

ANTI-P95HER2 ANTIBODIES AND METHODS FOR THEIR USE**FIELD OF THE INVENTION**

[0001] The present invention relates to novel anti-p95HER2 antibodies (as monoclonal antibodies or as used in other formats, such as bispecific or multi-specific formats) and compositions comprising such antibodies or cells activated by such antibodies for use in treating disorders associated with HER2, including p95HER2, such as human cancer therapy.

INCORPORATION BY REFERENCE OF A SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML file, created on April 17, 2024, is named ADAN-002-01WO.xml and is 692 KB in size.

BACKGROUND OF THE INVENTION

[0003] The epidermal growth factor receptor (EGFR) family (also known as the ErbB family) is a subgroup of the receptor tyrosine kinases (RTKs), which includes four members: EGFR/ErbB, HER2/ErbB2, HER3/ErbB3 and HER4/ErbB4. The ErbB family of receptors regulate, among other functions, control over events leading to cell growth, differentiation and migration. EGFR, HER2 and HER3 have been linked to development of cancer in normal cells and in the continued growth and/or metastatic spread of cancer cells. For example, both EGFR and HER2 are overexpressed by many epithelial cancers, and associated with disease progression, poor prognoses and poor drug response, as well as chemotherapy resistance in many epithelial cancers; FDA-approved therapeutics that are functional antagonists of these molecules have had significant success in mitigating EGFR- and HER2-driven disease.

[0004] Human epidermal growth factor receptor 2 (HER2, also known as ErbB2 or Neu; UniProtKB/Swiss-Prot No. P04626) has 1233 amino acids and is structurally similar to EGFR with an extracellular domain consisting of four subdomains I-IV, a transmembrane domain, a juxta-membrane domain, an intracellular cytoplasmic tyrosine kinase and a regulatory C-terminal domain (Yamamoto et al. (1986) *Nature* 319: 230-234).

[0005] HER2 has no known ligands, but is activated via formation of heteromeric complexes with other ErbB family members and thereby indirectly regulated by EGFR and HER3 ligands. HER2

is a heterodimerization partner of the three other EGFR receptors, enhancing the affinity of the other EGFR receptors for their ligands by slowing the rate of ligand-receptor complex dissociation. Thus, for example, HER2 enhances and prolongs signaling of the associated EGFR chain. Heterodimerization of HER2 and another ligand-bound receptor of the EGFR family induces cross-phosphorylation of the C-terminal amino acids that act as scaffolds for certain signaling molecules.

[0006] The HER2-HER3 complex is the most active among the various heterodimers, and HER2 also complements the kinase-deficient HER3 by providing an active kinase. Unlike some other EGFR family members, HER2 resists internalization and thus escapes lysosomal degradation such that it remains at the cellular membrane.

[0007] HER2 in normal tissues modulates signaling that is initiated through ligand-bound ErbB receptor. Like EGFR, HER2 is generally expressed in epithelial cells where it has a non-oncogenic role in regulating growth, differentiation, apoptosis and remodeling in normal mammary gland development.

[0008] Like EGFR, excess HER2 on the cell surface causes transformation of epithelial cells from multiple tissues. HER2 overexpression is linked with a range of human tumors, including 20-30% of invasive ductal carcinomas, and is a known predictor of poor survival in breast cancer patients.

[0009] In certain cancers, a heterogeneous group of truncated HER2 fragments, collectively known in the literature as p95HER2, can be detected. One of these fragments, the c-terminal fragment of HER2 with an N-terminus arising from methionine 611 of the full-length sequence of p185HER2 (p95-CTF611-HER2) has been discovered to be highly oncogenic due to the ability of the isoform to form stable homodimers that are constitutive kinases due to an unpaired cysteine residue that results in intermolecular disulfide bonding of the two monomers resulting in a forced active dimer. Hereafter, unless otherwise specified the term p95HER2 will refer to the isoform p95-CTF611-HER2. Given its oncogenic nature, unsurprisingly, p95HER2 is expressed in a subgroup of HER2-positive breast cancers.

BRIEF SUMMARY OF THE INVENTION

[0010] Unfortunately, p95-CTF611-HER2 isoform of HER2 is not recognized by most conventional treatments for HER2-overexpressing cancers, such as trastuzumab, pertuzumab, enhertu, and trastuzumab-DM-1, because the p95HER2 fragments lack the epitopes recognized by

these approved antibody-based current therapies. Thus, there is serious unmet medical need to address the oncogenic properties of p95-CTF611-HER2 in the broader population of HER2-driven diseases which include but are not limited to breast cancer.

[0011] The present invention is directed to novel peptides (e.g., antibodies and antibody fragments) that bind to p95HER2 (i.e., p95-CTF611-HER2, unless otherwise specified). The present invention also includes compositions comprising one or more of these peptides/antibodies, or fragments thereof, and/or immune cells that are modified to include and/or be activated by one or more of these antibodies, or fragments thereof, to treat a disease or condition, such as breast cancer. Antibodies of the present invention may similarly find use in the treatment of other HER2 overexpressing cancers, such as certain forms of ovarian and gastric cancer.

[0012] The presently disclosed antibodies may underly treatments that are far more effective than current therapies for ameliorating HER2 overexpressing cancers, particularly in patients that express p95HER2. The presently disclosed p95HER2 antibodies of the invention may be included as part of a treatment regime, which may include, for example, providing two or more such antibodies and/or multi-specific antibodies.

[0013] The present invention further relates to novel anti-p95HER2 antibodies (as monoclonal antibodies or as used in other formats, such as bispecific or multi-specific formats) and compositions comprising such antibodies or cells activated by such antibodies for use in treating disorders associated with p95HER2, such as human cancer therapy. The present invention also includes compositions comprising one or more of these peptides/antibodies, or fragments thereof, and/or immune cells that are modified to include and/or be activated by one or more of these antibodies, or fragments thereof, to treat a disease or condition, such as cancer. Antibodies of the present invention may similarly find use as a targeting arm of a bispecific or multi-specific format.

[0014] In one aspect, the present invention provides an anti-p95HER2 antibody or antibody fragment comprising: a heavy chain CDR3 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 2-65 and 514, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 2-65 and 514; a heavy chain CDR2 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 258-321 and 518, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence

identity with any of SEQ ID NOS: 258-321 and 518; a heavy chain CDR1 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 130-193 and 516, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 130-193 and 516; a light chain CDR3 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 66-129 and 515, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 66-129 and 515; a light chain CDR2 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 322-385 and 519, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 322-385 and 519; and/or a light chain CDR1 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 194-257 and 517, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 194-257 and 517.

[0015] In one aspect, the present invention provides an anti-p95HER2 antibody or antibody fragment comprising one or more of:

a heavy chain CDR3 sequence (VH) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 514;

a heavy chain CDR2 sequence (VH) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 518;

a heavy chain CDR1 sequence (VH) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 516;

a light chain CDR3 sequence (VL) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 515;

a light chain CDR2 sequence (VL) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 519; and a light chain CDR1 sequence (VL) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 517.

[0016] In one aspect, the present invention provides an anti-p95HER2 antibody or antibody fragment comprising a VH chain comprising one or more of:

a heavy chain CDR3 sequence (VH) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 514;

a heavy chain CDR2 sequence (VH) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 518; and

a heavy chain CDR1 sequence (VH) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 516.

[0017] In certain aspects, the anti-p95HER2 antibody further comprises a VL chain comprising one or more of:

a light chain CDR3 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 66-129 and 515, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 66-129 and 515;

a light chain CDR2 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 322-385 and 519, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 322-385 and 519; and

a light chain CDR1 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 194-257 and 517, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 194-257 and 517.

[0018] In one aspect, the present invention provides an anti-p95HER2 antibody or antibody fragment comprising a VL chain comprising one or more of:

a light chain CDR3 sequence (VL) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 515;

a light chain CDR2 sequence (VL) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 519; and

a light chain CDR1 sequence (VL) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 517.

[0019] Additionally or alternatively, an anti-p95HER2 antibody or antibody fragment of the present invention may comprise a heavy chain variable region encoded by a nucleic acid sequence and/or a nucleic acid sequence having at least 85%, at least 90% at least 95.5%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 841. Additionally or alternatively, an anti-p95HER2 antibody or antibody fragment of the present invention may comprise a light chain variable region encoded by a nucleic acid sequence and/or a nucleic acid sequence having at least 85%, at least 90% at least 95.5%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 842.

[0020] In certain aspects, the such an anti-p95HER2 antibody further comprises a VL chain comprising one or more of:

a heavy chain CDR3 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 2-65 and 514, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 2-65 and 514;

a heavy chain CDR2 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 258-321 and 518, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 258-321 and 518; and

a heavy chain CDR1 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 130-193 and 516, and/or a sequence that comprises an amino acid sequence having at

least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 130-193 and 516.

[0021] In certain aspects, the present invention provides an anti-p95HER2 antibody or antibody fragment comprising a heavy chain CDR3 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 2-65 and 514, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 2-65 and 514. Additionally or alternatively, an anti-p95HER2 antibody or antibody fragment of the present invention may comprise a light chain CDR3 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 66-129 and 515, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 66-129 and 515.

[0022] Additionally or alternatively, the present invention provides an anti-p95HER2 antibody or antibody fragment comprising a heavy chain CDR3 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 2-65 and 514, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 2-65 and 514, and a light chain CDR3 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 66-129 and 515, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 66-129 and 515.

[0023] Another aspect of the invention relates to nucleic acid molecules comprising a nucleotide sequence that encodes an antibody, VL variable region sequence, VH variable region sequence, VL CDR3 sequence, VH CDR3 sequence, VL CDR2 sequence, VH CDR2 sequence, VL CDR1 sequence, and/or VH CDR1 sequence as set forth herein. In certain aspects, the invention comprises a nucleic acid encoding at least a portion of an anti-p95HER2 antibody of the invention. In certain aspects, the nucleic acid encodes at least the VH sequence. In certain aspects, the VH chain, or portion thereof, is encoded by a nucleic acid having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% similarity with SEQ ID NO: 841. In certain aspects, the VH chain, or portion thereof, is encoded by a nucleic acid comprising SEQ ID NO: 841. In certain aspects, the VL chain, or portion thereof, is encoded by a nucleic acid having at least 95%, at least

96%, at least 97%, at least 98% or at least 99% similarity with SEQ ID NO: 842. In certain aspects, the VL chain, or portion thereof, is encoded by a nucleic acid comprising SEQ ID NO: 842.

[0024] A further aspect of the invention relates to an expression vector comprising a nucleic acid molecule as defined above. As noted above, expression vectors for use in the context of the present invention may be of any suitable type known in the art, e.g., a plasmid or a viral vector. In certain aspects, said vector comprises a nucleic acid comprising at least 95.5%, at least 96%, at least 97%, at least 98% or at least 99% similarity with one or both of SEQ ID NOS: 841 and 842.

[0025] A still further aspect of the invention relates to a host cell comprising a nucleic acid molecule as defined above, wherein said host cell is capable of expressing an anti-p95HER2 antibody encoded by said nucleic acid molecule.

[0026] Additionally or alternatively, an anti-p95HER2 antibody or antibody fragment of the present invention may comprise a heavy chain variable region comprising an amino acid sequence selected from one of SEQ ID NOS: 386-449, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 386-449. Additionally or alternatively, an anti-p95HER2 antibody or antibody fragment of the present invention may comprise a light chain variable region comprising an amino acid sequence selected from one of SEQ ID NOS: 450-513, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 450-513.

[0027] Additionally or alternatively, an anti-p95HER2 antibody or antibody fragment of the present invention may comprise a heavy chain variable region comprising an amino acid sequence selected from one of SEQ ID NOS: 386-449, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 386-449 and a light chain variable region comprising an amino acid sequence selected from one of SEQ ID NOS: 450-513, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 450-513.

[0028] In certain aspects, the present invention provides methods for treating a disorder, such as cancer, using one or more antibodies of the invention as described above, by, at least administering such antibodies to a subject, such as a human subject.

[0029] In certain aspects, the anti-p95HER2 antibodies of the invention are, or form a part of, a multispecific antibody.

[0030] Multispecific antibodies are monoclonal antibodies that have binding specificities for at least two different sites. In some embodiments, bispecific antibodies may bind to two different epitopes of p95HER2. In some embodiments, one of the binding specificities is for p95HER2 and the other is for any other antigen (e.g., a second biological molecule, e.g., a cell surface antigen, e.g., a tumor antigen), such as CD3 or epitopes thereof (e.g., CD3 ϵ or CD3 γ).

[0031] Accordingly, a bispecific anti-p95HER2 antibody may have binding specificities for p95HER2 and a second biological molecule. For example, in preferred aspects, a bispecific antibody/therapy of the invention includes an anti-p95HER2 antibody attached (e.g., conjugated) to an immune cell recruiter. Exemplary immune cells include, for example, T cells, macrophages, Natural Killer cells, and the like. Thus, for example, a bispecific p95HER2 antibody of invention may include an anti-p95HER2 antibody or fragment and a CD3 antibody or fragment that activates and/or recruits a T cell to a cell expressing p95HER2.

[0032] In certain aspects, the present invention provides antibody conjugates (ADCs) and/or compositions comprising such ADCs, wherein said ADCs comprise an anti-p95HER2 antibody of the invention linked or conjugated to another therapeutic agent, such as an anti-cancer agent, or targeting/delivery moiety, via a chemical linkage or scaffold. The invention further provides ADCs comprising two or more different anti-p95HER2 antibodies or fragment thereof, wherein each different anti-p95HER2 antibody or fragment targets a different p95HER2 fragment or epitope.

[0033] A further aspect of the invention relates to a nucleic acid molecule having a nucleotide sequence that encodes an anti-p95HER2 antibody or fragment thereof, as disclosed herein, as well as expression vectors comprising such a polynucleotide and host cells that have been transfected with such an expression vector.

[0034] Aspects of the invention also provide methods for producing the anti-p95HER2 antibodies, fragments thereof, and compositions of the invention.

[0035] The present invention also provides methods for treating a disease in a human or animal subject, in particular treatment of cancer in humans, by administering an anti-

p95HER2 antibody or composition of the invention to said subject. The invention also includes the use of one or more anti-p95HER2 antibodies of the invention for preparation of a medicament for use in treating a disease in a human or animal, in particular for the treatment of cancer in humans.

[0036] In some embodiments, the antibodies herein are full length antibodies. In some embodiments, the antibodies are an IgA, an IgD, an IgE, an IgG, or an IgM antibody. In some embodiments, the anti-p95HER2 antibody is an IgG antibody (e.g., an IgG1, IgG2, or IgG3 antibody).

[0037] In some embodiments, the antibodies herein are an antibody fragment. In some embodiments, the antibodies are an Fv fragment, a Fab fragment, a F(ab')₂ fragment, a Fab' fragment, a Fab'-SH, an scFv (sFv) fragment, and an scFv-Fc fragment. In some embodiments, the bispecific antibody is an scFv fragment. In some embodiments, the antibodies herein are monoclonal, human, humanized, or chimeric. In some embodiments, the antibodies herein are comprised of antibodies, for instance, but not limited to, antibodies with additional binding domains such as an scFv, yielding multi-valent bispecific therapeutics with increased avidity toward binding targets.

[0038] In some embodiments, the antibodies further comprise an Fc region. In some embodiments, the antibodies comprise one or more heavy chain constant domains, wherein the one or more heavy chain constant domains are selected from a first CH1 domain, a first CH2 domain, a first CH3 domain, a second CH1 domain, a second CH2 domain, and a second CH3 domain. In some embodiments, one or more heavy constant chain domains are paired with another heavy chain constant domain.

[0039] In some embodiments, a mutation in the Fc region reduces effector function, examples including but not limited to N297G or Leu234Ala/Leu235Ala.

DETAILED DESCRIPTION OF THE INVENTION

[0040] The present invention is directed to novel peptides (e.g., antibodies and antibody fragments) that bind to p95HER2 (i.e., p95-CTF611-HER2). The present invention also includes compositions comprising one or more of these peptides/antibodies, or fragments thereof, and/or immune cells that are modified to include and/or be activated by one or more of these antibodies, or fragments thereof, to treat a disease or condition, such as breast cancer. Antibodies of the present

invention may similarly find use in the treatment of other HER2 overexpressing cancers, such as certain forms of ovarian and gastric cancer.

[0041] The presently disclosed antibodies may underly treatments that are far more effective than current therapies for ameliorating HER2 overexpressing cancers, particularly in patients that express p95HER2 fragments. The presently disclosed p95HER2 antibodies of the invention may be included as part of a treatment regime, which may include, for example, providing two or more such antibodies, and/or in combination with other treatments such as chemotherapy.

[0042] The present invention is directed to novel peptides (e.g., antibodies and antibody fragments) that bind to one or more p95HER2 epitopes and/or fragments. The present invention also includes compositions comprising one or more of these peptides/antibodies, or fragments thereof, and/or immune cells that are modified to include and/or be activated by one or more of these antibodies, or fragments thereof, to treat a disease or condition, such as cancer.

[0043] The presently disclosed antibodies may provide treatments that are far more effective than current therapies than present anti-HER2 treatments, as no specific anti-p95HER2 exist. The presently disclosed anti-p95HER2 antibodies of the invention may be included as part of a treatment regime, which may include, for example, providing two or more such antibodies, and/or in combination with other treatments such as chemotherapy, antibody-drug-conjugates (ADCs), or tyrosine kinase inhibitors (TKIs).

Definitions

[0044] The term “antibody” or “antibody molecule” describes a functional component of serum and is often referred to either as a collection of molecules (antibodies or immunoglobulin) or as one molecule (the antibody molecule or immunoglobulin molecule). An antibody is capable of binding to or reacting with a specific antigenic determinant (the antigen or the antigenic epitope), which in turn may lead to induction of immunological effector mechanisms. An antibody is generally considered as monospecific, and a composition of antibodies may be monoclonal (i.e., consisting of identical antibody molecules) or polyclonal (i.e., a plurality of different antibodies that may react with the same or different epitopes on the same antigen or on distinct/different antigens). An antibody has a unique structure enabling it to bind specifically to its corresponding antigen, and all natural antibodies have the same overall basic structure of two identical light chains and two identical heavy chains.

[0045] As used herein, “antibody” or “antibodies” may include chimeric and single chain antibodies, as binding fragments of antibodies, such as Fab, Fv fragments or single chain Fv (scFv) fragments, and multimeric forms, e.g., dimeric IgA molecules or pentavalent IgM. Antibodies of the invention may be of human or non-human origin, for example a murine or other rodent-derived antibody, or a chimeric, humanized or reshaped antibody based e.g., on a murine antibody.

[0046] A heavy chain of an antibody typically includes a heavy chain variable region (VH) and a heavy chain constant region. The heavy chain constant region usually comprises three domains, referred to as CH1, CH2 and CH3. An antibody light chain includes a light chain variable region (VL) and a light chain constant region. The light chain constant region includes a single domain, referred to as CL. The VH and VL regions are subdivided into regions of hypervariability (“hypervariable regions”), which may be hypervariable in sequence and/or in looped structure. These regions are also referred to as complementarity determining regions (CDRs), which are interspersed with regions that are more conserved, termed framework regions (FRs). Each VH and VL typically includes three CDRs and four FRs, arranged from the amino terminus to the carboxy terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. Amino acid residues in the variable regions are often numbered using a standardized numbering method known as the Kabat numbering scheme (Kabat et al. (1991) Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., USA).

[0047] The antibody identifiers found in the tables of this application, e.g., “70702_01C18A”, refer to the specific antibodies.

[0048] As used herein, an antibody or fragment “derived from” or “based on” an antibody means that the “derived” antibody comprises, depending on the particular context, one of the following: the heavy chain CDR3 sequence of said specified antibody; the heavy chain CDR3 sequence and the light chain CDR3 sequence of said specified antibody; the heavy chain CDR1, CDR2 and CDR3 sequences and light chain CDR1, CDR2 and CDR3 sequences of said specified antibody; or the heavy chain variable region sequence and the light chain variable region sequence of said specified antibody, or a humanized variant of said heavy chain variable region sequence and/or light chain variable region sequence, or a heavy chain and/or light chain variable region sequence having at least 80%, 85%, 90% or 95% sequence identity, such as at least 96%, 97%, 98% or 99% sequence identity, with the respective heavy chain and light chain variable region sequences.

[0049] An antibody that is derived from or based on a specified antibody described herein will generally bind the same p95HER2 epitope as said specified antibody and will preferably exhibit substantially the same activity as said specified antibody.

[0050] The specificity of an antibody's interaction with a target antigen is driven, primarily, by the amino acid residues located in the six CDRs of the heavy and light chain. The amino acid sequences within CDRs are more variable between individual antibodies than sequences outside of CDRs. Since CDR sequences are responsible for most antibody-antigen interactions, antibodies that mimic the properties of a specific naturally occurring antibody, or any specific antibody with a given amino acid sequence, can be expressed by constructing expression vectors that express CDR sequences from the specific antibody grafted into framework sequences from a different antibody. This permits "humanization" of a non-human antibody, which will nonetheless substantially maintain the binding specificity and affinity of the original antibody. Nonetheless, in preferred aspects, the anti-p95HER2 antibodies are human antibodies.

[0051] A "chimeric antibody" means an antibody that includes one or more regions from one antibody and one or more regions from one or more different antibodies. A "chimeric antibody" is typically an antibody that is partially of human origin and partially of non-human origin. Chimeric antibodies may be preferred over non-human antibodies, as they have been shown to reduce the risk of a human anti-antibody response. A chimeric antibody may include an antibody in which the variable region sequences are murine sequences derived from immunization of a mouse, while the constant region sequences are human. In the case of a chimeric antibody, the non-human parts, which often include the framework regions of the variable region sequences, may be further altered in order to humanize the antibody.

[0052] In preferred aspects, the presently disclosed antibodies of the invention are derived from transgenic mice that contain human antibody gene segments, such that the antibodies are human antibodies derived by hybridoma technology from transgenic mice.

[0053] The terms "heavy chain variable region sequence" and "light chain variable region sequence" and similar terms as used herein with reference to any specific amino acid sequence encompass not only that specific sequence, but also any recombinant antibodies, human antibodies, including those derived from transgenic mice that contain human antibody gene segments, such that the antibodies are human antibodies derived by hybridoma technology, and/or humanized variants thereof.

[0054] As used herein, a reference to a heavy chain variable region sequence or a light chain variable region sequence with a particular minimum level of sequence identity compared to a specified heavy chain or light chain variable region sequence.

[0055] A “recombinant antibody” is an antibody that is expressed from a cell or cell line transfected with an expression vector (or possibly more than one expression vector, typically two expression vectors) comprising the coding sequence of the antibody, where said coding sequence is not naturally associated with the cell.

[0056] A “vector” is a nucleic acid molecule into which a nucleic acid sequence can be inserted for transport between different genetic environments and/or for expression in a host cell. A vector that carries regulatory elements for transcription of the nucleic acid sequence (at least a suitable promoter) is referred to as an “an expression vector”. The terms “plasmid” and “vector” may be used interchangeably. Expression vectors used in the context of the present invention may be of any suitable type known in the art, for example, a viral vectors or plasmids.

[0057] It is well-known in the art that antibodies exist as different isotypes, such as the human isotypes IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2, or the murine isotypes IgG1, IgG2a, IgG2b, IgG3 and IgA. An antibody of the invention may be of any isotype.

[0058] In certain aspects, compositions of the invention include antibody compositions comprising a plurality of individual anti-p95HER2 antibodies, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, or 10 or more different anti-p95HER2 antibodies.

[0059] A “CDR” or “complementarity determining region” refers to the “hypervariable” regions found in the variable domains of an antibody that are primarily responsible for determining the antibody's binding specificity. Each of the heavy and light chains of an antibody contain three CDR regions, referred to as CDR1, CDR2 and CDR3, of which CDR3 shows the greatest variability.

[0060] An “epitope” describes a part of a larger molecule (e.g., antigen or antigenic site) having antigenic or immunogenic activity in an animal. An epitope having immunogenic activity is a portion of a larger molecule that elicits an antibody response. An epitope having antigenic activity is a portion of a larger molecule to which an antibody immune-specifically binds. Antigenic epitopes are not necessarily immunogenic. An antigen is a substance to which an antibody or antibody fragment specifically binds, such as a toxin, virus, bacteria, protein or

DNA. An antigen or antigenic site may have more than one epitope and may be capable of stimulating an immune response.

[0061] Epitopes may be linear or conformational. A linear epitope generally consists of about 6 to 10 adjacent amino acids on a protein molecule that are recognized by an antibody. In contrast, a conformational epitope consists of amino acids that are not arranged sequentially, but where an antibody recognizes a particular three-dimensional structure. When a protein molecule folds into a three-dimensional structure, the amino acids forming the epitope are juxtaposed, enabling the antibody to recognize the conformational epitope. In a denatured protein, only linear epitopes are recognized. A conformational epitope, by definition, must be on the outside of the folded protein.

[0062] The term “distinct epitopes” refers to the fact that when two different antibodies of the invention bind distinct epitopes, there is less than 100% competition for antigen binding, preferably less than 80% competition for antigen binding, more preferably less than 50% competition for antigen binding, and most preferably as little competition as possible, such as less than about 25% competition for antigen binding.

[0063] Antibodies capable of competing with each other for binding to the same antigen may bind the same or overlapping epitopes or may have a binding site in the close vicinity of one another, so that competition is mainly caused by steric hindrance. An analysis for “distinct epitopes” of antibody pairs may be performed by methods known in the art, for example by way of binding experiments under saturating antibody conditions using either FACS (fluorescence activated cell sorting) or other flow cytometry analysis on cells expressing anti-p95HER2 and individual fluorescent labeled antibodies, or by Surface Plasmon Resonance (SPR) using anti-p95HER2 antigens attached to a flow cell surface.

[0064] Antibodies binding to different epitopes on the same antigen can have varying effects on the activity of the antigen to which they bind, depending on the location of the epitope. An antibody binding to an epitope in an active site of the antigen may block the function of the antigen completely, whereas another antibody binding at a different epitope may have no or little effect on the activity of the antigen alone. Such antibodies may, however, still activate complement and thereby result in the elimination of the antigen, and may result in synergistic effects when combined with one or more antibodies binding at different epitopes on the same antigen.

[0065] “Immunoglobulin” is a collective designation of the mixture of antibodies found in blood or serum, but may also be used to designate a mixture of antibodies derived from other sources.

[0066] The term “cognate V_H and V_L coding pair” describes an original pair of V_H and V_L coding sequences contained within or derived from the same antibody-producing cell. Thus, a cognate V_H and V_L pair represents the V_H and V_L pairing originally present in the donor from which such a cell is derived. The term “an antibody expressed from a V_H and V_L coding pair” indicates that an antibody or an antibody fragment is produced from a vector, plasmid or other polynucleotide containing the V_H and V_L coding sequence. When a cognate V_H and V_L coding pair is expressed, either as a complete antibody or as a stable fragment thereof, they preserve the binding affinity and specificity of the antibody originally expressed from the cell they are derived from. A library of cognate pairs is also termed a repertoire or collection of cognate pairs, and may be kept individually or pooled.

[0067] By “protein” or “polypeptide” is meant any chain of amino acids, regardless of length or post-translational modification. Proteins can exist as monomers or multimers, comprising two or more assembled polypeptide chains, fragments of proteins, polypeptides, oligopeptides, or peptides.

[0068] The term “head-to-head promoters” refers to a promoter pair being placed in close proximity so that transcription of two gene fragments driven by the promoters occurs in opposite directions. Head-to-head promoters are also known as bi-directional promoters.

[0069] The term “transfection” is herein used as a broad term for introducing foreign DNA into a cell. The term is also meant to cover other functional equivalent methods for introducing foreign DNA into a cell, such as e.g., transformation, infection, transduction or fusion of a donor cell and an acceptor cell.

[0070] As used herein, and unless otherwise specified, p95HER2 refers to the HER2 isoform p95-CTF611-HER2 and is intended to include variants, fragments, species, and homologs of p95-CTF611-HER2. Preferably, binding of an antibody of the invention to p95HER2 inhibits the growth of cells expressing p95HER2 fragments. In certain aspects, this inhibition is caused by inhibiting formation of heteromeric complexes between p95HER2 and other ErbB family members.

[0071] As used herein, the term “inhibits growth” (e.g., referring to cells) is intended to include any measurable decrease in the proliferation (increase in number of cells) or metabolism of a cell

when contacted with an anti-p95HER2 antibody as compared to the growth of the same cells in the absence of an anti-p95HER2 antibody, e.g., inhibition of growth of a cell culture by at least about 10%, and preferably more, such as at least about 20% or 30%, more preferably at least about 40% or 50%, such as at least about 60%, 70%, 80%, 90%, 99% or even 100%.

[0072] As used herein, the terms “inhibits dimerization” or “inhibits dimer formation” refer to any measurable reduction in the ability of p95HER2 to form dimers with e.g., EGFR, HER3 or HER4 as a result of binding of an anti-p95HER2 antibody compared to dimer formation in the absence of an anti-p95HER2 antibody.

[0073] The term “treatment” as used herein refers to administration of an anti-p95HER2 antibody, antibody composition of the invention, or composition of immune cells that express or are activated by an anti-p95HER2 antibody or fragment thereof, in a sufficient amount to ease, reduce, ameliorate or eradicate (cure) symptoms or disease states.

[0074] The percent identity between two sequences, e.g., variable region sequences, refers to the number of identical positions shared by the sequences (calculated as # of identical positions/total # of positions $\times$ 100), taking into account gaps that must be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences may be accomplished using readily available software. Suitable software programs are available from various sources, both for online use and for download, and for alignment of both protein and nucleotide sequences. One suitable program is ClustalW (Thompson et al. (1994) Nucleic Acids Res. 11; 22(22):4673-80), available from www.clustal.org.

[0075] An “acceptor human framework” for the purposes herein is a framework comprising the amino acid sequence of a light chain variable domain (VL) framework or a heavy chain variable domain (VH) framework derived from a human immunoglobulin framework or a human consensus framework, as defined below. An acceptor human framework “derived from” a human immunoglobulin framework or a human consensus framework may comprise the same amino acid sequence thereof, or it may contain amino acid sequence changes. In some embodiments, the number of amino acid changes are 10 or less, 9 or less, 8 or less, 7 or less, 6 or less, 5 or less, 4 or less, 3 or less, or 2 or less. In some embodiments, the VL acceptor human framework is identical in sequence to the VL human immunoglobulin framework sequence or human consensus framework sequence.

[0076] “Affinity” refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen). Unless indicated otherwise, as used herein, “binding affinity” refers to intrinsic binding affinity, which reflects a 1:1 interaction between members of a binding pair (e.g., antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (K_d). Affinity can be measured by common methods known in the art, including those described herein.

[0077] An “affinity matured” antibody refers to an antibody with one or more alterations in one or more hypervariable regions, compared to a parent antibody, which does not possess such alterations, such alterations resulting in an improvement in the affinity of the antibody for antigen.

[0078] The terms “anti-p95HER2 antibody” and “an antibody that binds to p95HER2” refer to an antibody that is capable of binding p95HER2 fragments with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting p95HER2. In one embodiment, the extent of binding of an anti-p95HER2 antibody to an unrelated, non-p95HER2 protein (e.g., the full HER2 protein) is less than about 10% of the binding of the antibody to p95HER2 as measured, e.g., by a radioimmunoassay (RIA).

[0079] In certain embodiments, an antibody that binds to p95HER2 has a dissociation constant (K_d) of $\leq 1 \mu\text{M}$, $\leq 100 \text{ nM}$, $\leq 10 \text{ nM}$, $\leq 1 \text{ nM}$, $\leq 0.1 \text{ nM}$, $\leq 0.01 \text{ nM}$, or $\leq 0.001 \text{ nM}$ (e.g., 10^{-6} M or less, e.g., from 10^{-8} M to 10^{-13} M , e.g., from 10^{-9} M to 10^{-13} M). In preferred aspects, this affinity range is the “optimal affinity range”, which retains anti-tumor activity but has reduced toxicity due to reduced cytokine release. In certain preferred aspects, the anti-p95HER2 antibody has a sub-nanomolar affinity range. In preferred aspects, the anti-p95HER2 antibody has an affinity in the range of between about 0.1 nM to 1 nM as measured by alanine scanning of the HC CDR3 of the antibody.

[0080] In certain embodiments, an anti-p95HER2 antibody binds to an epitope, variant, and/or specific of p95HER2 that is conserved among p95HER2 from different species, pathologies (e.g., cancers or different types of cancer), and/or individuals.

