875	gnl|Fabrus|VH1-69_IGHD2-2*01_IGHJ4*01	771	gnl|Fabrus|O1_IGKJ1*01	1100
876	gnl|Fabrus|VH1-69_IGHD2-8*01_IGHJ6*01	772	gnl|Fabrus|O1_IGKJ1*01	1100
877	gnl|Fabrus|VH1-69_IGHD3-16*01_IGHJ4*01	773	gnl|Fabrus|O1_IGKJ1*01	1100
878	gnl|Fabrus|VH1-69_IGHD3-3*01_IGHJ4*01	774	gnl|Fabrus|O1_IGKJ1*01	1100
879	gnl|Fabrus|VH1-69_IGHD4-17*01_IGHJ4*01	776	gnl|Fabrus|O1_IGKJ1*01	1100
880	gnl|Fabrus|VH1-69_IGHD5-12*01_IGHJ4*01	777	gnl|Fabrus|O1_IGKJ1*01	1100
881	gnl|Fabrus|VH1-69_IGHD6-19*01_IGHJ4*01	779	gnl|Fabrus|O1_IGKJ1*01	1100
882	gnl|Fabrus|VH1-69_IGHD7-27*01_IGHJ4*01	781	gnl|Fabrus|O1_IGKJ1*01	1100
883	gnl|Fabrus|VH4-34_IGHD1-7*01_IGHJ4*01	1017	gnl|Fabrus|O1_IGKJ1*01	1100
884	gnl|Fabrus|VH4-34_IGHD2-2*01_IGHJ4*01	1018	gnl|Fabrus|O1_IGKJ1*01	1100
885	gnl|Fabrus|VH4-34_IGHD3-16*01_IGHJ4*01	1019	gnl|Fabrus|O1_IGKJ1*01	1100
886	gnl|Fabrus|VH4-34_IGHD4-17*01_IGHJ4*01	1021	gnl|Fabrus|O1_IGKJ1*01	1100
887	gnl|Fabrus|VH4-34_IGHD5-12*01_IGHJ4*01	1022	gnl|Fabrus|O1_IGKJ1*01	1100
888	gnl|Fabrus|VH4-34_IGHD6-13*01_IGHJ4*01	1023	gnl|Fabrus|O1_IGKJ1*01	1100
889	gnl|Fabrus|VH4-34_IGHD6-25*01_IGHJ6*01	1024	gnl|Fabrus|O1_IGKJ1*01	1100
890	gnl|Fabrus|VH4-34_IGHD7-27*01_IGHJ4*01	1026	gnl|Fabrus|O1_IGKJ1*01	1100
891	gnl|Fabrus|VH2-26_IGHD1-20*01_IGHJ4*01	789	gnl|Fabrus|O1_IGKJ1*01	1100
892	gnl|Fabrus|VH2-26_IGHD2-2*01_IGHJ4*01	791	gnl|Fabrus|O1_IGKJ1*01	1100
893	gnl|Fabrus|VH2-26_IGHD3-10*01_IGHJ4*01	792	gnl|Fabrus|O1_IGKJ1*01	1100
894	gnl|Fabrus|VH2-26_IGHD4-11*01_IGHJ4*01	794	gnl|Fabrus|O1_IGKJ1*01	1100
895	gnl|Fabrus|VH2-26_IGHD5-18*01_IGHJ4*01	796	gnl|Fabrus|O1_IGKJ1*01	1100
896	gnl|Fabrus|VH2-26_IGHD6-13*01_IGHJ4*01	797	gnl|Fabrus|O1_IGKJ1*01	1100
897	gnl|Fabrus|VH2-26_IGHD7-27*01_IGHJ4*01	798	gnl|Fabrus|O1_IGKJ1*01	1100
898	gnl|Fabrus|VH5-51_IGHD1-14*01_IGHJ4*01	1044	gnl|Fabrus|O1_IGKJ1*01	1100
899	gnl|Fabrus|VH5-51_IGHD2-8*01_IGHJ4*01	1046	gnl|Fabrus|O1_IGKJ1*01	1100
900	gnl|Fabrus|VH5-51_IGHD3-3*01_IGHJ4*01	1048	gnl|Fabrus|O1_IGKJ1*01	1100
901	gnl|Fabrus|VH5-51_IGHD4-17*01_IGHJ4*01	1049	gnl|Fabrus|O1_IGKJ1*01	1100
902	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1050	gnl|Fabrus|O1_IGKJ1*01	1100

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
903	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1051	gnl|Fabrus|O1_IGKJ1*01	1100
904	gnl|Fabrus|VH5-51_IGHD6-25*01_IGHJ4*01	1052	gnl|Fabrus|O1_IGKJ1*01	1100
905	gnl|Fabrus|VH5-51_IGHD7-27*01_IGHJ4*01	1053	gnl|Fabrus|O1_IGKJ1*01	1100
906	gnl|Fabrus|VH6-1_IGHD1-1*01_IGHJ4*01	1054	gnl|Fabrus|O1_IGKJ1*01	1100
907	gnl|Fabrus|VH6-1_IGHD2-15*01_IGHJ4*01	1056	gnl|Fabrus|O1_IGKJ1*01	1100
908	gnl|Fabrus|VH6-1_IGHD3-3*01_IGHJ4*01	1059	gnl|Fabrus|O1_IGKJ1*01	1100
909	gnl|Fabrus|VH6-1_IGHD4-23*01_IGHJ4*01	1061	gnl|Fabrus|O1_IGKJ1*01	1100
910	gnl|Fabrus|VH6-1_IGHD4-11*01_IGHJ6*01	1060	gnl|Fabrus|O1_IGKJ1*01	1100
911	gnl|Fabrus|VH6-1_IGHD5-5*01_IGHJ4*01	1062	gnl|Fabrus|O1_IGKJ1*01	1100
912	gnl|Fabrus|VH6-1_IGHD6-13*01_IGHJ4*01	1063	gnl|Fabrus|O1_IGKJ1*01	1100
913	gnl|Fabrus|VH6-1_IGHD6-25*01_IGHJ6*01	1064	gnl|Fabrus|O1_IGKJ1*01	1100
914	gnl|Fabrus|VH6-1_IGHD7-27*01_IGHJ4*01	1065	gnl|Fabrus|O1_IGKJ1*01	1100
915	gnl|Fabrus|VH4-59_IGHD6-25*01_IGHJ3*01	1043	gnl|Fabrus|O1_IGKJ1*01	1100
916	gnl|Fabrus|VH3-48_IGHD6-6*01_IGHJ1*01	923	gnl|Fabrus|O1_IGKJ1*01	1100
917	gnl|Fabrus|VH3-30_IGHD6-6*01_IGHJ1*01	893	gnl|Fabrus|O1_IGKJ1*01	1100
918	gnl|Fabrus|VH3-66_IGHD6-6*01_IGHJ1*01	949	gnl|Fabrus|O1_IGKJ1*01	1100
919	gnl|Fabrus|VH3-53_IGHD5-5*01_IGHJ4*01	938	gnl|Fabrus|O1_IGKJ1*01	1100
920	gnl|Fabrus|VH2-5_IGHD5-12*01_IGHJ4*01	804	gnl|Fabrus|O1_IGKJ1*01	1100
921	gnl|Fabrus|VH2-70_IGHD5-12*01_IGHJ4*01	811	gnl|Fabrus|O1_IGKJ1*01	1100
922	gnl|Fabrus|VH3-15_IGHD5-12*01_IGHJ4*01	835	gnl|Fabrus|O1_IGKJ1*01	1100
923	gnl|Fabrus|VH3-15_IGHD3-10*01_IGHJ4*01	833	gnl|Fabrus|O1_IGKJ1*01	1100
924	gnl|Fabrus|VH3-49_IGHD5-18*01_IGHJ4*01	930	gnl|Fabrus|O1_IGKJ1*01	1100
925	gnl|Fabrus|VH3-49_IGHD6-13*01_IGHJ4*01	931	gnl|Fabrus|O1_IGKJ1*01	1100
926	gnl|Fabrus|VH3-72_IGHD5-18*01_IGHJ4*01	967	gnl|Fabrus|O1_IGKJ1*01	1100
927	gnl|Fabrus|VH3-72_IGHD6-6*01_IGHJ1*01	969	gnl|Fabrus|O1_IGKJ1*01	1100
928	gnl|Fabrus|VH3-73_IGHD5-12*01_IGHJ4*01	977	gnl|Fabrus|O1_IGKJ1*01	1100
929	gnl|Fabrus|VH3-73_IGHD4-23*01_IGHJ5*01	976	gnl|Fabrus|O1_IGKJ1*01	1100
930	gnl|Fabrus|VH3-43_IGHD3-22*01_IGHJ4*01	918	gnl|Fabrus|O1_IGKJ1*01	1100
931	gnl|Fabrus|VH3-43_IGHD6-13*01_IGHJ4*01	921	gnl|Fabrus|O1_IGKJ1*01	1100
932	gnl|Fabrus|VH3-9_IGHD3-22*01_IGHJ4*01	992	gnl|Fabrus|O1_IGKJ1*01	1100
933	gnl|Fabrus|VH3-9_IGHD1-7*01_IGHJ5*01	989	gnl|Fabrus|O1_IGKJ1*01	1100
934	gnl|Fabrus|VH3-9_IGHD6-13*01_IGHJ4*01	995	gnl|Fabrus|O1_IGKJ1*01	1100
935	gnl|Fabrus|VH4-39_IGHD3-10*01_IGHJ4*01	1030	gnl|Fabrus|O1_IGKJ1*01	1100
936	gnl|Fabrus|VH4-39_IGHD5-12*01_IGHJ4*01	1034	gnl|Fabrus|O1_IGKJ1*01	1100
937	gnl|Fabrus|VH1-18_IGHD6-6*01_IGHJ1*01	728	gnl|Fabrus|O1_IGKJ1*01	1100
938	gnl|Fabrus|VH1-24_IGHD5-12*01_IGHJ4*01	735	gnl|Fabrus|O1_IGKJ1*01	1100
939	gnl|Fabrus|VH1-2_IGHD1-1*01_IGHJ3*01	729	gnl|Fabrus|O1_IGKJ1*01	1100
940	gnl|Fabrus|VH1-3_IGHD6-6*01_IGHJ1*01	743	gnl|Fabrus|O1_IGKJ1*01	1100
941	gnl|Fabrus|VH1-45_IGHD3-10*01_IGHJ4*01	748	gnl|Fabrus|O1_IGKJ1*01	1100
942	gnl|Fabrus|VH1-46_IGHD1-26*01_IGHJ4*01	754	gnl|Fabrus|O1_IGKJ1*01	1100
943	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ6*01	1068	gnl|Fabrus|O1_IGKJ1*01	1100
944	gnl|Fabrus|VH2-70_IGHD3-9*01_IGHJ6*01	810	gnl|Fabrus|O1_IGKJ1*01	1100

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
945	gnl|Fabrus|VH1-58_IGHD3-10*01_IGHJ6*01	764	gnl|Fabrus|O1_IGKJ1*01	1100
946	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ2*01	1067	gnl|Fabrus|O1_IGKJ1*01	1100
947	gnl|Fabrus|VH4-28_IGHD3-9*01_IGHJ6*01	1002	gnl|Fabrus|O1_IGKJ1*01	1100
948	gnl|Fabrus|VH4-31_IGHD2-15*01_IGHJ2*01	1008	gnl|Fabrus|O1_IGKJ1*01	1100
949	gnl|Fabrus|VH2-5_IGHD3-9*01_IGHJ6*01	803	gnl|Fabrus|O1_IGKJ1*01	1100
950	gnl|Fabrus|VH1-8_IGHD2-15*01_IGHJ6*01	783	gnl|Fabrus|O1_IGKJ1*01	1100
951	gnl|Fabrus|VH2-70_IGHD2-15*01_IGHJ2*01	808	gnl|Fabrus|O1_IGKJ1*01	1100
952	gnl|Fabrus|VH3-38_IGHD3-10*01_IGHJ4*01	907	gnl|Fabrus|O1_IGKJ1*01	1100
953	gnl|Fabrus|VH3-16_IGHD1-7*01_IGHJ6*01	838	gnl|Fabrus|O1_IGKJ1*01	1100
954	gnl|Fabrus|VH3-73_IGHD3-9*01_IGHJ6*01	974	gnl|Fabrus|O1_IGKJ1*01	1100
955	gnl|Fabrus|VH3-11_IGHD3-9*01_IGHJ6*01	816	gnl|Fabrus|O1_IGKJ1*01	1100
956	gnl|Fabrus|VH3-11_IGHD6-6*01_IGHJ1*01	820	gnl|Fabrus|O1_IGKJ1*01	1100
957	gnl|Fabrus|VH3-20_IGHD5-12*01_IGHJ4*01	852	gnl|Fabrus|O1_IGKJ1*01	1100
958	gnl|Fabrus|VH3-16_IGHD2-15*01_IGHJ2*01	839	gnl|Fabrus|O1_IGKJ1*01	1100
959	gnl|Fabrus|VH3-7_IGHD6-6*01_IGHJ1*01	960	gnl|Fabrus|O1_IGKJ1*01	1100
960	gnl|Fabrus|VH3-16_IGHD6-13*01_IGHJ4*01	844	gnl|Fabrus|O1_IGKJ1*01	1100
961	gnl|Fabrus|VH3-23_IGHD1-1*01_IGHJ4*01	863	gnl|Fabrus|L25_IGKJ3*01	1094
962	gnl|Fabrus|VH3-23_IGHD2-15*01_IGHJ4*01	866	gnl|Fabrus|L25_IGKJ3*01	1094
963	gnl|Fabrus|VH3-23_IGHD3-22*01_IGHJ4*01	870	gnl|Fabrus|L25_IGKJ3*01	1094
964	gnl|Fabrus|VH3-23_IGHD4-11*01_IGHJ4*01	872	gnl|Fabrus|L25_IGKJ3*01	1094
965	gnl|Fabrus|VH3-23_IGHD5-12*01_IGHJ4*01	874	gnl|Fabrus|L25_IGKJ3*01	1094
966	gnl|Fabrus|VH3-23_IGHD5-5*01_IGHJ4*01	876	gnl|Fabrus|L25_IGKJ3*01	1094
967	gnl|Fabrus|VH3-23_IGHD6-13*01_IGHJ4*01	877	gnl|Fabrus|L25_IGKJ3*01	1094
968	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ4*01	880	gnl|Fabrus|L25_IGKJ3*01	1094
969	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ6*01	881	gnl|Fabrus|L25_IGKJ3*01	1094
970	gnl|Fabrus|VH1-69_IGHD1-14*01_IGHJ4*01	770	gnl|Fabrus|L25_IGKJ3*01	1094
971	gnl|Fabrus|VH1-69_IGHD2-2*01_IGHJ4*01	771	gnl|Fabrus|L25_IGKJ3*01	1094
972	gnl|Fabrus|VH1-69_IGHD2-8*01_IGHJ6*01	772	gnl|Fabrus|L25_IGKJ3*01	1094
973	gnl|Fabrus|VH1-69_IGHD3-16*01_IGHJ4*01	773	gnl|Fabrus|L25_IGKJ3*01	1094
974	gnl|Fabrus|VH1-69_IGHD3-3*01_IGHJ4*01	774	gnl|Fabrus|L25_IGKJ3*01	1094
975	gnl|Fabrus|VH1-69_IGHD4-17*01_IGHJ4*01	776	gnl|Fabrus|L25_IGKJ3*01	1094
976	gnl|Fabrus|VH1-69_IGHD5-12*01_IGHJ4*01	777	gnl|Fabrus|L25_IGKJ3*01	1094
977	gnl|Fabrus|VH1-69_IGHD6-19*01_IGHJ4*01	779	gnl|Fabrus|L25_IGKJ3*01	1094
978	gnl|Fabrus|VH1-69_IGHD7-27*01_IGHJ4*01	781	gnl|Fabrus|L25_IGKJ3*01	1094
979	gnl|Fabrus|VH4-34_IGHD1-7*01_IGHJ4*01	1017	gnl|Fabrus|L25_IGKJ3*01	1094
980	gnl|Fabrus|VH4-34_IGHD2-2*01_IGHJ4*01	1018	gnl|Fabrus|L25_IGKJ3*01	1094
981	gnl|Fabrus|VH4-34_IGHD3-16*01_IGHJ4*01	1019	gnl|Fabrus|L25_IGKJ3*01	1094
982	gnl|Fabrus|VH4-34_IGHD4-17*01_IGHJ4*01	1021	gnl|Fabrus|L25_IGKJ3*01	1094
983	gnl|Fabrus|VH4-34_IGHD5-12*01_IGHJ4*01	1022	gnl|Fabrus|L25_IGKJ3*01	1094
984	gnl|Fabrus|VH4-34_IGHD6-13*01_IGHJ4*01	1023	gnl|Fabrus|L25_IGKJ3*01	1094
985	gnl|Fabrus|VH4-34_IGHD6-25*01_IGHJ6*01	1024	gnl|Fabrus|L25_IGKJ3*01	1094
986	gnl|Fabrus|VH4-34_IGHD7-27*01_IGHJ4*01	1026	gnl|Fabrus|L25_IGKJ3*01	1094

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
987	gnl|Fabrus|VH2-26_IGHD1-20*01_IGHJ4*01	789	gnl|Fabrus|L25_IGKJ3*01	1094
988	gnl|Fabrus|VH2-26_IGHD2-2*01_IGHJ4*01	791	gnl|Fabrus|L25_IGKJ3*01	1094
989	gnl|Fabrus|VH2-26_IGHD3-10*01_IGHJ4*01	792	gnl|Fabrus|L25_IGKJ3*01	1094
990	gnl|Fabrus|VH2-26_IGHD4-11*01_IGHJ4*01	794	gnl|Fabrus|L25_IGKJ3*01	1094
991	gnl|Fabrus|VH2-26_IGHD5-18*01_IGHJ4*01	796	gnl|Fabrus|L25_IGKJ3*01	1094
992	gnl|Fabrus|VH2-26_IGHD6-13*01_IGHJ4*01	797	gnl|Fabrus|L25_IGKJ3*01	1094
993	gnl|Fabrus|VH2-26_IGHD7-27*01_IGHJ4*01	798	gnl|Fabrus|L25_IGKJ3*01	1094
994	gnl|Fabrus|VH5-51_IGHD1-14*01_IGHJ4*01	1044	gnl|Fabrus|L25_IGKJ3*01	1094
995	gnl|Fabrus|VH5-51_IGHD2-8*01_IGHJ4*01	1046	gnl|Fabrus|L25_IGKJ3*01	1094
996	gnl|Fabrus|VH5-51_IGHD3-3*01_IGHJ4*01	1048	gnl|Fabrus|L25_IGKJ3*01	1094
997	gnl|Fabrus|VH5-51_IGHD4-17*01_IGHJ4*01	1049	gnl|Fabrus|L25_IGKJ3*01	1094
998	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1050	gnl|Fabrus|L25_IGKJ3*01	1094
999	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1051	gnl|Fabrus|L25_IGKJ3*01	1094
1000	gnl|Fabrus|VH5-51_IGHD6-25*01_IGHJ4*01	1052	gnl|Fabrus|L25_IGKJ3*01	1094
1001	gnl|Fabrus|VH5-51_IGHD7-27*01_IGHJ4*01	1053	gnl|Fabrus|L25_IGKJ3*01	1094
1002	gnl|Fabrus|VH6-1_IGHD1-1*01_IGHJ4*01	1054	gnl|Fabrus|L25_IGKJ3*01	1094
1003	gnl|Fabrus|VH6-1_IGHD2-15*01_IGHJ4*01	1056	gnl|Fabrus|L25_IGKJ3*01	1094
1004	gnl|Fabrus|VH6-1_IGHD3-3*01_IGHJ4*01	1059	gnl|Fabrus|L25_IGKJ3*01	1094
1005	gnl|Fabrus|VH6-1_IGHD4-23*01_IGHJ4*01	1061	gnl|Fabrus|L25_IGKJ3*01	1094
1006	gnl|Fabrus|VH6-1_IGHD4-11*01_IGHJ6*01	1060	gnl|Fabrus|L25_IGKJ3*01	1094
1007	gnl|Fabrus|VH6-1_IGHD5-5*01_IGHJ4*01	1062	gnl|Fabrus|L25_IGKJ3*01	1094
1008	gnl|Fabrus|VH6-1_IGHD6-13*01_IGHJ4*01	1063	gnl|Fabrus|L25_IGKJ3*01	1094
1009	gnl|Fabrus|VH6-1_IGHD6-25*01_IGHJ6*01	1064	gnl|Fabrus|L25_IGKJ3*01	1094
1010	gnl|Fabrus|VH6-1_IGHD7-27*01_IGHJ4*01	1065	gnl|Fabrus|L25_IGKJ3*01	1094
1011	gnl|Fabrus|VH4-59_IGHD6-25*01_IGHJ3*01	1043	gnl|Fabrus|L25_IGKJ3*01	1094
1012	gnl|Fabrus|VH3-48_IGHD6-6*01_IGHJ1*01	923	gnl|Fabrus|L25_IGKJ3*01	1094
1013	gnl|Fabrus|VH3-30_IGHD6-6*01_IGHJ1*01	893	gnl|Fabrus|L25_IGKJ3*01	1094
1014	gnl|Fabrus|VH3-66_IGHD6-6*01_IGHJ1*01	949	gnl|Fabrus|L25_IGKJ3*01	1094
1015	gnl|Fabrus|VH3-53_IGHD5-5*01_IGHJ4*01	938	gnl|Fabrus|L25_IGKJ3*01	1094
1016	gnl|Fabrus|VH2-5_IGHD5-12*01_IGHJ4*01	804	gnl|Fabrus|L25_IGKJ3*01	1094
1017	gnl|Fabrus|VH2-70_IGHD5-12*01_IGHJ4*01	811	gnl|Fabrus|L25_IGKJ3*01	1094
1018	gnl|Fabrus|VH3-15_IGHD5-12*01_IGHJ4*01	835	gnl|Fabrus|L25_IGKJ3*01	1094
1019	gnl|Fabrus|VH3-15_IGHD3-10*01_IGHJ4*01	833	gnl|Fabrus|L25_IGKJ3*01	1094
1020	gnl|Fabrus|VH3-49_IGHD5-18*01_IGHJ4*01	930	gnl|Fabrus|L25_IGKJ3*01	1094
1021	gnl|Fabrus|VH3-49_IGHD6-13*01_IGHJ4*01	931	gnl|Fabrus|L25_IGKJ3*01	1094
1022	gnl|Fabrus|VH3-72_IGHD5-18*01_IGHJ4*01	967	gnl|Fabrus|L25_IGKJ3*01	1094
1023	gnl|Fabrus|VH3-72_IGHD6-6*01_IGHJ1*01	969	gnl|Fabrus|L25_IGKJ3*01	1094
1024	gnl|Fabrus|VH3-73_IGHD5-12*01_IGHJ4*01	977	gnl|Fabrus|L25_IGKJ3*01	1094
1025	gnl|Fabrus|VH3-73_IGHD4-23*01_IGHJ5*01	976	gnl|Fabrus|L25_IGKJ3*01	1094
1026	gnl|Fabrus|VH3-43_IGHD3-22*01_IGHJ4*01	918	gnl|Fabrus|L25_IGKJ3*01	1094
1027	gnl|Fabrus|VH3-43_IGHD6-13*01_IGHJ4*01	921	gnl|Fabrus|L25_IGKJ3*01	1094
1028	gnl|Fabrus|VH3-9_IGHD3-22*01_IGHJ4*01	992	gnl|Fabrus|L25_IGKJ3*01	1094

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1029	gnl|Fabrus|VH3-9_IGHD1-7*01_IGHJ5*01	989	gnl|Fabrus|L25_IGKJ3*01	1094
1030	gnl|Fabrus|VH3-9_IGHD6-13*01_IGHJ4*01	995	gnl|Fabrus|L25_IGKJ3*01	1094
1031	gnl|Fabrus|VH4-39_IGHD3-10*01_IGHJ4*01	1030	gnl|Fabrus|L25_IGKJ3*01	1094
1032	gnl|Fabrus|VH4-39_IGHD5-12*01_IGHJ4*01	1034	gnl|Fabrus|L25_IGKJ3*01	1094
1033	gnl|Fabrus|VH1-18_IGHD6-6*01_IGHJ1*01	728	gnl|Fabrus|L25_IGKJ3*01	1094
1034	gnl|Fabrus|VH1-24_IGHD5-12*01_IGHJ4*01	735	gnl|Fabrus|L25_IGKJ3*01	1094
1035	gnl|Fabrus|VH1-2_IGHD1-1*01_IGHJ3*01	729	gnl|Fabrus|L25_IGKJ3*01	1094
1036	gnl|Fabrus|VH1-3_IGHD6-6*01_IGHJ1*01	743	gnl|Fabrus|L25_IGKJ3*01	1094
1037	gnl|Fabrus|VH1-45_IGHD3-10*01_IGHJ4*01	748	gnl|Fabrus|L25_IGKJ3*01	1094
1038	gnl|Fabrus|VH1-46_IGHD1-26*01_IGHJ4*01	754	gnl|Fabrus|L25_IGKJ3*01	1094
1039	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ6*01	1068	gnl|Fabrus|L25_IGKJ3*01	1094
1040	gnl|Fabrus|VH2-70_IGHD3-9*01_IGHJ6*01	810	gnl|Fabrus|L25_IGKJ3*01	1094
1041	gnl|Fabrus|VH1-58_IGHD3-10*01_IGHJ6*01	764	gnl|Fabrus|L25_IGKJ3*01	1094
1042	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ2*01	1067	gnl|Fabrus|L25_IGKJ3*01	1094
1043	gnl|Fabrus|VH4-28_IGHD3-9*01_IGHJ6*01	1002	gnl|Fabrus|L25_IGKJ3*01	1094
1044	gnl|Fabrus|VH4-31_IGHD2-15*01_IGHJ2*01	1008	gnl|Fabrus|L25_IGKJ3*01	1094
1045	gnl|Fabrus|VH2-5_IGHD3-9*01_IGHJ6*01	803	gnl|Fabrus|L25_IGKJ3*01	1094
1046	gnl|Fabrus|VH1-8_IGHD2-15*01_IGHJ6*01	783	gnl|Fabrus|L25_IGKJ3*01	1094
1047	gnl|Fabrus|VH2-70_IGHD2-15*01_IGHJ2*01	808	gnl|Fabrus|L25_IGKJ3*01	1094
1048	gnl|Fabrus|VH3-38_IGHD3-10*01_IGHJ4*01	907	gnl|Fabrus|L25_IGKJ3*01	1094
1049	gnl|Fabrus|VH3-16_IGHD1-7*01_IGHJ6*01	838	gnl|Fabrus|L25_IGKJ3*01	1094
1050	gnl|Fabrus|VH3-73_IGHD3-9*01_IGHJ6*01	974	gnl|Fabrus|L25_IGKJ3*01	1094
1051	gnl|Fabrus|VH3-11_IGHD3-9*01_IGHJ6*01	816	gnl|Fabrus|L25_IGKJ3*01	1094
1052	gnl|Fabrus|VH3-11_IGHD6-6*01_IGHJ1*01	820	gnl|Fabrus|L25_IGKJ3*01	1094
1053	gnl|Fabrus|VH3-20_IGHD5-12*01_IGHJ4*01	852	gnl|Fabrus|L25_IGKJ3*01	1094
1054	gnl|Fabrus|VH3-16_IGHD2-15*01_IGHJ2*01	839	gnl|Fabrus|L25_IGKJ3*01	1094
1055	gnl|Fabrus|VH3-7_IGHD6-6*01_IGHJ1*01	960	gnl|Fabrus|L25_IGKJ3*01	1094
1056	gnl|Fabrus|VH3-16_IGHD6-13*01_IGHJ4*01	844	gnl|Fabrus|L25_IGKJ3*01	1094
1057	gnl|Fabrus|VH3-23_IGHD1-1*01_IGHJ4*01	863	gnl|Fabrus|A27_IGKJ1*01	1080
1058	gnl|Fabrus|VH3-23_IGHD2-15*01_IGHJ4*01	866	gnl|Fabrus|A27_IGKJ1*01	1080
1059	gnl|Fabrus|VH3-23_IGHD3-22*01_IGHJ4*01	870	gnl|Fabrus|A27_IGKJ1*01	1080
1060	gnl|Fabrus|VH3-23_IGHD4-11*01_IGHJ4*01	872	gnl|Fabrus|A27_IGKJ1*01	1080
1061	gnl|Fabrus|VH3-23_IGHD5-12*01_IGHJ4*01	874	gnl|Fabrus|A27_IGKJ1*01	1080
1062	gnl|Fabrus|VH3-23_IGHD5-5*01_IGHJ4*01	876	gnl|Fabrus|A27_IGKJ1*01	1080
1063	gnl|Fabrus|VH3-23_IGHD6-13*01_IGHJ4*01	877	gnl|Fabrus|A27_IGKJ1*01	1080
1064	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ4*01	880	gnl|Fabrus|A27_IGKJ1*01	1080
1065	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ6*01	881	gnl|Fabrus|A27_IGKJ1*01	1080
1066	gnl|Fabrus|VH1-69_IGHD1-14*01_IGHJ4*01	770	gnl|Fabrus|A27_IGKJ1*01	1080
1067	gnl|Fabrus|VH1-69_IGHD2-2*01_IGHJ4*01	771	gnl|Fabrus|A27_IGKJ1*01	1080
1068	gnl|Fabrus|VH1-69_IGHD2-8*01_IGHJ6*01	772	gnl|Fabrus|A27_IGKJ1*01	1080
1069	gnl|Fabrus|VH1-69_IGHD3-16*01_IGHJ4*01	773	gnl|Fabrus|A27_IGKJ1*01	1080
1070	gnl|Fabrus|VH1-69_IGHD3-3*01_IGHJ4*01	774	gnl|Fabrus|A27_IGKJ1*01	1080

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1071	gnl|Fabrus|VH1-69_IGHD4-17*01_IGHJ4*01	776	gnl|Fabrus|A27_IGKJ1*01	1080
1072	gnl|Fabrus|VH1-69_IGHD5-12*01_IGHJ4*01	777	gnl|Fabrus|A27_IGKJ1*01	1080
1073	gnl|Fabrus|VH1-69_IGHD6-19*01_IGHJ4*01	779	gnl|Fabrus|A27_IGKJ1*01	1080
1074	gnl|Fabrus|VH1-69_IGHD7-27*01_IGHJ4*01	781	gnl|Fabrus|A27_IGKJ1*01	1080
1075	gnl|Fabrus|VH4-34_IGHD1-7*01_IGHJ4*01	1017	gnl|Fabrus|A27_IGKJ1*01	1080
1076	gnl|Fabrus|VH4-34_IGHD2-2*01_IGHJ4*01	1018	gnl|Fabrus|A27_IGKJ1*01	1080
1077	gnl|Fabrus|VH4-34_IGHD3-16*01_IGHJ4*01	1019	gnl|Fabrus|A27_IGKJ1*01	1080
1078	gnl|Fabrus|VH4-34_IGHD4-17*01_IGHJ4*01	1021	gnl|Fabrus|A27_IGKJ1*01	1080
1079	gnl|Fabrus|VH4-34_IGHD5-12*01_IGHJ4*01	1022	gnl|Fabrus|A27_IGKJ1*01	1080
1080	gnl|Fabrus|VH4-34_IGHD6-13*01_IGHJ4*01	1023	gnl|Fabrus|A27_IGKJ1*01	1080
1081	gnl|Fabrus|VH4-34_IGHD6-25*01_IGHJ6*01	1024	gnl|Fabrus|A27_IGKJ1*01	1080
1082	gnl|Fabrus|VH4-34_IGHD7-27*01_IGHJ4*01	1026	gnl|Fabrus|A27_IGKJ1*01	1080
1083	gnl|Fabrus|VH2-26_IGHD1-20*01_IGHJ4*01	789	gnl|Fabrus|A27_IGKJ1*01	1080
1084	gnl|Fabrus|VH2-26_IGHD2-2*01_IGHJ4*01	791	gnl|Fabrus|A27_IGKJ1*01	1080
1085	gnl|Fabrus|VH2-26_IGHD3-10*01_IGHJ4*01	792	gnl|Fabrus|A27_IGKJ1*01	1080
1086	gnl|Fabrus|VH2-26_IGHD4-11*01_IGHJ4*01	794	gnl|Fabrus|A27_IGKJ1*01	1080
1087	gnl|Fabrus|VH2-26_IGHD5-18*01_IGHJ4*01	796	gnl|Fabrus|A27_IGKJ1*01	1080
1088	gnl|Fabrus|VH2-26_IGHD6-13*01_IGHJ4*01	797	gnl|Fabrus|A27_IGKJ1*01	1080
1089	gnl|Fabrus|VH2-26_IGHD7-27*01_IGHJ4*01	798	gnl|Fabrus|A27_IGKJ1*01	1080
1090	gnl|Fabrus|VH5-51_IGHD1-14*01_IGHJ4*01	1044	gnl|Fabrus|A27_IGKJ1*01	1080
1091	gnl|Fabrus|VH5-51_IGHD2-8*01_IGHJ4*01	1046	gnl|Fabrus|A27_IGKJ1*01	1080
1092	gnl|Fabrus|VH5-51_IGHD3-3*01_IGHJ4*01	1048	gnl|Fabrus|A27_IGKJ1*01	1080
1093	gnl|Fabrus|VH5-51_IGHD4-17*01_IGHJ4*01	1049	gnl|Fabrus|A27_IGKJ1*01	1080
1094	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1050	gnl|Fabrus|A27_IGKJ1*01	1080
1095	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1051	gnl|Fabrus|A27_IGKJ1*01	1080
1096	gnl|Fabrus|VH5-51_IGHD6-25*01_IGHJ4*01	1052	gnl|Fabrus|A27_IGKJ1*01	1080
1097	gnl|Fabrus|VH5-51_IGHD7-27*01_IGHJ4*01	1053	gnl|Fabrus|A27_IGKJ1*01	1080
1098	gnl|Fabrus|VH6-1_IGHD1-1*01_IGHJ4*01	1054	gnl|Fabrus|A27_IGKJ1*01	1080
1099	gnl|Fabrus|VH6-1_IGHD2-15*01_IGHJ4*01	1056	gnl|Fabrus|A27_IGKJ1*01	1080
1100	gnl|Fabrus|VH6-1_IGHD3-3*01_IGHJ4*01	1059	gnl|Fabrus|A27_IGKJ1*01	1080
1101	gnl|Fabrus|VH6-1_IGHD4-23*01_IGHJ4*01	1061	gnl|Fabrus|A27_IGKJ1*01	1080
1102	gnl|Fabrus|VH6-1_IGHD4-11*01_IGHJ6*01	1060	gnl|Fabrus|A27_IGKJ1*01	1080
1103	gnl|Fabrus|VH6-1_IGHD5-5*01_IGHJ4*01	1062	gnl|Fabrus|A27_IGKJ1*01	1080
1104	gnl|Fabrus|VH6-1_IGHD6-13*01_IGHJ4*01	1063	gnl|Fabrus|A27_IGKJ1*01	1080
1105	gnl|Fabrus|VH6-1_IGHD6-25*01_IGHJ6*01	1064	gnl|Fabrus|A27_IGKJ1*01	1080
1106	gnl|Fabrus|VH6-1_IGHD7-27*01_IGHJ4*01	1065	gnl|Fabrus|A27_IGKJ1*01	1080
1107	gnl|Fabrus|VH4-59_IGHD6-25*01_IGHJ3*01	1043	gnl|Fabrus|A27_IGKJ1*01	1080
1108	gnl|Fabrus|VH3-48_IGHD6-6*01_IGHJ1*01	923	gnl|Fabrus|A27_IGKJ1*01	1080
1109	gnl|Fabrus|VH3-30_IGHD6-6*01_IGHJ1*01	893	gnl|Fabrus|A27_IGKJ1*01	1080
1110	gnl|Fabrus|VH3-66_IGHD6-6*01_IGHJ1*01	949	gnl|Fabrus|A27_IGKJ1*01	1080
1111	gnl|Fabrus|VH3-53_IGHD5-5*01_IGHJ4*01	938	gnl|Fabrus|A27_IGKJ1*01	1080
1112	gnl|Fabrus|VH2-5_IGHD5-12*01_IGHJ4*01	804	gnl|Fabrus|A27_IGKJ1*01	1080

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1113	gnl|Fabrus|VH2-70_IGHD5-12*01_IGHJ4*01	811	gnl|Fabrus|A27_IGKJ1*01	1080
1114	gnl|Fabrus|VH3-15_IGHD5-12*01_IGHJ4*01	835	gnl|Fabrus|A27_IGKJ1*01	1080
1115	gnl|Fabrus|VH3-15_IGHD3-10*01_IGHJ4*01	833	gnl|Fabrus|A27_IGKJ1*01	1080
1116	gnl|Fabrus|VH3-49_IGHD5-18*01_IGHJ4*01	930	gnl|Fabrus|A27_IGKJ1*01	1080
1117	gnl|Fabrus|VH3-49_IGHD6-13*01_IGHJ4*01	931	gnl|Fabrus|A27_IGKJ1*01	1080
1118	gnl|Fabrus|VH3-72_IGHD5-18*01_IGHJ4*01	967	gnl|Fabrus|A27_IGKJ1*01	1080
1119	gnl|Fabrus|VH3-72_IGHD6-6*01_IGHJ1*01	969	gnl|Fabrus|A27_IGKJ1*01	1080
1120	gnl|Fabrus|VH3-73_IGHD5-12*01_IGHJ4*01	977	gnl|Fabrus|A27_IGKJ1*01	1080
1121	gnl|Fabrus|VH3-73_IGHD4-23*01_IGHJ5*01	976	gnl|Fabrus|A27_IGKJ1*01	1080
1122	gnl|Fabrus|VH3-43_IGHD3-22*01_IGHJ4*01	918	gnl|Fabrus|A27_IGKJ1*01	1080
1123	gnl|Fabrus|VH3-43_IGHD6-13*01_IGHJ4*01	921	gnl|Fabrus|A27_IGKJ1*01	1080
1124	gnl|Fabrus|VH3-9_IGHD3-22*01_IGHJ4*01	992	gnl|Fabrus|A27_IGKJ1*01	1080
1125	gnl|Fabrus|VH3-9_IGHD1-7*01_IGHJ5*01	989	gnl|Fabrus|A27_IGKJ1*01	1080
1126	gnl|Fabrus|VH3-9_IGHD6-13*01_IGHJ4*01	995	gnl|Fabrus|A27_IGKJ1*01	1080
1127	gnl|Fabrus|VH4-39_IGHD3-10*01_IGHJ4*01	1030	gnl|Fabrus|A27_IGKJ1*01	1080
1128	gnl|Fabrus|VH4-39_IGHD5-12*01_IGHJ4*01	1034	gnl|Fabrus|A27_IGKJ1*01	1080
1129	gnl|Fabrus|VH1-18_IGHD6-6*01_IGHJ1*01	728	gnl|Fabrus|A27_IGKJ1*01	1080
1130	gnl|Fabrus|VH1-24_IGHD5-12*01_IGHJ4*01	735	gnl|Fabrus|A27_IGKJ1*01	1080
1131	gnl|Fabrus|VH1-2_IGHD1-1*01_IGHJ3*01	729	gnl|Fabrus|A27_IGKJ1*01	1080
1132	gnl|Fabrus|VH1-3_IGHD6-6*01_IGHJ1*01	743	gnl|Fabrus|A27_IGKJ1*01	1080
1133	gnl|Fabrus|VH1-45_IGHD3-10*01_IGHJ4*01	748	gnl|Fabrus|A27_IGKJ1*01	1080
1134	gnl|Fabrus|VH1-46_IGHD1-26*01_IGHJ4*01	754	gnl|Fabrus|A27_IGKJ1*01	1080
1135	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ6*01	1068	gnl|Fabrus|A27_IGKJ1*01	1080
1136	gnl|Fabrus|VH2-70_IGHD3-9*01_IGHJ6*01	810	gnl|Fabrus|A27_IGKJ1*01	1080
1137	gnl|Fabrus|VH1-58_IGHD3-10*01_IGHJ6*01	764	gnl|Fabrus|A27_IGKJ1*01	1080
1138	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ2*01	1067	gnl|Fabrus|A27_IGKJ1*01	1080
1139	gnl|Fabrus|VH4-28_IGHD3-9*01_IGHJ6*01	1002	gnl|Fabrus|A27_IGKJ1*01	1080
1140	gnl|Fabrus|VH4-31_IGHD2-15*01_IGHJ2*01	1008	gnl|Fabrus|A27_IGKJ1*01	1080
1141	gnl|Fabrus|VH2-5_IGHD3-9*01_IGHJ6*01	803	gnl|Fabrus|A27_IGKJ1*01	1080
1142	gnl|Fabrus|VH1-8_IGHD2-15*01_IGHJ6*01	783	gnl|Fabrus|A27_IGKJ1*01	1080
1143	gnl|Fabrus|VH2-70_IGHD2-15*01_IGHJ2*01	808	gnl|Fabrus|A27_IGKJ1*01	1080
1144	gnl|Fabrus|VH3-38_IGHD3-10*01_IGHJ4*01	907	gnl|Fabrus|A27_IGKJ1*01	1080
1145	gnl|Fabrus|VH3-16_IGHD1-7*01_IGHJ6*01	838	gnl|Fabrus|A27_IGKJ1*01	1080
1146	gnl|Fabrus|VH3-73_IGHD3-9*01_IGHJ6*01	974	gnl|Fabrus|A27_IGKJ1*01	1080
1147	gnl|Fabrus|VH3-11_IGHD3-9*01_IGHJ6*01	816	gnl|Fabrus|A27_IGKJ1*01	1080
1148	gnl|Fabrus|VH3-11_IGHD6-6*01_IGHJ1*01	820	gnl|Fabrus|A27_IGKJ1*01	1080
1149	gnl|Fabrus|VH3-20_IGHD5-12*01_IGHJ4*01	852	gnl|Fabrus|A27_IGKJ1*01	1080
1150	gnl|Fabrus|VH3-16_IGHD2-15*01_IGHJ2*01	839	gnl|Fabrus|A27_IGKJ1*01	1080
1151	gnl|Fabrus|VH3-7_IGHD6-6*01_IGHJ1*01	960	gnl|Fabrus|A27_IGKJ1*01	1080
1152	gnl|Fabrus|VH3-16_IGHD6-13*01_IGHJ4*01	844	gnl|Fabrus|A27_IGKJ1*01	1080
1153	gnl|Fabrus|VH3-23_IGHD1-1*01_IGHJ4*01	863	gnl|Fabrus|A2_IGKJ1*01	1076
1154	gnl|Fabrus|VH3-23_IGHD2-15*01_IGHJ4*01	866	gnl|Fabrus|A2_IGKJ1*01	1076

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1155	gnl|Fabrus|VH3-23_IGHD3-22*01_IGHJ4*01	870	gnl|Fabrus|A2_IGKJ1*01	1076
1156	gnl|Fabrus|VH3-23_IGHD4-11*01_IGHJ4*01	872	gnl|Fabrus|A2_IGKJ1*01	1076
1157	gnl|Fabrus|VH3-23_IGHD5-12*01_IGHJ4*01	874	gnl|Fabrus|A2_IGKJ1*01	1076
1158	gnl|Fabrus|VH3-23_IGHD5-5*01_IGHJ4*01	876	gnl|Fabrus|A2_IGKJ1*01	1076
1159	gnl|Fabrus|VH3-23_IGHD6-13*01_IGHJ4*01	877	gnl|Fabrus|A2_IGKJ1*01	1076
1160	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ4*01	880	gnl|Fabrus|A2_IGKJ1*01	1076
1161	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ6*01	881	gnl|Fabrus|A2_IGKJ1*01	1076
1162	gnl|Fabrus|VH1-69_IGHD1-14*01_IGHJ4*01	770	gnl|Fabrus|A2_IGKJ1*01	1076
1163	gnl|Fabrus|VH1-69_IGHD2-2*01_IGHJ4*01	771	gnl|Fabrus|A2_IGKJ1*01	1076
1164	gnl|Fabrus|VH1-69_IGHD2-8*01_IGHJ6*01	772	gnl|Fabrus|A2_IGKJ1*01	1076
1165	gnl|Fabrus|VH1-69_IGHD3-16*01_IGHJ4*01	773	gnl|Fabrus|A2_IGKJ1*01	1076
1166	gnl|Fabrus|VH1-69_IGHD3-3*01_IGHJ4*01	774	gnl|Fabrus|A2_IGKJ1*01	1076
1167	gnl|Fabrus|VH1-69_IGHD4-17*01_IGHJ4*01	776	gnl|Fabrus|A2_IGKJ1*01	1076
1168	gnl|Fabrus|VH1-69_IGHD5-12*01_IGHJ4*01	777	gnl|Fabrus|A2_IGKJ1*01	1076
1169	gnl|Fabrus|VH1-69_IGHD6-19*01_IGHJ4*01	779	gnl|Fabrus|A2_IGKJ1*01	1076
1170	gnl|Fabrus|VH1-69_IGHD7-27*01_IGHJ4*01	781	gnl|Fabrus|A2_IGKJ1*01	1076
1171	gnl|Fabrus|VH4-34_IGHD1-7*01_IGHJ4*01	1017	gnl|Fabrus|A2_IGKJ1*01	1076
1172	gnl|Fabrus|VH4-34_IGHD2-2*01_IGHJ4*01	1018	gnl|Fabrus|A2_IGKJ1*01	1076
1173	gnl|Fabrus|VH4-34_IGHD3-16*01_IGHJ4*01	1019	gnl|Fabrus|A2_IGKJ1*01	1076
1174	gnl|Fabrus|VH4-34_IGHD4-17*01_IGHJ4*01	1021	gnl|Fabrus|A2_IGKJ1*01	1076
1175	gnl|Fabrus|VH4-34_IGHD5-12*01_IGHJ4*01	1022	gnl|Fabrus|A2_IGKJ1*01	1076
1176	gnl|Fabrus|VH4-34_IGHD6-13*01_IGHJ4*01	1023	gnl|Fabrus|A2_IGKJ1*01	1076
1177	gnl|Fabrus|VH4-34_IGHD6-25*01_IGHJ6*01	1024	gnl|Fabrus|A2_IGKJ1*01	1076
1178	gnl|Fabrus|VH4-34_IGHD7-27*01_IGHJ4*01	1026	gnl|Fabrus|A2_IGKJ1*01	1076
1179	gnl|Fabrus|VH2-26_IGHD1-20*01_IGHJ4*01	789	gnl|Fabrus|A2_IGKJ1*01	1076
1180	gnl|Fabrus|VH2-26_IGHD2-2*01_IGHJ4*01	791	gnl|Fabrus|A2_IGKJ1*01	1076
1181	gnl|Fabrus|VH2-26_IGHD3-10*01_IGHJ4*01	792	gnl|Fabrus|A2_IGKJ1*01	1076
1182	gnl|Fabrus|VH2-26_IGHD4-11*01_IGHJ4*01	794	gnl|Fabrus|A2_IGKJ1*01	1076
1183	gnl|Fabrus|VH2-26_IGHD5-18*01_IGHJ4*01	796	gnl|Fabrus|A2_IGKJ1*01	1076
1184	gnl|Fabrus|VH2-26_IGHD6-13*01_IGHJ4*01	797	gnl|Fabrus|A2_IGKJ1*01	1076
1185	gnl|Fabrus|VH2-26_IGHD7-27*01_IGHJ4*01	798	gnl|Fabrus|A2_IGKJ1*01	1076
1186	gnl|Fabrus|VH5-51_IGHD1-14*01_IGHJ4*01	1044	gnl|Fabrus|A2_IGKJ1*01	1076
1187	gnl|Fabrus|VH5-51_IGHD2-8*01_IGHJ4*01	1046	gnl|Fabrus|A2_IGKJ1*01	1076
1188	gnl|Fabrus|VH5-51_IGHD3-3*01_IGHJ4*01	1048	gnl|Fabrus|A2_IGKJ1*01	1076
1189	gnl|Fabrus|VH5-51_IGHD4-17*01_IGHJ4*01	1049	gnl|Fabrus|A2_IGKJ1*01	1076
1190	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1050	gnl|Fabrus|A2_IGKJ1*01	1076
1191	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1051	gnl|Fabrus|A2_IGKJ1*01	1076
1192	gnl|Fabrus|VH5-51_IGHD6-25*01_IGHJ4*01	1052	gnl|Fabrus|A2_IGKJ1*01	1076
1193	gnl|Fabrus|VH5-51_IGHD7-27*01_IGHJ4*01	1053	gnl|Fabrus|A2_IGKJ1*01	1076
1194	gnl|Fabrus|VH6-1_IGHD1-1*01_IGHJ4*01	1054	gnl|Fabrus|A2_IGKJ1*01	1076
1195	gnl|Fabrus|VH6-1_IGHD2-15*01_IGHJ4*01	1056	gnl|Fabrus|A2_IGKJ1*01	1076
1196	gnl|Fabrus|VH6-1_IGHD3-3*01_IGHJ4*01	1059	gnl|Fabrus|A2_IGKJ1*01	1076

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1197	gnl|Fabrus|VH6-1_IGHD4-23*01_IGHJ4*01	1061	gnl|Fabrus|A2_IGKJ1*01	1076
1198	gnl|Fabrus|VH6-1_IGHD4-11*01_IGHJ6*01	1060	gnl|Fabrus|A2_IGKJ1*01	1076
1199	gnl|Fabrus|VH6-1_IGHD5-5*01_IGHJ4*01	1062	gnl|Fabrus|A2_IGKJ1*01	1076
1200	gnl|Fabrus|VH6-1_IGHD6-13*01_IGHJ4*01	1063	gnl|Fabrus|A2_IGKJ1*01	1076
1201	gnl|Fabrus|VH6-1_IGHD6-25*01_IGHJ6*01	1064	gnl|Fabrus|A2_IGKJ1*01	1076
1202	gnl|Fabrus|VH6-1_IGHD7-27*01_IGHJ4*01	1065	gnl|Fabrus|A2_IGKJ1*01	1076
1203	gnl|Fabrus|VH4-59_IGHD6-25*01_IGHJ3*01	1043	gnl|Fabrus|A2_IGKJ1*01	1076
1204	gnl|Fabrus|VH3-48_IGHD6-6*01_IGHJ1*01	923	gnl|Fabrus|A2_IGKJ1*01	1076
1205	gnl|Fabrus|VH3-30_IGHD6-6*01_IGHJ1*01	893	gnl|Fabrus|A2_IGKJ1*01	1076
1206	gnl|Fabrus|VH3-66_IGHD6-6*01_IGHJ1*01	949	gnl|Fabrus|A2_IGKJ1*01	1076
1207	gnl|Fabrus|VH3-53_IGHD5-5*01_IGHJ4*01	938	gnl|Fabrus|A2_IGKJ1*01	1076
1208	gnl|Fabrus|VH2-5_IGHD5-12*01_IGHJ4*01	804	gnl|Fabrus|A2_IGKJ1*01	1076
1209	gnl|Fabrus|VH2-70_IGHD5-12*01_IGHJ4*01	811	gnl|Fabrus|A2_IGKJ1*01	1076
1210	gnl|Fabrus|VH3-15_IGHD5-12*01_IGHJ4*01	835	gnl|Fabrus|A2_IGKJ1*01	1076
1211	gnl|Fabrus|VH3-15_IGHD3-10*01_IGHJ4*01	833	gnl|Fabrus|A2_IGKJ1*01	1076
1212	gnl|Fabrus|VH3-49_IGHD5-18*01_IGHJ4*01	930	gnl|Fabrus|A2_IGKJ1*01	1076
1213	gnl|Fabrus|VH3-49_IGHD6-13*01_IGHJ4*01	931	gnl|Fabrus|A2_IGKJ1*01	1076
1214	gnl|Fabrus|VH3-72_IGHD5-18*01_IGHJ4*01	967	gnl|Fabrus|A2_IGKJ1*01	1076
1215	gnl|Fabrus|VH3-72_IGHD6-6*01_IGHJ1*01	969	gnl|Fabrus|A2_IGKJ1*01	1076
1216	gnl|Fabrus|VH3-73_IGHD5-12*01_IGHJ4*01	977	gnl|Fabrus|A2_IGKJ1*01	1076
1217	gnl|Fabrus|VH3-73_IGHD4-23*01_IGHJ5*01	976	gnl|Fabrus|A2_IGKJ1*01	1076
1218	gnl|Fabrus|VH3-43_IGHD3-22*01_IGHJ4*01	918	gnl|Fabrus|A2_IGKJ1*01	1076
1219	gnl|Fabrus|VH3-43_IGHD6-13*01_IGHJ4*01	921	gnl|Fabrus|A2_IGKJ1*01	1076
1220	gnl|Fabrus|VH3-9_IGHD3-22*01_IGHJ4*01	992	gnl|Fabrus|A2_IGKJ1*01	1076
1221	gnl|Fabrus|VH3-9_IGHD1-7*01_IGHJ5*01	989	gnl|Fabrus|A2_IGKJ1*01	1076
1222	gnl|Fabrus|VH3-9_IGHD6-13*01_IGHJ4*01	995	gnl|Fabrus|A2_IGKJ1*01	1076
1223	gnl|Fabrus|VH4-39_IGHD3-10*01_IGHJ4*01	1030	gnl|Fabrus|A2_IGKJ1*01	1076
1224	gnl|Fabrus|VH4-39_IGHD5-12*01_IGHJ4*01	1034	gnl|Fabrus|A2_IGKJ1*01	1076
1225	gnl|Fabrus|VH1-18_IGHD6-6*01_IGHJ1*01	728	gnl|Fabrus|A2_IGKJ1*01	1076
1226	gnl|Fabrus|VH1-24_IGHD5-12*01_IGHJ4*01	735	gnl|Fabrus|A2_IGKJ1*01	1076
1227	gnl|Fabrus|VH1-2_IGHD1-1*01_IGHJ3*01	729	gnl|Fabrus|A2_IGKJ1*01	1076
1228	gnl|Fabrus|VH1-3_IGHD6-6*01_IGHJ1*01	743	gnl|Fabrus|A2_IGKJ1*01	1076
1229	gnl|Fabrus|VH1-45_IGHD3-10*01_IGHJ4*01	748	gnl|Fabrus|A2_IGKJ1*01	1076
1230	gnl|Fabrus|VH1-46_IGHD1-26*01_IGHJ4*01	754	gnl|Fabrus|A2_IGKJ1*01	1076
1231	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ6*01	1068	gnl|Fabrus|A2_IGKJ1*01	1076
1232	gnl|Fabrus|VH2-70_IGHD3-9*01_IGHJ6*01	810	gnl|Fabrus|A2_IGKJ1*01	1076
1233	gnl|Fabrus|VH1-58_IGHD3-10*01_IGHJ6*01	764	gnl|Fabrus|A2_IGKJ1*01	1076
1234	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ2*01	1067	gnl|Fabrus|A2_IGKJ1*01	1076
1235	gnl|Fabrus|VH4-28_IGHD3-9*01_IGHJ6*01	1002	gnl|Fabrus|A2_IGKJ1*01	1076
1236	gnl|Fabrus|VH4-31_IGHD2-15*01_IGHJ2*01	1008	gnl|Fabrus|A2_IGKJ1*01	1076
1237	gnl|Fabrus|VH2-5_IGHD3-9*01_IGHJ6*01	803	gnl|Fabrus|A2_IGKJ1*01	1076
1238	gnl|Fabrus|VH1-8_IGHD2-15*01_IGHJ6*01	783	gnl|Fabrus|A2_IGKJ1*01	1076

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1239	gnl|Fabrus|VH2-70_IGHD2-15*01_IGHJ2*01	808	gnl|Fabrus|A2_IGKJ1*01	1076
1240	gnl|Fabrus|VH3-38_IGHD3-10*01_IGHJ4*01	907	gnl|Fabrus|A2_IGKJ1*01	1076
1241	gnl|Fabrus|VH3-16_IGHD1-7*01_IGHJ6*01	838	gnl|Fabrus|A2_IGKJ1*01	1076
1242	gnl|Fabrus|VH3-73_IGHD3-9*01_IGHJ6*01	974	gnl|Fabrus|A2_IGKJ1*01	1076
1243	gnl|Fabrus|VH3-11_IGHD3-9*01_IGHJ6*01	816	gnl|Fabrus|A2_IGKJ1*01	1076
1244	gnl|Fabrus|VH3-11_IGHD6-6*01_IGHJ1*01	820	gnl|Fabrus|A2_IGKJ1*01	1076
1245	gnl|Fabrus|VH3-20_IGHD5-12*01_IGHJ4*01	852	gnl|Fabrus|A2_IGKJ1*01	1076
1246	gnl|Fabrus|VH3-16_IGHD2-15*01_IGHJ2*01	839	gnl|Fabrus|A2_IGKJ1*01	1076
1247	gnl|Fabrus|VH3-7_IGHD6-6*01_IGHJ1*01	960	gnl|Fabrus|A2_IGKJ1*01	1076
1248	gnl|Fabrus|VH3-16_IGHD6-13*01_IGHJ4*01	844	gnl|Fabrus|A2_IGKJ1*01	1076
1249	gnl|Fabrus|VH3-23_IGHD1-1*01_IGHJ4*01	863	gnl|Fabrus|HerceptinLC	1086
1250	gnl|Fabrus|VH3-23_IGHD2-15*01_IGHJ4*01	866	gnl|Fabrus|HerceptinLC	1086
1251	gnl|Fabrus|VH3-23_IGHD3-22*01_IGHJ4*01	870	gnl|Fabrus|HerceptinLC	1086
1252	gnl|Fabrus|VH3-23_IGHD4-11*01_IGHJ4*01	872	gnl|Fabrus|HerceptinLC	1086
1253	gnl|Fabrus|VH3-23_IGHD5-12*01_IGHJ4*01	874	gnl|Fabrus|HerceptinLC	1086
1254	gnl|Fabrus|VH3-23_IGHD5-5*01_IGHJ4*01	876	gnl|Fabrus|HerceptinLC	1086
1255	gnl|Fabrus|VH3-23_IGHD6-13*01_IGHJ4*01	877	gnl|Fabrus|HerceptinLC	1086
1256	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ4*01	880	gnl|Fabrus|HerceptinLC	1086
1257	gnl|Fabrus|VH3-23_IGHD7-27*01_IGHJ6*01	881	gnl|Fabrus|HerceptinLC	1086
1258	gnl|Fabrus|VH1-69_IGHD1-14*01_IGHJ4*01	770	gnl|Fabrus|HerceptinLC	1086
1259	gnl|Fabrus|VH1-69_IGHD2-2*01_IGHJ4*01	771	gnl|Fabrus|HerceptinLC	1086
1260	gnl|Fabrus|VH1-69_IGHD2-8*01_IGHJ6*01	772	gnl|Fabrus|HerceptinLC	1086
1261	gnl|Fabrus|VH1-69_IGHD3-16*01_IGHJ4*01	773	gnl|Fabrus|HerceptinLC	1086
1262	gnl|Fabrus|VH1-69_IGHD3-3*01_IGHJ4*01	774	gnl|Fabrus|HerceptinLC	1086
1263	gnl|Fabrus|VH1-69_IGHD4-17*01_IGHJ4*01	776	gnl|Fabrus|HerceptinLC	1086
1264	gnl|Fabrus|VH1-69_IGHD5-12*01_IGHJ4*01	777	gnl|Fabrus|HerceptinLC	1086
1265	gnl|Fabrus|VH1-69_IGHD6-19*01_IGHJ4*01	779	gnl|Fabrus|HerceptinLC	1086
1266	gnl|Fabrus|VH1-69_IGHD7-27*01_IGHJ4*01	781	gnl|Fabrus|HerceptinLC	1086
1267	gnl|Fabrus|VH4-34_IGHD1-7*01_IGHJ4*01	1017	gnl|Fabrus|HerceptinLC	1086
1268	gnl|Fabrus|VH4-34_IGHD2-2*01_IGHJ4*01	1018	gnl|Fabrus|HerceptinLC	1086
1269	gnl|Fabrus|VH4-34_IGHD3-16*01_IGHJ4*01	1019	gnl|Fabrus|HerceptinLC	1086
1270	gnl|Fabrus|VH4-34_IGHD4-17*01_IGHJ4*01	1021	gnl|Fabrus|HerceptinLC	1086
1271	gnl|Fabrus|VH4-34_IGHD5-12*01_IGHJ4*01	1022	gnl|Fabrus|HerceptinLC	1086
1272	gnl|Fabrus|VH4-34_IGHD6-13*01_IGHJ4*01	1023	gnl|Fabrus|HerceptinLC	1086
1273	gnl|Fabrus|VH4-34_IGHD6-25*01_IGHJ6*01	1024	gnl|Fabrus|HerceptinLC	1086
1274	gnl|Fabrus|VH4-34_IGHD7-27*01_IGHJ4*01	1026	gnl|Fabrus|HerceptinLC	1086
1275	gnl|Fabrus|VH2-26_IGHD1-20*01_IGHJ4*01	789	gnl|Fabrus|HerceptinLC	1086
1276	gnl|Fabrus|VH2-26_IGHD2-2*01_IGHJ4*01	791	gnl|Fabrus|HerceptinLC	1086
1277	gnl|Fabrus|VH2-26_IGHD3-10*01_IGHJ4*01	792	gnl|Fabrus|HerceptinLC	1086
1278	gnl|Fabrus|VH2-26_IGHD4-11*01_IGHJ4*01	794	gnl|Fabrus|HerceptinLC	1086
1279	gnl|Fabrus|VH2-26_IGHD5-18*01_IGHJ4*01	796	gnl|Fabrus|HerceptinLC	1086
1280	gnl|Fabrus|VH2-26_IGHD6-13*01_IGHJ4*01	797	gnl|Fabrus|HerceptinLC	1086

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1281	gnl|Fabrus|VH2-26_IGHD7-27*01_IGHJ4*01	798	gnl|Fabrus|HerceptinLC	1086
1282	gnl|Fabrus|VH5-51_IGHD1-14*01_IGHJ4*01	1044	gnl|Fabrus|HerceptinLC	1086
1283	gnl|Fabrus|VH5-51_IGHD2-8*01_IGHJ4*01	1046	gnl|Fabrus|HerceptinLC	1086
1284	gnl|Fabrus|VH5-51_IGHD3-3*01_IGHJ4*01	1048	gnl|Fabrus|HerceptinLC	1086
1285	gnl|Fabrus|VH5-51_IGHD4-17*01_IGHJ4*01	1049	gnl|Fabrus|HerceptinLC	1086
1286	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1050	gnl|Fabrus|HerceptinLC	1086
1287	gnl|Fabrus|VH5-51_IGHD5-18*01_IGHJ4*01	1051	gnl|Fabrus|HerceptinLC	1086
1288	gnl|Fabrus|VH5-51_IGHD6-25*01_IGHJ4*01	1052	gnl|Fabrus|HerceptinLC	1086
1289	gnl|Fabrus|VH5-51_IGHD7-27*01_IGHJ4*01	1053	gnl|Fabrus|HerceptinLC	1086
1290	gnl|Fabrus|VH6-1_IGHD1-1*01_IGHJ4*01	1054	gnl|Fabrus|HerceptinLC	1086
1291	gnl|Fabrus|VH6-1_IGHD2-15*01_IGHJ4*01	1056	gnl|Fabrus|HerceptinLC	1086
1292	gnl|Fabrus|VH6-1_IGHD3-3*01_IGHJ4*01	1059	gnl|Fabrus|HerceptinLC	1086
1293	gnl|Fabrus|VH6-1_IGHD4-23*01_IGHJ4*01	1061	gnl|Fabrus|HerceptinLC	1086
1294	gnl|Fabrus|VH6-1_IGHD4-11*01_IGHJ6*01	1060	gnl|Fabrus|HerceptinLC	1086
1295	gnl|Fabrus|VH6-1_IGHD5-5*01_IGHJ4*01	1062	gnl|Fabrus|HerceptinLC	1086
1296	gnl|Fabrus|VH6-1_IGHD6-13*01_IGHJ4*01	1063	gnl|Fabrus|HerceptinLC	1086
1297	gnl|Fabrus|VH6-1_IGHD6-25*01_IGHJ6*01	1064	gnl|Fabrus|HerceptinLC	1086
1298	gnl|Fabrus|VH6-1_IGHD7-27*01_IGHJ4*01	1065	gnl|Fabrus|HerceptinLC	1086
1299	gnl|Fabrus|VH4-59_IGHD6-25*01_IGHJ3*01	1043	gnl|Fabrus|HerceptinLC	1086
1300	gnl|Fabrus|VH3-48_IGHD6-6*01_IGHJ1*01	923	gnl|Fabrus|HerceptinLC	1086
1301	gnl|Fabrus|VH3-30_IGHD6-6*01_IGHJ1*01	893	gnl|Fabrus|HerceptinLC	1086
1302	gnl|Fabrus|VH3-66_IGHD6-6*01_IGHJ1*01	949	gnl|Fabrus|HerceptinLC	1086
1303	gnl|Fabrus|VH3-53_IGHD5-5*01_IGHJ4*01	938	gnl|Fabrus|HerceptinLC	1086
1304	gnl|Fabrus|VH2-5_IGHD5-12*01_IGHJ4*01	804	gnl|Fabrus|HerceptinLC	1086
1305	gnl|Fabrus|VH2-70_IGHD5-12*01_IGHJ4*01	811	gnl|Fabrus|HerceptinLC	1086
1306	gnl|Fabrus|VH3-15_IGHD5-12*01_IGHJ4*01	835	gnl|Fabrus|HerceptinLC	1086
1307	gnl|Fabrus|VH3-15_IGHD3-10*01_IGHJ4*01	833	gnl|Fabrus|HerceptinLC	1086
1308	gnl|Fabrus|VH3-49_IGHD5-18*01_IGHJ4*01	930	gnl|Fabrus|HerceptinLC	1086
1309	gnl|Fabrus|VH3-49_IGHD6-13*01_IGHJ4*01	931	gnl|Fabrus|HerceptinLC	1086
1310	gnl|Fabrus|VH3-72_IGHD5-18*01_IGHJ4*01	967	gnl|Fabrus|HerceptinLC	1086
1311	gnl|Fabrus|VH3-72_IGHD6-6*01_IGHJ1*01	969	gnl|Fabrus|HerceptinLC	1086
1312	gnl|Fabrus|VH3-73_IGHD5-12*01_IGHJ4*01	977	gnl|Fabrus|HerceptinLC	1086
1313	gnl|Fabrus|VH3-73_IGHD4-23*01_IGHJ5*01	976	gnl|Fabrus|HerceptinLC	1086
1314	gnl|Fabrus|VH3-43_IGHD3-22*01_IGHJ4*01	918	gnl|Fabrus|HerceptinLC	1086
1315	gnl|Fabrus|VH3-43_IGHD6-13*01_IGHJ4*01	921	gnl|Fabrus|HerceptinLC	1086
1316	gnl|Fabrus|VH3-9_IGHD3-22*01_IGHJ4*01	992	gnl|Fabrus|HerceptinLC	1086
1317	gnl|Fabrus|VH3-9_IGHD1-7*01_IGHJ5*01	989	gnl|Fabrus|HerceptinLC	1086
1318	gnl|Fabrus|VH3-9_IGHD6-13*01_IGHJ4*01	995	gnl|Fabrus|HerceptinLC	1086
1319	gnl|Fabrus|VH4-39_IGHD3-10*01_IGHJ4*01	1030	gnl|Fabrus|HerceptinLC	1086
1320	gnl|Fabrus|VH4-39_IGHD5-12*01_IGHJ4*01	1034	gnl|Fabrus|HerceptinLC	1086
1321	gnl|Fabrus|VH1-18_IGHD6-6*01_IGHJ1*01	728	gnl|Fabrus|HerceptinLC	1086
1322	gnl|Fabrus|VH1-24_IGHD5-12*01_IGHJ4*01	735	gnl|Fabrus|HerceptinLC	1086

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1323	gnl|Fabrus|VH1-2_IGHD1-1*01_IGHJ3*01	729	gnl|Fabrus|HerceptinLC	1086
1324	gnl|Fabrus|VH1-3_IGHD6-6*01_IGHJ1*01	743	gnl|Fabrus|HerceptinLC	1086
1325	gnl|Fabrus|VH1-45_IGHD3-10*01_IGHJ4*01	748	gnl|Fabrus|HerceptinLC	1086
1326	gnl|Fabrus|VH1-46_IGHD1-26*01_IGHJ4*01	754	gnl|Fabrus|HerceptinLC	1086
1327	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ6*01	1068	gnl|Fabrus|HerceptinLC	1086
1328	gnl|Fabrus|VH2-70_IGHD3-9*01_IGHJ6*01	810	gnl|Fabrus|HerceptinLC	1086
1329	gnl|Fabrus|VH1-58_IGHD3-10*01_IGHJ6*01	764	gnl|Fabrus|HerceptinLC	1086
1330	gnl|Fabrus|VH7-81_IGHD2-21*01_IGHJ2*01	1067	gnl|Fabrus|HerceptinLC	1086
1331	gnl|Fabrus|VH4-28_IGHD3-9*01_IGHJ6*01	1002	gnl|Fabrus|HerceptinLC	1086
1332	gnl|Fabrus|VH4-31_IGHD2-15*01_IGHJ2*01	1008	gnl|Fabrus|HerceptinLC	1086
1333	gnl|Fabrus|VH2-5_IGHD3-9*01_IGHJ6*01	803	gnl|Fabrus|HerceptinLC	1086
1334	gnl|Fabrus|VH1-8_IGHD2-15*01_IGHJ6*01	783	gnl|Fabrus|HerceptinLC	1086
1335	gnl|Fabrus|VH2-70_IGHD2-15*01_IGHJ2*01	808	gnl|Fabrus|HerceptinLC	1086
1336	gnl|Fabrus|VH3-38_IGHD3-10*01_IGHJ4*01	907	gnl|Fabrus|HerceptinLC	1086
1337	gnl|Fabrus|VH3-16_IGHD1-7*01_IGHJ6*01	838	gnl|Fabrus|HerceptinLC	1086
1338	gnl|Fabrus|VH3-73_IGHD3-9*01_IGHJ6*01	974	gnl|Fabrus|HerceptinLC	1086
1339	gnl|Fabrus|VH3-11_IGHD3-9*01_IGHJ6*01	816	gnl|Fabrus|HerceptinLC	1086
1340	gnl|Fabrus|VH3-11_IGHD6-6*01_IGHJ1*01	820	gnl|Fabrus|HerceptinLC	1086
1341	gnl|Fabrus|VH3-20_IGHD5-12*01_IGHJ4*01	852	gnl|Fabrus|HerceptinLC	1086
1342	gnl|Fabrus|VH3-16_IGHD2-15*01_IGHJ2*01	839	gnl|Fabrus|HerceptinLC	1086
1343	gnl|Fabrus|VH3-7_IGHD6-6*01_IGHJ1*01	960	gnl|Fabrus|HerceptinLC	1086
1344	gnl|Fabrus|VH3-16_IGHD6-13*01_IGHJ4*01	844	gnl|Fabrus|HerceptinLC	1086
1345	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|O12_IGKJ1*01	1101
1346	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|O18_IGKJ1*01	1102
1347	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|A20_IGKJ1*01	1077
1348	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|A30_IGKJ1*01	1082
1349	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|L14_IGKJ1*01	1089
1350	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|L4/18a_IGKJ1*01	1095
1351	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|L5_IGKJ1*01	1096
1352	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|L8_IGKJ1*01	1097
1353	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|L23_IGKJ1*01	1092
1354	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|L11_IGKJ1*01	1087
1355	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|L12_IGKJ1*01	1088
1356	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|O1_IGKJ1*01	1100
1357	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|A17_IGKJ1*01	1075
1358	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|A2_IGKJ1*01	1076
1359	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|A23_IGKJ1*01	1078
1360	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|A27_IGKJ3*01	1081
1361	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|L2_IGKJ1*01	1090
1362	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|L6_IGKJ1*01	1097
1363	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|L25_IGKJ1*01	1094
1364	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|B3_IGKJ1*01	1085

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1365	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|B2_IGKJ1*01	1083
1366	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|A26_IGKJ1*01	1079
1367	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|A14_IGKJ1*01	1074
1368	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|L9_IGKJ2*01	1099
1369	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|A27_IGKJ1*01	1080
1370	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|B2_IGKJ3*01	1084
1371	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|L25_IGKJ3*01	1094
1372	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|RituxanLC	1103
1373	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|L22_IGKJ3*01	1091
1374	gnl|Fabrus|VH3-23_IGHD3-10*01_IGHJ4*01	868	gnl|Fabrus|HerceptinLC	1086
1375	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|O12_IGKJ1*01	1101
1376	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|O18_IGKJ1*01	1102
1377	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|A20_IGKJ1*01	1077
1378	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|A30_IGKJ1*01	1082
1379	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|L14_IGKJ1*01	1089
1380	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|L4/18a_IGKJ1*01	1095
1381	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|L5_IGKJ1*01	1096
1382	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|L8_IGKJ1*01	1097
1383	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|L23_IGKJ1*01	1092
1384	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|L11_IGKJ1*01	1087
1385	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|L12_IGKJ1*01	1088
1386	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|O1_IGKJ1*01	1100
1387	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|A17_IGKJ1*01	1075
1388	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|A2_IGKJ1*01	1076
1389	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|A23_IGKJ1*01	1078
1390	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|A27_IGKJ3*01	1081
1391	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|L2_IGKJ1*01	1090
1392	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|L6_IGKJ1*01	1097
1393	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|L25_IGKJ1*01	1094
1394	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|B3_IGKJ1*01	1085
1395	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|B2_IGKJ1*01	1083
1396	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|A26_IGKJ1*01	1079
1397	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|A14_IGKJ1*01	1074
1398	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|L9_IGKJ2*01	1099
1399	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|A27_IGKJ1*01	1080
1400	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|B2_IGKJ3*01	1084
1401	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|L25_IGKJ3*01	1094
1402	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|RituxanLC	1103
1403	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|L22_IGKJ3*01	1091
1404	gnl|Fabrus|VH4-31_IGHD6-6*01_IGHJ1*01	1015	gnl|Fabrus|HerceptinLC	1086
1405	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|O12_IGKJ1*01	1101
1406	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|O18_IGKJ1*01	1102

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1407	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|A20_IGKJ1*01	1077
1408	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|A30_IGKJ1*01	1082
1409	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|L14_IGKJ1*01	1089
1410	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|L4/18a_IGKJ1*01	1095
1411	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|L5_IGKJ1*01	1096
1412	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|L8_IGKJ1*01	1097
1413	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|L23_IGKJ1*01	1092
1414	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|L11_IGKJ1*01	1087
1415	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|L12_IGKJ1*01	1088
1416	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|O1_IGKJ1*01	1100
1417	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|A17_IGKJ1*01	1075
1418	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|A2_IGKJ1*01	1076
1419	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|A23_IGKJ1*01	1078
1420	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|A27_IGKJ3*01	1081
1421	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|L2_IGKJ1*01	1090
1422	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|L6_IGKJ1*01	1097
1423	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|L25_IGKJ1*01	1094
1424	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|B3_IGKJ1*01	1085
1425	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|B2_IGKJ1*01	1083
1426	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|A26_IGKJ1*01	1079
1427	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|A14_IGKJ1*01	1074
1428	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|L9_IGKJ2*01	1099
1429	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|A27_IGKJ1*01	1080
1430	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|B2_IGKJ3*01	1084
1431	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|L25_IGKJ3*01	1094
1432	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|RituxanLC	1103
1433	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|L22_IGKJ3*01	1091
1434	gnl|Fabrus|RituxanHC	721	gnl|Fabrus|HerceptinLC	1086
1435	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|O12_IGKJ1*01	1101
1436	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|O18_IGKJ1*01	1102
1437	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|A20_IGKJ1*01	1077
1438	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|A30_IGKJ1*01	1082
1439	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|L14_IGKJ1*01	1089
1440	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|L4/18a_IGKJ1*01	1095
1441	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|L5_IGKJ1*01	1096
1442	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|L8_IGKJ1*01	1097
1443	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|L23_IGKJ1*01	1092
1444	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|L11_IGKJ1*01	1087
1445	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|L12_IGKJ1*01	1088
1446	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|O1_IGKJ1*01	1100
1447	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|A17_IGKJ1*01	1075
1448	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|A2_IGKJ1*01	1076

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1449	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|A23_IGKJ1*01	1078
1450	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|A27_IGKJ3*01	1081
1451	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|L2_IGKJ1*01	1090
1452	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|L6_IGKJ1*01	1097
1453	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|L25_IGKJ1*01	1094
1454	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|B3_IGKJ1*01	1085
1455	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|B2_IGKJ1*01	1083
1456	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|A26_IGKJ1*01	1079
1457	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|A14_IGKJ1*01	1074
1458	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|L9_IGKJ2*01	1099
1459	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|A27_IGKJ1*01	1080
1460	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|B2_IGKJ3*01	1084
1461	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|L25_IGKJ3*01	1094
1462	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|RituxanLC	1103
1463	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|L22_IGKJ3*01	1091
1464	gnl|Fabrus|HerceptinHC	720	gnl|Fabrus|HerceptinLC	1086
1465	VH3-23_IGHD1-1*01>1_IGHJ1*01	1136	gnl|Fabrus|O12_IGKJ1*01	1101
1466	VH3-23_IGHD1-1*01>2_IGHJ1*01	1137	gnl|Fabrus|O12_IGKJ1*01	1101
1467	VH3-23_IGHD1-1*01>3_IGHJ1*01	1138	gnl|Fabrus|O12_IGKJ1*01	1101
1468	VH3-23_IGHD1-7*01>1_IGHJ1*01	1139	gnl|Fabrus|O12_IGKJ1*01	1101
1469	VH3-23_IGHD1-7*01>3_IGHJ1*01	1140	gnl|Fabrus|O12_IGKJ1*01	1101
1470	VH3-23_IGHD1-14*01>1_IGHJ1*01	1141	gnl|Fabrus|O12_IGKJ1*01	1101
1471	VH3-23_IGHD1-14*01>3_IGHJ1*01	1142	gnl|Fabrus|O12_IGKJ1*01	1101
1472	VH3-23_IGHD1-20*01>1_IGHJ1*01	1143	gnl|Fabrus|O12_IGKJ1*01	1101
1473	VH3-23_IGHD1-20*01>3_IGHJ1*01	1144	gnl|Fabrus|O12_IGKJ1*01	1101
1474	VH3-23_IGHD1-26*01>1_IGHJ1*01	1145	gnl|Fabrus|O12_IGKJ1*01	1101
1475	VH3-23_IGHD1-26*01>3_IGHJ1*01	1146	gnl|Fabrus|O12_IGKJ1*01	1101
1476	VH3-23_IGHD2-2*01>2_IGHJ1*01	1147	gnl|Fabrus|O12_IGKJ1*01	1101
1477	VH3-23_IGHD2-2*01>3_IGHJ1*01	1148	gnl|Fabrus|O12_IGKJ1*01	1101
1478	VH3-23_IGHD2-8*01>2_IGHJ1*01	1149	gnl|Fabrus|O12_IGKJ1*01	1101
1479	VH3-23_IGHD2-8*01>3_IGHJ1*01	1150	gnl|Fabrus|O12_IGKJ1*01	1101
1480	VH3-23_IGHD2-15*01>2_IGHJ1*01	1151	gnl|Fabrus|O12_IGKJ1*01	1101
1481	VH3-23_IGHD2-15*01>3_IGHJ1*01	1152	gnl|Fabrus|O12_IGKJ1*01	1101
1482	VH3-23_IGHD2-21*01>2_IGHJ1*01	1153	gnl|Fabrus|O12_IGKJ1*01	1101
1483	VH3-23_IGHD2-21*01>3_IGHJ1*01	1154	gnl|Fabrus|O12_IGKJ1*01	1101
1484	VH3-23_IGHD3-3*01>1_IGHJ1*01	1155	gnl|Fabrus|O12_IGKJ1*01	1101
1485	VH3-23_IGHD3-3*01>2_IGHJ1*01	1156	gnl|Fabrus|O12_IGKJ1*01	1101
1486	VH3-23_IGHD3-3*01>3_IGHJ1*01	1157	gnl|Fabrus|O12_IGKJ1*01	1101
1487	VH3-23_IGHD3-9*01>2_IGHJ1*01	1158	gnl|Fabrus|O12_IGKJ1*01	1101
1488	VH3-23_IGHD3-10*01>2_IGHJ1*01	1159	gnl|Fabrus|O12_IGKJ1*01	1101
1489	VH3-23_IGHD3-10*01>3_IGHJ1*01	1160	gnl|Fabrus|O12_IGKJ1*01	1101
1490	VH3-23_IGHD3-16*01>2_IGHJ1*01	1161	gnl|Fabrus|O12_IGKJ1*01	1101

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1491	VH3-23_IGHD3-16*01>3_IGHJ1*01	1162	gnl|Fabrus|O12_IGKJ1*01	1101
1492	VH3-23_IGHD3-22*01>2_IGHJ1*01	1163	gnl|Fabrus|O12_IGKJ1*01	1101
1493	VH3-23_IGHD3-22*01>3_IGHJ1*01	1164	gnl|Fabrus|O12_IGKJ1*01	1101
1494	VH3-23_IGHD4-4*01 (1) >2_IGHJ1*01	1165	gnl|Fabrus|O12_IGKJ1*01	1101
1495	VH3-23_IGHD4-4*01 (1) >3_IGHJ1*01	1166	gnl|Fabrus|O12_IGKJ1*01	1101
1496	VH3-23_IGHD4-11*01 (1) >2_IGHJ1*01	1167	gnl|Fabrus|O12_IGKJ1*01	1101
1497	VH3-23_IGHD4-11*01 (1) >3_IGHJ1*01	1168	gnl|Fabrus|O12_IGKJ1*01	1101
1498	VH3-23_IGHD4-17*01>2_IGHJ1*01	1169	gnl|Fabrus|O12_IGKJ1*01	1101
1499	VH3-23_IGHD4-17*01>3_IGHJ1*01	1170	gnl|Fabrus|O12_IGKJ1*01	1101
1500	VH3-23_IGHD4-23*01>2_IGHJ1*01	1171	gnl|Fabrus|O12_IGKJ1*01	1101
1501	VH3-23_IGHD4-23*01>3_IGHJ1*01	1172	gnl|Fabrus|O12_IGKJ1*01	1101
1502	VH3-23_IGHD5-5*01 (2) >1_IGHJ1*01	1173	gnl|Fabrus|O12_IGKJ1*01	1101
1503	VH3-23_IGHD5-5*01 (2) >2_IGHJ1*01	1174	gnl|Fabrus|O12_IGKJ1*01	1101
1504	VH3-23_IGHD5-5*01 (2) >3_IGHJ1*01	1175	gnl|Fabrus|O12_IGKJ1*01	1101
1505	VH3-23_IGHD5-12*01>1_IGHJ1*01	1176	gnl|Fabrus|O12_IGKJ1*01	1101
1506	VH3-23_IGHD5-12*01>3_IGHJ1*01	1177	gnl|Fabrus|O12_IGKJ1*01	1101
1507	VH3-23_IGHD5-18*01 (2) >1_IGHJ1*01	1178	gnl|Fabrus|O12_IGKJ1*01	1101
1508	VH3-23_IGHD5-18*01 (2) >2_IGHJ1*01	1179	gnl|Fabrus|O12_IGKJ1*01	1101
1509	VH3-23_IGHD5-18*01 (2) >3_IGHJ1*01	1180	gnl|Fabrus|O12_IGKJ1*01	1101
1510	VH3-23_IGHD5-24*01>1_IGHJ1*01	1181	gnl|Fabrus|O12_IGKJ1*01	1101
1511	VH3-23_IGHD5-24*01>3_IGHJ1*01	1182	gnl|Fabrus|O12_IGKJ1*01	1101
1512	VH3-23_IGHD6-6*01>1_IGHJ1*01	1183	gnl|Fabrus|O12_IGKJ1*01	1101
1513	VH3-23_IGHD1-1*01>1'_IGHJ1*01	1193	gnl|Fabrus|O12_IGKJ1*01	1101
1514	VH3-23_IGHD1-1*01>2'_IGHJ1*01	1194	gnl|Fabrus|O12_IGKJ1*01	1101
1515	VH3-23_IGHD1-1*01>3'_IGHJ1*01	1195	gnl|Fabrus|O12_IGKJ1*01	1101
1516	VH3-23_IGHD1-7*01>1'_IGHJ1*01	1196	gnl|Fabrus|O12_IGKJ1*01	1101
1517	VH3-23_IGHD1-7*01>3'_IGHJ1*01	1197	gnl|Fabrus|O12_IGKJ1*01	1101
1518	VH3-23_IGHD1-14*01>1'_IGHJ1*01	1198	gnl|Fabrus|O12_IGKJ1*01	1101
1519	VH3-23_IGHD1-14*01>2'_IGHJ1*01	1199	gnl|Fabrus|O12_IGKJ1*01	1101
1520	VH3-23_IGHD1-14*01>3'_IGHJ1*01	1200	gnl|Fabrus|O12_IGKJ1*01	1101
1521	VH3-23_IGHD1-20*01>1'_IGHJ1*01	1201	gnl|Fabrus|O12_IGKJ1*01	1101
1522	VH3-23_IGHD1-20*01>2'_IGHJ1*01	1202	gnl|Fabrus|O12_IGKJ1*01	1101
1523	VH3-23_IGHD1-20*01>3'_IGHJ1*01	1203	gnl|Fabrus|O12_IGKJ1*01	1101
1524	VH3-23_IGHD1-26*01>1'_IGHJ1*01	1204	gnl|Fabrus|O12_IGKJ1*01	1101
1525	VH3-23_IGHD1-26*01>3'_IGHJ1*01	1205	gnl|Fabrus|O12_IGKJ1*01	1101
1526	VH3-23_IGHD2-2*01>1'_IGHJ1*01	1206	gnl|Fabrus|O12_IGKJ1*01	1101
1527	VH3-23_IGHD2-2*01>3'_IGHJ1*01	1207	gnl|Fabrus|O12_IGKJ1*01	1101
1528	VH3-23_IGHD2-8*01>1'_IGHJ1*01	1208	gnl|Fabrus|O12_IGKJ1*01	1101
1529	VH3-23_IGHD2-15*01>1'_IGHJ1*01	1209	gnl|Fabrus|O12_IGKJ1*01	1101
1530	VH3-23_IGHD2-15*01>3'_IGHJ1*01	1210	gnl|Fabrus|O12_IGKJ1*01	1101
1531	VH3-23_IGHD2-21*01>1'_IGHJ1*01	1211	gnl|Fabrus|O12_IGKJ1*01	1101
1532	VH3-23_IGHD2-21*01>3'_IGHJ1*01	1212	gnl|Fabrus|O12_IGKJ1*01	1101

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1533	VH3-23_IGHD3-3*01>1'_IGHJ1*01	1213	gnl|Fabrus|O12_IGKJ1*01	1101
1534	VH3-23_IGHD3-3*01>3'_IGHJ1*01	1214	gnl|Fabrus|O12_IGKJ1*01	1101
1535	VH3-23_IGHD3-9*01>1'_IGHJ1*01	1215	gnl|Fabrus|O12_IGKJ1*01	1101
1536	VH3-23_IGHD3-9*01>3'_IGHJ1*01	1216	gnl|Fabrus|O12_IGKJ1*01	1101
1537	VH3-23_IGHD3-10*01>1'_IGHJ1*01	1217	gnl|Fabrus|O12_IGKJ1*01	1101
1538	VH3-23_IGHD3-10*01>3'_IGHJ1*01	1218	gnl|Fabrus|O12_IGKJ1*01	1101
1539	VH3-23_IGHD3-16*01>1'_IGHJ1*01	1219	gnl|Fabrus|O12_IGKJ1*01	1101
1540	VH3-23_IGHD3-16*01>3'_IGHJ1*01	1220	gnl|Fabrus|O12_IGKJ1*01	1101
1541	VH3-23_IGHD3-22*01>1'_IGHJ1*01	1221	gnl|Fabrus|O12_IGKJ1*01	1101
1542	VH3-23_IGHD4-4*01 (1) >1'_IGHJ1*01	1222	gnl|Fabrus|O12_IGKJ1*01	1101
1543	VH3-23_IGHD4-4*01 (1) >3'_IGHJ1*01	1223	gnl|Fabrus|O12_IGKJ1*01	1101
1544	VH3-23_IGHD4-11*01 (1) >1'_IGHJ1*01	1224	gnl|Fabrus|O12_IGKJ1*01	1101
1545	VH3-23_IGHD4-11*01 (1) >3'_IGHJ1*01	1225	gnl|Fabrus|O12_IGKJ1*01	1101
1546	VH3-23_IGHD4-17*01>1'_IGHJ1*01	1226	gnl|Fabrus|O12_IGKJ1*01	1101
1547	VH3-23_IGHD4-17*01>3'_IGHJ1*01	1227	gnl|Fabrus|O12_IGKJ1*01	1101
1548	VH3-23_IGHD4-23*01>1'_IGHJ1*01	1228	gnl|Fabrus|O12_IGKJ1*01	1101
1549	VH3-23_IGHD4-23*01>3'_IGHJ1*01	1229	gnl|Fabrus|O12_IGKJ1*01	1101
1550	VH3-23_IGHD5-5*01 (2) >1'_IGHJ1*01	1230	gnl|Fabrus|O12_IGKJ1*01	1101
1551	VH3-23_IGHD5-5*01 (2) >3'_IGHJ1*01	1231	gnl|Fabrus|O12_IGKJ1*01	1101
1552	VH3-23_IGHD5-12*01>1'_IGHJ1*01	1232	gnl|Fabrus|O12_IGKJ1*01	1101
1553	VH3-23_IGHD5-12*01>3'_IGHJ1*01	1233	gnl|Fabrus|O12_IGKJ1*01	1101
1554	VH3-23_IGHD5-18*01 (2) >1'_IGHJ1*01	1234	gnl|Fabrus|O12_IGKJ1*01	1101
1555	VH3-23_IGHD5-18*01 (2) >3'_IGHJ1*01	1235	gnl|Fabrus|O12_IGKJ1*01	1101
1556	VH3-23_IGHD5-24*01>1'_IGHJ1*01	1236	gnl|Fabrus|O12_IGKJ1*01	1101
1557	VH3-23_IGHD5-24*01>3'_IGHJ1*01	1237	gnl|Fabrus|O12_IGKJ1*01	1101
1558	VH3-23_IGHD6-6*01>1'_IGHJ1*01	1238	gnl|Fabrus|O12_IGKJ1*01	1101
1559	VH3-23_IGHD6-6*01>2'_IGHJ1*01	1239	gnl|Fabrus|O12_IGKJ1*01	1101
1560	VH3-23_IGHD6-6*01>3'_IGHJ1*01	1240	gnl|Fabrus|O12_IGKJ1*01	1101
1561	VH3-23_IGHD6-6*01>2_IGHJ1*01	1184	gnl|Fabrus|O12_IGKJ1*01	1101
1562	VH3-23_IGHD6-13*01>1_IGHJ1*01	1185	gnl|Fabrus|O12_IGKJ1*01	1101
1563	VH3-23_IGHD6-13*01>2_IGHJ1*01	1186	gnl|Fabrus|O12_IGKJ1*01	1101
1564	VH3-23_IGHD6-19*01>1_IGHJ1*01	1187	gnl|Fabrus|O12_IGKJ1*01	1101
1565	VH3-23_IGHD6-19*01>2_IGHJ1*01	1188	gnl|Fabrus|O12_IGKJ1*01	1101
1566	VH3-23_IGHD6-25*01>1_IGHJ1*01	1189	gnl|Fabrus|O12_IGKJ1*01	1101
1567	VH3-23_IGHD6-25*01>2_IGHJ1*01	1190	gnl|Fabrus|O12_IGKJ1*01	1101
1568	VH3-23_IGHD7-27*01>1_IGHJ1*01	1191	gnl|Fabrus|O12_IGKJ1*01	1101
1569	VH3-23_IGHD7-27*01>3_IGHJ1*01	1192	gnl|Fabrus|O12_IGKJ1*01	1101
1570	VH3-23_IGHD6-13*01>1'_IGHJ1*01	1241	gnl|Fabrus|O12_IGKJ1*01	1101
1571	VH3-23_IGHD6-13*01>2'_IGHJ1*01	1242	gnl|Fabrus|O12_IGKJ1*01	1101
1572	VH3-23_IGHD6-13*01>2_IGHJ1*01_B	1243	gnl|Fabrus|O12_IGKJ1*01	1101
1573	VH3-23_IGHD6-19*01>1'_IGHJ1*01	1244	gnl|Fabrus|O12_IGKJ1*01	1101
1574	VH3-23_IGHD6-19*01>2'_IGHJ1*01	1245	gnl|Fabrus|O12_IGKJ1*01	1101

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1575	VH3-23_IGHD6-19*01>2_IGHJ1*01_B	1246	gnl|Fabrus|O12_IGKJ1*01	1101
1576	VH3-23_IGHD6-25*01>1'_IGHJ1*01	1247	gnl|Fabrus|O12_IGKJ1*01	1101
1577	VH3-23_IGHD6-25*01>3'_IGHJ1*01	1248	gnl|Fabrus|O12_IGKJ1*01	1101
1578	VH3-23_IGHD7-27*01>1'_IGHJ1*01_B	1249	gnl|Fabrus|O12_IGKJ1*01	1101
1579	VH3-23_IGHD7-27*01>2'_IGHJ1*01	1250	gnl|Fabrus|O12_IGKJ1*01	1101
1580	VH3-23_IGHD1-1*01>1_IGHJ2*01	1251	gnl|Fabrus|O12_IGKJ1*01	1101
1581	VH3-23_IGHD1-1*01>2_IGHJ2*01	1252	gnl|Fabrus|O12_IGKJ1*01	1101
1582	VH3-23_IGHD1-1*01>3_IGHJ2*01	1253	gnl|Fabrus|O12_IGKJ1*01	1101
1583	VH3-23_IGHD1-7*01>1_IGHJ2*01	1254	gnl|Fabrus|O12_IGKJ1*01	1101
1584	VH3-23_IGHD1-7*01>3_IGHJ2*01	1255	gnl|Fabrus|O12_IGKJ1*01	1101
1585	VH3-23_IGHD1-14*01>1_IGHJ2*01	1256	gnl|Fabrus|O12_IGKJ1*01	1101
1586	VH3-23_IGHD1-14*01>3_IGHJ2*01	1257	gnl|Fabrus|O12_IGKJ1*01	1101
1587	VH3-23_IGHD1-20*01>1_IGHJ2*01	1258	gnl|Fabrus|O12_IGKJ1*01	1101
1588	VH3-23_IGHD1-20*01>3_IGHJ2*01	1259	gnl|Fabrus|O12_IGKJ1*01	1101
1589	VH3-23_IGHD1-26*01>1_IGHJ2*01	1260	gnl|Fabrus|O12_IGKJ1*01	1101
1590	VH3-23_IGHD1-26*01>3_IGHJ2*01	1261	gnl|Fabrus|O12_IGKJ1*01	1101
1591	VH3-23_IGHD2-2*01>2_IGHJ2*01	1262	gnl|Fabrus|O12_IGKJ1*01	1101
1592	VH3-23_IGHD2-2*01>3_IGHJ2*01	1263	gnl|Fabrus|O12_IGKJ1*01	1101
1593	VH3-23_IGHD2-8*01>2_IGHJ2*01	1264	gnl|Fabrus|O12_IGKJ1*01	1101
1594	VH3-23_IGHD2-8*01>3_IGHJ2*01	1265	gnl|Fabrus|O12_IGKJ1*01	1101
1595	VH3-23_IGHD2-15*01>2_IGHJ2*01	1266	gnl|Fabrus|O12_IGKJ1*01	1101
1596	VH3-23_IGHD2-15*01>3_IGHJ2*01	1267	gnl|Fabrus|O12_IGKJ1*01	1101
1597	VH3-23_IGHD2-21*01>2_IGHJ2*01	1268	gnl|Fabrus|O12_IGKJ1*01	1101
1598	VH3-23_IGHD2-21*01>3_IGHJ2*01	1269	gnl|Fabrus|O12_IGKJ1*01	1101
1599	VH3-23_IGHD3-3*01>1_IGHJ2*01	1270	gnl|Fabrus|O12_IGKJ1*01	1101
1600	VH3-23_IGHD3-3*01>2_IGHJ2*01	1271	gnl|Fabrus|O12_IGKJ1*01	1101
1601	VH3-23_IGHD3-3*01>3_IGHJ2*01	1272	gnl|Fabrus|O12_IGKJ1*01	1101
1602	VH3-23_IGHD3-9*01>2_IGHJ2*01	1273	gnl|Fabrus|O12_IGKJ1*01	1101
1603	VH3-23_IGHD3-10*01>2_IGHJ2*01	1274	gnl|Fabrus|O12_IGKJ1*01	1101
1604	VH3-23_IGHD3-10*01>3_IGHJ2*01	1275	gnl|Fabrus|O12_IGKJ1*01	1101
1605	VH3-23_IGHD3-16*01>2_IGHJ2*01	1276	gnl|Fabrus|O12_IGKJ1*01	1101
1606	VH3-23_IGHD3-16*01>3_IGHJ2*01	1277	gnl|Fabrus|O12_IGKJ1*01	1101
1607	VH3-23_IGHD3-22*01>2_IGHJ2*01	1278	gnl|Fabrus|O12_IGKJ1*01	1101
1608	VH3-23_IGHD3-22*01>3_IGHJ2*01	1279	gnl|Fabrus|O12_IGKJ1*01	1101
1609	VH3-23_IGHD4-4*01 (1) >2_IGHJ2*01	1280	gnl|Fabrus|O12_IGKJ1*01	1101
1610	VH3-23_IGHD4-4*01 (1) >3_IGHJ2*01	1281	gnl|Fabrus|O12_IGKJ1*01	1101
1611	VH3-23_IGHD4-11*01 (1) >2_IGHJ2*01	1282	gnl|Fabrus|O12_IGKJ1*01	1101
1612	VH3-23_IGHD4-11*01 (1) >3_IGHJ2*01	1283	gnl|Fabrus|O12_IGKJ1*01	1101
1613	VH3-23_IGHD4-17*01>2_IGHJ2*01	1284	gnl|Fabrus|O12_IGKJ1*01	1101
1614	VH3-23_IGHD4-17*01>3_IGHJ2*01	1285	gnl|Fabrus|O12_IGKJ1*01	1101
1615	VH3-23_IGHD4-23*01>2_IGHJ2*01	1286	gnl|Fabrus|O12_IGKJ1*01	1101
1616	VH3-23_IGHD4-23*01>3_IGHJ2*01	1287	gnl|Fabrus|O12_IGKJ1*01	1101

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1617	VH3-23_IGHD5-5*01 (2) >1_IGHJ2*01	1288	gnl|Fabrus|O12_IGKJ1*01	1101
1618	VH3-23_IGHD5-5*01 (2) >2_IGHJ2*01	1289	gnl|Fabrus|O12_IGKJ1*01	1101
1619	VH3-23_IGHD5-5*01 (2) >3_IGHJ2*01	1290	gnl|Fabrus|O12_IGKJ1*01	1101
1620	VH3-23_IGHD5-12*01>1_IGHJ2*01	1291	gnl|Fabrus|O12_IGKJ1*01	1101
1621	VH3-23_IGHD5-12*01>3_IGHJ2*01	1292	gnl|Fabrus|O12_IGKJ1*01	1101
1622	VH3-23_IGHD5-18*01 (2) >1_IGHJ2*01	1293	gnl|Fabrus|O12_IGKJ1*01	1101
1623	VH3-23_IGHD5-18*01 (2) >2_IGHJ2*01	1294	gnl|Fabrus|O12_IGKJ1*01	1101
1624	VH3-23_IGHD5-18*01 (2) >3_IGHJ2*01	1295	gnl|Fabrus|O12_IGKJ1*01	1101
1625	VH3-23_IGHD5-24*01>1_IGHJ2*01	1296	gnl|Fabrus|O12_IGKJ1*01	1101
1626	VH3-23_IGHD5-24*01>3_IGHJ2*01	1297	gnl|Fabrus|O12_IGKJ1*01	1101
1627	VH3-23_IGHD6-6*01>1_IGHJ2*01	1298	gnl|Fabrus|O12_IGKJ1*01	1101
1628	VH3-23_IGHD1-1*01>1'_IGHJ2*01	1308	gnl|Fabrus|O12_IGKJ1*01	1101
1629	VH3-23_IGHD1-1*01>2'_IGHJ2*01	1309	gnl|Fabrus|O12_IGKJ1*01	1101
1630	VH3-23_IGHD1-1*01>3'_IGHJ2*01	1310	gnl|Fabrus|O12_IGKJ1*01	1101
1631	VH3-23_IGHD1-7*01>1'_IGHJ2*01	1311	gnl|Fabrus|O12_IGKJ1*01	1101
1632	VH3-23_IGHD1-7*01>3'_IGHJ2*01	1312	gnl|Fabrus|O12_IGKJ1*01	1101
1633	VH3-23_IGHD1-14*01>1'_IGHJ2*01	1313	gnl|Fabrus|O12_IGKJ1*01	1101
1634	VH3-23_IGHD1-14*01>2'_IGHJ2*01	1314	gnl|Fabrus|O12_IGKJ1*01	1101
1635	VH3-23_IGHD1-14*01>3'_IGHJ2*01	1315	gnl|Fabrus|O12_IGKJ1*01	1101
1636	VH3-23_IGHD1-20*01>1'_IGHJ2*01	1316	gnl|Fabrus|O12_IGKJ1*01	1101
1637	VH3-23_IGHD1-20*01>2'_IGHJ2*01	1317	gnl|Fabrus|O12_IGKJ1*01	1101
1638	VH3-23_IGHD1-20*01>3'_IGHJ2*01	1318	gnl|Fabrus|O12_IGKJ1*01	1101
1639	VH3-23_IGHD1-26*01>1'_IGHJ2*01	1319	gnl|Fabrus|O12_IGKJ1*01	1101
1640	VH3-23_IGHD1-26*01>1_IGHJ2*01_B	1320	gnl|Fabrus|O12_IGKJ1*01	1101
1641	VH3-23_IGHD2-2*01>1'_IGHJ2*01	1321	gnl|Fabrus|O12_IGKJ1*01	1101
1642	VH3-23_IGHD2-2*01>3'_IGHJ2*01	1322	gnl|Fabrus|O12_IGKJ1*01	1101
1643	VH3-23_IGHD2-8*01>1'_IGHJ2*01	1323	gnl|Fabrus|O12_IGKJ1*01	1101
1644	VH3-23_IGHD2-15*01>1'_IGHJ2*01	1324	gnl|Fabrus|O12_IGKJ1*01	1101
1645	VH3-23_IGHD2-15*01>3'_IGHJ2*01	1325	gnl|Fabrus|O12_IGKJ1*01	1101
1646	VH3-23_IGHD2-21*01>1'_IGHJ2*01	1326	gnl|Fabrus|O12_IGKJ1*01	1101
1647	VH3-23_IGHD2-21*01>3'_IGHJ2*01	1327	gnl|Fabrus|O12_IGKJ1*01	1101
1648	VH3-23_IGHD3-3*01>1'_IGHJ2*01	1328	gnl|Fabrus|O12_IGKJ1*01	1101
1649	VH3-23_IGHD3-3*01>3'_IGHJ2*01	1329	gnl|Fabrus|O12_IGKJ1*01	1101
1650	VH3-23_IGHD3-9*01>1'_IGHJ2*01	1330	gnl|Fabrus|O12_IGKJ1*01	1101
1651	VH3-23_IGHD3-9*01>3'_IGHJ2*01	1331	gnl|Fabrus|O12_IGKJ1*01	1101
1652	VH3-23_IGHD3-10*01>1'_IGHJ2*01	1332	gnl|Fabrus|O12_IGKJ1*01	1101
1653	VH3-23_IGHD3-10*01>3'_IGHJ2*01	1333	gnl|Fabrus|O12_IGKJ1*01	1101
1654	VH3-23_IGHD3-16*01>1'_IGHJ2*01	1334	gnl|Fabrus|O12_IGKJ1*01	1101
1655	VH3-23_IGHD3-16*01>3'_IGHJ2*01	1335	gnl|Fabrus|O12_IGKJ1*01	1101
1656	VH3-23_IGHD3-22*01>1'_IGHJ2*01	1336	gnl|Fabrus|O12_IGKJ1*01	1101
1657	VH3-23_IGHD4-4*01 (1) >1'_IGHJ2*01	1337	gnl|Fabrus|O12_IGKJ1*01	1101
1658	VH3-23_IGHD4-4*01 (1) >3'_IGHJ2*01	1338	gnl|Fabrus|O12_IGKJ1*01	1101

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1659	VH3-23_IGHD4-11*01 (1) >1'_IGHJ2*01	1339	gnl|Fabrus|O12_IGKJ1*01	1101
1660	VH3-23_IGHD4-11*01 (1) >3'_IGHJ2*01	1340	gnl|Fabrus|O12_IGKJ1*01	1101
1661	VH3-23_IGHD4-17*01>1'_IGHJ2*01	1341	gnl|Fabrus|O12_IGKJ1*01	1101
1662	VH3-23_IGHD4-17*01>3'_IGHJ2*01	1342	gnl|Fabrus|O12_IGKJ1*01	1101
1663	VH3-23_IGHD4-23*01>1'_IGHJ2*01	1343	gnl|Fabrus|O12_IGKJ1*01	1101
1664	VH3-23_IGHD4-23*01>3'_IGHJ2*01	1344	gnl|Fabrus|O12_IGKJ1*01	1101
1665	VH3-23_IGHD5-5*01 (2) >1'_IGHJ2*01	1345	gnl|Fabrus|O12_IGKJ1*01	1101
1666	VH3-23_IGHD5-5*01 (2) >3'_IGHJ2*01	1346	gnl|Fabrus|O12_IGKJ1*01	1101
1667	VH3-23_IGHD5-12*01>1'_IGHJ2*01	1347	gnl|Fabrus|O12_IGKJ1*01	1101
1668	VH3-23_IGHD5-12*01>3'_IGHJ2*01	1348	gnl|Fabrus|O12_IGKJ1*01	1101
1669	VH3-23_IGHD5-18*01 (2) >1'_IGHJ2*01	1349	gnl|Fabrus|O12_IGKJ1*01	1101
1670	VH3-23_IGHD5-18*01 (2) >3'_IGHJ2*01	1350	gnl|Fabrus|O12_IGKJ1*01	1101
1671	VH3-23_IGHD5-24*01>1'_IGHJ2*01	1351	gnl|Fabrus|O12_IGKJ1*01	1101
1672	VH3-23_IGHD5-24*01>3'_IGHJ2*01	1352	gnl|Fabrus|O12_IGKJ1*01	1101
1673	VH3-23_IGHD6-6*01>1'_IGHJ2*01	1353	gnl|Fabrus|O12_IGKJ1*01	1101
1674	VH3-23_IGHD6-6*01>2'_IGHJ2*01	1354	gnl|Fabrus|O12_IGKJ1*01	1101
1675	VH3-23_IGHD6-6*01>3'_IGHJ2*01	1355	gnl|Fabrus|O12_IGKJ1*01	1101
1676	VH3-23_IGHD6-6*01>2_IGHJ2*01	1299	gnl|Fabrus|O12_IGKJ1*01	1101
1677	VH3-23_IGHD6-13*01>1_IGHJ2*01	1300	gnl|Fabrus|O12_IGKJ1*01	1101
1678	VH3-23_IGHD6-13*01>2_IGHJ2*01	1301	gnl|Fabrus|O12_IGKJ1*01	1101
1679	VH3-23_IGHD6-19*01>1_IGHJ2*01	1302	gnl|Fabrus|O12_IGKJ1*01	1101
1680	VH3-23_IGHD6-19*01>2_IGHJ2*01	1303	gnl|Fabrus|O12_IGKJ1*01	1101
1681	VH3-23_IGHD6-25*01>1_IGHJ2*01	1304	gnl|Fabrus|O12_IGKJ1*01	1101
1682	VH3-23_IGHD6-25*01>2_IGHJ2*01	1305	gnl|Fabrus|O12_IGKJ1*01	1101
1683	VH3-23_IGHD7-27*01>1_IGHJ2*01	1306	gnl|Fabrus|O12_IGKJ1*01	1101
1684	VH3-23_IGHD7-27*01>3_IGHJ2*01	1307	gnl|Fabrus|O12_IGKJ1*01	1101
1685	VH3-23_IGHD6-13*01>1'_IGHJ2*01	1356	gnl|Fabrus|O12_IGKJ1*01	1101
1686	VH3-23_IGHD6-13*01>2'_IGHJ2*01	1357	gnl|Fabrus|O12_IGKJ1*01	1101
1687	VH3-23_IGHD6-13*01>2_IGHJ2*01_B	1358	gnl|Fabrus|O12_IGKJ1*01	1101
1688	VH3-23_IGHD6-19*01>1'_IGHJ2*01	1359	gnl|Fabrus|O12_IGKJ1*01	1101
1689	VH3-23_IGHD6-19*01>2'_IGHJ2*01	1360	gnl|Fabrus|O12_IGKJ1*01	1101
1690	VH3-23_IGHD6-19*01>2_IGHJ2*01_B	1361	gnl|Fabrus|O12_IGKJ1*01	1101
1691	VH3-23_IGHD6-25*01>1'_IGHJ2*01	1362	gnl|Fabrus|O12_IGKJ1*01	1101
1692	VH3-23_IGHD6-25*01>3'_IGHJ2*01	1363	gnl|Fabrus|O12_IGKJ1*01	1101
1693	VH3-23_IGHD7-27*01>1'_IGHJ2*01	1364	gnl|Fabrus|O12_IGKJ1*01	1101
1694	VH3-23_IGHD7-27*01>2'_IGHJ2*01	1365	gnl|Fabrus|O12_IGKJ1*01	1101
1695	VH3-23_IGHD1-1*01>1_IGHJ3*01	1366	gnl|Fabrus|O12_IGKJ1*01	1101
1696	VH3-23_IGHD1-1*01>2_IGHJ3*01	1367	gnl|Fabrus|O12_IGKJ1*01	1101
1697	VH3-23_IGHD1-1*01>3_IGHJ3*01	1368	gnl|Fabrus|O12_IGKJ1*01	1101
1698	VH3-23_IGHD1-7*01>1_IGHJ3*01	1369	gnl|Fabrus|O12_IGKJ1*01	1101
1699	VH3-23_IGHD1-7*01>3_IGHJ3*01	1370	gnl|Fabrus|O12_IGKJ1*01	1101
1700	VH3-23_IGHD1-14*01>1_IGHJ3*01	1371	gnl|Fabrus|O12_IGKJ1*01	1101

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1701	VH3-23_IGHD1-14*01>3_IGHJ3*01	1372	gnl|Fabrus|O12_IGKJ1*01	1101
1702	VH3-23_IGHD1-20*01>1_IGHJ3*01	1373	gnl|Fabrus|O12_IGKJ1*01	1101
1703	VH3-23_IGHD1-20*01>3_IGHJ3*01	1374	gnl|Fabrus|O12_IGKJ1*01	1101
1704	VH3-23_IGHD1-26*01>1_IGHJ3*01	1375	gnl|Fabrus|O12_IGKJ1*01	1101
1705	VH3-23_IGHD1-26*01>3_IGHJ3*01	1376	gnl|Fabrus|O12_IGKJ1*01	1101
1706	VH3-23_IGHD2-2*01>2_IGHJ3*01	1377	gnl|Fabrus|O12_IGKJ1*01	1101
1707	VH3-23_IGHD2-2*01>3_IGHJ3*01	1378	gnl|Fabrus|O12_IGKJ1*01	1101
1708	VH3-23_IGHD2-8*01>2_IGHJ3*01	1379	gnl|Fabrus|O12_IGKJ1*01	1101
1709	VH3-23_IGHD2-8*01>3_IGHJ3*01	1380	gnl|Fabrus|O12_IGKJ1*01	1101
1710	VH3-23_IGHD2-15*01>2_IGHJ3*01	1381	gnl|Fabrus|O12_IGKJ1*01	1101
1711	VH3-23_IGHD2-15*01>3_IGHJ3*01	1382	gnl|Fabrus|O12_IGKJ1*01	1101
1712	VH3-23_IGHD2-21*01>2_IGHJ3*01	1383	gnl|Fabrus|O12_IGKJ1*01	1101
1713	VH3-23_IGHD2-21*01>3_IGHJ3*01	1384	gnl|Fabrus|O12_IGKJ1*01	1101
1714	VH3-23_IGHD3-3*01>1_IGHJ3*01	1385	gnl|Fabrus|O12_IGKJ1*01	1101
1715	VH3-23_IGHD3-3*01>2_IGHJ3*01	1386	gnl|Fabrus|O12_IGKJ1*01	1101
1716	VH3-23_IGHD3-3*01>3_IGHJ3*01	1387	gnl|Fabrus|O12_IGKJ1*01	1101
1717	VH3-23_IGHD3-9*01>2_IGHJ3*01	1388	gnl|Fabrus|O12_IGKJ1*01	1101
1718	VH3-23_IGHD3-10*01>2_IGHJ3*01	1389	gnl|Fabrus|O12_IGKJ1*01	1101
1719	VH3-23_IGHD3-10*01>3_IGHJ3*01	1390	gnl|Fabrus|O12_IGKJ1*01	1101
1720	VH3-23_IGHD3-16*01>2_IGHJ3*01	1391	gnl|Fabrus|O12_IGKJ1*01	1101
1721	VH3-23_IGHD3-16*01>3_IGHJ3*01	1392	gnl|Fabrus|O12_IGKJ1*01	1101
1722	VH3-23_IGHD3-22*01>2_IGHJ3*01	1393	gnl|Fabrus|O12_IGKJ1*01	1101
1723	VH3-23_IGHD3-22*01>3_IGHJ3*01	1394	gnl|Fabrus|O12_IGKJ1*01	1101
1724	VH3-23_IGHD4-4*01 (1) >2_IGHJ3*01	1395	gnl|Fabrus|O12_IGKJ1*01	1101
1725	VH3-23_IGHD4-4*01 (1) >3_IGHJ3*01	1396	gnl|Fabrus|O12_IGKJ1*01	1101
1726	VH3-23_IGHD4-11*01 (1) >2_IGHJ3*01	1397	gnl|Fabrus|O12_IGKJ1*01	1101
1727	VH3-23_IGHD4-11*01 (1) >3_IGHJ3*01	1398	gnl|Fabrus|O12_IGKJ1*01	1101
1728	VH3-23_IGHD4-17*01>2_IGHJ3*01	1399	gnl|Fabrus|O12_IGKJ1*01	1101
1729	VH3-23_IGHD4-17*01>3_IGHJ3*01	1400	gnl|Fabrus|O12_IGKJ1*01	1101
1730	VH3-23_IGHD4-23*01>2_IGHJ3*01	1401	gnl|Fabrus|O12_IGKJ1*01	1101
1731	VH3-23_IGHD4-23*01>3_IGHJ3*01	1402	gnl|Fabrus|O12_IGKJ1*01	1101
1732	VH3-23_IGHD5-5*01 (2) >1_IGHJ3*01	1403	gnl|Fabrus|O12_IGKJ1*01	1101
1733	VH3-23_IGHD5-5*01 (2) >2_IGHJ3*01	1404	gnl|Fabrus|O12_IGKJ1*01	1101
1734	VH3-23_IGHD5-5*01 (2) >3_IGHJ3*01	1405	gnl|Fabrus|O12_IGKJ1*01	1101
1735	VH3-23_IGHD5-12*01>1_IGHJ3*01	1406	gnl|Fabrus|O12_IGKJ1*01	1101
1736	VH3-23_IGHD5-12*01>3_IGHJ3*01	1407	gnl|Fabrus|O12_IGKJ1*01	1101
1737	VH3-23_IGHD5-18*01 (2) >1_IGHJ3*01	1408	gnl|Fabrus|O12_IGKJ1*01	1101
1738	VH3-23_IGHD5-18*01 (2) >2_IGHJ3*01	1409	gnl|Fabrus|O12_IGKJ1*01	1101
1739	VH3-23_IGHD5-18*01 (2) >3_IGHJ3*01	1410	gnl|Fabrus|O12_IGKJ1*01	1101
1740	VH3-23_IGHD5-24*01>1_IGHJ3*01	1411	gnl|Fabrus|O12_IGKJ1*01	1101
1741	VH3-23_IGHD5-24*01>3_IGHJ3*01	1412	gnl|Fabrus|O12_IGKJ1*01	1101
1742	VH3-23_IGHD6-6*01>1_IGHJ3*01	1413	gnl|Fabrus|O12_IGKJ1*01	1101

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1743	VH3-23_IGHD1-1*01>1'_IGHJ3*01	1423	gnl|Fabrus|O12_IGKJ1*01	1101
1744	VH3-23_IGHD1-1*01>2'_IGHJ3*01	1424	gnl|Fabrus|O12_IGKJ1*01	1101
1745	VH3-23_IGHD1-1*01>3'_IGHJ3*01	1425	gnl|Fabrus|O12_IGKJ1*01	1101
1746	VH3-23_IGHD1-7*01>1'_IGHJ3*01	1426	gnl|Fabrus|O12_IGKJ1*01	1101
1747	VH3-23_IGHD1-7*01>3'_IGHJ3*01	1427	gnl|Fabrus|O12_IGKJ1*01	1101
1748	VH3-23_IGHD1-14*01>1'_IGHJ3*01	1428	gnl|Fabrus|O12_IGKJ1*01	1101
1749	VH3-23_IGHD1-14*01>2'_IGHJ3*01	1429	gnl|Fabrus|O12_IGKJ1*01	1101
1750	VH3-23_IGHD1-14*01>3'_IGHJ3*01	1430	gnl|Fabrus|O12_IGKJ1*01	1101
1751	VH3-23_IGHD1-20*01>1'_IGHJ3*01	1431	gnl|Fabrus|O12_IGKJ1*01	1101
1752	VH3-23_IGHD1-20*01>2'_IGHJ3*01	1432	gnl|Fabrus|O12_IGKJ1*01	1101
1753	VH3-23_IGHD1-20*01>3'_IGHJ3*01	1433	gnl|Fabrus|O12_IGKJ1*01	1101
1754	VH3-23_IGHD1-26*01>1'_IGHJ3*01	1434	gnl|Fabrus|O12_IGKJ1*01	1101
1755	VH3-23_IGHD1-26*01>3'_IGHJ3*01	1435	gnl|Fabrus|O12_IGKJ1*01	1101
1756	VH3-23_IGHD2-2*01>1'_IGHJ3*01	1436	gnl|Fabrus|O12_IGKJ1*01	1101
1757	VH3-23_IGHD2-2*01>3'_IGHJ3*01	1437	gnl|Fabrus|O12_IGKJ1*01	1101
1758	VH3-23_IGHD2-8*01>1'_IGHJ3*01	1438	gnl|Fabrus|O12_IGKJ1*01	1101
1759	VH3-23_IGHD2-15*01>1'_IGHJ3*01	1439	gnl|Fabrus|O12_IGKJ1*01	1101
1760	VH3-23_IGHD2-15*01>3'_IGHJ3*01	1440	gnl|Fabrus|O12_IGKJ1*01	1101
1761	VH3-23_IGHD2-21*01>1'_IGHJ3*01	1441	gnl|Fabrus|O12_IGKJ1*01	1101
1762	VH3-23_IGHD2-21*01>3'_IGHJ3*01	1442	gnl|Fabrus|O12_IGKJ1*01	1101
1763	VH3-23_IGHD3-3*01>1'_IGHJ3*01	1443	gnl|Fabrus|O12_IGKJ1*01	1101
1764	VH3-23_IGHD3-3*01>3'_IGHJ3*01	1444	gnl|Fabrus|O12_IGKJ1*01	1101
1765	VH3-23_IGHD3-9*01>1'_IGHJ3*01	1445	gnl|Fabrus|O12_IGKJ1*01	1101
1766	VH3-23_IGHD3-9*01>3'_IGHJ3*01	1446	gnl|Fabrus|O12_IGKJ1*01	1101
1767	VH3-23_IGHD3-10*01>1'_IGHJ3*01	1447	gnl|Fabrus|O12_IGKJ1*01	1101
1768	VH3-23_IGHD3-10*01>3'_IGHJ3*01	1448	gnl|Fabrus|O12_IGKJ1*01	1101
1769	VH3-23_IGHD3-16*01>1'_IGHJ3*01	1449	gnl|Fabrus|O12_IGKJ1*01	1101
1770	VH3-23_IGHD3-16*01>3'_IGHJ3*01	1450	gnl|Fabrus|O12_IGKJ1*01	1101
1771	VH3-23_IGHD3-22*01>1'_IGHJ3*01	1451	gnl|Fabrus|O12_IGKJ1*01	1101
1772	VH3-23_IGHD4-4*01 (1) >1'_IGHJ3*01	1452	gnl|Fabrus|O12_IGKJ1*01	1101
1773	VH3-23_IGHD4-4*01 (1) >3'_IGHJ3*01	1453	gnl|Fabrus|O12_IGKJ1*01	1101
1774	VH3-23_IGHD4-11*01 (1) >1'_IGHJ3*01	1454	gnl|Fabrus|O12_IGKJ1*01	1101
1775	VH3-23_IGHD4-11*01 (1) >3'_IGHJ3*01	1455	gnl|Fabrus|O12_IGKJ1*01	1101
1776	VH3-23_IGHD4-17*01>1'_IGHJ3*01	1456	gnl|Fabrus|O12_IGKJ1*01	1101
1777	VH3-23_IGHD4-17*01>3'_IGHJ3*01	1457	gnl|Fabrus|O12_IGKJ1*01	1101
1778	VH3-23_IGHD4-23*01>1'_IGHJ3*01	1458	gnl|Fabrus|O12_IGKJ1*01	1101
1779	VH3-23_IGHD4-23*01>3'_IGHJ3*01	1459	gnl|Fabrus|O12_IGKJ1*01	1101
1780	VH3-23_IGHD5-5*01 (2) >1'_IGHJ3*01	1460	gnl|Fabrus|O12_IGKJ1*01	1101
1781	VH3-23_IGHD5-5*01 (2) >3'_IGHJ3*01	1461	gnl|Fabrus|O12_IGKJ1*01	1101
1782	VH3-23_IGHD5-12*01>1'_IGHJ3*01	1462	gnl|Fabrus|O12_IGKJ1*01	1101
1783	VH3-23_IGHD5-12*01>3'_IGHJ3*01	1463	gnl|Fabrus|O12_IGKJ1*01	1101
1784	VH3-23_IGHD5-18*01 (2) >1'_IGHJ3*01	1464	gnl|Fabrus|O12_IGKJ1*01	1101

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1785	VH3-23_IGHD5-18*01 (2) >3'_IGHJ3*01	1465	gnl|Fabrus|O12_IGKJ1*01	1101
1786	VH3-23_IGHD5-24*01>1'_IGHJ3*01	1466	gnl|Fabrus|O12_IGKJ1*01	1101
1787	VH3-23_IGHD5-24*01>3'_IGHJ3*01	1467	gnl|Fabrus|O12_IGKJ1*01	1101
1788	VH3-23_IGHD6-6*01>1'_IGHJ3*01	1468	gnl|Fabrus|O12_IGKJ1*01	1101
1789	VH3-23_IGHD6-6*01>2'_IGHJ3*01	1469	gnl|Fabrus|O12_IGKJ1*01	1101
1790	VH3-23_IGHD6-6*01>3'_IGHJ3*01	1470	gnl|Fabrus|O12_IGKJ1*01	1101
1791	VH3-23_IGHD6-6*01>2_IGHJ3*01	1414	gnl|Fabrus|O12_IGKJ1*01	1101
1792	VH3-23_IGHD6-13*01>1_IGHJ3*01	1415	gnl|Fabrus|O12_IGKJ1*01	1101
1793	VH3-23_IGHD6-13*01>2_IGHJ3*01	1416	gnl|Fabrus|O12_IGKJ1*01	1101
1794	VH3-23_IGHD6-19*01>1_IGHJ3*01	1417	gnl|Fabrus|O12_IGKJ1*01	1101
1795	VH3-23_IGHD6-19*01>2_IGHJ3*01	1418	gnl|Fabrus|O12_IGKJ1*01	1101
1796	VH3-23_IGHD6-25*01>1_IGHJ3*01	1419	gnl|Fabrus|O12_IGKJ1*01	1101
1797	VH3-23_IGHD6-25*01>2_IGHJ3*01	1420	gnl|Fabrus|O12_IGKJ1*01	1101
1798	VH3-23_IGHD7-27*01>1_IGHJ3*01	1421	gnl|Fabrus|O12_IGKJ1*01	1101
1799	VH3-23_IGHD7-27*01>3_IGHJ3*01	1422	gnl|Fabrus|O12_IGKJ1*01	1101
1800	VH3-23_IGHD6-13*01>1'_IGHJ3*01	1471	gnl|Fabrus|O12_IGKJ1*01	1101
1801	VH3-23_IGHD6-13*01>2'_IGHJ3*01	1472	gnl|Fabrus|O12_IGKJ1*01	1101
1802	VH3-23_IGHD6-13*01>1_IGHJ6*01	1473	gnl|Fabrus|O12_IGKJ1*01	1101
1803	VH3-23_IGHD6-19*01>1'_IGHJ3*01	1474	gnl|Fabrus|O12_IGKJ1*01	1101
1804	VH3-23_IGHD6-19*01>2'_IGHJ3*01	1475	gnl|Fabrus|O12_IGKJ1*01	1101
1805	VH3-23_IGHD6-19*01>3'_IGHJ3*01	1476	gnl|Fabrus|O12_IGKJ1*01	1101
1806	VH3-23_IGHD6-25*01>1'_IGHJ3*01	1477	gnl|Fabrus|O12_IGKJ1*01	1101
1807	VH3-23_IGHD6-25*01>3'_IGHJ3*01	1478	gnl|Fabrus|O12_IGKJ1*01	1101
1808	VH3-23_IGHD7-27*01>1'_IGHJ3*01	1479	gnl|Fabrus|O12_IGKJ1*01	1101
1809	VH3-23_IGHD7-27*01>2'_IGHJ3*01	1480	gnl|Fabrus|O12_IGKJ1*01	1101
1810	VH3-23_IGHD1-1*01>1_IGHJ4*01	1481	gnl|Fabrus|O12_IGKJ1*01	1101
1811	VH3-23_IGHD1-1*01>2_IGHJ4*01	1482	gnl|Fabrus|O12_IGKJ1*01	1101
1812	VH3-23_IGHD1-1*01>3_IGHJ4*01	1483	gnl|Fabrus|O12_IGKJ1*01	1101
1813	VH3-23_IGHD1-7*01>1_IGHJ4*01	1484	gnl|Fabrus|O12_IGKJ1*01	1101
1814	VH3-23_IGHD1-7*01>3_IGHJ4*01	1485	gnl|Fabrus|O12_IGKJ1*01	1101
1815	VH3-23_IGHD1-14*01>1_IGHJ4*01	1486	gnl|Fabrus|O12_IGKJ1*01	1101
1816	VH3-23_IGHD1-14*01>3_IGHJ4*01	1487	gnl|Fabrus|O12_IGKJ1*01	1101
1817	VH3-23_IGHD1-20*01>1_IGHJ4*01	1488	gnl|Fabrus|O12_IGKJ1*01	1101
1818	VH3-23_IGHD1-20*01>3_IGHJ4*01	1489	gnl|Fabrus|O12_IGKJ1*01	1101
1819	VH3-23_IGHD1-26*01>1_IGHJ4*01	1490	gnl|Fabrus|O12_IGKJ1*01	1101
1820	VH3-23_IGHD1-26*01>3_IGHJ4*01	1491	gnl|Fabrus|O12_IGKJ1*01	1101
1821	VH3-23_IGHD2-2*01>2_IGHJ4*01	1492	gnl|Fabrus|O12_IGKJ1*01	1101
1822	VH3-23_IGHD2-2*01>3_IGHJ4*01	1493	gnl|Fabrus|O12_IGKJ1*01	1101
1823	VH3-23_IGHD2-8*01>2_IGHJ4*01	1494	gnl|Fabrus|O12_IGKJ1*01	1101
1824	VH3-23_IGHD2-8*01>3_IGHJ4*01	1495	gnl|Fabrus|O12_IGKJ1*01	1101
1825	VH3-23_IGHD2-15*01>2_IGHJ4*01	1496	gnl|Fabrus|O12_IGKJ1*01	1101
1826	VH3-23_IGHD2-15*01>3_IGHJ4*01	1497	gnl|Fabrus|O12_IGKJ1*01	1101

