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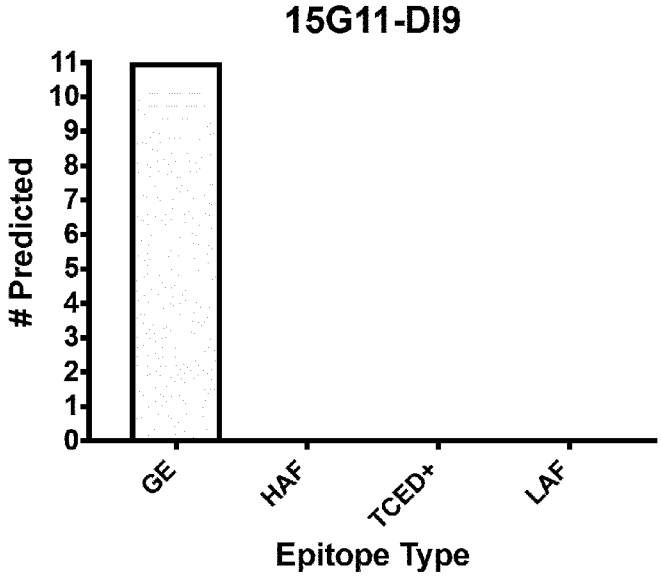
(54) Title: DE-IMMUNISED ANTI-ERBB3 ANTIBODIES

FIG. 14E



(57) Abstract: Provided herein are humanised and deimmunised antibody molecules that bind specifically to ERBB3 and related nucleic acid molecules, vectors and host cells. Also provided herein are medical uses of such antibody molecules.

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DE-IMMUNISED ANTI-ERBB3 ANTIBODIES

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of GB Patent Application No. 1804094.9, filed on March 14, 2018, the disclosure of which is hereby incorporated by reference in its entirety.

DESCRIPTION OF THE TEXT FILE SUBMITTED ELECTRONICALLY

The contents of the text file submitted electronically herewith are incorporated herein by reference in their entirety: A computer readable format copy of the Sequence Listing (filename: ULTH_001_01WO_SeqList_ST25.txt, date recorded: March 13, 2019, file size 141,221 bytes).

FIELD OF THE INVENTION

The invention relates to antibody molecules binding specifically to ERBB3 (also known as ErbB-3, HER3, LCCS2, MDA-BF-1, c-erbB-3, c-erbB3, erbB3-S, p180-ErbB3, p45-sErbB3, p85-sErbB3, erb-b2 receptor tyrosine kinase 3) and medical uses thereof.

BACKGROUND OF THE INVENTION

ERBB3 (also known as ErbB-3, HER3, LCCS2, MDA-BF-1, c-erbB-3, c-erbB3, erbB3-S, p180-ErbB3, p45-sErbB3, p85-sErbB3, and erb-b2 receptor tyrosine kinase 3) is a transmembrane receptor tyrosine kinase (RTK) protein that belongs to the immunoglobulin superfamily. ERBB3 lacks significant tyrosine kinase activity of its own, and is activated via heterodimerization with other related RTKs such as HER2, EGFR, and MET. This heterodimerization is primarily driven by the predominant ligand for ERBB3, which is Heregulin (HRG), also known as Neuregulin 1 (NRG1). ERBB3-HRG interaction triggers the tyrosine phosphorylation of ERBB3 by heterodimer partners and the activation of diverse intracellular signaling networks. Importantly, ERBB3 is the most potent activator of the PI3K/AKT signaling pathway in the EGFR family.

The ERBB3 receptor is often overexpressed in tumours of the head and neck, lung, breast, ovary, prostate, colon, pancreas, and gastrointestinal tract. The overexpression of ERBB3 is strongly linked with poor prognosis, and ERBB3 is believed to be influential in resistance mechanisms to radiotherapy and various chemotherapeutic and biotherapeutic drugs. As the preferred dimerization partner of HER2, amplified ERBB3 signaling in HER2+ breast tumours is believed to be partly responsible for resistance to trastuzumab therapy. Therapeutic antibodies that antagonise ERBB3 signalling by blocking its ability to dimerise with other key receptors have the potential to mediate anti-tumour effects, via two mechanisms: 1. Potent

inhibition of the ERBB3 signalling pathway by locking the receptors into a monomeric form. 2. Antibody effector-function mediated engagement of immune cells.

The majority of currently approved antibody therapeutics are derived from immunized rodents. Many of those antibodies have undergone a process known as “humanization”, via the “grafting” of murine Complementarity-Determining Regions (CDRs) into human v-gene framework sequences (see Nelson *et al.*, 2010, Nat Rev Drug Discov 9: 767-774). This process is often inaccurate and leads to a reduction in target binding affinity of the resulting antibody. To return the binding affinity of the original antibody, murine residues are usually introduced at key positions in the variable domain frameworks of the grafted v-domains (also known as “back-mutations”).

While antibodies humanized via CDR grafting and back mutations have been shown to induce lower immune response rates in the clinic in comparison to those with fully murine v-domains, antibodies humanized using this basic grafting method still carry significant clinical development risks due to the potential physical instability and immunogenicity motifs still housed in the grafted CDR loops. Antibodies such as anti-ERBB3, which potentially engage immune effector functions as part of their mechanism of action, are at particularly high risk of immunogenicity as they can encourage phagocytosis of ERBB3+ target cells, leading to antigen processing of the antibody along with the target cell. As animal testing of protein immunogenicity is often non-predictive of immune responses in man, antibody engineering for therapeutic use focuses on minimizing predicted human T-cell epitope content, non-human germline amino acid content and aggregation potential in the purified protein.

The ideal humanized antagonistic anti-ERBB3 antibody would therefore have as many residues as possible in the v-domains that are identical to those found in both the frameworks and CDRs of well-characterized human germline sequences. This high level of identity to high-stability germlines that are highly expressed in the maximum number of potential patients minimises the risk of a therapeutic antibody having unwanted immunogenicity in the clinic, or unusually high ‘cost of goods’ in manufacturing.

Townsend *et al.* (2015; PNAS 112: 15354-15359) describe a method for generating antibodies in which CDRs derived from rat, rabbit and mouse antibodies were grafted into preferred human frameworks and then subject to a human germ-lining approach termed “Augmented Binary Substitution”. Although the approach demonstrated a fundamental plasticity in the original antibody paratopes, in the absence of highly accurate antibody-antigen co-crystal structural data, it is still not possible to reliably predict which individual residues in the CDR loops of any given antibody can be converted to human germline, and

in what combination. Additionally, the Townsend et al. study did not address the addition of mutagenesis beyond the residues found in the human germline at positions where the removal of development risk motifs might be beneficial. This is a technological limitation which renders the process inherently inefficient, requiring an extra stage of modification of the starting antibody sequence. In addition, it cannot currently be accurately predicted what modifications in distal positions of the protein sequence of an individual v-domain, or even on the partner v-domain, might facilitate the removal of risk motifs while maintaining antigen binding affinity and specificity.

CDR germ-lining and development quality optimisation is thus a complex, multifactorial problem, as multiple functional properties of the molecule should preferably be maintained, including in this instance: target binding specificity, affinity to ERBB3 from both human and animal test species (e.g. rhesus monkey, also known as the rhesus macaque, i.e. *Macaca mulatta*), v-domain biophysical stability and/or IgG yield from protein expression platforms used in research, clinical and commercial supply. Antibody engineering studies have shown that mutation of even single residue positions in key CDRs can have dramatic effects on all of these desired molecular properties.

WO2011136911A2 describes an antagonistic murine anti-ERBB3 IgG molecule termed "24C05", and also the preparation of humanized forms (h24C05). Those humanized forms of 24C05 were produced using classical humanization techniques, i.e. by grafting of Kabat-defined murine CDRs into human heavy and light chain framework sequences, with some of the human framework residues being potentially back-mutated to the correspondingly positioned 24C05 murine residues. For reasons noted above, such humanized forms of 24C05 described in WO2011136911A2 are not ideal.

SUMMARY OF THE INVENTION

The present invention provides a number of anti-ERBB3 antibodies and medical uses thereof.

According to one aspect of the invention, there is provided an antibody molecule which specifically binds to human ERBB3, and optionally also to rhesus monkey ERBB3, or an antigen-binding portion thereof, wherein the antibody molecule or antigen-binding portion comprises a heavy chain variable region with:

an HCDR1 having amino acids in sequence in the following order: G-F-T-F-S-D-Y-G or any amino acid (such as S)-M-S (SEQ ID NO:1);

an HCDR2 having amino acids in sequence in the following order: V-S-T-I-S-D-G or any amino acid (such as S, D)-G-T or a conservative substitution of T (such as S)-Y or any amino

acid (such as T)-T or any amino acid (such as I)-Y-Y-P or any amino acid (such as A)-D-N or a conservative substitution of N (such as S)-V-K-G (SEQ ID NO:2); and
an HCDR3 having amino acids in sequence in the following order: E or any amino acid (such as M)-W or any amino acid (such as F, L, M, Q or Y)-G-D-Y or any amino acid (such as A, D, E, H, L, M, N, Q, S, T or W)-D-G-F or any amino acid (such as I, L, W, Y)-D-Y or any amino acid (such as A, D, E, F, H, I, K, L, M, N, Q, R, S, V, W) (SEQ ID NO:3).

In aspects of the invention, the HCDR1 of the antibody molecule or antigen-binding portion may exclude the sequence GFTFSDYAMS (SEQ ID NO:4; 24C05 murine/humanized antibody HCDR1 disclosed in WO2011136911A2; US20110256154A1), the HCDR2 of the antibody molecule or antigen-binding portion may exclude the sequence VSTISDGGTYTYYPDNVKG (SEQ ID NO:5; 24C05 murine/humanized antibody HCDR2 disclosed in WO2011136911A2; US20110256154A1), and/or the HCDR3 of the antibody molecule or antigen-binding portion may exclude the sequence EWGDYDGFDY (SEQ ID NO:6; 24C05 murine/humanized antibody HCDR3 disclosed in WO2011136911A2; US20110256154A1).

The antibody molecule or antigen-binding portion may further comprise a light chain variable region with:
an LCDR1 having amino acids in sequence in the following order: R-A-S-Q-E or any amino acid (such as S, I, N)-I-S-G or a conservative substitution of G (such as S, T)-Y-L-S or a conservative substitution of S (such as N) (SEQ ID NO:7);
an LCDR2 having amino acids in sequence in the following order: A or any amino acid (such as E)-A-S-T or a conservative substitution of T (such as S, N)-L-D or any amino acid (such as H, K, Q)-S or T (SEQ ID NO:8); and
an LCDR3 having amino acids in sequence in the following order: L or any amino acid (such as Q)-Q-Y or any amino acid (such as S)-D or any amino acid (such as Y)-S-Y or any amino acid (such as T, S)-P or any amino acid (such as H)-Y or any amino acid (such as L)-T (SEQ ID NO:9).

In aspects of the invention, the LCDR1 of the antibody molecule or antigen-binding portion may exclude the sequence RASQEISGYLS (SEQ ID NO:10; 24C05 murine/humanized antibody LCDR1 disclosed in WO2011136911A2; US20110256154A1), and/or the LCDR2 of the antibody molecule or antigen-binding portion may exclude the sequence AASTLDS (SEQ ID NO:11; 24C05 murine/humanized antibody LCDR2 disclosed in WO2011136911A2; US20110256154A1), and/or the LCDR3 of the antibody molecule or antigen-binding portion may exclude the sequence LQYDSYPYT (SEQ ID NO:12; 24C05 murine/humanized antibody LCDR3 disclosed in WO2011136911A2; US20110256154A1).

In some aspects, disclosed herein is an anti-ERBB3 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein

(a) the HCDR1 comprises the amino acid sequence G-F-T-F-S-D-Y-X_1-M-S, wherein X_1 is G or any other amino acid (SEQ ID NO:1);

(b) the HCDR2 comprises V-S-T-I-S-D-X_1-G-X_2-X_3-X_4-Y-Y-X_5-D-X_6-V-K-G, wherein X_1 is G or any other amino acid, X_2 is T or a conservative substitution of T, X_3 is Y or any other amino acid, X_4 is T or any other amino acid, X_5 is P or any other amino acid, and X_6 is N or a conservative substitution of N (SEQ ID NO:2);

(c) the HCDR3 comprises X_1-X_2-G-D-X_3-D-G-X_4-D-X_5, wherein X_1 is E or any other amino acid, X_2 is W or any other amino acid, X_3 is Y or any other amino acid, X_4 is F or any other amino acid, and X_5 is Y or any other amino acid (SEQ ID NO:3);

(d) the LCDR1 comprises R-A-S-Q-X_1-I-S-X_2-Y-L-X_3, wherein X_1 is E or any other amino acid, X_2 is G or a conservative substitution of G, and X_3 is S or a conservative substitution of S (SEQ ID NO:7);

(e) the LCDR2 comprises X_1-A-S-X_2-L-X_3-S, wherein X_1 is A or any other amino acid, X_2 is T or a conservative substitution of T, and X_3 is or D any other amino acid (SEQ ID NO:8); and

(f) the LCDR3 comprises X_1-Q-X_2-X_3-S-X_4-X_5-X_6-T, wherein X_1 is L or any other amino acid, X_2 is Y or any other amino acid, X_3 is D or any other amino acid, X_4 is Y or any other amino acid, X_5 is P or any other amino acid, and X_6 is Y or any other amino acid (SEQ ID NO:9). In some aspects, the LCDR2 comprises X_1-A-S-X_2-L-X_3-S (SEQ ID NO:8), wherein the seventh residue in the sequence is a conservative substitution of S (for example, T).

In some aspects, the invention provides an anti-ERBB3 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein

(a) the VH region amino acid sequence comprises HCDR1 of GFTFSDYSMS (SEQ ID NO: 24), HCDR2 of VSTISDSGTYTYYPDSVKG (SEQ ID NO: 25) and HCDR3 of EWGDYDGFDF (SEQ ID NO: 15); and the VL region amino acid sequence comprises LCDR1 of RASQEISTYLS (SEQ ID NO: 261), LCDR2 of AASTLQS (SEQ ID NO:26) and LCDR3 of LQYDSSPLT (SEQ ID NO: 262);

(b) the VH region amino acid sequence comprises HCDR1 of GFTFSDYSMS (SEQ ID NO: 24), HCDR2 of VSTISDSGTYTYYPDSVKG (SEQ ID NO: 25) and HCDR3 of EWGDYDGFDF (SEQ ID NO: 15); and the VL region amino acid sequence comprises

LCDR1 of RASQEISSYLS (SEQ ID NO: 21), LCDR2 of AASSLDT (SEQ ID NO: 263) and LCDR3 of LQYDSTPYT (SEQ ID NO: 23);

(c) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDSGSYTYYPDSVKG (SEQ ID NO:19) and HCDR3 of ELGDYDGFDY (SEQ ID NO:20); and the VL region amino acid sequence comprises LCDR1 of RASQEISSYLS (SEQ ID NO:21), LCDR2 of AASSLDS (SEQ ID NO:22) and LCDR3 of LQYDSTPYT (SEQ ID NO:23);

(d) the VH region amino acid sequence comprises HCDR1 of GFTFSDYSMS (SEQ ID NO:24), HCDR2 of VSTISDSGTYTYYPDSVKG (SEQ ID NO:25) and HCDR3 of EWGDYDGFDF (SEQ ID NO:15); and the VL region amino acid sequence comprises LCDR1 of RASQEISSYLS (SEQ ID NO:21), LCDR2 of AASTLQS (SEQ ID NO:26) and LCDR3 of LQYDSTPLT (SEQ ID NO:18);

(e) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDSGSYIYYADSVKG (SEQ ID NO:14) and HCDR3 of EWGDYDGFDF (SEQ ID NO:15); and the VL region amino acid sequence comprises LCDR1 of RASQSISSYLS (SEQ ID NO:16), LCDR2 of AASSLQS (SEQ ID NO:17) and LCDR3 of LQYDSTPLT (SEQ ID NO:18);

(f) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDSGSYIYYADSVKG (SEQ ID NO:14) and HCDR3 of EWGDYDGFDH (SEQ ID NO:27); and the VL region amino acid sequence comprises LCDR1 of RASQEISSYLS (SEQ ID NO:21), LCDR2 of AASSLQS (SEQ ID NO:17) and LCDR3 of LQYDSTPLT (SEQ ID NO:18);

(g) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDGGSYTYYADSVKG (SEQ ID NO:28) and HCDR3 of EWGDYDGFDE (SEQ ID NO:29); and the VL region amino acid sequence comprises LCDR1 of RASQSISGYLS (SEQ ID NO:30), LCDR2 of AASTLQS (SEQ ID NO:26) and LCDR3 of LQYDSTPYT (SEQ ID NO:23);

(h) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDGGSYTYYADNVKG (SEQ ID NO:31) and HCDR3 of EWGDYDGFDF (SEQ ID NO:15); and the VL region amino acid sequence comprises LCDR1 of RASQSISSYLS (SEQ ID NO:16), LCDR2 of AASTLQS (SEQ ID NO:26) and LCDR3 of LQYDSTPLT (SEQ ID NO:18); or

(i) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDSGSYIYYADSVKG (SEQ ID NO:14) and HCDR3 of EWGDYDGFDE (SEQ ID NO:29); and the VL region amino acid sequence comprises LCDR1 of RASQSISSYLS (SEQ ID NO:16), LCDR2 of AASSLQS (SEQ ID NO:17) and LCDR3 of LQYDSTPLT (SEQ ID NO:18).

In some aspects, disclosed herein is an anti-ERBB3 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein

the VH region amino acid sequence comprises:

(a) HCDR1 of SEQ ID NO: 13 or 24;

(b) HCDR2 of SEQ ID NO: 14, 19, 25, 28 or 31; and

(c) HCDR3 of SEQ ID NO: 15, 20, 27 or 29; and

the VL region amino acid sequence comprises:

(a') LCDR1 of SEQ ID NO: 16, 21, 30 or 261;

(b') LCDR2 of SEQ ID NO: 17, 22, 26 or 263; and

(c') LCDR3 of SEQ ID NO: 18, 23 or 262.

In some aspects, disclosed herein is an anti-ERBB3 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein

(a) the VH region amino acid sequence comprises SEQ ID NO:236 and the VL region amino acid sequence comprises SEQ ID NO:225;

(b) the VH region amino acid sequence comprises SEQ ID NO:232 and the VL region amino acid sequence comprises SEQ ID NO:221;

(c) the VH region amino acid sequence comprises SEQ ID NO:253 and the VL region amino acid sequence comprises SEQ ID NO:254; or

(d) the VH region amino acid sequence comprises SEQ ID NO:255 and the VL region amino acid sequence comprises SEQ ID NO:256.

Also provided according to the invention is an immunoconjugate comprising the antibody molecule or antigen-binding portion thereof as defined herein linked, fused or conjugated to a therapeutic agent.

In another aspect the invention provides a nucleic acid molecule encoding the antibody molecule or antigen-binding portion thereof as defined herein.

Further provided is a vector comprising the nucleic acid molecule of the invention.

Also provided is a host cell comprising the nucleic acid molecule or the vector of the invention as defined herein.

In a further aspect there is provided a method of producing an anti-ERBB3 antibody and/or an antigen-binding portion thereof, comprising culturing the host cell of the invention under

conditions that result in expression and/or production of the antibody and/or the antigen-binding portion thereof, and isolating the antibody and/or the antigen-binding portion thereof from the host cell or culture.

In another aspect of the invention there is provided a pharmaceutical composition comprising the antibody molecule or antigen-binding portion thereof of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein.

Further provided is a method for enhancing an immune response in a subject, comprising administering an effective amount of the antibody molecule or antigen-binding portion thereof of the invention as defined herein, or the immunoconjugate of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein, or the pharmaceutical composition of the invention as defined herein.

In a further aspect there is provided a method for treating or preventing cancer in a subject, comprising administering an effective amount of the antibody molecule or antigen-binding portion thereof of the invention as defined herein, or the immunoconjugate of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein, or the pharmaceutical composition of the invention as defined herein.

Further provided herein is an antibody molecule or antigen-binding portion thereof as defined herein, or the immunoconjugate as defined herein, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein, for use as a medicament. The invention also provides an antibody molecule or antigen-binding portion thereof of the invention as defined herein, or the immunoconjugate of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein, or the pharmaceutical composition of the invention as defined herein, for use in the treatment of cancer.

In another aspect the invention provides the antibody molecule, or antigen-binding portion thereof, or the immunoconjugate, or the nucleic acid molecule, or the vector for use, or the method of treatment of the invention as defined herein, for separate, sequential or simultaneous use in a combination with a second therapeutic agent, for example an anti-cancer agent.

In a further aspect there is provided the use of an antibody molecule or antigen-binding portion thereof of the invention as defined herein, or an immunoconjugate of the invention as defined herein, or a nucleic acid molecule of the invention as defined herein, or a vector of the invention as defined herein, or a pharmaceutical composition of the invention as defined herein, in the manufacture of a medicament for the treatment of cancer.

The invention also provides a method for treating or preventing an an autoimmune disease or an inflammatory disease in a subject, comprising administering an effective amount of the antibody molecule or antigen-binding portion thereof as defined herein, or the immunoconjugate as defined here, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein.

The autoimmune disease or inflammatory disease may be selected in all aspects from the group consisting of: arthritis, asthma, multiple sclerosis, psoriasis, Crohn's disease, inflammatory bowel disease, lupus, Grave's disease and Hashimoto's thyroiditis, and ankylosing spondylitis.

Also provided is an antibody molecule or antigen-binding portion thereof as defined herein, or the immunoconjugate as defined herein, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein, for use in the treatment of an autoimmune disease or an inflammatory disease.

Further provided is the use of an antibody molecule or antigen-binding portion thereof as defined herein, or an immunoconjugate as defined herein, or a nucleic acid molecule as defined herein, or a vector as defined herein, or a pharmaceutical composition as defined herein, in the manufacture of a medicament for the treatment of an autoimmune disease or an inflammatory disease.

The invention also provides a method for treating or preventing a cardiovascular disease or a fibrotic disease in a subject, comprising administering an effective amount of the antibody molecule or antigen-binding portion thereof as defined herein, or the immunoconjugate as defined here, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein.

Also provided is an antibody molecule or antigen-binding portion thereof as defined herein, or the immunoconjugate as defined herein, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein, for use in the treatment of a cardiovascular disease or a fibrotic disease.

Further provided is the use of an antibody molecule or antigen-binding portion thereof as defined herein, or an immunoconjugate as defined herein, or a nucleic acid molecule as defined herein, or a vector as defined herein, or a pharmaceutical composition as defined herein, in the manufacture of a medicament for the treatment of an autoimmune disease, an inflammatory disease or a fibrotic disease.

The cardiovascular disease in any aspect of the invention may for example be coronary heart disease or atherosclerosis.

The fibrotic disease in any aspect of the invention may be selected from the group consisting of myocardial infarction, angina, osteoarthritis, pulmonary fibrosis, cystic fibrosis, bronchitis and asthma.

The invention also provides a method of producing an antibody molecule which specifically binds to human ERBB3 and optionally also to rhesus monkey ERBB3, or an antigen-binding portion thereof, comprising the steps of:
(1) grafting anti-ERBB3 CDRs from a non-human source into a human v-domain framework to produce a humanized anti-ERBB3 antibody molecule or antigen-binding portion thereof;
(2) generating a phage library of clones of the humanized anti-ERBB3 antibody molecule or antigen-binding portion thereof comprising one or more mutations in the CDRs;
(3) screening the phage library for binding to human ERBB3 and optionally also to rhesus monkey ERBB3;
(4) selecting clones from the screening step (3) having binding specificity to human ERBB3 and optionally also to rhesus monkey ERBB3; and
(5) producing an antibody molecule which specifically binds to human ERBB3 and optionally also to rhesus monkey ERBB3, or an antigen-binding portion thereof from clones selected from step (4).