[0081] The term “cluster of differentiation 3” or “CD3,” as used herein, refers to any native CD3 from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated, including, for example, CD3 ϵ , CD3 γ , CD3 δ , and CD3 ζ chains. The term encompasses “full-length,” unprocessed CD3 (e.g., unprocessed or unmodified

CD3 ϵ or CD3 γ), as well as any form of CD3 that results from processing in the cell. The term also encompasses naturally occurring variants of CD3, including, for example, splice variants or allelic variants. CD3 includes, for example, human CD3 ϵ protein (NCBI RefSeq No. NP-000724), which is 207 amino acids in length, and human CD3 γ protein (NCBI RefSeq No. NP-000064), which is 182 amino acids in length.

[0082] The “class” of an antibody refers to the type of constant domain or constant region possessed by its heavy chain. There are five major classes of antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called α , δ , ϵ , γ , and μ , respectively.

[0083] “Effector functions” refer to those biological activities attributable to the Fc region of an antibody, which vary with the antibody isotype. Examples of antibody effector functions include: C1 q binding and complement dependent cytotoxicity (CDC); Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e.g., B cell receptor); and B cell activation.

[0084] An “effective amount” of a compound, for example, an anti-p95HER2 antibody of the invention or a composition (e.g., pharmaceutical composition) thereof, is at least the minimum amount required to achieve the desired therapeutic or prophylactic result, such as a measurable improvement or prevention of a particular disorder (e.g., a cell proliferative disorder, e.g., cancer). An effective amount herein may vary according to factors such as the disease state, age, sex, and weight of the patient, and the ability of the antibody to elicit a desired response in the individual. An effective amount is also one in which any toxic or detrimental effects of the treatment are outweighed by the therapeutically beneficial effects. For prophylactic use, beneficial or desired results include results such as eliminating or reducing the risk, lessening the severity, or delaying the onset of the disease, including biochemical, histological and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease. For therapeutic use, beneficial or desired results include clinical results such as decreasing one or more symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, enhancing effect of another medication such as via targeting, delaying the progression of the disease, and/or prolonging survival. In the case of cancer or tumor, an effective amount of the

drug may have the effect in reducing the number of cancer cells; reducing the tumor size; inhibiting (i.e., slow to some extent or desirably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and desirably stop) tumor metastasis; inhibiting to some extent tumor growth; and/or relieving to some extent one or more of the symptoms associated with the disorder. An effective amount can be administered in one or more administrations. For purposes of this invention, an effective amount of drug, compound, or pharmaceutical composition is an amount sufficient to accomplish prophylactic or therapeutic treatment either directly or indirectly. As is understood in the clinical context, an effective amount of a drug, compound, or pharmaceutical composition may or may not be achieved in conjunction with another drug, compound, or pharmaceutical composition. Thus, an “effective amount” may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable result may be or is achieved.

[0085] The term “Fc region” herein is used to define a C-terminal region of an immunoglobulin heavy chain that contains at least a portion of the constant region. The term includes native sequence Fc regions and variant Fc regions. In one embodiment, a human IgG heavy chain Fc region extends from Cys226, or from Pro230, to the carboxyl-terminus of the heavy chain. However, the C-terminal lysine (Lys447) of the Fc region may or may not be present. Unless otherwise specified herein, numbering of amino acid residues in the Fc region or constant region is according to the EU numbering system, also called the EU index, as described in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991. Fc regions may also contain variant sequences to confer unique therapeutic properties, for example but not limited to an N297G amino acid substitution that reduces Fc receptor binding.

[0086] “Framework” or “FR” refers to variable domain residues other than hypervariable region residues. The FR of a variable domain generally consists of four FR domains: FR1, FR2, FR3, and FR4. Accordingly, the HVR and FR sequences generally appear in the following sequence in VH (or VL): FR1-H1(L)-FR2-H2(L2)-FR3-H3(L3)-FR4.

[0087] The terms “full-length antibody,” “intact antibody,” and “whole antibody” are used herein interchangeably to refer to an antibody having a structure substantially similar to a native antibody structure or having heavy chains that contain an Fc region as defined herein.

[0088] A “human antibody” is one which possesses an amino acid sequence which corresponds to that of an antibody produced by a human or a human cell or derived from a non-human source that utilizes human antibody repertoires or other human antibody-encoding sequences. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues. Human antibodies can be produced using various techniques known in the art, including phage-display libraries. Hoogenboom and Winter, *J. Mol. Biol.*, 227:381 (1991); Marks et al., *J. Mol. Biol.*, 222:581 (1991). Also available for the preparation of human monoclonal antibodies are methods described in Cole et al., *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985); Boerner et al., *J. Immunol.* 147(1):86-95 (1991). See also van Dijk and van de Winkel, *Curr. Opin. Pharmacol.*, 5: 368-74 (2001). Human antibodies can be prepared by administering the antigen to a transgenic animal that has been modified to produce such antibodies in response to antigenic challenge, but whose endogenous loci have been disabled, e.g., immunized xenomice (see, e.g., U.S. Pat. Nos. 6,075,181 and 6,150,584 regarding XENOMOUSE™ technology). See also, for example, Li et al., *Proc. Natl. Acad. Sci. USA*, 103:3557-3562 (2006) regarding human antibodies generated via a human B-cell hybridoma technology.

[0089] For example, in preferred aspects, technologies such as AlivaMab Mouse technology are used to produce the anti-p95HER2 antibodies described herein. Generally, AlivaMab Mouse technology is used to generate panels of monoclonal antibodies (mAbs) against a human antigen of interest, such as those expressed by or associated with tumor cells, e.g., variants of p95HER2 and/or HER2.

[0090] The AlivaMab Mouse is a transgenic mouse that produces chimeric human-mouse monoclonal antibodies comprising fully human Fab and upper hinge regions and mouse middle hinge and Fc regions. Optimized constant domains facilitate the generation and identification of antibodies that retain structure-function characteristics. Antibodies produced using AlivaMab Mouse technology possess biophysical properties, which are predictive and comparable to that of fully human antibody counterparts.

[0091] Antibodies produced by AlivaMab Kappa Mice include a chimeric immunoglobulin heavy (IgH) chain and a human immunoglobulin kappa (IgK) light chain. Antibodies produced by AlivaMab Lambda Mice include a chimeric IgH chain and a human immunoglobulin lambda (IgK) light chain. The chimeric IgH chain of the AlivaMab Mouse antibodies include a human variable region comprising a human variable heavy (VH) domain, a human diversity heavy (DH) domain,

and a human joining heavy (JH) domain, a human constant heavy 1 (CH1) domain, a human upper hinge region (except for O μ , which is naturally missing an upper hinge region), a mouse middle hinge region, a mouse CH2 domain, and a mouse CH3 domain.

[0092] When a lead candidate antibody is discovered, the human heavy chain variable region is readily appended to a fully human constant region while maintaining the antigen-binding characteristics of the parent chimeric antibody that were developed *in vivo* in the AlivaMab Mouse. In one embodiment, the human heavy chain variable region, CH1 and, optionally, upper hinge region of the chimeric antibody are appended to human hinge, a human CH2 domain and a human CH3 domain in order to produce a fully human antibody.

[0093] Portions of variable regions from the antibodies produced from AlivaMab Mouse technology may include all or a combination of the complementarity determining regions (CDRs) of the VH and/or VL. The variable regions may be formatted with constant regions, either native or modified for various desired effector functions, in a standard antibody structure (two heavy chains with two light chains). The variable regions may also be formatted as multi-specific antibodies, e.g., bispecific antibodies binding to two different epitopes or to two different antigens. The variable regions may also be formatted as antibody fragments, e.g., single-domain antibodies comprising a single VH or VL, Fabs or Fab'2. The antibodies may also be used as antibody-drug conjugates, or carry other additions such as small molecule toxins, biologic toxins, cytokines, oligopeptides, or RNAs to increase therapeutic modality and/or increase safety.

[0094] Methods for producing the anti-p95HER2 antibodies of the invention using AlivaMab mouse technology may include immunizing AlivaMab Kappa Mice and AlivaMab Lambda Mice with an antigen of interest. Generally, within two weeks, the mice are sacrificed and terminal materials collected. Spleens and lymph nodes may be prepared and fused with myeloma cells (such as CRL-2016 cells) using a PEG based method as generally described in "Antibodies: A Laboratory Manual" (Harlow and Lane 1988 CSH Press) to establish hybridomas.

[0095] Hybridomas may be grown in 384-well tissue culture plates and supernatants from individual wells were screened by ELISA for production of antibodies recognizing the antigen of interest. Positive wells are then transferred to 48-well plates, expanded, and supernatants were collected for antigen binding confirmation by ELISA. Positive supernatants may also be counter-screened against a non-related histidine-tagged protein. Hybridoma lines each from AlivaMab Kappa Mice and AlivaMab Lambda Mice are confirmed to bind to the antigen specifically by

ELISA and are picked at random and single-cell cloned into 96-well plates. They are grown into colonies and the supernatant from these individual colonies is screened by ELISA to re-confirm monoclonal antibody binding to the antigen of interest. These supernatants are then screened by FACS to confirm binding to the native antigen expressed on cells.

[0096] AlivaMab Mouse technology and methods for producing antibodies using such technologies can be found in WO 2010/039900 and WO 2011/123708, which are incorporated herein in their entirety.

[0097] A “human consensus framework” is a framework which represents the most commonly occurring amino acid residues in a selection of human immunoglobulin VL or VH framework sequences. Generally, the selection of human immunoglobulin VL or VH sequences is from a subgroup of variable domain sequences. Generally, the subgroup of sequences is a subgroup as in Kabat et al., Sequences of Proteins of Immunological Interest, Fifth Edition, NIH Publication 91-3242, Bethesda Md. (1991), vols. 1-3. In one embodiment, for the VL, the subgroup is subgroup kappa I as in Kabat et al., supra. In one embodiment, for the VH, the subgroup is subgroup III as in Kabat et al., supra.

[0098] A “humanized” antibody refers to a chimeric antibody comprising amino acid residues from non-human HVRs and amino acid residues from human FRs. In certain embodiments, a humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the HVRs (e.g., CDRs) correspond to those of a non-human antibody, and all or substantially all of the FRs correspond to those of a human antibody. A humanized antibody optionally may comprise at least a portion of an antibody constant region derived from a human antibody. A “humanized form” of an antibody, e.g., a non-human antibody, refers to an antibody that has undergone humanization.

[0099] To “humanize” an antibody means that an antibody of wholly or partially of non-human origin, for example a murine antibody obtained from immunization of mice with an antigen of interest or a chimeric antibody based on such a murine antibody, can have amino acids replaced, particularly in the framework regions and constant domains of the heavy and light chains, to avoid or minimize an immune response in humans. It is known that all antibodies have the potential for eliciting a human anti-antibody response, which correlates to some extent with the degree of “humanness” of the antibody in question.

[0100] Non-human antibodies tend to be more immunogenic than human antibodies. Chimeric antibodies, where the foreign (usually rodent) constant regions have been replaced with sequences of human origin, have been shown to be less immunogenic than antibodies of fully foreign origin, and the most development efforts in therapeutic antibodies are trending towards the use of humanized or fully human antibodies. Preferably, chimeric antibodies or other antibodies of non-human origin are humanized to reduce the risk of a human anti-antibody response. For chimeric antibodies, humanization may include, for example, modification of the framework regions of the variable region sequences. Amino acid residues of a CDR may often not be altered during humanization, although in certain cases it may be desirable to alter individual CDR amino acid residues, for example to remove a glycosylation site, a deamidation site or an undesired cysteine residue.

[0101] Numerous methods for humanization of an antibody sequence are known in the art. A commonly used method is CDR grafting, which may involve identification of human germline gene counterparts to murine variable region genes and grafting of the murine CDR sequences into this framework. Since CDR grafting reduces the chance for binding specificity and affinity and the biological activity of a CDR grafted non-human antibody, back mutations are often introduced at selected positions of the CDR grafted antibody to retain the binding specificity and affinity. Amino acid residues that for back mutations may include those that are located at the surface of an antibody molecule. Another humanization technique for CDR grafting and back mutation is resurfacing, in which non-surface exposed residues of non-human origin are retained, while surface residues are altered to human variants.

[0102] Humanized antibodies and methods of making them are reviewed, e.g., in Almagro and Fransson, *Front. Biosci.* 13:1619-1633 (2008), and are further described, e.g., in Riechmann et al., *Nature* 332:323-329 (1988); Queen et al., *Proc. Nat'l Acad. Sci. USA* 86:10029-10033 (1989); U.S. Pat. Nos. 5,821,337, 7,527,791, 6,982,321, and 7,087,409; Kashmiri et al., *Methods* 36:25-34 (2005) (describing specificity determining region (SDR) grafting); Padlan, *Mol. Immunol.* 28:489-498 (1991) (describing "resurfacing"); Dall'Acqua et al., *Methods* 36:43-60 (2005) (describing "FR shuffling"); and Osbourn et al., *Methods* 36:61-68 (2005) and Klimka et al., *Br. J. Cancer*, 83:252-260 (2000) (describing the "guided selection" approach to FR shuffling).

[0103] Human framework regions that may be used for humanization include but are not limited to: framework regions selected using the "best-fit" method (see, e.g., Sims et al. *J. Immunol.*

151:2296 (1993)), framework regions derived from the consensus sequence of human antibodies of a particular subgroup of light or heavy chain variable regions (see, e.g., Carter et al. Proc. Natl. Acad. Sci. USA, 89:4285 (1992); and Presta et al. J. Immunol., 151:2623 (1993)); human mature (somatically mutated) framework regions or human germline framework regions (see, e.g., Almagro and Fransson, Front. Biosci. 13:1619-1633 (2008)); and framework regions derived from screening FR libraries (see, e.g., Baca et al., J. Biol. Chem. 272:10678-10684 (1997) and Rosok et al., J. Biol. Chem. 271:22611-22618 (1996)).

[0104] The term “hypervariable region” or “HVR” as used herein refers to each of the regions of an antibody variable domain which are hypervariable in sequence (“complementarity determining regions” or “CDRs”) and/or form structurally defined loops (“hypervariable loops”) and/or contain the antigen-contacting residues (“antigen contacts”). Generally, antibodies comprise six HVRs: three in the VH (H1, H2, H3), and three in the VL (L1, L2, L3). Unless otherwise indicated, HVR residues and other residues in the variable domain (e.g., FR residues) are numbered herein according to Kabat et al., *supra*.

[0105] An “immunoconjugate” is an antibody conjugated to one or more heterologous molecule(s), including but not limited to a cytotoxic agent.

[0106] A “subject” or an “individual” is a mammal. Mammals include, but are not limited to, domesticated animals (e.g., cows, sheep, cats, dogs, and horses), primates (e.g., humans and non-human primates such as monkeys), rabbits, and rodents (e.g., mice and rats). In certain embodiments, the subject or individual is a human.

[0107] An “isolated” antibody is one which has been separated from a component of its natural environment. In some embodiments, an antibody is purified to greater than 95% or 99% purity as determined by, for example, electrophoretic (e.g., SDS-PAGE, isoelectric focusing (IEF), capillary electrophoresis) or chromatographic (e.g., ion exchange or reverse phase HPLC). For review of methods for assessment of antibody purity, see, e.g., Flatman et al., J. Chromatogr. B 848:79-87 (2007).

[0108] An “isolated” nucleic acid refers to a nucleic acid molecule that has been separated from a component of its natural environment. An isolated nucleic acid includes a nucleic acid molecule contained in cells that ordinarily contain the nucleic acid molecule, but the nucleic acid molecule is present extrachromosomally or at a chromosomal location that is different from its natural chromosomal location.

[0109] “Isolated nucleic acid encoding an anti-p95HER2 antibody” refers to one or more nucleic acid molecules encoding antibody heavy and light chains (or fragments thereof), including such nucleic acid molecule(s) in a single vector or separate vectors, and such nucleic acid molecule(s) present at one or more locations in a host cell.

[0110] The term “monoclonal antibody” as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical and/or bind the same epitope, except for possible variant antibodies, e.g., containing naturally occurring mutations or arising during production of a monoclonal antibody preparation, such variants generally being present in minor amounts. In contrast to polyclonal antibody preparations, which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody of a monoclonal antibody preparation is directed against a single determinant on an antigen. Thus, the modifier “monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by a variety of techniques, including but not limited to the hybridoma method, recombinant DNA methods, phage-display methods, and methods utilizing transgenic animals containing all or part of the human immunoglobulin loci, such methods and other exemplary methods for making monoclonal antibodies being described herein.

[0111] “Native antibodies” refer to naturally occurring immunoglobulin molecules with varying structures. For example, native IgG antibodies are heterotetrameric glycoproteins of about 150,000 Daltons, composed of two identical light chains and two identical heavy chains that are disulfide-bonded. From N- to C-terminus, each heavy chain has a variable region (VH), also called a variable heavy domain or a heavy chain variable domain, followed by three constant domains (CH1, CH2, and CH3). Similarly, from N- to C-terminus, each light chain has a variable region (VL), also called a variable light domain or a light chain variable domain, followed by a constant light (CL) domain. The light chain of an antibody may be assigned to one of two types, called kappa (K) and lambda (A), based on the amino acid sequence of its constant domain.

[0112] The term “package insert” is used to refer to instructions customarily included in commercial packages of therapeutic products, which contain information about the indications,

usage, dosage, administration, combination therapy, contraindications, and/or warnings concerning the use of such therapeutic products.

[0113] The term “protein,” as used herein, refers to any native protein from any vertebrate source, including mammals such as primates (e.g., humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses “full-length,” unprocessed protein as well as any form of the protein that results from processing in the cell. The term also encompasses naturally occurring variants of the protein, e.g., splice variants or allelic variants.

[0114] The term “variable region” or “variable domain” refers to the domain of an antibody heavy or light chain that is involved in binding the antibody to antigen. The variable domains of the heavy chain and light chain (VH and VL, respectively) of a native antibody generally have similar structures, with each domain comprising four conserved framework regions (FRs) and three hypervariable regions (HVRs). (*See, e.g., Kindt et al. Kuby Immunology, 6th ed., W.H. Freeman and Co., page 91 (2007).*) A single VH or VL domain may be sufficient to confer antigen-binding specificity. Furthermore, antibodies that bind a particular antigen may be isolated using a VH or VL domain from an antibody that binds the antigen to screen a library of complementary VL or VH domains, respectively. *See, e.g., Portolano et al., J. Immunol. 150:880-887 (1993); Clarkson et al., Nature 352:624-628 (1991).*

[0115] As used herein, “administering” is meant a method of giving a dosage of a compound (e.g., an anti-p95HER2 antibody of the invention or a nucleic acid encoding an anti-p95HER2 antibody of the invention) or a composition (e.g., a pharmaceutical composition, e.g., a pharmaceutical composition including an anti-p95HER2 antibody of the invention) to a subject. The compositions utilized in the methods described herein can be administered, for example, intramuscularly, intravenously, intradermally, percutaneously, intraarterially, intraperitoneally, intralesionally, intracranially, intraarticularly, intraprostatically, intrapleurally, intratracheally, intranasally, intravitreally, intravaginally, intrarectally, topically, intratumorally, peritoneally, subcutaneously, subconjunctivally, intravesicularly, mucosally, intrapericardially, intraumbilically, intraocularly, orally, topically, locally, by inhalation, by injection, by infusion, by continuous infusion, by localized perfusion bathing target cells directly, by catheter, by lavage, in cremes, or in lipid compositions. The method of administration can vary depending on various factors (e.g., the compound or composition being administered, and the severity of the condition, disease, or disorder being treated).

[0116] As used herein, “somatic hypermutation” or “SHM” refers to the mutation of a polynucleotide sequence initiated by, or associated with the action of the Activation-Induced Cytidine Deaminase (AID), a functional AID mutant, uracil glycosylase and/or error prone polymerases on that polynucleotide sequence. As used herein, the term includes mutagenesis that occurs as a consequence of the error prone repair, including mutagenesis mediated by the mismatch repair machinery and related enzymes.

[0117] SHM is generally initiated by targeting AID to rearranged V(D)J and switch regions of Ig genes. The mutation rate of this programmed mutagenesis is a million-fold higher than the non-AID targeted genome of B cells. AID is a processive enzyme that binds single-stranded DNA and deaminates cytosines in DNA. Cytosine deamination generates highly mutagenic deoxy-uracil (U) in the DNA of the Ig loci. Mutagenic processing of uracil through the DNA damage response produces the entire spectrum of base substitutions, which characterizes SHM at and around an initial U lesion. At least five, identified mutagenic DNA damage response pathways are known to generate a well-defined SHM spectrum of C/G transitions, C/G transversions, and A/T mutations around this initial lesion. These pathways include (1) replication opposite template U generates transitions at C/G, (2) UNG2-dependent translesion synthesis (TLS) generates transversions at C/G, (3) a hybrid pathway comprising non-canonical mismatch repair (ncMMR) and UNG2-dependent TLS generates transversions at C/G, (4) ncMMR generates mutations at A/T, and (5) UNG2- and PCNA Ubiquitination (PCNA-Ub)-dependent mutations at A/T. Specific strand-biases of SHM spectra arise as a consequence of a biased AID targeting, ncMMR, and anti-mutagenic repriming. By elucidating the amino acid and/or nucleotide sequences of the CDR3 variable regions and/or one of CDR3 heavy chain (HC) and light chain (LC) variable regions of the anti-p95HER2 antibodies disclosed herein, the present inventors identified a series of “clusters” or “motifs” within the sequences. These clusters represent convergent somatic hypermutations (SHM) in the variable region sequences. Clustering may provide insight into the functionally related sequences and the diversity of the total population of antibodies and their variable region sequences. Sequences that are descendants from the same parent B cell or convergently evolved the sequences in the same cluster should be functionally more related than sequences belonging to other clusters. Convergent SHMs are likely functionally related mutations, e.g., they share a specific affinity for p95HER2, which may include a specific affinity for select p95HER2 epitopes/fragments and/or for p95HER2 fragments over fully expressed HER2 protein. These

SHM may inform the development of recombinant anti-p95HER2 antibodies with improved properties, such as specific binding for p95HER2 fragments.

Selected Embodiments

[0118] One aspect of the invention relates to various novel anti-p95HER2 antibodies and fragments thereof.

[0119] The presently disclosed antibodies may provide treatments that are far more effective than current therapies. The presently disclosed p95HER2 antibodies of the invention may be included as part of a treatment regime, which may include, for example, providing two or more such antibodies, and/or in combination with other treatments such as chemotherapy.

[0120] In one aspect, the invention relates to novel p95HER2 antigen binding peptides, which may be antibodies and/or fragments thereof. In certain aspects, the antibodies and/or fragments thereof bind to a p95HER2 fragment having an amino acid sequence of SEQ ID NO: 1, and/or a sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity to SEQ ID NO: 1 or a fragment thereof.

MPIWKFPDEEGACQPCPINCTHSCVDLDDKGCPAEQRASPLTKRRQQKIRKYTMRRLLQ
ETELVEPLTPSGAMPNQAQMRILKETELRKV (SEQ ID NO: 1)

[0121] In one aspect, the present invention provides an anti-p95HER2 antibody or antibody fragment comprising: a heavy chain CDR3 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 2-65 and 514, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 2-65 and 514; a heavy chain CDR2 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 258-321 and 518, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 258-321 and 518; a heavy chain CDR1 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 130-193 and 516, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 130-193 and 516; a light chain CDR3 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 66-129 and 515, and/or a sequence that comprises an amino acid sequence having

at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 66-129 and 515; a light chain CDR2 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 322-385 and 519, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 322-385 and 519; and/or a light chain CDR1 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 194-257 and 517, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 194-257 and 517.

[0122] In one aspect, the present invention provides an anti-p95HER2 antibody or antibody fragment comprising one or more of:

a heavy chain CDR3 sequence (VH) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 514;

a heavy chain CDR2 sequence (VH) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 518;

a heavy chain CDR1 sequence (VH) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 516;

a light chain CDR3 sequence (VL) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 515;

a light chain CDR2 sequence (VL) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 519; and

a light chain CDR1 sequence (VL) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 517.

[0123] In one aspect, the present invention provides an anti-p95HER2 antibody or antibody fragment comprising a VH chain comprising one or more of:

a heavy chain CDR3 sequence (VH) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 514;

a heavy chain CDR2 sequence (VH) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 518; and

a heavy chain CDR1 sequence (VH) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 516.

[0124] In certain aspects, the anti-p95HER2 antibody further comprises a VL chain comprising one or more of:

a light chain CDR3 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 66-129 and 515, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 66-129 and 515;

a light chain CDR2 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 322-385 and 519, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 322-385 and 519; and

a light chain CDR1 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 194-257 and 517, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 194-257 and 517.

[0125] In one aspect, the present invention provides an anti-p95HER2 antibody or antibody fragment comprising a VL chain comprising one or more of:

a light chain CDR3 sequence (VL) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 515;

a light chain CDR2 sequence (VL) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 519; and

a light chain CDR1 sequence (VL) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 517.

[0126] Additionally or alternatively, an anti-p95HER2 antibody or antibody fragment of the present invention may comprise a heavy chain variable region encoded by a nucleic acid sequence and/or a nucleic acid sequence having at least 85%, at least 90% at least 95.5%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 841. Additionally or alternatively, an anti-p95HER2 antibody or antibody fragment of the present invention may comprise a light chain variable region encoded by a nucleic acid sequence and/or a nucleic acid sequence having at least 85%, at least 90% at least 95.5%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 842.

SEQ ID NO: 841:

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCGGGGGGGTCCCTGAG
ACTCTCCTGTGCAGCCTCTGGATTCTCCTTCAGTAGCTATGCCTTGACCTGGGTCCGC
CAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCATCCATCAGTAGTAGTAGTCA
CAAATACTACGCAGACTCAGTGAAGGGCCGATTACCATCTCCAGAGACAACGCCA
AGAACTCACTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTCTATT
ACTGTGCGAAAACTACCCCTTTGACTACTGGGGCCAGGGAACCCTGGTCAACCGTCT
CCTCAG

SEQ ID NO: 842:

CAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACC
ATCTCCTGCACTGGAACCAGCAGTGATGTTGGGAGTTATAACCTTGCTCCTGGTAC
CAACACCACCCAGGCAAAGTCCCCAACTCATGATTTATGAGGGCAGTAAGCGGCC
CTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGAC
AATCTCTGGGCTCCAGGCTGAGGACGAGGCTGATTATTACTGCTGCTCATATGCAGG
TAGTAGCACTTTTCGTATTCGGCGGAGGGACCAAGCTGACCGTCCTAG

[0127] In certain aspects, such an anti-p95HER2 antibody further comprises a VL chain comprising one or more of:

a heavy chain CDR3 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 2-65 and 514, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 2-65 and 514;

a heavy chain CDR2 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 258-321 and 518, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 258-321 and 518; and

a heavy chain CDR1 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 130-193 and 516, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 130-193 and 516;

[0128] In certain aspects, the present invention provides an anti-p95HER2 antibody or antibody fragment comprising a heavy chain CDR3 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 2-65 and 514, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 2-65 and 514. Additionally or alternatively, an anti-p95HER2 antibody or antibody fragment of the present invention may comprise a light chain CDR3 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 66-129 and 515, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 66-129 and 515.

[0129] Additionally or alternatively, the present invention provides an anti-p95HER2 antibody or antibody fragment comprising a heavy chain CDR3 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 2-65 and 514, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 2-65 and 514, and a light chain CDR3 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 66-129 and 515, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 66-129 and 515.

[0130] Additionally or alternatively, an anti-p95HER2 antibody or antibody fragment of the present invention may comprise a heavy chain variable region comprising an amino acid sequence selected from one of SEQ ID NOS: 386-449, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 386-449. Additionally or alternatively, an anti-p95HER2 antibody or antibody fragment of the present invention may comprise a light chain variable region comprising an amino acid sequence selected from one of SEQ ID NOS: 450-513, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 450-513.

[0131] Additionally or alternatively, an anti-p95HER2 antibody or antibody fragment of the present invention may comprise a heavy chain variable region comprising an amino acid sequence selected from one of SEQ ID NOS: 386-449, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 386-449 and a light chain variable region comprising an amino acid sequence selected from one of SEQ ID NOS: 450-513, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 450-513.

[0132] Additionally or alternatively, an anti-p95HER2 antibody or antibody of the present invention comprises a heavy chain variable region and/or a light chain variable region sequence comprising the somatic hypermutations (SMH) of clusters: Clust 1.1; Clust 1.2; Clust 1.3; Clust 2.1; Clust 3.1; Clust 4.1; Clust 4.2; Clust 4.3; Clust 5.1; Clust 5.2; Clust 6.1; Clust 6.2; Clust 7.1; Clust 7.2; Clust 8.1; Clust 8.2; Clust 9.1; Clust 9.2; Clust 10.1; Clust 10.2; Clust 11.1; Clust 11.2; Clust 12.1; and/or Clust 12.2, as set forth in Tables 3-4. Additionally or alternatively, an anti-p95HER2 antibody or antibody of the present invention comprises a heavy chain variable region and/or a light chain variable region sequence comprising one or more of the somatic hypermutations (SMH), as set forth in Tables 3-4.

[0133] In certain aspects, the present invention provides compositions, including therapeutic compositions, comprising an anti-p95HER2 antibody or antibody fragment as described herein. In certain aspects, the present invention provides compositions, including therapeutic compositions,

two or more of the anti-p95HER2 antibodies disclosed herein. Certain compositions of the invention include a plurality of different anti-p95HER2 antibodies, as disclosed herein, wherein each different antibody binds to a distinct p95HER2 epitope or fragment.

[0134] In certain aspects, the present invention provides methods for treating breast cancer using compositions comprising one or more anti-p95HER2 antibodies, as described herein. In certain aspects, the administration of such a composition results in reduced p95HER2, HER2, and/or other Erb receptor expression, and/or HER2, p95HER2, and/or other Erb receptor internalization, and/or ligand-induced phosphorylation of HER3.

[0135] In certain aspects, the present invention provides immunoconjugates and/or compositions comprising such immunoconjugates, wherein said immunoconjugates comprise an anti-p95HER2 antibody of the invention conjugated to another therapeutic agent, such as an anti-cancer agent. The invention further provides immunoconjugates comprising two or more different anti-p95HER2 antibodies or fragment thereof, wherein each different anti-p95HER2 antibody or fragment targets a different p95HER2 fragment or epitope.

[0136] A further aspect of the invention relates to a nucleic acid molecule having a nucleotide sequence that encodes an anti-p95HER2 antibody or fragment thereof, as disclosed herein, as well as expression vectors comprising such a polynucleotide and host cells that have been transfected with such an expression vector.

[0137] Aspects of the invention also provide methods for producing the anti-p95HER2 antibodies, fragments thereof, and compositions of the invention.

[0138] The present invention also provides methods for treating a disease in a human or animal subject, in particular treatment of cancer in humans, by administering an anti-p95HER2 antibody or composition of the invention to said subject. The invention also includes the use of one or more anti-p95HER2 antibodies of the invention for preparation of a medicament for use in treating a disease in a human or animal, in particular for the treatment of cancer in humans.

[0139] Another embodiment of this aspect of the invention relates to an antibody composition comprising at least first and second anti-p95HER2 antibodies, wherein the first and second antibodies bind distinct epitopes of p95HER2, said first and second antibodies independently comprising a heavy chain CDR3 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 2-65 and 514, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least

99% sequence identity with any of SEQ ID NOS: 2-65 and 514. Additionally or alternatively, said first and second anti-p95HER2 antibodies comprise a light chain CDR3 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 66-129 and 515, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 66-129 and 515.

[0140] Another aspect of the invention relates to nucleic acid molecules comprising a nucleotide sequence that encodes an antibody, VL variable region sequence, VH variable region sequence, VL CDR3 sequence, VH CDR3 sequence, VL CDR2 sequence, VH CDR2 sequence, VL CDR1 sequence, and/or VH CDR1 sequence as set forth herein, and/or a sequence having an amino acid sequence comprising a sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% with any of SEQ ID NOS: 2-519.

[0141] Another aspect of the invention relates to nucleic acid molecules comprising a nucleotide sequence that encodes an antibody, VL variable region sequence, VH variable region sequence, VL CDR3 sequence, VH CDR3 sequence, VL CDR2 sequence, VH CDR2 sequence, VL CDR1 sequence, and/or VH CDR1 sequence as set forth herein. In certain aspects, the invention comprises a nucleic acid encoding at least a portion of an anti-p95HER2 antibody of the invention. In certain aspects, the nucleic acid encodes at least the VH sequence. In certain aspects, the VH chain, or portion thereof, is encoded by a nucleic acid having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% similarity with SEQ ID NO: 841. In certain aspects, the VH chain, or portion thereof, is encoded by a nucleic acid comprising SEQ ID NO: 841. In certain aspects, the VL chain, or portion thereof, is encoded by a nucleic acid having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% similarity with SEQ ID NO: 842. In certain aspects, the VL chain, or portion thereof, is encoded by a nucleic acid comprising SEQ ID NO: 842.