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1827	VH3-23_IGHD2-21*01>2_IGHJ4*01	1498	gnl|Fabrus|O12_IGKJ1*01	1101
1828	VH3-23_IGHD2-21*01>3_IGHJ4*01	1499	gnl|Fabrus|O12_IGKJ1*01	1101
1829	VH3-23_IGHD3-3*01>1_IGHJ4*01	1500	gnl|Fabrus|O12_IGKJ1*01	1101
1830	VH3-23_IGHD3-3*01>2_IGHJ4*01	1501	gnl|Fabrus|O12_IGKJ1*01	1101
1831	VH3-23_IGHD3-3*01>3_IGHJ4*01	1502	gnl|Fabrus|O12_IGKJ1*01	1101
1832	VH3-23_IGHD3-9*01>2_IGHJ4*01	1503	gnl|Fabrus|O12_IGKJ1*01	1101
1833	VH3-23_IGHD3-10*01>2_IGHJ4*01	1504	gnl|Fabrus|O12_IGKJ1*01	1101
1834	VH3-23_IGHD3-10*01>3_IGHJ4*01	1505	gnl|Fabrus|O12_IGKJ1*01	1101
1835	VH3-23_IGHD3-16*01>2_IGHJ4*01	1506	gnl|Fabrus|O12_IGKJ1*01	1101
1836	VH3-23_IGHD3-16*01>3_IGHJ4*01	1507	gnl|Fabrus|O12_IGKJ1*01	1101
1837	VH3-23_IGHD3-22*01>2_IGHJ4*01	1508	gnl|Fabrus|O12_IGKJ1*01	1101
1838	VH3-23_IGHD3-22*01>3_IGHJ4*01	1509	gnl|Fabrus|O12_IGKJ1*01	1101
1839	VH3-23_IGHD4-4*01 (1) >2_IGHJ4*01	1510	gnl|Fabrus|O12_IGKJ1*01	1101
1840	VH3-23_IGHD4-4*01 (1) >3_IGHJ4*01	1511	gnl|Fabrus|O12_IGKJ1*01	1101
1841	VH3-23_IGHD4-11*01 (1) >2_IGHJ4*01	1512	gnl|Fabrus|O12_IGKJ1*01	1101
1842	VH3-23_IGHD4-11*01 (1) >3_IGHJ4*01	1513	gnl|Fabrus|O12_IGKJ1*01	1101
1843	VH3-23_IGHD4-17*01>2_IGHJ4*01	1514	gnl|Fabrus|O12_IGKJ1*01	1101
1844	VH3-23_IGHD4-17*01>3_IGHJ4*01	1515	gnl|Fabrus|O12_IGKJ1*01	1101
1845	VH3-23_IGHD4-23*01>2_IGHJ4*01	1516	gnl|Fabrus|O12_IGKJ1*01	1101
1846	VH3-23_IGHD4-23*01>3_IGHJ4*01	1517	gnl|Fabrus|O12_IGKJ1*01	1101
1847	VH3-23_IGHD5-5*01 (2) >1_IGHJ4*01	1518	gnl|Fabrus|O12_IGKJ1*01	1101
1848	VH3-23_IGHD5-5*01 (2) >2_IGHJ4*01	1519	gnl|Fabrus|O12_IGKJ1*01	1101
1849	VH3-23_IGHD5-5*01 (2) >3_IGHJ4*01	1520	gnl|Fabrus|O12_IGKJ1*01	1101
1850	VH3-23_IGHD5-12*01>1_IGHJ4*01	1521	gnl|Fabrus|O12_IGKJ1*01	1101
1851	VH3-23_IGHD5-12*01>3_IGHJ4*01	1522	gnl|Fabrus|O12_IGKJ1*01	1101
1852	VH3-23_IGHD5-18*01 (2) >1_IGHJ4*01	1523	gnl|Fabrus|O12_IGKJ1*01	1101
1853	VH3-23_IGHD5-18*01 (2) >2_IGHJ4*01	1524	gnl|Fabrus|O12_IGKJ1*01	1101
1854	VH3-23_IGHD5-18*01 (2) >3_IGHJ4*01	1525	gnl|Fabrus|O12_IGKJ1*01	1101
1855	VH3-23_IGHD5-24*01>1_IGHJ4*01	1526	gnl|Fabrus|O12_IGKJ1*01	1101
1856	VH3-23_IGHD5-24*01>3_IGHJ4*01	1527	gnl|Fabrus|O12_IGKJ1*01	1101
1857	VH3-23_IGHD6-6*01>1_IGHJ4*01	1528	gnl|Fabrus|O12_IGKJ1*01	1101
1858	VH3-23_IGHD1-1*01>1'_IGHJ4*01	1538	gnl|Fabrus|O12_IGKJ1*01	1101
1859	VH3-23_IGHD1-1*01>2'_IGHJ4*01	1539	gnl|Fabrus|O12_IGKJ1*01	1101
1860	VH3-23_IGHD1-1*01>3'_IGHJ4*01	1540	gnl|Fabrus|O12_IGKJ1*01	1101
1861	VH3-23_IGHD1-7*01>1'_IGHJ4*01	1541	gnl|Fabrus|O12_IGKJ1*01	1101
1862	VH3-23_IGHD1-7*01>3'_IGHJ4*01	1542	gnl|Fabrus|O12_IGKJ1*01	1101
1863	VH3-23_IGHD1-14*01>1'_IGHJ4*01	1543	gnl|Fabrus|O12_IGKJ1*01	1101
1864	VH3-23_IGHD1-14*01>2'_IGHJ4*01	1544	gnl|Fabrus|O12_IGKJ1*01	1101
1865	VH3-23_IGHD1-14*01>3'_IGHJ4*01	1545	gnl|Fabrus|O12_IGKJ1*01	1101
1866	VH3-23_IGHD1-20*01>1'_IGHJ4*01	1546	gnl|Fabrus|O12_IGKJ1*01	1101
1867	VH3-23_IGHD1-20*01>2'_IGHJ4*01	1547	gnl|Fabrus|O12_IGKJ1*01	1101
1868	VH3-23_IGHD1-20*01>3'_IGHJ4*01	1548	gnl|Fabrus|O12_IGKJ1*01	1101

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1869	VH3-23_IGHD1-26*01>1'_IGHJ4*01	1549	gnl|Fabrus|O12_IGKJ1*01	1101
1870	VH3-23_IGHD1-26*01>1_IGHJ4*01_B	1550	gnl|Fabrus|O12_IGKJ1*01	1101
1871	VH3-23_IGHD2-2*01>1'_IGHJ4*01	1551	gnl|Fabrus|O12_IGKJ1*01	1101
1872	VH3-23_IGHD2-2*01>3'_IGHJ4*01	1552	gnl|Fabrus|O12_IGKJ1*01	1101
1873	VH3-23_IGHD2-8*01>1'_IGHJ4*01	1553	gnl|Fabrus|O12_IGKJ1*01	1101
1874	VH3-23_IGHD2-15*01>1'_IGHJ4*01	1554	gnl|Fabrus|O12_IGKJ1*01	1101
1875	VH3-23_IGHD2-15*01>3'_IGHJ4*01	1555	gnl|Fabrus|O12_IGKJ1*01	1101
1876	VH3-23_IGHD2-21*01>1'_IGHJ4*01	1556	gnl|Fabrus|O12_IGKJ1*01	1101
1877	VH3-23_IGHD2-21*01>3'_IGHJ4*01	1557	gnl|Fabrus|O12_IGKJ1*01	1101
1878	VH3-23_IGHD3-3*01>1'_IGHJ4*01	1558	gnl|Fabrus|O12_IGKJ1*01	1101
1879	VH3-23_IGHD3-3*01>3'_IGHJ4*01	1559	gnl|Fabrus|O12_IGKJ1*01	1101
1880	VH3-23_IGHD3-9*01>1'_IGHJ4*01	1560	gnl|Fabrus|O12_IGKJ1*01	1101
1881	VH3-23_IGHD3-9*01>3'_IGHJ4*01	1561	gnl|Fabrus|O12_IGKJ1*01	1101
1882	VH3-23_IGHD3-10*01>1'_IGHJ4*01	1562	gnl|Fabrus|O12_IGKJ1*01	1101
1883	VH3-23_IGHD3-10*01>3'_IGHJ4*01	1563	gnl|Fabrus|O12_IGKJ1*01	1101
1884	VH3-23_IGHD3-16*01>1'_IGHJ4*01	1564	gnl|Fabrus|O12_IGKJ1*01	1101
1885	VH3-23_IGHD3-16*01>3'_IGHJ4*01	1565	gnl|Fabrus|O12_IGKJ1*01	1101
1886	VH3-23_IGHD3-22*01>1'_IGHJ4*01	1566	gnl|Fabrus|O12_IGKJ1*01	1101
1887	VH3-23_IGHD4-4*01 (1) >1'_IGHJ4*01	1567	gnl|Fabrus|O12_IGKJ1*01	1101
1888	VH3-23_IGHD4-4*01 (1) >3'_IGHJ4*01	1568	gnl|Fabrus|O12_IGKJ1*01	1101
1889	VH3-23_IGHD4-11*01 (1) >1'_IGHJ4*01	1569	gnl|Fabrus|O12_IGKJ1*01	1101
1890	VH3-23_IGHD4-11*01 (1) >3'_IGHJ4*01	1570	gnl|Fabrus|O12_IGKJ1*01	1101
1891	VH3-23_IGHD4-17*01>1'_IGHJ4*01	1571	gnl|Fabrus|O12_IGKJ1*01	1101
1892	VH3-23_IGHD4-17*01>3'_IGHJ4*01	1572	gnl|Fabrus|O12_IGKJ1*01	1101
1893	VH3-23_IGHD4-23*01>1'_IGHJ4*01	1573	gnl|Fabrus|O12_IGKJ1*01	1101
1894	VH3-23_IGHD4-23*01>3'_IGHJ4*01	1574	gnl|Fabrus|O12_IGKJ1*01	1101
1895	VH3-23_IGHD5-5*01 (2) >1'_IGHJ4*01	1575	gnl|Fabrus|O12_IGKJ1*01	1101
1896	VH3-23_IGHD5-5*01 (2) >3'_IGHJ4*01	1576	gnl|Fabrus|O12_IGKJ1*01	1101
1897	VH3-23_IGHD5-12*01>1'_IGHJ4*01	1577	gnl|Fabrus|O12_IGKJ1*01	1101
1898	VH3-23_IGHD5-12*01>3'_IGHJ4*01	1578	gnl|Fabrus|O12_IGKJ1*01	1101
1899	VH3-23_IGHD5-18*01 (2) >1'_IGHJ4*01	1579	gnl|Fabrus|O12_IGKJ1*01	1101
1900	VH3-23_IGHD5-18*01 (2) >3'_IGHJ4*01	1580	gnl|Fabrus|O12_IGKJ1*01	1101
1901	VH3-23_IGHD5-24*01>1'_IGHJ4*01	1581	gnl|Fabrus|O12_IGKJ1*01	1101
1902	VH3-23_IGHD5-24*01>3'_IGHJ4*01	1582	gnl|Fabrus|O12_IGKJ1*01	1101
1903	VH3-23_IGHD6-6*01>1'_IGHJ4*01	1583	gnl|Fabrus|O12_IGKJ1*01	1101
1904	VH3-23_IGHD6-6*01>2'_IGHJ4*01	1584	gnl|Fabrus|O12_IGKJ1*01	1101
1905	VH3-23_IGHD6-6*01>3'_IGHJ4*01	1585	gnl|Fabrus|O12_IGKJ1*01	1101
1906	VH3-23_IGHD6-6*01>2_IGHJ4*01	1529	gnl|Fabrus|O12_IGKJ1*01	1101
1907	VH3-23_IGHD6-13*01>1_IGHJ4*01	1530	gnl|Fabrus|O12_IGKJ1*01	1101
1908	VH3-23_IGHD6-13*01>2_IGHJ4*01	1531	gnl|Fabrus|O12_IGKJ1*01	1101
1909	VH3-23_IGHD6-19*01>1_IGHJ4*01	1532	gnl|Fabrus|O12_IGKJ1*01	1101
1910	VH3-23_IGHD6-19*01>2_IGHJ4*01	1533	gnl|Fabrus|O12_IGKJ1*01	1101

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1911	VH3-23_IGHD6-25*01>1_IGHJ4*01	1534	gnl|Fabrus|O12_IGKJ1*01	1101
1912	VH3-23_IGHD6-25*01>2_IGHJ4*01	1535	gnl|Fabrus|O12_IGKJ1*01	1101
1913	VH3-23_IGHD7-27*01>1_IGHJ4*01	1536	gnl|Fabrus|O12_IGKJ1*01	1101
1914	VH3-23_IGHD7-27*01>3_IGHJ4*01	1537	gnl|Fabrus|O12_IGKJ1*01	1101
1915	VH3-23_IGHD6-13*01>1'_IGHJ4*01	1586	gnl|Fabrus|O12_IGKJ1*01	1101
1916	VH3-23_IGHD6-13*01>2'_IGHJ4*01	1587	gnl|Fabrus|O12_IGKJ1*01	1101
1917	VH3-23_IGHD6-13*01>2_IGHJ4*01_B	1588	gnl|Fabrus|O12_IGKJ1*01	1101
1918	VH3-23_IGHD6-19*01>1'_IGHJ4*01	1589	gnl|Fabrus|O12_IGKJ1*01	1101
1919	VH3-23_IGHD6-19*01>2'_IGHJ4*01	1590	gnl|Fabrus|O12_IGKJ1*01	1101
1920	VH3-23_IGHD6-19*01>2_IGHJ4*01_B	1591	gnl|Fabrus|O12_IGKJ1*01	1101
1921	VH3-23_IGHD6-25*01>1'_IGHJ4*01	1592	gnl|Fabrus|O12_IGKJ1*01	1101
1922	VH3-23_IGHD6-25*01>3'_IGHJ4*01	1593	gnl|Fabrus|O12_IGKJ1*01	1101
1923	VH3-23_IGHD7-27*01>1'_IGHJ4*01	1594	gnl|Fabrus|O12_IGKJ1*01	1101
1924	VH3-23_IGHD7-27*01>2'_IGHJ4*01	1595	gnl|Fabrus|O12_IGKJ1*01	1101
1925	VH3-23_IGHD1-1*01>1_IGHJ5*01	1596	gnl|Fabrus|O12_IGKJ1*01	1101
1926	VH3-23_IGHD1-1*01>2_IGHJ5*01	1597	gnl|Fabrus|O12_IGKJ1*01	1101
1927	VH3-23_IGHD1-1*01>3_IGHJ5*01	1598	gnl|Fabrus|O12_IGKJ1*01	1101
1928	VH3-23_IGHD1-7*01>1_IGHJ5*01	1599	gnl|Fabrus|O12_IGKJ1*01	1101
1929	VH3-23_IGHD1-7*01>3_IGHJ5*01	1600	gnl|Fabrus|O12_IGKJ1*01	1101
1930	VH3-23_IGHD1-14*01>1_IGHJ5*01	1601	gnl|Fabrus|O12_IGKJ1*01	1101
1931	VH3-23_IGHD1-14*01>3_IGHJ5*01	1602	gnl|Fabrus|O12_IGKJ1*01	1101
1932	VH3-23_IGHD1-20*01>1_IGHJ5*01	1603	gnl|Fabrus|O12_IGKJ1*01	1101
1933	VH3-23_IGHD1-20*01>3_IGHJ5*01	1604	gnl|Fabrus|O12_IGKJ1*01	1101
1934	VH3-23_IGHD1-26*01>1_IGHJ5*01	1605	gnl|Fabrus|O12_IGKJ1*01	1101
1935	VH3-23_IGHD1-26*01>3_IGHJ5*01	1606	gnl|Fabrus|O12_IGKJ1*01	1101
1936	VH3-23_IGHD2-2*01>2_IGHJ5*01	1607	gnl|Fabrus|O12_IGKJ1*01	1101
1937	VH3-23_IGHD2-2*01>3_IGHJ5*01	1608	gnl|Fabrus|O12_IGKJ1*01	1101
1938	VH3-23_IGHD2-8*01>2_IGHJ5*01	1609	gnl|Fabrus|O12_IGKJ1*01	1101
1939	VH3-23_IGHD2-8*01>3_IGHJ5*01	1610	gnl|Fabrus|O12_IGKJ1*01	1101
1940	VH3-23_IGHD2-15*01>2_IGHJ5*01	1611	gnl|Fabrus|O12_IGKJ1*01	1101
1941	VH3-23_IGHD2-15*01>3_IGHJ5*01	1612	gnl|Fabrus|O12_IGKJ1*01	1101
1942	VH3-23_IGHD2-21*01>2_IGHJ5*01	1613	gnl|Fabrus|O12_IGKJ1*01	1101
1943	VH3-23_IGHD2-21*01>3_IGHJ5*01	1614	gnl|Fabrus|O12_IGKJ1*01	1101
1944	VH3-23_IGHD3-3*01>1_IGHJ5*01	1615	gnl|Fabrus|O12_IGKJ1*01	1101
1945	VH3-23_IGHD3-3*01>2_IGHJ5*01	1616	gnl|Fabrus|O12_IGKJ1*01	1101
1946	VH3-23_IGHD3-3*01>3_IGHJ5*01	1617	gnl|Fabrus|O12_IGKJ1*01	1101
1947	VH3-23_IGHD3-9*01>2_IGHJ5*01	1618	gnl|Fabrus|O12_IGKJ1*01	1101
1948	VH3-23_IGHD3-10*01>2_IGHJ5*01	1619	gnl|Fabrus|O12_IGKJ1*01	1101
1949	VH3-23_IGHD3-10*01>3_IGHJ5*01	1620	gnl|Fabrus|O12_IGKJ1*01	1101
1950	VH3-23_IGHD3-16*01>2_IGHJ5*01	1621	gnl|Fabrus|O12_IGKJ1*01	1101
1951	VH3-23_IGHD3-16*01>3_IGHJ5*01	1622	gnl|Fabrus|O12_IGKJ1*01	1101
1952	VH3-23_IGHD3-22*01>2_IGHJ5*01	1623	gnl|Fabrus|O12_IGKJ1*01	1101

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1953	VH3-23_IGHD3-22*01>3_IGHJ5*01	1624	gnl|Fabrus|O12_IGKJ1*01	1101
1954	VH3-23_IGHD4-4*01 (1) >2_IGHJ5*01	1625	gnl|Fabrus|O12_IGKJ1*01	1101
1955	VH3-23_IGHD4-4*01 (1) >3_IGHJ5*01	1626	gnl|Fabrus|O12_IGKJ1*01	1101
1956	VH3-23_IGHD4-11*01 (1) >2_IGHJ5*01	1627	gnl|Fabrus|O12_IGKJ1*01	1101
1957	VH3-23_IGHD4-11*01 (1) >3_IGHJ5*01	1628	gnl|Fabrus|O12_IGKJ1*01	1101
1958	VH3-23_IGHD4-17*01>2_IGHJ5*01	1629	gnl|Fabrus|O12_IGKJ1*01	1101
1959	VH3-23_IGHD4-17*01>3_IGHJ5*01	1630	gnl|Fabrus|O12_IGKJ1*01	1101
1960	VH3-23_IGHD4-23*01>2_IGHJ5*01	1631	gnl|Fabrus|O12_IGKJ1*01	1101
1961	VH3-23_IGHD4-23*01>3_IGHJ5*01	1632	gnl|Fabrus|O12_IGKJ1*01	1101
1962	VH3-23_IGHD5-5*01 (2) >1_IGHJ5*01	1633	gnl|Fabrus|O12_IGKJ1*01	1101
1963	VH3-23_IGHD5-5*01 (2) >2_IGHJ5*01	1634	gnl|Fabrus|O12_IGKJ1*01	1101
1964	VH3-23_IGHD5-5*01 (2) >3_IGHJ5*01	1635	gnl|Fabrus|O12_IGKJ1*01	1101
1965	VH3-23_IGHD5-12*01>1_IGHJ5*01	1636	gnl|Fabrus|O12_IGKJ1*01	1101
1966	VH3-23_IGHD5-12*01>3_IGHJ5*01	1637	gnl|Fabrus|O12_IGKJ1*01	1101
1967	VH3-23_IGHD5-18*01 (2) >1_IGHJ5*01	1638	gnl|Fabrus|O12_IGKJ1*01	1101
1968	VH3-23_IGHD5-18*01 (2) >2_IGHJ5*01	1639	gnl|Fabrus|O12_IGKJ1*01	1101
1969	VH3-23_IGHD5-18*01 (2) >3_IGHJ5*01	1640	gnl|Fabrus|O12_IGKJ1*01	1101
1970	VH3-23_IGHD5-24*01>1_IGHJ5*01	1641	gnl|Fabrus|O12_IGKJ1*01	1101
1971	VH3-23_IGHD5-24*01>3_IGHJ5*01	1642	gnl|Fabrus|O12_IGKJ1*01	1101
1972	VH3-23_IGHD6-6*01>1_IGHJ5*01	1643	gnl|Fabrus|O12_IGKJ1*01	1101
1973	VH3-23_IGHD1-1*01>1'_IGHJ5*01	1653	gnl|Fabrus|O12_IGKJ1*01	1101
1974	VH3-23_IGHD1-1*01>2'_IGHJ5*01	1654	gnl|Fabrus|O12_IGKJ1*01	1101
1975	VH3-23_IGHD1-1*01>3'_IGHJ5*01	1655	gnl|Fabrus|O12_IGKJ1*01	1101
1976	VH3-23_IGHD1-7*01>1'_IGHJ5*01	1656	gnl|Fabrus|O12_IGKJ1*01	1101
1977	VH3-23_IGHD1-7*01>3'_IGHJ5*01	1657	gnl|Fabrus|O12_IGKJ1*01	1101
1978	VH3-23_IGHD1-14*01>1'_IGHJ5*01	1658	gnl|Fabrus|O12_IGKJ1*01	1101
1979	VH3-23_IGHD1-14*01>2'_IGHJ5*01	1659	gnl|Fabrus|O12_IGKJ1*01	1101
1980	VH3-23_IGHD1-14*01>3'_IGHJ5*01	1660	gnl|Fabrus|O12_IGKJ1*01	1101
1981	VH3-23_IGHD1-20*01>1'_IGHJ5*01	1661	gnl|Fabrus|O12_IGKJ1*01	1101
1982	VH3-23_IGHD1-20*01>2'_IGHJ5*01	1662	gnl|Fabrus|O12_IGKJ1*01	1101
1983	VH3-23_IGHD1-20*01>3'_IGHJ5*01	1663	gnl|Fabrus|O12_IGKJ1*01	1101
1984	VH3-23_IGHD1-26*01>1'_IGHJ5*01	1664	gnl|Fabrus|O12_IGKJ1*01	1101
1985	VH3-23_IGHD1-26*01>3'_IGHJ5*01	1665	gnl|Fabrus|O12_IGKJ1*01	1101
1986	VH3-23_IGHD2-2*01>1'_IGHJ5*01	1666	gnl|Fabrus|O12_IGKJ1*01	1101
1987	VH3-23_IGHD2-2*01>3'_IGHJ5*01	1667	gnl|Fabrus|O12_IGKJ1*01	1101
1988	VH3-23_IGHD2-8*01>1'_IGHJ5*01	1668	gnl|Fabrus|O12_IGKJ1*01	1101
1989	VH3-23_IGHD2-15*01>1'_IGHJ5*01	1669	gnl|Fabrus|O12_IGKJ1*01	1101
1990	VH3-23_IGHD2-15*01>3'_IGHJ5*01	1670	gnl|Fabrus|O12_IGKJ1*01	1101
1991	VH3-23_IGHD2-21*01>1'_IGHJ5*01	1671	gnl|Fabrus|O12_IGKJ1*01	1101
1992	VH3-23_IGHD2-21*01>3'_IGHJ5*01	1672	gnl|Fabrus|O12_IGKJ1*01	1101
1993	VH3-23_IGHD3-3*01>1'_IGHJ5*01	1673	gnl|Fabrus|O12_IGKJ1*01	1101
1994	VH3-23_IGHD3-3*01>3'_IGHJ5*01	1674	gnl|Fabrus|O12_IGKJ1*01	1101

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
1995	VH3-23_IGHD3-9*01>1'_IGHJ5*01	1675	gnl|Fabrus|O12_IGKJ1*01	1101
1996	VH3-23_IGHD3-9*01>3'_IGHJ5*01	1676	gnl|Fabrus|O12_IGKJ1*01	1101
1997	VH3-23_IGHD3-10*01>1'_IGHJ5*01	1677	gnl|Fabrus|O12_IGKJ1*01	1101
1998	VH3-23_IGHD3-10*01>3'_IGHJ5*01	1678	gnl|Fabrus|O12_IGKJ1*01	1101
1999	VH3-23_IGHD3-16*01>1'_IGHJ5*01	1679	gnl|Fabrus|O12_IGKJ1*01	1101
2000	VH3-23_IGHD3-16*01>3'_IGHJ5*01	1680	gnl|Fabrus|O12_IGKJ1*01	1101
2001	VH3-23_IGHD3-22*01>1'_IGHJ5*01	1681	gnl|Fabrus|O12_IGKJ1*01	1101
2002	VH3-23_IGHD4-4*01 (1) >1'_IGHJ5*01	1682	gnl|Fabrus|O12_IGKJ1*01	1101
2003	VH3-23_IGHD4-4*01 (1) >3'_IGHJ5*01	1683	gnl|Fabrus|O12_IGKJ1*01	1101
2004	VH3-23_IGHD4-11*01 (1) >1'_IGHJ5*01	1684	gnl|Fabrus|O12_IGKJ1*01	1101
2005	VH3-23_IGHD4-11*01 (1) >3'_IGHJ5*01	1685	gnl|Fabrus|O12_IGKJ1*01	1101
2006	VH3-23_IGHD4-17*01>1'_IGHJ5*01	1686	gnl|Fabrus|O12_IGKJ1*01	1101
2007	VH3-23_IGHD4-17*01>3'_IGHJ5*01	1687	gnl|Fabrus|O12_IGKJ1*01	1101
2008	VH3-23_IGHD4-23*01>1'_IGHJ5*01	1688	gnl|Fabrus|O12_IGKJ1*01	1101
2009	VH3-23_IGHD4-23*01>3'_IGHJ5*01	1689	gnl|Fabrus|O12_IGKJ1*01	1101
2010	VH3-23_IGHD5-5*01 (2) >1'_IGHJ5*01	1690	gnl|Fabrus|O12_IGKJ1*01	1101
2011	VH3-23_IGHD5-5*01 (2) >3'_IGHJ5*01	1691	gnl|Fabrus|O12_IGKJ1*01	1101
2012	VH3-23_IGHD5-12*01>1'_IGHJ5*01	1692	gnl|Fabrus|O12_IGKJ1*01	1101
2013	VH3-23_IGHD5-12*01>3'_IGHJ5*01	1693	gnl|Fabrus|O12_IGKJ1*01	1101
2014	VH3-23_IGHD5-18*01 (2) >1'_IGHJ5*01	1694	gnl|Fabrus|O12_IGKJ1*01	1101
2015	VH3-23_IGHD5-18*01 (2) >3'_IGHJ5*01	1695	gnl|Fabrus|O12_IGKJ1*01	1101
2016	VH3-23_IGHD5-24*01>1'_IGHJ5*01	1696	gnl|Fabrus|O12_IGKJ1*01	1101
2017	VH3-23_IGHD5-24*01>3'_IGHJ5*01	1697	gnl|Fabrus|O12_IGKJ1*01	1101
2018	VH3-23_IGHD6-6*01>1'_IGHJ5*01	1698	gnl|Fabrus|O12_IGKJ1*01	1101
2019	VH3-23_IGHD6-6*01>2'_IGHJ5*01	1699	gnl|Fabrus|O12_IGKJ1*01	1101
2020	VH3-23_IGHD6-6*01>3'_IGHJ5*01	1700	gnl|Fabrus|O12_IGKJ1*01	1101
2021	VH3-23_IGHD6-6*01>2_IGHJ5*01	1644	gnl|Fabrus|O12_IGKJ1*01	1101
2022	VH3-23_IGHD6-13*01>1_IGHJ5*01	1645	gnl|Fabrus|O12_IGKJ1*01	1101
2023	VH3-23_IGHD6-13*01>2_IGHJ5*01	1646	gnl|Fabrus|O12_IGKJ1*01	1101
2024	VH3-23_IGHD6-19*01>1_IGHJ5*01	1647	gnl|Fabrus|O12_IGKJ1*01	1101
2025	VH3-23_IGHD6-19*01>2_IGHJ5*01	1648	gnl|Fabrus|O12_IGKJ1*01	1101
2026	VH3-23_IGHD6-25*01>1_IGHJ5*01	1649	gnl|Fabrus|O12_IGKJ1*01	1101
2027	VH3-23_IGHD6-25*01>2_IGHJ5*01	1650	gnl|Fabrus|O12_IGKJ1*01	1101
2028	VH3-23_IGHD7-27*01>1_IGHJ5*01	1651	gnl|Fabrus|O12_IGKJ1*01	1101
2029	VH3-23_IGHD7-27*01>3_IGHJ5*01	1652	gnl|Fabrus|O12_IGKJ1*01	1101
2030	VH3-23_IGHD6-13*01>1'_IGHJ5*01	1701	gnl|Fabrus|O12_IGKJ1*01	1101
2031	VH3-23_IGHD6-13*01>2'_IGHJ5*01	1702	gnl|Fabrus|O12_IGKJ1*01	1101
2032	VH3-23_IGHD6-13*01>3'_IGHJ5*01	1703	gnl|Fabrus|O12_IGKJ1*01	1101
2033	VH3-23_IGHD6-19*01>1'_IGHJ5*01	1704	gnl|Fabrus|O12_IGKJ1*01	1101
2034	VH3-23_IGHD6-19*01>2'_IGHJ5*01	1705	gnl|Fabrus|O12_IGKJ1*01	1101
2035	VH3-23_IGHD6-19*01>2_IGHJ5*01_B	1706	gnl|Fabrus|O12_IGKJ1*01	1101
2036	VH3-23_IGHD6-25*01>1'_IGHJ5*01	1707	gnl|Fabrus|O12_IGKJ1*01	1101

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2037	VH3-23_IGHD6-25*01>3'_IGHJ5*01	1708	gnl|Fabrus|O12_IGKJ1*01	1101
2038	VH3-23_IGHD7-27*01>1'_IGHJ5*01	1709	gnl|Fabrus|O12_IGKJ1*01	1101
2039	VH3-23_IGHD7-27*01>2'_IGHJ5*01	1710	gnl|Fabrus|O12_IGKJ1*01	1101
2040	VH3-23_IGHD1-1*01>1_IGHJ6*01	1711	gnl|Fabrus|O12_IGKJ1*01	1101
2041	VH3-23_IGHD1-1*01>2_IGHJ6*01	1712	gnl|Fabrus|O12_IGKJ1*01	1101
2042	VH3-23_IGHD1-1*01>3_IGHJ6*01	1713	gnl|Fabrus|O12_IGKJ1*01	1101
2043	VH3-23_IGHD1-7*01>1_IGHJ6*01	1714	gnl|Fabrus|O12_IGKJ1*01	1101
2044	VH3-23_IGHD1-7*01>3_IGHJ6*01	1715	gnl|Fabrus|O12_IGKJ1*01	1101
2045	VH3-23_IGHD1-14*01>1_IGHJ6*01	1716	gnl|Fabrus|O12_IGKJ1*01	1101
2046	VH3-23_IGHD1-14*01>3_IGHJ6*01	1717	gnl|Fabrus|O12_IGKJ1*01	1101
2047	VH3-23_IGHD1-20*01>1_IGHJ6*01	1718	gnl|Fabrus|O12_IGKJ1*01	1101
2048	VH3-23_IGHD1-20*01>3_IGHJ6*01	1719	gnl|Fabrus|O12_IGKJ1*01	1101
2049	VH3-23_IGHD1-26*01>1_IGHJ6*01	1720	gnl|Fabrus|O12_IGKJ1*01	1101
2050	VH3-23_IGHD1-26*01>3_IGHJ6*01	1721	gnl|Fabrus|O12_IGKJ1*01	1101
2051	VH3-23_IGHD2-2*01>2_IGHJ6*01	1722	gnl|Fabrus|O12_IGKJ1*01	1101
2052	VH3-23_IGHD2-2*01>3_IGHJ6*01	1723	gnl|Fabrus|O12_IGKJ1*01	1101
2053	VH3-23_IGHD2-8*01>2_IGHJ6*01	1724	gnl|Fabrus|O12_IGKJ1*01	1101
2054	VH3-23_IGHD2-8*01>3_IGHJ6*01	1725	gnl|Fabrus|O12_IGKJ1*01	1101
2055	VH3-23_IGHD2-15*01>2_IGHJ6*01	1726	gnl|Fabrus|O12_IGKJ1*01	1101
2056	VH3-23_IGHD2-15*01>3_IGHJ6*01	1727	gnl|Fabrus|O12_IGKJ1*01	1101
2057	VH3-23_IGHD2-21*01>2_IGHJ6*01	1728	gnl|Fabrus|O12_IGKJ1*01	1101
2058	VH3-23_IGHD2-21*01>3_IGHJ6*01	1729	gnl|Fabrus|O12_IGKJ1*01	1101
2059	VH3-23_IGHD3-3*01>1_IGHJ6*01	1730	gnl|Fabrus|O12_IGKJ1*01	1101
2060	VH3-23_IGHD3-3*01>2_IGHJ6*01	1731	gnl|Fabrus|O12_IGKJ1*01	1101
2061	VH3-23_IGHD3-3*01>3_IGHJ6*01	1732	gnl|Fabrus|O12_IGKJ1*01	1101
2062	VH3-23_IGHD3-9*01>2_IGHJ6*01	1733	gnl|Fabrus|O12_IGKJ1*01	1101
2063	VH3-23_IGHD3-10*01>2_IGHJ6*01	1734	gnl|Fabrus|O12_IGKJ1*01	1101
2064	VH3-23_IGHD3-10*01>3_IGHJ6*01	1735	gnl|Fabrus|O12_IGKJ1*01	1101
2065	VH3-23_IGHD3-16*01>2_IGHJ6*01	1736	gnl|Fabrus|O12_IGKJ1*01	1101
2066	VH3-23_IGHD3-16*01>3_IGHJ6*01	1737	gnl|Fabrus|O12_IGKJ1*01	1101
2067	VH3-23_IGHD3-22*01>2_IGHJ6*01	1738	gnl|Fabrus|O12_IGKJ1*01	1101
2068	VH3-23_IGHD3-22*01>3_IGHJ6*01	1739	gnl|Fabrus|O12_IGKJ1*01	1101
2069	VH3-23_IGHD4-4*01 (1) >2_IGHJ6*01	1740	gnl|Fabrus|O12_IGKJ1*01	1101
2070	VH3-23_IGHD4-4*01 (1) >3_IGHJ6*01	1741	gnl|Fabrus|O12_IGKJ1*01	1101
2071	VH3-23_IGHD4-11*01 (1) >2_IGHJ6*01	1742	gnl|Fabrus|O12_IGKJ1*01	1101
2072	VH3-23_IGHD4-11*01 (1) >3_IGHJ6*01	1743	gnl|Fabrus|O12_IGKJ1*01	1101
2073	VH3-23_IGHD4-17*01>2_IGHJ6*01	1744	gnl|Fabrus|O12_IGKJ1*01	1101
2074	VH3-23_IGHD4-17*01>3_IGHJ6*01	1745	gnl|Fabrus|O12_IGKJ1*01	1101
2075	VH3-23_IGHD4-23*01>2_IGHJ6*01	1746	gnl|Fabrus|O12_IGKJ1*01	1101
2076	VH3-23_IGHD4-23*01>3_IGHJ6*01	1747	gnl|Fabrus|O12_IGKJ1*01	1101
2077	VH3-23_IGHD5-5*01 (2) >1_IGHJ6*01	1748	gnl|Fabrus|O12_IGKJ1*01	1101
2078	VH3-23_IGHD5-5*01 (2) >2_IGHJ6*01	1749	gnl|Fabrus|O12_IGKJ1*01	1101

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2079	VH3-23_IGHD5-5*01 (2) >3_IGHJ6*01	1750	gnl|Fabrus|O12_IGKJ1*01	1101
2080	VH3-23_IGHD5-12*01>1_IGHJ6*01	1751	gnl|Fabrus|O12_IGKJ1*01	1101
2081	VH3-23_IGHD5-12*01>3_IGHJ6*01	1752	gnl|Fabrus|O12_IGKJ1*01	1101
2082	VH3-23_IGHD5-18*01 (2) >1_IGHJ6*01	1753	gnl|Fabrus|O12_IGKJ1*01	1101
2083	VH3-23_IGHD5-18*01 (2) >2_IGHJ6*01	1754	gnl|Fabrus|O12_IGKJ1*01	1101
2084	VH3-23_IGHD5-18*01 (2) >3_IGHJ6*01	1755	gnl|Fabrus|O12_IGKJ1*01	1101
2085	VH3-23_IGHD5-24*01>1_IGHJ6*01	1756	gnl|Fabrus|O12_IGKJ1*01	1101
2086	VH3-23_IGHD5-24*01>3_IGHJ6*01	1757	gnl|Fabrus|O12_IGKJ1*01	1101
2087	VH3-23_IGHD6-6*01>1_IGHJ6*01	1758	gnl|Fabrus|O12_IGKJ1*01	1101
2088	VH3-23_IGHD6-6*01>2_IGHJ6*01	1759	gnl|Fabrus|O12_IGKJ1*01	1101
2089	VH3-23_IGHD5-12*01>3'_IGHJ6*01	1815	gnl|Fabrus|O12_IGKJ1*01	1101
2090	VH3-23_IGHD5-18*01(2)>1'_IGHJ6*01	1809	gnl|Fabrus|O12_IGKJ1*01	1101
2091	VH3-23_IGHD5-18*01(2)>3'_IGHJ6*01	1810	gnl|Fabrus|O12_IGKJ1*01	1101
2092	VH3-23_IGHD5-24*01>1'_IGHJ6*01	1811	gnl|Fabrus|O12_IGKJ1*01	1101
2093	VH3-23_IGHD5-24*01>3'_IGHJ6*01	1812	gnl|Fabrus|O12_IGKJ1*01	1101
2094	VH3-23_IGHD6-6*01>1'_IGHJ6*01	1813	gnl|Fabrus|O12_IGKJ1*01	1101
2095	VH3-23_IGHD6-6*01>2'_IGHJ6*01	1814	gnl|Fabrus|O12_IGKJ1*01	1101
2096	VH3-23_IGHD6-6*01>3'_IGHJ6*01	1815	gnl|Fabrus|O12_IGKJ1*01	1101
2097	VH3-23_IGHD1-1*01>1'_IGHJ6*01	1768	gnl|Fabrus|O12_IGKJ1*01	1101
2098	VH3-23_IGHD1-1*01>2'_IGHJ6*01	1769	gnl|Fabrus|O12_IGKJ1*01	1101
2099	VH3-23_IGHD1-1*01>3'_IGHJ6*01	1770	gnl|Fabrus|O12_IGKJ1*01	1101
2100	VH3-23_IGHD1-7*01>1'_IGHJ6*01	1771	gnl|Fabrus|O12_IGKJ1*01	1101
2101	VH3-23_IGHD1-7*01>3'_IGHJ6*01	1772	gnl|Fabrus|O12_IGKJ1*01	1101
2102	VH3-23_IGHD1-14*01>1'_IGHJ6*01	1773	gnl|Fabrus|O12_IGKJ1*01	1101
2103	VH3-23_IGHD1-14*01>2'_IGHJ6*01	1774	gnl|Fabrus|O12_IGKJ1*01	1101
2104	VH3-23_IGHD1-14*01>3'_IGHJ6*01	1775	gnl|Fabrus|O12_IGKJ1*01	1101
2105	VH3-23_IGHD1-20*01>1'_IGHJ6*01	1776	gnl|Fabrus|O12_IGKJ1*01	1101
2106	VH3-23_IGHD1-20*01>2'_IGHJ6*01	1777	gnl|Fabrus|O12_IGKJ1*01	1101
2107	VH3-23_IGHD1-20*01>3'_IGHJ6*01	1778	gnl|Fabrus|O12_IGKJ1*01	1101
2108	VH3-23_IGHD1-26*01>1'_IGHJ6*01	1779	gnl|Fabrus|O12_IGKJ1*01	1101
2109	VH3-23_IGHD1-26*01>1_IGHJ6*01_B	1780	gnl|Fabrus|O12_IGKJ1*01	1101
2110	VH3-23_IGHD2-2*01>2_IGHJ6*01_B	1781	gnl|Fabrus|O12_IGKJ1*01	1101
2111	VH3-23_IGHD2-2*01>3'_IGHJ6*01	1782	gnl|Fabrus|O12_IGKJ1*01	1101
2112	VH3-23_IGHD2-8*01>1'_IGHJ6*01	1783	gnl|Fabrus|O12_IGKJ1*01	1101
2113	VH3-23_IGHD2-15*01>1'_IGHJ6*01	1784	gnl|Fabrus|O12_IGKJ1*01	1101
2114	VH3-23_IGHD2-15*01>3'_IGHJ6*01	1785	gnl|Fabrus|O12_IGKJ1*01	1101
2115	VH3-23_IGHD2-21*01>1'_IGHJ6*01	1786	gnl|Fabrus|O12_IGKJ1*01	1101
2116	VH3-23_IGHD2-21*01>3'_IGHJ6*01	1787	gnl|Fabrus|O12_IGKJ1*01	1101
2117	VH3-23_IGHD3-3*01>1'_IGHJ6*01	1788	gnl|Fabrus|O12_IGKJ1*01	1101
2118	VH3-23_IGHD3-3*01>3'_IGHJ6*01	1789	gnl|Fabrus|O12_IGKJ1*01	1101
2119	VH3-23_IGHD3-9*01>1'_IGHJ6*01	1790	gnl|Fabrus|O12_IGKJ1*01	1101
2120	VH3-23_IGHD3-9*01>3'_IGHJ6*01	1791	gnl|Fabrus|O12_IGKJ1*01	1101

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2121	VH3-23_IGHD3-10*01>1'_IGHJ6*01	1792	gnl|Fabrus|O12_IGKJ1*01	1101
2122	VH3-23_IGHD3-10*01>3'_IGHJ6*01	1793	gnl|Fabrus|O12_IGKJ1*01	1101
2123	VH3-23_IGHD3-16*01>1'_IGHJ6*01	1794	gnl|Fabrus|O12_IGKJ1*01	1101
2124	VH3-23_IGHD3-16*01>3'_IGHJ6*01	1795	gnl|Fabrus|O12_IGKJ1*01	1101
2125	VH3-23_IGHD3-22*01>1'_IGHJ6*01	1796	gnl|Fabrus|O12_IGKJ1*01	1101
2126	VH3-23_IGHD4-4*01 (1) >1'_IGHJ6*01	1797	gnl|Fabrus|O12_IGKJ1*01	1101
2127	VH3-23_IGHD4-4*01 (1) >3'_IGHJ6*01	1798	gnl|Fabrus|O12_IGKJ1*01	1101
2128	VH3-23_IGHD4-11*01 (1) >1'_IGHJ6*01	1799	gnl|Fabrus|O12_IGKJ1*01	1101
2129	VH3-23_IGHD4-11*01 (1) >3'_IGHJ6*01	1800	gnl|Fabrus|O12_IGKJ1*01	1101
2130	VH3-23_IGHD4-17*01>1'_IGHJ6*01	1801	gnl|Fabrus|O12_IGKJ1*01	1101
2131	VH3-23_IGHD4-17*01>3'_IGHJ6*01	1802	gnl|Fabrus|O12_IGKJ1*01	1101
2132	VH3-23_IGHD4-23*01>1'_IGHJ6*01	1803	gnl|Fabrus|O12_IGKJ1*01	1101
2133	VH3-23_IGHD4-23*01>3'_IGHJ6*01	1804	gnl|Fabrus|O12_IGKJ1*01	1101
2134	VH3-23_IGHD5-5*01 (2) >1'_IGHJ6*01	1805	gnl|Fabrus|O12_IGKJ1*01	1101
2135	VH3-23_IGHD5-5*01 (2) >3'_IGHJ6*01	1806	gnl|Fabrus|O12_IGKJ1*01	1101
2136	VH3-23_IGHD5-12*01>1'_IGHJ6*01	1807	gnl|Fabrus|O12_IGKJ1*01	1101
2137	VH3-23_IGHD5-12*01>3'_IGHJ6*01	1808	gnl|Fabrus|O12_IGKJ1*01	1101
2138	VH3-23_IGHD5-18*01 (2) >1'_IGHJ6*01	1809	gnl|Fabrus|O12_IGKJ1*01	1101
2139	VH3-23_IGHD5-18*01 (2) >3'_IGHJ6*01	1810	gnl|Fabrus|O12_IGKJ1*01	1101
2140	VH3-23_IGHD5-24*01>1'_IGHJ6*01	1811	gnl|Fabrus|O12_IGKJ1*01	1101
2141	VH3-23_IGHD5-24*01>3'_IGHJ6*01	1812	gnl|Fabrus|O12_IGKJ1*01	1101
2142	VH3-23_IGHD6-6*01>1'_IGHJ6*01	1813	gnl|Fabrus|O12_IGKJ1*01	1101
2143	VH3-23_IGHD6-6*01>2'_IGHJ6*01	1814	gnl|Fabrus|O12_IGKJ1*01	1101
2144	VH3-23_IGHD6-6*01>3'_IGHJ6*01	1815	gnl|Fabrus|O12_IGKJ1*01	1101
2145	VH3-23_IGHD6-13*01>1'_IGHJ6*01	1816	gnl|Fabrus|O12_IGKJ1*01	1101
2146	VH3-23_IGHD6-13*01>2'_IGHJ6*01	1817	gnl|Fabrus|O12_IGKJ1*01	1101
2147	VH3-23_IGHD6-13*01>3'_IGHJ6*01	1818	gnl|Fabrus|O12_IGKJ1*01	1101
2148	VH3-23_IGHD6-19*01>1'_IGHJ6*01	1819	gnl|Fabrus|O12_IGKJ1*01	1101
2149	VH3-23_IGHD6-19*01>2'_IGHJ6*01	1820	gnl|Fabrus|O12_IGKJ1*01	1101
2150	VH3-23_IGHD6-19*01>3'_IGHJ6*01	1821	gnl|Fabrus|O12_IGKJ1*01	1101
2151	VH3-23_IGHD6-25*01>1'_IGHJ6*01	1822	gnl|Fabrus|O12_IGKJ1*01	1101
2152	VH3-23_IGHD6-25*01>3'_IGHJ6*01	1823	gnl|Fabrus|O12_IGKJ1*01	1101
2153	VH3-23_IGHD7-27*01>1'_IGHJ6*01	1824	gnl|Fabrus|O12_IGKJ1*01	1101
2154	VH3-23_IGHD7-27*01>2'_IGHJ6*01	1825	gnl|Fabrus|O12_IGKJ1*01	1101
2155	VH3-23_IGHD1-1*01>1_IGHJ1*01	1136	gnl|Fabrus|O18_IGKJ1*01	1102
2156	VH3-23_IGHD1-1*01>2_IGHJ1*01	1137	gnl|Fabrus|O18_IGKJ1*01	1102
2157	VH3-23_IGHD1-1*01>3_IGHJ1*01	1138	gnl|Fabrus|O18_IGKJ1*01	1102
2158	VH3-23_IGHD1-7*01>1_IGHJ1*01	1139	gnl|Fabrus|O18_IGKJ1*01	1102
2159	VH3-23_IGHD1-7*01>3_IGHJ1*01	1140	gnl|Fabrus|O18_IGKJ1*01	1102
2160	VH3-23_IGHD1-14*01>1_IGHJ1*01	1141	gnl|Fabrus|O18_IGKJ1*01	1102
2161	VH3-23_IGHD1-14*01>3_IGHJ1*01	1142	gnl|Fabrus|O18_IGKJ1*01	1102
2162	VH3-23_IGHD1-20*01>1_IGHJ1*01	1143	gnl|Fabrus|O18_IGKJ1*01	1102

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2163	VH3-23_IGHD1-20*01>3_IGHJ1*01	1144	gnl|Fabrus|O18_IGKJ1*01	1102
2164	VH3-23_IGHD1-26*01>1_IGHJ1*01	1145	gnl|Fabrus|O18_IGKJ1*01	1102
2165	VH3-23_IGHD1-26*01>3_IGHJ1*01	1146	gnl|Fabrus|O18_IGKJ1*01	1102
2166	VH3-23_IGHD2-2*01>2_IGHJ1*01	1147	gnl|Fabrus|O18_IGKJ1*01	1102
2167	VH3-23_IGHD2-2*01>3_IGHJ1*01	1148	gnl|Fabrus|O18_IGKJ1*01	1102
2168	VH3-23_IGHD2-8*01>2_IGHJ1*01	1149	gnl|Fabrus|O18_IGKJ1*01	1102
2169	VH3-23_IGHD2-8*01>3_IGHJ1*01	1150	gnl|Fabrus|O18_IGKJ1*01	1102
2170	VH3-23_IGHD2-15*01>2_IGHJ1*01	1151	gnl|Fabrus|O18_IGKJ1*01	1102
2171	VH3-23_IGHD2-15*01>3_IGHJ1*01	1152	gnl|Fabrus|O18_IGKJ1*01	1102
2172	VH3-23_IGHD2-21*01>2_IGHJ1*01	1153	gnl|Fabrus|O18_IGKJ1*01	1102
2173	VH3-23_IGHD2-21*01>3_IGHJ1*01	1154	gnl|Fabrus|O18_IGKJ1*01	1102
2174	VH3-23_IGHD3-3*01>1_IGHJ1*01	1155	gnl|Fabrus|O18_IGKJ1*01	1102
2175	VH3-23_IGHD3-3*01>2_IGHJ1*01	1156	gnl|Fabrus|O18_IGKJ1*01	1102
2176	VH3-23_IGHD3-3*01>3_IGHJ1*01	1157	gnl|Fabrus|O18_IGKJ1*01	1102
2177	VH3-23_IGHD3-9*01>2_IGHJ1*01	1158	gnl|Fabrus|O18_IGKJ1*01	1102
2178	VH3-23_IGHD3-10*01>2_IGHJ1*01	1159	gnl|Fabrus|O18_IGKJ1*01	1102
2179	VH3-23_IGHD3-10*01>3_IGHJ1*01	1160	gnl|Fabrus|O18_IGKJ1*01	1102
2180	VH3-23_IGHD3-16*01>2_IGHJ1*01	1161	gnl|Fabrus|O18_IGKJ1*01	1102
2181	VH3-23_IGHD3-16*01>3_IGHJ1*01	1162	gnl|Fabrus|O18_IGKJ1*01	1102
2182	VH3-23_IGHD3-22*01>2_IGHJ1*01	1163	gnl|Fabrus|O18_IGKJ1*01	1102
2183	VH3-23_IGHD3-22*01>3_IGHJ1*01	1164	gnl|Fabrus|O18_IGKJ1*01	1102
2184	VH3-23_IGHD4-4*01 (1) >2_IGHJ1*01	1165	gnl|Fabrus|O18_IGKJ1*01	1102
2185	VH3-23_IGHD4-4*01 (1) >3_IGHJ1*01	1166	gnl|Fabrus|O18_IGKJ1*01	1102
2186	VH3-23_IGHD4-11*01 (1) >2_IGHJ1*01	1167	gnl|Fabrus|O18_IGKJ1*01	1102
2187	VH3-23_IGHD4-11*01 (1) >3_IGHJ1*01	1168	gnl|Fabrus|O18_IGKJ1*01	1102
2188	VH3-23_IGHD4-17*01>2_IGHJ1*01	1169	gnl|Fabrus|O18_IGKJ1*01	1102
2189	VH3-23_IGHD4-17*01>3_IGHJ1*01	1170	gnl|Fabrus|O18_IGKJ1*01	1102
2190	VH3-23_IGHD4-23*01>2_IGHJ1*01	1171	gnl|Fabrus|O18_IGKJ1*01	1102
2191	VH3-23_IGHD4-23*01>3_IGHJ1*01	1172	gnl|Fabrus|O18_IGKJ1*01	1102
2192	VH3-23_IGHD5-5*01 (2) >1_IGHJ1*01	1173	gnl|Fabrus|O18_IGKJ1*01	1102
2193	VH3-23_IGHD5-5*01 (2) >2_IGHJ1*01	1174	gnl|Fabrus|O18_IGKJ1*01	1102
2194	VH3-23_IGHD5-5*01 (2) >3_IGHJ1*01	1175	gnl|Fabrus|O18_IGKJ1*01	1102
2195	VH3-23_IGHD5-12*01>1_IGHJ1*01	1176	gnl|Fabrus|O18_IGKJ1*01	1102
2196	VH3-23_IGHD5-12*01>3_IGHJ1*01	1177	gnl|Fabrus|O18_IGKJ1*01	1102
2197	VH3-23_IGHD5-18*01 (2) >1_IGHJ1*01	1178	gnl|Fabrus|O18_IGKJ1*01	1102
2198	VH3-23_IGHD5-18*01 (2) >2_IGHJ1*01	1179	gnl|Fabrus|O18_IGKJ1*01	1102
2199	VH3-23_IGHD5-18*01 (2) >3_IGHJ1*01	1180	gnl|Fabrus|O18_IGKJ1*01	1102
2200	VH3-23_IGHD5-24*01>1_IGHJ1*01	1181	gnl|Fabrus|O18_IGKJ1*01	1102
2201	VH3-23_IGHD5-24*01>3_IGHJ1*01	1182	gnl|Fabrus|O18_IGKJ1*01	1102
2202	VH3-23_IGHD6-6*01>1_IGHJ1*01	1183	gnl|Fabrus|O18_IGKJ1*01	1102
2203	VH3-23_IGHD1-1*01>1'_IGHJ1*01	1193	gnl|Fabrus|O18_IGKJ1*01	1102
2204	VH3-23_IGHD1-1*01>2'_IGHJ1*01	1194	gnl|Fabrus|O18_IGKJ1*01	1102

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2205	VH3-23_IGHD1-1*01>3'_IGHJ1*01	1195	gnl|Fabrus|O18_IGKJ1*01	1102
2206	VH3-23_IGHD1-7*01>1'_IGHJ1*01	1196	gnl|Fabrus|O18_IGKJ1*01	1102
2207	VH3-23_IGHD1-7*01>3'_IGHJ1*01	1197	gnl|Fabrus|O18_IGKJ1*01	1102
2208	VH3-23_IGHD1-14*01>1'_IGHJ1*01	1198	gnl|Fabrus|O18_IGKJ1*01	1102
2209	VH3-23_IGHD1-14*01>2'_IGHJ1*01	1199	gnl|Fabrus|O18_IGKJ1*01	1102
2210	VH3-23_IGHD1-14*01>3'_IGHJ1*01	1200	gnl|Fabrus|O18_IGKJ1*01	1102
2211	VH3-23_IGHD1-20*01>1'_IGHJ1*01	1201	gnl|Fabrus|O18_IGKJ1*01	1102
2212	VH3-23_IGHD1-20*01>2'_IGHJ1*01	1202	gnl|Fabrus|O18_IGKJ1*01	1102
2213	VH3-23_IGHD1-20*01>3'_IGHJ1*01	1203	gnl|Fabrus|O18_IGKJ1*01	1102
2214	VH3-23_IGHD1-26*01>1'_IGHJ1*01	1204	gnl|Fabrus|O18_IGKJ1*01	1102
2215	VH3-23_IGHD1-26*01>3'_IGHJ1*01	1205	gnl|Fabrus|O18_IGKJ1*01	1102
2216	VH3-23_IGHD2-2*01>1'_IGHJ1*01	1206	gnl|Fabrus|O18_IGKJ1*01	1102
2217	VH3-23_IGHD2-2*01>3'_IGHJ1*01	1207	gnl|Fabrus|O18_IGKJ1*01	1102
2218	VH3-23_IGHD2-8*01>1'_IGHJ1*01	1208	gnl|Fabrus|O18_IGKJ1*01	1102
2219	VH3-23_IGHD2-15*01>1'_IGHJ1*01	1209	gnl|Fabrus|O18_IGKJ1*01	1102
2220	VH3-23_IGHD2-15*01>3'_IGHJ1*01	1210	gnl|Fabrus|O18_IGKJ1*01	1102
2221	VH3-23_IGHD2-21*01>1'_IGHJ1*01	1211	gnl|Fabrus|O18_IGKJ1*01	1102
2222	VH3-23_IGHD2-21*01>3'_IGHJ1*01	1212	gnl|Fabrus|O18_IGKJ1*01	1102
2223	VH3-23_IGHD3-3*01>1'_IGHJ1*01	1213	gnl|Fabrus|O18_IGKJ1*01	1102
2224	VH3-23_IGHD3-3*01>3'_IGHJ1*01	1214	gnl|Fabrus|O18_IGKJ1*01	1102
2225	VH3-23_IGHD3-9*01>1'_IGHJ1*01	1215	gnl|Fabrus|O18_IGKJ1*01	1102
2226	VH3-23_IGHD3-9*01>3'_IGHJ1*01	1216	gnl|Fabrus|O18_IGKJ1*01	1102
2227	VH3-23_IGHD3-10*01>1'_IGHJ1*01	1217	gnl|Fabrus|O18_IGKJ1*01	1102
2228	VH3-23_IGHD3-10*01>3'_IGHJ1*01	1218	gnl|Fabrus|O18_IGKJ1*01	1102
2229	VH3-23_IGHD3-16*01>1'_IGHJ1*01	1219	gnl|Fabrus|O18_IGKJ1*01	1102
2230	VH3-23_IGHD3-16*01>3'_IGHJ1*01	1220	gnl|Fabrus|O18_IGKJ1*01	1102
2231	VH3-23_IGHD3-22*01>1'_IGHJ1*01	1221	gnl|Fabrus|O18_IGKJ1*01	1102
2232	VH3-23_IGHD4-4*01 (1) >1'_IGHJ1*01	1222	gnl|Fabrus|O18_IGKJ1*01	1102
2233	VH3-23_IGHD4-4*01 (1) >3'_IGHJ1*01	1223	gnl|Fabrus|O18_IGKJ1*01	1102
2234	VH3-23_IGHD4-11*01 (1) >1'_IGHJ1*01	1224	gnl|Fabrus|O18_IGKJ1*01	1102
2235	VH3-23_IGHD4-11*01 (1) >3'_IGHJ1*01	1225	gnl|Fabrus|O18_IGKJ1*01	1102
2236	VH3-23_IGHD4-17*01>1'_IGHJ1*01	1226	gnl|Fabrus|O18_IGKJ1*01	1102
2237	VH3-23_IGHD4-17*01>3'_IGHJ1*01	1227	gnl|Fabrus|O18_IGKJ1*01	1102
2238	VH3-23_IGHD4-23*01>1'_IGHJ1*01	1228	gnl|Fabrus|O18_IGKJ1*01	1102
2239	VH3-23_IGHD4-23*01>3'_IGHJ1*01	1229	gnl|Fabrus|O18_IGKJ1*01	1102
2240	VH3-23_IGHD5-5*01 (2) >1'_IGHJ1*01	1230	gnl|Fabrus|O18_IGKJ1*01	1102
2241	VH3-23_IGHD5-5*01 (2) >3'_IGHJ1*01	1231	gnl|Fabrus|O18_IGKJ1*01	1102
2242	VH3-23_IGHD5-12*01>1'_IGHJ1*01	1232	gnl|Fabrus|O18_IGKJ1*01	1102
2243	VH3-23_IGHD5-12*01>3'_IGHJ1*01	1233	gnl|Fabrus|O18_IGKJ1*01	1102
2244	VH3-23_IGHD5-18*01 (2) >1'_IGHJ1*01	1234	gnl|Fabrus|O18_IGKJ1*01	1102
2245	VH3-23_IGHD5-18*01 (2) >3'_IGHJ1*01	1235	gnl|Fabrus|O18_IGKJ1*01	1102
2246	VH3-23_IGHD5-24*01>1'_IGHJ1*01	1236	gnl|Fabrus|O18_IGKJ1*01	1102

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2247	VH3-23_IGHD5-24*01>3'_IGHJ1*01	1237	gnl|Fabrus|O18_IGKJ1*01	1102
2248	VH3-23_IGHD6-6*01>1'_IGHJ1*01	1238	gnl|Fabrus|O18_IGKJ1*01	1102
2249	VH3-23_IGHD6-6*01>2'_IGHJ1*01	1239	gnl|Fabrus|O18_IGKJ1*01	1102
2250	VH3-23_IGHD6-6*01>3'_IGHJ1*01	1240	gnl|Fabrus|O18_IGKJ1*01	1102
2251	VH3-23_IGHD7-27*01>1'_IGHJ6*01	1824	gnl|Fabrus|O18_IGKJ1*01	1102
2252	VH3-23_IGHD6-13*01>2_IGHJ6*01	1761	gnl|Fabrus|O18_IGKJ1*01	1102
2253	VH3-23_IGHD6-19*01>1_IGHJ6*01	1762	gnl|Fabrus|O18_IGKJ1*01	1102
2254	VH3-23_IGHD6-19*01>2_IGHJ6*01	1763	gnl|Fabrus|O18_IGKJ1*01	1102
2255	VH3-23_IGHD6-25*01>1_IGHJ6*01	1764	gnl|Fabrus|O18_IGKJ1*01	1102
2256	VH3-23_IGHD6-25*01>2_IGHJ6*01	1765	gnl|Fabrus|O18_IGKJ1*01	1102
2257	VH3-23_IGHD7-27*01>1_IGHJ6*01	1766	gnl|Fabrus|O18_IGKJ1*01	1102
2258	VH3-23_IGHD7-27*01>3_IGHJ6*01	1767	gnl|Fabrus|O18_IGKJ1*01	1102
2259	VH3-23_IGHD6-13*01>1'_IGHJ6*01	1816	gnl|Fabrus|O18_IGKJ1*01	1102
2260	VH3-23_IGHD6-13*01>2'_IGHJ6*01	1817	gnl|Fabrus|O18_IGKJ1*01	1102
2261	VH3-23_IGHD6-13*01>2_IGHJ6*01_B	1761	gnl|Fabrus|O18_IGKJ1*01	1102
2262	VH3-23_IGHD6-19*01>1'_IGHJ6*01	1819	gnl|Fabrus|O18_IGKJ1*01	1102
2263	VH3-23_IGHD6-19*01>2'_IGHJ6*01	1820	gnl|Fabrus|O18_IGKJ1*01	1102
2264	VH3-23_IGHD6-25*01>1_IGHJ6*01_B	1764	gnl|Fabrus|O18_IGKJ1*01	1102
2265	VH3-23_IGHD6-25*01>1'_IGHJ6*01	1822	gnl|Fabrus|O18_IGKJ1*01	1102
2266	VH3-23_IGHD6-25*01>3'_IGHJ6*01	1823	gnl|Fabrus|O18_IGKJ1*01	1102
2267	VH3-23_IGHD7-27*01>1'_IGHJ6*01	1824	gnl|Fabrus|O18_IGKJ1*01	1102
2268	VH3-23_IGHD7-27*01>2'_IGHJ6*01	1825	gnl|Fabrus|O18_IGKJ1*01	1102
2269	VH3-23_IGHD7-27*01>1'_IGHJ6*01	1824	gnl|Fabrus|A20_IGKJ1*01	1077
2270	VH3-23_IGHD6-13*01>2_IGHJ6*01	1761	gnl|Fabrus|A20_IGKJ1*01	1077
2271	VH3-23_IGHD6-19*01>1_IGHJ6*01	1762	gnl|Fabrus|A20_IGKJ1*01	1077
2272	VH3-23_IGHD6-19*01>2_IGHJ6*01	1763	gnl|Fabrus|A20_IGKJ1*01	1077
2273	VH3-23_IGHD6-25*01>1_IGHJ6*01	1764	gnl|Fabrus|A20_IGKJ1*01	1077
2274	VH3-23_IGHD6-25*01>2_IGHJ6*01	1765	gnl|Fabrus|A20_IGKJ1*01	1077
2275	VH3-23_IGHD7-27*01>1_IGHJ6*01	1766	gnl|Fabrus|A20_IGKJ1*01	1077
2276	VH3-23_IGHD7-27*01>3_IGHJ6*01	1767	gnl|Fabrus|A20_IGKJ1*01	1077
2277	VH3-23_IGHD6-13*01>1'_IGHJ6*01	1816	gnl|Fabrus|A20_IGKJ1*01	1077
2278	VH3-23_IGHD6-13*01>2'_IGHJ6*01	1817	gnl|Fabrus|A20_IGKJ1*01	1077
2279	VH3-23_IGHD6-13*01>2_IGHJ6*01_B	1761	gnl|Fabrus|A20_IGKJ1*01	1077
2280	VH3-23_IGHD6-19*01>1'_IGHJ6*01	1819	gnl|Fabrus|A20_IGKJ1*01	1077
2281	VH3-23_IGHD6-19*01>2'_IGHJ6*01	1820	gnl|Fabrus|A20_IGKJ1*01	1077
2282	VH3-23_IGHD6-25*01>1_IGHJ6*01_B	1764	gnl|Fabrus|A20_IGKJ1*01	1077
2283	VH3-23_IGHD6-25*01>1'_IGHJ6*01	1822	gnl|Fabrus|A20_IGKJ1*01	1077
2284	VH3-23_IGHD6-25*01>3'_IGHJ6*01	1823	gnl|Fabrus|A20_IGKJ1*01	1077
2285	VH3-23_IGHD7-27*01>1'_IGHJ6*01	1824	gnl|Fabrus|A20_IGKJ1*01	1077
2286	VH3-23_IGHD7-27*01>2'_IGHJ6*01	1825	gnl|Fabrus|A20_IGKJ1*01	1077
2287	VH3-23_IGHD1-1*01>1_IGHJ6*01	1711	gnl|Fabrus|L11_IGKJ1*01	1087
2288	VH3-23_IGHD1-1*01>2_IGHJ6*01	1712	gnl|Fabrus|L11_IGKJ1*01	1087

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2289	VH3-23_IGHD1-1*01>3_IGHJ6*01	1713	gnl|Fabrus|L11_IGKJ1*01	1087
2290	VH3-23_IGHD1-7*01>1_IGHJ6*01	1714	gnl|Fabrus|L11_IGKJ1*01	1087
2291	VH3-23_IGHD1-7*01>3_IGHJ6*01	1715	gnl|Fabrus|L11_IGKJ1*01	1087
2292	VH3-23_IGHD1-14*01>1_IGHJ6*01	1716	gnl|Fabrus|L11_IGKJ1*01	1087
2293	VH3-23_IGHD1-14*01>3_IGHJ6*01	1717	gnl|Fabrus|L11_IGKJ1*01	1087
2294	VH3-23_IGHD1-20*01>1_IGHJ6*01	1718	gnl|Fabrus|L11_IGKJ1*01	1087
2295	VH3-23_IGHD1-20*01>3_IGHJ6*01	1719	gnl|Fabrus|L11_IGKJ1*01	1087
2296	VH3-23_IGHD1-26*01>1_IGHJ6*01	1720	gnl|Fabrus|L11_IGKJ1*01	1087
2297	VH3-23_IGHD1-26*01>3_IGHJ6*01	1721	gnl|Fabrus|L11_IGKJ1*01	1087
2298	VH3-23_IGHD2-2*01>2_IGHJ6*01	1722	gnl|Fabrus|L11_IGKJ1*01	1087
2299	VH3-23_IGHD2-2*01>3_IGHJ6*01	1723	gnl|Fabrus|L11_IGKJ1*01	1087
2300	VH3-23_IGHD2-8*01>2_IGHJ6*01	1724	gnl|Fabrus|L11_IGKJ1*01	1087
2301	VH3-23_IGHD2-8*01>3_IGHJ6*01	1725	gnl|Fabrus|L11_IGKJ1*01	1087
2302	VH3-23_IGHD2-15*01>2_IGHJ6*01	1726	gnl|Fabrus|L11_IGKJ1*01	1087
2303	VH3-23_IGHD2-15*01>3_IGHJ6*01	1727	gnl|Fabrus|L11_IGKJ1*01	1087
2304	VH3-23_IGHD2-21*01>2_IGHJ6*01	1728	gnl|Fabrus|L11_IGKJ1*01	1087
2305	VH3-23_IGHD2-21*01>3_IGHJ6*01	1729	gnl|Fabrus|L11_IGKJ1*01	1087
2306	VH3-23_IGHD3-3*01>1_IGHJ6*01	1730	gnl|Fabrus|L11_IGKJ1*01	1087
2307	VH3-23_IGHD3-3*01>2_IGHJ6*01	1731	gnl|Fabrus|L11_IGKJ1*01	1087
2308	VH3-23_IGHD3-3*01>3_IGHJ6*01	1732	gnl|Fabrus|L11_IGKJ1*01	1087
2309	VH3-23_IGHD3-9*01>2_IGHJ6*01	1733	gnl|Fabrus|L11_IGKJ1*01	1087
2310	VH3-23_IGHD3-10*01>2_IGHJ6*01	1734	gnl|Fabrus|L11_IGKJ1*01	1087
2311	VH3-23_IGHD3-10*01>3_IGHJ6*01	1735	gnl|Fabrus|L11_IGKJ1*01	1087
2312	VH3-23_IGHD3-16*01>2_IGHJ6*01	1736	gnl|Fabrus|L11_IGKJ1*01	1087
2313	VH3-23_IGHD3-16*01>3_IGHJ6*01	1737	gnl|Fabrus|L11_IGKJ1*01	1087
2314	VH3-23_IGHD3-22*01>2_IGHJ6*01	1738	gnl|Fabrus|L11_IGKJ1*01	1087
2315	VH3-23_IGHD3-22*01>3_IGHJ6*01	1739	gnl|Fabrus|L11_IGKJ1*01	1087
2316	VH3-23_IGHD4-4*01 (1) >2_IGHJ6*01	1740	gnl|Fabrus|L11_IGKJ1*01	1087
2317	VH3-23_IGHD4-4*01 (1) >3_IGHJ6*01	1741	gnl|Fabrus|L11_IGKJ1*01	1087
2318	VH3-23_IGHD4-11*01 (1) >2_IGHJ6*01	1742	gnl|Fabrus|L11_IGKJ1*01	1087
2319	VH3-23_IGHD4-11*01 (1) >3_IGHJ6*01	1743	gnl|Fabrus|L11_IGKJ1*01	1087
2320	VH3-23_IGHD4-17*01>2_IGHJ6*01	1744	gnl|Fabrus|L11_IGKJ1*01	1087
2321	VH3-23_IGHD4-17*01>3_IGHJ6*01	1745	gnl|Fabrus|L11_IGKJ1*01	1087
2322	VH3-23_IGHD4-23*01>2_IGHJ6*01	1746	gnl|Fabrus|L11_IGKJ1*01	1087
2323	VH3-23_IGHD4-23*01>3_IGHJ6*01	1747	gnl|Fabrus|L11_IGKJ1*01	1087
2324	VH3-23_IGHD5-5*01 (2) >1_IGHJ6*01	1748	gnl|Fabrus|L11_IGKJ1*01	1087
2325	VH3-23_IGHD5-5*01 (2) >2_IGHJ6*01	1749	gnl|Fabrus|L11_IGKJ1*01	1087
2326	VH3-23_IGHD5-5*01 (2) >3_IGHJ6*01	1750	gnl|Fabrus|L11_IGKJ1*01	1087
2327	VH3-23_IGHD5-12*01>1_IGHJ6*01	1751	gnl|Fabrus|L11_IGKJ1*01	1087
2328	VH3-23_IGHD5-12*01>3_IGHJ6*01	1752	gnl|Fabrus|L11_IGKJ1*01	1087
2329	VH3-23_IGHD5-18*01 (2) >1_IGHJ6*01	1753	gnl|Fabrus|L11_IGKJ1*01	1087
2330	VH3-23_IGHD5-18*01 (2) >2_IGHJ6*01	1754	gnl|Fabrus|L11_IGKJ1*01	1087

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2331	VH3-23_IGHD5-18*01 (2) >3_IGHJ6*01	1755	gnl|Fabrus|L11_IGKJ1*01	1087
2332	VH3-23_IGHD5-24*01>1_IGHJ6*01	1756	gnl|Fabrus|L11_IGKJ1*01	1087
2333	VH3-23_IGHD5-24*01>3_IGHJ6*01	1757	gnl|Fabrus|L11_IGKJ1*01	1087
2334	VH3-23_IGHD6-6*01>1_IGHJ6*01	1758	gnl|Fabrus|L11_IGKJ1*01	1087
2335	VH3-23_IGHD1-1*01>1'_IGHJ6*01	1768	gnl|Fabrus|L11_IGKJ1*01	1087
2336	VH3-23_IGHD1-1*01>2'_IGHJ6*01	1769	gnl|Fabrus|L11_IGKJ1*01	1087
2337	VH3-23_IGHD1-1*01>3'_IGHJ6*01	1770	gnl|Fabrus|L11_IGKJ1*01	1087
2338	VH3-23_IGHD1-7*01>1'_IGHJ6*01	1771	gnl|Fabrus|L11_IGKJ1*01	1087
2339	VH3-23_IGHD1-7*01>3'_IGHJ6*01	1772	gnl|Fabrus|L11_IGKJ1*01	1087
2340	VH3-23_IGHD1-14*01>1'_IGHJ6*01	1773	gnl|Fabrus|L11_IGKJ1*01	1087
2341	VH3-23_IGHD1-14*01>2'_IGHJ6*01	1774	gnl|Fabrus|L11_IGKJ1*01	1087
2342	VH3-23_IGHD1-14*01>3'_IGHJ6*01	1775	gnl|Fabrus|L11_IGKJ1*01	1087
2343	VH3-23_IGHD1-20*01>1'_IGHJ6*01	1776	gnl|Fabrus|L11_IGKJ1*01	1087
2344	VH3-23_IGHD1-20*01>2'_IGHJ6*01	1777	gnl|Fabrus|L11_IGKJ1*01	1087
2345	VH3-23_IGHD1-20*01>3'_IGHJ6*01	1778	gnl|Fabrus|L11_IGKJ1*01	1087
2346	VH3-23_IGHD1-26*01>1'_IGHJ6*01	1779	gnl|Fabrus|L11_IGKJ1*01	1087
2347	VH3-23_IGHD1-26*01>1_IGHJ6*01_B	1780	gnl|Fabrus|L11_IGKJ1*01	1087
2348	VH3-23_IGHD2-2*01>2_IGHJ6*01_B	1781	gnl|Fabrus|L11_IGKJ1*01	1087
2349	VH3-23_IGHD2-2*01>3'_IGHJ6*01	1782	gnl|Fabrus|L11_IGKJ1*01	1087
2350	VH3-23_IGHD2-8*01>1'_IGHJ6*01	1783	gnl|Fabrus|L11_IGKJ1*01	1087
2351	VH3-23_IGHD2-15*01>1'_IGHJ6*01	1784	gnl|Fabrus|L11_IGKJ1*01	1087
2352	VH3-23_IGHD2-15*01>3'_IGHJ6*01	1785	gnl|Fabrus|L11_IGKJ1*01	1087
2353	VH3-23_IGHD2-21*01>1'_IGHJ6*01	1786	gnl|Fabrus|L11_IGKJ1*01	1087
2354	VH3-23_IGHD2-21*01>3'_IGHJ6*01	1787	gnl|Fabrus|L11_IGKJ1*01	1087
2355	VH3-23_IGHD3-3*01>1'_IGHJ6*01	1788	gnl|Fabrus|L11_IGKJ1*01	1087
2356	VH3-23_IGHD3-3*01>3'_IGHJ6*01	1789	gnl|Fabrus|L11_IGKJ1*01	1087
2357	VH3-23_IGHD3-9*01>1'_IGHJ6*01	1790	gnl|Fabrus|L11_IGKJ1*01	1087
2358	VH3-23_IGHD3-9*01>3'_IGHJ6*01	1791	gnl|Fabrus|L11_IGKJ1*01	1087
2359	VH3-23_IGHD3-10*01>1'_IGHJ6*01	1792	gnl|Fabrus|L11_IGKJ1*01	1087
2360	VH3-23_IGHD3-10*01>3'_IGHJ6*01	1793	gnl|Fabrus|L11_IGKJ1*01	1087
2361	VH3-23_IGHD3-16*01>1'_IGHJ6*01	1794	gnl|Fabrus|L11_IGKJ1*01	1087
2362	VH3-23_IGHD3-16*01>3'_IGHJ6*01	1795	gnl|Fabrus|L11_IGKJ1*01	1087
2363	VH3-23_IGHD3-22*01>1'_IGHJ6*01	1796	gnl|Fabrus|L11_IGKJ1*01	1087
2364	VH3-23_IGHD4-4*01 (1) >1'_IGHJ6*01	1797	gnl|Fabrus|L11_IGKJ1*01	1087
2365	VH3-23_IGHD4-4*01 (1) >3'_IGHJ6*01	1798	gnl|Fabrus|L11_IGKJ1*01	1087
2366	VH3-23_IGHD4-11*01 (1) >1'_IGHJ6*01	1799	gnl|Fabrus|L11_IGKJ1*01	1087
2367	VH3-23_IGHD4-11*01 (1) >3'_IGHJ6*01	1800	gnl|Fabrus|L11_IGKJ1*01	1087
2368	VH3-23_IGHD4-17*01>1'_IGHJ6*01	1801	gnl|Fabrus|L11_IGKJ1*01	1087
2369	VH3-23_IGHD4-17*01>3'_IGHJ6*01	1802	gnl|Fabrus|L11_IGKJ1*01	1087
2370	VH3-23_IGHD4-23*01>1'_IGHJ6*01	1803	gnl|Fabrus|L11_IGKJ1*01	1087
2371	VH3-23_IGHD4-23*01>3'_IGHJ6*01	1804	gnl|Fabrus|L11_IGKJ1*01	1087
2372	VH3-23_IGHD5-5*01 (2) >1'_IGHJ6*01	1805	gnl|Fabrus|L11_IGKJ1*01	1087

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2373	VH3-23_IGHD5-5*01 (2) >3'_IGHJ6*01	1806	gnl|Fabrus|L11_IGKJ1*01	1087
2374	VH3-23_IGHD5-12*01>1'_IGHJ6*01	1807	gnl|Fabrus|L11_IGKJ1*01	1087
2375	VH3-23_IGHD5-12*01>3'_IGHJ6*01	1808	gnl|Fabrus|L11_IGKJ1*01	1087
2376	VH3-23_IGHD5-18*01 (2) >1'_IGHJ6*01	1809	gnl|Fabrus|L11_IGKJ1*01	1087
2377	VH3-23_IGHD5-18*01 (2) >3'_IGHJ6*01	1810	gnl|Fabrus|L11_IGKJ1*01	1087
2378	VH3-23_IGHD5-24*01>1'_IGHJ6*01	1811	gnl|Fabrus|L11_IGKJ1*01	1087
2379	VH3-23_IGHD5-24*01>3'_IGHJ6*01	1812	gnl|Fabrus|L11_IGKJ1*01	1087
2380	VH3-23_IGHD6-6*01>1'_IGHJ6*01	1813	gnl|Fabrus|L11_IGKJ1*01	1087
2381	VH3-23_IGHD6-6*01>2'_IGHJ6*01	1814	gnl|Fabrus|L11_IGKJ1*01	1087
2382	VH3-23_IGHD6-6*01>3'_IGHJ6*01	1815	gnl|Fabrus|L11_IGKJ1*01	1087
2383	VH3-23_IGHD1-1*01>1_IGHJ6*01	1711	gnl|Fabrus|L12_IGKJ1*01	1088
2384	VH3-23_IGHD1-1*01>2_IGHJ6*01	1712	gnl|Fabrus|L12_IGKJ1*01	1088
2385	VH3-23_IGHD1-1*01>3_IGHJ6*01	1713	gnl|Fabrus|L12_IGKJ1*01	1088
2386	VH3-23_IGHD1-7*01>1_IGHJ6*01	1714	gnl|Fabrus|L12_IGKJ1*01	1088
2387	VH3-23_IGHD1-7*01>3_IGHJ6*01	1715	gnl|Fabrus|L12_IGKJ1*01	1088
2388	VH3-23_IGHD1-14*01>1_IGHJ6*01	1716	gnl|Fabrus|L12_IGKJ1*01	1088
2389	VH3-23_IGHD1-14*01>3_IGHJ6*01	1717	gnl|Fabrus|L12_IGKJ1*01	1088
2390	VH3-23_IGHD1-20*01>1_IGHJ6*01	1718	gnl|Fabrus|L12_IGKJ1*01	1088
2391	VH3-23_IGHD1-20*01>3_IGHJ6*01	1719	gnl|Fabrus|L12_IGKJ1*01	1088
2392	VH3-23_IGHD1-26*01>1_IGHJ6*01	1720	gnl|Fabrus|L12_IGKJ1*01	1088
2393	VH3-23_IGHD1-26*01>3_IGHJ6*01	1721	gnl|Fabrus|L12_IGKJ1*01	1088
2394	VH3-23_IGHD2-2*01>2_IGHJ6*01	1722	gnl|Fabrus|L12_IGKJ1*01	1088
2395	VH3-23_IGHD2-2*01>3_IGHJ6*01	1723	gnl|Fabrus|L12_IGKJ1*01	1088
2396	VH3-23_IGHD2-8*01>2_IGHJ6*01	1724	gnl|Fabrus|L12_IGKJ1*01	1088
2397	VH3-23_IGHD2-8*01>3_IGHJ6*01	1725	gnl|Fabrus|L12_IGKJ1*01	1088
2398	VH3-23_IGHD2-15*01>2_IGHJ6*01	1726	gnl|Fabrus|L12_IGKJ1*01	1088
2399	VH3-23_IGHD2-15*01>3_IGHJ6*01	1727	gnl|Fabrus|L12_IGKJ1*01	1088
2400	VH3-23_IGHD2-21*01>2_IGHJ6*01	1728	gnl|Fabrus|L12_IGKJ1*01	1088
2401	VH3-23_IGHD2-21*01>3_IGHJ6*01	1729	gnl|Fabrus|L12_IGKJ1*01	1088
2402	VH3-23_IGHD3-3*01>1_IGHJ6*01	1730	gnl|Fabrus|L12_IGKJ1*01	1088
2403	VH3-23_IGHD3-3*01>2_IGHJ6*01	1731	gnl|Fabrus|L12_IGKJ1*01	1088
2404	VH3-23_IGHD3-3*01>3_IGHJ6*01	1732	gnl|Fabrus|L12_IGKJ1*01	1088
2405	VH3-23_IGHD3-9*01>2_IGHJ6*01	1733	gnl|Fabrus|L12_IGKJ1*01	1088
2406	VH3-23_IGHD3-10*01>2_IGHJ6*01	1734	gnl|Fabrus|L12_IGKJ1*01	1088
2407	VH3-23_IGHD3-10*01>3_IGHJ6*01	1735	gnl|Fabrus|L12_IGKJ1*01	1088
2408	VH3-23_IGHD3-16*01>2_IGHJ6*01	1736	gnl|Fabrus|L12_IGKJ1*01	1088
2409	VH3-23_IGHD3-16*01>3_IGHJ6*01	1737	gnl|Fabrus|L12_IGKJ1*01	1088
2410	VH3-23_IGHD3-22*01>2_IGHJ6*01	1738	gnl|Fabrus|L12_IGKJ1*01	1088
2411	VH3-23_IGHD3-22*01>3_IGHJ6*01	1739	gnl|Fabrus|L12_IGKJ1*01	1088
2412	VH3-23_IGHD4-4*01 (1) >2_IGHJ6*01	1740	gnl|Fabrus|L12_IGKJ1*01	1088
2413	VH3-23_IGHD4-4*01 (1) >3_IGHJ6*01	1741	gnl|Fabrus|L12_IGKJ1*01	1088
2414	VH3-23_IGHD4-11*01 (1) >2_IGHJ6*01	1742	gnl|Fabrus|L12_IGKJ1*01	1088

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2415	VH3-23_IGHD4-11*01 (1) >3_IGHJ6*01	1743	gnl|Fabrus|L12_IGKJ1*01	1088
2416	VH3-23_IGHD4-17*01>2_IGHJ6*01	1744	gnl|Fabrus|L12_IGKJ1*01	1088
2417	VH3-23_IGHD4-17*01>3_IGHJ6*01	1745	gnl|Fabrus|L12_IGKJ1*01	1088
2418	VH3-23_IGHD4-23*01>2_IGHJ6*01	1746	gnl|Fabrus|L12_IGKJ1*01	1088
2419	VH3-23_IGHD4-23*01>3_IGHJ6*01	1747	gnl|Fabrus|L12_IGKJ1*01	1088
2420	VH3-23_IGHD5-5*01 (2) >1_IGHJ6*01	1748	gnl|Fabrus|L12_IGKJ1*01	1088
2421	VH3-23_IGHD5-5*01 (2) >2_IGHJ6*01	1749	gnl|Fabrus|L12_IGKJ1*01	1088
2422	VH3-23_IGHD5-5*01 (2) >3_IGHJ6*01	1750	gnl|Fabrus|L12_IGKJ1*01	1088
2423	VH3-23_IGHD5-12*01>1_IGHJ6*01	1751	gnl|Fabrus|L12_IGKJ1*01	1088
2424	VH3-23_IGHD5-12*01>3_IGHJ6*01	1752	gnl|Fabrus|L12_IGKJ1*01	1088
2425	VH3-23_IGHD5-18*01 (2) >1_IGHJ6*01	1753	gnl|Fabrus|L12_IGKJ1*01	1088
2426	VH3-23_IGHD5-18*01 (2) >2_IGHJ6*01	1754	gnl|Fabrus|L12_IGKJ1*01	1088
2427	VH3-23_IGHD5-18*01 (2) >3_IGHJ6*01	1755	gnl|Fabrus|L12_IGKJ1*01	1088
2428	VH3-23_IGHD5-24*01>1_IGHJ6*01	1756	gnl|Fabrus|L12_IGKJ1*01	1088
2429	VH3-23_IGHD5-24*01>3_IGHJ6*01	1757	gnl|Fabrus|L12_IGKJ1*01	1088
2430	VH3-23_IGHD6-6*01>1_IGHJ6*01	1758	gnl|Fabrus|L12_IGKJ1*01	1088
2431	VH3-23_IGHD1-1*01>1'_IGHJ6*01	1768	gnl|Fabrus|L12_IGKJ1*01	1088
2432	VH3-23_IGHD1-1*01>2'_IGHJ6*01	1769	gnl|Fabrus|L12_IGKJ1*01	1088
2433	VH3-23_IGHD1-1*01>3'_IGHJ6*01	1770	gnl|Fabrus|L12_IGKJ1*01	1088
2434	VH3-23_IGHD1-7*01>1'_IGHJ6*01	1771	gnl|Fabrus|L12_IGKJ1*01	1088
2435	VH3-23_IGHD1-7*01>3'_IGHJ6*01	1772	gnl|Fabrus|L12_IGKJ1*01	1088
2436	VH3-23_IGHD1-14*01>1'_IGHJ6*01	1773	gnl|Fabrus|L12_IGKJ1*01	1088
2437	VH3-23_IGHD1-14*01>2'_IGHJ6*01	1774	gnl|Fabrus|L12_IGKJ1*01	1088
2438	VH3-23_IGHD1-14*01>3'_IGHJ6*01	1775	gnl|Fabrus|L12_IGKJ1*01	1088
2439	VH3-23_IGHD1-20*01>1'_IGHJ6*01	1776	gnl|Fabrus|L12_IGKJ1*01	1088
2440	VH3-23_IGHD1-20*01>2'_IGHJ6*01	1777	gnl|Fabrus|L12_IGKJ1*01	1088
2441	VH3-23_IGHD1-20*01>3'_IGHJ6*01	1778	gnl|Fabrus|L12_IGKJ1*01	1088
2442	VH3-23_IGHD1-26*01>1'_IGHJ6*01	1779	gnl|Fabrus|L12_IGKJ1*01	1088
2443	VH3-23_IGHD1-26*01>1_IGHJ6*01_B	1780	gnl|Fabrus|L12_IGKJ1*01	1088
2444	VH3-23_IGHD2-2*01>2_IGHJ6*01_B	1781	gnl|Fabrus|L12_IGKJ1*01	1088
2445	VH3-23_IGHD2-2*01>3'_IGHJ6*01	1782	gnl|Fabrus|L12_IGKJ1*01	1088
2446	VH3-23_IGHD2-8*01>1'_IGHJ6*01	1783	gnl|Fabrus|L12_IGKJ1*01	1088
2447	VH3-23_IGHD2-15*01>1'_IGHJ6*01	1784	gnl|Fabrus|L12_IGKJ1*01	1088
2448	VH3-23_IGHD2-15*01>3'_IGHJ6*01	1785	gnl|Fabrus|L12_IGKJ1*01	1088
2449	VH3-23_IGHD2-21*01>1'_IGHJ6*01	1786	gnl|Fabrus|L12_IGKJ1*01	1088
2450	VH3-23_IGHD2-21*01>3'_IGHJ6*01	1787	gnl|Fabrus|L12_IGKJ1*01	1088
2451	VH3-23_IGHD3-3*01>1'_IGHJ6*01	1788	gnl|Fabrus|L12_IGKJ1*01	1088
2452	VH3-23_IGHD3-3*01>3'_IGHJ6*01	1789	gnl|Fabrus|L12_IGKJ1*01	1088
2453	VH3-23_IGHD3-9*01>1'_IGHJ6*01	1790	gnl|Fabrus|L12_IGKJ1*01	1088
2454	VH3-23_IGHD3-9*01>3'_IGHJ6*01	1791	gnl|Fabrus|L12_IGKJ1*01	1088
2455	VH3-23_IGHD3-10*01>1'_IGHJ6*01	1792	gnl|Fabrus|L12_IGKJ1*01	1088
2456	VH3-23_IGHD3-10*01>3'_IGHJ6*01	1793	gnl|Fabrus|L12_IGKJ1*01	1088

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2457	VH3-23_IGHD3-16*01>1'_IGHJ6*01	1794	gnl|Fabrus|L12_IGKJ1*01	1088
2458	VH3-23_IGHD3-16*01>3'_IGHJ6*01	1795	gnl|Fabrus|L12_IGKJ1*01	1088
2459	VH3-23_IGHD3-22*01>1'_IGHJ6*01	1796	gnl|Fabrus|L12_IGKJ1*01	1088
2460	VH3-23_IGHD4-4*01 (1) >1'_IGHJ6*01	1797	gnl|Fabrus|L12_IGKJ1*01	1088
2461	VH3-23_IGHD4-4*01 (1) >3'_IGHJ6*01	1798	gnl|Fabrus|L12_IGKJ1*01	1088
2462	VH3-23_IGHD4-11*01 (1) >1'_IGHJ6*01	1799	gnl|Fabrus|L12_IGKJ1*01	1088
2463	VH3-23_IGHD4-11*01 (1) >3'_IGHJ6*01	1800	gnl|Fabrus|L12_IGKJ1*01	1088
2464	VH3-23_IGHD4-17*01>1'_IGHJ6*01	1801	gnl|Fabrus|L12_IGKJ1*01	1088
2465	VH3-23_IGHD4-17*01>3'_IGHJ6*01	1802	gnl|Fabrus|L12_IGKJ1*01	1088
2466	VH3-23_IGHD4-23*01>1'_IGHJ6*01	1803	gnl|Fabrus|L12_IGKJ1*01	1088
2467	VH3-23_IGHD4-23*01>3'_IGHJ6*01	1804	gnl|Fabrus|L12_IGKJ1*01	1088
2468	VH3-23_IGHD5-5*01 (2) >1'_IGHJ6*01	1805	gnl|Fabrus|L12_IGKJ1*01	1088
2469	VH3-23_IGHD5-5*01 (2) >3'_IGHJ6*01	1806	gnl|Fabrus|L12_IGKJ1*01	1088
2470	VH3-23_IGHD5-12*01>1'_IGHJ6*01	1807	gnl|Fabrus|L12_IGKJ1*01	1088
2471	VH3-23_IGHD5-12*01>3'_IGHJ6*01	1808	gnl|Fabrus|L12_IGKJ1*01	1088
2472	VH3-23_IGHD5-18*01 (2) >1'_IGHJ6*01	1809	gnl|Fabrus|L12_IGKJ1*01	1088
2473	VH3-23_IGHD5-18*01 (2) >3'_IGHJ6*01	1810	gnl|Fabrus|L12_IGKJ1*01	1088
2474	VH3-23_IGHD5-24*01>1'_IGHJ6*01	1811	gnl|Fabrus|L12_IGKJ1*01	1088
2475	VH3-23_IGHD5-24*01>3'_IGHJ6*01	1812	gnl|Fabrus|L12_IGKJ1*01	1088
2476	VH3-23_IGHD6-6*01>1'_IGHJ6*01	1813	gnl|Fabrus|L12_IGKJ1*01	1088
2477	VH3-23_IGHD6-6*01>2'_IGHJ6*01	1814	gnl|Fabrus|L12_IGKJ1*01	1088
2478	VH3-23_IGHD6-6*01>3'_IGHJ6*01	1815	gnl|Fabrus|L12_IGKJ1*01	1088
2479	VH3-23_IGHD1-1*01>1_IGHJ6*01	1711	gnl|Fabrus|O1_IGKJ1*01	1100
2480	VH3-23_IGHD1-1*01>2_IGHJ6*01	1712	gnl|Fabrus|O1_IGKJ1*01	1100
2481	VH3-23_IGHD1-1*01>3_IGHJ6*01	1713	gnl|Fabrus|O1_IGKJ1*01	1100
2482	VH3-23_IGHD1-7*01>1_IGHJ6*01	1714	gnl|Fabrus|O1_IGKJ1*01	1100
2483	VH3-23_IGHD1-7*01>3_IGHJ6*01	1715	gnl|Fabrus|O1_IGKJ1*01	1100
2484	VH3-23_IGHD1-14*01>1_IGHJ6*01	1716	gnl|Fabrus|O1_IGKJ1*01	1100
2485	VH3-23_IGHD1-14*01>3_IGHJ6*01	1717	gnl|Fabrus|O1_IGKJ1*01	1100
2486	VH3-23_IGHD1-20*01>1_IGHJ6*01	1718	gnl|Fabrus|O1_IGKJ1*01	1100
2487	VH3-23_IGHD1-20*01>3_IGHJ6*01	1719	gnl|Fabrus|O1_IGKJ1*01	1100
2488	VH3-23_IGHD1-26*01>1_IGHJ6*01	1720	gnl|Fabrus|O1_IGKJ1*01	1100
2489	VH3-23_IGHD1-26*01>3_IGHJ6*01	1721	gnl|Fabrus|O1_IGKJ1*01	1100
2490	VH3-23_IGHD2-2*01>2_IGHJ6*01	1722	gnl|Fabrus|O1_IGKJ1*01	1100
2491	VH3-23_IGHD2-2*01>3_IGHJ6*01	1723	gnl|Fabrus|O1_IGKJ1*01	1100
2492	VH3-23_IGHD2-8*01>2_IGHJ6*01	1724	gnl|Fabrus|O1_IGKJ1*01	1100
2493	VH3-23_IGHD2-8*01>3_IGHJ6*01	1725	gnl|Fabrus|O1_IGKJ1*01	1100
2494	VH3-23_IGHD2-15*01>2_IGHJ6*01	1726	gnl|Fabrus|O1_IGKJ1*01	1100
2495	VH3-23_IGHD2-15*01>3_IGHJ6*01	1727	gnl|Fabrus|O1_IGKJ1*01	1100
2496	VH3-23_IGHD2-21*01>2_IGHJ6*01	1728	gnl|Fabrus|O1_IGKJ1*01	1100
2497	VH3-23_IGHD2-21*01>3_IGHJ6*01	1729	gnl|Fabrus|O1_IGKJ1*01	1100
2498	VH3-23_IGHD3-3*01>1_IGHJ6*01	1730	gnl|Fabrus|O1_IGKJ1*01	1100

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2499	VH3-23_IGHD3-3*01>2_IGHJ6*01	1731	gnl|Fabrus|O1_IGKJ1*01	1100
2500	VH3-23_IGHD3-3*01>3_IGHJ6*01	1732	gnl|Fabrus|O1_IGKJ1*01	1100
2501	VH3-23_IGHD3-9*01>2_IGHJ6*01	1733	gnl|Fabrus|O1_IGKJ1*01	1100
2502	VH3-23_IGHD3-10*01>2_IGHJ6*01	1734	gnl|Fabrus|O1_IGKJ1*01	1100
2503	VH3-23_IGHD3-10*01>3_IGHJ6*01	1735	gnl|Fabrus|O1_IGKJ1*01	1100
2504	VH3-23_IGHD3-16*01>2_IGHJ6*01	1736	gnl|Fabrus|O1_IGKJ1*01	1100
2505	VH3-23_IGHD3-16*01>3_IGHJ6*01	1737	gnl|Fabrus|O1_IGKJ1*01	1100
2506	VH3-23_IGHD3-22*01>2_IGHJ6*01	1738	gnl|Fabrus|O1_IGKJ1*01	1100
2507	VH3-23_IGHD3-22*01>3_IGHJ6*01	1739	gnl|Fabrus|O1_IGKJ1*01	1100
2508	VH3-23_IGHD4-4*01 (1) >2_IGHJ6*01	1740	gnl|Fabrus|O1_IGKJ1*01	1100
2509	VH3-23_IGHD4-4*01 (1) >3_IGHJ6*01	1741	gnl|Fabrus|O1_IGKJ1*01	1100
2510	VH3-23_IGHD4-11*01 (1) >2_IGHJ6*01	1742	gnl|Fabrus|O1_IGKJ1*01	1100
2511	VH3-23_IGHD4-11*01 (1) >3_IGHJ6*01	1743	gnl|Fabrus|O1_IGKJ1*01	1100
2512	VH3-23_IGHD4-17*01>2_IGHJ6*01	1744	gnl|Fabrus|O1_IGKJ1*01	1100
2513	VH3-23_IGHD4-17*01>3_IGHJ6*01	1745	gnl|Fabrus|O1_IGKJ1*01	1100
2514	VH3-23_IGHD4-23*01>2_IGHJ6*01	1746	gnl|Fabrus|O1_IGKJ1*01	1100
2515	VH3-23_IGHD4-23*01>3_IGHJ6*01	1747	gnl|Fabrus|O1_IGKJ1*01	1100
2516	VH3-23_IGHD5-5*01 (2) >1_IGHJ6*01	1748	gnl|Fabrus|O1_IGKJ1*01	1100
2517	VH3-23_IGHD5-5*01 (2) >2_IGHJ6*01	1749	gnl|Fabrus|O1_IGKJ1*01	1100
2518	VH3-23_IGHD5-5*01 (2) >3_IGHJ6*01	1750	gnl|Fabrus|O1_IGKJ1*01	1100
2519	VH3-23_IGHD5-12*01>1_IGHJ6*01	1751	gnl|Fabrus|O1_IGKJ1*01	1100
2520	VH3-23_IGHD5-12*01>3_IGHJ6*01	1752	gnl|Fabrus|O1_IGKJ1*01	1100
2521	VH3-23_IGHD5-18*01 (2) >1_IGHJ6*01	1753	gnl|Fabrus|O1_IGKJ1*01	1100
2522	VH3-23_IGHD5-18*01 (2) >2_IGHJ6*01	1754	gnl|Fabrus|O1_IGKJ1*01	1100
2523	VH3-23_IGHD5-18*01 (2) >3_IGHJ6*01	1755	gnl|Fabrus|O1_IGKJ1*01	1100
2524	VH3-23_IGHD5-24*01>1_IGHJ6*01	1756	gnl|Fabrus|O1_IGKJ1*01	1100
2525	VH3-23_IGHD5-24*01>3_IGHJ6*01	1757	gnl|Fabrus|O1_IGKJ1*01	1100
2526	VH3-23_IGHD6-6*01>1_IGHJ6*01	1758	gnl|Fabrus|O1_IGKJ1*01	1100
2527	VH3-23_IGHD1-1*01>1'_IGHJ6*01	1768	gnl|Fabrus|O1_IGKJ1*01	1100
2528	VH3-23_IGHD1-1*01>2'_IGHJ6*01	1769	gnl|Fabrus|O1_IGKJ1*01	1100
2529	VH3-23_IGHD1-1*01>3'_IGHJ6*01	1770	gnl|Fabrus|O1_IGKJ1*01	1100
2530	VH3-23_IGHD1-7*01>1'_IGHJ6*01	1771	gnl|Fabrus|O1_IGKJ1*01	1100
2531	VH3-23_IGHD1-7*01>3'_IGHJ6*01	1772	gnl|Fabrus|O1_IGKJ1*01	1100
2532	VH3-23_IGHD1-14*01>1'_IGHJ6*01	1773	gnl|Fabrus|O1_IGKJ1*01	1100
2533	VH3-23_IGHD1-14*01>2'_IGHJ6*01	1774	gnl|Fabrus|O1_IGKJ1*01	1100
2534	VH3-23_IGHD1-14*01>3'_IGHJ6*01	1775	gnl|Fabrus|O1_IGKJ1*01	1100
2535	VH3-23_IGHD1-20*01>1'_IGHJ6*01	1776	gnl|Fabrus|O1_IGKJ1*01	1100
2536	VH3-23_IGHD1-20*01>2'_IGHJ6*01	1777	gnl|Fabrus|O1_IGKJ1*01	1100
2537	VH3-23_IGHD1-20*01>3'_IGHJ6*01	1778	gnl|Fabrus|O1_IGKJ1*01	1100
2538	VH3-23_IGHD1-26*01>1'_IGHJ6*01	1779	gnl|Fabrus|O1_IGKJ1*01	1100
2539	VH3-23_IGHD1-26*01>1_IGHJ6*01_B	1780	gnl|Fabrus|O1_IGKJ1*01	1100
2540	VH3-23_IGHD2-2*01>2_IGHJ6*01_B	1781	gnl|Fabrus|O1_IGKJ1*01	1100

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2541	VH3-23_IGHD2-2*01>3'_IGHJ6*01	1782	gnl|Fabrus|O1_IGKJ1*01	1100
2542	VH3-23_IGHD2-8*01>1'_IGHJ6*01	1783	gnl|Fabrus|O1_IGKJ1*01	1100
2543	VH3-23_IGHD2-15*01>1'_IGHJ6*01	1784	gnl|Fabrus|O1_IGKJ1*01	1100
2544	VH3-23_IGHD2-15*01>3'_IGHJ6*01	1785	gnl|Fabrus|O1_IGKJ1*01	1100
2545	VH3-23_IGHD2-21*01>1'_IGHJ6*01	1786	gnl|Fabrus|O1_IGKJ1*01	1100
2546	VH3-23_IGHD2-21*01>3'_IGHJ6*01	1787	gnl|Fabrus|O1_IGKJ1*01	1100
2547	VH3-23_IGHD3-3*01>1'_IGHJ6*01	1788	gnl|Fabrus|O1_IGKJ1*01	1100
2548	VH3-23_IGHD3-3*01>3'_IGHJ6*01	1789	gnl|Fabrus|O1_IGKJ1*01	1100
2549	VH3-23_IGHD3-9*01>1'_IGHJ6*01	1790	gnl|Fabrus|O1_IGKJ1*01	1100
2550	VH3-23_IGHD3-9*01>3'_IGHJ6*01	1791	gnl|Fabrus|O1_IGKJ1*01	1100
2551	VH3-23_IGHD3-10*01>1'_IGHJ6*01	1792	gnl|Fabrus|O1_IGKJ1*01	1100
2552	VH3-23_IGHD3-10*01>3'_IGHJ6*01	1793	gnl|Fabrus|O1_IGKJ1*01	1100
2553	VH3-23_IGHD3-16*01>1'_IGHJ6*01	1794	gnl|Fabrus|O1_IGKJ1*01	1100
2554	VH3-23_IGHD3-16*01>3'_IGHJ6*01	1795	gnl|Fabrus|O1_IGKJ1*01	1100
2555	VH3-23_IGHD3-22*01>1'_IGHJ6*01	1796	gnl|Fabrus|O1_IGKJ1*01	1100
2556	VH3-23_IGHD4-4*01 (1) >1'_IGHJ6*01	1797	gnl|Fabrus|O1_IGKJ1*01	1100
2557	VH3-23_IGHD4-4*01 (1) >3'_IGHJ6*01	1798	gnl|Fabrus|O1_IGKJ1*01	1100
2558	VH3-23_IGHD4-11*01 (1) >1'_IGHJ6*01	1799	gnl|Fabrus|O1_IGKJ1*01	1100
2559	VH3-23_IGHD4-11*01 (1) >3'_IGHJ6*01	1800	gnl|Fabrus|O1_IGKJ1*01	1100
2560	VH3-23_IGHD4-17*01>1'_IGHJ6*01	1801	gnl|Fabrus|O1_IGKJ1*01	1100
2561	VH3-23_IGHD4-17*01>3'_IGHJ6*01	1802	gnl|Fabrus|O1_IGKJ1*01	1100
2562	VH3-23_IGHD4-23*01>1'_IGHJ6*01	1803	gnl|Fabrus|O1_IGKJ1*01	1100
2563	VH3-23_IGHD4-23*01>3'_IGHJ6*01	1804	gnl|Fabrus|O1_IGKJ1*01	1100
2564	VH3-23_IGHD5-5*01 (2) >1'_IGHJ6*01	1805	gnl|Fabrus|O1_IGKJ1*01	1100
2565	VH3-23_IGHD5-5*01 (2) >3'_IGHJ6*01	1806	gnl|Fabrus|O1_IGKJ1*01	1100
2566	VH3-23_IGHD5-12*01>1'_IGHJ6*01	1807	gnl|Fabrus|O1_IGKJ1*01	1100
2567	VH3-23_IGHD5-12*01>3'_IGHJ6*01	1808	gnl|Fabrus|O1_IGKJ1*01	1100
2568	VH3-23_IGHD5-18*01 (2) >1'_IGHJ6*01	1809	gnl|Fabrus|O1_IGKJ1*01	1100
2569	VH3-23_IGHD5-18*01 (2) >3'_IGHJ6*01	1810	gnl|Fabrus|O1_IGKJ1*01	1100
2570	VH3-23_IGHD5-24*01>1'_IGHJ6*01	1811	gnl|Fabrus|O1_IGKJ1*01	1100
2571	VH3-23_IGHD5-24*01>3'_IGHJ6*01	1812	gnl|Fabrus|O1_IGKJ1*01	1100
2572	VH3-23_IGHD6-6*01>1'_IGHJ6*01	1813	gnl|Fabrus|O1_IGKJ1*01	1100
2573	VH3-23_IGHD6-6*01>2'_IGHJ6*01	1814	gnl|Fabrus|O1_IGKJ1*01	1100
2574	VH3-23_IGHD6-6*01>3'_IGHJ6*01	1815	gnl|Fabrus|O1_IGKJ1*01	1100
2575	VH3-23_IGHD1-1*01>1_IGHJ5*01	1596	gnl|Fabrus|A2_IGKJ1*01	1076
2576	VH3-23_IGHD1-1*01>2_IGHJ5*01	1597	gnl|Fabrus|A2_IGKJ1*01	1076
2577	VH3-23_IGHD1-1*01>3_IGHJ5*01	1598	gnl|Fabrus|A2_IGKJ1*01	1076
2578	VH3-23_IGHD1-7*01>1_IGHJ5*01	1599	gnl|Fabrus|A2_IGKJ1*01	1076
2579	VH3-23_IGHD1-7*01>3_IGHJ5*01	1600	gnl|Fabrus|A2_IGKJ1*01	1076
2580	VH3-23_IGHD1-14*01>1_IGHJ5*01	1601	gnl|Fabrus|A2_IGKJ1*01	1076
2581	VH3-23_IGHD1-14*01>3_IGHJ5*01	1602	gnl|Fabrus|A2_IGKJ1*01	1076
2582	VH3-23_IGHD1-20*01>1_IGHJ5*01	1603	gnl|Fabrus|A2_IGKJ1*01	1076

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2583	VH3-23_IGHD1-20*01>3_IGHJ5*01	1604	gnl|Fabrus|A2_IGKJ1*01	1076
2584	VH3-23_IGHD1-26*01>1_IGHJ5*01	1605	gnl|Fabrus|A2_IGKJ1*01	1076
2585	VH3-23_IGHD1-26*01>3_IGHJ5*01	1606	gnl|Fabrus|A2_IGKJ1*01	1076
2586	VH3-23_IGHD2-2*01>2_IGHJ5*01	1607	gnl|Fabrus|A2_IGKJ1*01	1076
2587	VH3-23_IGHD2-2*01>3_IGHJ5*01	1608	gnl|Fabrus|A2_IGKJ1*01	1076
2588	VH3-23_IGHD2-8*01>2_IGHJ5*01	1609	gnl|Fabrus|A2_IGKJ1*01	1076
2589	VH3-23_IGHD2-8*01>3_IGHJ5*01	1610	gnl|Fabrus|A2_IGKJ1*01	1076
2590	VH3-23_IGHD2-15*01>2_IGHJ5*01	1611	gnl|Fabrus|A2_IGKJ1*01	1076
2591	VH3-23_IGHD2-15*01>3_IGHJ5*01	1612	gnl|Fabrus|A2_IGKJ1*01	1076
2592	VH3-23_IGHD2-21*01>2_IGHJ5*01	1613	gnl|Fabrus|A2_IGKJ1*01	1076
2593	VH3-23_IGHD2-21*01>3_IGHJ5*01	1614	gnl|Fabrus|A2_IGKJ1*01	1076
2594	VH3-23_IGHD3-3*01>1_IGHJ5*01	1615	gnl|Fabrus|A2_IGKJ1*01	1076
2595	VH3-23_IGHD3-3*01>2_IGHJ5*01	1616	gnl|Fabrus|A2_IGKJ1*01	1076
2596	VH3-23_IGHD3-3*01>3_IGHJ5*01	1617	gnl|Fabrus|A2_IGKJ1*01	1076
2597	VH3-23_IGHD3-9*01>2_IGHJ5*01	1618	gnl|Fabrus|A2_IGKJ1*01	1076
2598	VH3-23_IGHD3-10*01>2_IGHJ5*01	1619	gnl|Fabrus|A2_IGKJ1*01	1076
2599	VH3-23_IGHD3-10*01>3_IGHJ5*01	1620	gnl|Fabrus|A2_IGKJ1*01	1076
2600	VH3-23_IGHD3-16*01>2_IGHJ5*01	1621	gnl|Fabrus|A2_IGKJ1*01	1076
2601	VH3-23_IGHD3-16*01>3_IGHJ5*01	1622	gnl|Fabrus|A2_IGKJ1*01	1076
2602	VH3-23_IGHD3-22*01>2_IGHJ5*01	1623	gnl|Fabrus|A2_IGKJ1*01	1076
2603	VH3-23_IGHD3-22*01>3_IGHJ5*01	1624	gnl|Fabrus|A2_IGKJ1*01	1076
2604	VH3-23_IGHD4-4*01 (1) >2_IGHJ5*01	1625	gnl|Fabrus|A2_IGKJ1*01	1076
2605	VH3-23_IGHD4-4*01 (1) >3_IGHJ5*01	1626	gnl|Fabrus|A2_IGKJ1*01	1076
2606	VH3-23_IGHD4-11*01 (1) >2_IGHJ5*01	1627	gnl|Fabrus|A2_IGKJ1*01	1076
2607	VH3-23_IGHD4-11*01 (1) >3_IGHJ5*01	1628	gnl|Fabrus|A2_IGKJ1*01	1076
2608	VH3-23_IGHD4-17*01>2_IGHJ5*01	1629	gnl|Fabrus|A2_IGKJ1*01	1076
2609	VH3-23_IGHD4-17*01>3_IGHJ5*01	1630	gnl|Fabrus|A2_IGKJ1*01	1076
2610	VH3-23_IGHD4-23*01>2_IGHJ5*01	1631	gnl|Fabrus|A2_IGKJ1*01	1076
2611	VH3-23_IGHD4-23*01>3_IGHJ5*01	1632	gnl|Fabrus|A2_IGKJ1*01	1076
2612	VH3-23_IGHD5-5*01 (2) >1_IGHJ5*01	1633	gnl|Fabrus|A2_IGKJ1*01	1076
2613	VH3-23_IGHD5-5*01 (2) >2_IGHJ5*01	1634	gnl|Fabrus|A2_IGKJ1*01	1076
2614	VH3-23_IGHD5-5*01 (2) >3_IGHJ5*01	1635	gnl|Fabrus|A2_IGKJ1*01	1076
2615	VH3-23_IGHD5-12*01>1_IGHJ5*01	1636	gnl|Fabrus|A2_IGKJ1*01	1076
2616	VH3-23_IGHD5-12*01>3_IGHJ5*01	1637	gnl|Fabrus|A2_IGKJ1*01	1076
2617	VH3-23_IGHD5-18*01 (2) >1_IGHJ5*01	1638	gnl|Fabrus|A2_IGKJ1*01	1076
2618	VH3-23_IGHD5-18*01 (2) >2_IGHJ5*01	1639	gnl|Fabrus|A2_IGKJ1*01	1076
2619	VH3-23_IGHD5-18*01 (2) >3_IGHJ5*01	1640	gnl|Fabrus|A2_IGKJ1*01	1076
2620	VH3-23_IGHD5-24*01>1_IGHJ5*01	1641	gnl|Fabrus|A2_IGKJ1*01	1076
2621	VH3-23_IGHD5-24*01>3_IGHJ5*01	1642	gnl|Fabrus|A2_IGKJ1*01	1076
2622	VH3-23_IGHD6-6*01>1_IGHJ5*01	1643	gnl|Fabrus|A2_IGKJ1*01	1076
2623	VH3-23_IGHD1-1*01>1'_IGHJ5*01	1653	gnl|Fabrus|A2_IGKJ1*01	1076
2624	VH3-23_IGHD1-1*01>2'_IGHJ5*01	1654	gnl|Fabrus|A2_IGKJ1*01	1076

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2625	VH3-23_IGHD1-1*01>3'_IGHJ5*01	1655	gnl|Fabrus|A2_IGKJ1*01	1076
2626	VH3-23_IGHD1-7*01>1'_IGHJ5*01	1656	gnl|Fabrus|A2_IGKJ1*01	1076
2627	VH3-23_IGHD1-7*01>3'_IGHJ5*01	1657	gnl|Fabrus|A2_IGKJ1*01	1076
2628	VH3-23_IGHD1-14*01>1'_IGHJ5*01	1658	gnl|Fabrus|A2_IGKJ1*01	1076
2629	VH3-23_IGHD1-14*01>2'_IGHJ5*01	1659	gnl|Fabrus|A2_IGKJ1*01	1076
2630	VH3-23_IGHD1-14*01>3'_IGHJ5*01	1660	gnl|Fabrus|A2_IGKJ1*01	1076
2631	VH3-23_IGHD1-20*01>1'_IGHJ5*01	1661	gnl|Fabrus|A2_IGKJ1*01	1076
2632	VH3-23_IGHD1-20*01>2'_IGHJ5*01	1662	gnl|Fabrus|A2_IGKJ1*01	1076
2633	VH3-23_IGHD1-20*01>3'_IGHJ5*01	1663	gnl|Fabrus|A2_IGKJ1*01	1076
2634	VH3-23_IGHD1-26*01>1'_IGHJ5*01	1664	gnl|Fabrus|A2_IGKJ1*01	1076
2635	VH3-23_IGHD1-26*01>3'_IGHJ5*01	1665	gnl|Fabrus|A2_IGKJ1*01	1076
2636	VH3-23_IGHD2-2*01>1'_IGHJ5*01	1666	gnl|Fabrus|A2_IGKJ1*01	1076
2637	VH3-23_IGHD2-2*01>3'_IGHJ5*01	1667	gnl|Fabrus|A2_IGKJ1*01	1076
2638	VH3-23_IGHD2-8*01>1'_IGHJ5*01	1668	gnl|Fabrus|A2_IGKJ1*01	1076
2639	VH3-23_IGHD2-15*01>1'_IGHJ5*01	1669	gnl|Fabrus|A2_IGKJ1*01	1076
2640	VH3-23_IGHD2-15*01>3'_IGHJ5*01	1670	gnl|Fabrus|A2_IGKJ1*01	1076
2641	VH3-23_IGHD2-21*01>1'_IGHJ5*01	1671	gnl|Fabrus|A2_IGKJ1*01	1076
2642	VH3-23_IGHD2-21*01>3'_IGHJ5*01	1672	gnl|Fabrus|A2_IGKJ1*01	1076
2643	VH3-23_IGHD3-3*01>1'_IGHJ5*01	1673	gnl|Fabrus|A2_IGKJ1*01	1076
2644	VH3-23_IGHD3-3*01>3'_IGHJ5*01	1674	gnl|Fabrus|A2_IGKJ1*01	1076
2645	VH3-23_IGHD3-9*01>1'_IGHJ5*01	1675	gnl|Fabrus|A2_IGKJ1*01	1076
2646	VH3-23_IGHD3-9*01>3'_IGHJ5*01	1676	gnl|Fabrus|A2_IGKJ1*01	1076
2647	VH3-23_IGHD3-10*01>1'_IGHJ5*01	1677	gnl|Fabrus|A2_IGKJ1*01	1076
2648	VH3-23_IGHD3-10*01>3'_IGHJ5*01	1678	gnl|Fabrus|A2_IGKJ1*01	1076
2649	VH3-23_IGHD3-16*01>1'_IGHJ5*01	1679	gnl|Fabrus|A2_IGKJ1*01	1076
2650	VH3-23_IGHD3-16*01>3'_IGHJ5*01	1680	gnl|Fabrus|A2_IGKJ1*01	1076
2651	VH3-23_IGHD3-22*01>1'_IGHJ5*01	1681	gnl|Fabrus|A2_IGKJ1*01	1076
2652	VH3-23_IGHD4-4*01 (1) >1'_IGHJ5*01	1682	gnl|Fabrus|A2_IGKJ1*01	1076
2653	VH3-23_IGHD4-4*01 (1) >3'_IGHJ5*01	1683	gnl|Fabrus|A2_IGKJ1*01	1076
2654	VH3-23_IGHD4-11*01 (1) >1'_IGHJ5*01	1684	gnl|Fabrus|A2_IGKJ1*01	1076
2655	VH3-23_IGHD4-11*01 (1) >3'_IGHJ5*01	1685	gnl|Fabrus|A2_IGKJ1*01	1076
2656	VH3-23_IGHD4-17*01>1'_IGHJ5*01	1686	gnl|Fabrus|A2_IGKJ1*01	1076
2657	VH3-23_IGHD4-17*01>3'_IGHJ5*01	1687	gnl|Fabrus|A2_IGKJ1*01	1076
2658	VH3-23_IGHD4-23*01>1'_IGHJ5*01	1688	gnl|Fabrus|A2_IGKJ1*01	1076
2659	VH3-23_IGHD4-23*01>3'_IGHJ5*01	1689	gnl|Fabrus|A2_IGKJ1*01	1076
2660	VH3-23_IGHD5-5*01 (2) >1'_IGHJ5*01	1690	gnl|Fabrus|A2_IGKJ1*01	1076
2661	VH3-23_IGHD5-5*01 (2) >3'_IGHJ5*01	1691	gnl|Fabrus|A2_IGKJ1*01	1076
2662	VH3-23_IGHD5-12*01>1'_IGHJ5*01	1692	gnl|Fabrus|A2_IGKJ1*01	1076
2663	VH3-23_IGHD5-12*01>3'_IGHJ5*01	1693	gnl|Fabrus|A2_IGKJ1*01	1076
2664	VH3-23_IGHD5-18*01 (2) >1'_IGHJ5*01	1694	gnl|Fabrus|A2_IGKJ1*01	1076
2665	VH3-23_IGHD5-18*01 (2) >3'_IGHJ5*01	1695	gnl|Fabrus|A2_IGKJ1*01	1076
2666	VH3-23_IGHD5-24*01>1'_IGHJ5*01	1696	gnl|Fabrus|A2_IGKJ1*01	1076

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2667	VH3-23_IGHD5-24*01>3'_IGHJ5*01	1697	gnl|Fabrus|A2_IGKJ1*01	1076
2668	VH3-23_IGHD6-6*01>1'_IGHJ5*01	1698	gnl|Fabrus|A2_IGKJ1*01	1076
2669	VH3-23_IGHD6-6*01>2'_IGHJ5*01	1699	gnl|Fabrus|A2_IGKJ1*01	1076
2670	VH3-23_IGHD6-6*01>3'_IGHJ5*01	1700	gnl|Fabrus|A2_IGKJ1*01	1076
2671	VH3-23_IGHD1-1*01>1_IGHJ6*01	1711	gnl|Fabrus|L2_IGKJ1*01	1090
2672	VH3-23_IGHD1-1*01>2_IGHJ6*01	1712	gnl|Fabrus|L2_IGKJ1*01	1090
2673	VH3-23_IGHD1-1*01>3_IGHJ6*01	1713	gnl|Fabrus|L2_IGKJ1*01	1090
2674	VH3-23_IGHD1-7*01>1_IGHJ6*01	1714	gnl|Fabrus|L2_IGKJ1*01	1090
2675	VH3-23_IGHD1-7*01>3_IGHJ6*01	1715	gnl|Fabrus|L2_IGKJ1*01	1090
2676	VH3-23_IGHD1-14*01>1_IGHJ6*01	1716	gnl|Fabrus|L2_IGKJ1*01	1090
2677	VH3-23_IGHD1-14*01>3_IGHJ6*01	1717	gnl|Fabrus|L2_IGKJ1*01	1090
2678	VH3-23_IGHD1-20*01>1_IGHJ6*01	1718	gnl|Fabrus|L2_IGKJ1*01	1090
2679	VH3-23_IGHD1-20*01>3_IGHJ6*01	1719	gnl|Fabrus|L2_IGKJ1*01	1090
2680	VH3-23_IGHD1-26*01>1_IGHJ6*01	1720	gnl|Fabrus|L2_IGKJ1*01	1090
2681	VH3-23_IGHD1-26*01>3_IGHJ6*01	1721	gnl|Fabrus|L2_IGKJ1*01	1090
2682	VH3-23_IGHD2-2*01>2_IGHJ6*01	1722	gnl|Fabrus|L2_IGKJ1*01	1090
2683	VH3-23_IGHD2-2*01>3_IGHJ6*01	1723	gnl|Fabrus|L2_IGKJ1*01	1090
2684	VH3-23_IGHD2-8*01>2_IGHJ6*01	1724	gnl|Fabrus|L2_IGKJ1*01	1090
2685	VH3-23_IGHD2-8*01>3_IGHJ6*01	1725	gnl|Fabrus|L2_IGKJ1*01	1090
2686	VH3-23_IGHD2-15*01>2_IGHJ6*01	1726	gnl|Fabrus|L2_IGKJ1*01	1090
2687	VH3-23_IGHD2-15*01>3_IGHJ6*01	1727	gnl|Fabrus|L2_IGKJ1*01	1090
2688	VH3-23_IGHD2-21*01>2_IGHJ6*01	1728	gnl|Fabrus|L2_IGKJ1*01	1090
2689	VH3-23_IGHD2-21*01>3_IGHJ6*01	1729	gnl|Fabrus|L2_IGKJ1*01	1090
2690	VH3-23_IGHD3-3*01>1_IGHJ6*01	1730	gnl|Fabrus|L2_IGKJ1*01	1090
2691	VH3-23_IGHD3-3*01>2_IGHJ6*01	1731	gnl|Fabrus|L2_IGKJ1*01	1090
2692	VH3-23_IGHD3-3*01>3_IGHJ6*01	1732	gnl|Fabrus|L2_IGKJ1*01	1090
2693	VH3-23_IGHD3-9*01>2_IGHJ6*01	1733	gnl|Fabrus|L2_IGKJ1*01	1090
2694	VH3-23_IGHD3-10*01>2_IGHJ6*01	1734	gnl|Fabrus|L2_IGKJ1*01	1090
2695	VH3-23_IGHD3-10*01>3_IGHJ6*01	1735	gnl|Fabrus|L2_IGKJ1*01	1090
2696	VH3-23_IGHD3-16*01>2_IGHJ6*01	1736	gnl|Fabrus|L2_IGKJ1*01	1090
2697	VH3-23_IGHD3-16*01>3_IGHJ6*01	1737	gnl|Fabrus|L2_IGKJ1*01	1090
2698	VH3-23_IGHD3-22*01>2_IGHJ6*01	1738	gnl|Fabrus|L2_IGKJ1*01	1090
2699	VH3-23_IGHD3-22*01>3_IGHJ6*01	1739	gnl|Fabrus|L2_IGKJ1*01	1090
2700	VH3-23_IGHD4-4*01 (1) >2_IGHJ6*01	1740	gnl|Fabrus|L2_IGKJ1*01	1090
2701	VH3-23_IGHD4-4*01 (1) >3_IGHJ6*01	1741	gnl|Fabrus|L2_IGKJ1*01	1090
2702	VH3-23_IGHD4-11*01 (1) >2_IGHJ6*01	1742	gnl|Fabrus|L2_IGKJ1*01	1090
2703	VH3-23_IGHD4-11*01 (1) >3_IGHJ6*01	1743	gnl|Fabrus|L2_IGKJ1*01	1090
2704	VH3-23_IGHD4-17*01>2_IGHJ6*01	1744	gnl|Fabrus|L2_IGKJ1*01	1090
2705	VH3-23_IGHD4-17*01>3_IGHJ6*01	1745	gnl|Fabrus|L2_IGKJ1*01	1090
2706	VH3-23_IGHD4-23*01>2_IGHJ6*01	1746	gnl|Fabrus|L2_IGKJ1*01	1090
2707	VH3-23_IGHD4-23*01>3_IGHJ6*01	1747	gnl|Fabrus|L2_IGKJ1*01	1090
2708	VH3-23_IGHD5-5*01 (2) >1_IGHJ6*01	1748	gnl|Fabrus|L2_IGKJ1*01	1090