The method may comprise a further step of producing additional clones based on the clones selected in step (4), for example based on further exploratory mutagenesis at specific positions in the CDRs of the clones selected in step (4), to enhance humanization and/or minimise human T cell epitope content and/or improve manufacturing properties in the antibody molecule or antigen-binding portion thereof produced in step (5).

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1A – FIG. 1B. Direct binding ELISA and Alphascreen competition screening of library-derived anti-ERBB3 Fabs against human and rhesus ERBB3-Fc proteins.

Clones were derived from multiple phage selection branches where phage populations were selected on biotinylated human, or rhesus monkey ERBB3 proteins in each of rounds II-IV. 'Hammer-Hug' rounds were also performed in separate rounds II and III. After each round of selection, library-derived clones were screened as periplasmically-expressed Fab proteins, against both human (huERBB3) and rhesus (rhERBB3) in ELISA (FIG. 1A), and in blocking the binding of 24C05 IgG in binding to huERBB3 by Alphascreen (FIG. 1B). Mean ± SD values in each round are represented in grey bars.

FIG. 2A – FIG. 2B. Analysis of CDR residue tolerance for mutation to germline. A plot of murine amino acid retention frequencies in the CDRs of the ELISA-positive population of 658 unique Fab clones that demonstrated human and rhesus ERBB3 cross-reactivity is shown for V_L (SEQ ID NOs:32-34) (FIG. 2A) and V_H (SEQ ID NOs:35-37) (FIG. 2B) domains, respectively. Only those residues targeted for human/murine residue mutagenesis are plotted, other than in the HCDR3. CDR residues noted in parentheses on the X-axes were identical to those found in the human germlines used for grafting (IGKV1-39 and IGHV3-11). Those residues in the CDRs that are not in parentheses, but whose values are set at 0, were mutated to human germline during the grafting process. In both plots the dashed line in grey at 75% represents the cut off for tolerance of murine residue replacement by human germline.

FIG. 3A – FIG. 3B. Direct titration ELISA for IgG binding to human and rhesus ERBB3 proteins. Chimeric and humanized 24C05, library-derived and designer clones in human IgG1null format were titrated (in nM) in a direct binding ELISA against human (FIG. 3A) and rhesus (FIG. 3B) ERBB3-Fc proteins. All clones other than Isotype IgG1null control demonstrated binding activity against both orthologs of ERBB3.

FIG. 4. Epitope competition analysis of IgG1null proteins in Alphascreen. Anti-ERBB3 IgG1null clones were applied in an epitope competition assay using Alphascreen technology. In this assay, library-derived and designer IgGs were analysed for their retention of the h24C05 epitope by competing for h24C05 IgG1null binding to human ERBB3 protein, in solution. All clones analysed showed strong, concentration-dependent neutralisation of h24C05 binding to ERBB3.

FIG. 5A – FIG. 5B. Flow cytometric binding to human and rhesus ERBB3+ HEK-293 cells for library-derived and primary designer leads. Chimeric and humanized 24C05, library-derived and designer leads in IgG1null format were examined for specific binding on human (FIG. 5A) and rhesus (FIG. 5B) ERBB3-transfected HEK-293 cells. IgGs were tested at concentrations ranging from 0.008-500 nM. Concentration-dependent binding was observed against both human and rhesus cell lines for all ERBB3-specific antibodies but not isotype controls. No binding signals above background were observed against wild type HEK-293 cells.

FIG. 6A – FIG. 6B. T cell epitope peptide content in lead antibody v-domains. The v-domains of h24C05 (FIG. 6A) and 15G11 (FIG. 6B) antibodies were examined for the presence of Germline (GE), High Affinity Foreign (HAF), Low Affinity Foreign (LAF) and TCED+ T cell receptor epitopes. Both the VH and VL domains of each antibody were found to contain multiple high-risk human T cell epitopes. In 15G11, despite having germline frameworks and multiple human germline residue changes in the CDRs, the high-risk epitope content was significantly increased in comparison to h24C05, rather than the expected reduction.

FIG. 7A – FIG. 7D. In silico disruption of T cell epitope peptide content in lead antibody v-domains. The v-domains High Affinity Foreign (HAF), Low Affinity Foreign (LAF) and TCED+ T cell receptor epitopes found in 15G11 were targeted for ablation. In silico mutagenesis analyses were performed to identify non-germline amino acid changes that might maintain antibody binding function but ablate one or more 9-mer peptide epitopes. There analyses were performed for peptides found in the HCDR-1 (FIG. 7A), LCDR-1 (FIG. 7B), LCDR-2 (FIG. 7C) and LCDR-3 (FIG. 7D). Residues are numbered according to the Kabat numbering scheme, the 9-mer peptide sequence is highlighted and p1 and p9 positions indicated. Favoured epitope disrupting mutations are indicated above arrows in grey, disfavoured in black. A delta symbol next to an amino acid one-letter abbreviation means that this mutation would render the new peptide a germ line (GE) peptide. An asterisk next to an amino acid one-letter abbreviation refers to a disfavoured mutation because the use of that residue would create a new isomerisation development risk motif (DG). FIG. 7A shows SEQ ID NO:257. FIG. 7B shows SEQ ID NO:258. FIG. 7C shows SEQ ID NO:259. FIG. 7D shows SEQ ID NO:260.

FIG. 8A – FIG. 8B. Direct titration ELISA for 15G11-DI IgGs binding to human and rhesus ErbB3 proteins. Chimeric and humanized 24C05, isotype control IgG1 and 15G11-DI1 to DI11 clones in human IgG1 format were titrated (in nM) in a direct binding ELISA against human (FIG. 8A) and rhesus (FIG. 8B) ERBB3-Fc proteins. All clones other than Isotype IgG1 control demonstrated binding activity against both orthologs of ERBB3.

FIG. 9. Epitope competition analysis of IgG1 proteins in Alphascreen. Chimeric and humanized 24C05, isotype control IgG1 and 15G11-DI1 to DI11 clones in human IgG1 format were applied in an epitope competition assay using Alphascreen technology. In this assay, IgGs were analysed for their retention of the same functional epitope as h24C05 by competing for h24C05 IgG1 binding to human ERBB3 protein, in solution. All clones analysed showed strong, concentration-dependent neutralisation of h24C05 binding to ERBB3, with the exception of 15G11-DI11.

FIG. 10A – FIG. 10B. Flow cytometric binding to human and rhesus ERBB3+ HEK-293 cells for library-derived and primary designer leads. Chimeric and humanized 24C05, isotype control IgG1 and 15G11-DI1 to DI11 clones in human IgG1 format were examined

for specific binding on human (FIG. 10A) and rhesus (FIG. 10B) ERBB3-transfected HEK-293 cells. IgGs were tested at concentrations ranging from 0.008-500 nM. Concentration-dependent binding was observed against both human and rhesus transfected cells for all ERBB3-specific antibodies but not isotype controls.

FIG. 11. Development risk ELISAs. Chimeric and humanized 24C05, isotype control IgG1, clinical-stage control antibodies, and 15G11-DI1 to DI11 clones in human IgG1 format were examined for nonspecific binding to the negatively charged biomolecules Insulin and double-stranded DNA (dsDNA). All lead clones demonstrated binding scores below 10 (15G11-DI10 being an exception), significantly lower than either of the negative control IgG1 Ustekinumab and Bevacizumab analogs. Strong off-target binding to insulin or dsDNA, as observed for Bococizumab and Briakinumab analogues, has been shown to be a high-risk indicator of poor pharmacokinetics of therapeutic antibodies.

FIG. 12A – FIG. 12G. Cell-based ErbB2-ErbB3 antagonism assay. Chimeric and humanized 24C05, isotype control IgG1 and clones 15G11 (FIG. 12A), 16B09 (FIG. 12B), 15G11-DI5 (FIG. 12C), 15G11-DI6 (FIG. 12D), 15G11-DI7 (FIG. 12E), 15G11-DI8 (FIG. 12F), and 15G11-DI9 (FIG. 12G) in human IgG1 format were titrated in a human ErbB3 signalling reporter assay (DiscoverX PathHunter eXpress ErbB2-ErbB3 assay, performed according to manufacturer's instructions). All clones other than the Isotype control induced strong, concentration-dependent ErbB3 antagonism, with highly similar potencies to h24C05.

FIG. 13. Cell-based ErbB2-ErbB3 antagonism assay for 15G11-DI9. Chimeric and humanized 24C05, isotype control IgG1 and clone 15G11-DI9 in human IgG1 format were titrated in a human ErbB3 signalling reporter assay (DiscoverX PathHunter eXpress ErbB2-ErbB3 assay, performed according to manufacturer's instructions). All clones other than the Isotype control induced strong, concentration-dependent ErbB3 antagonism, as evidenced by fold inhibition of signal.

FIG. 14A – FIG. 14E. T cell epitope peptide content in lead antibody v-domains. The v-domains of 15G11-DI5 (FIG. 14A), 15G11-DI6 (FIG. 14B), 15G11-DI7 (FIG. 14C), 15G11-DI8 (FIG. 14D) and 15G11-DI9 (FIG. 14E) antibodies were examined for the presence of Germline (GE), High Affinity Foreign (HAF), Low Affinity Foreign (LAF) and TCED+ T cell receptor epitopes. In all lead clones, the high-risk epitope content was progressively reduced, and germline epitope content maintained from 15G11-DI5 to 15G11-DI9, with 15G11-DI9 containing no predicted foreign epitopes at all, coupled with high GE content, suggesting that this clone may be fully non-immunogenic in man.

DETAILED DESCRIPTION OF THE INVENTION

According to a first aspect of the invention, there is provided an antibody molecule which specifically binds to human ERBB3 and optionally also to rhesus monkey ERBB3, or an

antigen-binding portion thereof, wherein the antibody molecule or antigen-binding portion comprises a heavy chain variable region with:

an HCDR1 having amino acids in sequence in the following order: G-F-T-F-S-D-Y-G or any amino acid (such as S)-M-S (SEQ ID NO:1);

an HCDR2 having amino acids in sequence in the following order: V-S-T-I-S-D-G or any amino acid (such as S, D)-G-T or a conservative substitution of T (such as S)-Y or any amino acid (such as T)-T or any amino acid (such as I)-Y-Y-P or any amino acid (such as A)-D-N or a conservative substitution of N (such as S)-V-K-G (SEQ ID NO:2); and

an HCDR3 having amino acids in sequence in the following order: E or any amino acid (such as M)-W or any amino acid (such as F, L, M, Q or Y)-G-D-Y or any amino acid (such as A, D, E, H, L, M, N, Q, S, T or W)-D-G-F or any amino acid (such as I, L, W, Y)-D-Y or any amino acid (such as A, D, E, F, H, I, K, L, M, N, Q, R, S, V, W) (SEQ ID NO:3).

In some aspects an anti-ERBB3 antibody or antigen-binding portion provided herein specifically binds to a ERBB3 protein comprising or consisting of SEQ ID NO:246 or SEQ ID NO:247. In some aspects an anti-ERBB3 antibody or antigen-binding portion provided herein specifically binds to a ERBB3 protein having an amino acid sequence that is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% identical to SEQ ID NO:246 or SEQ ID NO:247.

In aspects of the invention, the HCDR1 of the antibody molecule or antigen-binding portion may exclude the sequence GFTFSDYAMS (SEQ ID NO:4; 24C05 murine/humanized antibody HCDR1 disclosed in WO2011136911A2; US20110256154A1), the HCDR2 of the antibody molecule or antigen-binding portion may exclude the sequence VSTISDGGTYTYYPDNVKG (SEQ ID NO:5; 24C05 murine/humanized antibody HCDR2 disclosed in WO2011136911A2; US20110256154A1), and/or the HCDR3 of the antibody molecule or antigen-binding portion may exclude the sequence EWGDYDGFDY (SEQ ID NO:6; 24C05 murine/humanized antibody HCDR3 disclosed in WO2011136911A2; US20110256154A1).

The antibody molecule or antigen-binding portion may further comprise a light chain variable region with:

an LCDR1 having amino acids in sequence in the following order: R-A-S-Q-E or any amino acid (such as S, I, N)-I-S-G or a conservative substitution of G (such as S, T)-Y-L-S or a conservative substitution of S (such as N) (SEQ ID NO:7);

an LCDR2 having amino acids in sequence in the following order: A or any amino acid (such as E)-A-S-T or a conservative substitution of T (such as S, N)-L-D or any amino acid (such as H, K, Q)-S or T (SEQ ID NO:8); and

an LCDR3 having amino acids in sequence in the following order: L or any amino acid (such as Q)-Q-Y or any amino acid (such as S)-D or any amino acid (such as Y)-S-Y or any amino acid (such as T, S)-P or any amino acid (such as H)-Y or any amino acid (such as L)-T (SEQ ID NO:9).

In aspects of the invention, the LCDR1 of the antibody molecule or antigen-binding portion may exclude the sequence RASQEISGYLS (SEQ ID NO:10; 24C05 murine/humanized antibody LCDR1 disclosed in WO2011136911A2; US20110256154A1), and/or the LCDR2 of the antibody molecule or antigen-binding portion may exclude the sequence AASTLDS (SEQ ID NO:11; 24C05 murine/humanized antibody LCDR2 disclosed in WO2011136911A2; US20110256154A1), and/or the LCDR3 of the antibody molecule or antigen-binding portion may exclude the sequence LQYDSYPYT (SEQ ID NO:12; 24C05 murine/humanized antibody LCDR3 disclosed in WO2011136911A2; US20110256154A1).

In some aspects, disclosed herein is an anti-ERBB3 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein

(a) the HCDR1 comprises the amino acid sequence G-F-T-F-S-D-Y-X_1-M-S, wherein X_1 is G or any other amino acid (for example, S) (SEQ ID NO:1);

(b) the HCDR2 comprises V-S-T-I-S-D-X_1-G-X_2-X_3-X_4-Y-Y-X_5-D-X_6-V-K-G, wherein X_1 is G or any other amino acid (for example, S or D), X_2 is T or a conservative substitution of T (for example, S), X_3 is Y or any other amino acid (for example, T), X_4 is T or any other amino acid (for example, I), X_5 is P or any other amino acid (for example, A), and X_6 is N or a conservative substitution of N (for example, S) (SEQ ID NO:2);

(c) the HCDR3 comprises X_1-X_2-G-D-X_3-D-G-X_4-D-X_5, wherein X_1 is E or any other amino acid (for example, M), X_2 is W or any other amino acid (for example, F, L, M, Q or Y), X_3 is Y or any other amino acid (for example, A, D, E, H, L, M, N, Q, S, T or W), X_4 is F or any other amino acid (for example, I, L, W or Y), and X_5 is Y or any other amino acid (for example, A, D, E, F, H, I, K, L, M, N, Q, R, S, V or W) (SEQ ID NO:3);

(d) the LCDR1 comprises R-A-S-Q-X_1-I-S-X_2-Y-L-X_3, wherein X_1 is E or any other amino acid (for example, S, I or N), X_2 is G or a conservative substitution of G (for example, S or T), and X_3 is S or a conservative substitution of S (for example, N) (SEQ ID NO:7);

(e) the LCDR2 comprises X_1-A-S-X_2-L-X_3-S, wherein X_1 is A or any other amino acid (for example, E), X_2 is T or a conservative substitution of T (for example, S or N), and X_3 is or D any other amino acid (for example, H, K or Q) (SEQ ID NO:8); and

(f) the LCDR3 comprises X_1-Q-X_2-X_3-S-X_4-X_5-X_6-T, wherein X_1 is L or any other amino acid (for example, Q), X_2 is Y or any other amino acid (for example, S), X_3 is D or any other amino acid (for example, Y), X_4 is Y or any other amino acid (for example, T or S), X_5 is P or any other amino acid (for example, H), and X_6 is Y or any other amino acid (for example, L) (SEQ ID NO:9). In some aspects, the LCDR2 comprises X_1-A-S-X_2-L-X_3-S (SEQ ID NO:8), wherein the seventh residue in the sequence is a conservative substitution of S (for example, T).

In some aspects, disclosed herein is an anti-ERBB3 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region comprising, in amino-terminal to carboxyl-terminal order, FR1-HCDR1-FR2-HCDR2-FR3-HCDR3-FR4 and a light chain variable (VL) region comprising, in amino-terminal to carboxyl-terminal order, FR1-LCDR1-FR2-LCDR2-FR3-LCDR3-FR4, wherein the HCDR1 is SEQ ID NO:1, the HCDR2 is SEQ ID NO:2, the HCDR3 is SEQ ID NO:3, the LCDR1 is SEQ ID NO:7, the LCDR2 is SEQ ID NO:8 and the LCDR3 is SEQ ID NO:9, wherein the heavy chain FR1, FR2, FR3 and FR4 amino acid sequences are the heavy chain FR1, FR2, FR3 and FR4 amino acid sequences in SEQ ID NO: 86 (see Table 2) and wherein the light chain FR1, FR2, FR3 and FR4 amino acid sequences are the light chain FR1, FR2, FR3 and FR4 amino acid sequences in SEQ ID NO: 88 (see Table 2).

As elaborated herein, the present inventors have succeeded for the first time in generating a number of optimized anti-ERBB3 antibody molecules using CDR sequences derived from the murine anti-ERBB3 antibody 24C05 disclosed in WO2011136911A2; US20110256154A1. In embodiments of the present invention, these antibody molecules have been selected to have binding specificity to both human ERBB3 as well as rhesus monkey ERBB3 (to facilitate *in vivo* studies in an appropriate animal test species). Further refining of the optimized antibody molecules as described herein has provided improved variable domain stability, higher expression yields, and/or reduced immunogenicity.

Preferred optimized anti-ERBB3 antibody molecules of the present invention do not necessarily have the maximum number of human germline substitutions at corresponding murine CDR or other (such as framework) amino acid positions. As elaborated in the experimental section below, we have found that “maximally humanized” antibody molecules are not necessary “maximally optimized” in terms of anti-ERBB3 binding characteristics and/or other desirable features.

The present invention encompasses modifications to the amino acid sequence of the antibody molecule or antigen-binding portion thereof as defined herein. For example, the

invention includes antibody molecules and corresponding antigen-binding portions thereof comprising functionally equivalent variable regions and CDRs which do not significantly affect their properties as well as variants which have enhanced or decreased activity and/or affinity. For example, the amino acid sequence may be mutated to obtain an antibody with the desired binding affinity to ERBB3. Insertions which include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues, are envisaged. Examples of terminal insertions include an antibody molecule with an N-terminal methionyl residue or the antibody molecule fused to an epitope tag. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody of an enzyme or a polypeptide which increases the half-life of the antibody in the blood circulation.

The antibody molecule or antigen-binding portion of the invention may include glycosylated and nonglycosylated polypeptides, as well as polypeptides with other post-translational modifications, such as, for example, glycosylation with different sugars, acetylation, and phosphorylation. The antibody molecule or antigen-binding portion of the invention may be mutated to alter such post-translational modifications, for example by adding, removing or replacing one or more amino acid residues to form or remove a glycosylation site.

The antibody molecule or antigen-binding portion of the invention may be modified for example by amino acid substitution to remove potential proteolytic sites in the antibody.

In the antibody molecule or antigen-binding portion thereof, the HCDR1 may have the amino acid sequence: G-F-T-F-S-D-Y-E/G/H/N/R/S/T/Q/V-M-S (SEQ ID NO:38); the HCDR2 may have the amino acid sequence: V-S-T-I-S-D-G/S/D-G-T/S-Y/T-T/I-Y-Y-P/A-D-N/S-V-K-G (SEQ ID NO:39); and the HCDR3 may have the amino acid sequence: E/M-W/F/L/M/Q/Y-G-D-Y/A/D/E/H/L/M/N/Q/S/T/W-D-G-F/I/L/W/Y-D-Y/A/D/E/F/H/I/K/L/M/N/Q/R/S/V/W (SEQ ID NO:40).

For example, the HCDR1 may have the amino acid sequence: G-F-T-F-S-D-Y-G/S-M-S (SEQ ID NO:41); the HCDR2 may have the amino acid sequence: V-S-T-I-S-D-G/S-G-S-Y/T-T/I-Y-Y-P/A-D-S-V-K-G (SEQ ID NO:42); and the HCDR3 may have the amino acid sequence: E-W/L/Y-G-D-Y-D-G-F-D-Y/E/F/H/N (SEQ ID NO:43).

In the antibody molecule or antigen-binding portion thereof, the LCDR1 may have the amino acid sequence: R-A-S-Q-E/S/I/N-I-S-G/S-Y-L-S/N (SEQ ID NO:44); the LCDR2 may have the amino acid sequence: A/E-A-S-T/S/N-L-D/H/K/Q-S (SEQ ID NO:45); and the LCDR3

may have the amino acid sequence: L/Q-Q-Y/S-D/Y-S-Y/T-P/H-Y/L-T (SEQ ID NO:46). In the antibody molecule or antigen-binding portion thereof, the LCDR1 may have the amino acid sequence: R-A-S-Q-E/S/I/N-I-S-G/S/T-Y-L-S/N; the LCDR2 may have the amino acid sequence: A/E-A-S-T/S/N-L-D/H/K/Q-S/T; and the LCDR3 may have the amino acid sequence: L/Q-Q-Y/S-D/Y-S-Y/T/S-P/H-Y/L-T.

For example, the LCDR1 may have the amino acid sequence: R-A-S-Q-E/S-I-S-G/S-Y-L-S/N (SEQ ID NO:47); the LCDR2 may have the amino acid sequence: A-A-S-T/S-L-D/Q-S (SEQ ID NO:48); and the LCDR3 may have the amino acid sequence: L-Q-Y-D/Y-S-T-P-Y/L-T (SEQ ID NO:49). For example, the LCDR1 may have the amino acid sequence: R-A-S-Q-E/S-I-S-G/S/T-Y-L-S/N; the LCDR2 may have the amino acid sequence: A-A-S-T/S-L-D/Q-S/T; and the LCDR3 may have the amino acid sequence: L-Q-Y-D/Y-S-T/S-P-Y/L-T.