[0142] A further aspect of the invention relates to an expression vector comprising a nucleic acid molecule as defined above. As noted above, expression vectors for use in the context of the present invention may be of any suitable type known in the art, e.g., a plasmid or a viral vector. In certain aspects, said vector comprises a nucleic acid comprising at least 95.5%, at least 96%, at least 97%, at least 98% or at least 99% similarity with one or both of SEQ ID NOS: 841 and 842.

[0143] A still further aspect of the invention relates to a host cell comprising a nucleic acid molecule as defined above, wherein said host cell is capable of expressing an anti-p95HER2 antibody encoded by said nucleic acid molecule.

[0144] In some embodiments, an antibody provided herein has a dissociation constant (K_d) of $\leq 1 \mu\text{M}$, $\leq 100 \text{ nM}$, $\leq 10 \text{ nM}$, $\leq 1 \text{ nM}$, $\leq 0.1 \text{ nM}$, $\leq 0.01 \text{ nM}$, or $\leq 0.001 \text{ nM}$ (e.g., 10^{-6} M or less, e.g., from 10^{-8} M to 10^{-13} M , e.g., from 10^{-9} M to 10^{-13} M). In certain preferred aspects, this affinity range is the “optimal affinity range”, which retains anti-tumor activity. In other preferred aspects, the anti-p95HER2 antibody has a sub-nanomolar affinity to promote receptor occupancy in low copy-number situations.

[0145] In some embodiments, K_d is measured by a radiolabeled antigen binding assay (RIA). In some embodiments, an RIA is performed with the Fab version of an antibody of interest and its antigen. For example, solution binding affinity of Fabs for antigen is measured by equilibrating Fab with a minimal concentration of (125I)-labeled antigen in the presence of a titration series of unlabeled antigen, then capturing bound antigen with an anti-Fab antibody-coated plate (see, e.g., Chen et al., J. Mol. Biol. 293:865-881(1999)).

[0146] In some embodiments, K_d is measured using a BIACORE® surface plasmon resonance assay. For example, an assay using a BIACORE®-2000 or a BIACORE®-3000 (BIAcore, Inc., Piscataway, N.J.) is performed at 25° C. with immobilized antigen CM5 chips at ~10 response units (RU). In one embodiment, carboxymethylated dextran biosensor chips (CM5, BIACORE, Inc.) are activated with N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) and N-hydroxysuccinimide (NHS) according to the supplier's instructions. Antigen is diluted with 10 mM sodium acetate, pH 4.8, to 5 g/ml (~0.2 M) before injection at a flow rate of 5 $\mu\text{l}/\text{minute}$ to achieve approximately 10 response units (RU) of coupled protein. Following the injection of antigen, 1 M ethanolamine is injected to block unreacted groups. For kinetics measurements, two-fold serial dilutions of Fab (0.78 nM to 500 nM) are injected in PBS with 0.05% polysorbate 20 (TWEEN-20™) surfactant (PBST) at 25° C. at a flow rate of approximately 25 $\mu\text{l}/\text{min}$. Association rates (k_{on}) and dissociation rates (k_{off}) are calculated using a simple one-to-one Langmuir binding model (BIACORE® Evaluation Software version 3.2) by simultaneously fitting the association and dissociation sensorgrams. The equilibrium dissociation constant (K_d) is calculated as the ratio k_{on}/k_{off} . See, for example, Chen et al., J. Mol. Biol. 293:865-881 (1999). If the on-rate exceeds $10^6 \text{ M}^{-1}\text{s}^{-1}$ by the surface plasmon resonance assay above, then the on-rate can be determined by

using a fluorescent quenching technique that measures the increase or decrease in fluorescence emission intensity (excitation=295 nm; emission=340 nm, 16 nm band-pass) at 25° C. of a 20 nM anti-antigen antibody (Fab form) in PBS, pH 7.2, in the presence of increasing concentrations of antigen as measured in a spectrometer, such as a stop-flow equipped spectrophotometer (Aviv Instruments) or a 8000-series SLM-AMINCO™ spectrophotometer (ThermoSpectronic) with a stirred cuvette.

[0147] In preferred aspects, the modality to estimate affinity is production of a monovalent anti-p95HER2 antibody followed by titration on live p95HER2 expressing cells and determination of MFI by flow cytometry to determine an EC50 value. Advantageously, this may represent an exacting context (monovalent and p95HER2 on cells) in which a therapeutic based on the anti-p95HER2 antibodies of the invention is used.

[0148] In some embodiments, an antibody provided herein is an antibody fragment. Antibody fragments include, but are not limited to, Fab, Fab', Fab'-SH, F(ab')2, Fv, and scFv fragments, and other fragments described below. For a review of certain antibody fragments, see Hudson et al. *Nat. Med.* 9:129-134 (2003). For a review of scFv fragments, see, e.g., Pluckthun, in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenberg and Moore eds., (Springer-Verlag, New York), pp. 269-315 (1994); see also WO 93/16185; and U.S. Pat. Nos. 5,571,894 and 5,587,458. For discussion of Fab and F(ab')2 fragments comprising salvage receptor binding epitope residues and having increased in vivo half-life, see U.S. Pat. No. 5,869,046.

[0149] Diabodies are antibody fragments with two antigen-binding sites that may be bivalent or bispecific. See, e.g., EP 404,097; WO 1993/01161; Hudson et al. *Nat. Med.* 9:129-134 (2003); and Hollinger et al. *Proc. Natl. Acad. Sci. USA* 90: 6444-6448 (1993). Triabodies and tetrabodies are also described in Hudson et al. *Nat. Med.* 9:129-134 (2003).

[0150] Single-domain antibodies are antibody fragments comprising all or a portion of the heavy chain variable domain or all or a portion of the light chain variable domain of an antibody. In certain embodiments, a single-domain antibody is a human single-domain antibody (Domantis, Inc., Waltham, Mass.; see, e.g., U.S. Pat. No. 6,248,516 B1).

[0151] Antibody fragments can be made by various techniques, including but not limited to proteolytic digestion of an intact antibody as well as production by recombinant host cells (e.g., *E. coli* or phage).

[0152] In some embodiments, an antibody provided herein is a chimeric antibody. Certain chimeric antibodies are described, e.g., in U.S. Pat. No. 4,816,567; and Morrison et al. Proc. Natl. Acad. Sci. USA, 81:6851-6855 (1984)). In one example, a chimeric antibody comprises a non-human variable region (e.g., a variable region derived from a mouse, rat, hamster, rabbit, or non-human primate, such as a monkey) and a human constant region. In a further example, a chimeric antibody is a "class switched" antibody in which the class or subclass has been changed from that of the parent antibody. Chimeric antibodies include antigen-binding fragments thereof.

[0153] In preferred embodiments, an antibody provided herein is a human antibody. Human antibodies can be produced using various techniques known in the art. Human antibodies are described generally in van Dijk and van de Winkel, Curr. Opin. Pharmacol. 5: 368-74 (2001) and Lonberg, Curr. Opin. Immunol. 20:450-459 (2008).

[0154] The human antibodies may be prepared by administering an immunogen to a transgenic animal that has been modified to produce intact human antibodies or intact antibodies with human variable regions in response to antigenic challenge. Such animals typically contain all or a portion of the human immunoglobulin loci, which replace the endogenous immunoglobulin loci, or which are present extra-chromosomally or integrated randomly into the animal's chromosomes. In such transgenic mice, the endogenous immunoglobulin loci have generally been inactivated. For a review of methods for obtaining human antibodies from transgenic animals, see Lonberg, Nat. Biotech. 23:1117-1125 (2005). See also, e.g., U.S. Pat. Nos. 6,075,181 and 6,150,584 describing XENOMOUSE™ technology; U.S. Pat. No. 5,770,429 describing HUMAB® technology; U.S. Pat. No. 7,041,870 describing K-M MOUSE® technology, and U.S. Patent Application Publication No. US 2007/0061900, describing VELOCIMOUSE® technology). Human variable regions from intact antibodies generated by such animals may be further modified, e.g., by combining with a different human constant region.

[0155] Human antibodies can also be made by hybridoma-based methods. Human myeloma and mouse-human heteromyeloma cell lines for the production of human monoclonal antibodies have been described. (See, e.g., Kozbor J. Immunol., 133: 3001 (1984); Brodeur et al., Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987); and Boerner et al., J. Immunol., 147: 86 (1991).) Human antibodies generated via human B-cell hybridoma technology are also described in Li et al., Proc. Natl. Acad. Sci. LISA. 103: 3557-3562 (2006). Additional methods include those described, for example, in U.S. Pat. No.

7,189,826 (describing production of monoclonal human IgM antibodies from hybridoma cell lines) and Ni, Xiandai Mianyixue, 26(4):265-268 (2006) (describing human-human hybridomas). Human hybridoma technology (Trioma technology) is also described in Vollmers and Brandlein, Histology and Histopathology, 20(3):927-937 (2005) and Vollmers and Brandlein, Methods and Findings in Experimental and Clinical Pharmacology, 27(3):185-91 (2005).

[0156] For example, in preferred aspects, technologies such as AlivaMab Mouse technology are used to produce the anti-p95HER2 antibodies described herein. AlivaMab Mouse technology is used to generate panels of monoclonal antibodies (mAbs) against p95HER2.

[0157] The AlivaMab Mouse is a transgenic mouse that produces chimeric human-mouse monoclonal antibodies comprising fully human Fab and upper hinge regions and mouse middle hinge and Fc regions. Optimized constant domains facilitate the generation and identification of antibodies that retain structure-function characteristics. Antibodies of the invention produced using AlivaMab Mouse technology possess biophysical properties, which are predictive and comparable to that of fully human antibody counterparts.

[0158] Antibodies of the invention may be produced by AlivaMab Kappa Mice, and may include a chimeric immunoglobulin heavy (IgH) chain and a human immunoglobulin kappa (IgK) light chain. The antibodies of the invention produced by AlivaMab Lambda Mice may include a chimeric IgH chain and a human immunoglobulin lambda (IgK) light chain. The chimeric IgH chain of the AlivaMab Mouse anti-p95HER2 antibodies may include a human variable region comprising a human variable heavy (VH) domain, a human diversity heavy (DH) domain, and a human joining heavy (JH) domain, a human constant heavy 1 (CH1) domain, a human upper hinge region (except for O_H, which is naturally missing an upper hinge region), a mouse middle hinge region, a mouse CH2 domain, and a mouse CH3 domain.

[0159] When an anti-p95HER2 antibody is discovered, the human heavy chain variable region is readily appended to a fully human constant region while maintaining the antigen-binding characteristics of the parent chimeric antibody that were developed *in vivo* in the AlivaMab Mouse. In one embodiment, the human heavy chain variable region, CH1 and, optionally, upper hinge region of the chimeric antibody are appended to human hinge, a human CH2 domain and a human CH3 domain in order to produce a fully human anti-p95HER2 antibody as disclosed herein.

[0160] Portions of variable regions from the antibodies produced from AlivaMab Mouse technology may include all or a combination of the complementarity determining regions (CDRs)

of the VH and/or VL. The variable regions may be formatted with constant regions, either native or modified for various desired effector functions, in a standard antibody structure (two heavy chains with two light chains). The variable regions may also be formatted as multi-specific antibodies, e.g., bispecific antibodies binding to two different epitopes or to two different antigens. The variable regions may also be formatted as antibody fragments, e.g., single-domain antibodies comprising a single VH or VL, Fabs or Fab'2. The antibodies may also be used as antibody-drug conjugates, or carry other additions such as small molecule toxins, biologic toxins, cytokines, oligopeptides, or RNAs to increase therapeutic modality and/or increase safety.

[0161] Methods for producing the anti-p95HER2 antibodies of the invention using AlivaMab mouse technology may include immunizing AlivaMab Kappa Mice and AlivaMab Lambda Mice with an antigen. Generally, within two weeks, the mice are sacrificed, and terminal materials collected. Spleens and lymph nodes may be prepared and fused with myeloma cells (such as CRL-2016 cells) using a PEG based method as generally described in "Antibodies: A Laboratory Manual" (Harlow and Lane 1988 CSH Press) to establish hybridomas.

[0162] Hybridomas may be grown in 384-well tissue culture plates and supernatants from individual wells were screened by ELISA for production of antibodies recognizing the antigen of interest. Positive wells are then transferred to 48-well plates, expanded, and supernatants were collected for antigen binding confirmation by ELISA. Positive supernatants may also be counter-screened against a non-related histidine-tagged protein. Hybridoma lines each from AlivaMab Kappa Mice and AlivaMab Lambda Mice are confirmed to bind to the antigen specifically by ELISA and are picked at random and single-cell cloned into 96-well plates. They are grown into colonies and the supernatant from these individual colonies is screened by ELISA to re-confirm monoclonal antibody binding to the antigen of interest. These supernatants are then screened by FACS to confirm binding to the native antigen expressed on cells.

[0163] AlivaMab Mouse technology and methods for producing antibodies using such technologies can be found in WO 2010/039900 and WO 2011/123708, which are incorporated herein in their entirety.

[0164] In certain methods for designing and/or producing the anti-p95HER2 antibodies of the invention, by elucidating the amino acid and/or nucleotide sequences of the CDR3 variable regions and/or one of CDR3 heavy chain (HC) and light chain (LC) variable regions of the anti-p95HER2 antibodies produced, for example, using AlivaMab Mouse technology, a series of "clusters" or

“motifs” are identified within the sequences. These clusters represent convergent somatic hypermutations (SHM) in the variable region sequences. Clustering may provide insight into the functionally related sequences and the diversity of the total population of antibodies and their variable region sequences. Sequences that are descendants from the same parent B cell or convergently evolved the sequences in the same cluster should be functionally more related than sequences belonging to other clusters. Convergent SHMs are likely functionally related mutations, e.g., they share a specific affinity for p95HER2. These SHM may inform the development of recombinant anti-p95HER2 antibodies with improved properties, such as specific binding for p95HER2 fragments.

[0165] Specific SHMs in the anti-p95HER2 antibody variable regions of the antibodies disclosed herein are found in Tables 1-4, with the amino acids representing an SHM indicated in bold, colored, and/or stylized lettering.

[0166] Human antibodies may also be generated by isolating Fv clone variable domain sequences selected from human-derived phage display libraries. Such variable domain sequences may then be combined with a desired human constant domain.

[0167] Antibodies of the invention may be isolated by screening combinatorial libraries for antibodies with the desired activity or activities. For example, a variety of methods is known in the art for generating phage display libraries and screening such libraries for antibodies possessing the desired binding characteristics. Such methods are reviewed, e.g., in Hoogenboom et al. in *Methods in Molecular Biology* 178:1-37 (O'Brien et al., ed., Human Press, Totowa, N.J., 2001) and further described, e.g., in the McCafferty et al., *Nature* 348:552-554; Clackson et al., *Nature* 352: 624-628 (1991); Marks et al., *J. Mol. Biol.* 222: 581-597 (1992); Marks and Bradbury, in *Methods in Molecular Biology* 248:161-175 (Lo, ed., Human Press, Totowa, N.J., 2003); Sidhu et al., *J. Mol. Biol.* 338(2): 299-310 (2004); Lee et al., *J. Mol. Biol.* 340(5): 1073-1093 (2004); Fellouse, *Proc. Natl. Acad. Sci. USA* 101(34): 12467-12472 (2004); and Lee et al., *J. Immunol. Methods* 284(1-2): 119-132(2004).

[0168] In certain phage display methods, repertoires of VH and VL genes are separately cloned by polymerase chain reaction (PCR) and recombined randomly in phage libraries, which can then be screened for antigen-binding phage as described in Winter et al., *Ann. Rev. Immunol.*, 12: 433-455 (1994). Phage typically display antibody fragments, either as single-chain Fv (scFv) fragments or as Fab fragments. Libraries from immunized sources provide high-affinity antibodies to the

immunogen without the requirement of constructing hybridomas. Alternatively, the naive repertoire can be cloned (e.g., from human) to provide a single source of 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 unrearranged V-gene segments from stem cells, and using PCR primers containing random sequence to encode the highly variable CDR3 regions, and/or accomplishing rearrangement in vitro, as described by Hoogenboom and Winter, J. Mol. Biol., 227: 381-388 (1992). Patent publications describing human antibody phage libraries include, for example: U.S. Pat. No. 5,750,373, and US Patent Publication Nos. 2005/0079574, 2005/0119455, 2005/0266000, 2007/0117126, 2007/0160598, 2007/0237764, 2007/0292936, and 2009/0002360.

[0169] Alternatively, in certain aspects, the present invention includes humanized variants of the antibodies described herein or humanized antibodies comprising a one or more of SEQ ID NOS: 2-513, or a fragment thereof. Methods for humanizing antibodies are well known in the art.

[0170] In certain aspects, the anti-p95HER2 antibodies of the invention are, or form a part of, a multispecific antibody.

[0171] Multispecific antibodies are monoclonal antibodies that have binding specificities for at least two different sites. In some embodiments, bispecific antibodies may bind to two different epitopes of p95HER2. In some embodiments, one of the binding specificities is for p95HER2 and the other is for any other antigen (e.g., a second biological molecule, e.g., a cell surface antigen, e.g., a tumor antigen), such as CD3 or epitopes thereof (e.g., CD3 ϵ or CD3 γ). Accordingly, a bispecific anti-p95HER2 antibody may have binding specificities for p95HER2 and a second biological molecule, e.g., a second p95HER2 epitope, another antigen, an immune cell, an immune cell recruiter, and the like.

[0172] Techniques for making multispecific antibodies include, but are not limited to, recombinant co-expression of two immunoglobulin heavy chain-light chain pairs having different specificities (see Milstein and Cuello, Nature 305: 537 (1983)), WO 93/08829, and Traunecker et al., EMBO J. 10: 3655 (1991)), and “knob-in-hole” engineering (see, e.g., U.S. Pat. No. 5,731,168). “Knob-in-hole” engineering of multispecific antibodies may be utilized to generate a first arm containing a knob and a second arm containing the hole into which the knob of the first arm may bind. The knob of the multispecific antibodies of the invention may be an anti-p95HER2 arm in one embodiment. Alternatively, the knob of the multispecific antibodies of the invention may be an

anti-target/antigen arm in one embodiment. The hole of the multispecific antibodies of the invention may be an anti-p95HER2 arm in one embodiment. Alternatively, the hole of the multispecific antibodies of the invention may be an anti-target/antigen arm in one embodiment.

[0173] There other ways of making multispecific antibodies. For example, multispecific antibodies may be engineered using immunoglobulin crossover (also known as Fab domain exchange or CrossMab format) technology (see e.g., WO2009/080253; Schaefer et al., Proc. Natl. Acad. Sci. USA, 108:11187-11192 (2011)). Multi-specific antibodies may also be made by engineering electrostatic steering effects for making antibody Fc-heterodimeric molecules (WO 2009/089004A1); cross-linking two or more antibodies or fragments (see, e.g., U.S. Pat. No. 4,676,980, and Brennan et al., Science, 229: 81 (1985)); using leucine zippers to produce bispecific antibodies (see, e.g., Kostelny et al., J. Immunol., 148(5):1547-1553 (1992)); using “diabody” technology for making bispecific antibody fragments (see, e.g., Hollinger et al., Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993)); and using single-chain Fv (scFv) dimers (see, e.g. Gruber et al., J. Immunol., 152:5368 (1994)); and preparing trispecific antibodies as described, e.g., in Tutt et al. J. Immunol 147: 60 (1991).

[0174] In certain embodiments, amino acid sequence variants of the anti-p95HER2 antibodies of the invention (e.g., bispecific anti-p95HER2 antibodies of the invention that bind to p95HER2 and a second biological molecule, e.g., a cell surface antigen, e.g., a tumor antigen, such as certain members and/or fragments of the epidermal growth factor receptor (HER/EGFR/ERBB) family, and/or one or more CD3 epitopes) are contemplated. For example, it may be desirable to modulate or alter the binding affinity and/or other biological properties of the antibody. Amino acid sequence variants of an antibody may be prepared by introducing appropriate modifications into the nucleotide sequence encoding the antibody, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution can be made to arrive at the final construct, provided that the final construct possesses the desired characteristics, for example, antigen-binding.

[0175] In certain aspects, the anti-p95HER2 antibodies of the invention are multi-specific antibodies. In certain aspects, the multi-specific antibodies are bispecific antibodies, trispecific antibodies, and/or of greater multi-specificity that exhibit specificity to p95HER2 and another molecule and/or another epitope/fragment of p95HER2 and/or HER2. For example, such

antibodies can bind to both p95HER2 and to an antigen that is important for targeting the antibody to a particular cell type or tissue (for example, to an antigen associated with a cancer antigen of a tumor being treated) and/or an antigen to activate or recruit immune cells. In some embodiments, multi-specific antibodies of the invention bind to molecules (receptors or ligands) involved in immunomodulatory pathways, such as CTLA4, TIM3, TIM4, OX40, CD40, GITR, 4-1-BB, CD27/CD70, ICOS, B7-H4, LIGHT, PD-1 or LAG3, which may provide control or modulation of the multi-specific antibodies' therapeutic effects. Furthermore, a multispecific antibody may bind to effector molecules such as cytokines (e.g., IL-7, IL-15, IL-12, IL-4 TGF-beta, IL-10, IL-17, IFNg, Flt3, BLys) and/or chemokines (e.g., CCL21). Methods are known in the art for producing bispecific antibodies.

[0176] In certain embodiments, antibody variants having one or more amino acid substitutions are provided. Sites of interest for substitutional mutagenesis include the HVRs and FRs. Conservative substitutions are shown in Table A under the heading of "preferred substitutions." More substantial changes are provided in Table A under the heading of "exemplary substitutions," and as further described below in reference to amino acid side chain classes. Amino acid substitutions may be introduced into an antibody of interest and the products screened for a desired activity, for example, chemical stability, retained/improved antigen binding, decreased immunogenicity, or improved ADCC or CDC.

TABLE A

Exemplary and Preferred Amino Acid Substitutions		
Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	Val; Leu; Ile	Val
Arg (R)	Lys; Gln; Asn	Lys
Asn (N)	Gln; His; Asp; Lys; Arg	Gln
Asp (D)	Glu; Asn	Glu
Cys (C)	Ser; Ala	Ser
Gln (Q)	Asn; Glu	Asn
Glu (E)	Asp; Gln	Asp

Gly (G)	Ala	Ala
His (H)	Asn; Gln; Lys; Arg	Arg
Ile (I)	Leu; Val; Met; Ala; Phe ; Norleucine	Leu
Leu (L)	Norleucine; Ile; Val; Met; Ala; Phe	Ile
Lys (K)	Arg; Gln; Asn	Arg
Met (M)	Leu; Phe; Ile	Leu
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr	Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Val; Ser	Ser
Trp (W)	Tyr; Phe	Tyr
Tyr (Y)	Trp; Phe; Thr; Ser	Phe
Val (V)	Ile; Leu; Met; Phe; Ala; Norleucine	Leu

[0177] Amino acids may be grouped according to common side-chain properties:

- (1) hydrophobic: Met, Ala, Val, Leu, Ile;
- (2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;
- (3) acidic: Asp, Glu;
- (4) basic: His, Lys, Arg;
- (5) residues that influence chain orientation: Gly, Pro;
- (6) aromatic: Trp, Tyr, Phe.

[0178] Non-conservative substitutions will entail exchanging a member of one of these classes for another class.

[0179] One type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (e.g., a humanized or human antibody). Generally, the resulting variant(s) selected for further study will have modifications (e.g., improvements) in certain biological properties (e.g., increased affinity, reduced immunogenicity) relative to the parent antibody and/or will have substantially retained certain biological properties of the parent antibody. An exemplary substitutional variant is an affinity matured antibody, which may be conveniently generated, e.g., using phage display-based affinity maturation techniques. Briefly,

one or more HVR residues are mutated and the variant antibodies displayed on phage and screened for a particular biological activity (e.g. binding affinity).

[0180] Alterations (e.g., substitutions) may be made in HVRs, e.g., to improve antibody affinity. Such alterations may be made in HVR “hotspots,” i.e., residues encoded by codons that undergo mutation at high frequency during the somatic maturation process (see, e.g., Chowdhury, *Methods Mol. Biol.* 207:179-196 (2008)), and/or residues that contact antigen, with the resulting variant VH or VL being tested for binding affinity. Affinity maturation by constructing and reselecting from secondary libraries has been described, e.g., in Hoogenboom et al. in *Methods in Molecular Biology* 178:1-37 (O'Brien et al., ed., Human Press, Totowa, N.J., (2001).) In some embodiments of affinity maturation, diversity is introduced into the variable genes chosen for maturation by any of a variety of methods (e.g., error-prone PCR, chain shuffling, or oligonucleotide-directed mutagenesis). A secondary library is then created. The library is then screened to identify any antibody variants with the desired affinity. Another method to introduce diversity involves HVR-directed approaches, in which several HVR residues (e.g., 4-6 residues at a time) are randomized. HVR residues involved in antigen binding may be specifically identified, e.g., using alanine scanning mutagenesis or modeling. CDR-H3 and CDR-L3 in particular are often targeted.

[0181] In certain embodiments, substitutions, insertions, or deletions may occur within one or more HVRs so long as such alterations do not substantially reduce the ability of the antibody to bind antigen. For example, conservative alterations (e.g., conservative substitutions as provided herein) that do not substantially reduce binding affinity may be made in HVRs. Such alterations may, for example, be outside of antigen contacting residues in the HVRs. In certain embodiments of the variant VH and VL sequences provided above, each HVR either is unaltered, or contains no more than one, two, or three amino acid substitutions.

[0182] A useful method for identification of residues or regions of an antibody that may be targeted for mutagenesis is called “alanine scanning mutagenesis” as described by Cunningham and Wells (1989) *Science*, 244:1081-1085. In this method, a residue or group of target residues (e.g., charged residues such as arg, asp, his, lys, and glu) are identified and replaced by a neutral or negatively charged amino acid (e.g., alanine or polyalanine) to determine whether the interaction of the antibody with antigen is affected. Further substitutions may be introduced at the amino acid locations demonstrating functional sensitivity to the initial substitutions. Alternatively, or additionally, a crystal structure of an antigen-antibody complex to identify contact points between

the antibody and antigen may be used. Such contact residues and neighboring residues may be targeted or eliminated as candidates for substitution. Variants may be screened to determine whether they contain the desired properties.

[0183] Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intra-sequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody to an enzyme or a polypeptide which increases the serum half-life of the antibody.

[0184] In certain embodiments, anti-p95HER2 antibodies of the invention can be altered to increase or decrease the extent to which the antibody is glycosylated. Addition or deletion of glycosylation sites to anti-p95HER2 antibody of the invention may be conveniently accomplished by altering the amino acid sequence such that one or more glycosylation sites is created or removed.

[0185] Where the antibody comprises an Fc region, the carbohydrate attached thereto may be altered. Native antibodies produced by mammalian cells typically comprise a branched, biantennary oligosaccharide that is generally attached by an N-linkage to Asn297 of the CH2 domain of the Fc region. See, e.g., Wright et al. TIBTECH 15:26-32 (1997). The oligosaccharide may include various carbohydrates, e.g., mannose, N-acetyl glucosamine (GlcNAc), galactose, and sialic acid, as well as a fucose attached to a GlcNAc in the "stem" of the biantennary oligosaccharide structure. In some embodiments, modifications of the oligosaccharide in an antibody of the invention may be made in order to create antibody variants with certain improved properties.

[0186] In one embodiment, anti-p95HER2 antibody variants are provided having a carbohydrate structure that lacks fucose attached (directly or indirectly) to an Fc region. For example, the amount of fucose in such antibody may be from 1% to 80%, from 1% to 65%, from 5% to 65%, or from 20% to 40%. The amount of fucose is determined by calculating the average amount of fucose within the sugar chain at Asn297, relative to the sum of all glycostructures attached to Asn 297 (e.g., complex, hybrid and high mannose structures) as measured by MALDI-TOF mass spectrometry, as described in WO 2008/077546, for example. Asn297 refers to the asparagine residue located at about position 297 in the Fc region (EU numbering of Fc region residues);

however, Asn297 may also be located about 3 amino acids upstream or downstream of position 297, i.e., between positions 294 and 300, due to minor sequence variations in antibodies. Such fucosylation variants may have improved ADCC function. See, e.g., US Patent Publication Nos. US 2003/0157108 (Presta, L.); US 2004/0093621 (Kyowa Hakko Kogyo Co., Ltd). Examples of publications related to “defucosylated” or “fucose-deficient” antibody variants include: 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; WO2002/031140; Okazaki et al. J. Mol. Biol. 336:1239-1249 (2004); Yamane-Ohnuki et al. Biotech. Bioeng. 87: 614 (2004). Examples of cell lines capable of 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 (see, e.g., Yamane-Ohnuki et al. Biotech. Bioeng. 87: 614 (2004); Kanda, Y. et al., Biotechnol. Bioeng., 94(4):680-688 (2006); and WO2003/085107).

[0187] Anti-p95HER2 antibody variants are further provided with bisected oligosaccharides, for example, in which a biantennary oligosaccharide attached to the Fc region of the antibody is bisected by GlcNAc. Such antibody variants may have reduced fucosylation and/or improved ADCC function. Examples of such antibody variants are described, e.g., in WO 2003/011878 (Jean-Mairet et al.); U.S. Pat. No. 6,602,684 (Umana et al.); and US 2005/0123546 (Umana et al.). Antibody variants with at least one galactose residue in the oligosaccharide attached to the Fc region are also provided. Such antibody variants may have improved CDC function. Such antibody variants are described, e.g., in WO 1997/30087 (Patel et al.); WO 1998/58964 (Raju, S.); and WO 1999/22764 (Raju, S.).

[0188] In certain embodiments, one or more amino acid modifications may be introduced into the Fc region of an anti-p95HER2 antibody of the invention thereby generating an Fc region variant (see e.g., US 2012/0251531). The Fc region variant may comprise a human Fc region sequence (e.g., a human IgG1, IgG2, IgG3 or IgG4 Fc region) comprising an amino acid modification (e.g., a substitution) at one or more amino acid positions. In certain embodiments, the invention contemplates an anti-p95HER2 antibody variant that possesses some but not all effector functions,

which make it a desirable candidate for applications in which the half-life of the antibody in vivo is important yet certain effector functions (such as complement and ADCC) are unnecessary or deleterious. In vitro and/or in vivo cytotoxicity assays can be conducted to confirm the reduction/depletion of CDC and/or ADCC activities. For example, Fc receptor (FcR) binding assays can be conducted to ensure that the antibody lacks FcγR binding (hence likely lacking ADCC activity), but retains FcRn binding ability. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express FcγRI, FcγRII and FcγRIII. FcR expression on hematopoietic cells is summarized on page 464 of Ravetch and Kinet, *Annu. Rev. Immunol.* 9:457-492 (1991). Non-limiting examples of in vitro assays to assess ADCC activity of a molecule of interest is described in U.S. Pat. No. 5,500,362 (see, e.g. Hellstrom, I. et al. *Proc. Nat'l Acad. Sci. USA* 83:7059-7063 (1986)) and Hellstrom, I et al., *Proc. Nat'l Acad. Sci. USA* 82:1499-1502 (1985); U.S. Pat. No. 5,821,337 (see Bruggemann, M. et al., *J. Exp. Med.* 166:1351-1361 (1987)). Alternatively, non-radioactive assays methods may be employed (see, for example, ACTITM non-radioactive cytotoxicity assay for flow cytometry (CellTechnology, Inc. Mountain View, Calif.; and CytoTox 96 non-radioactive cytotoxicity assay (Promega, Madison, Wis.). Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells.

[0189] Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed in vivo, e.g., in an animal model such as that disclosed in Clynes et al. *Proc. Nat'l Acad. Sci. USA* 95:652-656 (1998). C1q binding assays may also be carried out to confirm that the antibody is unable to bind C1q and hence lacks CDC activity. See, e.g., C1q and C3c binding ELISA in WO 2006/029879 and WO 2005/100402. To assess complement activation, a CDC assay may be performed (see, for example, Gazzano-Santoro et al. *J. Immunol. Methods* 202:163 (1996); Cragg, M. S. et al. *Blood*. 101:1045-1052 (2003); and Cragg, M. S. and M. J. Glennie *Blood*. 103:2738-2743 (2004)). FcRn binding and in vivo clearance/half-life determinations can also be performed using methods known in the art (see, e.g., Petkova, S. B. et al. *Int'l. Immunol.* 18(12):1759-1769 (2006)).

[0190] Antibodies with reduced effector function include those with substitution of one or more of Fc region residues 238, 265, 269, 270, 297, 327 and 329 (U.S. Pat. Nos. 6,737,056 and 8,219,149). Such Fc mutants include Fc mutants with substitutions at two or more of amino acid

positions 265, 269, 270, 297 and 327, including the so-called "DANA" Fc mutant with substitution of residues 265 and 297 to alanine (U.S. Pat. Nos. 7,332,581 and 8,219,149).