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2709	VH3-23_IGHD5-5*01 (2) >2_IGHJ6*01	1749	gnl|Fabrus|L2_IGKJ1*01	1090
2710	VH3-23_IGHD5-5*01 (2) >3_IGHJ6*01	1750	gnl|Fabrus|L2_IGKJ1*01	1090
2711	VH3-23_IGHD5-12*01>1_IGHJ6*01	1751	gnl|Fabrus|L2_IGKJ1*01	1090
2712	VH3-23_IGHD5-12*01>3_IGHJ6*01	1752	gnl|Fabrus|L2_IGKJ1*01	1090
2713	VH3-23_IGHD5-18*01 (2) >1_IGHJ6*01	1753	gnl|Fabrus|L2_IGKJ1*01	1090
2714	VH3-23_IGHD5-18*01 (2) >2_IGHJ6*01	1754	gnl|Fabrus|L2_IGKJ1*01	1090
2715	VH3-23_IGHD5-18*01 (2) >3_IGHJ6*01	1755	gnl|Fabrus|L2_IGKJ1*01	1090
2716	VH3-23_IGHD5-24*01>1_IGHJ6*01	1756	gnl|Fabrus|L2_IGKJ1*01	1090
2717	VH3-23_IGHD5-24*01>3_IGHJ6*01	1757	gnl|Fabrus|L2_IGKJ1*01	1090
2718	VH3-23_IGHD6-6*01>1_IGHJ6*01	1758	gnl|Fabrus|L2_IGKJ1*01	1090
2719	VH3-23_IGHD1-1*01>1'_IGHJ6*01	1768	gnl|Fabrus|L2_IGKJ1*01	1090
2720	VH3-23_IGHD1-1*01>2'_IGHJ6*01	1769	gnl|Fabrus|L2_IGKJ1*01	1090
2721	VH3-23_IGHD1-1*01>3'_IGHJ6*01	1770	gnl|Fabrus|L2_IGKJ1*01	1090
2722	VH3-23_IGHD1-7*01>1'_IGHJ6*01	1771	gnl|Fabrus|L2_IGKJ1*01	1090
2723	VH3-23_IGHD1-7*01>3'_IGHJ6*01	1772	gnl|Fabrus|L2_IGKJ1*01	1090
2724	VH3-23_IGHD1-14*01>1'_IGHJ6*01	1773	gnl|Fabrus|L2_IGKJ1*01	1090
2725	VH3-23_IGHD1-14*01>2'_IGHJ6*01	1774	gnl|Fabrus|L2_IGKJ1*01	1090
2726	VH3-23_IGHD1-14*01>3'_IGHJ6*01	1775	gnl|Fabrus|L2_IGKJ1*01	1090
2727	VH3-23_IGHD1-20*01>1'_IGHJ6*01	1776	gnl|Fabrus|L2_IGKJ1*01	1090
2728	VH3-23_IGHD1-20*01>2'_IGHJ6*01	1777	gnl|Fabrus|L2_IGKJ1*01	1090
2729	VH3-23_IGHD1-20*01>3'_IGHJ6*01	1778	gnl|Fabrus|L2_IGKJ1*01	1090
2730	VH3-23_IGHD1-26*01>1'_IGHJ6*01	1779	gnl|Fabrus|L2_IGKJ1*01	1090
2731	VH3-23_IGHD1-26*01>1_IGHJ6*01_B	1780	gnl|Fabrus|L2_IGKJ1*01	1090
2732	VH3-23_IGHD2-2*01>2_IGHJ6*01_B	1781	gnl|Fabrus|L2_IGKJ1*01	1090
2733	VH3-23_IGHD2-2*01>3'_IGHJ6*01	1782	gnl|Fabrus|L2_IGKJ1*01	1090
2734	VH3-23_IGHD2-8*01>1'_IGHJ6*01	1783	gnl|Fabrus|L2_IGKJ1*01	1090
2735	VH3-23_IGHD2-15*01>1'_IGHJ6*01	1784	gnl|Fabrus|L2_IGKJ1*01	1090
2736	VH3-23_IGHD2-15*01>3'_IGHJ6*01	1785	gnl|Fabrus|L2_IGKJ1*01	1090
2737	VH3-23_IGHD2-21*01>1'_IGHJ6*01	1786	gnl|Fabrus|L2_IGKJ1*01	1090
2738	VH3-23_IGHD2-21*01>3'_IGHJ6*01	1787	gnl|Fabrus|L2_IGKJ1*01	1090
2739	VH3-23_IGHD3-3*01>1'_IGHJ6*01	1788	gnl|Fabrus|L2_IGKJ1*01	1090
2740	VH3-23_IGHD3-3*01>3'_IGHJ6*01	1789	gnl|Fabrus|L2_IGKJ1*01	1090
2741	VH3-23_IGHD3-9*01>1'_IGHJ6*01	1790	gnl|Fabrus|L2_IGKJ1*01	1090
2742	VH3-23_IGHD3-9*01>3'_IGHJ6*01	1791	gnl|Fabrus|L2_IGKJ1*01	1090
2743	VH3-23_IGHD3-10*01>1'_IGHJ6*01	1792	gnl|Fabrus|L2_IGKJ1*01	1090
2744	VH3-23_IGHD3-10*01>3'_IGHJ6*01	1793	gnl|Fabrus|L2_IGKJ1*01	1090
2745	VH3-23_IGHD3-16*01>1'_IGHJ6*01	1794	gnl|Fabrus|L2_IGKJ1*01	1090
2746	VH3-23_IGHD3-16*01>3'_IGHJ6*01	1795	gnl|Fabrus|L2_IGKJ1*01	1090
2747	VH3-23_IGHD3-22*01>1'_IGHJ6*01	1796	gnl|Fabrus|L2_IGKJ1*01	1090
2748	VH3-23_IGHD4-4*01 (1) >1'_IGHJ6*01	1797	gnl|Fabrus|L2_IGKJ1*01	1090
2749	VH3-23_IGHD4-4*01 (1) >3'_IGHJ6*01	1798	gnl|Fabrus|L2_IGKJ1*01	1090
2750	VH3-23_IGHD4-11*01 (1) >1'_IGHJ6*01	1799	gnl|Fabrus|L2_IGKJ1*01	1090

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2751	VH3-23_IGHD4-11*01 (1) >3'_IGHJ6*01	1800	gnl|Fabrus|L2_IGKJ1*01	1090
2752	VH3-23_IGHD4-17*01>1'_IGHJ6*01	1801	gnl|Fabrus|L2_IGKJ1*01	1090
2753	VH3-23_IGHD4-17*01>3'_IGHJ6*01	1802	gnl|Fabrus|L2_IGKJ1*01	1090
2754	VH3-23_IGHD4-23*01>1'_IGHJ6*01	1803	gnl|Fabrus|L2_IGKJ1*01	1090
2755	VH3-23_IGHD4-23*01>3'_IGHJ6*01	1804	gnl|Fabrus|L2_IGKJ1*01	1090
2756	VH3-23_IGHD5-5*01 (2) >1'_IGHJ6*01	1805	gnl|Fabrus|L2_IGKJ1*01	1090
2757	VH3-23_IGHD5-5*01 (2) >3'_IGHJ6*01	1806	gnl|Fabrus|L2_IGKJ1*01	1090
2758	VH3-23_IGHD5-12*01>1'_IGHJ6*01	1807	gnl|Fabrus|L2_IGKJ1*01	1090
2759	VH3-23_IGHD5-12*01>3'_IGHJ6*01	1808	gnl|Fabrus|L2_IGKJ1*01	1090
2760	VH3-23_IGHD5-18*01 (2) >1'_IGHJ6*01	1809	gnl|Fabrus|L2_IGKJ1*01	1090
2761	VH3-23_IGHD5-18*01 (2) >3'_IGHJ6*01	1810	gnl|Fabrus|L2_IGKJ1*01	1090
2762	VH3-23_IGHD5-24*01>1'_IGHJ6*01	1811	gnl|Fabrus|L2_IGKJ1*01	1090
2763	VH3-23_IGHD5-24*01>3'_IGHJ6*01	1812	gnl|Fabrus|L2_IGKJ1*01	1090
2764	VH3-23_IGHD6-6*01>1'_IGHJ6*01	1813	gnl|Fabrus|L2_IGKJ1*01	1090
2765	VH3-23_IGHD6-6*01>2'_IGHJ6*01	1814	gnl|Fabrus|L2_IGKJ1*01	1090
2766	VH3-23_IGHD6-6*01>3'_IGHJ6*01	1815	gnl|Fabrus|L2_IGKJ1*01	1090
2767	VH3-23_IGHD1-1*01>1_IGHJ6*01	1711	gnl|Fabrus|L6_IGKJ1*01	1097
2768	VH3-23_IGHD1-1*01>2_IGHJ6*01	1712	gnl|Fabrus|L6_IGKJ1*01	1097
2769	VH3-23_IGHD1-1*01>3_IGHJ6*01	1713	gnl|Fabrus|L6_IGKJ1*01	1097
2770	VH3-23_IGHD1-7*01>1_IGHJ6*01	1714	gnl|Fabrus|L6_IGKJ1*01	1097
2771	VH3-23_IGHD1-7*01>3_IGHJ6*01	1715	gnl|Fabrus|L6_IGKJ1*01	1097
2772	VH3-23_IGHD1-14*01>1_IGHJ6*01	1716	gnl|Fabrus|L6_IGKJ1*01	1097
2773	VH3-23_IGHD1-14*01>3_IGHJ6*01	1717	gnl|Fabrus|L6_IGKJ1*01	1097
2774	VH3-23_IGHD1-20*01>1_IGHJ6*01	1718	gnl|Fabrus|L6_IGKJ1*01	1097
2775	VH3-23_IGHD1-20*01>3_IGHJ6*01	1719	gnl|Fabrus|L6_IGKJ1*01	1097
2776	VH3-23_IGHD1-26*01>1_IGHJ6*01	1720	gnl|Fabrus|L6_IGKJ1*01	1097
2777	VH3-23_IGHD1-26*01>3_IGHJ6*01	1721	gnl|Fabrus|L6_IGKJ1*01	1097
2778	VH3-23_IGHD2-2*01>2_IGHJ6*01	1722	gnl|Fabrus|L6_IGKJ1*01	1097
2779	VH3-23_IGHD2-2*01>3_IGHJ6*01	1723	gnl|Fabrus|L6_IGKJ1*01	1097
2780	VH3-23_IGHD2-8*01>2_IGHJ6*01	1724	gnl|Fabrus|L6_IGKJ1*01	1097
2781	VH3-23_IGHD2-8*01>3_IGHJ6*01	1725	gnl|Fabrus|L6_IGKJ1*01	1097
2782	VH3-23_IGHD2-15*01>2_IGHJ6*01	1726	gnl|Fabrus|L6_IGKJ1*01	1097
2783	VH3-23_IGHD2-15*01>3_IGHJ6*01	1727	gnl|Fabrus|L6_IGKJ1*01	1097
2784	VH3-23_IGHD2-21*01>2_IGHJ6*01	1728	gnl|Fabrus|L6_IGKJ1*01	1097
2785	VH3-23_IGHD2-21*01>3_IGHJ6*01	1729	gnl|Fabrus|L6_IGKJ1*01	1097
2786	VH3-23_IGHD3-3*01>1_IGHJ6*01	1730	gnl|Fabrus|L6_IGKJ1*01	1097
2787	VH3-23_IGHD3-3*01>2_IGHJ6*01	1731	gnl|Fabrus|L6_IGKJ1*01	1097
2788	VH3-23_IGHD3-3*01>3_IGHJ6*01	1732	gnl|Fabrus|L6_IGKJ1*01	1097
2789	VH3-23_IGHD3-9*01>2_IGHJ6*01	1733	gnl|Fabrus|L6_IGKJ1*01	1097
2790	VH3-23_IGHD3-10*01>2_IGHJ6*01	1734	gnl|Fabrus|L6_IGKJ1*01	1097
2791	VH3-23_IGHD3-10*01>3_IGHJ6*01	1735	gnl|Fabrus|L6_IGKJ1*01	1097
2792	VH3-23_IGHD3-16*01>2_IGHJ6*01	1736	gnl|Fabrus|L6_IGKJ1*01	1097

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2793	VH3-23_IGHD3-16*01>3_IGHJ6*01	1737	gnl|Fabrus|L6_IGKJ1*01	1097
2794	VH3-23_IGHD3-22*01>2_IGHJ6*01	1738	gnl|Fabrus|L6_IGKJ1*01	1097
2795	VH3-23_IGHD3-22*01>3_IGHJ6*01	1739	gnl|Fabrus|L6_IGKJ1*01	1097
2796	VH3-23_IGHD4-4*01 (1) >2_IGHJ6*01	1740	gnl|Fabrus|L6_IGKJ1*01	1097
2797	VH3-23_IGHD4-4*01 (1) >3_IGHJ6*01	1741	gnl|Fabrus|L6_IGKJ1*01	1097
2798	VH3-23_IGHD4-11*01 (1) >2_IGHJ6*01	1742	gnl|Fabrus|L6_IGKJ1*01	1097
2799	VH3-23_IGHD4-11*01 (1) >3_IGHJ6*01	1743	gnl|Fabrus|L6_IGKJ1*01	1097
2800	VH3-23_IGHD4-17*01>2_IGHJ6*01	1744	gnl|Fabrus|L6_IGKJ1*01	1097
2801	VH3-23_IGHD4-17*01>3_IGHJ6*01	1745	gnl|Fabrus|L6_IGKJ1*01	1097
2802	VH3-23_IGHD4-23*01>2_IGHJ6*01	1746	gnl|Fabrus|L6_IGKJ1*01	1097
2803	VH3-23_IGHD4-23*01>3_IGHJ6*01	1747	gnl|Fabrus|L6_IGKJ1*01	1097
2804	VH3-23_IGHD5-5*01 (2) >1_IGHJ6*01	1748	gnl|Fabrus|L6_IGKJ1*01	1097
2805	VH3-23_IGHD5-5*01 (2) >2_IGHJ6*01	1749	gnl|Fabrus|L6_IGKJ1*01	1097
2806	VH3-23_IGHD5-5*01 (2) >3_IGHJ6*01	1750	gnl|Fabrus|L6_IGKJ1*01	1097
2807	VH3-23_IGHD5-12*01>1_IGHJ6*01	1751	gnl|Fabrus|L6_IGKJ1*01	1097
2808	VH3-23_IGHD5-12*01>3_IGHJ6*01	1752	gnl|Fabrus|L6_IGKJ1*01	1097
2809	VH3-23_IGHD5-18*01 (2) >1_IGHJ6*01	1753	gnl|Fabrus|L6_IGKJ1*01	1097
2810	VH3-23_IGHD5-18*01 (2) >2_IGHJ6*01	1754	gnl|Fabrus|L6_IGKJ1*01	1097
2811	VH3-23_IGHD5-18*01 (2) >3_IGHJ6*01	1755	gnl|Fabrus|L6_IGKJ1*01	1097
2812	VH3-23_IGHD5-24*01>1_IGHJ6*01	1756	gnl|Fabrus|L6_IGKJ1*01	1097
2813	VH3-23_IGHD5-24*01>3_IGHJ6*01	1757	gnl|Fabrus|L6_IGKJ1*01	1097
2814	VH3-23_IGHD6-6*01>1_IGHJ6*01	1758	gnl|Fabrus|L6_IGKJ1*01	1097
2815	VH3-23_IGHD1-1*01>1'_IGHJ6*01	1768	gnl|Fabrus|L6_IGKJ1*01	1097
2816	VH3-23_IGHD1-1*01>2'_IGHJ6*01	1769	gnl|Fabrus|L6_IGKJ1*01	1097
2817	VH3-23_IGHD1-1*01>3'_IGHJ6*01	1770	gnl|Fabrus|L6_IGKJ1*01	1097
2818	VH3-23_IGHD1-7*01>1'_IGHJ6*01	1771	gnl|Fabrus|L6_IGKJ1*01	1097
2819	VH3-23_IGHD1-7*01>3'_IGHJ6*01	1772	gnl|Fabrus|L6_IGKJ1*01	1097
2820	VH3-23_IGHD1-14*01>1'_IGHJ6*01	1773	gnl|Fabrus|L6_IGKJ1*01	1097
2821	VH3-23_IGHD1-14*01>2'_IGHJ6*01	1774	gnl|Fabrus|L6_IGKJ1*01	1097
2822	VH3-23_IGHD1-14*01>3'_IGHJ6*01	1775	gnl|Fabrus|L6_IGKJ1*01	1097
2823	VH3-23_IGHD1-20*01>1'_IGHJ6*01	1776	gnl|Fabrus|L6_IGKJ1*01	1097
2824	VH3-23_IGHD1-20*01>2'_IGHJ6*01	1777	gnl|Fabrus|L6_IGKJ1*01	1097
2825	VH3-23_IGHD1-20*01>3'_IGHJ6*01	1778	gnl|Fabrus|L6_IGKJ1*01	1097
2826	VH3-23_IGHD1-26*01>1'_IGHJ6*01	1779	gnl|Fabrus|L6_IGKJ1*01	1097
2827	VH3-23_IGHD1-26*01>1_IGHJ6*01_B	1780	gnl|Fabrus|L6_IGKJ1*01	1097
2828	VH3-23_IGHD2-2*01>2_IGHJ6*01_B	1781	gnl|Fabrus|L6_IGKJ1*01	1097
2829	VH3-23_IGHD2-2*01>3'_IGHJ6*01	1782	gnl|Fabrus|L6_IGKJ1*01	1097
2830	VH3-23_IGHD2-8*01>1'_IGHJ6*01	1783	gnl|Fabrus|L6_IGKJ1*01	1097
2831	VH3-23_IGHD2-15*01>1'_IGHJ6*01	1784	gnl|Fabrus|L6_IGKJ1*01	1097
2832	VH3-23_IGHD2-15*01>3'_IGHJ6*01	1785	gnl|Fabrus|L6_IGKJ1*01	1097
2833	VH3-23_IGHD2-21*01>1'_IGHJ6*01	1786	gnl|Fabrus|L6_IGKJ1*01	1097
2834	VH3-23_IGHD2-21*01>3'_IGHJ6*01	1787	gnl|Fabrus|L6_IGKJ1*01	1097

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2835	VH3-23_IGHD3-3*01>1'_IGHJ6*01	1788	gnl|Fabrus|L6_IGKJ1*01	1097
2836	VH3-23_IGHD3-3*01>3'_IGHJ6*01	1789	gnl|Fabrus|L6_IGKJ1*01	1097
2837	VH3-23_IGHD3-9*01>1'_IGHJ6*01	1790	gnl|Fabrus|L6_IGKJ1*01	1097
2838	VH3-23_IGHD3-9*01>3'_IGHJ6*01	1791	gnl|Fabrus|L6_IGKJ1*01	1097
2839	VH3-23_IGHD3-10*01>1'_IGHJ6*01	1792	gnl|Fabrus|L6_IGKJ1*01	1097
2840	VH3-23_IGHD3-10*01>3'_IGHJ6*01	1793	gnl|Fabrus|L6_IGKJ1*01	1097
2841	VH3-23_IGHD3-16*01>1'_IGHJ6*01	1794	gnl|Fabrus|L6_IGKJ1*01	1097
2842	VH3-23_IGHD3-16*01>3'_IGHJ6*01	1795	gnl|Fabrus|L6_IGKJ1*01	1097
2843	VH3-23_IGHD3-22*01>1'_IGHJ6*01	1796	gnl|Fabrus|L6_IGKJ1*01	1097
2844	VH3-23_IGHD4-4*01 (1) >1'_IGHJ6*01	1797	gnl|Fabrus|L6_IGKJ1*01	1097
2845	VH3-23_IGHD4-4*01 (1) >3'_IGHJ6*01	1798	gnl|Fabrus|L6_IGKJ1*01	1097
2846	VH3-23_IGHD4-11*01 (1) >1'_IGHJ6*01	1799	gnl|Fabrus|L6_IGKJ1*01	1097
2847	VH3-23_IGHD4-11*01 (1) >3'_IGHJ6*01	1800	gnl|Fabrus|L6_IGKJ1*01	1097
2848	VH3-23_IGHD4-17*01>1'_IGHJ6*01	1801	gnl|Fabrus|L6_IGKJ1*01	1097
2849	VH3-23_IGHD4-17*01>3'_IGHJ6*01	1802	gnl|Fabrus|L6_IGKJ1*01	1097
2850	VH3-23_IGHD4-23*01>1'_IGHJ6*01	1803	gnl|Fabrus|L6_IGKJ1*01	1097
2851	VH3-23_IGHD4-23*01>3'_IGHJ6*01	1804	gnl|Fabrus|L6_IGKJ1*01	1097
2852	VH3-23_IGHD5-5*01 (2) >1'_IGHJ6*01	1805	gnl|Fabrus|L6_IGKJ1*01	1097
2853	VH3-23_IGHD5-5*01 (2) >3'_IGHJ6*01	1806	gnl|Fabrus|L6_IGKJ1*01	1097
2854	VH3-23_IGHD5-12*01>1'_IGHJ6*01	1807	gnl|Fabrus|L6_IGKJ1*01	1097
2855	VH3-23_IGHD5-12*01>3'_IGHJ6*01	1808	gnl|Fabrus|L6_IGKJ1*01	1097
2856	VH3-23_IGHD5-18*01 (2) >1'_IGHJ6*01	1809	gnl|Fabrus|L6_IGKJ1*01	1097
2857	VH3-23_IGHD5-18*01 (2) >3'_IGHJ6*01	1810	gnl|Fabrus|L6_IGKJ1*01	1097
2858	VH3-23_IGHD5-24*01>1'_IGHJ6*01	1811	gnl|Fabrus|L6_IGKJ1*01	1097
2859	VH3-23_IGHD5-24*01>3'_IGHJ6*01	1812	gnl|Fabrus|L6_IGKJ1*01	1097
2860	VH3-23_IGHD6-6*01>1'_IGHJ6*01	1813	gnl|Fabrus|L6_IGKJ1*01	1097
2861	VH3-23_IGHD6-6*01>2'_IGHJ6*01	1814	gnl|Fabrus|L6_IGKJ1*01	1097
2862	VH3-23_IGHD6-6*01>3'_IGHJ6*01	1815	gnl|Fabrus|L6_IGKJ1*01	1097
2863	VH3-23_IGHD1-1*01>1_IGHJ5*01	1596	gnl|Fabrus|L25_IGKJ1*01	1093
2864	VH3-23_IGHD1-1*01>2_IGHJ5*01	1597	gnl|Fabrus|L25_IGKJ1*01	1093
2865	VH3-23_IGHD1-1*01>3_IGHJ5*01	1598	gnl|Fabrus|L25_IGKJ1*01	1093
2866	VH3-23_IGHD1-7*01>1_IGHJ5*01	1599	gnl|Fabrus|L25_IGKJ1*01	1093
2867	VH3-23_IGHD1-7*01>3_IGHJ5*01	1600	gnl|Fabrus|L25_IGKJ1*01	1093
2868	VH3-23_IGHD1-14*01>1_IGHJ5*01	1601	gnl|Fabrus|L25_IGKJ1*01	1093
2869	VH3-23_IGHD1-14*01>3_IGHJ5*01	1602	gnl|Fabrus|L25_IGKJ1*01	1093
2870	VH3-23_IGHD1-20*01>1_IGHJ5*01	1603	gnl|Fabrus|L25_IGKJ1*01	1093
2871	VH3-23_IGHD1-20*01>3_IGHJ5*01	1604	gnl|Fabrus|L25_IGKJ1*01	1093
2872	VH3-23_IGHD1-26*01>1_IGHJ5*01	1605	gnl|Fabrus|L25_IGKJ1*01	1093
2873	VH3-23_IGHD1-26*01>3_IGHJ5*01	1606	gnl|Fabrus|L25_IGKJ1*01	1093
2874	VH3-23_IGHD2-2*01>2_IGHJ5*01	1607	gnl|Fabrus|L25_IGKJ1*01	1093
2875	VH3-23_IGHD2-2*01>3_IGHJ5*01	1608	gnl|Fabrus|L25_IGKJ1*01	1093
2876	VH3-23_IGHD2-8*01>2_IGHJ5*01	1609	gnl|Fabrus|L25_IGKJ1*01	1093

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2877	VH3-23_IGHD2-8*01>3_IGHJ5*01	1610	gnl|Fabrus|L25_IGKJ1*01	1093
2878	VH3-23_IGHD2-15*01>2_IGHJ5*01	1611	gnl|Fabrus|L25_IGKJ1*01	1093
2879	VH3-23_IGHD2-15*01>3_IGHJ5*01	1612	gnl|Fabrus|L25_IGKJ1*01	1093
2880	VH3-23_IGHD2-21*01>2_IGHJ5*01	1613	gnl|Fabrus|L25_IGKJ1*01	1093
2881	VH3-23_IGHD2-21*01>3_IGHJ5*01	1614	gnl|Fabrus|L25_IGKJ1*01	1093
2882	VH3-23_IGHD3-3*01>1_IGHJ5*01	1615	gnl|Fabrus|L25_IGKJ1*01	1093
2883	VH3-23_IGHD3-3*01>2_IGHJ5*01	1616	gnl|Fabrus|L25_IGKJ1*01	1093
2884	VH3-23_IGHD3-3*01>3_IGHJ5*01	1617	gnl|Fabrus|L25_IGKJ1*01	1093
2885	VH3-23_IGHD3-9*01>2_IGHJ5*01	1618	gnl|Fabrus|L25_IGKJ1*01	1093
2886	VH3-23_IGHD3-10*01>2_IGHJ5*01	1619	gnl|Fabrus|L25_IGKJ1*01	1093
2887	VH3-23_IGHD3-10*01>3_IGHJ5*01	1620	gnl|Fabrus|L25_IGKJ1*01	1093
2888	VH3-23_IGHD3-16*01>2_IGHJ5*01	1621	gnl|Fabrus|L25_IGKJ1*01	1093
2889	VH3-23_IGHD3-16*01>3_IGHJ5*01	1622	gnl|Fabrus|L25_IGKJ1*01	1093
2890	VH3-23_IGHD3-22*01>2_IGHJ5*01	1623	gnl|Fabrus|L25_IGKJ1*01	1093
2891	VH3-23_IGHD3-22*01>3_IGHJ5*01	1624	gnl|Fabrus|L25_IGKJ1*01	1093
2892	VH3-23_IGHD4-4*01 (1) >2_IGHJ5*01	1625	gnl|Fabrus|L25_IGKJ1*01	1093
2893	VH3-23_IGHD4-4*01 (1) >3_IGHJ5*01	1626	gnl|Fabrus|L25_IGKJ1*01	1093
2894	VH3-23_IGHD4-11*01 (1) >2_IGHJ5*01	1627	gnl|Fabrus|L25_IGKJ1*01	1093
2895	VH3-23_IGHD4-11*01 (1) >3_IGHJ5*01	1628	gnl|Fabrus|L25_IGKJ1*01	1093
2896	VH3-23_IGHD4-17*01>2_IGHJ5*01	1629	gnl|Fabrus|L25_IGKJ1*01	1093
2897	VH3-23_IGHD4-17*01>3_IGHJ5*01	1630	gnl|Fabrus|L25_IGKJ1*01	1093
2898	VH3-23_IGHD4-23*01>2_IGHJ5*01	1631	gnl|Fabrus|L25_IGKJ1*01	1093
2899	VH3-23_IGHD4-23*01>3_IGHJ5*01	1632	gnl|Fabrus|L25_IGKJ1*01	1093
2900	VH3-23_IGHD5-5*01 (2) >1_IGHJ5*01	1633	gnl|Fabrus|L25_IGKJ1*01	1093
2901	VH3-23_IGHD5-5*01 (2) >2_IGHJ5*01	1634	gnl|Fabrus|L25_IGKJ1*01	1093
2902	VH3-23_IGHD5-5*01 (2) >3_IGHJ5*01	1635	gnl|Fabrus|L25_IGKJ1*01	1093
2903	VH3-23_IGHD5-12*01>1_IGHJ5*01	1636	gnl|Fabrus|L25_IGKJ1*01	1093
2904	VH3-23_IGHD5-12*01>3_IGHJ5*01	1637	gnl|Fabrus|L25_IGKJ1*01	1093
2905	VH3-23_IGHD5-18*01 (2) >1_IGHJ5*01	1638	gnl|Fabrus|L25_IGKJ1*01	1093
2906	VH3-23_IGHD5-18*01 (2) >2_IGHJ5*01	1639	gnl|Fabrus|L25_IGKJ1*01	1093
2907	VH3-23_IGHD5-18*01 (2) >3_IGHJ5*01	1640	gnl|Fabrus|L25_IGKJ1*01	1093
2908	VH3-23_IGHD5-24*01>1_IGHJ5*01	1641	gnl|Fabrus|L25_IGKJ1*01	1093
2909	VH3-23_IGHD5-24*01>3_IGHJ5*01	1642	gnl|Fabrus|L25_IGKJ1*01	1093
2910	VH3-23_IGHD6-6*01>1_IGHJ5*01	1643	gnl|Fabrus|L25_IGKJ1*01	1093
2911	VH3-23_IGHD1-1*01>1'_IGHJ5*01	1653	gnl|Fabrus|L25_IGKJ1*01	1093
2912	VH3-23_IGHD1-1*01>2'_IGHJ5*01	1654	gnl|Fabrus|L25_IGKJ1*01	1093
2913	VH3-23_IGHD1-1*01>3'_IGHJ5*01	1655	gnl|Fabrus|L25_IGKJ1*01	1093
2914	VH3-23_IGHD1-7*01>1'_IGHJ5*01	1656	gnl|Fabrus|L25_IGKJ1*01	1093
2915	VH3-23_IGHD1-7*01>3'_IGHJ5*01	1657	gnl|Fabrus|L25_IGKJ1*01	1093
2916	VH3-23_IGHD1-14*01>1'_IGHJ5*01	1658	gnl|Fabrus|L25_IGKJ1*01	1093
2917	VH3-23_IGHD1-14*01>2'_IGHJ5*01	1659	gnl|Fabrus|L25_IGKJ1*01	1093
2918	VH3-23_IGHD1-14*01>3'_IGHJ5*01	1660	gnl|Fabrus|L25_IGKJ1*01	1093

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2919	VH3-23_IGHD1-20*01>1'_IGHJ5*01	1661	gnl|Fabrus|L25_IGKJ1*01	1093
2920	VH3-23_IGHD1-20*01>2'_IGHJ5*01	1662	gnl|Fabrus|L25_IGKJ1*01	1093
2921	VH3-23_IGHD1-20*01>3'_IGHJ5*01	1663	gnl|Fabrus|L25_IGKJ1*01	1093
2922	VH3-23_IGHD1-26*01>1'_IGHJ5*01	1664	gnl|Fabrus|L25_IGKJ1*01	1093
2923	VH3-23_IGHD1-26*01>3'_IGHJ5*01	1665	gnl|Fabrus|L25_IGKJ1*01	1093
2924	VH3-23_IGHD2-2*01>1'_IGHJ5*01	1666	gnl|Fabrus|L25_IGKJ1*01	1093
2925	VH3-23_IGHD2-2*01>3'_IGHJ5*01	1667	gnl|Fabrus|L25_IGKJ1*01	1093
2926	VH3-23_IGHD2-8*01>1'_IGHJ5*01	1668	gnl|Fabrus|L25_IGKJ1*01	1093
2927	VH3-23_IGHD2-15*01>1'_IGHJ5*01	1669	gnl|Fabrus|L25_IGKJ1*01	1093
2928	VH3-23_IGHD2-15*01>3'_IGHJ5*01	1670	gnl|Fabrus|L25_IGKJ1*01	1093
2929	VH3-23_IGHD2-21*01>1'_IGHJ5*01	1671	gnl|Fabrus|L25_IGKJ1*01	1093
2930	VH3-23_IGHD2-21*01>3'_IGHJ5*01	1672	gnl|Fabrus|L25_IGKJ1*01	1093
2931	VH3-23_IGHD3-3*01>1'_IGHJ5*01	1673	gnl|Fabrus|L25_IGKJ1*01	1093
2932	VH3-23_IGHD3-3*01>3'_IGHJ5*01	1674	gnl|Fabrus|L25_IGKJ1*01	1093
2933	VH3-23_IGHD3-9*01>1'_IGHJ5*01	1675	gnl|Fabrus|L25_IGKJ1*01	1093
2934	VH3-23_IGHD3-9*01>3'_IGHJ5*01	1676	gnl|Fabrus|L25_IGKJ1*01	1093
2935	VH3-23_IGHD3-10*01>1'_IGHJ5*01	1677	gnl|Fabrus|L25_IGKJ1*01	1093
2936	VH3-23_IGHD3-10*01>3'_IGHJ5*01	1678	gnl|Fabrus|L25_IGKJ1*01	1093
2937	VH3-23_IGHD3-16*01>1'_IGHJ5*01	1679	gnl|Fabrus|L25_IGKJ1*01	1093
2938	VH3-23_IGHD3-16*01>3'_IGHJ5*01	1680	gnl|Fabrus|L25_IGKJ1*01	1093
2939	VH3-23_IGHD3-22*01>1'_IGHJ5*01	1681	gnl|Fabrus|L25_IGKJ1*01	1093
2940	VH3-23_IGHD4-4*01 (1) >1'_IGHJ5*01	1682	gnl|Fabrus|L25_IGKJ1*01	1093
2941	VH3-23_IGHD4-4*01 (1) >3'_IGHJ5*01	1683	gnl|Fabrus|L25_IGKJ1*01	1093
2942	VH3-23_IGHD4-11*01 (1) >1'_IGHJ5*01	1684	gnl|Fabrus|L25_IGKJ1*01	1093
2943	VH3-23_IGHD4-11*01 (1) >3'_IGHJ5*01	1685	gnl|Fabrus|L25_IGKJ1*01	1093
2944	VH3-23_IGHD4-17*01>1'_IGHJ5*01	1686	gnl|Fabrus|L25_IGKJ1*01	1093
2945	VH3-23_IGHD4-17*01>3'_IGHJ5*01	1687	gnl|Fabrus|L25_IGKJ1*01	1093
2946	VH3-23_IGHD4-23*01>1'_IGHJ5*01	1688	gnl|Fabrus|L25_IGKJ1*01	1093
2947	VH3-23_IGHD4-23*01>3'_IGHJ5*01	1689	gnl|Fabrus|L25_IGKJ1*01	1093
2948	VH3-23_IGHD5-5*01 (2) >1'_IGHJ5*01	1690	gnl|Fabrus|L25_IGKJ1*01	1093
2949	VH3-23_IGHD5-5*01 (2) >3'_IGHJ5*01	1691	gnl|Fabrus|L25_IGKJ1*01	1093
2950	VH3-23_IGHD5-12*01>1'_IGHJ5*01	1692	gnl|Fabrus|L25_IGKJ1*01	1093
2951	VH3-23_IGHD5-12*01>3'_IGHJ5*01	1693	gnl|Fabrus|L25_IGKJ1*01	1093
2952	VH3-23_IGHD5-18*01 (2) >1'_IGHJ5*01	1694	gnl|Fabrus|L25_IGKJ1*01	1093
2953	VH3-23_IGHD5-18*01 (2) >3'_IGHJ5*01	1695	gnl|Fabrus|L25_IGKJ1*01	1093
2954	VH3-23_IGHD5-24*01>1'_IGHJ5*01	1696	gnl|Fabrus|L25_IGKJ1*01	1093
2955	VH3-23_IGHD5-24*01>3'_IGHJ5*01	1697	gnl|Fabrus|L25_IGKJ1*01	1093
2956	VH3-23_IGHD6-6*01>1'_IGHJ5*01	1698	gnl|Fabrus|L25_IGKJ1*01	1093
2957	VH3-23_IGHD6-6*01>2'_IGHJ5*01	1699	gnl|Fabrus|L25_IGKJ1*01	1093
2958	VH3-23_IGHD6-6*01>3'_IGHJ5*01	1700	gnl|Fabrus|L25_IGKJ1*01	1093
2959	VH3-23_IGHD1-1*01>1_IGHJ5*01	1596	gnl|Fabrus|B3_IGKJ1*01	1085
2960	VH3-23_IGHD1-1*01>2_IGHJ5*01	1597	gnl|Fabrus|B3_IGKJ1*01	1085

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
2961	VH3-23_IGHD1-1*01>3_IGHJ5*01	1598	gnl|Fabrus|B3_IGKJ1*01	1085
2962	VH3-23_IGHD1-7*01>1_IGHJ5*01	1599	gnl|Fabrus|B3_IGKJ1*01	1085
2963	VH3-23_IGHD1-7*01>3_IGHJ5*01	1600	gnl|Fabrus|B3_IGKJ1*01	1085
2964	VH3-23_IGHD1-14*01>1_IGHJ5*01	1601	gnl|Fabrus|B3_IGKJ1*01	1085
2965	VH3-23_IGHD1-14*01>3_IGHJ5*01	1602	gnl|Fabrus|B3_IGKJ1*01	1085
2966	VH3-23_IGHD1-20*01>1_IGHJ5*01	1603	gnl|Fabrus|B3_IGKJ1*01	1085
2967	VH3-23_IGHD1-20*01>3_IGHJ5*01	1604	gnl|Fabrus|B3_IGKJ1*01	1085
2968	VH3-23_IGHD1-26*01>1_IGHJ5*01	1605	gnl|Fabrus|B3_IGKJ1*01	1085
2969	VH3-23_IGHD1-26*01>3_IGHJ5*01	1606	gnl|Fabrus|B3_IGKJ1*01	1085
2970	VH3-23_IGHD2-2*01>2_IGHJ5*01	1607	gnl|Fabrus|B3_IGKJ1*01	1085
2971	VH3-23_IGHD2-2*01>3_IGHJ5*01	1608	gnl|Fabrus|B3_IGKJ1*01	1085
2972	VH3-23_IGHD2-8*01>2_IGHJ5*01	1609	gnl|Fabrus|B3_IGKJ1*01	1085
2973	VH3-23_IGHD2-8*01>3_IGHJ5*01	1610	gnl|Fabrus|B3_IGKJ1*01	1085
2974	VH3-23_IGHD2-15*01>2_IGHJ5*01	1611	gnl|Fabrus|B3_IGKJ1*01	1085
2975	VH3-23_IGHD2-15*01>3_IGHJ5*01	1612	gnl|Fabrus|B3_IGKJ1*01	1085
2976	VH3-23_IGHD2-21*01>2_IGHJ5*01	1613	gnl|Fabrus|B3_IGKJ1*01	1085
2977	VH3-23_IGHD2-21*01>3_IGHJ5*01	1614	gnl|Fabrus|B3_IGKJ1*01	1085
2978	VH3-23_IGHD3-3*01>1_IGHJ5*01	1615	gnl|Fabrus|B3_IGKJ1*01	1085
2979	VH3-23_IGHD3-3*01>2_IGHJ5*01	1616	gnl|Fabrus|B3_IGKJ1*01	1085
2980	VH3-23_IGHD3-3*01>3_IGHJ5*01	1617	gnl|Fabrus|B3_IGKJ1*01	1085
2981	VH3-23_IGHD3-9*01>2_IGHJ5*01	1618	gnl|Fabrus|B3_IGKJ1*01	1085
2982	VH3-23_IGHD3-10*01>2_IGHJ5*01	1619	gnl|Fabrus|B3_IGKJ1*01	1085
2983	VH3-23_IGHD3-10*01>3_IGHJ5*01	1620	gnl|Fabrus|B3_IGKJ1*01	1085
2984	VH3-23_IGHD3-16*01>2_IGHJ5*01	1621	gnl|Fabrus|B3_IGKJ1*01	1085
2985	VH3-23_IGHD3-16*01>3_IGHJ5*01	1622	gnl|Fabrus|B3_IGKJ1*01	1085
2986	VH3-23_IGHD3-22*01>2_IGHJ5*01	1623	gnl|Fabrus|B3_IGKJ1*01	1085
2987	VH3-23_IGHD3-22*01>3_IGHJ5*01	1624	gnl|Fabrus|B3_IGKJ1*01	1085
2988	VH3-23_IGHD4-4*01 (1) >2_IGHJ5*01	1625	gnl|Fabrus|B3_IGKJ1*01	1085
2989	VH3-23_IGHD4-4*01 (1) >3_IGHJ5*01	1626	gnl|Fabrus|B3_IGKJ1*01	1085
2990	VH3-23_IGHD4-11*01 (1) >2_IGHJ5*01	1627	gnl|Fabrus|B3_IGKJ1*01	1085
2991	VH3-23_IGHD4-11*01 (1) >3_IGHJ5*01	1628	gnl|Fabrus|B3_IGKJ1*01	1085
2992	VH3-23_IGHD4-17*01>2_IGHJ5*01	1629	gnl|Fabrus|B3_IGKJ1*01	1085
2993	VH3-23_IGHD4-17*01>3_IGHJ5*01	1630	gnl|Fabrus|B3_IGKJ1*01	1085
2994	VH3-23_IGHD4-23*01>2_IGHJ5*01	1631	gnl|Fabrus|B3_IGKJ1*01	1085
2995	VH3-23_IGHD4-23*01>3_IGHJ5*01	1632	gnl|Fabrus|B3_IGKJ1*01	1085
2996	VH3-23_IGHD5-5*01 (2) >1_IGHJ5*01	1633	gnl|Fabrus|B3_IGKJ1*01	1085
2997	VH3-23_IGHD5-5*01 (2) >2_IGHJ5*01	1634	gnl|Fabrus|B3_IGKJ1*01	1085
2998	VH3-23_IGHD5-5*01 (2) >3_IGHJ5*01	1635	gnl|Fabrus|B3_IGKJ1*01	1085
2999	VH3-23_IGHD5-12*01>1_IGHJ5*01	1636	gnl|Fabrus|B3_IGKJ1*01	1085
3000	VH3-23_IGHD5-12*01>3_IGHJ5*01	1637	gnl|Fabrus|B3_IGKJ1*01	1085
3001	VH3-23_IGHD5-18*01 (2) >1_IGHJ5*01	1638	gnl|Fabrus|B3_IGKJ1*01	1085
3002	VH3-23_IGHD5-18*01 (2) >2_IGHJ5*01	1639	gnl|Fabrus|B3_IGKJ1*01	1085

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3003	VH3-23_IGHD5-18*01 (2) >3_IGHJ5*01	1640	gnl|Fabrus|B3_IGKJ1*01	1085
3004	VH3-23_IGHD5-24*01>1_IGHJ5*01	1641	gnl|Fabrus|B3_IGKJ1*01	1085
3005	VH3-23_IGHD5-24*01>3_IGHJ5*01	1642	gnl|Fabrus|B3_IGKJ1*01	1085
3006	VH3-23_IGHD6-6*01>1_IGHJ5*01	1643	gnl|Fabrus|B3_IGKJ1*01	1085
3007	VH3-23_IGHD1-1*01>1'_IGHJ5*01	1653	gnl|Fabrus|B3_IGKJ1*01	1085
3008	VH3-23_IGHD1-1*01>2'_IGHJ5*01	1654	gnl|Fabrus|B3_IGKJ1*01	1085
3009	VH3-23_IGHD1-1*01>3'_IGHJ5*01	1655	gnl|Fabrus|B3_IGKJ1*01	1085
3010	VH3-23_IGHD1-7*01>1'_IGHJ5*01	1656	gnl|Fabrus|B3_IGKJ1*01	1085
3011	VH3-23_IGHD1-7*01>3'_IGHJ5*01	1657	gnl|Fabrus|B3_IGKJ1*01	1085
3012	VH3-23_IGHD1-14*01>1'_IGHJ5*01	1658	gnl|Fabrus|B3_IGKJ1*01	1085
3013	VH3-23_IGHD1-14*01>2'_IGHJ5*01	1659	gnl|Fabrus|B3_IGKJ1*01	1085
3014	VH3-23_IGHD1-14*01>3'_IGHJ5*01	1660	gnl|Fabrus|B3_IGKJ1*01	1085
3015	VH3-23_IGHD1-20*01>1'_IGHJ5*01	1661	gnl|Fabrus|B3_IGKJ1*01	1085
3016	VH3-23_IGHD1-20*01>2'_IGHJ5*01	1662	gnl|Fabrus|B3_IGKJ1*01	1085
3017	VH3-23_IGHD1-20*01>3'_IGHJ5*01	1663	gnl|Fabrus|B3_IGKJ1*01	1085
3018	VH3-23_IGHD1-26*01>1'_IGHJ5*01	1664	gnl|Fabrus|B3_IGKJ1*01	1085
3019	VH3-23_IGHD1-26*01>3'_IGHJ5*01	1665	gnl|Fabrus|B3_IGKJ1*01	1085
3020	VH3-23_IGHD2-2*01>1'_IGHJ5*01	1666	gnl|Fabrus|B3_IGKJ1*01	1085
3021	VH3-23_IGHD2-2*01>3'_IGHJ5*01	1667	gnl|Fabrus|B3_IGKJ1*01	1085
3022	VH3-23_IGHD2-8*01>1'_IGHJ5*01	1668	gnl|Fabrus|B3_IGKJ1*01	1085
3023	VH3-23_IGHD2-15*01>1'_IGHJ5*01	1669	gnl|Fabrus|B3_IGKJ1*01	1085
3024	VH3-23_IGHD2-15*01>3'_IGHJ5*01	1670	gnl|Fabrus|B3_IGKJ1*01	1085
3025	VH3-23_IGHD2-21*01>1'_IGHJ5*01	1671	gnl|Fabrus|B3_IGKJ1*01	1085
3026	VH3-23_IGHD2-21*01>3'_IGHJ5*01	1672	gnl|Fabrus|B3_IGKJ1*01	1085
3027	VH3-23_IGHD3-3*01>1'_IGHJ5*01	1673	gnl|Fabrus|B3_IGKJ1*01	1085
3028	VH3-23_IGHD3-3*01>3'_IGHJ5*01	1674	gnl|Fabrus|B3_IGKJ1*01	1085
3029	VH3-23_IGHD3-9*01>1'_IGHJ5*01	1675	gnl|Fabrus|B3_IGKJ1*01	1085
3030	VH3-23_IGHD3-9*01>3'_IGHJ5*01	1676	gnl|Fabrus|B3_IGKJ1*01	1085
3031	VH3-23_IGHD3-10*01>1'_IGHJ5*01	1677	gnl|Fabrus|B3_IGKJ1*01	1085
3032	VH3-23_IGHD3-10*01>3'_IGHJ5*01	1678	gnl|Fabrus|B3_IGKJ1*01	1085
3033	VH3-23_IGHD3-16*01>1'_IGHJ5*01	1679	gnl|Fabrus|B3_IGKJ1*01	1085
3034	VH3-23_IGHD3-16*01>3'_IGHJ5*01	1680	gnl|Fabrus|B3_IGKJ1*01	1085
3035	VH3-23_IGHD3-22*01>1'_IGHJ5*01	1681	gnl|Fabrus|B3_IGKJ1*01	1085
3036	VH3-23_IGHD4-4*01 (1) >1'_IGHJ5*01	1682	gnl|Fabrus|B3_IGKJ1*01	1085
3037	VH3-23_IGHD4-4*01 (1) >3'_IGHJ5*01	1683	gnl|Fabrus|B3_IGKJ1*01	1085
3038	VH3-23_IGHD4-11*01 (1) >1'_IGHJ5*01	1684	gnl|Fabrus|B3_IGKJ1*01	1085
3039	VH3-23_IGHD4-11*01 (1) >3'_IGHJ5*01	1685	gnl|Fabrus|B3_IGKJ1*01	1085
3040	VH3-23_IGHD4-17*01>1'_IGHJ5*01	1686	gnl|Fabrus|B3_IGKJ1*01	1085
3041	VH3-23_IGHD4-17*01>3'_IGHJ5*01	1687	gnl|Fabrus|B3_IGKJ1*01	1085
3042	VH3-23_IGHD4-23*01>1'_IGHJ5*01	1688	gnl|Fabrus|B3_IGKJ1*01	1085
3043	VH3-23_IGHD4-23*01>3'_IGHJ5*01	1689	gnl|Fabrus|B3_IGKJ1*01	1085
3044	VH3-23_IGHD5-5*01 (2) >1'_IGHJ5*01	1690	gnl|Fabrus|B3_IGKJ1*01	1085

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3045	VH3-23_IGHD5-5*01 (2) >3'_IGHJ5*01	1691	gnl|Fabrus|B3_IGKJ1*01	1085
3046	VH3-23_IGHD5-12*01>1'_IGHJ5*01	1692	gnl|Fabrus|B3_IGKJ1*01	1085
3047	VH3-23_IGHD5-12*01>3'_IGHJ5*01	1693	gnl|Fabrus|B3_IGKJ1*01	1085
3048	VH3-23_IGHD5-18*01 (2) >1'_IGHJ5*01	1694	gnl|Fabrus|B3_IGKJ1*01	1085
3049	VH3-23_IGHD5-18*01 (2) >3'_IGHJ5*01	1695	gnl|Fabrus|B3_IGKJ1*01	1085
3050	VH3-23_IGHD5-24*01>1'_IGHJ5*01	1696	gnl|Fabrus|B3_IGKJ1*01	1085
3051	VH3-23_IGHD5-24*01>3'_IGHJ5*01	1697	gnl|Fabrus|B3_IGKJ1*01	1085
3052	VH3-23_IGHD6-6*01>1'_IGHJ5*01	1698	gnl|Fabrus|B3_IGKJ1*01	1085
3053	VH3-23_IGHD6-6*01>2'_IGHJ5*01	1699	gnl|Fabrus|B3_IGKJ1*01	1085
3054	VH3-23_IGHD6-6*01>3'_IGHJ5*01	1700	gnl|Fabrus|B3_IGKJ1*01	1085
3055	VH3-23_IGHD1-1*01>1_IGHJ5*01	1596	gnl|Fabrus|A26_IGKJ1*01	1079
3056	VH3-23_IGHD1-1*01>2_IGHJ5*01	1597	gnl|Fabrus|A26_IGKJ1*01	1079
3057	VH3-23_IGHD1-1*01>3_IGHJ5*01	1598	gnl|Fabrus|A26_IGKJ1*01	1079
3058	VH3-23_IGHD1-7*01>1_IGHJ5*01	1599	gnl|Fabrus|A26_IGKJ1*01	1079
3059	VH3-23_IGHD1-7*01>3_IGHJ5*01	1600	gnl|Fabrus|A26_IGKJ1*01	1079
3060	VH3-23_IGHD1-14*01>1_IGHJ5*01	1601	gnl|Fabrus|A26_IGKJ1*01	1079
3061	VH3-23_IGHD1-14*01>3_IGHJ5*01	1602	gnl|Fabrus|A26_IGKJ1*01	1079
3062	VH3-23_IGHD1-20*01>1_IGHJ5*01	1603	gnl|Fabrus|A26_IGKJ1*01	1079
3063	VH3-23_IGHD1-20*01>3_IGHJ5*01	1604	gnl|Fabrus|A26_IGKJ1*01	1079
3064	VH3-23_IGHD1-26*01>1_IGHJ5*01	1605	gnl|Fabrus|A26_IGKJ1*01	1079
3065	VH3-23_IGHD1-26*01>3_IGHJ5*01	1606	gnl|Fabrus|A26_IGKJ1*01	1079
3066	VH3-23_IGHD2-2*01>2_IGHJ5*01	1607	gnl|Fabrus|A26_IGKJ1*01	1079
3067	VH3-23_IGHD2-2*01>3_IGHJ5*01	1608	gnl|Fabrus|A26_IGKJ1*01	1079
3068	VH3-23_IGHD2-8*01>2_IGHJ5*01	1609	gnl|Fabrus|A26_IGKJ1*01	1079
3069	VH3-23_IGHD2-8*01>3_IGHJ5*01	1610	gnl|Fabrus|A26_IGKJ1*01	1079
3070	VH3-23_IGHD2-15*01>2_IGHJ5*01	1611	gnl|Fabrus|A26_IGKJ1*01	1079
3071	VH3-23_IGHD2-15*01>3_IGHJ5*01	1612	gnl|Fabrus|A26_IGKJ1*01	1079
3072	VH3-23_IGHD2-21*01>2_IGHJ5*01	1613	gnl|Fabrus|A26_IGKJ1*01	1079
3073	VH3-23_IGHD2-21*01>3_IGHJ5*01	1614	gnl|Fabrus|A26_IGKJ1*01	1079
3074	VH3-23_IGHD3-3*01>1_IGHJ5*01	1615	gnl|Fabrus|A26_IGKJ1*01	1079
3075	VH3-23_IGHD3-3*01>2_IGHJ5*01	1616	gnl|Fabrus|A26_IGKJ1*01	1079
3076	VH3-23_IGHD3-3*01>3_IGHJ5*01	1617	gnl|Fabrus|A26_IGKJ1*01	1079
3077	VH3-23_IGHD3-9*01>2_IGHJ5*01	1618	gnl|Fabrus|A26_IGKJ1*01	1079
3078	VH3-23_IGHD3-10*01>2_IGHJ5*01	1619	gnl|Fabrus|A26_IGKJ1*01	1079
3079	VH3-23_IGHD3-10*01>3_IGHJ5*01	1620	gnl|Fabrus|A26_IGKJ1*01	1079
3080	VH3-23_IGHD3-16*01>2_IGHJ5*01	1621	gnl|Fabrus|A26_IGKJ1*01	1079
3081	VH3-23_IGHD3-16*01>3_IGHJ5*01	1622	gnl|Fabrus|A26_IGKJ1*01	1079
3082	VH3-23_IGHD3-22*01>2_IGHJ5*01	1623	gnl|Fabrus|A26_IGKJ1*01	1079
3083	VH3-23_IGHD3-22*01>3_IGHJ5*01	1624	gnl|Fabrus|A26_IGKJ1*01	1079
3084	VH3-23_IGHD4-4*01 (1) >2_IGHJ5*01	1625	gnl|Fabrus|A26_IGKJ1*01	1079
3085	VH3-23_IGHD4-4*01 (1) >3_IGHJ5*01	1626	gnl|Fabrus|A26_IGKJ1*01	1079
3086	VH3-23_IGHD4-11*01 (1) >2_IGHJ5*01	1627	gnl|Fabrus|A26_IGKJ1*01	1079

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3087	VH3-23_IGHD4-11*01 (1) >3_IGHJ5*01	1628	gnl|Fabrus|A26_IGKJ1*01	1079
3088	VH3-23_IGHD4-17*01>2_IGHJ5*01	1629	gnl|Fabrus|A26_IGKJ1*01	1079
3089	VH3-23_IGHD4-17*01>3_IGHJ5*01	1630	gnl|Fabrus|A26_IGKJ1*01	1079
3090	VH3-23_IGHD4-23*01>2_IGHJ5*01	1631	gnl|Fabrus|A26_IGKJ1*01	1079
3091	VH3-23_IGHD4-23*01>3_IGHJ5*01	1632	gnl|Fabrus|A26_IGKJ1*01	1079
3092	VH3-23_IGHD5-5*01 (2) >1_IGHJ5*01	1633	gnl|Fabrus|A26_IGKJ1*01	1079
3093	VH3-23_IGHD5-5*01 (2) >2_IGHJ5*01	1634	gnl|Fabrus|A26_IGKJ1*01	1079
3094	VH3-23_IGHD5-5*01 (2) >3_IGHJ5*01	1635	gnl|Fabrus|A26_IGKJ1*01	1079
3095	VH3-23_IGHD5-12*01>1_IGHJ5*01	1636	gnl|Fabrus|A26_IGKJ1*01	1079
3096	VH3-23_IGHD5-12*01>3_IGHJ5*01	1637	gnl|Fabrus|A26_IGKJ1*01	1079
3097	VH3-23_IGHD5-18*01 (2) >1_IGHJ5*01	1638	gnl|Fabrus|A26_IGKJ1*01	1079
3098	VH3-23_IGHD5-18*01 (2) >2_IGHJ5*01	1639	gnl|Fabrus|A26_IGKJ1*01	1079
3099	VH3-23_IGHD5-18*01 (2) >3_IGHJ5*01	1640	gnl|Fabrus|A26_IGKJ1*01	1079
3100	VH3-23_IGHD5-24*01>1_IGHJ5*01	1641	gnl|Fabrus|A26_IGKJ1*01	1079
3101	VH3-23_IGHD5-24*01>3_IGHJ5*01	1642	gnl|Fabrus|A26_IGKJ1*01	1079
3102	VH3-23_IGHD6-6*01>1_IGHJ5*01	1643	gnl|Fabrus|A26_IGKJ1*01	1079
3103	VH3-23_IGHD1-1*01>1'_IGHJ5*01	1653	gnl|Fabrus|A26_IGKJ1*01	1079
3104	VH3-23_IGHD1-1*01>2'_IGHJ5*01	1654	gnl|Fabrus|A26_IGKJ1*01	1079
3105	VH3-23_IGHD1-1*01>3'_IGHJ5*01	1655	gnl|Fabrus|A26_IGKJ1*01	1079
3106	VH3-23_IGHD1-7*01>1'_IGHJ5*01	1656	gnl|Fabrus|A26_IGKJ1*01	1079
3107	VH3-23_IGHD1-7*01>3'_IGHJ5*01	1657	gnl|Fabrus|A26_IGKJ1*01	1079
3108	VH3-23_IGHD1-14*01>1'_IGHJ5*01	1658	gnl|Fabrus|A26_IGKJ1*01	1079
3109	VH3-23_IGHD1-14*01>2'_IGHJ5*01	1659	gnl|Fabrus|A26_IGKJ1*01	1079
3110	VH3-23_IGHD1-14*01>3'_IGHJ5*01	1660	gnl|Fabrus|A26_IGKJ1*01	1079
3111	VH3-23_IGHD1-20*01>1'_IGHJ5*01	1661	gnl|Fabrus|A26_IGKJ1*01	1079
3112	VH3-23_IGHD1-20*01>2'_IGHJ5*01	1662	gnl|Fabrus|A26_IGKJ1*01	1079
3113	VH3-23_IGHD1-20*01>3'_IGHJ5*01	1663	gnl|Fabrus|A26_IGKJ1*01	1079
3114	VH3-23_IGHD1-26*01>1'_IGHJ5*01	1664	gnl|Fabrus|A26_IGKJ1*01	1079
3115	VH3-23_IGHD1-26*01>3'_IGHJ5*01	1665	gnl|Fabrus|A26_IGKJ1*01	1079
3116	VH3-23_IGHD2-2*01>1'_IGHJ5*01	1666	gnl|Fabrus|A26_IGKJ1*01	1079
3117	VH3-23_IGHD2-2*01>3'_IGHJ5*01	1667	gnl|Fabrus|A26_IGKJ1*01	1079
3118	VH3-23_IGHD2-8*01>1'_IGHJ5*01	1668	gnl|Fabrus|A26_IGKJ1*01	1079
3119	VH3-23_IGHD2-15*01>1'_IGHJ5*01	1669	gnl|Fabrus|A26_IGKJ1*01	1079
3120	VH3-23_IGHD2-15*01>3'_IGHJ5*01	1670	gnl|Fabrus|A26_IGKJ1*01	1079
3121	VH3-23_IGHD2-21*01>1'_IGHJ5*01	1671	gnl|Fabrus|A26_IGKJ1*01	1079
3122	VH3-23_IGHD2-21*01>3'_IGHJ5*01	1672	gnl|Fabrus|A26_IGKJ1*01	1079
3123	VH3-23_IGHD3-3*01>1'_IGHJ5*01	1673	gnl|Fabrus|A26_IGKJ1*01	1079
3124	VH3-23_IGHD3-3*01>3'_IGHJ5*01	1674	gnl|Fabrus|A26_IGKJ1*01	1079
3125	VH3-23_IGHD3-9*01>1'_IGHJ5*01	1675	gnl|Fabrus|A26_IGKJ1*01	1079
3126	VH3-23_IGHD3-9*01>3'_IGHJ5*01	1676	gnl|Fabrus|A26_IGKJ1*01	1079
3127	VH3-23_IGHD3-10*01>1'_IGHJ5*01	1677	gnl|Fabrus|A26_IGKJ1*01	1079
3128	VH3-23_IGHD3-10*01>3'_IGHJ5*01	1678	gnl|Fabrus|A26_IGKJ1*01	1079

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3129	VH3-23_IGHD3-16*01>1'_IGHJ5*01	1679	gnl|Fabrus|A26_IGKJ1*01	1079
3130	VH3-23_IGHD3-16*01>3'_IGHJ5*01	1680	gnl|Fabrus|A26_IGKJ1*01	1079
3131	VH3-23_IGHD3-22*01>1'_IGHJ5*01	1681	gnl|Fabrus|A26_IGKJ1*01	1079
3132	VH3-23_IGHD4-4*01 (1) >1'_IGHJ5*01	1682	gnl|Fabrus|A26_IGKJ1*01	1079
3133	VH3-23_IGHD4-4*01 (1) >3'_IGHJ5*01	1683	gnl|Fabrus|A26_IGKJ1*01	1079
3134	VH3-23_IGHD4-11*01 (1) >1'_IGHJ5*01	1684	gnl|Fabrus|A26_IGKJ1*01	1079
3135	VH3-23_IGHD4-11*01 (1) >3'_IGHJ5*01	1685	gnl|Fabrus|A26_IGKJ1*01	1079
3136	VH3-23_IGHD4-17*01>1'_IGHJ5*01	1686	gnl|Fabrus|A26_IGKJ1*01	1079
3137	VH3-23_IGHD4-17*01>3'_IGHJ5*01	1687	gnl|Fabrus|A26_IGKJ1*01	1079
3138	VH3-23_IGHD4-23*01>1'_IGHJ5*01	1688	gnl|Fabrus|A26_IGKJ1*01	1079
3139	VH3-23_IGHD4-23*01>3'_IGHJ5*01	1689	gnl|Fabrus|A26_IGKJ1*01	1079
3140	VH3-23_IGHD5-5*01 (2) >1'_IGHJ5*01	1690	gnl|Fabrus|A26_IGKJ1*01	1079
3141	VH3-23_IGHD5-5*01 (2) >3'_IGHJ5*01	1691	gnl|Fabrus|A26_IGKJ1*01	1079
3142	VH3-23_IGHD5-12*01>1'_IGHJ5*01	1692	gnl|Fabrus|A26_IGKJ1*01	1079
3143	VH3-23_IGHD5-12*01>3'_IGHJ5*01	1693	gnl|Fabrus|A26_IGKJ1*01	1079
3144	VH3-23_IGHD5-18*01 (2) >1'_IGHJ5*01	1694	gnl|Fabrus|A26_IGKJ1*01	1079
3145	VH3-23_IGHD5-18*01 (2) >3'_IGHJ5*01	1695	gnl|Fabrus|A26_IGKJ1*01	1079
3146	VH3-23_IGHD5-24*01>1'_IGHJ5*01	1696	gnl|Fabrus|A26_IGKJ1*01	1079
3147	VH3-23_IGHD5-24*01>3'_IGHJ5*01	1697	gnl|Fabrus|A26_IGKJ1*01	1079
3148	VH3-23_IGHD6-6*01>1'_IGHJ5*01	1698	gnl|Fabrus|A26_IGKJ1*01	1079
3149	VH3-23_IGHD6-6*01>2'_IGHJ5*01	1699	gnl|Fabrus|A26_IGKJ1*01	1079
3150	VH3-23_IGHD6-6*01>3'_IGHJ5*01	1700	gnl|Fabrus|A26_IGKJ1*01	1079
3151	VH3-23_IGHD1-1*01>1_IGHJ5*01	1596	gnl|Fabrus|A14_IGKJ1*01	1074
3152	VH3-23_IGHD1-1*01>2_IGHJ5*01	1597	gnl|Fabrus|A14_IGKJ1*01	1074
3153	VH3-23_IGHD1-1*01>3_IGHJ5*01	1598	gnl|Fabrus|A14_IGKJ1*01	1074
3154	VH3-23_IGHD1-7*01>1_IGHJ5*01	1599	gnl|Fabrus|A14_IGKJ1*01	1074
3155	VH3-23_IGHD1-7*01>3_IGHJ5*01	1600	gnl|Fabrus|A14_IGKJ1*01	1074
3156	VH3-23_IGHD1-14*01>1_IGHJ5*01	1601	gnl|Fabrus|A14_IGKJ1*01	1074
3157	VH3-23_IGHD1-14*01>3_IGHJ5*01	1602	gnl|Fabrus|A14_IGKJ1*01	1074
3158	VH3-23_IGHD1-20*01>1_IGHJ5*01	1603	gnl|Fabrus|A14_IGKJ1*01	1074
3159	VH3-23_IGHD1-20*01>3_IGHJ5*01	1604	gnl|Fabrus|A14_IGKJ1*01	1074
3160	VH3-23_IGHD1-26*01>1_IGHJ5*01	1605	gnl|Fabrus|A14_IGKJ1*01	1074
3161	VH3-23_IGHD1-26*01>3_IGHJ5*01	1606	gnl|Fabrus|A14_IGKJ1*01	1074
3162	VH3-23_IGHD2-2*01>2_IGHJ5*01	1607	gnl|Fabrus|A14_IGKJ1*01	1074
3163	VH3-23_IGHD2-2*01>3_IGHJ5*01	1608	gnl|Fabrus|A14_IGKJ1*01	1074
3164	VH3-23_IGHD2-8*01>2_IGHJ5*01	1609	gnl|Fabrus|A14_IGKJ1*01	1074
3165	VH3-23_IGHD2-8*01>3_IGHJ5*01	1610	gnl|Fabrus|A14_IGKJ1*01	1074
3166	VH3-23_IGHD2-15*01>2_IGHJ5*01	1611	gnl|Fabrus|A14_IGKJ1*01	1074
3167	VH3-23_IGHD2-15*01>3_IGHJ5*01	1612	gnl|Fabrus|A14_IGKJ1*01	1074
3168	VH3-23_IGHD2-21*01>2_IGHJ5*01	1613	gnl|Fabrus|A14_IGKJ1*01	1074
3169	VH3-23_IGHD2-21*01>3_IGHJ5*01	1614	gnl|Fabrus|A14_IGKJ1*01	1074
3170	VH3-23_IGHD3-3*01>1_IGHJ5*01	1615	gnl|Fabrus|A14_IGKJ1*01	1074

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3171	VH3-23_IGHD3-3*01>2_IGHJ5*01	1616	gnl|Fabrus|A14_IGKJ1*01	1074
3172	VH3-23_IGHD3-3*01>3_IGHJ5*01	1617	gnl|Fabrus|A14_IGKJ1*01	1074
3173	VH3-23_IGHD3-9*01>2_IGHJ5*01	1618	gnl|Fabrus|A14_IGKJ1*01	1074
3174	VH3-23_IGHD3-10*01>2_IGHJ5*01	1619	gnl|Fabrus|A14_IGKJ1*01	1074
3175	VH3-23_IGHD3-10*01>3_IGHJ5*01	1620	gnl|Fabrus|A14_IGKJ1*01	1074
3176	VH3-23_IGHD3-16*01>2_IGHJ5*01	1621	gnl|Fabrus|A14_IGKJ1*01	1074
3177	VH3-23_IGHD3-16*01>3_IGHJ5*01	1622	gnl|Fabrus|A14_IGKJ1*01	1074
3178	VH3-23_IGHD3-22*01>2_IGHJ5*01	1623	gnl|Fabrus|A14_IGKJ1*01	1074
3179	VH3-23_IGHD3-22*01>3_IGHJ5*01	1624	gnl|Fabrus|A14_IGKJ1*01	1074
3180	VH3-23_IGHD4-4*01 (1) >2_IGHJ5*01	1625	gnl|Fabrus|A14_IGKJ1*01	1074
3181	VH3-23_IGHD4-4*01 (1) >3_IGHJ5*01	1626	gnl|Fabrus|A14_IGKJ1*01	1074
3182	VH3-23_IGHD4-11*01 (1) >2_IGHJ5*01	1627	gnl|Fabrus|A14_IGKJ1*01	1074
3183	VH3-23_IGHD4-11*01 (1) >3_IGHJ5*01	1628	gnl|Fabrus|A14_IGKJ1*01	1074
3184	VH3-23_IGHD4-17*01>2_IGHJ5*01	1629	gnl|Fabrus|A14_IGKJ1*01	1074
3185	VH3-23_IGHD4-17*01>3_IGHJ5*01	1630	gnl|Fabrus|A14_IGKJ1*01	1074
3186	VH3-23_IGHD4-23*01>2_IGHJ5*01	1631	gnl|Fabrus|A14_IGKJ1*01	1074
3187	VH3-23_IGHD4-23*01>3_IGHJ5*01	1632	gnl|Fabrus|A14_IGKJ1*01	1074
3188	VH3-23_IGHD5-5*01 (2) >1_IGHJ5*01	1633	gnl|Fabrus|A14_IGKJ1*01	1074
3189	VH3-23_IGHD5-5*01 (2) >2_IGHJ5*01	1634	gnl|Fabrus|A14_IGKJ1*01	1074
3190	VH3-23_IGHD5-5*01 (2) >3_IGHJ5*01	1635	gnl|Fabrus|A14_IGKJ1*01	1074
3191	VH3-23_IGHD5-12*01>1_IGHJ5*01	1636	gnl|Fabrus|A14_IGKJ1*01	1074
3192	VH3-23_IGHD5-12*01>3_IGHJ5*01	1637	gnl|Fabrus|A14_IGKJ1*01	1074
3193	VH3-23_IGHD5-18*01 (2) >1_IGHJ5*01	1638	gnl|Fabrus|A14_IGKJ1*01	1074
3194	VH3-23_IGHD5-18*01 (2) >2_IGHJ5*01	1639	gnl|Fabrus|A14_IGKJ1*01	1074
3195	VH3-23_IGHD5-18*01 (2) >3_IGHJ5*01	1640	gnl|Fabrus|A14_IGKJ1*01	1074
3196	VH3-23_IGHD5-24*01>1_IGHJ5*01	1641	gnl|Fabrus|A14_IGKJ1*01	1074
3197	VH3-23_IGHD5-24*01>3_IGHJ5*01	1642	gnl|Fabrus|A14_IGKJ1*01	1074
3198	VH3-23_IGHD6-6*01>1_IGHJ5*01	1643	gnl|Fabrus|A14_IGKJ1*01	1074
3199	VH3-23_IGHD1-1*01>1'_IGHJ5*01	1653	gnl|Fabrus|A14_IGKJ1*01	1074
3200	VH3-23_IGHD1-1*01>2'_IGHJ5*01	1654	gnl|Fabrus|A14_IGKJ1*01	1074
3201	VH3-23_IGHD1-1*01>3'_IGHJ5*01	1655	gnl|Fabrus|A14_IGKJ1*01	1074
3202	VH3-23_IGHD1-7*01>1'_IGHJ5*01	1656	gnl|Fabrus|A14_IGKJ1*01	1074
3203	VH3-23_IGHD1-7*01>3'_IGHJ5*01	1657	gnl|Fabrus|A14_IGKJ1*01	1074
3204	VH3-23_IGHD1-14*01>1'_IGHJ5*01	1658	gnl|Fabrus|A14_IGKJ1*01	1074
3205	VH3-23_IGHD1-14*01>2'_IGHJ5*01	1659	gnl|Fabrus|A14_IGKJ1*01	1074
3206	VH3-23_IGHD1-14*01>3'_IGHJ5*01	1660	gnl|Fabrus|A14_IGKJ1*01	1074
3207	VH3-23_IGHD1-20*01>1'_IGHJ5*01	1661	gnl|Fabrus|A14_IGKJ1*01	1074
3208	VH3-23_IGHD1-20*01>2'_IGHJ5*01	1662	gnl|Fabrus|A14_IGKJ1*01	1074
3209	VH3-23_IGHD1-20*01>3'_IGHJ5*01	1663	gnl|Fabrus|A14_IGKJ1*01	1074
3210	VH3-23_IGHD1-26*01>1'_IGHJ5*01	1664	gnl|Fabrus|A14_IGKJ1*01	1074
3211	VH3-23_IGHD1-26*01>3'_IGHJ5*01	1665	gnl|Fabrus|A14_IGKJ1*01	1074
3212	VH3-23_IGHD2-2*01>1'_IGHJ5*01	1666	gnl|Fabrus|A14_IGKJ1*01	1074

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3213	VH3-23_IGHD2-2*01>3'_IGHJ5*01	1667	gnl|Fabrus|A14_IGKJ1*01	1074
3214	VH3-23_IGHD2-8*01>1'_IGHJ5*01	1668	gnl|Fabrus|A14_IGKJ1*01	1074
3215	VH3-23_IGHD2-15*01>1'_IGHJ5*01	1669	gnl|Fabrus|A14_IGKJ1*01	1074
3216	VH3-23_IGHD2-15*01>3'_IGHJ5*01	1670	gnl|Fabrus|A14_IGKJ1*01	1074
3217	VH3-23_IGHD2-21*01>1'_IGHJ5*01	1671	gnl|Fabrus|A14_IGKJ1*01	1074
3218	VH3-23_IGHD2-21*01>3'_IGHJ5*01	1672	gnl|Fabrus|A14_IGKJ1*01	1074
3219	VH3-23_IGHD3-3*01>1'_IGHJ5*01	1673	gnl|Fabrus|A14_IGKJ1*01	1074
3220	VH3-23_IGHD3-3*01>3'_IGHJ5*01	1674	gnl|Fabrus|A14_IGKJ1*01	1074
3221	VH3-23_IGHD3-9*01>1'_IGHJ5*01	1675	gnl|Fabrus|A14_IGKJ1*01	1074
3222	VH3-23_IGHD3-9*01>3'_IGHJ5*01	1676	gnl|Fabrus|A14_IGKJ1*01	1074
3223	VH3-23_IGHD3-10*01>1'_IGHJ5*01	1677	gnl|Fabrus|A14_IGKJ1*01	1074
3224	VH3-23_IGHD3-10*01>3'_IGHJ5*01	1678	gnl|Fabrus|A14_IGKJ1*01	1074
3225	VH3-23_IGHD3-16*01>1'_IGHJ5*01	1679	gnl|Fabrus|A14_IGKJ1*01	1074
3226	VH3-23_IGHD3-16*01>3'_IGHJ5*01	1680	gnl|Fabrus|A14_IGKJ1*01	1074
3227	VH3-23_IGHD3-22*01>1'_IGHJ5*01	1681	gnl|Fabrus|A14_IGKJ1*01	1074
3228	VH3-23_IGHD4-4*01 (1) >1'_IGHJ5*01	1682	gnl|Fabrus|A14_IGKJ1*01	1074
3229	VH3-23_IGHD4-4*01 (1) >3'_IGHJ5*01	1683	gnl|Fabrus|A14_IGKJ1*01	1074
3230	VH3-23_IGHD4-11*01 (1) >1'_IGHJ5*01	1684	gnl|Fabrus|A14_IGKJ1*01	1074
3231	VH3-23_IGHD4-11*01 (1) >3'_IGHJ5*01	1685	gnl|Fabrus|A14_IGKJ1*01	1074
3232	VH3-23_IGHD4-17*01>1'_IGHJ5*01	1686	gnl|Fabrus|A14_IGKJ1*01	1074
3233	VH3-23_IGHD4-17*01>3'_IGHJ5*01	1687	gnl|Fabrus|A14_IGKJ1*01	1074
3234	VH3-23_IGHD4-23*01>1'_IGHJ5*01	1688	gnl|Fabrus|A14_IGKJ1*01	1074
3235	VH3-23_IGHD4-23*01>3'_IGHJ5*01	1689	gnl|Fabrus|A14_IGKJ1*01	1074
3236	VH3-23_IGHD5-5*01 (2) >1'_IGHJ5*01	1690	gnl|Fabrus|A14_IGKJ1*01	1074
3237	VH3-23_IGHD5-5*01 (2) >3'_IGHJ5*01	1691	gnl|Fabrus|A14_IGKJ1*01	1074
3238	VH3-23_IGHD5-12*01>1'_IGHJ5*01	1692	gnl|Fabrus|A14_IGKJ1*01	1074
3239	VH3-23_IGHD5-12*01>3'_IGHJ5*01	1693	gnl|Fabrus|A14_IGKJ1*01	1074
3240	VH3-23_IGHD5-18*01 (2) >1'_IGHJ5*01	1694	gnl|Fabrus|A14_IGKJ1*01	1074
3241	VH3-23_IGHD5-18*01 (2) >3'_IGHJ5*01	1695	gnl|Fabrus|A14_IGKJ1*01	1074
3242	VH3-23_IGHD5-24*01>1'_IGHJ5*01	1696	gnl|Fabrus|A14_IGKJ1*01	1074
3243	VH3-23_IGHD5-24*01>3'_IGHJ5*01	1697	gnl|Fabrus|A14_IGKJ1*01	1074
3244	VH3-23_IGHD6-6*01>1'_IGHJ5*01	1698	gnl|Fabrus|A14_IGKJ1*01	1074
3245	VH3-23_IGHD6-6*01>2'_IGHJ5*01	1699	gnl|Fabrus|A14_IGKJ1*01	1074
3246	VH3-23_IGHD6-6*01>3'_IGHJ5*01	1700	gnl|Fabrus|A14_IGKJ1*01	1074
3247	VH3-23_IGHD1-1*01>1_IGHJ5*01	1596	gnl|Fabrus|A27_IGKJ1*01	1080
3248	VH3-23_IGHD1-1*01>2_IGHJ5*01	1597	gnl|Fabrus|A27_IGKJ1*01	1080
3249	VH3-23_IGHD1-1*01>3_IGHJ5*01	1598	gnl|Fabrus|A27_IGKJ1*01	1080
3250	VH3-23_IGHD1-7*01>1_IGHJ5*01	1599	gnl|Fabrus|A27_IGKJ1*01	1080
3251	VH3-23_IGHD1-7*01>3_IGHJ5*01	1600	gnl|Fabrus|A27_IGKJ1*01	1080
3252	VH3-23_IGHD1-14*01>1_IGHJ5*01	1601	gnl|Fabrus|A27_IGKJ1*01	1080
3253	VH3-23_IGHD1-14*01>3_IGHJ5*01	1602	gnl|Fabrus|A27_IGKJ1*01	1080
3254	VH3-23_IGHD1-20*01>1_IGHJ5*01	1603	gnl|Fabrus|A27_IGKJ1*01	1080

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3255	VH3-23_IGHD1-20*01>3_IGHJ5*01	1604	gnl|Fabrus|A27_IGKJ1*01	1080
3256	VH3-23_IGHD1-26*01>1_IGHJ5*01	1605	gnl|Fabrus|A27_IGKJ1*01	1080
3257	VH3-23_IGHD1-26*01>3_IGHJ5*01	1606	gnl|Fabrus|A27_IGKJ1*01	1080
3258	VH3-23_IGHD2-2*01>2_IGHJ5*01	1607	gnl|Fabrus|A27_IGKJ1*01	1080
3259	VH3-23_IGHD2-2*01>3_IGHJ5*01	1608	gnl|Fabrus|A27_IGKJ1*01	1080
3260	VH3-23_IGHD2-8*01>2_IGHJ5*01	1609	gnl|Fabrus|A27_IGKJ1*01	1080
3261	VH3-23_IGHD2-8*01>3_IGHJ5*01	1610	gnl|Fabrus|A27_IGKJ1*01	1080
3262	VH3-23_IGHD2-15*01>2_IGHJ5*01	1611	gnl|Fabrus|A27_IGKJ1*01	1080
3263	VH3-23_IGHD2-15*01>3_IGHJ5*01	1612	gnl|Fabrus|A27_IGKJ1*01	1080
3264	VH3-23_IGHD2-21*01>2_IGHJ5*01	1613	gnl|Fabrus|A27_IGKJ1*01	1080
3265	VH3-23_IGHD2-21*01>3_IGHJ5*01	1614	gnl|Fabrus|A27_IGKJ1*01	1080
3266	VH3-23_IGHD3-3*01>1_IGHJ5*01	1615	gnl|Fabrus|A27_IGKJ1*01	1080
3267	VH3-23_IGHD3-3*01>2_IGHJ5*01	1616	gnl|Fabrus|A27_IGKJ1*01	1080
3268	VH3-23_IGHD3-3*01>3_IGHJ5*01	1617	gnl|Fabrus|A27_IGKJ1*01	1080
3269	VH3-23_IGHD3-9*01>2_IGHJ5*01	1618	gnl|Fabrus|A27_IGKJ1*01	1080
3270	VH3-23_IGHD3-10*01>2_IGHJ5*01	1619	gnl|Fabrus|A27_IGKJ1*01	1080
3271	VH3-23_IGHD3-10*01>3_IGHJ5*01	1620	gnl|Fabrus|A27_IGKJ1*01	1080
3272	VH3-23_IGHD3-16*01>2_IGHJ5*01	1621	gnl|Fabrus|A27_IGKJ1*01	1080
3273	VH3-23_IGHD3-16*01>3_IGHJ5*01	1622	gnl|Fabrus|A27_IGKJ1*01	1080
3274	VH3-23_IGHD3-22*01>2_IGHJ5*01	1623	gnl|Fabrus|A27_IGKJ1*01	1080
3275	VH3-23_IGHD3-22*01>3_IGHJ5*01	1624	gnl|Fabrus|A27_IGKJ1*01	1080
3276	VH3-23_IGHD4-4*01 (1) >2_IGHJ5*01	1625	gnl|Fabrus|A27_IGKJ1*01	1080
3277	VH3-23_IGHD4-4*01 (1) >3_IGHJ5*01	1626	gnl|Fabrus|A27_IGKJ1*01	1080
3278	VH3-23_IGHD4-11*01 (1) >2_IGHJ5*01	1627	gnl|Fabrus|A27_IGKJ1*01	1080
3279	VH3-23_IGHD4-11*01 (1) >3_IGHJ5*01	1628	gnl|Fabrus|A27_IGKJ1*01	1080
3280	VH3-23_IGHD4-17*01>2_IGHJ5*01	1629	gnl|Fabrus|A27_IGKJ1*01	1080
3281	VH3-23_IGHD4-17*01>3_IGHJ5*01	1630	gnl|Fabrus|A27_IGKJ1*01	1080
3282	VH3-23_IGHD4-23*01>2_IGHJ5*01	1631	gnl|Fabrus|A27_IGKJ1*01	1080
3283	VH3-23_IGHD4-23*01>3_IGHJ5*01	1632	gnl|Fabrus|A27_IGKJ1*01	1080
3284	VH3-23_IGHD5-5*01 (2) >1_IGHJ5*01	1633	gnl|Fabrus|A27_IGKJ1*01	1080
3285	VH3-23_IGHD5-5*01 (2) >2_IGHJ5*01	1634	gnl|Fabrus|A27_IGKJ1*01	1080
3286	VH3-23_IGHD5-5*01 (2) >3_IGHJ5*01	1635	gnl|Fabrus|A27_IGKJ1*01	1080
3287	VH3-23_IGHD5-12*01>1_IGHJ5*01	1636	gnl|Fabrus|A27_IGKJ1*01	1080
3288	VH3-23_IGHD5-12*01>3_IGHJ5*01	1637	gnl|Fabrus|A27_IGKJ1*01	1080
3289	VH3-23_IGHD5-18*01 (2) >1_IGHJ5*01	1638	gnl|Fabrus|A27_IGKJ1*01	1080
3290	VH3-23_IGHD5-18*01 (2) >2_IGHJ5*01	1639	gnl|Fabrus|A27_IGKJ1*01	1080
3291	VH3-23_IGHD5-18*01 (2) >3_IGHJ5*01	1640	gnl|Fabrus|A27_IGKJ1*01	1080
3292	VH3-23_IGHD5-24*01>1_IGHJ5*01	1641	gnl|Fabrus|A27_IGKJ1*01	1080
3293	VH3-23_IGHD5-24*01>3_IGHJ5*01	1642	gnl|Fabrus|A27_IGKJ1*01	1080
3294	VH3-23_IGHD6-6*01>1_IGHJ5*01	1643	gnl|Fabrus|A27_IGKJ1*01	1080
3295	VH3-23_IGHD1-1*01>1'_IGHJ5*01	1653	gnl|Fabrus|A27_IGKJ1*01	1080
3296	VH3-23_IGHD1-1*01>2'_IGHJ5*01	1654	gnl|Fabrus|A27_IGKJ1*01	1080

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3297	VH3-23_IGHD1-1*01>3'_IGHJ5*01	1655	gnl|Fabrus|A27_IGKJ1*01	1080
3298	VH3-23_IGHD1-7*01>1'_IGHJ5*01	1656	gnl|Fabrus|A27_IGKJ1*01	1080
3299	VH3-23_IGHD1-7*01>3'_IGHJ5*01	1657	gnl|Fabrus|A27_IGKJ1*01	1080
3300	VH3-23_IGHD1-14*01>1'_IGHJ5*01	1658	gnl|Fabrus|A27_IGKJ1*01	1080
3301	VH3-23_IGHD1-14*01>2'_IGHJ5*01	1659	gnl|Fabrus|A27_IGKJ1*01	1080
3302	VH3-23_IGHD1-14*01>3'_IGHJ5*01	1660	gnl|Fabrus|A27_IGKJ1*01	1080
3303	VH3-23_IGHD1-20*01>1'_IGHJ5*01	1661	gnl|Fabrus|A27_IGKJ1*01	1080
3304	VH3-23_IGHD1-20*01>2'_IGHJ5*01	1662	gnl|Fabrus|A27_IGKJ1*01	1080
3305	VH3-23_IGHD1-20*01>3'_IGHJ5*01	1663	gnl|Fabrus|A27_IGKJ1*01	1080
3306	VH3-23_IGHD1-26*01>1'_IGHJ5*01	1664	gnl|Fabrus|A27_IGKJ1*01	1080
3307	VH3-23_IGHD1-26*01>3'_IGHJ5*01	1665	gnl|Fabrus|A27_IGKJ1*01	1080
3308	VH3-23_IGHD2-2*01>1'_IGHJ5*01	1666	gnl|Fabrus|A27_IGKJ1*01	1080
3309	VH3-23_IGHD2-2*01>3'_IGHJ5*01	1667	gnl|Fabrus|A27_IGKJ1*01	1080
3310	VH3-23_IGHD2-8*01>1'_IGHJ5*01	1668	gnl|Fabrus|A27_IGKJ1*01	1080
3311	VH3-23_IGHD2-15*01>1'_IGHJ5*01	1669	gnl|Fabrus|A27_IGKJ1*01	1080
3312	VH3-23_IGHD2-15*01>3'_IGHJ5*01	1670	gnl|Fabrus|A27_IGKJ1*01	1080
3313	VH3-23_IGHD2-21*01>1'_IGHJ5*01	1671	gnl|Fabrus|A27_IGKJ1*01	1080
3314	VH3-23_IGHD2-21*01>3'_IGHJ5*01	1672	gnl|Fabrus|A27_IGKJ1*01	1080
3315	VH3-23_IGHD3-3*01>1'_IGHJ5*01	1673	gnl|Fabrus|A27_IGKJ1*01	1080
3316	VH3-23_IGHD3-3*01>3'_IGHJ5*01	1674	gnl|Fabrus|A27_IGKJ1*01	1080
3317	VH3-23_IGHD3-9*01>1'_IGHJ5*01	1675	gnl|Fabrus|A27_IGKJ1*01	1080
3318	VH3-23_IGHD3-9*01>3'_IGHJ5*01	1676	gnl|Fabrus|A27_IGKJ1*01	1080
3319	VH3-23_IGHD3-10*01>1'_IGHJ5*01	1677	gnl|Fabrus|A27_IGKJ1*01	1080
3320	VH3-23_IGHD3-10*01>3'_IGHJ5*01	1678	gnl|Fabrus|A27_IGKJ1*01	1080
3321	VH3-23_IGHD3-16*01>1'_IGHJ5*01	1679	gnl|Fabrus|A27_IGKJ1*01	1080
3322	VH3-23_IGHD3-16*01>3'_IGHJ5*01	1680	gnl|Fabrus|A27_IGKJ1*01	1080
3323	VH3-23_IGHD3-22*01>1'_IGHJ5*01	1681	gnl|Fabrus|A27_IGKJ1*01	1080
3324	VH3-23_IGHD4-4*01 (1) >1'_IGHJ5*01	1682	gnl|Fabrus|A27_IGKJ1*01	1080
3325	VH3-23_IGHD4-4*01 (1) >3'_IGHJ5*01	1683	gnl|Fabrus|A27_IGKJ1*01	1080
3326	VH3-23_IGHD4-11*01 (1) >1'_IGHJ5*01	1684	gnl|Fabrus|A27_IGKJ1*01	1080
3327	VH3-23_IGHD4-11*01 (1) >3'_IGHJ5*01	1685	gnl|Fabrus|A27_IGKJ1*01	1080
3328	VH3-23_IGHD4-17*01>1'_IGHJ5*01	1686	gnl|Fabrus|A27_IGKJ1*01	1080
3329	VH3-23_IGHD4-17*01>3'_IGHJ5*01	1687	gnl|Fabrus|A27_IGKJ1*01	1080
3330	VH3-23_IGHD4-23*01>1'_IGHJ5*01	1688	gnl|Fabrus|A27_IGKJ1*01	1080
3331	VH3-23_IGHD4-23*01>3'_IGHJ5*01	1689	gnl|Fabrus|A27_IGKJ1*01	1080
3332	VH3-23_IGHD5-5*01 (2) >1'_IGHJ5*01	1690	gnl|Fabrus|A27_IGKJ1*01	1080
3333	VH3-23_IGHD5-5*01 (2) >3'_IGHJ5*01	1691	gnl|Fabrus|A27_IGKJ1*01	1080
3334	VH3-23_IGHD5-12*01>1'_IGHJ5*01	1692	gnl|Fabrus|A27_IGKJ1*01	1080
3335	VH3-23_IGHD5-12*01>3'_IGHJ5*01	1693	gnl|Fabrus|A27_IGKJ1*01	1080
3336	VH3-23_IGHD5-18*01 (2) >1'_IGHJ5*01	1694	gnl|Fabrus|A27_IGKJ1*01	1080
3337	VH3-23_IGHD5-18*01 (2) >3'_IGHJ5*01	1695	gnl|Fabrus|A27_IGKJ1*01	1080
3338	VH3-23_IGHD5-24*01>1'_IGHJ5*01	1696	gnl|Fabrus|A27_IGKJ1*01	1080

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3339	VH3-23_IGHD5-24*01>3'_IGHJ5*01	1697	gnl|Fabrus|A27_IGKJ1*01	1080
3340	VH3-23_IGHD6-6*01>1'_IGHJ5*01	1698	gnl|Fabrus|A27_IGKJ1*01	1080
3341	VH3-23_IGHD6-6*01>2'_IGHJ5*01	1699	gnl|Fabrus|A27_IGKJ1*01	1080
3342	VH3-23_IGHD6-6*01>3'_IGHJ5*01	1700	gnl|Fabrus|A27_IGKJ1*01	1080
3343	VH3-23_IGHD6-6*01>2_IGHJ1*01	1184	gnl|Fabrus|V1-11_IGLJ2*01	1104
3344	VH3-23_IGHD6-13*01>1_IGHJ1*01	1185	gnl|Fabrus|V1-11_IGLJ2*01	1104
3345	VH3-23_IGHD6-13*01>2_IGHJ1*01	1186	gnl|Fabrus|V1-11_IGLJ2*01	1104
3346	VH3-23_IGHD6-19*01>1_IGHJ1*01	1187	gnl|Fabrus|V1-11_IGLJ2*01	1104
3347	VH3-23_IGHD6-19*01>2_IGHJ1*01	1188	gnl|Fabrus|V1-11_IGLJ2*01	1104
3348	VH3-23_IGHD6-25*01>1_IGHJ1*01	1189	gnl|Fabrus|V1-11_IGLJ2*01	1104
3349	VH3-23_IGHD6-25*01>2_IGHJ1*01	1190	gnl|Fabrus|V1-11_IGLJ2*01	1104
3350	VH3-23_IGHD7-27*01>1_IGHJ1*01	1191	gnl|Fabrus|V1-11_IGLJ2*01	1104
3351	VH3-23_IGHD7-27*01>3_IGHJ1*01	1192	gnl|Fabrus|V1-11_IGLJ2*01	1104
3352	VH3-23_IGHD6-13*01>1'_IGHJ1*01	1241	gnl|Fabrus|V1-11_IGLJ2*01	1104
3353	VH3-23_IGHD6-13*01>2'_IGHJ1*01	1242	gnl|Fabrus|V1-11_IGLJ2*01	1104
3354	VH3-23_IGHD6-13*01>2_IGHJ1*01_B	1243	gnl|Fabrus|V1-11_IGLJ2*01	1104
3355	VH3-23_IGHD6-19*01>1'_IGHJ1*01	1244	gnl|Fabrus|V1-11_IGLJ2*01	1104
3356	VH3-23_IGHD6-19*01>2'_IGHJ1*01	1245	gnl|Fabrus|V1-11_IGLJ2*01	1104
3357	VH3-23_IGHD6-19*01>2_IGHJ1*01_B	1246	gnl|Fabrus|V1-11_IGLJ2*01	1104
3358	VH3-23_IGHD6-25*01>1'_IGHJ1*01	1247	gnl|Fabrus|V1-11_IGLJ2*01	1104
3359	VH3-23_IGHD6-25*01>3'_IGHJ1*01	1248	gnl|Fabrus|V1-11_IGLJ2*01	1104
3360	VH3-23_IGHD7-27*01>1'_IGHJ1*01_B	1249	gnl|Fabrus|V1-11_IGLJ2*01	1104
3361	VH3-23_IGHD7-27*01>2'_IGHJ1*01	1250	gnl|Fabrus|V1-11_IGLJ2*01	1104
3362	VH3-23_IGHD6-6*01>2_IGHJ2*01	1299	gnl|Fabrus|V1-11_IGLJ2*01	1104
3363	VH3-23_IGHD6-13*01>1_IGHJ2*01	1300	gnl|Fabrus|V1-11_IGLJ2*01	1104
3364	VH3-23_IGHD6-13*01>2_IGHJ2*01	1301	gnl|Fabrus|V1-11_IGLJ2*01	1104
3365	VH3-23_IGHD6-19*01>1_IGHJ2*01	1302	gnl|Fabrus|V1-11_IGLJ2*01	1104
3366	VH3-23_IGHD6-19*01>2_IGHJ2*01	1303	gnl|Fabrus|V1-11_IGLJ2*01	1104
3367	VH3-23_IGHD6-25*01>1_IGHJ2*01	1304	gnl|Fabrus|V1-11_IGLJ2*01	1104
3368	VH3-23_IGHD6-25*01>2_IGHJ2*01	1305	gnl|Fabrus|V1-11_IGLJ2*01	1104
3369	VH3-23_IGHD7-27*01>1_IGHJ2*01	1306	gnl|Fabrus|V1-11_IGLJ2*01	1104
3370	VH3-23_IGHD7-27*01>3_IGHJ2*01	1307	gnl|Fabrus|V1-11_IGLJ2*01	1104
3371	VH3-23_IGHD6-13*01>1'_IGHJ2*01	1356	gnl|Fabrus|V1-11_IGLJ2*01	1104
3372	VH3-23_IGHD6-13*01>2'_IGHJ2*01	1357	gnl|Fabrus|V1-11_IGLJ2*01	1104
3373	VH3-23_IGHD6-13*01>2_IGHJ2*01_B	1358	gnl|Fabrus|V1-11_IGLJ2*01	1104
3374	VH3-23_IGHD6-19*01>1'_IGHJ2*01	1359	gnl|Fabrus|V1-11_IGLJ2*01	1104
3375	VH3-23_IGHD6-19*01>2'_IGHJ2*01	1360	gnl|Fabrus|V1-11_IGLJ2*01	1104
3376	VH3-23_IGHD6-19*01>2_IGHJ2*01_B	1361	gnl|Fabrus|V1-11_IGLJ2*01	1104
3377	VH3-23_IGHD6-25*01>1'_IGHJ2*01	1362	gnl|Fabrus|V1-11_IGLJ2*01	1104
3378	VH3-23_IGHD6-25*01>3'_IGHJ2*01	1363	gnl|Fabrus|V1-11_IGLJ2*01	1104
3379	VH3-23_IGHD7-27*01>1'_IGHJ2*01	1364	gnl|Fabrus|V1-11_IGLJ2*01	1104
3380	VH3-23_IGHD7-27*01>2'_IGHJ2*01	1365	gnl|Fabrus|V1-11_IGLJ2*01	1104

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3381	VH3-23_IGHD6-6*01>2_IGHJ3*01	1414	gnl|Fabrus|V1-11_IGLJ2*01	1104
3382	VH3-23_IGHD6-13*01>1_IGHJ3*01	1415	gnl|Fabrus|V1-11_IGLJ2*01	1104
3383	VH3-23_IGHD6-13*01>2_IGHJ3*01	1416	gnl|Fabrus|V1-11_IGLJ2*01	1104
3384	VH3-23_IGHD6-19*01>1_IGHJ3*01	1417	gnl|Fabrus|V1-11_IGLJ2*01	1104
3385	VH3-23_IGHD6-19*01>2_IGHJ3*01	1418	gnl|Fabrus|V1-11_IGLJ2*01	1104
3386	VH3-23_IGHD6-25*01>1_IGHJ3*01	1419	gnl|Fabrus|V1-11_IGLJ2*01	1104
3387	VH3-23_IGHD6-25*01>2_IGHJ3*01	1420	gnl|Fabrus|V1-11_IGLJ2*01	1104
3388	VH3-23_IGHD7-27*01>1_IGHJ3*01	1421	gnl|Fabrus|V1-11_IGLJ2*01	1104
3389	VH3-23_IGHD7-27*01>3_IGHJ3*01	1422	gnl|Fabrus|V1-11_IGLJ2*01	1104
3390	VH3-23_IGHD6-13*01>1'_IGHJ3*01	1471	gnl|Fabrus|V1-11_IGLJ2*01	1104
3391	VH3-23_IGHD6-13*01>2'_IGHJ3*01	1472	gnl|Fabrus|V1-11_IGLJ2*01	1104
3392	VH3-23_IGHD6-13*01>3'_IGHJ6*01	1818	gnl|Fabrus|V1-11_IGLJ2*01	1104
3393	VH3-23_IGHD6-19*01>1'_IGHJ3*01	1474	gnl|Fabrus|V1-11_IGLJ2*01	1104
3394	VH3-23_IGHD6-19*01>2'_IGHJ3*01	1475	gnl|Fabrus|V1-11_IGLJ2*01	1104
3395	VH3-23_IGHD6-19*01>3'_IGHJ3*01	1476	gnl|Fabrus|V1-11_IGLJ2*01	1104
3396	VH3-23_IGHD6-25*01>1'_IGHJ3*01	1477	gnl|Fabrus|V1-11_IGLJ2*01	1104
3397	VH3-23_IGHD6-25*01>3'_IGHJ3*01	1478	gnl|Fabrus|V1-11_IGLJ2*01	1104
3398	VH3-23_IGHD7-27*01>1'_IGHJ3*01	1479	gnl|Fabrus|V1-11_IGLJ2*01	1104
3399	VH3-23_IGHD7-27*01>2'_IGHJ3*01	1480	gnl|Fabrus|V1-11_IGLJ2*01	1104
3400	VH3-23_IGHD6-6*01>2_IGHJ4*01	1529	gnl|Fabrus|V1-11_IGLJ2*01	1104
3401	VH3-23_IGHD6-13*01>1_IGHJ4*01	1530	gnl|Fabrus|V1-11_IGLJ2*01	1104
3402	VH3-23_IGHD6-13*01>2_IGHJ4*01	1531	gnl|Fabrus|V1-11_IGLJ2*01	1104
3403	VH3-23_IGHD6-19*01>1_IGHJ4*01	1532	gnl|Fabrus|V1-11_IGLJ2*01	1104
3404	VH3-23_IGHD6-19*01>2_IGHJ4*01	1533	gnl|Fabrus|V1-11_IGLJ2*01	1104
3405	VH3-23_IGHD6-25*01>1_IGHJ4*01	1534	gnl|Fabrus|V1-11_IGLJ2*01	1104
3406	VH3-23_IGHD6-25*01>2_IGHJ4*01	1535	gnl|Fabrus|V1-11_IGLJ2*01	1104
3407	VH3-23_IGHD7-27*01>1_IGHJ4*01	1536	gnl|Fabrus|V1-11_IGLJ2*01	1104
3408	VH3-23_IGHD7-27*01>3_IGHJ4*01	1537	gnl|Fabrus|V1-11_IGLJ2*01	1104
3409	VH3-23_IGHD6-13*01>1'_IGHJ4*01	1586	gnl|Fabrus|V1-11_IGLJ2*01	1104
3410	VH3-23_IGHD6-13*01>2'_IGHJ4*01	1587	gnl|Fabrus|V1-11_IGLJ2*01	1104
3411	VH3-23_IGHD6-13*01>2_IGHJ4*01_B	1588	gnl|Fabrus|V1-11_IGLJ2*01	1104
3412	VH3-23_IGHD6-19*01>1'_IGHJ4*01	1589	gnl|Fabrus|V1-11_IGLJ2*01	1104
3413	VH3-23_IGHD6-19*01>2'_IGHJ4*01	1590	gnl|Fabrus|V1-11_IGLJ2*01	1104
3414	VH3-23_IGHD6-19*01>2_IGHJ4*01_B	1591	gnl|Fabrus|V1-11_IGLJ2*01	1104
3415	VH3-23_IGHD6-25*01>1'_IGHJ4*01	1592	gnl|Fabrus|V1-11_IGLJ2*01	1104
3416	VH3-23_IGHD6-25*01>3'_IGHJ4*01	1593	gnl|Fabrus|V1-11_IGLJ2*01	1104
3417	VH3-23_IGHD7-27*01>1'_IGHJ4*01	1594	gnl|Fabrus|V1-11_IGLJ2*01	1104
3418	VH3-23_IGHD7-27*01>2'_IGHJ4*01	1595	gnl|Fabrus|V1-11_IGLJ2*01	1104
3419	VH3-23_IGHD6-6*01>2_IGHJ5*01	1644	gnl|Fabrus|V1-11_IGLJ2*01	1104
3420	VH3-23_IGHD6-13*01>1_IGHJ5*01	1645	gnl|Fabrus|V1-11_IGLJ2*01	1104
3421	VH3-23_IGHD6-13*01>2_IGHJ5*01	1646	gnl|Fabrus|V1-11_IGLJ2*01	1104
3422	VH3-23_IGHD6-19*01>1_IGHJ5*01	1647	gnl|Fabrus|V1-11_IGLJ2*01	1104

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3423	VH3-23_IGHD6-19*01>2_IGHJ5*01	1648	gnl|Fabrus|V1-11_IGLJ2*01	1104
3424	VH3-23_IGHD6-25*01>1_IGHJ5*01	1649	gnl|Fabrus|V1-11_IGLJ2*01	1104
3425	VH3-23_IGHD6-25*01>2_IGHJ5*01	1650	gnl|Fabrus|V1-11_IGLJ2*01	1104
3426	VH3-23_IGHD7-27*01>1_IGHJ5*01	1651	gnl|Fabrus|V1-11_IGLJ2*01	1104
3427	VH3-23_IGHD7-27*01>3_IGHJ5*01	1652	gnl|Fabrus|V1-11_IGLJ2*01	1104
3428	VH3-23_IGHD6-13*01>1'_IGHJ5*01	1701	gnl|Fabrus|V1-11_IGLJ2*01	1104
3429	VH3-23_IGHD6-13*01>2'_IGHJ5*01	1702	gnl|Fabrus|V1-11_IGLJ2*01	1104
3430	VH3-23_IGHD6-13*01>3'_IGHJ5*01	1703	gnl|Fabrus|V1-11_IGLJ2*01	1104
3431	VH3-23_IGHD6-19*01>1'_IGHJ5*01	1704	gnl|Fabrus|V1-11_IGLJ2*01	1104
3432	VH3-23_IGHD6-19*01>2'_IGHJ5*01	1705	gnl|Fabrus|V1-11_IGLJ2*01	1104
3433	VH3-23_IGHD6-19*01>2_IGHJ5*01_B	1706	gnl|Fabrus|V1-11_IGLJ2*01	1104
3434	VH3-23_IGHD6-25*01>1'_IGHJ5*01	1707	gnl|Fabrus|V1-11_IGLJ2*01	1104
3435	VH3-23_IGHD6-25*01>3'_IGHJ5*01	1708	gnl|Fabrus|V1-11_IGLJ2*01	1104
3436	VH3-23_IGHD7-27*01>1'_IGHJ5*01	1709	gnl|Fabrus|V1-11_IGLJ2*01	1104
3437	VH3-23_IGHD7-27*01>2'_IGHJ5*01	1710	gnl|Fabrus|V1-11_IGLJ2*01	1104
3438	VH3-23_IGHD6-6*01>2_IGHJ6*01	1759	gnl|Fabrus|V1-11_IGLJ2*01	1104
3439	VH3-23_IGHD6-6*01>2_IGHJ1*01	1184	gnl|Fabrus|V1-13_IGLJ5*01	1105
3440	VH3-23_IGHD6-13*01>1_IGHJ1*01	1185	gnl|Fabrus|V1-13_IGLJ5*01	1105
3441	VH3-23_IGHD6-13*01>2_IGHJ1*01	1186	gnl|Fabrus|V1-13_IGLJ5*01	1105
3442	VH3-23_IGHD6-19*01>1_IGHJ1*01	1187	gnl|Fabrus|V1-13_IGLJ5*01	1105
3443	VH3-23_IGHD6-19*01>2_IGHJ1*01	1188	gnl|Fabrus|V1-13_IGLJ5*01	1105
3444	VH3-23_IGHD6-25*01>1_IGHJ1*01	1189	gnl|Fabrus|V1-13_IGLJ5*01	1105
3445	VH3-23_IGHD6-25*01>2_IGHJ1*01	1190	gnl|Fabrus|V1-13_IGLJ5*01	1105
3446	VH3-23_IGHD7-27*01>1_IGHJ1*01	1191	gnl|Fabrus|V1-13_IGLJ5*01	1105
3447	VH3-23_IGHD7-27*01>3_IGHJ1*01	1192	gnl|Fabrus|V1-13_IGLJ5*01	1105
3448	VH3-23_IGHD6-13*01>1'_IGHJ1*01	1241	gnl|Fabrus|V1-13_IGLJ5*01	1105
3449	VH3-23_IGHD6-13*01>2'_IGHJ1*01	1242	gnl|Fabrus|V1-13_IGLJ5*01	1105
3450	VH3-23_IGHD6-13*01>2_IGHJ1*01_B	1243	gnl|Fabrus|V1-13_IGLJ5*01	1105
3451	VH3-23_IGHD6-19*01>1'_IGHJ1*01	1244	gnl|Fabrus|V1-13_IGLJ5*01	1105
3452	VH3-23_IGHD6-19*01>2'_IGHJ1*01	1245	gnl|Fabrus|V1-13_IGLJ5*01	1105
3453	VH3-23_IGHD6-19*01>2_IGHJ1*01_B	1246	gnl|Fabrus|V1-13_IGLJ5*01	1105
3454	VH3-23_IGHD6-25*01>1'_IGHJ1*01	1247	gnl|Fabrus|V1-13_IGLJ5*01	1105
3455	VH3-23_IGHD6-25*01>3'_IGHJ1*01	1248	gnl|Fabrus|V1-13_IGLJ5*01	1105
3456	VH3-23_IGHD7-27*01>1'_IGHJ1*01_B	1249	gnl|Fabrus|V1-13_IGLJ5*01	1105
3457	VH3-23_IGHD7-27*01>2'_IGHJ1*01	1250	gnl|Fabrus|V1-13_IGLJ5*01	1105
3458	VH3-23_IGHD6-6*01>2_IGHJ2*01	1299	gnl|Fabrus|V1-13_IGLJ5*01	1105
3459	VH3-23_IGHD6-13*01>1_IGHJ2*01	1300	gnl|Fabrus|V1-13_IGLJ5*01	1105
3460	VH3-23_IGHD6-13*01>2_IGHJ2*01	1301	gnl|Fabrus|V1-13_IGLJ5*01	1105
3461	VH3-23_IGHD6-19*01>1_IGHJ2*01	1302	gnl|Fabrus|V1-13_IGLJ5*01	1105
3462	VH3-23_IGHD6-19*01>2_IGHJ2*01	1303	gnl|Fabrus|V1-13_IGLJ5*01	1105
3463	VH3-23_IGHD6-25*01>1_IGHJ2*01	1304	gnl|Fabrus|V1-13_IGLJ5*01	1105
3464	VH3-23_IGHD6-25*01>2_IGHJ2*01	1305	gnl|Fabrus|V1-13_IGLJ5*01	1105

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3465	VH3-23_IGHD7-27*01>1_IGHJ2*01	1306	gnl|Fabrus|V1-13_IGLJ5*01	1105
3466	VH3-23_IGHD7-27*01>3_IGHJ2*01	1307	gnl|Fabrus|V1-13_IGLJ5*01	1105
3467	VH3-23_IGHD6-13*01>1'_IGHJ2*01	1356	gnl|Fabrus|V1-13_IGLJ5*01	1105
3468	VH3-23_IGHD6-13*01>2'_IGHJ2*01	1357	gnl|Fabrus|V1-13_IGLJ5*01	1105
3469	VH3-23_IGHD6-13*01>2_IGHJ2*01_B	1358	gnl|Fabrus|V1-13_IGLJ5*01	1105
3470	VH3-23_IGHD6-19*01>1'_IGHJ2*01	1359	gnl|Fabrus|V1-13_IGLJ5*01	1105
3471	VH3-23_IGHD6-19*01>2'_IGHJ2*01	1360	gnl|Fabrus|V1-13_IGLJ5*01	1105
3472	VH3-23_IGHD6-19*01>2_IGHJ2*01_B	1361	gnl|Fabrus|V1-13_IGLJ5*01	1105
3473	VH3-23_IGHD6-25*01>1'_IGHJ2*01	1362	gnl|Fabrus|V1-13_IGLJ5*01	1105
3474	VH3-23_IGHD6-25*01>3'_IGHJ2*01	1363	gnl|Fabrus|V1-13_IGLJ5*01	1105
3475	VH3-23_IGHD7-27*01>1'_IGHJ2*01	1364	gnl|Fabrus|V1-13_IGLJ5*01	1105
3476	VH3-23_IGHD7-27*01>2'_IGHJ2*01	1365	gnl|Fabrus|V1-13_IGLJ5*01	1105
3477	VH3-23_IGHD6-6*01>2_IGHJ3*01	1414	gnl|Fabrus|V1-13_IGLJ5*01	1105
3478	VH3-23_IGHD6-13*01>1_IGHJ3*01	1415	gnl|Fabrus|V1-13_IGLJ5*01	1105
3479	VH3-23_IGHD6-13*01>2_IGHJ3*01	1416	gnl|Fabrus|V1-13_IGLJ5*01	1105
3480	VH3-23_IGHD6-19*01>1_IGHJ3*01	1417	gnl|Fabrus|V1-13_IGLJ5*01	1105
3481	VH3-23_IGHD6-19*01>2_IGHJ3*01	1418	gnl|Fabrus|V1-13_IGLJ5*01	1105
3482	VH3-23_IGHD6-25*01>1_IGHJ3*01	1419	gnl|Fabrus|V1-13_IGLJ5*01	1105
3483	VH3-23_IGHD6-25*01>2_IGHJ3*01	1420	gnl|Fabrus|V1-13_IGLJ5*01	1105
3484	VH3-23_IGHD7-27*01>1_IGHJ3*01	1421	gnl|Fabrus|V1-13_IGLJ5*01	1105
3485	VH3-23_IGHD7-27*01>3_IGHJ3*01	1422	gnl|Fabrus|V1-13_IGLJ5*01	1105
3486	VH3-23_IGHD6-13*01>1'_IGHJ3*01	1471	gnl|Fabrus|V1-13_IGLJ5*01	1105
3487	VH3-23_IGHD6-13*01>2'_IGHJ3*01	1472	gnl|Fabrus|V1-13_IGLJ5*01	1105
3488	VH3-23_IGHD6-13*01>1_IGHJ6*01	1818	gnl|Fabrus|V1-13_IGLJ5*01	1105
3489	VH3-23_IGHD6-19*01>1'_IGHJ3*01	1474	gnl|Fabrus|V1-13_IGLJ5*01	1105
3490	VH3-23_IGHD6-19*01>2'_IGHJ3*01	1475	gnl|Fabrus|V1-13_IGLJ5*01	1105
3491	VH3-23_IGHD6-19*01>3'_IGHJ3*01	1476	gnl|Fabrus|V1-13_IGLJ5*01	1105
3492	VH3-23_IGHD6-25*01>1'_IGHJ3*01	1477	gnl|Fabrus|V1-13_IGLJ5*01	1105
3493	VH3-23_IGHD6-25*01>3'_IGHJ3*01	1478	gnl|Fabrus|V1-13_IGLJ5*01	1105
3494	VH3-23_IGHD7-27*01>1'_IGHJ3*01	1479	gnl|Fabrus|V1-13_IGLJ5*01	1105
3495	VH3-23_IGHD7-27*01>2'_IGHJ3*01	1480	gnl|Fabrus|V1-13_IGLJ5*01	1105
3496	VH3-23_IGHD6-6*01>2_IGHJ4*01	1529	gnl|Fabrus|V1-13_IGLJ5*01	1105
3497	VH3-23_IGHD6-13*01>1_IGHJ4*01	1530	gnl|Fabrus|V1-13_IGLJ5*01	1105
3498	VH3-23_IGHD6-13*01>2_IGHJ4*01	1531	gnl|Fabrus|V1-13_IGLJ5*01	1105
3499	VH3-23_IGHD6-19*01>1_IGHJ4*01	1532	gnl|Fabrus|V1-13_IGLJ5*01	1105
3500	VH3-23_IGHD6-19*01>2_IGHJ4*01	1533	gnl|Fabrus|V1-13_IGLJ5*01	1105
3501	VH3-23_IGHD6-25*01>1_IGHJ4*01	1534	gnl|Fabrus|V1-13_IGLJ5*01	1105
3502	VH3-23_IGHD6-25*01>2_IGHJ4*01	1535	gnl|Fabrus|V1-13_IGLJ5*01	1105
3503	VH3-23_IGHD7-27*01>1_IGHJ4*01	1536	gnl|Fabrus|V1-13_IGLJ5*01	1105
3504	VH3-23_IGHD7-27*01>3_IGHJ4*01	1537	gnl|Fabrus|V1-13_IGLJ5*01	1105
3505	VH3-23_IGHD6-13*01>1'_IGHJ4*01	1586	gnl|Fabrus|V1-13_IGLJ5*01	1105
3506	VH3-23_IGHD6-13*01>2'_IGHJ4*01	1587	gnl|Fabrus|V1-13_IGLJ5*01	1105

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3507	VH3-23_IGHD6-13*01>2_IGHJ4*01_B	1588	gnl|Fabrus|V1-13_IGLJ5*01	1105
3508	VH3-23_IGHD6-19*01>1'_IGHJ4*01	1589	gnl|Fabrus|V1-13_IGLJ5*01	1105
3509	VH3-23_IGHD6-19*01>2'_IGHJ4*01	1590	gnl|Fabrus|V1-13_IGLJ5*01	1105
3510	VH3-23_IGHD6-19*01>2_IGHJ4*01_B	1591	gnl|Fabrus|V1-13_IGLJ5*01	1105
3511	VH3-23_IGHD6-25*01>1'_IGHJ4*01	1592	gnl|Fabrus|V1-13_IGLJ5*01	1105
3512	VH3-23_IGHD6-25*01>3'_IGHJ4*01	1593	gnl|Fabrus|V1-13_IGLJ5*01	1105
3513	VH3-23_IGHD7-27*01>1'_IGHJ4*01	1594	gnl|Fabrus|V1-13_IGLJ5*01	1105
3514	VH3-23_IGHD7-27*01>2'_IGHJ4*01	1595	gnl|Fabrus|V1-13_IGLJ5*01	1105
3515	VH3-23_IGHD6-6*01>2_IGHJ5*01	1644	gnl|Fabrus|V1-13_IGLJ5*01	1105
3516	VH3-23_IGHD6-13*01>1_IGHJ5*01	1645	gnl|Fabrus|V1-13_IGLJ5*01	1105
3517	VH3-23_IGHD6-13*01>2_IGHJ5*01	1646	gnl|Fabrus|V1-13_IGLJ5*01	1105
3518	VH3-23_IGHD6-19*01>1_IGHJ5*01	1647	gnl|Fabrus|V1-13_IGLJ5*01	1105
3519	VH3-23_IGHD6-19*01>2_IGHJ5*01	1648	gnl|Fabrus|V1-13_IGLJ5*01	1105
3520	VH3-23_IGHD6-25*01>1_IGHJ5*01	1649	gnl|Fabrus|V1-13_IGLJ5*01	1105
3521	VH3-23_IGHD6-25*01>2_IGHJ5*01	1650	gnl|Fabrus|V1-13_IGLJ5*01	1105
3522	VH3-23_IGHD7-27*01>1_IGHJ5*01	1651	gnl|Fabrus|V1-13_IGLJ5*01	1105
3523	VH3-23_IGHD7-27*01>3_IGHJ5*01	1652	gnl|Fabrus|V1-13_IGLJ5*01	1105
3524	VH3-23_IGHD6-13*01>1'_IGHJ5*01	1701	gnl|Fabrus|V1-13_IGLJ5*01	1105
3525	VH3-23_IGHD6-13*01>2'_IGHJ5*01	1702	gnl|Fabrus|V1-13_IGLJ5*01	1105
3526	VH3-23_IGHD6-13*01>3'_IGHJ5*01	1703	gnl|Fabrus|V1-13_IGLJ5*01	1105
3527	VH3-23_IGHD6-19*01>1'_IGHJ5*01	1704	gnl|Fabrus|V1-13_IGLJ5*01	1105
3528	VH3-23_IGHD6-19*01>2'_IGHJ5*01	1705	gnl|Fabrus|V1-13_IGLJ5*01	1105
3529	VH3-23_IGHD6-19*01>2_IGHJ5*01_B	1706	gnl|Fabrus|V1-13_IGLJ5*01	1105
3530	VH3-23_IGHD6-25*01>1'_IGHJ5*01	1707	gnl|Fabrus|V1-13_IGLJ5*01	1105
3531	VH3-23_IGHD6-25*01>3'_IGHJ5*01	1708	gnl|Fabrus|V1-13_IGLJ5*01	1105
3532	VH3-23_IGHD7-27*01>1'_IGHJ5*01	1709	gnl|Fabrus|V1-13_IGLJ5*01	1105
3533	VH3-23_IGHD7-27*01>2'_IGHJ5*01	1710	gnl|Fabrus|V1-13_IGLJ5*01	1105
3534	VH3-23_IGHD6-6*01>2_IGHJ6*01	1759	gnl|Fabrus|V1-13_IGLJ5*01	1105
3535	VH3-23_IGHD6-6*01>2_IGHJ1*01	1184	gnl|Fabrus|V1-16_IGLJ6*01	1106
3536	VH3-23_IGHD6-13*01>1_IGHJ1*01	1185	gnl|Fabrus|V1-16_IGLJ6*01	1106
3537	VH3-23_IGHD6-13*01>2_IGHJ1*01	1186	gnl|Fabrus|V1-16_IGLJ6*01	1106
3538	VH3-23_IGHD6-19*01>1_IGHJ1*01	1187	gnl|Fabrus|V1-16_IGLJ6*01	1106
3539	VH3-23_IGHD6-19*01>2_IGHJ1*01	1188	gnl|Fabrus|V1-16_IGLJ6*01	1106
3540	VH3-23_IGHD6-25*01>1_IGHJ1*01	1189	gnl|Fabrus|V1-16_IGLJ6*01	1106
3541	VH3-23_IGHD6-25*01>2_IGHJ1*01	1190	gnl|Fabrus|V1-16_IGLJ6*01	1106
3542	VH3-23_IGHD7-27*01>1_IGHJ1*01	1191	gnl|Fabrus|V1-16_IGLJ6*01	1106
3543	VH3-23_IGHD7-27*01>3_IGHJ1*01	1192	gnl|Fabrus|V1-16_IGLJ6*01	1106
3544	VH3-23_IGHD6-13*01>1'_IGHJ1*01	1241	gnl|Fabrus|V1-16_IGLJ6*01	1106
3545	VH3-23_IGHD6-13*01>2'_IGHJ1*01	1242	gnl|Fabrus|V1-16_IGLJ6*01	1106
3546	VH3-23_IGHD6-13*01>2_IGHJ1*01_B	1243	gnl|Fabrus|V1-16_IGLJ6*01	1106
3547	VH3-23_IGHD6-19*01>1'_IGHJ1*01	1244	gnl|Fabrus|V1-16_IGLJ6*01	1106
3548	VH3-23_IGHD6-19*01>2'_IGHJ1*01	1245	gnl|Fabrus|V1-16_IGLJ6*01	1106