In specific embodiments of the invention, the antibody molecule or antigen-binding portion may comprise:

(a) the amino acid sequences RASQSISSYLS (SEQ ID NO:16; LCDR1), AASTLQS (SEQ ID NO:26; LCDR2), LQYDSTPLT (SEQ ID NO:18; LCDR3), GFTFSDYGMS (SEQ ID NO:13; HCDR1), VSTISDGGSYTYYADNVKG (SEQ ID NO:31; HCDR2), EWGDYDGFDF (SEQ ID NO:15; HCDR3), [Clone 15D10]; or

(b) the amino acid sequences RASQSISGYLS (SEQ ID NO:30; LCDR1), AASTLQS (SEQ ID NO:26; LCDR2), LQYDSTPYT (SEQ ID NO:23; LCDR3), GFTFSDYGMS (SEQ ID NO:13; HCDR1), VSTISDGGSYTYYADSVKG (SEQ ID NO:28; HCDR2), EWGDYDGFDE (SEQ ID NO:29; HCDR3), [Clone 17H10]; or

(c) the amino acid sequences RASQSISSYLN (SEQ ID NO:50; LCDR1), AASSLDS (SEQ ID NO:22; LCDR2), LQYDSTPLT (SEQ ID NO:18; LCDR3), GFTFSDYGMS (SEQ ID NO:13; HCDR1), VSTISDGGSYTYYADSVKG (SEQ ID NO:28; HCDR2), EYGDYDGFDY (SEQ ID NO:51; HCDR3), [Clone 09D12]; or

(d) the amino acid sequences RASQEISSYLS (SEQ ID NO:21; LCDR1), AASSLQS (SEQ ID NO:17; LCDR2), LQYDSTPLT (SEQ ID NO:18; LCDR3), GFTFSDYGMS (SEQ ID NO:13; HCDR1), VSTISDSGSYIYYADSVKG (SEQ ID NO:14; HCDR2), EWGDYDGFDH (SEQ ID NO:27; HCDR3), [Clone 15D03]; or

(e) the amino acid sequences RASQIISSYLS (SEQ ID NO:52; LCDR1), AASSLDS (SEQ ID NO:22; LCDR2), LQYYSTPLT (SEQ ID NO:53; LCDR3), GFTFSDYGMS (SEQ ID NO:13; HCDR1), VSTISDSGSYTYYADSVKG (SEQ ID NO:54; HCDR2), EWGDYDGFDN (SEQ ID NO:55; HCDR3), [Clone 11H02]; or

(f) the amino acid sequences RASQEISSYLS (SEQ ID NO:21; LCDR1), AASSLDS (SEQ ID NO:22; LCDR2), LQYDSTPYT (SEQ ID NO:23; LCDR3), GFTFSDYGMS (SEQ ID NO:13;

HCDR1), VSTISDSGSYTYYPDSVKG (SEQ ID NO:19; HCDR2), ELGDYDGFDY (SEQ ID NO:20; HCDR3), [Clone 15G11]; or

(g) the amino acid sequences RASQSISSYLS (SEQ ID NO:16; LCDR1), AASSLQS (SEQ ID NO:17; LCDR2), LQYDSTPLT (SEQ ID NO:18; LCDR3), GFTFSDYGMS (SEQ ID NO:13; HCDR1), VSTISDSGTTIYYADNVKG (SEQ ID NO:56; HCDR2), EYGDYDGFDY (SEQ ID NO:51; HCDR3), [Clone 15E02]; or

(h) the amino acid sequences RASQSISSYLS (SEQ ID NO:16; LCDR1), AASSLQS (SEQ ID NO:17; LCDR2), LQYDSTPLT (SEQ ID NO:18; LCDR3), GFTFSDYSMS (SEQ ID NO:24; HCDR1), VSTISDGGSYTYYPDSVKG (SEQ ID NO:57; HCDR2), ELGDYDGFDY (SEQ ID NO:20; HCDR3), [Clone 09HO2]; or

(i) the amino acid sequences RASQEISSYLS (SEQ ID NO:21; LCDR1), AASTLQS (SEQ ID NO:26; LCDR2), LQYDSTPLT (SEQ ID NO:18; LCDR3), GFTFSDYSMS (SEQ ID NO:24; HCDR1), VSTISDSGTYTYYPDSVKG (SEQ ID NO:25; HCDR2), EWGDYDGFDF (SEQ ID NO:15; HCDR3), [Clone 16B09]; or

(j) the amino acid sequences RASQSISSYLS (SEQ ID NO:16; LCDR1), AASSLQS (SEQ ID NO:17; LCDR2), LQYDSTPLT (SEQ ID NO:18; LCDR3), GFTFSDYGMS (SEQ ID NO:13; HCDR1), VSTISDSGSYIYYADSVKG (SEQ ID NO:14; HCDR2), ELGDYDGFDY (SEQ ID NO:20; HCDR3), [Clone MH1]; or

(k) the amino acid sequences RASQSISSYLS (SEQ ID NO:16; LCDR1), AASSLQS (SEQ ID NO:17; LCDR2), LQYDSTPLT (SEQ ID NO:18; LCDR3), GFTFSDYGMS (SEQ ID NO:13; HCDR1), VSTISDSGSYIYYADSVKG (SEQ ID NO:14; HCDR2), EWGDYDGFDF (SEQ ID NO:15; HCDR3), [Clone MH2]; or

(l) the amino acid sequences RASQSISSYLS (SEQ ID NO:16; LCDR1), AASSLQS (SEQ ID NO:17; LCDR2), LQYDSTPLT (SEQ ID NO:18; LCDR3), GFTFSDYSMS (SEQ ID NO:24; HCDR1), VSTISDSGSTIYYADSVKG (SEQ ID NO:58; HCDR2), EWGDYDGFDF (SEQ ID NO:15; HCDR3), [Clone MH3]; or

(m) the amino acid sequences RASQSISSYLS (SEQ ID NO:16; LCDR1), AASSLQS (SEQ ID NO:17; LCDR2), LQYDSTPLT (SEQ ID NO:18; LCDR3), GFTFSDYGMS (SEQ ID NO:13; HCDR1), VSTISDSGSYIYYADSVKG (SEQ ID NO:14; HCDR2), EWGDYDGFDE (SEQ ID NO:29; HCDR3), [Clone MH4]; or

(n) the amino acid sequences RASQSISSYLS (SEQ ID NO:16; LCDR1), AASSLQS (SEQ ID NO:17; LCDR2), LQYDSTPLT (SEQ ID NO:18; LCDR3), GFTFSDYGMS (SEQ ID NO:13; HCDR1), VSTISDSGSTIYYADSVKG (SEQ ID NO:58; HCDR2), EYGDYDGFDY (SEQ ID NO:51; HCDR3), [Clone MH5]; or

(o) the amino acid sequences RASQSISSYLN (SEQ ID NO:50; LCDR1), AASSLQS (SEQ ID NO:17; LCDR2), LQYDSTPLT (SEQ ID NO:18; LCDR3), GFTFSDYGMS (SEQ ID NO:13; HCDR1), VSTISDSGSTIYYADSVKG (SEQ ID NO:58; HCDR2), EYGDYDGFDY (SEQ ID NO:51; HCDR3), [Clone TTP]; or

(p) the amino acid sequences RASQEISTYLS (SEQ ID NO: 261; LCDR1), AASTLQS (SEQ ID NO:26; LCDR2), LQYDSSPLT (SEQ ID NO: 262; LCDR3), GFTFSDYSMS (SEQ ID NO: 24; HCDR1), VSTISDSGTYTYYPDSVKG (SEQ ID NO: 25; HCDR2), EWGDYDGFDF (SEQ ID NO: 15; HCDR3), [Clone 15G11-DI9]; or

(q) the amino acid sequences RASQEISSYLS (SEQ ID NO: 21; LCDR1), AASSLDT (SEQ ID NO: 263; LCDR2), LQYDSTPYT (SEQ ID NO: 23; LCDR3), GFTFSDYSMS (SEQ ID NO: 24; HCDR1), VSTISDSGTYTYYPDSVKG (SEQ ID NO: 25; HCDR2), EWGDYDGFDF (SEQ ID NO: 15; HCDR3), [Clone 15G11-DI5].

In some aspects, disclosed herein is an anti-ERBB3 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein

(a) the VH region amino acid sequence comprises HCDR1 of GFTFSDYSMS (SEQ ID NO: 24), HCDR2 of VSTISDSGTYTYYPDSVKG (SEQ ID NO: 25) and HCDR3 of EWGDYDGFDF (SEQ ID NO: 15); and the VL region amino acid sequence comprises LCDR1 of RASQEISTYLS (SEQ ID NO: 261), LCDR2 of AASTLQS (SEQ ID NO:26) and LCDR3 of LQYDSSPLT (SEQ ID NO: 262);

(b) the VH region amino acid sequence comprises HCDR1 of GFTFSDYSMS (SEQ ID NO: 24), HCDR2 of VSTISDSGTYTYYPDSVKG (SEQ ID NO: 25) and HCDR3 of EWGDYDGFDF (SEQ ID NO: 15); and the VL region amino acid sequence comprises LCDR1 of RASQEISSYLS (SEQ ID NO: 21), LCDR2 of AASSLDT (SEQ ID NO: 263) and LCDR3 of LQYDSTPYT (SEQ ID NO: 23);

(c) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDSGSYTYYPDSVKG (SEQ ID NO:19) and HCDR3 of ELGDYDGFDY (SEQ ID NO:20); and the VL region amino acid sequence comprises LCDR1 of RASQEISSYLS (SEQ ID NO:21), LCDR2 of AASSLDS (SEQ ID NO:22) and LCDR3 of LQYDSTPYT (SEQ ID NO:23);

(d) the VH region amino acid sequence comprises HCDR1 of GFTFSDYSMS (SEQ ID NO:24), HCDR2 of VSTISDSGTYTYYPDSVKG (SEQ ID NO:25) and HCDR3 of EWGDYDGFDF (SEQ ID NO:15); and the VL region amino acid sequence comprises LCDR1 of RASQEISSYLS (SEQ ID NO:21), LCDR2 of AASTLQS (SEQ ID NO:26) and LCDR3 of LQYDSTPLT (SEQ ID NO:18);

(e) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDSGSYIYYADSVKG (SEQ ID NO:14) and HCDR3 of EWGDYDGFDF (SEQ ID NO:15); and the VL region amino acid sequence comprises LCDR1 of RASQSISSYLS (SEQ ID NO:16), LCDR2 of AASSLQS (SEQ ID NO:17) and LCDR3 of LQYDSTPLT (SEQ ID NO:18);

(f) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDSGSYIYYADSVKG (SEQ ID NO:14) and HCDR3 of EWGDYDGFDH (SEQ ID NO:27); and the VL region amino acid sequence comprises LCDR1 of RASQEISSYLS (SEQ ID NO:21), LCDR2 of AASSLQS (SEQ ID NO:17) and LCDR3 of LQYDSTPLT (SEQ ID NO:18);

(g) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDGGSYTYYADSVKG (SEQ ID NO:28) and HCDR3 of EWGDYDGFDE (SEQ ID NO:29); and the VL region amino acid sequence comprises LCDR1 of RASQSISGYLS (SEQ ID NO:30), LCDR2 of AASTLQS (SEQ ID NO:26) and LCDR3 of LQYDSTPYT (SEQ ID NO:23);

(h) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDGGSYTYYADNVKG (SEQ ID NO:31) and HCDR3 of EWGDYDGFDF (SEQ ID NO:15); and the VL region amino acid sequence comprises LCDR1 of RASQSISSYLS (SEQ ID NO:16), LCDR2 of AASTLQS (SEQ ID NO:26) and LCDR3 of LQYDSTPLT (SEQ ID NO:18); or

(i) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDSGSYIYYADSVKG (SEQ ID NO:14) and HCDR3 of EWGDYDGFDE (SEQ ID NO:29); and the VL region amino acid sequence comprises LCDR1 of RASQSISSYLS (SEQ ID NO:16), LCDR2 of AASSLQS (SEQ ID NO:17) and LCDR3 of LQYDSTPLT (SEQ ID NO:18).

In some aspects, disclosed herein is an anti-ERBB3 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the VH region comprises any one of the VH region amino acid sequences in Table 7 or 8 and the VL region comprises any one of the VL region amino acid sequences in Table 6 or 8.

In some aspects, disclosed herein is an anti-ERBB3 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein

(a) the VH region amino acid sequence comprises SEQ ID NO:236 and the VL region amino acid sequence comprises SEQ ID NO:225;

(b) the VH region amino acid sequence comprises SEQ ID NO:232 and the VL region amino acid sequence comprises SEQ ID NO:221;

(c) the VH region amino acid sequence comprises SEQ ID NO:253 and the VL region amino acid sequence comprises SEQ ID NO:254;

(d) the VH region amino acid sequence comprises SEQ ID NO:255 and the VL region amino acid sequence comprises SEQ ID NO:256;

(e) the VH region amino acid sequence comprises SEQ ID NO:228 and the VL region amino acid sequence comprises SEQ ID NO:217;

(f) the VH region amino acid sequence comprises SEQ ID NO:229 and the VL region amino acid sequence comprises SEQ ID NO:218;

(g) the VH region amino acid sequence comprises SEQ ID NO:230 and the VL region amino acid sequence comprises SEQ ID NO:219;

(h) the VH region amino acid sequence comprises SEQ ID NO:231 and the VL region amino acid sequence comprises SEQ ID NO:220;

(i) the VH region amino acid sequence comprises SEQ ID NO:233 and the VL region amino acid sequence comprises SEQ ID NO:222;

(j) the VH region amino acid sequence comprises SEQ ID NO:234 and the VL region amino acid sequence comprises SEQ ID NO:223;

(k) the VH region amino acid sequence comprises SEQ ID NO:235 and the VL region amino acid sequence comprises SEQ ID NO:224;

(l) the VH region amino acid sequence comprises SEQ ID NO:237 and the VL region amino acid sequence comprises SEQ ID NO:226; or

(m) the VH region amino acid sequence comprises SEQ ID NO:238 and the VL region amino acid sequence comprises SEQ ID NO:227.

In some aspects, disclosed herein is an anti-ERBB3 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein

(a) the VH region amino acid sequence is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% identical to SEQ ID NO:236 and the VL region amino acid sequence is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% identical to SEQ ID NO:225;

(b) the VH region amino acid sequence is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% identical to SEQ ID NO:232 and the VL region amino acid sequence is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% identical to SEQ ID NO:221;

(c) the VH region amino acid sequence is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least

about 96%, at least about 97%, at least about 98% or at least about 99% identical to SEQ ID NO:253 and the VL region amino acid sequence is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% identical to SEQ ID NO:254; or

(d) the VH region amino acid sequence is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% identical to SEQ ID NO:255 and the VL region amino acid sequence is at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98% or at least about 99% identical to SEQ ID NO:256.

In some aspects, the antibody or antigen-binding portion as defined herein may be isolated.

The antibody molecule or antigen-binding portion as defined herein may cross-compete for binding to ERBB3 with an antibody or antigen-binding portion thereof comprising the sets of CDRs disclosed herein. In some embodiments, the invention provides an isolated anti-ERBB3 antibody or an antigen-binding portion thereof, wherein the antibody or antigen-binding portion cross-competes for binding to ERBB3 with the antibody or antigen-binding portion comprising the sets of CDRs disclosed herein; and (a) comprises fully germline human framework amino acid sequences; and/or (b) does not comprise an isomerization site in the LCDR2; and/or (c) does not comprise a 'DG' isomerization site in the HCDR2; and/or (d) does not comprise an oxidation site at position 2 in the HCDR3; and/or and/or (e) exhibits a reduced number of predicted foreign human T cell receptor binding peptides in its v-domains in comparison to h24C05; and/or (f) contains no predicted foreign human T cell receptor binding peptides in its v-domains. In some embodiments, the anti-ERBB3 antibody or an antigen-binding portion thereof does not comprise an oxidation site at position 2 (e.g., W) in the HCDR3.

The terms "cross-compete", "cross-competition", "cross-block", "cross-blocked" and "cross-blocking" are used interchangeably herein to mean the ability of an antibody or portion thereof to interfere with the binding directly or indirectly through allosteric modulation of the anti-ERBB3 antibodies of the invention to the target ERBB3 (e.g., human ERBB3). The extent to which an antibody or portion thereof is able to interfere with the binding of another to the target, and therefore whether it can be said to cross-block or cross-compete according to the invention, can be determined using competition binding assays. One example of a binding competition assay is Homogeneous Time Resolved Fluorescence

(HTRF). One particularly suitable quantitative cross-competition assay uses a FACS- or an AlphaScreen-based approach to measure competition between the labelled (e.g. His tagged, biotinylated or radioactive labelled) antibody or portion thereof and the other antibody or portion thereof in terms of their binding to the target. In general, a cross-competing antibody or portion thereof is, for example, one which will bind to the target in the cross-competition assay such that, during the assay and in the presence of a second antibody or portion thereof, the recorded displacement of the immunoglobulin single variable domain or polypeptide according to the invention is up to 100% (e.g. in a FACS based competition assay) of the maximum theoretical displacement (e.g. displacement by cold (e.g. unlabeled) antibody or fragment thereof that needs to be cross-blocked) by the potentially cross-blocking antibody or fragment thereof that is present in a given amount. Preferably, cross-competing antibodies or portions thereof have a recorded displacement that is between 10% and 100%, or between 50% and 100%.

The antibody molecule or antigen-binding portion as defined herein may comprise one or more substitutions, deletions and/or insertions which remove a post-translational modification (PTM) site, for example a glycosylation site (N-linked or O-linked), a deamination site, a phosphorylation site or an isomerisation/fragmentation site.

More than 350 types of PTM are known. Key forms of PTM include phosphorylation, glycosylation (*N*- and *O*-linked), sumoylation, palmitoylation, acetylation, sulfation, myristoylation, prenylation and methylation (of K and R residues). Statistical methods to identify putative amino acid sites responsible for specific PTMs are well known in the art (see Zhou *et al.*, 2016, Nature Protocols 1: 6588-1321). Removal of such a site for example by substitution, deletion and/or insertion and then optionally testing (experimentally and/or theoretically) for (a) binding activity and/or (b) loss of the PTM is contemplated.

For example, the 24C05 murine LCDR2 (as defined herein, i.e. the amino acid sequence AASTLDS (SEQ ID NO:11)) has been identified to have a putative isomerisation site at residue 6. Removal this site at equivalent positions in an LCDR2 of the invention, for example by substitution of D (such as to Q), is envisaged (as for example in clone MH2 and others found in Tables 3 and 4).

In a further example, the 24C05 murine HCDR2 (as defined herein, i.e. the amino acid sequence VSTISDGGTYTYYPDNVKG (SEQ ID NO:5)) has been identified to have a putative isomerisation site at residue 6 (D). Reduction in chemical modification risk this site at equivalent positions in an HCDR2 of the invention, for example by substitution of G (such

as to S, or D), is envisaged (as for example in clone 15G11 and others found in Tables 3 and 4).

In a further example, the 24C05 murine HCDR3 (as defined herein, i.e. the amino acid sequence EWGDYDGFDY (SEQ ID NO:6)) has been identified to have a putative oxidation site at residue 2 (W). Removal this site at equivalent positions in an LCDR1 of the invention, for example by substitution of W (such as to L or Y), is envisaged (as for example in clone 15G11 and others found in Tables 3 and 4).

The antibody molecule or antigen-binding portion thereof may be human, humanized or chimeric.

The antibody molecule or antigen-binding portion thereof may comprise one or more human variable domain framework scaffolds into which the CDRs have been inserted. For example, the VH region, the VL region, or both the VH and the VL region may comprise one or more human framework region amino acid sequences.

The antibody molecule or antigen-binding portion thereof may comprise an IGHV3-11 human germline scaffold into which the corresponding HCDR sequences have been inserted. The antibody molecule or antigen-binding portion thereof may comprise a VH region that comprises an IGHV3-11 human germline scaffold amino acid sequence into which a set of corresponding HCDR1, HCDR2 and HCDR3 amino acid sequences have been inserted.

The antibody molecule or antigen-binding portion thereof may comprise an IGKV1-39 human germline scaffold into which the corresponding LCDR sequences have been inserted. The antibody molecule or antigen-binding portion thereof may comprise a VL region that comprises an IGKV1-39 human germline scaffold amino acid sequence into which a set of corresponding LCDR1, LCDR2 and LCDR3 amino acid sequences have been inserted.

The antibody molecule or antigen-binding portion thereof may comprise an IGHV3-11 human germline scaffold into which the corresponding HCDR sequences have been inserted and an IGKV1-39 human germline scaffold into which the corresponding LCDR sequences have been inserted. The antibody molecule or antigen-binding portion thereof may comprise a VH region that comprises an IGHV3-11 human germline scaffold amino acid sequence into which a set of corresponding HCDR1, HCDR2 and HCDR3 amino acid sequences have been inserted and a VL region that comprises an IGKV1-39 human germline scaffold amino acid sequence into which a set of corresponding LCDR1, LCDR2 and LCDR3 amino acid sequences have been inserted. The HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3

amino acid sequences may be the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 amino acid sequences of any one of the clones in Table 4 (with all six CDR sequences being from the same clone).

In some aspects, the antibody molecule or antigen-binding portion thereof may comprise an immunoglobulin constant region. In some embodiments, the immunoglobulin constant region is IgG1, IgG2, IgG3, IgG4, IgA1 or IgA2. In additional embodiments, the immunoglobulin constant region is IgG1, IgG2, IgG3, IgG1null, IgG4(S228P), IgA1 or IgA2. The antibody molecule or antigen-binding portion thereof may comprise an immunologically inert constant region. In some aspects, an anti-ERBB3 antibody or antigen-binding portion thereof may comprise an immunoglobulin constant region comprising a wild-type human IgG1 constant region, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A or a human IgG1 constant region comprising the amino acid substitutions L234A, L235A, G237A and P331S. In some aspects, an anti-ERBB3 antibody or antigen-binding portion thereof may comprise an immunoglobulin constant region comprising a wild-type human IgG2 constant region or a wild-type human IgG4 constant region. In some aspects, an anti-ERBB3 antibody may comprise an immunoglobulin constant region comprising any one of the amino acid sequences in Table 9. The Fc region sequences in Table 9 begin at the CH1 domain. In some aspects, an anti-ERBB3 antibody may comprise an immunoglobulin constant region comprising an amino acid sequence of an Fc region of human IgG4, human IgG4(S228P), human IgG2, human IgG1, human IgG1-3M or human IgG1-4M. For example, the human IgG4(S228P) Fc region comprises the following substitution compared to the wild-type human IgG4 Fc region: S228P. For example, the human IgG1-3M Fc region comprises the following substitutions compared to the wild-type human IgG1 Fc region: L234A, L235A and G237A, while the human IgG1-4M Fc region comprises the following substitutions compared to the wild-type human IgG1 Fc region: L234A, L235A, G237A and P331S. In some aspects, a position of an amino acid residue in a constant region of an immunoglobulin molecule is numbered according to EU nomenclature (Ward *et al.*, 1995 *Therap. Immunol.* 2:77-94). In some aspects, an immunoglobulin constant region may comprise an RDELT (SEQ ID NO:248) motif or an REEM (SEQ ID NO:249) motif (underlined in Table 9). The REEM (SEQ ID NO:249) allotype is found in a smaller human population than the RDELT (SEQ ID NO:248) allotype. In some aspects, an anti-ERBB3 antibody may comprise an immunoglobulin constant region comprising any one of SEQ ID NOS:239-245. In some aspects, an anti-ERBB3 antibody may comprise the six CDR amino acid sequences of any one of the clones in Table 4 and any one of the Fc region amino acid sequences in Table 9. In some aspects, an anti-ERBB3 antibody may comprise an immunoglobulin heavy chain constant region comprising any one

of the Fc region amino acid sequences in Table 9 and an immunoglobulin light chain constant region that is a kappa light chain constant region or a lambda light chain constant region.

