ANTI-ERBB3 ANTIBODIES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. provisional patent application serial number 61/322,712, filed April 9, 2010; the entire content of which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The field of the invention is molecular biology, immunology and oncology. More particularly, the field is humanized antibodies that bind human ErbB3/HER3.

BACKGROUND

[0003] HER3/c-ErbB3 (referred to herein as ErbB3) is a member of the epidermal growth factor receptor (EGFR) family. ErbB3 binds neuregulin/heregulin (NRG/HRG). Receptors in the EGFR family are single transmembrane receptors with an intracellular tyrosine kinase domain. While the other EGFR family members, *i.e.*, EGFR/HER1/ErbB1, HER2/ErbB2, and HER4/ErbB4, each have tyrosine kinase activity, ErbB3 has little or no tyrosine kinase activity, and thus is "kinase-dead."

[0004] The extracellular domain (ECD) of the EGFR family contains four domains. Domains 1 and 3 (also known as domains L1 and L2) are responsible for ligand binding. Cysteine-rich domains 2 and 4 (also known as domains C1 and C2) are involved in dimerization with receptor partners. Upon ligand binding, the ECD undergoes conformational changes. The interaction of domains 2 and 4, which maintains the tethered (inactive) conformation of the receptor, is relieved, and an extended (active) conformation is adopted. The extended conformation favors dimerization with other receptor partners. HER2/ErbB2 is the only exception to this general rule, *i.e.*, Her2-ECD is constitutively in the extended conformation. No ligand for HER2 has been identified thus far.

[0005] Because ErbB3 lacks an intrinsic kinase activity, it must dimerize with another active tyrosine kinase receptor to be activated by tyrosine phosphorylation. Dimerization can occur between two different receptors (heterodimerization), *e.g.*, ErbB3 and EGFR/HER1/ErbB1, HER2/ErbB2, or HER4/ErbB4. Recently, ErbB3 was also shown to dimerize with MET. Upon association with another tyrosine kinase receptor, ErbB3 is activated by phosphorylation of at least nine tyrosine residues in the ErbB3 intracellular domain, and then rapidly associates with adaptors or downstream signaling molecules. Six of the ErbB3 phosphorylated tyrosine residues associate directly with the p85 subunit of Phosphatidylinositol 3-Kinase (PIK3), which results in activation of the cellular survival pathway controlled by the PI3K/Akt axis. Constitutive activation of ErbB3 by unregulated dimerization and/or unregulated phosphorylation of ErbB3 can lead to certain cancers.

[0006] Overexpression of ErbB3 is associated with poor prognosis in various carcinomas (*e.g.*, breast, ovarian, prostate, colorectal, pancreatic, gastric, and head and neck cancers). Overexpression of ErbB3 also correlates with local to distal metastasis in lung, gastric, and colorectal cancers, and bone invasion in prostate cancer (Sithanandam *et al.*, 2008, CANCER GENE THERAPY 15:413). Overexpression of ErbB3 has been linked to resistance to several cancer treatments, including treatment with EGFR tyrosine kinase inhibitors in non-small cell lung cancer (NSCLC) and head and neck cancers, treatment with Her2 inhibitor in breast cancers, and treatment with radiotherapy in pancreatic cancers. Moreover, overexpression of NRG, a ligand for ErbB3, was also linked to resistance to EGFR tyrosine kinase inhibitor treatment. Chen *et al.* describe the use of anti-ErbB3 monoclonal antibodies that inhibit NRG function and show growth inhibitory activity against breast and ovarian cancer cells (Chen *et al.*, 1996, J. BIOL. CHEM. 271: 7620).

[0007] There is a need for improved anti-ErbB3 antibodies that can be used as therapeutic agents.

SUMMARY

[0008] The invention is based on the discovery of a family of antibodies that specifically bind human ErbB3. The antibodies contain ErbB3 binding sites based on CDRs that specifically bind human ErbB3. When used as therapeutic agents, the antibodies are engineered, *e.g.*, humanized, to reduce or eliminate an immune response when administered to a human patient.

[0009] The antibodies disclosed herein prevent or inhibit the activation of human ErbB3. In some embodiments, the antibodies prevent ErbB3 from binding to a ligand, *e.g.*, NRG/HRG, thereby neutralizing the biological activity of ErbB3. In other embodiments, the anti-ErbB3 antibodies inhibit ErbB3 dimerization, thereby neutralizing the biological activity of ErbB3. The antibodies disclosed herein can be used to inhibit the proliferation of tumor cells *in vitro* or *in vivo*. When administered to a human cancer patient (or an animal model such as a mouse model), the antibodies inhibit or reduce tumor growth in the human patient (or animal model).

[0010] These and other aspects and advantages of the invention are illustrated by the following figures, detailed description and claims. As used herein, "including" means without limitation, and examples cited are non-limiting.

DESCRIPTION OF THE DRAWINGS

[0011] The invention can be more completely understood with reference to the following drawings.

[0012] FIG. 1 (prior art) is a schematic representation of a typical antibody.

[0013] FIG. 2 is a schematic diagram showing the amino acid sequence of the complete immunoglobulin heavy chain variable region of the antibodies denoted as 04D01, 09D03, 11G01, 12A07, 18H02, 22A02, and 24C05. The amino acid sequences for each antibody are aligned against one another, and Complementary Determining Sequences (CDR) (Kabat definition), CDR_1, CDR_2, and CDR_3, are identified in boxes. The unboxed sequences represent framework (FR) sequences.

[0014] FIG. 3 is a schematic diagram showing the CDR_1, CDR_2, and CDR_3 sequences (Kabat definition) for each of the immunoglobulin heavy chain variable region sequences in FIG. 2.

[0015] FIG. 4 is a schematic diagram showing the amino acid sequence of the complete immunoglobulin light chain variable region of antibodies 04D01, 09D03, 11G01, 12A07, 18H02, 22A02, and 24C05. The amino acid sequences for each antibody are aligned against one another, and CDR_1, CDR_2, and CDR_3 sequences (Kabat definition) are identified in boxes. The unboxed sequences represent framework (FR) sequences.

[0016] FIG. 5 is a schematic diagram showing the CDR_1, CDR_2, and CDR_3 sequences (Kabat definition) for each of the immunoglobulin light chain variable region sequences in FIG. 4.

[0017] FIGS. 6A and 6B are graphs summarizing results from an experiment to measure the neutralization activity of negative control (murine IgG (Δ)) and anti-ErbB3 monoclonal antibodies 04D01 (■), 12A07 (○), 18H02 (◊), 22A02 (●) and 24C05 (□) to inhibit NRG1-β1 binding to hErbB3 (FIG. 6A) and to measure the enhanced binding of NRG1-β1 to rhErbB3 by the anti-ErbB3 mAb 09D03 (▲) and 11G01 (*) (FIG. 6B).

[0018] FIG. 7 is a graph summarizing results from an experiment to measure the neutralization activity of negative control (murine IgG) and anti-ErbB3 monoclonal antibodies 04D01, 09D03, 11G01, 12A07, 18H02, 22A02 and 24C05 to inhibit NRG1-α1 binding to rhErbB3.

[0019] FIG. 8 is a graph summarizing results from an experiment to measure the cell surface recognition of the anti-ErbB3 antibodies of the chimeric protein Her2/3d2 expressed at the surface of CHO cells.

[0020] FIG. 9 is a graph summarizing results from an experiment to measure the anti-proliferation activity of negative control IgG (murine IgG (Δ)) and anti-ErbB3 monoclonal antibodies 04D01 (■), 09D03 (▼), 11G01 (♦), 12A07 (○), 18H02 (◊), 22A02 (●) and 24C05 (□) in BaF/3 cells expressing Her2 and ErbB3 in presence of NRG1-β1.

[0021] FIG. 10 is a graph summarizing results from an experiment to measure the anti-proliferation activity of anti-ErbB3 monoclonal antibodies 04D01 (■), 09D03 (▼),11G01 (♦), 12A07 (○), 18H02 (◊), 22A02 (●) and 24C05 (□) in MCF7 cells in the presence of NRG1-β1.

[0022] FIG. 11 is a graph summarizing results from an experiment to measure the anti-proliferation activity of negative control (murine IgG) and anti-ErbB3 monoclonal antibodies 04D01, 09D03, 11G01, 12A07, 18H02, 22A02 and 24C05 in SKBR-3 cells treated with 5 μg/ml of antibodies in the presence of serum.

[0023] FIG. 12 is graph summarizing results from an experiment to measure the inhibitory activity of negative control IgG and anti-ErbB3 monoclonal antibodies 04D01, 09D03, 11G01, 12A07, 18H02, 22A02 and 24C05 on the phosphorylation of ErbB3 induced by NRG in SKBR-3 cells. No antibody/no ligand and no antibody controls are also shown.

[0024] FIG. 13A and 13B are graphs representing results from an experiment to measure the inhibitory activity of anti-ErbB3 monoclonal antibodies 04D01, 09D03, 11G01, 12A07, 18H02, 22A02 and 24C05 on the phosphorylation of Akt in response to NRG1-β1 in MCF7 cells (FIG. 13A) and in DU145 cells (FIG. 13B) as determined by ELISA. No antibody/no ligand and no antibody controls are also shown.

[0025] FIG. 14 is a graph summarizing results from an experiment to measure the tumor inhibitory activity of the anti-ErbB3 antibodies 04D01 (Δ), 09D03 (*), 11G01 (□), 12A07 (▲), 18H02 (●), 22A02 (■), 24C05 (○) and a human IgG control (- -■- -) dosed at 20 mg/kg in a BxPC3 pancreatic tumor xenograft model in CB17 SCID mice (vehicle control, PBS (♦)).

[0026] FIG. 15 is a schematic diagram showing the amino acid sequences of the complete heavy chain variable region of 24C05 and the complete humanized heavy chain variable regions denoted as Sh24C05 Hv3-7, Sh24C05 Hv3-11, Sh24C05 Hv3-11 N62S, Sh24C05 Hv3-21, Sh24C05 Hv3-23, Sh24C05 Hv3-30, and Hu24C05 HvA. The amino acid sequences for each heavy chain variable regions are aligned against one another, and Complementary Determining Sequences (CDR) (Kabat definition), CDR_1, CDR_2, and CDR_3, are identified in boxes. The unboxed sequences represent framework (FR) sequences.

[0027] FIG. 16 is a schematic diagram showing the amino acid sequences of the complete light chain variable region of 24C05 and the complete humanized light chain variable regions denoted as Sh24C05 Kv1-9, Sh24C05 Kv1-16, Sh24C05 Kv1-17, Sh24C05 Kv1-33, Sh24C05 Kv1-39, and Hu24C05 KvA. The amino acid sequences for each light chain variable regions are aligned against one another, and CDR_1, CDR_2, and CDR_3 sequences (Kabat definition) are identified in boxes. The unboxed sequences represent framework (FR) sequences.

[0028] FIG. 17 are Biacore sensorgrams representing results from an experiment to measure the kinetic values of anti-ErbB3 monoclonal antibodies, Sh24C05-31 N62S-IgG1, Ab#6, U1-53, and U1-59.

[0029] FIG. 18A is a graph summarizing results from an experiment to measure the neutralization activity of negative control (human IgG (□)) and anti-ErbB3 monoclonal antibodies Sh24C05-25 N62S-IgG1 (▲), Sh24C05-25 N62S-IgG2 (Δ), Sh24C05-31 N62S-IgG1(●) and Sh24C05-31 N62S-IgG2 (○). FIG. 18B is a graph summarizing results from an experiment to measure the neutralization activity of human IgG (□) and anti-ErbB3 monoclonal antibodies Ab#6 IgG2 (▼) , U1-53 (◊) and U1-59 (■).

[0030] FIG. 19A is a graph summarizing results from an experiment to measure the inhibitory activity of negative control (human IgG (□)) and anti-ErbB3 monoclonal antibodies Sh24C05-25 N62S-IgG1 (▲), Sh24C05-25 N62S-IgG2 (Δ), Sh24C05-31 N62S-IgG1 (●) and Sh24C05-31 N62S-IgG2 (○) in BaF/3 cells expressing Her2 and ErbB3 in the presence of NRG1-β1. FIG. 19B is a graph summarizing results from an experiment to measure the inhibitory activity of human IgG (□) and anti-ErbB3 monoclonal antibodies Sh24C05-31 N62S-IgG1(●), Ab#6 IgG2 (∇), U1-53 (◊) and U1-59 (■) in BaF/3 cells expressing Her2 and ErbB3 in the presence of NRG1-β1.

[0031] FIG. 20 is a graph summarizing results from an experiment to measure the inhibitory activity of negative control (human IgG) and anti-ErbB3 monoclonal antibodies Sh24C05-25 N62S-IgG1, Sh24C05-25 N62S-IgG2, Sh24C05-31 N62S-IgG1, and Sh24C05-31 N62S-IgG2 on the steady state phosphorylation of ErbB3 in growing SKBR-3 cells.

[0032] FIG. 21 is a graph summarizing results from an experiment to measure the degradation of ErbB3 receptor by negative control (human IgG) and anti-ErbB3 monoclonal antibodies Sh24C05-25 N62S-IgG1, Sh24C05-25 N62S-IgG2, Sh24C05-31 N62S-IgG1, and Sh24C05-31 N62S-IgG2 in growing SKBR-3 cells.

[0033] FIG. 22 is a graph summarizing the results from an experiment to measure tumor inhibitory activity of a human IgG, murine IgG, or anti-ErbB3 monoclonal antibodies dosed at 2 mg/kg in a BxPC3 pancreatic tumor xenograft model in CB17 SCID mice (murine 24C05 (Δ), Sh24C05-31 N62S IgG1 (●), Sh24C05-31 N62S IgG2 (♦), Sh24C05-25 N62S IgG1(▲), Sh24C05-25 N62S IgG2 (■), vehicle control (□), murine IgG (x), and human IgG (◊)).

[0034] FIG. 23A is a graph summarizing the results from an experiment to measure tumor inhibitory activity of a murine IgG or anti-ErbB3 monoclonal antibodies dosed at 5 mg/kg in a Calu-3 non-small cell lung cancer xenograft model in NCR nude mice (vehicle control (□), murine IgG (x), Sh24C05-31 N62S IgG1 (▲), Ab#6 IgG2 (●), and U1-59 (■)).

[0035] FIG. 23B is a graph summarizing the results from an experiment to measure tumor inhibitory activity of a murine IgG or anti-ErbB3 monoclonal antibodies dosed at 10 mg/kg in a Calu-3 non-small cell lung cancer xenograft model in NCR nude mice (vehicle control (□), murine IgG (x), Sh24C05-31 N62S IgG1 (▲), Ab#6 IgG2 (●), and U1-59 (■)).

[0036] FIG. 23C is a graph summarizing the results from an experiment to measure tumor inhibitory activity of a murine IgG or anti-ErbB3 monoclonal antibodies dosed at 20 mg/kg in a

Calu-3 non-small cell lung cancer xenograft model in NCR nude mice (vehicle control (□), murine IgG (x), Sh24C05-31 N62S IgG1 (▲), Ab#6 IgG2 (●), and U1-59 (■)).

[0037] FIG. 24 is a graph summarizing the results from an experiment to measure tumor inhibitory activity of a human IgG, murine or anti-ErbB3 monoclonal antibodies in a MDA-MB-453 breast cancer xenograft model in NOD SCID mice (vehicle control (□), human IgG (x), Sh24C05-31 N62S IgG1 dosed at 5 mg/kg (◊), Sh24C05-31 N62S IgG1 dosed at 10 mg/kg (Δ), Sh24C05-31 N62S IgG1 dosed at 20 mg/kg (▲), Ab#6 IgG2 dosed at 10 mg/kg (●), and U1-59 dosed at 10 mg/kg (■)).

DETAILED DESCRIPTION

[0038] The ErbB3 antibodies disclosed herein are based on the antigen binding sites of certain monoclonal antibodies selected for their ability to neutralize the biological activity of human ErbB3 polypeptides. The antibodies contain immunoglobulin variable region CDR sequences that define a binding site for ErbB3. In some embodiments, the antibodies prevent ErbB3 from binding to a ligand, *e.g.*, NRG/HRG, thereby neutralizing the biological activity of ErbB3. In other embodiments, the anti-ErbB3 antibodies inhibit ErbB3 dimerization, thereby neutralizing the biological activity of ErbB3. In still other embodiments, the anti-ErbB3 antibodies inhibit phosphorylation of ErbB3 and downstream signaling.

[0039] Because of the neutralizing activity of these antibodies, they are useful for inhibiting the growth and/or proliferation of certain cancer cells and tumors. The antibodies can be engineered to minimize or eliminate an immune response when administered to a human patient. In some embodiments, the antibodies are fused or conjugated to other moieties, such as detectable labels or effector molecules such as small molecule toxins.

I. Antibodies that Bind ErbB3

[0040] In some embodiments, the antibody comprises: (a) an immunoglobulin heavy chain variable region comprising the structure CDR_{H1}-CDR_{H2}-CDR_{H3} and (b) immunoglobulin light chain variable region, wherein the heavy chain variable region and the light chain variable region together define a single binding site for binding human ErbB3. A CDR_{H1} comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 5 (**04D01**), SEQ ID NO:15 (**09D03**), SEQ ID NO: 25 (**11G01**), SEQ ID NO: 34 (**12A07**), SEQ ID NO: 41 (**18H02**), SEQ ID NO: 51 (**22A02**), SEQ ID NO: 57 (**24C05**), and SEQ ID NO: 75 (**24C05**); a CDR_{H2} comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 6

(**04D01**), SEQ ID NO:16 (**09D03**), SEQ ID NO: 26 (**11G01**), SEQ ID NO: 35 (**12A07**), SEQ ID NO: 42 (**18H02**), SEQ ID NO: 52 (**22A02**), SEQ ID NO: 58 (**24C05**), and SEQ ID NO: 148 (**Sh24C05 Hv3-11 N62S**); and a CDR_{H3} comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 7 (**04D01**), SEQ ID NO: 17 (**09D03**), SEQ ID NO: 27 (**11G01**), SEQ ID NO: 36 (**12A07**, **22A02**), SEQ ID NO: 43 (**18H02**), and SEQ ID NO: 59 (**24C05**). Throughout the specification a particular SEQ ID NO. is followed in parentheses by the antibody that was the origin of that sequence. For example, "SEQ ID NO: 5 (**04D01**)" means that SEQ ID NO: 5 comes from antibody 04D01.

[0041] In some embodiments, the antibody comprises an immunoglobulin heavy chain variable region comprising a CDR_{H1} comprising the amino acid sequence of SEQ ID NO: 5 (**04D01**), a CDR_{H2} comprising the amino acid sequence of SEQ ID NO: 6 (**04D01**), and a CDR_{H3} comprising the amino acid sequence of SEQ ID NO: 7 (**04D01**).

[0042] In some embodiments, the antibody comprises an immunoglobulin heavy chain variable region comprising a CDR_{H1} comprising the amino acid sequence of SEQ ID NO: 15 (**09D03**), a CDR_{H2} comprising the amino acid sequence of SEQ ID NO: 16 (**09D03**), and a CDR_{H3} comprising the amino acid sequence of SEQ ID NO: 17 (**09D03**).

[0043] In some embodiments, the antibody comprises an immunoglobulin heavy chain variable region comprising a CDR_{H1} comprising the amino acid sequence of SEQ ID NO: 25 (**11G01**), a CDR_{H2} comprising the amino acid sequence of SEQ ID NO: 26 (**11G01**), and a CDR_{H3} comprising the amino acid sequence of SEQ ID NO: 27 (**11G01**).

[0044] In some embodiments, the antibody comprises an immunoglobulin heavy chain variable region comprising a CDR_{H1} comprising the amino acid sequence of SEQ ID NO: 34 (**12A07**), a CDR_{H2} comprising the amino acid sequence of SEQ ID NO: 35 (**12A07**), and a CDR_{H3} comprising the amino acid sequence of SEQ ID NO: 36 (**12A07**, **22A02**).

[0045] In some embodiments, the antibody comprises an immunoglobulin heavy chain variable region comprising a CDR_{H1} comprising the amino acid sequence of SEQ ID NO: 41 (**18H02**), a CDR_{H2} comprising the amino acid sequence of SEQ ID NO: 42 (**18H02**), and a CDR_{H3} comprising the amino acid sequence of SEQ ID NO: 43 (**18H02**).

[0046] In some embodiments, the antibody comprises an immunoglobulin heavy chain variable region comprising a CDR_{H1} comprising the amino acid sequence of SEQ ID NO: 51

(**22A02**), a CDR_{H2} comprising the amino acid sequence of SEQ ID NO: 52 (**22A02**), and a CDR_{H3} comprising the amino acid sequence of SEQ ID NO: 36 (**12A07**, **22A02**).

[0047] In some embodiments, the antibody comprises an immunoglobulin heavy chain variable region comprising a CDR_{H1} comprising the amino acid sequence of SEQ ID NO: 57 (**24C05**) or SEQ ID NO: 75 (**24C05**), a CDR_{H2} comprising the amino acid sequence of SEQ ID NO: 58 (**24C05**), and a CDR_{H3} comprising the amino acid sequence of SEQ ID NO: 59 (**24C05**).

[0048] In certain embodiments, the antibody comprises an immunoglobulin heavy chain variable region comprising a CDR_{H1} comprising the amino acid sequence of SEQ ID NO: 57 (**24C05**), a CDR_{H2} comprising the amino acid sequence of SEQ ID NO: 58 (**24C05**), and a CDR_{H3} comprising the amino acid sequence of SEQ ID NO: 59 (**24C05**).

[0049] In other embodiments, the antibody comprises an immunoglobulin heavy chain variable region comprising a CDR_{H1} comprising the amino acid sequence of SEQ ID NO: 75 (**24C05**), a CDR_{H2} comprising the amino acid sequence of SEQ ID NO: 58 (**24C05**), and a CDR_{H3} comprising the amino acid sequence of SEQ ID NO: 59 (**24C05**).

[0050] In certain embodiments, the antibody comprises an immunoglobulin heavy chain variable region a CDR_{H1} comprising the amino acid sequence of SEQ ID NO: 57 (**24C05**) or SEQ ID NO: 75 (**24C05**), a CDR_{H2} comprising the amino acid sequence of SEQ ID NO: 148 (**Sh24C05 Hv3-11 N62S**), and a CDR_{H3} comprising the amino acid sequence of SEQ ID NO: 59 (**24C05**).

[0051] Preferably, the CDR_{H1}, CDR_{H2}, and CDR_{H3} sequences are interposed between human or humanized immunoglobulin FRs. The antibody can be an intact antibody or an antigen-binding antibody fragment.

[0052] In some embodiments, the antibody comprises (a) an immunoglobulin light chain variable region comprising the structure CDR_{L1}-CDR_{L2}-CDR_{L3}, and (b) an immunoglobulin heavy chain variable region, wherein the IgG light chain variable region and the IgG heavy chain variable region together define a single binding site for binding human ErbB3. A CDR_{L1} comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 8 (**04D01**, **12A07**, **22A02**), SEQ ID NO: 18 (**09D03**), SEQ ID NO: 28 (**11G01**), SEQ ID NO: 44 (**18H02**), and SEQ ID NO: 60 (**24C05**); a CDR_{L2} comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 9 (**04D01**, **11G01**, **12A07**, **22A02**), SEQ ID NO: 19

(**09D03**), SEQ ID NO: 45 (**18H02**), and SEQ ID NO: 61 (**24C05**); and a CDR_{L3} comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 10 (**04D01**, **12A07**, **22A02**), SEQ ID NO: 20 (**09D03**), SEQ ID NO: 29 (**11G01**), SEQ ID NO: 46 (**18H02**), and SEQ ID NO: 62 (**24C05**).

[0053] In some embodiments, the antibody comprises an immunoglobulin light chain variable region comprising: a CDR_{L1} comprising the amino acid sequence of SEQ ID NO: 8 (**04D01**, **12A07**, **22A02**); a CDR_{L2} comprising the amino acid sequence of SEQ ID NO: 9 (**04D01**, **11G01**, **12A07**, **22A02**); and a CDR_{L3} comprising the amino acid sequence of SEQ ID NO: 10 (**04D01**, **12A07**, **22A02**).

[0054] In some embodiments, the antibody comprises an immunoglobulin light chain variable region comprising: a CDR_{L1} comprising the amino acid sequence of SEQ ID NO: 18 (**09D03**); a CDR_{L2} comprising the amino acid sequence of SEQ ID NO: 19 (**09D03**); and a CDR_{L3} comprising the amino acid sequence of SEQ ID NO: 20 (**09D03**).

[0055] In some embodiments, the antibody comprises an immunoglobulin light chain variable region comprising: a CDR_{L1} comprising the amino acid sequence of SEQ ID NO: 28 (**11G01**); a CDR_{L2} comprising the amino acid sequence of SEQ ID NO: 9 (**04D01**, **11G01**, **12A07**, **22A02**); and a CDR_{L3} comprising the amino acid sequence of SEQ ID NO: 29 (**11G01**).

[0056] In some embodiments, the antibody comprises an immunoglobulin light chain variable region comprising: a CDR_{L1} comprising the amino acid sequence of SEQ ID NO: 44 (**18H02**); a CDR_{L2} comprising the amino acid sequence of SEQ ID NO: 45 (**18H02**); and a CDR_{L3} comprising the amino acid sequence of SEQ ID NO: 46 (**18H02**).

[0057] In one embodiment, the antibody comprises an immunoglobulin light chain variable region comprising: a CDR_{L1} comprising the amino acid sequence of SEQ ID NO: 60 (**24C05**); a CDR_{L2} comprising the amino acid sequence of SEQ ID NO: 61 (**24C05**); and a CDR_{L3} comprising the amino acid sequence of SEQ ID NO: 62 (**24C05**).

[0058] Preferably, the CDR_{L1}, CDR_{L2}, and CDR_{L3} sequences are interposed between human or humanized immunoglobulin FRs. The antibody can be an intact antibody or an antigen-binding antibody fragment.

[0059] In some embodiments, the antibody comprises: (a) an IgG heavy chain variable region comprising the structure CDR_{H1}-CDR_{H2}-CDR_{H3} and (b) an IgG light chain variable

region comprising the structure CDR_{L1}-CDR_{L2}-CDR_{L3}, wherein the heavy chain variable region and the light chain variable region together define a single binding site for binding human ErbB3. The CDR_{H1} is an amino acid sequence selected from the group consisting of SEQ ID NO: 5 (**04D01**), SEQ ID NO:15 (**09D03**), SEQ ID NO: 25 (**11G01**), SEQ ID NO: 34 (**12A07**), SEQ ID NO: 41 (**18H02**), SEQ ID NO: 51 (**22A02**), SEQ ID NO: 57 (**24C05**), and SEQ ID NO: 75 (**24C05**); the CDR_{H2} is an amino acid sequence selected from the group consisting of SEQ ID NO: 6 (**04D01**), SEQ ID NO:16 (**09D03**), SEQ ID NO: 26 (**11G01**), SEQ ID NO: 35 (**12A07**), SEQ ID NO: 42 (**18H02**), SEQ ID NO: 52 (**22A02**), SEQ ID NO: 58 (**24C05**), and SEQ ID NO: 148 (**Sh24C05 Hv3-11 N62S**); and the CDR_{H3} is an amino acid sequence selected from the group consisting of SEQ ID NO: 7 (**04D01**), SEQ ID NO: 17 (**09D03**), SEQ ID NO: 27 (**11G01**), SEQ ID NO: 36 (**12A07**, **22A02**), SEQ ID NO: 43 (**18H02**), and SEQ ID NO: 59 (**24C05**). The CDR_{L1} is an amino acid sequence selected from the group consisting of SEQ ID NO: 8 (**04D01**, **12A07**, **22A02**), SEQ ID NO: 18 (**09D03**), SEQ ID NO: 28 (**11G01**), SEQ ID NO: 44 (**18H02**), and SEQ ID NO: 60 (**24C05**); the CDR_{L2} is an amino acid sequence selected from the group consisting of SEQ ID NO: 9 (**04D01**, **11G01**, **12A07**, **22A02**), SEQ ID NO: 19 (**09D03**), SEQ ID NO: 45 (**18H02**), and SEQ ID NO: 61 (**24C05**); and the CDR_{L3} is an amino acid sequence selected from the group consisting of SEQ ID NO: 10 (**04D01**, **12A07**, **22A02**), SEQ ID NO: 20 (**09D03**), SEQ ID NO: 29 (**11G01**), SEQ ID NO: 46 (**18H02**), and SEQ ID NO: 62 (**24C05**).

[0060] In another embodiment, the antibody comprises an immunoglobulin heavy chain variable region selected from the group consisting of SEQ ID NO: 2 (**04D01**), SEQ ID NO: 12 (**09D03**), SEQ ID NO: 22 (**11G01**), SEQ ID NO: 31 (**12A07**), SEQ ID NO: 38 (**18H02**), SEQ ID NO: 48 (**22A02**), SEQ ID NO: 54 (**24C05**), and SEQ ID NO: 154 (**Sh24C05 Hv3-11 N62S**), and an immunoglobulin light chain variable region selected from the group consisting of SEQ ID NO: 4 (**04D01**), SEQ ID NO: 14 (**09D03**), SEQ ID NO: 24 (**11G01**), SEQ ID NO: 33 (**12A07**), SEQ ID NO: 40 (**18H02**), SEQ ID NO: 50 (**22A02**), SEQ ID NO: 56 (**24C05**), SEQ ID NO: 166 (**Sh24C05 Kv1-16**), and SEQ ID NO: 168 (**Sh24C05 Kv1-17**).

[0061] In another embodiment, the antibody comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2 (**04D01**), and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 4 (**04D01**).

[0062] In another embodiment, the antibody comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 12 (**09D03**), and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 14 (**09D03**).

[0063] In another embodiment, the antibody comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 22 (**11G01**), and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 24 (**11G01**).

[0064] In another embodiment, the antibody comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 31 (**12A07**), and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 33 (**12A07**).

[0065] In another embodiment, the antibody comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 38 (**18H02**), and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 40 (**18H02**).

[0066] In another embodiment, the antibody comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 48 (**22A02**), and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 50 (**22A02**).

[0067] In another embodiment, the antibody comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 54 (**24C05**), and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 56 (**24C05**).

[0068] In another embodiment, the antibody comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 154 (**Sh24C05 Hv3-11 N62S**), and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 166 (**Sh24C05 Kv1-16**).

[0069] In another embodiment, the antibody comprises an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 154 (**Sh24C05 Hv3-11**

N62S), and an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 168 (**Sh24C05 Kv1-17**).

[0070] In other embodiments, the antibody comprises (i) an immunoglobulin heavy chain selected from the group consisting of SEQ ID NO: 109 (**04D01**), SEQ ID NO: 113 (**09D03**), SEQ ID NO: 117 (**11G01**), SEQ ID NO: 121 (**12A07**), SEQ ID NO: 125 (**18H02**), SEQ ID NO: 129 (**22A07**), SEQ ID NO: 133 (**24C05**), SEQ ID NO: 190 (**Sh24C05 Hv3-11 N62S IgG1**), and SEQ ID NO: 192 (**Sh24C05 Hv3-11 N62S IgG2**), and (ii) an immunoglobulin light chain selected from the group consisting of SEQ ID NO: 111 (**04D01**), SEQ ID NO: 115 (**09D03**), SEQ ID NO: 119 (**11G01**), SEQ ID NO: 123 (**12A07**), SEQ ID NO: 127 (**18H02**), SEQ ID NO: 131 (**22A07**), SEQ ID NO: 135 (**24C05**), SEQ ID NO: 204 (**Sh24C05 Kv1-16 kappa**), and SEQ ID NO: 206 (**Sh24C05 Kv1-17 kappa**).

[0071] In another embodiment, the antibody comprises an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 109 (**04D01**), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 111 (**04D01**).

[0072] In another embodiment, the antibody comprises an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 113 (**09D03**), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 115 (**09D03**).

[0073] In another embodiment, the antibody comprises an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 117 (**11G01**), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 119 (**11G01**).

[0074] In another embodiment, the antibody comprises an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 121 (**12A07**), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 123 (**12A07**).

[0075] In another embodiment, the antibody comprises an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 125 (**18H02**), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 127 (**18H02**).

[0076] In another embodiment, the antibody comprises an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 129 (**22A02**), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 131 (**22A02**).

[0077] In another embodiment, the antibody comprises an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 133 (**24C05**), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 135 (**24C05**).

[0078] In another embodiment, the antibody comprises an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 190 (**Sh24C05 Hv3-11 N62S IgG1**), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 204 (**Sh24C05 Kv1-16 kappa**).

[0079] In another embodiment, the antibody comprises an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 192 (**Sh24C05 Hv3-11 N62S IgG2**), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 204 (**Sh24C05 Kv1-16 kappa**).

[0080] In another embodiment, the antibody comprises an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 190 (**Sh24C05 Hv3-11 N62S IgG1**), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 206 (**Sh24C05 Kv1-17 kappa**).

[0081] In another embodiment, the antibody comprises an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 192 (**Sh24C05 Hv3-11 N62S IgG2**), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 206 (**Sh24C05 Kv1-17 kappa**).

[0082] As used herein, unless otherwise indicated, the term "antibody" means an intact antibody (*e.g.*, an intact monoclonal antibody) or antigen-binding fragment of a antibody (*e.g.*, an antigen-binding fragment of a monoclonal antibody), including an intact antibody or antigen-binding fragment that has been modified, engineered, or chemically conjugated. Examples of antibodies that have been modified or engineered include chimeric antibodies, humanized antibodies, and multispecific antibodies (*e.g.*, bispecific antibodies). Examples of antigen-binding fragments include Fab, Fab', $(Fab')_2$, Fv, single chain antibodies (*e.g.*, scFv), minibodies, and diabodies. An example of a chemically conjugated antibody is an antibody conjugated to a toxin moiety.

[0083] Figure 1 shows a schematic representation of an intact monoclonal antibody that contains four polypeptide chains. Two of the polypeptide chains are called immunoglobulin heavy chains (H chains), and two of the polypeptide chains are called immunoglobulin light

chains (L chains). The immunoglobulin heavy and light chains are connected by an interchain disulfide bond. The immunoglobulin heavy chains are connected by interchain disulfide bonds. A light chain consists of one variable region (V_L in FIG. 1) and one constant region (C_L in FIG. 1). The heavy chain consists of one variable region (V_H in FIG. 1) and at least three constant regions (CH_1, CH_2 and CH_3 in FIG. 1). The variable regions determine the specificity of the antibody.

[0084] Each variable region contains three hypervariable regions known as complementarity determining regions (CDRs) flanked by four relatively conserved regions known as framework regions (FRs). The three CDRs, referred to as CDR_1, CDR_2, and CDR_3, contribute to the antibody binding specificity.

[0085] In certain embodiments, an isolated antibody that binds human ErbB3 comprises an immunoglobulin heavy chain variable region comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% identical to the entire variable region or the framework region sequence of SEQ ID NO: 2 (**04D01**), SEQ ID NO: 12 (**09D03**), SEQ ID NO: 22 (**11G01**), SEQ ID NO: 31 (**12A07**), SEQ ID NO: 38 (**18H02**), SEQ ID NO: 48 (**22A02**), SEQ ID NO: 54 (**24C05**), and SEQ ID NO: 154 (**Sh24C05 Hv3-11 N62S**).

[0086] In certain embodiments, an isolated antibody that binds human ErbB3 comprises an immunoglobulin light chain variable region comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% identical to the entire variable region or the framework region sequence of SEQ ID NO: 4 (**04D01**), SEQ ID NO: 14 (**09D03**), SEQ ID NO: 24 (**11G01**), SEQ ID NO: 33 (**12A07**), SEQ ID NO: 40 (**18H02**), SEQ ID NO: 50 (**22A02**), SEQ ID NO: 56 (**24C05**), SEQ ID NO: 166 (**Sh24C05 Kv1-16**), and SEQ ID NO: 168 (**Sh24C05 Kv1-17**).

[0087] In each of the foregoing embodiments, it is contemplated herein that immunoglobulin heavy chain variable region sequences and/or light chain variable region sequences that together bind human ErbB3 may contain amino acid alterations (*e.g.*, at least 1, 2, 3, 4, 5, or 10 amino acid substitutions, deletions, or additions) in the framework regions of the heavy and/or light chain variable regions.

[0088] In some embodiments, an isolated antibody binds hErbB3 with a K_D of 350 pM, 300 pM, 250 pM, 200 pM, 150 pM, 100 pM, 75 pM, 50 pM, 20 pM, 10 pM or lower. Unless otherwise specified, K_D values are determined by surface plasmon resonance methods. The

surface plasmon resonance methods can be performed using the conditions described, for example, in Examples 3 and 12, where the measurements were performed at 25°C and 37°C, respectively.

[0089] In some embodiments, the antibodies inhibit hErbB3 binding to NRG1-β1. For example, the antibodies can have an IC_{50} (concentration at 50% of maximum inhibition) of about 5 nM, 2 nM or lower, when assayed using the protocols described in Examples 4 and 13.

II. Production of Antibodies

[0090] Methods for producing antibodies disclosed herein are known in the art. For example, DNA molecules encoding light chain variable regions and heavy chain variable regions can be chemically synthesized using the sequence information provided herein. Synthetic DNA molecules can be ligated to other appropriate nucleotide sequences, including, *e.g.*, constant region coding sequences, and expression control sequences, to produce conventional gene expression constructs encoding the desired antibodies. Production of defined gene constructs is within routine skill in the art. Alternatively, the sequences provided herein can be cloned out of hybridomas by conventional hybridization techniques or polymerase chain reaction (PCR) techniques, using synthetic nucleic acid probes whose sequences are based on sequence information provided herein, or prior art sequence information regarding genes encoding the heavy and light chains of murine antibodies in hybridoma cells.

[0091] Nucleic acids encoding the antibodies disclosed herein can be incorporated (ligated) into expression vectors, which can be introduced into host cells through conventional transfection or transformation techniques. Exemplary host cells are *E. coli* cells, Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (*e.g.*, Hep G2), and myeloma cells that do not otherwise produce IgG protein. Transformed host cells can be grown under conditions that permit the host cells to express the genes that encode the immunoglobulin light and/or heavy chain variable regions.

[0092] Specific expression and purification conditions will vary depending upon the expression system employed. For example, if a gene is to be expressed in *E. coli*, it is first cloned into an expression vector by positioning the engineered gene downstream from a suitable bacterial promoter, *e.g.*, Trp or Tac, and a prokaryotic signal sequence. The expressed

secreted protein accumulates in refractile or inclusion bodies, and can be harvested after disruption of the cells by French press or sonication. The refractile bodies then are solubilized, and the proteins refolded and cleaved by methods known in the art.