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3549	VH3-23_IGHD6-19*01>2_IGHJ1*01_B	1246	gnl|Fabrus|V1-16_IGLJ6*01	1106
3550	VH3-23_IGHD6-25*01>1'_IGHJ1*01	1247	gnl|Fabrus|V1-16_IGLJ6*01	1106
3551	VH3-23_IGHD6-25*01>3'_IGHJ1*01	1248	gnl|Fabrus|V1-16_IGLJ6*01	1106
3552	VH3-23_IGHD7-27*01>1'_IGHJ1*01_B	1249	gnl|Fabrus|V1-16_IGLJ6*01	1106
3553	VH3-23_IGHD7-27*01>2'_IGHJ1*01	1250	gnl|Fabrus|V1-16_IGLJ6*01	1106
3554	VH3-23_IGHD6-6*01>2_IGHJ2*01	1299	gnl|Fabrus|V1-16_IGLJ6*01	1106
3555	VH3-23_IGHD6-13*01>1_IGHJ2*01	1300	gnl|Fabrus|V1-16_IGLJ6*01	1106
3556	VH3-23_IGHD6-13*01>2_IGHJ2*01	1301	gnl|Fabrus|V1-16_IGLJ6*01	1106
3557	VH3-23_IGHD6-19*01>1_IGHJ2*01	1302	gnl|Fabrus|V1-16_IGLJ6*01	1106
3558	VH3-23_IGHD6-19*01>2_IGHJ2*01	1303	gnl|Fabrus|V1-16_IGLJ6*01	1106
3559	VH3-23_IGHD6-25*01>1_IGHJ2*01	1304	gnl|Fabrus|V1-16_IGLJ6*01	1106
3560	VH3-23_IGHD6-25*01>2_IGHJ2*01	1305	gnl|Fabrus|V1-16_IGLJ6*01	1106
3561	VH3-23_IGHD7-27*01>1_IGHJ2*01	1306	gnl|Fabrus|V1-16_IGLJ6*01	1106
3562	VH3-23_IGHD7-27*01>3_IGHJ2*01	1307	gnl|Fabrus|V1-16_IGLJ6*01	1106
3563	VH3-23_IGHD6-13*01>1'_IGHJ2*01	1356	gnl|Fabrus|V1-16_IGLJ6*01	1106
3564	VH3-23_IGHD6-13*01>2'_IGHJ2*01	1357	gnl|Fabrus|V1-16_IGLJ6*01	1106
3565	VH3-23_IGHD6-13*01>2_IGHJ2*01_B	1358	gnl|Fabrus|V1-16_IGLJ6*01	1106
3566	VH3-23_IGHD6-19*01>1'_IGHJ2*01	1359	gnl|Fabrus|V1-16_IGLJ6*01	1106
3567	VH3-23_IGHD6-19*01>2'_IGHJ2*01	1360	gnl|Fabrus|V1-16_IGLJ6*01	1106
3568	VH3-23_IGHD6-19*01>2_IGHJ2*01_B	1361	gnl|Fabrus|V1-16_IGLJ6*01	1106
3569	VH3-23_IGHD6-25*01>1'_IGHJ2*01	1362	gnl|Fabrus|V1-16_IGLJ6*01	1106
3570	VH3-23_IGHD6-25*01>3'_IGHJ2*01	1363	gnl|Fabrus|V1-16_IGLJ6*01	1106
3571	VH3-23_IGHD7-27*01>1'_IGHJ2*01	1364	gnl|Fabrus|V1-16_IGLJ6*01	1106
3572	VH3-23_IGHD7-27*01>2'_IGHJ2*01	1365	gnl|Fabrus|V1-16_IGLJ6*01	1106
3573	VH3-23_IGHD6-6*01>2_IGHJ3*01	1414	gnl|Fabrus|V1-16_IGLJ6*01	1106
3574	VH3-23_IGHD6-13*01>1_IGHJ3*01	1415	gnl|Fabrus|V1-16_IGLJ6*01	1106
3575	VH3-23_IGHD6-13*01>2_IGHJ3*01	1416	gnl|Fabrus|V1-16_IGLJ6*01	1106
3576	VH3-23_IGHD6-19*01>1_IGHJ3*01	1417	gnl|Fabrus|V1-16_IGLJ6*01	1106
3577	VH3-23_IGHD6-19*01>2_IGHJ3*01	1418	gnl|Fabrus|V1-16_IGLJ6*01	1106
3578	VH3-23_IGHD6-25*01>1_IGHJ3*01	1419	gnl|Fabrus|V1-16_IGLJ6*01	1106
3579	VH3-23_IGHD6-25*01>2_IGHJ3*01	1420	gnl|Fabrus|V1-16_IGLJ6*01	1106
3580	VH3-23_IGHD7-27*01>1_IGHJ3*01	1421	gnl|Fabrus|V1-16_IGLJ6*01	1106
3581	VH3-23_IGHD7-27*01>3_IGHJ3*01	1422	gnl|Fabrus|V1-16_IGLJ6*01	1106
3582	VH3-23_IGHD6-13*01>1'_IGHJ3*01	1471	gnl|Fabrus|V1-16_IGLJ6*01	1106
3583	VH3-23_IGHD6-13*01>2'_IGHJ3*01	1472	gnl|Fabrus|V1-16_IGLJ6*01	1106
3584	VH3-23_IGHD6-13*01>1_IGHJ6*01	1818	gnl|Fabrus|V1-16_IGLJ6*01	1106
3585	VH3-23_IGHD6-19*01>1'_IGHJ3*01	1474	gnl|Fabrus|V1-16_IGLJ6*01	1106
3586	VH3-23_IGHD6-19*01>2'_IGHJ3*01	1475	gnl|Fabrus|V1-16_IGLJ6*01	1106
3587	VH3-23_IGHD6-19*01>3'_IGHJ3*01	1476	gnl|Fabrus|V1-16_IGLJ6*01	1106
3588	VH3-23_IGHD6-25*01>1'_IGHJ3*01	1477	gnl|Fabrus|V1-16_IGLJ6*01	1106
3589	VH3-23_IGHD6-25*01>3'_IGHJ3*01	1478	gnl|Fabrus|V1-16_IGLJ6*01	1106
3590	VH3-23_IGHD7-27*01>1'_IGHJ3*01	1479	gnl|Fabrus|V1-16_IGLJ6*01	1106

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3591	VH3-23_IGHD7-27*01>2'_IGHJ3*01	1480	gnl|Fabrus|V1-16_IGLJ6*01	1106
3592	VH3-23_IGHD6-6*01>2_IGHJ4*01	1529	gnl|Fabrus|V1-16_IGLJ6*01	1106
3593	VH3-23_IGHD6-13*01>1_IGHJ4*01	1530	gnl|Fabrus|V1-16_IGLJ6*01	1106
3594	VH3-23_IGHD6-13*01>2_IGHJ4*01	1531	gnl|Fabrus|V1-16_IGLJ6*01	1106
3595	VH3-23_IGHD6-19*01>1_IGHJ4*01	1532	gnl|Fabrus|V1-16_IGLJ6*01	1106
3596	VH3-23_IGHD6-19*01>2_IGHJ4*01	1533	gnl|Fabrus|V1-16_IGLJ6*01	1106
3597	VH3-23_IGHD6-25*01>1_IGHJ4*01	1534	gnl|Fabrus|V1-16_IGLJ6*01	1106
3598	VH3-23_IGHD6-25*01>2_IGHJ4*01	1535	gnl|Fabrus|V1-16_IGLJ6*01	1106
3599	VH3-23_IGHD7-27*01>1_IGHJ4*01	1536	gnl|Fabrus|V1-16_IGLJ6*01	1106
3600	VH3-23_IGHD7-27*01>3_IGHJ4*01	1537	gnl|Fabrus|V1-16_IGLJ6*01	1106
3601	VH3-23_IGHD6-13*01>1'_IGHJ4*01	1586	gnl|Fabrus|V1-16_IGLJ6*01	1106
3602	VH3-23_IGHD6-13*01>2'_IGHJ4*01	1587	gnl|Fabrus|V1-16_IGLJ6*01	1106
3603	VH3-23_IGHD6-13*01>2_IGHJ4*01_B	1588	gnl|Fabrus|V1-16_IGLJ6*01	1106
3604	VH3-23_IGHD6-19*01>1'_IGHJ4*01	1589	gnl|Fabrus|V1-16_IGLJ6*01	1106
3605	VH3-23_IGHD6-19*01>2'_IGHJ4*01	1590	gnl|Fabrus|V1-16_IGLJ6*01	1106
3606	VH3-23_IGHD6-19*01>2_IGHJ4*01_B	1591	gnl|Fabrus|V1-16_IGLJ6*01	1106
3607	VH3-23_IGHD6-25*01>1'_IGHJ4*01	1592	gnl|Fabrus|V1-16_IGLJ6*01	1106
3608	VH3-23_IGHD6-25*01>3'_IGHJ4*01	1593	gnl|Fabrus|V1-16_IGLJ6*01	1106
3609	VH3-23_IGHD7-27*01>1'_IGHJ4*01	1594	gnl|Fabrus|V1-16_IGLJ6*01	1106
3610	VH3-23_IGHD7-27*01>2'_IGHJ4*01	1595	gnl|Fabrus|V1-16_IGLJ6*01	1106
3611	VH3-23_IGHD6-6*01>2_IGHJ5*01	1644	gnl|Fabrus|V1-16_IGLJ6*01	1106
3612	VH3-23_IGHD6-13*01>1_IGHJ5*01	1645	gnl|Fabrus|V1-16_IGLJ6*01	1106
3613	VH3-23_IGHD6-13*01>2_IGHJ5*01	1646	gnl|Fabrus|V1-16_IGLJ6*01	1106
3614	VH3-23_IGHD6-19*01>1_IGHJ5*01	1647	gnl|Fabrus|V1-16_IGLJ6*01	1106
3615	VH3-23_IGHD6-19*01>2_IGHJ5*01	1648	gnl|Fabrus|V1-16_IGLJ6*01	1106
3616	VH3-23_IGHD6-25*01>1_IGHJ5*01	1649	gnl|Fabrus|V1-16_IGLJ6*01	1106
3617	VH3-23_IGHD6-25*01>2_IGHJ5*01	1650	gnl|Fabrus|V1-16_IGLJ6*01	1106
3618	VH3-23_IGHD7-27*01>1_IGHJ5*01	1651	gnl|Fabrus|V1-16_IGLJ6*01	1106
3619	VH3-23_IGHD7-27*01>3_IGHJ5*01	1652	gnl|Fabrus|V1-16_IGLJ6*01	1106
3620	VH3-23_IGHD6-13*01>1'_IGHJ5*01	1701	gnl|Fabrus|V1-16_IGLJ6*01	1106
3621	VH3-23_IGHD6-13*01>2'_IGHJ5*01	1702	gnl|Fabrus|V1-16_IGLJ6*01	1106
3622	VH3-23_IGHD6-13*01>3'_IGHJ5*01	1703	gnl|Fabrus|V1-16_IGLJ6*01	1106
3623	VH3-23_IGHD6-19*01>1'_IGHJ5*01	1704	gnl|Fabrus|V1-16_IGLJ6*01	1106
3624	VH3-23_IGHD6-19*01>2'_IGHJ5*01	1705	gnl|Fabrus|V1-16_IGLJ6*01	1106
3625	VH3-23_IGHD6-19*01>2_IGHJ5*01_B	1706	gnl|Fabrus|V1-16_IGLJ6*01	1106
3626	VH3-23_IGHD6-25*01>1'_IGHJ5*01	1707	gnl|Fabrus|V1-16_IGLJ6*01	1106
3627	VH3-23_IGHD6-25*01>3'_IGHJ5*01	1708	gnl|Fabrus|V1-16_IGLJ6*01	1106
3628	VH3-23_IGHD7-27*01>1'_IGHJ5*01	1709	gnl|Fabrus|V1-16_IGLJ6*01	1106
3629	VH3-23_IGHD7-27*01>2'_IGHJ5*01	1710	gnl|Fabrus|V1-16_IGLJ6*01	1106
3630	VH3-23_IGHD6-6*01>2_IGHJ6*01	1759	gnl|Fabrus|V1-16_IGLJ6*01	1106
3631	VH3-23_IGHD6-6*01>2_IGHJ1*01	1184	gnl|Fabrus|V1-2_IGLJ7*01	1108
3632	VH3-23_IGHD6-13*01>1_IGHJ1*01	1185	gnl|Fabrus|V1-2_IGLJ7*01	1108

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3633	VH3-23_IGHD6-13*01>2_IGHJ1*01	1186	gnl|Fabrus|V1-2_IGLJ7*01	1108
3634	VH3-23_IGHD6-19*01>1_IGHJ1*01	1187	gnl|Fabrus|V1-2_IGLJ7*01	1108
3635	VH3-23_IGHD6-19*01>2_IGHJ1*01	1188	gnl|Fabrus|V1-2_IGLJ7*01	1108
3636	VH3-23_IGHD6-25*01>1_IGHJ1*01	1189	gnl|Fabrus|V1-2_IGLJ7*01	1108
3637	VH3-23_IGHD6-25*01>2_IGHJ1*01	1190	gnl|Fabrus|V1-2_IGLJ7*01	1108
3638	VH3-23_IGHD7-27*01>1_IGHJ1*01	1191	gnl|Fabrus|V1-2_IGLJ7*01	1108
3639	VH3-23_IGHD7-27*01>3_IGHJ1*01	1192	gnl|Fabrus|V1-2_IGLJ7*01	1108
3640	VH3-23_IGHD6-13*01>1'_IGHJ1*01	1241	gnl|Fabrus|V1-2_IGLJ7*01	1108
3641	VH3-23_IGHD6-13*01>2'_IGHJ1*01	1242	gnl|Fabrus|V1-2_IGLJ7*01	1108
3642	VH3-23_IGHD6-13*01>2_IGHJ1*01_B	1243	gnl|Fabrus|V1-2_IGLJ7*01	1108
3643	VH3-23_IGHD6-19*01>1'_IGHJ1*01	1244	gnl|Fabrus|V1-2_IGLJ7*01	1108
3644	VH3-23_IGHD6-19*01>2'_IGHJ1*01	1245	gnl|Fabrus|V1-2_IGLJ7*01	1108
3645	VH3-23_IGHD6-19*01>2_IGHJ1*01_B	1246	gnl|Fabrus|V1-2_IGLJ7*01	1108
3646	VH3-23_IGHD6-25*01>1'_IGHJ1*01	1247	gnl|Fabrus|V1-2_IGLJ7*01	1108
3647	VH3-23_IGHD6-25*01>3'_IGHJ1*01	1248	gnl|Fabrus|V1-2_IGLJ7*01	1108
3648	VH3-23_IGHD7-27*01>1'_IGHJ1*01_B	1249	gnl|Fabrus|V1-2_IGLJ7*01	1108
3649	VH3-23_IGHD7-27*01>2'_IGHJ1*01	1250	gnl|Fabrus|V1-2_IGLJ7*01	1108
3650	VH3-23_IGHD6-6*01>2_IGHJ2*01	1299	gnl|Fabrus|V1-2_IGLJ7*01	1108
3651	VH3-23_IGHD6-13*01>1_IGHJ2*01	1300	gnl|Fabrus|V1-2_IGLJ7*01	1108
3652	VH3-23_IGHD6-13*01>2_IGHJ2*01	1301	gnl|Fabrus|V1-2_IGLJ7*01	1108
3653	VH3-23_IGHD6-19*01>1_IGHJ2*01	1302	gnl|Fabrus|V1-2_IGLJ7*01	1108
3654	VH3-23_IGHD6-19*01>2_IGHJ2*01	1303	gnl|Fabrus|V1-2_IGLJ7*01	1108
3655	VH3-23_IGHD6-25*01>1_IGHJ2*01	1304	gnl|Fabrus|V1-2_IGLJ7*01	1108
3656	VH3-23_IGHD6-25*01>2_IGHJ2*01	1305	gnl|Fabrus|V1-2_IGLJ7*01	1108
3657	VH3-23_IGHD7-27*01>1_IGHJ2*01	1306	gnl|Fabrus|V1-2_IGLJ7*01	1108
3658	VH3-23_IGHD7-27*01>3_IGHJ2*01	1307	gnl|Fabrus|V1-2_IGLJ7*01	1108
3659	VH3-23_IGHD6-13*01>1'_IGHJ2*01	1356	gnl|Fabrus|V1-2_IGLJ7*01	1108
3660	VH3-23_IGHD6-13*01>2'_IGHJ2*01	1357	gnl|Fabrus|V1-2_IGLJ7*01	1108
3661	VH3-23_IGHD6-13*01>2_IGHJ2*01_B	1358	gnl|Fabrus|V1-2_IGLJ7*01	1108
3662	VH3-23_IGHD6-19*01>1'_IGHJ2*01	1359	gnl|Fabrus|V1-2_IGLJ7*01	1108
3663	VH3-23_IGHD6-19*01>2'_IGHJ2*01	1360	gnl|Fabrus|V1-2_IGLJ7*01	1108
3664	VH3-23_IGHD6-19*01>2_IGHJ2*01_B	1361	gnl|Fabrus|V1-2_IGLJ7*01	1108
3665	VH3-23_IGHD6-25*01>1'_IGHJ2*01	1362	gnl|Fabrus|V1-2_IGLJ7*01	1108
3666	VH3-23_IGHD6-25*01>3'_IGHJ2*01	1363	gnl|Fabrus|V1-2_IGLJ7*01	1108
3667	VH3-23_IGHD7-27*01>1'_IGHJ2*01	1364	gnl|Fabrus|V1-2_IGLJ7*01	1108
3668	VH3-23_IGHD7-27*01>2'_IGHJ2*01	1365	gnl|Fabrus|V1-2_IGLJ7*01	1108
3669	VH3-23_IGHD6-6*01>2_IGHJ3*01	1414	gnl|Fabrus|V1-2_IGLJ7*01	1108
3670	VH3-23_IGHD6-13*01>1_IGHJ3*01	1415	gnl|Fabrus|V1-2_IGLJ7*01	1108
3671	VH3-23_IGHD6-13*01>2_IGHJ3*01	1416	gnl|Fabrus|V1-2_IGLJ7*01	1108
3672	VH3-23_IGHD6-19*01>1_IGHJ3*01	1417	gnl|Fabrus|V1-2_IGLJ7*01	1108
3673	VH3-23_IGHD6-19*01>2_IGHJ3*01	1418	gnl|Fabrus|V1-2_IGLJ7*01	1108
3674	VH3-23_IGHD6-25*01>1_IGHJ3*01	1419	gnl|Fabrus|V1-2_IGLJ7*01	1108

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3675	VH3-23_IGHD6-25*01>2_IGHJ3*01	1420	gnl|Fabrus|V1-2_IGLJ7*01	1108
3676	VH3-23_IGHD7-27*01>1_IGHJ3*01	1421	gnl|Fabrus|V1-2_IGLJ7*01	1108
3677	VH3-23_IGHD7-27*01>3_IGHJ3*01	1422	gnl|Fabrus|V1-2_IGLJ7*01	1108
3678	VH3-23_IGHD6-13*01>1'_IGHJ3*01	1471	gnl|Fabrus|V1-2_IGLJ7*01	1108
3679	VH3-23_IGHD6-13*01>2'_IGHJ3*01	1472	gnl|Fabrus|V1-2_IGLJ7*01	1108
3680	VH3-23_IGHD6-13*01>1_IGHJ6*01	1818	gnl|Fabrus|V1-2_IGLJ7*01	1108
3681	VH3-23_IGHD6-19*01>1'_IGHJ3*01	1474	gnl|Fabrus|V1-2_IGLJ7*01	1108
3682	VH3-23_IGHD6-19*01>2'_IGHJ3*01	1475	gnl|Fabrus|V1-2_IGLJ7*01	1108
3683	VH3-23_IGHD6-19*01>3'_IGHJ3*01	1476	gnl|Fabrus|V1-2_IGLJ7*01	1108
3684	VH3-23_IGHD6-25*01>1'_IGHJ3*01	1477	gnl|Fabrus|V1-2_IGLJ7*01	1108
3685	VH3-23_IGHD6-25*01>3'_IGHJ3*01	1478	gnl|Fabrus|V1-2_IGLJ7*01	1108
3686	VH3-23_IGHD7-27*01>1'_IGHJ3*01	1479	gnl|Fabrus|V1-2_IGLJ7*01	1108
3687	VH3-23_IGHD7-27*01>2'_IGHJ3*01	1480	gnl|Fabrus|V1-2_IGLJ7*01	1108
3688	VH3-23_IGHD6-6*01>2_IGHJ4*01	1529	gnl|Fabrus|V1-2_IGLJ7*01	1108
3689	VH3-23_IGHD6-13*01>1_IGHJ4*01	1530	gnl|Fabrus|V1-2_IGLJ7*01	1108
3690	VH3-23_IGHD6-13*01>2_IGHJ4*01	1531	gnl|Fabrus|V1-2_IGLJ7*01	1108
3691	VH3-23_IGHD6-19*01>1_IGHJ4*01	1532	gnl|Fabrus|V1-2_IGLJ7*01	1108
3692	VH3-23_IGHD6-19*01>2_IGHJ4*01	1533	gnl|Fabrus|V1-2_IGLJ7*01	1108
3693	VH3-23_IGHD6-25*01>1_IGHJ4*01	1534	gnl|Fabrus|V1-2_IGLJ7*01	1108
3694	VH3-23_IGHD6-25*01>2_IGHJ4*01	1535	gnl|Fabrus|V1-2_IGLJ7*01	1108
3695	VH3-23_IGHD7-27*01>1_IGHJ4*01	1536	gnl|Fabrus|V1-2_IGLJ7*01	1108
3696	VH3-23_IGHD7-27*01>3_IGHJ4*01	1537	gnl|Fabrus|V1-2_IGLJ7*01	1108
3697	VH3-23_IGHD6-13*01>1'_IGHJ4*01	1586	gnl|Fabrus|V1-2_IGLJ7*01	1108
3698	VH3-23_IGHD6-13*01>2'_IGHJ4*01	1587	gnl|Fabrus|V1-2_IGLJ7*01	1108
3699	VH3-23_IGHD6-13*01>2_IGHJ4*01_B	1588	gnl|Fabrus|V1-2_IGLJ7*01	1108
3700	VH3-23_IGHD6-19*01>1'_IGHJ4*01	1589	gnl|Fabrus|V1-2_IGLJ7*01	1108
3701	VH3-23_IGHD6-19*01>2'_IGHJ4*01	1590	gnl|Fabrus|V1-2_IGLJ7*01	1108
3702	VH3-23_IGHD6-19*01>2_IGHJ4*01_B	1591	gnl|Fabrus|V1-2_IGLJ7*01	1108
3703	VH3-23_IGHD6-25*01>1'_IGHJ4*01	1592	gnl|Fabrus|V1-2_IGLJ7*01	1108
3704	VH3-23_IGHD6-25*01>3'_IGHJ4*01	1593	gnl|Fabrus|V1-2_IGLJ7*01	1108
3705	VH3-23_IGHD7-27*01>1'_IGHJ4*01	1594	gnl|Fabrus|V1-2_IGLJ7*01	1108
3706	VH3-23_IGHD7-27*01>2'_IGHJ4*01	1595	gnl|Fabrus|V1-2_IGLJ7*01	1108
3707	VH3-23_IGHD6-6*01>2_IGHJ5*01	1644	gnl|Fabrus|V1-2_IGLJ7*01	1108
3708	VH3-23_IGHD6-13*01>1_IGHJ5*01	1645	gnl|Fabrus|V1-2_IGLJ7*01	1108
3709	VH3-23_IGHD6-13*01>2_IGHJ5*01	1646	gnl|Fabrus|V1-2_IGLJ7*01	1108
3710	VH3-23_IGHD6-19*01>1_IGHJ5*01	1647	gnl|Fabrus|V1-2_IGLJ7*01	1108
3711	VH3-23_IGHD6-19*01>2_IGHJ5*01	1648	gnl|Fabrus|V1-2_IGLJ7*01	1108
3712	VH3-23_IGHD6-25*01>1_IGHJ5*01	1649	gnl|Fabrus|V1-2_IGLJ7*01	1108
3713	VH3-23_IGHD6-25*01>2_IGHJ5*01	1650	gnl|Fabrus|V1-2_IGLJ7*01	1108
3714	VH3-23_IGHD7-27*01>1_IGHJ5*01	1651	gnl|Fabrus|V1-2_IGLJ7*01	1108
3715	VH3-23_IGHD7-27*01>3_IGHJ5*01	1652	gnl|Fabrus|V1-2_IGLJ7*01	1108
3716	VH3-23_IGHD6-13*01>1'_IGHJ5*01	1701	gnl|Fabrus|V1-2_IGLJ7*01	1108

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3717	VH3-23_IGHD6-13*01>2'_IGHJ5*01	1702	gnl|Fabrus|V1-2_IGLJ7*01	1108
3718	VH3-23_IGHD6-13*01>3'_IGHJ5*01	1703	gnl|Fabrus|V1-2_IGLJ7*01	1108
3719	VH3-23_IGHD6-19*01>1'_IGHJ5*01	1704	gnl|Fabrus|V1-2_IGLJ7*01	1108
3720	VH3-23_IGHD6-19*01>2'_IGHJ5*01	1705	gnl|Fabrus|V1-2_IGLJ7*01	1108
3721	VH3-23_IGHD6-19*01>2_IGHJ5*01_B	1706	gnl|Fabrus|V1-2_IGLJ7*01	1108
3722	VH3-23_IGHD6-25*01>1'_IGHJ5*01	1707	gnl|Fabrus|V1-2_IGLJ7*01	1108
3723	VH3-23_IGHD6-25*01>3'_IGHJ5*01	1708	gnl|Fabrus|V1-2_IGLJ7*01	1108
3724	VH3-23_IGHD7-27*01>1'_IGHJ5*01	1709	gnl|Fabrus|V1-2_IGLJ7*01	1108
3725	VH3-23_IGHD7-27*01>2'_IGHJ5*01	1710	gnl|Fabrus|V1-2_IGLJ7*01	1108
3726	VH3-23_IGHD6-6*01>2_IGHJ6*01	1759	gnl|Fabrus|V1-2_IGLJ7*01	1108
3727	VH3-23_IGHD6-6*01>2_IGHJ1*01	1184	gnl|Fabrus|V1-20_IGLJ6*01	1109
3728	VH3-23_IGHD6-13*01>1_IGHJ1*01	1185	gnl|Fabrus|V1-20_IGLJ6*01	1109
3729	VH3-23_IGHD6-13*01>2_IGHJ1*01	1186	gnl|Fabrus|V1-20_IGLJ6*01	1109
3730	VH3-23_IGHD6-19*01>1_IGHJ1*01	1187	gnl|Fabrus|V1-20_IGLJ6*01	1109
3731	VH3-23_IGHD6-19*01>2_IGHJ1*01	1188	gnl|Fabrus|V1-20_IGLJ6*01	1109
3732	VH3-23_IGHD6-25*01>1_IGHJ1*01	1189	gnl|Fabrus|V1-20_IGLJ6*01	1109
3733	VH3-23_IGHD6-25*01>2_IGHJ1*01	1190	gnl|Fabrus|V1-20_IGLJ6*01	1109
3734	VH3-23_IGHD7-27*01>1_IGHJ1*01	1191	gnl|Fabrus|V1-20_IGLJ6*01	1109
3735	VH3-23_IGHD7-27*01>3_IGHJ1*01	1192	gnl|Fabrus|V1-20_IGLJ6*01	1109
3736	VH3-23_IGHD6-13*01>1'_IGHJ1*01	1241	gnl|Fabrus|V1-20_IGLJ6*01	1109
3737	VH3-23_IGHD6-13*01>2'_IGHJ1*01	1242	gnl|Fabrus|V1-20_IGLJ6*01	1109
3738	VH3-23_IGHD6-13*01>2_IGHJ1*01_B	1243	gnl|Fabrus|V1-20_IGLJ6*01	1109
3739	VH3-23_IGHD6-19*01>1'_IGHJ1*01	1244	gnl|Fabrus|V1-20_IGLJ6*01	1109
3740	VH3-23_IGHD6-19*01>2'_IGHJ1*01	1245	gnl|Fabrus|V1-20_IGLJ6*01	1109
3741	VH3-23_IGHD6-19*01>2_IGHJ1*01_B	1246	gnl|Fabrus|V1-20_IGLJ6*01	1109
3742	VH3-23_IGHD6-25*01>1'_IGHJ1*01	1247	gnl|Fabrus|V1-20_IGLJ6*01	1109
3743	VH3-23_IGHD6-25*01>3'_IGHJ1*01	1248	gnl|Fabrus|V1-20_IGLJ6*01	1109
3744	VH3-23_IGHD7-27*01>1'_IGHJ1*01_B	1249	gnl|Fabrus|V1-20_IGLJ6*01	1109
3745	VH3-23_IGHD7-27*01>2'_IGHJ1*01	1250	gnl|Fabrus|V1-20_IGLJ6*01	1109
3746	VH3-23_IGHD6-6*01>2_IGHJ2*01	1299	gnl|Fabrus|V1-20_IGLJ6*01	1109
3747	VH3-23_IGHD6-13*01>1_IGHJ2*01	1300	gnl|Fabrus|V1-20_IGLJ6*01	1109
3748	VH3-23_IGHD6-13*01>2_IGHJ2*01	1301	gnl|Fabrus|V1-20_IGLJ6*01	1109
3749	VH3-23_IGHD6-19*01>1_IGHJ2*01	1302	gnl|Fabrus|V1-20_IGLJ6*01	1109
3750	VH3-23_IGHD6-19*01>2_IGHJ2*01	1303	gnl|Fabrus|V1-20_IGLJ6*01	1109
3751	VH3-23_IGHD6-25*01>1_IGHJ2*01	1304	gnl|Fabrus|V1-20_IGLJ6*01	1109
3752	VH3-23_IGHD6-25*01>2_IGHJ2*01	1305	gnl|Fabrus|V1-20_IGLJ6*01	1109
3753	VH3-23_IGHD7-27*01>1_IGHJ2*01	1306	gnl|Fabrus|V1-20_IGLJ6*01	1109
3754	VH3-23_IGHD7-27*01>3_IGHJ2*01	1307	gnl|Fabrus|V1-20_IGLJ6*01	1109
3755	VH3-23_IGHD6-13*01>1'_IGHJ2*01	1356	gnl|Fabrus|V1-20_IGLJ6*01	1109
3756	VH3-23_IGHD6-13*01>2'_IGHJ2*01	1357	gnl|Fabrus|V1-20_IGLJ6*01	1109
3757	VH3-23_IGHD6-13*01>2_IGHJ2*01_B	1358	gnl|Fabrus|V1-20_IGLJ6*01	1109
3758	VH3-23_IGHD6-19*01>1'_IGHJ2*01	1359	gnl|Fabrus|V1-20_IGLJ6*01	1109

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3759	VH3-23_IGHD6-19*01>2'_IGHJ2*01	1360	gnl|Fabrus|V1-20_IGLJ6*01	1109
3760	VH3-23_IGHD6-19*01>2_IGHJ2*01_B	1361	gnl|Fabrus|V1-20_IGLJ6*01	1109
3761	VH3-23_IGHD6-25*01>1'_IGHJ2*01	1362	gnl|Fabrus|V1-20_IGLJ6*01	1109
3762	VH3-23_IGHD6-25*01>3'_IGHJ2*01	1363	gnl|Fabrus|V1-20_IGLJ6*01	1109
3763	VH3-23_IGHD7-27*01>1'_IGHJ2*01	1364	gnl|Fabrus|V1-20_IGLJ6*01	1109
3764	VH3-23_IGHD7-27*01>2'_IGHJ2*01	1365	gnl|Fabrus|V1-20_IGLJ6*01	1109
3765	VH3-23_IGHD6-6*01>2_IGHJ3*01	1414	gnl|Fabrus|V1-20_IGLJ6*01	1109
3766	VH3-23_IGHD6-13*01>1_IGHJ3*01	1415	gnl|Fabrus|V1-20_IGLJ6*01	1109
3767	VH3-23_IGHD6-13*01>2_IGHJ3*01	1416	gnl|Fabrus|V1-20_IGLJ6*01	1109
3768	VH3-23_IGHD6-19*01>1_IGHJ3*01	1417	gnl|Fabrus|V1-20_IGLJ6*01	1109
3769	VH3-23_IGHD6-19*01>2_IGHJ3*01	1418	gnl|Fabrus|V1-20_IGLJ6*01	1109
3770	VH3-23_IGHD6-25*01>1_IGHJ3*01	1419	gnl|Fabrus|V1-20_IGLJ6*01	1109
3771	VH3-23_IGHD6-25*01>2_IGHJ3*01	1420	gnl|Fabrus|V1-20_IGLJ6*01	1109
3772	VH3-23_IGHD7-27*01>1_IGHJ3*01	1421	gnl|Fabrus|V1-20_IGLJ6*01	1109
3773	VH3-23_IGHD7-27*01>3_IGHJ3*01	1422	gnl|Fabrus|V1-20_IGLJ6*01	1109
3774	VH3-23_IGHD6-13*01>1'_IGHJ3*01	1471	gnl|Fabrus|V1-20_IGLJ6*01	1109
3775	VH3-23_IGHD6-13*01>2'_IGHJ3*01	1472	gnl|Fabrus|V1-20_IGLJ6*01	1109
3776	VH3-23_IGHD6-13*01>1_IGHJ6*01	1818	gnl|Fabrus|V1-20_IGLJ6*01	1109
3777	VH3-23_IGHD6-19*01>1'_IGHJ3*01	1474	gnl|Fabrus|V1-20_IGLJ6*01	1109
3778	VH3-23_IGHD6-19*01>2'_IGHJ3*01	1475	gnl|Fabrus|V1-20_IGLJ6*01	1109
3779	VH3-23_IGHD6-19*01>3'_IGHJ3*01	1476	gnl|Fabrus|V1-20_IGLJ6*01	1109
3780	VH3-23_IGHD6-25*01>1'_IGHJ3*01	1477	gnl|Fabrus|V1-20_IGLJ6*01	1109
3781	VH3-23_IGHD6-25*01>3'_IGHJ3*01	1478	gnl|Fabrus|V1-20_IGLJ6*01	1109
3782	VH3-23_IGHD7-27*01>1'_IGHJ3*01	1479	gnl|Fabrus|V1-20_IGLJ6*01	1109
3783	VH3-23_IGHD7-27*01>2'_IGHJ3*01	1480	gnl|Fabrus|V1-20_IGLJ6*01	1109
3784	VH3-23_IGHD6-6*01>2_IGHJ4*01	1529	gnl|Fabrus|V1-20_IGLJ6*01	1109
3785	VH3-23_IGHD6-13*01>1_IGHJ4*01	1530	gnl|Fabrus|V1-20_IGLJ6*01	1109
3786	VH3-23_IGHD6-13*01>2_IGHJ4*01	1531	gnl|Fabrus|V1-20_IGLJ6*01	1109
3787	VH3-23_IGHD6-19*01>1_IGHJ4*01	1532	gnl|Fabrus|V1-20_IGLJ6*01	1109
3788	VH3-23_IGHD6-19*01>2_IGHJ4*01	1533	gnl|Fabrus|V1-20_IGLJ6*01	1109
3789	VH3-23_IGHD6-25*01>1_IGHJ4*01	1534	gnl|Fabrus|V1-20_IGLJ6*01	1109
3790	VH3-23_IGHD6-25*01>2_IGHJ4*01	1535	gnl|Fabrus|V1-20_IGLJ6*01	1109
3791	VH3-23_IGHD7-27*01>1_IGHJ4*01	1536	gnl|Fabrus|V1-20_IGLJ6*01	1109
3792	VH3-23_IGHD7-27*01>3_IGHJ4*01	1537	gnl|Fabrus|V1-20_IGLJ6*01	1109
3793	VH3-23_IGHD6-13*01>1'_IGHJ4*01	1586	gnl|Fabrus|V1-20_IGLJ6*01	1109
3794	VH3-23_IGHD6-13*01>2'_IGHJ4*01	1587	gnl|Fabrus|V1-20_IGLJ6*01	1109
3795	VH3-23_IGHD6-13*01>2_IGHJ4*01_B	1588	gnl|Fabrus|V1-20_IGLJ6*01	1109
3796	VH3-23_IGHD6-19*01>1'_IGHJ4*01	1589	gnl|Fabrus|V1-20_IGLJ6*01	1109
3797	VH3-23_IGHD6-19*01>2'_IGHJ4*01	1590	gnl|Fabrus|V1-20_IGLJ6*01	1109
3798	VH3-23_IGHD6-19*01>2_IGHJ4*01_B	1591	gnl|Fabrus|V1-20_IGLJ6*01	1109
3799	VH3-23_IGHD6-25*01>1'_IGHJ4*01	1592	gnl|Fabrus|V1-20_IGLJ6*01	1109
3800	VH3-23_IGHD6-25*01>3'_IGHJ4*01	1593	gnl|Fabrus|V1-20_IGLJ6*01	1109

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3801	VH3-23_IGHD7-27*01>1'_IGHJ4*01	1594	gnl|Fabrus|V1-20_IGLJ6*01	1109
3802	VH3-23_IGHD7-27*01>2'_IGHJ4*01	1595	gnl|Fabrus|V1-20_IGLJ6*01	1109
3803	VH3-23_IGHD6-6*01>2_IGHJ5*01	1644	gnl|Fabrus|V1-20_IGLJ6*01	1109
3804	VH3-23_IGHD6-13*01>1_IGHJ5*01	1645	gnl|Fabrus|V1-20_IGLJ6*01	1109
3805	VH3-23_IGHD6-13*01>2_IGHJ5*01	1646	gnl|Fabrus|V1-20_IGLJ6*01	1109
3806	VH3-23_IGHD6-19*01>1_IGHJ5*01	1647	gnl|Fabrus|V1-20_IGLJ6*01	1109
3807	VH3-23_IGHD6-19*01>2_IGHJ5*01	1648	gnl|Fabrus|V1-20_IGLJ6*01	1109
3808	VH3-23_IGHD6-25*01>1_IGHJ5*01	1649	gnl|Fabrus|V1-20_IGLJ6*01	1109
3809	VH3-23_IGHD6-25*01>2_IGHJ5*01	1650	gnl|Fabrus|V1-20_IGLJ6*01	1109
3810	VH3-23_IGHD7-27*01>1_IGHJ5*01	1651	gnl|Fabrus|V1-20_IGLJ6*01	1109
3811	VH3-23_IGHD7-27*01>3_IGHJ5*01	1652	gnl|Fabrus|V1-20_IGLJ6*01	1109
3812	VH3-23_IGHD6-13*01>1'_IGHJ5*01	1701	gnl|Fabrus|V1-20_IGLJ6*01	1109
3813	VH3-23_IGHD6-13*01>2'_IGHJ5*01	1702	gnl|Fabrus|V1-20_IGLJ6*01	1109
3814	VH3-23_IGHD6-13*01>3'_IGHJ5*01	1703	gnl|Fabrus|V1-20_IGLJ6*01	1109
3815	VH3-23_IGHD6-19*01>1'_IGHJ5*01	1704	gnl|Fabrus|V1-20_IGLJ6*01	1109
3816	VH3-23_IGHD6-19*01>2'_IGHJ5*01	1705	gnl|Fabrus|V1-20_IGLJ6*01	1109
3817	VH3-23_IGHD6-19*01>2_IGHJ5*01_B	1706	gnl|Fabrus|V1-20_IGLJ6*01	1109
3818	VH3-23_IGHD6-25*01>1'_IGHJ5*01	1707	gnl|Fabrus|V1-20_IGLJ6*01	1109
3819	VH3-23_IGHD6-25*01>3'_IGHJ5*01	1708	gnl|Fabrus|V1-20_IGLJ6*01	1109
3820	VH3-23_IGHD7-27*01>1'_IGHJ5*01	1709	gnl|Fabrus|V1-20_IGLJ6*01	1109
3821	VH3-23_IGHD7-27*01>2'_IGHJ5*01	1710	gnl|Fabrus|V1-20_IGLJ6*01	1109
3822	VH3-23_IGHD6-6*01>2_IGHJ6*01	1759	gnl|Fabrus|V1-20_IGLJ6*01	1109
3823	VH3-23_IGHD6-6*01>2_IGHJ1*01	1184	gnl|Fabrus|V1-3_IGLJ1*01	1110
3824	VH3-23_IGHD6-13*01>1_IGHJ1*01	1185	gnl|Fabrus|V1-3_IGLJ1*01	1110
3825	VH3-23_IGHD6-13*01>2_IGHJ1*01	1186	gnl|Fabrus|V1-3_IGLJ1*01	1110
3826	VH3-23_IGHD6-19*01>1_IGHJ1*01	1187	gnl|Fabrus|V1-3_IGLJ1*01	1110
3827	VH3-23_IGHD6-19*01>2_IGHJ1*01	1188	gnl|Fabrus|V1-3_IGLJ1*01	1110
3828	VH3-23_IGHD6-25*01>1_IGHJ1*01	1189	gnl|Fabrus|V1-3_IGLJ1*01	1110
3829	VH3-23_IGHD6-25*01>2_IGHJ1*01	1190	gnl|Fabrus|V1-3_IGLJ1*01	1110
3830	VH3-23_IGHD7-27*01>1_IGHJ1*01	1191	gnl|Fabrus|V1-3_IGLJ1*01	1110
3831	VH3-23_IGHD7-27*01>3_IGHJ1*01	1192	gnl|Fabrus|V1-3_IGLJ1*01	1110
3832	VH3-23_IGHD6-13*01>1'_IGHJ1*01	1241	gnl|Fabrus|V1-3_IGLJ1*01	1110
3833	VH3-23_IGHD6-13*01>2'_IGHJ1*01	1242	gnl|Fabrus|V1-3_IGLJ1*01	1110
3834	VH3-23_IGHD6-13*01>2_IGHJ1*01_B	1243	gnl|Fabrus|V1-3_IGLJ1*01	1110
3835	VH3-23_IGHD6-19*01>1'_IGHJ1*01	1244	gnl|Fabrus|V1-3_IGLJ1*01	1110
3836	VH3-23_IGHD6-19*01>2'_IGHJ1*01	1245	gnl|Fabrus|V1-3_IGLJ1*01	1110
3837	VH3-23_IGHD6-19*01>2_IGHJ1*01_B	1246	gnl|Fabrus|V1-3_IGLJ1*01	1110
3838	VH3-23_IGHD6-25*01>1'_IGHJ1*01	1247	gnl|Fabrus|V1-3_IGLJ1*01	1110
3839	VH3-23_IGHD6-25*01>3'_IGHJ1*01	1248	gnl|Fabrus|V1-3_IGLJ1*01	1110
3840	VH3-23_IGHD7-27*01>1'_IGHJ1*01_B	1249	gnl|Fabrus|V1-3_IGLJ1*01	1110
3841	VH3-23_IGHD7-27*01>2'_IGHJ1*01	1250	gnl|Fabrus|V1-3_IGLJ1*01	1110
3842	VH3-23_IGHD6-6*01>2_IGHJ2*01	1299	gnl|Fabrus|V1-3_IGLJ1*01	1110

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3843	VH3-23_IGHD6-13*01>1_IGHJ2*01	1300	gnl|Fabrus|V1-3_IGLJ1*01	1110
3844	VH3-23_IGHD6-13*01>2_IGHJ2*01	1301	gnl|Fabrus|V1-3_IGLJ1*01	1110
3845	VH3-23_IGHD6-19*01>1_IGHJ2*01	1302	gnl|Fabrus|V1-3_IGLJ1*01	1110
3846	VH3-23_IGHD6-19*01>2_IGHJ2*01	1303	gnl|Fabrus|V1-3_IGLJ1*01	1110
3847	VH3-23_IGHD6-25*01>1_IGHJ2*01	1304	gnl|Fabrus|V1-3_IGLJ1*01	1110
3848	VH3-23_IGHD6-25*01>2_IGHJ2*01	1305	gnl|Fabrus|V1-3_IGLJ1*01	1110
3849	VH3-23_IGHD7-27*01>1_IGHJ2*01	1306	gnl|Fabrus|V1-3_IGLJ1*01	1110
3850	VH3-23_IGHD7-27*01>3_IGHJ2*01	1307	gnl|Fabrus|V1-3_IGLJ1*01	1110
3851	VH3-23_IGHD6-13*01>1'_IGHJ2*01	1356	gnl|Fabrus|V1-3_IGLJ1*01	1110
3852	VH3-23_IGHD6-13*01>2'_IGHJ2*01	1357	gnl|Fabrus|V1-3_IGLJ1*01	1110
3853	VH3-23_IGHD6-13*01>2_IGHJ2*01_B	1358	gnl|Fabrus|V1-3_IGLJ1*01	1110
3854	VH3-23_IGHD6-19*01>1'_IGHJ2*01	1359	gnl|Fabrus|V1-3_IGLJ1*01	1110
3855	VH3-23_IGHD6-19*01>2'_IGHJ2*01	1360	gnl|Fabrus|V1-3_IGLJ1*01	1110
3856	VH3-23_IGHD6-19*01>2_IGHJ2*01_B	1361	gnl|Fabrus|V1-3_IGLJ1*01	1110
3857	VH3-23_IGHD6-25*01>1'_IGHJ2*01	1362	gnl|Fabrus|V1-3_IGLJ1*01	1110
3858	VH3-23_IGHD6-25*01>3'_IGHJ2*01	1363	gnl|Fabrus|V1-3_IGLJ1*01	1110
3859	VH3-23_IGHD7-27*01>1'_IGHJ2*01	1364	gnl|Fabrus|V1-3_IGLJ1*01	1110
3860	VH3-23_IGHD7-27*01>2'_IGHJ2*01	1365	gnl|Fabrus|V1-3_IGLJ1*01	1110
3861	VH3-23_IGHD6-6*01>2_IGHJ3*01	1414	gnl|Fabrus|V1-3_IGLJ1*01	1110
3862	VH3-23_IGHD6-13*01>1_IGHJ3*01	1415	gnl|Fabrus|V1-3_IGLJ1*01	1110
3863	VH3-23_IGHD6-13*01>2_IGHJ3*01	1416	gnl|Fabrus|V1-3_IGLJ1*01	1110
3864	VH3-23_IGHD6-19*01>1_IGHJ3*01	1417	gnl|Fabrus|V1-3_IGLJ1*01	1110
3865	VH3-23_IGHD6-19*01>2_IGHJ3*01	1418	gnl|Fabrus|V1-3_IGLJ1*01	1110
3866	VH3-23_IGHD6-25*01>1_IGHJ3*01	1419	gnl|Fabrus|V1-3_IGLJ1*01	1110
3867	VH3-23_IGHD6-25*01>2_IGHJ3*01	1420	gnl|Fabrus|V1-3_IGLJ1*01	1110
3868	VH3-23_IGHD7-27*01>1_IGHJ3*01	1421	gnl|Fabrus|V1-3_IGLJ1*01	1110
3869	VH3-23_IGHD7-27*01>3_IGHJ3*01	1422	gnl|Fabrus|V1-3_IGLJ1*01	1110
3870	VH3-23_IGHD6-13*01>1'_IGHJ3*01	1471	gnl|Fabrus|V1-3_IGLJ1*01	1110
3871	VH3-23_IGHD6-13*01>2'_IGHJ3*01	1472	gnl|Fabrus|V1-3_IGLJ1*01	1110
3872	VH3-23_IGHD6-13*01>1_IGHJ6*01	1818	gnl|Fabrus|V1-3_IGLJ1*01	1110
3873	VH3-23_IGHD6-19*01>1'_IGHJ3*01	1474	gnl|Fabrus|V1-3_IGLJ1*01	1110
3874	VH3-23_IGHD6-19*01>2'_IGHJ3*01	1475	gnl|Fabrus|V1-3_IGLJ1*01	1110
3875	VH3-23_IGHD6-19*01>3'_IGHJ3*01	1476	gnl|Fabrus|V1-3_IGLJ1*01	1110
3876	VH3-23_IGHD6-25*01>1'_IGHJ3*01	1477	gnl|Fabrus|V1-3_IGLJ1*01	1110
3877	VH3-23_IGHD6-25*01>3'_IGHJ3*01	1478	gnl|Fabrus|V1-3_IGLJ1*01	1110
3878	VH3-23_IGHD7-27*01>1'_IGHJ3*01	1479	gnl|Fabrus|V1-3_IGLJ1*01	1110
3879	VH3-23_IGHD7-27*01>2'_IGHJ3*01	1480	gnl|Fabrus|V1-3_IGLJ1*01	1110
3880	VH3-23_IGHD6-6*01>2_IGHJ4*01	1529	gnl|Fabrus|V1-3_IGLJ1*01	1110
3881	VH3-23_IGHD6-13*01>1_IGHJ4*01	1530	gnl|Fabrus|V1-3_IGLJ1*01	1110
3882	VH3-23_IGHD6-13*01>2_IGHJ4*01	1531	gnl|Fabrus|V1-3_IGLJ1*01	1110
3883	VH3-23_IGHD6-19*01>1_IGHJ4*01	1532	gnl|Fabrus|V1-3_IGLJ1*01	1110
3884	VH3-23_IGHD6-19*01>2_IGHJ4*01	1533	gnl|Fabrus|V1-3_IGLJ1*01	1110

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3885	VH3-23_IGHD6-25*01>1_IGHJ4*01	1534	gnl|Fabrus|V1-3_IGLJ1*01	1110
3886	VH3-23_IGHD6-25*01>2_IGHJ4*01	1535	gnl|Fabrus|V1-3_IGLJ1*01	1110
3887	VH3-23_IGHD7-27*01>1_IGHJ4*01	1536	gnl|Fabrus|V1-3_IGLJ1*01	1110
3888	VH3-23_IGHD7-27*01>3_IGHJ4*01	1537	gnl|Fabrus|V1-3_IGLJ1*01	1110
3889	VH3-23_IGHD6-13*01>1'_IGHJ4*01	1586	gnl|Fabrus|V1-3_IGLJ1*01	1110
3890	VH3-23_IGHD6-13*01>2'_IGHJ4*01	1587	gnl|Fabrus|V1-3_IGLJ1*01	1110
3891	VH3-23_IGHD6-13*01>2_IGHJ4*01_B	1588	gnl|Fabrus|V1-3_IGLJ1*01	1110
3892	VH3-23_IGHD6-19*01>1'_IGHJ4*01	1589	gnl|Fabrus|V1-3_IGLJ1*01	1110
3893	VH3-23_IGHD6-19*01>2'_IGHJ4*01	1590	gnl|Fabrus|V1-3_IGLJ1*01	1110
3894	VH3-23_IGHD6-19*01>2_IGHJ4*01_B	1591	gnl|Fabrus|V1-3_IGLJ1*01	1110
3895	VH3-23_IGHD6-25*01>1'_IGHJ4*01	1592	gnl|Fabrus|V1-3_IGLJ1*01	1110
3896	VH3-23_IGHD6-25*01>3'_IGHJ4*01	1593	gnl|Fabrus|V1-3_IGLJ1*01	1110
3897	VH3-23_IGHD7-27*01>1'_IGHJ4*01	1594	gnl|Fabrus|V1-3_IGLJ1*01	1110
3898	VH3-23_IGHD7-27*01>2'_IGHJ4*01	1595	gnl|Fabrus|V1-3_IGLJ1*01	1110
3899	VH3-23_IGHD6-6*01>2_IGHJ5*01	1644	gnl|Fabrus|V1-3_IGLJ1*01	1110
3900	VH3-23_IGHD6-13*01>1_IGHJ5*01	1645	gnl|Fabrus|V1-3_IGLJ1*01	1110
3901	VH3-23_IGHD6-13*01>2_IGHJ5*01	1646	gnl|Fabrus|V1-3_IGLJ1*01	1110
3902	VH3-23_IGHD6-19*01>1_IGHJ5*01	1647	gnl|Fabrus|V1-3_IGLJ1*01	1110
3903	VH3-23_IGHD6-19*01>2_IGHJ5*01	1648	gnl|Fabrus|V1-3_IGLJ1*01	1110
3904	VH3-23_IGHD6-25*01>1_IGHJ5*01	1649	gnl|Fabrus|V1-3_IGLJ1*01	1110
3905	VH3-23_IGHD6-25*01>2_IGHJ5*01	1650	gnl|Fabrus|V1-3_IGLJ1*01	1110
3906	VH3-23_IGHD7-27*01>1_IGHJ5*01	1651	gnl|Fabrus|V1-3_IGLJ1*01	1110
3907	VH3-23_IGHD7-27*01>3_IGHJ5*01	1652	gnl|Fabrus|V1-3_IGLJ1*01	1110
3908	VH3-23_IGHD6-13*01>1'_IGHJ5*01	1701	gnl|Fabrus|V1-3_IGLJ1*01	1110
3909	VH3-23_IGHD6-13*01>2'_IGHJ5*01	1702	gnl|Fabrus|V1-3_IGLJ1*01	1110
3910	VH3-23_IGHD6-13*01>3'_IGHJ5*01	1703	gnl|Fabrus|V1-3_IGLJ1*01	1110
3911	VH3-23_IGHD6-19*01>1'_IGHJ5*01	1704	gnl|Fabrus|V1-3_IGLJ1*01	1110
3912	VH3-23_IGHD6-19*01>2'_IGHJ5*01	1705	gnl|Fabrus|V1-3_IGLJ1*01	1110
3913	VH3-23_IGHD6-19*01>2_IGHJ5*01_B	1706	gnl|Fabrus|V1-3_IGLJ1*01	1110
3914	VH3-23_IGHD6-25*01>1'_IGHJ5*01	1707	gnl|Fabrus|V1-3_IGLJ1*01	1110
3915	VH3-23_IGHD6-25*01>3'_IGHJ5*01	1708	gnl|Fabrus|V1-3_IGLJ1*01	1110
3916	VH3-23_IGHD7-27*01>1'_IGHJ5*01	1709	gnl|Fabrus|V1-3_IGLJ1*01	1110
3917	VH3-23_IGHD7-27*01>2'_IGHJ5*01	1710	gnl|Fabrus|V1-3_IGLJ1*01	1110
3918	VH3-23_IGHD6-6*01>2_IGHJ6*01	1759	gnl|Fabrus|V1-3_IGLJ1*01	1110
3919	VH3-23_IGHD1-1*01>1_IGHJ6*01	1711	gnl|Fabrus|V2-13_IGLJ2*01	1117
3920	VH3-23_IGHD1-1*01>2_IGHJ6*01	1712	gnl|Fabrus|V2-13_IGLJ2*01	1117
3921	VH3-23_IGHD1-1*01>3_IGHJ6*01	1713	gnl|Fabrus|V2-13_IGLJ2*01	1117
3922	VH3-23_IGHD1-7*01>1_IGHJ6*01	1714	gnl|Fabrus|V2-13_IGLJ2*01	1117
3923	VH3-23_IGHD1-7*01>3_IGHJ6*01	1715	gnl|Fabrus|V2-13_IGLJ2*01	1117
3924	VH3-23_IGHD1-14*01>1_IGHJ6*01	1716	gnl|Fabrus|V2-13_IGLJ2*01	1117
3925	VH3-23_IGHD1-14*01>3_IGHJ6*01	1717	gnl|Fabrus|V2-13_IGLJ2*01	1117
3926	VH3-23_IGHD1-20*01>1_IGHJ6*01	1718	gnl|Fabrus|V2-13_IGLJ2*01	1117

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3927	VH3-23_IGHD1-20*01>3_IGHJ6*01	1719	gnl|Fabrus|V2-13_IGLJ2*01	1117
3928	VH3-23_IGHD1-26*01>1_IGHJ6*01	1720	gnl|Fabrus|V2-13_IGLJ2*01	1117
3929	VH3-23_IGHD1-26*01>3_IGHJ6*01	1721	gnl|Fabrus|V2-13_IGLJ2*01	1117
3930	VH3-23_IGHD2-2*01>2_IGHJ6*01	1722	gnl|Fabrus|V2-13_IGLJ2*01	1117
3931	VH3-23_IGHD2-2*01>3_IGHJ6*01	1723	gnl|Fabrus|V2-13_IGLJ2*01	1117
3932	VH3-23_IGHD2-8*01>2_IGHJ6*01	1724	gnl|Fabrus|V2-13_IGLJ2*01	1117
3933	VH3-23_IGHD2-8*01>3_IGHJ6*01	1725	gnl|Fabrus|V2-13_IGLJ2*01	1117
3934	VH3-23_IGHD2-15*01>2_IGHJ6*01	1726	gnl|Fabrus|V2-13_IGLJ2*01	1117
3935	VH3-23_IGHD2-15*01>3_IGHJ6*01	1727	gnl|Fabrus|V2-13_IGLJ2*01	1117
3936	VH3-23_IGHD2-21*01>2_IGHJ6*01	1728	gnl|Fabrus|V2-13_IGLJ2*01	1117
3937	VH3-23_IGHD2-21*01>3_IGHJ6*01	1729	gnl|Fabrus|V2-13_IGLJ2*01	1117
3938	VH3-23_IGHD3-3*01>1_IGHJ6*01	1730	gnl|Fabrus|V2-13_IGLJ2*01	1117
3939	VH3-23_IGHD3-3*01>2_IGHJ6*01	1731	gnl|Fabrus|V2-13_IGLJ2*01	1117
3940	VH3-23_IGHD3-3*01>3_IGHJ6*01	1732	gnl|Fabrus|V2-13_IGLJ2*01	1117
3941	VH3-23_IGHD3-9*01>2_IGHJ6*01	1733	gnl|Fabrus|V2-13_IGLJ2*01	1117
3942	VH3-23_IGHD3-10*01>2_IGHJ6*01	1734	gnl|Fabrus|V2-13_IGLJ2*01	1117
3943	VH3-23_IGHD3-10*01>3_IGHJ6*01	1735	gnl|Fabrus|V2-13_IGLJ2*01	1117
3944	VH3-23_IGHD3-16*01>2_IGHJ6*01	1736	gnl|Fabrus|V2-13_IGLJ2*01	1117
3945	VH3-23_IGHD3-16*01>3_IGHJ6*01	1737	gnl|Fabrus|V2-13_IGLJ2*01	1117
3946	VH3-23_IGHD3-22*01>2_IGHJ6*01	1738	gnl|Fabrus|V2-13_IGLJ2*01	1117
3947	VH3-23_IGHD3-22*01>3_IGHJ6*01	1739	gnl|Fabrus|V2-13_IGLJ2*01	1117
3948	VH3-23_IGHD4-4*01 (1) >2_IGHJ6*01	1740	gnl|Fabrus|V2-13_IGLJ2*01	1117
3949	VH3-23_IGHD4-4*01 (1) >3_IGHJ6*01	1741	gnl|Fabrus|V2-13_IGLJ2*01	1117
3950	VH3-23_IGHD4-11*01 (1) >2_IGHJ6*01	1742	gnl|Fabrus|V2-13_IGLJ2*01	1117
3951	VH3-23_IGHD4-11*01 (1) >3_IGHJ6*01	1743	gnl|Fabrus|V2-13_IGLJ2*01	1117
3952	VH3-23_IGHD4-17*01>2_IGHJ6*01	1744	gnl|Fabrus|V2-13_IGLJ2*01	1117
3953	VH3-23_IGHD4-17*01>3_IGHJ6*01	1745	gnl|Fabrus|V2-13_IGLJ2*01	1117
3954	VH3-23_IGHD4-23*01>2_IGHJ6*01	1746	gnl|Fabrus|V2-13_IGLJ2*01	1117
3955	VH3-23_IGHD4-23*01>3_IGHJ6*01	1747	gnl|Fabrus|V2-13_IGLJ2*01	1117
3956	VH3-23_IGHD5-5*01 (2) >1_IGHJ6*01	1748	gnl|Fabrus|V2-13_IGLJ2*01	1117
3957	VH3-23_IGHD5-5*01 (2) >2_IGHJ6*01	1749	gnl|Fabrus|V2-13_IGLJ2*01	1117
3958	VH3-23_IGHD5-5*01 (2) >3_IGHJ6*01	1750	gnl|Fabrus|V2-13_IGLJ2*01	1117
3959	VH3-23_IGHD5-12*01>1_IGHJ6*01	1751	gnl|Fabrus|V2-13_IGLJ2*01	1117
3960	VH3-23_IGHD5-12*01>3_IGHJ6*01	1752	gnl|Fabrus|V2-13_IGLJ2*01	1117
3961	VH3-23_IGHD5-18*01 (2) >1_IGHJ6*01	1753	gnl|Fabrus|V2-13_IGLJ2*01	1117
3962	VH3-23_IGHD5-18*01 (2) >2_IGHJ6*01	1754	gnl|Fabrus|V2-13_IGLJ2*01	1117
3963	VH3-23_IGHD5-18*01 (2) >3_IGHJ6*01	1755	gnl|Fabrus|V2-13_IGLJ2*01	1117
3964	VH3-23_IGHD5-24*01>1_IGHJ6*01	1756	gnl|Fabrus|V2-13_IGLJ2*01	1117
3965	VH3-23_IGHD5-24*01>3_IGHJ6*01	1757	gnl|Fabrus|V2-13_IGLJ2*01	1117
3966	VH3-23_IGHD6-6*01>1_IGHJ6*01	1758	gnl|Fabrus|V2-13_IGLJ2*01	1117
3967	VH3-23_IGHD1-1*01>1'_IGHJ6*01	1768	gnl|Fabrus|V2-13_IGLJ2*01	1117
3968	VH3-23_IGHD1-1*01>2'_IGHJ6*01	1769	gnl|Fabrus|V2-13_IGLJ2*01	1117

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
3969	VH3-23_IGHD1-1*01>3'_IGHJ6*01	1770	gnl|Fabrus|V2-13_IGLJ2*01	1117
3970	VH3-23_IGHD1-7*01>1'_IGHJ6*01	1771	gnl|Fabrus|V2-13_IGLJ2*01	1117
3971	VH3-23_IGHD1-7*01>3'_IGHJ6*01	1772	gnl|Fabrus|V2-13_IGLJ2*01	1117
3972	VH3-23_IGHD1-14*01>1'_IGHJ6*01	1773	gnl|Fabrus|V2-13_IGLJ2*01	1117
3973	VH3-23_IGHD1-14*01>2'_IGHJ6*01	1774	gnl|Fabrus|V2-13_IGLJ2*01	1117
3974	VH3-23_IGHD1-14*01>3'_IGHJ6*01	1775	gnl|Fabrus|V2-13_IGLJ2*01	1117
3975	VH3-23_IGHD1-20*01>1'_IGHJ6*01	1776	gnl|Fabrus|V2-13_IGLJ2*01	1117
3976	VH3-23_IGHD1-20*01>2'_IGHJ6*01	1777	gnl|Fabrus|V2-13_IGLJ2*01	1117
3977	VH3-23_IGHD1-20*01>3'_IGHJ6*01	1778	gnl|Fabrus|V2-13_IGLJ2*01	1117
3978	VH3-23_IGHD1-26*01>1'_IGHJ6*01	1779	gnl|Fabrus|V2-13_IGLJ2*01	1117
3979	VH3-23_IGHD1-26*01>1_IGHJ6*01_B	1780	gnl|Fabrus|V2-13_IGLJ2*01	1117
3980	VH3-23_IGHD2-2*01>2_IGHJ6*01_B	1781	gnl|Fabrus|V2-13_IGLJ2*01	1117
3981	VH3-23_IGHD2-2*01>3'_IGHJ6*01	1782	gnl|Fabrus|V2-13_IGLJ2*01	1117
3982	VH3-23_IGHD2-8*01>1'_IGHJ6*01	1783	gnl|Fabrus|V2-13_IGLJ2*01	1117
3983	VH3-23_IGHD2-15*01>1'_IGHJ6*01	1784	gnl|Fabrus|V2-13_IGLJ2*01	1117
3984	VH3-23_IGHD2-15*01>3'_IGHJ6*01	1785	gnl|Fabrus|V2-13_IGLJ2*01	1117
3985	VH3-23_IGHD2-21*01>1'_IGHJ6*01	1786	gnl|Fabrus|V2-13_IGLJ2*01	1117
3986	VH3-23_IGHD2-21*01>3'_IGHJ6*01	1787	gnl|Fabrus|V2-13_IGLJ2*01	1117
3987	VH3-23_IGHD3-3*01>1'_IGHJ6*01	1788	gnl|Fabrus|V2-13_IGLJ2*01	1117
3988	VH3-23_IGHD3-3*01>3'_IGHJ6*01	1789	gnl|Fabrus|V2-13_IGLJ2*01	1117
3989	VH3-23_IGHD3-9*01>1'_IGHJ6*01	1790	gnl|Fabrus|V2-13_IGLJ2*01	1117
3990	VH3-23_IGHD3-9*01>3'_IGHJ6*01	1791	gnl|Fabrus|V2-13_IGLJ2*01	1117
3991	VH3-23_IGHD3-10*01>1'_IGHJ6*01	1792	gnl|Fabrus|V2-13_IGLJ2*01	1117
3992	VH3-23_IGHD3-10*01>3'_IGHJ6*01	1793	gnl|Fabrus|V2-13_IGLJ2*01	1117
3993	VH3-23_IGHD3-16*01>1'_IGHJ6*01	1794	gnl|Fabrus|V2-13_IGLJ2*01	1117
3994	VH3-23_IGHD3-16*01>3'_IGHJ6*01	1795	gnl|Fabrus|V2-13_IGLJ2*01	1117
3995	VH3-23_IGHD3-22*01>1'_IGHJ6*01	1796	gnl|Fabrus|V2-13_IGLJ2*01	1117
3996	VH3-23_IGHD4-4*01 (1) >1'_IGHJ6*01	1797	gnl|Fabrus|V2-13_IGLJ2*01	1117
3997	VH3-23_IGHD4-4*01 (1) >3'_IGHJ6*01	1798	gnl|Fabrus|V2-13_IGLJ2*01	1117
3998	VH3-23_IGHD4-11*01 (1) >1'_IGHJ6*01	1799	gnl|Fabrus|V2-13_IGLJ2*01	1117
3999	VH3-23_IGHD4-11*01 (1) >3'_IGHJ6*01	1800	gnl|Fabrus|V2-13_IGLJ2*01	1117
4000	VH3-23_IGHD4-17*01>1'_IGHJ6*01	1801	gnl|Fabrus|V2-13_IGLJ2*01	1117
4001	VH3-23_IGHD4-17*01>3'_IGHJ6*01	1802	gnl|Fabrus|V2-13_IGLJ2*01	1117
4002	VH3-23_IGHD4-23*01>1'_IGHJ6*01	1803	gnl|Fabrus|V2-13_IGLJ2*01	1117
4003	VH3-23_IGHD4-23*01>3'_IGHJ6*01	1804	gnl|Fabrus|V2-13_IGLJ2*01	1117
4004	VH3-23_IGHD5-5*01 (2) >1'_IGHJ6*01	1805	gnl|Fabrus|V2-13_IGLJ2*01	1117
4005	VH3-23_IGHD5-5*01 (2) >3'_IGHJ6*01	1806	gnl|Fabrus|V2-13_IGLJ2*01	1117
4006	VH3-23_IGHD5-12*01>1'_IGHJ6*01	1807	gnl|Fabrus|V2-13_IGLJ2*01	1117
4007	VH3-23_IGHD5-12*01>3'_IGHJ6*01	1808	gnl|Fabrus|V2-13_IGLJ2*01	1117
4008	VH3-23_IGHD5-18*01 (2) >1'_IGHJ6*01	1809	gnl|Fabrus|V2-13_IGLJ2*01	1117
4009	VH3-23_IGHD5-18*01 (2) >3'_IGHJ6*01	1810	gnl|Fabrus|V2-13_IGLJ2*01	1117
4010	VH3-23_IGHD5-24*01>1'_IGHJ6*01	1811	gnl|Fabrus|V2-13_IGLJ2*01	1117

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
4011	VH3-23_IGHD5-24*01>3'_IGHJ6*01	1812	gnl|Fabrus|V2-13_IGLJ2*01	1117
4012	VH3-23_IGHD6-6*01>1'_IGHJ6*01	1813	gnl|Fabrus|V2-13_IGLJ2*01	1117
4013	VH3-23_IGHD6-6*01>2'_IGHJ6*01	1814	gnl|Fabrus|V2-13_IGLJ2*01	1117
4014	VH3-23_IGHD6-6*01>3'_IGHJ6*01	1815	gnl|Fabrus|V2-13_IGLJ2*01	1117
4015	VH3-23_IGHD1-1*01>1_IGHJ6*01	1711	gnl|Fabrus|V2-14_IGLJ4*01	1118
4016	VH3-23_IGHD1-1*01>2_IGHJ6*01	1712	gnl|Fabrus|V2-14_IGLJ4*01	1118
4017	VH3-23_IGHD1-1*01>3_IGHJ6*01	1713	gnl|Fabrus|V2-14_IGLJ4*01	1118
4018	VH3-23_IGHD1-7*01>1_IGHJ6*01	1714	gnl|Fabrus|V2-14_IGLJ4*01	1118
4019	VH3-23_IGHD1-7*01>3_IGHJ6*01	1715	gnl|Fabrus|V2-14_IGLJ4*01	1118
4020	VH3-23_IGHD1-14*01>1_IGHJ6*01	1716	gnl|Fabrus|V2-14_IGLJ4*01	1118
4021	VH3-23_IGHD1-14*01>3_IGHJ6*01	1717	gnl|Fabrus|V2-14_IGLJ4*01	1118
4022	VH3-23_IGHD1-20*01>1_IGHJ6*01	1718	gnl|Fabrus|V2-14_IGLJ4*01	1118
4023	VH3-23_IGHD1-20*01>3_IGHJ6*01	1719	gnl|Fabrus|V2-14_IGLJ4*01	1118
4024	VH3-23_IGHD1-26*01>1_IGHJ6*01	1720	gnl|Fabrus|V2-14_IGLJ4*01	1118
4025	VH3-23_IGHD1-26*01>3_IGHJ6*01	1721	gnl|Fabrus|V2-14_IGLJ4*01	1118
4026	VH3-23_IGHD2-2*01>2_IGHJ6*01	1722	gnl|Fabrus|V2-14_IGLJ4*01	1118
4027	VH3-23_IGHD2-2*01>3_IGHJ6*01	1723	gnl|Fabrus|V2-14_IGLJ4*01	1118
4028	VH3-23_IGHD2-8*01>2_IGHJ6*01	1724	gnl|Fabrus|V2-14_IGLJ4*01	1118
4029	VH3-23_IGHD2-8*01>3_IGHJ6*01	1725	gnl|Fabrus|V2-14_IGLJ4*01	1118
4030	VH3-23_IGHD2-15*01>2_IGHJ6*01	1726	gnl|Fabrus|V2-14_IGLJ4*01	1118
4031	VH3-23_IGHD2-15*01>3_IGHJ6*01	1727	gnl|Fabrus|V2-14_IGLJ4*01	1118
4032	VH3-23_IGHD2-21*01>2_IGHJ6*01	1728	gnl|Fabrus|V2-14_IGLJ4*01	1118
4033	VH3-23_IGHD2-21*01>3_IGHJ6*01	1729	gnl|Fabrus|V2-14_IGLJ4*01	1118
4034	VH3-23_IGHD3-3*01>1_IGHJ6*01	1730	gnl|Fabrus|V2-14_IGLJ4*01	1118
4035	VH3-23_IGHD3-3*01>2_IGHJ6*01	1731	gnl|Fabrus|V2-14_IGLJ4*01	1118
4036	VH3-23_IGHD3-3*01>3_IGHJ6*01	1732	gnl|Fabrus|V2-14_IGLJ4*01	1118
4037	VH3-23_IGHD3-9*01>2_IGHJ6*01	1733	gnl|Fabrus|V2-14_IGLJ4*01	1118
4038	VH3-23_IGHD3-10*01>2_IGHJ6*01	1734	gnl|Fabrus|V2-14_IGLJ4*01	1118
4039	VH3-23_IGHD3-10*01>3_IGHJ6*01	1735	gnl|Fabrus|V2-14_IGLJ4*01	1118
4040	VH3-23_IGHD3-16*01>2_IGHJ6*01	1736	gnl|Fabrus|V2-14_IGLJ4*01	1118
4041	VH3-23_IGHD3-16*01>3_IGHJ6*01	1737	gnl|Fabrus|V2-14_IGLJ4*01	1118
4042	VH3-23_IGHD3-22*01>2_IGHJ6*01	1738	gnl|Fabrus|V2-14_IGLJ4*01	1118
4043	VH3-23_IGHD3-22*01>3_IGHJ6*01	1739	gnl|Fabrus|V2-14_IGLJ4*01	1118
4044	VH3-23_IGHD4-4*01 (1) >2_IGHJ6*01	1740	gnl|Fabrus|V2-14_IGLJ4*01	1118
4045	VH3-23_IGHD4-4*01 (1) >3_IGHJ6*01	1741	gnl|Fabrus|V2-14_IGLJ4*01	1118
4046	VH3-23_IGHD4-11*01 (1) >2_IGHJ6*01	1742	gnl|Fabrus|V2-14_IGLJ4*01	1118
4047	VH3-23_IGHD4-11*01 (1) >3_IGHJ6*01	1743	gnl|Fabrus|V2-14_IGLJ4*01	1118
4048	VH3-23_IGHD4-17*01>2_IGHJ6*01	1744	gnl|Fabrus|V2-14_IGLJ4*01	1118
4049	VH3-23_IGHD4-17*01>3_IGHJ6*01	1745	gnl|Fabrus|V2-14_IGLJ4*01	1118
4050	VH3-23_IGHD4-23*01>2_IGHJ6*01	1746	gnl|Fabrus|V2-14_IGLJ4*01	1118
4051	VH3-23_IGHD4-23*01>3_IGHJ6*01	1747	gnl|Fabrus|V2-14_IGLJ4*01	1118
4052	VH3-23_IGHD5-5*01 (2) >1_IGHJ6*01	1748	gnl|Fabrus|V2-14_IGLJ4*01	1118

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
4053	VH3-23_IGHD5-5*01 (2) >2_IGHJ6*01	1749	gnl|Fabrus|V2-14_IGLJ4*01	1118
4054	VH3-23_IGHD5-5*01 (2) >3_IGHJ6*01	1750	gnl|Fabrus|V2-14_IGLJ4*01	1118
4055	VH3-23_IGHD5-12*01>1_IGHJ6*01	1751	gnl|Fabrus|V2-14_IGLJ4*01	1118
4056	VH3-23_IGHD5-12*01>3_IGHJ6*01	1752	gnl|Fabrus|V2-14_IGLJ4*01	1118
4057	VH3-23_IGHD5-18*01 (2) >1_IGHJ6*01	1753	gnl|Fabrus|V2-14_IGLJ4*01	1118
4058	VH3-23_IGHD5-18*01 (2) >2_IGHJ6*01	1754	gnl|Fabrus|V2-14_IGLJ4*01	1118
4059	VH3-23_IGHD5-18*01 (2) >3_IGHJ6*01	1755	gnl|Fabrus|V2-14_IGLJ4*01	1118
4060	VH3-23_IGHD5-24*01>1_IGHJ6*01	1756	gnl|Fabrus|V2-14_IGLJ4*01	1118
4061	VH3-23_IGHD5-24*01>3_IGHJ6*01	1757	gnl|Fabrus|V2-14_IGLJ4*01	1118
4062	VH3-23_IGHD6-6*01>1_IGHJ6*01	1758	gnl|Fabrus|V2-14_IGLJ4*01	1118
4063	VH3-23_IGHD1-1*01>1'_IGHJ6*01	1768	gnl|Fabrus|V2-14_IGLJ4*01	1118
4064	VH3-23_IGHD1-1*01>2'_IGHJ6*01	1769	gnl|Fabrus|V2-14_IGLJ4*01	1118
4065	VH3-23_IGHD1-1*01>3'_IGHJ6*01	1770	gnl|Fabrus|V2-14_IGLJ4*01	1118
4066	VH3-23_IGHD1-7*01>1'_IGHJ6*01	1771	gnl|Fabrus|V2-14_IGLJ4*01	1118
4067	VH3-23_IGHD1-7*01>3'_IGHJ6*01	1772	gnl|Fabrus|V2-14_IGLJ4*01	1118
4068	VH3-23_IGHD1-14*01>1'_IGHJ6*01	1773	gnl|Fabrus|V2-14_IGLJ4*01	1118
4069	VH3-23_IGHD1-14*01>2'_IGHJ6*01	1774	gnl|Fabrus|V2-14_IGLJ4*01	1118
4070	VH3-23_IGHD1-14*01>3'_IGHJ6*01	1775	gnl|Fabrus|V2-14_IGLJ4*01	1118
4071	VH3-23_IGHD1-20*01>1'_IGHJ6*01	1776	gnl|Fabrus|V2-14_IGLJ4*01	1118
4072	VH3-23_IGHD1-20*01>2'_IGHJ6*01	1777	gnl|Fabrus|V2-14_IGLJ4*01	1118
4073	VH3-23_IGHD1-20*01>3'_IGHJ6*01	1778	gnl|Fabrus|V2-14_IGLJ4*01	1118
4074	VH3-23_IGHD1-26*01>1'_IGHJ6*01	1779	gnl|Fabrus|V2-14_IGLJ4*01	1118
4075	VH3-23_IGHD1-26*01>1_IGHJ6*01_B	1780	gnl|Fabrus|V2-14_IGLJ4*01	1118
4076	VH3-23_IGHD2-2*01>2_IGHJ6*01_B	1781	gnl|Fabrus|V2-14_IGLJ4*01	1118
4077	VH3-23_IGHD2-2*01>3'_IGHJ6*01	1782	gnl|Fabrus|V2-14_IGLJ4*01	1118
4078	VH3-23_IGHD2-8*01>1'_IGHJ6*01	1783	gnl|Fabrus|V2-14_IGLJ4*01	1118
4079	VH3-23_IGHD2-15*01>1'_IGHJ6*01	1784	gnl|Fabrus|V2-14_IGLJ4*01	1118
4080	VH3-23_IGHD2-15*01>3'_IGHJ6*01	1785	gnl|Fabrus|V2-14_IGLJ4*01	1118
4081	VH3-23_IGHD2-21*01>1'_IGHJ6*01	1786	gnl|Fabrus|V2-14_IGLJ4*01	1118
4082	VH3-23_IGHD2-21*01>3'_IGHJ6*01	1787	gnl|Fabrus|V2-14_IGLJ4*01	1118
4083	VH3-23_IGHD3-3*01>1'_IGHJ6*01	1788	gnl|Fabrus|V2-14_IGLJ4*01	1118
4084	VH3-23_IGHD3-3*01>3'_IGHJ6*01	1789	gnl|Fabrus|V2-14_IGLJ4*01	1118
4085	VH3-23_IGHD3-9*01>1'_IGHJ6*01	1790	gnl|Fabrus|V2-14_IGLJ4*01	1118
4086	VH3-23_IGHD3-9*01>3'_IGHJ6*01	1791	gnl|Fabrus|V2-14_IGLJ4*01	1118
4087	VH3-23_IGHD3-10*01>1'_IGHJ6*01	1792	gnl|Fabrus|V2-14_IGLJ4*01	1118
4088	VH3-23_IGHD3-10*01>3'_IGHJ6*01	1793	gnl|Fabrus|V2-14_IGLJ4*01	1118
4089	VH3-23_IGHD3-16*01>1'_IGHJ6*01	1794	gnl|Fabrus|V2-14_IGLJ4*01	1118
4090	VH3-23_IGHD3-16*01>3'_IGHJ6*01	1795	gnl|Fabrus|V2-14_IGLJ4*01	1118
4091	VH3-23_IGHD3-22*01>1'_IGHJ6*01	1796	gnl|Fabrus|V2-14_IGLJ4*01	1118
4092	VH3-23_IGHD4-4*01 (1) >1'_IGHJ6*01	1797	gnl|Fabrus|V2-14_IGLJ4*01	1118
4093	VH3-23_IGHD4-4*01 (1) >3'_IGHJ6*01	1798	gnl|Fabrus|V2-14_IGLJ4*01	1118
4094	VH3-23_IGHD4-11*01 (1) >1'_IGHJ6*01	1799	gnl|Fabrus|V2-14_IGLJ4*01	1118

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
4095	VH3-23_IGHD4-11*01 (1) >3'_IGHJ6*01	1800	gnl|Fabrus|V2-14_IGLJ4*01	1118
4096	VH3-23_IGHD4-17*01>1'_IGHJ6*01	1801	gnl|Fabrus|V2-14_IGLJ4*01	1118
4097	VH3-23_IGHD4-17*01>3'_IGHJ6*01	1802	gnl|Fabrus|V2-14_IGLJ4*01	1118
4098	VH3-23_IGHD4-23*01>1'_IGHJ6*01	1803	gnl|Fabrus|V2-14_IGLJ4*01	1118
4099	VH3-23_IGHD4-23*01>3'_IGHJ6*01	1804	gnl|Fabrus|V2-14_IGLJ4*01	1118
4100	VH3-23_IGHD5-5*01 (2) >1'_IGHJ6*01	1805	gnl|Fabrus|V2-14_IGLJ4*01	1118
4101	VH3-23_IGHD5-5*01 (2) >3'_IGHJ6*01	1806	gnl|Fabrus|V2-14_IGLJ4*01	1118
4102	VH3-23_IGHD5-12*01>1'_IGHJ6*01	1807	gnl|Fabrus|V2-14_IGLJ4*01	1118
4103	VH3-23_IGHD5-12*01>3'_IGHJ6*01	1808	gnl|Fabrus|V2-14_IGLJ4*01	1118
4104	VH3-23_IGHD5-18*01 (2) >1'_IGHJ6*01	1809	gnl|Fabrus|V2-14_IGLJ4*01	1118
4105	VH3-23_IGHD5-18*01 (2) >3'_IGHJ6*01	1810	gnl|Fabrus|V2-14_IGLJ4*01	1118
4106	VH3-23_IGHD5-24*01>1'_IGHJ6*01	1811	gnl|Fabrus|V2-14_IGLJ4*01	1118
4107	VH3-23_IGHD5-24*01>3'_IGHJ6*01	1812	gnl|Fabrus|V2-14_IGLJ4*01	1118
4108	VH3-23_IGHD6-6*01>1'_IGHJ6*01	1813	gnl|Fabrus|V2-14_IGLJ4*01	1118
4109	VH3-23_IGHD6-6*01>2'_IGHJ6*01	1814	gnl|Fabrus|V2-14_IGLJ4*01	1118
4110	VH3-23_IGHD6-6*01>3'_IGHJ6*01	1815	gnl|Fabrus|V2-14_IGLJ4*01	1118
4111	VH3-23_IGHD1-1*01>1_IGHJ6*01	1711	gnl|Fabrus|V2-15_IGLJ7*01	1118
4112	VH3-23_IGHD1-1*01>2_IGHJ6*01	1712	gnl|Fabrus|V2-15_IGLJ7*01	1119
4113	VH3-23_IGHD1-1*01>3_IGHJ6*01	1713	gnl|Fabrus|V2-15_IGLJ7*01	1119
4114	VH3-23_IGHD1-7*01>1_IGHJ6*01	1714	gnl|Fabrus|V2-15_IGLJ7*01	1119
4115	VH3-23_IGHD1-7*01>3_IGHJ6*01	1715	gnl|Fabrus|V2-15_IGLJ7*01	1119
4116	VH3-23_IGHD1-14*01>1_IGHJ6*01	1716	gnl|Fabrus|V2-15_IGLJ7*01	1119
4117	VH3-23_IGHD1-14*01>3_IGHJ6*01	1717	gnl|Fabrus|V2-15_IGLJ7*01	1119
4118	VH3-23_IGHD1-20*01>1_IGHJ6*01	1718	gnl|Fabrus|V2-15_IGLJ7*01	1119
4119	VH3-23_IGHD1-20*01>3_IGHJ6*01	1719	gnl|Fabrus|V2-15_IGLJ7*01	1119
4120	VH3-23_IGHD1-26*01>1_IGHJ6*01	1720	gnl|Fabrus|V2-15_IGLJ7*01	1119
4121	VH3-23_IGHD1-26*01>3_IGHJ6*01	1721	gnl|Fabrus|V2-15_IGLJ7*01	1119
4122	VH3-23_IGHD2-2*01>2_IGHJ6*01	1722	gnl|Fabrus|V2-15_IGLJ7*01	1119
4123	VH3-23_IGHD2-2*01>3_IGHJ6*01	1723	gnl|Fabrus|V2-15_IGLJ7*01	1119
4124	VH3-23_IGHD2-8*01>2_IGHJ6*01	1724	gnl|Fabrus|V2-15_IGLJ7*01	1119
4125	VH3-23_IGHD2-8*01>3_IGHJ6*01	1725	gnl|Fabrus|V2-15_IGLJ7*01	1119
4126	VH3-23_IGHD2-15*01>2_IGHJ6*01	1726	gnl|Fabrus|V2-15_IGLJ7*01	1119
4127	VH3-23_IGHD2-15*01>3_IGHJ6*01	1727	gnl|Fabrus|V2-15_IGLJ7*01	1119
4128	VH3-23_IGHD2-21*01>2_IGHJ6*01	1728	gnl|Fabrus|V2-15_IGLJ7*01	1119
4129	VH3-23_IGHD2-21*01>3_IGHJ6*01	1729	gnl|Fabrus|V2-15_IGLJ7*01	1119
4130	VH3-23_IGHD3-3*01>1_IGHJ6*01	1730	gnl|Fabrus|V2-15_IGLJ7*01	1119
4131	VH3-23_IGHD3-3*01>2_IGHJ6*01	1731	gnl|Fabrus|V2-15_IGLJ7*01	1119
4132	VH3-23_IGHD3-3*01>3_IGHJ6*01	1732	gnl|Fabrus|V2-15_IGLJ7*01	1119
4133	VH3-23_IGHD3-9*01>2_IGHJ6*01	1733	gnl|Fabrus|V2-15_IGLJ7*01	1119
4134	VH3-23_IGHD3-10*01>2_IGHJ6*01	1734	gnl|Fabrus|V2-15_IGLJ7*01	1119
4135	VH3-23_IGHD3-10*01>3_IGHJ6*01	1735	gnl|Fabrus|V2-15_IGLJ7*01	1119
4136	VH3-23_IGHD3-16*01>2_IGHJ6*01	1736	gnl|Fabrus|V2-15_IGLJ7*01	1119

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
4137	VH3-23_IGHD3-16*01>3_IGHJ6*01	1737	gnl|Fabrus|V2-15_IGLJ7*01	1119
4138	VH3-23_IGHD3-22*01>2_IGHJ6*01	1738	gnl|Fabrus|V2-15_IGLJ7*01	1119
4139	VH3-23_IGHD3-22*01>3_IGHJ6*01	1739	gnl|Fabrus|V2-15_IGLJ7*01	1119
4140	VH3-23_IGHD4-4*01 (1) >2_IGHJ6*01	1740	gnl|Fabrus|V2-15_IGLJ7*01	1119
4141	VH3-23_IGHD4-4*01 (1) >3_IGHJ6*01	1741	gnl|Fabrus|V2-15_IGLJ7*01	1119
4142	VH3-23_IGHD4-11*01 (1) >2_IGHJ6*01	1742	gnl|Fabrus|V2-15_IGLJ7*01	1119
4143	VH3-23_IGHD4-11*01 (1) >3_IGHJ6*01	1743	gnl|Fabrus|V2-15_IGLJ7*01	1119
4144	VH3-23_IGHD4-17*01>2_IGHJ6*01	1744	gnl|Fabrus|V2-15_IGLJ7*01	1119
4145	VH3-23_IGHD4-17*01>3_IGHJ6*01	1745	gnl|Fabrus|V2-15_IGLJ7*01	1119
4146	VH3-23_IGHD4-23*01>2_IGHJ6*01	1746	gnl|Fabrus|V2-15_IGLJ7*01	1119
4147	VH3-23_IGHD4-23*01>3_IGHJ6*01	1747	gnl|Fabrus|V2-15_IGLJ7*01	1119
4148	VH3-23_IGHD5-5*01 (2) >1_IGHJ6*01	1748	gnl|Fabrus|V2-15_IGLJ7*01	1119
4149	VH3-23_IGHD5-5*01 (2) >2_IGHJ6*01	1749	gnl|Fabrus|V2-15_IGLJ7*01	1119
4150	VH3-23_IGHD5-5*01 (2) >3_IGHJ6*01	1750	gnl|Fabrus|V2-15_IGLJ7*01	1119
4151	VH3-23_IGHD5-12*01>1_IGHJ6*01	1751	gnl|Fabrus|V2-15_IGLJ7*01	1119
4152	VH3-23_IGHD5-12*01>3_IGHJ6*01	1752	gnl|Fabrus|V2-15_IGLJ7*01	1119
4153	VH3-23_IGHD5-18*01 (2) >1_IGHJ6*01	1753	gnl|Fabrus|V2-15_IGLJ7*01	1119
4154	VH3-23_IGHD5-18*01 (2) >2_IGHJ6*01	1754	gnl|Fabrus|V2-15_IGLJ7*01	1119
4155	VH3-23_IGHD5-18*01 (2) >3_IGHJ6*01	1755	gnl|Fabrus|V2-15_IGLJ7*01	1119
4156	VH3-23_IGHD5-24*01>1_IGHJ6*01	1756	gnl|Fabrus|V2-15_IGLJ7*01	1119
4157	VH3-23_IGHD5-24*01>3_IGHJ6*01	1757	gnl|Fabrus|V2-15_IGLJ7*01	1119
4158	VH3-23_IGHD6-6*01>1_IGHJ6*01	1758	gnl|Fabrus|V2-15_IGLJ7*01	1119
4159	VH3-23_IGHD1-1*01>1'_IGHJ6*01	1768	gnl|Fabrus|V2-15_IGLJ7*01	1119
4160	VH3-23_IGHD1-1*01>2'_IGHJ6*01	1769	gnl|Fabrus|V2-15_IGLJ7*01	1119
4161	VH3-23_IGHD1-1*01>3'_IGHJ6*01	1770	gnl|Fabrus|V2-15_IGLJ7*01	1119
4162	VH3-23_IGHD1-7*01>1'_IGHJ6*01	1771	gnl|Fabrus|V2-15_IGLJ7*01	1119
4163	VH3-23_IGHD1-7*01>3'_IGHJ6*01	1772	gnl|Fabrus|V2-15_IGLJ7*01	1119
4164	VH3-23_IGHD1-14*01>1'_IGHJ6*01	1773	gnl|Fabrus|V2-15_IGLJ7*01	1119
4165	VH3-23_IGHD1-14*01>2'_IGHJ6*01	1774	gnl|Fabrus|V2-15_IGLJ7*01	1119
4166	VH3-23_IGHD1-14*01>3'_IGHJ6*01	1775	gnl|Fabrus|V2-15_IGLJ7*01	1119
4167	VH3-23_IGHD1-20*01>1'_IGHJ6*01	1776	gnl|Fabrus|V2-15_IGLJ7*01	1119
4168	VH3-23_IGHD1-20*01>2'_IGHJ6*01	1777	gnl|Fabrus|V2-15_IGLJ7*01	1119
4169	VH3-23_IGHD1-20*01>3'_IGHJ6*01	1778	gnl|Fabrus|V2-15_IGLJ7*01	1119
4170	VH3-23_IGHD1-26*01>1'_IGHJ6*01	1779	gnl|Fabrus|V2-15_IGLJ7*01	1119
4171	VH3-23_IGHD1-26*01>1_IGHJ6*01_B	1780	gnl|Fabrus|V2-15_IGLJ7*01	1119
4172	VH3-23_IGHD2-2*01>2_IGHJ6*01_B	1781	gnl|Fabrus|V2-15_IGLJ7*01	1119
4173	VH3-23_IGHD2-2*01>3'_IGHJ6*01	1782	gnl|Fabrus|V2-15_IGLJ7*01	1119
4174	VH3-23_IGHD2-8*01>1'_IGHJ6*01	1783	gnl|Fabrus|V2-15_IGLJ7*01	1119
4175	VH3-23_IGHD2-15*01>1'_IGHJ6*01	1784	gnl|Fabrus|V2-15_IGLJ7*01	1119
4176	VH3-23_IGHD2-15*01>3'_IGHJ6*01	1785	gnl|Fabrus|V2-15_IGLJ7*01	1119
4177	VH3-23_IGHD2-21*01>1'_IGHJ6*01	1786	gnl|Fabrus|V2-15_IGLJ7*01	1119
4178	VH3-23_IGHD2-21*01>3'_IGHJ6*01	1787	gnl|Fabrus|V2-15_IGLJ7*01	1119

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
4179	VH3-23_IGHD3-3*01>1'_IGHJ6*01	1788	gnl|Fabrus|V2-15_IGLJ7*01	1119
4180	VH3-23_IGHD3-3*01>3'_IGHJ6*01	1789	gnl|Fabrus|V2-15_IGLJ7*01	1119
4181	VH3-23_IGHD3-9*01>1'_IGHJ6*01	1790	gnl|Fabrus|V2-15_IGLJ7*01	1119
4182	VH3-23_IGHD3-9*01>3'_IGHJ6*01	1791	gnl|Fabrus|V2-15_IGLJ7*01	1119
4183	VH3-23_IGHD3-10*01>1'_IGHJ6*01	1792	gnl|Fabrus|V2-15_IGLJ7*01	1119
4184	VH3-23_IGHD3-10*01>3'_IGHJ6*01	1793	gnl|Fabrus|V2-15_IGLJ7*01	1119
4185	VH3-23_IGHD3-16*01>1'_IGHJ6*01	1794	gnl|Fabrus|V2-15_IGLJ7*01	1119
4186	VH3-23_IGHD3-16*01>3'_IGHJ6*01	1795	gnl|Fabrus|V2-15_IGLJ7*01	1119
4187	VH3-23_IGHD3-22*01>1'_IGHJ6*01	1796	gnl|Fabrus|V2-15_IGLJ7*01	1119
4188	VH3-23_IGHD4-4*01 (1) >1'_IGHJ6*01	1797	gnl|Fabrus|V2-15_IGLJ7*01	1119
4189	VH3-23_IGHD4-4*01 (1) >3'_IGHJ6*01	1798	gnl|Fabrus|V2-15_IGLJ7*01	1119
4190	VH3-23_IGHD4-11*01 (1) >1'_IGHJ6*01	1799	gnl|Fabrus|V2-15_IGLJ7*01	1119
4191	VH3-23_IGHD4-11*01 (1) >3'_IGHJ6*01	1800	gnl|Fabrus|V2-15_IGLJ7*01	1119
4192	VH3-23_IGHD4-17*01>1'_IGHJ6*01	1801	gnl|Fabrus|V2-15_IGLJ7*01	1119
4193	VH3-23_IGHD4-17*01>3'_IGHJ6*01	1802	gnl|Fabrus|V2-15_IGLJ7*01	1119
4194	VH3-23_IGHD4-23*01>1'_IGHJ6*01	1803	gnl|Fabrus|V2-15_IGLJ7*01	1119
4195	VH3-23_IGHD4-23*01>3'_IGHJ6*01	1804	gnl|Fabrus|V2-15_IGLJ7*01	1119
4196	VH3-23_IGHD5-5*01 (2) >1'_IGHJ6*01	1805	gnl|Fabrus|V2-15_IGLJ7*01	1119
4197	VH3-23_IGHD5-5*01 (2) >3'_IGHJ6*01	1806	gnl|Fabrus|V2-15_IGLJ7*01	1119
4198	VH3-23_IGHD5-12*01>1'_IGHJ6*01	1807	gnl|Fabrus|V2-15_IGLJ7*01	1119
4199	VH3-23_IGHD5-12*01>3'_IGHJ6*01	1808	gnl|Fabrus|V2-15_IGLJ7*01	1119
4200	VH3-23_IGHD5-18*01 (2) >1'_IGHJ6*01	1809	gnl|Fabrus|V2-15_IGLJ7*01	1119
4201	VH3-23_IGHD5-18*01 (2) >3'_IGHJ6*01	1810	gnl|Fabrus|V2-15_IGLJ7*01	1119
4202	VH3-23_IGHD5-24*01>1'_IGHJ6*01	1811	gnl|Fabrus|V2-15_IGLJ7*01	1119
4203	VH3-23_IGHD5-24*01>3'_IGHJ6*01	1812	gnl|Fabrus|V2-15_IGLJ7*01	1119
4204	VH3-23_IGHD6-6*01>1'_IGHJ6*01	1813	gnl|Fabrus|V2-15_IGLJ7*01	1119
4205	VH3-23_IGHD6-6*01>2'_IGHJ6*01	1814	gnl|Fabrus|V2-15_IGLJ7*01	1119
4206	VH3-23_IGHD6-6*01>3'_IGHJ6*01	1815	gnl|Fabrus|V2-15_IGLJ7*01	1119
4207	VH3-23_IGHD1-1*01>1_IGHJ6*01	1711	gnl|Fabrus|V2-17_IGLJ2*01	1120
4208	VH3-23_IGHD1-1*01>2_IGHJ6*01	1712	gnl|Fabrus|V2-17_IGLJ2*01	1120
4209	VH3-23_IGHD1-1*01>3_IGHJ6*01	1713	gnl|Fabrus|V2-17_IGLJ2*01	1120
4210	VH3-23_IGHD1-7*01>1_IGHJ6*01	1714	gnl|Fabrus|V2-17_IGLJ2*01	1120
4211	VH3-23_IGHD1-7*01>3_IGHJ6*01	1715	gnl|Fabrus|V2-17_IGLJ2*01	1120
4212	VH3-23_IGHD1-14*01>1_IGHJ6*01	1716	gnl|Fabrus|V2-17_IGLJ2*01	1120
4213	VH3-23_IGHD1-14*01>3_IGHJ6*01	1717	gnl|Fabrus|V2-17_IGLJ2*01	1120
4214	VH3-23_IGHD1-20*01>1_IGHJ6*01	1718	gnl|Fabrus|V2-17_IGLJ2*01	1120
4215	VH3-23_IGHD1-20*01>3_IGHJ6*01	1719	gnl|Fabrus|V2-17_IGLJ2*01	1120
4216	VH3-23_IGHD1-26*01>1_IGHJ6*01	1720	gnl|Fabrus|V2-17_IGLJ2*01	1120
4217	VH3-23_IGHD1-26*01>3_IGHJ6*01	1721	gnl|Fabrus|V2-17_IGLJ2*01	1120
4218	VH3-23_IGHD2-2*01>2_IGHJ6*01	1722	gnl|Fabrus|V2-17_IGLJ2*01	1120
4219	VH3-23_IGHD2-2*01>3_IGHJ6*01	1723	gnl|Fabrus|V2-17_IGLJ2*01	1120
4220	VH3-23_IGHD2-8*01>2_IGHJ6*01	1724	gnl|Fabrus|V2-17_IGLJ2*01	1120

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
4221	VH3-23_IGHD2-8*01>3_IGHJ6*01	1725	gnl|Fabrus|V2-17_IGLJ2*01	1120
4222	VH3-23_IGHD2-15*01>2_IGHJ6*01	1726	gnl|Fabrus|V2-17_IGLJ2*01	1120
4223	VH3-23_IGHD2-15*01>3_IGHJ6*01	1727	gnl|Fabrus|V2-17_IGLJ2*01	1120
4224	VH3-23_IGHD2-21*01>2_IGHJ6*01	1728	gnl|Fabrus|V2-17_IGLJ2*01	1120
4225	VH3-23_IGHD2-21*01>3_IGHJ6*01	1729	gnl|Fabrus|V2-17_IGLJ2*01	1120
4226	VH3-23_IGHD3-3*01>1_IGHJ6*01	1730	gnl|Fabrus|V2-17_IGLJ2*01	1120
4227	VH3-23_IGHD3-3*01>2_IGHJ6*01	1731	gnl|Fabrus|V2-17_IGLJ2*01	1120
4228	VH3-23_IGHD3-3*01>3_IGHJ6*01	1732	gnl|Fabrus|V2-17_IGLJ2*01	1120
4229	VH3-23_IGHD3-9*01>2_IGHJ6*01	1733	gnl|Fabrus|V2-17_IGLJ2*01	1120
4230	VH3-23_IGHD3-10*01>2_IGHJ6*01	1734	gnl|Fabrus|V2-17_IGLJ2*01	1120
4231	VH3-23_IGHD3-10*01>3_IGHJ6*01	1735	gnl|Fabrus|V2-17_IGLJ2*01	1120
4232	VH3-23_IGHD3-16*01>2_IGHJ6*01	1736	gnl|Fabrus|V2-17_IGLJ2*01	1120
4233	VH3-23_IGHD3-16*01>3_IGHJ6*01	1737	gnl|Fabrus|V2-17_IGLJ2*01	1120
4234	VH3-23_IGHD3-22*01>2_IGHJ6*01	1738	gnl|Fabrus|V2-17_IGLJ2*01	1120
4235	VH3-23_IGHD3-22*01>3_IGHJ6*01	1739	gnl|Fabrus|V2-17_IGLJ2*01	1120
4236	VH3-23_IGHD4-4*01 (1) >2_IGHJ6*01	1740	gnl|Fabrus|V2-17_IGLJ2*01	1120
4237	VH3-23_IGHD4-4*01 (1) >3_IGHJ6*01	1741	gnl|Fabrus|V2-17_IGLJ2*01	1120
4238	VH3-23_IGHD4-11*01 (1) >2_IGHJ6*01	1742	gnl|Fabrus|V2-17_IGLJ2*01	1120
4239	VH3-23_IGHD4-11*01 (1) >3_IGHJ6*01	1743	gnl|Fabrus|V2-17_IGLJ2*01	1120
4240	VH3-23_IGHD4-17*01>2_IGHJ6*01	1744	gnl|Fabrus|V2-17_IGLJ2*01	1120
4241	VH3-23_IGHD4-17*01>3_IGHJ6*01	1745	gnl|Fabrus|V2-17_IGLJ2*01	1120
4242	VH3-23_IGHD4-23*01>2_IGHJ6*01	1746	gnl|Fabrus|V2-17_IGLJ2*01	1120
4243	VH3-23_IGHD4-23*01>3_IGHJ6*01	1747	gnl|Fabrus|V2-17_IGLJ2*01	1120
4244	VH3-23_IGHD5-5*01 (2) >1_IGHJ6*01	1748	gnl|Fabrus|V2-17_IGLJ2*01	1120
4245	VH3-23_IGHD5-5*01 (2) >2_IGHJ6*01	1749	gnl|Fabrus|V2-17_IGLJ2*01	1120
4246	VH3-23_IGHD5-5*01 (2) >3_IGHJ6*01	1750	gnl|Fabrus|V2-17_IGLJ2*01	1120
4247	VH3-23_IGHD5-12*01>1_IGHJ6*01	1751	gnl|Fabrus|V2-17_IGLJ2*01	1120
4248	VH3-23_IGHD5-12*01>3_IGHJ6*01	1752	gnl|Fabrus|V2-17_IGLJ2*01	1120
4249	VH3-23_IGHD5-18*01 (2) >1_IGHJ6*01	1753	gnl|Fabrus|V2-17_IGLJ2*01	1120
4250	VH3-23_IGHD5-18*01 (2) >2_IGHJ6*01	1754	gnl|Fabrus|V2-17_IGLJ2*01	1120
4251	VH3-23_IGHD5-18*01 (2) >3_IGHJ6*01	1755	gnl|Fabrus|V2-17_IGLJ2*01	1120
4252	VH3-23_IGHD5-24*01>1_IGHJ6*01	1756	gnl|Fabrus|V2-17_IGLJ2*01	1120
4253	VH3-23_IGHD5-24*01>3_IGHJ6*01	1757	gnl|Fabrus|V2-17_IGLJ2*01	1120
4254	VH3-23_IGHD6-6*01>1_IGHJ6*01	1758	gnl|Fabrus|V2-17_IGLJ2*01	1120
4255	VH3-23_IGHD1-1*01>1'_IGHJ6*01	1768	gnl|Fabrus|V2-17_IGLJ2*01	1120
4256	VH3-23_IGHD1-1*01>2'_IGHJ6*01	1769	gnl|Fabrus|V2-17_IGLJ2*01	1120
4257	VH3-23_IGHD1-1*01>3'_IGHJ6*01	1770	gnl|Fabrus|V2-17_IGLJ2*01	1120
4258	VH3-23_IGHD1-7*01>1'_IGHJ6*01	1771	gnl|Fabrus|V2-17_IGLJ2*01	1120
4259	VH3-23_IGHD1-7*01>3'_IGHJ6*01	1772	gnl|Fabrus|V2-17_IGLJ2*01	1120
4260	VH3-23_IGHD1-14*01>1'_IGHJ6*01	1773	gnl|Fabrus|V2-17_IGLJ2*01	1120
4261	VH3-23_IGHD1-14*01>2'_IGHJ6*01	1774	gnl|Fabrus|V2-17_IGLJ2*01	1120
4262	VH3-23_IGHD1-14*01>3'_IGHJ6*01	1775	gnl|Fabrus|V2-17_IGLJ2*01	1120

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
4263	VH3-23_IGHD1-20*01>1'_IGHJ6*01	1776	gnl|Fabrus|V2-17_IGLJ2*01	1120
4264	VH3-23_IGHD1-20*01>2'_IGHJ6*01	1777	gnl|Fabrus|V2-17_IGLJ2*01	1120
4265	VH3-23_IGHD1-20*01>3'_IGHJ6*01	1778	gnl|Fabrus|V2-17_IGLJ2*01	1120
4266	VH3-23_IGHD1-26*01>1'_IGHJ6*01	1779	gnl|Fabrus|V2-17_IGLJ2*01	1120
4267	VH3-23_IGHD1-26*01>1_IGHJ6*01_B	1780	gnl|Fabrus|V2-17_IGLJ2*01	1120
4268	VH3-23_IGHD2-2*01>2_IGHJ6*01_B	1781	gnl|Fabrus|V2-17_IGLJ2*01	1120
4269	VH3-23_IGHD2-2*01>3'_IGHJ6*01	1782	gnl|Fabrus|V2-17_IGLJ2*01	1120
4270	VH3-23_IGHD2-8*01>1'_IGHJ6*01	1783	gnl|Fabrus|V2-17_IGLJ2*01	1120
4271	VH3-23_IGHD2-15*01>1'_IGHJ6*01	1784	gnl|Fabrus|V2-17_IGLJ2*01	1120
4272	VH3-23_IGHD2-15*01>3'_IGHJ6*01	1785	gnl|Fabrus|V2-17_IGLJ2*01	1120
4273	VH3-23_IGHD2-21*01>1'_IGHJ6*01	1786	gnl|Fabrus|V2-17_IGLJ2*01	1120
4274	VH3-23_IGHD2-21*01>3'_IGHJ6*01	1787	gnl|Fabrus|V2-17_IGLJ2*01	1120
4275	VH3-23_IGHD3-3*01>1'_IGHJ6*01	1788	gnl|Fabrus|V2-17_IGLJ2*01	1120
4276	VH3-23_IGHD3-3*01>3'_IGHJ6*01	1789	gnl|Fabrus|V2-17_IGLJ2*01	1120
4277	VH3-23_IGHD3-9*01>1'_IGHJ6*01	1790	gnl|Fabrus|V2-17_IGLJ2*01	1120
4278	VH3-23_IGHD3-9*01>3'_IGHJ6*01	1791	gnl|Fabrus|V2-17_IGLJ2*01	1120
4279	VH3-23_IGHD3-10*01>1'_IGHJ6*01	1792	gnl|Fabrus|V2-17_IGLJ2*01	1120
4280	VH3-23_IGHD3-10*01>3'_IGHJ6*01	1793	gnl|Fabrus|V2-17_IGLJ2*01	1120
4281	VH3-23_IGHD3-16*01>1'_IGHJ6*01	1794	gnl|Fabrus|V2-17_IGLJ2*01	1120
4282	VH3-23_IGHD3-16*01>3'_IGHJ6*01	1795	gnl|Fabrus|V2-17_IGLJ2*01	1120
4283	VH3-23_IGHD3-22*01>1'_IGHJ6*01	1796	gnl|Fabrus|V2-17_IGLJ2*01	1120
4284	VH3-23_IGHD4-4*01 (1) >1'_IGHJ6*01	1797	gnl|Fabrus|V2-17_IGLJ2*01	1120
4285	VH3-23_IGHD4-4*01 (1) >3'_IGHJ6*01	1798	gnl|Fabrus|V2-17_IGLJ2*01	1120
4286	VH3-23_IGHD4-11*01 (1) >1'_IGHJ6*01	1799	gnl|Fabrus|V2-17_IGLJ2*01	1120
4287	VH3-23_IGHD4-11*01 (1) >3'_IGHJ6*01	1800	gnl|Fabrus|V2-17_IGLJ2*01	1120
4288	VH3-23_IGHD4-17*01>1'_IGHJ6*01	1801	gnl|Fabrus|V2-17_IGLJ2*01	1120
4289	VH3-23_IGHD4-17*01>3'_IGHJ6*01	1802	gnl|Fabrus|V2-17_IGLJ2*01	1120
4290	VH3-23_IGHD4-23*01>1'_IGHJ6*01	1803	gnl|Fabrus|V2-17_IGLJ2*01	1120
4291	VH3-23_IGHD4-23*01>3'_IGHJ6*01	1804	gnl|Fabrus|V2-17_IGLJ2*01	1120
4292	VH3-23_IGHD5-5*01 (2) >1'_IGHJ6*01	1805	gnl|Fabrus|V2-17_IGLJ2*01	1120
4293	VH3-23_IGHD5-5*01 (2) >3'_IGHJ6*01	1806	gnl|Fabrus|V2-17_IGLJ2*01	1120
4294	VH3-23_IGHD5-12*01>1'_IGHJ6*01	1807	gnl|Fabrus|V2-17_IGLJ2*01	1120
4295	VH3-23_IGHD5-12*01>3'_IGHJ6*01	1808	gnl|Fabrus|V2-17_IGLJ2*01	1120
4296	VH3-23_IGHD5-18*01 (2) >1'_IGHJ6*01	1809	gnl|Fabrus|V2-17_IGLJ2*01	1120
4297	VH3-23_IGHD5-18*01 (2) >3'_IGHJ6*01	1810	gnl|Fabrus|V2-17_IGLJ2*01	1120
4298	VH3-23_IGHD5-24*01>1'_IGHJ6*01	1811	gnl|Fabrus|V2-17_IGLJ2*01	1120
4299	VH3-23_IGHD5-24*01>3'_IGHJ6*01	1812	gnl|Fabrus|V2-17_IGLJ2*01	1120
4300	VH3-23_IGHD6-6*01>1'_IGHJ6*01	1813	gnl|Fabrus|V2-17_IGLJ2*01	1120
4301	VH3-23_IGHD6-6*01>2'_IGHJ6*01	1814	gnl|Fabrus|V2-17_IGLJ2*01	1120
4302	VH3-23_IGHD6-6*01>3'_IGHJ6*01	1815	gnl|Fabrus|V2-17_IGLJ2*01	1120
4303	VH3-23_IGHD1-1*01>1_IGHJ6*01	1711	gnl|Fabrus|V2-6_IGLJ4*01	1122
4304	VH3-23_IGHD1-1*01>2_IGHJ6*01	1712	gnl|Fabrus|V2-6_IGLJ4*01	1122

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
4305	VH3-23_IGHD1-1*01>3_IGHJ6*01	1713	gnl|Fabrus|V2-6_IGLJ4*01	1122
4306	VH3-23_IGHD1-7*01>1_IGHJ6*01	1714	gnl|Fabrus|V2-6_IGLJ4*01	1122
4307	VH3-23_IGHD1-7*01>3_IGHJ6*01	1715	gnl|Fabrus|V2-6_IGLJ4*01	1122
4308	VH3-23_IGHD1-14*01>1_IGHJ6*01	1716	gnl|Fabrus|V2-6_IGLJ4*01	1122
4309	VH3-23_IGHD1-14*01>3_IGHJ6*01	1717	gnl|Fabrus|V2-6_IGLJ4*01	1122
4310	VH3-23_IGHD1-20*01>1_IGHJ6*01	1718	gnl|Fabrus|V2-6_IGLJ4*01	1122
4311	VH3-23_IGHD1-20*01>3_IGHJ6*01	1719	gnl|Fabrus|V2-6_IGLJ4*01	1122
4312	VH3-23_IGHD1-26*01>1_IGHJ6*01	1720	gnl|Fabrus|V2-6_IGLJ4*01	1122
4313	VH3-23_IGHD1-26*01>3_IGHJ6*01	1721	gnl|Fabrus|V2-6_IGLJ4*01	1122
4314	VH3-23_IGHD2-2*01>2_IGHJ6*01	1722	gnl|Fabrus|V2-6_IGLJ4*01	1122
4315	VH3-23_IGHD2-2*01>3_IGHJ6*01	1723	gnl|Fabrus|V2-6_IGLJ4*01	1122
4316	VH3-23_IGHD2-8*01>2_IGHJ6*01	1724	gnl|Fabrus|V2-6_IGLJ4*01	1122
4317	VH3-23_IGHD2-8*01>3_IGHJ6*01	1725	gnl|Fabrus|V2-6_IGLJ4*01	1122
4318	VH3-23_IGHD2-15*01>2_IGHJ6*01	1726	gnl|Fabrus|V2-6_IGLJ4*01	1122
4319	VH3-23_IGHD2-15*01>3_IGHJ6*01	1727	gnl|Fabrus|V2-6_IGLJ4*01	1122
4320	VH3-23_IGHD2-21*01>2_IGHJ6*01	1728	gnl|Fabrus|V2-6_IGLJ4*01	1122
4321	VH3-23_IGHD2-21*01>3_IGHJ6*01	1729	gnl|Fabrus|V2-6_IGLJ4*01	1122
4322	VH3-23_IGHD3-3*01>1_IGHJ6*01	1730	gnl|Fabrus|V2-6_IGLJ4*01	1122
4323	VH3-23_IGHD3-3*01>2_IGHJ6*01	1731	gnl|Fabrus|V2-6_IGLJ4*01	1122
4324	VH3-23_IGHD3-3*01>3_IGHJ6*01	1732	gnl|Fabrus|V2-6_IGLJ4*01	1122
4325	VH3-23_IGHD3-9*01>2_IGHJ6*01	1733	gnl|Fabrus|V2-6_IGLJ4*01	1122
4326	VH3-23_IGHD3-10*01>2_IGHJ6*01	1734	gnl|Fabrus|V2-6_IGLJ4*01	1122
4327	VH3-23_IGHD3-10*01>3_IGHJ6*01	1735	gnl|Fabrus|V2-6_IGLJ4*01	1122
4328	VH3-23_IGHD3-16*01>2_IGHJ6*01	1736	gnl|Fabrus|V2-6_IGLJ4*01	1122
4329	VH3-23_IGHD3-16*01>3_IGHJ6*01	1737	gnl|Fabrus|V2-6_IGLJ4*01	1122
4330	VH3-23_IGHD3-22*01>2_IGHJ6*01	1738	gnl|Fabrus|V2-6_IGLJ4*01	1122
4331	VH3-23_IGHD3-22*01>3_IGHJ6*01	1739	gnl|Fabrus|V2-6_IGLJ4*01	1122
4332	VH3-23_IGHD4-4*01 (1) >2_IGHJ6*01	1740	gnl|Fabrus|V2-6_IGLJ4*01	1122
4333	VH3-23_IGHD4-4*01 (1) >3_IGHJ6*01	1741	gnl|Fabrus|V2-6_IGLJ4*01	1122
4334	VH3-23_IGHD4-11*01 (1) >2_IGHJ6*01	1742	gnl|Fabrus|V2-6_IGLJ4*01	1122
4335	VH3-23_IGHD4-11*01 (1) >3_IGHJ6*01	1743	gnl|Fabrus|V2-6_IGLJ4*01	1122
4336	VH3-23_IGHD4-17*01>2_IGHJ6*01	1744	gnl|Fabrus|V2-6_IGLJ4*01	1122
4337	VH3-23_IGHD4-17*01>3_IGHJ6*01	1745	gnl|Fabrus|V2-6_IGLJ4*01	1122
4338	VH3-23_IGHD4-23*01>2_IGHJ6*01	1746	gnl|Fabrus|V2-6_IGLJ4*01	1122
4339	VH3-23_IGHD4-23*01>3_IGHJ6*01	1747	gnl|Fabrus|V2-6_IGLJ4*01	1122
4340	VH3-23_IGHD5-5*01 (2) >1_IGHJ6*01	1748	gnl|Fabrus|V2-6_IGLJ4*01	1122
4341	VH3-23_IGHD5-5*01 (2) >2_IGHJ6*01	1749	gnl|Fabrus|V2-6_IGLJ4*01	1122
4342	VH3-23_IGHD5-5*01 (2) >3_IGHJ6*01	1750	gnl|Fabrus|V2-6_IGLJ4*01	1122
4343	VH3-23_IGHD5-12*01>1_IGHJ6*01	1751	gnl|Fabrus|V2-6_IGLJ4*01	1122
4344	VH3-23_IGHD5-12*01>3_IGHJ6*01	1752	gnl|Fabrus|V2-6_IGLJ4*01	1122
4345	VH3-23_IGHD5-18*01 (2) >1_IGHJ6*01	1753	gnl|Fabrus|V2-6_IGLJ4*01	1122
4346	VH3-23_IGHD5-18*01 (2) >2_IGHJ6*01	1754	gnl|Fabrus|V2-6_IGLJ4*01	1122

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
4347	VH3-23_IGHD5-18*01 (2) >3_IGHJ6*01	1755	gnl|Fabrus|V2-6_IGLJ4*01	1122
4348	VH3-23_IGHD5-24*01>1_IGHJ6*01	1756	gnl|Fabrus|V2-6_IGLJ4*01	1122
4349	VH3-23_IGHD5-24*01>3_IGHJ6*01	1757	gnl|Fabrus|V2-6_IGLJ4*01	1122
4350	VH3-23_IGHD6-6*01>1_IGHJ6*01	1758	gnl|Fabrus|V2-6_IGLJ4*01	1122
4351	VH3-23_IGHD1-1*01>1'_IGHJ6*01	1768	gnl|Fabrus|V2-6_IGLJ4*01	1122
4352	VH3-23_IGHD1-1*01>2'_IGHJ6*01	1769	gnl|Fabrus|V2-6_IGLJ4*01	1122
4353	VH3-23_IGHD1-1*01>3'_IGHJ6*01	1770	gnl|Fabrus|V2-6_IGLJ4*01	1122
4354	VH3-23_IGHD1-7*01>1'_IGHJ6*01	1771	gnl|Fabrus|V2-6_IGLJ4*01	1122
4355	VH3-23_IGHD1-7*01>3'_IGHJ6*01	1772	gnl|Fabrus|V2-6_IGLJ4*01	1122
4356	VH3-23_IGHD1-14*01>1'_IGHJ6*01	1773	gnl|Fabrus|V2-6_IGLJ4*01	1122
4357	VH3-23_IGHD1-14*01>2'_IGHJ6*01	1774	gnl|Fabrus|V2-6_IGLJ4*01	1122
4358	VH3-23_IGHD1-14*01>3'_IGHJ6*01	1775	gnl|Fabrus|V2-6_IGLJ4*01	1122
4359	VH3-23_IGHD1-20*01>1'_IGHJ6*01	1776	gnl|Fabrus|V2-6_IGLJ4*01	1122
4360	VH3-23_IGHD1-20*01>2'_IGHJ6*01	1777	gnl|Fabrus|V2-6_IGLJ4*01	1122
4361	VH3-23_IGHD1-20*01>3'_IGHJ6*01	1778	gnl|Fabrus|V2-6_IGLJ4*01	1122
4362	VH3-23_IGHD1-26*01>1'_IGHJ6*01	1779	gnl|Fabrus|V2-6_IGLJ4*01	1122
4363	VH3-23_IGHD1-26*01>1_IGHJ6*01_B	1780	gnl|Fabrus|V2-6_IGLJ4*01	1122
4364	VH3-23_IGHD2-2*01>2_IGHJ6*01_B	1781	gnl|Fabrus|V2-6_IGLJ4*01	1122
4365	VH3-23_IGHD2-2*01>3'_IGHJ6*01	1782	gnl|Fabrus|V2-6_IGLJ4*01	1122
4366	VH3-23_IGHD2-8*01>1'_IGHJ6*01	1783	gnl|Fabrus|V2-6_IGLJ4*01	1122
4367	VH3-23_IGHD2-15*01>1'_IGHJ6*01	1784	gnl|Fabrus|V2-6_IGLJ4*01	1122
4368	VH3-23_IGHD2-15*01>3'_IGHJ6*01	1785	gnl|Fabrus|V2-6_IGLJ4*01	1122
4369	VH3-23_IGHD2-21*01>1'_IGHJ6*01	1786	gnl|Fabrus|V2-6_IGLJ4*01	1122
4370	VH3-23_IGHD2-21*01>3'_IGHJ6*01	1787	gnl|Fabrus|V2-6_IGLJ4*01	1122
4371	VH3-23_IGHD3-3*01>1'_IGHJ6*01	1788	gnl|Fabrus|V2-6_IGLJ4*01	1122
4372	VH3-23_IGHD3-3*01>3'_IGHJ6*01	1789	gnl|Fabrus|V2-6_IGLJ4*01	1122
4373	VH3-23_IGHD3-9*01>1'_IGHJ6*01	1790	gnl|Fabrus|V2-6_IGLJ4*01	1122
4374	VH3-23_IGHD3-9*01>3'_IGHJ6*01	1791	gnl|Fabrus|V2-6_IGLJ4*01	1122
4375	VH3-23_IGHD3-10*01>1'_IGHJ6*01	1792	gnl|Fabrus|V2-6_IGLJ4*01	1122
4376	VH3-23_IGHD3-10*01>3'_IGHJ6*01	1793	gnl|Fabrus|V2-6_IGLJ4*01	1122
4377	VH3-23_IGHD3-16*01>1'_IGHJ6*01	1794	gnl|Fabrus|V2-6_IGLJ4*01	1122
4378	VH3-23_IGHD3-16*01>3'_IGHJ6*01	1795	gnl|Fabrus|V2-6_IGLJ4*01	1122
4379	VH3-23_IGHD3-22*01>1'_IGHJ6*01	1796	gnl|Fabrus|V2-6_IGLJ4*01	1122
4380	VH3-23_IGHD4-4*01 (1) >1'_IGHJ6*01	1797	gnl|Fabrus|V2-6_IGLJ4*01	1122
4381	VH3-23_IGHD4-4*01 (1) >3'_IGHJ6*01	1798	gnl|Fabrus|V2-6_IGLJ4*01	1122
4382	VH3-23_IGHD4-11*01 (1) >1'_IGHJ6*01	1799	gnl|Fabrus|V2-6_IGLJ4*01	1122
4383	VH3-23_IGHD4-11*01 (1) >3'_IGHJ6*01	1800	gnl|Fabrus|V2-6_IGLJ4*01	1122
4384	VH3-23_IGHD4-17*01>1'_IGHJ6*01	1801	gnl|Fabrus|V2-6_IGLJ4*01	1122
4385	VH3-23_IGHD4-17*01>3'_IGHJ6*01	1802	gnl|Fabrus|V2-6_IGLJ4*01	1122
4386	VH3-23_IGHD4-23*01>1'_IGHJ6*01	1803	gnl|Fabrus|V2-6_IGLJ4*01	1122
4387	VH3-23_IGHD4-23*01>3'_IGHJ6*01	1804	gnl|Fabrus|V2-6_IGLJ4*01	1122
4388	VH3-23_IGHD5-5*01 (2) >1'_IGHJ6*01	1805	gnl|Fabrus|V2-6_IGLJ4*01	1122

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
4389	VH3-23_IGHD5-5*01 (2) >3'_IGHJ6*01	1806	gnl|Fabrus|V2-6_IGLJ4*01	1122
4390	VH3-23_IGHD5-12*01>1'_IGHJ6*01	1807	gnl|Fabrus|V2-6_IGLJ4*01	1122
4391	VH3-23_IGHD5-12*01>3'_IGHJ6*01	1808	gnl|Fabrus|V2-6_IGLJ4*01	1122
4392	VH3-23_IGHD5-18*01 (2) >1'_IGHJ6*01	1809	gnl|Fabrus|V2-6_IGLJ4*01	1122
4393	VH3-23_IGHD5-18*01 (2) >3'_IGHJ6*01	1810	gnl|Fabrus|V2-6_IGLJ4*01	1122
4394	VH3-23_IGHD5-24*01>1'_IGHJ6*01	1811	gnl|Fabrus|V2-6_IGLJ4*01	1122
4395	VH3-23_IGHD5-24*01>3'_IGHJ6*01	1812	gnl|Fabrus|V2-6_IGLJ4*01	1122
4396	VH3-23_IGHD6-6*01>1'_IGHJ6*01	1813	gnl|Fabrus|V2-6_IGLJ4*01	1122
4397	VH3-23_IGHD6-6*01>2'_IGHJ6*01	1814	gnl|Fabrus|V2-6_IGLJ4*01	1122
4398	VH3-23_IGHD6-6*01>3'_IGHJ6*01	1815	gnl|Fabrus|V2-6_IGLJ4*01	1122
4399	VH3-23_IGHD1-1*01>1_IGHJ6*01	1711	gnl|Fabrus|V2-7_IGLJ2*01	1123
4400	VH3-23_IGHD1-1*01>2_IGHJ6*01	1712	gnl|Fabrus|V2-7_IGLJ2*01	1123
4401	VH3-23_IGHD1-1*01>3_IGHJ6*01	1713	gnl|Fabrus|V2-7_IGLJ2*01	1123
4402	VH3-23_IGHD1-7*01>1_IGHJ6*01	1714	gnl|Fabrus|V2-7_IGLJ2*01	1123
4403	VH3-23_IGHD1-7*01>3_IGHJ6*01	1715	gnl|Fabrus|V2-7_IGLJ2*01	1123
4404	VH3-23_IGHD1-14*01>1_IGHJ6*01	1716	gnl|Fabrus|V2-7_IGLJ2*01	1123
4405	VH3-23_IGHD1-14*01>3_IGHJ6*01	1717	gnl|Fabrus|V2-7_IGLJ2*01	1123
4406	VH3-23_IGHD1-20*01>1_IGHJ6*01	1718	gnl|Fabrus|V2-7_IGLJ2*01	1123
4407	VH3-23_IGHD1-20*01>3_IGHJ6*01	1719	gnl|Fabrus|V2-7_IGLJ2*01	1123
4408	VH3-23_IGHD1-26*01>1_IGHJ6*01	1720	gnl|Fabrus|V2-7_IGLJ2*01	1123
4409	VH3-23_IGHD1-26*01>3_IGHJ6*01	1721	gnl|Fabrus|V2-7_IGLJ2*01	1123
4410	VH3-23_IGHD2-2*01>2_IGHJ6*01	1722	gnl|Fabrus|V2-7_IGLJ2*01	1123
4411	VH3-23_IGHD2-2*01>3_IGHJ6*01	1723	gnl|Fabrus|V2-7_IGLJ2*01	1123
4412	VH3-23_IGHD2-8*01>2_IGHJ6*01	1724	gnl|Fabrus|V2-7_IGLJ2*01	1123
4413	VH3-23_IGHD2-8*01>3_IGHJ6*01	1725	gnl|Fabrus|V2-7_IGLJ2*01	1123
4414	VH3-23_IGHD2-15*01>2_IGHJ6*01	1726	gnl|Fabrus|V2-7_IGLJ2*01	1123
4415	VH3-23_IGHD2-15*01>3_IGHJ6*01	1727	gnl|Fabrus|V2-7_IGLJ2*01	1123
4416	VH3-23_IGHD2-21*01>2_IGHJ6*01	1728	gnl|Fabrus|V2-7_IGLJ2*01	1123
4417	VH3-23_IGHD2-21*01>3_IGHJ6*01	1729	gnl|Fabrus|V2-7_IGLJ2*01	1123
4418	VH3-23_IGHD3-3*01>1_IGHJ6*01	1730	gnl|Fabrus|V2-7_IGLJ2*01	1123
4419	VH3-23_IGHD3-3*01>2_IGHJ6*01	1731	gnl|Fabrus|V2-7_IGLJ2*01	1123
4420	VH3-23_IGHD3-3*01>3_IGHJ6*01	1732	gnl|Fabrus|V2-7_IGLJ2*01	1123
4421	VH3-23_IGHD3-9*01>2_IGHJ6*01	1733	gnl|Fabrus|V2-7_IGLJ2*01	1123
4422	VH3-23_IGHD3-10*01>2_IGHJ6*01	1734	gnl|Fabrus|V2-7_IGLJ2*01	1123
4423	VH3-23_IGHD3-10*01>3_IGHJ6*01	1735	gnl|Fabrus|V2-7_IGLJ2*01	1123
4424	VH3-23_IGHD3-16*01>2_IGHJ6*01	1736	gnl|Fabrus|V2-7_IGLJ2*01	1123
4425	VH3-23_IGHD3-16*01>3_IGHJ6*01	1737	gnl|Fabrus|V2-7_IGLJ2*01	1123
4426	VH3-23_IGHD3-22*01>2_IGHJ6*01	1738	gnl|Fabrus|V2-7_IGLJ2*01	1123
4427	VH3-23_IGHD3-22*01>3_IGHJ6*01	1739	gnl|Fabrus|V2-7_IGLJ2*01	1123
4428	VH3-23_IGHD4-4*01 (1) >2_IGHJ6*01	1740	gnl|Fabrus|V2-7_IGLJ2*01	1123
4429	VH3-23_IGHD4-4*01 (1) >3_IGHJ6*01	1741	gnl|Fabrus|V2-7_IGLJ2*01	1123
4430	VH3-23_IGHD4-11*01 (1) >2_IGHJ6*01	1742	gnl|Fabrus|V2-7_IGLJ2*01	1123

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
4431	VH3-23_IGHD4-11*01 (1) >3_IGHJ6*01	1743	gnl|Fabrus|V2-7_IGLJ2*01	1123
4432	VH3-23_IGHD4-17*01>2_IGHJ6*01	1744	gnl|Fabrus|V2-7_IGLJ2*01	1123
4433	VH3-23_IGHD4-17*01>3_IGHJ6*01	1745	gnl|Fabrus|V2-7_IGLJ2*01	1123
4434	VH3-23_IGHD4-23*01>2_IGHJ6*01	1746	gnl|Fabrus|V2-7_IGLJ2*01	1123
4435	VH3-23_IGHD4-23*01>3_IGHJ6*01	1747	gnl|Fabrus|V2-7_IGLJ2*01	1123
4436	VH3-23_IGHD5-5*01 (2) >1_IGHJ6*01	1748	gnl|Fabrus|V2-7_IGLJ2*01	1123
4437	VH3-23_IGHD5-5*01 (2) >2_IGHJ6*01	1749	gnl|Fabrus|V2-7_IGLJ2*01	1123
4438	VH3-23_IGHD5-5*01 (2) >3_IGHJ6*01	1750	gnl|Fabrus|V2-7_IGLJ2*01	1123
4439	VH3-23_IGHD5-12*01>1_IGHJ6*01	1751	gnl|Fabrus|V2-7_IGLJ2*01	1123
4440	VH3-23_IGHD5-12*01>3_IGHJ6*01	1752	gnl|Fabrus|V2-7_IGLJ2*01	1123
4441	VH3-23_IGHD5-18*01 (2) >1_IGHJ6*01	1753	gnl|Fabrus|V2-7_IGLJ2*01	1123
4442	VH3-23_IGHD5-18*01 (2) >2_IGHJ6*01	1754	gnl|Fabrus|V2-7_IGLJ2*01	1123
4443	VH3-23_IGHD5-18*01 (2) >3_IGHJ6*01	1755	gnl|Fabrus|V2-7_IGLJ2*01	1123
4444	VH3-23_IGHD5-24*01>1_IGHJ6*01	1756	gnl|Fabrus|V2-7_IGLJ2*01	1123
4445	VH3-23_IGHD5-24*01>3_IGHJ6*01	1757	gnl|Fabrus|V2-7_IGLJ2*01	1123
4446	VH3-23_IGHD6-6*01>1_IGHJ6*01	1758	gnl|Fabrus|V2-7_IGLJ2*01	1123
4447	VH3-23_IGHD1-1*01>1'_IGHJ6*01	1768	gnl|Fabrus|V2-7_IGLJ2*01	1123
4448	VH3-23_IGHD1-1*01>2'_IGHJ6*01	1769	gnl|Fabrus|V2-7_IGLJ2*01	1123
4449	VH3-23_IGHD1-1*01>3'_IGHJ6*01	1770	gnl|Fabrus|V2-7_IGLJ2*01	1123
4450	VH3-23_IGHD1-7*01>1'_IGHJ6*01	1771	gnl|Fabrus|V2-7_IGLJ2*01	1123
4451	VH3-23_IGHD1-7*01>3'_IGHJ6*01	1772	gnl|Fabrus|V2-7_IGLJ2*01	1123
4452	VH3-23_IGHD1-14*01>1'_IGHJ6*01	1773	gnl|Fabrus|V2-7_IGLJ2*01	1123
4453	VH3-23_IGHD1-14*01>2'_IGHJ6*01	1774	gnl|Fabrus|V2-7_IGLJ2*01	1123
4454	VH3-23_IGHD1-14*01>3'_IGHJ6*01	1775	gnl|Fabrus|V2-7_IGLJ2*01	1123
4455	VH3-23_IGHD1-20*01>1'_IGHJ6*01	1776	gnl|Fabrus|V2-7_IGLJ2*01	1123
4456	VH3-23_IGHD1-20*01>2'_IGHJ6*01	1777	gnl|Fabrus|V2-7_IGLJ2*01	1123
4457	VH3-23_IGHD1-20*01>3'_IGHJ6*01	1778	gnl|Fabrus|V2-7_IGLJ2*01	1123
4458	VH3-23_IGHD1-26*01>1'_IGHJ6*01	1779	gnl|Fabrus|V2-7_IGLJ2*01	1123
4459	VH3-23_IGHD1-26*01>1_IGHJ6*01_B	1780	gnl|Fabrus|V2-7_IGLJ2*01	1123
4460	VH3-23_IGHD2-2*01>2_IGHJ6*01_B	1781	gnl|Fabrus|V2-7_IGLJ2*01	1123
4461	VH3-23_IGHD2-2*01>3'_IGHJ6*01	1782	gnl|Fabrus|V2-7_IGLJ2*01	1123
4462	VH3-23_IGHD2-8*01>1'_IGHJ6*01	1783	gnl|Fabrus|V2-7_IGLJ2*01	1123
4463	VH3-23_IGHD2-15*01>1'_IGHJ6*01	1784	gnl|Fabrus|V2-7_IGLJ2*01	1123
4464	VH3-23_IGHD2-15*01>3'_IGHJ6*01	1785	gnl|Fabrus|V2-7_IGLJ2*01	1123
4465	VH3-23_IGHD2-21*01>1'_IGHJ6*01	1786	gnl|Fabrus|V2-7_IGLJ2*01	1123
4466	VH3-23_IGHD2-21*01>3'_IGHJ6*01	1787	gnl|Fabrus|V2-7_IGLJ2*01	1123
4467	VH3-23_IGHD3-3*01>1'_IGHJ6*01	1788	gnl|Fabrus|V2-7_IGLJ2*01	1123
4468	VH3-23_IGHD3-3*01>3'_IGHJ6*01	1789	gnl|Fabrus|V2-7_IGLJ2*01	1123
4469	VH3-23_IGHD3-9*01>1'_IGHJ6*01	1790	gnl|Fabrus|V2-7_IGLJ2*01	1123
4470	VH3-23_IGHD3-9*01>3'_IGHJ6*01	1791	gnl|Fabrus|V2-7_IGLJ2*01	1123
4471	VH3-23_IGHD3-10*01>1'_IGHJ6*01	1792	gnl|Fabrus|V2-7_IGLJ2*01	1123
4472	VH3-23_IGHD3-10*01>3'_IGHJ6*01	1793	gnl|Fabrus|V2-7_IGLJ2*01	1123

Table 4. Exemplary Paired Nucleic Acid Library

	HEAVY CHAIN	SEQ ID NO	LIGHT CHAIN	SEQ ID NO
4473	VH3-23_IGHD3-16*01>1'_IGHJ6*01	1794	gnl|Fabrus|V2-7_IGLJ2*01	1123
4474	VH3-23_IGHD3-16*01>3'_IGHJ6*01	1795	gnl|Fabrus|V2-7_IGLJ2*01	1123
4475	VH3-23_IGHD3-22*01>1'_IGHJ6*01	1796	gnl|Fabrus|V2-7_IGLJ2*01	1123
4476	VH3-23_IGHD4-4*01 (1) >1'_IGHJ6*01	1797	gnl|Fabrus|V2-7_IGLJ2*01	1123
4477	VH3-23_IGHD4-4*01 (1) >3'_IGHJ6*01	1798	gnl|Fabrus|V2-7_IGLJ2*01	1123
4478	VH3-23_IGHD4-11*01 (1) >1'_IGHJ6*01	1799	gnl|Fabrus|V2-7_IGLJ2*01	1123
4479	VH3-23_IGHD4-11*01 (1) >3'_IGHJ6*01	1800	gnl|Fabrus|V2-7_IGLJ2*01	1123
4480	VH3-23_IGHD4-17*01>1'_IGHJ6*01	1801	gnl|Fabrus|V2-7_IGLJ2*01	1123
4481	VH3-23_IGHD4-17*01>3'_IGHJ6*01	1802	gnl|Fabrus|V2-7_IGLJ2*01	1123
4482	VH3-23_IGHD4-23*01>1'_IGHJ6*01	1803	gnl|Fabrus|V2-7_IGLJ2*01	1123
4483	VH3-23_IGHD4-23*01>3'_IGHJ6*01	1804	gnl|Fabrus|V2-7_IGLJ2*01	1123
4484	VH3-23_IGHD5-5*01 (2) >1'_IGHJ6*01	1805	gnl|Fabrus|V2-7_IGLJ2*01	1123
4485	VH3-23_IGHD5-5*01 (2) >3'_IGHJ6*01	1806	gnl|Fabrus|V2-7_IGLJ2*01	1123
4486	VH3-23_IGHD5-12*01>1'_IGHJ6*01	1807	gnl|Fabrus|V2-7_IGLJ2*01	1123
4487	VH3-23_IGHD5-12*01>3'_IGHJ6*01	1808	gnl|Fabrus|V2-7_IGLJ2*01	1123
4488	VH3-23_IGHD5-18*01 (2) >1'_IGHJ6*01	1809	gnl|Fabrus|V2-7_IGLJ2*01	1123
4489	VH3-23_IGHD5-18*01 (2) >3'_IGHJ6*01	1810	gnl|Fabrus|V2-7_IGLJ2*01	1123
4490	VH3-23_IGHD5-24*01>1'_IGHJ6*01	1811	gnl|Fabrus|V2-7_IGLJ2*01	1123
4491	VH3-23_IGHD5-24*01>3'_IGHJ6*01	1812	gnl|Fabrus|V2-7_IGLJ2*01	1123
4492	VH3-23_IGHD6-6*01>1'_IGHJ6*01	1813	gnl|Fabrus|V2-7_IGLJ2*01	1123
4493	VH3-23_IGHD6-6*01>2'_IGHJ6*01	1814	gnl|Fabrus|V2-7_IGLJ2*01	1123
4494	VH3-23_IGHD6-6*01>3'_IGHJ6*01	1815	gnl|Fabrus|V2-7_IGLJ2*01	1123

Typically, the addressable combinatorial germline libraries are spatially arrayed in a multiwell plate, such as a 96-well plate, wherein each well of the plate corresponds to one antibody that is different from the antibodies in all the other wells. The antibodies can be immobilized to the surface of the wells of the plate or can be present in solution. Alternatively, the antibodies are attached to a solid support, such as for example, a filter, chip, slide, bead or cellulose. The antibodies can also be identifiably labeled, such as for example, with a colored, chromogenic, luminescent, chemical, fluorescent or electronic label. The combinatorial addressable germline antibody libraries can be screened for binding or activity against a target protein to identify antibodies or portions thereof that bind to a target protein and/or modulate an activity of a target protein. By virtue of the fact that these libaries are arrayed, the identity of each individual member in the collection is known during screening thereby allowing facile identification of a "Hit" antibody. Screening for binding or a functional activity can be by any method known to one of skill in the art, for example, any described in Section E.1.