In some aspects, disclosed herein is an anti-ERBB3 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region, a light chain variable (VL) region and a heavy chain constant region, wherein

(a) the VH region amino acid sequence comprises HCDR1 of GFTFSDYSMS (SEQ ID NO: 24), HCDR2 of VSTISDSGTYTYYPDSVKG (SEQ ID NO: 25) and HCDR3 of EWGDYDGFDF (SEQ ID NO: 15); the VL region amino acid sequence comprises LCDR1 of RASQEISTYLS (SEQ ID NO: 261), LCDR2 of AASTLQS (SEQ ID NO:26) and LCDR3 of LQYDSSPLT (SEQ ID NO: 262); and the heavy chain constant region comprises any one of SEQ ID NOS: 239-245;

(b) the VH region amino acid sequence comprises HCDR1 of GFTFSDYSMS (SEQ ID NO: 24), HCDR2 of VSTISDSGTYTYYPDSVKG (SEQ ID NO: 25) and HCDR3 of EWGDYDGFDF (SEQ ID NO: 15); the VL region amino acid sequence comprises LCDR1 of RASQEISSYLS (SEQ ID NO: 21), LCDR2 of AASSLDT (SEQ ID NO: 263) and LCDR3 of LQYDSTPYT (SEQ ID NO: 23); and the heavy chain constant region comprises any one of SEQ ID NOS: 239-245;

(c) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDSGSYTYYPDSVKG (SEQ ID NO:19) and HCDR3 of ELGDYDGFDY (SEQ ID NO:20); the VL region amino acid sequence comprises LCDR1 of RASQEISSYLS (SEQ ID NO:21), LCDR2 of AASSLDS (SEQ ID NO:22) and LCDR3 of LQYDSTPYT (SEQ ID NO:23); and the heavy chain constant region comprises any one of SEQ ID NOS: 239-245;

(d) the VH region amino acid sequence comprises HCDR1 of GFTFSDYSMS (SEQ ID NO:24), HCDR2 of VSTISDSGTYTYYPDSVKG (SEQ ID NO:25) and HCDR3 of EWGDYDGFDF (SEQ ID NO:15); the VL region amino acid sequence comprises LCDR1 of RASQEISSYLS (SEQ ID NO:21), LCDR2 of AASTLQS (SEQ ID NO:26) and LCDR3 of LQYDSTPLT (SEQ ID NO:18); and the heavy chain constant region comprises any one of SEQ ID NOS: 239-245;

(e) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDSGSYIYYADSVKG (SEQ ID NO:14) and HCDR3 of EWGDYDGFDF (SEQ ID NO:15); the VL region amino acid sequence comprises LCDR1 of RASQSISSYLS (SEQ ID NO:16), LCDR2 of AASSLQS (SEQ ID NO:17) and LCDR3 of LQYDSTPLT (SEQ ID NO:18); and the heavy chain constant region comprises any one of SEQ ID NOS: 239-245;

(f) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDSGSYIYYADSVKG (SEQ ID NO:14) and HCDR3 of

EWGDYDGFDH (SEQ ID NO:27); the VL region amino acid sequence comprises LCDR1 of RASQEISSYLS (SEQ ID NO:21), LCDR2 of AASSLQS (SEQ ID NO:17) and LCDR3 of LQYDSTPLT (SEQ ID NO:18); and the heavy chain constant region comprises any one of SEQ ID NOS: 239-245;

(g) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDGGSYTYYADSVKG (SEQ ID NO:28) and HCDR3 of EWGDYDGFDE (SEQ ID NO:29); the VL region amino acid sequence comprises LCDR1 of RASQSISGYLS (SEQ ID NO:30), LCDR2 of AASTLQS (SEQ ID NO:26) and LCDR3 of LQYDSTPYT (SEQ ID NO:23); and the heavy chain constant region comprises any one of SEQ ID NOS: 239-245;

(h) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDGGSYTYYADNVKG (SEQ ID NO:31) and HCDR3 of EWGDYDGFDF (SEQ ID NO:15); the VL region amino acid sequence comprises LCDR1 of RASQSISSYLS (SEQ ID NO:16), LCDR2 of AASTLQS (SEQ ID NO:26) and LCDR3 of LQYDSTPLT (SEQ ID NO:18); and the heavy chain constant region comprises any one of SEQ ID NOS: 239-245; or

(i) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDSGSYIYYADSVKG (SEQ ID NO:14) and HCDR3 of EWGDYDGFDE (SEQ ID NO:29); the VL region amino acid sequence comprises LCDR1 of RASQSISSYLS (SEQ ID NO:16), LCDR2 of AASSLQS (SEQ ID NO:17) and LCDR3 of LQYDSTPLT (SEQ ID NO:18); and the heavy chain constant region comprises any one of SEQ ID NOS: 239-245.

In some aspects, disclosed herein is an anti-ERBB3 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region, a light chain variable (VL) region and a heavy chain constant region, wherein

(a) the VH region amino acid sequence comprises or consists of SEQ ID NO:236; the VL region amino acid sequence comprises or consists of SEQ ID NO:225; and the heavy chain constant region comprises a wild-type human IgG4 constant region, a human IgG4 constant region comprising the amino acid substitution S228P, a wild-type human IgG2 constant region; a wild-type human IgG1 constant region or a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A;

(b) the VH region amino acid sequence comprises or consists of SEQ ID NO:232; the VL region amino acid sequence comprises or consists of SEQ ID NO:221; and the heavy chain constant region comprises a wild-type human IgG4 constant region, a human IgG4 constant region comprising the amino acid substitution S228P, a wild-type human IgG2 constant region; a wild-type human IgG1 constant region or a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A;

(c) the VH region amino acid sequence comprises or consists of SEQ ID NO:253; the VL region amino acid sequence comprises or consists of SEQ ID NO:254; and the heavy chain constant region comprises a wild-type human IgG4 constant region, a human IgG4 constant region comprising the amino acid substitution S228P, a wild-type human IgG2 constant region; a wild-type human IgG1 constant region or a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A; or

(d) the VH region amino acid sequence comprises or consists of SEQ ID NO:255; the VL region amino acid sequence comprises or consists of SEQ ID NO:256; and the heavy chain constant region comprises a wild-type human IgG4 constant region, a human IgG4 constant region comprising the amino acid substitution S228P, a wild-type human IgG2 constant region; a wild-type human IgG1 constant region or a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A.

In some aspects, disclosed herein is an anti-ERBB3 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region, a light chain variable (VL) region and a heavy chain constant region, wherein

(a) the VH region amino acid sequence comprises or consists of SEQ ID NO:236; the VL region amino acid sequence comprises or consists of SEQ ID NO:225; and the heavy chain constant region comprises any one of SEQ ID NOS: 239-245;

(b) the VH region amino acid sequence comprises or consists of SEQ ID NO:232; the VL region amino acid sequence comprises or consists of SEQ ID NO:221; and the heavy chain constant region comprises any one of SEQ ID NOS: 239-245;

(c) the VH region amino acid sequence comprises or consists of SEQ ID NO:253; the VL region amino acid sequence comprises or consists of SEQ ID NO:254; and the heavy chain constant region comprises any one of SEQ ID NOS: 239-245; or

(d) the VH region amino acid sequence comprises or consists of SEQ ID NO:255; the VL region amino acid sequence comprises or consists of SEQ ID NO:256; and the heavy chain constant region comprises any one of SEQ ID NOS: 239-245.

In some aspects, an anti-ERBB3 antibody may be immune effector null. In some aspects, an anti-ERBB3 antibody or an antigen-binding portion thereof does not induce immune effector function and, optionally, suppresses immune effector function. In some aspects, an anti-ERBB3 antibody may lack measurable binding to human FcγRI, FcγRIIa, FcγRIIIa and FcγRIIIb receptors but maintain binding to human FcγRIIb receptor and optionally maintain binding to human FcRn receptor. FcγRI, FcγRIIa, FcγRIIIa and FcγRIIIb are examples of activating receptors. FcγRIIb is an example of an inhibitory receptor. FcRn is an example of a recycling receptor. In some aspects, binding affinity of an anti-ERBB3 antibody or an antigen-binding portion thereof for human Fc receptors may be measured by BIACORE®

analysis. In some aspects, Homogeneous Time Resolved Fluorescence (HTRF) can be used to study binding of an anti-ERBB3 antibody to human Fc receptors. In one example of HTRF, human IgG1 (wild type) is labelled, as is the full suite of Fc gamma receptors and then antibodies with engineered Fc fragments are used in titration competition. In some aspects, ERBB3-positive cells may be mixed with human white blood cells and anti-ERBB3 antibodies, and cell killing by CDC, ADCC and/or ADCP may be measured. In some aspects, an anti-ERBB3 antibody comprising an amino acid sequence of an Fc region of human IgG1-3M (see Table 9) is effector null. In some aspects, an anti-ERBB3 antibody comprising an amino acid sequence of an Fc region of human IgG1-3M (see Table 9) is not effector null.

The antibody molecule or antigen-binding portion thereof may be a Fab fragment, a $F(ab)_2$ fragment, an Fv fragment, a tetrameric antibody, a tetravalent antibody, a multispecific antibody (for example, a bispecific antibody), a domain-specific antibody, a single domain antibody, a monoclonal antibody or a fusion protein. In one embodiment, an antibody may be a bispecific antibody that binds specifically to a first antigen and a second antigen, wherein the first antigen is ERBB3 and the second antigen is not ERBB3. Antibody molecules and methods for their construction and use are described, in for example Holliger & Hudson (2005, Nature Biotechnol. 23(9): 1126-1136).

In another aspect of the invention, there is provided an immunoconjugate comprising the antibody molecule or antigen-binding portion thereof of the invention as defined herein linked to a therapeutic agent.

Examples of suitable therapeutic agents include cytotoxins, radioisotopes, chemotherapeutic agents, immunomodulatory agents, anti-angiogenic agents, antiproliferative agents, pro-apoptotic agents, and cytostatic and cytolytic enzymes (for example RNAses). Further therapeutic agents include a therapeutic nucleic acid, such as a gene encoding an immunomodulatory agent, an anti-angiogenic agent, an anti-proliferative agent, or a pro-apoptotic agent. These drug descriptors are not mutually exclusive, and thus a therapeutic agent may be described using one or more of the above terms.

Examples of suitable therapeutic agents for use in immunoconjugates include the taxanes, maytansines, CC-1065 and the duocarmycins, the calicheamicins and other enediynes, and the auristatins. Other examples include the anti-folates, vinca alkaloids, and the anthracyclines. Plant toxins, other bioactive proteins, enzymes (i.e., ADEPT), radioisotopes, photosensitizers may also be used in immunoconjugates. In addition, conjugates can be made using secondary carriers as the cytotoxic agent, such as liposomes or polymers, Suitable cytotoxins include an agent that inhibits or prevents the function of cells and/or

results in destruction of cells. Representative cytotoxins include antibiotics, inhibitors of tubulin polymerization, alkylating agents that bind to and disrupt DNA, and agents that disrupt protein synthesis or the function of essential cellular proteins such as protein kinases, phosphatases, topoisomerases, enzymes, and cyclins.

Representative cytotoxins include, but are not limited to, doxorubicin, daunorubicin, idarubicin, aclarubicin, zorubicin, mitoxantrone, epirubicin, carubicin, nogalamycin, menogaril, pitarubicin, valrubicin, cytarabine, gemcitabine, trifluridine, ancitabine, enocitabine, azacitidine, doxifluhdine, pentostatin, broxuhdine, capecitabine, cladhbine, decitabine, floxuhdine, fludarabine, gougerotin, puromycin, tegafur, tiazofuhn, adhamycin, cisplatin, carboplatin, cyclophosphamide, dacarbazine, vinblastine, vincristine, mitoxantrone, bleomycin, mechlorethamine, prednisone, procarbazine, methotrexate, flurouracils, etoposide, taxol, taxol analogs, platins such as cis-platin and carbo-platin, mitomycin, thiotepa, taxanes, vincristine, daunorubicin, epirubicin, actinomycin, authramycin, azaserines, bleomycins, tamoxifen, idarubicin, dolastatins/auristatins, hemiasterlins, esperamicins and maytansinoids.

Suitable immunomodulatory agents include anti-hormones that block hormone action on tumors and immunosuppressive agents that suppress cytokine production, down-regulate self-antigen expression, or mask MHC antigens.

Also provided is a nucleic acid molecule encoding the antibody molecule or antigen-binding portion thereof of the invention as defined herein. A nucleic acid molecule may encode (a) the VH region amino acid sequence; (b) the VL region amino acid sequence; or (c) both the VH and the VL region amino acid sequences of an anti-ERBB3 antibody or an antigen-binding portion thereof described herein. In some aspects, the nucleic acid molecule as defined herein may be isolated.

Further provided is a vector comprising the nucleic acid molecule of the invention as defined herein. The vector may be an expression vector.

Also provided is a host cell comprising the nucleic acid molecule or the vector of the invention as defined herein. The host cell may be a recombinant host cell.

In a further aspect there is provided a method of producing an anti-ERBB3 antibody and/or an antigen-binding portion thereof, comprising culturing the host cell of the invention under conditions that result in expression and/or production of the antibody and/or the antigen-

binding portion thereof, and isolating the antibody and/or the antigen-binding portion thereof from the host cell or culture.

In another aspect of the invention there is provided a pharmaceutical composition comprising the antibody molecule or antigen-binding portion thereof of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein.

The invention also provides a method for inhibiting ERBB3 signalling in a cell, the method comprising contacting the cell with an anti-ERBB3 antibody molecule or antigen-binding portion thereof described herein. In some embodiments, an anti-ERBB3 antibody molecule or antigen-binding portion of the invention locks ERBB3 into a monomeric form.

Further provided is a method for enhancing an immune response in a subject, comprising administering to the subject an effective amount of the antibody molecule or antigen-binding portion thereof of the invention as defined herein, or the immunoconjugate of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein, or the pharmaceutical composition of the invention as defined herein. In some embodiments, an anti-ERBB3 antibody molecule or antigen-binding portion of the invention engages a subject's immune cells via antibody effector-function mediated engagement.

In a further aspect there is provided a method for treating or preventing cancer in a subject, comprising administering to the subject an effective amount of the antibody molecule or antigen-binding portion thereof of the invention as defined herein, or the immunoconjugate of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein, or the pharmaceutical composition of the invention as defined herein.

For example, the cancer may be Gastrointestinal Stromal cancer (GIST), pancreatic cancer, melanoma, breast cancer, lung cancer, bronchial cancer, colorectal cancer, prostate cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma, or cancer of hematological tissues.

The invention also provides an antibody molecule or antigen-binding portion thereof of the invention as defined herein, or the immunoconjugate of the invention as defined herein, or the nucleic acid molecule of the invention as defined herein, or the vector of the invention as defined herein, or the pharmaceutical composition of the invention as defined herein, for use in the treatment of cancer.

In another aspect the invention provides the antibody molecule, or antigen-binding portion thereof, or the immunoconjugate, or the nucleic acid molecule, or the vector for use, or the method of treatment of the invention as defined herein, for separate, sequential or simultaneous use in a combination combined with a second therapeutic agent, for example an anti-cancer agent.

In a further aspect there is provided the use of an antibody molecule or antigen-binding portion thereof of the invention as defined herein, or an immunoconjugate of the invention as defined herein, or a nucleic acid molecule of the invention as defined herein, or a vector of the invention as defined herein, or a pharmaceutical composition of the invention as defined herein, in the manufacture of a medicament for the treatment of cancer.

The invention also provides a method for treating or preventing an autoimmune disease or an inflammatory disease in a subject, comprising administering to the subject an effective amount of the antibody molecule or antigen-binding portion thereof as defined herein, or the immunoconjugate as defined here, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein.

For example the autoimmune disease or inflammatory disease may be arthritis, asthma, multiple sclerosis, psoriasis, Crohn's disease, inflammatory bowel disease, lupus, Grave's disease and Hashimoto's thyroiditis, or ankylosing spondylitis.

Also provided is an antibody molecule or antigen-binding portion thereof as defined herein, or the immunoconjugate as defined herein, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein, for use in the treatment of an autoimmune disease or an inflammatory disease.

Further provided is the use of an antibody molecule or antigen-binding portion thereof as defined herein, or an immunoconjugate as defined herein, or a nucleic acid molecule as defined herein, or a vector as defined herein, or a pharmaceutical composition as defined herein, in the manufacture of a medicament for the treatment of an autoimmune disease or an inflammatory disease.

The invention also provides a method for treating or preventing a cardiovascular disease or a fibrotic disease in a subject, comprising administering to the subject an effective amount of the antibody molecule or antigen-binding portion thereof as defined herein, or the immunoconjugate as defined here, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein.

Also provided is an antibody molecule or antigen-binding portion thereof as defined herein, or the immunoconjugate as defined herein, or the nucleic acid molecule as defined herein, or the vector as defined herein, or the pharmaceutical composition as defined herein, for use in the treatment of a cardiovascular disease or a fibrotic disease.

Further provided is the use of an antibody molecule or antigen-binding portion thereof as defined herein, or an immunoconjugate as defined herein, or a nucleic acid molecule as defined herein, or a vector as defined herein, or a pharmaceutical composition as defined herein, in the manufacture of a medicament for the treatment of a cardiovascular disease or a fibrotic disease.

The cardiovascular disease in any aspect of the invention may for example be coronary heart disease or atherosclerosis.

For example, the fibrotic disease in any aspect of the invention may be myocardial infarction, angina, osteoarthritis, pulmonary fibrosis, asthma, cystic fibrosis or bronchitis.

In one embodiment, the invention provides an anti-ERBB3 antibody or an antigen-binding portion thereof comprising the amino acid sequences disclosed herein for use in therapy.

The pharmaceutical composition of the invention may comprise a pharmaceutically acceptable excipient, carrier or diluent. A pharmaceutically acceptable excipient may be a compound or a combination of compounds entering into a pharmaceutical composition which does not provoke secondary reactions and which allows, for example, facilitation of the administration of the anti-ERBB3 antibody molecule, an increase in its lifespan and/or in its efficacy in the body or an increase in its solubility in solution. These pharmaceutically acceptable vehicles are well known and will be adapted by the person skilled in the art as a function of the mode of administration of the anti-ERBB3 antibody molecule.

In some embodiments, the anti-ERBB3 antibody molecule may be provided in a lyophilised form for reconstitution prior to administration. For example, lyophilised antibody molecules

may be re-constituted in sterile water and mixed with saline prior to administration to an individual.

The anti-ERBB3 antibody molecules will usually be administered in the form of a pharmaceutical composition, which may comprise at least one component in addition to the antibody molecule. Thus pharmaceutical compositions may comprise, in addition to the anti-ERBB3 antibody molecule, a pharmaceutically acceptable excipient, carrier, buffer, stabilizer or other materials well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the efficacy of the anti-ERBB3 antibody molecule. The precise nature of the carrier or other material will depend on the route of administration, which may be by bolus, infusion, injection or any other suitable route, as discussed below.

For parenteral, for example sub-cutaneous or intra-venous administration, e.g. by injection, the pharmaceutical composition comprising the anti-ERBB3 antibody molecule may be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles, such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilizers, buffers, antioxidants and/or other additives may be employed as required including buffers such as phosphate, citrate and other organic acids; antioxidants, such as ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride; benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens, such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3'-pentanol; and m-cresol); low molecular weight polypeptides; proteins, such as serum albumin, gelatin or immunoglobulins; hydrophilic polymers, such as polyvinylpyrrolidone; amino acids, such as glycine, glutamine, asparagines, histidine, arginine, or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose or dextrins; chelating agents, such as EDTA; sugars, such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions, such as sodium; metal complexes (e.g. Zn-protein complexes); and/or non-ionic surfactants, such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

A pharmaceutical composition comprising an anti-ERBB3 antibody molecule may be administered alone or in combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated.

An anti-ERBB3 antibody molecule as described herein may be used in a method of treatment of the human or animal body, including prophylactic or preventative treatment (e.g. treatment before the onset of a condition in an individual to reduce the risk of the condition occurring

in the individual; delay its onset; or reduce its severity after onset). The method of treatment may comprise administering the anti-ERBB3 antibody molecule to an individual in need thereof.

Administration is normally in a "therapeutically effective amount", this being sufficient to show benefit to a patient. Such benefit may be at least amelioration of at least one symptom. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of what is being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the composition, the method of administration, the scheduling of administration and other factors known to medical practitioners. Prescription of treatment, e.g. decisions on dosage etc., is within the responsibility of general practitioners and other medical doctors and may depend on the severity of the symptoms and/or progression of a disease being treated. Appropriate doses of antibody molecules are well known in the art (Ledermann J.A. *et al.*, 1991, Int. J. Cancer 47: 659-664; Bagshawe K.D. *et al.*, 1991, Antibody, Immunoconjugates and Radiopharmaceuticals 4: 915-922). Specific dosages may be indicated herein or in the Physician's Desk Reference (2003) as appropriate for the type of medicament being administered may be used. A therapeutically effective amount or suitable dose of an antibody molecule may be determined by comparing its *in vitro* activity and *in vivo* activity in an animal model. Methods for extrapolation of effective dosages in mice and other test animals to humans are known. The precise dose will depend upon a number of factors, including whether the antibody is for prevention or for treatment, the size and location of the area to be treated, the precise nature of the antibody (e.g. whole antibody, fragment) and the nature of any detectable label or other molecule attached to the antibody.

A typical antibody dose will be in the range 100 µg to 1 g for systemic applications, and 1 µg to 1 mg for topical applications. An initial higher loading dose, followed by one or more lower doses, may be administered. Typically, the antibody will be a whole antibody, e.g. the IgG1, IgG1null or IgG4 isotype. This is a dose for a single treatment of an adult patient, which may be proportionally adjusted for children and infants, and also adjusted for other antibody formats in proportion to molecular weight. Treatments may be repeated at daily, twice-weekly, weekly or monthly intervals, at the discretion of the physician. The treatment schedule for an individual may be dependent on the pharmocokinetic and pharmacodynamic properties of the antibody composition, the route of administration and the nature of the condition being treated.

Treatment may be periodic, and the period between administrations may be about two weeks or more, e.g. about three weeks or more, about four weeks or more, about once a month or

more, about five weeks or more, or about six weeks or more. For example, treatment may be every two to four weeks or every four to eight weeks. Treatment may be given before, and/or after surgery, and/or may be administered or applied directly at the anatomical site of surgical treatment or invasive procedure. Suitable formulations and routes of administration are described above.

In some embodiments, anti-ERBB3 antibody molecules as described herein may be administered as sub-cutaneous injections. Sub-cutaneous injections may be administered using an auto-injector, for example for long or short-term prophylaxis/treatment.

In some embodiments, the therapeutic effect of the anti-ERBB3 antibody molecule may persist for several multiples of the antibody half-life in serum, depending on the dose. For example, the therapeutic effect of a single dose of the anti-ERBB3 antibody molecule may persist in an individual for 1 month or more, 2 months or more, 3 months or more, 4 months or more, 5 months or more, or 6 months or more.

The invention also provides a method of producing an antibody molecule which specifically binds to human ERBB3 and optionally also to rhesus monkey ERBB3 or an antigen-binding portion thereof, comprising the steps of:

(1) grafting anti-ERBB3 CDRs from a non-human source into a human v-domain framework to produce a humanized anti-ERBB3 antibody molecule or antigen-binding portion thereof;

(2) generating a phage library of clones of the humanized anti-ERBB3 antibody molecule or antigen-binding portion thereof comprising one or more mutations in the CDRs;

(3) selecting the phage library for binding to human ERBB3 and optionally also to rhesus monkey ERBB3;

(4) screening clones from the selection step (3) having binding specificity to human ERBB3 and optionally also to rhesus monkey ERBB3; and

(5) producing an antibody molecule which specifically binds to human ERBB3 and optionally also to rhesus monkey ERBB3, or an antigen-binding portion thereof from clones selected from step (4).

The method may comprise a further step of producing additional clones based on the clones selected in step (4), for example based on further exploratory mutagenesis at specific positions in the CDRs of the clones selected in step (4), to enhance humanization and/or minimise human T cell epitope content and/or improve manufacturing properties in the antibody molecule or antigen-binding portion thereof produced in step (5).

Refinements applicable to the above method are as described in Example 1 below.

As used herein, the term "ERBB3" refers to the ERBB3 protein and variants thereof that retain at least part of the biological activity of ERBB3. As used herein, ERBB3 includes all mammalian species of native sequence ERBB3, including human, rat, mouse and chicken. The term "ERBB3" is used to include variants, isoforms and species homologs of human ERBB3. Antibodies of the invention may cross-react with ERBB3 from species other than human, in particular ERBB3 from rhesus monkey (*Macaca mulatta*). Examples of human and rhesus ERBB3 amino acid sequences are provided in Table 10. In certain embodiments, the antibodies may be completely specific for human ERBB3 and may not exhibit non-human cross-reactivity.

As used herein, an "antagonist" as used in the context of the antibody of the invention or an "anti-ERBB3 antagonist antibody" (interchangeably termed "anti-ERBB3 antibody") refers to an antibody which is able to bind to ERBB3 and inhibit ERBB3 biological activity and/or downstream pathway(s) mediated by ERBB3 signalling. An anti-ERBB3 antagonist antibody encompasses antibodies that can block, antagonize, suppress or reduce (including significantly) ERBB3 biological activity, including downstream pathways mediated by ERBB3 signalling, such as receptor binding and/or elicitation of a cellular response to ERBB3. For the purposes of the present invention, it will be explicitly understood that the term "anti-ERBB3 antagonist antibody" encompass all the terms, titles, and functional states and characteristics whereby ERBB3 itself, and ERBB3 biological activity, or the consequences of the activity or biological activity, are substantially nullified, decreased, or neutralized in any meaningful degree.

The antibody "specifically binds" "specifically interacts", "preferentially binds", "binds" or "interacts" with ERBB3 if it binds with greater affinity, avidity, more readily and/or with greater duration than it binds to other receptors.