[0093] If a DNA construct encoding an antibody disclosed herein is to be expressed in eukayotic host cells, *e.g.*, CHO cells, it is first inserted into an expression vector containing a suitable eukaryotic promoter, a secretion signal, IgG enhancers, and various introns. This expression vector optionally contains sequences encoding all or part of a constant region, enabling an entire, or a part of, a heavy and/or light chain to be expressed. In some embodiments, a single expression vector contains both heavy and light chain variable regions to be expressed.

[0094] The gene construct can be introduced into eukaryotic host cells using conventional techniques. The host cells express V_L or V_H fragments, V_L-V_H heterodimers, V_H-V_L or V_L-V_H single chain polypeptides, complete heavy or light immunoglobulin chains, or portions thereof, each of which may be attached to a moiety having another function (*e.g.*, cytotoxicity). In some embodiments, a host cell is transfected with a single vector expressing a polypeptide expressing an entire, or part of, a heavy chain (*e.g.*, a heavy chain variable region) or a light chain (*e.g.*, a light chain variable region). In other embodiments, a host cell is transfected with a single vector encoding (a) a polypeptide comprising a heavy chain variable region and a polypeptide comprising a light chain variable region, or (b) an entire immunoglobulin heavy chain and an entire immunoglobulin light chain. In still other embodiments, a host cell is co-transfected with more than one expression vector (*e.g.*, one expression vector expressing a polypeptide comprising an entire, or part of, a heavy chain or heavy chain variable region, and another expression vector expressing a polypeptide comprising an entire, or part of, a light chain or light chain variable region).

[0095] A method of producing a polypeptide comprising an immunoglobulin heavy chain variable region or a polypeptide comprising an immunoglobulin light chain variable region may comprise growing a host cell transfected with an expression vector under conditions that permits expression of the polypeptide comprising the immunoglobulin heavy chain variable region or the polypeptide comprising the immunoglobulin light chain variable region. The polypeptide comprising a heavy chain variable region or the polypeptide comprising the light chain variable region then may be purified using techniques well known in the art, *e.g.*, affinity tags such as glutathione-S-transferase (GST) and histidine tags.

[0096] A method of producing a monoclonal antibody that binds human ErbB3, or an antigen-binding fragment of the antibody, may comprise growing a host cell transfected with: (a) an expression vector that encodes a complete or partial immunoglobulin heavy chain, and a separate expression vector that encodes a complete or partial immunoglobulin light chain; or (b) a single expression vector that encodes both chains (*e.g.*, complete or partial chains), under conditions that permit expression of both chains. The intact antibody (or antigen-binding fragment) can be harvested and purified using techniques well known in the art, *e.g.*, Protein A, Protein G, affinity tags such as glutathione-S-transferase (GST) and histidine tags. It is within ordinary skill in the art to express the heavy chain and the light chain from a single expression vector or from two separate expression vectors.

III. Modifications to the Antibodies

[0097] Methods for reducing or eliminating the antigenicity of antibodies and antibody fragments are known in the art. When the antibodies are to be administered to a human, the antibodies preferably are "humanized" to reduce or eliminate antigenicity in humans. Preferably, a humanized antibody has the same or substantially the same affinity for the antigen as the non-humanized mouse antibody from which it was derived.

[0098] In one humanization approach, chimeric proteins are created in which mouse immunoglobulin constant regions are replaced with human immunoglobulin constant regions. See, *e.g.*, Morrison *et al.*,1984, PROC. NAT. ACAD. SCI. 81:6851-6855, Neuberger *et al.*, 1984, NATURE 312:604-608; U.S. Patent Nos. 6,893,625 (Robinson); 5,500,362 (Robinson); and 4,816,567 (Cabilly).

[0100] In an approach known as CDR grafting, the CDRs of the light and heavy chain variable regions are grafted into frameworks from another species. For example, murine CDRs can be grafted into human FRs. In some embodiments, the CDRs of the light and heavy chain variable regions of an anti-ErbB3 antibody are grafted onto human FRs or consensus human FRs. To create consensus human FRs, FRs from several human heavy chain or light chain amino acid sequences are aligned to identify a consensus amino acid sequence. CDR grafting is described in U.S. Patent Nos. 7,022,500 (Queen); 6,982,321 (Winter); 6,180,370 (Queen); 6,054,297 (Carter); 5,693,762 (Queen); 5,859,205 (Adair); 5,693,761 (Queen); 5,565,332 (Hoogenboom); 5,585,089 (Queen); 5,530,101 (Queen); Jones *et al.* (1986) NATURE 321: 522-525; Riechmann *et al.* (1988) NATURE 332: 323-327; Verhoeyen *et al.* (1988) SCIENCE 239: 1534-1536; and Winter (1998) FEBS LETT 430: 92-94.

[0101] In an approach called "SUPERHUMANIZATION™," human CDR sequences are chosen from human germline genes, based on the structural similarity of the human CDRs to those of the mouse antibody to be humanized. See, *e.g.*, U.S. Patent No. 6,881,557 (Foote); and Tan *et al.*, 2002, J. IMMUNOL 169:1119-1125.

[0102] Other methods to reduce immunogenicity include "reshaping," "hyperchimerization," and "veneering/resurfacing." See, *e.g.*, Vaswami *et al.*,1998, ANNALS OF ALLERGY, ASTHMA, & IMMUNOL. 81:105; Roguska *et al.*, 1996, PROT. ENGINEER 9:895-904; and U.S. Patent No. 6,072,035 (Hardman). In the veneering/resurfacing approach, the surface accessible amino acid residues in the murine antibody are replaced by amino acid residues more frequently found at the same positions in a human antibody. This type of antibody resurfacing is described, *e.g.*, in U.S. Patent No. 5,639,641 (Pedersen).

[0103] Another approach for converting a mouse antibody into a form suitable for medical use in humans is known as ACTIVMAB™ technology (Vaccinex, Inc., Rochester, NY), which involves a vaccinia virus-based vector to express antibodies in mammalian cells. High levels of combinatorial diversity of IgG heavy and light chains are said to be produced. See, *e.g.*, U.S. Patent Nos. 6,706,477 (Zauderer); 6,800,442 (Zauderer); and 6,872,518 (Zauderer).

[0104] Another approach for converting a mouse antibody into a form suitable for use in humans is technology practiced commercially by KaloBios Pharmaceuticals, Inc. (Palo Alto, CA). This technology involves the use of a proprietary human "acceptor" library to produce an "epitope focused" library for antibody selection.

[0105] Another approach for modifying a mouse antibody into a form suitable for medical use in humans is HUMAN ENGINEERING™ technology, which is practiced commercially by XOMA (US) LLC. See, *e.g.*, PCT Publication No. WO 93/11794 and U.S. Patent Nos. 5,766,886; 5,770,196; 5,821,123; and 5,869,619.

[0106] Any suitable approach, including any of the above approaches, can be used to reduce or eliminate human immunogenicity of an antibody disclosed herein.

[0107] Methods of making multispecific antibodies are known in the art. Multi-specific antibodies include bispecific antibodies. Bispecific antibodies are antibodies that have binding specificities for at least two different epitopes. Exemplary bispecific antibodies bind to two different epitopes of the antigen of interest. Bispecific antibodies can be prepared as full length antibodies or antibody fragments (*e.g.*, $F(ab')_2$ bispecific antibodies and diabodies) as

described, for example, in Milstein *et al.*, NATURE 305:537-539 (1983), WO 93/08829, Traunecker et al., EMBO J., 10:3655-3659 (1991), WO 94/04690, Suresh *et al.*, METHODS IN ENZYMOLOGY, 121:210 (1986), WO96/27011, Brennan *et al.*, SCIENCE, 229: 81 (1985), Shalaby et al., J. EXP. MED., 175: 217-225 (1992), Kostelny *et al.*, J. IMMUNOL., 148(5):1547-1553 (1992), Hollinger *et al.*, PNAS, 90:6444-6448, Gruber *et al.*, J. IMMUNOL., 152:5368 (1994), Wu *et al.*, NAT. BIOTECHNOL., 25(11): 1290-1297, U.S. Patent Publication No. 2007/0071675, and Bostrom *et al.*, SCIENCE 323:1640-1644 (2009).

[0108] In some embodiments, the antibody is conjugated to an effector agent such as a small molecule toxin or a radionuclide using standard *in vitro* conjugation chemistries. If the effector agent is a polypeptide, the antibody can be chemically conjugated to the effector or joined to the effector as a fusion protein. Construction of fusion proteins is within ordinary skill in the art.

IV. Use of the Antibodies

[0109] The antibodies disclosed herein can be used to treat various forms of cancer, *e.g.*, breast, ovarian, prostate, cervical, colorectal, lung (*e.g.*, non-small cell lung cancer), pancreatic, gastric, skin, kidney, head and neck, and schwannoma cancers. The cancer cells are exposed to a therapeutically effective amount of the antibody so as to inhibit or reduce proliferation of the cancer cell. In some embodiments, the antibodies inhibit cancer cell proliferation by at least 40%, 50%, 60%, 70%, 80%, 90%, 95%, 98%, 99%, or 100%.

[0110] In some embodiments, the antibody inhibits or reduces proliferation of a tumor cell by inhibiting binding of human ErbB3 to an ErbB3 ligand, *e.g.*, Neuregulin/Heregulin especially NRGβ1/NRG1-β1/NRGβ1/HRGβ1 and NRGα1/NRG1-α1/NRGα1/HRGα1. The antibody can be used in a method to inhibit tumor growth in a human patient. The method comprises administering to the patient a therapeutically effective amount of the antibody.

[0111] Cancers associated with ErbB3 overexpression and/or activation include breast cancer, ovarian cancer, prostate cancer, cervical cancer, lung cancer (*e.g.*, non-small cell lung cancer), some forms of brain cancer (*e.g.*, schwannoma), melanomas, skin, kidney, and gastrointestinal cancers (*e.g.*, colorectal, pancreatic, gastric, head and neck).

[0112] As used herein, "treat, "treating" and "treatment" mean the treatment of a disease in a mammal, *e.g.*, in a human. This includes: (a) inhibiting the disease, *i.e.*, arresting its

development; and (b) relieving the disease, *i.e.*, causing regression of the disease state; and (c) curing the disease.

[0113] Generally, a therapeutically effective amount of active component is in the range of 0.1 mg/kg to 100 mg/kg, *e.g.*, 1 mg/kg to 100 mg/kg, 1 mg/kg to 10 mg/kg. The amount administered will depend on variables such as the type and extent of disease or indication to be treated, the overall health of the patient, the *in vivo* potency of the antibody, the pharmaceutical formulation, and the route of administration. The initial dosage can be increased beyond the upper level in order to rapidly achieve the desired blood-level or tissue level. Alternatively, the initial dosage can be smaller than the optimum, and the daily dosage may be progressively increased during the course of treatment. Human dosage can be optimized, *e.g.*, in a conventional Phase I dose escalation study designed to run from 0.5 mg/kg to 20 mg/kg. Dosing frequency can vary, depending on factors such as route of administration, dosage amount and the disease being treated. Exemplary dosing frequencies are once per day, once per week and once every two weeks. A preferred route of administration is parenteral, *e.g.*, intravenous infusion. Formulation of monoclonal antibody-based drugs is within ordinary skill in the art. In some embodiments, the monoclonal antibody is lyophilized and reconstituted in buffered saline at the time of administration.

[0114] For therapeutic use, an antibody preferably is combined with a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" means buffers, carriers, and excipients suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. The carrier(s) should be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient. Pharmaceutically acceptable carriers include buffers, solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is known in the art.

[0115] Pharmaceutical compositions containing antibodies disclosed herein can be presented in a dosage unit form and can be prepared by any suitable method. A pharmaceutical composition should be formulated to be compatible with its intended route of administration. Examples of routes of administration are intravenous (IV), intradermal, inhalation, transdermal, topical, transmucosal, and rectal administration. A preferred route of administration for

monoclonal antibodies is IV infusion. Useful formulations can be prepared by methods well known in the pharmaceutical art. For example, see *Remington's Pharmaceutical Sciences*, 18th ed. (Mack Publishing Company, 1990). Formulation components suitable for parenteral administration include a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as EDTA; buffers such as acetates, citrates or phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose.

[0116] For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor ELTM (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). The carrier should be stable under the conditions of manufacture and storage, and should be preserved against microorganisms. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol), and suitable mixtures thereof.

[0117] Pharmaceutical formulations preferably are sterile. Sterilization can be accomplished, for example, by filtration through sterile filtration membranes. Where the composition is lyophilized, filter sterilization can be conducted prior to or following lyophilization and reconstitution.

EXAMPLES

[0118] The following Examples are merely illustrative and are not intended to limit the scope or content of the invention in any way.

Example 1 – Production of Anti-hErbB3 Monoclonal Antibodies

[0119] Immunizations, fusions, and primary screens were conducted at Maine Biotechnology Services Inc. following the Repetitive Immunization Multiple Sites (RIMMS) protocol. Three AJ mice and three Balb/c mice were immunized with recombinant human ErbB3/Fc (R&D Systems, Cat. No. 348-RB). Two sets of immunization were performed with either cleaved rhErbB3 (Immunization A) or with cleaved rhErbB3 cross-linked to its ligand, recombinant human NRG1-β1/HRG1-β1-EGF domain (R&D Systems, Cat. No. 396-HB) (Immunization B). Two AJ mice per immunization with sera displaying high anti-ErbB3 activity by Enzyme Linked Immunosorbent Assay (ELISA) were chosen for subsequent fusion. Spleens and lymph nodes from the appropriate mice were harvested. B-cells then were

harvested and fused with a myeloma line. Fusion products were serially diluted onto forty 96-well plates to near clonality. A total of 5280 supernatants from the resulting fusions were screened for binding to recombinant rhErbB3/Fc, using ELISA. The same supernatants were also screened for their binding to human ErbB3 overexpressed in CHO cells (by Mesoscale electrochemiluminescence assay). Three hundred supernatants identified as containing antibodies against ErbB3 were further characterized by *in vitro* biochemical and cell-based assays as discussed below. A panel of hybridomas was selected, and the hybridomas were subcloned and expanded. Hybridoma cell lines were transferred to BioXCell (formerly Bio-Express) for antibody expression and purification by affinity chromatography on Protein G resin under standard conditions.

[0120] Anti-hErbB3 monoclonal antibody 04D01 was generated from Immunization A described above. Anti-hErbB3 monoclonal antibodies 09D03, 11G01, 12A07, 18H02, 22A02 and 24C05 were generated from Immunization B described above.

Example 2 – Sequence Analysis of anti-hErbB3 Monoclonal Antibodies

[0121] The light-chain isotype and heavy chain isotype of each monoclonal antibody in Example 1 was determined using the IsoStrip™ Mouse Monoclonal Antibody Isotyping Kit according the manufacturer's instructions (Roche Applied Science). All antibodies were determined to be Kappa light chain and IgG1 or IgG2b IgG heavy chain.

[0122] The heavy and light chain variable regions of the mouse monoclonal antibodies were sequenced using 5' RACE (Rapid Amplification of cDNA Ends). Total RNA was extracted from each monoclonal hybridoma cell line using the RNeasy® Miniprep kit according to the vendor's instructions (Qiagen). Full-length first strand cDNA containing 5' ends was generated using either the GeneRacer™ Kit (Invitrogen) or SMARTer™ RACE cDNA Amplification Kit (Clontech) according to the manufacturer's instructions using random primers for 5' RACE.

[0123] The variable regions of the Kappa and Heavy (IgG1or IgG2b) IgG chains were amplified by PCR, using KOD Hot Start Polymerase (Novagen) or Advantage 2 Polymerase Mix (Clontech) according to the manufacturer's instructions. For amplification of 5' cDNA ends in conjunction with the GeneRacer™ Kit, the GeneRacer™ 5' Primer, 5' cgactggagcacgaggacactga 3' (SEQ ID NO: 136) (Invitrogen) was used as a 5' primer. For amplification of 5' cDNA ends in conjunction with the SMARTer™ RACE cDNA

Amplification Kit , the Universal Primer Mix A primer (Clontech), a mix of 5'CTAATACGACTCACTATAGGGCAAGCAGTGGTATCAACGCAGAGT 3' (SEQ ID NO: 137) and 5' CTAATACGACTCACTATAGGGC 3' (SEQ ID NO: 138), was used as a 5' primer. Heavy chain variable regions were amplified using the above 5' primers and a 3' IgG1 Constant Region specific primer, either 5' TATGCAAGGCTTACAACCACA 3' (SEQ ID NO: 139) or 5' GCCAGTGGATAGACAGATGGGGGTGTCG 3' (SEQ ID NO: 140). IgG2b sequences were amplified with either 5' AGGACAGGGGTTGATTGTTGA 3' (SEQ ID NO: 141), 5' GGCCAGTGGATAGACTGATGGGGGTGTTGT 3' (SEQ ID NO: 142), or 5' GGAGGAACCAGTTGTATCTCCACACCCA 3' (SEQ ID NO: 143). Kappa chain variable regions were amplified with the above 5' primers and a 3' Kappa Constant Region specific primer, either 5' CTCATTCCTGTTGAAGCTCTTGACAAT 3' (SEQ ID NO: 144) or 5' CGACTGAGGCACCTCCAGATGTT 3' (SEQ ID NO: 145).

[0124] Individual PCR products were isolated by agarose gel electrophoresis and purified using the Qiaquick® Gel Purification kit according to the manufacturer's instructions (Qiagen). The PCR products were subsequently cloned into the pCR®4Blunt plasmid using the Zero Blunt® TOPO® PCR Cloning Kit according to the manufacturer's instructions (Invitrogen) and transformed into DH5-α bacteria (Invitrogen) through standard molecular biology techniques. Plasmid DNA isolated from transformed bacterial clones was sequenced using M13 Forward (5' GTAAAACGACGGCCAGT 3') (SEQ ID NO: 146) and M13 Reverse primers (5' CAGGAAACAGCTATGACC 3') (SEQ ID NO: 147) by Beckman Genomics, using standard dideoxy DNA sequencing methods to identify the sequence of the variable region sequences. The sequences were analyzed using Vector NTI software (Invitrogen) and the IMGT/V-Quest software to identify and confirm variable region sequences.

[0125] The nucleic acid sequences encoding and the protein sequences defining variable regions of the murine monoclonal antibodies are summarized below (amino terminal signal peptide sequences are not shown). CDR sequences (Kabat definition) are shown in bold/underlined in the amino acid sequences.

[0126] Nucleic Acid Sequence Encoding the Heavy Chain Variable Region of the 04D01 Antibody (SEQ ID NO: 1)

```
   1 caggtccaac tgcagcagcc tggggctgaa ctggtgaggc ctgggacttc agtgaagttg
  61 tcctgcaagg cttctggcta caccttcacc agccactggt tgcactgggt gaagcagagg
 121 cctggacaag gccttgagtg gatcggagtg cttgatcctt ctgatttta tagtaactac
 181 aatcaaaact tcaagggcaa ggccacattg actgtagaca catcctccag cacagcctac
 241 atgcagctca gcagcctgac atctgaggac tctgcggtct attactgtgc acgaggccta
 301 ctatccgggg actatgctat ggactactgg ggtcaaggaa cctcagtcac cgtctcctca
```

[0127] Protein Sequence Defining the Heavy Chain Variable Region of the 04D01 Antibody (SEQ ID NO: 2)

```
  1 qvqlqqpgae lvrpgtsvkl sckasgytft shwlhwvkqr pgqglewigv ldpsdfysny
 61 nqnfkgkatl tvdtssstay mqlssltsed savyycargl lsgdyamdyw gqgtsvtvss
```

[0128] Nucleic Acid Sequence Encoding the Kappa Chain Variable Region of the 04D01 Antibody (SEQ ID NO: 3)

```
   1 gatgttttga tgacccaaat tccactctcc ctgcctgtca gtcttggaga tcaagcctcc
  61 atctcttgca gatctagtca gagcattgta catagtaatg gaaacaccta tttagaatgg
 121 tacctgcaga aaccaggcca gtctccaaag tccctgatct acaaagtttc taaccgattt
 181 tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc
 241 agcagagtgg aggctgagga tctgggagtt tattactgct ttcaaggttc atatgttccg
 301 tggacgttcg gtggaggcac caagctggaa atcaaa
```

[0129] Protein Sequence Defining the Kappa Chain Variable Region of the 04D01 Antibody (SEQ ID NO: 4)

```
  1 dvlmtqipls lpvslgdqas iscrssqsiv hsngntylew ylqkpgqspk sliykvsnrf
 61 sgvpdrfsgs gsgtdftlki srveaedlgv yycfqgsyvp wtfgggtkle ik
```

[0130] Nucleic Acid Sequence Encoding the Heavy Chain Variable Region of the 09D03 Antibody (SEQ ID NO: 11)

```
   1 caggttactc taaaagagtc tggccctggg atattgcggc cctcccagac cctcagtctg
  61 acttgttctt tctctgggtt ttcactgagc acttttggtt tgagtgtagg ctggattcgt
 121 cagccttcag ggaagggtct ggagtggctg gcacacattt ggtgggatga tgataagtac
 181 tataacccag cccttaagag tcggctcaca atctccaagg atacctccaa aaaccaggta
 241 ttcctcaaga tcgccaatgt ggacactgca gatactgcca catactactg tgctcgaata
 301 ggggcggacg cccttccttt tgactactgg ggccaaggca ccactctcac agtctcctca
```

[0131] Protein Sequence Defining the Heavy Chain Variable Region of the 09D03 Antibody (SEQ ID NO: 12)

```
  1 qvtlkesgpg ilrpsqtlsl tcsfsgfsls tfglsvgwir qpsgkglewl ahiwwdddky
 61 ynpalksrlt iskdtsknqv flkianvdta dtatyycari gadalpfdyw gqgttltvss
```

[0132] Nucleic Acid Sequence Encoding the Kappa Chain Variable Region of the 09D03 Antibody (SEQ ID NO: 13)

```
  1 gatattgtgt tgactcagac tgcaccctct gtacctgtca ctcctggaga gtcagtatcc
 61 atctcctgca ggtctagtaa gagtctcctg catagtaatg gcaacactta cttgtattgg
121 ttcctgcaga ggccaggcca gtctcctcag ctcctgatat atcggatgtc caaccttgcc
181 tcaggagtcc cagacaggtt cagtggcagt gggtcaggaa ctgctttcac actgagaatc
241 agtagagtgg aggctgagga tgtgggtgtt tattactgta tgcaacatct agaatatcct
301 ttcacgttcg gctcggggac aaagttggaa ataaaa
```

[0133] Protein Sequence Defining the Kappa Chain Variable Region of the 09D03 Antibody (SEQ ID NO: 14)

```
  1 divltqtaps vpvtpgesvs iscrssksll hsngntylyw flqrpgqspq lliyrmsnla
 61 sgvpdrfsgs gsgtaftlri srveaedvgv yycmqhleyp ftfgsgtkle ik
```

[0134] Nucleic Acid Sequence Encoding the Heavy Chain Variable Region of the 11G01 Antibody (SEQ ID NO: 21)

```
  1 caggttcagc tgcaacagtc tgacgctgag ttggtgaaac ctggagcttc agtgaagata
 61 tcctgcaagg tttctggcta caccttcact gaccatatta ttcactggat gaagcagagg
121 cctgaacagg gcctggaatg gattggatat atttatccta gagatggtta tattaagtac
181 aatgagaagt tcaagggcaa ggccacattg actgcagaca aatcctccag cacagcctac
241 atgcaggtca acagcctgac atctgaggac tctgcagtct atttctgtgc aaggggttac
301 tattatgcta tggactactg gggtcaagga acctcagtca ccgtctcctc a
```

[0135] Protein Sequence Defining the Heavy Chain Variable Region of the 11G01 Antibody (SEQ ID NO: 22)

```
  1 qvqlqqsdae lvkpgasvki sckvsgytft dhiihwmkqr peqglewigy iyprdgyiky
 61 nekfkgkatl tadkssstay mqvnsltsed savyfcargy yyamdywgqg tsvtvss
```

[0136] Nucleic Acid Sequence Encoding the Kappa Chain Variable Region of the 11G01 Antibody (SEQ ID NO: 23)

```
   1 gatgttttga tgacccaaac tccactctcc ctgcctgtca gtcttggaga tcaagcctcc
  61 atctcttgca gatctagtca gagcattgta catagtattg gaaacaccta tttagaatgg
 121 tacctgcaga aaccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt
 181 tctggggtcc cagagaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc
 241 agcagagtgg aggctgagga tctgggagtt tattactgct ttcaaggttc acatgttcca
 301 ttcacgttcg gctcggggac aaagttggaa ataaaa
```

[0137] Protein Sequence Defining the Kappa Chain Variable Region of the 11G01 Antibody (SEQ ID NO: 24)

```
   1 dvlmtqtpls lpvslgdqas isc[rssqsiv] [hsigntyle]w ylqkpgqspk lliy[kvsnrf]
  61 [s]gvperfsgs gsgtdftlki srveaedlgv yyc[fqgshvp] [ft]fgsgtkle ik
```

[0138] Nucleic Acid Sequence Encoding the Heavy Chain Variable Region of the 12A07 Antibody (SEQ ID NO: 30)

```
   1 caggtccaac tgctgcagcc tggggctgag ctggtgaggc ctgggacttc agtgaagttg
  61 tcctgcaaga cttctggcta caccttctcc agctactgga tgcactgggt aaagcagagg
 121 cctggacaag gccttgagtg gatcggaatg attgatcctt ctgatgttta tactaactac
 181 aatccaaagt tcaagggcaa ggccacattg actgttgaca catcctccag cacagcctac
 241 atgcagctca gcagcctgac atctgaggac tctgcggtct attactgtgc aagaaactac
 301 tctggggact actggggcca aggcaccact ctcacagtct cctca
```

[0139] Protein Sequence Defining the Heavy Chain Variable Region of the 12A07 Antibody (SEQ ID NO: 31)

```
   1 qvqllqpgae lvrpgtsvkl scktsgytfs [sywmh]wvkqr pgqglewig[m] [idpsdvytny]
  61 [npkfkg]katl tvdtssstay mqlssltsed savyycar[ny] [sgdy]wgqgtt ltvss
```

[0140] Nucleic Acid Sequence Encoding the Kappa Chain Variable Region of the 12A07 Antibody (SEQ ID NO: 32)

```
   1 gatgttttga tgacccaaat tccactctcc ctgcctgtca gtcttggaga tcaagcctcc
  61 atctcttgta gatctagtca gagcattgtc catagtaatg gaaacaccta tttagaatgg
 121 tacctgcaga aaccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt
 181 tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc
 241 agcagagtgg aggctgagga tctgggagtt tattactgct ttcaaggttc atatgttccg
 301 tggacgttcg gtggaggcac caagctggaa atcaaa
```

[0141] Protein Sequence Defining the Kappa Chain Variable Region of the 12A07 Antibody (SEQ ID NO: 33)

```
  1 dvlmtqipls lpvslgdqas iscrssqsiv hsngntylew ylqkpgqspk lliykvsnrf
 61 sgvpdrfsgs gsgtdftlki srveaedlgv yycfqgsyvp wtfgggtkle ik
```

[0142] Nucleic Acid Sequence Encoding the Heavy Chain Variable Region of the 18H02 Antibody (SEQ ID NO: 37)

```
  1 cagatccagt tggtacagtc tggacctgaa ctgaagaagc ctggagaggc agtcaagatc
 61 tcctgcaagt cttctgggta taccttcaca acctatggaa tgagctgggt gaaacaggct
121 ccaggaaggg ctttaaagtg gatgggctgg ataaacacct actctggagt gccaacatat
181 gctgatgact tcaagggacg gtttgccttc tctttggaat cctctgccag cactgcctat
241 ttgcagatca acaacctcaa aaatgaggac acggctacat atttctgtgc aagagggagg
301 gatggttacc aagtggcctg gtttgcttac tggggccaag ggacgctggt cactgtctct
361 gca
```

[0143] Protein Sequence Defining the Heavy Chain Variable Region of the 18H02 Antibody (SEQ ID NO: 38)

```
  1 qiqlvqsgpe lkkpgeavki sckssgytft tygmswvkqa pgralkwmgw intysgvpty
 61 addfkgrfaf slessastay lqinnlkned tatyfcargr dgyqvawfay wgqgtlvtvs
121 a
```

[0144] Nucleic Acid Sequence Encoding the Kappa Chain Variable Region of the 18H02 Antibody (SEQ ID NO: 39)

```
  1 gaaacaactg tgacccagtc tccagcatcc ctgtccatgg ctataggaga taaagtcacc
 61 atcagatgca taaccagcac tgatattgat gatgatatga actggttcca gcagaagcca
121 ggggaacctc ctaagctcct tatttcagaa ggcaatactc ttcgtcctgg agtcccatcc
181 cgattctccg gcagtggcta tggtacagat tttattttta caattgaaaa catgctctct
241 gaagatgttg cagattacta ctgtttgcaa agtgataact tgccgtacac gttcggaggg
301 gggaccaagc tggaaataaa a
```

[0145] Protein Sequence Defining the Kappa Chain Variable Region of the 18H02 Antibody (SEQ ID NO: 40)

```
  1 ettvtqspas lsmaigdkvt ircitstdid ddmnwfqqkp geppkllise gntlrpgvps
 61 rfsgsgygtd fiftienmls edvadyyclq sdnlpytfgg gtkleik
```

[0146] Nucleic Acid Sequence Encoding the Heavy Chain Variable Region of the 22A02 Antibody (SEQ ID NO: 47)

```
   1 caggtccaac tgcagcagcc tggggctgag ctggtgaggc ctgggacttc agtgaagttg
  61 tcctgcaagg cttctggcta caccttcacc aactactgga tgcactgggt aaagcagagg
 121 cctggacaag gccttgagtg gatcggaatg attgatcctt ctgatagtta tactaactac
 181 aatccaaagt tcaagggtaa ggccacattg actgtagaca catcctccag cacagcctac
 241 atgcagctca gcagcctgac atctgaggac tctgcggtct attactgtgc aagaaactac
 301 tctggggact actggggcca aggcaccact ctcacagtct cctca
```

[0147] Protein Sequence Defining the Heavy Chain Variable Region of the 22A02 Antibody (SEQ ID NO: 48)

```
   1 qvqlqqpgae lvrpgtsvkl sckasgytft nywmhwvkqr pgqglewigm idpsdsytny
  61 npkfkgkatl tvdtssstay mqlssltsed savyycarny sgdywgqgtt ltvss
```

[0148] Nucleic Acid Sequence Encoding the Kappa Chain Variable Region of the 22A02 Antibody (SEQ ID NO: 49)

```
   1 gatgttttga tgacccaaac tccactctcc ctgcctgtca gtcttggaga tcaagcctcc
  61 atctcttgca gatctagtca gagcattgta catagtaatg gaaacaccta tttagaatgg
 121 tacctgcaga aaccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt
 181 tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc
 241 agcagagtgg aggctgagga tctgggagtt tattattgct ttcaaggttc atatgttccg
 301 tggacgttcg gtggaggcac caagctggaa atcaaa
```

[0149] Protein Sequence Defining the Kappa Chain Variable Region of the 22A02 Antibody (SEQ ID NO: 50)

```
   1 dvlmtqtpls lpvslgdqas iscrssqsiv hsngntylew ylqkpgqspk lliykvsnrf
  61 sgvpdrfsgs gsgtdftlki srveaedlgv yycfqgsyvp wtfgggtkle ik
```

[0150] Nucleic Acid Sequence Encoding the Heavy Chain Variable Region of the 24C05 Antibody (SEQ ID NO: 53)

```
   1 gaggtgcagc tggtggaatc tgggggaggc ttagtgaagc ctggagggtc cctgaaactc
  61 tcctgtgcag cctctggatt cactttcagt gactatgcca tgtcttgggt tcgccagact
 121 ccggaaaaga ggctggagtg ggtcgcaacc attagtgatg gtggtactta cacctactat
 181 ccagacaatg taaagggccg attcaccatc tccagagaca atgccaagaa caacctgtac
```

241 ctgcaaatga gccatctgaa gtctgaggac acagccatgt attactgtgc aagagaatgg
301 ggtgattacg acggatttga ctactggggc caaggcacca ctctcacagt ctcctcg

[0151] Protein Sequence Defining the Heavy Chain Variable Region of the 24C05 Antibody (SEQ ID NO: 54)

1 evqlvesggg lvkpggslkl scaasgftfs **dyams**wvrqt pekrlewva**t** **isdggtytyy**
61 **pdnvkg**rfti srdnaknnly lqmshlksed tamyycar**ew** **gdydgfdy**wg qgttltvss

[0152] Nucleic Acid Sequence Encoding the Kappa Chain Variable Region of the 24C05 Antibody (SEQ ID NO: 55)

1 gacatccaga tgacccagtc tccatcctcc ttatctgcct ctctgggaga aagagtcagt
61 ctcacttgtc gggcaagtca ggaaattagt ggttacttaa gctggcttca gcagaaacca
121 gatggaacta ttaaacgcct gatctacgcc gcatccactt tagattctgg tgtcccaaaa
181 aggttcagtg gcagtaggtc tgggtcagat tattctctca ccatcggcag ccttgagtct
241 gaagatcttg cagactatta ctgtctacaa tatgatagtt atccgtacac gttcggaggg
301 gggaccaagc tggaaataaa a

[0153] Protein Sequence Defining the Kappa Chain Variable Region of the 24C05 Antibody (SEQ ID NO: 56)

1 diqmtqspss lsaslgervs ltc**rasqeis** **gyls**wlqqkp dgtikrliy**a** **astlds**gvpk
61 rfsgsrsgsd ysltigsles edladyyc**lq** **ydsypyt**fgg gtkleik

[0154] The amino acid sequences defining the immunoglobulin heavy chain variable regions for the antibodies produced in Example 1 are aligned in FIG. 2. Amino terminal signal peptide sequences (for proper expression/secretion) are not shown. CDR_1, CDR_2, and CDR_3 (Kabat definition) are identified by boxes. FIG. 3 shows an alignment of the separate CDR_1, CDR_2, and CDR_3 sequences for each antibody.

[0155] The amino acid sequences defining the immunoglobulin light chain variable regions for the antibodies in Example 1 are aligned in FIG. 4. Amino terminal signal peptide sequences (for proper expression/secretion) are not shown. CDR_1, CDR_2 and CDR_3 are identified by boxes. FIG. 5 shows an alignment of the separate CDR_1, CDR_2, and CDR_3 sequences for each antibody.

[0156] Table 1 is a concordance chart showing the SEQ ID NO. of each sequence discussed in this Example.

Table 1

SEQ. ID NO.	Nucleic Acid or Protein
1	04D01 Heavy Chain Variable Region—nucleic acid
2	04D01 Heavy Chain Variable Region—protein
3	04D01 Light (kappa) Chain Variable Region—nucleic acid
4	04D01 Light (kappa) Chain Variable Region—protein
5	04D01 Heavy Chain CDR_1
6	04D01 Heavy Chain CDR_2
7	04D01 Heavy Chain CDR_3
8	04D01 Light (kappa) Chain CDR_1
9	04D01 Light (kappa) Chain CDR_2
10	04D01 Light (kappa) Chain CDR_3
11	09D03 Heavy Chain Variable Region—nucleic acid
12	09D03 Heavy Chain Variable Region—protein
13	09D03 Light (kappa) Chain Variable Region—nucleic acid
14	09D03 Light (kappa) Chain Variable Region—protein
15	09D03 Heavy Chain CDR_1
16	09D03 Heavy Chain CDR_2
17	09D03 Heavy Chain CDR_3
18	09D03 Light (kappa) Chain CDR_1
19	09D03 Light (kappa) Chain CDR_2
20	09D03 Light (kappa) Chain CDR_3
21	11G01 Heavy Chain Variable Region—nucleic acid
22	11G01 Heavy Chain Variable Region—protein
23	11G01 Light (kappa) Chain Variable Region—nucleic acid
24	11G01 Light (kappa) Chain Variable Region—protein
25	11G01 Heavy Chain CDR_1
26	11G01 Heavy Chain CDR_2
27	11G01 Heavy Chain CDR_3
28	11G01 Light (kappa) Chain CDR_1
9	11G01 Light (kappa) Chain CDR_2

Table 1 (Cont.)

SEQ. ID NO.	Nucleic Acid or Protein
29	11G01 Light (kappa) Chain CDR_3
30	12A07 Heavy Chain Variable Region—nucleic acid
31	12A07 Heavy Chain Variable Region—protein
32	12A07 Light (kappa) Chain Variable Region—nucleic acid
33	12A07 Light (kappa) Chain Variable Region—protein
34	12A07 Heavy Chain CDR_1
35	12A07 Heavy Chain CDR_2
36	12A07 Heavy Chain CDR_3
8	12A07 Light (kappa) Chain CDR_1
9	12A07 Light (kappa) Chain CDR_2
10	12A07 Light (kappa) Chain CDR_3
37	18H02 Heavy Chain Variable Region—nucleic acid
38	18H02 Heavy Chain Variable Region—protein
39	18H02 Light (kappa) Chain Variable Region—nucleic acid
40	18H02 Light (kappa) Chain Variable Region—protein
41	18H02 Heavy Chain CDR_1
42	18H02 Heavy Chain CDR_2
43	18H02 Heavy Chain CDR_3
44	18H02 Light (kappa) Chain CDR_1
45	18H02 Light (kappa) Chain CDR_2
46	18H02 Light (kappa) Chain CDR_3
47	22A02 Heavy Chain Variable Region—nucleic acid
48	22A02 Heavy Chain Variable Region—protein
49	22A02 Light (kappa) Chain Variable Region—nucleic acid
50	22A02 Light (kappa) Chain Variable Region—protein
51	22A02 Heavy Chain CDR_1
52	22A02 Heavy Chain CDR_2
36	22A02 Heavy Chain CDR_3
8	22A02 Light (kappa) Chain CDR_1
9	22A02 Light (kappa) Chain CDR_2

Table 1 (Cont.)

SEQ. ID NO.	Nucleic Acid or Protein
10	22A02 Light (kappa) Chain CDR_3
53	24C05 Heavy Chain Variable Region—nucleic acid
54	24C05 Heavy Chain Variable Region—protein
55	24C05 Light (kappa) Chain Variable Region—nucleic acid
56	24C05 Light (kappa) Chain Variable Region—protein
57	24C05 Heavy Chain CDR_1
58	24C05 Heavy Chain CDR_2
59	24C05 Heavy Chain CDR_3
60	24C05 Light (kappa) Chain CDR_1
61	24C05 Light (kappa) Chain CDR_2
62	24C05 Light (kappa) Chain CDR_3

[0157] Mouse monoclonal antibody heavy chain CDR sequences (Kabat, Chothia, and IMGT definitions) are shown in Table 2.