For example, as described in the Examples, an addressable antibody library is exemplified to screen for "Hits" against a target antigen using an MSD electrochemiluminescence binding assay or by ELISA. Since the library was addressable, the sequence of the identified "Hit" was immediately known. A similar assay is exemplified to identify a related antibody as discussed further below.

b. Identification of a Related Antibody

In the method provided herein, comparison to a related antibody that has reduced or less activity for the target antigen than the first antibody provides information of SAR that can be used for affinity maturation herein. In the method, residues to mutagenize in the antibody to be affinity matured are identified by comparison of the amino acid sequence of the variable heavy or light chain of the first antibody (e.g."Hit") with the corresponding amino acid sequence of the variable heavy or light chain of a related antibody. For purposes of practice of the method herein, a related antibody has sequence similarity or identity to the "Hit" antibody across the entire sequence of the antibody (heavy and light chain), but is not itself identical in sequence to the "Hit" antibody. In addition, the related antibody exhibits less activity (e.g. binding or binding affinity) for the target antigen than the first antibody.

In the method herein, once a first antibody is chosen for affinity maturation herein as set forth above, one or more related antibodies are selected. It is not necessary that the first antibody and related antibodies are identified from the same library or even using the same screening method. All that is necessary is that the related antibody has less activity to a target antigen than the first antibody and that the related antibody exhibits sequence similarity to the antibody that is being affinity matured. For convenience, a related antibody is typically identified using the same screening method and assay system used for identification of the first antibody. Hence, any of the methods of generating an antibody, including any of the antibody libraries, described in Section C.1 above can be used for identification of a related antibody. Exemplary of an antibody library is an addressable combinatorial antibody library described above and herein in the Examples. As previously mentioned, the addressable combinatorial antibody library has the benefit of immediate knowledge of the structure-activity relationship of all members of the library for binding to a target antigen. Hence, like a "Hit" antibody, the sequence and activity of a related antibody is immediately known. Accordingly, assessment of sequence similarity between a "Hit" and related antibody can be determined almost instantaneously upon completion of a screening assay for a target antigen.

Generally, the related antibody is an antibody that exhibits 80% of less of the activity of the first antibody, generally 5% to 80% of the activity, and in particular 5% to 50% of the activity, such as 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5% or less the activity towards

the target antigen compared to the first antibody. For example, the related antibody can be an antibody that does not bind or that shows negligible binding to the target antigen for which the "Hit" antibody binds (e.g. a level of binding that is the same or similar to binding of a negative control used in the assay). Thus, a related antibody can be initially identified because it does not specifically bind to the target antigen for which the chosen first antibody specifically binds. For example, a related antibody can exhibit a binding affinity that is 10^{-4} M or higher, for example, 10^{-4} M, 10^{-3} M, 10^{-2} M, or higher. In comparing an activity (e.g. binding and/or binding affinity) of first antibody to a related antibody, the same target antigen is used and activity is assessed in the same or similar assay. In addition, corresponding forms of the antibodies are compared such that the structure of the antibody also is the same (e.g. full-length antibody or fragment thereof such as a Fab).

A related antibody that is chosen for practice of the method is related to the first antibody because it exhibits sequence similarity or identity to a first antibody across its entire sequence (heavy and light chain) or across its variable heavy or variable light chain. For example, the amino acid sequence of the variable heavy chain and/or variable light chain of the related antibody is at least 50% identical in amino acid sequence to the first antibody, generally at least 75% identical in sequence, for example it is or is about 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical in amino acid sequence to the first antibody, typically at least at or about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95% similar in sequence. The related antibody is not identical to the first antibody in both the variable heavy and light chain, but can be identical to the first antibody in one of the variable heavy or light chains and exhibit less than 100% sequence similarity in the other chain. Thus, it is understood that for practice of the method, the variable portion of the related antibody used in the method is less than 100% identical to the identified "Hit" antibody. For example, in many instances, a related antibody might exhibit 100% sequence identity to the first antibody in the variable light chain sequence, but less than 100% sequence similarity to the first antibody in the variable heavy chain sequence, while still exhibiting a requisite sequence similarity. In that instance, only the variable heavy chain sequence of the related antibody is used in the practice of the method as described herein. Any method for determining sequence similarity known to one of skill in the art can be used as described elsewhere herein, including, but not limited to, manual methods or the use of available programs such as BLAST.

For example, a related antibody can contain a variable heavy chain that is identical to the variable heavy chain of the first antibody, and a variable light chain that exhibits sequence similarity to the first antibody. In other examples, neither the variable heavy or variable light

chain of the related antibody are identical to the amino acid sequence of the first antibody, but both exhibit sequence similarity to the first antibody. Thus, in some instances, a related antibody used in the method of affinity maturing the variable heavy chain of the first antibody is different from a related antibody used in the method of affinity maturing the variable light chain of the first antibody. Accordingly, more than one related antibody can be selected for practice of the method herein. For example, as exemplified in the examples, three related antibodies are selected for affinity maturation of the variable light chain. In either case, a variable chain (heavy or light) of a related antibody that exhibits sequence similarity to the corresponding heavy or light chain of the first antibody is used in the method to identify a region or regions in the first antibody that differ and thus are responsible for the differing binding abilities of the "first antibody and related antibodies. Such region or regions are targeted for affinity maturation and mutagenesis in the method herein as described further below.

Generally, the variable heavy and/or light chain of a first antibody and a related antibody are derived from the same or related, such as from the same gene family, antibody variable region germline segments. For example, a related antibody is encoded by a sequence of nucleic acids that contains one or more variable heavy chain V_H, D_H and/or J_H germline segments or variable light chain V_κ and J_κ or V_λ and J_λ germline segments that is not identical to, but is of the same gene family, as contained in the nucleic acid sequence encoding the first antibody. Typically, a related antibody is encoded by a sequence of nucleic acids that contains identical germline segments to the nucleic acid sequence encoding the first antibody, except that 1, 2, 3, 4, or 5 of the germline segments are different or related. For example, a related antibody is encoded by a nucleic acid sequence encoding the VH or VL chain that contains the same variable heavy chain V_H, and D_H germline segments, or the same variable light chain V_κ or V_λ germline segments, but different or related J_H, and J_κ or J_λ germline segments. As exemplified in the Examples, the variable heavy chain of a related antibody was chosen for practice of the method herein because it was encoded by a sequence of nucleic acids that contained identical variable heavy chain V_H and J_H germline segments (i.e., VH5-51 and IGHJ4*01) but had a different D_H germline segment (i.e., IGHD5-51*01>3 versus IGHD6-25*01) compared to the sequence of nucleic acids encoding the variable heavy chain sequence of the chosen "Hit". The sequence of the variable heavy chain of the related antibody exhibits 98 % sequence similarity to the first antibody. In another example, the variable heavy chain of a related antibody was chosen for practice of the method herein because it was encoded by a sequence of nucleic acids that contained identical V_H germline segments (i.e., VH1-46), but different J_H germline segments (i.e., IGHJ4*01 versus

IGHJ1*01), and related D_H germline segments (i.e., IGHD6-13*01 versus IGHD6-6*01, sharing the same gene family IGHD6) compared to the sequence of nucleic acids encoding the variable heavy chain sequence of the chosen first antibody. The sequence of the variable heavy chain of the related antibody exhibits 95 % sequence similarity to the first antibody.

One of skill in the art knows and is familiar with germline segment sequences of antibodies, and can identify the germline segment sequences encoding an antibody heavy or light chain. Exemplary antibody germline sources include but are not limited to databases at the National Center for Biotechnology Information (NCBI), the international ImMunoGeneTics information system® (IMGT), the Kabat database and the Tomlinson's VBase database (Lefranc (2003) *Nucleic Acids Res.*, 31:307-310; Martin *et al.*, Bioinformatics Tools for Antibody Engineering in Handbook of Therapeutic Antibodies, Wiley-VCH (2007), pp. 104-107). Germline segments also are known for non-humans. For example, an exemplary mouse germline databases is ABG database available at ibt.unam.mx/vir/v_mice.html. Germline segment sequences are known by various nomenclatures, including for example, IMGT gene names and defintions approved by the Human Genome Organization (HUGO) nomenclature committee, Lefranc, M.-P. *Exp Clin Immunogenet*, 18:100-116 (2001), Zachau, H.G. *Immunologist*, 4:49-54 (1996), Lefranc, M.-P. *Exp Clin Immunogenet*, 18:161-174 (2000), Kawasaki et al, *Genome Res*, 7:250-261 (1997), Lefranc, M.-P. *Exp Clin Immunogenet*, 18:242-254 (2001). Any desired naming convention can be used to identify antibody germline segments. One of skill in the art can identify a nucleic acid sequence using any desired naming convention. For example, for IMGT nomenclature, the first three letters indicate the locus (IGH, IGK or IGL), the fourth letter represents the gene (e.g., V for V-gene, D for D-gene, J for J-gene), the fifth position indicates the number of the subgroup, followed by a hyphen indicating the gene number classification. For alleles, the IMGT name is followed by an asterisk and a two figure number. U.S. Provisional Application Nos. 61/198,764 and 61/211,204 set forth exemplary human heavy chain and light chain (kappa and lambda) germline segment sequences.

c. Comparison of the amino acid sequences of the First Antibody and Related antibodies

Once a first antibody is chosen and a related antibody or antibodies are identified that have a related variable heavy chain and/or variable light chain, sequence comparison of the antibodies is effected. Comparison of the amino acid sequence of the variable heavy chain and/or the variable light chain of the parent or first antibody and the related antibody permits identification of regions that differ between the first antibody and the related antibody. Such region or regions are targeted for affinity maturation and mutagenesis.

In the method, the amino acid sequence of the VH chain and/or the VL chain of the parent first antibody is aligned to the respective VH chain or VL chain of at least one related antibody to identify regions of the polypeptide that differ, or vary, between the first antibody and related antibodies. The amino acid sequences of the antibodies can be aligned by any method commonly known in the art. The methods include manual alignment, computer assisted sequence alignment, and combinations thereof. A number of algorithms (which are generally computer implemented) for performing sequence alignment are widely available, or can be produced by one of skill. These methods include, e.g., the local homology algorithm of Smith and Waterman (1981) *Adv. Appl. Math.* 2:482; the homology alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443; the search for similarity method of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. (USA)* 85:2444; and/or by computerized implementations of these algorithms (e.g., GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package Release 7.0, Genetics Computer Group, 575 Science Dr., Madison, Wis.).

For example, software for performing sequence identity (and sequence similarity) analysis using the BLAST algorithm is described in Altschul *et al.*, (1990) *J. Mol. Biol.* 215:403-410. This software is publicly available, e.g., through the National Center for Biotechnology Information on the world wide web at ncbi.nlm.nih.gov. This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold. These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are then extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, a cutoff of 100, M=5, N=-4, and a comparison of both strands. For amino acid sequences, the BLASTP (BLAST Protein) program uses as defaults a wordlength (W) of 3, an

expectation (E) of 10, and the BLOSUM62 scoring matrix (see, Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915).

Additionally, the BLAST algorithm performs a statistical analysis of the similarity between two sequences (see, e.g., Karlin and Altschul (1993) *Proc. Nat'l. Acad. Sci. USA* 90:5873-5787). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences occurs by chance. For example, a nucleic acid is considered similar to a reference sequence (and, therefore, in this context, homologous) if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.1, or less than about 0.01, and or even less than about 0.001.

An additional example of an algorithm that is suitable for multiple DNA, or amino acid, sequence alignments is the CLUSTALW program (Thompson, J. D. *et al.*, (1994) *Nucl. Acids. Res.* 22: 4673-4680). CLUSTALW performs multiple pairwise comparisons between groups of sequences and assembles them into a multiple alignment based on homology. Gap open and Gap extension penalties can be, e.g., 10 and 0.05 respectively. For amino acid alignments, the BLOSUM algorithm can be used as a protein weight matrix. See, e.g., Henikoff and Henikoff (1992) *Proc. Natl. Acad. Sci. USA* 89: 10915-10919.

By aligning the amino acid sequences of the antibodies, one skilled in the art can identify regions that differ between the amino acid sequence of the first antibody and the related antibodies. A region that differs between the antibodies can occur along any portion of the VH chain and/or VL chain. Typically, a region that differs or varies occurs at a CDR or framework (FR) region, for example, CDR1, CDR2, CDR3, FR1, FR2, FR3 and/or FR4, and in particular in a CDR, for example CDR3. One of skill in the art knows and can identify the CDRs and FR based on Kabat or Chothia numbering (see e.g., Kabat, E.A. *et al.* (1991) *Sequences of Proteins of Immunological Interest*, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242, and Chothia, C. *et al.* (1987) *J. Mol. Biol.* 196:901-917). For example, based on Kabat numbering, CDR-L1 corresponds to residues L24-L34; CDR-L2 corresponds to residues L50-L56; CDR-L3 corresponds to residues L89-L97; CDR-H1 corresponds to residues H31-H35, 35a or 35b depending on the length; CDR-H2 corresponds to residues H50-H65; and CDR-H3 corresponds to residues H95-H102. For example, based on Kabat numbering, FR-L1 corresponds to residues L1-L23; FR-L2 corresponds to residues L35-L49; FR-L3 corresponds to residues L57-L88; FR-L4 corresponds to residues L98-L109; FR-H1 corresponds to residues H1-H30; FR-H2

corresponds to residues H36-H49; FR-H3 corresponds to residues H66-H94; and FR-H4 corresponds to residues H103-H113.

A region(s) that differs is identified as a target region because it contains at least one acid differences or variation at corresponding amino acid positions in the variable heavy chain and/or variable light chain amino acid sequence of a first antibody and a related antibody. A variant position includes an amino acid deletion, addition or substitution in the first antibody polypeptide as compared to the related antibody polypeptide. For purposes herein, an identified region contains one or more, typically two or more, for example, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more variant amino acid positions in at least one region of a variable chain of the first antibody antibody compared to a related antibody. In some examples, more then one region, for example, 1, 2, 3, 4 or more regions can be identified that contain at least one variant amino acid positions between a first antibody and a related antibody. Any one or more of the regions can be targeted for affinity maturation by mutagenesis. Generally, a CDR is targeted for mutagenesis.

d. Mutagenesis of an Identified Region

In the method, mutagenesis is performed on target residues within the identified target region. For example, some or up to all amino acid residues of the selected target region in the heavy chain and/or light chain of the first antibody are mutated, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 or more amino acid residues. Each target amino acid residue selected for mutagenesis can be mutated to all 19 other amino acid residues, or to a restricted subset thereof.

In one example, all amino acid residues in the identified target region, e.g. CDR3, can be subject to mutagenesis. In another example, a subset of amino acid residues in the selected target region can be subject to mutagenesis. For example, only the amino acid residues at positions that differ between the first antibody and related antibody are subject to mutagenesis. In another example, only the amino acid residues at positions that are the same between the first antibody and a related antibody are subject to mutagenesis. In an additional example, scanning mutagenesis is optionally performed to identify residues that increase binding to the target antigen. In such examples, only those residues that are identified as "UP" mutants as discussed below are subject to further saturation mutagenesis.

For example, typically, a CDR can contain 3 to 25 amino acid residues. All or subset of the amino acids within a CDR can be targeted for mutagenesis, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid residues can be targeted for mutagenesis. In some examples, all amino acids within a CDR are selected for mutagenesis. In other examples, only a subset of amino acids within a CDR are selected for

mutagenesis. In some instances, only one amino acid residue within a CDR is selected for mutagenesis. In other instances, two or more amino acids are selected for mutagenesis.

The amino acid residues that are selected for further mutagenesis can be modified by any method known to one of skill in the art. The amino acid residues can be modified rationally or can be modified by random mutagenesis. This can be accomplished by modifying the encoding DNA. One of skill in the art is familiar with mutagenesis methods. Mutagenesis methods include, but are not limited to, site-mediated mutagenesis, PCR mutagenesis, cassette mutagenesis, site-directed mutagenesis, random point mutagenesis, mutagenesis using uracil containing templates, oligonucleotide-directed mutagenesis, phosphorothioate-modified DNA mutagenesis, mutagenesis using gapped duplex DNA, point mismatch repair, mutagenesis using repair-deficient host strains, restriction-selection and restriction-purification, deletion mutagenesis, mutagenesis by total gene synthesis, double-strand break repair, and many others known to persons of skill. See, e.g., Arnold (1993) *Current Opinion in Biotechnology* 4:450-455; Bass *et al.*, (1988) *Science* 242:240-245; Botstein and Shortle (1985) *Science* 229:1193-1201; Carter *et al.*, (1985) *Nucl. Acids Res.* 13: 4431-4443; Carter (1986) *Biochem. J.* 237:1-7; Carter (1987) *Methods in Enzymol.* 154: 382-403; Dale *et al.*, (1996) *Methods Mol. Biol.* 57:369-374; Eghtedarzadeh and Henikoff (1986) *Nucl. Acids Res.* 14: 5115; Fritz *et al.*, (1988) *Nucl. Acids Res.* 16: 6987-6999; Grundstrom *et al.*, (1985) *Nucl. Acids Res.* 13: 3305-3316; Kunkel (1987) "The efficiency of oligonucleotide directed mutagenesis" in Nucleic Acids and Molecular Biology (Eckstein, F. and Lilley, D. M. J. eds., Springer Verlag, Berlin); Kunkel (1985) *Proc. Natl. Acad. Sci. USA* 82:488-492; Kunkel *et al.*, (1987) *Methods in Enzymol.* 154, 367-382; Kramer *et al.*, (1984) *Nucl. Acids Res.* 12: 9441-9456; Kramer and Fritz (1987) *Methods in Enzymol.* 154:350-367; Kramer *et al.*, (1984) *Cell* 38:879-887; Kramer *et al.*, (1988) *Nucl. Acids Res.* 16: 7207; Ling *et al.*, (1997) *Anal Biochem.* 254(2): 157-178; Lorimer and Pastan (1995) *Nucleic Acids Res.* 23, 3067-8; Mandecki (1986) *Proc. Natl. Acad. Sci. USA* 83:7177-7181; Nakamaye and Eckstein (1986) *Nucl. Acids Res.* 14: 9679-9698; Nambiar *et al.*, (1984) *Science* 223: 1299-1301; Sakamar and Khorana (1988) *Nucl. Acids Res.* 14: 6361-6372; Sayers *et al.*, (1988) *Nucl. Acids Res.* 16:791-802; Sayers *et al.*, (1988) *Nucl. Acids Res.* 16:803-814; Sieber *et al.*, (2001) *Nature Biotechnology* 19:456-460; Smith (1985) *Ann. Rev. Genet.* 19:423-462; Stemmer (1994) *Nature* 370, 389-91; Taylor *et al.*, (1985) *Nucl. Acids Res.* 13: 8749-8764; Taylor *et al.*, (1985) *Nucl. Acids Res.* 13: 8765-8787; Wells *et al.*, (1986) *Phil. Trans. R. Soc. Lond. A* 317: 415-423; Wells et al. (1985) *Gene* 34:315-323; Zoller and Smith (1982) *Nucleic Acids Res.* 10:6487-6500; Zoller and Smith (1983) *Methods in Enzymol.* 100:468-500; and Zoller and Smith (1987) *Methods in Enzymol.* 154:329-350. In some examples, the amino

acid residues are modified by NNK mutagenesis. In other examples, the amino acid residues are modified by cassette mutagenesis.

In some examples, selected target amino acid residues can be mutagenized individually such that each mutagenesis is performed by the replacement of a single amino acid residue at only one target position, such that each individual mutant generated is the single product of each single mutagenesis reaction. The single amino acid replacement mutagenesis reactions can be repeated for each of the replacing amino acids selected at each of the target positions in the selected region. Thus, a plurality of mutant protein molecules are produced, whereby each mutant protein contains a single amino acid replacement at only one of the target positions. The mutagenesis can be effected in an addressable array such that the identity of each mutant protein is known. For example, site-directed mutagenesis methods can be used to individually generate mutant proteins.

In other examples, a mutagenized antibody can be generated that has random amino acids at specific target positions in the variable heavy or light chain. Generally, selected target amino acid residues can be mutagenized simultaneously, i.e., one or more amino acid residues are mutagenized at the same time. For example, random mutagenesis methodology can be used such that target amino acids are replaced by all (or a group) of the 20 amino acids. Either single or multiple replacements at different amino acid positions are generated on the same molecule, at the same time. In this approach neither the amino acid position nor the amino acid type are restricted; and every possible mutation is generated and tested. Multiple replacements can randomly happen at the same time on the same molecule. The resulting collection of mutant molecules can be assessed for activity as described below, and those that exhibit binding are identified and sequenced.

In random mutagenesis methods, it is contemplated that any known method of introducing randomization into a sequence can be utilized. For example, error prone PCR can introduce random mutations into nucleic acid sequences encoding the polypeptide of interest (see, e.g., Hawkins *et al.*, *J. Mol. Biol.*, (1992) 226(3): 889-96). Briefly, PCR is run under conditions which compromise the fidelity of replication, thus introducing random mutations in sequences as those skilled in the art can accomplish.

Exemplary of a method of introducing randomization into one or more target amino acid positions is the use of a deoxyribonucleotide "doping strategy," which can cover the introduction of all 20 amino acids while minimizing the number of encoded stop codons. For example, NNK mutagenesis can be employed whereby N can be A, C, G, or T (nominally equimolar) and K is G or T (nominally equimolar). In other examples, NNS mutagenesis can be employed whereby S can be G or C. Thus, NNK or NNS (i) code for all the amino acids,

(ii) code for only one stop codon, and (iii) reduce the range of codon bias from 6:1 to 3:1. There are 32 possible codons resulting from the NNK motif: 1 for each of 12 amino acids, 2 for each of 5 amino acids, 3 for each of 3 amino acids, and only one of the three stop codons. Other alternatives include, but are not limited to: NNN which can provide all possible amino acids and all stops; NNY which eliminates all stops and still cover 14 of 20 amino acids; and NNR which covers 14 of 20 amino acids. The third nucleotide position in the codon can be custom engineered using any of the known degenerate mixtures. However, the group NNK, NNN, NNY, NNR, NNS covers the most commonly used doping strategies and the ones used herein.

Mutagenized proteins are expressed and assessed for activity to the target antigen. Any method known to one of skill in the art to assess activity, for example, as described further herein below in Section E.1, can be used. For example, exemplary binding assays include, but are not limited to immunoassays such as competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, Meso Scale Discovery electrochemiluminescence assays (MSD, Gaithersburg, Maryland), immunoprecipitation assays, ELISPOT, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays. Such assays are routine and well known in the art (see, e.g., Ausubel *et al.*, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). For example, in the methods provided herein, binding of an antibody to a target antigen is determined using an ECL binding assay. In another example, binding is determined by ELISA.

Identified mutant antibodies that exhibit improved or increased binding to the target antigen compared to the parent first antibody are identified. The amino acid mutations in the variable heavy or light chain in the identified mutant antibody can be determined. As discussed below, further mutagenesis and iterative screening can be effected on an identified mutant antibody to further optimize the activity for a target antigen. For example, the mutations of all mutant antibodies of a parent first antibody that were identified as exhibiting improved binding for a target antigen can be determined. All or a subset of the identified amino acid mutations can be combined to generate a combination mutant antibody.

2. SAR by Scanning Mutagenesis

Scanning mutagenesis is a simple and widely used technique in the determination of the functional role of protein residues. Scanning mutagenesis can be used in methods of

affinity maturation herein to determine SAR of a first antibody. Scanning mutagenesis can be performed on a first antibody without comparison to a related antibody. In other examples, scanning mutagenesis is optionally performed prior to mutagenesis of a target region above in order to more rationally identify amino acif residues to mutate.

In the scanning mutagenesis methods herein, every residue across the full-length of the variable heavy chain and/or variable light chain of the antibody is replaced by a scanning amino acid. Alternatively, every residue in a region of the variable heavy chain or variable light chain is replaced by a scanning amino acid. For example, at least one CDR (e.g. a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 or CDRL3) is selected for scanning. The scanning amino acid can be any amino acid, but is generally an alanine, theronine, proline or glycine. Amino acid substitution is typically effected by site-directed mutagenesis. Alanine is generally the substitution residue of choice since it eliminates the side chain beyond the [beta] carbon and yet does not alter the main-chain conformation (as can glycine or proline), nor does it impose extreme electrostatic or steric effects. Generally, all amino acid residues selected for mutageneis are scanned (e.g. mutated to) the same amino acid residue. Often, it is necessary to use other scanning amino acid residues. For example, if the target amino acid residue already is an alanine, then another amino acid residue such as threonine, proline or glycine can be used.

When performing scanning mutagenesis, all or a subset of amino acids across the full-length polypeptide or in a selected region are targeted for scanning mutagenesis, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more amino acid residues are subjected to scanning mutagenesis. In examples where scanning mutagenesis is performed in addition to comparison to a related antibody, all amino acid residues in a target region, or a subset or amino acid residues in a target region, are scanned. In one example, only the amino acid residues that differ between the first antibody and a related antibody are targeted for scanning mutagenesis. Generally, all amino acid residues in a target region are subjected to scanning mutagenesis. Mutagenized proteins are expressed and assessed for activity to the target antigen as described above and in Section E below.

Following scanning, scanned (e.g. mutated) antibodies are screened for an activity to identify amino acid residues for further mutation. Generally, most prior art scanning mutagenesis methods involve or are limited to identification of scanned positions that knock down or decrease the activity of the protein of interest. The rationale is that these residues are critical for activity in some way. For purposes of practice of the method herein, however, residues that are "Up" mutants are selected for further mutagenesis following scanning. These are antibodies that exhibit retained or increased activity when mutated to contain a

scanned amino acid compared to the parent antibody. Further, only residues with scanned substitutions that are in contact-making CDRs are selected. Thus in an exemplary embodiment, only residues with scanned substititutions that are in contact-making CDRs and that do not affect activity or confer an improvement are selected herein to further mutate individually to other amino acids.

A benefit of this approach is that generally antibodies that are selected for affinity maturation herein exhibit a micromolar or high nanomolar affinity. Such affinities mean that the antibodies exhibit a low interaction for the target antigen. This is in contrast to many proteins that are typically affinity matured that already are highly evolved for their functional activity. Thus, for antibodies selected for affinity maturation that exhibit a weaker activity for a target antigen, there is more opportunity to improve or optimize weak interactions. Thus, in practicing the method herein, scanned residues that result in an increased or retained activity of the antibody are selected for further mutagenesis. This, allows new interactions to take place, for example, creating new contact residues, that did not exist prior to affinity maturation.

Thus, in scanning mutagenesis methods herein, selected amino acids are subjected to scanning mutagenesis to identify those amino acid residues that are "Up" mutants (i.e. exhibit retained or increased activity). Further mutagenesis is performed only at scanned amino acid positions that exhibit a retained or an increase in activity to the target antigen compared to the parent antibody. An antibody that retains an activity to a target antigen can exhibit some increase or decrease in binding, but generally exhibits the same binding as the first antibody not containing the scanned mutation, for example, exhibits at least 75% of the binding activity, such as 75% to 120% of the binding, for example, 75 %, 80 %, 85 %, 90 %, 95 %, 100 %, 105 %, 110 % or 115 % of the binding. An antibody that exhibits increased activity to a target antigen generally exhibits greater than 115% of the activity, such as greater than 115 %, 120 %, 130 %, 140 %, 150 %, 200 % or more activity than the first antibody not containing the mutation. Thus, scanning mutagenesis can be employed to restrict the subset of target amino acid residues in the target region that are further mutagenized. Once identified, mutagenesis is performed on all or a subset of the amino acid residues as described in Section C.4 above. The further mutagenized antibodies are expressed and assessed for activity to the target antigen as described above and in Section E below. Antibodies that exhibit an improved or optimized activity compared to the first antibody are selected.

3. Further Optimization

The affinity maturation methods provided herein can be performed iteratively to further optimize antibodies. Additionally or alternatively, all or a subset of the amino acid

modifications within a variable heavy or light chain that result in improved or increased activity to the target antigen can be selected and combined and further assessed for activity. These intermediate antibodies also can be used as templates for further mutagenesis using the affinity maturation methods herein. In some examples, variable heavy or light chains with one or more amino acid modification(s) incorporated can be used as templates for further mutagenesis and optimization of activity. In addition, further regions of an antibody can be mutagenized.

The method further provides for optimization of regions of the variable heavy or light chain that were not initially selected for mutagenesis based on the amino acid sequence comparison of the first antibody and related antibodies. An additional region selected for further mutagenesis can occur along any portion of the variable heavy or light chain. For example, a further region can include a CDR or a framework region. Typically, a CDR, for example, CDR1, CDR2 and/or CDR3, is selected and targeted. Any one or more of the regions can be targeted for affinity maturation by mutagenesis. As exemplified in Examples 9 and 12 below, CDRH1 and CDRH2 are selected for additional mutagenesis.

Additional regions of the variable heavy or light chain can be subjected to further mutagenesis at the same time, or alternatively, they can be mutagenized iteratively. For example, mutations in one region that optimize an activity of the antibody can first be identified by further mutagenesis herein, followed by optimization of a second region. The selection of amino acid residues to mutagenize within a selected target region can be determined by the person practicing the method. In some examples, all amino acids in that region are targeted for mutagenesis. In other examples, only a subset of amino acids in that region are targeted for mutagenesis. In an additional example, scanning mutagenesis is performed to identify residues that increase or retain activity to the target antigen. In such examples, only residues that increase or do not affect binding affinity are further mutagenized to identify mutations that increase binding affinity to the target antigen. Typically, mutagenesis is performed for one or both of the heavy and/or light chain(s) independently of the other. The amino acid residues that are selected for further mutagenesis can be modified by any method known to one of skill in the art. Mutagenized proteins are expressed and assessed for binding to the target antigen. Exemplary binding assays are described in Section E.1 below.

The amino acid residues in a region that are selected for further mutagenesis can be modified by any method known to one of skill in the art, as described in Sections C.4 and C.5 above. In some examples, the selected amino acids are subjected to scanning mutagenesis to identify "Up" mutants for further mutagenesis. In other examples, the selected amino acids

are randomly mutagenized, for example, the amino acid residues are modified by saturation mutagenesis and/or cassette mutagenesis. Mutagenized proteins are expressed and assessed for activity to the target antigen, as described in Sections F and E. Antibodies containing amino acid mutations that increase activity to the target antigen are identified.

Combination mutants also can be generated. In the methods provided herein, amino acid mutations that result in increased activity of the antibody towards the target antigen can be combined to generate a variable heavy or light chain with multiple amino acid modifications. Typically, combination mutants have 2, 3, 4, 5, 6, 7, 8, 9, 10 or more mutations per variable heavy and/or light chain. In some examples, combination mutants contain two amino acid modifications. In other examples, combination mutants contain three or more amino acid modifications. As exemplified in Example 9 below, a variable heavy chain is generated containing 4 amino acid mutations.

In addition, intermediate antibodies containing multiple amino acid modifications within the variable heavy or light chain can be generated at any step in the method. A variable heavy and/or light chain of an intermediate antibody, i.e., one containing multiple previously identified amino acid modifications, can be used as a "template" for further mutagenesis and affinity maturation.

Further, the method herein provides for pairing of any modified heavy chains with any modified light chains thereby generating intermediate or affinity matured antibodies in which both the heavy and light chains contain mutations. Mutated heavy and light chains can be paired at any step in the method, expressed and assessed for binding to the target antigen. Thus, further optimization of an antibody can be achieved.

At any step in of further optimization in the methods herein, the affinity matured antibodies can be further evaluated for activity as described in Section E.

a. Complementarity Determining Regions

In some examples, a region is selected for further mutagenesis. Generally, a region is a CDR, for example, CDR1, CDR2 and/or CDR3 of the variable heavy or light chain. The amino acid residues within a variable heavy or light chain CDR can be identified by one of skill in the art. CDRs can be identified by any standard definition, including those of Kabat (see, e.g., Kabat et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition. NIH Publication No. 91-3242.); Chothia (see, e.g. Chothia & Lesk, (1987) *J Mol Biol.* 196(4):901-17; Al-Lazikani et al., (1997) *J Mol Biol.* 273(4):927-48); Abm (see, e.g., Martin et al., (1989) *Proc Natl Acad Sci USA* 86:9268-9272); or contact residues based on crystal structure data (see, e.g., MacCalllum et al., (1996) *J. Mol. Biol.* 262, 732-745). Amino acids

contained within heavy and light chain CDRs, as defined based on Kabat numbering, are described in Section C.3. above.

Typically, a CDR contains 3 to 25 residues, all or part of which can be targeted for further mutagenesis. For example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid residues can be targeted for mutagenesis. As exemplified in Example 9, only selected residues of CDRH1 were mutagenized whereas in Example 10, all residues within CDRL2 were mutagenized.

Selected amino acids are subjected to mutagenesis and the antibodies are expressed and assayed for activity to the target antigen as described in sections C.4 above and E. and F. below.

b. Framework Regions

In some examples, a region selected for further mutagenesis is part of a framework region, for example, FR1, FR2, FR3 and/or FR4, of the variable heavy or light chain. As is the case for CDRs, framework regions can be identified by any standard definition, according to the numbering of Kabat, Chothia, Abm or contact residues. Amino acids that make up the framework regions within the heavy and light chain variable regions as defined based on Kabat numbering are described in Section C.3. above. Typically, a framework region contains 11 to 32 amino acids. All or part of a framework region can be targeted for mutagenesis, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 or 32 amino acids can be subjected to full or partial saturation mutagenesis. A selected region with a framework region can include one or more amino acid residues. In some examples, only one amino acid residue is mutagenized. In other examples, two or more amino acid residues are mutagenized. Selected amino acid residues can be mutagenized individually, or alternatively, selected amino acid residues can be mutagenized simultaneously, i.e., one or more amino acid residues are mutagenized at the same time. For example, double mutants are generated and assayed for their ability to bind to the target antigen.

Selected amino acids are subjected to mutagenesis and the antibodies are expressed and assayed for activity to the target antigen as described in sections C.4 above and E. and F below.

c. Germline Swapping

In some examples, a region selected for further mutagenesis is a germline segment, i.e., a variable heavy chain V, D or J segment, or a variable kappa or lambda light chain V or J segment, e.g., V_H, D_H, J_H, V_κ, V_λ, J_κ, and J_λ. In a variable heavy chain, germline segment V_H contains amino acids within CDR1 and CDR2 while germline segments D_H and J_H contain

amino acid residues within CDR3. In a variable light chain, V germline segments (e.g., V_κ or V_λ) contain amino acid residues within CDR1, CDR2 and the 5' end of CDR3 while J germline segments (e.g., V_λ and J_κ) contain amino acid residues at the 3' end of CDR3. When a germline segment is targeted for mutagenesis, amino acid modifications are introduced into a variable heavy or light chain by swapping, or replacing, an entire germline segment with another germline segment of the same type. For example, a J_H germline segment, e.g., IGHJ1*01, is replaced with a different J_H germline segment, e.g., IGHJ2*01, or any other IGHJ germline segment. As exemplified in Example 13A and Figure 4A, swapping of IGHJ1*01 allows for simultaneous mutation of 6 amino acid residues within heavy chain CDR3 and a seventh residue within framework region 4. One germline segment is swapped, such as, for example, J_H, or alternatively, two germline segments can be swapped, for example, both D_H and J_H can be swapped within one variable heavy chain.

Typically, a D or J germline segment is selected for mutagenesis since these germline segments encode for CDR3 of both the heavy and light chain. More specifically, germline segments D_H, J_H, J_κ, and/or J_λ are selected. As exemplified in Example 13B, swapping of both D_H and J_H segments leads to an almost complete scan of heavy chain CDR3. As shown in Figure 4B, germline segment J_H is swapped with three different J_H segments serving to mutate 6 amino acids at the 3' end of CDRH3 and as shown in Figure 4C, 5 amino acids within the middle of CDRH3 are modified.

Germline swapped antibodies are expressed and assayed for activity to the target antigen as described in section E. and F below. Antibodies containing swapped germline segments that increase activity to the target antigen can be used as intermediate antibodies for further modifications, as described in this section herein.

D. METHOD OF ANTIBODY CONVERSION

Provided herein is a method of antibody conversion. The method is based on the elucidation that antibodies with varying affinities, while maintaining their specificity to a target antigen, can exhibit a range of activities ranging from agonist or activator-modulator activity to antagonist activity for the same target antigen. As described herein, the pharmacologic activity of antibodies is dependent on their affinity, with qualitatively different activities (activations vs. inhibition) occurring in antibodies recognizing the same epitope but with disparate affinities. It is contemplated herein that activation of an activity is due to the enhancement of signaling through receptor clustering and rapid on/off kinetics of the low affinity variant. In contrast, high affinity binders grab on to their ligand and do not let go, thereby preventing transmission of a signal. Thus, an antibody can have a therapeutic benefit

as a low affinity agonist or activator-modulator or as a high affinity antagonist of the same target antigen.

Nearly all antibodies in clinical use are high-affinity antagonists, despite the fact that multiple mechanisms of action are typically seen for several classes of small molecule drugs. For example, small molecule drugs have several mechanisms of action, including acting as antagonists, agonists, partial agonists or antagonists and modulators. In contrast, most antibody therapeutics act as antagonists. The discovery selection mechanisms in hybridoma and display-based systems drive affinity and dominant epitope binding. Thus, most methods of antibody engineering exhibit affinity-based bias. This is because most existing display-based libraries select antibodies based on the ability to rapidly identify high-affinity binders. For example, most methods rely on competitive selection based on target affinity. Thus, most existing methods, for example, traditional display-based methods that rely on competitive affinity screens can miss potential therapeutics simply because they are incompatible with high affinity.

Thus, provided herein are methods of antibody conversion, whereby antibodies are converted from antagonists to partial agonists, antagonists or activators-modulators, or can be converted from agonists or activators-modulators to antagonists or partial antagonists. The method is based on converting antibodies by modulating or altering the binding affinity of an antibody for the same target antigen in order to get a range of activities from antagonism, partial antagonism or activation-modulation. The methods combine mutagenesis approaches of a starting antibody with endpoint analysis for binding affinity and functional activity assessment of resulting activities. By employing random or rational mutagenesis strategies, libraries can be generated that can be screened through a wide dynamic range of affinities to identify antibodies with antagonist, partial antagonist or activator/modulator activities. In some examples, the libraries are in arrayed formats such that the identity of each member in the library is known. In another example, a structure/activity relationship (SAR) mutagensis strategy can be employed similar to the affinity maturation method described in Section C.

1. Choosing the Starting or Reference Antibody

In the method, a starting or reference antibody, or portion thereof, to be converted is chosen. The antibody that is chosen is one that 1) exhibits a known activity against a particular target antigen (e.g. antagonist or agonist), and 2) for which there would be a potential therapeutic benefit if the activity of the antibody was inversed or partially inversed. For example, an antibody that exhibits an antagonist or partial antagonist activity can be chosen, whereby an antibody exhibiting the inverse agonist, partial agonist or activator-modulator activity towards the same target antigen also is desired. In another example, an

antibody that exhibits an agonist, partial agonist or activator-modulator activity towards a target antigen can be chosen, whereby an antibody exhibiting the inverse antagonist or partial antagonist activity towards the same target antigen also is desired.

The first or starting antibody is an antibody that is known or that is identified as having an activity to a target antigen. The target antigen can be a polypeptide, carbohydrate, lipid, nucleic acid or a small molecule (e.g. neurotransmitter). The antibody can exhibit activity for the antigen expressed on the surface of a virus, bacterial, tumor or other cell, or exhibits an activity (e.g. binding) for the purified antigen. Generally, the target antigen is a protein that is a target for a therapeutic intervention. Exemplary target antigens include, but are not limited to, targets involved in cell proliferation and differentiation, cell migration, apoptosis and angiogenesis. Such targets include, but are not limited to, growth factors, cytokines, lymphocytic antigens, other cellular activators and receptors thereof. Exemplary of such targets include, membrane bound receptors, such as cell surface receptors, including, but are not limited to, a VEGFR-1, VEGFR-2, VEGFR-3 (vascular endothelial growth factor receptors 1, 2, and 3), a epidermal growth factor receptor (EGFR), ErbB-2, ErbB-b3, IGF-R1, C-Met (also known as hepatocyte growth factor receptor; HGFR), DLL4, DDR1 (discoidin domain receptor), KIT (receptor for c-kit), FGFR1, FGFR2, FGFR4 (fibroblast growth factor receptors 1, 2, and 4), RON (recepteur d'origine nantais; also known as macrophage stimulating 1 receptor), TEK (endothelial-specific receptor tyrosine kinase), TIE (tyrosine kinase with immunoglobulin and epidermal growth factor homology domains receptor), CSF1R (colony stimulating factor 1 receptor), PDGFRB (platelet-derived growth factor receptor B), EPHA1, EPHA2, EPHB1 (erythropoietin-producing hepatocellular receptor A1, A2 and B1), TNF-R1, TNF-R2, HVEM, LT-βR, CD20, CD3, CD25, NOTCH, G-CSF-R, GM-CSF-R and EPO-R. Other targets include membrane-bound proteins such as selected from among a cadherin, integrin, CD52 or CD44. Exemplary ligands that can be targets, include, but are not limited to, VEGF-A, VEGF-B, VEGF-C, VEGF-D, PIGF, EGF, HGF, TNF-α, LIGHT, BTLA, lymphotoxin (LT), IgE, G-CSF, GM-CSF and EPO.

The first or starting antibody that has activity for the target antigen is known in the art or is identified as having a particular activity for a target antigen or antigens. For example, any method for identifying or selecting antibodies against particular target antigens can be used to choose or select a starting antibody including, but not limited to, immunization and hybridoma screening approaches, display library screening methods (e.g. antibody phage display libraries), or addressable combinatorial antibody libraries. For example, methods of identifying antibodies with particular activities or affinities is described in Section B.2 herein. Further, it is understood that the description of the methods for choosing or selecting a first or

starting antibody described for the affinity maturation method herein in Section C.1, and in particular in section C.1.ai and ii, can also be used choose or select a first antibody to be converted in the antibody conversion method herein. In addition, any antibody that has been affinity matured, and which, typically, exhibits antagonist activity, can be selected as the starting or first antibody. As discussed elsewhere herein, affinity maturation methods are known in the art (see e.g. Section B.3). Also, the affinity maturation method described in Section C also can be used to identify an antibody, generally one with high affinity, that can be subsequently used in the conversion method herein.

If not known, the activity of a first or starting antibody can be determined. The binding affinity and/or functional activity (e.g. as an agonist, antagonist or activator-modulator) can be determined. Exemplary assays are described herein in Section E and in the Examples. The particular assay chosen depends on the target antigen and/or its requirements for activity. For example, DLL4 is a cell-surface ligand that activates the Notch1 receptor, also expressed on the cell surface. Thus, typically, cell-based assays are employed to assess activity. Exemplary of cell-based assays are reporter assays as described herein and in the Examples. Based on the descriptions herein, it is within the level of one of skill in the art to determine and or optimize a particular assay for each antibody.

2. Mutagenesis

Once a first or starting antibody is chosen, amino acid residues in the variable heavy chain and/or variable light chain are subjected to mutagenesis. Generally, amino acid residues in a CDR or CDRs are mutated, for example, residues in CDRL1, CDRL2, CDRL3, CDRH1, CDRH2 and/or CDRH3 of the antibody are mutated. For example, typically, a CDR can contain 3 to 25 amino acid residues. All or subset of the amino acids within a CDR can be targeted for mutagenesis, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 amino acid residues can be targeted for mutagenesis.

The amino acid residues that are selected for further mutagenesis can be modified by any method known to one of skill in the art. The amino acid residues can be modified rationally or can be modified by random mutagenesis. This can be accomplished by modifying the encoding DNA. One of skill in the art is familiar with mutagenesis methods. For example, any of the mutagenesis methods described in Section C.1.d can be used. In one example, if residues in the first or starting antibody are known that are involved in binding, those residues can be rationally targeted by any of a variety of mutagenesis strategies. In another example, random mutagenesis methods can be employed. Exemplary of such mutagenesis strategies introduce randomization into a sequence using methods know in the art, including but not limited to, error prone PCR or doping strategies. Mutagenized proteins

are expressed as described in Section F. Libraries or collections of variant antibodies can be generated and screened for conversion as described herein below. In some examples, the libraries are addressable libraries.

3. Selecting for a Converted Antibody

Mutagenized proteins are expressed and assessed for their binding affinity to the target antigen and/or for effects on modulation of a functional activity towards the target antigen. Converted antibodies are selected for that have a binding affinity and activity that is inversed (e.g. higher or lower; antagonist vs. agonist/activator-modulator) compared to the starting of first antibody.

a. Binding

In the first step of selection of a converted antibody, binding affinity is assessed. Any method known to one of skill in the art to assess activity, for example, as described further herein below in Section E.1, can be used. For example, exemplary binding assays include, but are not limited to immunoassays such as competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, Meso Scale Discovery electrochemiluminescence assays (MSD, Gaithersburg, Maryland), immunoprecipitation assays, ELISPOT, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays. Such assays are routine and well known in the art (see, e.g., Ausubel *et al.*, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). For example, in the methods provided herein, binding of an antibody to a target antigen is determined using an ECL binding assay. In another example, binding is determined by ELISA. As discussed elsewhere herein, comparison of binding affinities between a first antibody and a mutagenized antibody are typically made between antibodies that have the same structure, e.g. Fab compared to Fab of IgG compated to IgG.

For example, if an antagonist antibody is chosen as the first or starting antibody, an agonist, partial agonist or activator-modulator is selected by first testing the antibody for its binding affinity. Antibodies that exhibit a decreased binding affinity (e.g. higher binding affinity) than the first or starting antibody are selected. For example, antibodies are selected that exhibit a binding affinity that is decreased by 2-fold to 5000-fold, for example, 10-fold to 5000-fold, such as 100-fold to 1000-fold. For example, if the binding affinity of the first or starting antibody is 10^{-9} M, and antibody exhibiting a binding affinity of 10^{-7} M exhibits a 1000-fold decreased binding affinity.

In another example, if an agonist, partial agonist, or an activator-modulator antibody is chosen as the first or starting antibody, an antagonist or partial antagonist antibody is selected by first testing the antibody for its binding affinity. Antibodies that exhibit an enhanced or increased binding affinity (e.g. lower binding affinity) then the first or starting antibody are selected. For example, antibodies are selected that exhibit a binding affinity that is enhanced or increased by 10-fold to 10,000 fold, for example, 100-fold to 5000-fold, such as about 500-fold to 2500-fold. For example, if the binding affinity of the first or starting antibody is 10^{-7} M, an antibody exhibiting a binding affinity of 10^{-9} M is selected as exhibiting a 1000-fold increased or enhanced binding affinity.

b. Functional Activity

Mutagenized antibodies initially selected based on binding affinity are then selected for the inversed modulation of a functional activity. Assays to assess the functional activities are well known to those of skill in the art and can be empirically determined depending on the particular target protein. Typically, the assay is a cell-based assay. Exemplary assays, including exemplary cell lines, are described herein in Section E. The cells to be assayed express the particular target protein of interest. Control cells not expressing the protein also can be used to assess specificity. The assay that is employed is one that is capable of providing a read-out that that provides a quantitative assessment of activity, which can be readily assessed. For example, exemplary functional assays include reporter assays, whereby upon activation of a cell-surface receptor, for example by an exogenously added ligand, a reporter signal is induced that can be measured. In the presence of an antagonist or partial antagonist antibody to the cell-surface receptor or ligand, the measured read-out is decreased consistent with the inhibitory effect of the antibody. In contrast, in the presence of an agonist, partial agonist or activator-modulator, the measured read-out is increased consistent with an activating effect of the antibody.

For example, if the starting or first antibody is an antagonist of a target protein, mutant antibodies of the first antibody that are initially selected as having decreased binding affinity in a) above (e.g. higher binding affinity), are further tested for activity as an agonist, partial agonist and/or activator-modulator for the same target protein. Antibodies selected as being converted are those that exhibit an activating activity on the target protein. Thus, the presence of the antibody results in increased activity of the target protein, or on the end-point activity of the target protein, compared to the activity that is exhibited under the same activating conditions without the antibody present. For example, if a target protein is normally activated in the presence of a ligand, a set measured activity is achieved; in the additional presence of an agonist, partial agonist or activator-modulator antibody, the

measured activity is increased. In another example, if the target protein is a ligand that normally activates a receptor, the ligand-receptor interaction results in a set measured activity; in the additional presence of an antibody to the ligand the measured activity is increased. For example, activity of the target protein is increased by 1.2 to 2-fold, 2-fold to 1000-fold, for example, is increased 5-fold to 500-fold, such as 10-fold to 200-fold, for example, is increased 1.2-fold, 1.5-fold, 2-fold, 5-fold, 10-fold, 20-fold, 30-fold, 40-fold, 50-fold, 60-fold, 70-fold, 80-fold, 90-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold, 600-fold, 700-fold, 800-fold, 900-fold, 1000-fold or more compared to the activity of the target protein under the same activating conditions without the antibody present.

In another example, if the starting or first antibody is an agonist, partial agonist or activator-modulator of a target protein, mutant antibodies of the first antibody that are initially selected as having increased or enhanced binding affinity in a) above (e.g. lower binding affinity), are further tested for activity as an antagonist or partial antagonist for the same target protein. Antibodies selected as being converted are those that exhibit an inhibitory activity on the target protein. Thus, the presence of the antibody results in decreased activity of the target protein, or on the end-point activity of the target protein, compared to the activity that is exhibited under the same activating conditions without the antibody present. For example, if a target protein is normally activated in the presence of a ligand, a set measured activity is achieved; in the additional presence of an antagonist or partial antagonist antibody, the measured activity is decreased. In another example, if the target protein is a ligand that normally activates a receptor, the ligand-receptor interaction results in a set measured activity; in the additional presence of an antibody to the ligand the measured activity is decreased. For example, activity of the target protein is decreased by 1.2 to 2-fold, 2-fold to 1000-fold, for example, is decreased by 5-fold to 500-fold, such as 10-fold to 200-fold, for example, is deceased 1.2-fold, 1.5-fold, 2-fold, 5-fold, 10-fold, 20-fold, 30-fold, 40-fold, 50-fold, 60-fold, 70-fold, 80-fold, 90-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold, 600-fold, 700-fold, 800-fold, 900-fold, 1000-fold or more compared to the activity of the target protein under the same activating conditions without the antibody present.

In some examples of the antibody conversion method herein, the initial step of selecting an antibody based on an increased or decreased binding affinity is not performed. Hence, the method of antibody conversion herein can be effected directly by choosing a first or starting antibody as described herein, mutagenizing it as described herein, and directly testing the collection of mutant antibodies for an inverse functional activity of the first or starting antibody. Converted antibodies are selected that exhibit the inverse activity.

In practicing the method provided herein, typically only the variable heavy chain and/or variable light chain of the antibody is subjected to mutagenesis. The ultimate antibody that is selected typically at least contains a variable heavy chain and a variable light chain, or portion thereof sufficient to form an antigen binding site. It is understood, however, that the antibody also can include all or a portion of the constant heavy chain (e.g. one or more CH domains, such as CH1, CH2, CH3 and CH4, and/or a constant light chain (CL)). Hence, the antibody can include those that are full-length antibodies, and also include fragments or portions thereof including, for example, Fab, Fab', $F(ab')_2$, single-chain Fvs (scFv), Fv, dsFv, diabody, Fd and Fd' fragments, Fab fragments, scFv fragments, and scFab fragments. It also is understood that once the antibody is converted as provided herein, the resulting antibody can be produced as a full-length antibody or a fragment thereof, such as a Fab, Fab', $F(ab')_2$, single-chain Fvs (scFv), Fv, dsFv, diabody, Fd and Fd' fragments, Fab fragments, scFv fragments, and scFab fragments. Further, the constant region of any isotype can be used in the generation of full or partial antibody fragments, including IgG, IgM, IgA, IgD and IgE constant regions. Such constant regions can be obtained from any human or animal species. It is understood that activities and binding affinities can differ depending on the structure of an antibody, although it is not expected that an activity as, for example an agonist or antagonist, will substantially change. For example, generally a bivalent antibody, for example a bivalent $F(ab')_2$ fragment or full-length IgG, has a better binding affinity then a monovalent Fab antibody. As a result, where a Fab has a specified binding affinity for a particular target, it is excepted that the binding affinity is even greater for a full-length IgG that is bivalent.

The resulting converted antibodies are candidate therapeutics. Exemplary of practice of the method is described herein in the Examples. For example, Example 19 shows that two different anti-DLL4 germline antibodies, having low affinity for DLL4, exhibited agonist activity. Mutagenesis of each of the antibodies by the affinity maturation method described herein resulted in conversion of the antibodies to antagonist antibodies with higher affinity for the same target antigen.

E. Assays

Antibodies produced in the methods herein can be assessed for their activity towards the target antigen. Antibodies can be screened to identify mutant or modified antibodies that have improved binding affinity or that alter or modulate (increase or decrease) an activity of a target. Typically, the methods herein includes screening or testing antibodies for their binding to a target antigen. Other activities also can be assayed for, including but not limited

to cytotoxicity, differentiation or proliferation of cells, cell migration, apoptosis, angiogenesis and alteration of gene expression.

1. Binding Assays

The antibodies provided herein can be screened for their ability to bind a selected target by any method known to one of skill in the art. Exemplary target antigens are described in Section C.1. Binding assays can be performed in solution, suspension or on a solid support. For example, target antigens can be immobilized to a solid support (e.g. a carbon or plastic surface or chip) and contacted with antibody. Unbound antibody or target protein can be washed away and bound complexes can then be detected. Binding assays can be performed under conditions to reduce nonspecific binding, such as by using a high ionic strength buffer (e.g. 0.3-0.4 M NaCl) with nonionic detergent (e.g. 0.1% Triton X-100 or Tween 20) and/or blocking proteins (e.g. bovine serum albumin or gelatin). Negative controls also can be including in such assays as a measure of background binding. Binding affinities can be determined using Scatchard analysis (Munson *et al.*, *Anal. Biochem.,* 107:220 (1980)), BIACore or other methods known to one of skill in the art.

Exemplary binding assays include, but are not limited to immunoassays such as competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, Meso Scale Discovery (MSD, Gaithersburg, Maryland), immunoprecipitation assays, ELISPOT, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays. Such assays are routine and well known in the art (see, e.g., Ausubel *et al.*, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Other assay formats include liposome immunoassays (LIA), which use liposomes designed to bind specific molecules (e.g., antibodies) and release encapsulated reagents or markers. The released chemicals are then detected according to standard techniques (see Monroe *et al.*, (1986) *Amer. Clin. Prod. Rev.* 5:34-41).

Generally, binding is detected using a detectable moiety or label (e.g. an enzyme, a radionuclide, a fluorescent probe, electrochemiluminescent label, or a color dye) typically attached to the target or, if desired, directly to the antibody members in the library. Alternatively, binding can be detected by a further third reagent that itself is labeled or detectable. For example, detection of an antibody bound to a target protein can be achieved using a labeled capture molecule in a sandwich assay format. Other proteins capable of specifically binding immunoglobulin constant regions, such as protein A or protein G also can

be used as the label agent. These proteins exhibit a strong non-immunogenic reactivity with immunoglobulin constant regions from a variety of species (see, e.g., Kronval *et al.*, (1973) *J. Immunol.* 111:1401-1406; Akerstrom *et al.*, (1985) *J. Immunol.* 135:2589-2542). The detction agent can be modified with a detectable moiety, such as biotin, to which another molecule can specifically bind, such as streptavidin. A variety of detectable moieties are well known to those skilled in the art.

The choice of label or detectable group used in the assay is not critical, as long as it does not significantly interfere with the specific binding of the antibody used in the assay. Generally, the choice depends on sensitivity required, ease of conjugation with the compound, stability requirements, available instrumentation, and disposal provisions. One of skill in the art is familiar with labels and can identify a detectable label suitable for and compatible with the assay employed.

The detectable group can be any material having a detectable physical or chemical property. Such detectable labels have been well-developed in the field of immunoassays and, in general, most any label useful in such methods can be applied herein. Thus, a label is any composition detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Useful labels include magnetic beads (e.g., DYNABEADS™), fluorescent dyes (e.g., fluorescein isothiocyanate, Texas red, rhodamine, and the like), radiolabels (e.g., 3H, 125I, 35S, 14C, or 32P), enzymes (e.g., horse radish peroxidase, alkaline phosphatase and others commonly used in an ELISA), chemiluminescent labels (luciferin and 2,3-dihydrophtahlazinediones, e.g., luminol), and colorimetric labels such as colloidal gold or colored glass or plastic beads (e.g., polystyrene, polypropylene, latex, etc.). For a review of various labeling or signal producing systems that can be used, see e.g. United States Patent No. 4,391,904.

Means of detecting labels are well known to those of skill in the art. Thus, for example, where the label is a radioactive label, means for detection include a scintillation counter or photographic film as in autoradiography. Where the label is a fluorescent label, it can be detected by exciting the fluorochrome with the appropriate wavelength of light and detecting the resulting fluorescence. The fluorescence can be detected visually, by the use of electronic detectors such as charge coupled devices (CCDs) or photomultipliers and the like. Similarly, enzymatic labels can be detected by providing the appropriate substrates for the enzyme and detecting the resulting reaction product. Finally simple colorimetric labels can be detected simply by observing the color associated with the label.

Some assay formats do not require the use of labeled components. For instance, agglutination assays can be used to detect the presence of the target antibodies. In this case,

antigen-coated particles are agglutinated by samples containing the target antibodies. In this format, none of the components need be labeled and the presence of the target antibody is detected by simple visual inspection.

Alternatively, the antibodies provided herein can be screened for their ability to bind to cells, using whole cell panning, with or without subtractive panning. Screening can be done against live cells or against intact, mildly fixed target cells. Methods for whole cell panning have been described previously (see e.g. Siegel *et al.* (1997) *J. Immunol. Methods* 206:73-85 incorporated herein by reference). Other techniques for screening which can be applied include fluorescent activated cell sorting (FACs).

For high-throughput screening, assays can be multiplexed. Thus, the binding affinities of antibodies to a number of different target proteins can be determined at once. In one example, different target proteins can be separately labeled with different detectable moieities. For example, different antigens can be coupled to color-coded beads (Schwenk *et al.* (2007) Mol. Cell. Prot., 6:125-132). In another example, multi-spot plates can be used that permit assay multiplexing by absorption of up to 100 proteins in a locus of the plate (e.g. using Multi-Array or Multi-Spot plates from Meso Scale Discovery; MSD, Gaithersburg, MD). In such an example, antibodies can be screened by addition of a different antibody to each well of a multi-spot plate. The assay readily permits the screening of thousands of antibodies at once against numerous target proteins.

In the methods of screening herein, antibodies generally are identified that specifically bind to a target antigen, and that have an increased binding affinity compared to a first antibody. The increase in affinity, measured as decrease in Kd, can be achieved either through an increase in association rate (k_{on}), or a reduction in dissociation rate k_{off}, or both. For example, the binding affinity of the antibodies is determined to identify or select antibodies that have high affinity for a target protein. For example, the affinity matured antibodies generated by practice of the method can have a binding affinity for a target antigen that is 1×10^{-9} M or less, generally 1×10^{-9} M to 1×10^{-11} M, for example that is or is about 1×10^{-9} M, 2×10^{-9} M, 3×10^{-9} M, 4×10^{-9} M, 5×10^{-9} M, 6×10^{-9} M, 7×10^{-9} M, 8×10^{-9} M, 9×10^{-9} M, 1×10^{-10} M, 2×10^{-10} M, 3×10^{-10} M, 4×10^{-10} M, 5×10^{-10} M, 6×10^{-10} M, 7×10^{-10} M, 8×10^{-10} M, 9×10^{-10} M or less.

Any method known to one of skill in the art can be used to measure the binding affinity of an antibody. For example, the binding properties of an antibody can be assessed by performing a saturation binding assay, for example, a saturation ELISA, whereby binding to a target protein is assessed with increasing amounts of antibody. In such experiments, it is possible to assess whether the binding is dose-dependent and/or saturable. In addition, the

binding affinity can be extrapolated from the 50% binding signal. Typically, apparent binding affinity is measured in terms of its association constant (Ka) or dissociation constant (Kd) and determined using Scatchard analysis (Munson *et al.*, *Anal. Biochem.*, 107:220 (1980). For example, binding affinity to a target protein can be assessed in a competition binding assay in where increasing concentrations of unlabeled protein is added, such as by radioimmunoassay (RIA) or ELISA. Binding affinity also can be analyzed using BIAcore kinetic analysis. This involves analyzing the binding and dissociation of an antibody member from chips containing immobilized target proteins on their surface. The Biacore evaluation software generates the values of Ka and Kd by fitting the data to interaction models. It is understood that the binding affinity of an antibody can vary depending on the assay and conditions employed, although all assays for binding affinity provide a rough approximation. By performing various assays under various conditions it is possible to estimate the binding affinity of an antibody.

In addition, binding affinities can differ depending on the structure of an antibody. For example, generally a bivalent antibody, for example a bivalent F(ab')2 fragment or full-length IgG, has a better binding affinity then a monovalent Fab antibody. Hence, it is understood that where a Fab has a specified binding affinity for a particular target, it is excepted that the binding affinity is even greater for a full-length IgG that is bivalent.

2. Functional Activity

The antibodies generated by the method herein can be screened for their ability to modulate the functional activity of a target by any method known to one of skill in the art. Assays can be designed to identify antibodies capable of binding and/or modulating cell surface receptors. Such antibodies can either be agonists, mimicking the normal effects of receptor binding, or antagonists, inhibiting the normal effects of receptor binding. Of particular interest is the identification of agents which bind to the receptors and modulate intracellular signaling.

In some example, such assays are cell-based assays. Generally, assays are performed using cell lines known to express the target of interest. Such cells are known to one of skill in the art. For example, one can consult the ATCC Catalog (atcc.org) to identify cell lines. Also, if a particular cell type is desired, the means for obtaining such cells, and/or their instantly available source is known to those in the art. An analysis of the scientific literature can readily reveal appropriate choice of cells expressing any desired target. Table 5 lists exemplary cells lines that express targets of interest that can be screened in functional activities herein against antibody libraries provided herein.

Table 5. Cell lines expressing targets

Target	Cell Lines	References
GP IIb/IIIa	MEG-01 chronic myelogenous leukemia megakaryoblast cells (ATCC CRL-2021); UT-7 human leukemia cell ine	Ogura *et al.* Establishment of a novel human megakaryoblastic leukemia cell line, MEG- 01, with positive Philadelphia chromosome. Blood 66: 1384-1392, 1985; Komatsu *et al.* Establishment and Characterization of a Human Leukemic Cell Line with Megakaryocytic Features: Dependency on Granulocyte-Macrophage Colony-stimulating Factor, Interleukin 3, or Erythropoietin for Growth and Survival. Cancer Research 51:341-348 (1991)
GM-CSF-R	VA-ES-BJ epitheloid sarcoma cells (ATCC CRL-2138); TF1-HaRas; TF1-vRaf; TF1-vSrc; HL-60 (ATCC CCL-240); U-937 (ATCC CRL-1593.2); ML-2	Int J Oncol 1995;7:51-56; Ali Habib *et al.* A urokinase-activated recombinant diphtheria toxin targeting the granulocyte-macrophage colony-stimulating factor receptor is selectively cytotoxic to human acute myeloid leukemia blasts. Blood 104(7):2143-2148 (2004); Kiser *et al.* Oncogene-dependent engraftment of human myeloid leukemia cells in immunosuppressed mice. Leukemia 15(5):814-818 (2001)
VEGFA	Human A673 rhabdomyosarcoma cells (ATCC CRL-1598); Breast carcinoma MDA-MB-435 cells (ATCC); Bovine adrenal cortex-derived capillary endothelial cells	Gerber *et al.* Complete inhibition of rhabdomyosarcoma xenograft growth and neovascularization requires blockade of both tumor and host vascular endothelial growth factor. Cancer Res. 60(22):6253-8 (2000); Presta *et al.* Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Research, 57(20):4593-4599 (1997)
CD3	Jurkat E6.1 Human leukemic T cell lymphoblast (Sigma Aldrich 88042803)	Buhler *et al.* A bispecific diabody directed against prostate-specific membrane antigen and CD3 induces T-cell mediated lysis of prostate cancer cells. Cancer Immunol Immunother. 57(1):43-52 (2008)
EGFR	DiFi human colorectal carcinoma cells; A431 cells (ATCC CRL-1555); Caco-2 colorectal adenocarcinoma cells (ATCC HTB-37); HRT-18 colorectal adenocarcinoma cells (ATCC CCL-244); HT-29 colorectal adenocarcinoma cells (ATCC HTB-38)	Olive *et al.* Characterization of the DiFi rectal carcinoma cell line derived from a familial adenomatous polyposis patient. In Vitro Cell Dev Biol. 29A(3 Pt 1):239-248 (1993); Wu *et al.* Apoptosis induced by an anti-epidermal growth factor receptor monoclonal antibody in a human colorectal carcinoma cell line and its delay by insulin. Clin. Invest. 95(4): 1897-1905 (1995)
EPO receptor	A2780 ovarian cancer cells; UT-7 human leukemia cell ine	Jeong *et al.* Characterization of erythropoietin receptor and erythropoietin expression and function in human ovarian cancer cells. Int J Cancer. 122(2):274-280 (2008); Elliott *et al.* Activation of the Erythropoietin (EPO) Receptor by Bivalent Anti-EPO Receptor Antibodies. J Biol Chem. 271(40):24691-24697 (1996)
Her2/Neu receptor	BT-474 ductal carcinoma breast cancer cell (ATCC HTB-20); SK-BR-3 adenocarcinoma breast cancer cell (ATCC HTB-	Le *et al.* Roles of human epidermal growth factor receptor 2, c-jun NH2-terminal kinase, phosphoinositide 3-kinase, and p70 S6 kinase pathways in regulation of cyclin G2 expression in human breast cancer cells. Mol Cancer Ther. 6(11):2843-2857 (2007)

	30); MDA-MB-453 metastatic carcinoma cell line (ATCC HTB-131)	
cMet	H1993 lung adenocarcinoma cells (ATCC CRL-5909); H1838 lung adenocarcinoma cells (ATCC CRL-5899); SW 900 lung squamous cell carcinoma cells (ATCC HTB-59); H358 lung bronchioalveolar carcinoma cells (ATCC CRL-5807); SK-Lu-1 lung adenocarcinoma cells (ATCC HTB-57); H441 Non-small cell lung cancer cells (ATCC HTB-174)	Ma *et al.* Functional expression and mutations of c-Met and its therapeutic inhibition with SU11274 and small interfering RNA in non-small cell lung cancer. Cancer Res. 65(4):1479-1488 (2005); Ma *et al.* A selective small molecule c-MET Inhibitor, PHA665752, cooperates with rapamycin. Clin Cancer Res 11(6):2312-2319 (2005)
CD20	Ramos Burkitt's lymphoma B cells (ATCC CRL-1596); Raji Burkitt's lymphoma B cells (ATCC CCL-86): Daudi Burkitt's lymphoma B cells (ATCC CCL-213); 2F7 Burkitt's lymphoma B cells	Jazirehi *et al.* Rituximab (anti-CD20) selectively modifies Bcl-xL and apoptosis protease activating factor-1 (Apaf-1) expression and sensitizes human non-Hodgkin's lymphoma B cell lines to paclitaxel-induced apoptosis. Mol Cancer Ther. 2(11):1183-1193 (2003)

In addition, cells lines expressing a target of interest can be generated by transient or stable transfection with an expression vector expressing a target of interest. Methods of transfection and expression are known to those of skill in the art (see e.g., Kaufman R.J. (1990) Methods in Enzymology 185:537-566; Kaufman *et al.* (1990) Methods in Enzymology 185:537-566). In addition, any primary cell or cell line can be assessed for expression of a particular target (e.g. cell surface marker). Cell surface markers can be assayed using fluorescently labeled antibodies and FACS. Suitable cell lines include A549 (lung), HeLa , Jurkat, BJAB, Colo205, H1299 , MCF7, MDA-MB-231, PC3, HUMEC, HUVEC, and PrEC.

Any suitable functional effect can be measured, as described herein. For example, cellular morphology (e.g., cell volume, nuclear volume, cell perimeter, and nuclear perimeter), ligand binding, substrate binding, nuclease activity, apoptosis, chemotaxis or cell migrations, cell surface marker expression, cellular proliferation, GFP positivity and dye dilution assays (e.g., cell tracker assays with dyes that bind to cell membranes), DNA synthesis assays (e.g., 3H-thymidine and fluorescent DNA-binding dyes such as BrdU or

Hoechst dye with FACS analysis) and nuclear foci assays, are all suitable assays to identify potential modulators using a cell based system. Other functional activities that can be measured include, but are not limited to, ligand binding, substrate binding, endonuclease and/or exonuclease activity, transcriptional changes to both known and uncharacterized genetic markers (e.g., northern blots), changes in cell metabolism, changes related to cellular proliferation, cell surface marker expression, DNA synthesis, marker and dye dilution assays (e.g., GFP and cell tracker assays), contact inhibition, tumor growth in nude mice, and others.

For example, antibodies generated by the method provided herein can be assessed for their modulation of one or more phenotypes of a cell known to express a target protein. Phenotypic assays, kits and reagents for their use are well known to those skilled in the art and are herein used to screen antibody libraries. Representative phenotypic assays, which can be purchased from any one of several commercial vendors, include those for determining cell viability, cytotoxicity, proliferation or cell survival (Molecular Probes, Eugene, Oregon; PerkinElmer, Boston, Mass.), protein-based assays including enzymatic assays (Panvera, LLC, Madison, Wis.; BD Biosciences, Franklin Lakes, N.J.; Oncogene Research Products, San Diego, Calif.), cell regulation, signal transduction, inflammation, oxidative processes and apoptosis (Assay Designs Inc., Ann Arbor, Mich.), triglyceride accumulation (Sigma-Aldrich, St. Louis, Mo.), angiogenesis assays, tube formation assays, cytokine and hormone assays and metabolic assays (Chemicon International Inc., Temecula, Calif.; Amersham Biosciences, Piscataway, N.J.).

Cells determined to be appropriate for a particular phenotypic assay (i.e., A549, HeLa, Jurkat, BJAB, Colo205, H1299, MCF7, MDA-MB-231, PC3, HUMEC, HUVEC, and PrEC and any others known to express the target of interest) are treated with antibodies as well as control compounds. If necessary, a ligand for the receptor target is included so that activation of the receptor is effected. At the end of the treatment period, treated and untreated cells are analyzed by one or more methods specific for the assay to determine phenotypic outcomes and endpoints.

Phenotypic endpoints include changes in cell morphology over time or treatment dose as well as changes in levels of cellular components such as proteins, lipids, nucleic acids, hormones, saccharides or metals. Measurements of cellular status which include pH, stage of the cell cycle, intake or excretion of biological indicators by the cell, are also endpoints of interest.

The assays can be performed to assess the direct effects of an antibody on a target protein. For example, if the target protein is a cell surface receptor, an antibody can be added to assess whether the target protein directly modulates, such as by stimulation, the activity or

function of the receptor. In such instances, the antibody is deemed an agonist antibody. In other examples, if the target protein is a cell surface receptor, the activity of the receptor can be stimulated in the presence of a ligand or other stimulating agent in the presence or absence of the antibody to determine if the antibody modulates (e.g. inhibits) the actions of the antibody. For example, the antibody can act by blocking the ability of the ligand to interact with the receptor and/or otherwise induce a negative stimulatory signal. In such instances, the antibody is deemed to be an antagonist of the receptor. Thus, the methods of screening herein by functional activity permits identification of agonist and antagonist antibodies.

a. Differentiation

Cellular differentiation can be analyzed using any assay that allows a detection of a physical, chemical or phenotypic change. Various assays are used to quantitatively determine cellular proliferation and activation in response to an external stimuli. Cell proliferation assays are used to quantitatively determine cellular proliferation by incorporating a reagent into the DNA of newly synthesized cells upon cell division. Such reagents include, but are not limited to ^{3}H-thymidine, 5-bromo-2′-deoxyuridine (BrdU) and fluorescent Hoechst dyes. Cell viability assays are used to determine the number of healthy cells in a sample by staining cells with a dye and measuring how many cells uptake the dye based on the fact that living cells will exclude the dye. Such dyes include but are not limited to 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), 2,3-Bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide inner salt (XTT), and 4-[3-(4-iodophenyl)-2-(4-nitrophenyl)-2H-5-tetrazolio]-1,3-benzene disulfonate (WST-1). Uptake of the reagent is measured either colorimetrically using a spectrophotometer or by measuring radiation with a scintillation counter. Details of these methods are well-known to one skilled in the art.

Fluorescent dyes are commonly used for the detection of live cells and key functional activities in a variety of cell-based assays. There are several non-radioactive, fluorescence-based assays that are not dependent on cellular metabolism. The fluorescent dye binds nucleic acids and the fluorescence can then be measured quantitatively or qualitatively. Such dyes include, but are not limited to, propidium iodide and Hoechst 33342. The cell number can then be quantitated based on the fluorescence. DNA content can also be quantitated using the tools available in the imaging instruments. Details of these methods are well known to one skilled in the art.

The degree of invasiveness into Matrigel or some other extracellular matrix constituent can be used as an assay to identify antibodies that are capable of inhibiting abnormal cell proliferation and tumor growth. Tumor cells exhibit a good correlation between malignancy and invasiveness of cells into Matrigel or some other extracellular matrix

constituent. In this assay, tumorigenic cells are typically used as host cells. Therefore, antibodies can be identified by measuring changes in the level of invasiveness between the host cells before and after the introduction of potential modulators.

Briefly, the level of invasion of host cells can be measured by using filters coated with Matrigel or some other extracellular matrix constituent. Penetration into the gel, or through to the distal side of the filter, is rated as invasiveness, and rated histologically by number of cells and distance moved, or by prelabeling the cells with 125I and counting the radioactivity on the distal side of the filter or bottom of the dish. (see, e.g., Freshney, Culture of Animal Cells a Manual of Basic Technique, 3rd ed., Wiley-Liss, New York (1994), herein incorporated by reference).

b. Alteration of Gene Expression

Detection of binding and/or modulation of a target by an antibody can be accomplished by detecting a biological response, such as, for example, measuring Ca^{2+} ion flux, cAMP, IP3 , PIP3 or transcription of reporter genes. Analysis of the genotype of the cell (measurement of the expression of one or more of the genes of the cell using a reporter gene assay) after treatment is also used as an indicator of the efficacy or potency of the antibody. Hallmark genes, or those genes suspected to be associated with a signal transduction pathway are measured in both treated and untreated cells.

Assays can be performed that measure the activation of a reporter gene. Suitable reporter genes include endogenous genes as well as exogenous genes that are introduced into a cell by any of the standard methods familiar to the skilled artisan, such as transfection, electroporation, lipofection and viral infection. For example, cells expressing a recombinant receptor can be transfected with a reporter gene (e.g., chloramphenicol acetyltransferase, firefly luciferase, bacterial luciferase, β-galactosidase and alkaline phosphatase) operably linked to a response element. The cells are then incubated with antibodies and the expression of the reporter gene is compared to expression in control cells that do not express the recombinant receptor but that are essentially identical in other respects. A statistically significant change in reporter gene expression in the receptor-expressing cells is indicative of a test compound that interacts with the receptor. Furthermore, the protein of interest can be used as an indirect reporter via attachment to a second reporter such as red or green fluorescent protein (see, e.g., Mistili & Spector, (1997) *Nature Biotechnology* 15:961-964).

The reporter construct is typically transfected into a cell. After treatment with a potential modulator, the amount of reporter gene transcription, translation, or activity is measured according to standard techniques known to those of skill in the art. The use of a

reporter gene assay using luciferase to measure activiation of STAT5 directly or by induction of cyclin-D promoter is exemplified in Example 12.

c. Cytotoxicity Activity

Antibodies can be screened for their ability to directly induce apoptosis or programmed cell death or to indirectly induce apoptosis by blocking growth factor receptors, thereby effectively arresting proliferation. Antibodies also bind complement, leading to direct cell toxicity, known as complement dependent cytotoxicity (CDC). Thus, assays can be performed to assess complement-dependent cytotoxicity.

A variety of assays to assess apoptosis are known to one of skill in the art. For example, apoptosis assays include those that assay for the activation of a caspase, which are enzymes involved in apoptosis. Caspase assays are based on the measurement of zymogen processing to an active enzyme and proteolytic activity. A number of commercial kits and reagents are available to assess apoptosis based on caspase function including, but not limited to, PhiPhiLux (OncoImmunin, Inc.), Caspase 3 activity assay (Roche Applied science), Homogenous Caspase assay (Roche Applied Science), Caspase-Glo Assays (Promega), Apo-ONE Homogeneous Caspase-3/7 Assay (Promega), CaspACE Assay System Colorimetric or Fluormetric (Promega), EnzChek Caspase-3 Assay Kit (Invitrogen), Imag-iT LIVE green Caspase-3 and 7 Detection Kit (Invitrogen), Active Caspase-3 Detection Kits (Stratagene), Caspase-mediated Apoptosis Products (BioVision) and CasPASE Apoptosis Assay Kit (Genotech).

Assays for apoptosis include TUNEL and DNA fragmentation assays that measure the activation of nucleases and subsequent cleavage of DNA into 180 to 200 base pair increments. Such assays and kits are commercially available and include, but are not limited to, Apoptotic DNA Ladder Kit (Roche Applied Science), Cellular DNA Fragmentation ELISA (Roche Applied Science), Cell Death Detection ELISAPLUS (Roche Applied Science), In Situ Cell Death Detection Kit (Roche Applied Science), DeadEnd Fluorometirc or Colorimetric TUNEL System (Promega), APO-BrdU TUNEL Assay Kit (Invitrogen), and TUNEL Apoptosis Detection Kit (Upstate).

Other assays to assess apoptosis include, for example, cell permeability assays that evaluate the loss of membrane integrity. For example, to determine whether the antibody is able to induce cell death, loss of membrane integrity as evaluated by uptake of propidium iodide (PI), trypan blue, or 7-aminoactinomycin D (7AAD) can be assessed relative to untreated cells. In addition, commercial kits such as APOPercentage Assay (Biocolor Assays) can be used to measure apoptosis. Annexin V assays also can be employed. Annexin V binds to phosphatidylserine, which is normally found on the inner surface of the

cytoplasmic membrane. During apoptosis, phosphatidylserine is translocated to the outer surface and can be detected by Annexin V. For example, standard binding assays using a fluorescent labeled Annexin V can be used (e.g. Annexin V, Alex Fluor 350 Conjugate from Invitrogen). Apoptosis also can be measured by assessing the presence of other markers of apoptosis, assessing protein cleavage, and/or by mitochondrial and ATP/ADP assays. Such assays are routine and known to one of skill in the art.

For example, apoptosis analysis can be used as an assay to identify functional antibodies using cell lines, such as RKO or HCT116, or other cells expressing a target protein of interest. The cells can be co-transfected with a construct containing a marker gene, such as a gene that encodes green fluorescent protein, or a cell tracker dye. The apoptotic change can be determined using methods known in the art, such as DAPI staining and TUNEL assay using fluorescent microscope. For TUNEL assay, commercially available kit can be used (e.g., Fluorescein FragEL DNA Fragmentation Detection Kit (Oncogene Research Products, Cat.# QIA39) and Tetramethyl-rhodamine-5-dUTP (Roche, Cat. # 1534 378)). Cells contacted with an antibody exhibit, e.g., an increased apoptosis compared to control.

Cell death *in vitro* can be determined in the absence of complement and immune effector cells to distinguish cell death induced by antibody dependent cellular cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC). Thus, the assay for cell death can be performed using heat inactivated serum (i.e. in the absence of complement) and in the absence of immune effector cells.

3. In Vivo Assays

Once an affinity matured antibody or converted antibody is generated by the methods herein, it can be assessed in vivo assays associated with aberrant activity of the target. In general, the method involves administering an antibody to a subject, generally a non-human animal model for a disease or condition and determining the effect of the antibody on the on the disease or condition of the model animal. *In vivo* assays include controls, where suitable controls include a sample in the absence of the antibody. Generally a plurality of assay mixtures is run in parallel with different antibody concentrations to obtain a differential response to the various concentrations. Typically, one of these concentrations serves as a negative control, i.e. at zero concentration or below the level of detection.

Non-human animals models include those induced to have a disease such as by injection with disease and/or phenotype-inducing substances prior to administration of the antibodies to monitor the effects on disease progression. Genetic models also are useful. Animals, such as mice, can be generated which mimic a disease or condition by the overexpression, underexpression or knock-out of one or more genes. Such animals can be

generated by transgenic animal production techniques well-known in the art or using naturally-occurring or induced mutant strains. One of skill in the art is familiar with various animal models associated with particular targets.

Such animal model systems include, but are not limited to, mice, rats, rabbits, guinea pigs, sheep, goats, pigs, and non-human primates, e.g. baboons, chimpanzees and monkey. Any animal system well-known in the art can be used. Several aspects of the procedure can vary; said aspects include, but are not limited to, the temporal regime of administering the antibodies (e.g., prophylactic and/or therapeutic agents), whether such antibodies are administered separately or as an admixture, and the frequency of administration of the antibodies.

Recombinant (transgenic) animal models can be engineered by introducing the coding portion of the genes identified herein into the genome of animals of interest, using standard techniques for producing transgenic animals. Animals that can serve as a target for transgenic manipulation include, without limitation, mice, rats, rabbits, guinea pigs, sheep, goats, pigs, and non-human primates, e.g. baboons, chimpanzees and monkeys. Techniques known in the art to introduce a transgene into such animals include pronucleic microinjection (United States Patent No. 4,873,191); retrovirus-mediated gene transfer into germ lines (e.g., Van der Putten *et al.*, (1985) *Proc. Natl. Acad. Sci. USA* 82:6148-615); gene targeting in embryonic stem cells (Thompson *et al.*, (1989) *Cell* 56:313-321); electroporation of embryos (Lo, (1983) *Mol. Cel. Biol.* 3:1803-1814); sperm-mediated gene transfer (Lavitrano *et al.*, (1989) *Cell* 57:717-73). For review, see, for example, U.S. Pat. No. 4,736,866.

Animal models can be used to assess the efficacy of an antibody, a composition, or a combination therapy provided herein. Examples of animal models for lung cancer include, but are not limited to, lung cancer animal models (see e.g. Zhang *et al.*, (1994) *In Vivo* 8(5):755-69) and a transgenic mouse model with disrupted p53 function (see, e.g., Morris *et al.*, (1998) *J La State Med Soc* 150(4):179-85). An example of an animal model for breast cancer includes, but is not limited to, a transgenic mouse that overexpresses cyclin D1 (see, e.g., Hosokawa *et al.*, (2001) *Transgenic Res* 10(5):471-8). An example of an animal model for colon cancer includes, but is not limited to, a TCR b and p53 double knockout mouse (see, e.g., Kado *et al.*, (2001), *Cancer Res* 61(6):2395-8). Examples of animal models for pancreatic cancer include, but are not limited to, a metastatic model of Panc02 murine pancreatic adenocarcinoma (see, e.g., Wang *et al.*, (2001) *Int J Pancreatol* 29(1):37-46) and nu-nu mice generated in subcutaneous pancreatic tumors (see, e.g., Ghaneh *et al.*, (2001) *Gene Ther* 8(3):199-208). Examples of animal models for non-Hodgkin's lymphoma include, but are not limited to, a severe combined immunodeficiency ("SCID") mouse (see, e.g.,

Bryant *et al.*, (2000) *Lab Invest* 80(4):553-73) and an IgHmu-HOX11 transgenic mouse (see, e.g., Hough *et al.*, (1998) *Proc Natl Acad Sci USA* 95(23):13853-8). An example of an animal model for esophageal cancer includes, but is not limited to, a mouse transgenic for the human papillomavirus type 16 E7 oncogene (see, e.g., Herber *et al.*, (1996) *J Virol* 70(3):1873-81). Examples of animal models for colorectal carcinomas include, but are not limited to, Apc mouse models (see, e.g., Fodde & Smits, (2001) *Trends Mol Med* 7(8):369-73 and Kuraguchi *et al.*, (2000) *Oncogene* 19(50):5755-63).

Animal models for arthritis include, but are not limited to, rheumatoid arthritis rats (see e.g. Pearson, (1956) *Proc. Soc. Exp. Biol. Med.*, 91:95-101) and collagen induced arthritis in mice and rats (see e.g. Current Protocols in Immunology, Eds. J. E. Cologan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach and W. Strober, John Wiley & Sons, Inc., 1994). An example of an animal model for asthma, includes but is not limited to, a mouse model of pulmonary hypersensitivity (see e.g. Riese *et al.* (1998) *J. Clin. Invest.* 101:2351-2363 and Shi, *et al.* (1999) *Immunity* 10:197-206). Animal models for allogenic rejection include, but are not limited to, rat allogeneic heart transplant models (see e.g. Tanabe *et al.* (1994) *Transplantation* 58:23-27 and Tinubu *et al.* (1994) *J. Immunol.* 153:4330-4338) and rat heterocardiac allograft rejection (Jae-Hyuck Sim *et al.* (2002) *Proc Natl Acad Sci U.S.A.* 99(16):10617-10622). Steel mice are used as a model of human aplastic anemia (see e.g. Jones, (1983) *Exp. Hematol.*, 11:571-580). An example of an animal model for anemia, includes but is not limited to, hemolytic anemia guinea pigs (see e.g. Schreiber, *et al.* (1972) *J. Clin. Invest.* 51:575). An example of an animal model for neutropenia, includes but is not limited to, neutropenia neutropenic CD rats (see, e.g. Nohynek *et al.* (1997) Cancer Chemother. Pharmacol. 39:259-266).

F. Methods of Production of Antibodies

Nucleic acid molecules and antibodies generated by the methods provided herein can be made by any method known to one of skill in the art. Such procedures are routine and are well known to the skill artisan. They include routine molecular biology techniques including gene synthesis, PCR, ligation, cloning, transfection and purification techniques. A description of such procedures is provided below.

For example, nucleic acid sequences can be constructed using gene synthesis techniques as discussed herein above. Gene synthesis or routine molecular biology techniques also can be used to effect insertion, deletion, addition or replacement of nucleotides. For example, additional nucleotide sequences can be joined to a nucleic acid sequence. In one example linker sequences can be added, such as sequences containing restriction endonuclease sites for the purpose of cloning the synthetic gene into a vector, for

example, a protein expression vector or a vector designed for the amplification of the antibody constant region coding DNA sequences. Furthermore, additional nucleotide sequences specifying functional DNA elements can be operatively linked to a recombined germline encoding nucleic acid molecule. Examples of such sequences include, but are not limited to, promoter sequences designed to facilitate intracellular protein expression, and leader peptide sequences designed to facilitate protein secretion. Additional nucleotide sequences such as sequences specifying protein binding regions also can be linked to nucleic acid sequences. Such regions include, but are not limited to, sequences to facilitate uptake of recombined antibodies or fragments thereof into specific target cells, or otherwise enhance the pharmacokinetics of the synthetic gene.

Nucleic acid sequences can be further engineered as described herein, such as by mutagenesis, to generate mutant antibodies. Mutagenesis can be effected entirely through gene synthesis. For example, nucleic acid molecules can be designed manually or *in silico* for synthesis to encode mutant antibodies. The benefit of using gene synthesis methods is that the mutations can be effected so that the resulting nucleic acid molecules are in-frame and are "productive" as discussed herein above. Other methods of synthesis exist where randomization can be achieved during the gene synthesis. For example, a protocol has been developed by which synthesis of an oligonucleotide is "doped" with non-native phosphoramidites, resulting in randomization of the gene section targeted for random mutagenesis (Wang and Hoover (1997) J. Bacteriol., 179:5812-9). This method allows control of position selection while retaining a random substitution rate. Alternatively, mutagenesis can be effected through other molecular biology techniques. Generally, site-directed mutagenesis strategies can be employed.

Other current methods can be used to create mutant antibodies include, but are not limited to, error-prone polymerase chain reaction (Caldwell and Joyce (1992); Gram *et al.* (1992) *Proc. Natl. Acad. Sci.,* 89:3576-80); cassette mutagenesis in which the specific region to be optimized is replaced with a synthetically mutagenized oligonucleotide (Stemmer and Morris (1992) *Biotechniques*, 13:214-20); Arkin and Youvan (1992) *Proc. Natl. Acad. Sci.,* 89:7811-7815; Oliphant *et al.* (1986) Gene, 44:177-83; Hermes *et al.* (1990) *Proc. Natl. Acad. Sci,* 87:696-700); the use of mutator strains of hosts cells to add mutational frequency (Greener *et al.* (1997) *Mol. Biotechnol.*, 7:189-95); DNA shuffling (Crameri *et al.* (1998) *Nature*, 391:288-291; U.S. Patent No. 6,177,263; U.S. Patent No. 5,965,408; Ostermeier *et al.* (1999) Nat. Biotechnol., 17:1205-1209); and other random mutagenesis methods.

Antibodies provided herein can be generated or expressed as full-length antibodies or as antibodies that are less than full length, including, but not limited to Fabs, Fab hinge

fragment, scFv fragment, scFv tandem fragment and scFv hinge and scFv hinge(ΔE) fragments. Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies (see e.g. Morimoto et al. (1992) *Journal of Biochemical and Biophysical Methods*, 24:107-117; Brennance et al. (1985) *Science*, 229:81). Fragments also can be produced directly by recombinant host cells. Fab, Fv and scFv antibody fragments can all be expressed in and secreted from host cells, such as *E. coli*, thus allowing the facile production of large amounts of these fragments. Also, Fab'-SH fragments can be chemically coupled to form $F(ab')_2$ fragments (Carter et al. (1992) *Bio/Technology*, 10:163-167). According to another approach, $F(ab')_2$ fragments can be isolated directly from recombinant host cell culture. In other examples, the antibody of choice is a single chain Fv fragment (scFv) (see e.g. WO93/16185; US Patent No. 5,571,894 and U.S. Patent No. 5,587,458. 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 terminius of an sFv. The antibody fragment can also be a linear antibody (see e.g. U.S. Patent No. 5,641,870). Such linear antibody fragments can be monospecific or bispecific. Other techniques for the production of antibody fragments or antibody multimers are known to one of skill in the art.

For example, upon expression, antibody heavy and light chains pair by disulfide bond to form a full-length antibody or fragments thereof. For example, for expression of a full-length Ig, sequences encoding the V_H-C_H1-hinge-C_H2- C_H3 can be cloned into a first expression vector and sequences encoding the V_L-C_L domains can be cloned into a second expression vector. Upon co-expression with the second expression vector encoding the V_L-C_L domains, a full-length antibody is expressed. In another example, to generate a Fab, sequences encoding the V_H-C_H1 can be cloned into a first expression vector and sequences encoding the V_L-C_L domains can be cloned into a second expression vector. The heavy chain pairs with a light chain and a Fab monomer is generated. In this example, exemplary vectors include Plasmids A, C, D and E as described elsewhere herein. Sequences of C_H1, hinge, C_H2 and/or C_H3 of various IgG sub-types are known to one of skill in the art (see e.g. U.S. Published Application No. 20080248028; see also SEQ ID NO: 2922). Similarly, sequences of CL, lambda or kappa, also is known (see e.g. U.S. Published Application No. 20080248028; see also SEQ ID NOS: 2923-2924).

1. Vectors

Provided herein are vectors for expression of nucleic acid encoding variable heavy chain or a variable light chain. The nucleic acids encoding antibody polypeptides are typically cloned into a intermediate vector before transformation into prokaryotic or eukaryotic cells. Choice of vector can depend on the desired application. For example, after insertion of the nucleic acid, the vectors typically are used to transform host cells, for example, to amplify the antibody genes for replication and/or expression thereof. In such examples, a vector suitable for high level expression is used. In other cases, a vector is chosen that is compatible with display of the expressed polypeptide on the surface of the cell.

The nucleic acids encoding antibody polypeptides are typically cloned into a vector before transformation into prokaryotic or eukaryotic cells. Choice of vector can depend on the desired application. For example, after insertion of the nucleic acid, the vectors typically are used to transform host cells, for example, to amplify the antibody genes for replication and/or expression thereof. In such examples, a vector suitable for high level expression is used. Expression can be in any cell expression system known to one of skill in the art. Exemplary cells for expression include, but are not limited to, 293FS cells, HEK293-6E cells or CHO cells. Other expression vectors and host cells are described below.

Generally, nucleic acid encoding the heavy chain of an antibody is cloned into a vector and the nucleic acid encoding the light chain of an antibody is cloned into the vector. The genes can be cloned into a single vector for dual expression thereof, or into separate vectors. If desired, the vectors also can contain further sequences encoding additional constant region(s) or hinge regions to generate other antibody forms.

Many expression vectors are available and known to those of skill in the art for the expression of antibodies or portions thereof. The choice of an expression vector is influenced by the choice of host expression system. Such selection is well within the level of skill of the skilled artisan. In general, expression vectors can include transcriptional promoters and optionally enhancers, translational signals, and transcriptional and translational termination signals. Expression vectors that are used for stable transformation typically have a selectable marker which allows selection and maintenance of the transformed cells. In some cases, an origin of replication can be used to amplify the copy number of the vectors in the cells. Vectors also generally can contain additional nucleotide sequences operably linked to the ligated nucleic acid molecule (e.g. His tag, Flag tag). For purposes herein, vectors generally include sequences encoding the constant region. Thus, recombined antibodies or portions thereof also can be expressed as protein fusions. For example, a fusion can be generated to add additional functionality to a polypeptide. Examples of fusion proteins include, but are not limited to, fusions of a signal sequence, an epitope tag such as for localization, e.g. a his_6 tag

or a myc tag, or a tag for purification, for example, a GST fusion, and a sequence for directing protein secretion and/or membrane association.

For example, expression of the proteins can be controlled by any promoter/enhancer known in the art. Suitable bacterial promoters are well known in the art and described herein below. Other suitable promoters for mammalian cells, yeast cells and insect cells are well known in the art and some are exemplified below. Selection of the promoter used to direct expression of a heterologous nucleic acid depends on the particular application. Promoters which can be used include but are not limited to eukaryotic expression vectors containing the SV40 early promoter (Bernoist and Chambon, *Nature 290*:304-310 (1981)), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto *et al. Cell 22*:787-797 (1980)), the herpes thymidine kinase promoter (Wagner *et al.*, *Proc. Natl. Acad. Sci. USA 78*:1441-1445 (1981)), the regulatory sequences of the metallothionein gene (Brinster *et al.*, *Nature 296*:39-42 (1982)); prokaryotic expression vectors such as the β-lactamase promoter (Jay *et al.*, (1981) *Proc. Natl. Acad. Sci. USA 78*:5543) or the *tac* promoter (DeBoer *et al.*, *Proc. Natl. Acad. Sci. USA 80*:21-25 (1983)); see also "Useful Proteins from Recombinant Bacteria": in Scientific American *242*:79-94 (1980)); plant expression vectors containing the nopaline synthetase promoter (Herrara-Estrella *et al.*, *Nature 303*:209-213 (1984)) or the cauliflower mosaic virus 35S RNA promoter (Gardner *et al.*, *Nucleic Acids Res. 9*:2871 (1981)), and the promoter of the photosynthetic enzyme ribulose bisphosphate carboxylase (Herrera-Estrella *et al.*, *Nature 310*:115-120 (1984)); promoter elements from yeast and other fungi such as the Gal4 promoter, the alcohol dehydrogenase promoter, the phosphoglycerol kinase promoter, the alkaline phosphatase promoter, and the following animal transcriptional control regions that exhibit tissue specificity and have been used in transgenic animals: elastase I gene control region which is active in pancreatic acinar cells (Swift *et al.*, *Cell 38*:639-646 (1984); Ornitz *et al.*, *Cold Spring Harbor Symp. Quant. Biol. 50*:399-409 (1986); MacDonald, *Hepatology 7*:425-515 (1987)); insulin gene control region which is active in pancreatic beta cells (Hanahan *et al.*, *Nature 315*:115-122 (1985)), immunoglobulin gene control region which is active in lymphoid cells (Grosschedl *et al.*, *Cell 38*:647-658 (1984); Adams *et al.*, *Nature 318*:533-538 (1985); Alexander *et al.*, *Mol. Cell Biol. 7*:1436-1444 (1987)), mouse mammary tumor virus control region which is active in testicular, breast, lymphoid and mast cells (Leder *et al.*, *Cell 45*:485-495 (1986)), albumin gene control region which is active in liver (Pinckert *et al.*, *Genes and Devel. 1*:268-276 (1987)), alpha-fetoprotein gene control region which is active in liver (Krumlauf *et al.*, *Mol. Cell. Biol. 5*:1639-1648 (1985); Hammer *et al.*, *Science 235*:53-58 1987)), alpha-1 antitrypsin gene control region which is active in liver (Kelsey *et al.*, *Genes and Devel. 1*:161-171 (1987)),

beta globin gene control region which is active in myeloid cells (Magram *et al.*, *Nature 315*:338-340 (1985); Kollias *et al.*, *Cell 46*:89-94 (1986)), myelin basic protein gene control region which is active in oligodendrocyte cells of the brain (Readhead *et al.*, *Cell 48*:703-712 (1987)), myosin light chain-2 gene control region which is active in skeletal muscle (Shani, *Nature 314*:283-286 (1985)), and gonadotrophic releasing hormone gene control region which is active in gonadotrophs of the hypothalamus (Mason *et al.*, *Science 234*:1372-1378 (1986)).

In addition to the promoter, the expression vector typically contains a transcription unit or expression cassette that contains all the additional elements required for the expression of the antibody, or portion thereof, in host cells. A typical expression cassette contains a promoter operably linked to the nucleic acid sequence encoding the germline antibody chain and signals required for efficient polyadenylation of the transcript, ribosome binding sites and translation termination. Additional elements of the cassette can include enhancers. In addition, the cassette typically contains a transcription termination region downstream of the structural gene to provide for efficient termination. The termination region can be obtained from the same gene as the promoter sequence or can be obtained from different genes.

Some expression systems have markers that provide gene amplification such as thymidine kinase and dihydrofolate reductase. Alternatively, high yield expression systems not involving gene amplification are also suitable, such as using a baculovirus vector in insect cells, with a nucleic acid sequence encoding a germline antibody chain under the direction of the polyhedron promoter or other strong baculovirus promoter.

Exemplary expression vectors include any mammalian expression vector such as, for example, pCMV. For bacterial expression, such vectors include pBR322, pUC, pSKF, pET23D, and fusion vectors such as MBP, GST and LacZ. Exemplary of such a vector are bacterial expression vectors such as, for example, plasmid A, plasmid C, plasmid D and plasmid E, described herein. Other eukaryotic vectors, for example any containing regulatory elements from eukaryotic viruses can be used as eukaryotic expression vectors. These include, for example, SV40 vectors, papilloma virus vectors, and vectors derived from Epstein-Bar virus. Other exemplary eukaryotic vectors include pMSG, pAV009/A+, pMT010/A+, pMAMneo-5, baculovirus pDSCE, and any other vector allowing expression of proteins under the direction of the CMV promoter, SV40 early promoter, SV40 late promoter, metallothionein promoter, murine mammary tumor virus promoter, Rous sarcoma virus promoter, polyhedron promoter, or other promoters shown effective for expression in eukaryotes.

Vectors can be provided that contain a sequence of nucleotides that encodes a constant region of an antibody operably linked to the nucleic acid sequence encoding the

variable region of the antibody. The vector can include the sequence for one or all of a CH1, CH2, CH3 or CH4 and/or CL. Generally, such as for expression of Fabs, the vector contains the sequence for a CH1 or CL. In one example, nucleic acid encoding the heavy chain of an antibody, is ligated into a first expression vector and nucleic acid encoding the light chain of an antibody, is ligated into a second expression vector. The expression vectors can be the same or different, although generally they are sufficiently compatible to allow comparable expression of proteins (heavy and light chain) therefrom. The first and second expression vectors are generally co-transfected into host cells, typically at a 1:1 ratio. Exemplary of vectors include, but are not limited to, pγ1HC and pκLC (Tiller et al. (2008) *J Immunol. Methods*, 329:112-24). Other expression vectors include the light chain expression vector pAG4622 and the heavy chain expression vector pAH4604 (Coloma et al. (1992) *J Immunol. Methods*, 152:89-104). The pAG4622 vector contains the genomic sequence encoding the C-region domain of the human κ L chain and the gpt selectable marker. The pAH4604 vectors contain the hisD selectable marker and sequences encoding the human H chain γ1 C-region domain. In another example, the heavy and light chain can be cloned into a single vector that has expression cassettes for both the heavy and light chain. Other exemplary expression vectors include Plasmids A, C, D and E, described elsewhere herein.

For purposes herein, vectors are provided that contain a sequence of nucleotides that encodes a constant region of an antibody operably linked to the nucleic acid sequence encoding the recombined variable region of the antibody. The vector can include the sequence for one or all of a CH1, CH2, hinge, CH3 or CH4 and/or CL. Generally, such as for expression of Fabs, the vector contains the sequence for a CH1 (amino acids 1-103 of SEQ ID NO:2922) or CL (for kappa light chains, see SEQ ID NO:2923; for lambda light chains, see SEQ ID NO:2924). The sequences of constant regions or hinge regions are known to one of skill in the art (see e.g. U.S. Published Application No. 20080248028 and SEQ ID NOS:2922-2924, including CH1 (amino acids 1-103 of SEQ ID NO:2922), IgG1 hinge region (amino acids 104-119 of SEQ ID NO:2922), IgG1 CH2 (amino acids 120-223 of SEQ ID NO:2922), IgG1 CH3 (amino acids 224-330 of SEQ ID NO:2922), CL kappa (SEQ ID NO:2923) and CL lambda (SEQ ID NO:2924). Exemplary of such vectors containing a heavy chain constant region gene (e.g. CH1) are plasmids A and D, described herein. Exemplary of such vectors containing a light chain constant region genes are plasmids C and E, described herein.

Exemplary plasmid vectors for transformation of *E. coli* cells, include, for example, the ColE1 replication vectors described herein. Several features common to all these vectors include (a) a pBAD inducible promoter; (b) an AraC gene, which controls the pBAD promoter; (c) a synthetic ribosomal binding site (RBS) for efficient translation; (d) a ColE1

origin of replication, allowing for high copy expression; (e) a STII leader sequence, allowing for expressed proteins to be translocated to the periplasm; (f) a f1 origin of replication; and (g) a gene for conferring antibiotic resistance. Such plasmids include plasmid A (SEQ ID NO:84), plasmid C (SEQ ID NO:86), plasmid D (SEQ ID NO:85) and plasmid E (SEQ ID NO:87). Plasmid A and Plasmid D are utilized for expression of heavy chain antibody genes in as they contain a gene for the heavy chain constant region (CH1) operably linked to the inserted gene for the heavy chain variable region. The vectors contain NheI and NcoI restriction sites to allow for cloning of the recombined antibody genes described herein. Both vectors contain a pUC origin of replication, a ColE1 type origin of replication, and an aminoglycoside phosphotransferase gene conferring kanamycin resistance. Plasmid A contains a $(His)_6$ Tag and a Flag Tag for protein purification. Plasmid D contains both a $(His)_6$ Tag and a Flag Tag, and an additional LPETG tag, which allows for covalent attachment of the resulting protein using a sortase. Plasmid C and Plasmid E are utilized for expression of light chain antibody genes in as they contain a gene for the light chain constant region (CL) operably linked to the inserted gene for the light chain variable region. Plasmid C is specific for kappa light chains and contains BseWI and NcoI restriction sites to allow for cloning of the recombined antibody genes described herein. Plasmid E is specific for lambda light chains and contains AcrII and NcoI restriction sites to allow for cloning of the recombined antibody genes described herein. Both vectors contain a 3.3 origin of replication, a ColE1 type origin of replication, and a gene conferring chloramphenicol resistance. The vectors described above are designed to be utilized in a dual vector system, in which a light chain vector and a heavy chain vector are co-transformed. Thus, they contain two different but compatible ColE1 origins of replication utilized, one for heavy chains and one light chain. This allows for efficient expression of both chains of the antibody when the vectors are co-transformed and expressed.

Any methods known to those of skill in the art for the insertion of DNA fragments into a vector can be used to construct expression vectors containing a nucleic acid encoding an antibody chain. These methods can include *in vitro* recombinant DNA and synthetic techniques and *in vivo* recombinants (genetic recombination). The insertion into a cloning vector can, for example, be accomplished by ligating the DNA fragment into a cloning vector which has complementary cohesive termini. If the complementary restriction sites used to fragment the DNA are not present in the cloning vector, the ends of the DNA molecules can be enzymatically modified. Alternatively, any site desired can be produced by ligating nucleotide sequences (linkers) onto the DNA termini; these ligated linkers can contain

specific chemically synthesized nucleic acids encoding restriction endonuclease recognition sequences.

2. Cells and Expression Systems

Cells containing the vectors also are provided. Generally, any cell type that can be engineered to express heterologous DNA and has a secretory pathway is suitable. Expression hosts include prokaryotic and eukaryotic organisms such as bacterial cells (e.g. *E. coli*), yeast cells, fungal cells, Archea, plant cells, insect cells and animal cells including human cells. Expression hosts can differ in their protein production levels as well as the types of post-translational modifications that are present on the expressed proteins. Further, the choice of expression host is often related to the choice of vector and transcription and translation elements used. For example, the choice of expression host is often, but not always, dependent on the choice of precursor sequence utilized. For example, many heterologous signal sequences can only be expressed in a host cell of the same species (i.e., an insect cell signal sequence is optimally expressed in an insect cell). In contrast, other signal sequences can be used in heterologous hosts such as, for example, the human serum albumin (hHSA) signal sequence which works well in yeast, insect, or mammalian host cells and the tissue plasminogen activator pre/pro sequence which has been demonstrated to be functional in insect and mammalian cells (Tan *et al.*, (2002) *Protein Eng.* 15:337). The choice of expression host can be made based on these and other factors, such as regulatory and safety considerations, production costs and the need and methods for purification. Thus, the vector system must be compatible with the host cell used.

Expression in eukaryotic hosts can include expression in yeasts such as *Saccharomyces cerevisiae* and *Pichia pastoris*, insect cells such as *Drosophila* cells and *lepidopteran* cells, plants and plant cells such as tobacco, corn, rice, algae, and lemna. Eukaryotic cells for expression also include mammalian cells lines such as Chinese hamster ovary (CHO) cells or baby hamster kidney (BHK) cells. Eukaryotic expression hosts also include production in transgenic animals, for example, including production in serum, milk and eggs.

Recombinant molecules can be introduced into host cells via, for example, transformation, transfection, infection, electroporation and sonoporation, so that many copies of the gene sequence are generated. Generally, standard transfection methods are used to produce bacterial, mammalian, yeast, or insect cell lines that express large quantity of antibody chains, which is then purified using standard techniques (see e.g., Colley *et al.* (1989) J. Biol. Chem., 264:17619-17622; Guide to Protein Purification, in Methods in Enzymology, vol. 182 (Deutscher, ed.), 1990). Transformation of eukaryotic and prokaryotic

cells are performed according to standard techniques (see, e.g., Morrison (1977) J. Bact. 132:349-351; Clark-Curtiss and Curtiss (1983) Methods in Enzymology, 101, 347-362). For example, any of the well-known procedures for introducing foreign nucleotide sequences into host cells can be used. These include the use of calcium phosphate transfection, polybrene, protoplast fusion, electroporation, biolistics, liposomes, microinjection, plasma vectors, viral vectors and any other the other well known methods for introducing cloned genomic DNA, cDNA, synthetic DNA or other foreign genetic material into a host cell. Generally, for purposes herein, host cells are transfected with a first vector encoding at least a VH chain and a second vector encoding at least a VL chain. Thus, it is only necessary that the particular genetic engineering procedure used be capable of successfully introducing at least both genes into the host cell capable of expressing germline, or modified form thereof, antibody polypeptide.

Transformation of host cells with recombinant DNA molecules that incorporate the isolated recombined variable region gene, cDNA, or synthesized DNA sequence enables generation of multiple copies of the gene. Thus, the gene can be obtained in large quantities by growing transformants, isolating the recombinant DNA molecules from the transformants and, when necessary, retrieving the inserted gene from the isolated recombinant DNA. Generally, After the expression vector is introduced into the cells, the transfected cells are cultured under conditions favoring expression of the germline chain, which is recovered from the culture using standard purification techniques identified below.

Antibodies and portions thereof can be produced using a high throughput approach by any methods known in the art for protein production including *in vitro* and *in vivo* methods such as, for example, the introduction of nucleic acid molecules encoding antibodies or portions thereof into a host cell or host animal and expression from nucleic acid molecules encoding antibodies *in vitro*. Prokaryotes, especially *E. coli*, provide a system for producing large amounts of antibodies or portions thereof, and are particularly desired in applications of high-throughput expression and purification of proteins. Transformation of *E. coli* is a simple and rapid technique well known to those of skill in the art. *E. coli* host strains for high throughput expression include, but are not limited to, BL21 (EMD Biosciences) and LMG194 (ATCC). Exemplary of such an *E. coli* host strain is BL21. Vectors for high throughput expression include, but are not limited to, pBR322 and pUC vectors. Exemplary of such vectors are the vectors described herein, including plasmid A, plasmid C, plasmid D and plasmid E. Automation of expression and purification can facilitate high-throughput expression. For example, use of a Piccolo™ system (Wollerton *et al.* (2006) JALA, 11:291-

303), a fully automatic system that combines cell culture with automated harvesting, lysing and purification units, or other similar robotic system can be employed.

a. Prokaryotic Expression

Prokaryotes, especially *E. coli*, provide a system for producing large amounts of antibodies or portions thereof. Transformation of *E. coli* is a simple and rapid technique well known to those of skill in the art. Expression vectors for *E. coli* can contain inducible promoters that are useful for inducing high levels of protein expression and for expressing proteins that exhibit some toxicity to the host cells. Examples of inducible promoters include the lac promoter, the trp promoter, the hybrid tac promoter, the T7 and SP6 RNA promoters and the temperature regulated λP_L promoter.

Antibodies or portions thereof can be expressed in the cytoplasmic environment of *E. coli*. The cytoplasm is a reducing environment and for some molecules, this can result in the formation of insoluble inclusion bodies. Reducing agents such as dithiothreitol and β-mercaptoethanol and denaturants (e.g., such as guanidine-HCl and urea) can be used to resolubilize the proteins. An exemplary alternative approach is the expression of antibodies or fragments thereof in the periplasmic space of bacteria which provides an oxidizing environment and chaperonin-like and disulfide isomerases leading to the production of soluble protein. Typically, a leader sequence is fused to the protein to be expressed which directs the protein to the periplasm. The leader is then removed by signal peptidases inside the periplasm. There are three major pathways to translocate expressed proteins into the periplasm, namely the Sec pathway, the SRP pathway and the TAT pathway. Examples of periplasmic-targeting leader sequences include the pelB leader from the pectate lyase gene, the StII leader sequence, and the DsbA leader sequence. An exemplary leader sequence is a DsbA leader sequence. In some cases, periplasmic expression allows leakage of the expressed protein into the culture medium. The secretion of proteins allows quick and simple purification from the culture supernatant. Proteins that are not secreted can be obtained from the periplasm by osmotic lysis. Similar to cytoplasmic expression, in some cases proteins can become insoluble and denaturants and reducing agents can be used to facilitate solubilization and refolding. Temperature of induction and growth also can influence expression levels and solubility. Typically, temperatures between 25 °C and 37 °C are used. Mutations also can be used to increase solubility of expressed proteins. Typically, bacteria produce aglycosylated proteins. Thus, if proteins require glycosylation for function, glycosylation can be added *in vitro* after purification from host cells.

b. Yeast

Yeasts such as *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Yarrowia lipolytica*, *Kluyveromyces lactis,* and *Pichia pastoris* are useful expression hosts for recombined antibodies or portions thereof. Yeast can be transformed with episomal replicating vectors or by stable chromosomal integration by homologous recombination. Typically, inducible promoters are used to regulate gene expression. Examples of such promoters include AOX1, GAL1, GAL7, and GAL5 and metallothionein promoters such as CUP1. Expression vectors often include a selectable marker such as LEU2, TRP1, HIS3, and URA3 for selection and maintenance of the transformed DNA. Proteins expressed in yeast are often soluble. Co-expression with chaperonins such as Bip and protein disulfide isomerase can improve expression levels and solubility. Additionally, proteins expressed in yeast can be directed for secretion using secretion signal peptide fusions such as the yeast mating type alpha-factor secretion signal from Saccharomyces cerevisae and fusions with yeast cell surface proteins such as the Aga2p mating adhesion receptor or the *Arxula adeninivoran*s glucoamylase. A protease cleavage site such as for the Kex-2 protease, can be engineered to remove the fused sequences from the expressed polypeptides as they exit the secretion pathway. Yeast also is capable of glycosylation at Asn-X-Ser/Thr motifs.

c. Insects

Insect cells, particularly using baculovirus expression, are useful for expressing antibodies or portions thereof. Insect cells express high levels of protein and are capable of most of the post-translational modifications used by higher eukaryotes. Baculovirus have a restrictive host range which improves the safety and reduces regulatory concerns of eukaryotic expression. Typical expression vectors use a promoter for high level expression such as the polyhedrin promoter and p10 promoter of baculovirus. Commonly used baculovirus systems include the baculoviruses such as *Autographa californica* nuclear polyhedrosis virus (AcNPV), and the *Bombyx mori* nuclear polyhedrosis virus (BmNPV) and an insect cell line such as Sf9 derived from *Spodoptera frugiperda* and TN derived from *Trichoplusia ni.* For high-level expression, the nucleotide sequence of the molecule to be expressed is fused immediately downstream of the polyhedrin initiation codon of the virus. To generate baculovirus recombinants capable of expressing human antibodies, a dual-expression transfer, such as pAcUW51 (PharMingen) is utilized. Mammalian secretion signals are accurately processed in insect cells and can be used to secrete the expressed protein into the culture medium

An alternative expression system in insect cells is the use of stably transformed cells. Cell lines such as Sf9 derived cells from *Spodoptera frugiperda* and TN derived cells from *Trichoplusia ni* can be used for expression. The baculovirus immediate early gene promoter

IE1 can be used to induce consistent levels of expression. Typical expression vectors include the pIE1-3 and pI31-4 transfer vectors (Novagen). Expression vectors are typically maintained by the use of selectable markers such as neomycin and hygromycin.

d. Mammalian Cells

Mammalian expression systems can be used to express antibodies or portions thereof. Expression constructs can be transferred to mammalian cells by viral infection such as adenovirus or by direct DNA transfer such as liposomes, calcium phosphate, DEAE-dextran and by physical means such as electroporation and microinjection. Expression vectors for mammalian cells typically include an mRNA cap site, a TATA box, a translational initiation sequence (Kozak consensus sequence) and polyadenylation elements. Such vectors often include transcriptional promoter-enhancers for high-level expression, for example the SV40 promoter-enhancer, the human cytomegalovirus (CMV) promoter and the long terminal repeat of Rous sarcoma virus (RSV). These promoter-enhancers are active in many cell types. Tissue and cell-type promoters and enhancer regions also can be used for expression. Exemplary promoter/enhancer regions include, but are not limited to, those from genes such as elastase I, insulin, immunoglobulin, mouse mammary tumor virus, albumin, alpha fetoprotein, alpha 1 antitrypsin, beta globin, myelin basic protein, myosin light chain 2, and gonadotropic releasing hormone gene control. Selectable markers can be used to select for and maintain cells with the expression construct. Examples of selectable marker genes include, but are not limited to, hygromycin B phosphotransferase, adenosine deaminase, xanthine-guanine phosphoribosyl transferase, aminoglycoside phosphotransferase, dihydrofolate reductase and thymidine kinase. Antibodies are typically produced using a NEO^R/G418 system, a dihydrofolate reductase (DHFR) system or a glutamine synthetase (GS) system. The GS system uses joint expression vectors, such as pEE12/pEE6, to express both heavy chain and light chain. Fusion with cell surface signaling molecules such as TCR-ζ and $Fc_\varepsilon RI$-γ can direct expression of the proteins in an active state on the cell surface.