[0191] In certain embodiments, the proline at position 329 of a wild-type human Fc region in the antibody is substituted with glycine or arginine or an amino acid residue large enough to destroy the proline sandwich within the Fc/Fcγ receptor interface that is formed between the proline 329 of the Fc and tryptophan residues Trp 87 and Trp 110 of FcγRIII (Sondermann et al.: Nature 406, 267-273 (20 Jul. 2000)). In certain embodiments, the antibody comprises at least one further amino acid substitution. In one embodiment, the further amino acid substitution is S228P, E233P, L234A, L235A, L235E, N297A, N297D, or P331S, and still in another embodiment the at least one further amino acid substitution is L234A and L235A of the human IgG1 Fc region or S228P and L235E of the human IgG4 Fc region (see e.g., US 2012/0251531), and still in another embodiment the at least one further amino acid substitution is L234A and L235A and P329G of the human IgG1 Fc region.

[0192] Certain antibody variants with improved or diminished binding to FcRs are described. (See, e.g., U.S. Pat. No. 6,737,056; WO 2004/056312, and Shields et al., J. Biol. Chem. 9(2): 6591-6604 (2001).)

[0193] In certain embodiments, an antibody variant comprises an Fc region with one or more amino acid substitutions which improve ADCC, e.g., substitutions at positions 298, 333, and/or 334 of the Fc region (EU numbering of residues).

[0194] In some embodiments, alterations are made in the Fc region that result in altered (i.e., either improved or diminished) C1q binding and/or Complement Dependent Cytotoxicity (CDC), e.g., as described in U.S. Pat. No. 6,194,551, WO 99/51642, and Idusogie et al. J. Immunol. 164: 4178-4184 (2000).

[0195] Antibodies with increased half-lives and improved binding to the neonatal Fc receptor (FcRn), which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., J. Immunol. 117:587 (1976) and Kim et al., J. Immunol. 24:249 (1994)), are described in US2005/0014934A1 (Hinton et al.). Those antibodies comprise an Fc region with one or more substitutions therein which improve binding of the Fc region to FcRn. Such Fc variants include those with substitutions at one or more of Fc region residues: 238, 256, 265, 272, 286, 303, 305, 307, 311, 312, 317, 340, 356, 360, 362, 376, 378, 380, 382, 413, 424 or 434, e.g., substitution of Fc region residue 434

(U.S. Pat. No. 7,371,826). See also Duncan & Winter, *Nature* 322:738-40 (1988); U.S. Pat. Nos. 5,648,260; 5,624,821; and WO 94/29351 concerning other examples of Fc region variants.

[0196] In some aspects, the bispecific antibody comprises an Fc region comprising an N297G mutation. In some embodiments, the bispecific antibody comprising the N297G mutation comprises one or more heavy chain constant domains, wherein the one or more heavy chain constant domains are selected from a first CH1 domain, a first CH2 domain, a first CH3 domain, a second CH1 domain, second CH2 domain, and a second CH3 domain.

[0197] In certain embodiments, it may be desirable to create cysteine engineered antibodies in which one or more residues of an antibody are substituted with cysteine residues. In some embodiments, the substituted residues occur at accessible sites of the antibody. By substituting those residues with cysteine, reactive thiol groups are thereby positioned at accessible sites of the antibody and may be used to conjugate the antibody to other moieties, such as drug moieties or linker-drug moieties, to create an immunoconjugate, as described further herein. In certain embodiments, any one or more of the following residues may be substituted with cysteine: V205 (Kabat numbering) of the light chain; A118 (EU numbering) of the heavy chain; and S400 (EU numbering) of the heavy chain Fc region. Cysteine engineered antibodies may be generated as described, for example, in WO 2016/040856, which is incorporated by reference in its entirety herein, including any drawings.

[0198] In certain embodiments, the bispecific antibody provided herein may be further modified to contain additional non-proteinaceous moieties that are known in the art and readily available. The moieties suitable for derivatization of the antibody include but are not limited to water soluble polymers. Non-limiting examples of 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, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols (e.g., glycerol), polyvinyl alcohol, and mixtures thereof. Polyethylene glycol propionaldehyde may have advantages in manufacturing due to its stability in water. The polymer may be of any molecular weight, and may be branched or unbranched. The number of polymers attached to the antibody may vary, and if more than one polymer is attached, each 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, whether the antibody derivative will be used in a therapy under defined conditions, etc.

[0199] In another embodiment, conjugates of an antibody and nonproteinaceous moiety that may be selectively heated by exposure to radiation are provided. In one embodiment, the nonproteinaceous moiety is a carbon nanotube (Kam et al., Proc. Natl. Acad. Sci. USA 102: 11600-11605 (2005)). The radiation may be of any wavelength, and includes, but is not limited to, wavelengths that do not harm ordinary cells, but which heat the nonproteinaceous moiety to a temperature at which cells proximal to the antibody-nonproteinaceous moiety are killed.

[0200] The bispecific antibodies of the invention may be produced using recombinant methods and compositions, for example, as described in U.S. Pat. No. 4,816,567. In one embodiment, an isolated nucleic acid encoding an anti-p95HER2 antibody described herein is provided. Such nucleic acid may encode an amino acid sequence comprising the VL and/or an amino acid sequence comprising the VH of the antibody (e.g., the light and/or heavy chains of the antibody). In a further embodiment, one or more vectors (e.g., expression vectors) comprising such nucleic acid are provided. In a further embodiment, a host cell comprising such nucleic acid is provided. In one such embodiment, a host cell comprises (e.g., has been transformed with): (1) a vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antibody and an amino acid sequence comprising the VH of the antibody, or (2) a first vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antibody and a second vector comprising a nucleic acid that encodes an amino acid sequence comprising the VH of the antibody. In one embodiment, the host cell is eukaryotic, e.g., a Chinese Hamster Ovary (CHO) cell or lymphoid cell (e.g., YO, NS0, Sp20 cell). In one embodiment, a method of making a bispecific antibody is provided, wherein the method comprises culturing a host cell comprising a nucleic acid encoding the antibody under conditions suitable for expression of the antibody, and optionally recovering the antibody from the host cell (or host cell culture medium).

[0201] For recombinant production of an antibody, a nucleic acid encoding an antibody is isolated and inserted into one or more vectors for further cloning and/or expression in a host cell. Such nucleic acid may be readily isolated and sequenced using conventional procedures (e.g., by using

oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody).

[0202] Suitable host cells for cloning or expression of antibody-encoding vectors include prokaryotic or eukaryotic cells described herein. For example, antibodies may be produced in bacteria, in particular when glycosylation and Fc effector function are not needed. For expression of antibody fragments and polypeptides in bacteria, see, e.g., U.S. Pat. Nos. 5,648,237, 5,789,199, and 5,840,523. (See also Charlton, *Methods in Molecular Biology*, Vol. 248 (B. K. C. Lo, ed., Humana Press, Totowa, N.J., 2003), pp. 245-254, describing expression of antibody fragments in *E. coli*.) After expression, the antibody may be isolated from the bacterial cell paste in a soluble fraction and can be further purified.

[0203] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for antibody-encoding vectors, including fungi and yeast strains whose glycosylation pathways have been "humanized," resulting in the production of an antibody with a partially or fully human glycosylation pattern. See Gerngross, *Nat. Biotech.* 22:1409-1414 (2004), and Li et al., *Nat. Biotech.* 24:210-215 (2006).

[0204] Suitable host cells for the expression of glycosylated antibody are also derived from multicellular organisms (invertebrates and vertebrates). Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains have been identified which may be used in conjunction with insect cells, particularly for transfection of *Spodoptera frugiperda* cells.

[0205] Plant cell cultures can also be utilized as hosts. See, e.g., U.S. Pat. Nos. 5,959,177, 6,040,498, 6,420,548, 7,125,978, and 6,417,429 (describing PLANTIBODIES™ technology for producing antibodies in transgenic plants).

[0206] Vertebrate cells may also be used as hosts. For example, mammalian cell lines that are adapted to grow in suspension may be useful. Other examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7); human embryonic kidney line (293 or 293 cells as described, e.g., in Graham et al., *J. Gen Virol.* 36:59 (1977)); baby hamster kidney cells (BHK); mouse sertoli cells (TM4 cells as described, e.g., in Mather, *Biol. Reprod.* 23:243-251 (1980)); monkey kidney cells (CV1); African green monkey kidney cells (VERO-76); human cervical carcinoma cells (HELA); canine kidney cells (MDCK); buffalo rat liver cells (BRL 3A); human lung cells (W138); human liver cells (Hep G2); mouse mammary tumor (MMT 060562); TRI cells, as described, e.g., in Mather et al., *Annals N.Y. Acad. Sci.* 383:44-68 (1982); MRC 5

cells; and FS4 cells. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including DHFR-CHO cells (Urlaub et al., Proc. Natl. Acad. Sci. USA 77:4216 (1980)); and myeloma cell lines such as Y0, NS0 and Sp2/0. For a review of certain mammalian host cell lines suitable for antibody production, see, e.g., Yazaki and Wu, Methods in Molecular Biology, Vol. 248 (B. K. C. Lo, ed., Humana Press, Totowa, N.J.), pp. 255-268 (2003).

[0207] The antibodies of the invention may be identified, screened for, or characterized for their physical/chemical properties and/or biological activities by various assays known in the art.

[0208] In one aspect, the antibody of the invention is tested for its antigen binding activity, for example, by known methods such as ELISA, Western blot, etc. In another aspect, competition assays may be used to identify an antibody that competes with an anti-p95HER2 antibody of the invention for binding to p95HER2. In an exemplary competition assay, immobilized p95HER2 is incubated in a solution comprising a first labeled antibody that binds to p95HER2 and a second unlabeled antibody that is being tested for its ability to compete with the first antibody for binding to p95HER2. The second antibody may be present in a hybridoma supernatant. As a control, immobilized p95HER2 is incubated in a solution comprising the first labeled antibody but not the second unlabeled antibody. After incubation under conditions permissive for binding of the first antibody to p95HER2, excess unbound antibody is removed, and the amount of label associated with immobilized p95HER2 is measured. If the amount of label associated with immobilized p95HER2 is substantially reduced in the test sample relative to the control sample, then that indicates that the second antibody is competing with the first antibody for binding to p95HER2. See, e.g., Harlow and Lane (1988) Antibodies: A Laboratory Manual. Ch. 14 (Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.).

[0209] In one aspect, assays are provided for identifying antibodies having biological activity. Biological activity may include, for example, binding to p95HER2 (e.g., on a cell surface), or a peptide fragment thereof, either *in vivo*, *in vitro*, or *ex vivo*. In the case of a bispecific antibody of the invention, biological activity may also include, for example, effector cell activation (e.g., T cell (e.g., CD8+ and/or CD4+ T cell) activation), effector cell population expansion (i.e., an increase in T cell count), target cell population reduction (i.e., a decrease in the population of cells expressing the second biological molecule on their cell surfaces), and/or target cell killing. In some embodiments, the activity comprises ability to support B cell killing and/or the activation of the cytotoxic T cells.

[0210] In certain embodiments, any of the antibodies of the invention may be used to detect the presence of p95HER2 in a biological sample. The term “detecting” as used herein encompasses quantitative or qualitative detection. In certain embodiments, a biological sample comprises a cell or tissue. In certain embodiments, the method comprises contacting the biological sample with an anti-p95HER2 antibody as described herein under conditions permissive for binding of the bispecific antibody to p95HER2 and another antigen, and detecting whether a complex is formed between the bispecific antibody and p95HER2. Such method may be an *in vitro* or *in vivo* method.

[0211] In certain embodiments, labeled antibodies are provided. Labels include, but are not limited to, labels or moieties that are detected directly (such as fluorescent, chromophoric, electron-dense, chemiluminescent, and radioactive labels), as well as moieties, such as enzymes or ligands, that are detected indirectly, e.g., through an enzymatic reaction or molecular interaction. Exemplary labels include, but are not limited to, the radioisotopes ^{32}P , ^{14}C , ^{125}I , ^3H , and ^{131}I , fluorophores such as rare earth chelates or fluorescein and its derivatives, rhodamine and its derivatives, dansyl, umbelliferon, luciferases, e.g., firefly luciferase, and bacterial luciferase (see for example, U.S. Pat. No. 4,737,456, which is incorporated by reference in its entirety herein, including any drawings), luciferin, 2,3-dihydrophthalazinediones, horseradish peroxidase (HRP), alkaline phosphatase, β -galactosidase, glucoamylase, lysozyme, saccharide oxidases, e.g., glucose oxidase, galactose oxidase, and glucose-6-phosphate dehydrogenase, heterocyclic oxidases such as uricase and xanthine oxidase, coupled with an enzyme that employs hydrogen peroxide to oxidize a dye precursor such as HRP, lactoperoxidase, or microperoxidase, biotin/avidin, spin labels, bacteriophage labels, stable free radicals, and the like.

Production of Anti-p95HER2 Antibodies and Antibody Compositions

[0212] An additional aspect of the invention relates to methods for producing anti-p95HER2 antibodies and compositions of the invention. One embodiment of this aspect of the invention relates to a method for producing an anti-p95HER2 antibody as defined herein, comprising providing a host cell capable of expressing an anti-p95HER2 antibody, cultivating said host cell under conditions suitable for expression of the antibody, and isolating the resulting antibody.

[0213] An antibody or antibody composition of the present invention may be produced by methods generally known in the art for production of recombinant monoclonal or polyclonal antibodies. Thus, in the case of production of a single antibody of the invention, any method known in the art

for production of recombinant monoclonal antibodies may be used. For production of an antibody composition comprising two or more anti-p95HER2 antibodies of the invention, the individual antibodies may be produced separately, i.e., each antibody being produced in a separate bioreactor, or the individual antibodies may be produced together in single bioreactor. When the number of different antibodies in a composition is more than e.g., two or three, it will generally be preferably for reasons of cost efficiency to produce the antibodies together in a single bioreactor. On the other hand, when the composition only contains a small number of different antibodies, e.g., two, three or possibly four different antibodies, a decision to produce them separately in different bioreactors or together in a single bioreactor will have to be made based on the individual circumstances. If the antibody composition is produced in more than one bioreactor, the purified anti-p95HER2 antibody composition can be obtained by pooling the antibodies obtained from individually purified supernatants from each bioreactor. Various approaches are known in the art for production of a polyclonal antibody composition in multiple bioreactors, where the cell lines or antibody preparations are combined at a later point upstream or prior to or during downstream processing.

[0214] In the case of production of two or more individual antibodies in a single bioreactor, this may be performed, for example, based on site-specific integration of the antibody coding sequence into the genome of the individual host cells, ensuring that the V_H and V_L protein chains are maintained in their original pairing during production. Furthermore, the site-specific integration minimizes position effects, and therefore the growth and expression properties of the individual cells in the polyclonal cell line are expected to be very similar. Generally, the method involves the following: i) a host cell with one or more recombinase recognition sites; ii) an expression vector with at least one recombinase recognition site compatible with that of the host cell; iii) generation of a collection of expression vectors by transferring the selected V_H and V_L coding pairs from the screening vector to an expression vector such that a full-length antibody or antibody fragment can be expressed from the vector (such a transfer may not be necessary if the screening vector is identical to the expression vector); iv) transfection of the host cell with the collection of expression vectors and a vector coding for a recombinase capable of combining the recombinase recognition sites in the genome of the host cell with that in the vector; v) obtaining/generating a polyclonal cell line from the transfected host cell and vi) expressing and collecting the antibody composition from the polyclonal cell line.

[0215] An alternative approach is to produce two or more different antibodies in a single bioreactor. This method involves generation of a polyclonal cell line capable of expressing a polyclonal antibody or other polyclonal protein comprising two or more distinct members by a) providing a set of expression vectors, wherein each of said vectors comprises at least one copy of a distinct nucleic acid encoding a distinct member of the polyclonal protein, separately transfecting host cells with each of the expression vectors under conditions avoiding site-specific integration of the expression vectors into the genome of the cells, thereby obtaining two or more compositions of cells, each composition expressing one distinct member of the polyclonal protein, and c) mixing the at least two compositions of cells to obtain a polyclonal cell line.

[0216] The antibodies of the invention may be produced in various types of cells, including mammalian cells as well as non-mammalian eukaryotic or prokaryotic cells, such as plant cells, insect cells, yeast cells, fungi, *E. coli* etc. However, the antibodies are preferably produced in mammalian cells, for example CHO cells, COS cells, BHK cells, myeloma cells (e.g., Sp2/0 or NS0 cells), fibroblasts such as NIH 3T3, or immortalized human cells such as HeLa cells or HEK 293 cells.

[0217] Methods for transfecting a nucleic acid sequence into a host cell are well-known in the art (see, e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, 3rd Edition, 2001). For site-specific integration a suitable host cell will comprise one or more recombinase recognition sites in its genome. In this case, a suitable expression vector comprises a recombination recognition site matching the recombinase recognition site(s) of the host cell.

[0218] One embodiment of the present invention is thus a polyclonal cell line capable of expressing two or more anti-p95HER2 antibodies of the present invention. A further embodiment is a polyclonal cell line wherein each individual cell is capable of expressing a single V_H and V_L pair, and the polyclonal cell line as a whole is capable of expressing a collection of V_H and V_L pairs, where each V_H and V_L pair encodes an anti-p95HER2 antibody.

Therapeutic Compositions

[0219] Another aspect of the invention is a pharmaceutical composition comprising as an active ingredient at least one anti-p95HER2 antibody of the invention, or an anti-p95HER2 Fab or another anti-p95HER2 antibody fragment composition. Such compositions are intended for

amelioration, prevention and/or treatment of cancer. The pharmaceutical composition may be administered to a human or to a domestic animal.

[0220] In addition to at least one antibody of the invention or fragment thereof, the pharmaceutical composition will further comprise at least one pharmaceutically acceptable diluent, carrier or excipient. These may for example include preservatives, stabilizers, surfactants/wetting agents, emulsifying agents, solubilizers, salts for regulating the osmotic pressure and/or buffers. Solutions or suspensions may further comprise viscosity-increasing substances, such as sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone or gelatin. A suitable pH value for the pharmaceutical composition will generally be in the range of about 5.5 to 8.5, such as about 6 to 8, e.g., about 7, maintained where appropriate by use of a buffer.

[0221] Conventional pharmaceutical practice may be employed to provide suitable formulations or compositions to administer to e.g., cancer patients. The administration will typically be therapeutic, meaning that it is administered after a cancer condition has been diagnosed. Any appropriate route of administration may be employed, for example parenteral, intravenous, intra-arterial, subcutaneous, intramuscular, intraperitoneal, intranasal, aerosol, suppository or oral administration. Pharmaceutical compositions of the invention will typically be administered in the form of liquid solutions or suspensions, more typically aqueous solutions or suspensions, in particular isotonic aqueous solutions or suspensions.

[0222] As an alternative to a liquid formulation, the compositions of the invention may be prepared in lyophilized form comprising the at least one antibody alone or together with a carrier, for example mannitol, in which case the composition is reconstituted with a liquid such as sterile water prior to use.

[0223] The pharmaceutical compositions comprise from approximately 1% to approximately 95%, preferably from approximately 20% to approximately 90%, active ingredient. Pharmaceutical compositions according to the invention may e.g., be produced in unit dose form, such as in the form of ampoules, vials, suppositories, tablets or capsules. The formulations can be administered to human individuals in therapeutically or prophylactically effective amounts (e.g., amounts which prevent, eliminate, or reduce a pathological condition) to provide therapy for a cancerous disease or other condition. The preferred dosage of therapeutic agent to be administered is likely to depend on such variables as the severity of the cancer, the overall health status of the particular patient, the formulation of the compound excipients, and its route of administration.

Therapeutic Uses of Antibodies and Compositions According to the Invention

[0224] The anti-p95HER2 antibodies and pharmaceutical compositions according to the present invention may be used for the treatment or amelioration of a disease, in a mammal, in particular treatment of cancer in humans. A particular embodiment relates to a method for treating a human patient with a disorder characterized by overexpression of p95HER2, in particular cancer, the method comprising administering to said patient one or more anti-p95HER2 antibodies as defined herein or.

[0225] Some embodiments provide a method of treating or delaying the progression of a cell proliferative disorder or an autoimmune disorder in a subject in need thereof, the method comprising administering to the subject an effective amount any one of the antibodies described herein (in a monospecific, bi-specific, or multi-specific format). In another aspect, the invention features a method of enhancing or decreasing immune function in a subject having a cell proliferative disorder or an autoimmune disorder, the method comprising administering to the subject any one of the antibodies described herein (in a monospecific, bi-specific, or multi-specific format).

[0226] In any of the uses or methods set forth herein, the cell proliferative disorder can be cancer. In some embodiments, the cancer is selected from the group consisting of breast cancer, colorectal cancer, non-small cell lung cancer, salivary gland cancer, stomach cancer, ovarian cancer, uterine cancer, cervical cancer, pancreatic cancer, colorectal cancer, bladder cancer, prostate cancer, non-Hodgkin's lymphoma (NHL), B cell lymphoma, B cell leukemia, multiple myeloma, renal cancer, prostate cancer, liver cancer, head and neck cancer, melanoma, ovarian cancer, mesothelioma, glioblastoma, germinal-center B-cell-like (GCB) DLBCL, activated B-cell-like (ABC) DLBCL, follicular lymphoma (FL), mantle cell lymphoma (MCL), acute myeloid leukemia (AML), chronic lymphoid leukemia (CLL), marginal zone lymphoma (MZL), small lymphocytic leukemia (SLL), lymphoplasmacytic lymphoma (LL), Waldenstrom macroglobulinemia (WM), central nervous system lymphoma (CNSL), Burkitt's lymphoma (BL), B-cell prolymphocytic leukemia, Splenic marginal zone lymphoma, Hairy cell leukemia, Splenic lymphoma/leukemia, unclassifiable, Splenic diffuse red pulp small B-cell lymphoma, Hairy cell leukemia variant, Waldenstrom macroglobulinemia, Heavy chain diseases, a Heavy chain disease, γ Heavy chain disease, Heavy chain disease, Plasma cell myeloma, Solitary plasmacytoma of bone, Extraosseous plasmacytoma,

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), Nodal marginal zone lymphoma, Pediatric nodal marginal zone lymphoma, Pediatric follicular lymphoma, Primary cutaneous follicle centre lymphoma, T-cell/histiocyte rich large B-cell lymphoma, Primary DLBCL of the CNS, Primary cutaneous DLBCL, leg type, EBV-positive DLBCL of the elderly, DLBCL associated with chronic inflammation, Lymphomatoid granulomatosis, Primary mediastinal (thymic) large B-cell lymphoma, Intravascular large B-cell lymphoma, ALK-positive large B-cell lymphoma, Plasmablastic lymphoma, Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease, Primary effusion lymphoma: B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma, and B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma. In some embodiments, the preferred cancer is germinal-center B-cell-like (GCB) DLBCL, activated B-cell-like (ABC) DLBCL, follicular lymphoma (FL), mantle cell lymphoma (MCL), acute myeloid leukemia (AML), chronic lymphoid leukemia (CLL), marginal zone lymphoma (MZL), small lymphocytic leukemia (SLL), lymphoplasmacytic lymphoma (LL), Waldenstrom macroglobulinemia (WM), central nervous system lymphoma (CNSL), or Burkitt's lymphoma (BL).

[0227] In some embodiments, the autoimmune disorder is selected from the group consisting of rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus (SLE), Wegener's disease, inflammatory bowel disease, idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), autoimmune thrombocytopenia, multiple sclerosis, psoriasis, IgA nephropathy, IgM polyneuropathies, myasthenia gravis, vasculitis, diabetes mellitus, Reynaud's syndrome, Sjorgen's syndrome, glomerulonephritis, Neuromyelitis Optica (NMO), and IgG neuropathy.

[0228] In some embodiments, the antibody is in a kit comprising: (a) a composition comprising any one of the antibodies described herein (in a monospecific, bi-specific, or multi-specific format) and (b) a package insert comprising instructions for administering the composition to a subject to treat or delay progression of a cell proliferative disorder. In some embodiments, the antibody within the kit is lyophilized.

[0229] In any of the preceding uses or methods, the subject can be a human.

[0230] Antibody compositions of the invention are contemplated to be particularly applicable to treatment of cancers that overexpress p95HER2, for example certain epithelial cancers such as many breast cancers, ovarian cancers and gastric (stomach) cancers.

[0231] The present invention further includes anti-p95HER2 antibody compositions that include or are administered in conjunction with at least one chemotherapeutic or other anti-cancer compound for the simultaneous, separate or successive administration in cancer therapy. Exemplary chemotherapeutic agents include, for example, alkylating agents, for example platinum derivatives such as cisplatin, carboplatin or oxaliplatin; plant alkoids, for example paclitaxel, docetaxel or irinotecan; antitumor antibiotics, for example doxorubicin (adriamycin); topoisomerase inhibitors such as topotecan; and antimetabolites, for example fluorouracil or other fluoropyrimidines.

[0232] The presently disclosed anti-p95HER2 antibodies of the invention may also be used in adjunctive therapy. For example, in connection with tyrosine kinase inhibitors (TKIs). TKIs interact with the intracellular tyrosine kinase domain of receptors and inhibiting ligand-induced receptor phosphorylation by competing for an intracellular Mg-ATP binding site. Several TKIs to block HER2 kinase are in clinical development. *See* Spector et al. (2007) *Breast Cancer Res.* 9(2): 205.

[0233] In certain aspects, the anti-p95HER2 antibody compositions of the present invention may be used in combination with other antibody therapeutics, e.g., antibodies against p185HER2 (e.g., Herceptin and Perjeta), HER3, Met, EGFR (e.g., Erbitux® or Vectibix®) or VEGF (e.g., Avastin®). In yet other embodiments, the antibody compositions of the present invention may be used in combination with an agent known to stimulate cells of the immune system, such combination treatment leading to enhanced immune-mediated enhancement of the efficacy of the antibody compositions of the invention, for example, recombinant interleukins (e.g., IL-21 and IL-2).

[0234] One or more anti-cancer agents may be conjugated to the antibodies of the invention, including cytotoxic agents (e.g., conventional chemotherapy agents and other small molecule anti-cancer drugs), cytokines, toxins, and radionuclides.

Dose and Route of Administration

[0235] The antibodies and compositions of the invention will be administered in an effective amount for treatment of the condition in question, i.e., at dosages and for periods of time necessary to achieve a desired result. A therapeutically effective amount may vary according to factors such as the particular condition being treated, the age, sex and weight of the patient, and whether the anti-p95HER2 antibodies are being administered as a stand-alone treatment or in combination with one or more additional anti-cancer treatments.

[0236] An effective amount for tumor therapy may be measured by its ability to stabilize disease progression and/or ameliorate symptoms in a patient, and preferably to reverse disease progression, e.g., by reducing tumor size. The ability of an antibody or composition of the invention to inhibit cancer may be evaluated by in vitro assays, e.g., as described in the examples, as well as in suitable animal models that are predictive of the efficacy in human tumors. Suitable dosage regimens will be selected in order to provide an optimum therapeutic response in each particular situation, for example, administered as a single bolus or as a continuous infusion, and with possible adjustment of the dosage as indicated by the exigencies of each case.

[0237] In some embodiments, the antibody is administered to the subject in a dosage of about 0.01 mg/kg to about 10 mg/kg. In some embodiments, the antibody is administered to the subject in a dosage of about 0.1 mg/kg to about 10 mg/kg. In some embodiments, the antibody is administered to the subject in a dosage of about 1 mg/kg. In some embodiments, the antibody is administered subcutaneously, intravenously, intramuscularly, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally. In some embodiments, the antibody is administered subcutaneously. In some embodiments, the bispecific antibody is administered intravenously.

Pharmaceutical Formulations

[0238] Pharmaceutical formulations of the antibodies of the invention may be prepared by mixing such antibody having the desired degree of purity with one or more optional pharmaceutically acceptable carriers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Pharmaceutically acceptable carriers are generally nontoxic to recipients at the dosages and concentrations employed, and include, but are not limited to: buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl

ammonium chloride; hexamethonium chloride; benzalkonium chloride; benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g. Zn-protein complexes); and/or non-ionic surfactants such as polyethylene glycol (PEG). Exemplary pharmaceutically acceptable carriers herein further include interstitial drug dispersion agents such as soluble neutral-active hyaluronidase glycoproteins (sHASEGP), for example, human soluble PH-20 hyaluronidase glycoproteins, such as rHuPH20 (HYLENEX®, Baxter International, Inc.). Certain exemplary sHASEGPs and methods of use, including rHuPH20, are described in US Patent Publication Nos. 2005/0260186 and 2006/0104968. In one aspect, a sHASEGP is combined with one or more additional glycosaminoglycanases such as chondroitinases.

[0239] Exemplary lyophilized antibody formulations are described in U.S. Pat. No. 6,267,958. Aqueous antibody formulations include those described in U.S. Pat. No. 6,171,586 and WO2006/044908, the latter formulations including a histidine-acetate buffer.

[0240] The formulation herein may also contain more than one active ingredient as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. For example, it may be desirable to further provide an additional therapeutic agent (e.g., a chemotherapeutic agent, a cytotoxic agent, a growth inhibitory agent, and/or an anti-hormonal agent, such as those recited herein above). Such active ingredients are suitably present in combination in amounts that are effective for the purpose intended. Active ingredients may be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nano-capsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980).

[0241] Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the bispecific antibody, which matrices are in the form of shaped articles, for example, films, or microcapsules. The formulations to be used for in vivo administration are generally sterile. Sterility may be readily accomplished, e.g., by filtration through sterile filtration membranes.

EXAMPLES

Example 1

[0242] The present example provides the results of a hybridoma-based method used to generate multiple, different anti-p95HER2 antibodies of the invention.

[0243] Briefly, the multiple, different anti-p95HER2 antibodies were produced using hybridoma technology. Although the present inventors have used this methodology to produce a large number of anti-p95HER2 antibodies, this Example provides p95HER2-specific antibodies, antibody fragments, and amino acid sequence motifs discovered by the present inventors. By elucidating the amino acid and/or nucleotide sequences of these antibodies' CDR3 heavy chain (HC) and light chain (LC) variable regions, the present inventors identified a series of "clusters" or "motifs" within the sequences. These clusters represent convergent somatic hypermutations (SHM) in the variable region sequences. Clustering may provide insight into the functionally related sequences and the diversity of the total population of antibodies and their variable region sequences. Sequences that are descendants from the same parent B cell or convergently evolved the sequences in the same cluster should be functionally more related than sequences belonging to other clusters.

[0244] In the present Example, the variable chain region sequences were provided by different antibodies. Thus, any clustering can most likely be attributed to convergent SHM, which are likely functionally related mutations, e.g., they share a specific affinity for p95HER2. These SHM may inform the development of recombinant anti-p95HER2 antibodies with improved properties, such as specific binding for p95HER2 fragments.

Hybridomas

[0245] Hybridomas were produced that each expressed a different anti-p95HER2 antibody. Methods known in the art to generate antibodies and/or hybridoma cells are known in the art.

[0246] For example, different anti-p95HER2 antibodies are obtained from different populations of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical and/or bind the same epitope except for possible variants that arise during production of the monoclonal antibody, such variants generally being present in minor amounts.

[0247] By way of example, in certain hybridoma methods, a mouse or other appropriate host animal, such as a hamster, is immunized with a p95HER2 antigen to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may 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.

[0248] The hybridoma cells thus prepared are seeded and grown in a suitable culture medium that preferably 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.

[0249] In some embodiments, the myeloma cells are 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 these, in some embodiments, the myeloma cell lines are murine myeloma lines, such as those derived from mouse tumors. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies.

[0250] Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against p95HER2. In some embodiments, the binding specificity of monoclonal antibodies produced by hybridoma cells is determined by immunoprecipitation or by an in vitro binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA).

[0251] After hybridoma cells are identified that produce antibodies of the desired specificity, affinity, and/or activity, the clones may be subcloned by limiting dilution procedures and grown

by standard methods. Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown in vivo as ascites tumors in an animal.

[0252] 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, chromatography, gel electrophoresis, dialysis, or affinity chromatography.

[0253] DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). In some embodiments, the hybridoma cells serve as a source of such DNA. Once isolated, the DNA may 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 monoclonal antibodies in the recombinant host cells.

[0254] In a further embodiment, antibodies or antibody fragments can be isolated from antibody phage libraries generated using the techniques described in McCafferty et al., *Nature*, 348:552-554 (1990). Clackson et al., *Nature*, 352:624-628 (1991) and Marks et al., *J. Mol. Biol.*, 222:581-597 (1991) describe the isolation of murine and human antibodies, respectively, using phage libraries. Subsequent publications describe the production of high affinity (nM range) human antibodies by chain shuffling (Marks et al., *Bio/Technology*, 10:779-783 (1992)), as well as combinatorial infection and in vivo recombination as a strategy for constructing very large phage libraries (Waterhouse et al., *Nuc. Acids. Res.*, 21:2265-2266 (1993)). Thus, these techniques are viable alternatives to traditional monoclonal antibody hybridoma techniques for isolation of monoclonal antibodies.