Table 2

	Kabat		
	CDR1	**CDR2**	CDR3
04D01	SHWLH (SEQ ID NO: 5)	**VLDPSDFYSNYNQNFKG** (SEQ ID NO: 6)	GLLSGDYAMDY (SEQ ID NO: 7)
09D03	TFGLSVG (SEQ ID NO: 15)	**HIWWDDDKYYNPALKS** (SEQ ID NO: 16)	IGADALPFDY (SEQ ID NO: 17)
11G01	DHIIH (SEQ ID NO: 25)	**YIYPRDGYIKYNEKFKG** (SEQ ID NO: 26)	GYYYAMDY (SEQ ID NO: 27)
12A07	SYWMH (SEQ ID NO: 34)	**MIDPSDVYTNYNPKFKG** (SEQ ID NO: 35)	NYSGDY (SEQ ID NO: 36)
18H02	TYGMS (SEQ ID NO: 41)	**WINTYSGVPTYADDFKG** (SEQ ID NO: 42)	GRDGYQVAWFAY (SEQ ID NO: 43)
22A02	NYWMH (SEQ ID NO: 51)	**MIDPSDSYTNYNPKFKG** (SEQ ID NO: 52)	NYSGDY (SEQ ID NO: 36)

Table 2 (Cont.)

Kabat			
	CDR1	**CDR2**	CDR3
24C05	DYAMS (SEQ ID NO: 57)	**TISDGGTYTYYPDNVKG** (SEQ ID NO: 58)	EWGDYDGFDY (SEQ ID NO: 59)
Chothia			
	CDR1	CDR2	CDR3
04D01	**GYTFTSH** (SEQ ID NO: 63)	DPSDFY (SEQ ID NO: 64)	GLLSGDYAMDY (SEQ ID NO: 7)
09D03	**GFSLSTFGL** (SEQ ID NO: 65)	WWDDD (SEQ ID NO: 66)	IGADALPFDY (SEQ ID NO: 17)
11G01	**GYTFTDH** (SEQ ID NO: 67)	YPRDGY (SEQ ID NO: 68)	GYYYAMDY (SEQ ID NO: 27)
12A07	**GYTFSSY** (SEQ ID NO: 69)	DPSDVY (SEQ ID NO: 70)	NYSGDY (SEQ ID NO: 36)
18H02	**GYTFTTY** (SEQ ID NO: 71)	NTYSGV (SEQ ID NO: 72)	GRDGYQVAWFAY (SEQ ID NO: 43)
22A02	**GYTFTNY** (SEQ ID NO: 73)	DPSDSY (SEQ ID NO: 74)	NYSGDY (SEQ ID NO: 36)
24C05	**GFTFSDY** (SEQ ID NO: 75)	SDGGTY (SEQ ID NO: 76)	EWGDYDGFDY (SEQ ID NO: 59)
IMGT			
	CDR1	CDR2	**CDR3**
04D01	GYTFTSHW (SEQ ID NO: 77)	LDPSDFYS (SEQ ID NO: 78)	**ARGLLSGDYAMDY** (SEQ ID NO: 79)
09D03	GFSLSTFGLS (SEQ ID NO: 80)	IWWDDDK (SEQ ID NO: 81)	**ARIGADALPFDY** (SEQ ID NO: 82)
11G01	GYTFTDHI (SEQ ID NO: 83)	IYPRDGYI (SEQ ID NO: 84)	**ARGYYYAMDY** (SEQ ID NO: 85)
12A07	GYTFSSYW (SEQ ID NO: 86)	IDPSDVYT (SEQ ID NO: 87)	**ARNYSGDY** (SEQ ID NO: 88)

Table 2 (Cont.)

	IMGT		
	CDR1	CDR2	**CDR3**
18H02	GYTFTTYG (SEQ ID NO: 89)	INTYSGVP (SEQ ID NO: 90)	**ARGRDGYQVAWFAY** (SEQ ID NO: 91)
22A02	GYTFTNYW (SEQ ID NO: 92)	IDPSDSYT (SEQ ID NO: 93)	**ARNYSGDY** (SEQ ID NO: 88)
24C05	GFTFSDYA (SEQ ID NO: 94)	ISDGGTYT (SEQ ID NO: 95)	**AREWGDYDGFDY** (SEQ ID NO: 96)

[0158] Mouse monoclonal antibody Kappa light chain CDR sequences (Kabat, Chothia, and IMGT definitions) are shown in Table 3.

Table 3

	Kabat/Chothia		
	CDR1	**CDR2**	**CDR3**
04D01	**RSSQSIVHSNGNTYLE** (SEQ ID NO: 8)	**KVSNRFS** (SEQ ID NO: 9)	**FQGSYVPWT** (SEQ ID NO: 10)
09D03	**RSSKSLLHSNGNTYLY** (SEQ ID NO: 18)	**RMSNLAS** (SEQ ID NO: 19)	**MQHLEYPFT** (SEQ ID NO: 20)
11G01	**RSSQSIVHSIGNTYLE** (SEQ ID NO: 28)	**KVSNRFS** (SEQ ID NO: 9)	**FQGSHVPFT** (SEQ ID NO: 29)
12A07	**RSSQSIVHSNGNTYLE** (SEQ ID NO: 8)	**KVSNRFS** (SEQ ID NO: 9)	**FQGSYVPWT** (SEQ ID NO: 10)
18H02	**ITSTDIDDDMN** (SEQ ID NO: 44)	**EGNTLRP** (SEQ ID NO: 45)	**LQSDNLPYT** (SEQ ID NO: 46)
22A02	**RSSQSIVHSNGNTYLE** (SEQ ID NO: 8)	**KVSNRFS** (SEQ ID NO: 9)	**FQGSYVPWT** (SEQ ID NO: 10)
24C05	**RASQEISGYLS** (SEQ ID NO: 60)	**AASTLDS** (SEQ ID NO: 61)	**LQYDSYPYT** (SEQ ID NO: 62)

Table 3 (Cont.)

	IMGT		
	CDR1	CDR2	CDR3
04D01	QSIVHSNGNTY (SEQ ID NO: 97)	KVS	FQGSYVPWT (SEQ ID NO: 10)
09D03	KSLLHSNGNTY (SEQ ID NO: 98)	RMS	MQHLEYPFT (SEQ ID NO: 20)
11G01	QSIVHSIGNTY (SEQ ID NO: 99)	KVS	FQGSHVPFT (SEQ ID NO: 29)
12A07	QSIVHSNGNTY (SEQ ID NO: 97)	KVS	FQGSYVPWT (SEQ ID NO: 10)
18H02	TDIDDD (SEQ ID NO: 100)	EGN	LQSDNLPYT (SEQ ID NO: 46)
22A02	QSIVHSNGNTY (SEQ ID NO: 97)	KVS	FQGSYVPWT (SEQ ID NO: 10)
24C05	QEISGY (SEQ ID NO: 101)	AAS	LQYDSYPYT (SEQ ID NO: 62)

[0159] In Tables 2 and 3, the longest CDR sequences for the immunoglobulin heavy chain and light chain are shown in bold.

[0160] To create the complete heavy or kappa chain antibody sequences, each variable sequence above is combined with its respective constant region. For example, a complete heavy chain comprises a heavy variable sequence followed by the murine IgG1 or IgG2b heavy chain constant sequence and a complete kappa chain comprises a kappa variable sequence followed by the murine kappa light chain constant sequence.

[0161] Nucleic Acid Sequence Encoding the Murine IgG1 Heavy Chain Constant Region (SEQ ID NO: 102)

```
   1 gccaaaacga cacccccatc tgtctatcca ctggcccctg gatctgctgc ccaaactaac
  61 tccatggtga ccctgggatg cctggtcaag ggctatttcc ctgagccagt gacagtgacc
 121 tggaactctg gatccctgtc cagcggtgtg cacaccttcc cagctgtcct gcagtctgac
 181 ctctacactc tgagcagctc agtgactgtc ccctccagca cctggcccag ccagaccgtc
 241 acctgcaacg ttgcccaccc ggccagcagc accaaggtgg acaagaaaat tgtgcccagg
 301 gattgtggtt gtaagccttg catatgtaca gtcccagaag tatcatctgt cttcatcttc
 361 cccccaaagc ccaaggatgt gctcaccatt actctgactc ctaaggtcac gtgtgttgtg
 421 gtagacatca gcaaggatga tcccgaggtc cagttcagct ggtttgtaga tgatgtggag
 481 gtgcacacag ctcagacgca accccgggag gagcagttca acagcacttt ccgctcagtc
 541 agtgaacttc ccatcatgca ccaggactgg ctcaatggca aggagttcaa atgcagggtc
 601 aacagtgcag ctttccctgc ccccatcgag aaaaccatct ccaaaaccaa aggcagaccg
 661 aaggctccac aggtgtacac cattccacct cccaaggagc agatggccaa ggataaagtc
 721 agtctgacct gcatgataac agacttcttc cctgaagaca ttactgtgga gtggcagtgg
 781 aatgggcagc cagcggagaa ctacaagaac actcagccca tcatggacac agatggctct
 841 tacttcgtct acagcaagct caatgtgcag aagagcaact gggaggcagg aaatactttc
 901 acctgctctg tgttacatga gggcctgcac aaccaccata ctgagaagag cctctcccac
 961 tctcctggta aa
```

[0162] Protein Sequence Defining the Murine IgG1 Heavy Chain Constant Region (SEQ ID NO: 103)

```
   1 akttppsvyp lapgsaaqtn smvtlgclvk gyfpepvtvt wnsgslssgv htfpavlqsd
  61 lytlsssvtv psstwpsqtv tcnvahpass tkvdkkivpr dcgckpcict vpevssvfif
 121 ppkpkdvlti tltpkvtcvv vdiskddpev qfswfvddve vhtaqtqpre eqfnstfrsv
 181 selpimhqdw lngkefkcrv nsaafpapie ktisktkgrp kapqvytipp pkeqmakdkv
 241 sltcmitdff peditvewqw ngqpaenykn tqpimdtdgs yfvysklnvq ksnweagntf
 301 tcsvlheglh nhhtekslsh spgk
```

[0163] Nucleic Acid Sequence Encoding the Murine IgG2b Heavy Chain Constant Region (SEQ ID NO: 104)

```
   1 gccaaaacaa cacccccatc agtctatcca ctggcccctg ggtgtggaga tacaactggt
  61 tcctctgtga ctctgggatg cctggtcaag ggctacttcc ctgagtcagt gactgtgact
 121 tggaactctg gatccctgtc cagcagtgtg cacaccttcc cagctctcct gcagtctgga
 181 ctctacacta tgagcagctc agtgactgtc ccctccagca cctggccaag tcagaccgtc
 241 acctgcagcg ttgctcaccc agccagcagc accacggtgg acaaaaaact tgagcccagc
 301 gggcccattt caacaatcaa cccctgtcct ccatgcaagg agtgtcacaa atgcccagct
```

```
361 cctaacctcg agggtggacc atccgtcttc atcttccctc caaatatcaa ggatgtactc
421 atgatctccc tgacacccaa ggtcacgtgt gtggtggtgg atgtgagcga ggatgaccca
481 gacgtccaga tcagctggtt tgtgaacaac gtggaagtac acacagctca gacacaaacc
541 catagagagg attacaacag tactatccgg gtggtcagca ccctccccat ccagcaccag
601 gactggatga gtggcaagga gttcaaatgc aaggtcaaca acaaagacct cccatcaccc
661 atcgagagaa ccatctcaaa aattaaaggg ctagtcagag ctccacaagt atacatcttg
721 ccgccaccag cagagcagtt gtccaggaaa gatgtcagtc tcacttgcct ggtcgtgggc
781 ttcaaccctg gagacatcag tgtggagtgg accagcaatg ggcatacaga ggagaactac
841 aaggacaccg caccagtcct agactctgac ggttcttact tcatatatag caagctcaat
901 atgaaaacaa gcaagtggga gaaaacagat tccttctcat gcaacgtgag acacgagggt
961 ctgaaaaatt actacctgaa gaagaccatc tcccggtctc cgggtaaa
```

[0164] Protein Sequence Defining the Murine IgG2b Heavy Chain Constant Region (SEQ ID NO: 105)

```
  1 akttppsvyp lapgcgdttg ssvtlgclvk gyfpesvtvt wnsgslsssv htfpallqsg
 61 lytmsssvtv psstwpsqtv tcsvahpass ttvdkkleps gpistinpcp pckechkcpa
121 pnleggpsvf ifppnikdvl misltpkvtc vvvdvseddp dvqiswfvnn vevhtaqtqt
181 hredynstir vvstlpiqhq dwmsgkefkc kvnnkdlpsp iertiskikg lvrapqvyil
241 pppaeqlsrk dvsltclvvg fnpgdisvew tsnghteeny kdtapvldsd gsyfiyskln
301 mktskwektd sfscnvrheg lknyylkkti srspgk
```

[0165] Nucleic Acid Sequence Encoding the Murine Kappa Light Chain Constant Region (SEQ ID NO: 106)

```
  1 cgggctgatg ctgcaccaac tgtatccatc ttcccaccat ccagtgagca gttaacatct
 61 ggaggtgcct cagtcgtgtg cttcttgaac aacttctacc ccagagacat caatgtcaag
121 tggaagattg atggcagtga acgacaaaat ggtgtcctga acagttggac tgatcaggac
181 agcaaagaca gcacctacag catgagcagc accctcacat tgaccaagga cgagtatgaa
241 cgacataaca gctatacctg tgaggccact cacaagacat caacttcacc cattgtcaag
301 agcttcaaca ggaatgagtg t
```

[0166] Protein Sequence Defining the Murine Kappa Light Chain Constant Region (SEQ ID NO: 107)

```
  1 radaaptvsi fppsseqlts ggasvvcfln nfyprdinvk wkidgserqn gvlnswtdqd
 61 skdstysmss tltltkdeye rhnsytceat hktstspivk sfnrnec
```

[0167] The following sequences represent the actual or contemplated full length heavy and light chain sequences (*i.e.*, containing both the variable and constant regions sequences) for each antibody described in this Example. Signal sequences for proper secretion of the antibodies are also included at the 5' end of the DNA sequences or the amino terminal end of the protein sequences. The variable region sequences can be ligated to other constant region sequences, to produce active full length IgG heavy and light chains.

[0168] Nucleic Acid Sequence Encoding the Full Length Heavy Chain Sequence (Heavy Chain Variable Region and IgG1 Constant Region) of 04D01 (SEQ ID NO: 108)

```
   1 atgggatgga gctgtatcat tgtcctcttg gtatcaacag ctacaggtgt ccactcccag
  61 gtccaactgc agcagcctgg ggctgaactg gtgaggcctg ggacttcagt gaagttgtcc
 121 tgcaaggctt ctggctacac cttcaccagc cactggttgc actgggtgaa gcagaggcct
 181 ggacaaggcc ttgagtggat cggagtgctt gatccttctg atttttatag taactacaat
 241 caaaacttca agggcaaggc cacattgact gtagacacat cctccagcac agcctacatg
 301 cagctcagca gcctgacatc tgaggactct gcggtctatt actgtgcacg aggcctacta
 361 tccggggact atgctatgga ctactggggt caaggaacct cagtcaccgt ctcctcagcc
 421 aaaacgacac ccccatctgt ctatccactg gcccctggat ctgctgccca aactaactcc
 481 atggtgaccc tgggatgcct ggtcaagggc tatttccctg agccagtgac agtgacctgg
 541 aactctggat ccctgtccag cggtgtgcac accttcccag ctgtcctgca gtctgacctc
 601 tacactctga gcagctcagt gactgtcccc tccagcacct ggcccagcca gaccgtcacc
 661 tgcaacgttg cccacccggc cagcagcacc aaggtggaca agaaaattgt gcccagggat
 721 tgtggttgta agccttgcat atgtacagtc ccagaagtat catctgtctt catcttcccc
 781 ccaaagccca aggatgtgct caccattact ctgactccta aggtcacgtg tgttgtggta
 841 gacatcagca aggatgatcc cgaggtccag ttcagctggt ttgtagatga tgtggaggtg
 901 cacacagctc agacgcaacc ccgggaggag cagttcaaca gcactttccg ctcagtcagt
 961 gaacttccca tcatgcacca ggactggctc aatggcaagg agttcaaatg cagggtcaac
1021 agtgcagctt tccctgcccc catcgagaaa accatctcca aaaccaaagg cagaccgaag
1081 gctccacagg tgtacaccat tccacctccc aaggagcaga tggccaagga taaagtcagt
1141 ctgacctgca tgataacaga cttcttccct gaagacatta ctgtggagtg gcagtggaat
1201 gggcagccag cggagaacta caagaacact cagcccatca tggacacaga tggctcttac
1261 ttcgtctaca gcaagctcaa tgtgcagaag agcaactggg aggcaggaaa tactttcacc
1321 tgctctgtgt tacatgaggg cctgcacaac caccatactg agaagagcct ctcccactct
1381 cctggtaaa
```

[0169] Protein Sequence Defining the Full Length Heavy Chain Sequence (Heavy Chain Variable Region and IgG1 Constant Region) of 04D01 (SEQ ID NO: 109)

```
  1 mgwsciivll vstatgvhsq vqlqqpgael vrpgtsvkls ckasgytfts hwlhwvkqrp
 61 gqglewigvl dpsdfysnyn qnfkgkatlt vdtssstaym qlssltseds avyycargll
121 sgdyamdywg qgtsvtvssa kttppsvypl apgsaaqtns mvtlgclvkg yfpepvtvtw
181 nsgslssgvh tfpavlqsdl ytlsssvtvp sstwpsqtvt cnvahpasst kvdkkivprd
241 cgckpcictv pevssvfifp pkpkdvltit ltpkvtcvvv diskddpevq fswfvddvev
301 htaqtqpree qfnstfrsvs elpimhqdwl ngkefkcrvn saafpapiek tisktkgrpk
361 apqvytippp keqmakdkvs ltcmitdffp editvewqwn gqpaenyknt qpimdtdgsy
421 fvysklnvqk snweagntft csvlheglhn hhtekslshs pgk
```

[0170] Nucleic Acid Sequence Encoding the Full Length Light Chain Sequence (Kappa Chain Variable Region and Constant Region) of 04D01 (SEQ ID NO: 110)

```
  1 atgaagttgc ctgttaggct gttggtgctg atgttctgga ttcctgcttc cagcagtgat
 61 gttttgatga cccaaattcc actctccctg cctgtcagtc ttggagatca agcctccatc
121 tcttgcagat ctagtcagag cattgtacat agtaatggaa acacctattt agaatggtac
181 ctgcagaaac caggccagtc tccaaagtcc ctgatctaca aagtttctaa ccgattttct
241 ggggtcccag acaggttcag tggcagtgga tcagggacag atttcacact caagatcagc
301 agagtggagg ctgaggatct gggagtttat tactgctttc aaggttcata tgttccgtgg
361 acgttcggtg gaggcaccaa gctggaaatc aaacgggctg atgctgcacc aactgtatcc
421 atcttcccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg
481 aacaacttct accccagaga catcaatgtc aagtggaaga ttgatggcag tgaacgacaa
541 aatggtgtcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc
601 agcaccctca cattgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc
661 actcacaaga catcaacttc acccattgtc aagagcttca acaggaatga gtgt
```

[0171] Protein Sequence Defining the Full Length Light Chain Sequence (Kappa Chain Variable Region and Constant Region) of 04D01 (SEQ ID NO: 111)

```
  1 mklpvrllvl mfwipasssd vlmtqiplsl pvslgdqasi scrssqsivh sngntylewy
 61 lqkpgqspks liykvsnrfs gvpdrfsgsg sgtdftlkis rveaedlgvy ycfqgsyvpw
121 tfgggtklei kradaaptvs ifppsseqlt sggasvvcfl nnfyprdinv kwkidgserq
181 ngvlnswtdq dskdstysms stltltkdey erhnsytcea thktstspiv ksfnrnec
```

[0172] Nucleic Acid Sequence Encoding the Full Length Heavy Chain Sequence (Heavy Chain Variable Region and IgG2b Constant Region) of 09D03 (SEQ ID NO: 112)

```
   1 atgggcaggc ttacttcttc attcctgtta ctgattgtcc ctgcatatgt cctgtcccag
  61 gttactctaa aagagtctgg ccctgggata ttgcggccct cccagaccct cagtctgact
 121 tgttctttct ctgggttttc actgagcact tttggtttga gtgtaggctg gattcgtcag
 181 ccttcaggga agggtctgga gtggctggca cacatttggt gggatgatga taagtactat
 241 aacccagccc ttaagagtcg gctcacaatc tccaaggata cctccaaaaa ccaggtattc
 301 ctcaagatcg ccaatgtgga cactgcagat actgccacat actactgtgc tcgaataggg
 361 gcggacgccc ttccttttga ctactggggc caaggcacca ctctcacagt ctcctcagcc
 421 aaaacaacac ccccatcagt ctatccactg gcccctgggt gtggagatac aactggttcc
 481 tccgtgacct ctgggtgcct ggtcaagggg tacttccctg agccagtgac tgtgacttgg
 541 aactctggat ccctgtccag cagtgtgcac accttcccag ctctcctgca gtctggactc
 601 tacactatga gcagctcagt gactgtcccc tccagcacct ggccaagtca gaccgtcacc
 661 tgcagcgttg ctcacccagc cagcagcacc acggtggaca aaaaacttga gcccagcggg
 721 cccatttcaa caatcaaccc ctgtcctcca tgcaaggagt gtcacaaatg cccagctcct
 781 aacctcgagg gtggaccatc cgtcttcatc ttccctccaa atatcaagga tgtactcatg
 841 atctccctga cacccaaggt cacgtgtgtg gtggtggatg tgagcgagga tgacccagac
 901 gtccagatca gctggtttgt gaacaacgtg gaagtacaca cagctcagac acaaacccat
 961 agagaggatt acaacagtac tatccgggtg gtcagcaccc tccccatcca gcaccaggac
1021 tggatgagtg gcaaggagtt caaatgcaag gtgaacaaca aagacctccc atcacccatc
1081 gagagaacca tctcaaaaat taaagggcta gtcagagctc cacaagtata cactttgccg
1141 ccaccagcag agcagttgtc caggaaagat gtcagtctca cttgcctggt cgtgggcttc
1201 aaccctggag acatcagtgt ggagtggacc agcaatgggc atacagagga gaactacaag
1261 gacaccgcac cagttcttga ctctgacggt tcttacttca tatatagcaa gctcaatatg
1321 aaaacaagca agtgggagaa aacagattcc ttctcatgca acgtgagaca cgagggtctg
1381 aaaaattact acctgaagaa gaccatctcc cggtctccgg gtaaa
```

[0173] Protein Sequence Defining the Full Length Heavy Chain Sequence (Heavy Chain Variable Region and IgG2b Constant Region) of 09D03 (SEQ ID NO: 113)

```
   1 mgrltssfll livpayvlsq vtlkesgpgi lrpsqtlslt csfsgfslst fglsvgwirq
  61 psgkglewla hiwwdddkyy npalksrlti skdtsknqvf lkianvdtad tatyycarig
 121 adalpfdywg qgttltvssa kttppsvypl apgcgdttgs svtsgclvkg yfpepvtvtw
 181 nsgslsssvh tfpallqsgl ytmsssvtvp sstwpsqtvt csvahpasst tvdkklepsg
 241 pistinpcpp ckechkcpap nleggpsvfi fppnikdvlm isltpkvtcv vvdvseddpd
 301 vqiswfvnnv evhtaqtqth redynstirv vstlpiqhqd wmsgkefkck vnnkdlpspi
 361 ertiskikgl vrapqvytlp ppaeqlsrkd vsltclvvgf npgdisvewt snghteenyk
 421 dtapvldsdg syfiysklnm ktskwektds fscnvrhegl knyylkktis rspgk
```

[0174] Nucleic Acid Sequence Encoding the Full Length Light Chain Sequence (Kappa Chain Variable Region and Constant Region) of 09D03 (SEQ ID NO: 114)

```
   1 atgaggtgcc tagctgagtt cctggggctg cttgtgctct ggatccctgg agccattggg
  61 gatattgtgt tgactcagac tgcaccctct gtacctgtca ctcctggaga gtcagtatcc
 121 atctcctgca ggtctagtaa gagtctcctg catagtaatg gcaacactta cttgtattgg
 181 ttcctgcaga ggccaggcca gtctcctcag ctcctgatat atcggatgtc caaccttgcc
 241 tcaggagtcc cagacaggtt cagtggcagt gggtcaggaa ctgctttcac actgagaatc
 301 agtagagtgg aggctgagga tgtgggtgtt tattactgta tgcaacatct agaatatcct
 361 ttcacgttcg gctcggggac aaagttggaa ataaaacggg ctgatgctgc accaactgta
 421 tccatcttcc caccatccag tgagcagtta acatctggag gtgcctcagt cgtgtgcttc
 481 ttgaacaact tctaccccag agacatcaat gtcaagtgga agattgatgg cagtgaacga
 541 caaaatggtg tcctgaacag ttggactgat caggacagca aagacagcac ctacagcatg
 601 agcagcaccc tcacattgac caaggacgag tatgaacgac ataacagcta tacctgtgag
 661 gccactcaca agacatcaac ttcacccatt gtcaagagct tcaacaggaa tgagtgt
```

[0175] Protein Sequence Defining the Full Length Light Chain Sequence (Kappa Chain Variable Region and Constant Region) of 09D03 (SEQ ID NO: 115)

```
   1 mrclaeflgl lvlwipgaig divltqtaps vpvtpgesvs iscrssksll hsngntylyw
  61 flqrpgqspq lliyrmsnla sgvpdrfsgs gsgtaftlri srveaedvgv yycmqhleyp
 121 ftfgsgtkle ikradaaptv sifppsseql tsggasvvcf lnnfyprdin vkwkidgser
 181 qngvlnswtd qdskdstysm sstltltkde yerhnsytce athktstspi vksfnrnec
```

[0176] Nucleic Acid Sequence Encoding the Full Length Heavy Chain Sequence (Heavy Chain Variable Region and IgG1 Constant Region) of 11G01 (SEQ ID NO: 116)

```
   1 atggaatgga gctgggtctc tctcttcttc ctgtcagtaa ctacaggtgt ccactcccag
  61 gttcagctgc aacagtctga cgctgagttg gtgaaacctg gagcttcagt gaagatatcc
 121 tgcaaggttt ctggctacac cttcactgac catattattc actggatgaa gcagaggcct
 181 gaacagggcc tggaatggat tggatatatt tatcctagag atggttatat taagtacaat
 241 gagaagttca agggcaaggc cacattgact gcagacaaat cctccagcac agcctacatg
 301 caggtcaaca gcctgacatc tgaggactct gcagtctatt tctgtgcaag gggttactat
 361 tatgctatgg actactgggg tcaaggaacc tcagtcaccg tctcctcagc caaaacgaca
 421 cccccatctg tctatccact ggcccctgga tctgctgccc aaactaactc catggtgacc
 481 ctgggatgcc tggtcaaggg ctatttccct gagccagtga cagtgacctg gaactctgga
 541 tccctgtcca gcggtgtgca caccttccca gctgtcctgc agtctgacct ctacactctg
 601 agcagctcag tgactgtccc ctccagcacc tggcccagcc agaccgtcac ctgcaacgtt
 661 gcccacccgg ccagcagcac caaggtggac aagaaaattg tgcccaggga ttgtggttgt
 721 aagccttgca tatgtacagt cccagaagta tcatctgtct tcatcttccc cccaaagccc
```

781 aaggatgtgc tcaccattac tctgactcct aaggtcacgt gtgttgtggt agacatcagc
841 aaggatgatc ccgaggtcca gttcagctgg tttgtagatg atgtggaggt gcacacagct
901 cagacgcaac cccgggagga gcagttcaac agcactttcc gctcagtcag tgaacttccc
961 atcatgcacc aggactggct caatggcaag gagttcaaat gcagggtcaa cagtgcagct
1021 ttccctgccc ccatcgagaa aaccatctcc aaaaccaaag gcagaccgaa ggctccacag
1081 gtgtacacca ttccacctcc caaggagcag atggccaagg ataaagtcag tctgacctgc
1141 atgataacag acttcttccc tgaagacatt actgtggagt ggcagtggaa tgggcagcca
1201 gcggagaact acaagaacac tcagcccatc atggacacag atggctctta cttcgtctac
1261 agcaagctca atgtgcagaa gagcaactgg gaggcaggaa atactttcac ctgctctgtg
1321 ttacatgagg gcctgcacaa ccaccatact gagaagagcc tctcccactc tcctggtaaa

[0177] Protein Sequence Defining the Full Length Heavy Chain Sequence (Heavy Chain Variable Region and IgG1 Constant Region) of 11G01 (SEQ ID NO: 117)

1 mewswvslff lsvttgvhsq vqlqqsdael vkpgasvkis ckvsgytftd hiihwmkqrp
61 eqglewigyi yprdgyikyn ekfkgkatlt adkssstaym qvnsltseds avyfcargyy
121 yamdywgqgt svtvssaktt ppsvyplapg saaqtnsmvt lgclvkgyfp epvtvtwnsg
181 slssgvhtfp avlqsdlytl sssvtvpsst wpsqtvtcnv ahpasstkvd kkivprdcgc
241 kpcictvpev ssvfifppkp kdvltitltp kvtcvvvdis kddpevqfsw fvddvevhta
301 qtqpreeqfn stfrsvselp imhqdwlngk efkcrvnsaa fpapiektis ktkgrpkapq
361 vytipppkeq makdkvsltc mitdffpedi tvewqwngqp aenykntqpi mdtdgsyfvy
421 sklnvqksnw eagntftcsv lheglhnhht ekslshspgk

[0178] Nucleic Acid Sequence Encoding the Full Length Light Chain Sequence (Kappa Chain Variable Region and Constant Region) of 11G01 (SEQ ID NO: 118)

1 atgaagttgc ctgttaggct gttggtgctg atgttctgga ttcctgcttc cagaagtgat
61 gttttgatga cccaaactcc actctccctg cctgtcagtc ttggagatca agcctccatc
121 tcttgcagat ctagtcagag cattgtacat agtattggaa acacctattt agaatggtac
181 ctgcagaaac caggccagtc tccaaagctc ctgatctaca aagtttccaa ccgattttct
241 ggggtcccag agaggttcag tggcagtgga tcagggacag atttcacact caagatcagc
301 agagtggagg ctgaggatct gggagtttat tactgctttc aaggttcaca tgttccattc
361 acgttcggct cggggacaaa gttggaaata aaacgggctg atgctgcacc aactgtatcc
421 atcttcccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg
481 aacaacttct accccaaaga catcaatgtc aagtggaaga ttgatggcag tgaacgacaa
541 aatggcgtcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc
601 agcaccctca cgttgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc
661 actcacaaga catcaacttc acccattgtc aagagcttca acaggaatga gtgt

[0179] Protein Sequence Defining the Full Length Light Chain Sequence (Kappa Chain Variable Region and Constant Region) of 11G01 (SEQ ID NO: 119)

```
  1 mklpvrllvl mfwipasrsd vlmtqtplsl pvslgdqasi scrssqsivh signtylewy
 61 lqkpgqspkl liykvsnrfs gvperfsgsg sgtdftlkis rveaedlgvy ycfqgshvpf
121 tfgsgtklei kradaaptvs ifppsseqlt sggasvvcfl nnfypkdinv kwkidgserq
181 ngvlnswtdq dskdstysms stltltkdey erhnsytcea thktstspiv ksfnrnec
```

[0180] Nucleic Acid Sequence Encoding the Full Length Heavy Chain Sequence (Heavy Chain Variable Region and IgG1 Constant Region) of 12A07 (SEQ ID NO: 120)

```
   1 atgggatgga gctgtatcat tgtcctcttg gtatcaacag ctacatgtgt ccactcccag
  61 gtccaactgc tgcagcctgg ggctgagctg gtgaggcctg ggacttcagt gaagttgtcc
 121 tgcaagactt ctggctacac cttctccagc tactggatgc actgggtaaa gcagaggcct
 181 ggacaaggcc ttgagtggat cggaatgatt gatccttctg atgtttatac taactacaat
 241 ccaaagttca agggcaaggc cacattgact gttgacacat cctccagcac agcctacatg
 301 cagctcagca gcctgacatc tgaggactct gcggtctatt actgtgcaag aaactactct
 361 ggggactact ggggccaagg caccactctc acagtctcct cagccaaaac gacaccccca
 421 tctgtctatc cactggcccc tggatctgct gcccaaacta actccatggt gaccctggga
 481 tgcctggtca agggctattt ccctgagcca gtgacagtga cctggaactc tggatccctg
 541 tccagcggtg tgcacacctt cccagctgtc ctgcagtctg acctctacac tctgagcagc
 601 tcagtgactg tcccctccag cacctggccc agccagaccg tcacctgcaa cgttgcccac
 661 ccggccagca gcaccaaggt ggacaagaaa attgtgccca gggattgtgg ttgtaagcct
 721 tgcatatgta cagtcccaga agtatcatct gtcttcatct tccccccaaa gcccaaggat
 781 gtgctcacca ttactctgac tcctaaggtc acgtgtgttg tggtagacat cagcaaggat
 841 gatcccgagg tccagttcag ctggtttgta gatgatgtgg aggtgcacac agctcagacg
 901 caaccccggg aggagcagtt caacagcact ttccgctcag tcagtgaact tcccatcatg
 961 caccaggact ggctcaatgg caaggagttc aaatgcaggg tcaacagtgc agctttccct
1021 gcccccatcg agaaaaccat ctccaaaacc aaaggcagac cgaaggctcc acaggtgtac
1081 accattccac ctcccaagga gcagatggcc aaggataaag tcagtctgac ctgcatgata
1141 acagacttct tccctgaaga cattactgtg gagtggcagt ggaatgggca gccagcggag
1201 aactacaaga acactcagcc catcatggac acagatggct cttacttcgt ctacagcaag
1261 ctcaatgtgc agaagagcaa ctgggaggca ggaaatactt tcacctgctc tgtgttacat
1321 gagggcctgc acaaccacca tactgagaag agcctctccc actctcctgg taaa
```

[0181] Protein Sequence Defining the Full Length Heavy Chain Sequence (Heavy Chain Variable Region and IgG1 Constant Region) of 12A07 (SEQ ID NO: 121)

```
  1 mgwsciivll vstatcvhsq vqllqpgael vrpgtsvkls cktsgytfss ywmhwvkqrp
 61 gqglewigmi dpsdvytnyn pkfkgkatlt vdtssstaym qlssltseds avyycarnys
```

```
121 gdywgqgttl tvssakttpp svyplapgsa aqtnsmvtlg clvkgyfpep vtvtwnsgsl
181 ssgvhtfpav lqsdlytlss svtvpsstwp sqtvtcnvah passtkvdkk ivprdcgckp
241 cictvpevss vfifppkpkd vltitltpkv tcvvvdiskd dpevqfswfv ddvevhtaqt
301 qpreeqfnst frsvselpim hqdwlngkef kcrvnsaafp apiektiskt kgrpkapqvy
361 tipppkeqma kdkvsltcmi tdffpeditv ewqwngqpae nykntqpimd tdgsyfvysk
421 lnvqksnwea gntftcsvlh eglhnhhtek slshspgk
```

[0182] Nucleic Acid Sequence Encoding the Full Length Light Chain Sequence (Kappa Chain Variable Region and Constant Region) of 12A07 (SEQ ID NO: 122)

```
  1 atgaagttgc ctgttaggct gttggtgctg atgttctgga ttcctgcttc cagcagtgat
 61 gttttgatga cccaaattcc actctccctg cctgtcagtc ttggagatca agcctccatc
121 tcttgtagat ctagtcagag cattgtccat agtaatggaa acacctattt agaatggtac
181 ctgcagaaac caggccagtc tccaaagctc ctgatctaca aagtttccaa ccgattttct
241 ggggtcccag acaggttcag tggcagtgga tcagggacag atttcacact caagatcagc
301 agagtggagg ctgaggatct gggagtttat tactgctttc aaggttcata tgttccgtgg
361 acgttcggtg gaggcaccaa gctggaaatc aaacgggctg atgctgcacc aactgtatcc
421 atcttcccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg
481 aacaacttct accccagaga catcaatgtc aagtggaaga ttgatggcag tgaacgacaa
541 aatggtgtcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc
601 agcaccctca cattgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc
661 actcacaaga catcaacttc acccattgtc aagagcttca acaggaatga gtgt
```

[0183] Protein Sequence Defining the Full Length Light Chain Sequence (Kappa Chain Variable Region and Constant Region) of 12A07 (SEQ ID NO: 123)

```
  1 mklpvrllvl mfwipasssd vlmtqiplsl pvslgdqasi scrssqsivh sngntylewy
 61 lqkpgqspkl liykvsnrfs gvpdrfsgsg sgtdftlkis rveaedlgvy ycfqgsyvpw
121 tfgggtklei kradaaptvs ifppsseqlt sggasvvcfl nnfyprdinv kwkidgserq
181 ngvlnswtdq dskdstysms stltltkdey erhnsytcea thktstspiv ksfnrnec
```

[0184] Nucleic Acid Sequence Encoding the Full Length Heavy Chain Sequence (Heavy Chain Variable Region and IgG1 Constant Region) of 18H02 (SEQ ID NO: 124)

```
  1 atgggttggc tgtggaactt gctattcctg atggcagctg cccaaagtgc ccaagcacag
 61 atccagttgg tacagtctgg acctgaactg aagaagcctg gagaggcagt caagatctcc
121 tgcaagtctt ctgggtatac cttcacaacc tatggaatga gctgggtgaa acaggctcca
181 ggaagggctt taaagtggat gggctggata aacacctact ctggagtgcc aacatatgct
241 gatgacttca agggacggtt tgccttctct ttggaatcct ctgccagcac tgcctatttg
301 cagatcaaca acctcaaaaa tgaggacacg gctacatatt tctgtgcaag agggagggat
```

```
 361 ggttaccaag tggcctggtt tgcttactgg ggccaaggga cgctggtcac tgtctctgca
 421 gccaaaacga cacccccatc tgtctatcca ctggcccctg gatctgctgc ccaaactaac
 481 tccatggtga ccctgggatg cctggtcaag ggctatttcc ctgagccagt gacagtgacc
 541 tggaactctg gatccctgtc cagcggtgtg cacaccttcc cagctgtcct gcagtctgac
 601 ctctacactc tgagcagctc agtgactgtc ccctccagca cctggcccag ccagaccgtc
 661 acctgcaacg ttgcccaccc ggccagcagc accaaggtgg acaagaaaat tgtgcccagg
 721 gattgtggtt gtaagccttg catatgtaca gtcccagaag tatcatctgt cttcatcttc
 781 cccccaaagc ccaaggatgt gctcaccatt actctgactc ctaaggtcac gtgtgttgtg
 841 gtagacatca gcaaggatga tcccgaggtc agttcagct ggtttgtaga tgatgtggag
 901 gtgcacacag ctcagacgca accccgggag gagcagttca acagcacttt ccgctcagtc
 961 agtgaacttc ccatcatgca ccaggactgg ctcaatggca aggagttcaa atgcagggtc
1021 aacagtgcag ctttccctgc ccccatcgag aaaaccatct ccaaaaccaa aggcagaccg
1081 aaggctccac aggtgtacac cattccacct cccaaggagc agatggccaa ggataaagtc
1141 agtctgacct gcatgataac agacttcttc cctgaagaca ttactgtgga gtggcagtgg
1201 aatgggcagc cagcggagaa ctacaagaac actcagccca tcatggacac agatggctct
1261 tacttcgtct acagcaagct caatgtgcag aagagcaact gggaggcagg aaatactttc
1321 acctgctctg tgttacatga gggcctgcac aaccaccata ctgagaagag cctctcccac
1381 tctcctggta aatga
```