Many cell lines are available for mammalian expression including mouse, rat human, monkey, chicken and hamster cells. Exemplary cell lines include but are not limited to CHO, Balb/3T3, HeLa, MT2, mouse NS0 (nonsecreting) and other myeloma cell lines, hybridoma and heterohybridoma cell lines, lymphocytes, fibroblasts, Sp2/0, COS, NIH3T3, HEK293, 293S, 2B8, and HKB cells. Cell lines also are available adapted to serum-free media which facilitates purification of secreted proteins from the cell culture media. One such example is the serum free EBNA-1 cell line (Pham *et al.*, (2003) *Biotechnol. Bioeng. 84*:332-42.)

e. Plants

Transgenic plant cells and plants can be used to express proteins such as any antibody or portion thereof described herein. Expression constructs are typically transferred to plants using direct DNA transfer such as microprojectile bombardment and PEG-mediated transfer into protoplasts, and with agrobacterium-mediated transformation. Expression vectors can include promoter and enhancer sequences, transcriptional termination elements and translational control elements. Expression vectors and transformation techniques are usually divided between dicot hosts, such as *Arabidopsis* and tobacco, and monocot hosts, such as corn and rice. Examples of plant promoters used for expression include the cauliflower mosaic virus CaMV 35S promoter, the nopaline synthase promoter, the ribose bisphosphate carboxylase promoter and the maize ubiquitin-1 (*ubi*-1) promoter promoters. Selectable markers such as hygromycin, phosphomannose isomerase and neomycin phosphotransferase are often used to facilitate selection and maintenance of transformed cells. Transformed plant cells can be maintained in culture as cells, aggregates (callus tissue) or regenerated into whole plants. Transgenic plant cells also can include algae engineered to produce proteases or modified proteases (see for example, Mayfield *et al.* (2003) *PNAS 100*:438-442). Because plants have different glycosylation patterns than mammalian cells, this can influence the choice of protein produced in these hosts.

3. Purification

Antibodies and portions thereof are purified by any procedure known to one of skill in the art. The antibodies generated or used by the methods herein can be purified to substantial purity using standard protein purification techniques known in the art including but not limited to, SDS-PAGE, size fraction and size exclusion chromatography, ammonium sulfate precipitation, chelate chromatography, ionic exchange chromatography or column chromatography. For example, antibodies can be purified by column chromatography. Exemplary of a method to purify antibodies is by using column chromatography, wherein a solid support column material is linked to Protein G, a cell surface-associated protein from *Streptococcus*, that binds immunoglobulins with high affinity. The antibodies can be purified to 60%, 70%, 80% purity and typically at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% purity. Purity can be assessed by standard methods such as by SDS-PAGE and coomassie staining.

Methods for purification of antibodies or portions thereof from host cells depend on the chosen host cells and expression systems. For secreted molecules, proteins are generally purified from the culture media after removing the cells. For intracellular expression, cells can be lysed and the proteins purified from the extract. When transgenic organisms such as transgenic plants and animals are used for expression, tissues or organs can be used as starting

material to make a lysed cell extract. Additionally, transgenic animal production can include the production of polypeptides in milk or eggs, which can be collected, and if necessary further the proteins can be extracted and further purified using standard methods in the art.

When antibodies are expressed by transformed bacteria in large amounts, typically after promoter induction, although expression can be constitutive, the polypeptides can form insoluble aggregates. There are several protocols that are suitable for purification of polypeptide inclusion bodies known to one of skill in the art. Numerous variations will be apparent to those of skill in the art.

For example, in one method, the cell suspension is generally centrifuged and the pellet containing the inclusion bodies resuspended in buffer which does not dissolve but washes the inclusion bodies, e.g., 20 mM Tris-HCL (pH 7.2), 1 mM EDTA, 150 mM NaCl and 2% Triton-X 100, a non-ionic detergent. It can be necessary to repeat the wash step to remove as much cellular debris as possible. The remaining pellet of inclusion bodies can be resuspended in an appropriate buffer (e.g., 20 mM sodium phosphate, pH 6.8, 150 mM NaCl). Other appropriate buffers are apparent to those of skill in the art.

Alternatively, antibodies can be purified from bacteria periplasm. Where the polypeptide is exported into the periplasm of the bacteria, the periplasmic fraction of the bacteria can be isolated by cold osmotic shock in addition to other methods known to those of skill in the art. For example, in one method, to isolate recombinant polypeptides from the periplasm, the bacterial cells are centrifuged to form a pellet. The pellet is resuspended in a buffer containing 20% sucrose. To lyse the cells, the bacteria are centrifuged and the pellet is resuspended in ice-cold 5 mM $MgSO_4$ and kept in an ice bath for approximately 10 minutes. The cell suspension is centrifuged and the supernatant decanted and saved. The recombinant polypeptides present in the supernatant can be separated from the host proteins by standard separation techniques well known to those of skill in the art. These methods include, but are not limited to, the following steps: solubility fractionation, size differential filtration, and column chromatography.

G. Anti-DLL4 Activator/Modulator Antibodies and Uses Thereof

Provided herein are anti-DLL4 multimer antibodies that specifically bind to human Delta-like ligand 4 (DLL4) DLL4 and that are activator/modulators of DLL4 activity. Thus, the multimer antibodies can be used as antiangiogenic therapeutics to treat diseases or disorders characterized by excessive or aberrant angiogenesis, such as for example, cancer or macular degeneration.

1. DLL4

a. Structure

DLL4 (set forth in SEQ ID NO:2904; and encoded by a sequence of nucleotides set forth in SEQ ID NO:2905) is a transmembrane protein ligand for Notch transmembrane receptors. The extracellular region contains 8 EGF-like repeats, as well as a DSL domain that is conserved among all Notch ligands and is necessary for receptor binding. The protein also contains a transmembrane region, and a cytoplasmic tail lacking any catalytic motifs. Human DLL4 is a 685 amino acid protein and contains the following domains corresponding to amino acids set forth in SEQ ID NO:2904: signal peptide (amino acids 1-25); MNNL (amino acids 26-92); DSL (amino acids 155-217); EGF-Like 1 (EGF1; amino acids 221-251); EGF-Like 2 (EGF2; amino acids 252-282); EGF-Like 3 (EGF3; amino acids 284-322); EGF-Like 4 (EGF4; amino acids 324-360); EGF-Like 5 (EGF5; amino acids 366-400); EGF-Like 6 (EGF6; amino acids 402-438); EGF-Like 7 (EGF7; amino acids 440-476); EGF-Like 8 (EGF8; amino acids 480-518); transmembrane (amino acids 529-551); and cytoplasmic domain (amino acids 553-685).

b. Expression

DLL4 is expressed widely in a variety of tissues, but its expression is predominantly localized to the vasculature. It is required for normal vascular development and is expressed on tumor vessels. It is upregulated in blood vessels during tumor angiogenesis and expression is dependent on VEGF signaling. DLL4 also is expressed on activated macrophages exposed to proinflammatory stimuli such as lipopolysaccharide, interleukin-1β, Toll-like receptor 4 ligands and other proinflammatory stimuli and it's signaling through the Notch pathway plays a role in inflammatory states characterized by macrophage activation (Fung *et al.* (2007) *Circulation*, 115: 2948-2956).

c. Function

DLL4 binds to Notch receptors. The evolutionary conserved Notch pathway is a key regulator of many developmental processes as well as postnatal self-renewing organ systems. From invertebrates to mammals, Notch signaling guides cells through a myriad of cell fate decisions and incluences proliferation, differentiation and apoptosis (Miele and Osborne (1999) *J Cell Physiol.*, 181:393-409). The Notch family is made up of structurally conserved cell surface receptors that are activated by membrane bound ligands of the DSL gene family (named for Delta and Serrate from Drosophila and Lag-2 from *C. elegans*). Mammals have four receptors (Notch 1, Notch 2, Notch 3 and Notch 4) and five ligands (Jag 1, Jag 2, DLL1, DLL3, and DLL4). Upon activation by ligands presented on neighboring cells, Notch receptors undergo successive proteolytic cleavages; an extracellular cleavage mediated by an ADAM protease and a cleavage within the trnamembrane domain mediated by gamma secretase. This leads to the release of the Notch Intra-Cellular Domain (NICD), which

translocates into the nucleus and forms a transcriptional complex with the DNA binding protein, RBP-Jk (also known as CSL for CBF1/Su(H)/Lag-1) and other transcriptional cofactors. The primary target genes of Notch activation include the HES (Hairy/Enhance of Split) gene family and HES-related genes (Hey, CHF, HRT, HESR), which in turn regulate the downstream transcriptional effectors in a tissue and cell-type specific manner (Iso et al. (2003) *J Cell Physiol.*, 194:237-255; Li and Harris (2005) *Cancer Cell*, 8:1-3).

Signaling by Notch receptors implicate a variety of cellular processes including, but not limited to, the normal maintenance and leukemic transformation of hematopoietic stem cells (HSCs; Kopper & Hajdu (2004) *Pathol. Oncol. Res.*, 10:69-73); maintenance of neural stem cells including in their normal maintenance as well as in brain cancers (Kopper & Hajdu (2004) *Pathol. Oncol. Res.*, 10:69-73; Purow et al. (2005) *Cancer Res.* 65:2353-63; Hallahan et al., (2004) *Cancer Res.* 64:7794-800); generation of a number of human cancers including in lymphoblastic leukemia/lymphoma (Ellisen et al. (1991) *Cell*, 66:649-61; Robey et al. (1996) *Cell,* 87:483-92; Pear et al. (1996) *J. Exp. Med.* 183:2283-91; Yan et al. (2001) *Blood* 98:3793-9; Bellavia et al. (2000) *EMBO J.* 19:3337-48; Pear & Aster (2004) *Curr. Opin. Hematol.*, 11:416-33); breast cancer (Gallahan & Callahan (1987) *J. Virol.*, 61:66-74; Brennan & Brown (2003) *Breast Cancer Res.*, 5:69; Politi et al. (2004) *Semin. Cancer Biol.*, 14:341-7; Weijzen et al. (2002) *Nat. Med.*, 8:979-86; Parr et al. (2004) *Int. J. Mol. Med.*, 14:779-86); cervical cancer (Zagouras et al. (1995) *PNAS*, 92:6414-8); renal cell carcinomas (Rae et al (2000) *Int. J. Cancer*, 88:726-32); head and neck squamous cell carcinomas (Leethanakul et al (2000) *Oncogene*, 19:3220-4); endometrial cancers (Suzuki *et al.* (2000) *Int. J. Oncol.*, 17:1131-9); and neuroblastomas (van Limpt *et al.* (2000) *Med. Pediatr. Oncol.*, 35:554-8). The Notch pathway also is involved in multiple aspects of vascular development including proliferation, migration, smooth muscle differentiation, angiogenesis and arterial-venous differentiation (Iso *et al.* (2003) *Arterioscler. Thromb. Vasc. Biol.* 23: 543).

The Notch ligand DLL4, which interacts with Notch-1 (Uniprot accession No. P46531; SEQ ID NO:2906) and Notch-4 receptors (Uniprot accession No. Q99466; SEQ ID NO:2907), is expressed predominantly in the vasculature. Studies assessing the effects of overexpression of DLL4 have shown that DLL4 is a negative regulator of angiogenesis, endothelial cell proliferation, migration and vessel branching (see e.g. Trindade et al. (2008) Blood 1:112). One explanation for the antiangiogenic activity of DLL4 is that it is a VEGF responsive gene and acts as a negative regulator of VEGF signaling, which is a proangiogenic factor. Thus, targeting the activation of DLL4 promotes the antiangiogenic activity of DLL4.

In contrast, blocking DLL4 is associated with nonproductive angiogensis. Although DLL4 increases angiogenesis characterized by sprouting and branching of blood vessels, it

also is associated with a decrease in vessel function, thereby resulting in decreased tumor growth (Ridgway *et al.* (2006) *Nature*, 444:1083; Noguera-Troise *et al.* (2006) *Nature*, 444:1032). Accordingly, DLL4 function is associated with deregulated angiogenesis by uncoupling of tumor growth from tumor vascular density. Thus, blocking DLL4 signaling effectively reduces tumor growth by disrupting productive angiogenesis. Accordingly, targeting the inhibition of DLL4 also can be used to treat tumors undergoing angiogenesis (see e.g. International PCT application No. WO2009/085209).

2. Activator/Modulator Anti-DLL4 Multimer Antibodies

Provided herein are antibodies or antibody fragments thereof that are activator/modulators of DLL4 activity. The antibodies activate or increase the activity of DLL4, and thereby act as anti-angiogenic agents. For example, the antibody multimers provided herein increase the activity of DLL4-mediated receptor activation, for example activation of DLL4-mediated Notch -1 or Notch-4 signaling, compared to activation in the absence of the antibody multimer. DLL4-mediated activity is increased at least 1.1-fold, for example, between or about 1.2-fold to 5-fold, such as 1.1-fold, 1.2-, 1.3-, 1.4-, 1.5-, 1.6-, 1.7-, 1.8-, 1.9-, 2.0-, 2.5-, 3.0-, 3.5-, 4.0-, 4.5-, 5-fold or more in the presence of the antibody multimer compared to activation in its absence. Thus, the antibodies can be used to treat angiogenic diseases or disorders. In some examples, the antibodies provided herein are agonists. In other examples, the antibodies provided herein are activator/modulators of DLL4 by activating Notch signaling.

The antibody multimers provided herein exhibit rapid on/off kinetics for their binding site on DLL4. In particular, the antibody exhibits a fast k_{off}. For example, when assessed as a monomeric Ig fragment, antibodies provided herein have a k_{off} that is or is about between 1 s^{-1} to 5 x 10^{-2} s^{-1}, for example, 0.5 s^{-1} to 0.01 s^{-1}, such as for example, at or about 0.1 s^{-1}. For example, the k_{off} of antibodies provided herein, when assessed in Fab form, is at or about 5 x 10^{-2} s^{-1}, 4 x 10^{-2} s^{-1}, 3 x 10^{-2} s^{-1}, 2 x 10^{-2} s^{-1}, 1 x 10^{-2} s^{-1}, 0.02 s^{-1}, 0.03 s^{-1}, 0.04 s^{-1}, 0.05 s^{-1}, 0.06 s^{-1}, 0.07 s^{-1}, 0.08 s^{-1}, 0.09 s^{-1}, 0.1 s^{-1}, 0.2 s^{-1}, 0.3 s^{-1}, 0.4 s^{-1}, 0.5 s^{-1}, 0.6 s^{-1}, 0.7 s^{-1}, 0.8 s^{-1}, 0.9 s^{-1}, 1 s^{-1} or faster, so long as the antibody multimer specifically binds to DLL4. In some examples, the antibodies provided herein exhibit a dissociation half-life ($t_{1/2}$), when assessed as a monomeric Ig fragment, that is between 0.5 seconds (s) to 150 s, for example, 1 s to 100 s, 5 s to 50 s or 5 s to 10 s. For example, the $t_{1/2}$ of antibodies provided herein, when assessed as a monomeric Ig fragment, is or is about 1 s, 2 s, 3 s, 4 s, 5 s, 6 s, 7 s, 8 s, 9 s, 10 s, 20 s, 30 s, 40 s , 50 s, 60 s, 70 s, 80 s, 90 s, 100 s, 110 s, 120 s, 130 s, 140 s or 150 s. Methods to determine kinetic rate constants of antibodies are known to one of skill in the art. For example, surface plasmon resonance using Biacore™ instrument can be used (BiaCore Life

Science; GE Healthcare). Services offering Biacore instrumentation and other instrumentations are available (Biosensor Tools; Salt Lake City, UT; biosensortools.com/index.php).

Typically, antibody multimers provided herein exhibit a generally low binding affinity. For example, when assessed as a monomeric Ig fragment, antibodies provided herein exhibit a binding affinity that is 10^{-8} M or lower binding affinity. For example, the binding affinity is between 10^{-6} M to 10^{-8} M, such as between 4 x 10^{-6} M to 10^{-8} M, for example between 1 x10^{-7} M to 10^{-8} M. For example, the binding affinity of antibodies provided herein, as a monomeric Ig fragment, is at or about 1 x 10^{-6} M, 2 x 10^{-6} M , 3 x 10^{-6} M , 4 x 10^{-6} M, 5 x 10^{-6} M, 6 x 10^{-6} M, 7 x 10^{-6} M, 8 x 10^{-6} M, 9 x 10^{-6} M, 1 x 10^{-7} M, 2 x 10^{-7} M, 3 x 10^{-7} M, 4 x 10^{-7} M, 5 x 10^{-7} M, 6 x 10^{-7} M, 7 x 10^{-7} M, 8 x 10^{-7} M, 9 x 10^{-7} M or 1 x 10^{-8} M. Methods to assess binding affinity are known to one of skill in the art and are described elsewhere herein in Section E.

The antibodies provided herein are multimers, such that they contain at least two antigen-binding sites. Generally, the antibodies provided herein contain at least two variable heavy chain, or a sufficient portion thereof to bind antigen; and two variable light chains, or a sufficient portion thereof to bind antigen that are associated by a multimerization domain. The multimers can be dimers, trimers or higher-order multimers of monomeric immunoglobulin molecules. The multimers include those that are bivalent, trivalent, tetravalent, pentavalent, hexavalent, heptavalent, or greater valency (i.e., containing 2, 3, 4, 5, 6, 7 or more antigen-binding sites). For example, dimers of whole immunoglobulin molecules or of F(ab')2 fragments are tetravalent, whereas dimers of Fab fragments or scFv molecules are bivalent.

Individual antibodies within a multimer can have the same or different binding specificites. Typically, the multimers are monospecific, containing two or more antigen-binding domains that immunospecifically bind to the same epitope on DLL4. In some examples, antibody multimers can be generated that are multispecific, containing two or more antigen-binding domains that immunospecifically bind to two of more different epitopes. The epitopes can be DLL4 epitopes. In some examples, the antibody multimers bind an epitope in DLL4 and also bind an epitope in another different target antigen.

Techniques for engineering antibody multimers are known in the art, and include, for example, linkage of two or more variable heavy chains and variable light chains via covalent, non-covalent, or chemical linkage. Multimerization of antibodies can be accomplished through natural aggregation of antibodies or through chemical or recombinant linking techniques known in the art. Thus, multimerization between two antibody polypeptide chains

or antigen-binding fragments can be spontaneous, or can occur due to forced linkage of two or more polypeptides. In one example, antibody multimers can be generated by disulfide bonds formed between cysteine residues on different polypeptide chains. In another example, antibody multimers are generated by joining polypeptides via covalent or non-covalent interactions. In some examples, multimers can be generated form peptides such as peptide linkers (spacers), or peptides that have the property of promoting multimerization. In some examples, antibody multimers can be formed through chemical linkage, such as for example, by using heterobifunctional linkers.

For example, antibody multimers include antibodies that contain a light chain containing a VL-CL and a heavy chain containing a VH-CH1-hinge and a sufficient portion of CH2-CH3 (or CH4 if of an IgE or IgM class) to permit association of heavy chains. Upon purification, such antibodies (e.g. full length IgG1) spontaneously form aggregates containing antibody homodimers, and other higher-order antibody multimers. Exemplary of a constant region can include a constant region portion of an immunoglobulin molecule, such as from IgG1, IgG2, IgG3, IgG4, IgA, IgD, IgM, and IgE. Sequences of antibody regions are known and can be used to recombinantly generate antibody multimers (see e.g. US20080248028). For example, a light chain amino acid sequence can include the CL domain, kappa (set forth in SEQ ID NO:2923) or lambda (SEQ ID NO:2924). A heavy chain amino acid sequence can include one or more of a CH1, hinge, CH2, CH3 or CH4 from an IgG1 (SEQ ID NO:2922), IgG2 (SEQ ID NO: 2937), IgG3 (SEQ ID NO:2925), IgA (SEQ ID NO:2926 or 2927) or IgM (SEQ ID NO:2928 or 2929) subclass. In particular, antibody multimers provided herein are full-length antibodies that contain a light chain containing a VL-CL and a heavy chain containing a VH-CH1-hinge-CH2-CH3. For example, in such an antibody multimer, the resulting antibody molecule is at least a four chain molecule where each heavy chain is linked to a light chain by a disulfide bond, and the two heavy chains are linked to each other by disulfide bonds. Linkage of the heavy chains also is mediated by a flexible region of the heavy chain, known as the hinge region.

Alternatively, antibody homodimers can be formed through chemical linkage techniques known in the art. For example, heterobifunctional crosslinking agents, including, but not limited to, SMCC [succinimidyl 4-(maleimidomethyl)cyclohexane-1-carboxylate] and SATA [N-succinimidyl S-acethylthio-acetate] (available, for example, from Pierce Biotechnology, Inc. (Rockford, Ill.)) can be used to form antibody multimers. An exemplary protocol for the formation of antibody homodimers is given in Ghetie et al., *Proceedings of the National Academy of Sciences USA* (1997) 94:7509-7514. Antibody homodimers can be converted to Fab'2 homodimers through digestion with pepsin. Another way to form antibody

homodimers is through the use of the autophilic T15 peptide described in Zhao and Kohler, *The Journal of Immunology* (2002) 25:396-404.

ScFv dimers can also be formed through recombinant techniques known in the art. For example, such an antibody multimer contains a variable heavy chain connected to a variable light chain on the same polypeptide chain (VH-VL) connected by a peptide linker that is too short to allow pairing between the two domains on the same chain. This forces pairing with the complementary domains of another chain and promotes the assembly of a dimeric molecule with two functional antigen binding sites. An example of the construction of scFv dimers is given in Goel et al., (2000) *Cancer Research* 60:6964-6971.

Alternatively, antibodies can be made to multimerize through recombinant DNA techniques. IgM and IgA naturally form antibody multimers through the interaction with the mature J chain polypeptide (e.g., SEQ ID NO:2930). Non-IgA or non-IgM molecules, such as IgG molecules, can be engineered to contain the J chain interaction domain of IgA or IgM, thereby conferring the ability to form higher order multimers on the non-IgA or non-IgM molecules. (see, for example, Chintalacharuvu et al., (2001) *Clinical Immunology* 101:21-31. and Frigerio et al., (2000) *Plant Physiology* 123:1483-94). IgA dimers are naturally secreted into the lumen of mucosa-lined organs. This secretion is mediated through interaction of the J chain with the polymeric IgA receptor (pIgR) on epithelial cells. If secretion of an IgA form of an antibody (or of an antibody engineered to contain a J chain interaction domain) is not desired, it can be greatly reduced by expressing the antibody molecule in association with a mutant J chain that does not interact well with pIgR (e.g., SEQ ID NOS:2931-2933; Johansen et al., *The Journal of Immunology* (2001) 167:5185-5192). SEQ ID NO:2931 is a mutant form of a human mature J chain with C134S mutation compared to the mature form of human J chain (SEQ ID NO:2930). SEQ ID NO:2932 is a mutant form of a human mature J chain with amino acids 113-137 deleted compared to the mature form of human J chain (SEQ ID NO:2930). SEQ ID NO:2933 shows a mutant form of human mature J chain with C109S and C134S mutation compared to the mature form of human J chain (SEQ ID NO:2930). Expression of an antibody with one of these mutant J chains will reduce its ability to bind to the polymeric IgA receptor on epithelial cells, thereby reducing transport of the antibody across the epithelial cell and its resultant secretion into the lumen of mucosa lined organs.

Antibody multimers may be purified using any suitable method known in the art, including, but not limited to, size exclusion chromatography. Exemplary methods for purifying antibodies are described elsewhere herein.

Exemplary antibodies

An exemplary antibody multimer provided herein contains a variable heavy chain that contains a CDRH1 (corresponding to amino acid positions 26-35 based on kabat numbering) that has a sequence of amino acids of SYYMH (SEQ ID NO:2920), such as GYTFTSYYMH (SEQ ID NO: 2908), a CDRH2 (corresponding to amino acid positions 50-65 based on kabat numbering) that has a sequence of amino acids of IINPSGGSTSYAQKFQG (SEQ ID NO:2909), and a CDRH3 (corresponding to amino acid positions 95-102) that has a sequence of amino acids of EEYSSSSAEYFQH (SEQ ID NO:2910); and contains a variable light chain that contains a CDRL1 (corresponding to amino acid positions 24 to 33 or 34 based on kabat numbering) that has a sequence of amino acids of RASQSVSSYLA (SEQ ID NO: 2911), a CDRL2 (corresponding to amino acid positions 50-56 based on kabat numbering) that has a sequence of amino acids of amino acids of DASNRAT (SEQ ID NO:2912), and a CDRL3 (corresponding to amino acid positions 89-97 based on kabat numbering) that has a sequence of amino acids of QQRSNWPPWT (SEQ ID NO:2913). Also provided are antibody multimers that have a variable heavy chain containing a CDRH1, CDRH2 and CDRH3 that is at least 70% identical to any of SEQ ID NOS:2908-2910 , respectively and a variable light chain containing a CDRL1, CDRL2, and CDRL3 that is at least 70% identical to any of SEQ ID NOS:2911-2913, respectively, whereby the antibody multimer binds to DLL4 and is an activator of DLL4. For example, sequence identity can be at or about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, or more. For example, the antibody multimer is an antibody that at least contains a variable heavy chain set forth in SEQ ID NO:88 and a variable light chain set forth in SEQ ID NO:107, or a variable heavy chain or variable light chain that is at least 60% identical to SEQ ID NO:88 and/or 107, respectively. The antibody can be multimerized as described herein above. For example, provided herein is an antibody multimer that has a heavy chain containing a variable heavy chain region set forth in SEQ ID NO:88, and a CH1-hinge-CH2-CH3 set forth in SEQ ID NO: 2922, and contains a light chain containing a variable light chain set forth in SEQ ID NO:107 and a kappa or lambda CL chain set forth in SEQ ID NO:2923 or 2924.

In another example, an exemplary antibody multimer provided herein contains a variable heavy chain that contains a CDRH1 (corresponding to amino acid positions 26-35 based on kabat numbering) that has a sequence of amino acids of SYWIG (SEQ ID NO: 2921), such as GYSFTSYWIG (SEQ ID NO:2914), a CDRH2 (corresponding to amino acid positions 50-65 based on kabat numbering) that has a sequence of amino acids of IIYPGDSDTRYSPSFQG (SEQ ID NO:2915), and a CDRH3 (corresponding to amino acid positions 95-102) that has a sequence of amino acids of RGYSYGYDYFDY (SEQ ID NO:2916); a contains a variable light chain that contains CDRL1 (corresponding to amino

acid positions 24 to 33 or 34 based on kabat numbering) that has a sequence of amino acids of GLSSGSVSTSYYPS (SEQ ID NO:2917); a CDRL2 (corresponding to amino acid positions 50-56 based on kabat numbering) that has a sequence of amino acids of amino acids of STNTRSS (SEQ ID NO: 2918); and a CDRL3 (corresponding to amino acid positions 89-97 based on kabat numbering) that has a sequence of amino acids of VLYMGSGISYV (SEQ ID NO:2919). Also provided are antibody multimers that have a variable heavy chain containing a CDRH1, CDRH2 and CDRH3 that is at least 70% identical to any of SEQ ID NOS:2914-2916 , respectively and a variable light chain containing a CDRL1, CDRL2, and CDRL3 that is at least 70% identical to any of SEQ ID NOS:2917-2919, respectively, whereby the antibody multimer binds to DLL4 and is an activator of DLL4. For example, sequence identity can be at or about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, or more. For example, the antibody multimer is an antibody that at least contains a variable heavy chain set forth in SEQ ID NO:89 and a variable light chain set forth in SEQ ID NO:108, or a variable heavy chain or variable light chain that is at least 60% identical to SEQ ID NO:89 and/or 108, respectively. The antibody can be multimerized as described herein above. For example, provided herein is an antibody multimer that has a heavy chain containing a variable heavy chain region set forth in SEQ ID NO:89, and a CH1-hinge-CH2-CH3 set forth in SEQ ID NO: 2922, and contains a light chain containing a variable light chain set forth in SEQ ID NO:108 and a kappa or lambda CL chain set forth in SEQ ID NO:2923 or 2924.

In some examples, that anti-DLL4 antibody multimers provided herein include activator/modulators of DLL4 activity, with the proviso that the antibody is not an antibody that has a heavy chain containing a variable heavy chain set forth in SEQ ID NO:88 and a variable light chain set forth in SEQ ID NO:107; or is not an antibody that has a heavy chain containing a variable heavy chain set forth in SEQ ID NO:89 and a variable light chain set forth in SEQ ID NO:108.

3. Modifications

The anti-DLL4 antibody multimers provided herein can be further modified so long as the antibody retains binding to DLL4 and is an activator of DLL4 activity. Modification of an anti-DLL4 antibody multimer provided herein can improve one or more properties of the antibody, including, but not limited to, decreasing the immunogenicity of the antibody; improving the half-life of the antibody, such as reducing the susceptibility to proteolysis and/or reducing susceptibility to oxidation; altering or improving of the binding properties of the antibody; and/or modulating the effector functions of the antibody. Exemplary modifications include modification of the primary sequence of the antibody and/or alteration

of the post-translational modification of an antibody. Exemplary post-translational modifications include, for example, glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization with protecting/blocking group, proteolytic cleavage, and linkage to a cellular ligand or other protein. Other exemplary modifications include attachment of one or more heterologous peptides to the antibody to alter or improve one or more properties of the antibody.

Generally, the modifications do not result in increased immunogenicity of the antibody or antigen-binding fragment thereof or significantly negatively affect the binding of the antibody to DLL4 or its activity as an activator. Methods of assessing the binding of the modified antibodies to DLL4 are provided herein and are known in the art. For example, modified antibodies can be assayed for binding to DLL4 by methods such as, but not limited to, ELISA or FACS binding assays. Methods to assess activating activity of the antibody also are known to one of skill in the art and described elsewhere herein, for examples, in the Examples. For example, activity can be determined using a reporter assay for activity of a Notch receptor.

Modification of the anti-DLL4 antibodies produced herein can include one or more amino acid substitutions, deletions or additions, compared to the parent antibody from which it was derived. Methods for modification of polypeptides, such as antibodies, are known in the art and can be employed for the modification of any antibody or antigen-binding fragment provided herein. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide molecule encoding an antibody or an antigen-binding fragment provided herein in order to produce a polypeptide with one or more amino acid substitutions. Exemplary techniques for introducing mutations include, but are not limited to, site-directed mutagenesis and PCR-mediated mutagenesis.

The antibodies can be recombinantly fused to a heterologous polypeptide at the N-terminus or C-terminus or chemically conjugated, including covalent and non-covalent conjugation, to a heterologous polypeptide or other composition. The fusion does not necessarily need to be direct, but can occur through a linker peptide. In some examples, the linker peptide contains a protease cleavage site which allows for removal of the purification peptide following purification by cleavage with a protease that specifically recognizes the protease cleavage site.

For example, the anti-DLL4 antibodies provided herein can be modified by the attachment of a heterologous peptide to facilitate purification. Generally such peptides are expressed as a fusion protein containing the antibody fused to the peptide at the C- or N-terminus of the antibody. Exemplary peptides commonly used for purification include, but

are not limited to, hexa-histidine peptides, hemagglutinin (HA) peptides, and flag tag peptides (see *e.g.*, Wilson *et al.* (1984) *Cell* 37:767; Witzgall *et al.* (1994) *Anal Biochem* 223:2, 291-8). In another example, the anti-DLL4 antibodies provided herein can be modified by the covalent attachment of any type of molecule, such as a diagnostic or therapeutic molecule. Exemplary diagnostic and therapeutic moieties include, but are not limited to, drugs, radionucleotides, toxins, fluorescent molecules (see, *e.g.* International PCT Publication Nos. WO 92/08495; WO 91/14438; WO 89/12624; U.S. Pat. No. 5,314,995; and EP 396,387). Diagnostic polypeptides or diagnostic moieties can be used, for example, as labels for *in vivo* or *in vitro* detection. In a further example, anti-DLL4 antibody multimers provided herein can be modified by attachment to other molecules or moieties, such as any that increase the half-life, stability, immunogenicity or that affect or alter the targeting of the antibody *in vivo*.

Exemplary modifications are described herein below. It is within the level of one of skill in the art to modify any of the antibodies provided herein depending on the particular application of the antibody.

a. Modifications to reduce immunogenicity

In some examples, the antibodies provided herein can be modified to reduce the immunogenicity in a subject, such as a human subject. For example, one or more amino acids in the antibody can be modified to alter potential epitopes for human T-cells in order to eliminate or reduce the immunogenicity of the antibody when exposed to the immune system of the subject. Exemplary modifications include substitutions, deletions and insertion of one or more amino acids, which eliminate or reduce the immunogenicity of the antibody. Generally, such modifications do not alter the binding specificity of the antibody for its respective antigen. Reducing the immunogenicity of the antibody can improve one or more properties of the antibody, such as, for example, improving the therapeutic efficacy of the antibody and/or increasing the half-life of the antibody *in vivo*.

b. Glycosylation

The anti-DLL4 antibodies provided herein can be modified by either N-linked or O-linked glycosylation. N-linked glycosylation includes the attachment of a carbohydrate moiety to the side chain of an asparagine residue within the tripeptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline. O-linked glycosylation includes the attachment of one of the sugars N-aceylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine can also be used. The anti-DLL4 antibodies can be further modified to incorporate additional glycosylation sites by altering the amino acid sequence such that it contains one or more of the above-described tripeptide sequences (for

N-linked glycosylation sites). The alteration can also be made by the addition of, or substitution by, one or more serine or threonine residues to the sequence of the original antibody (for O-linked glycosylation sites). Where the antibody comprises an Fc region, the carbohydrate attached thereto can be altered (see, e.g., U.S. Patent Pub. Nos. 2003/0157108, 2005/0123546 and US 2004/0093621; International Patent Pub. Nos. WO 2003/011878, WO 1997/30087, WO 1998/58964, WO 1999/22764; and U.S. Pat. No. 6,602,684).

For example, a glycosylation variantion is in the Fc region of the antibody, wherein a carbohydrate structure attached to the Fc region lacks fucose. Such variants have improved ADCC function. Optionally, the Fc region further contains one or more amino acid substitutions therein which further improve ADCC, for example, substitutions at positions 298, 333, and/or 334 of the Fc region (Eu numbering of residues) (see, e.g., US 2003/0157108; WO 2000/61739; WO 2001/29246; US 2003/0115614; US 2002/0164328; US 2004/0093621; US 2004/0132140; US 2004/0110704; US 2004/0110282; US 2004/0109865; WO 2003/085119; WO 2003/084570; WO 2005/035586; WO 2005/035778; WO2005/053742; Okazaki et al. *J. Mol. Biol.* 336:1239-1249 (2004); Yamane-Ohnuki et al. *Biotech. Bioeng.* 87: 614 (2004)). Examples of cell lines producing defucosylated antibodies include Lec13 CHO cells deficient in protein fucosylation (Ripka et al. *Arch. Biochem. Biophys.* 249:533-545 (1986); US Pat Appl No US 2003/0157108 A1, Presta, L; and WO 2004/056312 A1, Adams et al., especially at Example 11), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene, FUT8, knockout CHO cells (Yamane-Ohnuki et al. *Biotech. Bioeng.* 87: 614 (2004)).

c. Fc Modifications

The anti-DLL4 antibody multimers provided herein can contain wild-type or modified Fc region. The antibodies provided herein can be engineered to contain modified Fc regions. In some examples, the Fc region can be modified to alter one or more properties of the Fc polypeptide. For example, the Fc region can be modified to alter (*i.e.* increase or decrease) effector functions compared to the effector function of an Fc region of a wild-type immunoglobulin heavy chain. Thus, a modified Fc domain can have altered affinity, including but not limited to, increased or low or no affinity for the Fc receptor. Altering the affinity of an Fc region for a receptor can modulate the effector functions induced by the Fc domain.

In one example, an Fc region is used that is modified for optimized binding to certain FcγRs to better mediate effector functions, such as for example, antibody-dependent cellular cytotoxicity, ADCC. Such modified Fc regions can contain modifications at one or more of amino acid residues (according to the Kabat numbering scheme, Kabat *et al.* (1991)

Sequences of Proteins of Immunological Interest, U.S. Department of Health and Human Services), including, but not limited to, amino acid positions 249, 252, 259, 262, 268, 271, 273, 277, 280, 281, 285, 287, 296, 300, 317, 323, 343, 345, 346, 349, 351, 352, 353, and 424. For example, modifications in an Fc region can be made corresponding to any one or more of G119S, G119A, S122D, S122E, S122N, S122Q, S122T, K129H, K129Y, D132Y, R138Y, E141Y, T143H, V147I, S150E, H151D, E155Y, E155I, E155H, K157E, G164D, E166L, E166H, S181A, S181D, S187T, S207G, S207I, K209T, K209E, K209D, A210D, A213Y, A213L, A213I, I215D, I215E, I215N, I215Q, E216Y, E216A, K217T, K217F, K217A, and P279L of the exemplary Fc sequence set forth in SEQ ID NO:2922, or combinations thereof. A modified Fc containing these mutations can have enhanced binding to an FcR such as, for example, the activating receptor FcγIIIa and/or can have reduced binding to the inhibitory receptor FcγRIIb (see e.g., US 2006/0024298). Fc regions modified to have increased binding to FcRs can be more effective in facilitating the destruction of the fungal cells in patients.

In some examples, the antibodies or antigen-binding fragments provided herein can be further modified to improve the interaction of the antibody with the FcRn receptor in order to increase the *in vivo* half-life and pharmacokinetics of the antibody (see, *e.g.* U.S. Patent No. 7,217,797; and U.S Pat. Pub. Nos. 2006/0198840 and 2008/0287657). FcRn is the neonatal FcR, the binding of which recycles endocytosed antibody from the endosomes back to the bloodstream. This process, coupled with preclusion of kidney filtration due to the large size of the full length molecule, results in favorable antibody serum half-lives ranging from one to three weeks. Binding of Fc to FcRn also plays a role in antibody transport.

Exemplary modifications of the Fc region include but are not limited to, mutation of the Fc described in U.S. Patent No. 7,217,797; U.S Pat. Pub. Nos. 2006/0198840, 2006/0024298 and 2008/0287657; and International Patent Pub. No. WO 2005/063816, such as mutations at one or more of amino acid residues (Kabat numbering, Kabat *et al.* (1991)) 251-256, 285-90, 308-314, in the C_H2 domain and/or amino acids residues 385-389, and 428-436 in the C_H3 domain of the Fc heavy chain constant region, where the modification alters Fc receptor binding affinity and/or serum half-life relative to unmodified antibody. In some examples, the Fc region is modified at one or more of amino acid positions 250, 251, 252, 254, 255, 256, 263, 308, 309, 311, 312 and 314 in the C_H2 domain and/or amino acid positions 385, 386, 387, 389, 428, 433, 434, 436, and 459 in the C_H3 domain of the Fc heavy chain constant region. Such modifications correspond to amino acids Gly120, Pro121, Ser122, Phe124 Leu125, Phe126, Thr133, Pro174, Arg175, Glu177, Gln178, and Asn180 in the C_H2 domain and amino acids Gln245, Val246, Ser247, Thr249, Ser283, Gly285, Ser286,

Phe288, and Met311 in the C_H3 domain in an exemplary Fc sequence set forth in SEQ ID NO:2922 In some examples, the modification is at one or more surface-exposed residues, and the modification is a substitution with a residue of similar charge, polarity or hydrophobicity to the residue being substituted.

In particular examples, a Fc heavy chain constant region is modified at one or more of amino acid positions 251, 252, 254, 255, and 256 (Kabat numbering), where position 251 is substituted with Leu or Arg, position 252 is substituted with Tyr, Phe, Ser, Trp or Thr, position 254 is substituted with Thr or Ser, position 255 is substituted with Leu, Gly, Ile or Arg, and/or position 256 is substituted with Ser, Arg, Gln, Glu, Asp, Ala, Asp or Thr. In some examples, a Fc heavy chain constant region is modified at one or more of amino acid positions 308, 309, 311, 312, and 314 (Kabat numbering), where position 308 is substituted with Thr or Ile, position 309 is substituted with Pro, position 311 is substituted with serine or Glu, position 312 is substituted with Asp, and/or position 314 is substituted with Leu. In some examples, a Fc heavy chain constant region is modified at one or more of amino acid positions 428, 433, 434, and 436 (Kabat numbering), where position 428 is substituted with Met, Thr, Leu, Phe, or Ser, position 433 is substituted with Lys, Arg, Ser, Ile, Pro, Gln, or His, position 434 is substituted with Phe, Tyr, or His, and/or position 436 is substituted with His, Asn, Asp, Thr, Lys, Met, or Thr. In some examples, a Fc heavy chain constant region is modified at one or more of amino acid positions 263 and 459 (Kabat numbering), where position 263 is substituted with Gln or Glu and/or position 459 is substituted with Leu or Phe.

In some examples, a Fc heavy chain constant region can be modified to enhance binding to the complement protein C1q. In addition to interacting with FcRs, Fc also interact with the complement protein C1q to mediate complement dependent cytotoxicity (CDC). C1q forms a complex with the serine proteases C1r and C1s to form the C1 complex. C1q is capable of binding six antibodies, although binding to two IgGs is sufficient to activate the complement cascade. Similar to Fc interaction with FcRs, different IgG subclasses have different affinity for C1q, with IgG1 and IgG3 typically binding substantially better than IgG2 and IgG4. Thus, a modified Fc having increased binding to C1q can mediate enhanced CDC, and can enhance destruction of fungal cells. Exemplary modifications in an Fc region that increase binding to C1q include, but are not limited to, amino acid modifications at positions 345 and 253 (Kabat numbering). Exemplary modifications are include those corresponding to K209W, K209Y, and E216S in an exemplary Fc sequence set forth in SEQ ID NO:2922.

In another example, a variety of Fc mutants with substitutions to reduce or ablate binding with FcγRs also are known. Such muteins are useful in instances where there is a need for reduced or eliminated effector function mediated by Fc. This is often the case where

antagonism, but not killing of the cells bearing a target antigen is desired. Exemplary of such an Fc is an Fc mutein described in U.S. Patent No. 5,457,035, which is modified at amino acid positions 248, 249 and 251 (Kabat numbering). In an exemplary Fc sequence set forth in amino acids 100-330 of SEQ ID NO:2922, amino acid 118 is modified from Leu to Ala, amino acid 119 is modified from Leu to Glu, and amino acid 121 is modified from Gly to Ala. Similar mutations can be made in any Fc sequence such as, for example, the exemplary Fc sequence. This mutein exhibits reduced affinity for Fc receptors.

d. Pegylation

The anti-DLL4 antibody multimers provided herein can be conjugated to polymer molecules, or water soluble polymers, such as high molecular weight polyethylene glycol (PEG) to increase half-life and/or improve their pharmacokinetic profiles. Water soluble polymers include, but are not limited to, polyethylene glycol (PEG), copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1,3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids (either homopolymers or random copolymers), and dextran or poly(n-vinyl pyrrolidone)polyethylene glycol, propropylene glycol homopolymers, prolypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols (e.g., glycerol), polyvinyl alcohol, and mixtures thereof. Polyethylene glycol propionaldehyde can have advantages in manufacturing due to its stability in water. The polymer can be of any molecular weight, and can be branched or unbranched. The number of polymers attached to the antibody can vary, and if more than one polymer is attached, they can be the same or different molecules. In general, the number and/or type of polymers used for derivatization can be determined based on considerations including, but not limited to, the particular properties or functions of the antibody to be improved, and whether the antibody derivative will be used in a therapy under defined conditions.

Conjugation can be carried out by techniques known to those skilled in the art. Conjugation of therapeutic antibodies with PEG has been shown to enhance pharmacodynamics while not interfering with function (see, *e.g.*, Deckert *et al.*, *Int. J. Cancer* 87: 382-390, 2000; Knight *et al.*, *Platelets* 15: 409-418, 2004; Leong *et al.*, *Cytokine* 16: 106-119, 2001; and Yang *et al.*, *Protein Eng.* 16: 761-770, 2003). PEG can be attached to the antibodies or antigen-binding fragments with or without a multifunctional linker either through site-specific conjugation of the PEG to the N- or C-terminus of the antibodies or antigen-binding fragments or via epsilon-amino groups present on lysine residues. Linear or branched polymer derivatization that results in minimal loss of biological activity can be used. The degree of conjugation can be monitored by SDS-PAGE and mass spectrometry to

ensure proper conjugation of PEG molecules to the antibodies. Unreacted PEG can be separated from antibody-PEG conjugates by, *e.g.,* size exclusion or ion-exchange chromatography. PEG-derivatized antibodies can be tested for binding activity to DLL4 as well as for *in vivo* efficacy using methods known to those skilled in the art, for example, by functional assays described herein.

4. COMPOSITIONS, FORMULATIONS, ADMINISTRATION AND ARTICLES OF MANUFACTURE/KITS

a. Compositions and Formulations

The antibody multimers provided herein can be provided as a formulation for administration. While it is possible for the active ingredient to be administered alone, generally it is present as a pharmaceutical formulation. Compositions or formulations contain at least one active ingredient, together with one or more acceptable carriers thereof. Each carrier must be both pharmaceutically and physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the patient. Formulations include those suitable for oral, rectal, nasal, or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations can conveniently be presented in unit dosage form and can be prepared by methods well known in the art of pharmacy. See, e.g., Gilman, *et al.* (eds. 1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences, 17th ed. (1990), Mack Publishing Co., Easton, Pa.; Avis, *et al.* (eds. 1993) Pharmaceutical Dosage Forms: Parenteral Medications Dekker, NY; Lieberman, *et al.* (eds. 1990) Pharmaceutical Dosage Forms: Tablets Dekker, NY; and Lieberman, *et al.* (eds. 1990) Pharmaceutical Dosage Forms: Disperse Systems Dekker, NY.

The route of antibody administration is in accord with known methods, e.g., injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, subcutaneous, intraocular, intraarterial, intrathecal, inhalation or intralesional routes, topical or by sustained release systems as noted below. The antibody is typically administered continuously by infusion or by bolus injection. One can administer the antibodies in a local or systemic manner.

The antibody multimers provided herein can be prepared in a mixture with a pharmaceutically acceptable carrier. Techniques for formulation and administration of the compounds are known to one of skill in the art (see *e.g.* "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, Pa.). This therapeutic composition can be administered intravenously or through the nose or lung, preferably as a liquid or powder aerosol (lyophilized). The composition also can be administered parenterally or

subcutaneously as desired. When administered systematically, the therapeutic composition should be sterile, pyrogen-free and in a parenterally acceptable solution having due regard for pH, isotonicity, and stability. These conditions are known to those skilled in the art.

Therapeutic formulations can be administered in many conventional dosage formulations. Briefly, dosage formulations of the antibodies provided herein are prepared for storage or administration by mixing the compound having the desired degree of purity with physiologically acceptable carriers, excipients, or stabilizers. Such materials are non-toxic to the recipients at the dosages and concentrations employed, and can include buffers such as TRIS HCl, phosphate, citrate, acetate and other organic acid salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidinone; amino acids such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium and/or nonionic surfactants such as TWEEN, PLURONICS or polyethyleneglycol.

When used for *in vivo* administration, the antibody multimer formulation should be sterile and can be formulated according to conventional pharmaceutical practice. This is readily accomplished by filtration through sterile filtration membranes, prior to or following lyophilization and reconstitution. The antibody ordinarily will be stored in lyophilized form or in solution. Other vehicles such as naturally occurring vegetable oil like sesame, peanut, or cottonseed oil or a synthetic fatty vehicle like ethyl oleate or the like may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

Pharmaceutical compositions suitable for use include compositions wherein one or more antibody multimers are contained in an amount effective to achieve their intended purpose. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. Therapeutically effective dosages can be determined by using in vitro and in vivo methods.

An effective amount of antibody to be employed therapeutically will depend, for example, upon the therapeutic objectives, the route of administration, and the condition of the patient. In addition, the attending physician takes into consideration various factors known to modify the action of drugs including severity and type of disease, body weight, sex, diet, time and route of administration, other medications and other relevant clinical factors. Accordingly, it will be necessary for the therapist to titer the dosage and modify the route of

administration as required to obtain the optimal therapeutic effect. Typically, the clinician will administer antibody until a dosage is reached that achieves the desired effect. The progress of this therapy is easily monitored by conventional assays.

For any antibody containing a peptide, the therapeutically effective dose can be estimated initially from cell culture assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the EC50 as determined in cell culture (e.g., the concentration of the test molecule which promotes or inhibits cellular proliferation or differentiation). Such information can be used to more accurately determine useful doses in humans.

Toxicity and therapeutic efficacy of the antibody multimers described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD50 and ED50. Molecules which exhibit high therapeutic indices can be used. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such molecules lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g., Fingl *et al.*, 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1, p.1).

Dosage amount and interval can be adjusted individually to provide plasma levels of the antibody which are sufficient to promote or inhibit cellular proliferation or differentiation or minimal effective concentration (MEC). The MEC will vary for each antibody, but can be estimated from in vitro data using described assays. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using MEC value. Antibody molecules should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%.

In cases of local administration or selective uptake, the effective local concentration of the antibody may not be related to plasma concentration.

A typical daily dosage might range of antibody multimers provided herein is from about 1 μ/kg to up to 1000 mg/kg or more, depending on the factors mentioned above.

Typically, the clinician will administer the molecule until a dosage is reached that achieves the desired effect. The progress of this therapy is easily monitored by conventional assays.

Depending on the type and severity of the disease, from about 0.001 mg/kg to abut 1000 mg/kg, such as about 0.01 mg to 100 mg/kg, for example about 0.010 to 20 mg/kg of the antibody multimer, is an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. For repeated administrations over several days or longer, depending on the condition, the treatment is repeated until a desired suppression of disease symptoms occurs or the desired improvement in the patient's condition is achieved. However, other dosage regimes also are contemplated.

b. Articles of Manufacture and Kits

Pharmaceutical compounds of selected antibodies or nucleic acids encoding selected antibodies, or a derivative or a biologically active portion thereof can be packaged as articles of manufacture containing packaging material, a pharmaceutical composition which is effective for treating the disease or disorder, and a label that indicates that selected antibody or nucleic acid molecule is to be used for treating the disease or disorder.

The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are well known to those of skill in the art. See, for example, U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252, each of which is incorporated herein in its entirety. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of formulations of the compounds and compositions provided herein are contemplated as are a variety of treatments for any EPO-mediated disease or disorder or therapeutic polypeptide-mediated disease or disorder.

Antibodies and nucleic acid molecules encoding the antibodies thereof also can be provided as kits. Kits can include a pharmaceutical composition described herein and an item for administration. For example, a selected antibody can be supplied with a device for administration, such as a syringe, an inhaler, a dosage cup, a dropper, or an applicator. The kit can, optionally, include instructions for application including dosages, dosing regimens and instructions for modes of administration. Kits also can include a pharmaceutical composition described herein and an item for diagnosis. For example, such kits can include an item for measuring the concentration, amount or activity of the antibody in a subject.

5. Methods of Treatment and Uses

Provided herein are methods of treatment or uses of anti-DLL4 antibody multimers to treat diseases that manifest aberrant angiogenesis or neovascularization. Angiogenesis is a

process by which new blood vessels are formed. It occurs for example, in a healthy body for healing wounds and for restoring blood flow to tissues after injury or insult. In females, angiogenesis also occurs during the monthly reproductive cycle to rebuild the uterus lining, to mature the egg during ovulation and during pregnancy to build the placenta. In some situations 'too much' angiogenesis can be detrimental, such as angiogenesis that supplies blood to tumor foci, in inflammatory responses and other aberrant angiogenic-related conditions. The growth of tumors, or sites of proliferation in chronic inflammation, generally requires the recruitment of neighboring blood vessels and vascular endothelial cells to support their metabolic requirements. This is because the diffusion is limited for oxygen in tissues. Exemplary conditions associated with angiogenesis include, but are not limited to solid tumors and hematologic malignancies such as lymphomas, acute leukemia, and multiple myeloma, where increased numbers of blood vessels are observed in the pathologic bone marrow.

Hence, angiogenesis is implicated in the pathogenesis of a variety of disorders. These include solid tumors and metastasis, atherosclerosis, retrolental fibroplasia, hemangiomas, chronic inflammation, intraocular neovascular diseases such as proliferative retinopathies, e.g., diabetic retinopathy, age-related macular degeneration (AMD), neovascular glaucoma, immune rejection of transplanted corneal tissue and other tissues, rheumatoid arthritis, and psoriasis. Folkman et al., *J. Biol. Chem.* 267:10931-34 (1992); Klagsbrun et al., *Annu. Rev. Physiol.* 53:217-39 (1991); and Garner A., "Vascular diseases," In: Pathobiology of Ocular Disease. A Dynamic Approach, Garner A., Klintworth G K, eds., 2nd Edition (Marcel Dekker, NY, 1994), pp 1625-1710.

In the case of tumor growth, angiogenesis appears to be crucial for the transition from hyperplasia to neoplasia, and for providing nourishment for the growth and metastasis of the tumor. Folkman et al., *Nature* 339:58 (1989). The neovascularization allows the tumor cells to acquire a growth advantage and proliferative autonomy compared to the normal cells. A tumor usually begins as a single aberrant cell which can proliferate only to a size of a few cubic millimeters due to the distance from available capillary beds, and it can stay 'dormant' without further growth and dissemination for a long period of time. Some tumor cells then switch to the angiogenic phenotype to activate endothelial cells, which proliferate and mature into new capillary blood vessels. These newly formed blood vessels not only allow for continued growth of the primary tumor, but also for the dissemination and recolonization of metastatic tumor cells. Accordingly, a correlation has been observed between density of microvessels in tumor sections and patient survival in breast cancer as well as in several other tumors. Weidner et al., *N. Engl. J. Med.* 324:1-6 (1991); Horak et al., *Lancet* 340:1120-24

(1992); Macchiarini et al., *Lancet* 340:145-46 (1992). The precise mechanisms that control the angiogenic switch is not well understood, but it is believed that neovascularization of tumor mass results from the net balance of a multitude of angiogenesis stimulators and inhibitors (Folkman, *Nat. Med.* 1(1):27-31 (1995)).

Angiogenesis also play a role in inflammatory diseases. These diseases have a proliferative component, similar to a tumor focus. In rheumatoid arthritis, one component of this is characterized by aberrant proliferation of synovial fibroblasts, resulting in pannus formation. The pannus is composed of synovial fibroblasts which have some phenotypic characteristics with transformed cells. As a pannus grows within the joint it expresses many proangiogenic signals, and experiences many of the same neo-angiogenic requirements as a tumor. The need for additional blood supply, neoangiogenesis, is critical. Similarly, many chronic inflammatory conditions also have a proliferative component in which some of the cells composing it may have characteristics usually attributed to transformed cells.

Another example of a condition involving excess angiogenesis is diabetic retinopathy (Lip et al. Br J Ophthalmology 88: 1543, 2004)). Diabetic retinopathy has angiogenic, inflammatory and proliferative components; overexpression of VEGF, and angiopoietin-2 are common. This overexpression is likely required for disease-associated remodeling and branching of blood vessels, which then supports the proliferative component of the disease.

Hence, provided herein are methods of treatment with anti-DLL4 antibody multimers for angiogenic diseases and conditions. Such diseases or conditions include, but are not limited to, inflammatory diseases, immune diseases, cancers, and other diseases that manifest aberrant angiogenesis and abnormal vascularization. Cancers include breast, lung, colon, gastric cancers, pancreatic cancers and others. Inflammatory diseases, include, for example, diabetic retinopathies and/or neuropathies and other inflammatory vascular complications of diabetes, autoimmune diseases, including autoimmune diabetes, atherosclerosis, Crohn's disease, diabetic kidney disease, cystic fibrosis, endometriosis, diabetes-induced vascular injury, inflammatory bowel disease, Alzheimers disease and other neurodegenerative diseases. Treatment can be effected by administering by suitable route formulations of the antibody multimers, which can be provided in compositions as polypeptides. In some examples, the antibody multimers can be linked to targeting agents, for targeted delivery or encapsulated in delivery vehicles, such as liposomes.

For example, treatments using the anti-DLL4 multimers provided herein, include, but are not limited to treatment of diabetes-related diseases and conditions including periodontal, autoimmune, vascular, and tubulointerstitial diseases. Treatments using the anti-DLL4 antibody multimers also include treatment of ocular disease including macular degeneration,

cardiovascular disease, neurodegenerative disease including Alzheimer's disease, inflammatory diseases and conditions including rhematoid arthritis, and diseases and conditions associated with cell proliferation including cancers. One of skill in the art can assess based on the type of disease to be treated, the severity and course of the disease, whether the molecule is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to therapy, and the discretion of the attending physician appropriate dosage of a molecule to administer.

Combination Therapy

Anti-DLL4 antibody multimers provided herein can be administered in combination with another therapy. For example, anti-DLL4 antibody multimers are used in combinations with anti-cancer therapeutics or anti-neovascularization therapeutics to treat various neoplastic or non-neoplastic conditions. In one embodiment, the neoplastic or non-neoplastic condition is characterized by pathological disorder associated with aberrant or undesired angiogenesis. Exemplary combination therapies also include any set forth in U.S. Published application No. 20090246199. The anti-DLL4 antibody multimer can be administered serially or in combination with another agent that is effective for those purposes, either in the same composition or as separate compositions. The anti-DLL4 antibody multimers can be administered sequentially, simultaneously or intermittently with a therapeutic agent. Alternatively, or additionally, multiple inhibitors of DLL4 can be administered.

The administration of the anti-DLL4 antibody multimer can be done simultaneously, e.g., as a single composition or as two or more distinct compositions using the same or different administration routes. Alternatively, or additionally, the administration can be done sequentially, in any order. In certain embodiments, intervals ranging from minutes to days, to weeks to months, can be present between the administrations of the two or more compositions. For example, the anti-cancer agent can be administered first, followed by the DLL4 antibody multimer. Simultaneous administration or administration of the anti-DLL4 antibody multimer first also is contemplated.

The effective amounts of therapeutic agents administered in combination with an anti-DLL4 antibody multimer will be at the physician's or veterinarian's discretion. Dosage administration and adjustment is done to achieve maximal management of the conditions to be treated. The dose will additionally depend on such factors as the type of therapeutic agent to be used and the specific patient being treated. Suitable dosages for the anti-cancer agent are those presently used and can be lowered due to the combined action (synergy) of the anti-cancer agent and the anti-DLL4 antibody multimer.

Typically, the anti-DLL4 antibody multimer and anti-cancer agents are suitable for the same or similar diseases to block or reduce a pathological disorder such as tumor growth or growth of a cancer cell. In one embodiment the anti-cancer agent is an anti-angiogenesis agent. Antiangiogenic therapy in relationship to cancer is a cancer treatment strategy aimed at inhibiting the development of tumor blood vessels required for providing nutrients to support tumor growth. Because angiogenesis is involved in both primary tumor growth and metastasis, the antiangiogenic treatment is generally capable of inhibiting the neoplastic growth of tumor at the primary site as well as preventing metastasis of tumors at the secondary sites, therefore allowing attack of the tumors by other therapeutics.

Many anti-angiogenic agents have been identified and are known in the arts, including those listed herein, e.g., listed under Definitions, and by, e.g., Carmeliet and Jain, *Nature* 407:249-257 (2000); Ferrara et al., *Nature Reviews. Drug Discovery*, 3:391-400 (2004); and Sato *Int. J. Clin. Oncol.*, 8:200-206 (2003). See also, US Patent Application US20030055006. In one embodiment, an anti-DLL4 antibody multimer is used in combination with an anti-VEGF neutralizing antibody (or fragment) and/or another VEGF antagonist or a VEGF receptor antagonist including, but not limited to, for example, soluble VEGF receptor (e.g., VEGFR-1, VEGFR-2, VEGFR-3, neuropillins (e.g., NRP1, NRP2)) fragments, aptamers capable of blocking VEGF or VEGFR, neutralizing anti-VEGFR antibodies, low molecule weight inhibitors of VEGFR tyrosine kinases (RTK), antisense strategies for VEGF, ribozymes against VEGF or VEGF receptors, antagonist variants of VEGF; and any combinations thereof. Alternatively, or additionally, two or more angiogenesis inhibitors can optionally be co-administered to the patient in addition to VEGF antagonist and other agent. In certain embodiment, one or more additional therapeutic agents, e.g., anti-cancer agents, can be administered in combination with anti-DLL4 antibody multimer, the VEGF antagonist, and an anti-angiogenesis agent.

In certain aspects, other therapeutic agents useful for combination angiogenic or tumor therapy with a anti-DLL4 antibody mulitmer include other cancer therapies, (e.g., surgery, radiological treatments (e.g., involving irradiation or administration of radioactive substances), chemotherapy, treatment with anti-cancer agents listed herein and known in the art, or combinations thereof). Alternatively, or additionally, two or more antibodies binding the same or two or more different antigens disclosed herein can be co-administered to the patient. Sometimes, it can be beneficial to also administer one or more cytokines to the patient.

H. EXAMPLES

The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention.

EXAMPLE 1

Generation of Mutant Fab antibodies

In this Example, mutant Fab antibodies were generated by alanine-scanning, NNK mutagenesis, and ligation of oligo pairs into BsaI modified plasmids that allow cloning of any modified CDR region in a high-throughput manner.

A. Alanine scanning mutagenesis

Alanine mutants were generated by overlapping PCR using the parent heavy or light chain DNA as a template. Forward and reverse primers that specifically generate the desired mutation at the target codon were used to amplify the parent DNA in the appropriate plasmid.

In the first round of PCR, two separate PCR reactions with different primer pairs were used to amplify two segments of the gene. The first reaction used the specific reverse primer with an EcoRI forward primer and amplified the first half of the gene. The second reaction used the specific forward primer with an FLXhoI reverse primer and amplified the second half of the gene. The gene segments were generated using 20 cycles of PCR with the following conditions: 94 °C for 30 sec; 50 °C for 30 sec; and 72 °C for 90 sec. The PCR products were isolated and purified from 1% agarose gel and mixed together as a template for the second round of PCR. In the second round of PCR, EcoRI forward and FLXhoI reverse primers were used to amplify the full length gene product. The gene product was generated using 20 cycles of PCR with the following conditions: 94 °C for 30 sec; 55 °C for 30 sec; and 72 °C for 90 sec.

The PCR product was isolated and subsequently digested with EcoRI and XhoI (New England Biolabs) and ligated into the similarly digested plasmid. After transformation of the ligation product in *E. coli* DH5α and plating, individual colonies were selected and grown in a 96-well block containing 1.5 ml of Terrific Broth (EMD, San Diego, CA) supplemented with 50 μg/ml Kanamycin, and 0.4 % glucose, and grown at 37 °C overnight. The DNA was isolated using a mini-prep kit (Qiagen) and alanine mutations were confirmed by DNA sequencing.

As an example, Table 6 sets forth primer pairs used to generate the mutant VH5-51_IGHD5-18*01>3_IGHJ4*01 R99A and VH1-46_IGHD6-6*01_IGHJ1*01 E100A. Primers R99A_F and R99A_R were utilized to specifically amplify the R99 to alanine mutation. Primers E100A_F and E100A_R were utilized to specifically amplify the E100 to alanine mutation. Primers EcoRI_F and FLXhoI_R were utilized to amplify the remaining segments of the gene.

Table 6. Example primer pairs for alanine scanning mutagenesis		
Primer	**Sequence**	**SEQ ID NO**
VH5-51_IGHD5-18*01>3_IGHJ4*01		
R99A_F	GCCATGTATTACTGTGCGAGA**GCC**GGATACAGCTATGGTTACGAC	1
R99A_R	GTCGTAACCATAGCTGTATCC**GGC**TCTCGCACAGTAATACATGGC	2
VH1-46_IGHD6-6*01_IGHJ1*01		
E100A_F	GTGTATTACTGTGCGAGAGAG**GCC**TATAGCAGCTCGTCCGCTG	3
E100A_R	CAGCGGACGAGCTGCTATAG**GCC**TCTCTCGCACAGTAATACAC	4
Plasmid A and D		
EcoRI_F	TTGGGCGAATTCCCTAGATAATTAATTAGGAGG	5
FLXhoI_R	TTAAACCTCGAGCCGCGGTTCATTAAAG	6

B. NNK mutagenesis by overlapping PCR

NNK mutagenesis by overlapping PCR was carried out as described above for alanine scanning mutagenesis, with initial primers that generate the desired NNK mutations. Therefore, in the first round of PCR, specific primer pairs were used in which the target codon was replaced with NNK (forward) and MNN (reverse). For example, Table 7 below sets forth forward and reverse primers used to generate VH5-51_IGHD5-18*01>3_IGHJ4*01 G100 NNK mutants and VH1-46_IGHD6-6*01_IGHJ1*01 S102 NNK mutants.

Individual clones were subjected to DNA sequencing (by BATJ, Inc., San Diego, CA) to identify the amino acid substitution. Depending on the number of colonies picked per NNK mutation reaction, mutation rate varies—as low as 4 to 5 amino acid changes, and as high as 18 to 19 amino acid changes per mutation were observed.

Table 7. Example primer pairs for NNK mutagenesis		
Primer	**Sequence**	**SEQ ID NO**
VH5-51_IGHD5-18*01>3_IGHJ4*01		
G100_NNK_F	GTATTACTGTGCGAGACGT**NNK**TACAGCTATGGTTACGAC	7
G100_NNK_R	GTCGTAACCATAGCTGTA**MNN**ACGTCTCGCACAGTAATAC	8
VH1-46_IGHD6-6*01_IGHJ1*01		
S102_NNK_F	TGCGAGAGAGGGGTAT**NNK**AGCAGCTGGTACGACT	9
S102_NNK_R	AGTCGTACCAGCTGCT**MNN**ATACCCCTCTCTCGCA	10

C. Cassette mutagenesis using type II restriction enzyme based digestion and ligation of oligo pairs

In this example, Fab mutants were generated in a in a high-throughput manner by cloning of specific synthetic CDR1, CDR2 and/or CDR3 sequences into plasmids previously modified to contain BsaI cloning sites. Specifically, for each heavy or light chain, three vectors each were generated whereby a BsaI restriction site was incorporated at both the 5' and 3' end of each CDR region. To generate Fab mutants, forward and reverse primers encoding a CDR with specific mutations and additionally BsaI overlapping ends were synthesized and annealed. These cassettes, or mutated CDR regions, were then ligated into the corresponding BsaI digested vector, thereby generating a plasmid containing a specifically modified CDR region.

For example, specific primers were synthesized (IDT, see Table 8 below) and used to generate three vectors each for heavy chains VH1-46_IGHD6-6*01_IGHJ1*01 and VH5-51_IGHD5-18*01>3_IGHJ4*01 and light chains L6_IGKJ1*01 and V3-4_IGLJ1*01, to incorporate a BsaI site at the beginning and end of CDR1, CDR2 and CDR3. The vectors were generated as described above using the specific forward and reverse primers in the first round of PCR and the parent heavy or light chain DNA as a template. Individual clones were subjected to DNA sequencing (by BATJ, Inc., San Diego, CA) to confirm the incorporation of two BsaI sites in each CDR.

Subsequentely, each BsaI containing plasmid was digested with BsaI (New England Biolabs) and the DNA was gel purified. Specific primers were synthesized (IDT) to generate desired mutants. Briefly, 1 μl of each forward and reverse primer were annealed by heating to 95 °C in TE for 2 min, followed by slow cooling to room temperature. 1 μl of the annealed primers were then ligated with 2 ng of the BsaI digested vector and transformed into *E. coli* DH5a cell. Mutations were confirmed by DNA sequencing. The ligation reactions can be carried out in a 96-well plate thereby allowing for high-throughput mutagenesis.

For example, Table 8-9 below sets forth primers to generate VH1-46_IGHD6-6*01_IGHJ1*01_APFF CDR2 mutants.

Table 8. BsaI restriction enzyme mutagenesis primers

Primer	Sequence	SEQ ID NO
VH1-46_C DR1_F	gagacctactatggttcgggtctctgggtgcgacaggcc	11
VH1-46_C DR2_F	gagacctactatggttcgggtctcaagttccagggcagagtcac	12
VH1-46_C DR3_F	gagacctactatggttcgggtctctggggccagggcac	13
VH5-51_C DR1_F	gagacctactatggttcgggtctctgggtgcgccagatg	14
VH5-51_C DR2_F	gagacctactatggttcgggtctccaggtcaccatctcagccg	15
VH5-51_C DR3_F	gagacctactatggttcgggtctctggggccaaggaaccc	16
L6_CDR1_F	gagacctactatggttcgggtctctggtaccaacagaaacctggc	17
L6_CDR2_F	gagacctactatggttcgggtctcggcatcccagccagg	18
L6_CDR3_F	gagacctactatggttcgggtctcttcggccaagggacca	19
V3-4_CDR1_F	gagacctactatggttcgggtctctggtaccagcagacccca	20
V3-4_CDR2_F	gagacctactatggttcgggtctcggggtccctgatcgcttc	21
V3-4_CDR3_F	gagacctactatggttcgggtctcttcggaactgggaccaag	22
Lambda_BSA_F	gagtggagacgaccacaccc	23
VH1-46_C DR1_R	GAGACCCGAACCATAGTAGGTCTCAGATGCCTTGCAGGAAACC	24
VH1-46_C DR2_R	GAGACCCGAACCATAGTAGGTCTCTCCCATCCACTCAAGCCC	25
VH1-46_C DR3_R	GAGACCCGAACCATAGTAGGTCTCTCTCGCACAGTAATACACGGC	26
VH5-51_C DR1_R	GAGACCCGAACCATAGTAGGTCTCAGAACCCTTACAGGAGATCTTCA	27
VH5-51_C DR2_R	GAGACCCGAACCATAGTAGGTCTCCCCCATCCACTCCAGGC	28
VH5-51_C DR3_R	GAGACCCGAACCATAGTAGGTCTCTCTCGCACAGTAATACATGGC	29
L6_CDR1_R	GAGACCCGAACCATAGTAGGTCTCGCAGGAGAGGGTGGCTC	30
L6_CDR2_R	GAGACCCGAACCATAGTAGGTCTCATAGATGAGGAGCCTGGGAG	31

L6_CDR3_R	GAGACCCGAACCATAGTAGGTCTCACAGTAATAAACTGCAAAATCTTCAG	32
V3-4_CDR1_R	GAGACCCGAACCATAGTAGGTCTCACAAGTGAGTGTGACTGTCCCT	33
V3-4_CDR2_R	GAGACCCGAACCATAGTAGGTCTCGTAGATGAGCGTGCGTGG	34
V3-4_CDR3_R	GAGACCCGAACCATAGTAGGTCTCACAGTAATAATCAGATTCATCATCTGC	35

Table 9. VH1-46_IGHD6-6*01_IGHJ1*01_APFF_CDR2 BsaI mutagenesis primers

Primer	Sequence	SEQ ID NO
A_ILPTH_F	tgggaataattctccctactggtcatagcacaagctacgcacaga	36
A_VLPTH_F	tgggaatagtgctccctactggtcatagcacaagctacgcacaga	37
A_ALPTH_F	tgggaatagctctccctactggtcatagcacaagctacgcacaga	38
A_GLPTH_F	tgggaataggcctccctactggtcatagcacaagctacgcacaga	39
A_TLPTH_F	tgggaataaccctccctactggtcatagcacaagctacgcacaga	40
A_SLPTH_F	tgggaatatccctccctactggtcatagcacaagctacgcacaga	41
A_YLPTH_F	tgggaatatacctccctactggtcatagcacaagctacgcacaga	42
A_WLPTH_F	tgggaatatggctccctactggtcatagcacaagctacgcacaga	43
A_HLPTH_F	tgggaatacacctccctactggtcatagcacaagctacgcacaga	44
A_RLPTH_F	tgggaatacgcctccctactggtcatagcacaagctacgcacaga	45
A_ELPTH_F	tgggaatagaactccctactggtcatagcacaagctacgcacaga	46
A_NLPTH_F	tgggaataaacctccctactggtcatagcacaagctacgcacaga	47
A_TLVTH_F	tgggaataaccctcgtgactggtcatagcacaagctacgcacaga	48
A_TLATH_F	tgggaataaccctcgctactggtcatagcacaagctacgcacaga	49
A_TLGTH_F	tgggaataaccctcggcactggtcatagcacaagctacgcacaga	50
A_TLTTH_F	tgggaataaccctcaccactggtcatagcacaagctacgcacaga	51
A_TLSTH_F	tgggaataaccctctccactggtcatagcacaagctacgcacaga	52
A_TLYTH_F	tgggaataaccctctacactggtcatagcacaagctacgcacaga	53
A_TLWTH_F	tgggaataaccctctggactggtcatagcacaagctacgcacaga	54
A_TLHTH_F	tgggaataaccctccacactggtcatagcacaagctacgcacaga	55
A_TLRTH_F	tgggaataaccctccgcactggtcatagcacaagctacgcacaga	56
A_TLETH_F	tgggaataaccctcgaaactggtcatagcacaagctacgcacaga	57
A_TLNTH_F	tgggaataaccctcggcactggtcatagcacaagctacgcacaga	58
A_TLMTH_F	tgggaataaccctcatgactggtcatagcacaagctacgcacaga	59
A_ILPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGAATTATT	60
A_VLPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGCACTATT	61
A_ALPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGAGCTATT	62
A_GLPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGGCCTATT	63
A_TLPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGGGTTATT	64
A_SLPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGGGATATT	65
A_YLPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGGTATATT	66
A_WLPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGCCATATT	67
A_HLPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGGTGTATT	68
A_RLPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGGCGTATT	69
A_ELPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGTTCTATT	70
A_NLPTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGGGAGGTTTATT	71
A_TLVTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTCACGAGGGTTATT	72
A_TLATH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTAGCGAGGGTTATT	73
A_TLGTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTGCCGAGGGTTATT	74
A_TLTTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTGGTGAGGGTTATT	75
A_TLSTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTGGAGAGGGTTATT	76
A_TLYTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTGTAGAGGGTTATT	77
A_TLWTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTCCAGAGGGTTATT	78

A_TLHTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTGTGGAGGGTTATT	79
A_TLRTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTGCGGAGGGTTATT	80
A_TLETH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTTTCGAGGGTTATT	81
A_TLNTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTGCCGAGGGTTATT	82
A_TLMTH_R	AACTTCTGTGCGTAGCTTGTGCTATGACCAGTCATGAGGGTTATT	83

EXAMPLE 2

Cloning and High throughput Growth and Purification of Fab libraries

In this Example, Fab antibodies were generated by cloning heavy or light chain variable region DNA into their respective plasmids followed by co-transformation and high throughput protein growth/purification.

A. Cloning and Co-transformation of Variable Heavy and Light Chains

DNA encoding a heavy or light chain variable region was cloned into plasmids containing constant heavy or light chains as appropriate for co-transformation and expression of combinatorial Fabs. Plasmid A (SEQ ID NO:84) and plasmid D (SEQ ID NO:85) contain heavy chain constant regions sequences. Plasmid C (SEQ ID NO:86) contains a kappa light chain constant region sequence and Plasmid E (SEQ ID NO:87) contains a lambda light chain constant region sequence.

DNA encoding a variable heavy chain was digested with Nhe I and Nco I and ligated into Plasmid A with a StII leader sequence using standard molecular techniques. DNA encoding a variable kappa light chain was digested with NcoI and BsiWI and DNA encoding a variable lambda chain was digested with NcoI and AvrII, and were ligated into Plasmid C or Plasmid E, respectively, with a StII leader sequence, using standard molecular biology techniques.

Plasmid A and one of either Plasmid C or Plasmid E, each containing various combinations of variable heavy and light chains, were co-transformed into *E. coli*. The process was repeated for all combinations of heavy and light chains. Briefly, plasmid A (encoding a Fab heavy chain) and plasmid C or Plasmid E (encoding a Fab light chain) were resuspended separately in TE buffer to a final concentration of 1 ng/μl. One (1) μL of heavy chain plasmid and 1 μL of light chain plasmid were combined in a PCR tube or a PCR plate and were mixed with 20 μL ice cold LMG194 competent cells. The transformation reaction was incubated on ice for 10 minutes followed by heat shock in a preheated PCR block at 42 °C for 45 seconds. The tube was then placed on ice for an additional 2 minutes followed by addition of 200 μL SOC medium. The cells were allowed to recover for 1.5 hours at 37 °C. A 100 μL aliquot of the transformation culture was used to inoculate 0.9 mL LB (Luria-Bertani Broth) containing 0.4% (w/v) glucose, 17 μg/mL kanamycin (Sigma Aldrich) and 34 μg/mL chloramphenicol (Sigma Aldrich). The culture was grown at 30 °C with vigorous

shaking for 20 hours. The transformation culture was grown and purified using the Piccolo™ system as described below.

B. High throughput Growth and Purification of Fab antibodies

Following transformation, the cells were grown overnight in 2 ml deep well 96-well plates (VWR) block covered with breathable tape. The overnight culture was used directly for inoculation in Piccolo™ (Wollerton *et al.* (2006) JALA, 11:291-303.)

High throughput, parallel expression and purification of Fab antibodies was performed using Piccolo™ (The Automation Partnership (TAP)), which automates protein expression and purification. The expression and purification parameters for Piccolo™ were prepared using Run Composer software (TAP). A 'Strain File' was generated mapping the location of each clone in the seed culture plate. This was submitted to the Run Composer software and the basic machine settings were set as follows: Pre-induction Incubator set at 30° C; Expression Incubator 1 set at 16 °C; Centrifuge set at 6 °C and 5000 x *g*; Media Pump 1 primed with TB (Terrific Broth; per liter contains 12 g tryptone, 24 g yeast extract, 9.4 g potassium phosphate, dibasic, and 2.2 g potassium phosphate, monobasic) (EMD Biosciences; catalog No. 71754), 50 μg/mL kanamycin (Sigma Aldrich), 35 μg/mL chloramphenicol (Sigma Aldrich), 0.4% (w/v) glucose (Sigma Aldrich) and 0.015% (v/v) Antifoam 204 (Sigma Aldrich); Inducer Pump 1 primed with 0.2% (w/v) arabinose (EMD Biosciences); Incubator Gassing Rate set at 2 sec with 51% oxygen, 0.1 mL inoculation volume; Induction Statistic Mean set w/o Outliers (i.e. block mean OD_{600} determined after excluding the 3 highest and 3 lowest values); culture vessel blocks (CVB) pre-induction delay set at 1 hr 20 min and Expression Incubator Acclimatization set at 30 min.

The seed cultures were prepared and loaded into Piccolo™ along with the necessary labware: 24-well culture vessel blocks (CVBs; The Automation Partnership), 24-well Filter Plates (The Automation Partnership), 24-well Output Plates (Seahorse Bioscience) and Pipette Tip Boxes (MBP) as specified by the manufacturer. The TB media supplemented as described above, arabinose inducer and associated pumps were prepared under sterile conditions and attached to the machine. The centrifuge counterbalance weight was set and placed inside the centrifuge. Lastly, purification reagents were prepared and attached to the system pumps (lysis buffer, resin, wash buffer and elution buffer as described below). Once this was complete, the machine was started and processing began.

Before inoculation, the inocula were mapped to specific wells of 24-well CVB, and expression and induction conditions were set as described below. Each well of the CVBs was filled with 10 mL of TB media supplemented as described above prior to inoculation from the

seed plate. Each well of each CVB was inoculated with 0.1 mL seed culture and then returned to the storage carousel to await scheduled admission to pre-induction incubation. Once a CVB was queued to begin pre-induction incubation it was removed from the storage carousel and coupled to an aeration assembly (which provides agitation, well sealing and a means for controlled administration of oxygen/air) and then placed in the pre-induction incubator set at 30 °C. OD_{600} readings were taken upon commencement of incubation and approximately every 30 minutes thereafter. Piccolo operation control software monitors the OD_{600} measurements to predict when each CVB will reach the 1.0 OD_{600} set point. Approximately 30 minutes prior to the CVB reaching the OD_{600} set point the assembly was moved to the expression incubator to equilibrate to the expression temperature of 20 °C, and then the cultures in the CVB were induced by addition of 0.032% arabinose inducer followed by 45 hours of expression.

Following culture inoculation and growth induction of cultures, the cells were harvested and lysed for purification of Fabs. Piccolo™ was used for purification of the expressed Fab proteins using an automated expression and purification 'Lifecycle' of a whole culture purification. After controlled expression, CVBs were chilled for 30 minutes at 6 °C in the storage carousel prior to lysis. The CVB was moved to the liquid handling bed and lysis buffer (2.5 mL of Popculture with 1:1000 Lysonase (EMD Biosciences)) was added to each well with thorough mixing. The lysis proceeded for 10 minutes and then the CVB was centrifuged for 10 minutes at 5000 x *g* to pellet cell debris. During centrifugation, a Filter Plate was placed in the filter bed and resin (2 mL of a 50% slurry of Ni-charged His-Bind resin (EMD Biosciences)) was added to each well. Soluble lysate was added to the corresponding wells of the filter plate containing resin and allowed to bind for 10 minutes prior to draining to waste. Wash buffer (12 mL of wash buffer (50 mM Sodium Phosphate, 300 mM NaCl, 30 mM Imidazole, pH 8.0)) was added in two steps to each well and allowed to drain to waste. Finally, an Output Plate was placed under the Filter Plate in the filter bed and IMAC elution buffer (50 mM Sodium Phosphate, 300 mM NaCl, 500 mM Imidazole) was added in two steps draining into the output plate. The output plate was returned to the storage carousel as was all other labware. Once this process was complete for each CVB in the designed run, the machine was unloaded.

EXAMPLE 3

Orthogonal Secondary Purification of Fab antibodies

To rapidly further purify partially pure Fabs generated after the Piccolo™ process, an orthogonal method of purification was developed. Fabs were expressed and purified as described above in Example 2 using the Piccolo™ machine.

Two different affinity resins were used depending on the light chain classes. Fabs with a kappa light chain were further purified on Protein G column (GE Healthcare), and Fabs with a lambda light chain were further purified on CaptureSelect Fab Lambda affinity column (BAC, Netherlands). First, the protein samples were transferred to a deep well 96-well block (VWR). Approximately 1.8 mL of the IMAC elution per Fab sample was purified on either a 1 mL Hi-Trap Protein G column or a 0.5 mL CaptureSelect Fab Lambda affinity column at 4 °C using the Akta purifier (GE Healthcare) and A-905 autosampler (GE Healthcare) according to the manufacturer's protocol. Protein concentration was determined by measuring absorbance at A280 on a Molecular Dynamic plate reader and calculated from the exctinction coefficient of the corresponding Fab. Extinction coefficients are calculated based on the total numbers of Tyrosine + Tryptophane + Phenylalanine in the Fab heavy and light chains. Following purification using the Piccolo™ system, expressed protein was generally less than 20% pure. After orthogonal purification with protein G, Fab purity was greater than 95% pure as indicated by SDS-PAGE.

EXAMPLE 4

Electrochemiluminescence Binding Assay

In this example, an electrochemiluminescence (ECL) binding assay was used to screen a Fab library (e.g. see Table 4) for antibodies capable of binding to one of nine different antigens, including the human epidermal growth factor 2 receptor (ErbB2), epidermal growth factor receptor (EGF R), hepatocyte growth factor receptor (HGF R/c-Met), Notch-1, CD44, insulin-like growth factor-1 soluble receptor (IGF-1 sR), P-cadherin, erythropoietin receptor (Epo R) and delta-like protein 4 (DLL4). In an ECL assay, an antigen-antibody interaction is detected by addition of a detection antibody labeled with ruthenium tri-bispyridine-(4-methysulfone) ($Ru(bpy)_2^{2+}$). Upon application of an electric current, the $Ru(bpy)_2^{2+}$-label undergoes an oxidation-reduction cycle in the presence of a co-reactant and light is emitted. A signal is only generated when the $Ru(bpy)_2^{2+}$-label is in close proximity to the electrode, eliminating the need for washing. Detected light intensity is proportional to the amount of captured protein.

Recombinant human proteins were obtained from R&D Systems and included: rHuman ErbB2/Fc Chimera, CF (Cat# 1129-ER); rHuman EGF R/Fc Chimera, CF (Cat# 344-ER); rHuman HGF R/c-MET/Fc Chimera, CF (Cat# 358-MT/CF); rHuman Notch-1/Fc

Chimera, CF (Cat# 3647-TK); rHuman CD44/Fc Chimera, CF (Cat# 3660-CD); rHuman IGF-1 sR,(IGF-1 sR), CF (Cat# 391-GR); rHuman P-Cadherin/Fc Chimera, CF (Cat# 861-PC); rHuman Erythropoietin R/Fc Chimera, CF (Cat# 963-ER); and Recombinant Human DLL4 (Cat# 1506-D4/CF).

A. Multispot ECL assay for binding to multiple antigens

Each of the antigens listed above were immobilized onto each well of 10 plates by spotting 50 nanoliters (nl) of each protein (of a 60 μg/mL antigen) on the surface of a 96-well Multi-Spot 10 Highbind plate (Meso Scale Discovery; Gaithersburg MD). Spot 10 was left blank as a control.

An 150 μl aliquot of 1% Bovine Serum Albumin (BSA) in Tris-buffered Saline Tween (TBST) was added to each well and allowed to incubate for 30 min at 20 °C followed by washing and tap drying to completely remove any residual solution. Subsequently, a 12.5 μl aliquot of 1% BSA TBST was added to each well followed by the addition of a 12.5 μl aliquot of a purified Fab. The plate was sealed and incubated for 1 hour at 20 °C with shaking.

Detection antibodies were prepared by individually conjugating both goat anti-human Kappa light chain polyclonal antibody (K3502-1MG, Sigma-Aldrich) and goat anti-human Lambda light chain polyclonal antibody (L1645-1ML, Sigma-Aldrich) with Ruthenium (II) tris-bipyridine-(4-methylsulfone)-N-hydroxysuccinimide (SULFO-TAG NHS-ester, Meso Scale Discovery) according to the manufacturer's instructions. TAG-detection antibody at 25 μl was added to each well and allowed to incubate for 1 hour at 20 °C with shaking. Finally, 15 μl of Read Buffer P with Surfactant (Cat # R92PC-1, Meso Scale Discovery) was added to each well. The electrochemiluminescence was measured using a Sector Imager 2400 (Meso Scale Discovery). Data was analyzed by comparing the ECL signals for an antigen to the blank of each well. A signal to blank ratio of 4 or more was considered a "Hit" Fab.

Using the Multispot ECL assay antibodies were identified that bind to the selected antigens. Table 10, below, lists the Fabs (including the heavy chain and light chain) that were identified as "hits" using the Multispot ECL assay and the target(s) of the identified Fab "hit." Several Fabs were identified that bind to multiple targets. For example, VH1-46_IGHD6-13*01_IGH41*01 & B3_IGKJ1*01, shows affinity for both Human ErbB2/Fc and Human Erythropoietin R/Fc chimeras; Fab VH1-46_IGHD2-15*01_IGHJ2*01 & L12_IGKJ1*01 binds to EGF R, Epo R and DLL4 and Fab VH1-46_IGHD3-10*01_IGHJ4*01 & L12_IGKJ1*01 binds to Notch-1, P-cadherin and DLL4.

TABLE 10: IDENTIFIED FAB "HITS"

Target	Heavy Chain	SEQ ID NO	Light Chain	SEQ ID NO
rHuman DLL4	VH1-46_IGHD6-6*01_IGHJ1*01	88	L6_IGKJ1*01	107
rHuman DLL4	VH5-51_IGHD5-18*01>3_IGHJ4*01	89	V3-4_IGLJ1*01	108
rHuman DLL4	VH6-1_IGHD3-3*01_IGHJ4*01	90	V4-3_IGLJ4*01	109
rHuman ErbB2/Fc chimera	VH4-31_IGHD1-26*01_IGHJ2*01	91	A27_IGKJ1*01	110
rHuman Epo R/Fc chimera	VH1-46_IGHD3-10*01_IGHJ4*01	92	B3_IGKJ1*01	111
rHuman ErbB2/Fc chimera and rHuman Epo R/Fc chimera	VH1-46_IGHD6-13*01_IGHJ4*01	93	B3_IGKJ1*01	111
Epo R/Fc chimera	VH4-28_IGHD7-27*01_IGHJ1*01	94	L2_IGKJ1*01	112
Epo R/Fc chimera	VH4-31_IGHD7-27*01_IGHJ5*01	95	L2_IGKJ1*01	112
ErbB2/Fc chimera	VH2-5_IGHD7-27*01_IGHJ2*01	96	L2_IGKJ1*01	112
Epo R/Fc chimera	VH1-46_IGHD7-27*01_IGHJ2*01	97	A27_IGKJ1*01	110
ErbB2/Fc chimera	VH1-69_IGHD1-1*01_IGHJ6*01	98	A17_IGKJ1*01	113
Epo R/Fc chimera and EGF R/Fc chimera	VH1-46_IGHD2-15*01_IGHJ2*01	99	L2_IGKJ1*01	112
EGF R/Fc chimera, Notch-1/Fc chimera, P-cadherin/Fc chimera, Epo R/Fc chimera and DLL4	VH1-46_IGHD6-13*01_IGHJ4*01	93	L2_IGKJ1*01	112
DLL4	VH4-34_IGHD7-27*01_IGHJ4*01	100	L5_IGKJ1*01	114
Notch-1/Fc chimera, P-cadherin/Fc chimera, Epo R/Fc chimera and DLL4	VH1-46_IGHD6-13*01_IGHJ4*01	93	A27_IGKJ1*01	110
P-cadherin/Fc chimera	VH1-46_IGHD7-27*01_IGHJ2*01	97	L6_IGKJ1*01	107
DLL4	VH1-3_IGHD4-23*01_IGHJ4*01	101	L12_IGKJ1*01	115
EGF R/Fc chimera, Epo R/Fc chimera and DLL4	VH1-46_IGHD2-15*01_IGHJ2*01	99	L12_IGKJ1*01	115
Notch-1/Fc chimera, P-cadherin/Fc chimera and DLL4	VH1-46_IGHD3-10*01_IGHJ4*01	92	L12_IGKJ1*01	115
DLL4	VH1-8_IGHD2-2*01_IGHJ6*01	102	L12_IGKJ1*01	115
Epo R/Fc chimera	VH1-46_IGHD3-10*01_IGHJ4*01	92	O1_IGKJ1*01	116
Epo R/Fc chimera and DLL4	VH1-46_IGHD6-13*01_IGHJ4*01	93	O1_IGKJ1*01	116
DLL4	VH4-34_IGHD7-27*01_IGHJ4*01	100	V1-4_IGLJ4*01	117
DLL4	VH4-31_IGHD2-15*01_IGHJ2*01	103	V1-4_IGLJ4*01	117
DLL4	VH4-34_IGHD7-27*01_IGHJ4*01	100	V4-6_IGLJ4*01	118
P-cadherin/Fc chimera and Epo R/Fc chimera	VH3-23_IGHD3-10*01>3_IGHJ6*01	104	O12_IGKJ1*01	119

P-cadherin/Fc chimera	VH3-23_IGHD3-10*01>1'_IGHJ3*01	105	O12_IGKJ1*01	119

To confirm a "Hit" from the initial Multispot ECL screening, a Fab concentration dependent titration was carried out to determine the Fab-antigen binding affinity. The Multispot ECL assay procedure was the same as described above, except that the concentration of Fab antibody was varied between wells from 0.1 nM to 2.4 μM as indicated in the Tables below depending on each Fab tested. The data are set forth in Tables 11-33 below.

Table 11. Binding affinity of Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01

Fab[nM]	2383	595.8	148.9	37.2	9.3	2.3	0.6	0.1
ErbB2/Fc	454	321	247	384	354	291	215	306
EGF R/Fc	621	403	290	228	424	289	309	311
HGF R/Fc	762	353	205	207	324	253	256	286
Notch-1/Fc	690	306	375	402	492	333	337	378
CD44/Fc	559	372	348	356	396	317	238	323
IGF-1 sR	527	335	322	295	315	231	313	241
P-Cadherin/Fc	728	617	687	649	452	401	321	235
EPO R/Fc	658	378	373	315	306	429	337	373
DLL4	11794	17203	16253	16717	13210	3055	508	317
Blank	344	285	218	199	287	234	226	201

Table 12. Binding affinity of Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01

Fab[nM]	154	51	17	6
ErbB2/Fc	1593	1248	1033	873
EGF R/Fc	1398	816	805	742
HGF R/Fc	1520	1044	914	831
Notch-1/Fc	929	685	558	464
CD44/Fc	960	651	518	547
IGF-1 sR	1396	1051	872	854
P-Cadherin/Fc	1733	854	542	358
EPO R/Fc	1195	750	620	548
DLL4	40392	17025	7158	1946
Blank	447	335	143	191

Table 13. Binding affinity of Fab VH6-1_IGHD3-3*01_IGHJ4*01 & V4-3_IGLJ4*01								
Fab[nM]	**480**	**240**	**120**	**60**	**30**	**15**	**7.5**	**3.8**
ErbB2/Fc	965	833	822	777	726	713	695	714
EGF R/Fc	877	690	658	679	585	584	582	511
HGF R/Fc	951	834	785	623	640	694	558	519
Notch-1/Fc	545	368	472	415	425	508	392	383
CD44/Fc	541	470	442	434	484	454	444	419
IGF-1 sR	741	625	813	654	697	705	642	463
P-Cadherin/Fc	596	383	450	372	440	351	352	281
EPO R/Fc	621	478	431	423	325	397	443	407
DLL4	1532	1273	938	875	736	690	598	462
Blank	362	316	363	237	213	261	217	198

Table 14. Binding affinity of Fab VH4-31_IGHD1-26*01_IGHJ2*01 & A27_IGKJ1*01								
Fab[nM]	**410**	**205**	**102.5**	**51.3**	**25.6**	**12.8**	**6.4**	**3.2**
ErbB2/Fc	5422	5260	4355	3588	2992	2255	1796	868
EGF R/Fc	734	595	455	379	373	320	249	254
HGF R/Fc	753	735	425	456	382	258	234	294
Notch-1/Fc	804	722	607	408	270	249	279	275
CD44/Fc	767	613	461	409	332	273	240	295
IGF-1 sR	600	565	443	316	311	323	209	313
P-Cadherin/Fc	814	769	714	424	323	245	197	206
EPO R/Fc	797	595	587	498	409	338	264	233
DLL4	859	599	550	474	384	268	256	242
Blank	637	430	437	337	345	227	133	172

Table 15. Binding affinity of Fab VH1-46_IGHD3-10*01_IGHJ4*01 & B3_IGKJ1*01								
Fab[nM]	**1410**	**705**	**352.5**	**176.3**	**88.1**	**44.1**	**22**	**11**
ErbB2/Fc	932	671	514	448	200	347	363	216
EGF R/Fc	1071	692	769	428	376	428	312	201
HGF R/Fc	903	839	606	418	392	336	203	268
Notch-1/Fc	1034	958	715	664	440	331	389	404
CD44/Fc	885	693	556	376	340	302	317	296
IGF-1 sR	426	630	528	393	273	309	347	289
P-Cadherin/Fc	1059	827	649	532	278	343	215	270
EPO R/Fc	4314	4894	4105	3519	3368	2387	2241	1824
DLL4	1265	981	660	460	434	388	342	254
Blank	709	483	494	346	301	200	289	212

Table 16. Binding affinity of Fab VH1-46_IGHD6-13*01_IGHJ4*01 & B3_IGKJ1*01								
Fab[nM]	**1000**	**500**	**250**	**125**	**62.5**	**31.3**	**15.6**	**7.8**
ErbB2/Fc	8731	10241	11026	12956	13124	13911	14791	13220
EGF R/Fc	2236	1468	1138	860	602	447	346	379
HGF R/Fc	2109	1371	1221	778	578	299	293	282
Notch-1/Fc	2267	1975	1241	802	536	563	418	486
CD44/Fc	1966	1685	1175	764	591	439	473	409
IGF-1 sR	1667	1334	993	654	491	385	349	353
P-Cadherin/Fc	4495	3447	2784	1481	1173	1105	971	695
EPO R/Fc	8594	10305	8535	9237	7749	7878	8357	6765
DLL4	2785	2319	1560	912	715	528	525	407
Blank	1133	680	590	403	268	250	294	316

Table 17. Binding affinity of Fab VH4-28_IGHD7-27*01_IGHJ1*01 & L2_IGKJ1*01		
Fab[nM]	**360**	**36**
ErbB2/Fc	647	600
EGF R/Fc	957	711
HGF R/Fc	581	613
Notch-1/Fc	1026	773
CD44/Fc	740	679
IGF-1 sR	535	486
P-Cadherin/Fc	636	693
EPO R/Fc	4715	2977
DLL4	866	799
Blank	462	413

Table 18. Binding affinity of Fab VH1-46_IGHD2-15*01_IGHJ2*01 & L2_IGKJ1*01				
Fab[μM]	**0.25**	**0.0625**	**0.01563**	**0.00391**
ErbB2/Fc	29608	9033	4495	1667
EGF R/Fc	116674	94778	70836	35936
HGF R/Fc	13427	4108	1998	913
Notch-1/Fc	21447	5848	2800	1282
CD44/Fc	23015	6746	3182	1295
IGF-1 sR	11050	3150	1742	822
P-Cadherin/Fc	25459	7739	4945	1962
EPO R/Fc	49177	21136	11342	5022
DLL4	27691	8051	4015	1551
Blank	6344	1738	906	576

Table 19. Binding affinity of Fab VH1-46_IGHD6-13*01_IGHJ4*01 & L2_IGKJ1*01				
Fab[μM]	**1.19**	**0.2975**	**0.07438**	**0.01859**
ErbB2/Fc	38410	15111	7551	5531
EGF R/Fc	62454	42213	16605	11750
HGF R/Fc	45494	17396	6611	4566
Notch-1/Fc	72018	37503	21990	17565
CD44/Fc	47145	28601	10922	7322
IGF-1 sR	35187	17389	5804	3779
P-Cadherin/Fc	69710	26043	14807	11672
EPO R/Fc	192967	167064	153692	188065
DLL4	74900	34726	20719	18888
Blank	24999	5019	2504	1776

Table 20. Binding affinity of Fab VH4-34_IGHD7-27*01_IGHJ4*01 & L5_IGKJ1*01				
Fab[μM]	**0.51**	**0.1275**	**0.03188**	**0.00797**
ErbB2/Fc	1532	857	584	493
EGF R/Fc	2363	1061	694	530
HGF R/Fc	1989	853	693	419
Notch-1/Fc	2773	1497	849	654
CD44/Fc	2012	926	653	490
IGF-1 sR	2236	1045	765	564
P-Cadherin/Fc	2389	957	775	502
EPO R/Fc	2624	1067	789	566
DLL4	5183	2382	1282	872
Blank	1096	530	536	364

Table 21. Binding affinity of Fab VH1-46_IGHD6-13*01_IGHJ4*01 & A27_IGKJ1*01			
Fab[μM]	**0.48**	**0.096**	**0.0192**
ErbB2/Fc	11287	3365	2313
EGF R/Fc	14638	4509	3115
HGF R/Fc	8002	2328	1582
Notch-1/Fc	15931	4802	3041
CD44/Fc	13445	4320	2915
IGF-1 sR	8927	2449	1826
P-Cadherin/Fc	15595	6654	5040
EPO R/Fc	70938	57356	62037
DLL4	16065	5586	3555
Blank	2945	917	751

Table 22. Binding affinity of Fab VH1-46_IGHD7-27*01_IGHJ2*01 & L6_IGKJ1*01			
Fab[μM]	**1.56**	**0.312**	**0.0624**
ErbB2/Fc	7577	3659	2146
EGF R/Fc	7832	4328	2415
HGF R/Fc	10267	4691	2453
Notch-1/Fc	9447	4462	2352
CD44/Fc	7595	4171	2110
IGF-1 sR	6913	3508	2034
P-Cadherin/Fc	15016	7098	4226
EPO R/Fc	9480	5020	2678
DLL4	10897	5484	2585
Blank	4357	1977	960

Table 23. Binding affinity of Fab VH1-3_IGHD4-23*01_IGHJ4*01 & L12_IGKJ1*01				
Fab[nM]	**60**	**15**	**3.75**	**0.9375**
ErbB2/Fc	2155	740	291	268
EGF R/Fc	2563	842	371	224
HGF R/Fc	2298	743	394	243
Notch-1/Fc	2886	1058	375	348
CD44/Fc	2355	748	307	251
IGF-1 sR	2666	859	314	204
P-Cadherin/Fc	2662	837	331	191
EPO R/Fc	3214	970	358	238
DLL4	17270	7728	1569	453
Blank	1433	536	191	153

Table 24. Binding affinity of Fab VH1-46_IGHD2-15*01_IGHJ2*01 & L12_IGKJ1*01				
Fab[nM]	**280**	**70**	**17.5**	**4.375**
ErbB2/Fc	3953	1358	541	384
EGF R/Fc	6667	2574	1305	542
HGF R/Fc	3564	1289	565	193
Notch-1/Fc	4382	1492	680	480
CD44/Fc	4069	1370	664	424
IGF-1 sR	3533	1319	626	369
P-Cadherin/Fc	5400	1817	949	469
EPO R/Fc	8496	2485	1262	594
DLL4	8111	2747	1219	558
Blank	1691	635	304	305

Table 25. Binding affinity of Fab VH1-46_IGHD3-10*01_IGHJ4*01 & L12_IGKJ1*01				
Fab[nM]	**920**	**230**	**57.5**	**14.375**
ErbB2/Fc	10924	4078	2447	1594
EGF R/Fc	13406	5723	3858	2672
HGF R/Fc	10708	3934	2297	1600
Notch-1/Fc	20086	9737	5886	4206
CD44/Fc	9698	3817	2313	1488
IGF-1 sR	10246	4764	2833	1746
P-Cadherin/Fc	16666	6484	4110	2318
EPO R/Fc	16429	6949	4038	2718
DLL4	73638	119436	144126	125422
Blank	4082	1656	954	738

Table 26. Binding affinity of Fab VH1-8_IGHD2-2*01_IGHJ6*01 & L12_IGKJ1*01				
Fab[nM]	**130**	**32.5**	**8.1**	**2.0**
ErbB2/Fc	1533	556	557	382
EGF R/Fc	1746	645	560	424
HGF R/Fc	1882	525	551	356
Notch-1/Fc	1759	706	612	539
CD44/Fc	1754	573	528	447
IGF-1 sR	1973	561	518	367
P-Cadherin/Fc	1845	556	573	250
EPO R/Fc	2151	673	660	433
DLL4	7738	2989	1548	605
Blank	1153	473	435	316

Table 27. Binding affinity of Fab FabVH1-46_IGHD3-10*01_IGHJ4*01 & O1_IGKJ1*01				
Fab[nM]	**1570**	**392.5**	**98.1**	**24.5**
ErbB2/Fc	1263	539	247	241
EGF R/Fc	2481	744	4386	317
HGF R/Fc	1638	581	335	211
Notch-1/Fc	1639	749	313	434
CD44/Fc	1381	498	265	267
IGF-1 sR	1428	466	309	239
P-Cadherin/Fc	1793	459	347	257
EPO R/Fc	6121	5863	5628	4531
DLL4	2701	735	402	339
Blank	866	338	210	149

Table 28. Binding affinity of Fab VH1-46_IGHD6-13*01_IGHJ4*01 & O1_IGKJ1*01				
Fab[nM]	**930**	**232.5**	**58.1**	**14.5**
ErbB2/Fc	2225	779	322	274
EGF R/Fc	3110	803	444	357
HGF R/Fc	2344	790	432	373
Notch-1/Fc	2206	778	388	317
CD44/Fc	1917	607	375	212
IGF-1 sR	1915	569	343	234
P-Cadherin/Fc	2438	655	478	277
EPO R/Fc	3009	1472	829	660
DLL4	8162	3586	1876	1149
Blank	1206	460	225	117

Table 29. Binding affinity of Fab VH4-34_IGHD7-27*01_IGHJ4*01 & V1-4_IGLJ4*01				
Fab[nM]	**580**	**145**	**36.3**	**9.1**
ErbB2/Fc	1712	1123	1029	987
EGF R/Fc	1631	856	831	800
HGF R/Fc	2341	1173	1065	894
Notch-1/Fc	1585	860	633	754
CD44/Fc	1228	692	629	607
IGF-1 sR	1364	794	799	788
P-Cadherin/Fc	2240	850	684	589
EPO R/Fc	1579	845	722	697
DLL4	4420	2140	1399	1030
Blank	679	357	314	276

Table 30. Binding affinity of Fab VH4-31_IGHD2-15*01_IGHJ2*01 & V1-4_IGLJ4*01				
Fab[nM]	**210**	**52.5**	**13.1**	**3.3**
ErbB2/Fc	1977	1511	930	1031
EGF R/Fc	1617	1109	824	847
HGF R/Fc	2060	1286	981	849
Notch-1/Fc	1972	1323	669	726
CD44/Fc	1395	897	708	621
IGF-1 sR	1431	911	814	743
P-Cadherin/Fc	4410	2161	1062	678
EPO R/Fc	2123	1319	776	695
DLL4	4108	1951	1107	922
Blank	833	467	376	359

Table 31. Binding affinity of Fab VH4-34_IGHD7-27*01_IGHJ4*01 & V4-6_IGLJ4*01				
Fab[nM]	**340**	**170**	**85.0**	**42.5**
ErbB2/Fc	1226	964	844	866
EGF R/Fc	1208	826	1001	528
HGF R/Fc	1238	757	998	607
Notch-1/Fc	1209	816	780	649
CD44/Fc	959	660	693	522
IGF-1 sR	1042	832	891	646
P-Cadherin/Fc	1160	744	709	421
EPO R/Fc	1255	790	817	494
DLL4	2332	1462	1311	877
Blank	554	262	292	162

Table 32. Binding affinity of Fab VH3-23_IGHD3-10*01>3_IGHJ6*01 & O12_IGKJ1*01				
Fab[nM]	**120**	**12**	**1.2**	**0.12**
ErbB2/Fc	17294	4358	677	287
EGF R/Fc	14925	1984	464	272
HGF R/Fc	15917	2703	412	287
Notch-1/Fc	14382	2582	660	218
CD44/Fc	13519	1321	341	291
IGF-1 sR	13265	1135	181	175
P-Cadherin/Fc	61714	28490	1684	318
EPO R/Fc	33268	10966	1014	260
DLL4	20627	2510	319	210
Blank	6749	573	227	264

Table 33. Binding affinity of Fab VH3-23_IGHD3-10*01>1'_IGHJ3*01 & O12_IGKJ1*01		
Fab[nM]	**421.12**	**42.112**
ErbB2/Fc	868	524
EGF R/Fc	765	422
HGF R/Fc	1202	565
Notch-1/Fc	1061	437
CD44/Fc	903	360
IGF-1 sR	1065	364
P-Cadherin/Fc	2949	1546
EPO R/Fc	1299	759
DLL4	1090	404
Blank	639	323

B. 96-well plate ECL assay for binding to DLL4

A similar ECL assay was performed as above, except only one antigen was immobilized to a single-spot per well plate for testing. Recombinant Human DLL4 (Cat# 1506-D4/CF) was immobilized onto a 96-well plate by adding 5 μL (of 10 μg/ml DLL4 in PBS + 0.03% Triton-X-100) to each well and incubating overnight at 20 °C. One well was

left blank as a control. The protein was removed and an 150 µl aliquot of 1% BSA in TBST was added to each well and allowed to incubate for 1 hour at 20 °C followed by washing 2 times with 150 µl TBST and tap drying to completely remove any residual solution. Subsequently, 25 µl aliquot of each Fab (with 1% BSA with TBST) was added to each well. The plate was sealed and incubated for 1 hour at 20 °C with shaking. As described in Examples 7 and 12, two different combinations of antigen and Fab concentrations were utilized. In one experiment, 5 µL of 30 µg/mL antigen was used to coat the plate and each Fab was tested at a concentration of 0.02 µM. In the other experiment, 5 µL of 15 µg/mL antigen was used to coat the plate and each Fab was tested at a concentration of 0.004 µM.

The Fab was subsequently removed and 25 µl anti-human Kappa Ruthenium antibody or anti-human Lambda Ruthenium antibody (1 µg/ml in 1% BSA with TBST) was added to each well and allowed to incubate for 1 hour at 20 °C with shaking. Finally, 15 µl of Read Buffer P with Surfactant (Cat # R92PC-1, Meso Scale Discovery) was added to each well. The electrochemiluminescence was measured using a Sector Imager 2400 (Meso Scale Discovery). Data was analyzed by comparing the ECL signals for an antigen to the blank of each well. A signal to blank ratio of 4 or more was considered a "Hit" Fab. The results are depicted in Examples 7-15 below.

EXAMPLE 5

Surface Plasmon Resonance

In this example, the binding affinities of selected Fabs to recombinant human DLL4 (R&D Systems) were analyzed using Surface Plasmon Resonance (SPR) (Biosensor Tools, Salt Lake City, UT). The Fabs include germline antibodies identified in the initial ECL screen as binding to DLL4 (as shown in Example 4).

The results are shown in Table 34 below. Table 34 sets forth the Fab, the k_a ($M^{-1}s^{-1}$), the k_d (s^{-1}), and the K_D (nM) and the standard deviation (in parentheses). Germline Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 has an average K_D of 4.8 µM. Germline Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 binds DLL4 with an average K_D of 730 nM. Germline Fab VH6-1_IGHD3-3*01_IGHJ4*01 & V4-3_IGLJ4*01 has an average binding affinity of 38 µM while germline Fab VH1-46_IGHD3-10*01_IGHJ4*01 & L12_IGKJ1*01 has an average K_D of 500 nM.

Table 34. Binding affinity of DLL4 Fabs						
Heavy Chain	SEQ ID NO	Light Chain	SEQ ID NO	k_a ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_D (nM)
VH5-51_IGHD5-18*01>3_IGHJ4*01	89	V3-4_IGLJ1*01	108	n/a	n/a	4800(200)
VH1-46_IGHD6-6*01_IGHJ1*01	88	L6_IGKJ1*01	107	1.63(3)e5	0.101(2)	730(130)
VH6-1_IGHD3-3*01_IGHJ4*01	90	V4-3_IGLJ4*01	109	n/a	n/a	38000(4000)
VH1-46_IGHD3-10*01_IGHJ4*01	92	L12_IGKJ1*01	115	5(1)e5	0.29(2)	500(100)

EXAMPLE 6

ELISA Binding Assay

In this example, an ELISA binding assay was used to determine the binding of Fab antibodies to DLL4.

A. 96-well plate

Briefly, 50µl of a 0.5 µg/ml solution of DLL4 in 100 mM $NaHCO_3$, pH 9 was added to each well of a 96-well Costar plate (Cat # 3370, Corning Inc.) and allowed to incubate for 1 hour at room temperature. The plate was blocked by adding 1% BSA in Tris-buffered Saline Tween (TBST) and incubating for 1 hour at room temperature followed by washing 2 times with 150 µl TBST. A Fab antibody was serially diluted in 1% BSA in TBST, starting at a concentration of 1000 nM. A 50 µl aliquot of each serial dilution was added, in triplicate, to each well and the plate was incubated for 1 hour at room temperature followed by washing 2 times with TBST. 50 µl of goat anti-DDDDK tag HRP conjugated polyclonal antibody diluted 1:1000 in 1% BSA TBST (Cat # AB1238-200, Abcam), was added to each well and the plate was incubated for 30 minutes at room temperature followed by washing 3 times with 200 µl TBST. Finally, 100 µl TMB one-component reagent (Cat # TMBW-1000-01, BioFax) was added and allowed to develop for 2 minutes at room temperature. The reaction was immediately halted by the addition of 100 µl 0.5 M H_2S0_4 and the absorbance at 450 nm was measured using an ELISA plate reader. Results using this assay are depicted in Examples 9 and 10.

B. 384-well plate

Briefly, 10µl of a 0.5 µg/ml solution of DLL4 in 100 mM $NaHCO_3$, pH 9 was added to each well of a 384-well Nunc Maxisorp plate (Cat # 464718, Nalgene Nunc International) and allowed to incubate for 90 minutes at room temperature. The plate was blocked by adding 1% BSA in Tris-buffered Saline Tween (TBST) and incubating for 1 hour at room temperature followed by washing 2 times with 100 µl TBST. Fab antibody was serially diluted in 1% BSA in TBST, starting at a concentration of 1000 nM. A 20 µl aliquot of each

serial dilution was added, in triplicate, to each well and the plate was incubated for 1 hour at room temperature followed by washing 2 times with 100 µl TBST. Depending on the light chain, 20 µl of goat anti-kappa HRP conjugated polyclonal antibody, diluted 1:1000 in 1% BSA TBST (Cat # A7164-1mL, Sigma-Aldrich) or goat anti-lambda HRP conjugated polyclonal antibody, diluted 1:1000 in 1% BSA TBST (Cat # L1645-1ml, Sigma-Aldrich) was added to each well and the plate was incubated for 1 hour at room temperature followed by washing 4 times with 100 µl TBST. Finally, 25 µl TMB one-component reagent reagent (Cat # TMBW-1000-01, BioFax) was added and allowed to develop for 1-5 minutes at room temperature. The reaction was immediately halted by the addition of 25 µl 0.5 M H_2S0_4 and the absorbance at 450 nm was measured using an ELISA plate reader. Results using this assay are depicted in Examples 9 and 10.

EXAMPLE 7

Affinity Maturation of th Heavy Chain of Anti-DLL4 "Hit" VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01

a. Summary

The heavy and light chain amino acid sequence of Fab "Hit" VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 (SEQ ID NOS:88 and 107) against DLL4, identified in Example 4 using the Multispot ECL binding assay, was aligned with the heavy and light chain amino acid sequence of a related "non-Hit" Fab antibody that had a related heavy or light chain but did not bind to DLL4. Based on the alignment, amino acid residues that differed between the "Hit" and "non-Hit" antibodies were identified in each of the heavy and light chain as potential amino acids involved in binding for subsequent affinity maturation. Affinity maturation of the heavy chain is described in Examples 7-9. Affinity maturation of the light chain is described in Example 10.

Briefly, the identified amino acid residues were subjected to alanine-scanning mutagenesis and resultant mutant Fabs tested to assess the affect of the mutation on binding of the antibody to DLL4. Mutated residues that did not affect binding of the antibody to DLL4 were identified and subjected to further mutagenesis using overlapping PCR with NNK mutagenesis. Mutant antibodies were assessed for DLL4 binding, and mutations that improved binding to DLL4 were identified. Combinations mutants were generated containing each of the identified single mutants; combination mutants were further assayed for binding to DLL4. Further optimization was performed by mutating other regions of the antibody. By this method, anti-DLL4 antibodies were generated with significantly improved binding

affinity for DLL4 compared to the parent "Hit" VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 Fab antibody.

b. Affinity Maturation of Heavy Chain

i. Identification of the CDR potential binding site

The amino acid sequence of the heavy chain (SEQ ID NO:88) for the parent "Hit" VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 was aligned with the amino acid sequence of a related heavy chain (SEQ ID NO:93) of a non-Hit that was identified as not binding to DLL4, i.e. VH1-46_IGHD6-13*01_IGHJ4*01 & L6_IGKJ1*01. "Hit" Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 had an ECL signal/blank ratio of 23.1 while that of the non-Hit Fab VH1-46_IGHD6-13*01_IGHJ4*01 & L6_IGKJ1*01 was only 2.4. These two Fabs are related because they share the same V_H germline segment. Further, the D_H germline segment is of the same gene family (i.e. IGHD6). The sequence alignment is set forth in Figure 1. Based on the alignment, amino acid residues were identified that differed between the "Hit" and "non-Hit," thus accounting for the differences in binding of the "Hit" and "non-Hit" anti-DLL4 antibodies. The identified amino acid residues were located in CDR3, which was identified as the region of the heavy chain that is important for binding affinity.

ii. Alanine scanning of CDR3

Alanine scanning mutagenesis was performed on amino acid residues in the CDR3 of the heavy chain sequence of parent Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 to identify amino acid residues that do not appear to be involved in DLL4 binding. Alanine-scanning of the CDR3 region of the heavy chain sequence of parent Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 was performed by mutating every residue of the CDR3 region to an alanine, except amino acid residues A106, Y108, and F109. The mutant Fab antibodies were expressed and purified as described in Example 2 above.

Purified Fab alanine mutants were tested for binding to DLL4 using the ECL 96-well plate assay as described in Example 4B. 5 μL of 10 μg/mL recombinant Human DLL4 antigen was coated to to a 96-well plate, and tested Fab mutants were added at a concentration of 0.04 μM. As a control, background binding of the Fab to a blank well of the 96-well plate also was determined. The data were depicted as a Signal/Noise ratio of the ECL signal, which is the ratio of the ECL signal for binding to DLL4 divided by the ECL signal for residual binding to the plate. Table 35 sets forth the mutant Fabs tested and the Signal/Noise ratio observed for binding to DLL4. The results show that mutation of E100, Y101, S105, E107 or Q110 with alanine caused a reduction in the ECL signal and therefore decreased binding affinity to DLL4. These residues, therefore, appeared to be involved in the DLL4

binding and were not further mutagenized. In contrast, mutation of S102, S103, S104 or H111 with alanine resulted in either an increased ECL signal or no difference in ECL signal compared to the parent and thus either improved binding affinity or did not affect binding affinity to DLL4. Accordingly, these residues were identified as residues for further mutagenesis.

The ECL binding experiments above were repeated, except with varying concentrations of mutant Fab and DLL4 protein. Table 36 sets forth the mutant Fab, the ECL signal, and the Signal/Noise ratio for two different concentrations of DLL4 antigen and mutant Fab. The results are consistent for both assays and confirm the initial results above. Substitution of E100, Y101, S105, E107 or Q110 with alanine caused a reduction in ECL signal for binding to DLL4 while substitution of S102, S103, S104 or H111 with alanine either improved the ECL signal for binding or did not affect the ECL signal for binding to DLL4.

Table 35. Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 alanine mutant binding data

Fab				Signal/Noise (0.04 μM)
Heavy Chain	**SEQ ID NO**	**Light Chain**	**SEQ ID NO**	
E100A	129	L6_IGKJ1*01	107	0.9
Y101A	130	L6_IGKJ1*01	107	0.8
S102A	124	L6_IGKJ1*01	107	5.6
S103A	131	L6_IGKJ1*01	107	3.5
S104A	122	L6_IGKJ1*01	107	1.3
S105A	132	L6_IGKJ1*01	107	0.8
E107A	133	L6_IGKJ1*01	107	0.7
Q110A	134	L6_IGKJ1*01	107	0.9
H111A	135	L6_IGKJ1*01	107	2.4
parental	88	L6_IGKJ1*01	107	3.1

Table 36. Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 alanine mutant binding data

Fab			0.02 μM Fab 30 μg/mL DLL4		0.004 μM Fab 15 μg/mL DLL4	
Heavy Chain	**SEQ ID NO**	**Light Chain (SEQ ID NO:107)**	**ECL Signal**	**Signal/ Noise**	**ECL Signal**	**Signal/ Noise**
VH1-46_IGHD6-6*01_IGHJ1*01	88	L6_IGKJ1*01	8714	23.0	4261	29.2
E100A	129	L6_IGKJ1*01	1296	3.4	536	3.7
Y101A	130	L6_IGKJ1*01	237	0.6	340	2.3
S102A	124	L6_IGKJ1*01	19056	50.3	10338	70.8
S103A	131	L6_IGKJ1*01	11553	30.5	5150	35.3
S104A	122	L6_IGKJ1*01	163452	431.3	3614	24.8
S105A	132	L6_IGKJ1*01	1103	2.9	181	1.2

E107A	133	L6_IGKJ1*01	338	0.9	146	1.0
Q110A	134	L6_IGKJ1*01	257	0.7	128	0.9
H111A	135	L6_IGKJ1*01	11582	30.6	5023	34.4

iii. NNK mutagenesis of heavy chain amino acid residues S102, S103, S104

Following alanine scanning mutagenesis of CDR3, heavy chain amino acid residues S102, S103 and S104 were selected for further mutation using overlapping PCR with NNK mutagenesis as described in Example 1 using parent Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 as a template.

The binding affinity of each generated Fab mutant for DLL4 was determined using the 96-well plate ECL assay described in Example 4 with varying concentrations of Fab and DLL4 protein. Table 37 sets forth the Signal/Noise ratio for each of the S102, S103 and S104 NNK mutants. Fab NNK mutants were selected at random prior to sequencing and therefore several mutants, such as S103L, were purified and tested multiple times giving consistent results. Three mutations in Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 were identified that resulted in a Fab with an increased signal/noise ratio and therefore improved binding affinity to DLL4. Two Fab mutants, S102A and S103P, each had an signal/noise ratio for DLL4 approximately 3-fold greater than parent Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01. A third mutant, heavy chain Fab mutant S104F, had a signal/noise ratio for binding to DLL4 at least 4-fold greater than that of parent Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01. Two additional mutations were identified that resulted in a slight increase in the signal/noise ratio for binding to DLL4, namely Fab heavy chain mutants S103A and S104H.

Table 37. NNK mutagenesis of Fab VH1-46_IGHD6-6*01_IGHJ1*01 and L6_IGKJ1*01 at amino acid residues S102, S103 and S104

Fab			0.02 μM Fab 30 μg/mL DLL4	0.004 μM Fab 15 μg/mL DLL4
Heavy Chain	**SEQ ID NO**	**Light Chain (SEQ ID NO:107)**	**Signal/Noise**	**Signal/Noise**
VH1-46_IGHD6-6*01_IGHJ1*01	88	L6_IGKJ1*01	19.5	25.0
VH1-46_IGHD6-6*01_IGHJ1*01	88	L6_IGKJ1*01	24.8	19.5
VH1-46_IGHD6-6*01_IGHJ1*01	88	L6_IGKJ1*01	20.3	28.3
S102Q	136	L6_IGKJ1*01	40.6	31.9
S102V	137	L6_IGKJ1*01	35.9	36.5
S102I	138	L6_IGKJ1*01	35.3	34.5

Table 37. NNK mutagenesis of Fab VH1-46_IGHD6-6*01_IGHJ1*01 and L6_IGKJ1*01 at amino acid residues S102, S103 and S104				
Fab			0.02 μM Fab 30 μg/mL DLL4	0.004 μM Fab 15 μg/mL DLL4
Heavy Chain	SEQ ID NO	Light Chain (SEQ ID NO:107)	Signal/Noise	Signal/Noise
S102A	124	L6_IGKJ1*01	**51.7**	**69.8**
S102G	139	L6_IGKJ1*01	5.1	5.2
S103stop	234	L6_IGKJ1*01	0.8	1.1
S103L	140	L6_IGKJ1*01	25.8	36.6
S103W	141	L6_IGKJ1*01	16.3	25.0
S103L	140	L6_IGKJ1*01	27.0	36.8
S103L	140	L6_IGKJ1*01	39.8	44.9
S103F	142	L6_IGKJ1*01	16.4	20.7
S103L	140	L6_IGKJ1*01	22.5	30.7
S103L	140	L6_IGKJ1*01	18.7	28.1
S103N	143	L6_IGKJ1*01	18.8	23.8
S103H	144	L6_IGKJ1*01	21.7	31.7
S103C	145	L6_IGKJ1*01	27.1	27.4
S103L	140	L6_IGKJ1*01	22.1	36.3
S103L	140	L6_IGKJ1*01	24.0	40.4
S103A	131	L6_IGKJ1*01	**30.9**	**44.5**
S103A	131	L6_IGKJ1*01	**29.1**	**32.9**
S103L	140	L6_IGKJ1*01	26.6	30.7
S103G	146	L6_IGKJ1*01	9.1	8.3
S103W	141	L6_IGKJ1*01	25.8	38.8
S103F	142	L6_IGKJ1*01	21.9	21.2
S103P	123	L6_IGKJ1*01	**59.7**	**82.4**
S103N	143	L6_IGKJ1*01	13.4	22.4
S104G	147	L6_IGKJ1*01	23.4	20.0
S104C	148	L6_IGKJ1*01	9.9	8.4
S104H	149	L6_IGKJ1*01	**24.9**	**79.2**
S104L	150	L6_IGKJ1*01	23.5	43.8
S104R	151	L6_IGKJ1*01	23.4	28.6
S104G	147	L6_IGKJ1*01	45.5	67.8
S104F	121	L6_IGKJ1*01	**76.5**	**134.2**
S104L	150	L6_IGKJ1*01	24.8	25.6

The Fab heavy chain mutants, S102A, S103A, S103P, S104H and S104F, each containing a mutation in the heavy chain parent Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01, were subsequently re-assayed using the ECL multispot assay as describe in Example 4A to confirm the observed increased binding affinity for DLL4. Each Fab mutant was tested against a panel of antigens at two different Fab concentrations. The results are set forth in Tables 38-39 below. Table 29 sets forth the results for the ECL signal and signal/noise ratio of each mutant for binding to DLL4. Table 38 sets forth the signal/noise

ratio for binding to all of the tested antigens. The results show that the heavy chain mutants S102A, S103P, S104H and S104F all have increased signals for binding to DLL4 as compared to parent Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01, and additionally these mutants bind in a dose-dependent and antigen specific manner. Further, the results show that the signal for binding of heavy chain mutant S103A to DLL4 is about the same as binding of parent Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01.