[0255] The DNA also may be modified, for example, by substituting the coding sequence for human heavy- and light chain constant domains in place of the homologous murine sequences, or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide.

Sequencing

[0256] Briefly, a cDNA library was created from anti-p95HER2 antibody mRNA obtained from a hybridoma culture of cells that express different anti-p95HER2 antibodies.

[0257] The sequences were aligned and all the unique anti-p95HER2 antibody sequences identified. Alignments the sequences revealed the uniqueness of each particular sequence and their corresponding antibodies. The antibody variable sequences of each different antibody were analyzed using a custom AlivaAlign sequencing software.

[0258] The identified CDR3, CDR2, and CDR1 HC and VL sequences are provided in Table 1 as SEQ ID NOS: 2-385. The corresponding heavy chain variable region and light chain variable region sequences are provided in Table 2 as SEQ ID NOS: 386-449 and 450-513 respectively. As shown in Table 2, the heavy and light chain variable sequences were paired and identified to a particular antibody.

Clustering

[0259] The HC and VL chain variable region sequences were clustered using an algorithm that assigned sequences to a cluster when they shared identical hV, hJ, IV, and IJ genes, had identical HCDR3 lengths and were at least 90% identical (Hamming distance) for their HCDR3s within the cluster.

[0260] Table 3 provides the identified SMH for each heavy and light chain variable region sequence. In Table 3, the respective HC and VL variable region sequences are identifiable and pairable by the identity of their associated anti-p95HER2 antibody.

[0261] Table 4 provides data that informs the listed clusters of the anti-p95HER2 antibodies. The table also shows gene usage for heavy and light chains as well as difference to germline sequences as a percentage. The corresponding and paired HC and VL CDR3 sequences are also provided. Within each cluster are related sequences or “subclusters”, e.g., 1.1 and 1.2. Surprisingly, some antibodies, although independently produced/developed, possessed identical heavy and/or light chain nucleotide sequences between the antibodies.

Incorporation by Reference

[0262] References and citations to other documents, such as patents, patent applications, patent publications, journals, books, papers, web contents, publicly accessible databases, have been made

throughout this disclosure. All such documents are hereby incorporated herein by reference in their entirety for all purposes.

Equivalents

[0263] Various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full contents of this document, including references to the scientific and patent literature cited herein. The subject matter herein contains important information, exemplification and guidance that can be adapted to the practice of this invention in its various embodiments and equivalents thereof.

TABLE 1		
CDR3 Sequences		
CDR3 VH Amino Acid Sequences	Isotype	SEQ ID NO
AADRIGENYYYYGMDV	VH	SEQ ID NO: 2
AADRTGENYYYYGMDV	VH	SEQ ID NO: 3
AADRIGENYYYYGMDV	VH	SEQ ID NO: 4
ARTGDTDYYGMDV	VH	SEQ ID NO: 5
ARTGDTDYYGMDV	VH	SEQ ID NO: 6
ARSSSSDYYYYGLDV	VH	SEQ ID NO: 7
ARSSSSDYYYYGLDV	VH	SEQ ID NO: 8
ARGLNFDY	VH	SEQ ID NO: 9
ARGLNFDY	VH	SEQ ID NO: 10
ARGLNFDY	VH	SEQ ID NO: 11
ASKLDFDY	VH	SEQ ID NO: 12
ASKLDFDY	VH	SEQ ID NO: 13
ARSPLGAVTGAFDY	VH	SEQ ID NO: 14
ARSPLGAVTGAFDY	VH	SEQ ID NO: 15
ARKAGGDY	VH	SEQ ID NO: 16

ARKAGGDY	VH	SEQ ID NO: 17
ARDGMGFDY	VH	SEQ ID NO: 18
ARDGMGFDY	VH	SEQ ID NO: 19
AREELGFDY	VH	SEQ ID NO: 20
AREELGFDY	VH	SEQ ID NO: 21
ARDERGFDY	VH	SEQ ID NO: 22
ARDERGFDY	VH	SEQ ID NO: 23
ARDELGFDY	VH	SEQ ID NO: 24
ARDELGFDY	VH	SEQ ID NO: 25
ARDGGLGFDY	VH	SEQ ID NO: 26
ARDGGLGFDY	VH	SEQ ID NO: 27
ARDQIGFDI	VH	SEQ ID NO: 28
ARESQVGFDY	VH	SEQ ID NO: 29
ARDRTGFDY	VH	SEQ ID NO: 30
AREGGTGFDN	VH	SEQ ID NO: 31
AREGGTGFDN	VH	SEQ ID NO: 32
AREGLGFDY	VH	SEQ ID NO: 33
ATRLAFDY	VH	SEQ ID NO: 34
AREGIGFDY	VH	SEQ ID NO: 35
AREELGFDY	VH	SEQ ID NO: 36
ATRLAFDY	VH	SEQ ID NO: 37
VADRVVSNHYYGMDV	VH	SEQ ID NO: 38
AADRIGDRYYGMDV	VH	SEQ ID NO: 39
ARALTGTFDY	VH	SEQ ID NO: 40
AVGAFFDY	VH	SEQ ID NO: 41

TTGELGTDY	VH	SEQ ID NO: 42
TTGELGTDY	VH	SEQ ID NO: 43
ARDVLGFDY	VH	SEQ ID NO: 44
ARVLIGFDY	VH	SEQ ID NO: 45
TGGGFFHC	VH	SEQ ID NO: 46
AREVSTGFDY	VH	SEQ ID NO: 47
ARDGTGFDY	VH	SEQ ID NO: 48
ARSPLGAVTGAFDY	VH	SEQ ID NO: 49
AADRIEGATGDYYGMDV	VH	SEQ ID NO: 50
AADRIEGATGDYYGMDV	VH	SEQ ID NO: 51
ARDEMGFDY	VH	SEQ ID NO: 52
VADRVGTDYYGMDV	VH	SEQ ID NO: 53
VADRVGTDYYGMDV	VH	SEQ ID NO: 54
AKETGDY	VH	SEQ ID NO: 55
TTGYYYASSDYFDY	VH	SEQ ID NO: 56
AREGLGFDY	VH	SEQ ID NO: 57
AKDQGGGFDY	VH	SEQ ID NO: 58
ARIRGWDDAFDI	VH	SEQ ID NO: 59
ARERLGFDY	VH	SEQ ID NO: 60
ARDYYDSSDYLTGVFDI	VH	SEQ ID NO: 61
ARATVTSSYFDY	VH	SEQ ID NO: 62
AADRVWGRDYYGMDV	VH	SEQ ID NO: 63
TRANWGFDY	VH	SEQ ID NO: 64
AREGLGFDS	VH	SEQ ID NO: 65
AKNYPFDY	VH	SEQ ID NO: 514

CDR3 VL Amino Acid Sequences	Isotype	SEQ ID NO
MQALQTPYT	VL	SEQ ID NO: 66
MQARQTPYT	VL	SEQ ID NO: 67
MQALQTPYT	VL	SEQ ID NO: 68
MQARQTPLT	VL	SEQ ID NO: 69
MQARQTPLT	VL	SEQ ID NO: 70
MQARQAPLT	VL	SEQ ID NO: 71
MQARQAPLT	VL	SEQ ID NO: 72
AAWDDSLNGLV	VL	SEQ ID NO: 73
AAWDDSLNGLV	VL	SEQ ID NO: 74
AAWDDSLNGLV	VL	SEQ ID NO: 75
VAWDDSLNGVV	VL	SEQ ID NO: 76
AAWDDSLNGLV	VL	SEQ ID NO: 77
MQSTQFIT	VL	SEQ ID NO: 78
MQATQFIT	VL	SEQ ID NO: 79
MQGTHWPLT	VL	SEQ ID NO: 80
MQGTHWPLT	VL	SEQ ID NO: 81
QSADSSGTYV	VL	SEQ ID NO: 82
QSADSSGTYV	VL	SEQ ID NO: 83
QSADSSGTYV	VL	SEQ ID NO: 84
QSADNSGSYV	VL	SEQ ID NO: 85
QSADSSGTYV	VL	SEQ ID NO: 86
QSADSSGTYV	VL	SEQ ID NO: 87
QSADSSGTYV	VL	SEQ ID NO: 88
QSADSSGTYV	VL	SEQ ID NO: 89

QSADSSGTYV	VL	SEQ ID NO: 90
QSADSSGTYV	VL	SEQ ID NO: 91
AAWDDSLSGYV	VL	SEQ ID NO: 92
QSADSSGTYL	VL	SEQ ID NO: 93
QSADSSGTYV	VL	SEQ ID NO: 94
QSADSSGTYV	VL	SEQ ID NO: 95
MQRIEFPSTYT	VL	SEQ ID NO: 96
QSADSSGTYV	VL	SEQ ID NO: 97
MQGTHWPLT	VL	SEQ ID NO: 98
QAADSSGSYYV	VL	SEQ ID NO: 99
LQHDNFWLT	VL	SEQ ID NO: 100
MQGTHWPLT	VL	SEQ ID NO: 101
MQALQTPFT	VL	SEQ ID NO: 102
MQALQTPYT	VL	SEQ ID NO: 103
MQGTHFPLT	VL	SEQ ID NO: 104
GTWHSNSKTWV	VL	SEQ ID NO: 105
SALDSSLSAV	VL	SEQ ID NO: 106
GTWHSNSKTWV	VL	SEQ ID NO: 107
QSADSSGTYV	VL	SEQ ID NO: 108
QSADGISTYNYV	VL	SEQ ID NO: 109
GTWHSNSKTWV	VL	SEQ ID NO: 110
LLYYGGAYVV	VL	SEQ ID NO: 111
QSADSSGTYV	VL	SEQ ID NO: 112
AAWDDTLSTV	VL	SEQ ID NO: 113
MQPRQTPYT	VL	SEQ ID NO: 114

GTWDSALSAGHVV	VL	SEQ ID NO: 115
QSADSSGTFYV	VL	SEQ ID NO: 116
MQALQTPLT	VL	SEQ ID NO: 117
MQGINWPIT	VL	SEQ ID NO: 118
MQCTHWPPT	VL	SEQ ID NO: 119
GTWHSSSKTWV	VL	SEQ ID NO: 120
QSADSSGTYV	VL	SEQ ID NO: 121
VLYMGSGIWV	VL	SEQ ID NO: 122
MIWHSSAVV	VL	SEQ ID NO: 123
QSADSSGTYV	VL	SEQ ID NO: 124
MQATQFIT	VL	SEQ ID NO: 125
QSYDSSLSGYV	VL	SEQ ID NO: 126
MQSLQTPFT	VL	SEQ ID NO: 127
GTWDNSLSAGV	VL	SEQ ID NO: 128
QSADSSGTSYV	VL	SEQ ID NO: 129
CSYAGSSTFV	VL	SEQ ID NO: 515
CDR1 Sequences		
CDR1 VH Amino Acid Sequences	Isotype	SEQ ID NO
GFTFTTSA	VH	SEQ ID NO: 130
GFTFTSSA	VH	SEQ ID NO: 131
GFTFTSSA	VH	SEQ ID NO: 132
GFTFSSYD	VH	SEQ ID NO: 133
GFTFSSYD	VH	SEQ ID NO: 134
GFTFSNYD	VH	SEQ ID NO: 135
GFTFSNYD	VH	SEQ ID NO: 136
GFTFSSNA	VH	SEQ ID NO: 137

GFTFSRTA	VH	SEQ ID NO: 138
GFTFSRNS	VH	SEQ ID NO: 139
GFTFSSYS	VH	SEQ ID NO: 140
GFTFSSFS	VH	SEQ ID NO: 141
GFTFSSYS	VH	SEQ ID NO: 142
GFTFSTYS	VH	SEQ ID NO: 143
GFTFSSYW	VH	SEQ ID NO: 144
GFTFSSYW	VH	SEQ ID NO: 145
GGSISSYY	VH	SEQ ID NO: 146
GGSFSSYY	VH	SEQ ID NO: 147
GGSISSNH	VH	SEQ ID NO: 148
GGSISSYY	VH	SEQ ID NO: 149
GGSINSYY	VH	SEQ ID NO: 150
GGSISSYY	VH	SEQ ID NO: 151
GGSISSYY	VH	SEQ ID NO: 152
GGSFNNYY	VH	SEQ ID NO: 153
GGSISSYY	VH	SEQ ID NO: 154
GGSISSYY	VH	SEQ ID NO: 155
GGSISSYY	VH	SEQ ID NO: 156
GGSISSYY	VH	SEQ ID NO: 157
GGSISNHY	VH	SEQ ID NO: 158
GGSITNYY	VH	SEQ ID NO: 159
GGSITNYY	VH	SEQ ID NO: 160
GFTFSSYW	VH	SEQ ID NO: 161
GFTFSSYW	VH	SEQ ID NO: 162

GGSISSYY	VH	SEQ ID NO: 163
GGSISSNH	VH	SEQ ID NO: 164
GFTFSNYW	VH	SEQ ID NO: 165
GFTFTNSA	VH	SEQ ID NO: 166
GFTFISSA	VH	SEQ ID NO: 167
GGSFSSGGHY	VH	SEQ ID NO: 168
GFTFSNYW	VH	SEQ ID NO: 169
GFTFSNAW	VH	SEQ ID NO: 170
GFTFSNAW	VH	SEQ ID NO: 171
GGSISSYY	VH	SEQ ID NO: 172
GFTFSSYW	VH	SEQ ID NO: 173
GFTFSDAW	VH	SEQ ID NO: 174
GHTFTRY	VH	SEQ ID NO: 175
GGSISSDY	VH	SEQ ID NO: 176
GFTFSSYS	VH	SEQ ID NO: 177
GFTFTSSA	VH	SEQ ID NO: 178
GFTFTSSA	VH	SEQ ID NO: 179
DGSISTYY	VH	SEQ ID NO: 180
GFTFTSSA	VH	SEQ ID NO: 181
GFTFTSSA	VH	SEQ ID NO: 182
GFTFSSYA	VH	SEQ ID NO: 183
GFTFSNAW	VH	SEQ ID NO: 184
GGSISSYY	VH	SEQ ID NO: 185
GFTFRSYA	VH	SEQ ID NO: 186
GFSLSNARMG	VH	SEQ ID NO: 187

GGSINYY	VH	SEQ ID NO: 188
GFTFSSYG	VH	SEQ ID NO: 189
GGSISSYY	VH	SEQ ID NO: 190
GFTFTSSA	VH	SEQ ID NO: 191
GFSFSGSS	VH	SEQ ID NO: 192
GFTFSSYW	VH	SEQ ID NO: 193
GFSFSSYA	VH	SEQ ID NO: 516
CDR1 VL Amino Acid Sequences	Isotype	SEQ ID NO
QSLHLSNGYNY	VL	SEQ ID NO: 194
QSLHLSNGYNY	VL	SEQ ID NO: 195
QSLHLSNGYNY	VL	SEQ ID NO: 196
QSLHLSNGYNY	VL	SEQ ID NO: 197
QSLHLSNGYNY	VL	SEQ ID NO: 198
QSLYSNGYNY	VL	SEQ ID NO: 199
QSLYSNGYNY	VL	SEQ ID NO: 200
NSNIGSNT	VL	SEQ ID NO: 201
SSNIGSNT	VL	SEQ ID NO: 202
SSNIGSNT	VL	SEQ ID NO: 203
SSNIGSNT	VL	SEQ ID NO: 204
SSNIGSNT	VL	SEQ ID NO: 205
QSLVHSDGNTY	VL	SEQ ID NO: 206
QSLVHRDGNTY	VL	SEQ ID NO: 207
QSLVSSDGNTY	VL	SEQ ID NO: 208
QSLVYSDGNTY	VL	SEQ ID NO: 209
ALPKQY	VL	SEQ ID NO: 210

ALPKLY	VL	SEQ ID NO: 211
ALPKLY	VL	SEQ ID NO: 212
ALSKKY	VL	SEQ ID NO: 213
ALPRQY	VL	SEQ ID NO: 214
ALPKQY	VL	SEQ ID NO: 215
ALPKKY	VL	SEQ ID NO: 216
TLPKQY	VL	SEQ ID NO: 217
TLPKQY	VL	SEQ ID NO: 218
ALPKQY	VL	SEQ ID NO: 219
SSNIGSNY	VL	SEQ ID NO: 220
ALPKIY	VL	SEQ ID NO: 221
TLPKKY	VL	SEQ ID NO: 222
ALPKLY	VL	SEQ ID NO: 223
QSL LDSNDGNTC	VL	SEQ ID NO: 224
ALPKLY	VL	SEQ ID NO: 225
QSLVYSDGNTY	VL	SEQ ID NO: 226
ALPKQY	VL	SEQ ID NO: 227
QDIDDD	VL	SEQ ID NO: 228
QSLVYSDGNTY	VL	SEQ ID NO: 229
QSL LHSNGYNY	VL	SEQ ID NO: 230
QSL LHSNGYNY	VL	SEQ ID NO: 231
QSLVHNDGDTY	VL	SEQ ID NO: 232
SGFSVGDFW	VL	SEQ ID NO: 233
SNIVGNQG	VL	SEQ ID NO: 234
SGFSVGDFW	VL	SEQ ID NO: 235

ALPKQY	VL	SEQ ID NO: 236
ALPKQY	VL	SEQ ID NO: 237
SGFSVGDFW	VL	SEQ ID NO: 238
TGAVTSDYY	VL	SEQ ID NO: 239
ALPKQY	VL	SEQ ID NO: 240
SSNIGNNY	VL	SEQ ID NO: 241
QSLHLSNGYNY	VL	SEQ ID NO: 242
SSNIGNNY	VL	SEQ ID NO: 243
ALPKQY	VL	SEQ ID NO: 244
QSLHLSNGYNY	VL	SEQ ID NO: 245
QSLVYSDGNTF	VL	SEQ ID NO: 246
QSLVYSDGNTY	VL	SEQ ID NO: 247
SGFSVGDFW	VL	SEQ ID NO: 248
TLPKQY	VL	SEQ ID NO: 249
SGSVSTSY	VL	SEQ ID NO: 250
SGINVGTyr	VL	SEQ ID NO: 251
ALPKLY	VL	SEQ ID NO: 252
QSLVHSDGNTY	VL	SEQ ID NO: 253
SSNIGAGYD	VL	SEQ ID NO: 254
QSLHLSNGYNY	VL	SEQ ID NO: 255
SSNIGNNY	VL	SEQ ID NO: 256
ALPKQY	VL	SEQ ID NO: 257
SSDVGSYNL	VL	SEQ ID NO: 517
CDR2 Sequences		
CDR2 VH Amino Acid Sequences	Isotype	SEQ ID NO
IVVGSGNT	VH	SEQ ID NO: 258

IVVGSNT	VH	SEQ ID NO: 259
IVVASNT	VH	SEQ ID NO: 260
IDTAGDT	VH	SEQ ID NO: 261
IDTAGDT	VH	SEQ ID NO: 262
IGTADDT	VH	SEQ ID NO: 263
IGTADDT	VH	SEQ ID NO: 264
ISSSSYI	VH	SEQ ID NO: 265
ISSSTYI	VH	SEQ ID NO: 266
ISSSSYI	VH	SEQ ID NO: 267
ISSTSYI	VH	SEQ ID NO: 268
ISSSSYI	VH	SEQ ID NO: 269
IGGSTSTI	VH	SEQ ID NO: 270
SSSSSTI	VH	SEQ ID NO: 271
IKQDGSEK	VH	SEQ ID NO: 272
IKQDGSEK	VH	SEQ ID NO: 273
IYTSGST	VH	SEQ ID NO: 274
IYTSGST	VH	SEQ ID NO: 275
IYSSGST	VH	SEQ ID NO: 276
IYTSGNT	VH	SEQ ID NO: 277
IHTSGST	VH	SEQ ID NO: 278
IYTSGST	VH	SEQ ID NO: 279
IYTSGST	VH	SEQ ID NO: 280
IYASGNT	VH	SEQ ID NO: 281
IYYSGST	VH	SEQ ID NO: 282
IYYSGST	VH	SEQ ID NO: 283

IYTSGST	VH	SEQ ID NO: 284
IYTTGST	VH	SEQ ID NO: 285
IYTSGNT	VH	SEQ ID NO: 286
IYTSGST	VH	SEQ ID NO: 287
IYTSGST	VH	SEQ ID NO: 288
IKQDGSEK	VH	SEQ ID NO: 289
IKQDGSEK	VH	SEQ ID NO: 290
FYTSGSN	VH	SEQ ID NO: 291
IYSSGST	VH	SEQ ID NO: 292
IKQDGSEK	VH	SEQ ID NO: 293
IVVGSNT	VH	SEQ ID NO: 294
IVVGSNT	VH	SEQ ID NO: 295
IYYSGST	VH	SEQ ID NO: 296
IKQDGSEK	VH	SEQ ID NO: 297
IKRKIDGGTT	VH	SEQ ID NO: 298
IKRKIDGGTT	VH	SEQ ID NO: 299
IYTSNT	VH	SEQ ID NO: 300
IKQDGSEK	VH	SEQ ID NO: 301
IKSKTDGGTT	VH	SEQ ID NO: 302
INPSGGGK	VH	SEQ ID NO: 303
IYTSGST	VH	SEQ ID NO: 304
IGGSTSTI	VH	SEQ ID NO: 305
IVVGSNT	VH	SEQ ID NO: 306
IVVGSNT	VH	SEQ ID NO: 307
IYSSGST	VH	SEQ ID NO: 308

IVVGSNT	VH	SEQ ID NO: 309
IVVGSNT	VH	SEQ ID NO: 310
ISGSYGST	VH	SEQ ID NO: 311
IKSKTDGGTI	VH	SEQ ID NO: 312
IYTSGST	VH	SEQ ID NO: 313
ISGSGGST	VH	SEQ ID NO: 314
IFSNDK	VH	SEQ ID NO: 315
IYTSGNT	VH	SEQ ID NO: 316
IWYDGSKK	VH	SEQ ID NO: 317
IYTSGST	VH	SEQ ID NO: 318
IVIGSNT	VH	SEQ ID NO: 319
IRSKAKSYAT	VH	SEQ ID NO: 320
IKQDGVKK	VH	SEQ ID NO: 321
ISSSSHK	VH	SEQ ID NO: 518
CDR2 VL Amino Acid Sequences	Isotype	SEQ ID NO
LGS	VL	SEQ ID NO: 322
LGS	VL	SEQ ID NO: 323
LGS	VL	SEQ ID NO: 324
LGS	VL	SEQ ID NO: 325
LGS	VL	SEQ ID NO: 326
LGS	VL	SEQ ID NO: 327
LGS	VL	SEQ ID NO: 328
SNN	VL	SEQ ID NO: 329
SNN	VL	SEQ ID NO: 330
SNN	VL	SEQ ID NO: 331

RNN	VL	SEQ ID NO: 332
SNN	VL	SEQ ID NO: 333
KIS	VL	SEQ ID NO: 334
KIS	VL	SEQ ID NO: 335
KIS	VL	SEQ ID NO: 336
KVS	VL	SEQ ID NO: 337
KDS	VL	SEQ ID NO: 338
KDS	VL	SEQ ID NO: 339
KDS	VL	SEQ ID NO: 340
KDS	VL	SEQ ID NO: 341
KDS	VL	SEQ ID NO: 342
KDS	VL	SEQ ID NO: 343
KDS	VL	SEQ ID NO: 344
KDS	VL	SEQ ID NO: 345
KDS	VL	SEQ ID NO: 346
KDS	VL	SEQ ID NO: 347
SNN	VL	SEQ ID NO: 348
KDT	VL	SEQ ID NO: 349
KDS	VL	SEQ ID NO: 350
KDS	VL	SEQ ID NO: 351
TLS	VL	SEQ ID NO: 352
KDS	VL	SEQ ID NO: 353
KVS	VL	SEQ ID NO: 354
KDS	VL	SEQ ID NO: 355
EGT	VL	SEQ ID NO: 356

KVS	VL	SEQ ID NO: 357
LGS	VL	SEQ ID NO: 358
LGS	VL	SEQ ID NO: 359
KIS	VL	SEQ ID NO: 360
YHSDSDK	VL	SEQ ID NO: 361
RNN	VL	SEQ ID NO: 362
YHSDSNK	VL	SEQ ID NO: 363
KDS	VL	SEQ ID NO: 364
KDI	VL	SEQ ID NO: 365
YHSDSNK	VL	SEQ ID NO: 366
STS	VL	SEQ ID NO: 367
KDS	VL	SEQ ID NO: 368
SNN	VL	SEQ ID NO: 369
LGS	VL	SEQ ID NO: 370
DNN	VL	SEQ ID NO: 371
KDN	VL	SEQ ID NO: 372
LGS	VL	SEQ ID NO: 373
KVS	VL	SEQ ID NO: 374
KVS	VL	SEQ ID NO: 375
YHSDSNK	VL	SEQ ID NO: 376
KDS	VL	SEQ ID NO: 377
STN	VL	SEQ ID NO: 378
YKSDSNK	VL	SEQ ID NO: 379
KDS	VL	SEQ ID NO: 380
KIS	VL	SEQ ID NO: 381

GNS	VL	SEQ ID NO: 382
LGS	VL	SEQ ID NO: 383
DNN	VL	SEQ ID NO: 384
KDS	VL	SEQ ID NO: 385
EGS	VL	SEQ ID NO: 519

[0264] Table 2 provides exemplary anti-p95HER2 antibody variable region sequences. The table below provides the liabilities / SHM of specific residues of in the sequences provided in Table 2.

Letter Style	Liabilities/SHM
Bold Only – e.g., “ LMK ”	SHM
Italics Only – e.g., “ <i>LMK</i> ”	Aberrant Cysteine / Binding
Underline – e.g., “ <u>LMK</u> ”	Deamidation
Bold & Italics – e.g., “ <i>LMK</i> ”	Glycosylation
Bold & Underline – e.g., “ <u>LMK</u> ”	Isomerization (D[DGHST])
Underline + Italics – e.g., “ <u><i>LMK</i></u> ”	Oxidation

Table 2 -- anti-p95HER2 antibody Variable Region Sequences				
Antibody	HC Sequence		LC Sequence	
70702_0 1C18A	EVQLLESGGGLVQPGGSLRLSCA <u>DS</u> GFTFRSYAMSWVRQAPGKGL EWVSAISGGSTYYA <u>DS</u> VKGRF TISRDNKNTLYLQMNSLRAEDT AVYYCAKDDQGGFDYWGQGTL VTVSS	SEQ ID NO: 386	QTVVLTQEPSFSVSPGGTVTLTC GLSSGSVSTSYPSWYQQTPGQ APRTLITYSTNTRSSGVPDFRSGS ILGNKAALHTTGAQA <u>DD</u> ESDYV CVLYM <u>G</u> SGIIWVFGGGTKLTVL	SEQ ID NO: 450
70702_0 1G16A	QVQLQESGPGLVKPSETLSLTCTV SGGSISYYWSWIRQPAAGKLEWI GRIYTSGSTINYNPSLKSRTMSV <u>D</u> <u>T</u> SKNQFSLKLSVTAA <u>DT</u> AVYYC ARDQIGFDIWGGQGTMTVTSS	SEQ ID NO: 387	QSVLTQPPSASGTPGQRVTISCS GSSSNIGSNVYVWYQQLPGTA PKLLIYSNNQRPSGVPDFRSGS KSGTASLASGLRSEDEADYY CAA <u>WDD</u> SLSGYVFGTGKTV L	SEQ ID NO: 451
70702_0 1O21A	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSSY <u>I</u> MSWVRQAPGKGLE WVANIK <u>QDG</u> SEKYYV <u>DS</u> VKDRF TISRDN <u>AKNS</u> LNQMNSLRAEDT AVYYCARVLIIGFDYWGQGTLVT VSS	SEQ ID NO: 388	SYELTQPPSVSVSPGQTARITCS GDALPKQYAYWYQQKPGQAP VLVICKDIERPSGIPERFSGSSG TTVTLTISGVQAEDEADYYCQS <u>ADG</u> ISTYNYVFGTGKTVTL	SEQ ID NO: 452
70702_0 2D05A	EVQLVESGGGLVKPGGSLRLSCA ASGFTFSSNALTWVRQAPGKGLE WVSSISSSSSYYIA <u>DS</u> VKGRFTIS	SEQ ID NO: 389	QSVLTQPPSASGTPGQRVTISCS GSSSNIGSNVTNWNWYQQLPGTA PKLLIYSNNQRPSGVPDFRSGS KSGTASLASGLQSEDEADYY	SEQ ID NO: 453

	RDNARNSLYLQMN <u>SLRAADT</u> AV YYCARGLNFDYWGGQGLVTVSS		CAA <u>DD</u> SLNGLVFGGGTKLTV L	
70702_0 2M01A	EVQLVESGGGLVKPGGSLRLSCA ASGFTFS <u>RTALT</u> WVRQAPGKGLE WVSSISSTSYIYY <u>ADSV</u> KGRFTIS RDNAKNSLYLQMN <u>SLRAEDT</u> AV YYCARGLNFDYWGGQGLVTVSS	SEQ ID NO: 390	QSVLTQPPSASGTPGQQRVTISCS GSSSNIGSNTVNWYQQLPGTAP KLLIY <u>SNNRR</u> PSGVPDRFSGSK SGTSASLAISGLQSEDEADYYC AA <u>DD</u> SLNGLVFGGGTKLTVL	SEQ ID NO: 454
70702_0 4N16A	EVQLVESGGGLVKPGGSLRLSCA ASGFTFS <u>D</u> A <u>MSWVR</u> QAPGKGL EWVGRIKSKT <u>DGG</u> TTDFAAPVKG RFTISR <u>DD</u> SKNTLYLQMN <u>SLKTED</u> <u>I</u> AVYYCTGGGFF <u>HC</u> WGGQGLVT VSS	SEQ ID NO: 391	QPVLTQPSHSASSGASVRLTC MLNSGFSGVGD <u>F</u> <u>IRWY</u> QQKPG NPPLYLLYYHS <u>DS</u> NKGGQSGV PSRFGSNDASANAGILRISGLQ PEDEADYYCGT <u>HSNS</u> SKT <u>V</u> F GGGTKLTVL	SEQ ID NO: 455
70702_0 4O12A	QVQLQESGPGLVKPSETLSLTCTV SGGSISSYYWSWIRQAPAGKGLEWI GRIYTSGSTNYPNPSLKSRVTMSV <u>D</u> <u>TSKNQ</u> FSKLSSVTA <u>ADT</u> AVYYC <u>ARDG</u> M/GFDYWGGQGLVTVSS	SEQ ID NO: 392	SYELTQPPSVSVSPGQTARITCS GDALPKQYAYWYQQKPGQAP VLVIYK <u>DS</u> ERPSGIPERFSGSSS GTTVLTISGVQAEDEADYYC QSA <u>DS</u> SGTYYYVFGTGTKVTVL	SEQ ID NO: 456
70702_0 5A18A	EVQLVESGGGLVKPGGSLRLSCA ASGFTFSSYSMTWVRQAPGKGLE WVSSISSTSYIYY <u>ADSV</u> KGRFTIS RDNAKNSLYLQMN <u>SLRAEDT</u> AV YYCASKLDFDYWGQGLVTVSS	SEQ ID NO: 393	QSVLTQPPSASGTPGQQRV <u>I</u> PCS GSSSNIGSNTVNWYQQLPGTAP KLLIY <u>RNNQ</u> WPSGVPDFRFGS KSGTASLA <u>IRGLQ</u> SEDEADYY CVA <u>DD</u> SLNGLVFGGGTKLTV L	SEQ ID NO: 457
70702_0 6A06A	EVQLVESGGGLVKPGGSLRLSCA ASGFTFSR <u>NSIH</u> WVRQAPGKGLE WVSSISSTSYIYY <u>ADSV</u> KGRFTIS	SEQ ID NO: 394	QSVLTQPPSASGTPGQQRVTISCS GSSSNIGSNTVNWYQQLPGTAP KLLIY <u>SNNQR</u> PSGVPDFRFGSK	SEQ ID NO: 458