[0185] Protein Sequence Defining the Full Length Heavy Chain Sequence (Heavy Chain Variable Region and IgG1 Constant Region) of 18H02 (SEQ ID NO: 125)

```
   1 mgwlwnllfl maaaqsaqaq iqlvqsgpel kkpgeavkis ckssgytftt ygmswvkqap
  61 gralkwmgwi ntysgvptya ddfkgrfafs lessastayl qinnlknedt atyfcargrd
 121 gyqvawfayw gqgtlvtvsa akttppsvyp lapgsaaqtn smvtlgclvk gyfpepvtvt
 181 wnsgslssgv htfpavlqsd lytlsssvtv psstwpsqtv tcnvahpass tkvdkkivpr
 241 dcgckpcict vpevssvfif ppkpkdvlti tltpkvtcvv vdiskddpev qfswfvddve
 301 vhtaqtqpre eqfnstfrsv selpimhqdw lngkefkcrv nsaafpapie ktisktkgrp
 361 kapqvytipp pkeqmakdkv sltcmitdff peditvewqw ngqpaenykn tqpimdtdgs
 421 yfvysklnvq ksnweagntf tcsvlheglh nhhtekslsh spgk
```

[0186] Nucleic Acid Sequence Encoding the Full Length Light Chain Sequence (Kappa Chain Variable Region and Constant Region) of 18H02 (SEQ ID NO: 126)

```
   1 atgttctcac tagctcttct cctcagtctt cttctcctct gtgtctctga ttctagggca
  61 gaaacaactg tgacccagtc tccagcatcc ctgtccatgg ctataggaga taaagtcacc
 121 atcagatgca taaccagcac tgatattgat gatgatatga actggttcca gcagaagcca
 181 ggggaacctc ctaagctcct tatttcagaa ggcaatactc ttcgtcctgg agtcccatcc
 241 cgattctccg gcagtggcta tggtacagat tttattttta caattgaaaa catgctctct
 301 gaagatgttg cagattacta ctgtttgcaa agtgataact tgccgtacac gttcggaggg
 361 gggaccaagc tggaaataaa acgggctgat gctgcaccaa ctgtatccat cttcccacca
```

```
421 tccagtgagc agttaacatc tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac
481 cccagagaca tcaatgtcaa gtggaagatt gatggcagtg aacgacaaaa tggtgtcctg
541 aacagttgga ctgatcagga cagcaaagac agcacctaca gcatgagcag caccctcaca
601 ttgaccaagg acgagtatga acgacataac agctatacct gtgaggccac tcacaagaca
661 tcaacttcac ccattgtcaa gagcttcaac aggaatgagt gttag
```

[0187] Protein Sequence Defining the Full Length Light Chain Sequence (Kappa Chain Variable Region and Constant Region) of 18H02 (SEQ ID NO: 127)

```
  1 mfslalllsl lllcvsdsra ettvtqspas lsmaigdkvt ircitstdid ddmnwfqqkp
 61 geppkllise gntlrpgvps rfsgsgygtd fiftienmls edvadyyclq sdnlpytfgg
121 gtkleikrad aaptvsifpp sseqltsgga svvcflnnfy prdinvkwki dgserqngvl
181 nswtdqdskd stysmsstlt ltkdeyerhn sytceathkt stspivksfn rnec
```

[0188] Nucleic Acid Sequence Encoding the Full Length Heavy Chain Sequence (Heavy Chain Variable Region and IgG1 Constant Region) of 22A02 (SEQ ID NO: 128)

```
   1 atgggatgga gctgtatcat tgtcctcttg gtatcaacag ctacaggtgt ccactcccag
  61 gtccaactgc agcagcctgg ggctgagctg gtgaggcctg ggacttcagt gaagttgtcc
 121 tgcaaggctt ctggctacac cttcaccaac tactggatgc actgggtaaa gcagaggcct
 181 ggacaaggcc ttgagtggat cggaatgatt gatccttctg atagttatac taactacaat
 241 ccaaagttca agggtaaggc cacattgact gtagacacat cctccagcac agcctacatg
 301 cagctcagca gcctgacatc tgaggactct gcggtctatt actgtgcaag aaactactct
 361 ggggactact ggggccaagg caccactctc acagtctcct cagccaaaac gacaccccca
 421 tctgtctatc cactggcccc tggatctgct gcccaaacta actccatggt gaccctggga
 481 tgcctggtca agggctattt ccctgagcca gtgacagtga cctggaactc tggatccctg
 541 tccagcggtg tgcacacctt cccagctgtc ctgcagtctg acctctacac tctgagcagc
 601 tcagtgactg tcccctccag cacctggccc agccagaccg tcacctgcaa cgttgcccac
 661 ccggccagca gcaccaaggt ggacaagaaa attgtgccca gggattgtgg ttgtaagcct
 721 tgcatatgta cagtcccaga agtatcatct gtcttcatct tccccccaaa gcccaaggat
 781 gtgctcacca ttactctgac tcctaaggtc acgtgtgttg tggtagacat cagcaaggat
 841 gatcccgagg tccagttcag ctggtttgta gatgatgtgg aggtgcacac agctcagacg
 901 caaccccggg aggagcagtt caacagcact ttccgctcag tcagtgaact tcccatcatg
 961 caccaggact ggctcaatgg caaggagttc aaatgcaggg tcaacagtgc agctttccct
1021 gcccccatcg agaaaaccat ctccaaaacc aaaggcagac cgaaggctcc acaggtgtac
1081 accattccac ctcccaagga gcagatggcc aaggataaag tcagtctgac ctgcatgata
1141 acagacttct tccctgaaga cattactgtg gagtggcagt ggaatgggca gccagcggag
1201 aactacaaga acactcagcc catcatggac acagatggct cttacttcgt ctacagcaag
1261 ctcaatgtgc agaagagcaa ctgggaggca ggaaatactt tcacctgctc tgtgttacat
1321 gagggcctgc acaaccacca tactgagaag agcctctccc actctcctgg taaa
```

[0189] Protein Sequence Defining the Full Length Heavy Chain Sequence (Heavy Chain Variable Region and IgG1 Constant Region) of 22A02 (SEQ ID NO: 129)

```
  1 mgwsciivll vstatgvhsq vqlqqpgael vrpgtsvkls ckasgytftn ywmhwvkqrp
 61 gqglewigmi dpsdsytnyn pkfkgkatlt vdtssstaym qlssltseds avyycarnys
121 gdywgqgttl tvssakttpp svyplapgsa aqtnsmvtlg clvkgyfpep vtvtwnsgsl
181 ssgvhtfpav lqsdlytlss svtvpsstwp sqtvtcnvah passtkvdkk ivprdcgckp
241 cictvpevss vfifppkpkd vltitltpkv tcvvvdiskd dpevqfswfv ddvevhtaqt
301 qpreeqfnst frsvselpim hqdwlngkef kcrvnsaafp apiektiskt kgrpkapqvy
361 tipppkeqma kdkvsltcmi tdffpeditv ewqwngqpae nykntqpimd tdgsyfvysk
421 lnvqksnwea gntftcsvlh eglhnhhtek slshspgk
```

[0190] Nucleic Acid Sequence Encoding the Full Length Light Chain Sequence (Kappa Chain Variable Region and Constant Region) of 22A02 (SEQ ID NO: 130)

```
  1 atgaagttgc ctgttaggct gttggtgctg atgttctgga ttcctgcttc cagcagtgat
 61 gttttgatga cccaaactcc actctccctg cctgtcagtc ttggagatca agcctccatc
121 tcttgcagat ctagtcagag cattgtacat agtaatggaa acacctattt agaatggtac
181 ctgcagaaac caggccagtc tccaaagctc ctgatctaca aagtttccaa ccgattttct
241 ggggtcccag acaggttcag tggcagtgga tcagggacag atttcacact caagatcagc
301 agagtggagg ctgaggatct gggagtttat tattgctttc aaggttcata tgttccgtgg
361 acgttcggtg gaggcaccaa gctggaaatc aaacgggctg atgctgcacc aactgtatcc
421 atcttcccac catccagtga gcagttaaca tctggaggtg cctcagtcgt gtgcttcttg
481 aacaacttct accccagaga catcaatgtc aagtggaaga ttgatggcag tgaacgacaa
541 aatggtgtcc tgaacagttg gactgatcag gacagcaaag acagcaccta cagcatgagc
601 agcaccctca cattgaccaa ggacgagtat gaacgacata acagctatac ctgtgaggcc
661 actcacaaga catcaacttc acccattgtc aagagcttca acaggaatga gtgt
```

[0191] Protein Sequence Defining the Full Length Light Chain Sequence (Kappa Chain Variable Region and Constant Region) of 22A02 (SEQ ID NO: 131)

```
  1 mklpvrllvl mfwipasssd vlmtqtplsl pvslgdqasi scrssqsivh sngntylewy
 61 lqkpgqspkl liykvsnrfs gvpdrfsgsg sgtdftlkis rveaedlgvy ycfqgsyvpw
121 tfgggtklei kradaaptvs ifppsseqlt sggasvvcfl nnfyprdinv kwkidgserq
181 ngvlnswtdq dskdstysms stltltkdey erhnsytcea thktstspiv ksfnrnec
```

[0192] Nucleic Acid Sequence Encoding the Full Length Heavy Chain Sequence (Heavy Chain Variable Region and IgG1 Constant Region) of 24C05 (SEQ ID NO: 132)

```
   1 atgaacttcg ggctcagctt gatgttcctt gtccttgtct taaaaggtgt ccagtgtgag
  61 gtgcagctgg tggaatctgg gggaggctta gtgaagcctg gagggtccct gaaactctcc
 121 tgtgcagcct ctggattcac tttcagtgac tatgccatgt cttgggttcg ccagactccg
 181 gaaaagaggc tggagtgggt cgcaaccatt agtgatggtg gtacttacac ctactatcca
 241 gacaatgtaa agggccgatt caccatctcc agagacaatg ccaagaacaa cctgtacctg
 301 caaatgagcc atctgaagtc tgaggacaca gccatgtatt actgtgcaag agaatggggt
 361 gattacgacg gatttgacta ctggggccaa ggcaccactc tcacagtctc ctcggccaaa
 421 acgacacccc catctgtcta tccactggcc cctggatctg ctgcccaaac taactccatg
 481 gtgaccctgg gatgcctggt caagggctat ttccctgagc cagtgacagt gacctggaac
 541 tctggatccc tgtccagcgg tgtgcacacc ttcccagctg tcctgcagtc tgacctctac
 601 actctgagca gctcagtgac tgtcccctcc agcacctggc ccagccagac cgtcacctgc
 661 aacgttgccc acccggccag cagcaccaag gtggacaaga aaattgtgcc cagggattgt
 721 ggttgtaagc cttgcatatg tacagtccca gaagtatcat ctgtcttcat cttccccca
 781 aagcccaagg atgtgctcac cattactctg actcctaagg tcacgtgtgt tgtggtagac
 841 atcagcaagg atgatcccga ggtccagttc agctggtttg tagatgatgt ggaggtgcac
 901 acagctcaga cgcaaccccg ggaggagcag ttcaacagca ctttccgctc agtcagtgaa
 961 cttcccatca tgcaccagga ctggctcaat ggcaaggagt tcaaatgcag ggtcaacagt
1021 gcagctttcc ctgcccccat cgagaaaacc atctccaaaa ccaaaggcag accgaaggct
1081 ccacaggtgt acaccattcc acctcccaag gagcagatgg ccaaggataa agtcagtctg
1141 acctgcatga taacagactt cttccctgaa gacattactg tggagtggca gtggaatggg
1201 cagccagcgg agaactacaa gaacactcag cccatcatgg acacagatgg ctcttacttc
1261 gtctacagca agctcaatgt gcagaagagc aactgggagg caggaaatac tttcacctgc
1321 tctgtgttac atgagggcct gcacaaccac catactgaga agagcctctc ccactctcct
1381 ggtaaa
```

[0193] Protein Sequence Defining the Full Length Heavy Chain Sequence (Heavy Chain Variable Region and IgG1 Constant Region) of 24C05 (SEQ ID NO: 133)

```
   1 mnfglslmfl vlvlkgvqce vqlvesgggl vkpggslkls caasgftfsd yamswvrqtp
  61 ekrlewvati sdggtytyyp dnvkgrftis rdnaknnlyl qmshlksedt amyycarewg
 121 dydgfdywgq gttltvssak ttppsvypla pgsaaqtnsm vtlgclvkgy fpepvtvtwn
 181 sgslssgvht fpavlqsdly tlsssvtvps stwpsqtvtc nvahpasstk vdkkivprdc
 241 gckpcictvp evssvfifpp kpkdvltitl tpkvtcvvvd iskddpevqf swfvddvevh
 301 taqtqpreeq fnstfrsvse lpimhqdwln gkefkcrvns aafpapiekt isktkgrpka
 361 pqvytipppk eqmakdkvsl tcmitdffpe ditvewqwng qpaenykntq pimdtdgsyf
 421 vysklnvqks nweagntftc svlheglhnh htekslshsp gk
```

[0194] Nucleic Acid Sequence Encoding the Full Length Light Chain Sequence (Kappa Chain Variable Region and Constant Region) of 24C05 (SEQ ID NO: 134)

```
   1 atggacatga gggttcctgc tcacgttttt ggcttcttgt tgctctggtt tccaggtacc
  61 agatgtgaca tccagatgac ccagtctcca tcctccttat ctgcctctct gggagaaaga
 121 gtcagtctca cttgtcgggc aagtcaggaa attagtggtt acttaagctg gcttcagcag
 181 aaaccagatg gaactattaa acgcctgatc tacgccgcat ccactttaga ttctggtgtc
 241 ccaaaaaggt tcagtggcag taggtctggg tcagattatt ctctcaccat cggcagcctt
 301 gagtctgaag atcttgcaga ctattactgt ctacaatatg atagttatcc gtacacgttc
 361 ggaggggggа ccaagctgga aataaaacgg gctgatgctg caccaactgt atccatcttc
 421 ccaccatcca gtgagcagtt aacatctgga ggtgcctcag tcgtgtgctt cttgaacaac
 481 ttctacccca gagacatcaa tgtcaagtgg aagattgatg gcagtgaacg acaaaatggt
 541 gtcctgaaca gttggactga tcaggacagc aaagacagca cctacagcat gagcagcacc
 601 ctcacattga ccaaggacga gtatgaacga cataacagct atacctgtga ggccactcac
 661 aagacatcaa cttcacccat tgtcaagagc ttcaacagga atgagtgt
```

[0195] Protein Sequence Defining the Full Length Light Chain Sequence (Kappa Chain Variable Region and Constant Region) of 24C05 (SEQ ID NO: 135)

```
   1 mdmrvpahvf gflllwfpgt rcdiqmtqsp sslsaslger vsltcrasqe isgylswlqq
  61 kpdgtikrli yaastldsgv pkrfsgsrsg sdysltigsl esedladyyc lqydsypytf
 121 gggtkleikr adaaptvsif ppsseqltsg gasvvcflnn fyprdinvkw kidgserqng
 181 vlnswtdqds kdstysmsst ltltkdeyer hnsytceath ktstspivks fnrnec
```

[0196] For convenience, Table 4 provides a concordance chart showing the correspondence between the full length sequences of the antibodies discussed in this Example with those presented in the Sequence Listing.

Table 4

SEQ ID NO.	Nucleic Acid or Protein
108	04D01 Heavy Variable + IgG1 Constant—nucleic acid
109	04D01 Heavy Variable + IgG1 Constant—protein
110	04D01 Kappa Variable + Constant—nucleic acid
111	04D01 Kappa Variable + Constant—protein
112	09D03 Heavy Variable + IgG2b Constant—nucleic acid
113	09D03 Heavy Variable + IgG2b Constant—protein
114	09D03 Kappa Variable + Constant—nucleic acid

Table 4 (Cont.)

SEQ ID NO.	Nucleic Acid or Protein
115	09D03 Kappa Variable + Constant—protein
116	11G01 Heavy Variable + IgG1 Constant—nucleic acid
117	11G01 Heavy Variable + IgG1 Constant—protein
118	11G01 Kappa Variable + Constant—nucleic acid
119	11G01 Kappa Variable + Constant—protein
120	12A07 Heavy Variable + IgG1 Constant—nucleic acid
121	12A07 Heavy Variable + IgG1 Constant—protein
122	12A07 Kappa Variable + Constant—nucleic acid
123	12A07 Kappa Variable + Constant—protein
124	18H02 Heavy Variable + IgG1 Constant—nucleic acid
125	18H02 Heavy Variable + IgG1 Constant—protein
126	18H02 Kappa Variable + Constant—nucleic acid
127	18H02 Kappa Variable + Constant—protein
128	22A02 Heavy Variable + IgG1 Constant—nucleic acid
129	22A02 Heavy Variable + IgG1 Constant—protein
130	22A02 Kappa Variable + Constant—nucleic acid
131	22A02 Kappa Variable + Constant—protein
132	24C05 Heavy Variable + IgG1 Constant—nucleic acid
133	24C05 Heavy Variable + IgG1 Constant—protein
134	24C05 Kappa Variable + Constant—nucleic acid
135	24C05 Kappa Variable + Constant—protein

Example 3 – Binding Affinities

[0197] The binding affinities and kinetics of the binding of monoclonal antibodies 04D01, 09D03, 11G01, 12A07, 18H02, 22A02 and 24C05 to recombinant human ErbB3/Fc fusion protein (rhErbB3-Fc) were measured by surface plasmon resonance using a Biacore® T100 (Biacore) instrument.

[0198] Rabbit anti-mouse IgGs (Biacore, Cat. No. BR-1008-38) were immobilized on carboxymethylated dextran CM4 sensor chips (Biacore, Cat. No. BR-1005-34) by amine

coupling (BIAcore, Cat. No. BR-1000-50) using a standard coupling protocol according to vendor's instructions. The analyses were performed at 25°C, using PBS (Invitrogen, Cat. No. 14040-133) containing 0.05% surfactant P20 (Biacore, Cat. No. BR-1000-54) as running buffer.

[0199] The antibodies were captured in individual flow cells at a flow rate of 10 µl/minute. Injection time was varied for each antibody to yield an R_{max} between 30 and 60 RU. Buffer or rhErbB3-Fc diluted in running buffer was injected sequentially over a reference surface (no antibody captured) and the active surface (antibody to be tested) for 300 seconds at 60 µl/minute. The dissociation phase was monitored for up to 3600 seconds. The surface was then regenerated with two 60-seconds injection of 10 mM Glycine-HCl, pH 1.7 (made from Glycine pH 1.5 (Biacore, Cat. No. BR-1003-54) and pH 2.0 (Biacore, Cat. No. BR-1003-55)) at a flow rate of 60 µl/minute. The rhErbB3-Fc concentration range tested was 0.125 nM to 20 nM.

[0200] Kinetic parameters were determined using the kinetic function of the BIAevaluation software (Biacore) with double reference subtraction. Kinetic parameters for each antibody, k_a (association rate constant), k_d (dissociation rate constant) and K_D (equilibrium dissociation constant) were determined. Kinetic values of the monoclonal antibodies on rhErbB3-Fc at 25°C are summarized in Table 5.

Table 5

Antibody	k_a (1/Ms)	Standard Deviation	k_d (1/s)	Standard Deviation	K_D (M)	Standard Deviation	n
04D01	3.8E+05	3.0E+04	9.3E-05	1.9E-05	2.5E-10	5.6E-11	5
09D03	2.7E+05	3.2E+04	2.0E-05	1.2E-05	8.0E-11	5.5E-11	3
11G01	2.7E+05	9.2E+04	2.2E-05	9.6E-06	9.1E-11	5.5E-11	4
12A07	6.2E+05	8.1E+04	1.9E-04	1.0E-04	3.0E-10	1.4E-10	3
18H02	2.8E+05	3.1E+04	2.5E-05	8.8E-06	9.1E-11	3.7E-11	4
22A02	7.0E+05	8.1E+04	2.2E-04	1.4E-04	3.2E-10	2.4E-10	3
24C05	1.5E+06	2.0E+05	9.2E-06	3.0E-06	6.5E-12	2.8E-12	4

[0201] The data in Table 5 demonstrate that the antibodies bind rhErbB3 with a K_D of about 350 pM or less, 250 pM or less, 200 pM or less, 150 pM or less, 100 pM or less, 50 pM or less, or 10 pM or less.

Example 4 – Neutralization Activity

[0202] In this example, the antibodies produced in Example 1 were tested for ability to inhibit rhErbB3 binding to NRG1-β1 and NRG1-α1. The antibodies were tested by electrochemiluminescence (ECL) assay for inhibition of hErbB3 binding to NRG1-β1. MA2400 96-well standard binding plates (Meso Scale Discovery, Cat. No. L15XA-6) were coated with 50 µl of 0.5 µg/mL rhErbB3/Fc (R&D systems, Cat. No. 348-RB) in PBS (Invitrogen, Cat. No. 14040-133) for overnight at 4°C with no agitation. The plates then were washed 3 times with PBS+0.1% Tween20 (Sigma P5927) and blocked with 200 µl of PBS containing 5% BSA (Sera Care Life Sciences, Cat. No. AP-4510-80) for 1.5 hour at room temperature. After washing the plates 3 times with PBS, 25 µl of the antibody dilutions were added to the plates for another hour at room temperature with agitation. Ligand NRG1-β1 (R&D Systems, Cat. No. 377-HB, 26kDa) was added to the wells at the final concentration of 0.25 µg/ml. The plates were washed three times with PBS and incubated with 25 µl of 1 µg/mL biotinylated antibody against human NRG1-β1(R&D systems, Cat. No BAF377) preincubated for one hour with SULTO-TAG Streptavidin (Meso Scale Discovery, Cat. No R32AD-5) for one hour at room temperature with agitation. The plates then were washed 3 times with PBS, and 150 µl of 1X read buffer (Meso Scale Discovery, Cat. No. R92TC-1) was added to each well before the plates were analyzed on a Sector® Imager 2400 (Meso Scale Discovery) instrument.

[0203] The interaction of NRG1-β1 with ErbB3 was inhibited by antibodies 04D01, 12A07, 18H02, 22A02 and 24C05 (FIG. 6A). The interaction of NRG1-β1 with rhErbB3 was enhanced by antibody 09D03, but not as well as by antibody 11G01 (FIG. 6B).

[0204] The murine anti-human ErbB3 antibody IC_{50} values for neutralization of NRG1-β1 binding to rhErbB3 for the antibodies (*i.e.*, 04D01, 12A07, 18H02, 22A02 and 24C05) were calculated and are summarized in Table 6.

Table 6

	IC_{50} (nM)		
Antibody	Average	Standard Deviation	n
04D01	0.2232	0.0711	4
12A07	0.2351	0.0530	4
18H02	0.3460	0.0873	4
22A02	0.2418	0.0755	4
24C05	0.3367	0.0764	4

[0205] The results show that antibodies 04D01, 12A07, 18H02, 22A02, and 24C05 efficiently neutralized NRG1-β1 binding to rhErbB3. Antibodies 09D03 and 11G01 enhanced hNRG1-β1 binding to hErbB3.

[0206] The antibodies were tested by ECL assay for inhibition of hErbB3 binding to the second ErbB3 ligand, NRG1-α1. To assay inhibition of binding of NRG1-α1 to rhErbB3, the same method used for NRG1-β1 was used, except for the following changes: concentrations of plated rhErbB3/Fc (R&D 4518-RB) and of ligand NRG1-α1 (Thermo Scientific, RP-317-P1AX) were 1μg/ml and 1.5 μg/ml, respectively.

[0207] The interaction of NRG1-α1 with rhErbB3 was inhibited by 11G01, 12A07, 18H02, 22A02, and 24C05 IgG1, and was enhanced by antibody 09D03 (FIG. 7).

Example 5- Binding to ErbB3 domain II

[0208] In this example, the antibodies produced in Example 1 were tested for binding to the dimerization domain (domain 2) of hErbB3-ECD. Domain 2 of hErbB3 (118 amino acids, position 210-327) was cloned in place of domain 2 of Her2 (119 amino acids, position AA220-338) into the full-length Her2 receptor. The hybrid construct Her2/3d2 was cloned into pLenti6.3 and packaged by transient transfection of 293T cells into a Lentivirus using the ViraPower™ Lentiviral Support Kit (Invitrogen, Cat. No. K497000). CHO cells were infected with the lentivirus expressing the Her2/3d2 hybrid protein. The binding of the anti-ErbB3 hybridoma supernatants to Her2/3d2 were tested on these engineered CHO cells by ECL with sulfo-tagged anti-mouse antibodies. Data on the binding of the hybridoma supernatants to the chimeric protein Her2/3d2 expressed on the cell surface of CHO cells are summarized in FIG.

8. These results show that antibodies 09D03 and 11G01 bound to the ErbB3 domain II, AA210-327.

Example 6 – Anti-Proliferative Activity

[0209] This example describes a characterization of the antibodies produced in Example 1 for their ability to inhibit NRG1-β1 dependent proliferation of cells. Antibodies were tested in the BaF/3 cell system engineered to express both human Her2 and ErbB3 and in the human MCF7 breast cancer cells which naturally express both Her2 and ErbB3 and grow in response to NRG1-β1 stimulation.

[0210] BaF/3 cells were infected by two lentiviruses engineered to express human Her2 or human ErbB3. Infected cells were selected with blasticidin (15 μg/ml; Invitrogen, Cat. No. R21001) and individual colonies were isolated and tested for expression of both receptors. Her2/ErbB3 expressing clones were maintained in culture under blasticidin selection with [80% RPMI Medium 1640 (GIBCO, Cat. No. 11875-093), 10% fetal bovine serum (GIBCO, Cat. No. 10438-026) and 10% WEHI cell conditioned media {90% ISCOVE's Modified Dulbecco's Medium (GIBCO, Cat. No.12440053), 10% fetal bovine serum (GIBCO, Cat. No. 10438-026) + 2 mM L-glutamine (GIBCO, Cat. No.25030-081) + 0.0025 mM mercaptoethanol (Invitrogen, Cat. No. 21985-023)}]. To screen for antagonistic ErbB3 antibodies, cells were rinsed with PBS, and grown in the absence of blasticidin and WEHI conditioned media. Assays were conducted in a 96-well plate (5,000 cells/well) in the presence of NRG1-β1 (100 ng/ml) and various concentrations of antibodies (0.018-5000 ng/ml in 100 μl final volume). MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assays were conducted 3-4 days post NRG1-β1 stimulation.

[0211] An example of the dose-dependent inhibition of NRG1-β1 dependent cell proliferation of Her2/ErbB3-BaF/3 by murine anti-human ErbB3 antibodies is shown in FIG. 9. Inhibition data of NRG1-β1 dependent Her2/ErbB3-BaF/3 cell line proliferation with monoclonal antibodies (*i.e.,* 04D01, 09D03, 11G01, 12A07, 18H02, 22A02 and 24C05) are summarized in Table 7.

Table 7

Her2/ErbB3-BaF/3, NRG1-β1 dep. Proliferation			
Antibody	IC_{50} (nM)-Average	Standard deviation	n
04D01	0.373	0.061	3
09D03	1.395	0.268	3
11G01	1.934	0.116	3
12A07	0.854	0.059	3
18H02	1.930	0.276	3
22A02	1.291	0.151	3
24C05	0.145	0.031	3

[0212] The results in Table 7 show that antibodies 04D01, 09D03, 11G01, 12A07, 18H02, 22A02 and 24C05 strongly inhibited NRG1-β1-induced proliferation of BaF/3 cells expressing Her2/ErbB3.

[0213] MCF7 cells (ATCC, Cat. No. HTB-22) were maintained as recommended by ATCC. Cells were plated at 5,000 cells/well in a 96-well plate. Cells were starved overnight in the absence of serum. The following day, NRG1-β1 (40 ng/ml) and various concentrations of antibodies (12.8 pg/ml-20 μg/ml in 100 μl final volume) were added to the cells. MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assays were conducted three days post NRG1-β1 stimulation.

[0214] An example of the dose-dependent inhibition of NRG1-β1 dependent proliferation of MCF7 cells by murine anti-human ErbB3 antibodies is shown in FIG. 10. Inhibition data of NRG1-β1 dependent MCF7 cell proliferation with antibodies 04D01, 09D03, 11G01, 12A07, 18H02, 22A02 and 24C05 are summarized in Table 8.

Table 8

MCF7 cells, NRG1-β1 dependent Proliferation			
Antibody	IC_{50} (nM)-Average	Standard deviation	n
04D01	0.47	0.23	3
09D03	2.28	0.60	3
11G01	1.98	1.34	3
12A07	0.74	0.48	3
18H02	1.00	0.20	3
22A02	1.62	0.60	3
24C05	0.39	0.04	3

[0215] The results in Table 8 demonstrate that antibodies 04D01, 09D03, 11G01, 12A07, 18H02, 22A02, and 24C05 strongly inhibited NRG1-β1-induced proliferation of MCF7 cells.

[0216] The antibodies produced in Example 1 were also tested for their ability to inhibit proliferation of ErbB3 expressing human cancer cells. Breast cancer cells SKBR-3 overexpress Her2 and are sensitive to Her2-specific inhibitory antibodies.

[0217] SKBR-3 cells (ATCC, Cat. No. HTB-30) were maintained as recommended by ATCC. Cells were plated at 5,000 cells/well in a 96-well plate in the presence of 5 μg/ml of antibodies but without exogenous NRG1-β1. MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assays were conducted after three days in culture.

[0218] An example of inhibition of cell proliferation of SKBR-3 cells by murine anti-human ErbB3 antibodies is shown in FIG. 11. The results in FIG. 11 show that antibodies 04D01, 09D03, 11G01, 12A07, 18H02, 22A02 and 24C05 inhibited proliferation of SKBR-3 cells.

Example 7 – Inhibition of downstream signaling

[0219] This example describes a characterization of the antibodies produced in Example 1 for their ability to inhibit NRG1-β1 dependent phosphorylation of ErbB3 and the downstream kinase Akt, as the readout for PI3K activation. These antibodies were also tested for their ability to inhibit steady state phosphorylation of ErbB3 and Akt in exponentially growing cells.

[0220] Breast cancer cells SKBR-3 and MCF7 and prostate cancer cells DU145 were maintained as recommended by ATCC. Cells were starved overnight in 0% FBS, treated for one hour with 5 μg/ml of antibody followed by NRG1-β1 stimulation. Lysates were either analyzed by ELISA with the Phospho-ErbB3 kit from R&D Systems (Cat. No DYC1769) or with the Phospho-Akt ELISA kit from Cell Signaling (Cat. No 7143).

[0221] An example of the inhibition of the NRG1-β1 induced phosphorylation of ErbB3 in SKBR-3 cells by murine anti-human ErbB3 antibodies is shown in FIG. 12. The results in FIG.12 demonstrated that antibodies 04D01, 09D03, 11G01, 12A07, 18H02, 22A02 and 24C05 inhibited at least 50% of the phosphorylation of ErbB3 induced by NRG1-β1 in SKBR-3 cells.

[0222] An example of the inhibition of the NRG1-β1 induced phosphorylation of Akt in MCF7 and DU145 cells by murine anti-human ErbB3 antibodies is shown in FIG. 13A and FIG. 13B, respectively. The results in FIG. 13A and 13B demonstrated that antibodies 04D01, 09D03, 11G01, 12A07, 18H02, 22A02 and 24C05 inhibited at least 80% of the phosphorylation of Akt in response to the NRG1-β1 in both MCF7 and DU145 cells.

[0223] The capacity of the anti-ErbB3 antibodies to inhibit the steady state phosphorylation status of ErbB3 and Akt in a breast cancer cell line SKBR-3 and a pancreatic cancer cell line BxPC3 were tested by treating these exponentially growing cells for one hour in presence of antibodies at 5 μg/ml.

[0224] Western blot analysis of these experiments demonstrated that antibodies 04D01, 09D03, 11G01, 12A07, 18H02, 22A02 and 24C05 inhibited the steady state level of phosphorylation of Akt and ErbB3 in both SKBR-3 and BxPC3 cells.

Example 8 – Inhibition of NRG1-β1-induced EGFR phosphorylation

[0225] In this example, the antibodies produced in Example 1 were tested for their ability to inhibit NRG1-β1 dependent phosphorylation of EGFR in the ovarian cancer cell line NCI/ADR-RES. NCI/ADR-RES cells (DTP/DCTD NCI tumor repository) were starved overnight in 0% FBS, pre-treated with antibody (5 μg/ml) for one hour followed by NRG1-β1 (20 ng/ml) stimulation for 15 minutes. The phosphorylation of EGFR on tyrosine 1068 was analyzed by Western blot. The results of this experiment demonstrated that antibodies 04D01, 09D03, 11G01, 12A07, 18H02, 22A02 and 24C05 inhibited the phosphorylation of EGFR in response to the NRG1-β1 in NCI/ADR-RES cells.

Example 9 – Inhibition of EGF-induced ErbB3 phosphorylation

[0226] In this example, the antibodies produced in Example 1 were tested for their ability to inhibit EGF dependent phosphorylation of ErbB3 in the EGFR overexpressing, epidermoid cancer cell line A431. A431 cells (ATCC, Cat. No CRL-1555) were starved overnight in 0% FBS, pre-treated with antibody (5 μg/ml) for one hour followed by EGF (R&D Systems, Cat. No. 236-EG) (50 ng/ml) stimulation for 15 minutes. The phosphorylation of ErbB3 was analyzed by Western blot. The results of this experiment demonstrated that antibodies 04D01, 09D03, 12A07, 18H02, 22A02 and 24C05 inhibited to various extents the phosphorylation of ErbB3 in response to the EGF in A431 cells.

Example 10 – Inhibition of NRG1-β1-induced Her2/ErbB3 heterodimer formation

[0227] This example describes a characterization of the antibodies produced in Example 1 for their ability to inhibit the formation of the Her2/ErbB3 dimer in response to NRG1-β1 in SKBR-3 cells. Breast cancer cells SKBR-3 were starved overnight in 0% FBS, treated for one hour with 5 μg/ml of antibody followed by NRG1-β1 stimulation (30 ng/ml, 30 min). Lysates were immunoprecipitated with anti-Her2 antibody (R&D Systems, Cat. No. BAF1129) and analyzed by Western blot with polyclonal anti-ErbB3 antibody (Santa Cruz, Cat. No. SC285).

[0228] The results of this experiment demonstrated that antibodies 04D01, 09D03, 11G01, 12A07, 18H02, 22A02 and 24C05 inhibited NRG1-β1-induced Her2/ErbB3 dimer formation in SKBR-3 cells.

Example 11 – Inhibition of BxPC3 tumor xenograft growth

[0229] The ability of murine monoclonal antibodies produced in Example 1 to inhibit tumor growth was tested in a pancreatic BxPC3 xenograft model. Human pancreatic BxPC3 cells were grown in culture in 37°C in an atmosphere containing 5% CO2, using RMPI medium containing 10% fetal bovine serum. BxPC3 cells were inoculated subcutaneously into the flank of 8-week old female CB.17 SCID mice (Taconic Labs) with 10 x 10^6 cells per mouse in 50% matrigel (BD Biosciences, Cat No. 356237). Tumor measurements were taken twice weekly using vernier calipers. Tumor volume was calculated using the formula: width x width x length /2. When tumors reached approximately 200 mm^3, the mice were randomized into 9 groups of 10 mice each. One group received PBS and another received human IgG control (huIgG). Each of the other eight groups received one of the antibody, 04D01, 09D03, 18H02, 11G01, 24C05, 22A02, or 12A07. All antibodies were dosed at 20 mg/kg body weight, twice

per week, by intra-peritoneal injection for 6 weeks. Tumor volumes and mouse body weights were recorded twice per week. Tumor growth inhibition was analyzed using ANOVA and is expressed as percent inhibition compared to the PBS control.

[0230] The results in FIG. 14 show that antibody 24C05 inhibited tumor growth by 76% in this model ($p<0.001$). Antibodies 04D01, 18H02 and 11G01 also inhibited tumor growth in this model at 64%, 71%, and 72%, respectively ($p<0.001$). Antibodies 12A07 and 22A02 demonstrated the least activity, *i.e.*, near 40% tumor growth inhibition, while antibody 09D03 gave 60% tumor growth inhibition in this model.

Example 12 – Humanization of Anti-ErbB3 Antibodies

A. Construction of Humanized and Chimeric Anti-ErbB3 Antibodies

[0231] This Example describes the humanization of the murine antibody designated 24C05, and the characterization of the resulting humanized antibodies. The humanized anti-ErbB3 antibodies were designed using the SUPERHUMANIZATION™ method (Arana Therapeutics Ltd. and Hwang, W.Y. *et al.* (2005) METHODS 36:35-42) or the CDR grafting method with back mutations (some human framework residues were changed to murine residues) (*See e.g.*, U.S. Patent Nos. 5,530,101; 5,693,761; 5,693,762; 5,585,089; 6,180,370; 7,022,500). With the exception of heavy chain CDR1, the Kabat CDR definitions were used for CDR grafting onto human frameworks. A combination of Kabat and Chothia definitions were used for grafting heavy CDR1. The designed amino acid sequences were converted to codon-optimized DNA sequences and synthesized by DNA2.0, Inc. to include (in the following order): 5' HindIII restriction site, Kozak consensus sequence, amino terminal signal sequence, humanized variable region, human IgG1 or Kappa constant region, stop codon, and a 3' EcoRI restriction site. Additionally, one humanized heavy chain, Sh24C05 Hv3-11 Heavy IgG1, was mutated using overlap extension PCR to enhance humanization, resulting in the Sh24C05 Hv3-11 N62S heavy chain IgG1. A human IgG2 version of the Sh24C05 Hv3-11 N62S heavy chain was also constructed.