Table 38. Binding affinity of Fab VH1-46_IGHD6-6*01_IGHJ1*01 and L6_IGKJ1*01 heavy chain mutants S102A, S103A, S103P, S104H, and S104F for DLL4

Heavy Chain	SEQ ID NO	Light Chain (SEQ ID NO:107)	Fab [μM]	Signal	Blank	Signal / Noise
S103A	131	L6_IGKJ1*01	0.1	7108	225	31.6
S103A	131	L6_IGKJ1*01	0.01	1192	265	4.5
S103P	123	L6_IGKJ1*01	0.1	19284	139	138.7
S103P	123	L6_IGKJ1*01	0.01	4095	179	22.9
S104H	149	L6_IGKJ1*01	0.1	20053	227	88.3
S104H	149	L6_IGKJ1*01	0.01	4159	154	27.0
S104F	121	L6_IGKJ1*01	0.1	27072	139	194.8
S104F	121	L6_IGKJ1*01	0.01	4283	280	15.3
Parent	88	L6_IGKJ1*01	0.1	7002	171	40.9
Parent	88	L6_IGKJ1*01	0.01	1030	210	4.9
S102A	124	L6_IGKJ1*01	0.1	15754	220	71.6
S102A	124	L6_IGKJ1*01	0.01	2598	259	10.0

Table 39. Binding affinity and specificity of Fab VH1-46_IGHD6-6*01_IGHJ1*01 and L6_IGKJ1*01 heavy chain mutants S102A, S103A, S103P, S104H, and S104F

	Fab [μM]	ErbB2	EGFR	HGFR	Notch-1	CD44	IGF-1	P-Cad	EPOR	DLL4
S103A	0.1	1.0	1.2	1.0	1.2	1.4	1.2	1.4	1.4	31.6
S103A	0.01	0.9	1.3	1.2	1.4	1.3	1.1	1.3	1.1	4.5
S103P	0.1	2.2	2.3	1.9	2.6	2.1	2.0	1.4	2.4	138.7
S103P	0.01	2.0	1.8	1.2	1.8	1.5	1.0	1.1	1.8	22.9
S104H	0.1	1.0	0.6	0.8	0.8	1.1	1.0	0.8	1.0	88.3
S104H	0.01	1.0	1.0	1.0	1.4	1.4	1.5	1.0	1.2	27.0
S104F	0.1	1.8	2.0	1.6	2.6	1.9	1.7	1.4	2.1	194.8
S104F	0.01	0.7	0.8	0.6	0.8	0.8	0.6	0.4	0.7	15.3
Parent	0.1	1.2	1.2	1.3	1.7	1.8	1.6	1.6	1.2	40.9
Parent	0.01	1.0	0.9	0.9	0.5	1.1	0.8	1.0	1.0	4.9
S102A	0.1	0.8	0.9	0.5	1.4	1.3	1.3	1.0	1.3	71.6
S102A	0.01	1.0	0.8	0.5	0.6	0.9	0.5	0.2	0.8	10.0

iv. Combination mutants based on NNK mutagenesis results

Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 heavy chain mutants S102A, S103P and S104F, identified as contributing to increased binding to DLL4, were combined to generate a triple mutant. The triple mutant is designated as Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F & L6_IGKJ1*01 (H:APF & L:wt). The binding

affinity and specificity of the Fab APF triple mutant was determined using both the ECL multispot assay and ELISA.

The ECL multispot assay described in Example 4A was used to compare the specificity and binding affinity of the APF triple mutant and the parent antibody for binding to DLL4 and other antigens at various concentrations of antibody. Table 40 sets forth the signal/noise ratio for binding of the parent and APF triple mutant against the tested antigens. The results show that the heavy chain APF triple mutant binds DLL4 with 10-fold greater binding affinity than the parent antibody. Additionally, the APF triple mutant specifically binds DLL4, since no detectable signal was observed for binding to any other tested antigen.

The binding of the APF triple mutant to DLL4 was further analyzed by ELISA as described in Example 6 at Fab concentrations of 125 nm to 1000 nm antibody. The results are set forth in Table 41 below. At the tested concentrations, the parent Fab antibody did not show a detectable signal for binding to DLL4. In contrast, the APF triple mutant had a detectable signal evidencing DLL4 binding in a concentration dependent manner. These results confirm that the ECL assay is more sensitive then the ELISA assay.

Table 40. Binding affinity and specificity of triple mutant Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F (APF) & L6_IGKJ1*01 (SEQ ID NOS:125 and 107) as compared to parent Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 (SEQ ID NOS:88 and 107)

	Fab [μM]	ErbB2	EGFR	HGFR	Notch-1	CD44	IGF-1	P-Cad	EPOR	DLL4
Wt	500.00	0.3	0.7	0.3	0.8	0.4	0.4	0.2	0.8	16.2
	50.00	0.6	0.9	0.6	0.6	0.3	0.5	0.7	0.9	33.5
	5.00	1.0	1.0	0.9	0.8	1.3	1.1	0.9	1.1	32.5
	0.50	1.0	1.4	0.6	2.0	1.0	1.2	1.3	0.9	2.9
S102A, S103P, S104F	500.00	1.7	5.5	2.2	4.2	2.4	1.5	3.4	10.4	181.4
	50.00	0.7	1.0	0.7	1.1	0.7	0.5	0.9	1.6	274.5
	5.00	1.1	1.1	0.8	0.9	1.3	1.1	1.0	1.8	482.1
	0.50	1.0	1.1	0.8	1.4	1.0	1.3	0.8	0.9	34.5

Table 41. Binding affinity of triple mutant Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F (APF) & L6_IGKJ1*01 (SEQ ID NOS:125 and 107) as compared to parent Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 (SEQ ID NOS:88 and 107)

Fab [nM]	Wildtype	Blank	S102A, S103P, S104F	Blank
1000	0.071	0.060	0.463	0.080
500	0.070	0.069	0.307	0.074
250	0.069	0.064	0.231	0.071
125	0.070	0.066	0.173	0.075

EXAMPLE 8

Further optimization of the heavy chain of anti-DLL4 APF triple mutant for binding to DLL4

In this example, the heavy chain of the APF triple mutant described and generated in Example 7 was further optimized to improve its binding affinity for DLL4. The APF triple mutant Fab was used as a template for further mutagenesis of heavy chain amino acid residues in the remaining CDR regions of the antibody heavy chain. Amino acid residue G55 of CDR2 and amino acid residues E100, A106, Y108, F109, and H111 of CDR3 were subjected to mutagenesis using overlapping PCR with NNK mutagenesis, as described above in Example 1.

The Fab APF triple mutant containing further mutations at amino acid residues E100, A106, Y108, F109, and H111 were tested for binding to DLL4 and other antigens using the ECL Multispot Assay at a concentration of 10 nM Fab. The results are set forth in Tables 42-43 below. The Signal/Noise ratio of each mutant Fab tested for binding to DLL4 is set forth in Table 42. Table 43 sets forth the ECL signal and blank (background binding to control well containing no antigen) for the binding of each mutant Fab to various tested antigens. Amino acid mutations designated with X (for any amino acid) did not show appreciable binding and therefore were not sequenced to identify the exact mutation. The results show that mutation of amino acid residues G55, E100, A106, Y108, or F109 with any other amino acid generally caused a reduction in binding affinity to DLL4 as evidenced by a reduction in ECL signal while substitution of H111 either improved binding affinity or did not affect binding affinity to DLL4 as evidenced by an increased ECL signal or no change in ECL signal. In particular, Fab heavy chain mutant VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F & L6_IGKJ1*01 (H:APFF & L:wt) had a 2 to 4-fold better signal/noise ratio for binding to DLL4 than the Fab APF triple mutant. Additionally, none of the mutants showed any appreciable binding to any of the other tested antigens (see Table 43 below.)

Table 42. NNK mutagenesis of Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F (APF) & L6_IGKJ1*01 at amino acid residues G55, E100, A106, Y108, F109 and H111

Fab [10 nM]			
Heavy	**SEQ ID NO**	**Light (SEQ ID NO:107)**	**Signal/Noise**
S102A/S103P/S104F	125	L6_IGKJ1*01	12.8
S102A/S103P/S104F	125	L6_IGKJ1*01	10.4
S102A/S103P/S104F G55W	152	L6_IGKJ1*01	8.0
S102A/S103P/S104F G55X	235	L6_IGKJ1*01	1.4
S102A/S103P/S104F G55X	235	L6_IGKJ1*01	1.1
S102A/S103P/S104F G55X	235	L6_IGKJ1*01	1.0
S102A/S103P/S104F G55X	235	L6_IGKJ1*01	0.8

S102A/S103P/S104F G55X	235	L6_IGKJ1*01	0.6
S102A/S103P/S104F G55D	153	L6_IGKJ1*01	1.2
S102A/S103P/S104F	125	L6_IGKJ1*01	11.1
S102A/S103P/S104F G55X	235	L6_IGKJ1*01	1.3
S102A/S103P/S104F E100X	236	L6_IGKJ1*01	1.2
S102A/S103P/S104F E100X	236	L6_IGKJ1*01	1.0
S102A/S103P/S104F	125	L6_IGKJ1*01	20.4
S102A/S103P/S104F E100X	236	L6_IGKJ1*01	1.1
S102A/S103P/S104F E100X	236	L6_IGKJ1*01	1.0
S102A/S103P/S104F E100X	236	L6_IGKJ1*01	1.7
S102A/S103P/S104F E100X	236	L6_IGKJ1*01	1.2
S102A/S103P/S104F E100X	236	L6_IGKJ1*01	1.5
S102A/S103P/S104F	125	L6_IGKJ1*01	14.9
S102A/S103P/S104F A106X	237	L6_IGKJ1*01	0.7
S102A/S103P/S104F A106X	237	L6_IGKJ1*01	0.9
S102A/S103P/S104F A106X	237	L6_IGKJ1*01	1.2
S102A/S103P/S104F A106X	237	L6_IGKJ1*01	1.7
S102A/S103P/S104F A106X	237	L6_IGKJ1*01	1.1
S102A/S103P/S104F A106X	237	L6_IGKJ1*01	1.5
S102A/S103P/S104F A106X	237	L6_IGKJ1*01	1.9
S102A/S103P/S104F	125	L6_IGKJ1*01	16.0
S102A/S103P/S104F	125	L6_IGKJ1*01	13.8
S102A/S103P/S104F A106X	237	L6_IGKJ1*01	1.1
S102A/S103P/S104F Y108X	238	L6_IGKJ1*01	0.9
S102A/S103P/S104F Y108X	238	L6_IGKJ1*01	1.6
S102A/S103P/S104F Y108X	238	L6_IGKJ1*01	11.7
S102A/S103P/S104F Y108X	238	L6_IGKJ1*01	1.2
S102A/S103P/S104F	125	L6_IGKJ1*01	17.6
S102A/S103P/S104F Y108X	238	L6_IGKJ1*01	6.2
S102A/S103P/S104F	125	L6_IGKJ1*01	18.0
S102A/S103P/S104F A106E	154	L6_IGKJ1*01	4.3
S102A/S103P/S104F Y108X	238	L6_IGKJ1*01	8.0
S102A/S103P/S104F Y108X	238	L6_IGKJ1*01	0.8
S102A/S103P/S104F F109X	239	L6_IGKJ1*01	1.1
S102A/S103P/S104F F109X	239	L6_IGKJ1*01	1.2
S102A/S103P/S104F	125	L6_IGKJ1*01	9.9
S102A/S103P/S104F F109X	239	L6_IGKJ1*01	4.5
S102A/S103P/S104F F109X	239	L6_IGKJ1*01	0.9
S102A/S103P/S104F	125	L6_IGKJ1*01	12.0
S102A/S103P/S104F F109X	239	L6_IGKJ1*01	1.0
S102A/S103P/S104F F109X	239	L6_IGKJ1*01	1.3
S102A/S103P/S104F F109X	239	L6_IGKJ1*01	26.4
S102A/S103P/S104F	125	L6_IGKJ1*01	1.8
S102A/S103P/S104F H111X	240	L6_IGKJ1*01	1.1
S102A/S103P/S104F **H111F**	126	L6_IGKJ1*01	**42.5**
S102A/S103P/S104F	125	L6_IGKJ1*01	14.5
S102A/S103P/S104F	125	L6_IGKJ1*01	13.7
S102A/S103P/S104F H111X	240	L6_IGKJ1*01	2.4
S102A/S103P/S104F	125	L6_IGKJ1*01	12.3
S102A/S103P/S104F H111X	240	L6_IGKJ1*01	12.4

S102A/S103P/S104F H111X	240	L6_IGKJ1*01	6.2
S102A/S103P/S104F	125	L6_IGKJ1*01	24.7
S102A/S103P/S104F H111S	155	L6_IGKJ1*01	24.0

Table 43. NNK mutagenesis of Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F (APF) & L6_IGKJ1*01 at amino acid residues G55, E100, A106, Y108, F109 and H111

Heavy Chain [10 nM Fab]	Erb B2	EG F R	HGF R	Notch -1	CD 44	IGF-1	P-Cad	EP O R	Blank
APF	330	272	306	257	189	241	297	304	271
APF	157	237	272	334	96	197	208	329	204
APF G55W	334	312	365	327	159	250	391	296	271
APF G55X	284	190	331	333	165	330	234	275	317
APF G55X	189	280	182	208	256	202	190	235	301
APF G55X	145	207	277	436	298	228	301	339	314
APF G55X	323	307	301	334	257	247	357	261	324
APF G55X	113	192	254	182	172	192	128	279	235
APF G55D	302	272	268	302	173	191	243	329	248
APF	340	216	171	130	236	174	256	285	239
APF G55X	305	352	377	383	234	248	440	343	245
APF E100X	273	273	322	265	291	309	271	304	222
APF E100X	358	287	318	358	304	249	226	284	297
APF	91	159	212	181	127	238	59	159	95
APF E100X	314	365	451	418	262	177	430	327	326
APF E100X	357	267	379	171	257	241	205	222	229
APF E100X	172	158	188	142	197	169	206	140	132
APF E100X	229	285	306	144	159	177	249	324	273
APF E100X	279	267	395	293	295	355	436	302	220
APF	314	241	388	304	188	291	396	303	243
APF A106X	200	170	441	336	158	241	267	309	366
APF A106X	288	244	319	153	276	221	235	248	283
APF A106X	306	428	452	268	268	320	336	398	390
APF A106X	349	350	324	270	239	215	367	239	157
APF A106X	24	253	177	319	297	248	368	258	232
APF A106X	393	406	380	434	339	404	506	333	237
APF A106X	174	238	122	63	296	246	159	161	247
APF	202	138	190	189	199	190	152	179	214
APF	378	277	317	370	262	207	422	312	306
APF A106X	273	324	240	331	242	229	251	308	249
APF Y108X	270	300	294	315	169	285	285	384	385
APF Y108X	283	272	236	306	321	258	313	334	167
APF Y108X	322	253	314	314	295	240	189	345	219
APF Y108X	405	355	438	464	376	334	340	399	321
APF	413	324	269	390	385	270	301	421	320
APF Y108X	336	320	276	297	208	343	246	178	211
APF	200	255	258	336	214	230	280	228	198
APF A106E	189	226	212	156	192	312	308	204	219
APF Y108X	239	261	277	292	325	337	333	271	368
APF Y108X	388	355	423	348	248	380	469	276	336
APF F109X	378	397	429	362	440	400	509	479	428

Table 43. NNK mutagenesis of Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F (APF) & L6_IGKJ1*01 at amino acid residues G55, E100, A106, Y108, F109 and H111									
Heavy Chain [10 nM Fab]	**Erb B2**	**EG F R**	**HGF R**	**Notch -1**	**CD 44**	**IGF-1**	**P-Cad**	**EP O R**	**Blank**
APF F109X	405	444	462	544	324	442	503	441	402
APF	513	460	339	433	298	318	338	252	372
APF F109X	294	442	433	382	350	272	379	440	387
APF F109X	417	334	371	446	235	320	416	463	438
APF	356	371	434	363	417	293	293	389	344
APF F109X	304	241	246	369	392	320	351	340	347
APF F109X	350	399	340	217	338	407	314	376	331
APF F109X	147	158	298	249	334	260	206	241	148
APF	221	296	319	251	221	344	449	222	182
APF H111X	410	414	382	427	362	488	607	430	476
APF H111F	370	409	493	356	360	345	461	343	290
APF	381	206	379	450	363	453	384	326	487
APF	391	428	426	299	400	434	433	480	472
APF H111X	395	315	298	380	322	387	392	443	454
APF	525	467	422	376	345	361	305	494	363
APF H111X	91	292	134	297	164	158	143	291	186
APF H111X	207	188	256	177	192	142	223	181	185
APF	302	394	200	283	340	213	118	343	204
APF H111S	314	286	235	272	244	136	178	277	203

The APF triple mutant and APFF mutant were further compared for binding to DLL4 using the ECL Multispot Assay. The Fab antibodies were assayed at various concentrations to assess the dose dependence for binding to DLL4. The Fab antibodies also were assayed against various antigens to assess the specificity. The APFF mutant was tested in duplicate. Table 44 sets forth the signal/noise ratio for binding to DLL4. The results show that the H:APFF & L:wt mutant exhibits slightly increased affinity (70 nM) for DLL4 as compared to the H:APF & L:wt mutant (122 nM). Additionally, the results in Table 45, which depict the ECL signal observed in the assay, confirm that both Fab mutants specifically bind to DLL4 compared to other antigens tested.

Table 44. Binding affinity of Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F (APF) & L6_IGKJ1*01 versus Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF) & L6_IGKJ1*01			
Heavy Chain	S102A/S103P/S104F (SEQ ID NO:125)	S102A/S103P/S104F/H111F (SEQ ID NO:126)	S102A/S103P/S104F/H111F (SEQ ID NO:126)
Light Chain	L6_IGKJ1*01 (SEQ ID NO:107)	L6_IGKJ1*01 (SEQ ID NO:107)	L6_IGKJ1*01 (SEQ ID NO:107)
Fab [nM]	**Signal/Noise**		
500.00	65.9	47.3	54.8
50.00	207.3	239.1	355.7
5.00	260.4	747.6	282.9
0.50	46.9	87.6	36.6

Table 45. Binding affinity and specificity of Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F (APF) & L6_IGKJ1*01 versus Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF) & L6_IGKJ1*01

	Fab [μM]	Erb B2	EGF R	HGF R	Notch -1	CD 44	IGF-1	P-Cad	EPO R	DLL4	Blank
S102A S103P S104F	500.00	1578	1477	760	785	874	613	1008	1213	28930	439
	50.00	672	585	525	509	557	558	652	768	80005	386
	5.00	401	356	309	338	343	300	547	423	54938	211
	0.50	199	152	182	230	207	190	161	235	6666	142
S102A S103P S104F H111F	500.00	908	2409	945	1607	1282	722	1011	4722	26937	570
	50.00	394	452	368	559	449	283	349	736	79372	332
	5.00	225	229	208	260	168	232	290	294	76254	102
	0.50	130	137	104	158	129	94	106	122	8322	95
S102A S103P S104F H111F	500.00	712	2895	723	1333	1143	736	785	4966	27150	495
	50.00	503	552	380	470	550	485	453	879	79326	223
	5.00	286	303	258	304	313	323	280	423	75810	268
	0.50	222	266	215	265	279	184	201	298	7539	206

EXAMPLE 9

Further optimization of the heavy chain of anti-DLL4 APFF mutant for binding to DLL4

In this Example, the heavy chain amino acid sequence of the APFF mutant that was affinity matured for binding to DLL4 as described in Examples 7 and 8, was used as a template for further mutations of other CDR regions of the antibody polypeptide. Mutant Fabs were expressed and assayed for binding to DLL4.

i. Alanine scanning of CDR1

Heavy chain APFF mutant was used as a template for alanine scanning mutagenesis of amino acid residues in CDR1 (amino acids 26-35) to determine residues involved in antibody binding to DLL4. Alanine scanning was performed by mutating only residues T28, F29, T30, S31 and Y33 of CDR1 to an alanine. The mutant Fab antibodies were expressed and purified as described in Example 2 above.

Purified Fab alanine mutants were tested at a concentration of 10 nM for binding to DLL4 and other antigens using the ECL multispot binding assay. The results for the ECL assay are set forth in Tables 46 and 47. Table 46 sets forth forth the mutant Fabs and the Signal/Noise ratio for binding to DLL4. The results show that mutation of amino acid residues F29 and Y33 with alanine caused a reduction in the signal/noise ratio for binding to DLL4. Thus, these residues were not selected for further mutagenesis. Mutation of amino acid residues T28, T30 or S31 with alanine resulted in a slight increase in the signal/noise ratio for binding to DLL4 compared to the parent heavy chain APFF mutant. Table 47, which sets forth the ECL signal for binding to various antigens and to a blank well containing no

antigen, shows that all antibodies tested exhibited specificity for DLL4. Table 46 also depicts the results of an ELISA assay performed as described in Example 6 using 100 nM of Fab mutant. The results of the ELISA also show that amino acid residue Y33 is involved in DLL4 binding. The differing results observed in the ECL assay compared to the ELISA are likely due to the fact that the ELISA assay selects for long off-rates whereas the ECL assay detects equilibrium binding. Therefore a mutant with a reduced on-rate but improved off rate can exhibit strong binding by ELISA, but it will not necessarily correlate to a strong ECL signal. In contrast, a mutant with an improved on-rate but reduced off rate can exhibit weak binding by ELISA.

A further experiment was performed to confirm binding of the alanine mutants to DLL4 using an ECL Assay. Table 48 sets forth the ECL signal for DLL4 antigen and blank and signal/ration of each mutant Fab for binding to DLL4. Table 40 sets forth the ECL signals of each mutant Fab for binding to all tested antigens. The results in Tables 48 and 49 confirm the ECL results observed in Tables 46 and 47, respectively.

Table 46. Binding of Fab heavy chain VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF) & L6_IGKJ1 CDR1 alanine mutants to DLL4

Fab			ECL Signal/Noise [10 nM Fab]	ELISA (Signal-Noise)
Heavy Chain VH1-46_IGHD6-6*01_IGHJ1*01	SEQ ID NO	Light Chain (SEQ ID NO:107)		
S102A/S103P/S104F/H111F	126	L6_IGKJ1*01	202.2	0.78
S102A/S103P/S104F/H111F T28A	156	L6_IGKJ1*01	334.0	0.77
S102A/S103P/S104F/H111F F29A	157	L6_IGKJ1*01	189.8	0.67
S102A/S103P/S104F/H111F T30A	158	L6_IGKJ1*01	456.9	0.64
S102A/S103P/S104F/H111F S31A	159	L6_IGKJ1*01	453.3	0.47
S102A/S103P/S104F/H111F Y33A	160	L6_IGKJ1*01	136.3	0.09

Table 47. Binding and specificity of Fab heavy chain VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF) & L6_IGKJ1 CDR1 alanine mutants

Heavy Chain	Erb B2	EGF R	HGF R	Notch -1	CD 44	IGF -1	P-Cad	EPO R	DLL4	Blank
APFF	354	383	347	369	404	397	347	438	78437	388
APFF T28A	411	389	427	432	471	408	381	480	140295	420
APFF F29A	244	293	404	374	414	315	276	466	80652	425
APFF T30A	272	427	413	270	439	356	275	428	140273	307
APFF S31A	207	394	398	333	379	405	255	454	137810	304
APFF Y33A	394	372	345	244	294	308	383	373	26978	198

Table 48. Binding of Fab heavy chain VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF) & L6_IGKJ1*01 CDR1 alanine mutants to DLL4				
Heavy Chain VH1-46_IGHD6-6*01_IGHJ1*01	Light Chain (SEQ ID NO:107)	Signal	Blank	Signal/ Noise
S102A/S103P/S104F/H111F T28A	L6_IGKJ1*01	181427	449	404.1
S102A/S103P/S104F/H111F F29A	L6_IGKJ1*01	109225	459	238.0
S102A/S103P/S104F/H111F T30A	L6_IGKJ1*01	177678	353	503.3
S102A/S103P/S104F/H111F S31A	L6_IGKJ1*01	176308	333	529.5
APFF	L6_IGKJ1*01	196536	283	694.5
S102A/S103P/S104F/H111F Y33A	L6_IGKJ1*01	59547	265	224.7

Table 49. Binding and specificity of Fab heavy chain VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF) & L6_IGKJ1*01 CDR1 alanine mutants										
Heavy Chain	Erb B2	EGF R	HGF R	Notch -1	CD 44	IGF-1	P-Cad	EPO R	DLL4	Blank
APFF T28A	316	329	353	478	497	377	477	477	181427	449
APFF F29A	1292	537	512	6089	978	439	508	1055	109225	459
APFF T30A	408	351	353	368	396	343	337	479	177678	353
APFF S31A	253	377	358	427	235	268	262	507	176308	333
APFF	263	279	252	389	425	342	318	536	196536	283
APFF Y33A	298	281	248	334	290	227	178	430	59547	265

ii. Alanine scanning of CDR2

Heavy chain APFF mutant was used as a template for alanine scanning mutagenesis of amino acid residues in CDR2 (amino acids 50-66) to determine residues involved in antibody binding to DLL4. Amino acid residues Y60 to G66 were not mutated. The mutant Fab antibodies were expressed and purified as described in Example 2 above.

Purified Fab alanine mutants were tested at a concentration of 10 nM for binding to DLL4 using the ECL multispot binding assay. The results for the ECL assay are set forth in Tables 50 and 51. Table 50 sets forth the mutant Fabs and the Signal/Noise ratio for binding to DLL4. The results show that mutation of amino acid residues I50, G55, S57, T58, or S59 with alanine caused a reduction in the signal/noise ratio for binding to DLL4, and thus these residues were not further mutagenized. In contrast, mutation of amino acid residues I51, N52, P53, S54 or G56 with alanine improved the signal/noise ratio for binding to DLL4 2- to 4-fold over the parent heavy chain APFF mutant, and thus these residues were identified as residues for further mutagenesis. Table 51, which sets forth the ECL signals for binding various antigens and to a blank well containing no antigen, shows that all antibodies tested exhibited specificity for DLL4. Table 50 also depicts the results of an ELISA assay performed as described in Example 6 using 100 nM of Fab mutant. The results of the ELISA generally confirmed the results observed by the ECL assay. Mutation of amino acid residues I50, G55,

S57, T58 and S59 exhibited decreased binding to DLL4 compared to the parent APFF mutant as observed by ELISA.

Table 50. Binding of Fab heavy chain VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F CDR1 and CDR2 alanine mutants to DLL4

Fab			Signal/Noise [10 nM Fab]	ELISA (Signal-Noise)
Heavy Chain VH1-46_IGHD6-6*01_IGHJ1*01	SEQ ID NO	Light Chain (SEQ ID NO:107)		
APFF	126	L6_IGKJ1*01	202.2	0.78
S102A/S103P/S104F/H111F I50A	161	L6_IGKJ1*01	9.8	0.01
S102A/S103P/S104F/H111F I51A	162	L6_IGKJ1*01	637.2	0.49
S102A/S103P/S104F/H111F N52A	163	L6_IGKJ1*01	721.1	0.60
S102A/S103P/S104F/H111F P53A	164	L6_IGKJ1*01	462.3	0.41
S102A/S103P/S104F/H111F G55A	166	L6_IGKJ1*01	44.2	0.02
S102A/S103P/S104F/H111F G56A	167	L6_IGKJ1*01	441.5	1.60
S102A/S103P/S104F/H111F S57A	168	L6_IGKJ1*01	293.1	0.39
S102A/S103P/S104F/H111F T58A	169	L6_IGKJ1*01	142.4	0.14
S102A/S103P/S104F/H111F S59A	170	L6_IGKJ1*01	17.1	0.02
S102A/S103P/S104F/H111F S54A	165	L6_IGKJ1*01	122.1	0.255
APFF	126	L6_IGKJ1*01	71.1	0.123

Table 51. Binding and specificity of Fab heavy chain VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F CDR1 and CDR2 alanine mutants

Heavy Chain	Erb B2	EGF R	HGF R	Notch -1	CD 44	IGF -1	P-Cad	EPO R	DLL4	Blank
APFF	354	383	347	369	404	397	347	438	78437	388
I50A	369	402	301	297	326	247	313	252	2668	271
I51A	344	373	440	312	391	383	144	380	159290	250
N52A	378	340	369	383	362	362	353	468	168745	234
P53A	203	439	337	393	378	374	390	427	151173	327
G55A	474	217	221	381	365	392	426	305	14500	328
G56A	279	355	313	331	330	422	214	466	189405	429
S57A	304	302	388	365	439	417	232	477	112266	383
T58A	320	384	304	289	318	271	294	329	47422	333
S59A	312	358	280	333	346	273	339	382	4502	264

iii. NNK mutagenesis of CDR2 residues N52, S54 and G56

The Fab heavy chain APFF mutant was subsequently used as a template for further mutagenesis of amino acid residues N52, S54, G56 using NNK mutagenesis, as described above.

Fab heavy chain mutants containing mutations of amino acid residues N52, S65 and G56 in the parent APFF mutant template H:APFF & L:wt were tested for binding to DLL4 using the 96-well plate DLL4 ECL binding assay described in Example 4B and the ELISA assay described in Example 6. Table 52 depicts the ECL and ELISA signal for binding to DLL4 for the various mutants tested. Double mutants, such as I51T/N52V, were

inadvertently generated during the PCR reaction. Several Fab mutants that contained a combination of two mutations at a specific amino acid position are designated as such. For example, G56E/D indicates the tested antibody was a mixture of two Fabs, one containing the mutation G56E and the other containing the mutation G56D. Both the ECL and ELISA results show that several Fab heavy chain mutants containing mutations in the Fab APFF mutant, including N52L, N52W, S54T, G56H and G56W, all bind DLL4 with greater affinity than the parent Fab APFF mutant.

Table 52. Binding of Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF) & L6_IGKJ1*01 NNK heavy chain mutants to DLL4

Fab			ECL Signal [10 nM Fab]	ELISA Signal [100 nM Fab]
Heavy Chain VH1-46_IGHD6-6*01_IGHJ1*01 Mutant	SEQ ID NO	Light Chain (SEQ ID NO:107)		
S102A/S103P/S104F/H111F I51T/N52V	171	L6_IGKJ1*01	**71708**	**1.23**
S102A/S103P/S104F/H111F N52G	172	L6_IGKJ1*01	55584	0.47
S102A/S103P/S104F/H111F N52T	173	L6_IGKJ1*01	66771	0.61
S102A/S103P/S104F/H111F N52P	174	L6_IGKJ1*01	44756	0.18
APFF	126	L6_IGKJ1*01	42782	0.18
S102A/S103P/S104F/H111F N52L	**175**	**L6_IGKJ1*01**	**75452**	**1.06**
S102A/S103P/S104F/H111F N52W	**176**	**L6_IGKJ1*01**	**87011**	**0.42**
S102A/S103P/S104F/H111F N52Y	177	L6_IGKJ1*01	24501	0.01
S102A/S103P/S104F/H111F N52R	183	L6_IGKJ1*01	21642	0.01
S102A/S103P/S104F/H111F N52V	178	L6_IGKJ1*01	64665	0.24
S102A/S103P/S104F/H111F N52S	179	L6_IGKJ1*01	62211	0.28
S102A/S103P/S104F/H111F N52Q	180	L6_IGKJ1*01	60646	0.10
S102A/S103P/S104F/H111F N52K	181	L6_IGKJ1*01	67116	0.45
S102A/S103P/S104F/H111F N52A	163	L6_IGKJ1*01	52534	0.12
S102A/S103P/S104F/H111F G56V	182	L6_IGKJ1*01	68585	0.23
S102A/S103P/S104F/H111F G56E/G	241	L6_IGKJ1*01	61039	0.21
S102A/S103P/S104F/H111F G56V/N	242	L6_IGKJ1*01	68876	0.25
S102A/S103P/S104F/H111F G56S	184	L6_IGKJ1*01	65728	0.18
S102A/S103P/S104F/H111F G56K	185	L6_IGKJ1*01	66152	0.19
S102A/S103P/S104F/H111F G56E/D	243	L6_IGKJ1*01	70474	0.24
S102A/S103P/S104F/H111F G56T	186	L6_IGKJ1*01	60689	0.20
S102A/S103P/S104F/H111F G56L	187	L6_IGKJ1*01	64709	0.12
S102A/S103P/S104F/H111F G56A	167	L6_IGKJ1*01	63058	0.24
APFF	126	L6_IGKJ1*01	51792	0.09
S102A/S103P/S104F/H111F G56R	188	L6_IGKJ1*01	64277	0.20
S102A/S103P/S104F/H111F G56H	**189**	**L6_IGKJ1*01**	**68804**	**0.65**
S102A/S103P/S104F/H111F G56I	190	L6_IGKJ1*01	76973	0.23
S102A/S103P/S104F/H111F G56L	187	L6_IGKJ1*01	63372	0.19
S102A/S103P/S104F/H111F G56W	**191**	**L6_IGKJ1*01**	**69571**	**0.54**
S102A/S103P/S104F/H111F G56A	167	L6_IGKJ1*01	65124	0.26
S102A/S103P/S104F/H111F S54I	192	L6_IGKJ1*01	18450	0.03
APFF	126	L6_IGKJ1*01	46641	0.07
S102A/S103P/S104F/H111F S54E	193	L6_IGKJ1*01	36826	0.04
S102A/S103P/S104F/H111F S54R	194	L6_IGKJ1*01	26284	0.02

S102A/S103P/S104F/H111F S54G	195	L6_IGKJ1*01	47033	0.06
S102A/S103P/S104F/H111F S54T	**196**	**L6_IGKJ1*01**	**57232**	**0.08**
S102A/S103P/S104F/H111F S54L	197	L6_IGKJ1*01	28172	0.02
S102A/S103P/S104F/H111F S54V	198	L6_IGKJ1*01	22155	0.00
S102A/S103P/S104F/H111F S54Q	264	L6_IGKJ1*01	41757	0.07
S102A/S103P/S104F/H111F S54A	165	L6_IGKJ1*01	32598	0.02
S102A/S103P/S104F/H111F S54N	199	L6_IGKJ1*01	31710	0.02
S102A/S103P/S104F/H111F S54P	200	L6_IGKJ1*01	10059	0.00
S102A/S103P/S104F/H111F I50T/S54P	201	L6_IGKJ1*01	229	0.00
S102A/S103P/S104F/H111F S54A	165	L6_IGKJ1*01	35277	0.02
S102A/S103P/S104F/H111F S54A/S59N	202	L6_IGKJ1*01	17305	0.100
APFF	126	L6_IGKJ1*01	42886	0.06

iv. Further mutagenesis of CDR2 amino acid residue I51

A Fab mutant containing N52L, S54T and G56H was generated. Thus, the resulting Fab mutant contains seven mutations in the heavy chain of the antibody: S102A/S103P/S104F/H111F N52L/S54T/G56H, and is designated Fab mutant VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F N52L/S54T/G56H & L6_IGKJ1*01 (H:APFF LTH & L:wt). The H:APFF LTH mutant was used as a template for further NNK mutagenesis of CDR2 amino acid residue I51. The I51 mutants were tested for binding to DLL4 using the 96-well plate ECL binding assay described in Example 4B and ELISA described in Example 6. The results are depicted in Table 53, which sets forth the ECL and ELISA signals. The results show that mutation of amino acid residue I51 to valine (I51V) in the H:APFF LTH parent backbone caused a further increase in binding affinity to DLL4 compared to the H:APFF LTH parent.

Table 53. Binding of Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF) & L6_IGKJ1*01 I51 NNK heavy chain mutants to DLL4

Fab			ECL Signal [10 nM Fab]	ELISA Signal [100 nM Fab]
Heavy Chain VH1-46_IGHD6-6*01_IGHJ1*01 Mutant	**SEQ ID NO**	**Light Chain (SEQ ID NO:107)**		
S102A/S103P/S104F/H111F/ N52L/S54T/G56H (APFF LTH)	203	L6_IGKJ1*01	165312	1.101
S102A/S103P/S104F/H111F/ I51A/N52L/S54T/G56H (APFF ALTH)	204	L6_IGKJ1*01	142542	0.620
S102A/S103P/S104F/H111F/ I51T/N52L/S54T/G56H (APFF TLTH)	205	L6_IGKJ1*01	123199	0.641
S102A/S103P/S104F/H111F/ I51Y/N52L/S54T/G56H (APFF YLTH)	206	L6_IGKJ1*01	154612	0.513
S102A/S103P/S104F/H111F/ I51H/N52L/S54T/G56H (APFF HLTH)	207	L6_IGKJ1*01	155073	0.647
S102A/S103P/S104F/H111F/ I51E/N52L/S54T/G56H (APFF ELTH)	208	L6_IGKJ1*01	166549	0.995
S102A/S103P/S104F/H111F/ I51V/N52L/S54T/G56H (APFF VLTH)	**209**	**L6_IGKJ1*01**	**192273**	**1.105**

S102A/S103P/S104F/H111F/ I51G/N52L/S54T/G56H (APFF GLTH)	210	L6_IGKJ1*01	130722	0.407
S102A/S103P/S104F/H111F/ I51S/N52L/S54T/G56H (APFF SLTH)	211	L6_IGKJ1*01	134860	0.786
S102A/S103P/S104F/H111F/ I51W/N52L/S54T/G56H (APFF WLTH)	212	L6_IGKJ1*01	126271	0.088
S102A/S103P/S104F/H111F/ I51R/N52L/S54T/G56H (APFF RLTH)	213	L6_IGKJ1*01	92415	0.512
S102A/S103P/S104F/H111F/ I51N/N52L/S54T/G56H (APFF NLTH)	214	L6_IGKJ1*01	125869	1.091

v. NNK mutagenesis of CDR2 amino acid residue P53

Fab mutant VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F I51T/N52L/S54T/G56H & L6_IGKJ1*01 (H:APFF TLTH) was used as a template for NNK mutagenesis of CDR2 amino acid residue P53. The P53 mutants were tested for binding to DLL4 using the 96-well plate ECL binding assay described in Example 4B and ELISA assay described in Example 6. Table 54 sets forth the ECL and ELISA signals. The results show that mutation of Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F I51T/N52L/S54T/G56H (H:APFF TLTH) & L6_IGKJ1*01 heavy chain residue P53 to alanine (P53A) causes an increase in binding affinity to DLL4 compared to the H:APFF TLTH mutant.

Table 54. Binding of Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF) & L6_IGKJ1*01 P53 NNK heavy chain mutants to DLL4

Fab			ECL Signal [10 nM Fab]	ELISA Signal [100 nM Fab]
Heavy Chain VH1-46_IGHD6-6*01_IGHJ1*01 Mutant	**SEQ ID NO**	**Light Chain (SEQ ID NO:107)**		
S102A/S103P/S104F/H111F/ I51T/N52L/S54T/G56H (APFF TLTH)	205	L6_IGKJ1*01	123199	0.641
S102A/S103P/S104F/H111F/ I51T/N52L/P53V/S54T/G56H (APFF TLVTH)	215	L6_IGKJ1*01	91483	0.035
S102A/S103P/S104F/H111F/ I51T/N52L/P53G/S54T/G56H (APFF TLGTH)	216	L6_IGKJ1*01	103398	0.018
S102A/S103P/S104F/H111F/ I51T/N52L/P53S/S54T/G56H (APFF TLSTH)	217	L6_IGKJ1*01	135290	0.076
S102A/S103P/S104F/H111F/ I51T/N52L/P53W/S54T/G56H (APFF TLWTH)	218	L6_IGKJ1*01	126454	0.433
S102A/S103P/S104F/H111F/ I51T/N52L/P53R/S54T/G56H (APFF TLRTH)	219	L6_IGKJ1*01	63200	0.070
S102A/S103P/S104F/H111F/ I51T/N52L/P53N/S54T/G56H (APFF TLNTH)	220	L6_IGKJ1*01	113788	0.021
S102A/S103P/S104F/H111F/ I51T/N52L/P53A/S54T/G56H (APFF TLATH)	**221**	**L6_IGKJ1*01**	**163025**	**0.330**
S102A/S103P/S104F/H111F/	222	L6_IGKJ1*01	124867	0.219

I51T/N52L/P53T/S54T/G56H (APFF TLTTH)				
S102A/S103P/S104F/H111F/ I51T/N52L/P53Y/S54T/G56H (APFF TLYTH)	223	L6_IGKJ1*01	99517	0.274
S102A/S103P/S104F/H111F/ I51T/N52L/P53H/S54T/G56H (APFF TLHTH)	224	L6_IGKJ1*01	107908	0.287
S102A/S103P/S104F/H111F/ I51T/N52L/P53E/S54T/G56H (APFF TLETH)	225	L6_IGKJ1*01	91504	0.017
S102A/S103P/S104F/H111F/ I51T/N52L/P53M/S54T/G56H (APFF TLMTH)	226	L6_IGKJ1*01	105485	0.341

Heavy chain mutants APFF LTH (SEQ ID NO:203), APFF ELTH (SEQ ID NO: 208), APPF VLTH (SEQ ID NO: 209), APFF NLTH (SEQ ID NO: 214), APFF TLATH (SEQ ID NO: 221) and APFF I51T/N52V (SEQ ID NO: 171) were each paired with parent light chain L6_IGKJ1*01 (SEQ ID NO:107) and further analyzed for binding to DLL4 by ELISA using 2-fold serial dilutions of Fab, starting at a concentration of 20 nM. The results are set forth in Table 55 below. The results show that Fabs containing heavy chain mutants APFF LTH (SEQ ID NO:206), APFF ELTH (SEQ ID NO: 208), APPF VLTH (SEQ ID NO: 209) and APFF NLTH (SEQ ID NO: 214) bind DLL4 with a Kd of approximately between 1 nM and 10 nM. Fabs containing heavy chain mutants APFF TLATH (SEQ ID NO: 221) and APFF I51T/N52V (SEQ ID NO:171) have lower affinity for DLL4 as compared to the other tested Fabs. Heavy chain mutant APFF TLATH has an approximate Kd greater than 100 nM and heavy chain mutant APFF I51T/N52V has a Kd between 10 and 100 nM.

Table 55. Heavy chain Fab mutant VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF) & L6_IGKJ1*01 (SEQ ID NO:107) binding to DLL4 by ELISA

Fab [nM]	APFF LTH	APFF ELTH	APFF VLTH	APFF NLTH	APFF TLATH	APFF I51T/N52V
20	2.402	2.290	2.052	1.627	1.109	0.648
10	2.345	2.168	1.854	1.362	0.875	0.506
5	2.477	2.333	2.198	1.751	1.272	0.724
2.5	2.151	1.982	1.656	1.165	0.592	0.358
1.3	0.653	0.402	0.252	0.143	0.078	0.055
0.63	1.367	1.010	0.785	0.419	0.227	0.115
0.31	2.402	2.290	2.052	1.627	1.109	0.648
0.16	2.345	2.168	1.854	1.362	0.875	0.506

vi. NNK mutagenesis of framework amino acid residue S84

Fab heavy chain APFF mutant was used as a template for further mutagenesis of amino acid residue S84 in the framework region of the heavy chain using overlapping PCR with NNK mutagenesis, as described above. The resulting mutants were tested for binding to DLL4 and other antigens using the ECL Multispot binding assay as described in Example 4A and ELISA as described in Example 6. The results for the ECL and ELISA are set forth in

Tables 56. Table 56 sets forth mutant Fabs and the Signal/Noise ratio for binding to DLL4 by the ECL method or the ELISA assay. Table 57 sets forth the ECL signals of each mutant Fab for binding to all tested antigens. In general, the results show that Fab heavy chain VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F S84 mutants showed no increase in binding to DLL4 by either ECL or ELISA. One mutant, Fab heavy chain VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F S84T (SEQ ID NO:233), showed greater binding to DLL4 by the ECL MSD assay but had the same binding by ELISA.

Table 56. Binding of Fab heavy chain VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F S84 NNK mutants to DLL4

Fab			Signal/Blank [10 nM Fab]	ELISA (Signal-Noise)
Heavy Chain VH1-46_IGHD6-6*01_IGHJ1*01	SEQ ID NO	Light Chain (SEQ ID NO:107)		
S102A/S103P/S104F/H111F S84G	227	L6_IGKJ1*01	346.1	0.53
S102A/S103P/S104F/H111F S84Q	228	L6_IGKJ1*01	413.1	0.39
S102A/S103P/S104F/H111F S84N	229	L6_IGKJ1*01	497.4	0.47
S102A/S103P/S104F/H111F S84H	230	L6_IGKJ1*01	457.0	0.41
S102A/S103P/S104F/H111F S84R	231	L6_IGKJ1*01	432.9	0.26
S102A/S103P/S104F/H111F S84K	232	L6_IGKJ1*01	447.6	0.29
S102A/S103P/S104F/H111F S84T	233	L6_IGKJ1*01	1079.0	0.40
S102A/S103P/S104F/H111F	126	L6_IGKJ1*01	441.3	0.57
S102A/S103P/S104F/H111F	126	L6_IGKJ1*01	309.9	0.24
S102A/S103P/S104F/H111F	126	L6_IGKJ1*01	584.6	0.26
S102A/S103P/S104F/H111F	126	L6_IGKJ1*01	718.7	0.37

Table 57. Binding and specificity of Fab heavy chain VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F S84 NNK mutants

Heavy Chain	Erb B2	EGF R	HGF R	Notch -1	CD 44	IGF -1	P-Cad	EPO R	DLL4	Blank
APFF S84G	299	435	419	473	457	395	434	429	130821	378
APFF S84Q	311	347	255	416	372	373	357	288	122273	296
APFF S84N	307	337	375	309	251	324	167	415	134783	271
APFF S84H	301	306	374	331	382	353	319	318	138028	302
APFF S84R	372	435	392	377	335	395	310	393	139388	322
APFF S84K	354	301	317	400	386	405	517	528	164261	367
APFF S84T	297	293	274	372	352	281	180	328	162923	151
APFF	379	425	332	429	470	468	399	437	149144	338
APFF	292	329	237	377	326	357	277	449	126118	407
APFF	351	209	176	359	332	306	138	414	148493	254
APFF	322	409	263	417	316	173	240	328	132249	184

EXAMPLE 10

Affinity Maturation of the Light Chain of Identified "Hit" Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 Against DLL4

In this Example, the light chain of parent "Hit" Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 against DLL4 was subjected to affinity maturation similar to the affinity maturation of the heavy chain as described in Examples 7-9 above.

i. Identification of the CDR potential binding site

The amino acid sequence of the light chain (SEQ ID NO:107) for the "Hit" VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 was aligned with the amino acid sequence of related light chains of three "non-Hits" that were identified as not binding to DLL4 (see Table 58 below) These four Fabs are related because they share the same J_L germline segment. Further, the V_L germline segment is of the same subgroup (i.e. IGKV3). The sequence alignment is set forth in Figure 2. Based on the alignment, amino acid residues were identified that differed between the "Hit" and "non-Hits," thus accounting for the differences in binding affinity of the "Hit" and "non-Hits." The identified amino acid residues were located in CDR3, which was identified as the region of the light chain that is important for binding affinity.

Table 58. "Hit" and "non-Hit" Antibodies for Light Chain Sequence Alignment

Heavy Chain	SEQ ID NO	Light Chain	SEQ ID NO	ECL signal/ blank
VH1-46_IGHD6-6*01_IGHJ1*01	88	L6_IGKJ1*01	107	23.1
VH1-46_IGHD6-6*01_IGHJ1*01	88	A27_IGKJ1*01	110	1.3
VH1-46_IGHD6-6*01_IGHJ1*01	88	L25_IGKJ1*01	120	1.4
VH1-46_IGHD6-6*01_IGHJ1*01	88	L2_IGKJ1*01	112	1.4

NNK mutagenesis of CDR3

Amino acid residues R91, S92, N93, and W94 of CDR3 of the light chain L6_IGKJ1*01 were mutated by NNK mutagenesis using overlapping PCR to further identify amino acid residues that are in binding to DLL4. CDR3 amino acid residues Q89, Q90, P95, P96, W97 and T98 were conserved among the four aligned light chains (see Figure 2), and therefore were not subjected to NNK mutagenesis. Heavy chain triple mutant APF (see e.g. Example 7; Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F (H:APF) & L6_IGKJ1*01) was used as a parent template for NNK mutagenesis of amino acid residues R91 and S92. Heavy chain quadruple mutant APFF (see e.g., Example 9; Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (H:APFF) & L6_IGKJ1*01) was used as a parent template for NNK mutagenesis of amino acid residues S92, N93 and W94. Amino acid mutations designated with X (for any amino acid) did not show appreciable binding and therefore were not sequenced to identify the exact mutation. The resulting mutants were assayed using the ECL multispot assay as described in Example 4A. The results are set forth in Tables 59 and 60 below. Amino acid mutations designated with X (for any amino acid) did not show appreciable binding and therefore were not sequenced to identify the exact mutation. The results show that mutagenesis of amino acid residues R91, S92, N93 and W94 caused a reduction in ECL signal for binding to DLL4 compared either

the APF or APFF parent template antibody, and therefore these residues were not further mutagenized.

Table 59. NNK mutagenesis of Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F (APF) (SEQ ID NO:125) & L6_IGKJ1*01 or Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF) (SEQ ID NO:126) & L6_IGKJ1*01 at light chain amino acid residues R91, S92, N93 and W94

Fab			Signal	Blank	Signal/ Blank
Heavy Chain VH1-46_IGHD6-6*01_IGHJ1*01	Light Chain L6_IGKJ1*01	SEQ ID NO			
S102A/S103P/S104F	R91P	247	1280	271	4.7
S102A/S103P/S104F	R91L	248	375	273	1.4
S102A/S103P/S104F	parent	107	2585	229	11.3
S102A/S103P/S104F	R91G	249	292	209	1.4
S102A/S103P/S104F	R91X	361	1673	262	6.4
S102A/S103P/S104F	parent	107	2442	287	8.5
S102A/S103P/S104F	R91Q	250	817	261	3.1
S102A/S103P/S104F	R91X	361	248	296	0.8
S102A/S103P/S104F	S92X	362	180	259	0.7
S102A/S103P/S104F	S92X	362	255	395	0.6
S102A/S103P/S104F	S92X	362	2911	244	11.9
S102A/S103P/S104F	parent	107	2832	224	12.6
S102A/S103P/S104F	S92N	251	2092	271	7.7
S102A/S103P/S104F	S92X	362	701	140	5.0
S102A/S103P/S104F	S92X	362	2204	342	6.4
S102A/S103P/S104F	S92C	252	401	338	1.2
S102A/S103P/S104F	parent	107	3482	271	12.8
S102A/S103P/S104F	parent	107	2123	204	10.4
S102A/S103P/ S104F/H111F	N93Y	253	1385	270	5.1
S102A/S103P/ S104F/H111F	N93S	254	6436	206	31.2
S102A/S103P/ S104F/H111F	N93H	255	14711	331	44.4
S102A/S103P/ S104F/H111F	N93Q	256	704	239	2.9
S102A/S103P/ S104F/H111F	W94R	257	75771	256	296.0
S102A/S103P/ S104F/H111F	W94S	258	108653	479	226.8
S102A/S103P/ S104F/H111F	W94T	259	23228	438	53.0
S102A/S103P/ S104F/H111F	W94L	260	11613	200	58.1
S102A/S103P/ S104F/H111F	W94P	261	332	169	2.0
S102A/S103P/ S104F/H111F	W94M	262	33801	241	140.3
S102A/S103P/ S104F/H111F	S92P	263	2412	292	8.3
S102A/S103P/ S104F/H111F	S92P	263	446	166	2.7
S102A/S103P/ S104F/H111F	S92A/X	363	1755	265	6.6
S102A/S103P/ S104F/H111F	S92Q	265	348	255	1.4
S102A/S103P/ S104F/H111F	S92V	266	327	317	1.0
S102A/S103P/ S104F/H111F	parent	107	164982	282	585.0
S102A/S103P/ S104F/H111F	parent	107	164992	277	595.6
S102A/S103P/ S104F/H111F	parent	107	164224	274	599.4
S102A/S103P/ S104F/H111F	S92T	267	54083	278	194.5
S102A/S103P/ S104F/H111F	S92C	252	1343	348	3.9
S102A/S103P/ S104F/H111F	S92C	252	1263	504	2.5

S102A/S103P/ S104F/H111F	S92C	252	1229	428	2.9
S102A/S103P/ S104F/H111F	S92R	252	418	252	1.7
S102A/S103P/ S104F/H111F	S92G	269	89202	254	351.2
S102A/S103P/ S104F/H111F	S92V	266	405	225	1.8
S102A/S103P/ S104F/H111F	S92M	271	390	201	1.9
S102A/S103P/ S104F/H111F	S92N	251	824	224	3.7
S102A/S103P/ S104F/H111F	S92G	269	80151	294	272.6
S102A/S103P/ S104F/H111F	S92G	269	80671	208	387.8
S102A/S103P/ S104F/H111F	parent	107	188914	309	611.4
S102A/S103P/ S104F/H111F	S92R	268	587	219	2.7
S102A/S103P/ S104F/H111F	S92P	263	484	220	2.2
S102A/S103P/ S104F/H111F	S92P	263	4751	296	16.1
S102A/S103P/ S104F/H111F	S92G	269	91432	325	281.3

Table 60. NNK mutagenesis of Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F (APF) (SEQ ID NO:125) & L6_IGKJ1*01 or Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF) (SEQ ID NO:126) & L6_IGKJ1*01 at light chain amino acid residues R91, S92, N93 and W94

Heavy Chain	Light Chain	Erb B2	EGF R	HGF R	Notch-1	CD44	IGF-1	P-Cad	EPO R	DLL4	Blank
APF	R91P	333	216	273	228	252	199	296	275	1280	271
APF	R91L	526	367	255	383	236	382	437	459	375	273
APF	parent	331	363	307	398	223	223	189	252	2585	229
APF	R91G	236	271	239	170	163	260	235	306	292	209
APF	R91X	268	329	279	297	254	282	180	193	1673	262
APF	parent	317	226	344	358	205	162	250	319	2442	287
APF	R91Q	234	290	325	229	268	210	314	263	817	261
APF	R91X	219	210	341	138	191	269	324	193	248	296
APF	S92X	262	163	260	82	228	208	176	208	180	259
APF	S92X	258	209	267	354	257	264	323	327	255	395
APF	S92X	257	306	334	272	270	216	326	220	2911	244
APF	parent	149	279	275	171	197	168	171	0	2832	224
APF	S92N	293	346	405	193	316	211	240	304	2092	271
APF	S92X	298	228	131	135	99	200	290	227	701	140
APF	S92X	248	300	333	243	279	247	266	309	2204	342
APF	S92C	295	143	335	125	156	303	265	302	401	338
APF	parent	330	272	306	257	189	241	297	304	3482	271
APF	parent	157	237	272	334	96	197	208	329	2123	204
APFF	N93Y	369	464	380	453	333	318	499	541	1385	270
APFF	N93S	351	364	328	345	346	238	321	420	6436	206
APFF	N93H	307	347	307	342	345	268	293	425	14711	331
APFF	N93Q	240	337	309	310	452	256	304	477	704	239
APFF	W94R	283	325	293	375	443	303	364	546	75771	256
APFF	W94S	351	419	453	486	469	450	466	506	108653	479
APFF	W94T	396	414	377	418	453	387	481	432	23228	438
APFF	W94L	274	257	187	369	309	263	296	333	11613	200
APFF	W94P	299	267	275	228	241	187	268	292	332	169
APFF	W94M	244	302	302	321	327	340	346	435	33801	241
APFF	S92P	219	345	242	346	282	236	354	391	2412	292

APFF	S92P	268	317	256	328	292	280	307	385	446	166
APFF	S92A/X	212	268	252	242	228	193	325	262	1755	265
APFF	S92Q	282	332	373	351	312	246	340	330	348	255
APFF	S92V	188	319	230	262	248	244	373	371	327	317
APFF	parent	259	290	321	380	346	249	302	1062	164982	282
APFF	parent	311	307	267	266	351	221	299	467	164992	277
APFF	parent	236	266	339	279	367	305	283	473	164224	274
APFF	S92T	237	295	290	231	290	308	387	424	54083	278
APFF	S92C	425	452	472	439	458	471	786	601	1343	348
APFF	S92C	573	638	616	611	646	666	930	845	1263	504
APFF	S92C	526	588	589	642	554	642	805	742	1229	428
APFF	S92R	272	292	265	386	365	248	387	318	418	252
APFF	S92G	274	273	238	296	263	229	213	405	89202	254
APFF	S92V	246	305	288	347	331	237	390	368	405	225
APFF	S92M	301	367	346	385	304	271	328	340	390	201
APFF	S92N	242	293	243	407	336	312	271	314	824	224
APFF	S92G	384	347	296	280	306	257	294	428	80151	294
APFF	S92G	228	160	314	203	284	297	238	418	80671	208
APFF	parent	289	326	185	310	277	336	295	433	188914	309
APFF	S92R	266	322	315	437	358	256	410	395	587	219
APFF	S92P	240	332	281	399	367	282	321	378	484	220
APFF	S92P	299	315	222	397	393	296	288	495	4751	296
APFF	S92G	377	420	287	541	413	323	402	543	91432	325

iii. NNK mutagenesis of CDR1

Amino acid residues S28, S30, S31, and Y32 of CDR1 of the light chain L6_IGKJ1*01 were mutated by NNK mutagenesis using overlapping PCR to further identify amino acid residues that are important for binding to DLL4. The APF triple mutant (see e.g. Example 7; Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F (H:APF) & L6_IGKJ1*01) was used as a template for NNK mutagenesis of S30 and Y32. The APFF heavy chain quadruple mutant (see e.g. Example 9; Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (H:APFF) & L6_IGKJ1*01) was used as a template for NNK mutagenesis of S28, S30 and S31. The resulting mutants were assayed using the ECL multispot assay as described in Example 4A above. The results are set forth in Tables 61 and 62 below. Double mutants, such as R24G/Q27L, were inadvertently generated during the PCR reaction. Amino acid mutations designated with X (for any amino acid) did not show appreciable binding and therefore were not sequenced to identify the exact mutation. The results show that mutagenesis of amino acid residue Y32 caused a reduction in binding affinity to DLL4 compared to the APF parent template, and therefore this residue was not further mutagenized. Mutagenesis of amino acid residue S28, S30 and S31 either improved binding affinity or did not affect binding affinity to DLL4 compared to the APF or APFF parent templates, and thus these residues were identified as residues for further mutagenesis.

Three light chain mutants, namely L6_IGKJ1*01 S28D, S30N, and S31H, slightly increased antibody binding affinity to DLL4.

Table 61. NNK mutagenesis of Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F (APF) (SEQ ID NO:125) & L6_IGKJ1*01 or Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF) (SEQ ID NO:126) & L6_IGKJ1*01 at light chain amino acid residues S28, S30, S31 and Y32

Heavy Chain VH1-46_IGHD6-6*01_IGHJ1*01	Light Chain L6_IGKJ1*01	SEQ ID NO	Signal	Blank	Signal/ Blank
S102A/S103P/S104F	S30W	300	791	186	4.3
S102A/S103P/S104F	parent	107	803	125	6.4
S102A/S103P/S104F	S30X	364	101	112	0.9
S102A/S103P/S104F	S30R	298	745	95	7.8
S102A/S103P/S104F	S30X	364	593	204	2.9
S102A/S103P/S104F	S30T	297	1016	206	4.9
S102A/S103P/S104F	S30X	364	1374	204	6.7
S102A/S103P/S104F	S30X	364	1299	210	6.2
S102A/S103P/S104F	S30L	296	1627	235	6.9
S102A/S103P/S104F	Y32X	365	648	196	3.3
S102A/S103P/S104F	Y32X	365	817	193	4.2
S102A/S103P/S104F	Y32X	365	1753	261	6.7
S102A/S103P/S104F	Y32X	365	1209	155	7.8
S102A/S103P/S104F	R24G/Q27L	276	197	87	2.3
S102A/S103P/S104F	Y32V	277	427	164	2.6
S102A/S103P/S104F	Y32S	278	1031	210	4.9
S102A/S103P/S104F	parent	107	4266	256	16.7
S102A/S103P/S104F	Y32X	365	293	253	1.2
S102A/S103P/S104F	parent	107	3052	242	12.6
S102A/S103P/ S104F/H111F	S28G	279	182961	343	533.4
S102A/S103P/ S104F/H111F	S28K	280	124246	395	314.5
S102A/S103P/ S104F/H111F	S28V	281	83083	237	350.6
S102A/S103P/ S104F/H111F	S28F	282	133659	249	536.8
S102A/S103P/ S104F/H111F	parent	107	182026	400	455.1
S102A/S103P/ S104F/H111F	S28P	244	178227	393	453.5
S102A/S103P/ S104F/H111F	S28T	283	159288	305	522.3
S102A/S103P/ S104F/H111F	S28L	284	72299	329	219.8
S102A/S103P/ S104F/H111F	S28Q	285	133486	353	378.1
S102A/S103P/ S104F/H111F	S28A	286	156761	332	472.2
S102A/S103P/ S104F/H111F	S28N	287	203926	262	778.3
S102A/S103P/ S104F/H111F	S28H	288	209433	344	608.8
S102A/S103P/ S104F/H111F	S28I	289	106041	343	309.2
S102A/S103P/ S104F/H111F	S28R	290	110363	449	245.8
S102A/S103P/ S104F/H111F	S28W	291	165026	303	544.6
S102A/S103P/ S104F/H111F	S28M	292	108166	322	335.9
S102A/S103P/ S104F/H111F	S28E	293	184227	420	438.6
S102A/S103P/ S104F/H111F	S30C	294	128661	915	140.6
S102A/S103P/ S104F/H111F	S30D	295	225396	397	567.7
S102A/S103P/ S104F/H111F	S30L	296	198641	379	524.1
S102A/S103P/ S104F/H111F	S30T	297	122207	407	300.3

S102A/S103P/ S104F/H111F	S30R	298	145575	416	349.9
S102A/S103P/ S104F/H111F	S30P	299	1143	262	4.4
S102A/S103P/ S104F/H111F	parent	107	207955	306	679.6
S102A/S103P/ S104F/H111F	S30W	300	190872	289	660.5
S102A/S103P/ S104F/H111F	S30Y/S	366	143412	294	487.8
S102A/S103P/ S104F/H111F	S30Q	302	202637	198	1023.4
S102A/S103P/ S104F/H111F	S30A	303	183649	356	515.9
S102A/S103P/ S104F/H111F	S30G	304	180489	272	663.6
S102A/S103P/ S104F/H111F	S30N	245	174926	352	496.9
S102A/S103P/ S104F/H111F	S30P	299	1262	302	4.2
S102A/S103P/ S104F/H111F	S30G	304	177646	351	506.1
S102A/S103P/ S104F/H111F	S30A	303	186732	184	1014.8
S102A/S103P/ S104F/H111F	S30T	297	136426	392	348.0
S102A/S103P/ S104F/H111F	S30V	305	141111	284	496.9
S102A/S103P/ S104F/H111F	S30R	298	189471	278	681.6
S102A/S103P/ S104F/H111F	S30Q	302	196711	327	601.6
S102A/S103P/ S104F/H111F	S31T	306	191253	332	576.1
S102A/S103P/ S104F/H111F	S31N	307	177897	294	605.1
S102A/S103P/ S104F/H111F	S31K	246	179257	511	350.8
S102A/S103P/ S104F/H111F	parent	107	171775	442	388.6
S102A/S103P/ S104F/H111F	S31L	308	155112	416	372.9
S102A/S103P/ S104F/H111F	S31M	309	167080	442	378.0
S102A/S103P/ S104F/H111F	S31F	310	188723	411	459.2
S102A/S103P/ S104F/H111F	S31I	311	173649	321	541.0
S102A/S103P/ S104F/H111F	S31V	312	176358	345	511.2
S102A/S103P/ S104F/H111F	S31H	313	221327	264	838.4
S102A/S103P/ S104F/H111F	S31A	314	192365	218	882.4
S102A/S103P/ S104F/H111F	S31P	315	53282	341	156.3
S102A/S103P/ S104F/H111F	S31D	316	154331	493	313.0
S102A/S103P/ S104F/H111F	S31R	317	166188	298	557.7
S102A/S103P/ S104F/H111F	S31Y	318	187896	284	661.6
S102A/S103P/ S104F/H111F	S31Q	319	165030	407	405.5
S102A/S103P/ S104F/H111F	S31E	320	171114	331	517.0
S102A/S103P/ S104F/H111F	S31G	321	65521	231	283.6

Table 62. NNK mutagenesis of Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F (APF) (SEQ ID NO:125) & L6_IGKJ1*01 or Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF) (SEQ ID NO:126) & L6_IGKJ1*01 at light chain amino acid residues S28, S30, S31 and Y32

Heavy Chain	Light Chain	Erb B2	EGF R	HGF R	Notch-1	CD44	IGF-1	P-Cad	EPO R	DLL4	Blank
APF	S30W	73	132	62	105	186	157	39	30	791	186
APF	parent	61	161	86	135	66	217	117	105	803	125
APF	S30X	119	67	75	45	6	56	83	93	101	112
APF	S30R	35	140	108	155	89	86	39	87	745	95
APF	S30X	319	99	122	231	239	144	224	227	593	204
APF	S30T	243	274	297	127	229	204	195	207	1016	206
APF	S30X	213	188	337	247	223	176	233	267	1374	204
APF	S30X	210	218	311	79	156	207	262	211	1299	210
APF	S30L	244	288	250	296	240	193	260	259	1627	235
APF	Y32X	240	223	259	241	203	170	199	248	648	196
APF	Y32X	155	93	176	148	147	142	38	190	817	193

APF	Y32X	125	240	299	168	236	247	260	214	1753	261
APF	Y32X	124	256	167	255	147	139	148	170	1209	155
APF	R24G/Q27L	225	252	185	177	119	49	236	191	197	87
APF	Y32V	156	57	283	56	120	151	186	144	427	164
APF	Y32S	154	208	222	137	162	175	51	230	1031	210
APF	parent	223	268	205	344	200	332	285	366	4266	256
APF	Y32X	275	266	358	306	206	304	382	374	293	253
APF	parent	383	296	265	107	273	132	366	254	3052	242
APFF	S28G	334	360	333	324	436	360	491	494	182961	343
APFF	S28K	270	386	355	395	464	348	443	477	124246	395
APFF	S28V	231	327	338	289	380	284	344	446	83083	237
APFF	S28F	242	283	223	367	402	275	336	413	133659	249
APFF	parent	333	406	432	350	451	386	368	539	182026	400
APFF	S28P	427	370	318	416	365	392	605	492	178227	393
APFF	S28T	271	321	371	249	368	355	676	380	159288	305
APFF	S28L	222	378	317	392	365	346	418	404	72299	329
APFF	S28Q	345	517	380	331	420	404	809	437	133486	353
APFF	S28A	348	351	377	440	502	378	521	424	156761	332
APFF	S28N	363	325	406	243	399	331	447	440	203926	262
APFF	S28H	381	435	346	482	513	355	447	517	209433	344
APFF	S28I	265	386	369	442	412	353	416	450	106041	343
APFF	S28R	318	403	378	425	378	437	395	542	110363	449
APFF	S28W	316	283	414	349	404	489	385	489	165026	303
APFF	S28M	271	320	305	382	313	341	410	360	108166	322
APFF	S28E	389	396	401	433	461	361	393	513	184227	420
APFF	S30C	1007	1187	1229	1472	1081	1027	1686	1792	128661	915
APFF	S30D	284	325	312	415	434	357	543	496	225396	397
APFF	S30L	270	406	315	389	295	332	351	540	198641	379
APFF	S30T	332	360	375	413	423	410	370	497	122207	407
APFF	S30R	434	456	458	576	455	404	465	571	145575	416
APFF	S30P	391	394	328	544	334	356	348	520	1143	262
APFF	parent	412	386	349	565	411	409	466	540	207955	306
APFF	S30W	289	398	399	372	500	471	342	542	190872	289
APFF	S30Y/S	319	299	345	306	346	283	429	520	143412	294
APFF	S30Q	262	353	339	243	400	342	298	423	202637	198
APFF	S30A	251	322	414	380	390	400	454	561	183649	356
APFF	S30G	404	387	355	382	427	393	369	485	180489	272
APFF	S30N	241	400	297	296	437	362	396	525	174926	352
APFF	S30P	358	385	383	346	411	312	413	418	1262	302
APFF	S30G	260	298	263	346	343	304	397	480	177646	351
APFF	S30A	295	337	311	364	451	342	317	475	186732	184
APFF	S30T	269	383	320	375	521	401	418	470	136426	392
APFF	S30V	279	412	394	294	375	365	333	536	141111	284
APFF	S30R	404	395	452	313	472	422	442	525	189471	278
APFF	S30Q	340	381	344	326	411	354	393	376	196711	327
APFF	S31T	285	351	432	261	384	303	332	423	191253	332
APFF	S31N	197	246	300	267	384	379	342	363	177897	294
APFF	S31K	262	355	221	334	370	505	471	522	179257	511
APFF	parent	312	370	347	367	457	433	450	438	171775	442
APFF	S31L	288	375	319	365	371	405	346	427	155112	416
APFF	S31M	352	380	293	474	488	445	510	573	167080	442
APFF	S31F	295	342	280	349	256	267	369	599	188723	411
APFF	S31I	222	363	303	421	506	365	444	500	173649	321
APFF	S31V	300	363	288	374	384	335	360	509	176358	345
APFF	S31H	307	373	352	421	426	350	480	504	221327	264

APFF	S31A	383	415	309	424	406	334	361	461	192365	218
APFF	S31P	372	488	431	461	466	404	493	594	53282	341
APFF	S31D	479	438	429	510	471	407	451	596	154331	493
APFF	S31R	313	331	261	358	423	374	270	465	166188	298
APFF	S31Y	236	320	197	351	445	293	361	604	187896	284
APFF	S31Q	392	390	329	383	438	415	379	548	165030	407
APFF	S31E	313	297	324	460	390	367	273	441	171114	331
APFF	S31G	311	391	378	426	381	301	384	414	65521	231

Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (H:APFF) & L6_IGKJ1*01 light chain mutants S28D, S28H, S30N and S31H were subsequently re-assayed for binding to DLL4 by ELISA. The results are set forth in Table 63 below. The results show that Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (H:APFF) & L6_IGKJ1*01 light chain mutants S28N, and S31H slightly increase binding affinity to DLL4 compared to the H:APFF parental template antibody. By ELISA at the concentrations tested, the Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (H:APFF) & L6_IGKJ1*01 light chain mutant S28H and S30D did not increase binding affinity to DLL4 compared to the APFF parental template antibody.

Table 63. Binding affinity of VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (H:APFF) & L6_IGKJ1*01 Fab mutants to DLL4

Heavy Chain	**S102A/S103P/S104F/H111F (SEQ ID NO:126)**					
Light Chain	**L6_IGKJ1*01 (SEQ ID NO:107)**	**S28N (SEQ ID NO:287)**	**S28H (SEQ ID NO:288)**	**S30D (SEQ ID NO:295)**	**L6_IGKJ1*01 (SEQ ID NO:107)**	**S31H (SEQ ID NO:313)**
400 nM	0.13	0.19	0.13	0.13	0.13	0.20
200 nM	0.10	0.17	0.14	0.11	0.08	0.11
100 nM	0.07	0.13	0.09	0.09	0.07	0.09
50 nM	0.06	0.07	0.05	0.06	0.04	0.05
25 nM	0.02	0.04	0.03	0.03	0.02	0.03
25 nM	0.03	0.05	0.03	0.03	0.02	0.03
0	0.00	0.00	0.01	0.00	0.00	0.00
0	0.00	0.00	0.00	0.01	0.01	0.00

iv. Combination mutants based on NNK mutagenesis of CDR1

Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (H:APFF) & L6_IGKJ1*01 light chain mutants S28D, S30N and S31H were combined into one triple mutant, designated as Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (H:APFF) & L6_IGKJ1*01 S28D/S30N/S31H (L:NDH) (H:APFF & L:NDH). The binding affinity of the H:APFF & L:NDH mutant to DLL4 was assayed using both ELISA and the 96-well plate ECL assay. Additionally, the light chain triple mutant L6_IGKJ1*01 S28D/S30N/S31H (L:NDH) was assayed in combination with heavy chain mutants VH1-

46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F/G56A (H:APFF G56A) and VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F/S54A (H:APFF S54A).

The results are set forth in Tables 64 and 65 below. The results show the antibody mutant APFF-NDH binds DLL4 with 4-fold increased affinity as compared to parent antibody APFF mutant. The antibody Fab H:APFF G56A & L:NDH resulted in 8-fold greater affinity for binding to DLL4 as compared to the H:APFF & L:wt parental antibody mutant, and also exhibited increased binding affinity compared to the other antibodies tested. The antibody Fab H:APFF S54A & L:NDH resulted in a slight decrease in binding affinity compared to the H:APFF & L:NDH antibody mutant. Table 65 provides a comparison of binding affinity of antibodies containing the triple light chain mutant and various mutated heavy chain mutants. The results in Tables 64 and 65 show that the H:APFF G56A & L:NDH, containing 5 mutations in the heavy chain and three mutations in the light chain, exhibited the highest binding affinity of the antibodies tested.

Table 64. Binding affinity of VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 Fab mutants

Heavy Chain	APFF (SEQ ID NO:126)	APFF (SEQ ID NO:126)	APFF G56A (SEQ ID NO:167)	APFF G56A (SEQ ID NO:167)	APFF S54A (SEQ ID NO:165)
Light Chain	Parent (SEQ ID NO:107)	S28N/ S30D/ S31H (SEQ ID NO:323)	Parent (SEQ ID NO:107)	S28N/ S30D/ S31H (SEQ ID NO:323)	S28N/ S30D/ S31H (SEQ ID NO:323)
100 nM	0.072	0.259	0.338	0.453	0.213
75 nM	0.072	0.268	0.399	0.543	0.212
50 nM	0.060	0.202	0.301	0.366	0.154
0	0.006	0.002	0.002	0.002	0.000

Table 65. Binding affinity of VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 Fab mutants

Fab				ECL Signal [10 nM Fab]	ELISA Signal [100 nM Fab]
Heavy Chain VH1-46_IGHD6-6*01_IGHJ1*01	SEQ ID NO	Light Chain L6_IGKJ1*01	SEQ ID NO		
S102A/S103P/S104F/H111F	126	S28N/S30D/S31H	323	48997	0.08
S102A/S103P/ S104F/H111F/G56A	167	S28N/S30D/S31H	323	71603	0.20
S102A/S103P/S104F/H111F/S54A	165	S28N/ S30D/S31H	323	46700	0.08

v. Alanine scanning of CDR2

Amino acid residues D50, A51, S52, N53, R54, A55 and T56 of CDR2 of the light chain L6_IGKJ1*01 were mutated by alanine scanning mutagenesis to further identify amino acid residues that are important for binding to DLL4. Amino acid residues A51 and A55 were mutated to threonine. The APFF heavy chain quadruple mutant (see e.g. Example 9; Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (H:APFF) & L6_IGKJ1*01) was used as a template.

The results are set forth in Table 66 below. The results show that mutation of amino acid residues D50, R54 and T56 with alanine and substitution of amino acid residue A51 with

threonine caused a reduction in ECL signal for binding to DLL4 and therefore these residues were not further mutagenized. Mutation of amino acid residues S52 and N53 with alanine and mutation of amino acid residue A55 with threonine either improved the ECL signal or did not affect the ECL signal for binding to DLL4 and therefore these residues were identified as amino acid residues for further mutagenesis.

Table 66. Binding affinity of Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF) & L6_IGKJ1*01 CDR2 alanine mutants

Heavy Chain VH1-46_IGHD6-6*01_IGHJ1*01	SEQ ID NO	Light Chain L6_IGKJ1*01	SEQ ID NO	Signal [10 nM Fab]
S102A/S103P/S104F/H111F	126	wildtype	107	13516
S102A/S103P/S104F/H111F	126	D50A	324	4231
S102A/S103P/S104F/H111F	126	A51T	325	2849
S102A/S103P/S104F/H111F	126	S52A	326	19311
S102A/S103P/S104F/H111F	126	N53A	327	14166
S102A/S103P/S104F/H111F	126	R54A	328	11626
S102A/S103P/S104F/H111F	126	A55T	329	13228
S102A/S103P/S104F/H111F	126	T56A	330	7260

vi. NNK mutagenesis of CDR2 residues S52, N53, and A55

Fab mutant H:APFF & L:NDH (see Example 10 above; VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (H:APFF) & L6_IGKJ1*01 S28D/S30N/S31H (L:NDH)) was used as a template for NNK mutagenesis of CDR2 amino acid residues S52, N53 and A55. The Fab mutants were tested for binding to DLL4 using the 96-well plate ECL binding assay and ELISA. Table 67 sets forth the ECL and ELISA signals. Amino acid mutations designated with X (for any amino acid) did not show appreciable binding and therefore were not sequenced to identify the exact mutation. The results show that various mutants of H:APFF & L:NDH exhibited greater ECL and ELISA signals for binding to DLL4 as compared to the parental H:APFF & L:NDH, including those having further mutations S52T, S52L, N53H, A55S and A55G in the light chain.

Light chain mutants H:APFF & L:NDH S52T, H:APFF & L:NDH S52L, H:APFF & L:NDH S52T/S, H:APFF & L:NDH S52X, H:APFF & L:NDH N53H, H:APFF & L:NDH A55S and H:APFF & L:NDH A55G were further analyzed for binding to DLL4 by ELISA using 2-fold serial dilutions of Fab, starting at a concentration of 100 nM. The results are set forth in Table 68 below. Antibody mutants H:APFF & L:NDH S52L, H:APFF & L:NDH A55S and H:APFF & L:NDH A55G had a slightly increased affinity for binding to DLL4 as compared to the parental H:APFF & L:NDH mutant. All of the Fab light chain mutants bind DLL4 within the same range of affinity as the parental H:APFF & L:NDH mutant.

Table 67. Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (H:APFF) & L6_IGKJ1*01 S28N/S30D/S31H (L:NDH) light chain CDR2 NNK mutant binding data

Fab	ECL	ELISA

Heavy Chain VH1-46_IGHD6-6*01_IGHJ1*01 (SEQ ID NO:126)	Light Chain	SEQ ID NO	Signal	(Avgerage signal-noise)
S102A/S103P/S104F/H111F	**S28N/S30D/S31H S52L**	**331**	**17810**	**0.285**
S102A/S103P/S104F/H111F	S28N/S30D/S31H S52G/V	367	17589	0.233
S102A/S103P/S104F/H111F	S28N/S30D/S31H S52T/S	368	17769	0.261
S102A/S103P/S104F/H111F	S28N/S30D/S31H S52R	333	20009	0.244
S102A/S103P/S104F/H111F	S28N/S30D/S31H S52S/Y	369	15572	0.218
S102A/S103P/S104F/H111F	S28N/S30D/S31H S52X	370	2757	0.077
S102A/S103P/S104F/H111F	S28N/S30D/S31H S52X	370	15250	0.232
S102A/S103P/S104F/H111F	S28N/S30D/S31H S52X	370	16779	0.299
S102A/S103P/S104F/H111F	S28N/S30D/S31H S52X	370	16012	0.303
S102A/S103P/S104F/H111F	S28N/S30D/S31H S52X	370	15424	0.272
S102A/S103P/S104F/H111F	S28N/S30D/S31H S52X	370	16839	0.366
S102A/S103P/S104F/H111F	S28N/S30D/S31H S52X	370	15263	0.273
S102A/S103P/S104F/H111F	S28N/S30D/S31H S52W	334	16341	0.177
S102A/S103P/S104F/H111F	S28N/S30D/S31H S52R	333	20497	0.179
S102A/S103P/S104F/H111F	NDH	323	18697	0.165
S102A/S103P/S104F/H111F	S28N/S30D/S31H S52N/X	371	20512	0.221
S102A/S103P/S104F/H111F	S28N/S30D/S31H S52R	333	20573	0.243
S102A/S103P/S104F/H111F	S28N/S30D/S31H S52P/X	372	19361	0.233
S102A/S103P/S104F/H111F	**S28N/S30D/S31H S52T**	**332**	**20097**	**0.263**
S102A/S103P/S104F/H111F	S28N/S30D/S31H S52M	337	19458	0.185
S102A/S103P/S104F/H111F	S28N/S30D/S31H N53X	373	12235	0.106
S102A/S103P/S104F/H111F	S28N/S30D/S31H N53E	338	17553	0.204
S102A/S103P/S104F/H111F	S28N/S30D/S31H N53X	373	200	0.000
S102A/S103P/S104F/H111F	S28N/S30D/S31H N53X	373	9412	0.110
S102A/S103P/S104F/H111F	S28N/S30D/S31H N53G	339	20572	0.163
S102A/S103P/S104F/H111F	S28N/S30D/S31H N53X	373	15916	0.132
S102A/S103P/S104F/H111F	S28N/S30D/S31H N53X	373	3627	-0.001
S102A/S103P/S104F/H111F	S28N/S30D/S31H N53M	340	17793	0.162
S102A/S103P/S104F/H111F	S28N/S30D/S31H N53X	373	13341	0.161
S102A/S103P/S104F/H111F	S28N/S30D/S31H N53C/F	374	18046	0.266
S102A/S103P/S104F/H111F	**S28N/S30D/S31H N53H**	**342**	**20061**	**0.230**
S102A/S103P/S104F/H111F	S28N/S30D/S31H N53X	373	14078	0.139
S102A/S103P/S104F/H111F	S28N/S30D/S31H N53X	373	456	0.060
S102A/S103P/S104F/H111F	S28N/S30D/S31H N53M/L	375	16809	0.166
S102A/S103P/S104F/H111F	S28N/S30D/S31H N53P	343	18132	0.120
S102A/S103P/S104F/H111F	S28N/S30D/S31H N53X	373	203	0.015
S102A/S103P/S104F/H111F	S28N/S30D/S31H N53A	344	14213	0.151
S102A/S103P/S104F/H111F	S28N/S30D/S31H N53X	373	14322	0.127
S102A/S103P/S104F/H111F	S28N/S30D/S31H N53X	373	260	-0.001
S102A/S103P/S104F/H111F	S28N/S30D/S31H A55R	345	9031	0.106
S102A/S103P/S104F/H111F	S28N/S30D/S31H A55C	346	8226	0.146
S102A/S103P/S104F/H111F	S28N/S30D/S31H A55X	376	14187	0.202
S102A/S103P/S104F/H111F	**S28N/S30D/S31H A55S**	**347**	**20047**	**0.383**
S102A/S103P/S104F/H111F	S28N/S30D/S31H A55X	376	899	0.019
S102A/S103P/S104F/H111F	**S28N/S30D/S31H A55G**	**348**	**21381**	**0.323**
S102A/S103P/S104F/H111F	S28N/S30D/S31H A55X	376	8799	0.092
S102A/S103P/S104F/H111F	S28N/S30D/S31H A55X	376	5320	0.068
S102A/S103P/S104F/H111F	NDH	323	17201	0.214
S102A/S103P/S104F/H111F	S28N/S30D/S31H A55X	376	13643	0.116
S102A/S103P/S104F/H111F	S28N/S30D/S31H A55X	376	275	0.016

S102A/S103P/S104F/H111F	S28N/S30D/S31H A55X	376	1370	0.010
S102A/S103P/S104F/H111F	S28N/S30D/S31H A55X	376	13611	0.151
S102A/S103P/S104F/H111F	S28N/S30D/S31H A55X	376	167	0.007
S102A/S103P/S104F/H111F	**S28N/S30D/S31H A55G**	**348**	**18042**	**0.301**
S102A/S103P/S104F/H111F	S28N/S30D/S31H A55X	376	296	0.023
S102A/S103P/S104F/H111F	**S28N/S30D/S31H A55G**	**348**	**19264**	**0.298**
S102A/S103P/S104F/H111F	S28N/S30D/S31H A55X	376	5246	0.068

Table 68. Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF) (SEQ ID NO:126) & L6_IGKJ1*01 S28N/S30D/S31H (NDH) light chain S52, N53 and A55 mutant binding to DLL4 by ELISA

Fab [nM]	H L	APFF NDH/ S52L	APFF NDH/ S52T/ S	APFF NDH/ S52X	APFF NDH/ S52T	APFF NDH/ N53H	APFF NDH/ A55S	APFF NDH/ A55G	APFF NDH
100		0.791	0.696	0.686	0.653	0.608	0.858	0.814	0.686
50		0.546	0.500	0.508	0.490	0.416	0.588	0.510	0.507
25		0.335	0.297	0.309	0.323	0.238	0.407	0.316	0.310
12.5		0.215	0.186	0.192	0.215	0.167	0.258	0.198	0.192
6.25		0.142	0.115	0.125	0.130	0.109	0.154	0.125	0.125
3.125		0.095	0.088	0.096	0.099	0.089	0.108	0.093	0.096

vii. NNK mutagenesis of framework 3 residues S76 and F62

Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (H:APFF) and L6_IGKJ1*01 was used as template for further mutagenesis of amino acid residues S76 and F62 in the framework 3 region of the light chain. These residues were mutated using overlapping PCR with NNK mutagenesis, as described above. Binding to DLL4 was assayed using an ECL Multispot assay as described in Example 4A or in an ELISA assay as described in Example 6. The results are set forth in Tables 69-71, below. The results show that mutation of amino acid residues S76 and F62 caused a decrease in the ECL and ELISA signals for binding to DLL4.

Table 69. Binding affinity of Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF) & L6_IGKJ1*01 S76 and F62 Mutants

Heavy Chain VH1-46_IGHD6-6*01_IGHJ1*01	SEQ ID NO	Light Chain L6_IGKJ1*01	SEQ ID NO	Signal [10 nM Fab]
S102A/S103P/S104F/H111F	126	S76L	351	13688
S102A/S103P/S104F/H111F	126	S76T	352	15747
S102A/S103P/S104F/H111F	126	S76G	353	13404
S102A/S103P/S104F/H111F	126	wildtype	107	13516
S102A/S103P/S104F/H111F	126	S76A/K	377	16525
S102A/S103P/S104F/H111F	126	S76Y	355	14825
S102A/S103P/S104F/H111F	126	F62L	356	261

Table 70. Binding affinity of Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (H:APFF) & L6_IGKJ1*01 S76 and F62 Mutants

Heavy Chain VH1-46_IGHD6-6*01_IGHJ1*01	SEQ ID NO	Light Chain L6_IGKJ1*01	SEQ ID NO	ECL Signal/Noise	ELISA (Signal-Noise)
S102A/S103P/S104F/H111F	126	S76E	357	217.5	0.36
S102A/S103P/S104F/H111F	126	S76Q	358	187.3	0.32
S102A/S103P/S104F/H111F	126	S76P	359	100.0	0.29
S102A/S103P/S104F/H111F	126	S76N	360	118.2	0.28
S102A/S103P/S104F/H111F	126	wildtype	107	441.3	0.57
S102A/S103P/S104F/H111F	126	wildtype	107	309.9	0.24
S102A/S103P/S104F/H111F	126	wildtype	107	584.6	0.26
S102A/S103P/S104F/H111F	126	wildtype	107	718.7	0.37

Table 71. Binding affinity and specificity of Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (H:APFF) (SEQ ID NO:126) & L6_IGKJ1*01 S76 and F62 Mutants

Light	Erb B2	EGF R	HGF R	Notch-1	CD44	IGF-1	P-Cad	EPO R	DLL4	Blank
S76E	277	266	228	313	439	336	338	440	51555	237
S76Q	264	324	386	255	287	188	364	430	48330	258
S76P	260	331	394	402	313	347	271	371	29787	298
S76N	436	385	429	298	369	378	329	384	51989	440
wildtype	379	425	332	429	470	468	399	437	149144	338
wildtype	292	329	237	377	326	357	277	449	126118	407
wildtype	351	209	176	359	332	306	138	414	148493	254
wildtype	322	409	263	417	316	173	240	328	132249	184

EXAMPLE 11

Heavy chain and light chain Fab combination mutants

Heavy chain and light chain mutants that were identified in Examples 7-10 as contributing to binding to DLL4 were paired into various combination mutants. Heavy chain mutants included VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F N52L/S54T/G56H (H:APFF LTH), VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F I51A/N52L/S54T/G56H (H:APFF ALTH), and VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F I51V/N52L/S54T/G56H (H:APFF VLTH). Light chain mutants included L6_IGKJ1*01 S28D/S30N/S31H S52L/A55S (L:NDH LS) and L6_IGKJ1*01 S28D/S30N/S31H S52L/A55G (L:NDH LG).

Table 72 below sets forth the Fabs and the ECL signal for binding to DLL4. In general, Fabs with H:APFF LTH and H:APFF VLTH heavy chains had an increased ECL signal for binding to DLL4 as compared to a Fab with a heavy chain H:APFF ALTH. Depending on the antibody tested, the particular light chain mutants also further affected binding to DLL4. Similar results were obtained by ELISA (Table 73). The mutants were further analyzed for binding to DLL4 by ELISA using 3-fold serial dilutions of Fab, starting at a concentration of 20 nM. The results are set forth in Table 73 below. Antibodies

containing the H:APFF LTH and APFF H:VLTH heavy chain mutations had approximately 10-fold increased binding affinity to DLL4 compared to the antibody mutants containing the heavy chain mutant H:APFF ALTH.

Table 72. Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (H:APFF) & L6_IGKJ1*01 S28N/S30D/S31H (L:NDH) CDR2 combination mutants

Fab				
Heavy Chain VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF)	SEQ ID NO	Light Chain L6_IGKJ1*01 S28N/S30D/S31H (NDH)	SEQ ID NO	ECL Signal
N52L/S54T/G56H (LTH)	203	(NDH)	323	6023
N52L/S54T/G56H (LTH)	203	S52L/A55G (NDH LG)	349	9007
N52L/S54T/G56H (LTH)	203	S52L/A55S (NDH LS)	350	11493
I51A/N52L/S54T/G56H (ALTH)	204	(NDH)	323	1840
I51A/N52L/S54T/G56H (ALTH)	204	S52L/A55G (NDH LG)	349	1759
I51A/N52L/S54T/G56H (ALTH)	204	S52L/A55S (NDH LS)	350	3720
I51V/N52L/S54T/G56H (VLTH)	209	(NDH)	323	9789
I51V/N52L/S54T/G56H (VLTH)	209	S52L/A55G (NDH LG)	349	12246
I51V/N52L/S54T/G56H (VLTH)	209	S52L/A55S (NDH LS)	350	8000

Table 73. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ*01 mutant binding to DLL4 by ELISA

Heavy Chain VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF)	Light Chain L6_IGKJ1*01 S28N/S30D/S31H (NDH)	20	6.67	2.22	0.74
N52L/S54T/G56H (LTH)	(NDH)	0.863	0.739	0.463	0.270
N52L/S54T/G56H (LTH)	S52L/A55G (NDH LG)	1.008	0.880	0.594	0.368
N52L/S54T/G56H (LTH)	S52L/A55S (NDH LS)	1.054	0.916	0.557	0.398
I51A/N52L/S54T/G56H (ALTH)	(NDH)	0.391	0.232	0.069	0.024
I51A/N52L/S54T/G56H (ALTH)	S52L/A55G (NDH LG)	0.390	0.212	0.069	0.028
I51A/N52L/S54T/G56H (ALTH)	S52L/A55S (NDH LS)	0.458	0.282	0.040	0.046
I51V/N52L/S54T/G56H (VLTH)	(NDH)	0.979	0.776	0.608	0.288
I51V/N52L/S54T/G56H (VLTH)	S52L/A55G (NDH LG)	1.057	0.916	0.755	0.397
I51V/N52L/S54T/G56H (VLTH)	S52L/A55S (NDH LS)	0.910	0.747	0.523	0.263

Summary

As a result of affinity maturation, the affinity of parental Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 for binding to DLL4 was increased 430-fold. Table 75 below sets for the binding affinity of the various affinity matured antibodies for DLL4, as determined by SPR (see Example 5). Parent Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 binds DLL4 with a K_D of 730 nM. Mutation of four heavy chain amino acids, namely S102A/S103P/S104F/H111F (H:APFF), resulted in a Fab with 10-fold increased affinity for DLL4 (K_D = 70.6 nM). Affinity matured heavy and light chain mutant Fab H:APFF VLTH & L:NDH LS has a K_D of 1.7 nM, a 430-fold increase in binding affinity for DLL4.

Table 75. Surface Plasmon Resonance Binding affinity of DLL4 Fabs				
Heavy Chain	Light Chain	k_a ($x10^5$) ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_D (nM)
VH1-46_IGHD6-6*01_IGHJ1*01 (parental)	L6_IGKJ1*01 (parental)	1.63 (±3)	0.101 (±2)	730 (±130)
VH1-46_IGHD6-6*01_IGHJ1*01 S104F	L6_IGKJ1*01	5.0 (±0.8)	0.19 (±0.01)	380 (±60)
VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F (APF)	L6_IGKJ1*01	4.05 (±0.05)	0.0492 (±0.0004)	122 (±1)
VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF)	L6_IGKJ1*01	4.25 (±0.04)	0.0300 (±0.0002)	70.6 (±0.7)
VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111Y (APFY)	L6_IGKJ1*01	3.40 (±0.03)	0.0317 (±0.0002)	93.1 (±0.9)
VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F (APF)	L6_IGKJ1*01 S31K	3.50 (±0.05)	0.0392 (0.0004)	112 (±2)
VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F G56H (APFF G56H)	L6_IGKJ1*01	3.51 (±1.84)	0.0101 (±0.000716)	32.7 (±11.6)
VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F (APFF)	L6_IGKJ1*01 S28N/S30D/S31H (NDH)	4.44	0.0689	*155.2 and 14
VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F I51V/N52L/S54T/G56H (APFF VLTH)	L6_IGKJ1*01 S28N/S30D/S31H (NDH)	4.30 (±1.45)	0.00113 (±0.000138)	2.7 (±0.6)
VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F I51V/N52L/S54T/G56H (APFF VLTH)	L6_IGKJ1*01 S28N/S30D/S31H S52L/A55S (NDH LS)	6.84 (±2.51)	0.00109 (±0.000106)	1.7 (±0.5)

*Fab Fab VH1-46_IGHD6-6*01_IGHJ1*01 S102A/S103P/S104F/H111F & L6_IGKJ1*01 S28N/S30D/S31H displays 2-site binding: 89% with Kd of 155.2 nM and 10% with Kd of 14 nM.

EXAMPLE 12

Affinity Maturation of Identified Parent "Hit" Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 Against DLL4

The parent "Hit" Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 (SEQ ID NOS:89 and 108) against DLL4, identified in Example 4 using the electroluminescence Meso Scale Discovery (MSD) multispot binding assay, was subjected to affinity maturation as described above in Examples 7-11. By this method, an anti-DLL4 antibody was generated with significantly improved binding affinity for DLL4 compared to the parent "Hit" VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 Fab antibody.

A. Heavy Chain

1. Identification of the CDR potential binding site

The amino acid sequence of the heavy chain (SEQ ID NO:89) for the parent "Hit" VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 was aligned with the amino acid sequence of a related heavy chain (SEQ ID NO:106) of a non-Hit that was identified as not binding to DLL4, i.e. VH5-51_IGHD6-25*01_IGHJ4*01. These two Fabs are related because they share the same V_H and J_H germline segments. The sequence alignment is set forth in Figure 3. Based on the alignment, amino acid residues were identified that differed between the "Hit" and "non-Hit," thus accounting for the differences in binding of the "Hit" and "non-Hit" antibody for DLL4. The identified amino acid residues were located in CDR3, which was identified as the region of the heavy chain that is important for binding affinity.

2. Alanine scanning of CDR3

Alanine scanning mutagenesis was performed on amino acid residues in the CDR3 of the heavy chain sequence of parent Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 to identify amino acid residues that do not appear to be involved in DLL4 binding. Alanine-scanning of the CDR3 region of the heavy chain was performed by mutating every residue of the CDR3 region to an alanine, except amino acid residues Y107, F108, D109, and Y110. Purified Fab alanine mutants were tested for binding to DLL4. The results are set forth in Table 76. Mutation of R99, Y101, S102, Y103, Y105, or D106 with alanine caused a reduction in the ECL signal for binding to DLL4, and therefore these residues were not further mutagenized. In contrast, mutation of G100 or G104 with alanine either resulted in an increased ECL signal or did not affect the ECL signal for binding to DLL4, and thus these residues were identified as residues for further mutagenesis. The results were confirmed in a repeat experiment using varying concentrations of mutant Fab and DLL4 protein (see Table 77).

Table 76. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 alanine mutant binding data

Heavy Chain VH5-51_IGHD5-18*01_IGHJ4*01	SEQ ID NO	Light Chain	SEQ ID NO	Signal/ Noise (0.04 μM)
wildtype	89	V3-4_IGLJ1*01	108	14.7
R99A	382	V3-4_IGLJ1*01	108	1.3
G100A	383	V3-4_IGLJ1*01	108	30.4
Y101A	384	V3-4_IGLJ1*01	108	1.2
S102A	385	V3-4_IGLJ1*01	108	2
Y103A	386	V3-4_IGLJ1*01	108	1.2
G104A	387	V3-4_IGLJ1*01	108	15.5
Y105A	388	V3-4_IGLJ1*01	108	9.6
D106A	389	V3-4_IGLJ1*01	108	1.2
wildtype	89	V3-4_IGLJ1*01	108	15.5

Table 77. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 alanine mutant binding data				
Fab			0.1 μM Fab 30 μg/mL DLL4	0.02 μM Fab 15 μg/mL DLL4
Heavy Chain VH5-51_IGHD5-18*01_IGHJ4*01	SEQ ID NO	Light Chain (SEQ ID NO:108)	Signal/ Noise	Signal/ Noise
wildtype	89	V3-4_IGLJ1*01	24.0	15.2
R99A	382	V3-4_IGLJ1*01	1.1	1.0
G100A	383	V3-4_IGLJ1*01	53.3	24.2
Y101A	384	V3-4_IGLJ1*01	1.1	1.3
S102A	385	V3-4_IGLJ1*01	4.7	1.8
Y103A	386	V3-4_IGLJ1*01	4.0	1.5
G104A	387	V3-4_IGLJ1*01	41.5	12.5
Y105A	388	V3-4_IGLJ1*01	1.0	1.0
D106A	389	V3-4_IGLJ1*01	1.3	1.0

3. NNK mutagenesis of heavy chain amino acid residues G100 and G104

Following alanine scanning mutagenesis of CDR3, heavy chain amino acid residues G100 and G104 were selected for further mutation using overlapping PCR with NNK mutagenesis using wildtype Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 as a template, similar to the experiment described in Example 7.b.iii above. The results are set forth in Table 78 below. Amino acid mutations designated with X (for any amino acid) did not show appreciable binding and therefore were not sequenced to identify the exact mutation. Two mutations, G100K and G104T, in the heavy chain were identified that resulted in a Fab with an improved ECL signal for binding to DLL4. Each mutant exhibited an ECL signal for binding to DLL4 approximately 2-fold greater than parent Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01.

Table 78. NNK mutagenesis of parent Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 at amino acid residues G100 and G104				
Fab			0.1 μM Fab 30 μg/mL DLL4	0.02 μM Fab 15 μg/mL DLL4
Heavy Chain VH5-51_IGHD5-18*01_IGHJ4*01	SEQ ID NO	Light Chain (SEQ ID NO:108)	Signal/ Noise	Signal/Noise
G100L	390	V3-4_IGLJ1*01	27.2	13.0
G104stop	436	V3-4_IGLJ1*01	1.0	1.1
G100L	390	V3-4_IGLJ1*01	66.2	32.5
G100D	391	V3-4_IGLJ1*01	5.8	2.0
G100T	392	V3-4_IGLJ1*01	26.0	11.0
G100K	**378**	**V3-4_IGLJ1*01**	**133.9**	**72.6**
G100R	379	V3-4_IGLJ1*01	90.6	39.9
G100L	390	V3-4_IGLJ1*01	40.2	15.6
G100L	390	V3-4_IGLJ1*01	59.0	28.7

G104D	393	V3-4_IGLJ1*01	42.5	23.2
G104A	387	V3-4_IGLJ1*01	6.7	2.6
G104L	394	V3-4_IGLJ1*01	28.4	9.3
G104P	395	V3-4_IGLJ1*01	1.0	1.0
wildtype	89	V3-4_IGLJ1*01	31.4	13.2
G104R	396	V3-4_IGLJ1*01	23.2	9.1
G104T	380	V3-4_IGLJ1*01	45.4	20.2
G104X	437	V3-4_IGLJ1*01	44.5	22.5
G104T	**380**	**V3-4_IGLJ1*01**	**63.2**	**29.0**
G104stop	436	V3-4_IGLJ1*01	1.2	0.9
G104M	397	V3-4_IGLJ1*01	29.1	12.3
wildtype	89	V3-4_IGLJ1*01	32.6	15.6
G104L	394	V3-4_IGLJ1*01	23.4	10.8
G104stop	436	V3-4_IGLJ1*01	1.0	1.0
G104K	398	V3-4_IGLJ1*01	17.6	9.1
wildtype	89	V3-4_IGLJ1*01	42.4	17.6
G104R	396	V3-4_IGLJ1*01	20.4	7.8
G104S	399	V3-4_IGLJ1*01	47.8	25.6
G104R/Y101H	400	V3-4_IGLJ1*01	1.2	1.0
G104T	**380**	**V3-4_IGLJ1*01**	**67.8**	**35.8**

4. Combination mutant based on NNK mutagenesis of CDR3

Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 heavy chain mutants G100K and G104T, identified as having increased binding affinity to DLL4, were combined to generate a double mutant, designated as Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T & V3-4_IGLJ1*01 (H:KT). The binding of the KT double mutant to DLL4 was compared to the binding of the parent Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 to DLL4 by assaying various concentrations each antibody. The results are set forth in Tables 79-80 below. The results show that the KT double mutant exhibits an increased ECL signal for binding to DLL4 as compared to the parent Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01. Both Fabs exhibit specific binding to DLL4 as compared to the various other tested antigens (see Table 80).

Table 79. Binding affinity of double mutant Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T & V3-4_IGLJ1*01 (SEQ ID NO:108) as compared to wildtype Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01

Heavy Chain	Wildtype (SEQ ID NO:89)	G100K, G104T (SEQ ID NO:381)	Wildtype (SEQ ID NO:89)	G100K, G104T (SEQ ID NO:381)
Fab [μM]	**Signal**	**Signal**	**Signal/Noise**	**Signal/Noise**
200.00	4750	69079	36.3	76.9
20.00	2199	45123	21.1	157.2
2.00	443	5379	2.2	72.7
0.20	348	350	3.0	3.0

Table 80. Binding affinity and specificity of double mutant Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T & V3-4_IGLJ1*01 as compared to wildtype Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01

Heavy Chain	Fab [μM]	ErbB2	EGFR	HGFR	Notch-1	CD44	IGF-1	P-Cad	EPOR	DLL4
Wt	200.00	3.1	2.9	3.5	1.3	1.6	2.8	1.5	2.2	36.3
	20.00	4.4	2.5	4.0	1.6	2.6	1.8	0.9	2.0	21.1
	2.00	1.8	1.1	1.8	1.5	1.1	1.6	1.1	1.2	2.2
	0.20	2.6	3.4	3.1	1.7	1.4	2.9	1.5	2.5	3.0
G100K, G104T	200.00	1.7	1.6	1.7	1.7	1.4	1.5	2.0	1.7	76.9
	20.00	1.2	1.1	0.9	1.2	1.1	1.1	1.1	1.1	157.2
	2.00	3.2	3.8	6.0	1.9	3.5	3.7	4.3	4.1	72.7
	0.20	2.5	1.5	2.4	1.9	1.3	1.9	1.7	1.7	3.0

B. Further optimization of the Heavy Chain

1. Summary

The heavy chain of the KT double mutant described and generated above was further optimized to improve its binding for DLL4. The heavy chain mutant KT double mutant was used as a template for further mutagenesis of heavy chain amino acid residues in the CDR1 (amino acids 26-35), CDR2 (amino acid residues 50-66) and framework region of the heavy chain by alanine scanning mutagenesis.

2. Alaninie scanning of residues in CDR1

Alanine scanning was performed by mutating every amino acid residue of CDR1, except G26. Three additional flanking amino acid residues, namely G24, I34, and G35 were also mutated to alanine. Purified Fab alanine mutants were tested for binding to DLL4 using the ECL multispot binding assay. The results are set forth in Tables 81-83 below. Mutation of amino acid residues Y27, F29, T30, S31, Y32, W33, or I34 with alanine caused a reduction in the ECL and ELISA signals for binding to DLL4, and thus these residues were not further mutagenized. Mutation of amino acid residues G24, S28, or G35 with alanine either improved the ECL signal or did not affect the ECL signal for binding to DLL4, and thus these residues were identified as residues for further mutagenesis. ELISA experiments also were performed, but little or no detectable signal was observed in the ELISA experiments (Table 81). Table 83 shows that the tested antibodies exhibit specificity for DLL4 compared to other tested antigens.

Table 81. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (KT) & V3-4_IGLJ1*01 CDR1 alanine mutant binding data

Fab			ECL Signal/ Blank	ELISA (Signal-Noise)
Heavy Chain VH5-51_IGHD5-18*01_IGHJ4*01	SEQ ID NO	Light Chain (SEQ ID NO:108)		
G100K/G104T G24A	401	V3-4_IGLJ1*01	122.1	0.02
G100K/G104T I34A	402	V3-4_IGLJ1*01	2.6	0.01
G100K/G104T G35A	403	V3-4_IGLJ1*01	180.5	0.02
G100K/G104T S28A	404	V3-4_IGLJ1*01	112.1	0.01
G100K/G104T	381	V3-4_IGLJ1*01	85.9	0.00

G100K/G104T F29A	405	V3-4_IGLJ1*01	67.9	0.02
G100K/G104T T30A	406	V3-4_IGLJ1*01	69.4	0.00
G100K/G104T	381	V3-4_IGLJ1*01	188.0	0.00
G100K/G104T W33A	407	V3-4_IGLJ1*01	3.0	0.02
G100K/G104T	381	V3-4_IGLJ1*01	153.3	0.01

Table 82. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (KT) & V3-4_IGLJ1*01 CDR1 alanine mutant binding data

Fab			ECL Signal/ Blank
Heavy Chain VH5-51_IGHD5-18*01_IGHJ4*01	SEQ ID NO	Light Chain (SEQ ID NO:108)	
G100K/G104T	381	V3-4_IGLJ1*01	49.2
G100K/G104T Y27A	2899	V3-4_IGLJ1*01	9.1
G100K/G104T S31A	2900	V3-4_IGLJ1*01	3.0
G100K/G104T Y32A	2901	V3-4_IGLJ1*01	2.7

Table 83. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (KT) & V3-4_IGLJ1*01 CDR1 alanine mutant binding data

Heavy Chain	Erb B2	EGFR	HGFR	Notch-1	CD44	IGF-1	P-Cad	EPOR	DLL4	Blank
KT G24A	869	757	803	493	547	879	212	551	45546	373
KT I34A	1149	883	1084	564	608	923	349	505	772	300
KT G35A	911	760	939	400	624	899	305	506	53618	297
KT S28A	1072	839	1040	432	497	924	317	586	35439	316
KT	1095	852	838	543	579	877	319	554	36440	424
KT F29A	1040	887	985	601	621	945	502	586	22867	337
KT T30A	1071	853	868	539	698	968	438	553	24346	351
KT	1068	915	936	507	633	964	346	497	45120	240
KT W33A	921	761	735	561	513	788	302	424	731	240
KT	1098	768	867	437	540	781	226	421	32658	213

3. NNK mutagenesis of amino acid residues G24, S28 and G35

Following alanine scanning mutagenesis of CDR1, heavy chain amino acid residues G24, S28 and G35 were selected for further mutation using overlapping PCR with NNK mutagenesis using the heavy chain KT double mutant as a template. The results are set forth in Table 84 below. Amino acid mutations designated with X (for any amino acid) did not show appreciable binding and therefore were not sequenced to identify the exact mutation. Several Fab mutants that contained a combination of two mutations at a specific amino acid position are designated as such. For example, G24S/T indicates the tested antibody was a mixture of two Fabs, one containing the mutation G24S and the other containing the mutation G24T. The results show that mutation of additional amino acids (G24L, S28R, S28K and G35V) in the heavy chain of the KT double mutant result in increase the ECL signal for binding to DLL4 compared to the parental KT double mutant template.

Table 84. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (KT) & V3-

4_IGLJ1*01 CDR1 NNK mutant binding data				
Fab			ECL Signal	ELISA (Signal-Noise)
Heavy Chain VH5-51_IGHD5-18*01_IGHJ4*01	SEQ ID NO	Light Chain (SEQ ID NO:108)		
G100K/G104T G24L	**408**	**V3-4_IGLJ1*01**	**19617**	**0.09**
G100K/G104T G24X	438	V3-4_IGLJ1*01	291	0.03
G100K/G104T G24X	438	V3-4_IGLJ1*01	13304	0.06
G100K/G104T G24X	438	V3-4_IGLJ1*01	250	0.03
G100K/G104T G24X	438	V3-4_IGLJ1*01	10339	0.06
G100K/G104T G24X	438	V3-4_IGLJ1*01	7395	0.05
G100K/G104T G24X	438	V3-4_IGLJ1*01	1294	0.03
G100K/G104T G24X	438	V3-4_IGLJ1*01	4299	0.04
G100K/G104T G24X	438	V3-4_IGLJ1*01	319	0.02
G100K/G104T G24S/T	439	V3-4_IGLJ1*01	22221	0.09
G100K/G104T G24X	438	V3-4_IGLJ1*01	9771	0.06
G100K/G104T G24X	438	V3-4_IGLJ1*01	7554	0.05
G100K/G104T G24L/G	440	V3-4_IGLJ1*01	7970	0.05
G100K/G104T G24X	438	V3-4_IGLJ1*01	517	0.04
G100K/G104T G24X	438	V3-4_IGLJ1*01	1267	0.04
G100K/G104T G24X	438	V3-4_IGLJ1*01	12665	0.05
G100K/G104T G24X	438	V3-4_IGLJ1*01	12614	0.06
G100K/G104T G24X	438	V3-4_IGLJ1*01	8746	0.05
G100K/G104T G24X	438	V3-4_IGLJ1*01	2330	0.04
G100K/G104T G24X	438	V3-4_IGLJ1*01	7003	0.05
G100K/G104T S28R	**411**	**V3-4_IGLJ1*01**	**36903**	**0.25**
G100K/G104T S28X	441	V3-4_IGLJ1*01	1882	0.06
G100K/G104T S28K	**412**	**V3-4_IGLJ1*01**	**32324**	**0.28**
G100K/G104T S28X	441	V3-4_IGLJ1*01	5811	0.06
G100K/G104T G24R	410	V3-4_IGLJ1*01	4203	0.06
G100K/G104T S28X	441	V3-4_IGLJ1*01	6855	0.05
G100K/G104T S28X	441	V3-4_IGLJ1*01	356	0.03
G100K/G104T S28X	441	V3-4_IGLJ1*01	8482	0.05
G100K/G104T S28R	**411**	**V3-4_IGLJ1*01**	**64124**	**0.49**
G100K/G104T S28X	441	V3-4_IGLJ1*01	14585	0.10
G100K/G104T S28X	441	V3-4_IGLJ1*01	10205	0.07
G100K/G104T S28X	441	V3-4_IGLJ1*01	834	0.04
G100K/G104T S28X	441	V3-4_IGLJ1*01	4605	0.04
G100K/G104T S28X	441	V3-4_IGLJ1*01	344	0.03
G100K/G104T S28X	441	V3-4_IGLJ1*01	8017	0.05
G100K/G104T S28X	441	V3-4_IGLJ1*01	9895	0.05
G100K/G104T S28R	**411**	**V3-4_IGLJ1*01**	**51418**	**0.29**
G100K/G104T S28N	413	V3-4_IGLJ1*01	17255	0.09
G100K/G104T S28X	441	V3-4_IGLJ1*01	7681	0.05
G100K/G104T G35X	442	V3-4_IGLJ1*01	6027	0.05
G100K/G104T G35X	442	V3-4_IGLJ1*01	302	0.02
G100K/G104T G35T	414	V3-4_IGLJ1*01	14452	0.07
G100K/G104T G35X	442	V3-4_IGLJ1*01	937	0.04
G100K/G104T G35X	442	V3-4_IGLJ1*01	4954	0.05
G100K/G104T G35X	442	V3-4_IGLJ1*01	812	0.03

G100K/G104T G35X	442	V3-4_IGLJ1*01	1088	0.04
G100K/G104T G35X	442	V3-4_IGLJ1*01	1231	0.03
G100K/G104T G35X	442	V3-4_IGLJ1*01	5067	0.04
G100K/G104T G35A	403	V3-4_IGLJ1*01	19695	0.06
G100K/G104T G35V	**416**	**V3-4_IGLJ1*01**	**21169**	**0.09**
G100K/G104T G35X	442	V3-4_IGLJ1*01	2122	0.04
G100K/G104T G35X	442	V3-4_IGLJ1*01	1426	0.04
G100K/G104T G35X	442	V3-4_IGLJ1*01	326	0.03
G100K/G104T G35X	442	V3-4_IGLJ1*01	3106	0.03
G100K/G104T G35X	442	V3-4_IGLJ1*01	1373	0.03
G100K/G104T G35X	442	V3-4_IGLJ1*01	5986	0.06
G100K/G104T G35X	442	V3-4_IGLJ1*01	3787	0.04
G100K/G104T G35X	442	V3-4_IGLJ1*01	4871	0.04
G100K/G104T G35X	442	V3-4_IGLJ1*01	370	0.03
G100K/G104T G35X	442	V3-4_IGLJ1*01	841	0.04

4. Combination mutants of G24, S28 and G35

Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (KT) & V3-4_IGLJ1*01 heavy chain mutants G24L, G24T, G24A, S28R and G35V were combined to generate antibodies containing three to five mutations in the heavy chain. The mutants generated are set forth in Table 85. The mutants were assessed for binding to DLL4 using an ECL assay. All combination mutants exhibited greater ECL signals for binding to DLL4 compared to the KT double mutant. The results show that the mutant Fab H:KT TRV & L:wt had the greatest affinity towards binding to DLL4.

Table 85. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (KT) & V3-4_IGLJ1*01 CDR1 combination mutants

Fab				ECL Signal
Heavy Chain VH5-51_IGHD5-18*01_IGHJ4*01	SEQ ID NO	Light Chain	SEQ ID NO	
G100K/G104T (KT)	381	V3-4_IGLJ1*01	108	588
G100K/G104T/S28R (KT S28R)	411	V3-4_IGLJ1*01	108	6423
G100K/G104T/G24L/S28R/G35V (KT LRV)	417	V3-4_IGLJ1*01	108	15333
G100K/G104T/G24T/S28R/G35V (KT TRV)	**430**	**V3-4_IGLJ1*01**	**108**	**26072**
G100K/G104T/G24A/S28R/G35V (KT ARV)	431	V3-4_IGLJ1*01	108	17357

5. Alanine scanning of CDR2

The KT double mutant was used as a template for alanine scanning mutagenesis of CDR2 (amino acids 50-58) to determine residues important for antibody binding to DLL4. Purified Fab alanine mutants were tested for binding to DLL4 using the ECL multispot binding assay. The results are set forth in Tables 86-88 below. Mutation of amino acid residues I50, I51, Y52, P53, G54, D55, or D57 with alanine caused a reduction in the ECL signal for binding to DLL4, and thus these residues were not targeted for further mutagenesis.

Substitution of amino acid residues S56 or T58 with alanine either improved the ECL signal or did not affect the ECL signal for binding to DLL4, and thus these residues were subjected to further mutagenesis. Similar experiments also were performed by ELISA, although little to no detectable signal was observed. Table 88 shows that all antibodies exhibit specificity for DLL4.

Table 86. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (KT) & V3-4_IGLJ1*01 CDR2 alanine mutant binding data

Fab			ECL Signal/ Blank	ELISA (Signal-Noise)
Heavy Chain VH5-51_IGHD5-18*01_IGHJ4*01	SEQ ID NO	Light Chain (SEQ ID NO:108)		
G100K/G104T D57A	418	V3-4_IGLJ1*01	2.8	0.01
G100K/G104T	381	V3-4_IGLJ1*01	85.9	0.00
G100K/G104T	381	V3-4_IGLJ1*01	188.0	0.00
G100K/G104T	381	V3-4_IGLJ1*01	153.3	0.01
G100K/G104T I50A	419	V3-4_IGLJ1*01	40.9	0.02
G100K/G104T I51A	420	V3-4_IGLJ1*01	30.6	0.01
G100K/G104T Y52A	421	V3-4_IGLJ1*01	2.7	0.04
G100K/G104T P53A	422	V3-4_IGLJ1*01	57.7	0.00
G100K/G104T D55A	423	V3-4_IGLJ1*01	2.5	0.00

Table 87. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (KT) & V3-4_IGLJ1*01 CDR2 alanine mutant binding data

Fab			ECL Signal/ Blank
Heavy Chain VH5-51_IGHD5-18*01_IGHJ4*01	SEQ ID NO	Light Chain (SEQ ID NO:108)	
G100K/G104T	381	V3-4_IGLJ1*01	49.2
G100K/G104T G54A	2902	V3-4_IGLJ1*01	4.1
G100K/G104T S56A	2903	V3-4_IGLJ1*01	55
G100K/G104T T58A	425	V3-4_IGLJ1*01	101.9

Table 88. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (KT) & V3-4_IGLJ1*01 CDR1 and CDR2 alanine mutant binding data

Heavy Chain	Erb B2	EGFR	HGFR	Notch-1	CD44	IGF-1	P-Cad	EPOR	DLL4	Blank
KT D57A	1203	915	1126	523	600	982	365	456	888	321
KT	1095	852	838	543	579	877	319	554	36440	424
KT	1068	915	936	507	633	964	346	497	45120	240
KT	1098	768	867	437	540	781	226	421	32658	213
KT I50A	925	794	822	443	632	785	343	523	9682	237
KT I51A	1092	803	875	612	517	828	432	497	6578	215
KT Y52A	989	745	803	566	591	827	334	584	735	277
KT P53A	1145	976	1000	536	556	943	424	563	2013	349

									5	
KT D55A	1028	729	856	683	606	898	310	479	761	306

6. NNK mutagenesis of amino acid residues T58 and S56

Following alanine scanning mutagenesis of CDR2, heavy chain amino acid residues T58 and S56 were selected for further mutation using overlapping PCR with NNK mutagenesis using the H:KT & L:wt double mutant as a template. The results are set forth in Table 89 below. Amino acid mutations designated with X (for any amino acid) did not show appreciable binding and therefore were not sequenced to identify the exact mutation. Mutation of heavy chain KT amino acid residue T58 to alanine (T58A) and aspartic acid (T58D) resulted in an increase in ECL signal for binding to DLL4.

Table 89. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (H:KT) & V3-4_IGLJ1*01 CDR1 and CDR2 T58 and S56 NNK mutant binding data

Fab			ECL Signal	ELISA (Signal-Noise)
Heavy Chain VH5-51_IGHD5-18*01_IGHJ4*01	SEQ ID NO	Light Chain (SEQ ID NO:108)		
G100K/G104T T58D/K	443	V3-4_IGLJ1*01	823	0.03
G100K/G104T/T58X	444	V3-4_IGLJ1*01	5040	0.03
G100K/G104T /T58X	444	V3-4_IGLJ1*01	765	0.03
G100K/G104T /T58X	444	V3-4_IGLJ1*01	520	0.02
G100K/G104T /T58A	**425**	**V3-4_IGLJ1*01**	**12938**	**0.07**
G100K/G104T /T58X	444	V3-4_IGLJ1*01	2272	0.03
G100K/G104T /T58X	444	V3-4_IGLJ1*01	1059	0.03
G100K/G104T /T58X	444	V3-4_IGLJ1*01	619	0.03
G100K/G104T /T58X	444	V3-4_IGLJ1*01	2994	0.04
G100K/G104T /T58X	444	V3-4_IGLJ1*01	7341	0.05
G100K/G104T /T58X	444	V3-4_IGLJ1*01	1422	0.03
G100K/G104T /T58X	444	V3-4_IGLJ1*01	5119	0.05
G100K/G104T /T58D	**424**	**V3-4_IGLJ1*01**	**11468**	**0.07**
G100K/G104T /T58D	**424**	**V3-4_IGLJ1*01**	**10459**	**0.06**
G100K/G104T /T58X	444	V3-4_IGLJ1*01	476	0.03
G100K/G104T /T58X	444	V3-4_IGLJ1*01	1421	0.03
G100K/G104T /T58X	444	V3-4_IGLJ1*01	658	0.03
G100K/G104T /T58X	444	V3-4_IGLJ1*01	4278	0.03
G100K/G104T /S56X	445	V3-4_IGLJ1*01	1436	0.04
G100K/G104T /S56X	445	V3-4_IGLJ1*01	1553	0.03
G100K/G104T /S56X	445	V3-4_IGLJ1*01	1372	0.04
G100K/G104T /S56X	445	V3-4_IGLJ1*01	585	0.03
G100K/G104T /S56X	445	V3-4_IGLJ1*01	1165	0.03
G100K/G104T /S56X	445	V3-4_IGLJ1*01	335	0.03
G100K/G104T /S56X	445	V3-4_IGLJ1*01	1139	0.04
G100K/G104T /S56X	445	V3-4_IGLJ1*01	3206	0.04
G100K/G104T /S56X	445	V3-4_IGLJ1*01	3239	0.03
G100K/G104T /S56G	426	V3-4_IGLJ1*01	8433	0.05
G100K/G104T /S56X	445	V3-4_IGLJ1*01	1125	0.03
G100K/G104T /S56X	445	V3-4_IGLJ1*01	1927	0.04

G100K/G104T /S56X	445	V3-4_IGLJ1*01	502	0.04
G100K/G104T /S56X	445	V3-4_IGLJ1*01	1509	0.04
G100K/G104T /S56X	445	V3-4_IGLJ1*01	1951	0.03
G100K/G104T /S56X	445	V3-4_IGLJ1*01	4317	0.04
G100K/G104T /S56X	445	V3-4_IGLJ1*01	2065	0.04
G100K/G104T /S56X	445	V3-4_IGLJ1*01	1486	0.02

7. Mutagenesis of amino acid residues S84 and D109

The heavy chain KT double mutant was used as a template for mutagenesis of amino acid residues S84 and D109. These amino acid residues were mutated using overlapping PCR with NNK mutagenesis or by alanine scanning. The results are shown in Tables 90-92 below, which depict ECL and ELISA results for binding to DLL4 or various antigens. Mutation of heavy chain residues S84 and D109 caused a reduction in ECL signal for binding to DLL4 as compared to heavy chain mutant Fab KT & V3-4_IGLJ*01.

Table 90. Binding of Fab heavy chain VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (H:KT) & V3-4_IGLJ1*01 S84 and D109A mutants to DLL4

Fab			ECL Signal	ELISA (Signal-Noise)
Heavy Chain VH5-51_IGHD5-18*01_IGHJ4*01	SEQ ID NO	Light Chain (SEQ ID NO:108)		
G100K/G104T S84V	427	V3-4_IGLJ1*01	37.7	0.02
G100K/G104T S84L	428	V3-4_IGLJ1*01	3.2	0.00
G100K/G104T D109A	429	V3-4_IGLJ1*01	76.8	0.00
G100K/G104T	381	V3-4_IGLJ1*01	85.9	0.00

Table 91. Binding and specificity of Fab heavy chain VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (H:KT) & V3-4_IGLJ1*01 S84 and D109A mutants to DLL4

Heavy Chain	Erb B2	EGF R	HGF R	Notch -1	CD4 4	IGF-1	P-Cad	EP O R	DLL 4	Blan k
S84V	1042	805	811	505	577	914	362	484	8889	236
S84L	1092	864	933	410	545	908	320	458	713	223
D109A	1099	791	846	443	538	967	406	612	21807	284
G100K/G104T	1095	852	838	543	579	877	319	554	36440	424

Table 92. Binding of Fab heavy chain VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (H:KT) & V3-4_IGLJ1*01 S84I to DLL4

Heavy Chain VH5-51_IGHD5-18*01_IGHJ4*01	SEQ ID NO	Light Chain (SEQ ID NO:108)	ECL Signal
G100K/G104T	381	V3-4_IGLJ1*01	9355
G100K/G104T S84I	409	V3-4_IGLJ1*01	7937

C. Light Chain

1. Alanine scanning of CDR3

Alanine scanning mutagenesis was performed on amino acid residues in the CDR3 of the light chain of parent Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (H:KT) & V3-4_IGLJ*01 to identify amino acid residues that do not appear to be involved in DLL4 binding. Alanine scanning mutagenesis was performed by mutation of every residue of CDR3. Purified Fab alanine mutants were tested at a concentration of 0.04 μM for binding to DLL4 using the ECL multispot assay. The results are set forth in Tables 93-94 below. The results show that mutation of amino acid residues L92, Y93, G95, G97, I98, or S99 with alanine resulted in reduced binding to DLL4, and therefore these residues were not further mutagenized. Substitution of V91, M94, or S96 with alanine either improved binding or did not affect binding to DLL4 and thus these residues were identified as residues for further mutagenesis.