An "antibody molecule" is an immunoglobulin molecule capable of specific binding to a target, such as a carbohydrate, polynucleotide, lipid, polypeptide, etc., through at least one antigen recognition site, located in the variable region of the immunoglobulin molecule. As used herein, the term "antibody molecule" encompasses not only intact polyclonal or monoclonal antibodies, but also any antigen binding fragment (for example, an "antigen-binding portion") or single chain thereof, fusion proteins comprising an antibody, and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site including, for example without limitation, scFv, single domain antibodies (for example, shark and camelid antibodies), maxibodies, minibodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv.

An “antibody molecule” encompasses an antibody of any class, such as IgG, IgA, or IgM (or sub-class thereof), and the antibody need not be of any particular class. Depending on the antibody amino acid sequence of the constant region of its heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), for example IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. The heavy-chain constant regions that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

The term “antigen binding portion” of an antibody molecule, as used herein, refers to one or more fragments of an intact antibody that retain the ability to specifically bind to ERBB3. Antigen binding functions of an antibody molecule can be performed by fragments of an intact antibody. Examples of binding fragments encompassed within the term “antigen binding portion” of an antibody molecule include Fab; Fab'; F(ab')2; an Fd fragment consisting of the VH and CH1 domains; an Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a single domain antibody (dAb) fragment, and an isolated complementarity determining region (CDR).

The term “Fc region” is used to define a C-terminal region of an immunoglobulin heavy chain. The “Fc region” may be a native sequence Fc region or a variant Fc region. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy chain Fc region is usually defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The numbering of the residues in the Fc region is that of the EU index as in Kabat. The Fc region of an immunoglobulin generally comprises two constant domains, CH2 and CH3. As is known in the art, an Fc region can be present in dimer or monomeric form.

A “variable region” of an antibody refers to the variable region of the antibody light chain or the variable region of the antibody heavy chain, either alone or in combination. As known in the art, the variable regions of the heavy and light chain each consist of four framework regions (FRs) connected by three complementarity determining regions (CDRs) also known as hypervariable regions, and contribute to the formation of the antigen binding site of antibodies. When choosing FR to flank CDRs, for example when humanizing or optimizing an antibody, FRs from antibodies which contain CDR sequences in the same canonical class are preferred.

The CDR definitions used in the present application combine the domains used in the many disparate, often conflicting schemes that have been created in the field, which are based on the combination of immunoglobulin repertoire analyses and structural analyses of antibodies in isolation and in their co-crystals with antigens (see review by Swindells *et al.*, 2016, abYsis: Integrated Antibody Sequence and Structure-Management, Analysis, and Prediction. J Mol Biol. [PMID: 27561707; Epub 22 August 2016]). The CDR definition used herein (a "Unified" definition) incorporates the lessons of all such prior insights and includes all appropriate loop positions required to sample the full residue landscape that potentially mediates target-binding complementarity.

Table 1 shows the amino acid sequences of the 24C05 murine anti-ERBB3 antibody CDRs as defined herein (a "Unified" scheme), in comparison to well-known alternative systems for defining the same CDRs.

As used herein the term "conservative substitution" refers to replacement of an amino acid with another amino acid which does not significantly deleteriously change the functional activity. A preferred example of a "conservative substitution" is the replacement of one amino acid with another amino acid which has a value ≥ 0 in the following BLOSUM 62 substitution matrix (see Henikoff & Henikoff, 1992, PNAS 89: 10915-10919):

	A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V
A	4	-1	-2	-2	0	-1	-1	0	-2	-1	-1	-1	-1	-2	-1	1	0	-3	-2	0
R	-1	5	0	-2	-3	1	0	-2	0	-3	-2	2	-1	-3	-2	-1	-1	-3	-2	-3
N	-2	0	6	1	-3	0	0	0	1	-3	-3	0	-2	-3	-2	1	0	-4	-2	-3
D	-2	-2	1	6	-3	0	2	-1	-1	-3	-4	-1	-3	-3	-1	0	-1	-4	-3	-3
C	0	-3	-3	-3	9	-3	-4	-3	-3	-1	-1	-3	-1	-2	-3	-1	-1	-2	-2	-1
Q	-1	1	0	0	-3	5	2	-2	0	-3	-2	1	0	-3	-1	0	-1	-2	-1	-2
E	-1	0	0	2	-4	2	5	-2	0	-3	-3	1	-2	-3	-1	0	-1	-3	-2	-2
G	0	-2	0	-1	-3	-2	-2	6	-2	-4	-4	-2	-3	-3	-2	0	-2	-2	-3	-3
H	-2	0	1	-1	-3	0	0	-2	8	-3	-3	-1	-2	-1	-2	-1	-2	-2	2	-3
I	-1	-3	-3	-3	-1	-3	-3	-4	-3	4	2	-3	1	0	-3	-2	-1	-3	-1	3
L	-1	-2	-3	-4	-1	-2	-3	-4	-3	2	4	-2	2	0	-3	-2	-1	-2	-1	1
K	-1	2	0	-1	-3	1	1	-2	-1	-3	-2	5	-1	-3	-1	0	-1	-3	-2	-2
M	-1	-1	-2	-3	-1	0	-2	-3	-2	1	2	-1	5	0	-2	-1	-1	-1	-1	1
F	-2	-3	-3	-3	-2	-3	-3	-3	-1	0	0	-3	0	6	-4	-2	-2	1	3	-1
P	-1	-2	-2	-1	-3	-1	-1	-2	-2	-3	-3	-1	-2	-4	7	-1	-1	-4	-3	-2
S	1	-1	1	0	-1	0	0	0	-1	-2	-2	0	-1	-2	-1	4	1	-3	-2	-2
T	0	-1	0	-1	-1	-1	-1	-2	-2	-1	-1	-1	-1	-2	-1	1	5	-2	-2	0
W	-3	-3	-4	-4	-2	-2	-3	-2	-2	-3	-2	-3	-1	1	-4	-3	-2	11	2	-3
Y	-2	-2	-2	-3	-2	-1	-2	-3	2	-1	-1	-2	-1	3	-3	-2	-2	2	7	-1
V	0	-3	-3	-3	-1	-2	-2	-3	-3	3	1	-2	1	-1	-2	-2	0	-3	-1	4.

The term "monoclonal antibody" (Mab) refers to an antibody, or antigen-binding portion thereof, that is derived from a single copy or clone, including for example any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced. Preferably, a

monoclonal antibody of the invention exists in a homogeneous or substantially homogeneous population.

A “humanized” antibody molecule refers to a form of non-human (for example, murine) antibody molecules, or antigen-binding portion thereof, that are chimeric immunoglobulins, immunoglobulin chains, or fragments thereof (such as Fv, Fab, Fab', F(ab')2 or other antigen-binding sub-sequences of antibodies) that contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies may be human immunoglobulins (recipient antibody) in which residues from a CDR of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity.

“Human antibody or fully human antibody” refers to an antibody molecule, or antigen-binding portion thereof, derived from transgenic mice carrying human antibody genes or from human cells.

The term “chimeric antibody” is intended to refer to an antibody molecule, or antigen-binding portion thereof, in which the variable region sequences are derived from one species and the constant region sequences are derived from another species, such as an antibody molecule in which the variable region sequences are derived from a mouse antibody and the constant region sequences are derived from a human antibody.

“Antibody-drug conjugate” and “immunoconjugate” refer to an antibody molecule, or antigen-binding portion thereof, including antibody derivatives that binds to ERBB3, which is conjugated to cytotoxic, cytostatic and/or therapeutic agents.

Antibody molecules of the invention, or antigen-binding portion thereof, can be produced using techniques well known in the art, for example recombinant technologies, phage display technologies, synthetic technologies or combinations of such technologies or other technologies readily known in the art.

The term “isolated molecule” (where the molecule is, for example, a polypeptide, a polynucleotide, or an antibody) is a molecule that by virtue of its origin or source of derivation (1) is not associated with naturally associated components that accompany it in its native state, (2) is substantially free of other molecules from the same species (3) is expressed by a cell from a different species, or (4) does not occur in nature. Thus, a molecule that is chemically synthesized, or expressed in a cellular system different from the cell from which it naturally originates, will be “isolated” from its naturally associated components. A molecule

also may be rendered substantially free of naturally associated components by isolation, using purification techniques well known in the art. Molecule purity or homogeneity may be assayed by a number of means well known in the art. For example, the purity of a polypeptide sample may be assayed using polyacrylamide gel electrophoresis and staining of the gel to visualize the polypeptide using techniques well known in the art. For certain purposes, higher resolution may be provided by using HPLC or other means well known in the art for purification.

The term “epitope” refers to that portion of a molecule capable of being recognized by and bound by an antibody molecule, or antigen-binding portion thereof, at one or more of the antibody molecule's antigen-binding regions. Epitopes can consist of defined regions of primary secondary or tertiary protein structure and includes combinations of secondary structural units or structural domains of the target recognised by the antigen binding regions of the antibody, or antigen-binding portion thereof. Epitopes can likewise consist of a defined chemically active surface grouping of molecules such as amino acids or sugar side chains and have specific three-dimensional structural characteristics as well as specific charge characteristics. The term “antigenic epitope” as used herein, is defined as a portion of a polypeptide to which an antibody molecule can specifically bind as determined by any method well known in the art, for example, by conventional immunoassays, antibody competitive binding assays or by x-ray crystallography or related structural determination methods (for example NMR).

The term “binding affinity” or “KD” refers to the dissociation rate of a particular antigen-antibody interaction. The KD is the ratio of the rate of dissociation, also called the “off-rate (k_{off})”, to the association rate, or “on-rate (k_{on})”. Thus, K_D equals k_{off} / k_{on} and is expressed as a molar concentration (M). It follows that the smaller the K_D, the stronger the affinity of binding. Therefore, a K_D of 1 μM indicates weak binding affinity compared to a K_D of 1 nM. KD values for antibodies can be determined using methods well established in the art. One method for determining the KD of an antibody is by using surface plasmon resonance (SPR), typically using a biosensor system such as a Biacore® system.

The term “potency” is a measurement of biological activity and may be designated as IC_{50}, or effective concentration of an antibody or antibody drug conjugate to the antigen ERBB3 to inhibit 50% of activity measured in a ERBB3 activity assay as described herein.

The phrase “effective amount” or “therapeutically effective amount” as used herein refers to an amount necessary (at dosages and for periods of time and for the means of administration) to achieve the desired therapeutic result. An effective amount is at least the

minimal amount, but less than a toxic amount, of an active agent which is necessary to impart therapeutic benefit to a subject.

The term "inhibit" or "neutralize" as used herein with respect to bioactivity of an antibody molecule of the invention means the ability of the antibody to substantially antagonize, prohibit, prevent, restrain, slow, disrupt, eliminate, stop, reduce or reverse for example progression or severity of that which is being inhibited including, but not limited to, a biological activity or binding interaction of the antibody molecule to ERBB3.

A "host cell" includes an individual cell or cell culture that can be or has been a recipient for vector(s) for incorporation of polynucleotide inserts. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in morphology or in genomic DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation. A host cell includes cells transfected in vivo with a polynucleotide(s) of this invention.

As used herein, "vector" means a construct, which is capable of delivering, and, preferably, expressing, one or more gene(s) or sequence(s) of interest in a host cell. Examples of vectors include, but are not limited to, viral vectors, naked DNA or RNA expression vectors, plasmid, cosmid or phage vectors, DNA or RNA expression vectors associated with cationic condensing agents, DNA or RNA expression vectors encapsulated in liposomes, and certain eukaryotic cells, such as producer cells.

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, delaying the progression of, delaying the onset of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as defined above. The term "treating" also includes adjuvant and neoadjuvant treatment of a subject. For the avoidance of doubt, reference herein to "treatment" includes reference to curative, palliative and prophylactic treatment. For the avoidance of doubt, references herein to "treatment" also include references to curative, palliative and prophylactic treatment.

It is understood that wherever embodiments are described herein with the language "comprising," otherwise analogous embodiments described in terms of "consisting of" and/or "consisting essentially of" are also provided.

Where aspects or embodiments of the invention are described in terms of a Markush group or other grouping of alternatives, the present invention encompasses not only the entire group listed as a whole, but each member of the group individually and all possible subgroups of the main group, but also the main group absent one or more of the group members. The present invention also envisages the explicit exclusion of one or more of any of the group members in the claimed invention.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In case of conflict, the present specification, including definitions, will control. Throughout this specification and claims, the word “comprise,” or variations such as “comprises” or “comprising” will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Any example(s) following the term “e.g.” or “for example” is not meant to be exhaustive or limiting.

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry and immunology, which are within the skill of the art.

Particular non-limiting embodiments of the present invention will now be described with reference to accompanying drawings.

EXAMPLE 1. Generation of optimized anti-ERBB3 therapeutic antibodies

Introduction

In this example, we successfully generated a panel of antagonistic, optimized anti-ERBB3 antibodies. These anti-ERBB3 antibodies are well expressed, biophysically stable, highly soluble and of maximized amino acid sequence identity to preferred human germlines.

Materials and methods

ERBB3 library generation and selection

The ERBB3 Fab mutagenesis repertoire was assembled by mass oligo synthesis and PCR. This library was designed to sample the germline human CDR residue or murine CDR residue at all positions where the sequences differed, but also sampled all amino acids other than cysteine at key selected CDR positions e.g. in HCDR1 and HCDR3. The amplified Fab repertoire was then cloned via restriction-ligation into a phagemid vector, transformed into *E.coli* TG-1 cells, and the phage repertoire rescued essentially as previously described in detail (Finlay *et al.*, 2011, Methods Mol Biol 681: 383-401).

Phage selections were performed by coating streptavidin magnetic microbeads with biotinylated ERBB3 target protein (either human or rhesus), washing the beads thrice with PBS and resuspending in PBS pH7.4 plus 5% skim milk protein. These beads were coated at 100 nM target protein in round 1 of selection, followed by reduced antigen concentrations in three successive rounds. In each round, phage were eluted using trypsin before re-infection into TG1 cells.

Periplasmic extracts production (small-scale)

Production of soluble Fabs in individual *E. coli* clones was performed. *E. coli* TG1 cells in logarhythmic growth phase were induced with isopropyl 1-thio-β-D-galactopyranoside. Periplasmic extracts containing soluble Fab were generated by a freeze/thaw cycle: Bacterial cell pellets were frozen at -20 °C for overnight and then thawed at room temperature and resuspended in PBS pH 7.4. The supernatants containing the soluble Fab were collected after shaking at room temperature and centrifugation.

IgG expression and purification

Mammalian codon-optimized synthetic genes encoding the heavy and light chain variable domains of the lead panel anti-ERBB3 antibodies plus the m24C05 and h24C05 were cloned into mammalian expression vectors comprising IgG1null ('IgG1null'; human IgG1 containing L234A, L235A, G237A mutations in the lower hinge that abrogate normal immunoglobulin Fc effector functions) or IgG1 and human C_κ domains, respectively. Co-transfection of heavy

and light chain containing vector in mammalian expression system was performed, followed by protein A-based purification of the IgG, quantification and QC on denaturing and non-denaturing SDS-PAGE.

Direct binding ELISA for Fab and IgG

Binding and cross-reactivity of the lead panel to the recombinant proteins was initially assessed by binding ELISA. The human ERBB3 human Fc tagged recombinant protein and the rhesus monkey ERBB3 human Fc tagged recombinant protein were coated to the surface of MaxiSorp™ flat-bottom 96 well plate at 1 µg/ml. The purified IgG samples were titrated in two fold serial dilutions starting from 500 nM to 0.008 nM and allowed to bind to the coated antigens. The Fabs were detected using mouse anti-c-myc antibody followed by donkey anti-mouse IgG conjugated to horseradish peroxidase. The IgGs were detected using the mouse anti-human IgG conjugated to horseradish peroxidase. Binding signals were visualized with 3,3',5,5'-Tetramethylbenzidine Substrate Solution (TMB) and the absorbance measured at 450 nm.

Alphascreen epitope competition assay for IgG1nullnull antibodies

The AlphaScreen assay (Perkin Elmer) was performed in a 25 µl final volume in 384-well white microtiter plates (Greiner). The reaction buffer contained 1xPBS pH 7.3 (Oxoid, Cat. nr. BR0014G) and 0.05 % (v/v) Tween® 20 (Sigma, Cat. nr. P9416). Purified IgG samples were titrated in three fold serial dilutions starting at 100 nM final concentration and incubated with biotinylated human ERBB3-His (Acrobiosystems) at 1 nM final concentration for 20 minutes at room temperature. The parental IgG and the anti-human IgG1 Acceptor beads at were added and the mix was incubated for 1 hour at room temperature. Followed by addition of the Streptavidin Donor beads and incubation for 30 minutes at room temperature. The emission of light was measured in the EnVision multilabel plate reader (Perkin Elmer) and analysed using the EnVision manager software. Values were reported as Counts Per Second (CPS) and corrected for crosstalk.

Biacore® analyses of IgG affinity for monomeric human and rhesus ERBB3 in solution

Affinity (KD) of purified IgGs was determined via SPR with antigen in-solution on a Biacore® 3000 (GE). A mouse anti-human antibody (CH1 specific) was immobilized on a CM5 Sensor Chip to a level of 2000 RU in acetate buffer at pH 4.5 using amine coupling following the Wizard instructions for two channels. One channel was used for background signal correction. The standard running buffer HBS-EP pH 7.4 was used. Regeneration was performed with a single injection of 10 µl of 10 mM Glycine at pH 1.5 at 20 µl/minute. IgG samples were injected for 2 minutes at 50 nM at 30 µl/min followed by an off-rate of 60 seconds. The monomeric antigen (human ERBB3 His tagged or rhesus monkey ERBB3 His

tag) was injected in two fold serial dilutions from 3 nM down to 0.2 nM, for 2 minutes at 30 µl/min followed by an off-rate of 300 seconds. The obtained sensorgrams were analysed using the Biacore® 3000 evaluation (BIAevaluation) software. The KD was calculated by simultaneous fitting of the association and dissociation phases to a 1:1 Langmuir binding model.

Flow cytometry of IgGs

Purified IgGs were tested in FACs for binding to human and rhesus monkey ERBB3 expressed on transiently transfected HEK-293 cells and HEK-293 wild-type cells. The IgG samples were titrated in three-fold serial dilutions starting at 500 nM to 0.008 nM. Binding of IgGs was detected with a mouse anti-human IgG conjugated to FITC. Results were analyzed by examining the Mean Fluorescence Intensity (MFI) of 10000 cells per sample in the BL-1 channel detector of a flow cytometer (AttuneTM NxT Acoustic Focusing Cytometer, Invitrogen/ ThermoFisher Scientific). The EC50 values were calculated using the MFI values in GraphPad Prism software (GraphPad Software, La Jolla, CA) and 4 parameters.

Antibody v-domain T cell epitope content: *in silico* analyses

In silico technologies (Abzena, Ltd.), which are based on identifying the location of T cell epitopes in therapeutic antibodies and proteins, were used for assessing potential immunogenicity in antibody v-domains. iTope™ was used to analyse the VL and a VH sequences of key leads for peptides with promiscuous high affinity binding to human MHC class II. Promiscuous high affinity MHC class II binding peptides are thought to correlate with the presence of T cell epitopes that are high risk indicators for clinical immunogenicity of drug proteins. The iTope™ software predicts favourable interactions between amino acid side chains of a peptide and specific binding pockets (in particular pocket positions; p1, p4, p6, p7 and p9) within the open-ended binding grooves of 34 human MHC class II alleles. These alleles represent the most common HLA-DR alleles found world-wide with no weighting attributed to those found most prevalently in any particular ethnic population. Twenty of the alleles contain the ‘open’ p1 configuration and 14 contain the ‘closed’ configuration where glycine at position 83 is replaced by a valine. The location of key binding residues is achieved by the *in silico* generation of 9mer peptides that overlap by eight amino acids spanning the test protein sequence. This process successfully discriminates with high accuracy between peptides that either bind or do not bind MHC class II molecules.

In addition, the sequences were analysed using TCED™ (T Cell Epitope Database™) search for matches to T cell epitopes previously identified by *in vitro* human T cell epitope mapping analyses of other protein sequences. The TCED™ is used to search any test sequence

against a large (>10,000 peptides) database of peptides derived from unrelated protein and antibody sequences.

Results and Discussion

CDR grafting onto preferred human germline v-genes

The CDRs of an antagonistic murine anti-ERBB3 IgG 24C05 (24C05; see WO2011136911A2 and Table 2) were initially introduced to human germline immunoglobulin v-domain framework sequence scaffolds using CDR grafting. To bias our engineering efforts towards final lead therapeutic IgG compounds with optimal drug-like properties, we chose to graft the CDRs of the parental antibody onto "preferred" germline scaffolds IGHV3-11 and IGKV1-39, which are known to have good solubility, high physical stability and are used at high frequency in the expressed human antibody repertoire.

Those scaffolds and grafted CDR definitions are outlined in Table 2. While this process of CDR grafting is well known, it is still problematic to predict whether a given set of human v-domain sequences will act as suitable acceptor frameworks for non-human CDR grafting. The use of unsuitable frameworks can lead to the loss of target binding function, protein stability issues or even impaired expression of the final IgG. The IGHV3-11/IGKV1-39 graft was therefore taken forward as the template for CDR mutagenesis and selection of improved clones.

Library generation and screening

The CDR-grafted IGKV1-39/IGHV3-11 v-domain sequences were combined into a Fab phage display format and a mutagenesis library cassette was generated by oligo synthesis and assembly. The final Fab library was ligated into a phage display vector and transformed into *E. coli* via electroporation to generate 1.2 x 10^9 independent clones. Library build quality was verified by sequencing 96 clones, across both v-domains. This sequencing data showed that the positions encoding either the murine or human germline residue at each position of variance had been effectively sampled at a frequency of approximately 50% and that positions intended to encode all amino acids exhibited full coverage. Libraries were rescued using helper phage M13 and selections performed on biotinylated human and rhesus monkey ERBB3-Fc proteins in multiple separate branches.

Post-selection screening and DNA sequencing revealed the presence of 658 human and rhesus ERBB3-binding Fab clones that exhibited strong binding to human and rhesus ERBB3 in ELISA (Fig. 1A) and >50% inhibition of 24C05 IgG1null binding to human ERBB3 in Alphascreen assay (Fig. 1B). Amongst these 658 clones, the framework sequences remained fully germline while humanizing mutations were also observed in all CDRs (Table

3). Lead clones were ranked based on level of CDR germlining versus ELISA and Alphascreen signals for binding to both human and rhesus ERBB3-Fc. The v-domains of the 9 top clones from this ranking were then sub-cloned into IgG expression vectors for further testing as below (Table 4).

While germ-lining mutations were observed in all CDRs for the lead clones derived directly from library selections, it remained possible that sequence analyses might allow further clones to be designed to have maximal humanization. The 658 sequence-unique hits with binding signals against human and rhesus protein were therefore used to analyse the retention frequency for murine amino acids in the CDRs of this functionally characterized population. Positional amino acid retention frequency was expressed as a percentage found in the V_L and V_H domains (Fig. 2A&B, respectively). Murine residues with RF < 75% were regarded as positions that are possibly not essential to the target-binding paratope and are likely to be open to germ-lining, in a series of combinatorial designs (Table 4). In a surprising finding for such a high-affinity starting clone, only a minority of murine residues were found to be highly positively selected. Indeed, only 3 of the 9 murine residues in the HCDR1 and HCDR2 exhibited retention frequency above 75% (Fig. 2A). This analysis strongly suggested that the VH sequence outside the HCDR3 could possibly be rendered very close in germline identity to IGHV3-11. In the V_L domain, only 4 of 10 murine CDR residues derived from the h24C05 sequence were retained with frequencies >75% (Fig. 3A).