[0232] The anti-ErbB3 antibody chains humanized according to the SUPERHUMANIZATION™ method, as described herein, are designated with the prefix "Sh" before the antibody chain name. The anti-ErbB3 antibody chains humanized by the CDR grafting method with back mutations, as described herein, are designated with the prefix "Hu" before the antibody chain name.

[0233] Chimeric (murine variable region and human constant region) 24C05 heavy (human IgG1) and light (human Kappa) chains were also constructed. The murine variable regions were fused to the human constant region using overlap extension PCR, including (in the following order): 5' HindIII restriction site, Kozak consensus sequence, amino terminal signal sequence, mouse variable region, human IgG1 or Kappa constant region, stop codon, and 3' EcoRI restriction site.

[0234] The humanized and chimeric heavy chains were subcloned into pEE6.4 (Lonza Biologics) via HindIII and EcoRI sites using In-Fusion™ PCR cloning (Clontech). The humanized and chimeric Kappa light chains were subcloned into pEE14.4 (Lonza Biologics) via HindIII and EcoRI sites using In-Fusion™ PCR cloning.

[0235] Humanized antibody chains or chimeric antibody chains were transiently transfected into 293T cells to produce antibody. Antibody was either purified or used in cell culture media supernatant for subsequent *in vitro* analysis. Binding of the chimeric and humanized antibodies to human ErbB3 was measured as described below. The results are summarized in Table 15.

[0236] Additionally, some humanized antibody heavy and light chain combinations were stably expressed in CHOK1SV cells using the GS System™ (Lonza Biologics) in order to produce large quantities of purified humanized antibody. A single expression vector was constructed by combining pEE6.4 and pEE14.4 based vectors. First, pEE6.4 containing full length humanized heavy chain cDNA was digested with NotI and SalI to isolate the hCMV-MIE promoter + full length humanized heavy chain cDNA + SV40 polyA fragment. This fragment was inserted into the pEE14.4 vector already containing full length humanized light chain cDNA via NotI/SalI sites, thus creating an expression vector that simultaneously expresses heavy and light chains. The combined heavy and light chain vector was linearized and transfected into CHOK1SV cells. Stable clones were selected in the presence of methionine sulfoximine.

[0237] Each of the possible combinations of the humanized immunoglobulin heavy chain and immunoglobulin light chain variable regions are set forth below in Table 9.

Table 9

Light Chain Variable Region	Heavy Chain Variable Region
Hu24C05 KvA (SEQ ID NO: 174)	Hu24C05 HvA (SEQ ID NO: 162)
Hu24C05 KvA (SEQ ID NO: 174)	Sh24C05 Hv3-21 (SEQ ID NO: 156)
Hu24C05 KvA (SEQ ID NO: 174)	Sh24C05 Hv3-23 (SEQ ID NO: 158)
Hu24C05 KvA (SEQ ID NO: 174)	Sh24C05 Hv3-30 (SEQ ID NO: 160)
Hu24C05 KvA (SEQ ID NO: 174)	Sh24C05 Hv3-7 (SEQ ID NO: 150)
Hu24C05 KvA (SEQ ID NO: 174)	Sh24C05 Hv3-11 (SEQ ID NO: 152)
Hu24C05 KvA (SEQ ID NO: 174)	Sh24C05 Hv3-11 N62S (SEQ ID NO: 154)
Sh24C05 Kv1-16 (SEQ ID NO: 166)	Hu24C05 HvA (SEQ ID NO: 162)
Sh24C05 Kv1-16 (SEQ ID NO: 166)	Sh24C05 Hv3-21 (SEQ ID NO: 156)
Sh24C05 Kv1-16 (SEQ ID NO: 166)	Sh24C05 Hv3-23 (SEQ ID NO: 158)
Sh24C05 Kv1-16 (SEQ ID NO: 166)	Sh24C05 Hv3-30 (SEQ ID NO: 160)
Sh24C05 Kv1-16 (SEQ ID NO: 166)	Sh24C05 Hv3-7 (SEQ ID NO: 150)
Sh24C05 Kv1-16 (SEQ ID NO: 166)	Sh24C05 Hv3-11 (SEQ ID NO: 152)
Sh24C05 Kv1-16 (SEQ ID NO: 166)	Sh24C05 Hv3-11 N62S (SEQ ID NO: 154)
Sh24C05 Kv1-17 (SEQ ID NO: 168)	Hu24C05 HvA (SEQ ID NO: 162)
Sh24C05 Kv1-17 (SEQ ID NO: 168)	Sh24C05 Hv3-21 (SEQ ID NO: 156)
Sh24C05 Kv1-17 (SEQ ID NO: 168)	Sh24C05 Hv3-23 (SEQ ID NO: 158)
Sh24C05 Kv1-17 (SEQ ID NO: 168)	Sh24C05 Hv3-30 (SEQ ID NO: 160)
Sh24C05 Kv1-17 (SEQ ID NO: 168)	Sh24C05 Hv3-7 (SEQ ID NO: 150)
Sh24C05 Kv1-17 (SEQ ID NO: 168)	Sh24C05 Hv3-11 (SEQ ID NO: 152)
Sh24C05 Kv1-17 (SEQ ID NO: 168)	Sh24C05 Hv3-11 N62S (SEQ ID NO: 154)
Sh24C05 Kv1-33 (SEQ ID NO: 170)	Hu24C05 HvA(SEQ ID NO: 162)
Sh24C05 Kv1-33 (SEQ ID NO: 170)	Sh24C05 Hv3-21 (SEQ ID NO: 156)
Sh24C05 Kv1-33 (SEQ ID NO: 170)	Sh24C05 Hv3-23 (SEQ ID NO: 158)
Sh24C05 Kv1-33 (SEQ ID NO: 170)	Sh24C05 Hv3-30 (SEQ ID NO: 160)
Sh24C05 Kv1-33 (SEQ ID NO: 170)	Sh24C05 Hv3-7 (SEQ ID NO: 150)
Sh24C05 Kv1-33 (SEQ ID NO: 170)	Sh24C05 Hv3-11 (SEQ ID NO: 152)
Sh24C05 Kv1-33 (SEQ ID NO: 170)	Sh24C05 Hv3-11 N62S (SEQ ID NO: 154)
Sh24C05 Kv1-9 (SEQ ID NO: 164)	Hu24C05 HvA(SEQ ID NO: 162)

Table 9 (Cont.)

Light Chain Variable Region	Heavy Chain Variable Region
Sh24C05 Kv1-9 (SEQ ID NO: 164)	Sh24C05 Hv3-21 (SEQ ID NO: 156)
Sh24C05 Kv1-9 (SEQ ID NO: 164)	Sh24C05 Hv3-23 (SEQ ID NO: 158)
Sh24C05 Kv1-9 (SEQ ID NO: 164)	Sh24C05 Hv3-30 (SEQ ID NO: 160)
Sh24C05 Kv1-9 (SEQ ID NO: 164)	Sh24C05 Hv3-7 (SEQ ID NO: 150)
Sh24C05 Kv1-9 (SEQ ID NO: 164)	Sh24C05 Hv3-11 (SEQ ID NO: 152)
Sh24C05 Kv1-9 (SEQ ID NO: 164)	Sh24C05 Hv3-11 N62S (SEQ ID NO: 154)
Sh24C05 Kv1-39 (SEQ ID NO: 172)	Hu24C05 HvA (SEQ ID NO: 162)
Sh24C05 Kv1-39 (SEQ ID NO: 172)	Sh24C05 Hv3-21 (SEQ ID NO: 156)
Sh24C05 Kv1-39 (SEQ ID NO: 172)	Sh24C05 Hv3-23 (SEQ ID NO: 158)
Sh24C05 Kv1-39 (SEQ ID NO: 172)	Sh24C05 Hv3-30 (SEQ ID NO: 160)
Sh24C05 Kv1-39 (SEQ ID NO: 172)	Sh24C05 Hv3-7 (SEQ ID NO: 150)
Sh24C05 Kv1-39 (SEQ ID NO: 172)	Sh24C05 Hv3-11 (SEQ ID NO: 152)
Sh24C05 Kv1-39 (SEQ ID NO: 172)	Sh24C05 Hv3-11 N62S (SEQ ID NO: 154)

[0238] The nucleic acid sequences encoding and the protein sequences defining variable regions of the humanized 24C05 antibodies are summarized below (amino terminal signal peptide sequences are not shown). CDR sequences (Kabat definition) are shown in bold and are underlined in the amino acid sequences.

[0239] Nucleic Acid Sequence Encoding the Sh24C05 Hv3-7 Heavy Chain Variable Region (SEQ ID NO: 149)

```
  1 gaggttcagc tggtggaatc tggcggtggg cttgtacaac caggaggctc cctcagactg
 61 agttgtgccg cttcagggtt cacattctcc gactatgcga tgtcatgggt gcgccaagca
121 cccgggaaag gactggagtg ggttgccact atcagcgatg gcggaacgta tacctattac
181 cctgacaatg tgaagggtcg gttcaccatt tccagggata acgcaaagaa cagtctctac
241 ctgcagatga acagcctgag ggctgaggac accgccgtct actactgcgc ccgagaatgg
301 ggagattatg atgggtttga ctattggggc cagggcactt tggtgacagt cagttct
```

[0240] Protein Sequence Defining the Sh24C05 Hv3-7 Heavy Chain Variable Region (SEQ ID NO: 150)

```
  1 evqlvesggg lvqpggslrl scaasgftfs dyamswvrqa pgkglewvat isdggtytyy
 61 pdnvkgrfti srdnaknsly lqmnslraed tavyycarew gdydgfdywg qgtlvtvss
```

[0241] Nucleic Acid Sequence Encoding the Sh24C05 Hv3-11 Heavy Chain Variable Region (SEQ ID NO: 151)

```
  1 caagttcagc tggtggaatc tggcggtggg cttgtaaagc caggaggctc cctcagactg
 61 agttgtgccg cttcagggtt cacattctcc gactatgcga tgtcatggat caggcaagca
121 cccgggaaag gactggagtg ggttagcact atcagcgatg gcggaacgta tacctattac
181 cctgacaatg tgaagggtcg gttcaccatt tccagggata acgcaaagaa cagtctctac
241 cttcagatga acagcctgag ggctgaggac accgccgtct actactgcgc ccgagaatgg
301 ggagattatg atgggtttga ctattggggc cagggcactt tggtgacagt cagttct
```

[0242] Protein Sequence Defining the Sh24C05 Hv3-11 Heavy Chain Variable Region (SEQ ID NO: 152)

```
  1 qvqlvesggg lvkpggslrl scaasgftfs dyamswirqa pgkglewvst isdggtytyy
 61 pdnvkgrfti srdnaknsly lqmnslraed tavyycarew gdydgfdywg qgtlvtvss
```

[0243] Nucleic Acid Sequence Encoding the Sh24C05 Hv3-11 N62S Heavy Chain Variable Region (SEQ ID NO: 153)

```
  1 caagttcagc tggtggaatc tggcggtggg cttgtaaagc caggaggctc cctcagactg
 61 agttgtgccg cttcagggtt cacattctcc gactatgcga tgtcatggat caggcaagca
121 cccgggaaag gactggagtg ggttagcact atcagcgatg gcggaacgta tacctattac
181 cctgactccg tgaagggtcg gttcaccatt tccagggata acgcaaagaa cagtctctac
241 cttcagatga acagcctgag ggctgaggac accgccgtct actactgcgc ccgagaatgg
301 ggagattatg atgggtttga ctattggggc cagggcactt tggtgacagt cagttct
```

[0244] Protein Sequence Defining the Sh24C05 Hv3-11 N62S Heavy Chain Variable Region (SEQ ID NO: 154)

```
  1 qvqlvesggg lvkpggslrl scaasgftfs dyamswirqa pgkglewvst isdggtytyy
 61 pdsvkgrfti srdnaknsly lqmnslraed tavyycarew gdydgfdywg qgtlvtvss
```

[0245] Nucleic Acid Sequence Encoding the Sh24C05 Hv3-21 Heavy Chain Variable Region (SEQ ID NO: 155)

```
   1 gaggttcagc tggtggaatc tggcggtggg cttgtaaagc caggaggctc cctcagactg
  61 agttgtgccg cttcagggtt cacattctcc gactatgcga tgtcatgggt gcgccaagca
 121 cccgggaaag gactggagtg ggttagcact atcagcgatg gcggaacgta tacctattac
 181 cctgacaatg tgaagggtcg gttcaccatt tccagggata acgcaaagaa cagtctctat
 241 ttgcagatga acagcctgag ggctgaggac accgccgtct actactgcgc ccgagaatgg
 301 ggagattatg atgggtttga ctattggggc cagggcactt tggtgacagt cagttct
```

[0246] Protein Sequence Defining the Sh24C05 Hv3-21 Heavy Chain Variable Region (SEQ ID NO: 156)

```
   1 evqlvesggg lvkpggslrl scaasgftfs dyamswvrqa pgkglewvst isdggtytyy
  61 pdnvkgrfti srdnaknsly lqmnslraed tavyycarew gdydgfdywg qgtlvtvss
```

[0247] Nucleic Acid Sequence Encoding the Sh24C05 Hv3-23 Heavy Chain Variable Region (SEQ ID NO: 157)

```
   1 gaggttcagc ttctggaatc tggcggtggg cttgtacagc caggaggctc cctcagactg
  61 agttgtgccg cttcagggtt cacattctcc gactatgcga tgtcatgggt gcgccaagca
 121 cccgggaaag gactggagtg ggtttcaact atcagcgatg gcggaacgta tacctattac
 181 cctgacaatg tgaagggtcg gttcaccatt tccagggata acagcaagaa cacactctat
 241 ctccagatga acagcctgag ggctgaggac accgccgtct actactgcgc ccgagaatgg
 301 ggagattatg atgggtttga ctattggggc cagggcactt tggtgacagt cagttct
```

[0248] Protein Sequence Defining the Sh24C05 Hv3-23 Heavy Chain Variable Region (SEQ ID NO: 158)

```
   1 evqllesggg lvqpggslrl scaasgftfs dyamswvrqa pgkglewvst isdggtytyy
  61 pdnvkgrfti srdnskntly lqmnslraed tavyycarew gdydgfdywg qgtlvtvss
```

[0249] Nucleic Acid Sequence Encoding the Sh24C05 Hv3-30 Heavy Chain Variable Region (SEQ ID NO: 159)

```
   1 caggttcagc tggtggaatc tggcggtggg gtagtacaac caggacggtc cctcagactg
  61 agttgtgccg cttcagggtt cacattctcc gactatgcga tgtcatgggt gcgccaagca
 121 cccgggaaag gactggagtg ggttgccact atcagcgatg gcggaacgta tacctattac
 181 cctgacaatg tgaagggtcg gttcaccatt tccagggata actcaaagaa caccctctat
 241 ctccaaatga gtagcctgag ggctgaggac accgccgtct actactgcgc ccgagaatgg
 301 ggagattatg atgggtttga ctattggggc cagggcactt tggtgacagt cagttct
```

[0250] Protein Sequence Defining the Sh24C05 Hv3-30 Heavy Chain Variable Region (SEQ ID NO: 160)

```
  1 qvqlvesggg vvqpgrslrl scaasgftfs dyamswvrqa pgkglewvat isdggtytyy
 61 pdnvkgrfti srdnskntly lqmsslraed tavyycarew gdydgfdywg qgtlvtvss
```

[0251] Nucleic Acid Sequence Encoding the Hu24C05 HvA Heavy Chain Variable Region (SEQ ID NO: 161)

```
  1 gaggttcagc tggtggaatc tggcggtggg cttgtaaagc caggaggctc cctcagactg
 61 agttgtgccg cttcagggtt cacattctcc gactatgcga tgtcatgggt gcgccaagca
121 cccgggaaag gactggagtg ggttgccact atcagcgatg gcggaacgta tacctattac
181 cctgacaatg tgaagggtcg gttcaccatt tccagggata acgcaaagaa cagtctctac
241 cttcagatga acagcctgag ggctgaggac accgccgtct actactgcgc ccgagaatgg
301 ggagattatg atgggtttga ctattggggc cagggcactt tggtgacagt cagttct
```

[0252] Protein Sequence Defining the Hu24C05 HvA Heavy Chain Variable Region (SEQ ID NO: 162)

```
  1 evqlvesggg lvkpggslrl scaasgftfs dyamswvrqa pgkglewvat isdggtytyy
 61 pdnvkgrfti srdnaknsly lqmnslraed tavyycarew gdydgfdywg qgtlvtvss
```

[0253] Nucleic Acid Sequence Encoding the Sh24C05 Kv1-9 Kappa Chain Variable Region (SEQ ID NO: 163)

```
  1 gatattcagt tgacccaatc acctagcttc ctctcagctt ccgtgggcga cagagttacc
 61 ataacctgtc gggcaagcca ggagatttct gggtacctgt cctggtacca acagaagccc
121 ggaaaagccc ctaagctgtt gatctatgct gcgtcaacct tggatagcgg tgtcccgagt
181 cgattctccg gttctggctc cggaacagag ttcactctga caatttctag ccttcagcca
241 gaagatttcg ccacgtacta ttgcctccag tacgacagct atccctatac atttgggcag
301 ggcactaaac tggagatcaa a
```

[0254] Protein Sequence Defining the Sh24C05 Kv1-9 Kappa Chain Variable Region (SEQ ID NO: 164)

```
  1 diqltqspsf lsasvgdrvt itcrasqeis glswyqqkp gkapklliya astldsgvps
 61 rfsgsgsgte ftltisslqp edfatyyclq ydsypytfgq gtkleik
```

[0255] Nucleic Acid Sequence Encoding the Sh24C05 Kv1-16 Kappa Chain Variable Region (SEQ ID NO: 165)

```
  1 gatattcaga tgacccaatc acctagcagt ctctcagctt ccgtgggcga cagagttacc
 61 ataacctgtc gggcaagcca ggagatttct gggtacctgt cctggtttca acagaagccc
121 ggaaaggccc cgaagagctt gatctatgct gcgtcaacct tggatagcgg tgtcccgagt
181 cgattctccg gttctggctc cggaaccgac tttactctga caatttctag ccttcagcca
241 gaagatttcg ccacgtacta ttgcctccag tacgacagct atccctatac atttgggcag
301 ggcactaaac tggagatcaa a
```

[0256] Protein Sequence Defining the Sh24C05 Kv1-16 Kappa Chain Variable Region (SEQ ID NO: 166)

```
  1 diqmtqspss lsasvgdrvt itcrasqeis gylswfqqkp gkapksliya astldsgvps
 61 rfsgsgsgtd ftltisslqp edfatyyclq ydsypytfgq gtkleik
```

[0257] Nucleic Acid Sequence Encoding the Sh24C05 Kv1-17 Kappa Chain Variable Region (SEQ ID NO: 167)

```
  1 gatattcaga tgacccaatc acctagcagt ctctcagctt ccgtgggcga cagagttacc
 61 ataacctgtc gggcaagcca ggagatttct gggtacctgt cctggtatca acagaagccc
121 ggaaaagccc caaagaggtt gatctatgct gcgtcaacct tggatagcgg tgtcccgagt
181 cgattctccg gttctggctc cggaaccgag ttcactctga caatttctag ccttcagcca
241 gaagatttcg ccacgtacta ttgcctccag tacgacagct atccctatac atttgggcag
301 ggcactaaac tggagatcaa a
```

[0258] Protein Sequence Defining the Sh24C05 Kv1-17 Kappa Chain Variable Region (SEQ ID NO: 168)

```
  1 diqmtqspss lsasvgdrvt itcrasqeis gylswyqqkp gkapkrliya astldsgvps
 61 rfsgsgsgte ftltisslqp edfatyyclq ydsypytfgq gtkleik
```

[0259] Nucleic Acid Sequence Encoding the Sh24C05 Kv1-33 Kappa Chain Variable Region (SEQ ID NO: 169)

```
  1 gatattcaga tgacccaatc acctagcagt ctctcagctt ccgtgggcga cagagttacc
 61 ataacctgtc gggcaagcca ggagatttct gggtacctgt cctggtacca acagaagccc
121 ggaaaggccc ccaagctgtt gatctatgct gcgtcaacct tggatagcgg tgtcccgagt
181 cgattctccg gttctggctc cggaacagac tttactttta caatttctag ccttcagcca
241 gaggacatcg ccacgtacta ttgcctccag tacgacagct atccctatac atttgggcag
301 ggcactaaac tggagatcaa a
```

[0260] Protein Sequence Defining the Sh24C05 Kv1-33 Kappa Chain Variable Region (SEQ ID NO: 170)

```
  1 diqmtqspss lsasvgdrvt itcrasqeis glswyqqkp gkapklliya astldsgvps
 61 rfsgsgsgtd ftftisslqp ediatyyclq ydsypytfgq gtkleik
```

[0261] Nucleic Acid Sequence Encoding the Sh24C05 Kv1-39 Kappa Chain Variable Region (SEQ ID NO: 171)

```
  1 gatattcaga tgacccaatc acctagcagt ctctcagctt ccgtgggcga cagagttacc
 61 ataacctgtc gggcaagcca ggagatttct gggtacctgt cctggtatca acagaagccc
121 ggaaaagccc ctaagctgtt gatctatgct gcgtcaacct tggatagcgg tgtcccgagt
181 cgattctccg gttctggctc cggaactgac ttcactctga caatttctag ccttcagcca
241 gaagatttcg ccacgtacta ttgcctccag tacgacagct atccctatac atttgggcag
301 ggcactaaac tggagatcaa a
```

[0262] Protein Sequence Defining the Sh24C05 Kv1-39 Kappa Chain Variable Region (SEQ ID NO: 172)

```
  1 diqmtqspss lsasvgdrvt itcrasqeis glswyqqkp gkapklliya astldsgvps
 61 rfsgsgsgtd ftltisslqp edfatyyclq ydsypytfgq gtkleik
```

[0263] Nucleic Acid Sequence Encoding the Hu24C05 KvA Kappa Chain Variable Region (SEQ ID NO: 173)

```
  1 gatattcaga tgacccaatc acctagcagt ctctcagctt ccgtgggcga cagagttacc
 61 ataacctgtc gggcaagcca ggagatttct gggtacctgt cctggctgca acagaagccc
121 ggaggcgcca tcaagaggtt gatctatgct gcgtcaacct tggatagcgg tgtcccgagt
181 cgattctccg gttctggctc cggaagtgac tacactctga caatttctag ccttcagcca
241 gaagatttcg ccacgtacta ttgcctccag tacgacagct atccctatac atttgggcag
301 ggcactaaac tggagatcaa a
```

[0264] Protein Sequence Defining the Hu24C05 KvA Kappa Chain Variable Region (SEQ ID NO: 174)

```
  1 diqmtqspss lsasvgdrvt itcrasqeis glswlqqkp ggaikrliya astldsgvps
 61 rfsgsgsgsd ytltisslqp edfatyyclq ydsypytfgq gtkleik
```

[0265] The amino acid sequences defining the immunoglobulin heavy chain variable regions for the antibodies produced in Example 12 are aligned in FIG. 15. Amino terminal signal peptide sequences (for proper expression/secretion) are not shown. CDR_1, CDR_2, and CDR_3 (Kabat definition) are identified by boxes.

[0266] The amino acid sequences defining the immunoglobulin light chain variable regions for the antibodies in Example 12 are aligned in FIG. 16. Amino terminal signal peptide sequences (for proper expression/secretion) are not shown. CDR_1, CDR_2 and CDR_3 are identified by boxes.

[0267] Table 10 is a concordance chart showing the SEQ ID NO. of each sequence discussed in this Example.

Table 10

SEQ. ID NO.	Nucleic Acid or Protein
149	Sh24C05 Hv3-7 Heavy Chain Variable Region—nucleic acid
150	Sh24C05 Hv3-7 Heavy Chain Variable Region—protein
57	Sh24C05 Hv3-7 Heavy Chain CDR_1
58	Sh24C05 Hv3-7 Heavy Chain CDR_2
59	Sh24C05 Hv3-7 Heavy Chain CDR_3
151	Sh24C05 Hv3-11 Heavy Chain Variable Region—nucleic acid
152	Sh24C05 Hv3-11 Heavy Chain Variable Region—protein
57	Sh24C05 Hv3-11 Heavy Chain CDR_1
58	Sh24C05 Hv3-11 Heavy Chain CDR_2
59	Sh24C05 Hv3-11 Heavy Chain CDR_3
153	Sh24C05 Hv3-11 N62S Heavy Chain Variable Region—nucleic acid
154	Sh24C05 Hv3-11 N62S Heavy Chain Variable Region—protein
57	Sh24C05 Hv3-11 N62S Heavy Chain CDR_1
148	Sh24C05 Hv3-11 N62S Heavy Chain CDR_2
59	Sh24C05 Hv3-11 N62S Heavy Chain CDR_3
155	Sh24C05 Hv3-21 Heavy Chain Variable Region—nucleic acid
156	Sh24C05 Hv3-21 Heavy Chain Variable Region—protein

Table 10 (Cont.)

SEQ. ID NO.	Nucleic Acid or Protein
57	Sh24C05 Hv3-21 Heavy Chain CDR_1
58	Sh24C05 Hv3-21 Heavy Chain CDR_2
59	Sh24C05 Hv3-21 Heavy Chain CDR_3
157	Sh24C05 Hv3-23 Heavy Chain Variable Region—nucleic acid
158	Sh24C05 Hv3-23 Heavy Chain Variable Region—protein
57	Sh24C05 Hv3-23 Heavy Chain CDR_1
58	Sh24C05 Hv3-23 Heavy Chain CDR_2
59	Sh24C05 Hv3-23 Heavy Chain CDR_3
159	Sh24C05 Hv3-30 Heavy Chain Variable Region—nucleic acid
160	Sh24C05 Hv3-30 Heavy Chain Variable Region—protein
57	Sh24C05 Hv3-30 Heavy Chain CDR_1
58	Sh24C05 Hv3-30 Heavy Chain CDR_2
59	Sh24C05 Hv3-30 Heavy Chain CDR_3
161	Hu24C05 HvA Heavy Chain Variable Region—nucleic acid
162	Hu24C05 HvA Heavy Chain Variable Region—protein
57	Hu24C05 HvA Heavy Chain CDR_1
58	Hu24C05 HvA Heavy Chain CDR_2
59	Hu24C05 HvA Heavy Chain CDR_3
163	Sh24C05 Kv1-9 Light (kappa) Chain Variable Region—nucleic acid
164	Sh24C05 Kv1-9 Light (kappa) Chain Variable Region—protein
60	Sh24C05 Kv1-9 Light (kappa) Chain CDR_1
61	Sh24C05 Kv1-9 Light (kappa) Chain CDR_2
62	Sh24C05 Kv1-9 Light (kappa) Chain CDR_3
165	Sh24C05 Kv1-16 Light (kappa) Chain Variable Region—nucleic acid
166	Sh24C05 Kv1-16 Light (kappa) Chain Variable Region—protein

Table 10 (Cont.)

SEQ. ID NO.	Nucleic Acid or Protein
60	Sh24C05 Kv1-16 Light (kappa) Chain CDR_1
61	Sh24C05 Kv1-16 Light (kappa) Chain CDR_2
62	Sh24C05 Kv1-16 Light (kappa) Chain CDR_3
167	Sh24C05 Kv1-17 Light (kappa) Chain Variable Region—nucleic acid
168	Sh24C05 Kv1-17 Light (kappa) Chain Variable Region—protein
60	Sh24C05 Kv1-17 Light (kappa) Chain CDR_1
61	Sh24C05 Kv1-17 Light (kappa) Chain CDR_2
62	Sh24C05 Kv1-17 Light (kappa) Chain CDR_3
169	Sh24C05 Kv1-33 Light (kappa) Chain Variable Region—nucleic acid
170	Sh24C05 Kv1-33 Light (kappa) Chain Variable Region—protein
60	Sh24C05 Kv1-33 Light (kappa) Chain CDR_1
61	Sh24C05 Kv1-33 Light (kappa) Chain CDR_2
62	Sh24C05 Kv1-33 Light (kappa) Chain CDR_3
171	Sh24C05 Kv1-39 Light (kappa) Chain Variable Region—nucleic acid
172	Sh24C05 Kv1-39 Light (kappa) Chain Variable Region—protein
60	Sh24C05 Kv1-39 Light (kappa) Chain CDR_1
61	Sh24C05 Kv1-39 Light (kappa) Chain CDR_2
62	Sh24C05 Kv1-39 Light (kappa) Chain CDR_3
173	Hu24C05 KvA Light (kappa) Chain Variable Region—nucleic acid
174	Hu24C05 KvA Light (kappa) Chain Variable Region—protein
60	Hu24C05 KvA Light (kappa) Chain CDR_1
61	Hu24C05 KvA Light (kappa) Chain CDR_2
62	Hu24C05 KvA Light (kappa) Chain CDR_3

[0268] Humanized monoclonal antibody heavy chain CDR sequences (Kabat, Chothia, and IMGT definitions) are shown in Table 11.

Table 11

Kabat			
	CDR1	**CDR2**	CDR3
24C05	DYAMS (SEQ ID NO: 57)	**TISDGGTYTYYPDNVKG** (SEQ ID NO: 58)	EWGDYDGFDY (SEQ ID NO: 59)
Sh24C05 Hv3-7	DYAMS (SEQ ID NO: 57)	**TISDGGTYTYYPDNVKG** (SEQ ID NO: 58)	EWGDYDGFDY (SEQ ID NO: 59)
Sh24C05 Hv3-11	DYAMS (SEQ ID NO: 57)	**TISDGGTYTYYPDNVKG** (SEQ ID NO: 58)	EWGDYDGFDY (SEQ ID NO: 59)
Sh24C05 Hv3-11 N62S	DYAMS (SEQ ID NO: 57)	**TISDGGTYTYYPDSVKG** (SEQ ID NO: 148)	EWGDYDGFDY (SEQ ID NO: 59)
Sh24C05 Hv3-21	DYAMS (SEQ ID NO: 57)	**TISDGGTYTYYPDNVKG** (SEQ ID NO: 58)	EWGDYDGFDY (SEQ ID NO: 59)
Sh24C05 Hv3-23	DYAMS (SEQ ID NO: 57)	**TISDGGTYTYYPDNVKG** (SEQ ID NO: 58)	EWGDYDGFDY (SEQ ID NO: 59)
Sh24C05 Hv3-30	DYAMS (SEQ ID NO: 57)	**TISDGGTYTYYPDNVKG** (SEQ ID NO: 58)	EWGDYDGFDY (SEQ ID NO: 59)
Hu24C05 HvA	DYAMS (SEQ ID NO: 57)	**TISDGGTYTYYPDNVKG** (SEQ ID NO: 58)	EWGDYDGFDY (SEQ ID NO: 59)
Chothia			
	CDR1	CDR2	CDR3
24C05	**GFTFSDY** (SEQ ID NO: 75)	SDGGTY (SEQ ID NO: 76)	EWGDYDGFDY (SEQ ID NO: 59)
Sh24C05 Hv3-7	**GFTFSDY** (SEQ ID NO: 75)	SDGGTY (SEQ ID NO: 76)	EWGDYDGFDY (SEQ ID NO: 59)
Sh24C05 Hv3-11	**GFTFSDY** (SEQ ID NO: 75)	SDGGTY (SEQ ID NO: 76)	EWGDYDGFDY (SEQ ID NO: 59)
Sh24C05 Hv3-11 N62S	**GFTFSDY** (SEQ ID NO: 75)	SDGGTY (SEQ ID NO: 76)	EWGDYDGFDY (SEQ ID NO: 59)

Table 11 (Cont.)

Chothia			
	CDR1	CDR2	CDR3
Sh24C05 Hv3-21	**GFTFSDY** (SEQ ID NO: 75)	SDGGTY (SEQ ID NO: 76)	EWGDYDGFDY (SEQ ID NO: 59)
Sh24C05 Hv3-23	**GFTFSDY** (SEQ ID NO: 75)	SDGGTY (SEQ ID NO: 76)	EWGDYDGFDY (SEQ ID NO: 59)
Sh24C05 Hv3-30	**GFTFSDY** (SEQ ID NO: 75)	SDGGTY (SEQ ID NO: 76)	EWGDYDGFDY (SEQ ID NO: 59)
Hu24C05 HvA	**GFTFSDY** (SEQ ID NO: 75)	SDGGTY (SEQ ID NO: 76)	EWGDYDGFDY (SEQ ID NO: 59)
IMGT			
	CDR1	CDR2	**CDR3**
24C05	GFTFSDYA (SEQ ID NO: 94)	ISDGGTYT (SEQ ID NO: 95)	**AREWGDYDGFDY** (SEQ ID NO: 96)
Sh24C05 Hv3-7	GFTFSDYA (SEQ ID NO: 94)	ISDGGTYT (SEQ ID NO: 95)	**AREWGDYDGFDY** (SEQ ID NO: 96)
Sh24C05 Hv3-11	GFTFSDYA (SEQ ID NO: 94)	ISDGGTYT (SEQ ID NO: 95)	**AREWGDYDGFDY** (SEQ ID NO: 96)
Sh24C05 Hv3-11 N62S	GFTFSDYA (SEQ ID NO: 94)	ISDGGTYT (SEQ ID NO: 95)	**AREWGDYDGFDY** (SEQ ID NO: 96)
Sh24C05 Hv3-21	GFTFSDYA (SEQ ID NO: 94)	ISDGGTYT (SEQ ID NO: 95)	**AREWGDYDGFDY** (SEQ ID NO: 96)
Sh24C05 Hv3-23	GFTFSDYA (SEQ ID NO: 94)	ISDGGTYT (SEQ ID NO: 95)	**AREWGDYDGFDY** (SEQ ID NO: 96)
Sh24C05 Hv3-30	GFTFSDYA (SEQ ID NO: 94)	ISDGGTYT (SEQ ID NO: 95)	**AREWGDYDGFDY** (SEQ ID NO: 96)
Hu24C05 HvA	GFTFSDYA (SEQ ID NO: 94)	ISDGGTYT (SEQ ID NO: 95)	**AREWGDYDGFDY** (SEQ ID NO: 96)

[0269] Humanized monoclonal antibody Kappa light chain CDR sequences (Kabat,

Chothia, and IMGT definitions) are shown in Table 12.

Table 12

Kabat/Chothia			
	CDR1	**CDR2**	**CDR3**
24C05	**RASQEISGYLS** (SEQ ID NO: 60)	**AASTLDS** (SEQ ID NO: 61)	**LQYDSYPYT** (SEQ ID NO: 62)
Sh24C05 Kv1-9	**RASQEISGYLS** (SEQ ID NO: 60)	**AASTLDS** (SEQ ID NO: 61)	**LQYDSYPYT** (SEQ ID NO: 62)
Sh24C05 Kv1-16	**RASQEISGYLS** (SEQ ID NO: 60)	**AASTLDS** (SEQ ID NO: 61)	**LQYDSYPYT** (SEQ ID NO: 62)
Sh24C05 Kv1-17	**RASQEISGYLS** (SEQ ID NO: 60)	**AASTLDS** (SEQ ID NO: 61)	**LQYDSYPYT** (SEQ ID NO: 62)
Sh24C05 Kv1-33	**RASQEISGYLS** (SEQ ID NO: 60)	**AASTLDS** (SEQ ID NO: 61)	**LQYDSYPYT** (SEQ ID NO: 62)
Sh24C05 Kv1-39	**RASQEISGYLS** (SEQ ID NO: 60)	**AASTLDS** (SEQ ID NO: 61)	**LQYDSYPYT** (SEQ ID NO: 62)
Hu24C05 KvA	**RASQEISGYLS** (SEQ ID NO: 60)	**AASTLDS** (SEQ ID NO: 61)	**LQYDSYPYT** (SEQ ID NO: 62)
IMGT			
	CDR1	CDR2	CDR3
24C05	QEISGY (SEQ ID NO: 101)	AAS	LQYDSYPYT (SEQ ID NO: 62)
Sh24C05 Kv1-9	QEISGY (SEQ ID NO: 101)	AAS	LQYDSYPYT (SEQ ID NO: 62)
Sh24C05 Kv1-16	QEISGY (SEQ ID NO: 101)	AAS	LQYDSYPYT (SEQ ID NO: 62)
Sh24C05 Kv1-17	QEISGY (SEQ ID NO: 101)	AAS	LQYDSYPYT (SEQ ID NO: 62)
Sh24C05 Kv1-33	QEISGY (SEQ ID NO: 101)	AAS	LQYDSYPYT (SEQ ID NO: 62)

Table 12 (Cont.)

	IMGT		
	CDR1	CDR2	CDR3
Sh24C05 Kv1-39	QEISGY (SEQ ID NO: 101)	AAS	LQYDSYPYT (SEQ ID NO: 62)
Hu24C05 KvA	QEISGY (SEQ ID NO: 101)	AAS	LQYDSYPYT (SEQ ID NO: 62)

[0270] In Tables 11 and 12, the longest CDR sequences for the immunoglobulin heavy chain and light chain are shown in bold.

[0271] To create the complete chimeric and humanized heavy or kappa chain antibody sequences, each variable sequence above is combined with its respective human constant region. For example, a complete heavy chain comprises a heavy variable sequence followed by a human IgG1 heavy chain constant sequence or a human IgG2 heavy chain constant sequence. A complete kappa chain comprises a kappa variable sequence followed by the human kappa light chain constant sequence.