	RDNAKNSLYLQMNSLRAEDTAV YYCARGLNFDYWGGQGLVTVSS		SGTSASLAI SL QSEDEAVVYC AA// DD SLNGLVFGGGTKLTVL	
70702_0 6M21A	QVHLVQSGAEVKKPGASVKVSC RASGHITFRYYMHVVRQAPGQG LEWMGHINPSGGGKINAQKFQGR VTMT RD TSTSTVYMELSSLRSED TAVVYCAR EV STGFDYWGGQGL VTVSS	SEQ ID NO: 395	QTVVTQEP SL TVSPGGIVTLTC ASSTGAVTSDYYPNWFWQKPG QVPRSLISSTSNKHSWTPARFS GSLLGKKAALTL SGV QPEDEA EYYCLLYYGGAYVVF GG GTKL TVL	SEQ ID NO: 459
70702_0 7P03A	EVQLVESGGGLVKPGGSLRLSCA ASGFTFSFS HH WVRQAPGKGLE WVSSIS SS SYIYYA DS VKGRFTIS RDNAKNSLYLQMNSLRAEDTAV YYCASKLDFDYWGQGLVTVSS	SEQ ID NO: 396	QSVLTQPPSASGTPGQRVTFSC SGSSNIGSNTVNWYQQLPGTA PKLLIYSNNQRPSGV PD RFSGS KSGTSASLAI SL QSEDEADFY CAA// DD SLNGLVFGGGTKLTV L	SEQ ID NO: 460
70702_0 8L02A	QVQLQESGPGLVKPSETLSLTCTV SGGSFSSYYWFWIRQAPAGKGLE WIGRIYTSGSTNYKSLKSRVTMS V DT SKNQVSLKLSVTAADTAVY YCAR DGM GFDYWGGQGLVTVSS	SEQ ID NO: 397	SYELTQPPSVSVSPGQTARIACS GDALPKLYAYWYQKPGQAP VLV MC AD SERPSGIPERFSGSS GTTVTLTISGVQAEDEADYYC QSA DS SGTYVVF GT GTKVTVL	SEQ ID NO: 461
70702_0 8P13A	QVQLQESGPGLVKPSETLSLTCTV SGGSIS SS YYWSWIRQAPAGKLEWI GRIYTSGSTNYPNPSLKSRVTMSV D TSKNQFSKLKLSVTAADTAVVYC ARDELGF FD YWGGQGLVTVSS	SEQ ID NO: 398	SYELTQPPSVSVSPGQTARITCS GDALPKKYVYWYQKPGQAP VLVIYK D SERPSGIPERFSGSS GTTVTLTISGVQAEDEADYYC QSA DS SGTYVVF GT GTKVTVL	SEQ ID NO: 462
70702_0 9B19A	QVQLQESGPGLVKPSETLSLTCTV SGGSIS SS YYWSWIRQAPAGKLEWI GHIYTS GN TNYPNPSLKSRVTMSV	SEQ ID NO: 399	SYELTQPPSVSVSPGQTARITCS GDALSKKYVYWYQKPGQAP VLVIYK D SERPSGIPERFSGSNS	SEQ ID NO: 463

	D TSKNQFSLKLSSVTAAD DT AFYY CAREELGFDYWGGTLVTVSS		GTTVTLTISGVQAEDEADYYC QSADNSGSYVFGTGTKVTVL	
70702_0 9J24A	QVTLKESGPVLVKPIETILTCTV SGFSLSNARMGVSWIRPPGKAL EWLAHIFSNDEKSYSRSLKSRLTI SK DT SKSQVVLTLTNMDPV DT AT YYCARIRG DD AFDIWGGGFMV TVSS	SEQ ID NO: 400	QAVLTQPSSLSASPGASALTC TLRSGINVGTIRIYVYQQKPGS PPQYLLRYK DS SNKQQSGVPS RFSGSKDASANA GILLISGLQSE DEADYYCM HH HSSAVVFGGGT KLTVL	SEQ ID NO: 464
70702_1 1A22A	QVQLQESGPGLVKPSETLSLTCTV SGGSISSYYWSWIRQPAGKGLEWI GYIYSGSTKYNP S LKSRVTISV D T SKNQFSLKLSSVTAAD DT AVYYC ARD GG GLGFDYWGGGTLVTVSS	SEQ ID NO: 401	SYELTQPPSVSVSPGQTARITCS GETLPKQYVYWFQQKPGQAP VMVYK DS ERPSGIPERFSGSSS GTTVTLTISGVQAEDEADYYC QSAD DS SGTYVFGTGTKVTVL	SEQ ID NO: 465
70702_1 1D23A	QVQLQESGPGLVKPSETLSLTCTV SGGSISSYYWSWIRQPAGKGLEWI GRIYTTGSTNYPN S LKSRVTMSV DT SKIQFSLKLSSVTAAD DT AVYY CARESQVGFDYWGGGTLVTVSS	SEQ ID NO: 402	SYELTQPPSVSVSPGQTARITCS GDALPKIYVYVYQQKPGQAPV LVVIYK DT ERPSGIPERFSGSSG TTVTLTISGVQAEDEADYYCQS AD SS SGTYLFGGGTKLTVL	SEQ ID NO: 466
70702_1 1G03A	QVQLQESGPGLVKPSETLSLTCTV SGGSISS D YWSWIRQPAGKGLEWI GRIYTSNSTNYPN S LKSRVTMSV D T SKNQFSLKLNSVTVA DT SVYYC ARD GT GTGFDYWGGGTLVTVSS	SEQ ID NO: 403	SYELTQPPSVSVSPGQTARITCS GDALPKQYAYWYQQKPGQAP VLVIYK DS ERPSGIPERFSGSSS GTTVTLTISGVQAEDEADYYC QSAD DS SGTYVFGTGTKVTVL	SEQ ID NO: 467
70702_1 1K17A	QVQLQESGPGLVKPSETLSLACTV SGGSINNYWSWIRQPAGKVLEW IGHIYTSNTNYPN S LKSRVTMSV	SEQ ID NO: 404	SYELTQPPSVSVSPGQTARITCS GDALPKLYAYWYQQKPGQAP VLVIYK DS ERPSGIPERFSGSSS	SEQ ID NO: 468

	D TSKNQFSLKLTSTVTAAD T AVYY CARERLGF D YWGQGTLVTVSS		GTTVTLTISGVQAED E ADYYC QSA D SSGTYVFGTGKVTVL	
70702_1 1L20A1	EVQLVESGGGLIQPGGSLRLSCVA SGFTFSYMSWVRQAPGKGLEW VSYIGGSTSTIYVAD S VKGRFAIS RDNAKNSLYLQMNSLRDE D TAV YYCARSPLGAVTGAFDYWGQGT LVTVSS	SEQ ID NO: 405	QSVLTQPPSASGTPGQRVTISCS GSSSNIGNNVYVY H QLPGTA SKLLIYNNQRPSPGVPDRFSGS KSGTASLAISGLRSEDEADYY CAA/ DD TLSGVFGGKLTIV	SEQ ID NO: 469
70702_1 1L20A2	EVQLVESGGGLIQPGGSLRLSCVA SGFTFSYMSWVRQAPGKGLEW VSYIGGSTSTIYVAD S VKGRFAIS RDNAKNSLYLQMNSLRDE D TAV YYCARSPLGAVTGAFDYWGQGT LVTVSS	SEQ ID NO: 406	DIVMTQTPLSPPVTLGQPASISC RSSQSLVH SD GNTYLSWLQQR PGQPPRVLIYKISNRFSGVPDFR SGSGAGTDFILKISRVEAEDVG VYYCA Q STQFIFGQGTRL E I	SEQ ID NO: 470
70702_1 4A13A	QVQLQESGPGLVKPSETLSLTCTV SGGSFNYYW T WIRQAPAGKGLE WIGHIYASGNTNFTPSLKSRTVM SV D TSKNQFSLKLSSTVTAAD T AV YYCARD E LGF D YWGQGTLVTVS S	SEQ ID NO: 407	SYELTQPPSVSVSPGQTARITCS G DILPKQYVYVYQQKPGQAP VVV Y YK D SERPSGIPERFSGSS GTTVTLTISGVQAED E ADYYC QSA D SSGTYVYVFGTGKVTVL	SEQ ID NO: 471
70702_1 4A20A	QVQLQESGPGLVKPSETLSLTCTV SGGSISN H YWSWIRQAPAGKGLEW IGRIYTS G NTNYPNPSLKSRTMSV D TSKNQFSLKLSSTVTAAD T AVY F CARDRTGF D YWGQGTLVTVSA	SEQ ID NO: 408	SYELTQPPSVSVSPGQTARITCS G DILPK K YAYVYQQKPGQAP VSVIYK D SERPSGIPERFYGS GTTVTLTISGVQAED E ADYYC QSA D SSGTYVYVFGTGKVTVL	SEQ ID NO: 472
70702_1 4B22A	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSTYSMTWVRQAP G RGLE	SEQ ID NO: 409	DIVMTQTPLSPPVTLGQPA A ISC RSSQSLV H RD G NTYLSWLQQR	SEQ ID NO: 473

	WVSYSSSSSTIYY <u>DS</u> V/KGRFTIS RDNAKNSLYLQM <u>NS</u> LRDE <u>DT</u> AV YYCARSPLGAVTGAFDYWGQGT LVTVSS		PGQPPRVLIYKISNRFSVGPDRF SGSGAGTDFTLKISRVEAEDVG VYYC <u>Q</u> ATQFITFGQGTREIK	
70702_1 4C17A	QVQLQESGPGLVKPSETLSLTCTV SGGSISYYWNWIRQPPGKGLEWI GYIYSGSTKFNPSLKSRVHSV <u>DT</u> SKNQFSCLKRSVTAA <u>DT</u> AVYYCA R <u>DG</u> GLGFDYWGGQTLVTVSS	SEQ ID NO: 410	SYELTQPPSVSVSPGQTARITCS GEALPKQYVYW <u>F</u> QKPGQAP VLVIYK <u>DS</u> ERPSGIPERFSGSS GTTVTLTISGVQAEDVYVC QSA <u>DS</u> SGTYVVFGTGTVTL	SEQ ID NO: 474
70702_1 4E02A	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSSY <u>F</u> MSWVRQAPGKGLE WV/ANIKQ <u>DG</u> SEKYYV <u>DS</u> V/KGRF TISRDNAKNSLYLQM <u>NS</u> LRAE <u>DT</u> AVYYCARKAGGDYWGGQTLVT VSS	SEQ ID NO: 411	DVVMTQSPSLPVTILGQPASIS CRSSQSLVSS <u>DG</u> NTYLIWFQQR PGQSPRRLIYKISNR <u>DS</u> GVDPDRF SGSGSGTDFTLKISRVEAEDVG VYYC <u>M</u> QGT <u>H</u> <u>I</u> PLTFGQGTRE IK	SEQ ID NO: 475
70702_1 4F23A1	QVQLQESGPGLVKPSETLSLTCTV SGGSITNYYYWNWIRQAPGKGLE WIGRIYTSNSTNYPNPSLKSRVTMS V <u>DT</u> SKNQFSCLKSSVTAA <u>DT</u> AVY FCAREGGTGFDNWGGQTLVTVSS	SEQ ID NO: 412	SYELTQPPSVSVSPGQTARITCS GDALPKLYAYWYQKPGQAP VLVIYK <u>DS</u> ERPSGIPERFSGSS GTTVTLTISGVQAEDVYVC QSA <u>DS</u> SGTYVVFGTGTVTL	SEQ ID NO: 476
70702_1 4F23A2	QVQLQESGPGLVKPSETLSLTCTV SGGSITNYYYWNWIRQAPGKGLE WIGRIYTSNSTNYPNPSLKSRVTMS V <u>DT</u> SKNQFSCLKSSVTAA <u>DT</u> AVY FCAREGGTGFDNWGGQTLVTVSS	SEQ ID NO: 413	DIVMTQTPLSLPVTPEPASISC RSSQSLL <u>DS</u> <u>NDG</u> NTCZDWYLQ KPGQSPQLLYTLTYRASGVDP RFSGSGSGTDFTLKISRVEAED VGVVYCMQRIEFP <u>S</u> <u>M</u> YTFGQG TKLEIK	SEQ ID NO: 477

70702_1 4H04A	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSY W MSWVRQAPGKGLE WVANI KQD GSEK KYV DS VKGRF TISRDN AKNS LYLQMN SLRAEDT AVYYCAREGLGFDYWGQGTLLV VSS	SEQ ID NO: 414	SYELTPPPSVSVSPGQTARITCS GDALPKLYSYWYQQKPGQAP VLVIYK DS ERPSGIPERFSGSS GTTVTLTISGVQAEDADYYC QS AD SSGTYVVFGTGTKVTVL	SEQ ID NO: 478
70702_1 4H12A1	QMQLMQSGPEVKKPGTSVKVSC KASGFTFTSSAMQWVRQARGQR LEWIGWIVVSGGNTNYAQKFQER VTITRDMSTSTAYMELSSLRSE DT AVYYCAADRIEGATGDYYG MDV WGQGTITVTVSS	SEQ ID NO: 415	DIVMTQSPLSLPVTGPASISC RSSQSLHLSNGYNYLDWYLQK PGQSPQLLIYLGSNRASGV PDR FSGSGGTIDFTLKISRVEAEDV GVYH CM Q PR QTPYTFGQGTKL EIK	SEQ ID NO: 479
70702_1 4H12A2	QMQLMQSGPEVKKPGTSVKVSC KASGFTFTSSAMQWVRQARGQR LEWIGWIVVSGGNTNYAQKFQER VTITRDMSTSTAYMELSSLRSE DT AVYYCAADRIEGATGDYYG MDV WGQGTITVTVSS	SEQ ID NO: 416	QSVLTQPPSVSAAPGQKV TISC SGSSNIGNN YLSWY QQLPGTA PKLLIYDNNKRPSGIPDRFSGSK SGTSATLGITGLQTGDEADYYC GT WDS ALSAGHVVF GGT RLT VL	SEQ ID NO: 480
70702_1 4J12A	EMPLVESGGDLVQPGGSLRLSCA ASGFTFSY W MSWVRQAPGKGLE WVANI KQD GSEK KYV DS VKGRF TISRDN AKNS LYLQMN SLRAEDT AVYYCATRLAFDYWGQGTLLV SS	SEQ ID NO: 417	DVVMTQSPLSLPVTLGQPASIS CRSSQSLVYS DG NTYLNWFQQ RPGQSPRLIYKVSNR DS GV PD RFSGSGGTIDFTLKISRVEAED VGVYYC M Q GTH W PLTFGGGT KVEIK	SEQ ID NO: 481
70702_1 4O05A	QVQLQESGPGLVKPSETLSLTCTV SGGSISSYYWSWIRQPA GK GLEWI GRIYTS G STNYPN SLKSRVTMSVD	SEQ ID NO: 418	SYELTPPPSVSVSPGQTARITCS GEALPKQYVWYQQKPGQAP VLVIYK DS ERPSGIPERFSGSS	SEQ ID NO: 482

	<u>T</u> SKNQFSLKLT <u>S</u> VTAAD <u>T</u> AVYYC ARDERGFDYWGGGTLVTVSS		GTTVTLTISGVQAED <u>E</u> ADYYC QSA <u>D</u> SSSGTYVYVFGTGTKVTV	
70702_1 4008A	QVQLQESGPGLVKPSETLSVTCTV SGGSISSYYW <u>S</u> WIRQPAKGLEWI GHFYTSGSNNYNPSLKRRVTMSL <u>D</u> TSKNQFSLKLSVTAA <u>D</u> TAVYY CAREGIGFDYWGGGNLVTVSS	SEQ ID NO: 419	SYELTPPPSVSVSPGQTARITCS GDALPKQYVYWYQQKPGQAP VLVYK <u>D</u> SERPSGIPERFSGSSS GTTVTLTISGVQAED <u>E</u> ADYYC QAA <u>D</u> SSSGSYVYVFGTGTKVTVL	SEQ ID NO: 483
70702_1 5C18A	QMQLVQSGPEVKKPGTSVKVSCR ASGFTFTTSAMQWVRQARGQRL EWIGWIVVSGGNTKYAQKFQER VTITRDMSTSTAYMEVSSLSRSED <u>T</u> AVYYCAADRIGENYYYG <u>M</u> DVW GQGTTVTVSS	SEQ ID NO: 420	DIVMTQSPLSLPVTPGEPASISC RSSQSLHHSNGYNYLDWYLQK PGQSPQLLIYLGSNRASGVPRD FSGSGGTDFTLKISRVEAEDV GVYYC <u>M</u> QALQTPYTFGQGTKL EIK	SEQ ID NO: 484
70702_1 5D20A	QVQLVESGGGVVQPGRSRLRSCA ASGFTFSSYGMHWVRQAPGKGL EWVAFI <u>I</u> Y <u>D</u> GSKKYYTESVKGR FTISR <u>D</u> HISKNTLYLQMNSLRAED <u>T</u> AVYYCARDYY <u>D</u> SSDYLTGVFDI WGQGTMTVTVSS	SEQ ID NO: 421	DIVMTQTPLSPPVTLGQPASISC RSSQSLVHS <u>D</u> GNTYLSWLQQR PGQPPRLLIYKISNRFSGVPDRF SGSGAGTDFTLKISRVEAEDVG VYYC <u>M</u> QATQTFITFGQGTLEIK	SEQ ID NO: 485
70702_1 5E14A1	QVLLQESGPGLVKPSETLSLTCTV SGGSISSNNHWSWIRQPAKGLEW IGHIYSSSGSTKYNPSLKSRVTMSL <u>D</u> TSKNQFSLKLSVTAA <u>D</u> TAVYY CAREELGFDYWGGGTRVTVSS	SEQ ID NO: 422	SYELTPPPSVSVSPGQTARITCS GDALPKLYAYWYQQKPGQAP VLVYK <u>D</u> SERPSGIPERFSGSSS GTTVTLTISGVQAED <u>E</u> ADYYC QSA <u>D</u> SSSGTYVYVFGTGTKVTVL	SEQ ID NO: 486
70702_1 5E14A2	QVLLQESGPGLVKPSETLSLTCTV SGGSISSNNHWSWIRQPAKGLEW IGHIYSSSGSTKYNPSLKSRVTMSL	SEQ ID NO: 423	ETTLTQSPAEMSATPGDKV/NIS CKASQD <u>I</u> DDDMNWNYYQQKPGE AAFIHQEGTTLVPGIPRFSGSG	SEQ ID NO: 487

	DT SKNQFSLKLSVTAAD FA VVY CAREELGFDYWGQGT RV TVSS		YGTDFTLTLNNIVSEDAAYYFC LQHDN FL //TFGRG TK VEIK	
70702_1 5K04A	EGQLVESGGGLVQPGGSLRLS CE ASGFTFSNY//MSWVRQAPG KG L EWVANIKQ DG SEKYV VDS VKGR FTISRDNAKNSLYLQMN SLRAED T AVVYCATRLAFDYWGQGT LV VSS	SEQ ID NO: 424	DVVM TQ SPLSLPVT LG Q P ASIS CRSSQSLVYS DC NTY L NW FQ Q RPGQSPRR LIYK VSNR DS GV PD RFSGSGSGTDFTLKISRVEAED VGVVY CM Q Q GIH//PLTFGQGT RLEIK	SEQ ID NO: 488
70702_1 5K13A	QMQLVQSGPEVK K PGTSVKV SCK ASGFTFTSSAIQWVRQARG QR LE WIGWIVVSGNT KCAQK FQ ER VT ISRDMSTSTVYME LSLRSEDI AV YYCAADRTGENYY YGMD VW GQ GTTVTVSS	SEQ ID NO: 425	DVVM TQ SPLSLPVT GP E P ASIS RSSQSL HR NGYNYLDWY LQ K PGQSPQL LIY LGSNRASGV PD R FSGSGSGTDFTLKISRVEAEDV GVVY CM Q AR QTPYTFGQGT KL EIK	SEQ ID NO: 489
70702_1 6A10A	QMQLVQSGPEVK T PGTSVKV SCK ASGFTFTSSAVQWVRQARG QR LE WIGWIVVASGNT FAQK F RE RV T ITRDMSTSTAYME LSLRSEDI AV YYCAADRIGENYY YGMD VW GQ GTTVTVSS	SEQ ID NO: 426	DVVM TQ SPLSLPVT GP E P ASIS RSSQSL HS NGYNYLDWY LQ K SGQSPQL LIY LGSNRASGV PD R FSGSGSGTDFTLKISRVEAEDV GVVY CM Q AL QTPYTFGQGT KL EIK	SEQ ID NO: 490
70702_1 6A18A1	EVQLVESGGGLVQPGGSLRLS CA ASGFTFSY//MSWVRQAPG KG LE WVANIKQ DG SEKYV VDS VKGRF TISRDNAKNSLYLQMN SLRAEDT AVVY CARK AGGDYWGQGT LV VSS	SEQ ID NO: 427	DVVM TQ SPLSLPVT LG Q P ATIS CRSSQSLVYS DC NTY L KW FQ Q RPGQAPRR LIYK VSKR DS GV PD RFSGSGSGTDFTLKISRVEAED VGVVY CM Q Q GIH//PLTFGQGT RLEIK	SEQ ID NO: 491

70702_1 6A18A2	QVQLQESGPGLVKPSETLSLTCTV SGGSISSYYW ^{SWIR} QPA ^{GK} GLEWI GRIYTS ^{STN} YNPSLKSRVTMSV ^D <u>T</u> SKNQFSLKLSVTA ^{ADT} AVYYC ARATVTS ^{SYFDY} WGQGTILVTVSS	SEQ ID NO: 428	QSVLTQPPSVSGAPQQRVTISC TGSSNIGAGYDVHWYQQLP ^G TAPKLLIYGN ^{SNR} PSGVPDRFS GSKSGTASLAITGLQAEDEAD YYCQSY ^{DSSL} SGYVFGTGT ^{KV} TVL	SEQ ID NO: 492
70702_1 6C22A	QVQLQESGPGLVKPSETLSLTCTV SGGSINSYYW ^{SWIR} QPA ^{GK} GLEW IGRIHTSG ^{TNC} NP ^{SLK} SRVAMSI <u>D</u> TSKNQFSLKLSVIAA ^{DT} AVYY CARDERGF ^{DY} WGQGTILVTVSS	SEQ ID NO: 429	SYELTQPPSVSVSPGQTARITCS GDALP ^{RQY} VYVYQQKPGQAP VLVIYK ^D SERPSGIPERFSGSS GTTVTLTISGVQAEDEADYYC QSA ^{DSS} SGTYVFGTGT ^{KV} TVL	SEQ ID NO: 493
70702_1 6J21A	QVQLQESGPGLVKPSETLSLTCTV <u>S</u> DGSIS ^{TY} YW ^{SWIR} QPA ^{GK} GLEW IGRIYSSG ^{STN} YNPSLKSRVTMS ^{ID} <u>T</u> SKNQFSLKLSVTA ^{ADT} AVYYC ARDEM ^{GFDY} WGQGTILVTVSS	SEQ ID NO: 430	SYELTQPPSVSVSPGQTARITCS GDALP ^{KQY} AYWYQQKPGQAP VLVIYK ^D NERPSGIPERFSGSS GTAVTLTISGVQAEDEADYYC QSA ^{DSS} SGTFYVFGTGT ^{KV} TVL	SEQ ID NO: 494
70702_1 7A10A1	QMQLVQSGPEVKKPGTSVKVSK ASGFTFTSSAMQWVRQARGQRLE WIGWIVVGS ^{GNT} KYAQKFQERV TITRDMST ^S RAYMELSSLRSE ^{DTA} VYYCVADR ^V GT ^{DY} YG ^M DVWGQ GTTVTVSS	SEQ ID NO: 431	DIVMTQSP ^{LSL} LPVTPEEPASISC RSSQSL ^{LHS} NGYN ^{YLD} WYLQK PGQSPQLLIY ^{LGS} NRASGV ^{PDR} FSGSGSGTDFTLKISRVEAEDV GVVYVC ^M QALQTPLTFGGG ^T KV EIK	SEQ ID NO: 495
70702_1 7A10A2	QMQLVQSGPEVKKPGTSVKVSK ASGFTFTSSAMQWVRQARGQRLE WIGWIVVGS ^{GNT} KYAQKFQERV TITRDMST ^S RAYMELSSLRSE ^{DTA}	SEQ ID NO: 432	DVVM ^T QSP ^{LSL} LPVT ^{LGP} ASIS CRSSQSLVY ^{SDG} NTFLNWFQ ^Q RPGQSP ^{RRL} IYK ^{VSNR} ^D SGV ^{PD} RFSGSGSGTDFTLKISRVEAED	SEQ ID NO: 496

	VYYC VADRV GTDYYGMDVWGQ GTTVTVSS		VGIYYSMQQIN//PITFGQCTRL EIK	
70702_1 7B04A	QMLVQSGPEVKKPGTSVKVSCK ASGFTFTNSAMQWVRQARGRL EWIGWIVVGSNTNYAQKFQERV TTRDMSTSTAYMELSSLRSEDTIA VYYC VADRVVSNHYYGMDVWG QGTTVTVSS	SEQ ID NO: 433	DIVMTQSPLSLPVPGEPAISIC RSSQSLLHSNGYNYLDWYLQK PGQSPQLLIYLGSNRASGVDPDR FSGSGSGTDFTLKISRVEAEDV GVYYCMAQALQTPFTFGPGTKV DIK	SEQ ID NO: 497
70702_1 7E14A	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSYDMHWVRQVVGKGL EWVSAIDT AGDT YYPGSKGRFT ISRENAKNSLYLQMNSLRAGDTIA VYYCARTGDT YD YYGMDVWGQ TTVTVSS	SEQ ID NO: 434	DIVMTQSPLSLPVPGEPAISIC RSSQSLLHSNGYNYLDWYLQK PGQSPQLLIYLGSNRASGVDPDR FSGSGSGTDFTLKISRVEAEDV GLYYCMAQARQTPLTFGGGKTV EIK	SEQ ID NO: 498
70702_1 7K07A	QMLVQSGPEVKKPGTSVKVSCK TSGFTFTSSAMQWVRQARGRL WIGWIVIGSNTNYAQKFQERVTI TRDMSTSTAYMELSSLRSEDTAV YYCAADRVHGRDYYGMDVWGQ GTTVTVSS	SEQ ID NO: 435	DIVMTQSPLSLPVPGEPAISIC RSSQSLLHSNGYNYLDWYLQK PGQSPQLLIYLGSNRASGVDPDR FSGSGSGTDFTLKISRVEAEDV GVYYCMAQSLQTPTFTFGPGTKV DIK	SEQ ID NO: 499
70702_1 7O17A	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSYDMHWVRQVVGKGL EWVSAIDT AGDT YYPGSKGRFT ISRENAKNSLYLQMNSLRAGDTIA VYYCARTGDT YD YYGMDVWGQ TTVTVSS	SEQ ID NO: 436	DIVMTQSPLSLPVPGEPAISIC RSSQSLLHSNGYNYLDWYLQK PGQSPQLLIYLGSNRASGVDPDR FSGSGSGTDFTLKISRVEAEDV GLYYCMAQARQTPLTFGGGKTV EIK	SEQ ID NO: 500

70702_1 7P02A	QMLVQSGPEVKKPGTSVKVSKK ASGFTFISSAMQWVRQARGORRE WIGWIVVSGGNTKYAQKFQERV TITRDMSTSTAYMELSSLSRSEDTA VYYCAADRIGDRYYGMDVWGQ GTTVTVSS	SEQ ID NO: 437	DIVMTQSPSLSPVTPGEPASISC RSSQSLHNSNGYNYLDWYLQK PGQSPQLLIYLGSNRASGVDPDR FSGSGSGTDFTLKISRVEAEDV GVYYCMQALQTPYTFGGGTKL EIK	SEQ ID NO: 501
70702_1 8D08A	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSNYDMHWVRLTTGKGL EWVSAIGTADDTYYPGSVKGRFT ISRENAKNSLYLQMNSLRAGDTA VYYCARSSSDYYYGLDVWGQ TTVTTVSS	SEQ ID NO: 438	DIGMTQSPSLSPVTPGEPASISC RSSQSLLYSNGYNYLDWYLQK PGQSPQLLIYLGSNRASGVDPDR FSGSGSGTDFTLKISRVEAEDV GIYYCMQARQAPLTFGGGTKV EIK	SEQ ID NO: 502
70702_1 9F16A	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSNYDMHWVRLTTGKGL EWVSAIGTADDTYYPGSVKGRFT ISRENAKNSLYLQMNSLRAGDTA VYYCARSSSDYYYGLDVWGQ TTVTTVSS	SEQ ID NO: 439	DIGMTQSPSLSPVTPGEPASISC RSSQSLLYSNGYNYLDWYLQK PGQSPQLLIYLGSNRASGVDPDR FSGSGSGTDFTLKISRVEAEDV GIYYCMQARQAPLTFGGGTKV EIK	SEQ ID NO: 503
70702_1 9G11A	QVQLQESGPGLVKPSQTLSTCTV SGGSFSSGGHYWSWIRQHPGKGL EWIGFIYYSGSTYYNPSLKSRITISI DTSKNQFSLKLSVTAADTAVVY CARALTGTFDYWGQGLVTIVSS	SEQ ID NO: 440	DIVMTQTPLSPPVTLGQPASISC RSSQSLVHNDGDTYLSWLQQR PGQPPRLLIYKISNRFSGVPDRF SGSGAGTDFTLKISRVEAEDVG VYYCMQQTGFHPLTFGGGTKVE IK	SEQ ID NO: 504
70702_1 9H16A	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMSWVRQAPGKGLE WVSTISGSYGSTYYADSVKGRFTI	SEQ ID NO: 441	DVVMQTQSPSLSPVTLGQPASIS CRSSQSLVYSDGNTYLNWFHQ RPGQSPRRLIYKVSKRDSGVDPD RFSGSGSGTDFTLKISRVEAED	SEQ ID NO: 505

	SRDNSKNTLYLQMNSLRAEDTAV YYCAKETGDYWGQGTLVTVSS		VGLYYCMQC/H/PPTFGGGTK VEIK	
70702_2 0A07A	EVQLVESGGGLGQPGGSLKLSCA ASGFTFSNMHWVRQAPGKGLE WVGRIRSKAKSYATAYAAASVKG RFTISRDDSKNTAYLQMNSLKTE DTALYYCTRANWGFQDYWGQGT LVTVSS	SEQ ID NO: 442	QSVLTQPPSVSAAPGQKVITSC SGSSNIGNNNYVSWYQQLPGT APKLLYDNNKRPSGIPDRFSGS KSGTSAITLGITGLQTGDEADYY CGTWDNSLSAGVFGGGTKLTV L	SEQ ID NO: 506
70702_2 0A08A	EVQLVESGGGLVQPGGSLRLSCA VSGFTFSNYMNNWVRQAPGKGL EWVANIKQDDGSEKYYVDSVKGR FTISRDNAKNSLYLQMNSLRAED TAVYYCAVGAFFDYWGQGTLV TVSS	SEQ ID NO: 443	QPVLTQPSHSAASSGASVRLTC MLSSGFSVGDFWIRWYQQKPG NPPRYLLYYHSDSDKGGQSGV PSRFGSNDASANAAGILRISGLQ PEDEADYYCGTWSHNSKTWVF GGGTKLTVL	SEQ ID NO: 507
70702_2 0B05A1	EVQLVESGGGLVKPGGSLRLSCA ASGFTFSNAWMSWVRQAPGKGL EWVGRIKRKIDGGTTDYAAPVK GRFTISRDDSKNTLYLQMNSLKTE DTGVVYCTTGELGTDYWGQGT LVTVSS	SEQ ID NO: 444	QAQLTQPPSVSKGLRQTATLTC TGNINIVGNQGAAWLQQHQG HPPKLLSYRNNNRPSGISERFSA SRSGNTASLTITGLQPEDEADY YCSALDSSLSAVFGSGTKVTVL	SEQ ID NO: 508
70702_2 0B05A2	EVQLVESGGGLVKPGGSLRLSCA ASGFTFSNAWMSWVRQAPGKGL EWVGRIKRKIDGGTTDYAAPVK GRFTISRDDSKNTLYLQMNSLKTE DTGVVYCTTGELGTDYWGQGT LVTVSS	SEQ ID NO: 445	QPVLTQPSHSAASSGASVRLTC MLSSGFSVGDFWIRWYQQKPG NPPRYLLYYHSDSNKGGQSGV PSRFGSNDASANAAGILRISGLQ PEDEADYYCGTWSHNSKTWVF GGGTKLTVL	SEQ ID NO: 509