Designs containing combinations of those murine residues with RF > 75% with those also heavily-selected in the lead clone population were given the prefix “MH” (MH = Maximally Humanized). In total 5 MH clones were generated. In addition, a ‘TTP’ (TTP = Total Theoretically Possible) clone was generated which combined the 6 most humanized CDR sequences found in the high-functioning, epitope-competing Fab screen. The MH, TTP and library-derived clone v-domains (Table 4) were generated by gene synthesis and (along with the control antibodies), cloned into human expression vectors for production in IgG1null format. All IgGs were readily expressed and purified from transient transfections of mammalian cells.

Lead IgG specificity and potency characteristics

The purified IgGs described above were then tested for binding to human and rhesus ERBB3 in direct titration ELISA format (Fig. 3A&B). This analysis demonstrated that the majority of library derived and designer (MH) clones retained binding activity for human and/or rhesus ERBB3 that was equivalent to, or improved over, the h24C05 IgG1null.

An Alphascreen assay was established to allow the testing of IgGs for epitope competition with h24C05 IgG binding to biotinylated monomeric human ERBB3. In this assay, the top-performing library-derived and designer IgGs were more effectively differentiated. While all clones exhibited full, concentration-dependent neutralisation, and the majority of clones exhibited equivalent or improved competition for the h24C05 epitope over h24C05 (Fig. 4), some exhibited less potent epitope competition including MH1.

Biacore® analyses of binding affinity were performed for all IgGs to solution-phase, monomeric human and rhesus ERBB3 proteins. In all cases, accurate 1:1 binding affinities with low Chi^2 values were obtained (Table 5). These analyses showed that library-derived clones which consistently gave the highest EC50 and IC50 values in Fab and IgG ELISA and Alphascreen assays also showed highest affinity binding to human and rhesus ERBB3 (Table 5). Importantly, these improvements in affinity were recapitulated in rhesus binding, with the majority of these clones exhibiting affinities within 3-fold of the human ERBB3 affinity. Affinity differentials of less than 4-fold between human and rhesus target orthologs are highly beneficial in pre-clinical drug development analyses as they allow significantly better design and interpretation of e.g. monkey safety, PK and PD modelling experiments.

In addition, comparison of the affinities of MH and TTP clones confirmed the influence of the LCDR1 in maintaining binding affinity, as mutations of the residues 'S>N' at positions 11 in that CDR resulted in approximately 2-fold loss of KD for clones TTP in comparison to clone MH5, against human ERBB3 (Table 5). Comparison of clones MH2 and MH3 also confirmed that the mutation of HCDR1 residue 8 (A to S) and HCDR2 residue 10 (Y to T) in MH3 also led to an approximately 3-fold reduction in binding affinity for human and rhesus ERBB3 in comparison to clone MH2 (Table 5).

The findings outlined above confirmed that the multiple clones could retain high binding affinity (in the pM range), epitope specificity and species cross-reactivity of h24C05, while retaining only minimal non-germline amino acid content in the VH and VL domains (excluding the HCDR3, for which there is no corresponding germline). This near-complete germlining of the VH domain significantly reduced immunogenic potential in man. In addition, the gemlining mutations observed in multiple clones led to the removal or improvement of several amino acid degradation motifs found in the murine CDRs of h24C05 that are a known risk for manufacturing and clinical development qualities in antibody molecules: A putative isomerization risk at LCDR2 position 6 (D) was removed via mutation to Q, a 'DG' aspartic acid isomerisation motif in HCDR2 position 6 and 7 was converted to the lower-risk motif 'DS', and a putative oxidation risk at HCDR3 position 2 (W) was removed by mutation to Y or L. These improvements in primary sequence were not possible to predict *a priori* and are

of direct consequence in both manufacturing and clinical development of an antibody therapeutic as they are all potential stability risk motifs, leading to intrinsic product heterogeneity. Such risk motifs can lead to costly development issues where multiple process modifications must be made to maximise intact antibody yield and to minimise product heterogeneity. Degradation motifs are also a clinical development risk, as accelerated antibody breakdown in the body can reduce both half-life and potency of the molecule.

Flow cytometric analyses of lead IgG binding specificity at the cell membrane

Antibodies to ERBB3 were analysed for concentration-dependent binding at the cell surface via flow cytometry. HEK-293 cells were transiently transfected with either human or rhesus ERBB3 full-length cDNAs. Anti-ERBB3 IgGs and an isotype control were then all tested in IgG1null format, over a concentration range of 500-0.008 nM for binding to human (Fig. 5A) and rhesus (Fig. 5B) transfected cells. All IgGs other than the isotype control showed strong concentration-dependent binding to human and rhesus ERBB3+ cells, with a maximum MFI in each case being >20-fold higher than observed background signals for IgG1 isotype control.

Antibody v-domain T cell epitope analyses

In silico technologies (Abzena, Ltd.), which are based on identifying the location of T cell epitopes in therapeutic antibodies and proteins, were used for assessing the immunogenicity of both the h24C05 and lead antibody 15G11 v-domains. Analysis of the v-domain sequences was performed with overlapping 9mer peptides (with each overlapping the last peptide by 8 residues) which were tested against each of the 34 MHC class II allotypes. Each 9mer was scored based on the potential 'fit' and interactions with the MHC class II molecules. The peptide scores calculated by the software lie between 0 and 1. Peptides that produced a high mean binding score (>0.55 in the iTope™ scoring function) were highlighted and, if >50% of the MHC class II binding peptides (i.e. 17 out of 34 alleles) had a high binding affinity (score >0.6), such peptides were defined as 'high affinity' MHC class II binding peptides which are considered a high risk for containing CD4+ T cell epitopes. Low affinity MHC class II binding peptides bind a high number of alleles (>50%) with a binding score >0.55 (but without a majority >0.6). Further analysis of the sequences was performed using the TCED™. The sequences were used to interrogate the TCED™ by BLAST search in order to identify any high sequence homology between peptides (T cell epitopes) from unrelated proteins/antibodies that stimulated T cell responses in previous *in vitro* T cell epitope mapping studies performed at Abzena Ltd.

Peptides were grouped into four classes: High Affinity Foreign ('HAF' – high immunogenicity risk), Low Affinity Foreign ('LAF' – lower immunogenicity risk), TCED+ (previously identified epitope in TCED database), and Germline Epitope ('GE' - human germline peptide sequence with high MHC Class II binding affinity). Germline Epitope 9mer peptides are unlikely to have immunogenic potential due to T cell tolerance, as validated by previous studies with a wide range of germline peptides. Importantly, such germline v-domain epitopes (aided further by similar sequences in the human antibody constant regions) also compete for MHC Class II occupancy at the membrane of antigen presenting cells, reducing the risk of foreign peptide presentation being sufficient to achieve the 'activation threshold' required for T cell stimulation. High GE content is therefore a beneficial quality in clinical development of an antibody therapeutic.

This analysis showed that despite the replacement with several murine residues with human germline equivalents in the CDRs of the key lead 15G11, the method of Townsend *et al.* had not led to significant beneficial changes in peptide epitope content in comparison to h24C05 (Fig. 6A, Fig. 6B). On the contrary, while 15G11 had improved GE content (11) over h24C05 (10), 15G11 had unexpectedly increased immunogenicity risk rather than decreased, as it contained not only 2 new LAF epitopes, but had also gained a high-risk TCED+ LAF in the HCDR-1. As the v-domain framework regions (i.e. outside the CDR sequences) of both antibodies were germline in sequence (Table 2), all changes in predicted immunogenicity in 15G11 came about as a result of the germlining of CDR residues.

As the method of Townsend *et al.* had failed to improve either the potency or immunogenicity risk of lead clone 15G11 over h24C05, the potential of further non-human germline mutagenesis in the CDRs was examined. Selection of specific amino acid changes was influenced by the available biophysical and biochemical data, e.g. constraints on modification of the parental 15G11 sequence taking into consideration secondary and tertiary protein structures as well as potential interactions of amino acid side chains with the core of the protein. Additionally, selection of amino acid changes was influenced by the frequency of occurrence of any particular amino acid at any given position in the human repertoire. The aim was therefore to avoid introducing amino acids that never occur at a given position and that would be more likely to adversely affect the structure. The amino acid cysteine was not considered at any point to avoid introducing an unpaired cysteine residue, which could potentially lead to aggregation issues. Each epitope was analysed individually to identify residues that would remove or reduce promiscuous MHC class II binding and, subsequently, the proposed epitope variants were analysed in the context of the whole 15G11 sequence to ensure that novel potential epitopes were not introduced in

adjacent regions. Increased value was placed on the use of mutations that had been observed to be tolerated in the functionally-selected population of CDR sequences (Table 3). This process was applied to four key predicted epitopes.

Epitope 1 was the highest risk (TCED+) epitope identified and partially overlaps with VH CDR1 (Fig. 7A). As such, performing any substitutions within this region could potentially impact on binding to antigen. By iTope™ analysis, this region consists of one T cell epitope with a p1 anchor at Y32 (Kabat numbering). Only a limited number of changes were assessed for Framework 2 as this region is highly conserved between antibodies, with several residues playing a role in forming the VH:VL interface. In contrast to Framework regions, CDRs show greater sequence diversity, although this diversity is substantially less pronounced for VH CDR1 and 2 compared with VH CDR3. Within the VH CDR1 region, it was observed that for a number of given positions, several amino acid substitutions were able to completely abrogate potential T cell epitope binding. However, in many cases, these amino acids are almost never observed in that given position, and so these amino acids were discarded. Suggested sequence changes are illustrated in Fig. 7A. Two epitope-ablating variants were prioritised in this peptide: YSMSWIRQA (SED ID NO:250) and YGMSWVRQA (SEQ ID NO:251) (mutation underlined in both cases). The first mutation G>S could potentially ablate the TCED+ epitope, whereas the second mutation I>V could potentially render the peptide sequence a GE.

Epitope 2 lies primarily within VL CDR1 and, as such, performing any substitutions within this region could potentially impact on binding to antigen. By iTope™ analysis, this region consists of one potential T cell epitope with a p1 anchor at I29. Changes were kept to a minimum in Framework 2 as this region is very highly conserved between antibodies, with several residues playing a role in forming the VH:VL interface. In contrast to Framework regions, CDRs show greater sequence diversity, although this diversity is substantially less pronounced for VLs compared with VHs and for VL CDR1 and 2 compared with VL CDR3. Within the VL CDR1 region, it was observed that for a number of given positions, several amino acid substitutions were able to completely abrogate potential T cell epitope binding. However, in many cases, these amino acids are almost never observed in that given position, and so these amino acids were discarded. Suggested sequence changes are illustrated in Fig. 7B.

Epitope 3 overlaps partially with VL CDR2 and, as such, performing any mutations within this region could potentially impact on binding to antigen. By iTope™ analysis, this region consists of one potential T cell epitope with a p1 anchor at I48. Changes to Framework 2 were kept to a minimum as this region is highly conserved between antibodies. In contrast

to Framework regions, CDRs show greater sequence diversity, although this diversity is less pronounced for VL CDRs compared with VH CDRs. From iTope™ analysis, it was observed that the majority of amino acid substitutions at almost all positions within the core 9-mer were detrimental, with increased binding observed for almost all substitutions. A limited number of amino acid substitutions were identified that abrogate potential T cell epitope binding, however, these amino acids are almost never observed in that given position, and so these amino acids were discarded. Suggested sequence changes are illustrated in Fig. 7C. Importantly, in the analysis, as so many changes in this region were potentially detrimental, selected full CDR variants in the LCDR-2 (Tables 3 and 4) were examined for their TCR epitope risk. Surprisingly, the LCDR-2 sequence AASTLQS (SEQ ID NO:26) was found to fully ablate the HAF peptide risk of this epitope, and a similar high-risk HAF epitope in h24C05 (IYAASTLDS (SEQ ID NO:252)). As a result, this CDR sequence was prioritised for inclusion in a subset of new variants.

Epitope 4 lies completely within VL CDR3 and, as such, performing any substitutions within this region could potentially impact on binding to antigen. By iTope™ analysis, this region consists of one potential T cell epitope with a p1 anchor at L89. No Framework changes were considered. In contrast to Framework regions, CDRs show greater sequence diversity, especially for CDR3, and so amino acid substitutions were not discarded in this region on the basis of occurrence. Several single amino acid substitutions were observed to partially abrogate the binding of both potential T cell epitopes. Suggested single amino acid substitution changes that have an effect on Epitope 4 are illustrated in Fig. 7D.

As there were a number of potential variants to be sampled in each epitope, 11 new variants of 15G11 were designed in an attempt to find an ideal combination that could retain potency but lead to a fully deimmunised clone. For these 15 IgGs the VL v-domain sequences are shown in Table 6, with the VH domains in Table 7. These IgGs were cloned and expressed in IgG1 form, before functional testing as below.

15G11-DI variants - IgG specificity and potency characteristics

'DI' variant IgGs 15G11-DI1-11 were first examined for their binding characteristics by ELISA on human (Fig. 8A) and rhesus (Fig. 8B) ErbB3. Against both human and rhesus ErbB3, all clones other than 15G11-DI11 exhibited strong target binding with curves overlapping with both m24C05 and h24C05.

As ELISA binding is strongly influenced by avidity effects, we then performed a high-sensitivity, solution-phase, Alphascreen competition assay to simultaneously examine the target binding affinity and epitope competition retention with h24C05 (Fig. 9). In this assay,

all IgGs other than 15G11-DI11 showed full, concentration dependent inhibition of h24C05 to human ErbB3, with potencies generally being equivalent to, or improved over h24C05 (Fig. 9). IgGs m24C05 and h24C05 exhibited IC50 values of 0.16 nM and 1.25nM, respectively, which correlates with the Biacore® affinity value differential between those two IgGs shown in Table 5. Exceptions were 15G11-DI3, 15G11-DI4, 15G11-DI10 and 15G11-DI11, whose potencies appeared to be lower than h24C05.

In flow cytometric analyses of binding to human and rhesus ErbB3 (Fig 10A, B), all clones showed fully saturating, overlapping binding curves. Clones 15G11-DI5, 15G11-DI6, 15G11-DI7, 15G11-DI8 and 15G11-DI9 exhibited highest binding to both human and rhesus ErbB3, approximately equivalent to both m24C05 and h24C05.

A key developability factor in CDR-engineered antibodies for therapeutic use is a lack of 'polyreactivity'. Polyreactivity is a significant risk to the pharmacokinetic and safety qualities of any antibody. To ensure the deimmunised lead antibodies were not at risk, they were examined in established polyreactivity binding ELISA assays against dsDNA and human insulin (Avery et al. mAbs, 2018). The majority of IgGs tested in this assay (15G11-DI10 being an exception) showed no sign of polyreactive binding as they exhibited signals below the risk cut-off of 10 and at, or below, the signals of the negative control, clinically successful antibodies Bevacizumab and Ustekinumab (Fig. 11). The positive control antibodies Bococizumab and Briakinumab exhibited the expected strong signals in these assays.

To ascertain if the full biological potency of ErbB3 inhibition had been retained in the key deimmunised leads, clones 15G11, 16B09, 15G11-DI5, 15G11-DI6, 15G11-DI7, 15G11-DI8 and 15G11-DI9 were all analysed over a broad concentration range in the DiscoverX PathHunter eXpress ErbB2-ErbB3 functional assay (Fig. 12A-G). These analyses demonstrated that clones 15G11 (Fig. 12A), 16B09 (Fig. 12B), 15G11-DI5 (Fig. 12C) and 15G11-DI6 (Fig. 12D) all maintained near-identical potency to both m24C05 and h24C05. Clones 15G11-DI7 (Fig. 12E) and 15G11-DI8 (Fig. 12F) exhibited slightly reduced potency. For 15G11-DI9, the curve fit of its data was unreliable (Fig. 12C), so the experiment was repeated and the fit improved, with 15G11-DI9 also showing near identical potency to h24C05 and m24C05, as evidenced by the overlapping response curves (Fig. 13).

For these deimmunised key leads, TCR epitope content was again examined (Fig. 14A - FIG. 14E) and this demonstrated that clones 15G11-DI8 and 15G11-DI9 exhibited significantly reduced immunogenicity risk in comparison to h24C05 and 15G11 where the initial germlining process had, unexpectedly, actually increased risk over h24C05 (Fig. 6A,

Fig. 6B). Indeed, clone 15G11-DI9 was found to be fully inert, containing no predicted foreign TCR epitopes at all and only a large number of GE peptides (11).

The combined analyses outlined herein demonstrated that, surprisingly, deep sampling of both germline and non-germline amino acids in the CDRs of these antibodies allowed the simultaneous optimisation of target binding specificity, immunogenicity risk, potency, biophysical stability and chemical stability risks in multiple final molecules. These findings also demonstrate that the beneficial deimmunising outcomes described here could not be achieved using the method of Townsend *et al.* (2015; PNAS 112: 15354-15359).

Although the present invention has been described with reference to preferred or exemplary embodiments, those skilled in the art will recognize that various modifications and variations to the same can be accomplished without departing from the spirit and scope of the present invention and that such modifications are clearly contemplated herein. No limitation with respect to the specific embodiments disclosed herein and set forth in the appended claims is intended nor should any be inferred.

No limitation with respect to the specific embodiments disclosed herein and set forth in the appended claims is intended nor should any be inferred. All documents, or portions of documents, cited herein, including but not limited to patents, patent applications, articles, books, and treatises, are hereby expressly incorporated by reference in their entirety for any purpose. In the event that one or more of the incorporated documents or portions of documents define a term that contradicts that term's definition in the application, the definition that appears in this application controls. However, mention of any reference, article, publication, patent, patent publication, and patent application cited herein is not, and should not be taken as an acknowledgment, or any form of suggestion, that they constitute valid prior art or form part of the common general knowledge in any country in the world.

Table 1. Amino acid sequences of 24C05 anti-ERBB3 CDRs as defined here ("Unified" scheme) in comparison to alternative definitions.

Scheme	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
Unified	GFTFSDYAMS (SEQ ID NO:59)	VSTISDGGTYTYYPDNVKG (SEQ ID NO:65)	EWGDYDGFDY (SEQ ID NO:72)	RASQEISGYLS (SEQ ID NO:76)	AASTLDS (SEQ ID NO:80)	LQYDSYPYT (SEQ ID NO:82)
Kabat	DYAMS (SEQ ID NO:60)	TISDGGTYTYYPDNVKG (SEQ ID NO:66)	EWGDYDGFDY (SEQ ID NO:72)	RASQEISGYLS (SEQ ID NO:76)	AASTLDS (SEQ ID NO:80)	LQYDSYPYT (SEQ ID NO:)
Chotia	GFTFSDY (SEQ ID NO:61)	SDGGTY (SEQ ID NO:67)	EWGDYDGFDY (SEQ ID NO:72)	RASQEISGYLS (SEQ ID NO:76)	AASTLDS (SEQ ID NO:80)	LQYDSYPYT (SEQ ID NO:82)
IMGT	GFTFSDYA (SEQ ID NO:62)	ISDGGTYT (SEQ ID NO:68)	AREWGDYDGFDY (SEQ ID NO:73)	QEISGY (SEQ ID NO:77)	AAS	LQYDSYPYT (SEQ ID NO:82)
AHo	ASGFTFSDYAMS (SEQ ID NO:63)	ISDGGTYTYYPDNVKG (SEQ ID NO:69)	EWGDYDGFD (SEQ ID NO:74)	ASQEISGY (SEQ ID NO:78)	AASTLDS (SEQ ID NO:80)	YDSYPY (SEQ ID NO:83)
AbM	GFTFSDYAMS (SEQ ID NO:59)	TISDGGTYTY (SEQ ID NO:70)	EWGDYDGFDY (SEQ ID NO:72)	RASQEISGYLS (SEQ ID NO:76)	AASTLDS (SEQ ID NO:80)	LQYDSYPYT (SEQ ID NO:82)
Contact	SDYAMS (SEQ ID NO:64)	VSTISDGGTYTY (SEQ ID NO:71)	AREWGDYDGFD (SEQ ID NO:75)	ISGYLSWY (SEQ ID NO:79)	LLIYAASTLD (SEQ ID NO:81)	LQYDSYPY (SEQ ID NO:84)

Table 2. Amino acid sequence of h24C05 anti-ERBB3 v-domains and human germline CDR grafts.

V DOMAIN	Human germline[1]	Amino acid sequence[2]
h24C05-VH	IGHV3-11	QVQLVESGGGLVKPGGSLRLSCAAS**GFTFSDYAMS**WIRQAPGKGLEW**VSTISDGGTYTYYPDNVKG**RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR**EWGDYDGFDY**WGQGTLVTVSS (SEQ ID NO:85)
VH graft	IGHV3-11[3]	QVQLVESGGGLVKPGGSLRLSCAAS**GFTFSDYAMS**WIRQAPGKGLEW**VSTISDGGTYTYYPDNVKG**RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR**EWGDYDGFDY**WGQGTLVTVSS (SEQ ID NO:86)
h24C05-VL	IGKV1-16	DIQMTQSPSSLSASVGDRVTITC**RASQEISGYLS**WFQQKPGKAPKSLIY**AASTLDS**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**LQYDSYPYT**FGGGTKVEIK (SEQ ID NO:87)
VL graft	IGKV1-39[3]	DIQMTQSPSSLSASVGDRVTITC**RASQEISGYLS**WYQQKPGKAPKLLIY**AASTLDS**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**LQYDSYPYT**FGGGTKVEIK (SEQ ID NO:88)

[1]Human germline definitions used for grafting, based on IMGT system. [2]CDR residues are in bold and underlined. As noted above, the "Unified" CDR definitions used in this manuscript are an expanded definition in comparison to the classical Kabat definition. Each sequence above shows the framework regions (FRs) and the CDRs in the following order: FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4. [3]Grafts are fully germline in the framework regions, used as the template for CDR mutant library construction.

Table 3. Amino acid sequences of unique CDRs from 658 unique anti-ERBB3 v-domains.