[0272] Nucleic Acid Sequence Encoding the Human IgG1 Heavy Chain Constant Region (SEQ ID NO: 175)

```
   1 gcctcaacaa aaggaccaag tgtgttccca ctcgccccta gcagcaagag tacatccggg
  61 ggcactgcag cactcggctg cctcgtcaag gattattttc cagagccagt aaccgtgagc
 121 tggaacagtg gagcactcac ttctggtgtc catacttttc ctgctgtcct gcaaagctct
 181 ggcctgtact cactcagctc cgtcgtgacc gtgccatctt catctctggg cactcagacc
 241 tacatctgta atgtaaacca caagcctagc aatactaagg tcgataagcg ggtggaaccc
 301 aagagctgcg acaagactca cacttgtccc ccatgccctg cccctgaact tctgggcggt
 361 cccagcgtct ttttgttccc accaaagcct aaagatactc tgatgataag tagaacaccc
 421 gaggtgacat gtgttgttgt agacgtttcc cacgaggacc cagaggttaa gttcaactgg
 481 tacgttgatg gagtcgaagt acataatgct aagaccaagc ctagagagga gcagtataat
 541 agtacatacc gtgtagtcag tgttctcaca gtgctgcacc aagactggct caacggcaaa
 601 gaatacaaat gcaaagtgtc caacaaagca ctcccagccc ctatcgagaa gactattagt
 661 aaggcaaagg ggcagcctcg tgaaccacag gtgtacactc tgccacccag tagagaggaa
 721 atgacaaaga accaagtctc attgacctgc ctggtgaaag gcttctaccc cagcgacatc
 781 gccgttgagt gggagagtaa cggtcagcct gagaacaatt acaagacaac ccccccagtg
 841 ctggatagtg acgggtcttt ctttctgtac agtaagctga ctgtggacaa gtcccgctgg
 901 cagcagggta acgtcttcag ctgttccgtg atgcacgagg cattgcacaa ccactacacc
 961 cagaagtcac tgagcctgag cccagggaag
```

[0273] Protein Sequence Defining the Human IgG1 Heavy Chain Constant Region (SEQ ID NO: 176)

```
  1 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss
 61 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg
121 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn
181 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree
241 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw
301 qqgnvfscsv mhealhnhyt qkslslspgk
```

[0274] Nucleic Acid Sequence Encoding the Human IgG2 Heavy Chain Constant Region (SEQ ID NO: 177)

```
  1 gcctccacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag
 61 agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg
121 tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca
181 ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg cacccagacc
241 tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc
301 aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc
361 ctcttccccc caaaacccaa ggacaccctc atgatctccc ggaccccctga ggtcacgtgc
421 gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc
481 gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt
541 gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc
601 aaggtctcca acaaaggcct cccagccccc atcgagaaaa ccatctccaa aaccaaaggg
661 cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac
721 caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg
781 gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac
841 ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac
901 gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc
961 tccctgtctc cgggtaaa
```

[0275] Protein Sequence Defining the Human IgG2 Heavy Chain Constant Region (SEQ ID NO: 178)

```
  1 astkgpsvfp lapcsrstse staalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss
 61 glyslssvvt vpssnfgtqt ytcnvdhkps ntkvdktver kccvecppcp appvagpsvf
121 lfppkpkdtl misrtpevtc vvvdvshedp evqfnwyvdg vevhnaktkp reeqfnstfr
181 vvsvltvvhq dwlngkeykc kvsnkglpap iektisktkg qprepqvytl ppsreemtkn
241 qvsltclvkg fypsdiavew esngqpenny kttppmldsd gsfflysklt vdksrwqqgn
301 vfscsvmhea lhnhytqksl slspgk
```

[0276] Nucleic Acid Sequence Encoding the Human Kappa Light Chain Constant Region (SEQ ID NO: 179)

```
  1 cgcacagttg ctgcccccag cgtgttcatt ttcccaccta gcgatgagca gctgaaaagc
 61 ggtactgcct ctgtcgtatg cttgctcaac aacttttacc cacgtgaggc taaggtgcag
121 tggaaagtgg ataatgcact tcaatctgga aacagtcaag agtccgtgac agaacaggac
181 agcaaagact caacttattc actctcttcc accctgactc tgtccaaggc agactatgaa
241 aaacacaagg tatacgcctg cgaggttaca caccagggtt tgtctagtcc tgtcaccaag
301 tccttcaata ggggcgaatg t
```

[0277] Protein Sequence Defining the Human Kappa Light Chain Constant Region (SEQ ID NO: 180)

```
  1 rtvaapsvfi fppsdeqlks gtasvvclln nfypreakvq wkvdnalqsg nsqesvteqd
 61 skdstyslss tltlskadye khkvyacevt hqglsspvtk sfnrgec
```

[0278] The following sequences represent the actual or contemplated full length heavy and light chain sequences (*i.e.*, containing both the variable and constant regions sequences) for each antibody described in this Example. Signal sequences for proper secretion of the antibodies are also included at the 5' end of the DNA sequences or the amino terminal end of the protein sequences. It is also contemplated herein that the variable region sequences can be ligated to other constant region sequences to produce active full length IgG heavy and light chains.

[0279] Nucleic Acid Sequence Encoding the Full Length Chimeric 24C05 Heavy Chain (Mouse Heavy Chain Variable Region and Human IgG1 Constant Region) (SEQ ID NO: 181)

```
  1 atgaacttcg ggctcagctt gatgttcctt gtccttgtct taaaaggtgt ccagtgtgag
 61 gtgcagctgg tggaatctgg gggaggctta gtgaagcctg gagggtccct gaaactctcc
121 tgtgcagcct ctggattcac tttcagtgac tatgccatgt cttgggttcg ccagactccg
181 gaaaagaggc tggagtgggt cgcaaccatt agtgatggtg gtacttacac ctactatcca
241 gacaatgtaa agggccgatt caccatctcc agagacaatg ccaagaacaa cctgtacctg
301 caaatgagcc atctgaagtc tgaggacaca gccatgtatt actgtgcaag agaatggggt
361 gattacgacg gatttgacta ctggggccaa ggcaccactc tcacagtctc ctcggcctca
421 acaaaaggac caagtgtgtt cccactcgcc cctagcagca agagtacatc cgggggcact
481 gcagcactcg gctgcctcgt caaggattat tttccagagc cagtaaccgt gagctggaac
541 agtggagcac tcacttctgg tgtccatact tttcctgctg tcctgcaaag ctctggcctg
601 tactcactca gctccgtcgt gaccgtgcca tcttcatctc tgggcactca gacctacatc
661 tgtaatgtaa accacaagcc tagcaatact aaggtcgata agcgggtgga acccaagagc
```

```
 721 tgcgacaaga ctcacacttg tcccccatgc cctgcccctg aacttctggg cggtcccagc
 781 gtctttttgt tcccaccaaa gcctaaagat actctgatga taagtagaac acccgaggtg
 841 acatgtgttg ttgtagacgt ttcccacgag gacccagagg ttaagttcaa ctggtacgtt
 901 gatggagtcg aagtacataa tgctaagacc aagcctagag aggagcagta taatagtaca
 961 taccgtgtag tcagtgttct cacagtgctg caccaagact ggctcaacgg caaagaatac
1021 aaatgcaaag tgtccaacaa agcactccca gcccctatcg agaagactat tagtaaggca
1081 aaggggcagc ctcgtgaacc acaggtgtac actctgccac ccagtagaga ggaaatgaca
1141 aagaaccaag tctcattgac ctgcctggtg aaaggcttct accccagcga catcgccgtt
1201 gagtgggaga gtaacggtca gcctgagaac aattacaaga caacccccca agtgctggat
1261 agtgacgggt ctttctttct gtacagtaag ctgactgtgg acaagtcccg ctggcagcag
1321 ggtaacgtct tcagctgttc cgtgatgcac gaggcattgc acaaccacta cacccagaag
1381 tcactgagcc tgagcccagg gaag
```

[0280] Protein Sequence Defining the Full Length Chimeric 24C05 Heavy Chain (Mouse Heavy Chain Variable Region and Human IgG1 Constant Region) (SEQ ID NO: 182)

```
   1 mnfglslmfl vlvlkgvqce vqlvesgggl vkpggslkls caasgftfsd yamswvrqtp
  61 ekrlewvati sdggtytyyp dnvkgrftis rdnaknnlyl qmshlksedt amyycarewg
 121 dydgfdywgq gttltvssas tkgpsvfpla psskstsggt aalgclvkdy fpepvtvswn
 181 sgaltsgvht fpavlqssgl yslssvvtvp ssslgtqtyi cnvnhkpsnt kvdkrvepks
 241 cdkthtcppc papellggps vflfppkpkd tlmisrtpev tcvvvdvshe dpevkfnwyv
 301 dgvevhnakt kpreeqynst yrvvsvltvl hqdwlngkey kckvsnkalp apiektiska
 361 kgqprepqvy tlppsreemt knqvsltclv kgfypsdiav ewesngqpen nykttppvld
 421 sdgsfflysk ltvdksrwqq gnvfscsvmh ealhnhytqk slslspgk
```

[0281] Nucleic Acid Sequence Encoding the Full Length Chimeric 24C05 Light Chain (Mouse Kappa Chain Variable Region and Human Kappa Constant Region) (SEQ ID NO: 183)

```
   1 atggacatga gggttcctgc tcacgttttt ggcttcttgt tgctctggtt tccaggtacc
  61 agatgtgaca tccagatgac ccagtctcca tcctccttat ctgcctctct gggagaaaga
 121 gtcagtctca cttgtcgggc aagtcaggaa attagtggtt acttaagctg gcttcagcag
 181 aaaccagatg gaactattaa acgcctgatc tacgccgcat ccactttaga ttctggtgtc
 241 ccaaaaaggt tcagtggcag taggtctggg tcagattatt ctctcaccat cggcagcctt
 301 gagtctgaag atcttgcaga ctattactgt ctacaatatg atagttatcc gtacacgttc
 361 ggaggggggа ccaagctgga aataaaacgc acagtcgccg ctccctccgt gttcatcttt
 421 ccaccaagtg atgagcaact gaagtctggt actgcttcag tcgtgtgtct gctgaacaat
 481 ttctaccctc gagaagccaa agtccaatgg aaggtagaca acgcactgca gtccggcaat
 541 agccaagaat cagttaccga acaggattca aaggacagta catattccct gagcagcact
 601 ctgaccctgt caaaggccga ttacgagaaa cacaaggtct atgcttgcga agtgacacat
 661 cagggactgt ccagcccagt gacaaaatct tttaaccgtg gggagtgt
```

[0282] Protein Sequence Defining the Full Length Chimeric 24C05 Light Chain (Mouse Kappa Chain Variable Region and Human Kappa Constant Region) (SEQ ID NO: 184)

```
  1 mdmrvpahvf gflllwfpgt rcdiqmtqsp sslsaslger vsltcrasqe isgylswlqq
 61 kpdgtikrli yaastldsgv pkrfsgsrsg sdysltigsl esedladyyc lqydsypytf
121 gggtkleikr tvaapsvfif ppsdeqlksg tasvvcllnn fypreakvqw kvdnalqsgn
181 sqesvteqds kdstyslsst ltlskadyek hkvyacevth qglsspvtks fnrgec
```

[0283] Nucleic Acid Sequence Encoding the Full Length Humanized sh24C05 Hv3-7 Heavy Chain (Humanized Heavy Chain Variable Region and Human IgG1 Constant Region) (SEQ ID NO: 185)

```
   1 atggacatga gagttcctgc tcagctgctc gggttgctgt tgctttggct ccggggtgct
  61 aggtgcgagg ttcagctggt ggaatctggc ggtgggcttg tacaaccagg aggctccctc
 121 agactgagtt gtgccgcttc agggttcaca ttctccgact atgcgatgtc atgggtgcgc
 181 caagcacccg ggaaaggact ggagtgggtt gccactatca gcgatggcgg aacgtatacc
 241 tattaccctg acaatgtgaa gggtcggttc accatttcca gggataacgc aaagaacagt
 301 ctctacctgc agatgaacag cctgagggct gaggacaccg ccgtctacta ctgcgcccga
 361 gaatggggag attatgatgg gtttgactat tggggccagg gcactttggt gacagtcagt
 421 tctgcctcaa caaaaggacc aagtgtgttc ccactcgccc ctagcagcaa gagtacatcc
 481 gggggcactg cagcactcgg ctgcctcgtc aaggattatt ttccagagcc agtaaccgtg
 541 agctggaaca gtggagcact cacttctggt gtccatactt ttcctgctgt cctgcaaagc
 601 tctggcctgt actcactcag ctccgtcgtg accgtgccat cttcatctct gggcactcag
 661 acctacatct gtaatgtaaa ccacaagcct agcaatacta aggtcgataa gcgggtggaa
 721 cccaagagct gcgacaagac tcacacttgt cccccatgcc ctgcccctga acttctgggc
 781 ggtcccagcg tctttttgtt cccaccaaag cctaaagata ctctgatgat aagtagaaca
 841 cccgaggtga catgtgttgt tgtagacgtt tcccacgagg acccagaggt taagttcaac
 901 tggtacgttg atggagtcga agtacataat gctaagacca agcctagaga ggagcagtat
 961 aatagtacat accgtgtagt cagtgttctc acagtgctgc accaagactg gctcaacggc
1021 aaagaataca aatgcaaagt gtccaacaaa gcactcccag cccctatcga gaagactatt
1081 agtaaggcaa aggggcagcc tcgtgaacca caggtgtaca ctctgccacc cagtagagag
1141 gaaatgacaa agaaccaagt ctcattgacc tgcctggtga aaggcttcta ccccagcgac
1201 atcgccgttg agtgggagag taacggtcag cctgagaaca attacaagac aacccccca
1261 gtgctggata gtgacgggtc tttctttctg tacagtaagc tgactgtgga caagtcccgc
1321 tggcagcagg gtaacgtctt cagctgttcc gtgatgcacg aggcattgca caaccactac
1381 acccagaagt cactgagcct gagcccaggg aag
```

[0284] Protein Sequence Defining the Full Length Humanized Sh24C05 Hv3-7 Heavy Chain (Humanized Heavy Chain Variable Region and Human IgG1 Constant Region) (SEQ ID NO: 186)

```
   1 mdmrvpaqll glllwlrga rcevqlvesg gglvqpggsl rlscaasgft fsdyamswvr
  61 qapgkglewv atisdggtyt yypdnvkgrf tisrdnakns lylqmnslra edtavyycar
 121 ewgdydgfdy wgqgtlvtvs sastkgpsvf plapssksts ggtaalgclv kdyfpepvtv
 181 swnsgaltsg vhtfpavlqs sglyslssvv tvpssslgtq tyicnvnhkp sntkvdkrve
 241 pkscdkthtc ppcpapellg gpsvflfppk pkdtlmisrt pevtcvvvdv shedpevkfn
 301 wyvdgvevhn aktkpreeqy nstyrvvsvl tvlhqdwlng keykckvsnk alpapiekti
 361 skakgqprep qvytlppsre emtknqvslt clvkgfypsd iavewesngq pennykttpp
 421 vldsdgsffl yskltvdksr wqqgnvfscs vmhealhnhy tqkslslspg k
```

[0285] Nucleic Acid Sequence Encoding the Full Length Humanized Sh24C05 Hv3-11 Heavy Chain (Humanized Heavy Chain Variable Region and Human IgG1 Constant Region) (SEQ ID NO: 187)

```
   1 atggacatga gagttcctgc tcagctgctc gggttgctgt tgctttggct ccggggtgct
  61 aggtgccaag ttcagctggt ggaatctggc ggtgggcttg taaagccagg aggctccctc
 121 agactgagtt gtgccgcttc agggttcaca ttctccgact atgcgatgtc atggatcagg
 181 caagcacccg ggaaaggact ggagtgggtt agcactatca gcgatggcgg aacgtatacc
 241 tattaccctg acaatgtgaa gggtcggttc accatttcca gggataacgc aaagaacagt
 301 ctctaccttc agatgaacag cctgagggct gaggacaccg ccgtctacta ctgcgcccga
 361 gaatggggag attatgatgg gtttgactat tggggccagg gcactttggt gacagtcagt
 421 tctgcctcaa caaaaggacc aagtgtgttc ccactcgccc ctagcagcaa gagtacatcc
 481 gggggcactg cagcactcgg ctgcctcgtc aaggattatt ttccagagcc agtaaccgtg
 541 agctggaaca gtggagcact cacttctggt gtccatactt ttcctgctgt cctgcaaagc
 601 tctggcctgt actcactcag ctccgtcgtg accgtgccat cttcatctct gggcactcag
 661 acctacatct gtaatgtaaa ccacaagcct agcaatacta aggtcgataa gcgggtggaa
 721 cccaagagct gcgacaagac tcacacttgt cccccatgcc ctgcccctga acttctgggc
 781 ggtcccagcg tctttttgtt cccaccaaag cctaaagata ctctgatgat aagtagaaca
 841 cccgaggtga catgtgttgt tgtagacgtt tcccacgagg acccagaggt taagttcaac
 901 tggtacgttg atggagtcga agtacataat gctaagacca agcctagaga ggagcagtat
 961 aatagtacat accgtgtagt cagtgttctc acagtgctgc accaagactg gctcaacggc
1021 aaagaataca aatgcaaagt gtccaacaaa gcactcccag cccctatcga gaagactatt
1081 agtaaggcaa aggggcagcc tcgtgaacca caggtgtaca ctctgccacc cagtagagag
1141 gaaatgacaa agaaccaagt ctcattgacc tgcctggtga aaggcttcta ccccagcgac
1201 atcgccgttg agtgggagag taacggtcag cctgagaaca attacaagac aacccccca
```

```
1261 gtgctggata gtgacgggtc tttctttctg tacagtaagc tgactgtgga caagtcccgc
1321 tggcagcagg gtaacgtctt cagctgttcc gtgatgcacg aggcattgca caaccactac
1381 acccagaagt cactgagcct gagcccaggg aag
```

[0286] Protein Sequence Defining the Full Length Humanized Sh24C05 Hv3-11 Heavy Chain (Humanized Heavy Chain Variable Region and Human IgG1 Constant Region) (SEQ ID NO: 188)

```
   1 mdmrvpaqll glllwlrga rcqvqlvesg gglvkpggsl rlscaasgft fsdyamswir
  61 qapgkglewv stisdggtyt yypdnvkgrf tisrdnakns lylqmnslra edtavyycar
 121 ewgdydgfdy wgqgtlvtvs sastkgpsvf plapssksts ggtaalgclv kdyfpepvtv
 181 swnsgaltsg vhtfpavlqs sglyslssvv tvpssslgtq tyicnvnhkp sntkvdkrve
 241 pkscdkthtc ppcpapellg gpsvflfppk pkdtlmisrt pevtcvvvdv shedpevkfn
 301 wyvdgvevhn aktkpreeqy nstyrvvsvl tvlhqdwlng keykckvsnk alpapiekti
 361 skakgqprep qvytlppsre emtknqvslt clvkgfypsd iavewesngq pennykttpp
 421 vldsdgsffl yskltvdksr wqqgnvfscs vmhealhnhy tqkslslspg k
```

[0287] Nucleic Acid Sequence Encoding the Full Length Humanized Sh24C05 Hv3-11 N62S IgG1 Heavy Chain (Humanized Heavy Chain Variable Region and Human IgG1 Constant Region) (SEQ ID NO: 189)

```
   1 atggacatga gagttcctgc tcagctgctc gggttgctgt tgctttggct ccggggtgct
  61 aggtgccaag ttcagctggt ggaatctggc ggtgggcttg taaagccagg aggctccctc
 121 agactgagtt gtgccgcttc agggttcaca ttctccgact atgcgatgtc atggatcagg
 181 caagcacccg ggaaaggact ggagtgggtt agcactatca gcgatggcgg aacgtatacc
 241 tattaccctg actccgtgaa gggtcggttc accatttcca gggataacgc aaagaacagt
 301 ctctaccttc agatgaacag cctgagggct gaggacaccg ccgtctacta ctgcgcccga
 361 gaatggggag attatgatgg gtttgactat tggggccagg gcactttggt gacagtcagt
 421 tctgcctcaa caaaaggacc aagtgtgttc ccactcgccc ctagcagcaa gagtacatcc
 481 gggggcactg cagcactcgg ctgcctcgtc aaggattatt ttccagagcc agtaaccgtg
 541 agctggaaca gtggagcact cacttctggt gtccatactt ttcctgctgt cctgcaaagc
 601 tctggcctgt actcactcag ctccgtcgtg accgtgccat cttcatctct gggcactcag
 661 acctacatct gtaatgtaaa ccacaagcct agcaatacta aggtcgataa gcgggtggaa
 721 cccaagagct gcgacaagac tcacacttgt cccccatgcc ctgcccctga acttctgggc
 781 ggtcccagcg tctttttgtt cccaccaaag cctaaagata ctctgatgat aagtagaaca
 841 cccgaggtga catgtgttgt tgtagacgtt tcccacgagg acccagaggt taagttcaac
 901 tggtacgttg atggagtcga agtacataat gctaagacca agcctagaga ggagcagtat
 961 aatagtacat accgtgtagt cagtgttctc acagtgctgc accaagactg gctcaacggc
1021 aaagaataca aatgcaaagt gtccaacaaa gcactcccag cccctatcga gaagactatt
```

```
1081 agtaaggcaa aggggcagcc tcgtgaacca caggtgtaca ctctgccacc cagtagagag
1141 gaaatgacaa agaaccaagt ctcattgacc tgcctggtga aaggcttcta ccccagcgac
1201 atcgccgttg agtgggagag taacggtcag cctgagaaca attacaagac aacccccccа
1261 gtgctggata gtgacgggtc tttctttctg tacagtaagc tgactgtgga caagtcccgc
1321 tggcagcagg gtaacgtctt cagctgttcc gtgatgcacg aggcattgca caaccactac
1381 acccagaagt cactgagcct gagcccaggg aag
```

[0288] Protein Sequence Defining the Full Length Humanized Sh24C05 Hv3-11 N62S IgG1 Heavy Chain (Humanized Heavy Chain Variable Region and Human IgG1 Constant Region) (SEQ ID NO: 190)

```
   1 mdmrvpaqll glllwlrga rcqvqlvesg gglvkpggsl rlscaasgft fsdyamswir
  61 qapgkglewv stisdggtyt yypdsvkgrf tisrdnakns lylqmnslra edtavyycar
 121 ewgdydgfdy wgqgtlvtvs sastkgpsvf plapssksts ggtaalgclv kdyfpepvtv
 181 swnsgaltsg vhtfpavlqs sglyslssvv tvpssslgtq tyicnvnhkp sntkvdkrve
 241 pkscdkthtc ppcpapellg gpsvflfppk pkdtlmisrt pevtcvvvdv shedpevkfn
 301 wyvdgvevhn aktkpreeqy nstyrvvsvl tvlhqdwlng keykckvsnk alpapiekti
 361 skakgqprep qvytlppsre emtknqvslt clvkgfypsd iavewesngq pennykttpp
 421 vldsdgsffl yskltvdksr wqqgnvfscs vmhealhnhy tqkslslspg k
```

[0289] Nucleic Acid Sequence Encoding the Full Length Humanized Sh24C05 Hv3-11 N62S IgG2 Heavy Chain (Humanized Heavy Chain Variable Region and Human IgG2 Constant Region) (SEQ ID NO: 191)

```
   1 atggacatga gagttcctgc tcagctgctc gggttgctgt tgctttggct ccggggtgct
  61 aggtgccaag ttcagctggt ggaatctggc ggtgggcttg taaagccagg aggctccctc
 121 agactgagtt gtgccgcttc agggttcaca ttctccgact atgcgatgtc atggatcagg
 181 caagcacccg ggaaaggact ggagtgggtt agcactatca gcgatggcgg aacgtatacc
 241 tattaccctg actccgtgaa gggtcggttc accatttcca gggataacgc aaagaacagt
 301 ctctaccttc agatgaacag cctgagggct gaggacaccg ccgtctacta ctgcgcccga
 361 gaatggggag attatgatgg gtttgactat tggggccagg gcactttggt gacagtcagt
 421 tctgcctcca ccaagggccc atcggtcttc cccctggcgc cctgctccag gagcacctcc
 481 gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg
 541 tcgtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc
 601 tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcacccag
 661 acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag
 721 cgcaaatgtt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc
 781 ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg
 841 tgcgtggtgg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac
```

```
 901 ggcgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc
 961 cgtgtggtca gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag
1021 tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaaccaaa
1081 gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag
1141 aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag
1201 tgggagagca atgggcagcc ggagaacaac tacaagacca cacctcccat gctggactcc
1261 gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg
1321 aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc
1381 ctctccctgt ctccgggtaa a
```

[0290] Protein Sequence Defining the Full Length Humanized Sh24C05 Hv3-11 N62S IgG2 Heavy Chain (Humanized Heavy Chain Variable Region and Human IgG2 Constant Region) (SEQ ID NO: 192)

```
   1 mdmrvpaqll glllwlrga rcqvqlvesg gglvkpggsl rlscaasgft fsdyamswir
  61 qapgkglewv stisdggtyt yypdsvkgrf tisrdnakns lylqmnslra edtavyycar
 121 ewgdydgfdy wgqgtlvtvs sastkgpsvf plapcsrsts estaalgclv kdyfpepvtv
 181 swnsgaltsg vhtfpavlqs sglyslssvv tvpssnfgtq tytcnvdhkp sntkvdktve
 241 rkccvecppc pappvagpsv flfppkpkdt lmisrtpevt cvvvdvshed pevqfnwyvd
 301 gvevhnaktk preeqfnstf rvvsvltvvh qdwlngkeyk ckvsnkglpa piektisktk
 361 gqprepqvyt lppsreemtk nqvsltclvk gfypsdiave wesngqpenn ykttppmlds
 421 dgsfflyskl tvdksrwqqg nvfscsvmhe alhnhytqks lslspgk
```

[0291] Nucleic Acid Sequence Encoding the Full Length Humanized Sh24C05 Hv3-21 Heavy Chain (Humanized Heavy Chain Variable Region and Human IgG1 Constant Region) (SEQ ID NO: 193)

```
   1 atggacatga gagttcctgc tcagctgctc gggttgctgt tgctttggct ccggggtgct
  61 aggtgcgagg ttcagctggt ggaatctggc ggtgggcttg taaagccagg aggctccctc
 121 agactgagtt gtgccgcttc agggttcaca ttctccgact atgcgatgtc atgggtgcgc
 181 caagcacccg ggaaaggact ggagtgggtt agcactatca gcgatggcgg aacgtatacc
 241 tattaccctg acaatgtgaa gggtcggttc accatttcca gggataacgc aaagaacagt
 301 ctctatttgc agatgaacag cctgagggct gaggacaccg ccgtctacta ctgcgcccga
 361 gaatggggag attatgatgg gtttgactat tggggccagg gcactttggt gacagtcagt
 421 tctgcctcaa caaaaggacc aagtgtgttc ccactcgccc ctagcagcaa gagtacatcc
 481 gggggcactg cagcactcgg ctgcctcgtc aaggattatt ttccagagcc agtaaccgtg
 541 agctggaaca gtggagcact cacttctggt gtccatactt ttcctgctgt cctgcaaagc
 601 tctggcctgt actcactcag ctccgtcgtg accgtgccat cttcatctct gggcactcag
 661 acctacatct gtaatgtaaa ccacaagcct agcaatacta aggtcgataa gcgggtggaa
 721 cccaagagct gcgacaagac tcacacttgt cccccatgcc ctgcccctga acttctgggc
 781 ggtcccagcg tctttttgtt cccaccaaag cctaaagata ctctgatgat aagtagaaca
```

```
 841 cccgaggtga catgtgttgt tgtagacgtt tcccacgagg acccagaggt taagttcaac
 901 tggtacgttg atggagtcga agtacataat gctaagacca agcctagaga ggagcagtat
 961 aatagtacat accgtgtagt cagtgttctc acagtgctgc accaagactg gctcaacggc
1021 aaagaataca aatgcaaagt gtccaacaaa gcactcccag cccctatcga gaagactatt
1081 agtaaggcaa aggggcagcc tcgtgaacca caggtgtaca ctctgccacc cagtagagag
1141 gaaatgacaa agaaccaagt ctcattgacc tgcctggtga aaggcttcta ccccagcgac
1201 atcgccgttg agtgggagag taacggtcag cctgagaaca attacaagac aacccccccа
1261 gtgctggata gtgacgggtc tttctttctg tacagtaagc tgactgtgga caagtcccgc
1321 tggcagcagg gtaacgtctt cagctgttcc gtgatgcacg aggcattgca caaccactac
1381 acccagaagt cactgagcct gagcccaggg aag
```

[0292] Protein Sequence Defining the Full Length Humanized 24C05 Hv3-21 Heavy Chain (Humanized Heavy Chain Variable Region and Human IgG1 Constant Region) (SEQ ID NO: 194)

```
   1 mdmrvpaqll glllwlrga rcevqlvesg gglvkpggsl rlscaasgft fsdyamswvr
  61 qapgkglewv stisdggtyt yypdnvkgrf tisrdnakns lylqmnslra edtavyycar
 121 ewgdydgfdy wgqgtlvtvs sastkgpsvf plapssksts ggtaalgclv kdyfpepvtv
 181 swnsgaltsg vhtfpavlqs sglyslssvv tvpssslgtq tyicnvnhkp sntkvdkrve
 241 pkscdkthtc ppcpapellg gpsvflfppk pkdtlmisrt pevtcvvvdv shedpevkfn
 301 wyvdgvevhn aktkpreeqy nstyrvvsvl tvlhqdwlng keykckvsnk alpapiekti
 361 skakgqprep qvytlppsre emtknqvslt clvkgfypsd iavewesngq pennykttpp
 421 vldsdgsffl yskltvdksr wqqgnvfscs vmhealhnhy tqkslslspg k
```

[0293] Nucleic Acid Sequence Encoding the Full Length Humanized Sh24C05 Hv3-23 Heavy Chain (Humanized Heavy Chain Variable Region and Human IgG1 Constant Region) (SEQ ID NO: 195)

```
   1 atggacatga gagttcctgc tcagctgctc gggttgctgt tgctttggct ccggggtgct
  61 aggtgcgagg ttcagcttct ggaatctggc ggtgggcttg tacagccagg aggctccctc
 121 agactgagtt gtgccgcttc agggttcaca ttctccgact atgcgatgtc atgggtgcgc
 181 caagcacccg ggaaaggact ggagtgggtt tcaactatca gcgatggcgg aacgtatacc
 241 tattaccctg acaatgtgaa gggtcggttc accatttcca gggataacag caagaacaca
 301 ctctatctcc agatgaacag cctgagggct gaggacaccg ccgtctacta ctgcgcccga
 361 gaatggggag attatgatgg gtttgactat tggggccagg gcactttggt gacagtcagt
 421 tctgcctcaa caaaaggacc aagtgtgttc ccactcgccc ctagcagcaa gagtacatcc
 481 gggggcactg cagcactcgg ctgcctcgtc aaggattatt ttccagagcc agtaaccgtg
 541 agctggaaca gtggagcact cacttctggt gtccatactt ttcctgctgt cctgcaaagc
 601 tctggcctgt actcactcag ctccgtcgtg accgtgccat cttcatctct gggcactcag
```

```
 661 acctacatct gtaatgtaaa ccacaagcct agcaatacta aggtcgataa gcgggtggaa
 721 cccaagagct gcgacaagac tcacacttgt cccccatgcc ctgcccctga acttctgggc
 781 ggtcccagcg tctttttgtt cccaccaaag cctaaagata ctctgatgat aagtagaaca
 841 cccgaggtga catgtgttgt tgtagacgtt tcccacgagg acccagaggt taagttcaac
 901 tggtacgttg atggagtcga agtacataat gctaagacca agcctagaga ggagcagtat
 961 aatagtacat accgtgtagt cagtgttctc acagtgctgc accaagactg gctcaacggc
1021 aaagaataca aatgcaaagt gtccaacaaa gcactcccag cccctatcga gaagactatt
1081 agtaaggcaa aggggcagcc tcgtgaacca caggtgtaca ctctgccacc cagtagagag
1141 gaaatgacaa agaaccaagt ctcattgacc tgcctggtga aaggcttcta ccccagcgac
1201 atcgccgttg agtgggagag taacggtcag cctgagaaca attacaagac aacccccccа
1261 gtgctggata gtgacgggtc tttctttctg tacagtaagc tgactgtgga caagtcccgc
1321 tggcagcagg gtaacgtctt cagctgttcc gtgatgcacg aggcattgca caaccactac
1381 acccagaagt cactgagcct gagcccaggg aag
```

[0294] Protein Sequence Defining the Full Length Humanized Sh24C05 Hv3-23 Heavy Chain (Humanized Heavy Chain Variable Region and Human IgG1 Constant Region) (SEQ ID NO: 196)

```
   1 mdmrvpaqll glllwlrga rcevqllesg gglvqpggsl rlscaasgft fsdyamswvr
  61 qapgkglewv stisdggtyt yypdnvkgrf tisrdnsknt lylqmnslra edtavyycar
 121 ewgdydgfdy wgqgtlvtvs sastkgpsvf plapssksts ggtaalgclv kdyfpepvtv
 181 swnsgaltsg vhtfpavlqs sglyslssvv tvpssslgtq tyicnvnhkp sntkvdkrve
 241 pkscdkthtc ppcpapellg gpsvflfppk pkdtlmisrt pevtcvvvdv shedpevkfn
 301 wyvdgvevhn aktkpreeqy nstyrvvsvl tvlhqdwlng keykckvsnk alpapiekti
 361 skakgqprep qvytlppsre emtknqvslt clvkgfypsd iavewesngq pennykttpp
 421 vldsdgsffl yskltvdksr wqqgnvfscs vmhealhnhy tqkslslspg k
```

[0295] Nucleic Acid Sequence Encoding the Full Length Humanized Sh24C05 Hv3-30 Heavy Chain (Humanized Heavy Chain Variable Region and Human IgG1 Constant Region) (SEQ ID NO: 197)

```
   1 atggacatga gagttcctgc tcagctgctc gggttgctgt tgctttggct ccggggtgct
  61 aggtgccagg ttcagctggt ggaatctggc ggtggggtag tacaaccagg acggtccctc
 121 agactgagtt gtgccgcttc agggttcaca ttctccgact atgcgatgtc atgggtgcgc
 181 caagcacccg ggaaaggact ggagtgggtt gccactatca gcgatggcgg aacgtatacc
 241 tattaccctg acaatgtgaa gggtcggttc accatttcca gggataactc aaagaacacc
 301 ctctatctcc aaatgagtag cctgagggct gaggacaccg ccgtctacta ctgcgcccga
 361 gaatggggag attatgatgg gtttgactat tggggccagg gcactttggt gacagtcagt
 421 tctgcctcaa caaaaggacc aagtgtgttc ccactcgccc ctagcagcaa gagtacatcc
```

```
 481 gggggcactg cagcactcgg ctgcctcgtc aaggattatt ttccagagcc agtaaccgtg
 541 agctggaaca gtggagcact cacttctggt gtccatactt ttcctgctgt cctgcaaagc
 601 tctggcctgt actcactcag ctccgtcgtg accgtgccat cttcatctct gggcactcag
 661 acctacatct gtaatgtaaa ccacaagcct agcaatacta aggtcgataa gcgggtggaa
 721 cccaagagct gcgacaagac tcacacttgt cccccatgcc ctgcccctga acttctgggc
 781 ggtcccagcg tctttttgtt cccaccaaag cctaaagata ctctgatgat aagtagaaca
 841 cccgaggtga catgtgttgt tgtagacgtt tcccacgagg acccagaggt taagttcaac
 901 tggtacgttg atggagtcga agtacataat gctaagacca agcctagaga ggagcagtat
 961 aatagtacat accgtgtagt cagtgttctc acagtgctgc accaagactg gctcaacggc
1021 aaagaataca aatgcaaagt gtccaacaaa gcactcccag cccctatcga gaagactatt
1081 agtaaggcaa aggggcagcc tcgtgaacca caggtgtaca ctctgccacc cagtagagag
1141 gaaatgacaa agaaccaagt ctcattgacc tgcctggtga aaggcttcta ccccagcgac
1201 atcgccgttg agtgggagag taacggtcag cctgagaaca attacaagac aacccccccca
1261 gtgctggata gtgacgggtc tttctttctg tacagtaagc tgactgtgga caagtcccgc
1321 tggcagcagg gtaacgtctt cagctgttcc gtgatgcacg aggcattgca caaccactac
1381 acccagaagt cactgagcct gagcccaggg aag
```

[0296] Protein Sequence Defining the Full Length Humanized of Sh24C05 Hv3-30 Heavy Chain (Humanized Heavy Chain Variable Region and Human IgG1 Constant Region) (SEQ ID NO: 198)

```
   1 mdmrvpaqll glllwlrga rcqvqlvesg ggvvqpgrsl rlscaasgft fsdyamswvr
  61 qapgkglewv atisdggtyt yypdnvkgrf tisrdnsknt lylqmsslra edtavyycar
 121 ewgdydgfdy wgqgtlvtvs sastkgpsvf plapssksts ggtaalgclv kdyfpepvtv
 181 swnsgaltsg vhtfpavlqs sglyslssvv tvpssslgtq tyicnvnhkp sntkvdkrve
 241 pkscdkthtc ppcpapellg gpsvflfppk pkdtlmisrt pevtcvvvdv shedpevkfn
 301 wyvdgvevhn aktkpreeqy nstyrvvsvl tvlhqdwlng keykckvsnk alpapiekti
 361 skakgqprep qvytlppsre emtknqvslt clvkgfypsd iavewesngq pennykttpp
 421 vldsdgsffl yskltvdksr wqqgnvfscs vmhealhnhy tqkslslspg k
```

[0297] Nucleic Acid Sequence Encoding the Full Length Humanized Hu24C05 HvA Heavy Chain (Humanized Heavy Chain Variable Region and Human IgG1 Constant Region) (SEQ ID NO: 199)

```
   1 atggacatga gagttcctgc tcagctgctc gggttgctgt tgctttggct ccggggtgct
  61 aggtgcgagg ttcagctggt ggaatctggc ggtgggcttg taaagccagg aggctccctc
 121 agactgagtt gtgccgcttc agggttcaca ttctccgact atgcgatgtc atgggtgcgc
 181 caagcacccg ggaaaggact ggagtgggtt gccactatca gcgatggcgg aacgtatacc
 241 tattaccctg acaatgtgaa gggtcggttc accatttcca gggataacgc aaagaacagt
```

```
 301 ctctaccttc agatgaacag cctgagggct gaggacaccg ccgtctacta ctgcgcccga
 361 gaatggggag attatgatgg gtttgactat tggggccagg gcactttggt gacagtcagt
 421 tctgcctcaa caaaaggacc aagtgtgttc ccactcgccc ctagcagcaa gagtacatcc
 481 gggggcactg cagcactcgg ctgcctcgtc aaggattatt ttccagagcc agtaaccgtg
 541 agctggaaca gtggagcact cacttctggt gtccatactt ttcctgctgt cctgcaaagc
 601 tctggcctgt actcactcag ctccgtcgtg accgtgccat cttcatctct gggcactcag
 661 acctacatct gtaatgtaaa ccacaagcct agcaatacta aggtcgataa gcgggtggaa
 721 cccaagagct gcgacaagac tcacacttgt cccccatgcc ctgcccctga acttctgggc
 781 ggtcccagcg tctttttgtt cccaccaaag cctaaagata ctctgatgat aagtagaaca
 841 cccgaggtga catgtgttgt tgtagacgtt tcccacgagg acccagaggt taagttcaac
 901 tggtacgttg atggagtcga agtacataat gctaagacca agcctagaga ggagcagtat
 961 aatagtacat accgtgtagt cagtgttctc acagtgctgc accaagactg gctcaacggc
1021 aaagaataca aatgcaaagt gtccaacaaa gcactcccag cccctatcga gaagactatt
1081 agtaaggcaa aggggcagcc tcgtgaacca caggtgtaca ctctgccacc cagtagagag
1141 gaaatgacaa agaaccaagt ctcattgacc tgcctggtga aaggcttcta ccccagcgac
1201 atcgccgttg agtgggagag taacggtcag cctgagaaca attacaagac aacccccccа
1261 gtgctggata gtgacgggtc tttctttctg tacagtaagc tgactgtgga caagtcccgc
1321 tggcagcagg gtaacgtctt cagctgttcc gtgatgcacg aggcattgca caaccactac
1381 acccagaagt cactgagcct gagcccaggg aag
```