70702_2 0C01A	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSY#MSWVRQAPGKGLE WVANI KQDG VKKYYV DS VKGRF TISRDN AK NSLYLQMN SLRAEDT AVYYCAREGLGF DS WGQGTLVTVSS	SEQ ID NO: 446	SYELTPPSVSVSPGQTARITCS GDALPKQYAYWYQQKPGQAP VLVIYK DS ERPSGIPERFSGSS GTTVTLTISGVQAEDEADYYC Q SA DS SGTYYVFGTGTKVTVL	SEQ ID NO: 510
70702_2 0J03A	QVQLRESGPGLVKPSETLSLTCTV SGGSISYYWSWIRQ S AGKGLEWI GHYTSNTNYP SLK SRVTMSV DT SKNQFSLNLSVTA ADT AVYY CARDVLGFDYWGGQGLVTVSS	SEQ ID NO: 447	SYELTPPSVSVSPGQTARITCS GDALPKQYVYWYQQKPGQAP VLVIYK DS ERPSGIPERFSGSS GTTVTLTISGVQAEDEADYYCQ S AD SS GTYYVFGTGTKVTVL	SEQ ID NO: 511
70702_2 0L07A	EVQLVESGGGLVKPGGSLRLSCA ASGFTFSNA#MSWVRQAPGKGL EWVGRIKSKT DD GGTIDYAAPVKG RFTISR DD SKNTLSLQMN SLK TED T AVYYCTTGYYA SSD YYFDYW GQGTLVTVSS	SEQ ID NO: 448	QPVLTQPSHSASSGASVRLTC MLSSGFSGVDF#IRWYQQKPG NPPRFLLYYHS DS NKGQSGV PSRFGSNDASAN AGIL RISGLQ PEDETYYCGT#HSSSKT#VF GGGTKLVTVL	SEQ ID NO: 512
70702_2 1A09A	QVQLQESGPGLVKPSETLSLTCTV SGGSISYYWSWIRQ P AGKGLEWI GHYTS GT KYN PSL KSRVTMSV DT SKNQSLSLSSVTA ADT AVYY CAREGLGFDYWGGQGLVTVSS	SEQ ID NO: 449	SYELTPPSVSVSPGQTARITCS G DT LPKQYAYWYQQKPGQAP VLVIYK DS ERPSGIPERFSGSS GTTVTLTISGVQAEDEADYYC Q SA DS SGTYYVFGTGTKVTVL	SEQ ID NO: 513

Table 3 -- SHM Liabilities										
Antibody	Heavy Chain									
	SHM	Missing Cysteines	Aberrant Cysteines	CDR3 Aberrant Cysteines	Deamidation	CDR3 Deamidation	Glycosylation	CDR3 Glycosylation	Isomerization (D[DCHST])	Oxidation
70702_0 1C18A S30R	A24D S30R			False	NS/74 NS/84	False		False	DS/24 DS/62 DT/90	
70702_0 1G16A				False		False		False	DT/72 DT/89	
70702_0 1O21A	G66D Y80N			False	NA/74 NS/77 NS/84	False		False	DG/54 DS/62 DT/90	CDR1
70702_0 2D05A	Y32N S33A M34L N35T K76R E89A			False	NA/32 NA/74 NS/77 NS/84	False		False	DS/62 DT/90	
70702_0 2M01A	S31R Y32T S33A M34L N35T S56T			False	NA/74 NS/77 NS/84	False		False	DS/62 DT/90	
70702_0 4N16A	N31D Y62F D105H Y106C	C106		True	NS/86	False		False	DG/56 DD/75 DT/92	CDR1
70702_0 4O12A				False		False		False	DT/72 DT/89 DG/98	CDR3
70702_0 5A18A	N35T S54T			False	NA/74 NS/77 NS/84	False		False	DS/62 DT/90	
70702_0 6A06A	S31R Y32N M34I N35H			False	NS/32 NA/74 NS/77 NS/84	False		False	DS/62 DT/90	

Table 3 -- SHM Liabilities										
Antibody	Heavy Chain									
	SHM	Missing Cysteines	Aberrant Cysteines	CDR3 Aberrant Cysteines	Deamidation	CDR3 Deamidation	Glycosylation	CDR3 Glycosylation	Isomerization (D[DGHST])	Oxidation
70702_0 6M21A	Q3H			False	NA/60	False		False	DT/73 DT/90	
	K23R									
	Y27H									
	S31R									
	S57G									
	T58K									
70702_0 7P03A	S59I									
	Y60N									
	Y32F			False	NA/74 NS/77	False		False	DS/62 DT/90	
	M34I				NS/84					
70702_0 8L02A	N35H									
	I29F			False		False		False	DT/72 DT/89	CDR3
	S35T								DG/98	
	N60K									
	P61S									
70702_0 8P13A	F78V									
				False		False		False	DT/72 DT/89	
70702_0 9B19A										
	R50H			False		False		False	DT/72 DT/89	
	S56N									
70702_0 9J24A	V92F									
	T63R			False	NA/31	False		False	DT/74 DT/91	CDR1
	M84L								DD/104	CDR3
	T114P									
70702_1 1A22A	N58K			False		False		False	DT/72 DT/89	
									DG/98	
70702_1 1D23A	S54T			False		False		False	DT/72 DT/89	
	N76I									
70702_1 1G03A	Y32D			False	NS/83	False		False	DT/72 DT/89	
	S83N								DG/98	

Table 3 -- SHM Liabilities										
Antibody	Heavy Chain									
	SHM	Missing Cysteines	Aberrant Cysteines	CDR3 Aberrant Cysteines	Deamidation	CDR3 Deamidation	Glycosylation	CDR3 Glycosylation	Isomerization (D[DCHST])	Oxidation
70702.1 1K17A	A87V									
	A91S									
	T21A									
	S30N			False		False		False	DT/72 DT/89	
	S31N									
	G44V									
70702.1 1L20A1	R50H									
	S56N									
	S83T									
	V12I									
	A23V			False	NA/74 NS/77 NS/84	False		False	DS/62 DT/90	
	N35S									
70702.1 1L20A2	S52G									
	S53G									
	S55T									
	T69A									
	V12I			False	NA/74 NS/77 NS/84	False		False	DS/62 DT/90	
	A23V									
70702.1 4A13A	N35S									
	S52G									
	S53G									
	S55T									
	T69A									
	I29F			False		False		False	DT/72 DT/89	
	S30N									
	S31N									
	S35T									
	R50H									
	T53A									
	S56N									

Table 3 -- SHM Liabilities										
Antibody	Heavy Chain									
	SHM	Missing Cysteines	Aberrant Cysteines	CDR3 Aberrant Cysteines	Deamidation	CDR3 Deamidation	Glycosylation	CDR3 Glycosylation	Isomerization (D[DGHST])	Oxidation
	Y59F N60T									
70702_1 4A20A	S31N Y32H S56N Y94F			False		False		False	DT/72 DT/89	
70702_1 4B22A	S31T N35T K43R I51S			False	NA/74 NS/77 NS/84	False		False	DS/62 DT/90	
70702_1 4C17A	S35N N58K Y59F T68I S83R			False		False		False	DT/72 DT/89 DG/98	
70702_1 4E02A				False	NA/74 NS/77 NS/84	False		False	DG/54 DS/62 DT/90	CDR1
70702_1 4F23A1	S30T S31N S35N Y94F Y105N			False		False		False	DT/72 DT/89	
70702_1 4F23A2	S30T S31N S35N Y94F Y105N			False		False		False	DT/72 DT/89	
70702_1 4H04A	Y59K			False	NA/74 NS/77 NS/84	False		False	DG/54 DS/62 DT/90	CDR1

Table 3 -- SHM Liabilities											
Heavy Chain											
Antibody	SHM	Missing Cysteines	Aberrant Cysteines	CDR3 Aberrant Cysteines	Deamidation	CDR3 Deamidation	Glycosylation	CDR3 Glycosylation	Isomerization (D[DGHS])	Oxidation	
70702_1 4H12A1	V5M V102E			False		False		False	DT/90	CDR3	
70702_1 4H12A2	V5M V102E			False		False		False	DT/90	CDR3	
70702_1 4J12A	V2M Q3P G10D			False	NA/74 NS/77 NS/84	False		False	DG/54 DS/62 DT/90	CDR1	
70702_1 4O05A	S83T			False		False		False	DT/72 DT/89		
70702_1 4O08A	L20V R50H I51F T57N S65R V71L S83N T109N			False	NS/83	False		False	DT/72 DT/89		
70702_1 5C18A	K23R S31T N59K L83V			False		False		False	DT/90	CDR3	
70702_1 5D20A	V50F N57K A61T D62E N74H G105D			False	NS/84	False		False	DG/54 DH/73 DT/90 DS/102	CDR2	
70702_1 5E14A1	Q3L Y32N Y33H			False		False		False	DT/72 DT/89		

Table 3 -- SHM Liabilities										
Antibody	Heavy Chain									
	SHM	Missing Cysteines	Aberrant Cysteines	CDR3 Aberrant Cysteines	Deamidation	CDR3 Deamidation	Glycosylation	CDR3 Glycosylation	Isomerization (D[DCHST])	Oxidation
70702_1 5E14A2	R50H									
	I53S									
	N58K									
	V71L									
	L110R									
70702_1 5K04A	Q3L			False		False		False	DT/72 DT/89	
	Y32N									
	Y33H									
	R50H									
	I53S									
70702_1 5K13A	N58K									
	V71L									
	L110R									
	V2G			False	NA/74 NS/77 NS/84	False		False	DG/54 DS/62 DT/90	CDR1
	A23E									
70702_1 6A10A	S31N		C59	False		False		False	DT/90	CDR3
	M34I									
	N59K									
	Y60C									
	T71S									
70702_1 6A18A1	A79V			False		False		False	DT/90	CDR3
	K13T									
	G54A									
	Y60F									
	Q65R			False	NA/74 NS/77 NS/84	False		False	DG/54 DS/62 DT/90	CDR1
70702_1 6A18A2				False		False		False	DT/72 DT/89	

Table 3 -- SHM Liabilities										
Antibody	Heavy Chain									
	SHM	Missing Cysteines	Aberrant Cysteines	CDR3 Aberrant Cysteines	Deamidation	CDR3 Deamidation	Glycosylation	CDR3 Glycosylation	Isomerization (D[DGHST])	Oxidation
70702_1 6C22A	S30N Y52H Y59C T68A V71I T86I		C58	False	NS/30	False		False	DT/72 DT/89	
70702_1 6J21A	G26D S31T T53S V71I S83R			False		False		False	DG/26 DT/72 DT/89	CDR3
70702_1 7A10A1	N59K T78R A97V V102G			False		False		False	DT/90	CDR3
70702_1 7A10A2	N59K T78R A97V V102G			False		False		False	DT/90	CDR3
70702_1 7B04A	S31N A97V			False	NS/31	False		False	DT/90	CDR3
70702_1 7E14A	A40V G52D			False	NA/73 NS/76 NS/83	False		False	DT/52 DT/56 DT/89 DT/100	CDR3
70702_1 7K07A	A24T V53I			False		False		False	DT/90	CDR3 CDR3
70702_1 7O17A	A40V G52D			False	NA/73 NS/76 NS/83	False		False	DT/52 DT/56 DT/89 DT/100	CDR3
70702_1 7P02A	T30I L45R N59K			False		False		False	DT/90	CDR3

Table 3 -- SHM Liabilities										
Antibody	Heavy Chain									
	SHM	Missing Cysteines	Aberrant Cysteines	CDR3 Aberrant Cysteines	Deamidation	CDR3 Deamidation	Glycosylation	CDR3 Glycosylation	Isomerization (D[DGHST])	Oxidation
70702_1 8D08A	S31N			False	NA/73 NS/76 NS/83	False		False	DD/55 DT/89	
	Q39L									
	A40T									
	G55D									
	M107L									
70702_1 9F16A	S31N			False	NA/73 NS/76 NS/83	False		False	DD/55 DT/89	
	Q39L									
	A40T									
	G55D									
	M107L									
70702_1 9G11A	I29F			False	NS/85	False		False	DT/74 DT/91	
	Y34H									
	Y52F									
	V69I									
	V73I									
70702_1 9I16A	S85N									
	A50T			False	NS/84	False		False	DS/62 DT/90	
	G55Y									
	V12G			False	NS/86	False		False	DD/75 DT/92	CDR3
	T28S									
70702_2 0A07A	A33S									
	N56K									
	V95L									
	A24V			False	NA/74 NS/77 NS/84	False		False	DG/54 DS/62 DT/90	CDR1
	S31N									
70702_2 0B05A1	S35N									
	S53R			False	NA/31 NS/86	False		False	DG/56 DD/75 DT/92	CDR1
	T55I									
	A94G									

Table 3 – SHM Liabilities										
Antibody	Heavy Chain									
	SHM	Missing Cysteines	Aberrant Cysteines	CDR3 Aberrant Cysteines	Deamidation	CDR3 Deamidation	Glycosylation	CDR3 Glycosylation	Isomerization (D DCHST)	Oxidation
70702_2 0B05A2	S53R T55I A94G			False	NA/31 NS/86	False		False	DG/56 DD/75 DT/92	CDR1
70702_2 0C01A	S56V E57K Y105S			False	NA/74 NS/77 NS/84	False		False	DG/54 DS/62 DT/90 DS/104	CDR1
70702_2 0J03A	Q5R V12L P40S R50H S56N K81N S83N			False	NS/83	False		False	DT/72 DT/89	
70702_2 0L07A	T60I Y82S D105A G108D			False	NA/31 NS/86	False		False	DG/56 DD/75 DT/92	CDR1
70702_2 1A09A	R50H N58K F78L			False		False		False	DT/72 DT/89	

Table 3 (Continued) – SHM Liabilities										
Antibody	Light Chain									
	SHM	Missing Cysteines	Aberrant Cysteines	CDR3 Aberrant Cysteines	Deamidation	CDR3 Deamidation	Glycosylation	CDR3 Glycosylation	Isomerization (D DCHST)	Oxidation
70702_0 1C18A				False		False		False	DD/83	CDR3 CDR3

Table 3 (Continued) -- SHM Liabilities										
Light Chain										
Antibody	SHM	Missing Cysteines	Aberrant Cysteines	CDR3 Aberrant Cysteines	Deamidation	CDR3 Deamidation	Glycosylation	CDR3 Glycosylation	Isomerization (D[DGHS])	Oxidation
70702_0 1G16A				False		False		False	DD/93	CDR3
70702_0 1O21A	Y48C S51I S92G S93I G94S		C48	False		False		False	DG/91	
70702_0 2D05A	S26N			False	NS/26 NG/97	True		False	DD/93	CDR3
70702_0 2M01A	Q54R			False	NG/97	True		False	DD/93	CDR3
70702_0 4N16A	S25N			False	NS/25 NA/77 NS/102	True		False	DS/55	CDR1 CDR3 CDR3
70702_0 4O12A				False		False		False	DS/50 DS/91	
70702_0 5A18A	T19I S21P S51R R55W S77R A90V			False	NG/97	True		False	DD/93	CDR3
70702_0 6A06A	L40F D86V			False	NG/97	True		False	DD/93	CDR3
70702_0 6M21A	G32D A45V A48S Y51S			False		False		False		
70702_0 7P03A	I20F Y87F			False	NG/97	True		False	DD/93	CDR3

Table 3 (Continued) -- SHM Liabilities										
Light Chain										
Antibody	SHM	Missing Cysteines	Aberrant Cysteines	CDR3 Aberrant Cysteines	Deamidation n	CDR3 Deamidation	Glycosylation	CDR3 Glycosylation	Isomerization (D[DCGHST])	Oxidation
70702_0 8L02A	T21A Q30L I47M Y48C		C48	False		False		False	DS/50 DS/91	
70702_0 8P13A	Q30K A32V			False		False		False	DS/50 DS/91	
70702_0 9B19A	P28S Q30K A32V S65N S92N T95S			False	NS/65 NS/92	True		False	DS/50	
70702_0 9J24A	D57N			False	NA/77	False		False	DS/55	CDR3 CDR3
70702_1 1A22A	D25E A26T A32V Y35F L45M			False		False		False	DS/50 DS/91	
70702_1 1D23A	Q30I A32V S51T			False		False		False	DT/50 DS/91	
70702_1 1G03A				False		False		False	DS/50 DS/91	
70702_1 1K17A	Q30L			False		False		False	DS/50 DS/91	
70702_1 1L20A1	S31N Q38H P45S S95T			False		False		False	DD/93	CDR3

Table 3 (Continued) -- SHM Liabilities										
Light Chain										
Antibody	SHM	Missing Cysteines	Aberrant Cysteines	CDR3 Aberrant Cysteines	Deamidation	CDR3 Deamidation	Glycosylation	CDR3 Glycosylation	Isomerization (D[IGHST])	Oxidation
70702_1 1L20A2	L51V A96S			False		False		False	DG/33	CDR3
70702_1 4A13A	A26T A32V L45V I47T			False		False		False	DT/25 DS/50 DS/91	
70702_1 4A20A	A26T Q30K L45S S62Y			False		False		False	DT/25 DS/50 DS/91	
70702_1 4B22A	S20A S32R L51V			False		False		False	DG/33	CDR3
70702_1 4C17A	D25E A32V Y35F			False		False		False	DS/50 DS/91	
70702_1 4E02A	Y31S N39I V56I			False		False		False	DG/33 DS/60	CDR3 CDR3
70702_1 4F23A1	Q30L			False		False		False	DS/50 DS/91	
70702_1 4F23A2	D33N Y38C		C38	False		False		FALSE	DS/31 DG/34	CDR3 CDR3
70702_1 4H04A	Q30L A32S			False		False		False	DS/50 DS/91	
70702_1 4H12A1	Y92H A96P L97R			False	NG/33	False		False		CDR3

Table 3 (Continued) -- SHM Liabilities										
Light Chain										
Antibody	SHM	Missing Cysteines	Aberrant Cysteines	CDR3 Aberrant Cysteines	Deamidation	CDR3 Deamidation	Glycosylation	CDR3 Glycosylation	Isomerization (D[IGHST])	Oxidation
70702_1 4H12A2	V34L S95A K108R			False		False		False	DS/93	CDR3
70702_1 4J12A				False		False		False	DG/33 DS/60	CDR3 CDR3
70702_1 4Q05A	D25E A32V			False		False		False	DS/50 DS/91	
70702_1 4Q08A	A32V S89A T95S			False		False		False	DS/50 DS/91	
70702_1 5C18A				False	NG/33	False		False		CDR3
70702_1 5D20A				False		False		False	DG/33	CDR3
70702_1 5E14A1	Q30L			False		False		False	DS/50 DS/91	
70702_1 5E14A2	A51G I75L E79V Q100R			False		False	NISC/20	False	DD/30	CDR3
70702_1 5K04A				False		False		False	DG/33 DS/60	CDR3 CDR3
70702_1 5K13A	S32R L97R			False	NG/33	False		False		CDR3
70702_1 6A10A	P45S K79Q			False	NG/33	False		False		CDR3
70702_1 6A18A1	S20T N39K S48A N58K			False		False		False	DG/33 DS/60	CDR3 CDR3

Table 3 (Continued) -- SHM Liabilities										
Light Chain										
Antibody	SHM	Missing Cysteines	Aberrant Cysteines	CDR3 Aberrant Cysteines	Deamidation n	CDR3 Deamidation	Glycosylation	CDR3 Glycosylation	Isomerization (D/DGHSST)	Oxidation
70702_1 6A18A2				False	NS/53	False		False	DS/94	
70702_1 6C22A	K29R A32V			False		False		False	DS/50 DS/91	
70702_1 6J21A	S51N T69A			False		False		False	DS/91	
70702_1 7A10A1	G16E			False	NG/33	False		False		CDR3
70702_1 7A10A2	Y37F V90I C93S T97I H98N			False		False		False	DG/33 DS/60	CDR3 CDR3 CDR3
70702_1 7B04A				False	NG/33	False		False		CDR3
70702_1 7E14A	V90L L97R			False	NG/33	False		False		CDR3
70702_1 7K07A	A96S			False	NG/33	False		False		CDR3
70702_1 7O17A	V90L L97R			False	NG/33	False		False		CDR3
70702_1 7P02A				False	NG/33	False		False		CDR3
70702_1 8D08A	V3G H31Y V90I L97R T99A			False	NG/33	False		False		CDR3
70702_1 9F16A	V3G H31Y			False	NG/33	False		False		CDR3

Table 3 (Continued) -- SHM Liabilities										
Light Chain										
Antibody	SHM	Missing Cysteines	Aberrant Cysteines	CDR3 Aberrant Cysteines	Deamidation n	CDR3 Deamidation	Glycosylation	CDR3 Glycosylation	Isomerization (D[IGHST])	Oxidation
	V90I L97R T99A									
70702_1 9G11A	S32N N35D A96G Q98H			False		False		False	DG/33 DT/35	CDR3
70702_1 9I16A	Q42H N58K V90L G96C		C96	True		False		False	DG/33 DS/60	CDR3 CDR3
70702_2 0A07A	S94N			False	NS/94	True		False		CDR3
70702_2 0A08A	N57D			False	NA/77 NS/102	True		False	DS/55	CDR1 CDR3 CDR3
70702_2 0B05A1				False	NS/25	False		False	DS/93	
70702_2 0B05A2				False	NA/77 NS/102	True		False	DS/55	CDR1 CDR3 CDR3
70702_2 0C01A				False		False		False	DS/50 DS/91	
70702_2 0J03A	A32V T69I			False		False		False	DS/50 DS/91	
70702_2 0L07A	Y48F A92T N102S			False	NA/77	False		False	DS/55	CDR1 CDR3 CDR3

Table 3 (Continued) -- SHM Liabilities										
Light Chain										
Antibody	SHM	Missing Cysteines	Aberrant Cysteines	CDR3 Aberrant Cysteines	Deamidation	CDR3 Deamidation	Glycosylation	CDR3 Glycosylation	Isomerization (DIGHST)	Oxidation
70702_2 1A09A	A26T			False		False		False	DT/25 DS/50 DS/91	

Table 4 - Clustering																			
Clusters	Identicals	Heavy Chain							Light Chain										
		Antibody / Isotype	V Gene	V % Match	D Gene	D % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence	Isotype	V Gene	V % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence
1. 1		70702_15 C18 A / IGH G2a	IG HV 1-58	98.3%	IGH D3-16	100.0%	IG HJ 6	100.0%	GFTFT TSA (SEQ ID NO: 520)	IVVGS GNT (SEQ ID NO: 584)	AADR IGEN YYYG MDV (SEQ ID NO: 648)	I G K	IGK V2-28	100.0%	IG KJ 2	97.4%	QSL L HSN GYN Y (SEQ ID NO: 712)	LGS (SEQ ID NO: 322)	MQA LQTP YT (SEQ ID NO: 777)
		70702_15 K13 A / IGH G1	IG HV 1-58	98.0%	IGH D7-27	100.0%	IG HJ 6	100.0%	GFTFT SSA (SEQ ID NO: 521)	IVVGS GNT (SEQ ID NO: 585)	AADR TGEN YYYG MDV (SEQ ID NO: 649)	I G K	IGK V2-28	99.0%	IG KJ 2	100.0%	QSL L HRN GYN Y (SEQ ID NO: 713)	LGS (SEQ ID NO: 322)	MQA RQTP YT (SEQ ID NO: 778)

Table 4 - Clustering																			
Clusters	Identicals	Heavy Chain							Light Chain										
		Antibody / Isotype	V Gene	V % Match	D Gene	D % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence	Isotype	V Gene	V % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence
1. 3		7070 2_16 A10 A / IGH G2a	IG HV 1- 58	98. 0%	IGH D3- 16	100. 0%	IG HJ 6	98.1 %	GFTFT SSA (SEQ ID NO: 522)	IVVAS GNT (SEQ ID NO: 586)	AADR IGEN YYYG MDV (SEQ ID NO: 650)	I G K	IGK V2- 28	99. 3%	IG KJ 2	100. 0%	QSL HSN GYN Y (SEQ ID NO: 714)	LGS (SEQ ID NO: 322)	MQA LQTP YT (SEQ ID NO: 779)
	2. 1	identical_2	7070 2_17 E14 A / IGH G1	IG HV 3- 13	99. 0%	IGH D7- 27	100. 0%	IG HJ 6	100. 0%	GFTFS SYD (SEQ ID NO: 523)	IDTA GDT (SEQ ID NO: 587)	ARTG DTDY YGMD V (SEQ ID NO: 651)	I G K	IGK V2- 28	99. 0%	IG KJ 4	100. 0%	QSL HSN GYN Y (SEQ ID NO: 715)	LGS (SEQ ID NO: 322)
2. 1	identical_2	7070 2_17 O17 A / IGH G1	IG HV 3- 13	99. 0%	IGH D7- 27	100. 0%	IG HJ 6	100. 0%	GFTFS SYD (SEQ ID NO: 524)	IDTA GDT (SEQ ID NO: 588)	ARTG DTDY YGMD V (SEQ ID NO: 652)	I G K	IGK V2- 28	99. 0%	IG KJ 4	100. 0%	QSL HSN GYN Y (SEQ ID NO: 716)	LGS (SEQ ID NO: 322)	MQA RQTP LT (SEQ ID NO: 781)

Table 4 - Clustering																			
Clusters	Identicals	Heavy Chain						Light Chain						CDR3 Sequence	CDR2 Sequence	CDR1 Sequence			
		Antibody / Isotype	V Gene	V % Match	D Gene	D % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence	Isotype	V Gene				V % Match	J Gene	J % Match
3. 1	identical	7070 2.18 D08 A / IGH G1	IG HV 3-13	98.3%	IGH D6-6	100.0%	IG HJ 6	98.2%	GFTFS NYD (SEQ ID NO: 525)	IGTA DDT (SEQ ID NO: 589)	ARSSS SDYY YGLD V (SEQ ID NO: 653)	I G K	IGK V2-28	97.7%	IG KJ 4	100.0%	QSL L YSN GYN Y (SEQ ID NO: 717)	LGS (SEQ ID NO: 322)	MQA RQAP LT (SEQ ID NO: 782)
									GFTFS NYD (SEQ ID NO: 526)	IGTA DDT (SEQ ID NO: 590)	ARSSS SDYY YGLD V (SEQ ID NO: 654)	I G K	IGK V2-28	97.7%	IG KJ 4	100.0%	QSL L YSN GYN Y (SEQ ID NO: 718)	LGS (SEQ ID NO: 322)	MQA RQAP LT (SEQ ID NO: 783)
4. 1		7070 2.02 D05 A / IGH G2b	IG HV 3-21	97.3%	IGH D6-19	100.0%	IG HJ 4	100.0%	GFTFS SNA (SEQ ID NO: 527)	ISSSS SYI (SEQ ID NO: 591)	ARGL NFDY (SEQ ID NO: 655)	I G L	IGL V1-44	99.7%	IG LJ 2	100.0%	NSNI GSNT (SEQ ID NO: 719)	SNN (SEQ ID NO: 329)	AAW DDS L NGL V (SEQ ID NO: 784)
									GFTFS RTA (SEQ ID NO: 528)	ISSSS TYI (SEQ ID NO: 592)	ARGL NFDY (SEQ ID NO: 656)	I G L	IGL V1-44	99.3%	IG LJ 2	97.1%	SSNI GSNT (SEQ ID NO: 720)	SNN (SEQ ID NO: 329)	AAW DDS L NGL V (SEQ ID NO: 784)
4. 2		7070 2.02 M01 A /	IG HV 3-21	96.9%	IGH D6-19	100.0%	IG HJ 4	100.0%	GFTFS RTA (SEQ ID NO: 529)	ISSSS TYI (SEQ ID NO: 593)	ARGL NFDY (SEQ ID NO: 657)	I G L	IGL V1-44	99.3%	IG LJ 2	97.1%	SSNI GSNT (SEQ ID NO: 721)	SNN (SEQ ID NO: 329)	AAW DDS L NGL V (SEQ ID NO: 784)

Table 4 - Clustering																				
Clusters	Identicals	Heavy Chain								Light Chain										
		Antibody / Isotype	V Gene	V % Match	D Gene	D % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence	Isotype	V Gene	V % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence	
4. 3		IGH G2a							ID NO: 528)	ID NO: 592)	ID NO: 656)						NO: 720)	NO: 329)	(SEQ ID NO: 785)	
		7070 2_06 A06 A/ IGH G2b	IG HV 3- 21	98. 6%	IGH D6- 19	100. 0%	IG HJ 4	100. 0%	GFTFS RNS (SEQ ID NO: 529)	ISSSS SYI (SEQ ID NO: 593)	ARGL NFDY (SEQ ID NO: 657)	I G L	IGL V1- 44	99. 3%	IG LJ 2	100. 0%	SSNI GSNT (SEQ ID NO: 721)	SNN (SEQ ID NO: 329)	AAW DDSSL NGL V (SEQ ID NO: 786)	
5. 1		7070 2_05 A18 A/ IGH G2a	IG HV 3- 21	98. 0%	IGH D1- 1	100. 0%	IG HJ 4	100. 0%	GFTFS SYS (SEQ ID NO: 530)	ISSTS SYI (SEQ ID NO: 594)	ASKL DFDY (SEQ ID NO: 658)	I G L	IGL V1- 44	97. 3%	IG LJ 2	100. 0%	SSNI GSNT (SEQ ID NO: 722)	RNN (SEQ ID NO: 332)	V/AW DDSSL NGV V (SEQ ID NO: 787)	
5. 2		7070 2_07 P03A / IGH G1	IG HV 3- 21	97. 6%	IGH D1- 1	100. 0%	IG HJ 4	100. 0%	GFTFS SFS (SEQ ID NO: 531)	ISSSS SYI (SEQ ID NO: 595)	ASKL DFDY (SEQ ID NO: 659)	I G L	IGL V1- 44	99. 0%	IG LJ 2	100. 0%	SSNI GSNT (SEQ ID NO: 723)	SNN (SEQ ID NO: 329)	AAW DDSSL NGL V (SEQ ID NO: 788)	

Table 4 - Clustering																			
Clusters	Identicals	Heavy Chain							Light Chain										
		Antibody / Isotype	V Gene	V % Match	D Gene	D % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence	Isotype	V Gene	V % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence
6. 1		7070 2_11 L20 A2 / IGH G2a	IG HV 3- 48	97. 6%	IGH D7- 27	100. 0%	IG HJ 4	100. 0%	GFTFS SYS (SEQ ID NO: 532)	IGGST STI (SEQ ID NO: 596)	ARSP LGAV TGAF DY (SEQ ID NO: 660)	I G K	IGK V2- 24	99. 3%	IG KJ 5	97.1 %	QSLV HSD GNT Y (SEQ ID NO: 724)	KIS (SEQ ID NO: 334)	MQS TQFI T (SEQ ID NO: 789)
6. 2		7070 2_14 B22 A / IGH G1	IG HV 3- 48	98. 3%	IGH D7- 27	100. 0%	IG HJ 4	100. 0%	GFTFS TYS (SEQ ID NO: 533)	SSSSS STI (SEQ ID NO: 597)	ARSP LGAV TGAF DY (SEQ ID NO: 661)	I G K	IGK V2- 24	98. 7%	IG KJ 5	100. 0%	QSLV HRD GNT Y (SEQ ID NO: 725)	KIS (SEQ ID NO: 334)	MQA TQFI T (SEQ ID NO: 790)
7. 1		7070 2_14 E02 A / IGH G2a	IG HV 3-7	10 0.0 %	IGH D3- 16	100. 0%	IG HJ 4	100. 0%	GFTFS SYW (SEQ ID NO: 534)	IKQD GSEK (SEQ ID NO: 598)	ARKA GGDY (SEQ ID NO: 662)	I G K	IGK V2- 30	99. 0%	IG KJ 5	100. 0%	QSLV SSDG NTY (SEQ ID NO: 726)	KIS (SEQ ID NO: 334)	MQG THW PLT (SEQ ID NO: 791)
7. 2		7070 2_16 A18 A1 /	IG HV 3-7	99. 7%	IGH D3- 16	100. 0%	IG HJ 4	100. 0%	GFTFS SYW (SEQ ID NO: 535)	IKQD GSEK (SEQ ID NO: 599)	ARKA GGDY (SEQ ID NO: 663)	I G K	IGK V2- 30	98. 3%	IG KJ 5	100. 0%	QSLV YSD GNT Y (SEQ ID NO: 727)	KVS (SEQ ID NO: 337)	MQG THW PLT (SEQ ID NO: 792)