Table 93. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (H:KT) & V3-4_IGLJ1*01 alanine mutant binding data

Fab				ECL Signal/ Noise
Heavy Chain VH5-51_IGHD5-18*01_IGHJ4*01	SEQ ID NO	Light Chain V3-4_IGLJ1*01	SEQ ID NO	
G100K/G104T	381	Parental	108	49.2
G100K/G104T	381	V91A	446	48.5
G100K/G104T	381	L92A	447	30.3
G100K/G104T	381	Y93A	448	21.3
G100K/G104T	381	M94A	449	53.1
G100K/G104T	381	G95A	450	34.4
G100K/G104T	381	G97A	451	24.7
G100K/G104T	381	S96A	452	57.9
G100K/G104T	381	I98A	453	32.6
G100K/G104T	381	S99A	454	41.0

Table 94. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (H:KT) & V3-4_IGLJ1*01 CDR3 alanine mutant binding data

Light Chain	Erb B2	EGF R	HGF R	Notch-1	CD44	IGF-1	P-Cad	EPO R	DLL4	Blank
V91A	1118	833	1107	682	632	1031	484	675	33377	372
L92A	1374	1012	1172	693	695	959	326	582	11698	328
Y93A	1404	918	1130	725	700	1049	497	602	8107	388
M94A	1203	1126	1151	574	633	1094	472	614	35311	388
G95A	1250	995	999	707	657	1091	345	637	10445	341
G97A	1292	1059	1112	660	642	1034	474	528	14892	248
S96A	1275	1004	1115	715	678	927	491	684	32312	321
I98A	1375	1054	1227	700	708	1098	359	584	15096	1623
S99A	1323	956	909	674	670	943	500	693	18191	394

2. NNK mutagenesis of CDR3 amino acid residues V91, M94 and S96

Following alanine scanning mutagenesis of CDR3, light chain amino acid residues V91, M94 and S96 were selected for further mutation using overlapping PCR with NNK mutagenesis using Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T & V3-4_IGLJ*01 as a template. The resulting mutants were assayed using the ECL multispot assay as described in Example 4 or by ELISA as described in Example 6. The results are set forth in Table 95. The ECL results show that V3-4_IGLJ*01 amino acid mutants M94R, S96M and S96E exhibited increased binding to DLL4. No detectable signal was observed by ELISA for any of the mutants tested.

Table 95. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (H:KT) & V3-4_IGLJ1*01 V91, M94 and S96 NNK mutant binding data

Fab			ECL Signal [10 nM Fab]	ELISA Signal [100 nM Fab]
Heavy Chain VH5-51_IGHD5-18*01>3_IGHJ4*01 (SEQ ID NO:381)	Light Chain V3-4_IGLJ1*01	SEQ ID NO		
G100K/G104T	V91P	455	920	0.06
G100K/G104T	V91T	456	32717	0.01
G100K/G104T	V91S	457	32077	0.01
G100K/G104T	V91L	458	41576	0.02
G100K/G104T	V91R	459	13432	0.00
G100K/G104T	V91A	446	35576	0.01
G100K/G104T	parent	108	42851	0.01
G100K/G104T	V91C	460	38330	0.02
G100K/G104T	V91E	461	22524	0.00
G100K/G104T	V91W	462	12523	0.00
G100K/G104T	V91N	463	46674	0.00
G100K/G104T	V91I	464	51236	0.01
G100K/G104T	V91G	465	45254	0.01
G100K/G104T	V91H	466	27123	0.01
G100K/G104T	V91A	446	33817	0.02
G100K/G104T	M94E	467	32481	0.01
G100K/G104T	M94S	468	49579	0.02
G100K/G104T	M94G	469	20338	0.01
G100K/G104T	M94L	470	46770	0.02
G100K/G104T	M94P	471	39930	0.01
G100K/G104T	M94V	472	47326	0.02
G100K/G104T	M94D	473	52677	0.01
G100K/G104T	**M94R**	**474**	**77777**	**0.01**
G100K/G104T	M94N	475	51284	0.01
G100K/G104T	M94T	476	43017	0.02
G100K/G104T	M94F	477	26330	0.01
G100K/G104T	M94A	449	33484	0.01
G100K/G104T	M94A	449	37962	0.00
G100K/G104T	S96W	478	52299	0.02
G100K/G104T	S96G	479	40377	0.01
G100K/G104T	S96P	480	53997	0.03

G100K/G104T	S96A/E	579	43247	0.02
G100K/G104T	S96R	481	54259	0.02
G100K/G104T	S96L	482	39950	0.02
G100K/G104T	**S96M**	**483**	**61737**	**0.02**
G100K/G104T	S96E	484	57030	0.02
G100K/G104T	parent	108	36614	0.01
G100K/G104T	S96V	485	42293	0.01
G100K/G104T	S96A	452	1128	0.00

3. Combination mutants of M94 and S96

V3-4_IGLJ1*01 light chain mutants M94R and S96M, identified as contributing to increased binding to DLL4, were combined to generate a double mutant. The double mutant is designated as V3-4_IGLJ1*01 M94R/S96M (L:RM). The binding affinity of the L:RM double mutant, as paired with various heavy chain mutants including H:KT, H:KT S28R, H:KT LRV, H:KT TRV, and H:KT ARV, was determined by ECL assay as described in Example 4. The results are set forth in Table 96 below. Fab H:KT TRV & L:RM exhibited the greatest ECL signal for binding to DLL4 compared to other Fab antibodies tested..

The mutant Fabs above were further analyzed for binding to DLL4 by ELISA as described in Example 6 using 3-fold serial dilutions of Fab, starting at a concentration of 20 nM. The results are set forth in Table 97 below. Similar to the ECL results, Fab H:KT TRV & L:RM exhibited the greatest ELISA signal for binding to DLL4 compared to other mutant Fab antibodies tested.

Table 96. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (KT) & V3-4_IGLJ1*01 CDR3 combination mutants

Fab				ECL Signal
Heavy Chain VH5-51_IGHD5-18*01_IGHJ4*01	SEQ ID NO	Light Chain V3-4_IGLJ1*01	SEQ ID NO	
G100K/G104T	381	M94R/S96M	486	564
G100K/G104T S28R	411	M94R/S96M	486	530
G100K/G104T G24L/S28R/G35V	417	M94R/S96M	486	889
G100K/G104T G24T/S28R/G35V	**430**	**M94R/S96M**	486	**17277**
G100K/G104T G24A/S28R/G35V	431	M94R/S96M	486	1202

Table 97. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ*01 mutant binding to DLL4 by ELISA

Heavy Chain VH5-51_IGHD5-18*01>3_IGHJ4*01	Light Chain V3-4_IGLJ*01	20	6.67	2.22	0.74
G100K/G104T	parent	0.018	0.042	0.014	0.019
G100K/G104T S28R	parent	0.009	0.003	0.000	0.000
G100K/G104T G24L/S28R/G35V	parent	0.027	0.005	0.000	0.006
G100K/G104T G24T/S28R/G35V	parent	0.054	0.023	0.000	0.002
G100K/G104T G24A/S28R/G35V	parent	0.054	0.025	0.002	0.008
G100K/G104T	M94R/S96M	0.087	0.023	0.007	0.000
G100K/G104T S28R	M94R/S96M	0.011	0.001	0.003	0.000

G100K/G104T G24L/S28R/G35V	M94R/S96M	0.003	0.000	0.000	0.000
G100K/G104T G24T/S28R/G35V	**M94R/S96M**	**0.122**	**0.062**	**0.028**	**0.006**
G100K/G104T G24A/S28R/G35V	M94R/S96M	0.006	0.034	0.000	0.000

4. Alanine scanning of CDR1 of light chain

Heavy chain KT double mutant (Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T & V3-4_IGLJ*01) was used as a template for alanine scanning mutagenesis of CDR1 (amino acids 23-33) of the light chain to determine residues important for antibody binding to DLL4.

Purified Fab alanine mutants were tested for at a concentration of 100 nM for binding to DLL4 using the ECL multispot binding assay as described in Example 4A. The results are set forth in Table 98 below. Mutation of amino acid residues Y33, Y34 and P35 with alanine resulted in reduced binding to DLL4 as evidenced by the reduced ECL signal. Mutation of amino acid residues G23, L24, S25, S26, G27, S28, V29, S30, T31, and S32 with alanine either improved binding or did not affect binding to DLL4 as evidenced by an increased ECL signal or no change in ECL signal compared to the parent KT double mutant having no mutations in the light chain.

Table 98. Binding affinity of Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (H:KT) & V3-4_IGLJ*01 light chain CDR1 and CDR2 alanine mutants

Heavy Chain VH5-51_IGHD5-18*03_IGHJ4*01 (SEQ ID NO:381)	Light Chain V3-4_IGLJ1*01	SEQ ID NO	ECL Signal
G100K/G104T	wildtype	108	9355
G100K/G104T	L24A	487	9631
G100K/G104T	S26A	488	11673
G100K/G104T	G27A	489	10680
G100K/G104T	S28A	490	11488
G100K/G104T	V29A	491	9323
G100K/G104T	S30A	492	10342
G100K/G104T	T31A	493	13507
G100K/G104T	S32A	494	10377
G100K/G104T	Y33A	495	7705
G100K/G104T	Y34A	496	2198
G100K/G104T	P35A	497	8255
G100K/G104T	S36A	498	9690
G100K/G104T	G23A	499	13487
G100K/G104T	S25A	500	10150

5. NNK Mutagenesis of amino acid residue G23

Following alanine scanning mutagenesis of CDR1, the light chain amino acid residue G23 was selected for further NNK mutagenesis using the Fab H:KT & L:wt double mutant as a template. The ECL and ELISA signals are set forth in Table 99 below. Amino acid

mutations designated with X (for any amino acid) did not show appreciable binding and therefore were not sequenced to identify the exact mutation.

Table 99. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (H:KT) & V3-4_IGLJ*01 CDR1 G23 NNK mutant binding data

Fab			ECL Signal	ELISA Signal
Heavy Chain VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (SEQ ID NO:381)	Light Chain	SEQ ID NO		
G100K/G104T	G23R	501	68243	0.11
G100K/G104T	G23X	580	61919	0.10
G100K/G104T	G23X	580	327	0.09
G100K/G104T	G23X	580	68201	0.12
G100K/G104T	G23X	580	384	0.09
G100K/G104T	G23X	580	67230	0.11
G100K/G104T	G23X	580	70515	0.09
G100K/G104T	G23X	580	56769	0.10
G100K/G104T	G23X	580	322	0.09
G100K/G104T	G23L	502	67320	0.10
G100K/G104T	G23L	502	67618	0.10
G100K/G104T	G23X	580	66603	0.12
G100K/G104T	G23X	580	62101	0.10
G100K/G104T	G23X	580	50904	0.10
G100K/G104T	G23X	580	61718	0.11
G100K/G104T	G23X	580	67917	0.11
G100K/G104T	G23X	580	414	0.09
G100K/G104T	G23X	580	52864	0.10
G100K/G104T	G23X	580	53493	0.10

6. Alanine scanning of CDR2

Heavy chain KT double mutant (Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T & V3-4_IGLJ*01) was used as a template for alanine scanning mutagenesis of CDR2 (amino acids 52-58) to determine residues important for antibody binding to DLL4.

Purified Fab alanine mutants were tested for binding to DLL4 using the ECL multispot binding assay as described in Example 4. The results are set forth in Table 100 below. Mutation of amino acid residues S52, T53, N54, T55, R56, S57 and S58 with alanine either improved binding or did not affect binding to DLL4 as evidenced by an increased ECL signal or no change in ECL signal compared to the parent KT double mutant having no mutations in the light chain.

Table 100. Binding affinity of Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (H:KT) & V3-4_IGLJ*01 light chain CDR2 alanine mutants

Heavy Chain VH5-51_IGHD5-18*03_IGHJ4*01 (SEQ ID NO:381)	Light Chain V3-4_IGLJ1*01	SEQ ID NO	ECL Signal

G100K/G104T	wildtype	108	9355
G100K/G104T	S52A	503	15240
G100K/G104T	T53A	504	13197
G100K/G104T	N54A	505	12936
G100K/G104T	T55A	506	12717
G100K/G104T	R56A	507	16833
G100K/G104T	S57A	508	12612
G100K/G104T	S58A	509	12557
G100K/G104T	R56A	507	13609

7. NNK Mutagenesis of amino acid residues S52 and R56

Following alanine scanning mutagenesis of CDR2, light chain amino acid residues S52 and R56 were selected for further NNK mutagenesis using the heavy chain KT double mutant as a template. The ECL and ELISA signals are set forth in Table 101 below. Amino acid mutations designated with X (for any amino acid) did not show appreciable binding and therefore were not sequenced to identify the exact mutation. Light chain mutants S52G, R56Y/S, R56A and R56G exhibited increased binding to DLL4 as assessed by both ECL and ELISA.

Various Fabs, containing various combinations of mutations of the heavy chain and light chain, were further analyzed for binding to DLL4 by ELISA using 2-fold serial dilutions of Fab, starting at a concentration of 100 nM. The results are set forth in Table 102 below. Fab H:KT S28R & L:wt exhibited the greatest binding to DLL4 as evidenced by the ELISA signal compared to other Fab mutants tested.

Table 101. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (KT) & V3-4_IGLJ*01 CDR1 S52 and R56 NNK mutant binding data

Fab			ECL Signal	ELISA Signal
Heavy Chain VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (SEQ ID NO:381)	**Light Chain V3-4_IGLJ*01**	**SEQ ID NO**		
G100K/G104T	S52X	581	64794	0.10
G100K/G104T	S52X	581	58732	0.10
G100K/G104T	S52C	511	64255	0.10
G100K/G104T	S52X	581	84622	0.13
G100K/G104T	S52X	581	78239	0.14
G100K/G104T	S52X	581	62099	0.11
G100K/G104T	S52X	581	76278	0.14
G100K/G104T	S52X	581	84797	0.15
G100K/G104T	**S52G**	**510**	**85929**	**0.21**
G100K/G104T	**S52G**	**510**	**86660**	**0.18**
G100K/G104T	S52X	581	81950	0.13
G100K/G104T	S52X	581	79552	0.11
G100K/G104T	S52X	581	84470	0.14
G100K/G104T	S52X	581	356	0.09
G100K/G104T	S52R	512	85879	0.15

G100K/G104T	S52X	581	84017	0.16
G100K/G104T	S52X	581	67861	0.14
G100K/G104T	S52X	581	100221	0.17
G100K/G104T	S52X	581	61304	0.12
G100K/G104T	R56X	582	69586	0.13
G100K/G104T	R56X	582	75844	0.15
G100K/G104T	R56X	582	93607	0.13
G100K/G104T	R56X	582	58626	0.11
G100K/G104T	R56X	582	82996	0.14
G100K/G104T	R56X	582	71685	0.12
G100K/G104T	R56X	582	73639	0.11
G100K/G104T	R56I	513	94265	0.13
G100K/G104T	**R56Y/S**	**583**	**95103**	**0.28**
G100K/G104T	R56X	582	367	0.09
G100K/G104T	R56X	582	82747	0.26
G100K/G104T	R56X	582	80011	0.16
G100K/G104T	R56D	515	87363	0.19
G100K/G104T	**R56G**	**516**	**93708**	**0.19**
G100K/G104T	**R56A**	**507**	**83853**	**0.27**
G100K/G104T	R56X	582	91910	0.15
G100K/G104T	R56X	582	58466	0.11
G100K/G104T	R56X	582	45685	0.11
G100K/G104T	R56X	582	55229	0.12

Table 102. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ*01 mutant binding to DLL4 by ELISA

Fab [nM]	H	KT G24L	KT S28R	KT G35V	KT T58A	KT T58D	KT	KT	KT
	L	parent	parent	parent	parent	parent	S52G	R56Y	R56A
100		0.298	0.529	0.271	0.253	0.219	0.209	0.231	0.251
50		0.245	0.456	0.232	0.209	0.230	0.194	0.211	0.239
25		0.221	0.365	0.232	0.220	0.218	0.227	0.205	0.227
12.5		0.233	0.309	0.244	0.230	0.223	0.215	0.184	0.212
6.25		0.278	0.303	0.245	0.249	0.224	0.207	0.182	0.200
3.125		0.257	0.246	0.251	0.244	0.252	0.216	0.180	0.213

H – heavy chain
L – Light Chain

8. Mutagenesis of framework 3 amino acid residue T78

The KT heavy chain double mutant (Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (H:KT) & V3-4_IGLJ*01) was used as a template for further mutagenesis of amino acid residue T78 in the framework 3 region of the light chain. This residue was mutated using overlapping PCR with NNK mutagenesis. Table 103 sets forth the ECL signal for binding to DLL4. Mutation of amino acid residue T78 either improved binding or did not affect binding to DLL4 as evidenced by an increased ECL signal or no change in ECL signal compared to the parent KT double mutant having no mutations in the light chain. Two additional light chain double mutants G23A/N175K (in the constant region) and S52A/A116T

(in the framework 4 region) also were generated and they exhibited improved binding for DLL4 compared to the KT double mutant template antibody as evidenced by an increased ECL signal.

Table 103. Binding affinity of Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (H:KT) & V3-4_IGLJ*01 light chain mutants

Heavy Chain VH5-51_IGHD5-18*03_IGHJ4*01 (SEQ ID NO:381)	Light Chain V3-4_IGLJ1*01	SEQ ID NO	ECL Signal
G100K/G104T	wildtype	108	9355
G100K/G104T	T78S	518	7554
G100K/G104T	T78E	519	10559
G100K/G104T	T78Y/M	584	12364
G100K/G104T	T78L	522	9554
G100K/G104T	T78K	523	9620
G100K/G104T	T78V	524	9833
G100K/G104T	G23A,N175K	525	17828
G100K/G104T	S25A,A116T	526	12178

9. Paired mutants of heavy chain KT TRV

The SPR data (see Example 5 and Table 108) for Fabs H:KT TRV & V3-4_IGLJ1*01 and H:KT TRV & L:RM indicated that these Fabs have a short off-rate. Thus, in order to increase binding affinity of these antibodies, heavy chain H:KT TRV was paired with various V3-4_IGLJ1*01 light chain mutants and the binding affinity towards DLL4 was assayed by ELISA since the ELISA assay selects for long off-rates whereas the ECL assay detects equilibrium binding.

Purified Fab mutants were tested for binding to DLL4 using ELISA performed as described in Example 6 at a concentration of 100 nM Fab. The results for the ELISA assay are set forth in Table 104. Fabs containing light chain mutants V91A, T31A, S52A, T53A, S57A, V91L, S96G and S96P exhibited increased binding to DLL4 as compared to a Fab with parental light chain V3-4_IGLJ1*01 as evidenced by a greater ELISA signal-blank.

Table 104. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T G24T/S28R/G35V (H:KT TRV) & V3-4_IGLJ1*01 light chain mutant binding data

Fab				ELISA Signal-blank (100nM Fab)
Heavy Chain VH5-51_IGHD5-18*01_IGHJ4*01	SEQ ID NO	Light Chain V3-4_IGLJ1*01	SEQ ID NO	
G100K/G104T G24T/S28R/G35V	**430**	**V91A**	**446**	**0.606**
G100K/G104T G24T/S28R/G35V	430	L92A	447	0.186
G100K/G104T G24T/S28R/G35V	430	Y93A	448	0.185
G100K/G104T G24T/S28R/G35V	430	M94A	449	0.277
G100K/G104T G24T/S28R/G35V	430	G95A	450	0.216
G100K/G104T G24T/S28R/G35V	430	S96A	452	0.436
G100K/G104T G24T/S28R/G35V	430	G97A	451	0.129
G100K/G104T G24T/S28R/G35V	430	I98A	453	0.162
G100K/G104T G24T/S28R/G35V	430	S99A	454	0.300

G100K/G104T G24T/S28R/G35V	430	T78S	518	0.093
G100K/G104T G24T/S28R/G35V	430	T78E	519	0.217
G100K/G104T G24T/S28R/G35V	430	T78Y/M	584	0.459
G100K/G104T G24T/S28R/G35V	430	T78L	522	0.347
G100K/G104T G24T/S28R/G35V	430	T78K	523	0.480
G100K/G104T G24T/S28R/G35V	430	T78V	524	0.340
G100K/G104T G24T/S28R/G35V	430	G23A	499	0.405
G100K/G104T G24T/S28R/G35V	430	L24A	487	0.244
G100K/G104T G24T/S28R/G35V	430	S25A	500	0.483
G100K/G104T G24T/S28R/G35V	430	S26A	488	0.395
G100K/G104T G24T/S28R/G35V	430	G27A	489	0.398
G100K/G104T G24T/S28R/G35V	430	S28A	490	0.478
G100K/G104T G24T/S28R/G35V	430	V29A	491	0.394
G100K/G104T G24T/S28R/G35V	430	S30A	492	0.344
G100K/G104T G24T/S28R/G35V	**430**	**T31A**	**493**	**0.552**
G100K/G104T G24T/S28R/G35V	430	S32A	494	0.502
G100K/G104T G24T/S28R/G35V	430	Y33A	495	0.301
G100K/G104T G24T/S28R/G35V	430	Y34A	496	0.085
G100K/G104T G24T/S28R/G35V	430	P35A	497	0.236
G100K/G104T G24T/S28R/G35V	430	S36A	498	0.380
G100K/G104T G24T/S28R/G35V	**430**	**S52A**	**503**	**0.574**
G100K/G104T G24T/S28R/G35V	**430**	**T53A**	**504**	**0.532**
G100K/G104T G24T/S28R/G35V	430	N54A	505	0.318
G100K/G104T G24T/S28R/G35V	430	T55A	506	0.382
G100K/G104T G24T/S28R/G35V	430	R56A	507	0.442
G100K/G104T G24T/S28R/G35V	**430**	**S57A**	**508**	**0.598**
G100K/G104T G24T/S28R/G35V	430	S58A	509	0.451
G100K/G104T G24T/S28R/G35V	**430**	**V91L**	**458**	**0.734**
G100K/G104T G24T/S28R/G35V	430	V91P	455	0.078
G100K/G104T G24T/S28R/G35V	430	V91T	456	0.197
G100K/G104T G24T/S28R/G35V	430	V91S	457	0.264
G100K/G104T G24T/S28R/G35V	430	V91R	459	0.025
G100K/G104T G24T/S28R/G35V	430	V91A	446	0.529
G100K/G104T G24T/S28R/G35V	430	Parent	108	0.393
G100K/G104T G24T/S28R/G35V	430	V91C	460	0.625
G100K/G104T G24T/S28R/G35V	430	V91E	461	0.152
G100K/G104T G24T/S28R/G35V	430	V91W	462	0.080
G100K/G104T G24T/S28R/G35V	430	V91N	463	0.203
G100K/G104T G24T/S28R/G35V	430	V91I	464	0.336
G100K/G104T G24T/S28R/G35V	430	V91G	465	0.248
G100K/G104T G24T/S28R/G35V	430	V91H	466	0.127
G100K/G104T G24T/S28R/G35V	430	M94T	476	0.395
G100K/G104T G24T/S28R/G35V	430	M94E	467	0.171
G100K/G104T G24T/S28R/G35V	430	M94S	468	0.195
G100K/G104T G24T/S28R/G35V	430	M94G	469	0.199
G100K/G104T G24T/S28R/G35V	430	M94L	470	0.388
G100K/G104T G24T/S28R/G35V	430	M94P	471	0.256
G100K/G104T G24T/S28R/G35V	430	M94V	472	0.315
G100K/G104T G24T/S28R/G35V	430	M94D	473	0.070
G100K/G104T G24T/S28R/G35V	430	M94R	474	0.197
G100K/G104T G24T/S28R/G35V	430	M94N	475	0.205
G100K/G104T G24T/S28R/G35V	430	M94F	477	0.317
G100K/G104T G24T/S28R/G35V	430	M94A	449	0.216
G100K/G104T G24T/S28R/G35V	430	S96W	478	0.261
G100K/G104T G24T/S28R/G35V	**430**	**S96G**	**479**	**0.562**

G100K/G104T G24T/S28R/G35V	**430**	**S96P**	**480**	**0.813**
G100K/G104T G24T/S28R/G35V	430	S96A/E	579	0.538
G100K/G104T G24T/S28R/G35V	430	S96R	481	0.499
G100K/G104T G24T/S28R/G35V	430	S96L	482	0.355
G100K/G104T G24T/S28R/G35V	430	S96M	483	0.358
G100K/G104T G24T/S28R/G35V	430	S96E	484	0.439
G100K/G104T G24T/S28R/G35V	430	Parent	108	0.437
G100K/G104T G24T/S28R/G35V	430	S96V	485	0.452
G100K/G104T G24T/S28R/G35V	430	Parent	108	0.455
G100K/G104T G24T/S28R/G35V	430	Parent	108	0.430

10. Cassette Mutagenesis Using Type II Restriction Enzyme Ligatioin of amino acid residues S52, T53 and S57

Following analysis of paired Fab mutants of heavy chain H:KT TRV, light chain double mutant V3-4_IGLJ1*01 V91L/S96P (L:LP) was generated. Three additional light chain amino acid residues (S52, T53 and S57) that exhibited increased binding to DLL4 by ELISA (see Table 103 above) were selected for further mutagenesis using type II restriction enzyme ligation using Fab H: KT TRV & L:LP as a template. The ELISA signals are set forth in Table 105 below. Light chain mutants L:LP S52G, L:LP S52M, L:LP S52N and L:LP S52H exhibited increased binding to DLL4 as assessed by ELISA.

Four Fabs, containing various combinations of mutations of the heavy chain and light chain, were further analyzed for binding to DLL4 by ELISA using 3-fold serial dilutions of Fab, starting at a concentration of 100 nM. The results are set forth in Table 106 below. Fab H:KT TRV & L:LP S52G exhibited the greatest binding to DLL4 as evidenced by the ELISA signal compared to other Fab mutants tested.

Table 105. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T G24T/S28R/G35V (H:KT TRV) & V3-4_IGLJ1*01 V91L/S96P (L:LP) light chain mutant binding data

Fab				ELISA Signal-blank (100nM Fab)
Heavy Chain VH5-51_IGHD5-18*01_IGHJ4*01	SEQ ID NO	Light Chain V3-4_IGLJ1*01	SEQ ID NO	
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S52F	527	0.33
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S52L	528	0.40
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S52I	529	0.42
G100K/G104T G24T/S28R/G35V	**430**	**V91L/S96P S52M**	**530**	**0.46**
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S52V	531	0.44
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S52P	532	0.32
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S52T	533	0.34
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S52Y	534	0.41
G100K/G104T G24T/S28R/G35V	**430**	**V91L/S96P S52H**	**535**	**0.44**
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S52Q	536	0.39
G100K/G104T G24T/S28R/G35V	**430**	**V91L/S96P S52N**	**537**	**0.45**
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S52K	538	0.32
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S52D	539	0.39
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S52E	540	0.38
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S52W	541	0.29
G100K/G104T G24T/S28R/G35V	**430**	**V91L/S96P S52G**	**543**	**0.53**
G100K/G104T G24T/S28R/G35V	430	V91L/S96P	544	0.39

G100K/G104T G24T/S28R/G35V	430	V91L/S96P T53F	545	0.15
G100K/G104T G24T/S28R/G35V	430	V91L/S96P T53L	546	0.18
G100K/G104T G24T/S28R/G35V	430	V91L/S96P T53I	547	0.30
G100K/G104T G24T/S28R/G35V	430	V91L/S96P T53M	548	0.01
G100K/G104T G24T/S28R/G35V	430	V91L/S96P T53V	549	0.29
G100K/G104T G24T/S28R/G35V	430	V91L/S96P T53S	550	0.18
G100K/G104T G24T/S28R/G35V	430	V91L/S96P T53P	551	0.39
G100K/G104T G24T/S28R/G35V	430	V91L/S96P T53Y	552	0.22
G100K/G104T G24T/S28R/G35V	430	V91L/S96P T53H	553	0.14
G100K/G104T G24T/S28R/G35V	430	V91L/S96P T53Q	554	0.11
G100K/G104T G24T/S28R/G35V	430	V91L/S96P T53N	555	0.15
G100K/G104T G24T/S28R/G35V	430	V91L/S96P T53K	556	0.12
G100K/G104T G24T/S28R/G35V	430	V91L/S96P T53D	557	0.16
G100K/G104T G24T/S28R/G35V	430	V91L/S96P T53E	558	0.09
G100K/G104T G24T/S28R/G35V	430	V91L/S96P T53W	559	0.06
G100K/G104T G24T/S28R/G35V	430	V91L/S96P T53R	560	0.05
G100K/G104T G24T/S28R/G35V	430	V91L/S96P T53G	561	0.08
G100K/G104T G24T/S28R/G35V	430	V91L/S96P	544	0.30
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S57F	562	0.10
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S57L	563	0.30
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S57I	564	0.24
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S57M	565	0.30
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S57V	566	0.34
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S57P	567	0.36
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S57T	568	0.30
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S57Y	569	0.28
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S57H	570	0.21
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S57Q	571	0.21
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S57N	572	0.24
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S57K	573	0.17
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S57D	574	0.17
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S57E	575	0.20
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S57W	576	0.12
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S57R	577	0.18
G100K/G104T G24T/S28R/G35V	430	V91L/S96P S57G	578	0.23
G100K/G104T G24T/S28R/G35V	430	V91L/S96P	544	0.29

Table 106. Binding affinity of Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T G24T/S28R/G35V (H:KT TRV) & V3-4_IGLJ1*01 light chain mutants

Light Chain	Wildtype (SEQ ID NO:108)	V91L/S96P (SEQ ID NO:544)	V91L/S96P S52M (SEQ ID NO:530)	V91L/S96P S52G (SEQ ID NO:543)
Fab [μM]	**Signal**	**Signal**	**Signal**	**Signal**
100	0.16	0.34	0.24	0.69
33.33	0.08	0.19	0.12	0.35
11.11	0.04	0.07	0.06	0.17
3.70	0.03	0.03	0.03	0.06
1.23	0.01	0.03	0.03	0.03
0.41	0.01	0.02	0.03	0.01
0.14	0.00	0.03	0.02	0.02
0.05	0.01	0.02	0.02	0.02

11. Paired Fab mutants

Twenty four mutant Fabs, containing various combinations of mutations of the heavy chain and light chain, were further analyzed for binding to DLL4 by ELISA using 2-fold serial dilutions of Fab, starting at a concentration of 100 nM. The results are set forth in Table 107 below. Fabs H:KT TRV & L:LP S52K and H:KT TRV & L:LP S52G exhibited the greatest binding affinity to DLL4 as evidenced by the ELISA signal compared to other Fab mutants tested. Fabs H:KT TRV & L:LP S52H and H:KT TRV & L:LP S52N had slightly reduced binding affinity to DLL4 as compared to Fabs H:KT TRV & L:LP S52K and H:KT TRV & L:LP S52G.

Table 107. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ*01 mutant binding to DLL4 by ELISA

Heavy Chain VH5-51_IGHD5-18*01>3_IGHJ4*01	Light Chain V3-4_IGLJ*01	100	50	25	12.5
G100K/G104T G24L/S28R/G35V Y105H (SEQ ID NO:432)	Wildtype	0.23	0.20	0.19	0.21
G100K/G104T G24T/S28R/G35V Y105N (SEQ ID NO:433)	Wildtype	0.25	0.18	0.19	0.21
G100K/G104T G24A/S28R/G35V Y107F (SEQ ID NO:434)	Wildtype	0.28	0.24	0.20	0.21
G100K/G104T G24L/S28R/G35V D109Q (SEQ ID NO:435)	Wildtype	0.30	0.25	0.22	0.24
G100K/G104T G24T/S28R/G35V	V91L/S96P	1.00	0.81	0.58	0.45
G100K	Wildtype	0.20	0.19	0.18	0.19
Wildtype	Wildtype	0.17	0.16	0.18	0.17
G104T	Wildtype	0.17	0.17	0.18	0.19
G100K/G104T	Wildtype	0.18	0.18	0.16	0.18
G100K/G104T G24T/S28R/G35V	Wildtype	0.45	0.32	0.26	0.23
G100K/G104T S28R	Wildtype	0.26	0.23	0.20	0.18
G100K/G104T G24A/S28R/G35V	V91L/S96P S52V	0.95	0.74	0.60	0.43
G100K/G104T G24L/S28R/G35V	V91L/S96P S52F	0.99	0.69	0.49	0.42
G100K/G104T G24T/S28R/G35V	V91L/S96P S52L	1.02	0.78	0.58	0.43
G100K/G104T G24A/S28R/G35V	V91L/S96P S52I	1.04	0.82	0.60	0.40
G100K/G104T G24L/S28R/G35V	V91L/S96P S52M	1.01	0.80	0.59	0.41
G100K/G104T G24T/S28R/G35V	**V91L/S96P S52G**	**1.14**	**1.02**	**0.90**	**0.63**
G100K/G104T G24A/S28R/G35V	V91L/S96P S52P	1.00	0.79	0.59	0.43
G100K/G104T G24L/S28R/G35V	V91L/S96P S52T	0.99	0.79	0.62	0.41
G100K/G104T G24T/S28R/G35V	V91L/S96P S52Y	0.90	0.72	0.56	0.41
G100K/G104T G24A/S28R/G35V	**V91L/S96P S52H**	**1.09**	**0.91**	**0.73**	**0.50**
G100K/G104T G24L/S28R/G35V	V91L/S96P S52Q	0.96	0.81	0.67	0.47
G100K/G104T G24T/S28R/G35V	**V91L/S96P S52N**	**1.05**	**0.90**	**0.86**	**0.65**
G100K/G104T G24T/S28R/G35V	**V91L/S96P S52K**	**1.23**	**1.03**	**0.79**	**0.56**

Summary

As a result of affinity maturation, the affinity of parental Hit Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 for binding to DLL4 was increased 130-fold (see SPR data in Table 108 below). Parental Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 binds DLL4 with a K_D of 4.8 μM. Heavy chain mutant Fab H:KT & L:wt has

13-fold increased affinity for DLL4 (K_D = 355 nM). Affinity matured heavy and light chain mutant Fab H:KT TRV & L:wt has a K_D of 36.2 nM, a 130-fold increase in binding affinity for DLL4. Affinity matured heavy and light chain mutant Fabs H:KT TRV & L:LP and H:KT TRV & L:LP S52G have a K_D of 3.3 and 5.0 nM, respectively, a 1000-fold increase in binding affinity for DLL4.

Table 108. Binding affinity of VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 DLL4 mutant Fabs by Surface Plasmon Resonance

Heavy Chain	Light Chain	k_a ($x10^5$) ($M^{-1}s^{-1}$)	k_d ($x10^{-3}$) (s^{-1})	K_D (nM)
VH5-51_IGHD5-18*01>3_IGHJ4*01 (parental)	V3-4_IGLJ1*01 (parental)	n/a	n/a	4800 (±200)
VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T (KT)	V3-4_IGLJ1*01	0.645 (±0.092)	0.023 (±0.004)	355 (±7)
VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T S28R (KT S28R)	V3-4_IGLJ1*01	7.4 (±0.6)	0.0845 (±0.0050)	114 (±6)
VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T G24T/S28R/G35V (KT TRV)	V3-4_IGLJ1*01	20.90 (±6.24)	0.0717 (±0.00351)	36.2 (±8.5)
VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T G24T/S28R/G35V (KT TRV)	V3-4_IGLJ1*01 M94R/S96M (RM)	25.30 (±4.16)	0.101 (±0.0153)	40.3 (±9.3)
VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T G24T/S28R/G35V (KT TRV)	V3-4_IGLJ1*01 V91L/S96P (LP)	110	36	3.3
VH5-51_IGHD5-18*01>3_IGHJ4*01 G100K/G104T G24T/S28R/G35V (KT TRV)	V3-4_IGLJ1*01 V91L/S96P S52G (LP S52G)	29.6	14.7	5.0

EXAMPLE 13

Germline Segment Swapping

In this example, two antibody "Hit" Fabs against DLL4, identified in Example 4 using the Multispot ECL binding assay, were subjected to mutagenesis by J-swapping or D-swapping of the J_H or D_H germline segments, respectively. J-swapping involves substitution of the parent "Hit" Fab J_H germline segment with a different J_H germline segment. D-swapping involves substitution of the parent "Hit" D_H germline segment with a different D_H germline segment. Since the D_H germline segment constitutes the 5' end of the heavy chain CDR3 and J_H segment constitutes the 3' end of the heavy chain CDR3, D-swapping and J-swapping allow for facile mutagenesis of this important antibody binding region.

A. Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01

For Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01, J-swapping of IGHJ1*01 with IGHJ2*01, IGHJ4*01, and IGHJ5*01 allowed analysis of the 3' end of CDR3 from amino acid residues A106 to H111 (see Figure 4A). Purified Fab J-swapped mutants were tested for binding to DLL4 using the ECL assay as described in Example 4. The results

are set forth in Tables 109-110 below. The results show that swapping of IGHJ1*01 with either IGHJ2*01, IGHJ4*01, or IGHJ5*01 reduced binding of the antibody to DLL4 as assessed by a decreased ECL signal compared to the parent template antibody containing the IGHJ1*01 J_H germline segment.

Table 109. Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 J-swap binding data

Heavy Chain	SEQ ID NO	Light Chain	SEQ ID NO	Signal/ Noise (0.04 µM)
VH1-46_IGHD6-6*01_**IGHJ2*01**	585	L6_IGKJ1*01	107	0.8
wildtype	88	L6_IGKJ1*01	107	1.7
VH1-46_IGHD6-6*01_**IGHJ4*01**	586	L6_IGKJ1*01	107	0.8
VH1-46_IGHD6-6*01_**IGHJ5*01**	587	L6_IGKJ1*01	107	0.8

Table 110. Fab VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 J-swap mutant binding data

Fab		0.02 µM Fab 30 µg/mL DLL4		0.004 µM Fab 15 µg/mL DLL4	
Heavy Chain	Light Chain	ECL Signal	Signal/ Noise	ECL Signal	Signal/ Noise
IGHJ2*01	L6_IGKJ1*01	232	0.6	185	1.3
wildtype	L6_IGKJ1*01	8714	23.0	4261	29.2
IGHJ4*01	L6_IGKJ1*01	203	0.5	178	1.2
IGHJ5*01	L6_IGKJ1*01	244	0.6	137	0.9

B. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ*01

For Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ*01, J-swapping of IGHJ4*01 with IGHJ1*01, IGHJ3*01, and IGHJ5*01 allowed analysis of the 3' end of CDR3 from amino acid residues 106-110 (see Figure 4B). D-swapping of IGHD5-18*01 with IGHD5-12*01 and IGHD5-24*01 allowed analysis of the 5' end of CDR3 from amino acid residues 100-104 (see Figure 4C). Purified J-swapped and D-swapped mutants were tested for binding to DLL4 using the ECL assay as described in Example 4. The ECL results for binding to DLL4 are set forth in Tables 111-112 below. The results show that swapping of IGHJ4*01 with either IGHJ1*01, IGHJ3*01, or IGHJ5*01 reduced binding of the antibody to DLL4 as assessed by a decreased ECL signal compared to the parent template antibody containing the IGHJ4*01 J_H germline segment.. Additionally, swapping of IGHD5-18*01 with IGHD5-12*01 or IGHD5-24*01 reduced binding of the antibody to DLL4 as assessed by a decreased ECL signal compared to the parent template antibody containing the IGHD5-18*01 D_H germline segment.

Table 111. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ*01 D-swap and J-swap mutant binding data

Heavy Chain	SEQ	Light Chain	SEQ	Signal/

VH5-51_IGHD5-18*01>3_IGHJ4*01	ID NO		ID NO	Noise (0.04 μM)
IGHJ1*01	588	V3-4_IGLJ1*01	108	1.2
wildtype	89	V3-4_IGLJ1*01	108	14.7
IGHJ3*01	589	V3-4_IGLJ1*01	108	3.1
IGHJ5*01	590	V3-4_IGLJ1*01	108	1.2
IGHD5-12*01	591	V3-4_IGLJ1*01	108	1.2
IGHD5-24*01	592	V3-4_IGLJ1*01	108	1.3
wildtype	89	V3-4_IGLJ1*01	108	15.5

Table 112. Fab VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ*01 D-swap and J-swap mutant binding data

Fab			0.1 μM Fab 30 μg/mL DLL4	0.02 μM Fab 15 μg/mL DLL4
Heavy Chain VH5-51_IGHD5-18*01_IGHJ4*01	SEQ ID NO	Light Chain (SEQ ID NO:108)	Signal/ Noise	Signal/ Noise
IGHJ1*01	588	V3-4_IGLJ1*01	1.0	1.1
wildtype	89	V3-4_IGLJ1*01	24.0	15.2
IGHJ3*01	589	V3-4_IGLJ1*01	7.9	3.5
IGHJ5*01	590	V3-4_IGLJ1*01	1.0	0.9
IGHD5-12*01	591	V3-4_IGLJ1*01	1.1	1.2
IGHD5-24*01	592	V3-4_IGLJ1*01	1.7	1.0

EXAMPLE 14

Affinity Maturation of Fab VH3-23_IGHD2-21*01>3_IGHJ6*01 & V2-13_IGLJ2*01 Against Hepatocyte Growth Factor Receptor

Fab VH3-23_IGHD2-21*01>3_IGHJ6*01 & V2-13_IGLJ2*01 (SEQ ID NOS:2803 and 594) against hepatocyte growth factor receptor (HGFR; C-Met) identified using the electroluminescence Meso Scale Discovery (MSD) multispot binding assay, was subjected to affinity maturation as described above in Examples 7-9. Mutations of amino acid residues were carried out by ligation of oligo pairs using method described in Example 1C.

i. Identification of the CDR potential binding site

The amino acid sequence of the heavy chain (SEQ ID NO:2803) for the parent "Hit" VH3-23_IGHD2-21*01>3_IGHJ6*01 & V2-13_IGLJ2*01 was aligned with the amino acid sequences of three heavy chains (SEQ ID NOS:2797, 2799 and 2801) of three related "Hits" that also bind HGFR, albeit with slightly reduced affinity. These four Fabs share the same V_H and J_H germline segments. The sequence alignment is set forth in Figure 5. Based on the alignment, amino acid residues were identified that differed between the "Hit" and the related "Hits", thus accounting for differences in binding of the "Hit" and related "Hits" for HGFR.

The identified amino acid residues were located in CDR3, which was identified as the region of the heavy chain that is important for binding affinity.

ii. Alanine scanning of Heavy Chain CDR3

CDR3 of the heavy chain sequence of parent Fab VH3-23_IGHD2-21*01>3_IGHJ6*01 & V2-13_IGLJ2*01 (SEQ ID NOS:2803 and 594) was subjected to alanine scanning mutagenesis and analyzed using the ECL multispot assay using 100 nM Fab. The results are set forth in Table 113 below. Mutation of amino acid residues E99, V102, V103, V104, and I105 with alanine and A106 with threonine caused a significant reduction in binding to HGFR as assessed by a decreased ECL signal. Mutation of H100, I101, I107, and S108 with alanine slightly reduced binding to HGFR as assessed by a decreased ECL signal.

Table 113. Binding of Fab VH3-23_IGHD2-21*01>3_IGHJ6*01 & V2-13_IGLJ2*01 CDR3 alanine mutants to HGFR

	SEQ ID NO	Erb B2	EGF R	HGF R	Notch-1	CD44	IGF-1	P-Cad	EPO R	DLL4
Wt	2803	2.4	2.8	18.5	1.7	1.6	0.9	12.7	16.5	1.3
E99A	595	2.5	2.3	5.8	1.9	1.4	1.1	9.7	11.6	1.4
H100A	596	1.3	1.8	14.1	1.0	1.0	1.0	4.8	7.2	2.2
I101A	597	2.8	3.0	14.8	1.7	1.2	1.1	23.2	26.6	1.5
V102A	598	1.4	1.4	5.3	1.0	1.0	1.0	4.9	8.3	1.4
V103A	599	0.9	1.1	2.2	0.8	0.7	0.9	3.9	6.2	1.0
V104A	600	1.3	1.4	2.3	1.3	1.1	1.1	2.6	5.3	1.4
I105A	601	1.0	1.1	1.1	1.2	0.9	1.1	1.2	5.5	1.1
A106T	602	1.3	1.4	6.9	1.5	1.3	1.4	2.3	3.2	1.9
I107A	603	4.8	4.3	13.7	2.7	1.5	1.1	19.6	43.6	3.6
S108A	604	1.9	2.0	12.9	1.5	1.3	1.2	4.8	9.5	2.3

iii. NNK mutagenesis of Y113

Amino acid residue Y113 of the heavy chain sequence of Fab VH3-23_IGHD2-21*01>3_IGHJ6*01 H100E/S108P (H:EP) & V2-13_IGLJ2*01 (SEQ ID NOS:593 and 594) was subjected to NNK mutagenesis and analyzed using the ECL multispot assay using 20 nM Fab. The results are set forth in Table 114 below. EP mutants Y113G, Y113I, Y113S, Y113T, Y113N, Y113N and Y113W had increased binding to HGFR as compared to heavy chain EP as evidenced by an increase in ECL signal.

Table 114. Binding of Fab VH3-23_IGHD2-21*01>3_IGHJ6*01 H100E/S108P (EP) & V2-13_IGLJ2*01 mutants to HGFR

	SEQ ID NO	Erb B2	EGF R	HGF R	Notch-1	CD44	IGF-1	P-Cad	EPO R	DLL 4
Parent	593	4.1	4.2	33.4	2.1	1.8	1.6	20.6	39.4	2.3
Y113G	605	11.7	8.4	**104.6**	2.3	1.7	1.7	27.5	126.1	2.3
Y113I	606	40.7	17.8	**178.9**	5.5	3.7	3.3	58.6	116.5	5.0
Y113S	607	19.1	9.2	**133.1**	3.3	2.3	1.8	41.0	142.2	3.0

Y113P	608	1.6	1.4	13.0	1.4	1.1	1.4	2.3	2.1	1.6
Y113T	609	35.4	18.9	**185.0**	6.1	4.1	3.1	65.9	174.4	5.5
Y113H	610	6.3	3.6	**107.1**	1.7	1.4	1.5	16.0	55.9	2.0
Y113N	611	28.4	11.0	**122.6**	4.3	2.4	1.6	38.5	114.2	3.1
Y113E	612	50.6	20.0	48.6	7.3	3.9	3.4	41.8	142.0	5.3
Y113W	613	21.8	11.7	**130.8**	4.2	3.9	1.9	44.3	169.8	3.3
Y113R	614	48.4	19.3	76.4	9.4	6.5	3.4	56.3	183.2	4.6

iv. NNK mutagenesis of Y109, Y110, Y111, Y112 and Y114

Amino acid residues Y109, Y110, Y111, Y112 and Y114 of the heavy chain sequence of Fab VH3-23_IGHD2-21*01>3_IGHJ6*01 H100E/S108P/Y113G (EPG) & V2-13_IGLJ2*01 (SEQ ID NOS:605 and 594) were subjected to NNK mutagenesis and analyzed using the ECL multispot assay using 20 nM Fab. The results are set forth in Table 115 below. Mutation of EPG heavy chain residue Y110 to isoleucine resulted in increased binding to HGFR as evidenced by an increased ECL signal as compared to heavy chain EPG. EPG mutants Y109W, Y112, Y112T and Y112W had slightly increased binding to HGFR as compared to heavy chain EPG as evidenced by a slight increase in ECL signal.

Table 115. Binding of Fab VH3-23_IGHD2-21*01>3_IGHJ6*01 H100E/S108P/Y113G (EPG) & V2-13_IGLJ2*01 Y109, Y110, Y111, Y112, and Y114 mutants to HGFR

	SEQ ID NO	Erb B2	EGF R	HGF R	Notch -1	CD4 4	IGF -1	P-Cad	EPO R	DLL 4
Parent	2803	4.1	4.2	33.4	2.1	1.8	1.6	20.6	39.4	2.3
EPG	605	11.7	8.4	104.6	2.3	1.7	1.7	27.5	126.1	2.3
Y109L	615	2.1	2.2	52.9	1.9	1.6	1.7	4.0	22.1	2.0
Y109P	616	1.5	1.6	1.8	1.1	1.1	1.4	1.9	1.8	1.6
Y109T	617	1.7	1.4	16.0	1.7	1.1	1.3	2.1	6.0	1.5
Y109H	618	1.7	1.4	27.7	1.2	1.1	1.2	3.9	18.3	1.4
Y109Q	619	1.3	1.7	14.7	1.3	1.3	1.1	2.2	3.1	1.2
Y109D	620	1.3	1.4	2.9	1.3	1.0	1.4	1.8	2.0	1.4
Y109W	621	16.1	11.1	**125.3**	4.4	2.4	1.5	32.0	168.8	4.3
Y109R	622	2.0	1.8	39.6	1.4	1.0	1.3	7.4	30.1	1.5
Y109G	623	1.4	2.0	8.7	1.5	1.5	1.6	2.7	11.1	1.9
Y110I	624	11.4	8.6	**163.2**	2.5	1.7	1.4	39.0	73.7	2.0
Y110S	625	1.0	1.3	13.1	0.8	1.0	1.1	1.9	4.5	1.2
Y110P	626	0.9	1.1	4.8	1.1	1.2	1.2	1.7	2.9	1.4
Y110T	627	0.8	1.8	21.1	2.3	1.6	1.8	1.0	3.5	1.8
Y110H	628	2.2	1.7	8.8	1.4	1.4	1.3	2.9	3.7	1.9
Y110N	629	1.2	0.9	2.3	1.3	0.8	0.9	1.2	1.6	1.2
Y110E	630	1.7	1.6	1.8	1.5	1.3	1.4	2.0	2.2	1.8
Y110W	631	16.5	7.6	110.2	3.2	2.1	2.3	38.8	116.8	3.9
Y110R	632	2.1	1.6	3.9	1.6	1.3	1.4	3.3	4.8	1.8
Y110G	633	1.3	1.5	1.0	1.6	1.0	1.4	0.8	2.0	1.3
Y111I	634	1.7	1.9	10.2	1.8	1.3	1.0	1.9	6.9	1.5
Y111S	635	2.1	1.8	23.9	1.9	1.2	1.3	5.0	30.1	1.7
Y111P	636	1.6	1.5	1.7	1.6	1.3	1.2	1.3	1.9	1.4

Y111T	637	2.6	2.6	42.0	2.0	1.8	1.2	6.2	38.8	2.2
Y111H	638	3.0	2.9	37.5	1.5	1.3	1.2	7.7	49.8	1.6
Y111N	639	1.5	1.4	17.0	1.3	0.9	0.8	2.9	9.3	1.1
Y111E	640	1.5	1.4	2.2	1.5	1.1	1.4	2.3	2.9	1.5
Y111W	641	26.5	16.3	121.4	5.3	3.4	1.4	49.2	195.3	2.8
Y111R	642	3.3	2.6	24.3	2.3	1.4	1.3	15.7	22.6	1.4
Y111G	643	2.2	1.5	18.8	1.9	1.3	1.1	5.0	10.0	1.7
Y112I	644	25.0	21.5	**126.2**	10.4	6.5	2.1	43.1	81.7	3.7
Y112S	645	3.5	2.3	67.9	2.3	1.5	1.3	7.1	31.0	1.7
Y112P	646	2.3	1.8	41.8	1.4	1.1	1.1	5.0	32.2	1.5
Y112T	647	8.8	8.4	**137.6**	2.1	1.8	1.2	25.5	90.9	1.7
Y112H	648	3.4	2.7	86.6	1.8	1.4	1.7	9.7	40.6	1.8
Y112N	649	1.2	1.3	29.5	0.8	0.9	1.1	1.9	4.2	1.3
Y112E	650	1.4	1.5	7.3	1.2	1.1	1.2	2.0	4.7	1.3
Y112W	651	25.5	18.7	**127.0**	9.2	5.8	2.1	50.5	156.8	3.2
Y112R	652	5.9	3.7	120.5	2.7	1.6	1.5	30.0	85.1	2.6
Y112G	653	1.4	1.7	10.0	2.1	1.2	1.0	2.3	7.9	1.3
Y114I	654	11.4	7.1	82.2	2.6	1.8	1.4	22.6	161.8	2.4
Y114S	655	8.7	5.0	48.9	2.9	1.4	1.3	15.8	68.5	2.2
Y114P	656	1.4	1.2	2.7	1.4	1.1	0.9	1.3	2.3	1.1
Y114T	657	1.4	1.3	1.8	1.8	1.1	1.1	1.7	2.0	1.6
Y114H	658	12.5	8.7	67.5	3.3	1.8	1.4	27.0	119.7	2.3
Y114N	659	3.5	2.6	23.1	2.0	1.2	1.2	5.9	35.0	1.6
Y114E	660	7.4	6.8	18.2	3.3	1.5	1.5	13.9	69.2	2.2
Y114W	661	9.3	6.6	56.7	2.2	1.6	1.1	16.7	51.5	1.9
Y114R	662	6.4	4.3	70.4	2.0	1.4	1.1	15.6	61.8	1.9
Y114G	663	3.2	2.1	14.7	1.6	1.2	1.2	6.4	15.8	1.7

v. Alanine scanning of Heavy Chain CDR1

CDR1 of the heavy chain sequence of Fab VH3-23_IGHD2-21*01>3_IGHJ6*01 H100E/S108P/Y113G (H:EPG) & V2-13_IGLJ2*01 (SEQ ID NOS:605 and 594) was subjected to alanine scanning mutagenesis and analyzed using the ECL multispot assay using 20 nM Fab. The results are set forth in Table 116 below. Mutation of amino acid residues F27 and A33 with alanine resulted in reduced binding to HGFR as evidenced by a reduced ECL signal. Mutation of amino acid residues G26, T28, F29, S30, S31, Y32, M34, and S35 with alanine either improved binding or did not affect binding to HGFR as evidenced by an increased ECL signal or no change in ECL signal compared to the EPG triple mutant having no mutations in the light chain.

Table 116. Binding of Fab VH3-23_IGHD2-21*01>3_IGHJ6*01 H100E/S108P/Y113G (H:EPG) & V2-13_IGLJ2*01 CDR1 alanine mutants to HGFR

	SEQ ID NO	Erb B2	EGF R	HGF R	Notch -1	CD4 4	IGF -1	P-Cad	EPO R	DLL 4
G26A	664	12.1	7.5	110.9	2.3	2.0	1.6	29.4	161.3	2.7
F27A	665	6.1	3.6	87.3	1.4	1.3	1.1	14.8	64.2	1.7
T28A	666	13.3	8.7	**140.3**	2.2	1.8	1.3	32.6	180.5	2.2

F29A	667	11.6	8.1	120.5	2.4	1.5	1.4	32.7	157.6	2.5
S30A	668	11.4	8.9	118.3	2.4	1.7	1.3	26.8	153.7	2.0
S31A	669	12.4	9.1	121.2	2.1	1.7	1.3	32.4	143.5	4.3
Y32A	670	5.8	4.1	104.7	1.9	1.4	1.6	14.7	65.8	2.3
A33T	671	6.3	5.3	35.7	1.7	1.2	1.1	25.9	114.3	1.8
M34A	672	12.0	9.8	129.2	2.5	1.9	1.3	32.2	197.6	2.6
S35A	673	12.0	8.3	108.5	2.6	1.8	1.3	32.4	184.4	2.4
Parent	2803	4.1	4.2	33.4	2.1	1.8	1.6	20.6	39.4	2.3
EPG	605	11.7	8.4	104.6	2.3	1.7	1.7	27.5	126.1	2.3

vi. Alanine scanning of Heavy Chain CDR2

CDR2 of the heavy chain sequence of Fab VH3-23_IGHD2-21*01>3_IGHJ6*01 H100E/S108P/Y113G (H:EPG) & V2-13_IGLJ2*01 (SEQ ID NOS:605 and 594) was subjected to alanine scanning mutagenesis and analyzed using the ECL multispot assay using 20 nM Fab. The results are set forth in Table 117 below. Mutation of amino acid residues I51, G56, Y59, and A61 with alanine resulted in reduced binding to HGFR as evidenced by a reduced ECL signal. Double mutant S46A/G47A had reduced binding to HGFR as evidenced by a reduced ECL signal. Mutation of amino acid residues G53, S54 G55, S57, T58, Y60, D62, V64 and K65 with alanine either improved binding or did not affect binding to HGFR as evidenced by an increased ECL signal or no change in ECL signal compared to the H:EPG triple mutant having no mutations in the light chain.

Table 117. Binding of Fab VH3-23_IGHD2-21*01>3_IGHJ6*01 H100E/S108P (H:EP) or H100E/S108P/Y113G (H:EPG) & V2-13_IGLJ2*01 CDR2 alanine mutants to HGFR

	SEQ ID NO	Erb B2	EGF R	HGF R	Notch -1	CD4 4	IGF -1	P-Cad	EPO R	DLL 4
Parent	2803	4.1	4.2	33.4	2.1	1.8	1.6	20.6	39.4	2.3
EPG	605	11.7	8.4	104.6	2.3	1.7	1.7	27.5	126.1	2.3
I51A	674	9.4	5.3	77.4	2.8	1.6	1.3	20.3	112.6	2.2
S52A/ G53A	675	8.3	5.2	85.0	2.2	1.5	1.4	16.7	75.6	2.3
G53A	676	16.7	10.9	**159.2**	3.9	2.5	1.8	36.5	222.6	3.1
S54A	677	15.1	8.9	115.2	2.8	1.9	1.3	33.4	160.7	2.4
G55A	678	11.1	7.7	111.3	2.5	1.7	1.3	26.9	143.0	2.1
G56A	679	9.5	6.8	79.4	2.7	1.6	1.4	23.6	100.0	2.3
S57A	680	12.9	8.7	124.0	3.4	1.8	1.7	33.0	150.8	2.5
T58A	681	15.9	9.6	**167.0**	3.1	1.5	1.2	36.9	158.1	2.3
Y59A	682	1.6	1.4	3.3	2.1	1.4	1.3	2.4	2.5	2.8
Y60A	683	11.5	6.2	112.7	2.6	1.5	1.2	25.3	109.8	2.3
A61T	684	11.2	7.1	81.4	2.9	2.0	1.6	20.9	146.7	2.6
D62A	685	21.7	11.6	**154.4**	3.5	2.0	1.4	45.8	244.1	2.4
EP V64A	686	16.5	9.1	100.9	3.0	2.2	1.2	30.6	172.9	2.7
EP	687	12.1	7.1	95.8	3.0	1.7	1.4	21.6	120.4	2.5

K65A										

EXAMPLE 15

Affinity Maturation of Fab VH3-23_IGHD3-10*01>3_IGHJ6*01 & O12_IGKJ1*01 Against P-cadherin and Epo

Fab VH3-23_IGHD3-10*01>3_IGHJ6*01 & V2-13_IGLJ2*01 (SEQ ID NOS:688 and 594) against P-cadherin and EPO, identified as described in Example 4 using the electroluminescence Meso Scale Discovery (MSD) multispot binding assay, was subjected to affinity maturation as described above in Examples 7-9.

vii. NNK mutagenesis of CDR3 amino acid residues R104, Y110, Y112, Y113, and Y114

CDR3 amino acid residues R104, Y110, Y112, Y113, and Y114 were mutagenized using NNK mutagenesis and tested for their ability to bind P-cadherin and EPO by ECL multispot assay. The results are set forth in Table 118 below. Mutant -3Y is a deletion mutant in which tyrosines 110, 111 and 112 were deleted. Mutation of amino acid residue Y115 to proline (Y115P) and Y110 to valine (Y110V) resulted an increased binding to both P-cadherin and EPO as compared to the wildtype template antibody as evidenced by an increase in ECL binding signal. Mutation of amino acid residue Y111 to arginine (Y111R) resulted in an increase in binding to P-cadherin as compared to wildtype as evidenced by an increase in ECL binding signal. Additionally, as set forth in Table 116 below, mutants Y115P, Y110V and Y111R all bind P-cadherin as evidenced by ELISA binding results.

Table 118. Binding of Fab VH3-23_IGHD3-10*01>3_IGHJ6*01 & O12_IGKJ1*01 NNK mutants

	SEQ ID NO	Erb B2	EGF R	HGF R	Notch -1	CD44	IGF-1	P-Cad	EPO R	DLL4
Y114N	689	1.1	1.0	1.2	1.2	1.2	1.0	1.7	1.3	1.2
Y114T	690	0.8	0.8	1.2	0.7	0.9	0.7	1.3	1.2	0.9
Y114I	691	1.2	1.4	1.5	1.1	1.2	0.7	1.1	1.4	1.2
Y115P	692	3.4	2.7	4.3	1.7	1.3	1.7	**27.2**	**37.0**	4.2
Y115R	693	1.9	1.7	2.0	1.7	1.5	1.4	4.7	3.9	1.9
Y115G	694	1.9	2.0	2.1	1.7	1.5	1.9	9.7	17.0	2.7
Y115E	695	1.3	1.1	1.3	0.8	1.4	1.0	1.3	1.4	1.1
R104A	696	1.8	1.4	2.3	2.0	1.3	1.1	9.3	8.5	2.7
-3Y	697	1.2	1.4	1.1	0.7	0.9	1.0	1.1	1.7	1.3
Y110V	698	1.5	1.2	2.0	1.3	1.1	1.1	**17.2**	**10.8**	2.0
Y110S	699	1.6	1.2	1.4	1.4	1.4	1.1	1.5	1.4	1.4
Y110P	700	1.3	1.6	1.5	1.6	1.4	1.2	1.1	1.7	1.5
Y110G	701	1.3	1.2	0.9	1.4	0.9	1.2	1.0	1.4	1.3
Y110R	702	2.5	2.1	3.0	2.8	1.4	2.5	11.3	9.2	3.0
Y111S	703	1.2	1.3	1.3	1.3	1.0	0.9	1.4	1.5	1.2
Y111D	704	1.2	0.9	1.1	2.0	1.4	1.4	1.1	1.1	1.1
Y111R	705	2.5	2.4	3.2	3.0	1.5	1.9	**11.9**	7.3	2.9

Y112A	706	1.3	1.5	0.8	1.1	1.5	1.4	1.1	1.6	1.2
Y112G	707	2.9	2.1	2.3	3.3	2.5	2.3	1.4	1.6	2.2
Y112Q	708	1.5	1.2	1.4	1.7	1.4	1.6	3.0	2.4	1.8
Y112P	709	0.9	1.0	1.1	1.1	1.1	0.8	1.4	0.9	1.0
Y112V	710	1.6	1.2	1.3	1.4	1.0	0.8	9.8	4.3	2.0
Y113H	711	1.4	1.4	1.6	1.0	1.0	1.2	7.3	5.1	1.8
Y113L	712	0.8	1.6	1.0	1.5	1.2	1.4	1.4	1.7	1.4
Y113W	713	1.8	1.5	2.0	1.4	1.4	1.2	5.6	4.0	1.8
Y113E	714	1.1	1.1	1.2	1.3	1.3	1.0	1.2	1.6	1.4
Y113P	715	1.3	1.4	1.4	1.4	0.8	1.2	2.0	2.0	1.3
Y113K	716	0.9	1.1	1.2	1.2	1.0	0.8	1.2	1.3	1.3
Y114K	717	0.8	0.9	0.9	1.0	0.8	0.6	1.0	1.2	1.1
Y114F	718	1.1	1.1	1.4	1.0	1.0	1.1	2.0	2.1	1.2
Y114R	719	2.0	2.0	2.4	2.4	1.6	1.5	2.9	2.3	2.4
wt	688	1.8	1.4	1.6	1.2	0.9	1.1	9.2	7.9	1.6
wt	688	1.6	1.5	2.0	1.4	1.3	1.4	9.5	9.3	1.7

Example 16

Binding to DLL4 expressed on the surface of CHO cells

In this example, Fabs H:APFF VLTH & L:NDH LS (SEQ ID NOS:209 and 350; identified as exhibiting about 1.7 nM affinity as shown in Table 75) and H:KT TRV & L:LP S52G (SEQ ID NOS:430 and 543; identified as exhibiting about 5 nM affinity as shown in Table 108) were tested for their ability to bind to DLL4 expressed on the surface of CHO cells as detected by flow cytometry.

To generate a DLL4 expression construct, human DLL4 cDNA (SEQ ID NO:2905, Accession No. BC106950; and encoding amino acids set forth in SEQ ID NO:2904, Accession No. AAI06951) in pCR-BluntII-TOPO (SEQ ID NO:2934) as a glycerol stock was obtained from Open Biosystems (Clone ID# 40034887). The stock was streaked on kanamycin agar plates and a colony picked for purification of the DNA. DNA was obtained with Purelink™ Quick Plasmid Miniprep Kit (Invitrogen, Catalog # K210010).

Full-length DLL4 was digested out from the OpenBiosystems vector and ligated into pCDNA5/FRT (SEQ ID NO:2935; Invitrogen Catalog # K601001) between NheI and NotI. Ligation was performed with Rapid DNA Ligation Kit (Roche, Catalog # 11 635 379 001) and cells transformed using heat shock into One Shot® Max Efficiency® DH5α™-T1^R Competent Cells (Invitrogen, Catalog # 12297016). Cells were selected on carbenicillin plates. Colonies were picked and inoculated overnight in luria broth (LB) containing 1:1000 100 mg/mL carbenicillin. Plasmid DNA was extracted by miniprep (Invitrogen; Catalog # K210011).

Using Invitrogen's LipofectamineTM Transfection Reagent, pcDNA5/FRT containing full-length DLL4 and pOG44 recombinase vector (SEQ ID NO:2936; Invitrogen

Catalog # K601001) were transfected into Invitrogen's Flp-InTM-CHO Cell Line (Cat. No. R75807) according to Flp-InTM System protocol. Cells were approximately 90% confluent in a 12-well plate. Transfected cells were selected with 400μg/ml Hygromycin after a couple days. Colonies were picked about 5 days after and transferred into a 10 cm^2 tissue culture dish. These cell lines were maintained with hygromycin selection

CHO cells expressing full-length DLL4 and control CHO cells were detached from tissue culture plates (BD Falcon 10 cm^2) using Accutase™ Enzyme Cell Detachment Medium (Cat# 00-4555-56, eBioscience). After washing the cells in 2% Bovine Serum Albumin in Phosphate Buffered Saline (2% BSA/PBS), 10 nM to 50 nM Fab in 2% BSA/PBS was added and incubated at on ice for 30 minutes. The cells were washed one time with 2% BSA/PBS and mouse anti-human kappa-PE antibody (diluted 1:100, Cat# MH10514, Invitrogen) or mouse anti-human lambda-PE antibody (diluted 1:100, Cat# MH10614, Invitrogen) was added and incubated on ice for 10 minutes. Secondary antibody mouse anti-human kappa-PE alone (without Fab) was used as a control for DLL4-expressing CHO cells. The cells were then washed twice in 2% BSA/PBS and analyzed by flow cytometry on a BD FACSAria. The results show that the tested Fabs bind DLL4 expressed on the surface of CHO cells. Neither Fab showed significant binding to CHO cells without DLL4 over-expression.

Example 17

Inhibition of DLL4-Notch interaction by Flow Cytometry

In this example, three DLL4 binding Fabs were functionally screened for their ability to block the binding of Notch-Fc to DLL4. In this assay, DLL4-expressing CHO cells were incubated in the presence of both Fab and biotinylated-Notch-Fc. Streptavidin-PE was used as a detection molecule. If Notch-Fc binds to DLL4-expressing CHO cells, these cells will be detected by a PE signal at 578 nm. Alternatively, if the Fab blocks the binding of Notch-Fc to DLL4, the DLL4-expressing CHO cells will not be labeled or detected. The tested Fabs included H:APFF VLTH & L:NDH LS (SEQ ID NOS:209 and 350), H:KT TRV & V3-4_IGLJ1*01 (SEQ ID NOS:430 and 108) and H:KT TRV & L:LP S52G (SEQ ID NOS:430 and 543).

In short, CHO cells expressing full-length DLL4 (CHO-DLL4) as described in Example 16 were detached from tissue culture plates using Accutase™ Enzyme Cell Detachment Medium (Cat# 00-4555-56, eBioscience). Fab was 5-fold serially diluted in 2% BSA/PBS from a starting concentration of 50 nM. Notch-FC (cat# 3647-TK-050, R&D Systems) was biotinylated following using EZ-Link NHS-Biotin Reagent (cat# 20217. Pierce) according to the manufacturers instructions. Detached cells were treated with 250 nM

biotinylated Notch-FC in 2% BSA/PBS and 30 μL Fab for 30 minutes on ice. PE-labeled streptavidin (Cat# 21627, Pierce-Thermo Scientific) was then added to a final dilution of 1:5 followed by incubation for 10 minutes at room temperature. The cells were then washed twice in 2% BSA/PBS and analyzed by flow cytometry on a BD FACSAria.

The results are set forth in Table 119 below. All three Fabs effectively block Notch-Fc binding to CHO-DLL4. Fab H:APFF VLTH & L:NDH LS completely blocks the binding of Notch to DLL4 by 80% at a Fab concentration of 2 nM. Fab H:KT TRV & V3-4_IGLJ1*01 blocks the binding of Notch to DLL4 by 50% at a concentration of 50 nM Fab. Fab H:KT TRV & L:LP S52G blocks the binding of Notch to DLL4 by 80% at a concentration of 50 nM Fab.

Table 119. Inhibition of DLL4-Notch interaction

Fab [nM]	H:APFF VLTH & L:NDH LS	H:KT TRV & L:wt	H:KT TRV & L:LP S52G
50	30	141	105
10	30	244	190
2	117	448	250
0.4	277	Not tested	324
0	531	531	531

Example 18

IgG Cloning and Expression

In this example, Fab antibodies that bind to DLL4 were converted into IgGs by cloning into the pFUSE vectors. Briefly, sequences encoding heavy and light chains were cloned separately into the pFUSE family of vectors (pFUSE-hIgG2-Fc2, Cat# pfuse-hfc2, InvivoGen; SEQ ID NO:2938)) behind the included IL-2 signal sequence. These two vectors were then co-transformed into 293F cells and the protein was expressed and purified.

Light Chain: The Sequence encoding the Fab light chain (excluding the N-terminal *E. coli* sorting signal Met Ala) was amplified by PCR with primers containing EcoRI and NheI ends. The amplified Fab light chain was subcloned into pFUSE-hIgG2-Fc2, previously digested with EcoRI and NheI. The Fab light chain immediately follows the IL-2 signal sequence, and completely replaces the Fc sequence in pFUSE-hIgG2-Fc2.

Heavy Chain: A full-length IgG1 heavy chain sequence (SEQ ID NO:2922) also including a NheI site between VH and CH1-CH2-CH3 was synthesized by Genscript, amplified by PCR with primers containing EcoRI and XbaI ends, and subcloned into pFUSE-hIgG2-Fc2, previously digested with EcoRI and NheI. Ligation of the XbaI and NheI compatible cohesive ends eliminates both sties at this position, making the NheI site between VH and CH1-CH2-CH3 of the IgG1 heavy chain sequence unique. The sequence encoding Fab heavy

chain (excluding the N-terminal *E. coli* sorting signal Met Ala) was amplified by PCR with EcoRI and NheI ends. The vector containing the full length IgG1 heavy chain was then digested with EcoRI and NheI, which removed the VH sequence, and the amplified Fab heavy chain was subcloned into the digested vector. Thus the Fab Heavy chain was subcloned between IL-2 and the IgGI heavy chain.

Protein Expression and Purification: To produce IgG, the heavy and light chain plasmids were co-transfected into 293F cells (Cat# R790-07, Invitrogen) using 293fectin (Cat# 12347, Invitrogen) per manufacturer's instructions. Cells grown in serum-free 293Freestyle media (Cat# 12338026, Invitrogen) were transfected at 1×106 cells/ml in 50 ml spinner flask. Cell culture media were harvested 3 and 6 days after transfection and pooled together for purification by column chromatography using Protein-G Sepharose (GE Healthcare). IgG elution fractions were pooled and dialysed into PBS.

Example 19

Activity of Antibodies by DLL4-Notch interaction by a Reporter Assay

In this example, two DLL4 binding antibodies were assayed for their ability to inhibit DLL4-dependent Notch 1 signaling using a luciferase reporter assay. Reporter cells were generated by stably transfecting human glioma T98G cells, known for the presence of Notch 1 on their cell surface (see Purow et al. (2005) Cancer Res., 65:2353-63), with a Notch reporter plasmid (p6xCBF) containing six C promoter binding factor-1 (CBF-1) responsive elements (set forth in SEQ ID NO:2939; see Nefedova et al. (2004), Blood. 103(9):3503-10). Subsequent addition of DLL4-CHO cells (see Example 16 above) to the reporter T98G cells results in expression of firefly luciferase due to the Notch1-DLL4 interaction. Disruption of the Notch1-DLL4 by a DLL4 binding antibody therefore causes a decrease in luciferase expression.

A. Notch reporter plasmids

A reporter construct containing six C promoter binding factor-1 (CBF-1) response elements (set forth in SEQ ID NO:2939; CBF Notch-response elements are indicated by bold; ggtacctgagctcgctagcgatctggtgtaaacacgcc**gtgggaa**aaaatttatggatctggtgtaaacacgcc**gtgggaa**aaaatttatggagctcgctagcgatctggtgtaaacacgcc**gtgggaa**aaaatttatggatctggtgtaaacacgcc**gtgggaa**aaaatttatgctcgaggatctggtgtaaacacgcc**gtgggaa**aaaatttatggatctggtgtaaacacgcc**gtgggaa**aaaatttatgaagctt;) was digested with KpnI and HindIII. The digested product was then into the luciferase reporter vectors pGL4.26 (SEQ ID NO:2940; Promega, Catalog # E8441)) at the KpnI and HindIII sites. The pGL4.26 vector allows for hygromycin selection, which facilitates the production of a cell line with a stably-integrated copy of the reporter. Also, the use of pGL4.26

eliminates the need to transiently transfect the reporter and normalize for variable transfection efficiency.

B. Assay

T98G cells from ATCC (No. CRL-1690™) were plated onto a 96-well tissue culture plate at 20,000 cells per well in Eagle's Minimum Essential Media (EMEM, Invitrogen) supplemented with 10% Fetal Bovine Serum (BSA, Invitrogen) and 1X penicillin/streptomycin/glutamine (P/S/G, Invitrogen).

The following day, T98G cells were transfected with the Notch reporter construct expressing Firefly luciferase (p6xCBF) and stable integrants were selected with 200ug/ml Hygromycin B (Invitrogen). CHO cells expressing DLL4 or control CHO cells were propagated in F12 media (Invitrogen) supplemented with 10% FBS and P/S/G. Separately, T98G Notch reporter cells (2×10^5 cells/well) in EMEM with 10% FBS and P/S/G were plated onto 96-well tissue culture plates. Notch-expressing T98G cells were stimulated by CHO-DLL4 or control CHO cells (1×10^5 cells/well). Media on T98G cells was replaced by 100 µl of serum free F12 media supplemented with P/S/G. Fabs H:APFF VLTH & L:NDH LS (SEQ ID NOS:209 and 350) and H:KT TRV & L:LP S52G (SEQ ID NOS:430 and 543) and their corresponding IgGs, and control Fab (that does not bind DLL4; VH6-1_IGHD6-13*01_IGHJ4*01 and V2-17_IGLJ2*01 set forth in SEQ ID NOS: 2152 and 2941, respectively) were added at 100, 20, 4 and 0.8 nM. In addition, the non-affinity matured germline parent Fabs also were tested to determine their Notch reporter response. For this, corresponding IgGs of VH5-51_IGHD5-18*01>3_IGHJ4*01 & V3-4_IGLJ1*01 (set forth in SEQ ID NOS: 89 and 108; the parent germline Fab of H:KT TRV & L:LP S52G) and VH1-46_IGHD6-6*01_IGHJ1*01 & L6_IGKJ1*01 (set forth in SEQ ID NOS:88 and 107; the parent germline Fab of H:APFF VLTH & L:NDH LS) were control IgG was added at 200, 100 and 20 nM.

After 24 hours, luciferase-reporter expression was measured with Bright-Glo luciferase assay reagent (Cat# E2620, Promega). Luminenscence was read using a Wallac Victor II model 1420 plate reader. Each condition was performed in quadruplicate.

The results are depicted in Tables 120 below. The results in Table 120 show that incubation of the T98G reporter cells with CHO-DLL4 resulted in 8- to 9- fold increase in Notch1 reporter levels compared to those incubated with CHO cells alone. The Notch1 activation remained constant in the presence of the control Fab that does not bind to DLL4. The activation was reduced in the presence of increasing concentration of anti-DLL4 antibody Fabs H:APFF VLTH & L:NDH LS and H:KT TRV & L:LP S52G. The reduction was even more pronounced with an IgG version of H:APFF VLTH & L:NDH LS ($IC_{50} \sim 6$ nM), which

was almost 10-fold more efficient than the corresponding Fab. The IgG version of H:KT TRV & L:LP S52G was also more effective than the corresponding Fab, displaying about 30% reduction in Notch1 activation at 0.8 nM. Neither Fab nor IgG form of H:KT TRV & L:LP S52G showed complete suppression of Notch1 activation at higher concentrations (>100 nM). The results show that the IgG H:APFF VLTH & L:NDH LS is a complete inhibitor, whereas IgG H:KT TRV & L:LP S52G is a partial antagonist of the DLL4-Notch activation.

TABLE 120

Cell type	treatment	Conc [nM]	1	2	3	4	Avg ± SE
CHO-DLL4	**VH6-1 IGH36-13*01 IGHJ4*01 and V2-17_IGLJ2*01 (control Fab)**	0.8	4482	4541	3908	4221	4288 ± 144
		4	4809	4921	4187	4520	4609 ± 164
		20	5402	4988	4323	4546	4815 ± 240
		100	4821	4813	4034	4473	4535 ± 186
	H:KT TRV & L:LP S52G (Fab)	0.8	4878	4716	4078	4278	4488 ± 186
		4	4792	4771	4321	4469	4588 ± 116
		20	4245	4371	4148	4075	4210 ± 64
		100	3321	3483	3012	3083	3225 ± 109
	H:KT TRV & L:LP S52G (IgG)	0.8	3711	3485	3092	3292	3395 ± 132
		4	3276	3339	3091	2911	3154 ± 97
		20	3020	2904	2598	2652	2794 ± 101
		100	2811	2545	2276	2519	2538 ± 109
	H:APFF VLTH & L:NDH LS (Fab)	0.8	4739	4886	3818	4076	4380 ±257
		4	4837	4877	4251	4667	4658 ± 143
		20	4376	4482	3960	3993	4203 ± 133
		100	2397	2285	2148	2169	2250 ± 58
	H:APFF VLTH & L:NDH LS (IgG)	0.8	4445	4521	3899	3985	4213 ± 158
		4	4261	3862	3949	3765	3959 ± 107
		20	1250	1269	1174	1191	1221 ± 23
		100	757	807	678	688	733 ± 30
CHO	**VH6-1 IGH36-13*01**	0.8	572	569	555	583	570 ± 6
		4	557	547	539	450	523 ± 25

TABLE 120							
Cell type	**treatment**	**Conc [nM]**	**1**	**2**	**3**	**4**	**Avg ± SE**
	IGHJ4*01 and V2-17_IGLJ2*01 (control Fab)	20	508	532	550	476	517 ± 16
		100	488	487	491	464	483 ± 6

Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

CLAIMS:

1. A method of affinity maturation of a first antibody or portion thereof for a target antigen, comprising:

a) identifying a related antibody or portion thereof that exhibits a reduced activity for the target antigen than the corresponding form of a first antibody, wherein the related antibody or portion thereof contains a related variable heavy chain or a related variable light chain that is either:

one in which the corresponding variable heavy chain or variable light chain of the related antibody exhibits at least 75% amino acid sequence identity to the variable heavy chain or variable light chain of the first antibody but does not exhibit 100% sequence identity therewith; or

one in which at least one of the V_H, D_H and J_H germline segments of the nucleic acid molecule encoding the variable heavy chain of the related antibody is identical to one of the V_H, D_H and J_H germline segments of the nucleic acid molecule encoding the variable heavy chain of the first antibody and/or at least one of the V_κ and J_κ or at least one of the V_λ and J_λ germline segments of the nucleic acid molecule encoding the variable light chain is identical to one of the V_κ and J_κ or V_λ and J_λ germline segments of the nucleic acid molecule encoding the variable light chain of the first antibody ; and

b) comparing the amino acid sequence of the variable heavy chain or variable light chain of the first antibody to the amino acid sequence of the corresponding related variable heavy chain or variable light chain of the related antibody;

c) identifying a target region within the variable heavy chain or variable light chain of a first antibody, whereby a target region is a region in the first antibody that exhibits at least one amino acid difference compared to the same region in the related antibody;

d) producing a plurality of modified antibodies each comprising a variable heavy chain and a variable light chain, or a portion thereof, wherein at least one of the variable heavy chain or variable light chain is modified in its target region by replacement of a single amino acid residue, whereby the target region in each of the plurality of antibodies contains replacement of an amino acid to a different amino acid compared to the first antibody;

e) screening each of the plurality of modified antibodies for an activity to the target antigen; and

f) selecting those modified antibodies that exhibit increased activity for the target antigen compared to the first antibody.

2. The method of claim 1, wherein the plurality of modified antibodies in d) are produced by producing a plurality of nucleic acid molecules that encode modified forms of a variable heavy chain or a variable light chain of the first antibody, wherein the nucleic acid molecules contain one codon encoding an amino acid in the target region that encodes a different amino acid from the unmodified variable heavy or variable light chain, whereby each nucleic acid molecule of the plurality encodes a variable heavy chain or variable light chain that is modified in its target region by replacement of a single amino acid residue.

3. The method of claim 1, wherein the target region in the first antibody exhibits 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid differences compared to the corresponding region in the related antibody.

4. The method of any of claims 1-3, wherein the related antibody is 1, 2, 3, 4, or 5 related antibodies.

5. The method of any of claims 1-4, wherein an activity is selected from among binding, signal transduction, differentiation, alteration of gene expression, cellular proliferation, apoptosis, chemotaxis, cytotoxicity, cancer cell invasion, endothelial cell proliferation and tube formation.

6. The method of claim 5, wherein the activity is binding and binding is assessed by a method selected from among an immunoassay, whole cell panning and surface plasmon resonance (SPR).

7. The method of claim 6, wherein the immunoassay is selected from among a radioimmunoassay, enzyme linked immunosorbent assay (ELISA) and electrochemiluminescence assay.

8. The method of claim 7 wherein the electrochemiluminescence assay is meso scale discovery (MSD).

9. The method of any of claims 1-8, wherein the first antibody binds to the target antigen when the antibody is in a Fab form with a binding affinity that is 10^{-4} M or lower; 10^{-4} M to 10^{-8} M; or at or about 10^{-4} M, 10^{-5} M, 10^{-6} M, 10^{-7} M, 10^{-8} M, or lower.

10. The method of any of claims 1-9, wherein the related antibody or portion thereof exhibits 80% or less activity than the corresponding form of the first antibody; 5% to 80% of the activity of the corresponding form of the first antibody; or less than or about 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5% or less activity than the corresponding form of the first antibody.

11. The method of any of claims 1-9, wherein the related antibody exhibits the same or similar level of activity to the target antigen compared to a negative control.

12. The method of any of claims 1-11, wherein the related antibody exhibits a binding affinity that is less than the binding affinity of the first antibody, whereby the binding affinity of the related antibody in its Fab form is 10^{-4} M or lower; 10^{-4} M to 10^{-8} M; or at or about 10^{-4} M, 10^{-5} M, 10^{-6} M, 10^{-7} M, 10^{-8} M or lower.

13. The method of any of claims 1-12, wherein a target region is identified within the variable heavy chain of the first antibody, and steps d) – f) are performed therefrom.

14. The method of any of claims 1-12, wherein a target region is identified within the variable light chain of the first antibody, and steps d) – f) are performed therefrom.

15. The method of any of claims 1-12, wherein:

a target region is identified within the variable heavy chain of the first antibody and steps d) - f) are performed therefrom; and

separately and independently a target region is identified within the variable light chain of the first antibody, and steps d) – f) are performed therefrom.

16. The method of any of claims 1-15, wherein a related antibody that contains the related corresponding variable heavy chain is different than a related antibody that contains the related corresponding variable light chain.

17. The method of any of claims 1-15, wherein a related antibody that contains the related corresponding variable heavy chain is the same as a related antibody that contains the related corresponding variable light chain.

18. The method of any of claims 1-17, wherein the variable heavy chain or variable light chain of the first antibody exhibits at least 80% or more sequence identity with the corresponding related variable heavy chain or variable light chain of the related antibody; 80% to 99% of the sequence identity with the corresponding related variable heavy chain or variable light chain of the related antibody; or at least or about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity with the corresponding related variable heavy chain or variable light chain of the related antibody.

19. The method of any of claims 1-18, wherein the variable heavy chain or variable light chain of the first antibody exhibits at least 95% sequence identity with the corresponding related variable heavy chain or variable light chain of the related antibody.

20. The method of any of claims 1-19, wherein the related antibody contains a related variable heavy chain or variable light chain that is one in which at least one of the V_H, D_H and J_H germline segments of the nucleic acid molecule encoding the variable heavy chain of the first antibody is identical to one of the V_H, D_H and J_H germline segments of the nucleic acid molecule encoding the variable heavy chain of the related antibody; and/or at least one of the V_κ and J_κ or at least one of the V_λ and J_λ germline segments of the nucleic acid molecule

encoding the variable light chain of the first antibody is identical to one of the V_κ and J_κ or V_λ and J_λ germline segments of the nucleic acid molecule encoding the variable light chain of the related antibody.

21. The method of any of claims 1-20, wherein:

the related antibody contains a related variable heavy chain or variable light that is one in which at least one of the V_H, D_H and J_H germline segments of the nucleic acid molecule encoding the variable heavy chain of the first antibody is from the same gene family as one of the V_H, D_H and J_H germline segments of the nucleic acid molecule encoding the variable heavy chain of the related antibody; and/or at least one of the V_κ and J_κ or at least one of the V_λ and J_λ germline segments of the nucleic acid molecule encoding the variable light chain of the first antibody is from the same gene family as one of the V_κ and J_κ or V_λ and J_λ germline segments of the nucleic acid molecule encoding the variable light chain of the related antibody.

22. The method of claim 20 or claim 21, wherein the variable heavy chain or variable light chain of the first antibody exhibits at least 60% or more sequence identity with the corresponding related variable heavy chain or variable light chain of the related antibody; 60% to 99% of the sequence identity with the corresponding related variable heavy chain or variable light chain of the related antibody; or at least or about 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity with the corresponding related variable heavy chain or variable light chain of the related antibody.

23. The method of any of claims 1-22, wherein the target region is selected from among a CDR1, CDR2, CDR3, FR1, FR2, FR3 and FR4.

24. The method of any of claims 1-23, wherein the target region is a CDR1, CDR2 or CDR3.

25. The method of any of claims 1-24, wherein:

a) the first antibody is identified by screening a combinatorial antibody library;

b) the combinatorial antibody library is produced by a method comprising:

i) combining a V_H, a D_H and a J_H human germline segment or portion thereof in frame to generate a sequence of a nucleic acid molecule encoding a VH chain or a portion thereof

ii) combining a V_κ and a J_κ human germline segment or portion thereof, or a V_λ and a J_λ germline segment or portion thereof in frame to generate a sequence of a nucleic acid molecule encoding a VL chain or a portion thereof, wherein:

in step i) and ii) each of the portions of the V_H, D_H, J_H, V_κ, J_κ, V_λ or J_λ are sufficient to produce an antibody or portion thereof containing a VH or VL or portion thereof that forms a sufficient antigen binding site;

iii) repeating step i) and ii) a plurality of times to generate sequences of a plurality of different nucleic acid molecules;

iv) synthesizing the nucleic acid molecules to produce two libraries, wherein:

the first library comprises nucleic acid molecules encoding a VH chain or a portion thereof; and

the second library comprises nucleic acid molecules encoding a VL chain or a portion thereof;

v) introducing a nucleic acid molecule from the first library and from the second library into a cell and repeating this a plurality of times to produce a library of cells, wherein each cell contains nucleic acid molecules encoding a different combination of VH and VL from every other cell in the library of cells; and

vi) growing the cells to express the antibodies or portions thereof in each cell, thereby producing a plurality of antibodies or portion thereof, wherein each antibody or portion thereof in the library comprises a different combination of a VH and a VL chain or a sufficient portion thereof to form an antigen binding site from all other antibodies or portions thereof in the library; and

c) screening of the library is effected by:

i) contacting an antibody or portion thereof in the library with a target protein;

ii) assessing binding of the antibody or portion thereof with the target protein and/or whether the antibody or portion thereof modulates a functional activity of the target protein; and

iii) identifying an antibody or portion thereof that exhibits an activity for the target protein, wherein the identified antibody or portion thereof is a first antibody.

26. The method of claim 25, wherein the related antibody also is identified by screening a combinatorial antibody library by steps a) - c), whereby the related antibody exhibits reduced activity for the target antigen compared to the first antibody.

27. The method of claim 25 or claim 26, wherein the library is an addressable library, whereby:

in step iv) the synthesized nucleic acid sequences are individually addressed, thereby generating a first addressed nucleic acid library and a second addressed nucleic acid library;

in step v) the cells are addressed, wherein each locus comprises a cell that contains nucleic acid molecules encoding a different combination of a VH and a VL from every other cell in the addressed library of cells; and

in step vi) the plurality of antibodies or portions thereof are addressed, wherein:

the antibodies or portions thereof at each locus in the library are the same antibody and are different from those at each and every other locus; and

the identity of the antibody or portion thereof is known by its address.

28. The method of claim 27, wherein the antibodies in the addressable library are arranged in a spatial array, wherein each individual locus of the array corresponds to a different antibody member.

29. The method of claim 28, wherein the spatial array is a multiwell plate.

30. The method of claim 28, wherein the antibodies in the addressable library are attached to a solid support selected from among a filter, chip, slide, bead or cellulose, and the different antibody members are immobilized to the surface thereof.

31. The method of any of claims 1-30, wherein the target antigen is a polypeptide, carbohydrate, lipid, nucleic acid or a small molecule.

32. The method of any of claims 1-31, wherein the target antigen is expressed on the surface of a virus, bacteria, tumor or other cell, or is a recombinant protein or peptide.

33. The method of any of claims 1-32, wherein the target antigen is a protein that is a target for therapeutic intervention.

34. The method of any of claims 1-33, wherein the target antigen is involved in cell proliferation and differentiation, cell migration, apoptosis or angiogenesis.

35. The method of any of claims 1-34, wherein the target antigen is selected from among a VEGFR-1, VEGFR-2, VEGFR-3 (vascular endothelial growth factor receptors 1, 2, and 3), a epidermal growth factor receptor (EGFR), ErbB-2, ErbB-3, IGF-R1, C-Met (also known as hepatocyte growth factor receptor; HGFR), DLL4, DDR1 (discoidin domain receptor), KIT (receptor for c-kit), FGFR1, FGFR2, FGFR4 (fibroblast growth factor receptors 1, 2, and 4), RON (recepteur d'origine nantais; also known as macrophage stimulating 1 receptor), TEK (endothelial-specific receptor tyrosine kinase), TIE (tyrosine kinase with immunoglobulin and epidermal growth factor homology domains receptor), CSF1R (colony stimulating factor 1 receptor), PDGFRB (platelet-derived growth factor receptor B), EPHA1, EPHA2, EPHB1 (erythropoietin-producing hepatocellular receptor A1, A2 and B1), TNF-R1, TNF-R2, HVEM, LT-βR, CD20, CD3, CD25, NOTCH, G-CSF-R, GM-CSF-R, EPO-R., a cadherin, an integrin, CD52, CD44, VEGF-A, VEGF-B, VEGF-C,

VEGF-D, PIGF, EGF, HGF, TNF-α, LIGHT, BTLA, lymphotoxin (LT), IgE, G-CSF, GM-CSF and EPO.

36. The method of any of claims 1-35, wherein a subset of the amino acid residues in the target region are modified by amino acid replacement.

37. The method of any of claims 1-36, wherein only the amino acid residues that differ between the first antibody and related antibody in the target region are modified by amino acid replacement.

38. The method of any of claims 1-36, wherein only the amino acid residues that are the same between the first antibody and the related antibody in the target region are modified by amino acid replacement.

39. The method of any of claims 1-35, wherein all of the amino acids residues in the target region are modified by amino acid replacement.

40. The method of any of claims 1-39, wherein each amino acid residue that is modified in the target region is modified to all 19 other amino acid residues, or a restricted subset thereof.

41. The method of any of claims 2-40, wherein the plurality of nucleic acid molecules are generated by a method selected from among PCR mutagenesis, cassette mutagenesis, site-directed mutagenesis, random point mutagenesis, mutagenesis using uracil containing templates, oligonucleotide-directed mutagenesis, phosphorothioate-modified DNA mutagenesis, mutagenesis using gapped duplex DNA, point mismatch repair, mutagenesis using repair-deficient host strains, restriction-selection and restriction-purification, deletion mutagenesis, mutagenesis by total gene synthesis, and double-strand break repair.

42. The method of any of claims 2-40, wherein the plurality of nucleic acid molecules are generated by a method selected from among NNK, NNS, NNN, NNY or NNR mutagenesis.

43. The method of any of claims 1-42, further comprising before step d),

g) performing scanning mutagenesis of the first antibody comprising producing a plurality of modified antibodies comprising a variable heavy chain and a variable light chain, or a portion thereof, wherein at least one of the variable heavy chain or variable light chain is one that is modified by replacement of a single amino acid residue with a scanned amino acid residue in the target region, whereby each of the plurality of antibodies contains replacement of an amino acid in the target region compared to the first antibody;

h) screening each of the plurality of modified antibodies for an activity to the target antigen; and

i) selecting a second antibody from among the modified antibodies that exhibits retained or increased activity for the target antigen compared to the first antibody not containing the amino acid replacement, whereby the second antibody is used in place of the first antibody in step b).

44. The method of claim 43, wherein the plurality of modified antibodies in step g) are produced by producing a plurality of nucleic acid molecules that encode modified forms of a variable heavy chain or a variable light chain of the first antibody containing the target region, wherein the nucleic acid molecules contain one codon that encodes a scanned amino acid in the target region compared to the corresponding codon of the unmodified variable heavy or variable light chain that does not encode the scanned amino acid, whereby each nucleic acid molecule of the plurality encodes a variable heavy chain or variable light chain that is modified by replacement of a single amino acid residue to the same scanned amino acid residue in the target region.

45. The method of any of claims 43-44, wherein a second antibody is selected that exhibits an activity that is at least 75% or more of the activity of the corresponding form of the first antibody; is at least 75% to 200% of the activity of the corresponding form of the first antibody; or is at least or about 75%, 80%, 85%, 90%, 95%, 100%, 105%, 110%, 115%, 120%, 130%, 140%, 150%, 200% or more of the activity of the corresponding form of the first antibody.

46. The method of any of claims 43-45, further comprising after step i) determining the amino acid residue position that is modified in the second antibody to contain a neutral amino acid compared to the first antibody not containing the amino acid replacement.

47. The method of any of claims 43-46, wherein the scanned amino acid is selected from among alanine, threonine, proline and glycine.

48. The method of claim 47, wherein the amino acid is alanine.

49. The method of any of claims 43-46, wherein the scanned amino acid is a non-natural amino acid.

50. The method of any of claims 43-49, wherein a subset of the amino acid residues in the target region are modified by amino acid replacement to a scanned amino acid.

51. The method of any of claims 44-50, wherein only the amino acid residues that differ between the first antibody and related antibody in the target region are modified by amino acid replacement to a scanned amino acid.

52. The method of any of claims 44-51, wherein only the amino acid residues that are the same between the first antibody and the related antibody in the target region are modified by amino acid replacement to a scanned amino acid.

53. The method of any of claims 44-52, wherein all of the amino acids in the target region are modified by amino acid replacement to a scanned amino acid.

54. The method of any of claims 1-53, wherein the selected modified antibody exhibits 2-fold, 5-fold, 10-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold, 600-fold, 700-fold, 800-fold, 900-fold, 1000-fold, 2000-fold, 3000-fold, 4000-fold, 5000-fold, 10000-fold or more improved activity for the target antigen compared to the first antibody.

55. The method of any of claims 1-54, wherein the modified antibody exhibits a binding affinity that is greater than the binding affinity of the first antibody and is 1×10^{-9} M or less; 1×10^{-9} M to 1×10^{-11} M; or is or is about 1×10^{-9} M, 2×10^{-9} M, 3×10^{-9} M, 4×10^{-9} M, 5×10^{-9} M, 6×10^{-9} M, 7×10^{-9} M, 8×10^{-9} M, 9×10^{-9} M, 1×10^{-10} M, 2×10^{-10} M, 3×10^{-10} M, 4×10^{-10} M, 5×10^{-10} M, 6×10^{-10} M, 7×10^{-10} M, 8×10^{-10} M, 9×10^{-10} M or less.

56. The method of any of claims 1-55, further comprising determining the amino acid modifications that are altered in the modified antibody compared to the first antibody not containing the amino acid replacements.

57. The method of any of claims 1-56 that is repeated iteratively, wherein a modified antibody identified in step g) is selected and used in step a) as the first antibody for subsequent affinity maturation thereof.

58. The method of any of claims 1-57, wherein one or more amino acid replacements in the target region of one or more variable heavy chains or one or more variable light chains of selected modified antibodies are combined to generate a further modified antibody, whereby the further modified antibodies are screened for an activity to the target antigen to identify a further modified antibody that exhibits an increased activity for the target antigen compared to the first antibody and to the selected modified antibodies.

59. The method of any of claims 1-58, comprising:

performing steps a) - f) on the variable heavy chain of the first antibody and selecting first modified antibodies each containing an amino acid replacement in the target region;

performing steps a) - f) independently and separately on the variable light chain of the first antibody and selecting second modified antibodies each containing an amino acid replacement in the target region;

combining the variable heavy chain of a first modified antibody with the variable light chain of a second modified antibody to generate a plurality of different third modified

antibodies each comprising an amino acid replacement in the target region of the variable heavy chain and variable light chain; and

screening each of the plurality of third modified antibodies for binding to the target antigen; and

selecting those third modified antibodies that exhibit an increased activity for the target antigen compared to the first and second modified antibodies.

60. The method of any of claims 1-59, further comprising after selecting a first modified antibody in step f):

j) selecting another different region within the variable heavy chain or variable light chain of the first modified antibody for further mutagenesis;

k) producing a plurality of nucleic acid molecules that encode modified forms of the variable heavy chain or variable light chain of the first modified antibody, wherein the nucleic acid molecules contain one codon encoding an amino acid in the selected region that encodes a different amino acid from the first modified variable heavy or variable light chain, whereby each nucleic acid molecule of the plurality encodes a variable heavy chain or variable light chain that is modified in the selected region by replacement of a single amino acid residue;

l) producing a plurality of further modified antibodies each comprising a variable heavy chain and a variable light chain, or a portion thereof, wherein at least one of the variable heavy chain or variable light chain is one produced in step k), whereby the selected region in each of the plurality of antibodies contains replacement of an amino acid to a different amino acid compared to the first modified antibody;

m) screening each of the plurality of further modified antibodies for binding to the target antigen; and

n) selecting those further modified antibodies that exhibit increased activity for the target antigen compared to the first modified antibody.

61. The method of claim 60, wherein the different region is selected from among a CDR1, CDR2, CDR3, FR1, FR2, FR3 and FR4.

62. The method of any of claims 1-61, wherein the antibody comprising a variable heavy chain and a variable light chain, or a portion thereof, is selected from among a Fab, Fab', $F(ab')_2$, single-chain Fv (scFv), Fv, dsFv, diabody, Fd and Fd' fragment, Fab fragment, Fd fragments scFv fragment, and scFab fragment.

63. A method of affinity maturation of an antibody or portion thereof for a target antigen, comprising:

a) performing scanning mutagenesis of a first antibody comprising producing a plurality of nucleic acid molecules that encode modified forms of a variable heavy chain or a

variable light chain of a first antibody, wherein the nucleic acid molecules contain one codon that encodes another amino acid compared to the corresponding codon of the unmodified variable heavy or variable light chain that does not encode the other amino acid, whereby each nucleic acid molecule of the plurality encodes a variable heavy chain or variable light chain that is modified by replacement of a single amino acid residue to another amino acid such that every position across the full-length of the encoded variable heavy or light chain is replaced or every position in a selected region of the encoded variable heavy or variable light chain is replaced, whereby each replacement is to the same amino acid residue;

b) producing a plurality of modified antibodies each comprising a variable heavy chain and a variable light chain, or a portion thereof, wherein at least one of the variable heavy chain or variable light chain is one produced in step a), whereby each of the plurality of antibodies contains replacement of an amino acid position with another amino acid compared to the first antibody;

c) screening each of the plurality of modified antibodies for an activity to the target antigen;

d) selecting a second antibody from among the modified antibodies that exhibits retained or increased activity for the target antigen compared to the first antibody not containing the amino acid replacement;

e) performing further mutagenesis of the second antibody comprising producing a plurality of nucleic acid molecules that encode modified forms of a variable heavy chain or a variable light chain of the second antibody, wherein the nucleic acid molecules contain one codon encoding an amino acid at the scanned amino acid position that encodes a different amino acid than the scanned amino acid in the second antibody, whereby each nucleic acid molecule of the plurality encodes a variable heavy chain or variable light chain that is modified at the scanned amino acid position by a single amino acid residue; and

f) producing a plurality of further modified antibodies each comprising a variable heavy chain and a variable light chain, or a portion thereof, wherein at least one of the variable heavy chain or variable light chain is one produced in step e), whereby the scanned amino acid position contains replacement to a different amino acid compared to the second antibody;

g) screening each of the plurality of further modified antibodies for an activity to the target antigen; and

h) selecting a third antibody that exhibits increased activity for the target antigen compared to the first antibody or compared to the second antibody.

64. The method of claim 63, wherein in step a) every position in a region of the encoded variable heavy or variable light chain is replaced.

65. The method of claim 64, wherein the selected region is a complementary determining region in the variable heavy chain or variable light chain selected from among a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3.

66. The method of any of claims 63-65, wherein a second antibody is selected that exhibits an activity that is at least 75% or more of the activity of the corresponding form of the first antibody; is 75% to 200% of the activity of the corresponding form of the first antibody; or is at least or about 75%, 80%, 85%, 90%, 95%, 100%, 105%, 110%, 115%, 120%, 130%, 140%, 150%, 200% or more of the activity of the corresponding form of the first antibody.

67. The method of any of claims 63-66, further comprising after step d) determining the amino acid residue position that is modified in the second antibody to contain a scanned amino acid compared to the first antibody not containing the amino acid replacement.

68. The method of any of claims 63-67, wherein the other amino acid is selected from among alanine, threonine, proline and glycine.

69. The method of claim 68, wherein the amino acid is alanine.

70. The method of any of claims 63-67, wherein the other amino acid is a non-natural amino acid.

71. The method of any of claims 63-70, where each of the plurality of nucleic acid molecules encodes a variable heavy chain or variable light chain that is modified by replacement of a single amino acid residue to the same scanned amino acid.

72. The method of any of claims 63-71, wherein:

in step e) the scanned amino acid position is modified by amino acid replacement to all other amino acid residues, or to a restricted subset thereof.

73. The method of claim 72, wherein the modification does not include amino acid replacement to the scanned amino acid or to the original amino acid at that position in the first antibody.

74. The method of any of claims 63-73, wherein the plurality of nucleic acid molecules produced in step e) are generated by a method selected from among PCR mutagenesis, cassette mutagenesis, site-directed mutagenesis, random point mutagenesis, mutagenesis using uracil containing templates, oligonucleotide-directed mutagenesis, phosphorothioate-modified DNA mutagenesis, mutagenesis using gapped duplex DNA, point mismatch repair, mutagenesis using repair-deficient host strains, restriction-selection and

restriction-purification, deletion mutagenesis, mutagenesis by total gene synthesis, and double-strand break repair.

75. The method of any of claims 63-73, wherein the plurality of nucleic acid molecules produced in step e) are generated by a method selected from among NNK, NNS, NNN, NNY or NNR mutagenesis.

76. The method of any of claims 63-75, wherein an activity is selected from among binding, signal transduction, differentiation, alteration of gene expression, cellular proliferation, apoptosis, chemotaxis, cytotoxicity, cancer cell invasion, endothelial cell proliferation and tube formation.

77. The method of claim 76, wherein the activity is binding and binding is assessed by a method selected from among an immunoassay, whole cell panning and surface plasmon resonance (SPR).

78. The method of claim 77, wherein the immunoassay is selected from among a radioimmunoassay, enzyme linked immunosorbent assay (ELISA) and electrochemiluminescence assay.

79. The method of claim 78, wherein the electrochemiluminescence assay is meso scale discovery (MSD).

80. The method of any of claims 63-79, wherein the target antigen is a polypeptide, carbohydrate, lipid, nucleic acid or a small molecule.

81. The method of any of claims 63-80, wherein the target antigen is expressed on the surface of a virus, bacteria, tumor or other cell, or is a recombinant protein or peptide.

82. The method of any of claims 63-81, wherein the target antigen is a protein that is a target for therapeutic intervention.

83. The method of any of claims 63-82, wherein the target antigen is involved in cell proliferation and differentiation, cell migration, apoptosis or angiogenesis.

84. The method of any of claims 63-83, wherein the target antigen is selected from among a VEGFR-1, VEGFR-2, VEGFR-3 (vascular endothelial growth factor receptors 1, 2, and 3), a epidermal growth factor receptor (EGFR), ErbB-2, ErbB-3, IGF-R1, C-Met (also known as hepatocyte growth factor receptor; HGFR), DLL4, DDR1 (discoidin domain receptor), KIT (receptor for c-kit), FGFR1, FGFR2, FGFR4 (fibroblast growth factor receptors 1, 2, and 4), RON (recepteur d'origine nantais; also known as macrophage stimulating 1 receptor), TEK (endothelial-specific receptor tyrosine kinase), TIE (tyrosine kinase with immunoglobulin and epidermal growth factor homology domains receptor), CSF1R (colony stimulating factor 1 receptor), PDGFRB (platelet-derived growth factor receptor B), EPHA1, EPHA2, EPHB1 (erythropoietin-producing hepatocellular receptor A1,

A2 and B1), TNF-R1, TNF-R2, HVEM, LT-βR, CD20, CD3, CD25, NOTCH, G-CSF-R, GM-CSF-R, EPO-R., a cadherin, an integrin, CD52, CD44, VEGF-A, VEGF-B, VEGF-C, VEGF-D, PIGF, EGF, HGF, TNF-α, LIGHT, BTLA, lymphotoxin (LT), IgE, G-CSF, GM-CSF and EPO.

85. The method of any of claims 63-84, wherein the first antibody binds to the target antigen with a binding affinity when the antibody is in a Fab form that is 10^{-4} M or lower; 10^{-4} M to 10^{-8} M; or that is at or about 10^{-4} M, 10^{-5} M, 10^{-6} M, 10^{-7} M, 10^{-8} M, or lower.

86. The method of any of claims 63-85, wherein scanning mutagenesis is performed within the variable heavy chain of the first antibody, and steps a) – h) are performed therefrom.

87. The method of any of claims 63-86, wherein scanning mutagenesis is performed within the variable light chain of the first antibody, and steps a) - h) are performed therefrom.

88. The method of any of claims 63-87, wherein:

scanning mutagenesis is performed within the variable heavy chain of the first antibody and steps a) - h) are performed therefrom; and

separately and independently scanning mutagenesis is performed within the variable light chain of the first antibody, and steps a) - h) are performed therefrom.

89. The method of any of claims 63-88, wherein the third antibody exhibits at least 2-fold improved activity for the target antigen compared to the first antibody or the second antibody; 2-fold to 10000-fold or 2-fold to 1000-fold improved activity for the target antigen compared to the first antibody or the second antibody; or at least 2-fold, 5-fold, 10-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold, 600-fold, 700-fold, 800-fold, 900-fold, 1000-fold, 2000-fold, 3000-fold, 4000-fold, 5000-fold, 10000-fold or more improved activity for the target antigen compared to the first antibody or the second antibody.

90. The method of any of claims 63-89, wherein the third antibody exhibits a binding affinity that is greater than the binding affinity of the first antibody and is 1×10^{-9} M or less; is 1×10^{-9} M to 1×10^{-11} M; or is or is about 1×10^{-9} M, 2×10^{-9} M, 3×10^{-9} M, 4×10^{-9} M, 5×10^{-9} M, 6×10^{-9} M, 7×10^{-9} M, 8×10^{-9} M, 9×10^{-9} M, 1×10^{-10} M, 2×10^{-10} M, 3×10^{-10} M, 4×10^{-10} M, 5×10^{-10} M, 6×10^{-10} M, 7×10^{-10} M, 8×10^{-10} M, 9×10^{-10} M or less.

91. The method of any of claims 63-90, further comprising determining the amino acid modifications that are altered in the third antibody compared to the first antibody not containing the amino acid replacements.

92. The method of any of claims 63-91 that is repeated iteratively, wherein the third antibody identified in step h) is selected and used in step a) as the first antibody for subsequent maturation thereof, whereby the amino acid residue that is modified is not further modified in subsequent iterations of the method.

93. The method of any of claims 63-92, wherein one or more amino acid replacement in one or more variable heavy chains or one or more variable light chains of selected third antibodies are combined to generate a further modified antibody, whereby the further modified antibodies are screened for an activity to the target antigen to identify a further modified antibody that exhibits an increased activity for the target antigen compared to the first antibody, second antibody and to the selected third antibodies.

94. The method of any of claims 63-93, comprising:

performing steps a) - h) on the variable heavy chain of the first antibody and selecting third antibodies each containing an amino acid replacement in the variable heavy chain compared to the corresponding variable heavy chain of the first antibody;

performing steps a) - h) independently and separately on the variable light chain of the first antibody and selecting different third modified antibodies each containing an amino replacement in the variable light chain compared to the corresponding variable light chain of the first antibody;

combining the variable heavy chain of a third antibody with the variable light chain of a different third antibody to generate a plurality of different further modified antibodies each comprising an amino acid replacement of the variable heavy chain and variable light chain compared to the corresponding variable heavy chain and variable light chain of the first antibody;

screening each of the plurality of further modified antibodies for binding to the target antigen; and

selecting those fourth antibodies that exhibit an increased activity for the target antigen compared to the first antibody, second antibody, and third antibodies.

95. The method of any of claims 63-94, further comprising after selecting a third antibody in step h)

i) selecting another different region within the variable heavy chain or variable light chain of the third antibody for further mutagenesis;

j) producing a plurality of nucleic acid molecules that encode modified forms of the variable heavy chain or variable light chain of the third antibody, wherein the nucleic acids molecules contain one codon encoding an amino acid in the selected region that encodes a different amino acid from the first modified variable heavy or variable light chain, whereby

each nucleic acid molecule of the plurality encodes a variable heavy chain or variable light chain that is modified in the selected region by replacement of a single amino acid residue;

k) producing a plurality of further modified antibodies each comprising a variable heavy chain and a variable light chain, or a portion thereof, wherein at least one of the variable heavy chain or variable light chain is one produced in step j), whereby the selected region in each of the plurality of antibodies contains replacement of an amino acid to a different amino acid compared to the third antibody;

l) screening each of the plurality of further modified antibodies for binding to the target antigen; and

m) selecting those further modified antibodies that exhibit increased activity for the target antigen compared to the third antibody.

96. The method of claim 95, wherein the different region is selected from among a CDR1, CDR2, CDR3, FR1, FR2, FR3 and FR4.

97. The method of any of claims 63-96, wherein the antibody comprising a variable heavy chain and a variable light chain, or a portion thereof, is selected from among a Fab, Fab', $F(ab')_2$, single-chain Fv (scFv), Fv, dsFv, diabody, Fd and Fd' fragment, Fab fragment, Fd fragment, scFv fragment, and scFab fragment.

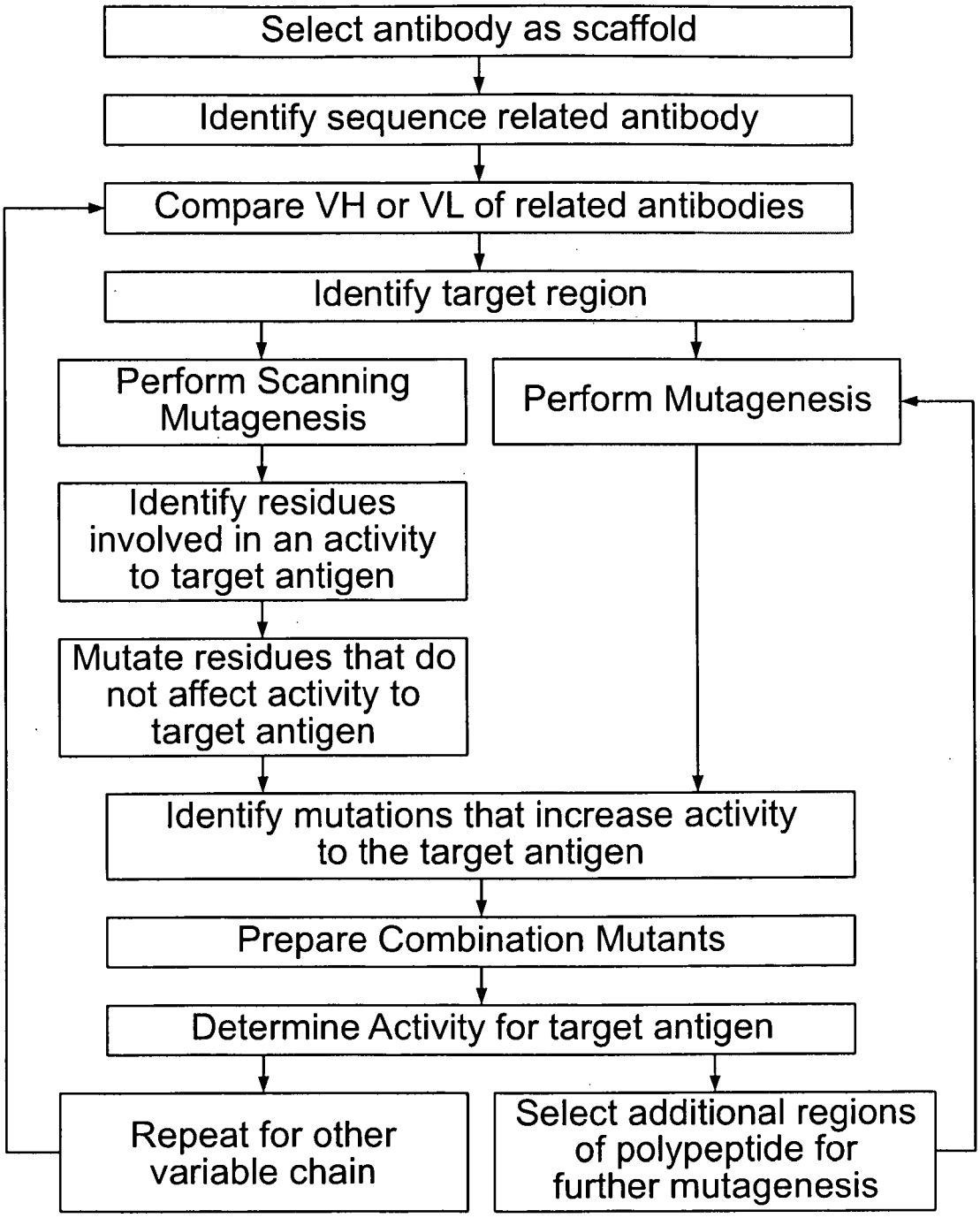
Select antibody as scaffold
Identify sequence related antibody
Compare VH or VL of related antibodies
Identify target region
Perform Scanning Mutagenesis
Perform Mutagenesis
Identify residues involved in an activity to target antigen
Mutate residues that do not affect activity to target antigen
Identify mutations that increase activity to the target antigen
Prepare Combination Mutants
Determine Activity for target antigen
Repeat for other variable chain
Select additional regions of polypeptide for further mutagenesis

FIG. 1

```
                                                              CDRH1                   CDRH2
VH1-46_IGHD6-6*01_IGHJ1*01   QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSY 60
VH1-46_IGHD6-13*01_IGHJ4*01  QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSY 60
                             ************************************************************
                                                                        CDRH3
VH1-46_IGHD6-6*01_IGHJ1*01   AQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAREEYSSSSAEYFQHWGQGTLVTV 120
VH1-46_IGHD6-13*01_IGHJ4*01  AQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAREGYSSSWYDYFDYWGQGTLVTV 120
                             *************************************** ****  :**:.:*********
VH1-46_IGHD6-6*01_IGHJ1*01   SS 122
VH1-46_IGHD6-13*01_IGHJ4*01  SS 122
                             **
```

FIG. 2A

```
                                         CDRL1                      CDRL2
L6_IGKJ1*01     EIVLTQSPATLSLSPGERATLSCRASQSVSSY-LAWYQQKPGQAPRLLIYDASNRATGIP 59
A27_IGKJ1*01    EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIP 60
L25_IGKJ1*01    EIVMTQSPATLSLSPGERATLSCRASQSVSSSYLSWYQQKPGQAPRLLIYGASTRATGIP 60
L2_IGKJ1*01     EIVMTQSPATLSVSPGERATLSCRASQSVSSN-LAWYQQKPGQAPRLLIYGASTRATGIP 59
                ***:****.***:*****************  *:**************.**.******
                                                     CDRL3
L6_IGKJ1*01     ARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPWTFGQGTKVEIK 108
A27_IGKJ1*01    DRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKVEIK 109
L25_IGKJ1*01    ARFSGSGSGTDFTLTISSLQPEDFAVYYCQQDYNLPPWTFGQGTKVEIK 109
L2_IGKJ1*01     ARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYNNWPPWTFGQGTKVEIK 108
                 *********:****** *: **********    **************
```

FIG. 2B

```
                                    CDRH1                                   CDRH2
VH5-51_IGHD5-18*01>3_IGHJ4*01  EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIYPGDSDTRY  60
VH5-51_IGHD6-25*01_IGHJ4*01    EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIYPGDSDTRY  60
                               ************************************************************

                                                                CDRH3
VH5-51_IGHD5-18*01>3_IGHJ4*01  SPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARRGYSYGYDYFDYWGQGTLVTVS  120
VH5-51_IGHD6-25*01_IGHJ4*01    SPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARQGYSSGYDYFDYWGQGTLVTVS  120
                               ********************************.*** **********************

VH5-51_IGHD5-18*01>3_IGHJ4*01  S 121
VH5-51_IGHD6-25*01_IGHJ4*01    S 121
                               *
```

FIG. 3

```
VH1-46_IGHD6-6*01_IGHJ1*01   QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSY 60
VH1-46_IGHD6-6*01_IGHJ2*01   QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSY 60
VH1-46_IGHD6-6*01_IGHJ4*01   QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSY 60
VH1-46_IGHD6-6*01_IGHJ5*01   QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSY 60
                             ************************************************************
                                                                 CDRH3
VH1-46_IGHD6-6*01_IGHJ1*01   AQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAREEYSSSSAEYFQHWGQGTLVTV 120
VH1-46_IGHD6-6*01_IGHJ2*01   AQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAREEYSSSSYWYFDLWGRGTLVTV 120
VH1-46_IGHD6-6*01_IGHJ4*01   AQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAREEYSSSSD-YFDYWGQGTLVTV 119
VH1-46_IGHD6-6*01_IGHJ5*01   AQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAREEYSSSSDNYFDYWGQGTLVTV 120
                             *********************************************  **: **:******

VH1-46_IGHD6-6*01_IGHJ1*01   SS 122
VH1-46_IGHD6-6*01_IGHJ2*01   SS 122
VH1-46_IGHD6-6*01_IGHJ4*01   SS 121
VH1-46_IGHD6-6*01_IGHJ5*01   SS 122
                             **
```

FIG. 4A

```
VH5-51_IGHD5-18*01>3_IGHJ1*01   EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIYPGDSDTRY 60
VH5-51_IGHD5-18*01>3_IGHJ3*01   EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIYPGDSDTRY 60
VH5-51_IGHD5-18*01>3_IGHJ4*01   EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIYPGDSDTRY 60
VH5-51_IGHD5-18*01>3_IGHJ5*01   EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIYPGDSDTRY 60
                                ************************************************************
                                                                    CDRH3
VH5-51_IGHD5-18*01>3_IGHJ1*01   SPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARRGYSYGYAEYFQHWGQGTLVTV 120
VH5-51_IGHD5-18*01>3_IGHJ3*01   SPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARRGYSYGYD-AFDVWGQGTLVTV 119
VH5-51_IGHD5-18*01>3_IGHJ4*01   SPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARRGYSYGYD-YFDYWGQGTLVTV 119
VH5-51_IGHD5-18*01>3_IGHJ5*01   SPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARRGYSYGYDNWFDSWGQGTLVTV 120
                                *********************************************   *: *********

VH5-51_IGHD5-18*01>3_IGHJ1*01   SS 122
VH5-51_IGHD5-18*01>3_IGHJ3*01   SS 121
VH5-51_IGHD5-18*01>3_IGHJ4*01   SS 121
VH5-51_IGHD5-18*01>3_IGHJ5*01   SS 122
                                **
```

FIG. 4B

```
VH5-51_IGHD5-18*01>3_IGHJ4*01  EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIYPGDSDTRY 60
VH5-51_IGHD5-12*01_IGHJ4*01    EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIYPGDSDTRY 60
VH5-51_IGHD5-24*01_IGHJ4*01    EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIYPGDSDTRY 60
                               ************************************************************

                                                                CDRH3
VH5-51_IGHD5-18*01>3_IGHJ4*01  SPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARRGYS-YGYDYFDYWGQGTLVTV 119
VH5-51_IGHD5-12*01_IGHJ4*01    SPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARRGYSGYDYFDYWGQGTLVTV 120
VH5-51_IGHD5-24*01_IGHJ4*01    SPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARRRDG-YNYDYFDYWGQGTLVTV 119
                               ************************************   * ********************

VH5-51_IGHD5-18*01>3_IGHJ4*01  SS 121
VH5-51_IGHD5-12*01_IGHJ4*01    SS 122
VH5-51_IGHD5-24*01_IGHJ4*01    SS 121
                               **
```

FIG. 4C

```
                                                CDRH1                                                CDRH2
VH3-23_IGHD2-2*01>3_IGHJ6*01     EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSISGSGGSTYY  60
VH3-23_IGHD2-8*01>3_IGHJ6*01     EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSISGSGGSTYY  60
VH3-23_IGHD2-15*01>3_IGHJ6*01    EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSISGSGGSTYY  60
VH3-23_IGHD2-21*01>3_IGHJ6*01    EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSISGSGGSTYY  60
                                 ************************************************************

                                                                CDRH3
VH3-23_IGHD2-2*01>3_IGHJ6*01     ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKEDIVVPAAMSYYYYYYGMDVW  120
VH3-23_IGHD2-8*01>3_IGHJ6*01     ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKEDIVLMVYAISYYYYYYGMDVW  120
VH3-23_IGHD2-15*01>3_IGHJ6*01    ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKEDIVVVVAATSYYYYYYGMDVW  120
VH3-23_IGHD2-21*01>3_IGHJ6*01    ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKEHIVV-IAISYYYYYYGMDVW  119
                                 ************************************.**::  * ************

VH3-23_IGHD2-2*01>3_IGHJ6*01     GQGTLVTVSSAS  132
VH3-23_IGHD2-8*01>3_IGHJ6*01     GQGTLVTVSSAS  132
VH3-23_IGHD2-15*01>3_IGHJ6*01    GQGTLVTVSSAS  132
VH3-23_IGHD2-21*01>3_IGHJ6*01    GQGTLVTVSSAS  131
                                 ************
```

FIG. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/055489

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/00 C07K16/28

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, SCISEARCH, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2010/054007 A1 (FABRUS LLC [US]; SMIDER VAUGHN [US]; GRAZIANO JAMES [US]; MAO HELEN HO) 14 May 2010 (2010-05-14) pages 402,427; tables 64-77	1-97
X,P	MAO HONGYUAN ET AL: "Spatially addressed combinatorial protein libraries for recombinant antibody discovery and optimization" NATURE BIOTECHNOLOGY, vol. 28, no. 11, November 2010 (2010-11), pages 1195-1202+2PP, XP002617400 ISSN: 1087-0156 DOI: 10.1038/nbt.1694 the whole document	1-97

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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 document 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
19 January 2011	09/02/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Domingues, Helena

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/055489

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HOOGENBOOM H R: "Selecting and screening recombinant antibody libraries" NATURE BIOTECHNOLOGY, vol. 23, no. 9, 1 September 2005 (2005-09-01), pages 1105-1116, XP002348401 NATUREPUBLISHING GROUP, NEW YORK, NY, US ISSN: 1087-0156 DOI: 10.1038/NBT1126 the whole document	1-97
Y	RAJPAL A ET AL: "A general method for greatly improving the affinity of antibodies by using combinatorial libraries" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES (PNAS), vol. 102, no. 24, 1 June 2005 (2005-06-01), pages 8466-8471, XP002347095 ISSN: 0027-8424 DOI: 10.1073/PNAS.0503543102 the whole document	1-97
Y	SCHIER R ET AL: "Isolation of picomolar affinity anti-c-erbB-2 single-chain Fv by molecular evolution of the complementary determining regions in the center of the antibody binding site" JOURNAL OF MOLECULAR BIOLOGY, vol. 263, no. 4, 8 November 1996 (1996-11-08), pages 551-567, XP002573971 LONDON, GB ISSN: 0022-2836 the whole document	1-97
A	HOEY T ET AL: "DLL4 Blockade Inhibits Tumor Growth and Reduces Tumor-Initiating Cell Frequency" CELL STEM CELL, vol. 5, no. 2, 7 August 2009 (2009-08-07), pages 168-177, XP002564818 CELL PRESS, US ISSN: 1934-5909 DOI: 10.1016/J.STEM.2009.05.019 [retrieved on 2009-08-06] the whole document	1-97

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/055489

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010054007 A1	14-05-2010	WO 2010054010 A1	14-05-2010