[0298] Protein Sequence Defining the Full Length Humanized Hu24C05 HvA Heavy Chain (Humanized Heavy Chain Variable Region and Human IgG1 Constant Region) (SEQ ID NO: 200)

```
   1 mdmrvpaqll glllwlrga rcevqlvesg gglvkpggsl rlscaasgft fsdyamswvr
  61 qapgkglewv atisdggtyt yypdnvkgrf tisrdnakns lylqmnslra edtavyycar
 121 ewgdydgfdy wgqgtlvtvs sastkgpsvf plapssksts ggtaalgclv kdyfpepvtv
 181 swnsgaltsg vhtfpavlqs sglyslssvv tvpssslgtq tyicnvnhkp sntkvdkrve
 241 pkscdkthtc ppcpapellg gpsvflfppk pkdtlmisrt pevtcvvvdv shedpevkfn
 301 wyvdgvevhn aktkpreeqy nstyrvvsvl tvlhqdwlng keykckvsnk alpapiekti
 361 skakgqprep qvytlppsre emtknqvslt clvkgfypsd iavewesngq pennykttpp
 421 vldsdgsffl yskltvdksr wqqgnvfscs vmhealhnhy tqkslslspg k
```

[0299] Nucleic Acid Sequence Encoding the Full Length Humanized Sh24C05 Kv1-9 Light Chain (Humanized Kappa Chain Variable Region and Human Constant Region) (SEQ ID NO: 201)

```
   1 atggacatga gggtgcccgc tcaactgctg gggctgctgc tgctgtggct gagaggagct
  61 cgttgcgata ttcagttgac ccaatcacct agcttcctct cagcttccgt gggcgacaga
```

```
121 gttaccataa cctgtcgggc aagccaggag atttctgggt acctgtcctg gtaccaacag
181 aagcccggaa aagcccctaa gctgttgatc tatgctgcgt caaccttgga tagcggtgtc
241 ccgagtcgat tctccggttc tggctccgga acagagttca ctctgacaat ttctagcctt
301 cagccagaag atttcgccac gtactattgc ctccagtacg acagctatcc ctatacattt
361 gggcagggca ctaaactgga gatcaaacgc acagttgctg cccccagcgt gttcattttc
421 ccacctagcg atgagcagct gaaaagcggt actgcctctg tcgtatgctt gctcaacaac
481 ttttacccac gtgaggctaa ggtgcagtgg aaagtggata atgcacttca atctggaaac
541 agtcaagagt ccgtgacaga acaggacagc aaagactcaa cttattcact ctcttccacc
601 ctgactctgt ccaaggcaga ctatgaaaaa cacaaggtat acgcctgcga ggttacacac
661 cagggtttgt ctagtcctgt caccaagtcc ttcaataggg gcgaatgt
```

[0300] Protein Sequence Defining the Full Length Humanized Sh24C05 Kv1-9 Light Chain (Humanized Kappa Chain Variable Region and Human Constant Region) (SEQ ID NO: 202)

```
  1 mdmrvpaqll glllwlrga rcdiqltqsp sflsasvgdr vtitcrasqe isgylswyqq
 61 kpgkapklli yaastldsgv psrfsgsgsg teftltissl qpedfatyyc lqydsypytf
121 gqgtkleikr tvaapsvfif ppsdeqlksg tasvvcllnn fypreakvqw kvdnalqsgn
181 sqesvteqds kdstyslsst ltlskadyek hkvyacevth qglsspvtks fnrgec
```

[0301] Nucleic Acid Sequence Encoding the Full Length Humanized Sh24C05 Kv1-16 Light Chain (Humanized Kappa Chain Variable Region and Human Constant Region) (SEQ ID NO: 203)

```
  1 atggacatga gggtgcccgc tcaactgctg gggctgctgc tgctgtggct gagaggagct
 61 cgttgcgata ttcagatgac ccaatcacct agcagtctct cagcttccgt gggcgacaga
121 gttaccataa cctgtcgggc aagccaggag atttctgggt acctgtcctg gtttcaacag
181 aagcccggaa aggccccgaa gagcttgatc tatgctgcgt caaccttgga tagcggtgtc
241 ccgagtcgat tctccggttc tggctccgga accgacttta ctctgacaat ttctagcctt
301 cagccagaag atttcgccac gtactattgc ctccagtacg acagctatcc ctatacattt
361 gggcagggca ctaaactgga gatcaaacgc acagttgctg cccccagcgt gttcattttc
421 ccacctagcg atgagcagct gaaaagcggt actgcctctg tcgtatgctt gctcaacaac
481 ttttacccac gtgaggctaa ggtgcagtgg aaagtggata atgcacttca atctggaaac
541 agtcaagagt ccgtgacaga acaggacagc aaagactcaa cttattcact ctcttccacc
601 ctgactctgt ccaaggcaga ctatgaaaaa cacaaggtat acgcctgcga ggttacacac
661 cagggtttgt ctagtcctgt caccaagtcc ttcaataggg gcgaatgt
```

[0302] Protein Sequence Defining the Full Length Humanized Sh24C05 Kv1-16 Light Chain (Humanized Kappa Chain Variable Region and Human Constant Region) (SEQ ID NO: 204)

```
  1 mdmrvpaqll glllwlrga rcdiqmtqsp sslsasvgdr vtitcrasqe isgylswfqq
 61 kpgkapksli yaastldsgv psrfsgsgsg tdftltissl qpedfatyyc lqydsypytf
121 gqgtkleikr tvaapsvfif ppsdeqlksg tasvvcllnn fypreakvqw kvdnalqsgn
181 sqesvteqds kdstyslsst ltlskadyek hkvyacevth qglsspvtks fnrgec
```

[0303] Nucleic Acid Sequence Encoding the Full Length Humanized Sh24C05 Kv1-17 Light Chain (Humanized Kappa Chain Variable Region and Human Constant Region) (SEQ ID NO: 205)

```
  1 atggacatga gggtgcccgc tcaactgctg gggctgctgc tgctgtggct gagaggagct
 61 cgttgcgata ttcagatgac ccaatcacct agcagtctct cagcttccgt gggcgacaga
121 gttaccataa cctgtcgggc aagccaggag atttctgggt acctgtcctg gtatcaacag
181 aagcccggaa aagccccaaa gaggttgatc tatgctgcgt caaccttgga tagcggtgtc
241 ccgagtcgat tctccggttc tggctccgga accgagttca ctctgacaat ttctagcctt
301 cagccagaag atttcgccac gtactattgc ctccagtacg acagctatcc ctatacattt
361 gggcagggca ctaaactgga gatcaaacgc acagttgctg cccccagcgt gttcattttc
421 ccacctagcg atgagcagct gaaaagcggt actgcctctg tcgtatgctt gctcaacaac
481 ttttacccac gtgaggctaa ggtgcagtgg aaagtggata atgcacttca atctggaaac
541 agtcaagagt ccgtgacaga acaggacagc aaagactcaa cttattcact ctcttccacc
601 ctgactctgt ccaaggcaga ctatgaaaaa cacaaggtat acgcctgcga ggttacacac
661 cagggtttgt ctagtcctgt caccaagtcc ttcaataggg gcgaatgt
```

[0304] Protein Sequence Defining the Full Length Humanized Sh24C05 Kv1-17 Light Chain (Humanized Kappa Chain Variable Region and Human Constant Region) (SEQ ID NO: 206)

```
  1 mdmrvpaqll glllwlrga rcdiqmtqsp sslsasvgdr vtitcrasqe isgylswyqq
 61 kpgkapkrli yaastldsgv psrfsgsgsg teftltissl qpedfatyyc lqydsypytf
121 gqgtkleikr tvaapsvfif ppsdeqlksg tasvvcllnn fypreakvqw kvdnalqsgn
181 sqesvteqds kdstyslsst ltlskadyek hkvyacevth qglsspvtks fnrgec
```

[0305] Nucleic Acid Sequence Encoding the Full Length Humanized sh24C05 Kv1-33 Light Chain (Humanized Kappa Chain Variable Region and Human Constant Region) (SEQ ID NO: 207)

```
   1 atggacatga gggtgcccgc tcaactgctg gggctgctgc tgctgtggct gagaggagct
  61 cgttgcgata ttcagatgac ccaatcacct agcagtctct cagcttccgt gggcgacaga
 121 gttaccataa cctgtcgggc aagccaggag atttctgggt acctgtcctg gtaccaacag
 181 aagcccggaa aggcccccaa gctgttgatc tatgctgcgt caaccttgga tagcggtgtc
 241 ccgagtcgat tctccggttc tggctccgga acagacttta cttttacaat ttctagcctt
 301 cagccagagg acatcgccac gtactattgc ctccagtacg acagctatcc ctatacattt
 361 gggcagggca ctaaactgga gatcaaacgc acagttgctg cccccagcgt gttcattttc
 421 ccacctagcg atgagcagct gaaaagcggt actgcctctg tcgtatgctt gctcaacaac
 481 ttttacccac gtgaggctaa ggtgcagtgg aaagtggata atgcacttca atctggaaac
 541 agtcaagagt ccgtgacaga acaggacagc aaagactcaa cttattcact ctcttccacc
 601 ctgactctgt ccaaggcaga ctatgaaaaa cacaaggtat acgcctgcga ggttacacac
 661 cagggtttgt ctagtcctgt caccaagtcc ttcaataggg gcgaatgt
```

[0306] Protein Sequence Defining the Full Length Humanized Sh24C05 Kv1-33 Light Chain (Humanized Kappa Chain Variable Region and Human Constant Region) (SEQ ID NO: 208)

```
   1 mdmrvpaqll glllwlrga rcdiqmtqsp sslsasvgdr vtitcrasqe isgylswyqq
  61 kpgkapklli yaastldsgv psrfsgsgsg tdftftissl qpediatyyc lqydsypytf
 121 gqgtkleikr tvaapsvfif ppsdeqlksg tasvvcllnn fypreakvqw kvdnalqsgn
 181 sqesvteqds kdstyslsst ltlskadyek hkvyacevth qglsspvtks fnrgec
```

[0307] Nucleic Acid Sequence Encoding the Full Length Humanzied Sh24C05 Kv1-39 Light Chain (Humanized Kappa Chain Variable Region and Human Constant Region) (SEQ ID NO: 209)

```
   1 atggacatga gggtgcccgc tcaactgctg gggctgctgc tgctgtggct gagaggagct
  61 cgttgcgata ttcagatgac ccaatcacct agcagtctct cagcttccgt gggcgacaga
 121 gttaccataa cctgtcgggc aagccaggag atttctgggt acctgtcctg gtatcaacag
 181 aagcccggaa aagcccctaa gctgttgatc tatgctgcgt caaccttgga tagcggtgtc
 241 ccgagtcgat tctccggttc tggctccgga actgacttca ctctgacaat ttctagcctt
 301 cagccagaag atttcgccac gtactattgc ctccagtacg acagctatcc ctatacattt
 361 gggcagggca ctaaactgga gatcaaacgc acagttgctg cccccagcgt gttcattttc
 421 ccacctagcg atgagcagct gaaaagcggt actgcctctg tcgtatgctt gctcaacaac
 481 ttttacccac gtgaggctaa ggtgcagtgg aaagtggata atgcacttca atctggaaac
```

```
541 agtcaagagt ccgtgacaga acaggacagc aaagactcaa cttattcact ctcttccacc
601 ctgactctgt ccaaggcaga ctatgaaaaa cacaaggtat acgcctgcga ggttacacac
661 cagggtttgt ctagtcctgt caccaagtcc ttcaataggg gcgaatgt
```

[0308] Protein Sequence Defining the Full Length Humanized Sh24C05 Kv1-39 Light Chain (Humanized Kappa Chain Variable Region and Human Constant Region) (SEQ ID NO: 210)

```
  1 mdmrvpaqll glllwlrga rcdiqmtqsp sslsasvgdr vtitcrasqe isgylswyqq
 61 kpgkapklli yaastldsgv psrfsgsgsg tdftltissl qpedfatyyc lqydsypytf
121 gqgtkleikr tvaapsvfif ppsdeqlksg tasvvcllnn fypreakvqw kvdnalqsgn
181 sqesvteqds kdstyslsst ltlskadyek hkvyacevth qglsspvtks fnrgec
```

[0309] Nucleic Acid Sequence Encoding the Full Length Humanized Hu24C05 KvA Light Chain (Humanized Kappa Chain Variable Region and Human Constant Region) (SEQ ID NO: 211)

```
  1 atggacatga gggtgcccgc tcaactgctg gggctgctgc tgctgtggct gagaggagct
 61 cgttgcgata ttcagatgac ccaatcacct agcagtctct cagcttccgt gggcgacaga
121 gttaccataa cctgtcgggc aagccaggag atttctgggt acctgtcctg gctgcaacag
181 aagccccgag gcgccatcaa gaggttgatc tatgctgcgt caaccttgga tagcggtgtc
241 ccgagtcgat tctccggttc tggctccgga agtgactaca ctctgacaat ttctagcctt
301 cagccagaag atttcgccac gtactattgc ctccagtacg acagctatcc ctatacattt
361 gggcagggca ctaaactgga gatcaaacgc acagttgctg cccccagcgt gttcattttc
421 ccacctagcg atgagcagct gaaaagcggt actgcctctg tcgtatgctt gctcaacaac
481 ttttacccac gtgaggctaa ggtgcagtgg aaagtggata atgcacttca atctggaaac
541 agtcaagagt ccgtgacaga acaggacagc aaagactcaa cttattcact ctcttccacc
601 ctgactctgt ccaaggcaga ctatgaaaaa cacaaggtat acgcctgcga ggttacacac
661 cagggtttgt ctagtcctgt caccaagtcc ttcaataggg gcgaatgt
```

[0310] Protein Sequence Defining the Full Length Humanized Hu24C05 KvA Light Chain (Humanized Kappa Chain Variable Region and Human Constant Region) (SEQ ID NO: 212)

```
  1 mdmrvpaqll glllwlrga rcdiqmtqsp sslsasvgdr vtitcrasqe isgylswlqq
 61 kpggaikrli yaastldsgv psrfsgsgsg sdytltissl qpedfatyyc lqydsypytf
121 gqgtkleikr tvaapsvfif ppsdeqlksg tasvvcllnn fypreakvqw kvdnalqsgn
181 sqesvteqds kdstyslsst ltlskadyek hkvyacevth qglsspvtks fnrgec
```

[0311] For convenience, Table 13 provides a concordance chart showing the SEQ ID NO. of each sequence discussed in this Example.

Table 13

SEQ ID NO.	Nucleic Acid or Protein
175	Human IgG1 constant—nucleic acid
176	Human IgG1 constant—protein
177	Human IgG2 constant—nucleic acid
178	Human IgG2 constant—protein
179	Human Kappa constant—nucleic acid
180	Human Kappa constant—protein
181	Chimeric 24C05 Mouse Heavy Chain Variable + Human IgG1 constant—nucleic acid
182	Chimeric 24C05 Mouse Heavy Chain Variable + Human IgG1 constant—protein
183	Chimeric 24C05 Mouse Light Chain Variable + Human Kappa constant—nucleic acid
184	Chimeric 24C05 Mouse Light Chain Variable + Human Kappa constant—protein
185	Humanized Sh24C05 Hv3-7 Heavy Human Variable + Human IgG1 constant—nucleic acid
186	Humanized Sh24C05 Hv3-7 Heavy Human Variable + Human IgG1 constant—protein
187	Humanized Sh24C05 Hv3-11 Heavy Human Variable + Human IgG1 constant—nucleic acid
188	Humanized Sh24C05 Hv3-11 Heavy Human Variable + Human IgG1 constant—protein
189	Humanized Sh24C05 Hv3-11 N62S IgG1 Heavy Human Variable + Human IgG1 constant—nucleic acid
190	Humanized Sh24C05 Hv3-11 N62S IgG1 Heavy Human Variable + Human IgG1 constant—protein
191	Humanized Sh24C05 Hv3-11 N62S IgG2 Heavy Human Variable + Human IgG2 constant—nucleic acid
192	Humanized Sh24C05 Hv3-11 N62S IgG2 Heavy Human Variable + Human IgG2 constant—protein

Table 13 (Cont.)

SEQ ID NO.	Nucleic Acid or Protein
193	Humanized Sh24C05 Hv3-21Heavy Human Variable + Human IgG1 constant—nucleic acid
194	Humanized Sh24C05 Hv3-21 Heavy Human Variable + Human IgG1 constant—protein
195	Humanized Sh24C05 Hv3-23 Heavy Human Variable + Human IgG1 constant—nucleic acid
196	Humanized Sh24C05 Hv3-23 Heavy Human Variable + Human IgG1 constant—protein
197	Humanized Sh24C05 Hv3-30 Heavy Human Variable + Human IgG1 constant—nucleic acid
198	Humanized Sh24C05 Hv3-30 Heavy Human Variable + Human IgG1 constant—protein
199	Humanized Hu24C05 HvA Heavy Human Variable + Human IgG1 constant—nucleic acid
200	Humanized Hu24C05 HvA Heavy Human Variable + Human IgG1 constant—protein
201	Humanized Sh24C05 Kv1-9 Human Variable + Human Kappa constant—nucleic acid
202	Humanized Sh24C05 Kv1-9 Human Variable + Human Kappa constant—protein
203	Humanized Sh24C05 Kv1-16 Human Variable + Human Kappa constant—nucleic acid
204	Humanized Sh24C05 Kv1-16 Human Variable + Human Kappa constant—protein
205	Humanized Sh24C05 Kv1-17 Human Variable + Human Kappa constant—nucleic acid
206	Humanized Sh24C05 Kv1-17 Human Variable + Human Kappa constant—protein
207	Humanized Sh24C05 Kv1-33 Human Variable + Human Kappa constant—nucleic acid
208	Humanized Sh24C05 Kv1-33 Human Variable + Human Kappa constant—protein
209	Humanized Sh24C05 Kv1-39 Human Variable + Human Kappa constant—nucleic acid
210	Humanized Sh24C05 Kv1-39 Human Variable + Human Kappa constant—protein

Table 13 (Cont.)

SEQ ID NO.	Nucleic Acid or Protein
211	Humanized Hu24C05 KvA Human Variable + Human Kappa constant—nucleic acid
212	Humanized Hu24C05 KvA Human Variable + Human Kappa constant—protein

[0312] Table 14 below shows antibodies containing chimeric immunoglobulin heavy and light chains and each of the possible combinations of the full-length humanized immunoglobulin heavy and light chains.

Table 14

Antibody Name	Light Chain	Heavy Chain
Sh24C05-1	24C05 Chimeric Kappa (SEQ ID NO: 184)	GP203 24C05 Chimeric Heavy IgG1 (SEQ ID NO: 182)
Sh24C05-14	Hu24C05 KvA Kappa (SEQ ID NO: 212)	Hu24C05 HvA IgG1 (SEQ ID NO: 200)
Sh24C05-15	Hu24C05 KvA Kappa (SEQ ID NO: 212)	Sh24C05 Hv3-21 Heavy IgG1 (SEQ ID NO: 194)
Sh24C05-16	Hu24C05 KvA Kappa (SEQ ID NO: 212)	Sh24C05 Hv3-23 Heavy IgG1 (SEQ ID NO: 196)
Sh24C05-17	Hu24C05 KvA Kappa (SEQ ID NO: 212)	Sh24C05 Hv3-30 Heavy IgG1 (SEQ ID NO: 198)
Sh24C05-18	Hu24C05 KvA Kappa (SEQ ID NO: 212)	Sh24C05 Hv3-7 Heavy IgG1 (SEQ ID NO: 186)
Sh24C05-19	Hu24C05 KvA Kappa (SEQ ID NO: 212)	Sh24C05 Hv3-11 Heavy IgG1 (SEQ ID NO: 188)
Sh24C05-19 N62S IgG1	Hu24C05 KvA Kappa (SEQ ID NO: 212)	Sh24C05 Hv3-11 N62S Heavy IgG1 (SEQ ID NO: 190)
Sh24C05-19 N62S IgG2	Hu24C05 KvA Kappa (SEQ ID NO: 212)	Sh24C05 Hv3-11 N62S Heavy IgG2 (SEQ ID NO: 192)
Sh24C05-20	Sh24C05 Kv1-16 Kappa (SEQ ID NO: 204)	Hu24C05 HvA IgG1 (SEQ ID NO: 200)

Table 14 (Cont.)

Antibody Name	Light Chain	Heavy Chain
Sh24C05-21	Sh24C05 Kv1-16 Kappa (SEQ ID NO: 204)	Sh24C05 Hv3-21 Heavy IgG1 (SEQ ID NO: 194)
Sh24C05-22	Sh24C05 Kv1-16 Kappa (SEQ ID NO: 204)	Sh24C05 Hv3-23 Heavy IgG1 (SEQ ID NO: 196)
Sh24C05-23	Sh24C05 Kv1-16 Kappa (SEQ ID NO: 204)	Sh24C05 Hv3-30 Heavy IgG1 (SEQ ID NO: 198)
Sh24C05-24	Sh24C05 Kv1-16 Kappa (SEQ ID NO: 204)	Sh24C05 Hv3-7 Heavy IgG1 (SEQ ID NO: 186)
Sh24C05-25	Sh24C05 Kv1-16 Kappa (SEQ ID NO: 204)	Sh24C05 Hv3-11 Heavy IgG1 (SEQ ID NO: 188)
Sh24C05-25 N62S IgG1	Sh24C05 Kv1-16 Kappa (SEQ ID NO: 204)	Sh24C05 Hv3-11 N62S Heavy IgG1 (SEQ ID NO: 190)
Sh24C05-25 N62S IgG2	Sh24C05 Kv1-16 Kappa (SEQ ID NO: 204)	Sh24C05 Hv3-11 N62S Heavy IgG2 (SEQ ID NO: 192)
Sh24C05-26	Sh24C05 Kv1-17 Kappa (SEQ ID NO: 206)	Hu24C05 HvA IgG1 (SEQ ID NO: 200)
Sh24C05-27	Sh24C05 Kv1-17 Kappa (SEQ ID NO: 206)	Sh24C05 Hv3-21 Heavy IgG1 (SEQ ID NO: 194)
Sh24C05-28	Sh24C05 Kv1-17 Kappa (SEQ ID NO: 206)	Sh24C05 Hv3-23 Heavy IgG1 (SEQ ID NO: 196)
Sh24C05-29	Sh24C05 Kv1-17 Kappa (SEQ ID NO: 206)	Sh24C05 Hv3-30 Heavy IgG1 (SEQ ID NO: 198)
Sh24C05-30	Sh24C05 Kv1-17 Kappa (SEQ ID NO: 206)	Sh24C05 Hv3-7 Heavy IgG1 (SEQ ID NO: 186)
Sh24C05-31	Sh24C05 Kv1-17 Kappa (SEQ ID NO: 206)	Sh24C05 Hv3-11 Heavy IgG1 (SEQ ID NO: 188)
Sh24C05-31 N62S IgG1	Sh24C05 Kv1-17 Kappa (SEQ ID NO: 206)	Sh24C05 Hv3-11 N62S Heavy IgG1 (SEQ ID NO: 190)
Sh24C05-31 N62S IgG2	Sh24C05 Kv1-17 Kappa (SEQ ID NO: 206)	Sh24C05 Hv3-11 N62S Heavy IgG2 (SEQ ID NO: 192)

Table 14 (Cont.)

Antibody Name	Light Chain	Heavy Chain
Sh24C05-32	Sh24C05 Kv1-33 Kappa (SEQ ID NO: 208)	Hu24C05 HvA IgG1 (SEQ ID NO: 200)
Sh24C05-33	Sh24C05 Kv1-33 Kappa (SEQ ID NO: 208)	Sh24C05 Hv3-21 Heavy IgG1 (SEQ ID NO: 194)
Sh24C05-34	Sh24C05 Kv1-33 Kappa (SEQ ID NO: 208)	Sh24C05 Hv3-23 Heavy IgG1 (SEQ ID NO: 196)
Sh24C05-35	Sh24C05 Kv1-33 Kappa (SEQ ID NO: 208)	Sh24C05 Hv3-30 Heavy IgG1 (SEQ ID NO: 198)
Sh24C05-36	Sh24C05 Kv1-33 Kappa (SEQ ID NO: 208)	Sh24C05 Hv3-7 Heavy IgG1 (SEQ ID NO: 186)
Sh24C05-37	Sh24C05 Kv1-33 Kappa (SEQ ID NO: 208)	Sh24C05 Hv3-11 Heavy IgG1 (SEQ ID NO: 188)
Sh24C05-37 N62S IgG1	Sh24C05 Kv1-33 Kappa (SEQ ID NO: 208)	Sh24C05 Hv3-11 N62S Heavy IgG1 (SEQ ID NO: 190)
Sh24C05-37 N62S IgG2	Sh24C05 Kv1-33 Kappa (SEQ ID NO: 208)	Sh24C05 Hv3-11 N62S Heavy IgG2 (SEQ ID NO: 192)
Sh24C05-38	Sh24C05 Kv1-9 Kappa (SEQ ID NO: 202)	Hu24C05 HvA IgG1 (SEQ ID NO: 200)
Sh24C05-39	Sh24C05 Kv1-9 Kappa (SEQ ID NO: 202)	Sh24C05 Hv3-21 Heavy IgG1 (SEQ ID NO: 194)
Sh24C05-40	Sh24C05 Kv1-9 Kappa (SEQ ID NO: 202)	Sh24C05 Hv3-23 Heavy IgG1 (SEQ ID NO: 196)
Sh24C05-41	Sh24C05 Kv1-9 Kappa (SEQ ID NO: 202)	Sh24C05 Hv3-30 Heavy IgG1 (SEQ ID NO: 198)
Sh24C05-42	Sh24C05 Kv1-9 Kappa (SEQ ID NO: 202)	Sh24C05 Hv3-7 Heavy IgG1 (SEQ ID NO: 186)
Sh24C05-43	Sh24C05 Kv1-9 Kappa (SEQ ID NO: 202)	Sh24C05 Hv3-11 Heavy IgG1 (SEQ ID NO: 188)
Sh24C05-43 N62S IgG1	Sh24C05 Kv1-9 Kappa (SEQ ID NO: 202)	Sh24C05 Hv3-11 N62S Heavy IgG1 (SEQ ID NO: 190)

Table 14 (Cont.)

Antibody Name	Light Chain	Heavy Chain
Sh24C05-43 N62S IgG2	Sh24C05 Kv1-9 Kappa (SEQ ID NO: 202)	Sh24C05 Hv3-11 N62S Heavy IgG2 (SEQ ID NO: 192)
Sh24C05-44	Sh24C05 Kv1-39 Kappa (SEQ ID NO: 210)	Hu24C05 HvA IgG1 (SEQ ID NO: 200)
Sh24C05-45	Sh24C05 Kv1-39 Kappa (SEQ ID NO: 210)	Sh24C05 Hv3-21 Heavy IgG1 (SEQ ID NO: 194)
Sh24C05-46	Sh24C05 Kv1-39 Kappa (SEQ ID NO: 210)	Sh24C05 Hv3-23 Heavy IgG1 (SEQ ID NO: 196)
Sh24C05-47	Sh24C05 Kv1-39 Kappa (SEQ ID NO: 210)	Sh24C05 Hv3-30 Heavy IgG1 (SEQ ID NO: 198)
Sh24C05-48	Sh24C05 Kv1-39 Kappa (SEQ ID NO: 210)	Sh24C05 Hv3-7 Heavy IgG1 (SEQ ID NO: 186)
Sh24C05-49	Sh24C05 Kv1-39 Kappa (SEQ ID NO: 210)	Sh24C05 Hv3-11 Heavy IgG1 (SEQ ID NO: 188)
Sh24C05-49 N62S IgG1	Sh24C05 Kv1-39 Kappa (SEQ ID NO: 210)	Sh24C05 Hv3-11 N62S Heavy IgG1 (SEQ ID NO: 190)
Sh24C05-49 N62S IgG2	Sh24C05 Kv1-39 Kappa (SEQ ID NO: 210)	Sh24C05 Hv3-11 N62S Heavy IgG2 (SEQ ID NO: 192)

[0313] The antibody construct containing the full length chimeric heavy and light chains is designated below:

Chimeric 24C05 = Full Length Chimeric 24C05 Heavy Chain (Mouse Variable Region and Human IgG1 Constant Region) (SEQ ID NO: 182) plus Full Length Chimeric 24C05 Light Chain (Mouse Variable Region and Human Kappa Constant Region) (SEQ ID NO: 184)

[0314] Four of the possible antibody constructs containing the full length immunoglobulin heavy and light chains containing humanized variable regions are designated below:

Sh24C05-25 N62S IgG1 = Humanized Sh24C05 Hv3-11 N62S Heavy Chain Variable Region and Human IgG1 Constant Region (SEQ ID NO: 190) plus Sh24C05 Kv1-16 Light Chain Variable Region and Human Kappa Constant Region (SEQ ID NO: 204)

Sh24C05-25 N62S IgG2 = Humanized Sh24C05 Hv3-11 N62S Heavy Chain Variable Region and Human IgG2 Constant Region (SEQ ID NO: 192) plus Sh24C05 Kv1-16 Light Chain Variable Region and Human Kappa Constant Region (SEQ ID NO: 204)

Sh24C05-31 N62S IgG1 = Humanized Sh24C05 Hv3-11 N62S Heavy Chain Variable Region and Human IgG1 Constant Region (SEQ ID NO: 190) plus Sh24C05 Kv1-17 Light Chain Variable Region and Human Kappa Constant Region (SEQ ID NO: 206)

Sh24C05-31 N62S IgG2 = Humanized Sh24C05 Hv3-11 N62S Heavy Chain Variable Region and Human IgG2 Constant Region (SEQ ID NO: 192) plus Sh24C05 Kv1-17 Light Chain Variable Region and Human Kappa Constant Region (SEQ ID NO: 206)

B. Binding Affinities of Humanized and Chimeric Anti-ErbB3 Monoclonal Antibodies

[0315] The binding affinities and kinetics of interaction of monoclonal antibodies produced in Example 12 against recombinant human ErbB3 monomeric protein (cleaved rhErbB3) were measured by surface plasmon resonance using a Biacore® T100 (Biacore) instrument. Monomeric ErbB3 was obtained by protease cleavage of rhErbB3-Fc (R&D Systems, Cat. No. 348-RB).

[0316] Goat anti-human IgG Fc (Jackson ImmunoResearch, Catalog No. 109-005-098) was immobilized on carboxymethylated dextran CM4 sensor chips (Biacore, Catalog No. BR-1005-34) by amine coupling (Biacore, Catalog No. BR-1000-50) using a standard coupling protocol according to the vendor's instructions. The analyses were performed at 37°C using PBS (Invitrogen, Catalog No. 14040-133) containing 0.05% surfactant P20 (Biacore, Catalog No. BR-1000-54) as running buffer.

[0317] The antibodies were captured in individual flow cells at a flow rate of 60 µl/minute. Injection time was varied for each antibody to yield an R_{max} between 30 and 60 RU. Buffer or cleaved rhErbB3 diluted in running buffer was injected sequentially over a reference

surface (no antibody captured) and the active surface (antibody to be tested) for 300 seconds at 60 µl/minute. The dissociation phase was monitored for up to 1200 seconds. The surface was then regenerated with two 60 second injections of Glycine pH 2.25 (made from Glycine pH 2.0 (Biacore, Catalog No. BR-1003-55) and pH 2.5 (Biacore, Catalog No. BR-1003-56)) at 60 µl/minute. For the initial screening, only one or two concentrations of cleaved rhErbB3 were tested, typically 5.0 and 1.25 nM (results are summarized in Table 15).

[0318] Kinetic parameters were determined using the kinetic function of the BIAevaluation software (Biacore) with double reference subtraction. Kinetic parameters for each antibody, k_a (association rate constant), k_d (dissociation rate constant) and K_D (equilibrium dissociation constant) were determined. The initial monoclonal antibodies were screened using cell culture media supernatant containing secreted antibody, and kinetic values of the monoclonal antibodies on cleaved rhErbB3 at 37°C are summarized in Table 15.

Table 15

Antibody	k_a (1/Ms)	k_d (1/s)	K_D (M)	n
Sh24C05-1	2.52E+06	4.48E-04	1.78E-10	3
Sh24C05-14	2.88E+06	4.98E-04	1.73E-10	2
Sh24C05-15	2.67E+06	4.99E-04	1.87E-10	2
Sh24C05-16	2.75E+06	4.04E-04	1.47E-10	2
Sh24C05-17	2.79E+06	4.17E-04	1.50E-10	2
Sh24C05-18	2.88E+06	4.63E-04	1.61E-10	2
Sh24C05-19	3.00E+06	2.55E-04	8.55E-11	2
Sh24C05-20	2.67E+06	5.91E-04	2.21E-10	2
Sh24C05-21	3.11E+06	6.62E-04	2.20E-10	2
Sh24C05-22	2.79E+06	6.01E-04	2.16E-10	2
Sh24C05-23	2.79E+06	7.21E-04	2.63E-10	2
Sh24C05-24	2.90E+06	6.28E-04	2.18E-10	2
Sh24C05-25	2.63E+06	4.59E-04	1.75E-10	2
Sh24C05-26	3.36E+06	7.39E-04	2.20E-10	2
Sh24C05-27	3.34E+06	7.98E-04	2.40E-10	2
Sh24C05-28	3.26E+06	6.14E-04	1.89E-10	2

Table 15 (cont.)

Antibody	k_a (1/Ms)	k_d (1/s)	K_D (M)	n
Sh24C05-29	3.25E+06	5.88E-04	1.82E-10	2
Sh24C05-30	4.48E+06	7.87E-04	1.90E-10	2
Sh24C05-31	3.47E+06	2.92E-04	8.65E-11	2
Sh24C05-32	9.98E+06	6.02E-03	6.03E-10	1
Sh24C05-33	4.02E+06	4.33E-03	1.08E-09	1
Sh24C05-34	1.09E+07	6.00E-03	5.52E-10	1
Sh24C05-35	8.44E+06	5.53E-03	6.55E-10	1
Sh24C05-36	5.18E+06	4.34E-03	8.37E-10	1
Sh24C05-37	5.94E+06	2.00E-03	3.74E-10	2
Sh24C05-38	2.71E+07	1.54E-02	5.67E-10	1
Sh24C05-39	1.18E+07	9.67E-03	8.19E-10	1
Sh24C05-40	2.11E+07	1.06E-02	5.03E-10	1
Sh24C05-41	1.81E+07	1.21E-02	6.69E-10	1
Sh24C05-42	7.35E+06	6.82E-03	9.27E-10	1
Sh24C05-43	6.16E+06	3.58E-03	5.82E-10	1
Sh24C05-44	7.96E+06	5.12E-03	6.44E-10	1
Sh24C05-45	8.57E+06	6.06E-03	7.07E-10	1
Sh24C05-46	7.99E+06	4.40E-03	5.51E-10	1
Sh24C05-47	7.98E+06	4.41E-03	5.53E-10	1
Sh24C05-48	8.72E+06	4.90E-03	5.62E-10	1
Sh24C05-49	4.08E+06	1.70E-03	4.16E-10	2

[0319] The results in Table 15 demonstrate that the chimeric and each of the humanized 24C05 antibodies have fast association rates (k_a), very slow disassociation rates (k_d) and very high affinities (K_D). In particular, the antibodies have affinities ranging from about 87 pM to about 1 nM.

[0320] The binding affinities and kinetics of certain purified monoclonal antibodies were also determined. To further characterize certain antibodies, the surface plasmon

resonance experiments described above were conducted using concentrations of cleaved rhErbB3 between 0.3125 nM and 5.0 nM (a 2-fold serial dilution).

[0321] The kinetic values of certain purified monoclonal antibodies (*i.e.*, Sh24C05-1, Sh24C05-25, Sh24C05-25 N62S IgG1, Sh24C05-25 N62S IgG2, Sh24C05-31, Sh24C05-31 N62S IgG1, and Sh24C05-31 N62S IgG2) on cleaved rhErbB3 at 37°C are summarized in Table 16.

Table 16

Antibody	k_a (1/Ms)	k_d (1/s)	K_D (M)	n
Sh24C05-1	3.5E+06	4.4E-04	1.4E-10	3
Sh24C05-25	4.0E+06	5.0E-04	1.3E-10	4
Sh24C05-25 N62S IgG1	2.9E+06	4.5E-04	1.6E-10	4
Sh24C05-25 N62S IgG2	2.7E+06	3.4E-04	1.2E-10	4
Sh24C05-31	4.7E+06	2.8E-04	6.3E-11	3
Sh24C05-31 N62S IgG1	3.5E+06	2.7E-04	7.6E-11	6
Sh24C05-31 N62S IgG2	3.2E+06	2.4E-04	7.4E-11	3

[0322] The results in Table 16 demonstrate the purified antibodies have a have affinities ranging from about 63 pM to about 160 pM when tested at 37°C.

C. Comparison of Other Anti-ErbB3 Antibodies

[0323] Three human antibodies that inhibit the function of human ErbB3 were constructed and expressed using published information. One antibody, referred to as Ab #6, was constructed as a human IgG2/Lambda antibody based the disclosure of Schoeberl *et al.*, US 2009/0291085 (Merrimack Pharmaceuticals, Inc.). Two additional antibodies, referred to as U1-53 and U1-59, were constructed as human IgG1/Kappa antibodies based on the disclosure of Rothe *et al.*, US 2008/0124345 (U3 Pharma AG and Amgen, Inc.).

[0324] Kinetic parameters for the Ab#6, U1-53, and U1-59 antibodies were determined by Biacore at 37°C using cleaved rhErbB3 (monomer) as described above (*See* Section B. Binding Affinities of Humanized and Chimeric Anti-ErbB3 Monoclonal Antibodies). Both Biacore sensorgrams (FIG. 17) and kinetic values (Table 17) are displayed for each antibody.