LCDR1	LCDR2	LCDR3	HCDR1	HCDR2	HCDR2	HCDR3
RASQSISSYLS (SEQ ID NO:16)	AASSLDS (SEQ ID NO:22)	LQYDSTPYT (SEQ ID NO:23)	GFTFSDYAMS (SEQ ID NO:109)	VGTISDGGTTIYYADNVKG (SEQ ID NO:117)	VSTISDSGSYIYYADSVKG (SEQ ID NO:14)	EFGDYDGFDF (SEQ ID NO:181)
RASQEISSYLS (SEQ ID NO:21)	AASSLQS (SEQ ID NO:17)	LQYYSYPYT (SEQ ID NO:98)	GFTFSDYEMS (SEQ ID NO:110)	VSTISDDGSTTYYADSVKG (SEQ ID NO:118)	VSTISDSGSYIYYPDNVKG (SEQ ID NO:155)	EFGDYDGFDY (SEQ ID NO:182)
RASQIISSYLS (SEQ ID NO:52)	AASTLQS (SEQ ID NO:26)	LQYDSTPLT (SEQ ID NO:18)	GFTFSDYGMS (SEQ ID NO:13)	VSTISDGGSTIYYADNVKG (SEQ ID NO:119)	VSTISDSGSYIYYPDSVKG (SEQ ID NO:156)	ELGDYDGFDY (SEQ ID NO:20)
RASQSISSYLN (SEQ ID NO:50)	AASNLQS (SEQ ID NO:93)	QQYDSYPYT (SEQ ID NO:99)	GFTFSDYHMS (SEQ ID NO:111)	VSTISDGGSTIYYADSVKG (SEQ ID NO:120)	VSTISDSGSYTYYADNVKG (SEQ ID NO:157)	ELGDYDGWDY (SEQ ID NO:183)
RASQSISGYLN (SEQ ID NO:89)	AASSLHS (SEQ ID NO:94)	LQYYSTPLT (SEQ ID NO:53)	GFTFSDYNMS (SEQ ID NO:112)	VSTISDGGSTIYYPDNVKG (SEQ ID NO:121)	VSTISDSGSYTYYADSVKG (SEQ ID NO:54)	EMGDYDGFDY (SEQ ID NO:184)
RASQEISSYLN (SEQ ID NO:90)	EASSLDS (SEQ ID NO:95)	LQYDSYPLT (SEQ ID NO:100)	GFTFSDYQMS (SEQ ID NO:113)	VSTISDGGSTIYYPDSVKG (SEQ ID NO:122)	VSTISDSGSYTYYPDNVKG (SEQ ID NO:158)	EQGDYDGFDI (SEQ ID NO:185)
RASQSISGYLS (SEQ ID NO:30)	AASSLKS (SEQ ID NO:96)	QQYDSTPYT (SEQ ID NO:101)	GFTFSDYRMS (SEQ ID NO:114)	VSTISDGGSTTYYADNVKG (SEQ ID NO:123)	VSTISDSGSYTYYPDSVKG (SEQ ID NO:19)	EWGDADGFDY (SEQ ID NO:186)
RASQEISGYLN (SEQ ID NO:91)	EASSLQS (SEQ ID NO:97)	LQSDSTPYT (SEQ ID NO:102)	GFTFSDYSMS (SEQ ID NO:24)	VSTISDGGSTTYYADSVKG (SEQ ID NO:124)	VSTISDSGTTIYYADNVKG (SEQ ID NO:56)	EWGDDDGFDY (SEQ ID NO:187)
RASQNISSYLS (SEQ ID NO:92)		LQSDSTPLT (SEQ ID NO:103)	GFTFSDYTMS (SEQ ID NO:115)	VSTISDGGSTTYYPDNVKG (SEQ ID NO:125)	VSTISDSGTTIYYADSVKG (SEQ ID NO:159)	EWGDEDGFDY (SEQ ID NO:188)
		QQYDSYPLT (SEQ ID NO:104)	GFTFSDYVMS (SEQ ID NO:116)	VSTISDGGSTTYYPDSVKG (SEQ ID NO:126)	VSTISDSGTTTYYADNVKG (SEQ ID NO:160)	EWGDHDGFDY (SEQ ID NO:189)
		LQYYSYPLT (SEQ ID NO:105)		VSTISDGGSYIYYADNVKG (SEQ ID NO:127)	VSTISDSGTTTYYADSVKG (SEQ ID NO:161)	EWGDLDGFDY (SEQ ID NO:190)
		LQYYSTPYT (SEQ ID NO:106)		VSTISDGGSYIYYADSVKG (SEQ ID NO:128)	VSTISDSGTTTYYPDNVKG (SEQ ID NO:162)	EWGDMDGFDR (SEQ ID NO:191)

		QQYDSTPLT (SEQ ID NO:107)		VSTISDGGSYIYYPDNVKG (SEQ ID NO:129)	VSTISDSGTTTYYPDSVKG (SEQ ID NO:163)	EWGDMDGFDY (SEQ ID NO:192)
		LQYDSYHLT (SEQ ID NO:108)		VSTISDGGSYIYYPDSVKG (SEQ ID NO:130)	VSTISDSGTYIYYADNVKG (SEQ ID NO:164)	EWGDNDGFDY (SEQ ID NO:193)
				VSTISDGGSYTYYADNVKG (SEQ ID NO:31)	VSTISDSGTYIYYADSVKG (SEQ ID NO:165)	EWGDQDGFDY (SEQ ID NO:194)
				VSTISDGGSYTYYADSVKG (SEQ ID NO:28)	VSTISDSGTYIYYPDNVKG (SEQ ID NO:166)	EWGDSDGFDY (SEQ ID NO:195)
				VSTISDGGSYTYYPDNVKG (SEQ ID NO:131)	VSTISDSGTYIYYPDSVKG (SEQ ID NO:167)	EWGDTDGFDY (SEQ ID NO:196)
				VSTISDGGSYTYYPDSVKG (SEQ ID NO:57)	VSTISDSGTYTYYADNVKG (SEQ ID NO:168)	EWGDWDGFDY (SEQ ID NO:197)
				VSTISDGGTTIYYADNVKG (SEQ ID NO:132)	VSTISDSGTYTYYADSVKG (SEQ ID NO:169)	EWGDYDGCDY (SEQ ID NO:198)
				VSTISDGGTTIYYADSVKG (SEQ ID NO:133)	VSTISDSGTYTYYPDNVKG (SEQ ID NO:170)	EWGDYDGFDA (SEQ ID NO:199)
				VSTISDGGTTIYYPDSVKG (SEQ ID NO:134)	VSTISDSGTYTYYPDSVKG (SEQ ID NO:25)	EWGDYDGFDD (SEQ ID NO:200)
				VSTISDGGTTTYYADNVKG (SEQ ID NO:135)	VSTISNSGTYTYYADSVKG (SEQ ID NO:171)	EWGDYDGFDE (SEQ ID NO:29)
				VSTISDGGTTTYYADSVKG (SEQ ID NO:136)	VSTISSGGSYIYYPDSVKG (SEQ ID NO:172)	EWGDYDGFDF (SEQ ID NO:15)
				VSTISDGGTTTYYPDNVKG (SEQ ID NO:137)	VSTISSGGSYTYYPDSVKG (SEQ ID NO:173)	EWGDYDGFDH (SEQ ID NO:27)
				VSTISDGGTTTYYPDSVKG (SEQ ID NO:138)	VSTISSSGSYTYYADNVKG (SEQ ID NO:174)	EWGDYDGFDI (SEQ ID NO:201)
				VSTISDGGTYIYYADNVKG	VSTISSSGTTTYYADSVKG	EWGDYDGFDK

					(SEQ ID NO:139)	(SEQ ID NO:175)			(SEQ ID NO:202)
					VSTISDGGTYIYYADSVKG (SEQ ID NO:140)	VSTISSSGTYIYYADNVKG (SEQ ID NO:176)			EWGDYDGFDL (SEQ ID NO:203)
					VSTISDGGTYIYYPDNVKG (SEQ ID NO:141)	VSYISDGGSYIYYADSVKG (SEQ ID NO:177)			EWGDYDGFDM (SEQ ID NO:204)
					VSTISDGGTYIYYPDSVKG (SEQ ID NO:142)	VSYISDGGSYTYYADNVKG (SEQ ID NO:178)			EWGDYDGFDN (SEQ ID NO:55)
					VSTISDGGTYTYYADNVKG (SEQ ID NO:143)	VSYISDGGTTIYYADSVKG (SEQ ID NO:179)			EWGDYDGFDQ (SEQ ID NO:205)
					VSTISDGGTYTYYADSVKG (SEQ ID NO:144)	VSYISDSGTYTYYPDSVKG (SEQ ID NO:180)			EWGDYDGFDR (SEQ ID NO:206)
					VSTISDGGTYTYYPDNVKG (SEQ ID NO:145)				EWGDYDGFDS (SEQ ID NO:207)
					VSTISDGGTYTYYPDSVKG (SEQ ID NO:146)				EWGDYDGFDV (SEQ ID NO:208)
					VSTISDSGSTIYYADNVKG (SEQ ID NO:147)				EWGDYDGFDW (SEQ ID NO:209)
					VSTISDSGSTIYYADSVKG (SEQ ID NO:58)				EWGDYDGFDY (SEQ ID NO:210)
					VSTISDSGSTIYYPDNVKG (SEQ ID NO:148)				EWGDYDGFHY (SEQ ID NO:211)
					VSTISDSGSTIYYPDSVKG (SEQ ID NO:149)				EWGDYDGIDY (SEQ ID NO:212)
					VSTISDSGSTTYYADNVKG (SEQ ID NO:150)				EWGDYDGLDY (SEQ ID NO:213)
					VSTISDSGSTTYYADSVKG (SEQ ID NO:151)				EWGDYDGWDY

	VSTISDSGSTTYYPDNVKG (SEQ ID NO:152)					EWGDYDGYDY (SEQ ID NO:215)
	VSTISDSGSTTYYPDSVKG (SEQ ID NO:153)					EYGDYDGFDY (SEQ ID NO:51)
	VSTISDSGSYIYYADNVKG (SEQ ID NO:154)					MWGDYDGFDY (SEQ ID NO:216)

Table 4. Amino acid sequences of CDRs of unique, library-derived and designer, human/rhesus cross-reactive anti-ERBB3 IgGs.

Clone	LCDR1	LCDR2	LCDR3	HCDR1	HCDR2	HCDR3
15D10	RASQSISSYLS (SEQ ID NO:16)	AASTLQS (SEQ ID NO:26)	LQYDSTPLT (SEQ ID NO:18)	GFTFSDYGMS (SEQ ID NO:13)	VSTISDGGSYTYYADNVKG (SEQ ID NO:31)	EWGDYDGFDF (SEQ ID NO:15)
17H10	RASQSISGYLS (SEQ ID NO:30)	AASTLQS (SEQ ID NO:26)	LQYDSTPYT (SEQ ID NO:23)	GFTFSDYGMS (SEQ ID NO:13)	VSTISDGGSYTYYADSVKG (SEQ ID NO:28)	EWGDYDGFDE (SEQ ID NO:29)
09D12	RASQSISSYLN (SEQ ID NO:50)	AASSLDS (SEQ ID NO:22)	LQYDSTPLT (SEQ ID NO:18)	GFTFSDYGMS (SEQ ID NO:13)	VSTISDGGSYTYYADSVKG (SEQ ID NO:28)	EYGDYDGFDY (SEQ ID NO:51)
15D03	RASQEISSYLS (SEQ ID NO:21)	AASSLQS (SEQ ID NO:17)	LQYDSTPLT (SEQ ID NO:18)	GFTFSDYGMS (SEQ ID NO:13)	VSTISDSGSYIYYADSVKG (SEQ ID NO:14)	EWGDYDGFDH (SEQ ID NO:27)
11H02	RASQIISSYLS (SEQ ID NO:52)	AASSLDS (SEQ ID NO:22)	LQYYSTPLT (SEQ ID NO:53)	GFTFSDYGMS (SEQ ID NO:13)	VSTISDSGSYTYYADSVKG (SEQ ID NO:54)	EWGDYDGFDN (SEQ ID NO:55)
15G11	RASQEISSYLS (SEQ ID NO:21)	AASSLDS (SEQ ID NO:22)	LQYDSTPYT (SEQ ID NO:23)	GFTFSDYGMS (SEQ ID NO:13)	VSTISDSGSYTYYPDSVKG (SEQ ID NO:19)	ELGDYDGFDY (SEQ ID NO:20)
15E02	RASQSISSYLS (SEQ ID NO:16)	AASSLQS (SEQ ID NO:17)	LQYDSTPLT (SEQ ID NO:18)	GFTFSDYGMS (SEQ ID NO:13)	VSTISDSGTTIYYADNVKG (SEQ ID NO:56)	EYGDYDGFDY (SEQ ID NO:51)
09H02	RASQSISSYLS (SEQ ID NO:16)	AASSLQS (SEQ ID NO:17)	LQYDSTPLT (SEQ ID NO:18)	GFTFSDYSMS (SEQ ID NO:24)	VSTISDGGSYTYYPDSVKG (SEQ ID NO:57)	ELGDYDGFDY (SEQ ID NO:20)
16B09	RASQEISSYLS (SEQ ID NO:21)	AASTLQS (SEQ ID NO:26)	LQYDSTPLT (SEQ ID NO:18)	GFTFSDYSMS (SEQ ID NO:24)	VSTISDSGTYTYYPDSVKG (SEQ ID NO:25)	EWGDYDGFDF (SEQ ID NO:15)
TTP	RASQSISSYLN (SEQ ID NO:50)	AASSLQS (SEQ ID NO:17)	LQYDSTPLT (SEQ ID NO:18)	GFTFSDYGMS (SEQ ID NO:13)	VSTISDSGSTIYYADSVKG (SEQ ID NO:58)	EYGDYDGFDY (SEQ ID NO:51)
MH1	RASQSISSYLS (SEQ ID NO:16)	AASSLQS (SEQ ID NO:17)	LQYDSTPLT (SEQ ID NO:18)	GFTFSDYGMS (SEQ ID NO:13)	VSTISDSGSYIYYADSVKG (SEQ ID NO:14)	ELGDYDGFDY (SEQ ID NO:20)
MH2	RASQSISSYLS (SEQ ID NO:16)	AASSLQS (SEQ ID NO:17)	LQYDSTPLT (SEQ ID NO:18)	GFTFSDYGMS (SEQ ID NO:13)	VSTISDSGSYIYYADSVKG (SEQ ID NO:14)	EWGDYDGFDF (SEQ ID NO:15)
MH3	RASQSISSYLS (SEQ ID NO:16)	AASSLQS (SEQ ID NO:17)	LQYDSTPLT (SEQ ID NO:18)	GFTFSDYSMS (SEQ ID NO:24)	VSTISDSGSTIYYADSVKG (SEQ ID NO:58)	EWGDYDGFDF (SEQ ID NO:15)
MH4	RASQSISSYLS (SEQ ID NO:16)	AASSLQS (SEQ ID NO:17)	LQYDSTPLT (SEQ ID NO:18)	GFTFSDYGMS (SEQ ID NO:13)	VSTISDSGSYIYYADSVKG (SEQ ID NO:14)	EWGDYDGFDE (SEQ ID NO:29)
MH5	RASQSISSYLS (SEQ ID NO:16)	AASSLQS (SEQ ID NO:17)	LQYDSTPLT (SEQ ID NO:18)	GFTFSDYGMS (SEQ ID NO:13)	VSTISDSGSTIYYADSVKG (SEQ ID NO:58)	EYGDYDGFDY (SEQ ID NO:51)

Table 5. BIACORE® affinity values for IgG binding to human and rhesus monomeric ERBB3.

	Human ERBB3				Rhesus ERBB3			
Clone name	ka (1/Ms)	kd (1/s)	Chi2	KD (nM)	ka (1/Ms)	kd (1/s)	Chi2	KD (nM)
24C05	4.60E+07	6.70E-04	0.117	0.014	1.80E+07	4.40E-04	0.02	0.024
h24C05	2.50E+07	9.60E-04	0.164	0.039	4.10E+06	7.40E-04	0.037	0.18
15G11	1.60E+07	1.20E-03	0.141	0.078	3.30E+06	1.10E-03	0.041	0.33
16B09	1.60E+07	1.40E-03	0.223	0.089	1.30E+07	2.70E-03	0.044	0.21
15D10	1.40E+07	1.90E-03	0.195	0.14	3.30E+06	1.80E-03	0.057	0.54
17H10	9.30E+06	1.70E-03	0.165	0.19	2.70E+06	1.80E-03	0.035	0.65
15D03	1.10E+07	3.00E-03	0.204	0.26	1.80E+07	4.70E-03	0.117	0.26
MH4	1.10E+07	2.90E-03	0.158	0.26	2.20E+07	4.70E-03	0.099	0.21
MH2	1.10E+07	2.90E-03	0.177	0.27	2.00E+07	4.80E-03	0.099	0.23
09D12	1.30E+07	3.50E-03	0.149	0.27	1.10E+07	7.40E-03	0.049	0.69
09H02	3.10E+06	1.30E-03	0.272	0.43	1.10E+07	2.70E-03	0.027	0.25
MH1	6.80E+06	3.50E-03	0.124	0.51	1.30E+07	5.60E-03	0.081	0.45
15E02	6.30E+06	3.90E-03	0.229	0.61	3.70E+06	9.50E-03	0.034	2.5
MH5	5.80E+06	4.10E-03	0.166	0.71	1.20E+07	6.00E-03	0.076	0.51
MH3	7.60E+06	6.50E-03	0.143	0.85	1.80E+07	1.10E-02	0.057	0.63
TTP	6.20E+07	7.30E-02	1.21	1.2	ND	ND	ND	ND
11H02	6.10E+06	8.10E-03	1.04	1.3	1.70E+07	3.70E-02	0.332	2.1

Table 6. Amino acid sequences of VL-domains of unique, deimmunised anti-ERBB3 IgGs.

Clone	VL
15G11-DI1	DIQMTQSPSSLSASVGDRVTITCRASQEISSYLSWYQQKPGKAPKLLIYAASSLDTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQYDSTPYTFGGGTKVEIK (SEQ ID NO:217)
15G11-DI2	DIQMTQSPSSLSASVGDRVTITCRASQEISTYLSWYQQKPGKAPKLLIYAASSLDTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQYDSTPYTFGGGTKVEIK (SEQ ID NO:218)
15G11-DI3	DIQMTQSPSSLSASVGDRVTITCRASQEISSYLSWYQQKPGKAPKLLIYAASSLDTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQYDSSPYTFGGGTKVEIK (SEQ ID NO:219)
15G11-DI4	DIQMTQSPSSLSASVGDRVTITCRASQEISTYLSWYQQKPGKAPKLLIYAASSLDTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQYDSSPYTFGGGTKVEIK (SEQ ID NO:220)
15G11-DI5	DIQMTQSPSSLSASVGDRVTITCRASQEISSYLSWYQQKPGKAPKLLIYAASSLDTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQYDSTPYTFGGGTKVEIK (SEQ ID NO:221)
15G11-DI6	DIQMTQSPSSLSASVGDRVTITCRASQEISTYLSWYQQKPGKAPKLLIYAASSLDTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQYDSTPYTFGGGTKVEIK (SEQ ID NO:222)
15G11-DI7	DIQMTQSPSSLSASVGDRVTITCRASQEISSYLSWYQQKPGKAPKLLIYAASSLDTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQYDSSPYTFGGGTKVEIK (SEQ ID NO:223)
15G11-DI8	DIQMTQSPSSLSASVGDRVTITCRASQEISTYLSWYQQKPGKAPKLLIYAASSLDTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQYDSSPYTFGGGTKVEIK (SEQ ID NO:224)
15G11-DI9	DIQMTQSPSSLSASVGDRVTITCRASQEISTYLSWYQQKPGKAPKLLIYAASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQYDSSPLTFGGGTKVEIK (SEQ ID NO:225)
15G11-DI10	DIQMTQSPSSLSASVGDRVTITCRASQEISSYLSWYQQKPGKAPKLLAYAASSLDSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQYDSTPYTFGGGTKVEIK (SEQ ID NO:226)
15G11-DI11	DIQMTQSPSSLSASVGDRVTITCRASQEASSYLSWYQQKPGKAPKLLAYAASSLDSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCLQYDSSPYTFGGGTKVEIK (SEQ ID NO:227)

Table 7. Amino acid sequences of VH-domains of unique, deimmunised anti-ERBB3 IgGs.

Clone	VH
15G11-DI1	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMSWVRQAPGKGLEWVSTISDSGSYTYYPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARELGDYDGFDYWGQG TLVTVSS (SEQ ID NO:228)
15G11-DI2	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMSWVRQAPGKGLEWVSTISDSGSYTYYPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARELGDYDGFDYWGQG TLVTVSS (SEQ ID NO:229)
15G11-DI3	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMSWVRQAPGKGLEWVSTISDSGSYTYYPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARELGDYDGFDYWGQG TLVTVSS (SEQ ID NO:230)
15G11-DI4	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMSWVRQAPGKGLEWVSTISDSGSYTYYPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARELGDYDGFDYWGQG TLVTVSS (SEQ ID NO:231)
15G11-DI5	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYSMSWIRQAPGKGLEWVSTISDSGTYTYYPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREWGDYDGFDFWGQG TLVTVSS (SEQ ID NO:232)
15G11-DI6	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYSMSWIRQAPGKGLEWVSTISDSGTYTYYPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREWGDYDGFDFWGQG TLVTVSS (SEQ ID NO:233)
15G11-DI7	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYSMSWIRQAPGKGLEWVSTISDSGTYTYYPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREWGDYDGFDFWGQG TLVTVSS (SEQ ID NO:234)
15G11-DI8	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYSMSWIRQAPGKGLEWVSTISDSGTYTYYPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREWGDYDGFDFWGQG TLVTVSS (SEQ ID NO:235)
15G11-DI9	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYSMSWIRQAPGKGLEWVSTISDSGTYTYYPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREWGDYDGFDFWGQG TLVTVSS (SEQ ID NO:236)
15G11-DI10	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMSWVRQAPGKGLEWVSTISDSGSYTYYPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARELGDYDGFDYWGQG TLVTVSS (SEQ ID NO:237)
15G11-DI11	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMSWVRQAPGKGLEWVSTISDSGSYTYYPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARELGDYDGFDYWGQG TLVTVSS (SEQ ID NO:238)

Table 8. Examples of antibody variable region amino acid sequences.

Antibody 15G11-DI9 heavy chain variable (VH) region
QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYSMSWIRQAPGKGLEWVSTISDSGTYTY
YPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREWGDYDGFDFWGQGTLVTV
SS (SEQ ID NO:236)

Antibody 15G11-DI9 light chain variable (VL) region
DIQMTQSPSSLSASVGDRVTITCRASQEISTYLSWYQQKPGKAPKLLIYAASTLQSGVPSR
FSGSGSGTDFTLTISSLQPEDFATYYCLQYDSSPLTFGGGTKVEIK (SEQ ID NO:225)

Antibody 15G11-DI5 heavy chain variable (VH) region
QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYSMSWIRQAPGKGLEWVSTISDSGTYTY
YPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREWGDYDGFDFWGQGTLVTV
SS (SEQ ID NO:232)

Antibody 15G11-DI5 light chain variable (VL) region
DIQMTQSPSSLSASVGDRVTITCRASQEISSYLSWYQQKPGKAPKLLIYAASSLDTGVPSR
FSGSGSGTDFTLTISSLQPEDFATYYCLQYDSTPYTFGGGTKVEIK (SEQ ID NO:221)

Antibody 15G11 heavy chain variable (VH) region
QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMSWIRQAPGKGLEWVSTISDSGSYTY
YPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARELGDYDGFDYWGQGTLVTVS
S (SEQ ID NO:253)

Antibody 15G11 light chain variable (VL) region
DIQMTQSPSSLSASVGDRVTITCRASQEISSYLSWYQQKPGKAPKLLIYAASSLDSGVPSR
FSGSGSGTDFTLTISSLQPEDFATYYCLQYDSTPYTFGGGTKVEIK (SEQ ID NO:254)

Antibody 16B09 heavy chain variable (VH) region
QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYSMSWIRQAPGKGLEWVSTISDSGTYTY
YPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREWGDYDGFDFWGQGTLVTV
SS (SEQ ID NO:255)

Antibody 16B09 light chain variable (VL) region
DIQMTQSPSSLSASVGDRVTITCRASQEISSYLSWYQQKPGKAPKLLIYAASTLQSGVPSR
FSGSGSGTDFTLTISSLQPEDFATYYCLQYDSTPLTFGGGTKVEIK (SEQ ID NO:256)

Table 9. Examples of antibody Fc region amino acid sequences.

Human IgG4 wild type
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSQED PEVQFNWYVDGVEVHNAKTKPREEQFNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ
EGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO:239)

Human IgG4(S228P)
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSQED PEVQFNWYVDGVEVHNAKTKPREEQFNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQ
EGNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO:240)

Human IgG1 wild type

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGG
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:241)

Human IgG1-3M
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGA
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:242)

Human IgG2 wild type
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSV
FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTF
RVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDISVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQ
GNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:243)

Human IgG1 wild type “REEM” allotype
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGG
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:244)

Human IgG1-3M “REEM” allotype
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGA
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN
STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:245)

Table 10. Examples of ERBB3 protein amino acid sequences.