Table 4 - Clustering																			
Clusters	Identicals	Antibody / Isotype	Heavy Chain							Light Chain									
			V Gene	V % Match	D Gene	D % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence	Isotype	V Gene	V % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence
8. 1		IGH G2b															ID NO: 727)		NO: 792)
		7070 2_04 O12 A / IGH G1	IG HV 4-4	10 0.0 %	IGH D1- 26	100. 0%	IG HJ 4	100. 0%	GGSS SY (SEQ ID NO: 536)	IYTS ST (SEQ ID NO: 600)	ARDG MGFD Y (SEQ ID NO: 664)	I G L	IGL V3- 25	10 0.0 %	IG LJ 1	100. 0%	ALPK QY (SEQ ID NO: 728)	KDS (SEQ ID NO: 338)	QSA DSSG TY (SEQ ID NO: 793)
8. 2		7070 2_08 L02 A / IGH G1	IG HV 4-4	98. 3%	IGH D1- 26	100. 0%	IG HJ 4	100. 0%	GGSF SSYY (SEQ ID NO: 537)	IYTS ST (SEQ ID NO: 601)	ARDG MGFD Y (SEQ ID NO: 665)	I G L	IGL V3- 25	98. 6%	IG LJ 1	100. 0%	ALPK LY (SEQ ID NO: 729)	KDS (SEQ ID NO: 338)	QSA DSSG TY (SEQ ID NO: 794)
		7070 2_15 E14 A1 / IGH G1	IG HV 4-4	96. 6%	IGH D7- 27	100. 0%	IG HJ 4	97.7 %	GGSS SNH (SEQ ID NO: 538)	IYSS ST (SEQ ID NO: 602)	AREE LGFD Y (SEQ ID NO: 666)	I G L	IGL V3- 25	99. 3%	IG LJ 1	100. 0%	ALPK LY (SEQ ID NO: 730)	KDS (SEQ ID NO: 338)	QSA DSSG TY (SEQ ID NO: 795)

Table 4 - Clustering																			
Clusters	Identicals	Antibody / Isotype	Heavy Chain						Light Chain										
			V Gene	V % Match	D Gene	D % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence	Isotype	V Gene	V % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence
9.2		7070 2_09 B19 A/ IGH G2b	IG HV 4-4	98.0%	IGH D7- 27	100.0%	IG HJ 4	100.0%	GG SIS SY Y (SEQ ID NO: 539)	IYTSG NT (SEQ ID NO: 603)	AREE LGFD Y (SEQ ID NO: 667)	I G L	IGL V3- 25	97.9%	IG LJ 1	100.0%	ALSK KY (SEQ ID NO: 731)	KDS (SEQ ID NO: 338)	QSA DNS GSY V (SEQ ID NO: 796)
10.1		7070 2_16 C22 A/ IGH G1	IG HV 4-4	96.9%			IG HJ 4	100.0%	GG SIN SY Y (SEQ ID NO: 540)	IHTSG ST (SEQ ID NO: 604)	ARDE RGFD Y (SEQ ID NO: 668)	I G L	IGL V3- 25	99.0%	IG LJ 1	100.0%	ALPR QY (SEQ ID NO: 732)	KDS (SEQ ID NO: 338)	QSA DSSG TY Y V (SEQ ID NO: 797)
10.2		7070 2_14 O05 A/ IGH G1	IG HV 4-4	98.6%			IG HJ 4	100.0%	GG SIS SY Y (SEQ ID NO: 541)	IYTSG ST (SEQ ID NO: 605)	ARDE RGFD Y (SEQ ID NO: 669)	I G L	IGL V3- 25	99.3%	IG LJ 1	100.0%	ALPK QY (SEQ ID NO: 733)	KDS (SEQ ID NO: 338)	QSA DSSG TY Y V (SEQ ID NO: 798)
11.1		7070 2_08 P13A /	IG HV 4-4	100.0%	IGH D7- 27	100.0%	IG HJ 4	100.0%	GG SIS SY Y (SEQ ID NO: 541)	IYTSG ST (SEQ ID NO: 605)	ARDE LGFD Y (SEQ ID NO: 669)	I G L	IGL V3- 25	99.3%	IG LJ 1	100.0%	ALPK KY (SEQ ID NO: 733)	KDS (SEQ ID NO: 338)	QSA DSSG TY Y V (SEQ ID NO: 798)

Table 4 - Clustering																						
Clusters	Identicals	Antibody / Isotype	Heavy Chain						Light Chain						CDR3 Sequence	CDR2 Sequence	CDR1 Sequence	J % Match	J Gene	V % Match	V Gene	Isotype
			V Gene	V % Match	D Gene	D % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence	V Gene	V % Match	J Gene								
		7070 2_01 G16 A / IGH G1	IG HV 4-4	99. 7%	IGH D3- 16	100. 0%	IG HJ 3	100. 0%	GGGIS SVY (SEQ ID NO: 546)	IYTS ST (SEQ ID NO: 610)	ARDQ IGFDI (SEQ ID NO: 674)	I G L	IGL V1- 47	99. 7%	IG LJ 1	100. 0%	SSNI GSN Y (SEQ ID NO: 738)	SNN (SEQ ID NO: 329)	AAW DDSL SGV V (SEQ ID NO: 803)			
		7070 2_11 D23 A / IGH G1	IG HV 4-4	99. 3%	IGH D1- 26	100. 0%	IG HJ 4	100. 0%	GGGIS SVY (SEQ ID NO: 547)	IYTT ST (SEQ ID NO: 611)	ARES QVGF DY (SEQ ID NO: 675)	I G L	IGL V3- 25	98. 6%	IG LJ 2	100. 0%	ALPK IY (SEQ ID NO: 739)	KDT (SEQ ID NO: 349)	QSA DSSG TYL (SEQ ID NO: 804)			
		7070 2_14 A20 A / IGH G1	IG HV 4-4	98. 3%	IGH D1- 1	100. 0%	IG HJ 4	100. 0%	GGGIS NHV (SEQ ID NO: 548)	IYTS NT (SEQ ID NO: 612)	ARDR TGFD Y (SEQ ID NO: 676)	I G L	IGL V3- 25	97. 9%	IG LJ 1	100. 0%	TLPK KY (SEQ ID NO: 740)	KDS (SEQ ID NO: 338)	QSA DSSG TYV (SEQ ID NO: 805)			
		7070 2_14 F23A 1 /	IG HV 4-4	98. 6%	IGH D2- 8	100. 0%	IG HJ 4	97.7 %	GGGIT NYV (SEQ ID NO: 549)	IYTS ST (SEQ ID NO: 613)	AREG GTGF DN (SEQ	I G L	IGL V3- 25	99. 7%	IG LJ 1	100. 0%	ALPK LY (SEQ ID	KDS (SEQ ID NO: 338)	QSA DSSG TYV (SEQ			

Table 4 - Clustering																						
Clusters	Identicals	Antibody / Isotype	Heavy Chain						Light Chain						CDR3 Sequence	CDR2 Sequence	CDR1 Sequence	J % Match	J Gene	V % Match	V Gene	Isotype
			V Gene	V % Match	D Gene	D % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence	Isotype	V Gene	V % Match								
		IGH G1								ID NO: 677)						NO: 741)						ID NO: 806)
		7070 2_14 F23A 2 / IGH G1	IG HV 4-4	98.6%	IGH D2-8	100.0%	IG HJ 4	97.7%	GGSTIT NYY (SEQ ID NO: 550)	IYTSG ST (SEQ ID NO: 614)	AREG GTGF DN (SEQ ID NO: 678)	I G K	IGK V2-40	99.0%	IG KJ 2	100.0%	QSLD DSN DGN TC (SEQ ID NO: 742)	TLS (SEQ ID NO: 352)	MQRI EFPS MYT (SEQ ID NO: 807)			
		7070 2_14 H04 A / IGH G1	IG HV 3-7	99.3%			IG HJ 4	100.0%	GFTFS SYW (SEQ ID NO: 551)	IKQD GSEK (SEQ ID NO: 615)	AREG LGFD Y (SEQ ID NO: 679)	I G L	IGL V3-25	99.0%	IG LJ 1	100.0%	ALPK LY (SEQ ID NO: 743)	KDS (SEQ ID NO: 338)	QSA DSSG TYY V (SEQ ID NO: 808)			
		7070 2_14 J12A / IGH G1	IG HV 3-7	99.0%	IGH D3-9	100.0%	IG HJ 4	100.0%	GFTFS SYW (SEQ ID NO: 552)	IKQD GSEK (SEQ ID NO: 616)	ATRL AFDY (SEQ ID NO: 680)	I G K	IGK V2-30	100.0%	IG KJ 4	100.0%	QSLV YSD GNT Y (SEQ ID NO: 744)	KVS (SEQ ID NO: 337)	MQG THW PLT (SEQ ID NO: 809)			

Table 4 - Clustering																			
Clusters	Identicals	Antibody / Isotype	Heavy Chain						Light Chain						CDR3 Sequence	CDR2 Sequence	CDR1 Sequence		
			V Gene	V % Match	D Gene	D % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence	Isotype	V Gene	V % Match				J Gene	J % Match
		7070 2_14 O08 A	IG HV 4-4	96. 9%	IGH D2- 21	100. 0%	IG HJ 4	97.7 %	GG SIS SYV (SEQ ID NO: 553)	FYTS GSN (SEQ ID NO: 617)	AREGI GFDY (SEQ ID NO: 681)	I G L	IGL V3- 25	99. 0%	IG LJ 1	100. 0%	ALPK QY (SEQ ID NO: 745)	KDS (SEQ ID NO: 338)	QAA DSSG SYV V (SEQ ID NO: 810)
		7070 2_15 E14 A2 / IGH G1	IG HV 4-4	96. 6%	IGH D7- 27	100. 0%	IG HJ 4	97.7 %	GG SIS SNH (SEQ ID NO: 554)	IYSSG ST (SEQ ID NO: 618)	AREE LGFD Y (SEQ ID NO: 682)	I G K	IGK V5- 2	98. 9%	IG KJ 1	97.3 %	QDID DD (SEQ ID NO: 746)	EGT (SEQ ID NO: 356)	LQH DNFL WT (SEQ ID NO: 811)
		7070 2_15 K04 A / IGH G1	IG HV 3-7	99. 0%	IGH D3- 9	100. 0%	IG HJ 4	100. 0%	GFTFS NYW (SEQ ID NO: 555)	IKQD GSEK (SEQ ID NO: 619)	ATRL AFDY (SEQ ID NO: 683)	I G K	IGK V2- 30	10 0.0 %	IG KJ 5	100. 0%	QSLV YSD GNT Y (SEQ ID NO: 747)	KVS (SEQ ID NO: 337)	MQG THW PLT (SEQ ID NO: 812)
		7070 2_17 B04 A /	IG HV 1- 58	99. 3%	IGH D2- 2	100. 0%	IG HJ 6	100. 0%	GFTFT NSA (SEQ ID NO: 556)	IVVGS GNT (SEQ ID NO: 620)	VADR VVS N HYYG MDV (SEQ	I G K	IGK V2- 28	10 0.0 %	IG KJ 3	97.4 %	QSL L HSN GYN Y (SEQ	LGS (SEQ ID NO: 322)	MQA LQTP FT (SEQ ID

Table 4 - Clustering																			
Clusters	Identicals	Antibody / Isotype	Heavy Chain						Light Chain						CDR3 Sequence	CDR2 Sequence	CDR1 Sequence		
			V Gene	V % Match	D Gene	D % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence	Isotype	V Gene	V % Match				J Gene	J % Match
		IGH G1								ID NO: 684)						ID NO: 748)		NO: 813)	
		7070 2_17 P02A / IGH G1	IG HV 1- 58	98. 3%	IGH D3- 3	100. 0%	IG HJ 6	100. 0%	GFTFI SSA (SEQ ID NO: 557)	IVVGS GNT (SEQ ID NO: 621)	AADR IGDR YYGM DV (SEQ ID NO: 685)	I G K	I IGK V2- 28	10 0.0 %	IG KJ 2	100. 0%	QSLI HSN GYN Y (SEQ ID NO: 749)	LGS (SEQ ID NO: 322)	MQA LQTP YT (SEQ ID NO: 814)
		7070 2_19 G11 A/ IGH G1	IG HV 4- 31	98. 0%	IGH D7- 27	100. 0%	IG HJ 4	100. 0%	GGSF SSGG HY (SEQ ID NO: 558)	IYYSG ST (SEQ ID NO: 622)	ARAL TGTF DY (SEQ ID NO: 686)	I G K	I IGK V2- 24	98. 7%	IG KJ 4	100. 0%	QSLV HND GDT Y (SEQ ID NO: 750)	KIS (SEQ ID NO: 334)	MQG THFP LT (SEQ ID NO: 815)
		7070 2_20 A08 A/ IGH G1	IG HV 3-7	98. 3%	IGH D1- 26	100. 0%	IG HJ 4	100. 0%	GFTFS NYW (SEQ ID NO: 559)	IKQD GSEK (SEQ ID NO: 623)	AVGA FFDY (SEQ ID NO: 687)	I G L	I IGL V5- 52	99. 7%	IG LJ 3	100. 0%	SGFS VGD FW (SEQ ID NO: 751)	YHS DSD K (SEQ ID NO: 361)	GTW HSNS KTW V (SEQ ID NO: 816)

Table 4 - Clustering																			
Clusters	Identicals	Heavy Chain										Light Chain							
		Antibody / Isotype	V Gene	V % Match	D Gene	D % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence	Isotype	V Gene	V % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence
		7070 2_20 B05 A1 / IGH G1	IG HV 3- 15	99. 0%	IGH D7- 27	100. 0%	IG HJ 4	100. 0%	GFTFS NAW (SEQ ID NO: 560)	IKRK1 DGGT T (SEQ ID NO: 624)	TTGE LGTD Y (SEQ ID NO: 688)	I G L	IGL V10 -54	10 0.0 %	IG LJ 6	100. 0%	SNIV GNQ G (SEQ ID NO: 752)	RNN (SEQ ID NO: 332)	SALD SSLS AV (SEQ ID NO: 817)
		7070 2_20 B05 A2 / IGH G1	IG HV 3- 15	99. 0%	IGH D7- 27	100. 0%	IG HJ 4	100. 0%	GFTFS NAW (SEQ ID NO: 561)	IKRK1 DGGT T (SEQ ID NO: 625)	TTGE LGTD Y (SEQ ID NO: 689)	I G L	IGL V5- 52	10 0.0 %	IG LJ 3	100. 0%	SGFS VGD FW (SEQ ID NO: 753)	YHS DSN K (SEQ ID NO: 366)	GTW HSNS KTW V (SEQ ID NO: 818)
		7070 2_20 J05A / IGH G1	IG HV 4-4	96. 6%	IGH D7- 27	100. 0%	IG HJ 4	100. 0%	GGGIS SYV (SEQ ID NO: 562)	IYTS NT (SEQ ID NO: 626)	ARDV LGFD Y (SEQ ID NO: 690)	I G L	IGL V3- 25	99. 0%	IG LJ 1	100. 0%	ALPK QY (SEQ ID NO: 754)	KDS (SEQ ID NO: 338)	QSA DSSG TYV V (SEQ ID NO: 819)
		7070 2_01 O21 A /	IG HV 3-7	98. 6%	IGH D2- 8	100. 0%	IG HJ 4	100. 0%	GFTFS SYW (SEQ ID NO: 563)	IKQD GSEK (SEQ ID NO: 627)	ARVLI GFDY (SEQ ID NO: 691)	I G L	IGL V3- 25	97. 9%	IG LJ 1	100. 0%	ALPK QY (SEQ ID NO: 754)	KDI (SEQ ID NO: 365)	QSA DGIS TYN YV (SEQ ID NO: 819)

Table 4 - Clustering																			
Clusters	Identicals	Antibody / Isotype	Heavy Chain						Light Chain										
			V Gene	V % Match	D Gene	D % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence	Isotype	V Gene	V % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence
		IGH G2a															NO: 755)		ID NO: 820)
		7070 2_04 N16 A / IGH G2a	IG HV 3-15	99.0%			IG HJ 4	95.5%	GFTFS DAW (SEQ ID NO: 564)	IKSKT DGGT T (SEQ ID NO: 628)	TGGG FFHC (SEQ ID NO: 692)	I G L	IGL V5-52	99.4%	IG LJ 3	97.3%	SGFS VGD FW (SEQ ID NO: 756)	YHS DSN K (SEQ ID NO: 366)	GTW HSNS KTW V (SEQ ID NO: 821)
		7070 2_06 M21 A / IGH G2a	IG HV 1-46	97.0%	IGH D1-1	100.0%	IG HJ 4	100.0%	GHTF TRY Y (SEQ ID NO: 565)	INPSG GGK (SEQ ID NO: 629)	AREV STGF DY (SEQ ID NO: 693)	I G L	IGL V7-43	98.3%	IG LJ 2	100.0%	TGA VTSD VY (SEQ ID NO: 757)	STS (SEQ ID NO: 367)	LLYY GGA YVV (SEQ ID NO: 822)
		7070 2_11 G03 A / IGH G2a	IG HV 4-44	98.6%			IG HJ 4	100.0%	GGSIS SDY (SEQ ID NO: 566)	IYTSG ST (SEQ ID NO: 630)	ARDG TGFD Y (SEQ ID NO: 694)	I G L	IGL V3-25	10.0%	IG LJ 1	100.0%	ALPK QY (SEQ ID NO: 758)	KDS (SEQ ID NO: 338)	QSA DSSG TY Y V (SEQ ID NO: 823)

Table 4 - Clustering																				
	Clusters	Identicals	Heavy Chain							Light Chain							CDR3 Sequence	CDR2 Sequence	CDR1 Sequence	
			Antibody / Isotype	V Gene	V % Match	D Gene	D % Match	J Gene	J % Match	CDR1 Sequence	J % Match	V Gene	V % Match	J Gene	J % Match	Isotype				
			7070 2_11 L20 A1 / IGH G2a	IG HV 3- 48	97. 6%	IGH D7- 27	100. 0%	IG HJ 4	100. 0%	GFTFS SYS (SEQ ID NO: 567)	IGGST STI (SEQ ID NO: 631)	ARSP LGAV TGAF DY (SEQ ID NO: 695)	I G L	I G L V1- 47	97. 3%	IG LJ 3	100. 0%	SSNI GNN Y (SEQ ID NO: 759)	SNN (SEQ ID NO: 329)	AAW DDTL SGV (SEQ ID NO: 824)
			7070 2_14 H12 A1 / IGH G2a	IG HV 1- 58	99. 3%	IGH D1- 26	93.8 %	IG HJ 6	100. 0%	GFTFT SSA (SEQ ID NO: 568)	IVVGS GNT (SEQ ID NO: 632)	AADR IEGAT GDYY GMDV (SEQ ID NO: 696)	I G K	I G K V2- 28	98. 7%	IG KJ 2	97.4 %	QSLI HSN GYN Y (SEQ ID NO: 760)	LGS (SEQ ID NO: 322)	MQP RQTP YT (SEQ ID NO: 825)
			7070 2_14 H12 A2 / IGH G2a	IG HV 1- 58	99. 3%	IGH D1- 26	93.8 %	IG HJ 6	100. 0%	GFTFT SSA (SEQ ID NO: 569)	IVVGS GNT (SEQ ID NO: 633)	AADR IEGAT GDYY GMDV (SEQ ID NO: 697)	I G L	I G L V1- 51	99. 0%	IG LJ 2	97.4 %	SSNI GNN Y (SEQ ID NO: 761)	DNN (SEQ ID NO: 371)	GTW DSAL SAG HV (SEQ ID NO: 826)
			7070 2_16 J21A /	IG HV 4-4	98. 3%	IGH D2- 8	100. 0%	IG HJ 4	100. 0%	DGSIS TYY (SEQ ID NO: 570)	IYSSG ST (SEQ ID NO: 634)	ARDE MGFD Y (SEQ ID NO: 698)	I G L	I G L V3- 25	99. 3%	IG LJ 1	100. 0%	ALPK QY (SEQ ID NO: 761)	KDN (SEQ ID NO: 372)	QSA DSSG TFYV (SEQ ID NO: 827)

Table 4 - Clustering																			
Clusters	Identicals	Heavy Chain							Light Chain										
		Antibody / Isotype	V Gene	V % Match	D Gene	D % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence	Isotype	V Gene	V % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence
		IGH G2a									ID NO: 698)						NO: 762)		NO: 827)
		7070 2_17 A10 A1 / IGH G2a	IG HV 1- 58	97.6%	IGH D4- 23	90.0%	IG HJ 6	100.0%	GFTFT SSA (SEQ ID NO: 571)	IVVGS GNT (SEQ ID NO: 635)	VADR VGTID YYGM DV (SEQ ID NO: 699)	I G K	IGK V2- 28	99.7%	IG KJ 4	100.0%	QSL HSN GYN Y (SEQ ID NO: 763)	LGS (SEQ ID NO: 322)	MQA LQIP LT (SEQ ID NO: 828)
		7070 2_17 A10 A2 / IGH G2a	IG HV 1- 58	97.6%	IGH D4- 23	90.0%	IG HJ 6	100.0%	GFTFT SSA (SEQ ID NO: 572)	IVVGS GNT (SEQ ID NO: 636)	VADR VGTID YYGM DV (SEQ ID NO: 700)	I G K	IGK V2- 30	98.3%	IG KJ 5	100.0%	QSLV YSD GNTF (SEQ ID NO: 764)	KVS (SEQ ID NO: 337)	MQGI NWPI T (SEQ ID NO: 829)
		7070 2_19 116A	IG HV 3- 23	99.0%			IG HJ 4	100.0%	GFTFS SYA (SEQ ID NO: 573)	ISGSY GST (SEQ ID NO: 637)	AKET GDY (SEQ ID NO: 701)	I G K	IGK V2- 30	98.7%	IG KJ 4	100.0%	QSLV YSD GNT Y (SEQ ID NO: 765)	KVS (SEQ ID NO: 337)	MOC THW PPT (SEQ ID NO: 830)
		7070 2_20 L07	IG HV	99.3%	IGH D3- 22	92.0%	IG HJ 4	100.0%	GFTFS NAW (SEQ ID NO: 574)	IKSKT DGGT I (SEQ ID NO: 638)	TTGY YYAS SDYY (SEQ ID NO: 702)	I G L	IGL V5- 52	99.0%	IG LJ 3	100.0%	SGFS VGD FW (SEQ ID NO: 766)	YHS DSN K (SEQ ID NO: 338)	GTW HSS KTW (SEQ ID NO: 831)

Table 4 - Clustering																			
Clusters	Identicals	Antibody / Isotype	Heavy Chain						Light Chain										
			V Gene	V % Match	D Gene	D % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence	Isotype	V Gene	V % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence
		7070 2_11 K17 A / IGH G2b	IG HV 4-4	97.6%	IGH D7- 27	100.0%	IG HJ 4	100.0%	GGGIN NYY (SEQ ID NO: 578)	IYTSG NT (SEQ ID NO: 642)	ARER LGFD Y (SEQ ID NO: 706)	I G L	IGL V3- 25	99.0%	IG LJ 1	100.0%	ALPK LY (SEQ ID NO: 770)	KDS (SEQ ID NO: 338)	QSA DSSG TYV (SEQ ID NO: 835)
		7070 2_15 D20 A / IGH G2b	IG HV 3-33	98.0%	IGH D3- 22	95.7%	IG HJ 3	100.0%	GFTFS SYG (SEQ ID NO: 579)	IWYD GSKK (SEQ ID NO: 643)	ARDY YDSS DYL GVFDI (SEQ ID NO: 707)	I G K	IGK V2- 24	10.0%	IG KJ 5	100.0%	QSLV HSD GNT Y (SEQ ID NO: 771)	KIS (SEQ ID NO: 334)	MQA TQFI T (SEQ ID NO: 836)
		7070 2_16 A18 A2 / IGH G2b	IG HV 4-4	10.0%	IGH D4- 17	100.0%	IG HJ 4	100.0%	GGGIS SYV (SEQ ID NO: 580)	IYTSG ST (SEQ ID NO: 644)	ARAT VTSS YFDY (SEQ ID NO: 708)	I G L	IGL V1- 40	10.0%	IG LJ 1	100.0%	SSNI GAG YD (SEQ ID NO: 772)	GNS (SEQ ID NO: 382)	QSY DSSL SGY V (SEQ ID NO: 837)
		7070 2_17 K07 A /	IG HV 1-58	99.0%	IGH D7- 27	100.0%	IG HJ 6	100.0%	GFTFT SSA (SEQ ID NO: 581)	IVIGS GNT (SEQ ID NO: 645)	AADR VWGR DYYG MDV (SEQ	I G K	IGK V2- 28	99.7%	IG KJ 3	100.0%	QSL HSN GYN Y (SEQ	LGS (SEQ ID NO: 322)	MQS LQTP FT (SEQ ID

Table 4 - Clustering																
Clusters	Identicals	Antibody / Isotype	Heavy Chain							Light Chain						
			V Gene	V % Match	D Gene	D % Match	J Gene	J % Match	CDR1 Sequence	CDR2 Sequence	CDR3 Sequence	Isotype	V Gene	V % Match	J Gene	J % Match
		IGH G2b									ID NO: 709)					ID NO: 838)
		7070 2_20 A07 A / IGH G2b	IGH HV 3-73	98.0%	IGH D7-27	100.0%	IGH HJ 4	100.0%	GFSEFS GSS (SEQ ID NO: 582)	IRSKA KSYA T (SEQ ID NO: 646)	TRAN WGFD Y (SEQ ID NO: 710)	I G L	IGL V1-51	99.7%	IG LJ 3	100.0%
		7070 2_20 C01 A / IGH G2b	IGH HV 3-7	98.6%			IGH HJ 4	97.7%	GFTFS SYW (SEQ ID NO: 583)	IKQD GVKK (SEQ ID NO: 647)	AREG LGFD S (SEQ ID NO: 711)	I G L	IGL V3-25	100.0%	IG LJ 1	100.0%
											ALPK QY (SEQ ID NO: 775)					GTW DNSL SAG V (SEQ ID NO: 839)
											KDS (SEQ ID NO: 338)					QSA DSSG TSYV (SEQ ID NO: 840)

CLAIMS

What is claimed is:

1. An anti-p95HER2 antibody or antibody fragment comprising:
 - a heavy chain CDR3 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 2-65 and 514, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 2-65 and 514;
 - a heavy chain CDR2 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 258-321 and 518, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 258-321 and 518;
 - a heavy chain CDR1 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 130-193 and 516, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 130-193 and 516;
 - a light chain CDR3 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 66-129 and 515, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 66-129 and 515;
 - a light chain CDR2 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 322-385 and 519, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 322-385 and 519; and/or
 - a light chain CDR1 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 194-257 and 517, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 194-257 and 517.

2. The an anti-p95HER2 antibody or antibody fragment of claim 1, wherein the antibody or antibody fragment comprises one or more of:

a heavy chain CDR3 sequence (VH) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 514;

a heavy chain CDR2 sequence (VH) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 518;

a heavy chain CDR1 sequence (VH) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 516;

a light chain CDR3 sequence (VL) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 515;

a light chain CDR2 sequence (VL) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 519; and

a light chain CDR1 sequence (VL) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 517.

3. The anti-p95HER2 antibody or antibody fragment of claim 1, wherein the antibody or antibody fragment comprises a heavy chain (VH) CDR3 comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 514.

4. The anti-p95HER2 antibody or antibody fragment of claim 1, wherein the antibody or antibody fragment comprises a light chain CDR3 sequence (VL) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at

least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 515.

5. The anti-p95HER2 antibody or antibody fragment of claim 1, wherein the antibody or antibody fragment comprises a heavy chain (VH) CDR1 comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 516.

6. The anti-p95HER2 antibody or antibody fragment of claim 1, wherein the antibody or antibody fragment comprises a light chain CDR1 sequence (VL) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 517.

7. The anti-p95HER2 antibody or antibody fragment of claim 1, wherein the antibody or antibody fragment comprises a heavy chain (VH) CDR2 comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 518.

8. The anti-p95HER2 antibody or antibody fragment of claim 1, wherein the antibody or antibody fragment comprises a light chain CDR2 sequence (VL) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 519.

9. The anti-p95HER2 antibody or antibody fragment of claim 1, wherein the antibody or fragment comprises a heavy chain variable region encoded by a nucleic acid sequence having at least 95.5%, at least 96%, at least 97%, at least 98% at least 99%, or at least 100% sequence identity with a SEQ ID NO: 841.

10. The anti-p95HER2 antibody or antibody fragment of claim 1, wherein the antibody or fragment comprises a light chain variable region encoded by a nucleic acid sequence having at least 95.5%, at least 96%, at least 97%, at least 98% at least 99%, or at least 100% sequence identity with a SEQ ID NO: 842.

11. A therapeutic composition comprising an anti-p95HER2 antibody or antibody fragment comprising:

a heavy chain CDR3 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 2-65 and 514, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 2-65 and 514;

a heavy chain CDR2 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 258-321 and 518, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 258-321 and 518;

a heavy chain CDR1 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 130-193 and 516, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 130-193 and 516;

a light chain CDR3 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 66-129 and 515, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 66-129 and 515;

a light chain CDR2 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 322-385 and 519, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 322-385 and 519; and/or

a light chain CDR1 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 194-257 and 517, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 194-257 and 517.

12. The therapeutic composition of claim 11, wherein the antibody or antibody fragment comprises one or more of:

a heavy chain CDR3 sequence (VH) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 514;

a heavy chain CDR2 sequence (VH) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 518;

a heavy chain CDR1 sequence (VH) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 516;

a light chain CDR3 sequence (VL) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 515;

a light chain CDR2 sequence (VL) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 519; and

a light chain CDR1 sequence (VL) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 517.

13. The therapeutic composition of claim 11, wherein the antibody or antibody fragment comprises a heavy chain (VH) CDR3 comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 514.

14. The therapeutic composition of claim 11, wherein the antibody or antibody fragment comprises a light chain CDR3 sequence (VL) comprising an amino acid and/or a sequence that

comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 515.

15. The therapeutic composition of claim 11, wherein the antibody or antibody fragment comprises a heavy chain (VH) CDR1 comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 516.

16. The therapeutic composition of claim 11, wherein the antibody or antibody fragment comprises a light chain CDR1 sequence (VL) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 517.

17. The therapeutic composition of claim 11, wherein the antibody or antibody fragment comprises a heavy chain (VH) CDR2 comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 518.

18. The therapeutic composition of claim 11, wherein the antibody or antibody fragment comprises a light chain CDR2 sequence (VL) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 519.

19. The therapeutic composition of claim 11, wherein the antibody or fragment comprises a heavy chain variable region encoded by a nucleic acid sequence having at least 95.5%, at least 96%, at least 97%, at least 98% at least 99%, or at least 100% sequence identity with a SEQ ID NO: 841.

20. The therapeutic composition of claim 11, wherein the antibody or fragment comprises a light chain variable region encoded by a nucleic acid sequence having at least 95.5%, at least 96%, at least 97%, at least 98% at least 99%, or at least 100% sequence identity with a SEQ ID NO: 842.

21. A method of treating a cancer patient with a therapeutic composition comprising at least one anti-p95HER2 antibody or fragment thereof, wherein said anti-p95HER2 antibody or fragment comprises:

a heavy chain CDR3 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 2-65 and 514, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 2-65 and 514;

a heavy chain CDR2 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 258-321 and 518, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 258-321 and 518;

a heavy chain CDR1 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 130-193 and 516, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 130-193 and 516;

a light chain CDR3 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 66-129 and 515, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 66-129 and 515;

a light chain CDR2 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 322-385 and 519, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 322-385 and 519; and/or

a light chain CDR1 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 194-257 and 517, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 194-257 and 517.

22. The method of claim 21, wherein said anti-p95HER2 antibody or fragment comprises:

a heavy chain CDR3 sequence (VH) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 514;

a heavy chain CDR2 sequence (VH) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 518;

a heavy chain CDR1 sequence (VH) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 516;

a light chain CDR3 sequence (VL) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 515;

a light chain CDR2 sequence (VL) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 519; and

a light chain CDR1 sequence (VL) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 517.

23. A bispecific antibody or multi-specific antibody that binds to p95HER2 and another antigen, comprising:

a targeting arm of the bispecific antibody or multi-specific antibody comprises an anti-p95HER2 antibody or antibody fragment comprising:

a a heavy chain CDR3 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 2-65 and 514, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 2-65 and 514;

a heavy chain CDR2 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 258-321 and 518, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 258-321 and 518;

a heavy chain CDR1 sequence (VH) comprising an amino acid sequence selected from one of SEQ ID NOS: 130-193 and 516, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 130-193 and 516;

a light chain CDR3 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 66-129 and 515, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 66-129 and 515;

a light chain CDR2 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 322-385 and 519, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 322-385 and 519; and/or

a light chain CDR1 sequence (VL) comprising an amino acid sequence selected from one of SEQ ID NOS: 194-257 and 517, and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with any of SEQ ID NOS: 194-257 and 517.

24. The bispecific antibody or multi-specific antibody of claim 23, wherein s antibody or multi-specific antibody:

a heavy chain CDR3 sequence (VH) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 514;

a heavy chain CDR2 sequence (VH) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 518;

a heavy chain CDR1 sequence (VH) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 516;

a light chain CDR3 sequence (VL) comprising an amino acid and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 515;

a light chain CDR2 sequence (VL) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 519; and

a light chain CDR1 sequence (VL) comprising an amino acid sequence and/or a sequence that comprises an amino acid sequence having at least 85%, at least 90% at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity with SEQ ID NO: 517.