Table 17

Antibody	k_a (1/Ms)	k_d (1/s)	K_D (M)	n
Sh24C05-31 N62S IgG1	3.5+06	2.7E-04	7.6E-11	6
Ab#6	9.3E+05	1.9E-04	2.3E-10	3
U1-59	1.8E+06	9.4E-04	5.3E-10	3
U1-53	-	-	-	-

[0325] The results in Table 17 demonstrate that the overall equilibrium dissociation constant (K_D) for the Sh24C05-31 N62S IgG1 (76 pM) was smaller (*i.e.*, higher affinity) than the K_D for the Ab#6 and U1-59 antibodies (230 pM ($p<0.01$) and 530 pM ($p<0.0005$), respectively). The equilibrium dissociation constant (K_D) for U1-53 could not determined because of poor curve fits (see FIG. 17, which shows a fast K_{off} rate of U1-53). The K_D of Ab #6, U1-53, and U1-59 antibodies can also be compared with other humanized 24C05 variants by comparing Tables 16 and 17.

[0326] Therefore, the affinity for Sh24C05-31 N62S IgG1 is significantly higher than the affinity of Ab#6 and U1-59 as disclosed herein.

Example 13 – Neutralization Activity of the humanized Anti-ErbB3 Antibodies

[0327] In this example, the humanized antibodies produced in Example 12 were tested for their ability to inhibit rhErbB3 binding to NRG1-β1 by ECL assay. Multi-array 96-well standard binding plates (Meso Scale Discovery, Cat. No. L15XA-3) were coated with 50 µl of 0.5 µg/mL rhErbB3/Fc (R&D systems, Cat. No. 348-RB) in PBS (Invitrogen, Cat. No. 14040-133) for one hour at room temperature with no agitation. The plates then were washed three times with PBS+0.1% Tween20 (Sigma P5927) and blocked with 200 µl of 100% Horse Serum, heat inactivated (GIBCO, Cat. No. 26050-088) for 1.5 hours at room temperature. After washing the plates three times with PBS+0.1% Tween, 25 µl of the antibody dilutions

were added to the plates for another hour at room temperature with agitation. Ligand NRG1-β1 (R&D Systems, Cat. No. 377-HB, 26kDa) was added to the wells at a final concentration of 0.25 μg/ml. The plates were washed three times with PBS+0.1% Tween and incubated with 25 μl of 1 μg/mL biotinylated antibody against human NRG1-β1 (R&D systems, Cat. No BAF377) preincubated for one hour with SULTO-TAG Streptavidin (Meso Scale Discovery, Cat. No R32AD-5) for one hour at room temperature with agitation. The plates then were washed three times with PBS+0.1% Tween, and 150 μl of 1X read buffer (Meso Scale Discovery, Cat. No. R92TC-1) was added to each well before the plates were analyzed on a Sector® Imager 2400 (Meso Scale Discovery) instrument.

[0328] The interaction of NRG1-β1 with rhErbB3 was inhibited by antibodies Sh24C05-25 N62S-IgG1, Sh24C05-25 N62S-IgG2, Sh24C05-31 N62S-IgG1, and Sh24C05-31 N62S-IgG2 (FIG. 18A). The Ab#6 IgG2 antibody as described in Schoeberl *et al.* (*supra*) and the U1-53 and U1-59 antibodies as described in Rothe *et al.* (*supra*) were also tested for their ability to inhibit ErbB3 binding to NRG1-β1. As shown in FIG. 18B, each of the Ab#6 IgG2, U1-53, and U1-59 antibodies inhibited ErbB3 binding to NRG1-β1.

[0329] The IC_{50} values for neutralization of NRG1-β1 binding to hErbB3 for the humanized 24C05 antibodies (*i.e.*, Sh24C05-25 N62S-IgG1, Sh24C05-25 N62S-IgG2, Sh24C05-31 N62S-IgG1, and Sh24C05-31 N62S-IgG2) were calculated and are summarized in Table 18. The IC_{50} values for the NRG1-β1 neutralization activity of the anti-ErbB3 human antibodies Ab#6 IgG2, U1-53 and U1-59 are also shown in Table 18.

Table 18

	IC_{50} (nM)		
Antibody	Average	Standard Deviation	n
Sh24C05-25 N62S-IgG1	0.1219	0.0173	4
Sh24C05-25 N62S-IgG2	0.1117	0.0154	4
Sh24C05-31 N62S-IgG1	0.1242	0.0391	5
Sh24C05-31 N62S-IgG2	0.0860	0.0588	4
U1-53	0.1128	0.0615	3
U1-59	0.3181	0.0274	3
Ab#6 IgG2	1.5161	0.5883	5

[0330] The results in Table 18 demonstrate that antibodies Sh24C05-25 N62S-IgG1, Sh24C05-25 N62S-IgG2, Sh24C05-31 N62S-IgG1, and Sh24C05-31 N62S-IgG2 efficiently neutralized NRG1-β1 binding to rhErbB3. While the anti-ErbB3 human antibodies Ab#6 IgG2, U1-53 and U1-59 also showed neutralization activity, the humanized Sh24C05 antibodies (*i.e.*, Sh24C05-25 N62S-IgG1, Sh24C05-25 N62S-IgG2, Sh24C05-31 N62S-IgG1, and Sh24C05-31 N62S-IgG2) had superior neutralization capacity than U1-59 or Ab#6 IgG2.

Example 14 – Anti-Proliferative Activity

[0331] In this example, the humanized antibodies produced in Example 12 were tested for their ability to inhibit NRG1-β1 dependent proliferation of cells in the BaF/3 cell system engineered to express both human Her2 and ErbB3.

[0332] BaF/3 cells expressing Her2 and ErbB3 receptors as described in Example 6 were treated with anti-ErbB3 antibodies in the absence of WEHI conditioned media but in the presence of NRG1-β1 (100 ng/ml). Assays were conducted in a 96-well plate (5,000 cells/well) in the presence of NRG1-β1 (100 ng/ml) and various concentrations of antibodies (0.018-5000 ng/ml in 100 µl of final volume). MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assays were conducted 3-4 days post NRG1-β1 stimulation.

[0333] The results demonstrate that Sh24C05-25 N62S-IgG1, Sh24C05-25 N62S-IgG2, Sh24C05-31 N62S-IgG1, and Sh24C05-31 N62S-IgG2 inhibited NRG induced Her2/ErbB3-BaF/3 cell proliferation in a dose dependent manner (FIG. 19A).

[0334] The IC_{50} values for the inhibition of NRG1-β1 dependent Her2/ErbB3-BaF/3 cell line proliferation with the humanized 24C05 antibodies (*i.e.*, Sh24C05-25 N62S-IgG1, Sh24C05-25 N62S-IgG2, Sh24C05-31 N62S-IgG1, Sh24C05-31 N62S-IgG2) were calculated and are summarized in Table 19.

Table 19

Her2/ErbB3-BaF/3, NRG1-β1 Dependent Proliferation			
Antibody	IC_{50} (nM)-Average	Standard deviation	n
Sh24C05-25 N62S-IgG1	0.0981	0.0187	2
Sh24C05-25 N62S-IgG2	0.2482	0.0124	2
Sh24C05-31 N62S-IgG1	0.1245	0.0181	5
Sh24C05-31 N62S-IgG2	0.2392	0.0217	2
U1-53	0.8128	0.0268	3
U1-59	0.8364	0.0434	5
Ab#6 IgG2	6.3015	0.8577	2

[0335] The results in Table 19 demonstrate that antibodies Sh24C05-25 N62S-IgG1, Sh24C05-25 N62S-IgG2, Sh24C05-31 N62S-IgG1, and Sh24C05-31 N62S-IgG2 strongly inhibited NRG1-β1-induced proliferation of BaF/3 cells expressing Her2/ErbB3.

[0336] The inhibitory activity of anti-ErbB3 Ab#6 IgG2, U1-53 and U1-59 antibodies were also tested in the NRG1-β1 dependent Her2/ErbB3-BaF/3 cells proliferation assay. As shown in FIG. 19B, the results demonstrate that the Ab#6 IgG2, U1-53 and U1-59 antibodies inhibited NRG induced Her2/ErbB3-BaF/3 cell proliferation in a dose dependent manner. Inhibition data of NRG1-β1 dependent Her2/ErbB3-BaF/3 cell proliferation with antibodies Ab#6 IgG2, U1-53 and U1-59 are summarized in Table 19. The results in Table 19 demonstrate that antibodies Ab#6 IgG2, U1-53, and U1-59 inhibited NRG1-β1-induced proliferation of Her2/ErbB3-BaF/3 cells. A comparison of the inhibitory activity of the tested anti-ErbB3 antibodies in the NRG1-β1 dependent Her2/ErbB3-BaF/3 cells proliferation assay indicates that the inhibitory activity of the humanized Sh24C05 antibodies is superior to the inhibitory activity of the Ab#6 IgG2, U1-53 and U1-59 antibodies (*e.g.*, the IC_{50} was 0.1245 nM for Sh24C05-31 N62S-IgG1 compared to 0.8128 nM for U1-53).

Example 15 – Inhibition of Downstream Signaling in SKBR-3 Cells

[0337] This example describes a characterization of the humanized antibodies produced in Example 12 for their ability to degrade total ErbB3 and inhibit phosphorylation of ErbB3 in exponentially growing SKBR-3 cells.

[0338] The breast cancer SKBR-3 cells were maintained as recommended by ATCC. Cells maintained in full serum condition were treated for 1, 2, 4 or 6 hours with 40 μg/ml of anti-ErbB3 antibody (*i.e.*, Sh24C05-25 N62S-IgG1, Sh24C05-25 N62S-IgG2, Sh24C05-31 N62S-IgG1, and Sh24C05-31 N62S-IgG2). Lysates were either analyzed by ELISA with the Total-ErbB3 and the Phospho-ErbB3 kit from R&D Systems (Cat. No DYC234 and Cat. No DYC1769, respectively).

[0339] The results demonstrate that anti-ErbB3 antibodies Sh24C05-25 N62S-IgG1, Sh24C05-25 N62S-IgG2, Sh24C05-31 N62S-IgG1, and Sh24C05-31 N62S-IgG2 inhibit at least 50% of the phosphorylation of ErbB3 in exponentially growing SKBR-3 cells (FIG. 20).

[0340] The results also demonstrate that anti-ErbB3 antibodies Sh24C05-25 N62S-IgG1, Sh24C05-25 N62S-IgG2, Sh24C05-31 N62S-IgG1, and Sh24C05-31 N62S-IgG2 degraded at least 50% of the total ErbB3 receptor present in exponentially growing SKBR-3 cells (FIG. 21).

Example 16 – Inhibition of BxPC3 Tumor Xenograft Growth

[0341] The ability of the humanized monoclonal antibodies produced in Example 12 to inhibit tumor growth were tested in a BxPC3 pancreatic xenograft model. Human pancreatic BxPC3 cells were grown in culture in 37°C in an atmosphere containing 5% CO2, using RMPI medium containing 10% fetal bovine serum. BxPC3 cells were inoculated subcutaneously into the flank of 8-week old female CB.17 SCID mice (Taconic Labs) with 10 x 10^6 cells per mouse in 50% matrigel (BD Biosciences, Cat No. 356237). Tumor measurements were taken twice weekly using vernier calipers. Tumor volume was calculated using the formula: width x width x length/2. When tumors reached approximately 200 mm^3, the mice were randomized into 8 groups of 10 mice each. One group received PBS, another received huIgG control, and another received muIgG control. Each of the remaining five groups received one of the antibodies (*i.e.*, murine 24C05, Sh24C05-25 N62S-IgG1, Sh24C05-25 N62S-IgG2, Sh24C05-31 N62S-IgG1 or Sh24C05-31 N62S-IgG2). All of the antibodies were dosed at 2 mg/kg body weight, twice per week, by intra-peritoneal injection for 7 weeks. Tumor volumes and mouse body weights were recorded twice per week. Tumor growth inhibition was analyzed using ANOVA and is expressed as percent inhibition compared to the PBS control.

[0342] The tested humanized antibodies were active *in vivo*. All four humanized anti-ErbB3 antibodies had similar efficacy in the BxPC3 model when dosed at 2 mg/kg, ranging from 75-80% tumor growth inhibition ($p<0.001$) (*i.e.*, Sh24C05-25 N62S-IgG1, 75%;

Sh24C05-25 N62S-IgG2, 76%; Sh24C05-31 N62S-IgG1, 79%; and Sh24C05-31 N62S-IgG2, 80%) at day 28 of the study (FIG. 22). The murine antibody demonstrated 65% tumor growth inhibition in this study ($p<0.05$). These results suggest similar potency and activity of the four humanized antibodies in this model.

[0343] The ability of the humanized monoclonal antibodies U1-53, U1-59, and Ab#6 IgG2 to inhibit tumor growth were also tested in a BxPC3 xenograft model. Using the protocol described above, BxPC3 tumors were generated in CB.17 SCID mice. When tumors reached approximately 200 mm^3, the mice were randomized into 11 groups of 10 mice each. One group received PBS and another received huIgG control. Each of the other nine groups received one of the humanized antibodies (*i.e.*, Sh24C05-31 N62S-IgG1, U1-53, U1-59, or Ab#6 IgG2). The antibodies were dosed either at 0.5 mg/kg, 1 mg/kg, or 5 mg/kg body weight, twice per week, by intra-peritoneal injection for 7 weeks. Tumor volumes and mouse body weights were recorded twice per week. Tumor growth inhibition was analyzed using ANOVA and is expressed as percent inhibition compared to the PBS control.

[0344] Tumor growth inhibition data determined at day 29 following treatment with one of the humanized antibodies (*i.e.*, Sh24C05-31 N62S-IgG1, U1-59, or Ab#6 IgG2) is shown in Table 20.

Table 20

Gr.	Treatment		Tumor Growth Inhibition (%)	ANOVA Analysis (Compared to PBS)	ANOVA Analysis (Compared to hIgG)
	Agent	mg/kg			
1	PBS	-	NA	NA	NA
2	hIgG	5	29.2	NS	NS
3	Sh24C05-31 N62S-IgG1	0.5	63.3	$P < 0.001$	$P < 0.01$
4	Sh24C05-31 N62S-IgG1	1	75.0	$P < 0.001$	$P < 0.001$
5	Sh24C05-31 N62S-IgG1	5	76.5	$P < 0.001$	$P < 0.001$
6	Ab#6 IgG2	0.5	31.5	$P < 0.05$	NS
7	Ab#6 IgG2	1	2.1	NS	NS
8	Ab#6 IgG2	5	40.6	$P < 0.001$	NS

Table 20 (Cont.)

Gr.	Treatment		Tumor Growth Inhibition (%)	ANOVA Analysis (Compared to PBS)	ANOVA Analysis (Compared to hIgG)
	Agent	mg/kg			
9	U1-59	0.5	32.6	P < 0.01	NS
10	U1-59	1	52.9	P < 0.001	NS
11	U1-59	5	60.3	P < 0.001	P < 0.05

[0345] The results demonstrate that Sh24C05-31 N62S-IgG1 showed the greatest tumor growth inhibition by day 29 (76.5%, p<0.001) at a dose of 5 mg/kg in the BxPC3 pancreatic xenograft model. The U1-59 and Ab#6 IgG2 antibodies demonstrated approximately 60% and 41% tumor growth inhibition at a dose of 5 mg/kg in the BxPC3 model, respectively (P < 0.001).

[0346] The results also demonstrate that Sh24C05-31 N62S-IgG1 showed the greatest tumor growth inhibition by day 29 at a dose of 0.5 mg/kg (63.3%, p<0.001) and at a dose of 1 mg/kg (75.0%, p<0.001) in the BxPC3 pancreatic xenograft model. The U1-59 and AB#6 IgG2 antibodies demonstrate approximately 33% (p < 0.01) and 31% (p < 0.05) tumor growth inhibition at a dose of 0.5 mg/kg in the BxPC3 model, respectively. The U1-59 and AB#6 IgG2 antibodies demonstrated approximately 53% (p < 0.001) and 2% (not significant) tumor growth inhibition at a dose of 1.0 mg/kg in the BxPC3 model, respectively.

Example 17 – Inhibition of Calu-3 Tumor Xenograft Growth

[0347] The ability of the humanized monoclonal antibodies produced in Example 12 to inhibit tumor growth was tested in a Calu-3 non-small cell lung cancer xenograft model. The ability of the humanized monoclonal antibodies U1-59 and Ab#6 IgG2, as described in Example 12, to inhibit tumor growth were also tested in the same model.

[0348] Human Non-Small Cell Lung Cancer Calu-3 cells were grown in culture in 37°C in an atmosphere containing 5% CO2, using EMEM medium containing 10% fetal bovine serum. Calu-3 cells were inoculated subcutaneously into the flank of 8-week old female NCR nude mice (Taconic Labs) with 10 x 10^6 cells per mouse in 50% matrigel (BD Biosciences, Cat No. 356237). Tumor measurements were taken twice weekly using vernier calipers. Tumor volume was calculated using the formula: width x width x length/2.

[0349] When tumors reached approximately 200 mm^3, the mice were randomized into 11 groups of 10 mice each. One group received PBS and another received muIgG control. Each of the other nine groups received one of the humanized antibodies (*i.e.*, Sh24C05-31 N62S-IgG1, U1-59, or Ab#6 IgG2) at a dose of either 5 mg/kg, 10 mg/kg or 20 mg/kg body weight, twice per week, by intra-peritoneal injection for 4 weeks. Tumor volumes and mouse body weights were recorded twice per week. Tumor growth inhibition was analyzed using ANOVA and is expressed as percent inhibition compared to the PBS control.

[0350] Tumor growth inhibition data determined at day 26 following treatment with one of the humanized antibodies (*i.e.*, Sh24C05-31 N62S-IgG1, U1-59, or Ab#6 IgG2) is shown in Table 21.

Table 21

Gr.	Treatment		Tumor Growth Inhibition (%)	ANOVA Analysis (Compared to PBS)	ANOVA Analysis (Compared to hIgG)
	Agent	mg/kg			
1	PBS	-	NA	NA	NA
2	muIgG	20	-1.2	NS	NA
3	Sh24C05-31 N62S-IgG1	5	62.3	P < 0.001	P < 0.001
4	Sh24C05-31 N62S-IgG1	10	62.0	P < 0.001	P < 0.001
5	Sh24C05-31 N62S-IgG1	20	69.0	P < 0.001	P < 0.001
6	Ab#6 IgG2	5	24.7	NS	NS
7	Ab#6 IgG2	10	35.9	P < 0.01	P < 0.01
8	Ab#6 IgG2	20	48.4	P < 0.001	P < 0.001
9	U1-59	5	47.8	P < 0.001	P < 0.001
10	U1-59	10	56.7	P < 0.001	P < 0.001
11	U1-59	20	57.7	P < 0.001	P < 0.001

[0351] The results using the Calu-3 non-small cell lung cancer xenograft model demonstrate that Sh24C05-31 N62S-IgG1 showed the greatest tumor growth inhibition by day 26 at all doses tested (*i.e.*, 5 mg/kg, 10 mg/kg, and 20 mg/kg of body weight).

[0352] For example, at the 10mg/kg dose, Sh24C05-31 N62S-IgG1 showed the greatest tumor growth inhibition by day 26 (62%, P<0.001) when compared to Ab#6 IgG2 (36%, NS) or U1-59 (57%, P<0.001). At the 20 mg/kg dose, Sh24C05-31 N62S-IgG1 also showed the greatest tumor growth inhibition by day 26 (69%, P<0.001) when compared to Ab#6 IgG2 (48%, P < 0.001) or U1-59 (58%, P<0.001).

Example 18– Inhibition of MDA-MB-453 Tumor Xenograft Growth

[0353] The ability of the humanized monoclonal antibodies produced in Example 12 to inhibit tumor growth were tested in a MDA-MB-453 breast xenograft model (which is a HER2 positive breast model). The ability of the humanized monoclonal antibodies U1-59 and Ab#6 IgG2, as described in Example 12, to inhibit tumor growth were also tested in the same model.

[0354] Human Breast MDA-MB-453 cells were grown in culture in 37°C in an atmosphere containing 0% CO2, using Leibovitz ATCC medium (Cat No. 30-2008) containing 10% fetal bovine serum. MDA-MB-453 cells were inoculated subcutaneously into the flank of 8-week old female NOD SCID mice (Taconic Labs) with 20 x 10^6 cells per mouse in 50% matrigel (BD Biosciences, Cat No. 356237). Tumor measurements were taken twice weekly using vernier calipers. Tumor volume was calculated using the formula: width x width x length/2.

[0355] When tumors reached approximately 200 mm^3, the mice were randomized into 7 groups of 10 mice each. One group received PBS and another received huIgG control. Each of the other nine groups received one of the humanized antibodies (*i.e.*, Sh24C05-31 N62S-IgG1, U1-59, or Ab#6 IgG2). Sh24C05-31 N62S-IgG1 was dosed either at 5 mg/kg, 10 mg/kg, or 20 mg/kg body weight, twice per week, by intra-peritoneal injection for more than 10 weeks; U1-59, or Ab#6 were dosed at 10 mg/kg with the same frequency. Tumor volumes and mouse body weights were recorded twice per week. Tumor growth inhibition was analyzed using ANOVA and is expressed as percent inhibition compared to the PBS control.

[0356] Tumor growth inhibition data determined at day 71 following treatment with one of the humanized antibodies (*i.e.*, Sh24C05-31 N62S-IgG1, U1-59, or Ab#6 IgG2) is shown in Table 22.

Table 22

Gr.	Treatment		Tumor Growth Inhibition (%)	ANOVA Analysis (Compared to PBS)	ANOVA Analysis (Compared to hIgG)
	Agent	mg/kg			
1	PBS	-	NA	NA	NA
2	hIgG	20	28.87	p<0.001	p<0.001
3	Sh24C05-31 N62S-IgG1	5	86.57	p<0.001	p<0.001
4	Sh24C05-31 N62S-IgG1	10	84.09	p<0.001	p<0.001
5	Sh24C05-31 N62S-IgG1	20	85.26	p<0.001	p<0.001
6	Ab#6 IgG2	10	62.48	p<0.001	p<0.001
7	U1-59	10	83.93	p<0.001	p<0.001

[0357] The results using the MDA-MB-453 xenograft model demonstrate that Sh24C05-31 N62S-IgG1 showed potent tumor growth inhibition by day 71 at all doses tested (*i.e.*, 5 mg/kg, 10 mg/kg, and 20 mg/kg of body weight).

[0358] The results also demonstrate that at the 10mg/kg dose, Sh24C05-31 N62S-IgG1 showed greater tumor growth inhibition by day 71 (84%, P<0.001) when compared to Ab#6 IgG2 (62%, P<0.001). Sh24C05-31 N62S-IgG1 showed equivalent tumor growth inhibition as U1-59 at the same dose.

INCORPORATION BY REFERENCE

[0359] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

[0360] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing

description, and all changes that come within the meaning and the range of equivalency of the claims are intended to be embraced therein.

[00361] What is claimed is:

1. An isolated antibody that binds human ErbB3 comprising an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region selected from the group consisting of:

(a) (i) an immunoglobulin heavy chain variable region comprising a CDR_{H1} comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 57 (**24C05**) and SEQ ID NO: 75 (**24C05**), a CDR_{H2} comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 58 (**24C05**) and SEQ ID NO: 148 (**Sh24C05 Hv3-11 N62S**), and a CDR_{H3} comprising the amino acid sequence of SEQ ID NO:59 (**24C05**);

(ii) an immunoglobulin light chain variable region comprising a CDR_{L1} comprising the amino acid sequence of SEQ ID NO: 60 (**24C05**), a CDR_{L2} comprising the amino acid sequence of SEQ ID NO: 61 (**24C05**), and a CDR_{L3} comprising the amino acid sequence of SEQ ID NO: 62 (**24C05**) and

(b) (i) an immunoglobulin heavy chain variable region comprising a CDR_{H1} comprising the amino acid sequence of SEQ ID NO: 5 (**04D01**), a CDR_{H2} comprising the amino acid sequence of SEQ ID NO: 6 (**04D01**), and a CDR_{H3} comprising the amino acid sequence of SEQ ID NO: 7 (**04D01**); and

(ii) an immunoglobulin light chain variable region comprising a CDR_{L1} comprising the s amino acid sequence of SEQ ID NO: 8 (**04D01**), a CDR_{L2} comprising the amino acid sequence of SEQ ID NO: 9 (**04D01**), and a CDR_{L3} comprising the amino acid sequence of SEQ ID NO: 10 (**04D01**);

(c) (i) an immunoglobulin heavy chain variable region comprising a CDR_{H1} comprising the amino acid sequence of SEQ ID NO: 15 (**09D03**), a CDR_{H2} comprising the amino acid sequence of SEQ ID NO: 16 (**09D03**), and a CDR_{H3} comprising the amino acid sequence of SEQ ID NO: 17 (**09D03**); and

(ii) an immunoglobulin light chain variable region comprising a CDR_{L1} comprising the amino acid sequence of SEQ ID NO: 18 (**09D03**), a CDR_{L2} comprising the amino acid sequence of SEQ ID NO: 19 (**09D03**), and a CDR_{L3} comprising the amino acid sequence of SEQ ID NO: 20 (**09D03**);

(d) (i) an immunoglobulin heavy chain variable region comprising a CDR_{H1} comprising the s amino acid sequence of SEQ ID NO: 25 **(11G01)**, a CDR_{H2} comprising the amino acid sequence of SEQ ID NO: 26 **(11G01)**, and a CDR_{H3} comprising the amino acid sequence of SEQ ID NO: 27 **(11G01)**; and

(ii) an immunoglobulin light chain variable region comprising a CDR_{L1} comprising the amino acid sequence of SEQ ID NO: 28 **(11G01)**, a CDR_{L2} comprising the amino acid sequence of SEQ ID NO: 9 **(11G01)**, and a CDR_{L3} comprising the amino acid sequence of SEQ ID NO: 29 **(11G01)**;

(e) (i) an immunoglobulin heavy chain variable region comprising a CDR_{H1} comprising the amino acid sequence of SEQ ID NO: 34 **(12A07)**, a CDR_{H2} comprising the amino acid sequence of SEQ ID NO: 35 **(12A07)**, and a CDR_{H3} comprising the amino acid sequence of SEQ ID NO: 36 **(12A07)**; and

(ii) an immunoglobulin light chain variable region comprising a CDR_{L1} comprising the amino acid sequence of SEQ ID NO: 8 **(12A07)**, a CDR_{L2} comprising the amino acid sequence of SEQ ID NO: 9 **(12A07)**, and a CDR_{L3} comprising the amino acid sequence of SEQ ID NO: 10 **(12A07)**;

(f) (i) an immunoglobulin heavy chain variable region comprising a CDR_{H1} comprising the amino acid sequence of SEQ ID NO: 41 **(18H02)**, a CDR_{H2} comprising the amino acid sequence of SEQ ID NO: 42 **(18H02)**, and a CDR_{H3} comprising the amino acid sequence of SEQ ID NO: 43 **(18H02)**; and

(ii) an immunoglobulin light chain variable region comprising a CDR_{L1} comprising the amino acid sequence of SEQ ID NO: 44 **(18H02)**, a CDR_{L2} comprising the amino acid sequence of SEQ ID NO: 45 **(18H02)**, and a CDR_{L3} comprising the amino acid sequence of SEQ ID NO: 46 **(18H02)**; and

(g) (i) an immunoglobulin heavy chain variable region comprising a CDR_{H1} comprising the amino acid sequence of SEQ ID NO: 51 **(22A02)**, a CDR_{H2} comprising the amino acid sequence of SEQ ID NO: 52 **(22A02)**, and a CDR_{H3} comprising the amino acid sequence of SEQ ID NO: 36 **(22A02)**; and

(ii) an immunoglobulin light chain variable region comprising a CDR_{L1} comprising the amino acid sequence of SEQ ID NO: 8 **(22A02)**, a CDR_{L2} comprising the amino acid

sequence of SEQ ID NO: 9 (**22A02**), and a CDR_{L3} comprising the amino acid sequence of SEQ ID NO: 10 (**22A02**).

2. The antibody of claim 1, wherein the immunoglobulin heavy chain variable region comprises a CDR_{H1} comprising the amino acid sequence of SEQ ID NO: 57 (**24C05**), a CDR_{H2} comprising the amino acid sequence of SEQ ID NO: 58 (**24C05**), and a CDR_{H3} comprising the amino acid sequence of SEQ ID NO: 59 (**24C05**); and

the immunoglobulin light chain variable region comprises a CDR_{L1} comprising the amino acid sequence of SEQ ID NO: 60 (**24C05**), a CDR_{L2} comprising the amino acid sequence of SEQ ID NO: 61 (**24C05**), and a CDR_{L3} comprising the amino acid sequence of SEQ ID NO: 62 (**24C05**).

3. The antibody of claim 1, wherein the immunoglobulin heavy chain variable region comprises a CDR_{H1} comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 57 (**24C05**) and SEQ ID NO: 75 (**24C05**), a CDR_{H2} comprising the amino acid sequence of SEQ ID NO: 148 (**Sh24C05 Hv3-11 N62S**), and a CDR_{H3} comprising the amino acid sequence of SEQ ID NO:59 (**24C05**); and

wherein the immunoglobulin light chain variable region comprises a CDR_{L1} comprising the amino acid sequence of SEQ ID NO: 60 (**24C05**), a CDR_{L2} comprising the amino acid sequence of SEQ ID NO: 61 (**24C05**), and a CDR_{L3} comprising the amino acid sequence of SEQ ID NO: 62 (**24C05**).

4. The antibody of any one of claims 1-3, wherein the CDR sequences are interposed between human and humanized framework sequences.

5. The antibody of any one of claims 1-3, wherein the antibody is an antigen-binding fragment.

6. An isolated nucleic acid comprising a nucleotide sequence encoding an immunoglobulin heavy chain variable region of any one of claims 1-3.

7. An isolated nucleic acid comprising a nucleotide sequence encoding an immunoglobulin light chain variable region of claim any one of claims 1-3.

8. An expression vector comprising the nucleic acid of claim 6.

9. An expression vector comprising the nucleic acid of claim 7.

10. The expression vector of claim 9, further comprising the nucleic acid of claim 6.

11. A host cell comprising the expression vector of claim 8.

12. A host cell comprising the expression vector of claim 9.

13. A host cell comprising the expression vector of claim 10.

14. The host cell comprising of claim 12, further comprising the expression vector of claim 8.

15. A method of producing a polypeptide comprising an immunoglobulin heavy chain variable region or an immunoglobulin light chain variable region, the method comprising:

(a) growing the host cell of claim 11 or 12 under conditions so that the host cell expresses the polypeptide comprising the immunoglobulin heavy chain variable region or the immunoglobulin light chain variable region; and

(b) purifying the polypeptide comprising the immunoglobulin heavy chain variable region or the immunoglobulin light chain variable region.

16. A method of producing an antibody that binds human ErbB3 or an antigen binding fragment of the antibody, the method comprising:

(a) growing the host cell of claim 13 or 14 under conditions so that the host cell expresses a polypeptide comprising the immunoglobulin heavy chain variable region and/or the immunoglobulin light chain variable region, thereby producing the antibody or the antigen-binding fragment of the antibody; and

(b) purifying the antibody or the antigen-binding fragment of the antibody.

17. An isolated antibody that binds human ErbB3 comprising an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region selected from the group consisting of:

(a) an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 54 (**24C05**), and

an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 56 (**24C05**);

(b) an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 154 (**Sh24C05 Hv3-11 N62S**), and

an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 168 **(Sh24C05 Kv1-17)**;

(c) an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 154 **(Sh24C05 Hv3-11 N62S)**, and

an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 166 **(Sh24C05 Kv1-16)**;

(d) an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2 **(04D01)**, and

an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 4 **(04D01)**;

(e) an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 12 **(09D03)**, and

an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 14 **(09D03)**;

(f) an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 22 **(11G01)**, and

an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 24 **(11G01)**;

(g) an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 31 **(12A07)**, and

an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 33 **(12A07)**;

(h) an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 38 **(18H02)**, and

an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 40 **(18H02)**; and

(i) an immunoglobulin heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 48 **(22A02)**, and

an immunoglobulin light chain variable region comprising the amino acid sequence of SEQ ID NO: 50 **(22A02)**.

18. The antibody of claim 17, wherein the immunoglobulin heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 54 **(24C05)**, and the immunoglobulin light chain variable region comprises the amino acid sequence of SEQ ID NO: 56 **(24C05)**.

19. The antibody of claim 17, wherein the immunoglobulin heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 154 **(Sh24C05 Hv3-11 N62S)**, and the immunoglobulin light chain variable region comprises the amino acid sequence of SEQ ID NO: 168 **(Sh24C05 Kv1-17)**.

20. The antibody of claim 17, wherein the immunoglobulin heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 154 **(Sh24C05 Hv3-11 N62S)**, and the immunoglobulin light chain variable region comprises the amino acid sequence of SEQ ID NO: 166 **(Sh24C05 Kv1-16)**.

21. An isolated nucleic acid comprising a nucleotide sequence encoding an immunoglobulin heavy chain variable region of any one of claims 17-20.

22. An isolated nucleic acid comprising a nucleotide sequence encoding an immunoglobulin light chain variable region of any one of claims 17-20.

23. An expression vector containing the nucleic acid of claim 21.

24. An expression vector containing the nucleic acid of claim 22.

25. The expression vector of claim 24, further comprising the nucleic acid of claim 21.

26. A host cell comprising the expression vector of claim 23.

27. A host cell comprising the expression vector of claim 24.

28. A host cell comprising the expression vector of claim 25.

29. The host of claim 27, further comprising the expression vector of claim 23.

30. A method of producing a polypeptide comprising an immunoglobulin heavy chain variable region or an immunoglobulin light chain variable region, the method comprising:

(a) growing the host cell of claim 26 or 27 under conditions so that the host cell expresses the polypeptide comprising the immunoglobulin heavy chain variable region or the immunoglobulin light chain variable region; and

(b) purifying the polypeptide comprising the immunoglobulin heavy chain variable region or the immunoglobulin light chain variable region.

31. A method of producing an antibody that binds human ErbB3 or an antigen binding fragment of the antibody, the method comprising:

(a) growing the host cell of claim 28 or 29 under conditions so that the host cell expresses a polypeptide comprising the immunoglobulin heavy chain variable region and/or the immunoglobulin light chain variable region, thereby producing the antibody or the antigen-binding fragment of the antibody; and

(b) purifying the antibody or the antigen-binding fragment of the antibody.

32. An isolated antibody that binds human ErbB3 comprising an immunoglobulin heavy chain and an immunoglobulin light chain selected from the group consisting of:

(a) an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 133 (**24C05**), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 135 (**24C05**);

(b) an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 190 (**Sh24C05 Hv3-11 N62S IgG1**), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 206 (**Sh24C05 Kv1-17 kappa**);

(c) an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 190 (**Sh24C05 Hv3-11 N62S IgG1**), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 204 (**Sh24C05 Kv1-16 kappa**);

(d) an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 109 (**04D01**), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 111 (**04D01**);

(e) an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 113 (**09D03**) , and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 115 (**09D03**);

(f) an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 117 (**11G01**), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 119 (**11G01**);

(g) an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 121 (**12A07**), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 123 (**12A07**);

(h) an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 125 (**18H02**), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 127 (**18H024**); and

(i) an immunoglobulin heavy chain comprising the amino acid sequence of SEQ ID NO: 129 (**22A02**), and an immunoglobulin light chain comprising the amino acid sequence of SEQ ID NO: 131 (**22A02**).

33. The antibody of claim 32, wherein the immunoglobulin heavy chain comprises the amino acid sequence of SEQ ID NO: 133 (**24C05**), and the immunoglobulin light chain comprises the amino acid sequence of SEQ ID NO: 135 (**24C05**).

34. The antibody of claim 32, wherein the immunoglobulin heavy chain comprises the amino acid sequence of SEQ ID NO: 190 (**Sh24C05 Hv3-11 N62S IgG1**), and the immunoglobulin light chain comprises the amino acid sequence of SEQ ID NO: 206 (**Sh24C05 Kv1-17 kappa**).

35. The antibody of claim 32, wherein the immunoglobulin heavy chain comprises the amino acid sequence of SEQ ID NO: 190 (**Sh24C05 Hv3-11 N62S IgG1**), and the immunoglobulin light chain comprises the amino acid sequence of SEQ ID NO: 204 (**Sh24C05 Kv1-16 kappa**).

36. The antibody of any one of claims 17-20 or 32-35, wherein the antibody is an antigen binding fragment.

37. An isolated nucleic acid comprising a nucleotide sequence encoding an immunoglobulin heavy chain of any one of claims 32-35.

38. An isolated nucleic acid comprising a nucleotide sequence encoding an immunoglobulin light chain of any one of claims 32-35.

39. An expression vector containing the nucleic acid of claim 37.

40. An expression vector containing the nucleic acid of claim 38.

41. The expression vector of claim 40, further comprising the nucleic acid of claim 37.

42. A host cell comprising the expression vector of claim 39.

43. A host cell comprising the expression vector of claim 40.

44. A host cell comprising the expression vector of claim 41.

45. The host of claim 43, further comprising the expression vector of claim 39.

46. A method of producing a polypeptide comprising an immunoglobulin heavy chain variable region or an immunoglobulin light chain variable region, the method comprising:

(a) growing the host cell of claim 42 or 43 under conditions so that the host cell expresses the polypeptide comprising the immunoglobulin heavy chain variable region or the immunoglobulin light chain variable region; and

(b) purifying the polypeptide comprising the immunoglobulin heavy chain variable region or the immunoglobulin light chain variable region.

47. A method of producing an antibody that binds human ErbB3 or an antigen binding fragment of the antibody, the method comprising:

(a) growing the host cell of claim 44 or 45 under conditions so that the host cell expresses a polypeptide comprising the immunoglobulin heavy chain variable region and/or the immunoglobulin light chain variable region, thereby producing the antibody or the antigen-binding fragment of the antibody; and

(b) purifying the antibody or the antigen-binding fragment of the antibody.

48. The antibody of any one of claims 1-5, 17-20, or 32-36, wherein the antibody has a K_D of 200 pM or lower as measured by surface plasmon resonance.

49. A method of inhibiting or reducing proliferation of a tumor cell comprising exposing the cell to an effective amount of the antibody of any one of claims 1-5, 17-20, or 32-36 to inhibit or reduce proliferation of the tumor cell.

50. A method of inhibiting or reducing tumor growth in a mammal, the method comprising exposing the mammal to an effective amount of the antibody of any one of claims 1-5, 17-20, or 32-36 to inhibit or reduce proliferation of the tumor.

51. A method of treating cancer in a mammal, the method comprising administering an effective amount of the antibody of any one of claims 1-5, 17-20, or 32-36 to a mammal in need thereof.

52. The method of claim 51, wherein the cancer is selected from the group consisting of breast, ovarian, prostate, cervical, colorectal, lung, pancreatic, gastric, skin, kidney, and head and neck, and schwannoma cancers.

53. The method of claim 51, wherein the cancer is selected from the group consisting of breast, lung, and pancreatic cancers.

54. The method of claim 51, wherein the mammal is a human.