Human ERBB3 sequence
MRANDALQVLGLLFSLARGSEVGNSQAVCPGTLNGLSVTGDAENQYQTLYKLYERCEVVM
GNLEIVLTGHNADLSFLQWIREVTGYVLVAMNEFSTLPLPNLRVVRGTQVYDGKFAIFVM
LNYNTNSSHALRQLRLTQLTEILSGGVYIEKNDKLCHMDTIDWRDIVRDRDAEIVVKDNG
RSCPPCHEVCKGRCWGPGSEDCQTLTKTICAPQCNGHCFGPNPNQCCHDECAGGCSGPQD
TDCFACRHFNDSGACVPRCPQPLVYNKLTFQLEPNPHTKYQYGGVCVASCPHNFVVDQTS
CVRACPPDKMEVDKNGLKMCEPCGGLCPKACEGTGSGSRFQTVDSSNIDGFVNCTKILGN
LDFLITGLNGDPWHKIPALDPEKLNVFRTVREITGYLNIQSWPPHMHNFSVFSNLTTIGG
RSLYNRGFSLLIMKNLNVTSLGFRSLKEISAGRIYISANRQLCYHHSLNWTKVLRGPTEE
RLDIKHNRPRRDCVAEGKVCDPLCSSGGCWGPGPGQCLSCRNYSRGGVCVTHCNFLNGEP
REFAHEAECFSCHPECQPMEGTATCNGSGSDTCAQCAHFRDGPHCVSSCPHGVLGAKGPI
YKYPDVQNECRPCHENCTQGCKGPELQDCLGQTLVLIGKTHLTMALTVIAGLVVIFMMLG
GTFLYWRGRRIQNKRAMRRYLERGESIEPLDPSEKANKVLARIFKETELRKLKVLGSGVF
GTVHKGVWIPEGESIKIPVCIKVIEDKSGRQSFQAVTDHMLAIGSLDHAHIVRLLGLCPG
SSLQLVTQYLPLGSLLDHVRQHRGALGPQLLLNWGVQIAKGMYYLEEHGMVHRNLAARNV

LLKSPSQVQVADFGVADLLPPDDKQLLYSEAKTPIKWMALESIHFGKYTHQSDVWSYGVT
VWELMTFGAEPYAGLRLAEVPDLLEKGERLAQPQICTIDVYMVMVKCWMIDENIRPTFKE
LANEFTRMARDPPRYLVIKRESGPGIAPGPEPHGLTNKKLEEVELEPELDLDLDLEAEED
NLATTTLGSALSLPVGTLNRPRGSQSLLSPSSGYMPMNQGNLGESCQESAVSGSSERCPR
PVSLHPMPRGCLASESSEGHVTGSEAELQEKVSMCRSRSRSRSPRPRGDSAYHSQRHSLL
TPVTPLSPPGLEEEDVNGYVMPDTHLKGTPSSREGTLSSVGLSSVLGTEEEDEDEEYEYM
NRRRRHSPPHPPRPSSLEELGYEYMDVGSDLSASLGSTQSCPLHPVPIMPTAGTTPDEDY
EYMNRQRDGGGPGGDYAAMGACPASEQGYEEMRAFQGPGHQAPHVHYARLKTLRSLEATD
SAFDNPDYWHSRLFPKANAQRT (SEQ ID NO:246)

Rhesus monkey ERBB3 sequence

MRANGALQVLGLLFNLARGSEVGNSQAVCPGTLNGLSVTGDAENQYQTLYKLYERCEVVM
GNLEIVLTGHNADLSFLQWIREVTGYVLVAMNEFSTLPLPNLRVVRGTQVYDGKFAIFVM
LNYNTNSSHALRQLRLTQLTEILSGGVYIEKNDKLCHMDTIDWKDIVRDQDAEIVVKDNG
RSCPLCHEVCKGRCWGPGPEDCQTLTKTICAPQCNGHCFGPNPNQCCHDECAGGCSGPQD
TDCFACRHFNDSGACVPRCPQPLVYNKLTFQLEPNPHTKYQYGGVCVASCPHNFVVDQTS
CVRACPPDKMEVDKNGLKMCEPCGGLCPKACEGTGSGSRFQTVDSSNIDGFVNCTKILGN
LDFLITGLNGDPWHKIPALDPEKLNVFRTVREITGYLNIQSWPPHMYNFSVFSNLTTIGG
RSLYNRGFSLLIMKNLNVTSLGFRSLKEISAGRIYISANRQLCYHHSLNWTKVLRGPTEE
RLDIKHNRPRRDCVAEGKVCDPLCSSGGCWGPGPGQCLSCRNYSRGGVCVTHCNFLNGEP
REFAHEAECFSCHPECQPMEGTATCNGSGSDTCAQCAHFRDGPHCVSSCPHGVLGAKGPI
YKYPDVQNECRPCHENCTQGCKGPELQDCLGQTLVLIGKTHLTMALTVIAGLVVIFMMLG
GTFLYWRGRRIQNKRAMRRYLERGESIEPLDPSEKANKVLARIFKETELRKLKVLGSGVF
GTVHKGVWIPEGESIKIPVCIKIIEDKSGRQSFQAVTDHMLAIGSLDHAHIVRLLGLCPG
SSLQLVTQYLPLGSLLDHVRQHRGALGPQLLLNWGVQIAKGMYYLEEHGMVHRNLAARNV
LLKSPSQVQVADFGVADLLPPDDKQLLYSEAKTPIKWMALESIHFGKYTHQSDVWSYGVT
VWELMTFGAEPYAGLRLAEVPDLLEKGERLAQPQICTIDVYMVMVKCWMIDENIRPTFKE
LANEFTRMARDPPRYLVIKRESGPGIAPGPEPHGLTNKKLEEVELEPELDLDLDLEAEED
NLATTTLGSALSLPVGTLNRPRGSQSLLSPSSGYMPMNQGNLGEACQESAVSGSSEWCPR
PVSLHPMPRGCLASESSEGHVTGSEAELQEKVSTCRSRSRSRSPRPRGDSAYHSQRHSLL
TPVTPLSPPGLEEEDVNGYVMPDTHLKGTPSSREGTLSSVGLSSVLGTEEEDEDEEYEYM
NRRRRHSPPRPPRPSSLEELGYEYMDVGSDLSASLGSTQSCPLHPVPVMPTAGTTPDEDY
EYMNRQRGGSGPGGDYAAMGACPASEQGYEEMRAFQGPGHQAPHVHYAHLKTLRSLEATD
SAFDNPDYWHSRLFPKANAQRT (SEQ ID NO:247)

CLAIMS

1. An anti-ERBB3 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein

(a) the VH region amino acid sequence comprises HCDR1 of GFTFSDYSMS (SEQ ID NO: 24), HCDR2 of VSTISDSGTYTYYPDSVKG (SEQ ID NO: 25) and HCDR3 of EWGDYDGFDF (SEQ ID NO: 15); and the VL region amino acid sequence comprises LCDR1 of RASQEISTYLS (SEQ ID NO: 261), LCDR2 of AASTLQS (SEQ ID NO:26) and LCDR3 of LQYDSSPLT (SEQ ID NO: 262);

(b) the VH region amino acid sequence comprises HCDR1 of GFTFSDYSMS (SEQ ID NO: 24), HCDR2 of VSTISDSGTYTYYPDSVKG (SEQ ID NO: 25) and HCDR3 of EWGDYDGFDF (SEQ ID NO: 15); and the VL region amino acid sequence comprises LCDR1 of RASQEISSYLS (SEQ ID NO: 21), LCDR2 of AASSLDT (SEQ ID NO: 263) and LCDR3 of LQYDSTPYT (SEQ ID NO: 23);

(c) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDSGSYTYYPDSVKG (SEQ ID NO:19) and HCDR3 of ELGDYDGFDY (SEQ ID NO:20); and the VL region amino acid sequence comprises LCDR1 of RASQEISSYLS (SEQ ID NO:21), LCDR2 of AASSLDS (SEQ ID NO:22) and LCDR3 of LQYDSTPYT (SEQ ID NO:23), [Clone 15G11]; or

(d) the VH region amino acid sequence comprises HCDR1 of GFTFSDYSMS (SEQ ID NO:24), HCDR2 of VSTISDSGTYTYYPDSVKG (SEQ ID NO:25) and HCDR3 of EWGDYDGFDF (SEQ ID NO:15); and the VL region amino acid sequence comprises LCDR1 of RASQEISSYLS (SEQ ID NO:21), LCDR2 of AASTLQS (SEQ ID NO:26) and LCDR3 of LQYDSTPLT (SEQ ID NO:18); [Clone 16B09]

(e) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDSGSYIYYADSVKG (SEQ ID NO:14) and HCDR3 of EWGDYDGFDF (SEQ ID NO:15); and the VL region amino acid sequence comprises LCDR1 of RASQSISSYLS (SEQ ID NO:16), LCDR2 of AASSLQS (SEQ ID NO:17) and LCDR3 of LQYDSTPLT (SEQ ID NO:18);

(f) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDSGSYIYYADSVKG (SEQ ID NO:14) and HCDR3 of EWGDYDGFDH (SEQ ID NO:27); and the VL region amino acid sequence comprises LCDR1 of RASQEISSYLS (SEQ ID NO:21), LCDR2 of AASSLQS (SEQ ID NO:17) and LCDR3 of LQYDSTPLT (SEQ ID NO:18);

(g) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDGGSYTYYADSVKG (SEQ ID NO:28) and HCDR3 of EWGDYDGFDE (SEQ ID NO:29); and the VL region amino acid sequence comprises

LCDR1 of RASQSISGYLS (SEQ ID NO:30), LCDR2 of AASTLQS (SEQ ID NO:26) and LCDR3 of LQYDSTPYT (SEQ ID NO:23);

(h) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDGGSYTYYADNVKG (SEQ ID NO:31) and HCDR3 of EWGDYDGFDF (SEQ ID NO:15); and the VL region amino acid sequence comprises LCDR1 of RASQSISSYLS (SEQ ID NO:16), LCDR2 of AASTLQS (SEQ ID NO:26) and LCDR3 of LQYDSTPLT (SEQ ID NO:18); or

(i) the VH region amino acid sequence comprises HCDR1 of GFTFSDYGMS (SEQ ID NO:13), HCDR2 of VSTISDSGSYIYYADSVKG (SEQ ID NO:14) and HCDR3 of EWGDYDGFDE (SEQ ID NO:29); and the VL region amino acid sequence comprises LCDR1 of RASQSISSYLS (SEQ ID NO:16), LCDR2 of AASSLQS (SEQ ID NO:17) and LCDR3 of LQYDSTPLT (SEQ ID NO:18).

2. The antibody or antigen-binding portion of claim 1, wherein

(a) the VH region amino acid sequence comprises SEQ ID NO:236 and the VL region amino acid sequence comprises SEQ ID NO:225;

(b) the VH region amino acid sequence comprises SEQ ID NO:232 and the VL region amino acid sequence comprises SEQ ID NO:221;

(c) the VH region amino acid sequence comprises SEQ ID NO:253 and the VL region amino acid sequence comprises SEQ ID NO:254; or

(d) the VH region amino acid sequence comprises SEQ ID NO:255 and the VL region amino acid sequence comprises SEQ ID NO:256.

3. An anti-ERBB3 antibody or an antigen-binding portion thereof, wherein the antibody comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein

(a) the HCDR1 comprises the amino acid sequence G-F-T-F-S-D-Y-X_1-M-S, wherein X_1 is G or any other amino acid (SEQ ID NO:1);

(b) the HCDR2 comprises V-S-T-I-S-D-X_1-G-X_2-X_3-X_4-Y-Y-X_5-D-X_6-V-K-G, wherein X_1 is G or any other amino acid, X_2 is T or a conservative substitution of T, X_3 is Y or any other amino acid, X_4 is T or any other amino acid, X_5 is P or any other amino acid, and X_6 is N or a conservative substitution of N (SEQ ID NO:2);

(c) the HCDR3 comprises X_1-X_2-G-D-X_3-D-G-X_4-D-X_5, wherein X_1 is E or any other amino acid, X_2 is W or any other amino acid, X_3 is Y or any other amino acid, X_4 is F or any other amino acid, and X_5 is Y or any other amino acid (SEQ ID NO:3);

(d) the LCDR1 comprises R-A-S-Q-X_1-I-S-X_2-Y-L-X_3, wherein X_1 is E or any other amino acid, X_2 is G or a conservative substitution of G, and X_3 is S or a conservative substitution of S (SEQ ID NO:7);

(e) the LCDR2 comprises X_1-A-S-X_2-L-X_3-S, wherein X_1 is A or any other amino acid, X_2 is T or a conservative substitution of N, and X_3 is or D any other amino acid (SEQ ID NO:8); and

(f) the LCDR3 comprises X_1-Q-X_2-X_3-S-X_4-X_5-X_6-T, wherein X_1 is L or any other amino acid, X_2 is Y or any other amino acid, X_3 is D or any other amino acid, X_4 is Y or any other amino acid, X_5 is P or any other amino acid, and X_6 is Y or any other amino acid (SEQ ID NO:9).

4. An anti-ERBB3 antibody or an antigen-binding portion thereof, wherein the antibody or antigen-binding portion cross-competes for binding to ERBB3 with the antibody or antigen-binding portion of any one of claims 1-3; and

(a) comprises fully germline human framework amino acid sequences; and/or

(b) does not comprise an isomerization site in the LCDR2; and/or

(c) does not comprise a 'DG' isomerization site in the HCDR2; and/or

(d) does not comprise an oxidation site at position 2 in the HCDR3; and/or

(e) exhibits a reduced number of predicted foreign human T cell receptor binding peptides in its v-domains in comparison to h24C05; and/or

(f) contains no predicted foreign human T cell receptor binding peptides in its v-domains.

5. The antibody or antigen-binding portion of any one of claims 1-4, wherein the antibody is human, humanized or chimeric.

6. The antibody or antigen-binding portion of any one of claims 1-5, wherein the VH region, the VL region, or both the VH and the VL region comprise one or more human framework region amino acid sequences.

7. The antibody or antigen-binding portion of any one of claims 1-6, wherein the VH region, the VL region, or both the VH and the VL region comprise a human variable region framework scaffold amino acid sequence into which the CDRs have been inserted.

8. The antibody or antigen-binding portion of claim 1 or 3, wherein the VH region comprises an IGHV3-11 human germline scaffold amino acid sequence into which the HCDR1, HCDR2 and HCDR3 amino acid sequences have been inserted.

9. The antibody or antigen-binding portion of any one of claims 1, 3 and 8, wherein the VL region comprises an IGKV1-39 human germline scaffold amino acid sequence into which the LCDR1, LCDR2 and LCDR3 amino acid sequences have been inserted.

10. The antibody or antigen-binding portion of any one of claims 1-9, wherein the antibody comprises an immunoglobulin constant region.

11. The antibody or antigen-binding portion of claim 10, wherein the immunoglobulin constant region is IgG, IgE, IgM, IgD, IgA or IgY.

12. The antibody or antigen-binding portion of claim 11, wherein the immunoglobulin constant region IgG1, IgG2, IgG3, IgG4, IgA1 or IgA2.

13. The antibody or antigen-binding portion of claim 10, wherein the immunoglobulin constant region is immunologically inert.

14. The antibody or antigen-binding portion of claim 10, wherein the immunoglobulin constant region is a wild-type human IgG4 constant region, a human IgG4 constant region comprising the amino acid substitution S228P, a wild-type human IgG1 constant region, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A or a wild-type human IgG2 constant region.

15. The antibody or antigen-binding portion of claim 10, wherein the immunoglobulin constant region comprises any one of SEQ ID NOS:239-245.

16. The antigen-binding portion of any one of claims 1-15, wherein the antibody or antigen-binding portion is an Fab, an Fab', an $F(ab')_2$, an Fd, an Fv, an scFv, a single domain antibody (dAb), a maxibody, a minibody, an intrabody, a diabody, a triabody, a tetrabody, a v-NAR or a bis-scFv.

17. The antibody or antigen-binding portion of any one of claims 1-16, wherein the antibody is monoclonal.

18. The antibody or antigen-binding portion of any one of claims 1-17, wherein the antibody is a tetrameric antibody, a tetravalent antibody or a multispecific antibody.

19. The antibody or antigen-binding portion of any one of claims 1-18, wherein the antibody is a bispecific antibody that binds specifically to a first antigen and a second antigen, wherein the first antigen is ERBB3 and the second antigen is not ERBB3.

20. The antibody or antigen-binding portion of any one of claims 1-19, wherein the antibody or antigen-binding portion binds specifically to (a) human ERBB3 or (b) human ERBB3 and rhesus ERBB3.

21. An immunoconjugate comprising the antibody or antigen-binding portion of any one of claims 1-20 linked to a therapeutic agent.

22. The immunoconjugate of claim 21, wherein the therapeutic agent is a cytotoxin, a radioisotope, a chemotherapeutic agent, an immunomodulatory agent, an anti-angiogenic agent, an antiproliferative agente, a pro-apoptotic agent, a cytostatic enzyme, a cytolytic enzymes, a therapeutic nucleic acid, an anti-angiogenic agent, an anti-proliferative agent, or a pro-apoptotic agent.

23. A pharmaceutical composition comprising the antibody or antigen-binding portion of any one of claims 1-20 or the immunoconjugate of claim 21 or 22, and a pharmaceutically acceptable carrier, diluent or excipient.

24. A nucleic acid molecule encoding
(a) the VH region amino acid sequence;
(b) the VL region amino acid sequence; or
(c) both the VH and the VL region amino acid sequences
of the antibody or antigen-binding portion of any one of claims 1-20.

25. An expression vector comprising the nucleic acid molecule of claim 24.

26. A recombinant host cell comprising the nucleic acid molecule of claim 24 or the expression vector of claim 25.

27. A method of producing an anti-ERBB3 antibody or an antigen-binding portion thereof, the method comprising:
culturing a recombinant host cell comprising the expression vector of claim 25 under conditions whereby the nucleic acid molecule is expressed, thereby producing the antibody or antigen-binding portion; and
isolating the antibody or antigen-binding portion from the host cell or culture.

28. A method for enhancing an immune response in a subject, comprising administering to the subject a therapeutically effective amount of the antibody or antigen-binding portion of any one of claims 1-20, the immunoconjugate of claim 21 or 22 or the pharmaceutical composition of claim 23.

29. A method of treating cancer, an autoimmune disease, an inflammatory disease, a cardiovascular disease or a fibrotic disease in a subject, comprising administering to the subject a therapeutically effective amount of the antibody or antigen-binding portion of any one of claims 1-20, the immunoconjugate of claim 21 or 22 or the pharmaceutical composition of claim 23.

30. The method of claim 29, wherein the cancer is Gastrointestinal Stromal cancer (GIST), pancreatic cancer, melanoma, breast cancer, lung cancer, bronchial cancer, colorectal cancer, prostate cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma or cancer of hematological tissues.

31. The method of claim 29, wherein the autoimmune disease or the inflammatory disease is arthritis, asthma, multiple sclerosis, psoriasis, Crohn's disease, inflammatory bowel disease, lupus, Grave's disease, Hashimoto’s thyroiditis or ankylosing spondylitis.

32. The method of claim 29, wherein the cardiovascular disease is coronary heart disease or atherosclerosis.

33. The method of claim 29, wherein the fibrotic disease is myocardial infarction, angina, osteoarthritis, pulmonary fibrosis, cystic fibrosis, bronchitis or asthma.

34. The antibody or antigen-binding portion of any one of claims 1-20, the immunoconjugate of claim 21 or 22 or the pharmaceutical composition of claim 23 for use in the treatment of cancer, an autoimmune disease, an inflammatory disease, a cardiovascular disease or a fibrotic disease.

35. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 24, wherein the cancer is

Gastrointestinal Stromal cancer (GIST), pancreatic cancer, melanoma, breast cancer, lung cancer, bronchial cancer, colorectal cancer, prostate cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma or cancer of hematological tissues.

36. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 34, wherein the autoimmune disease or the inflammatory disease is arthritis, asthma, multiple sclerosis, psoriasis, Crohn's disease, inflammatory bowel disease, lupus, Grave's disease, Hashimoto's thyroiditis or ankylosing spondylitis.

37. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 34, wherein the cardiovascular disease is coronary heart disease or atherosclerosis.

38. The antibody or antigen-binding portion, the immunoconjugate or the pharmaceutical composition for use according to claim 34, wherein the fibrotic disease is myocardial infarction, angina, osteoarthritis, pulmonary fibrosis, cystic fibrosis, bronchitis or asthma.

39. The antibody or antigen-binding portion of any one of claims 1-20, the immunoconjugate of claim 21 or 22 or the pharmaceutical composition of claim 23, for use as a medicament.

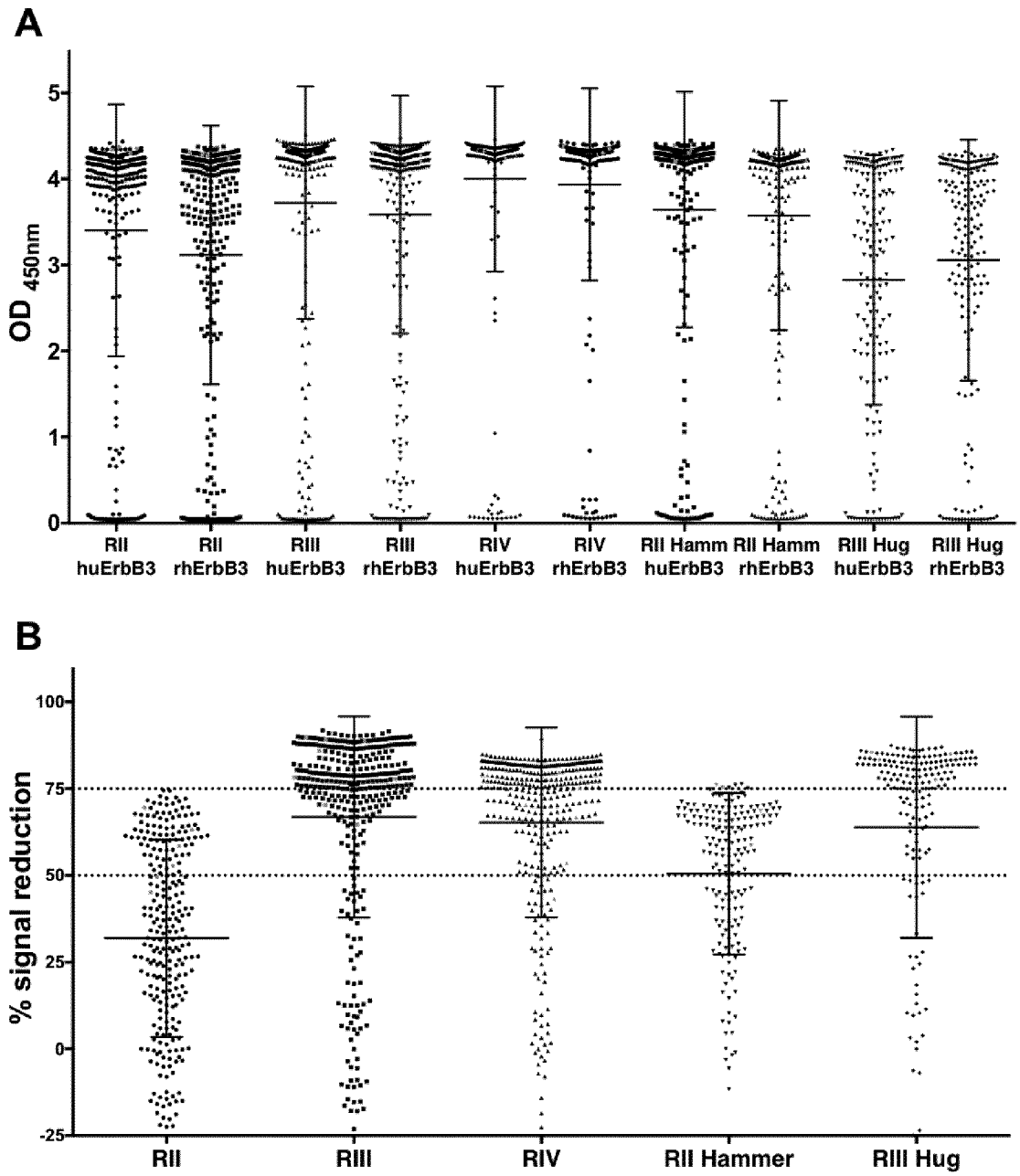

A
OD 450nm
0
1
2
3
4
5
RII huErbB3
RII rhErbB3
RIII huErbB3
RIII rhErbB3
RIV huErbB3
RIV rhErbB3
RII Hamm huErbB3
RII Hamm rhErbB3
RIII Hug huErbB3
RIII Hug rhErbB3
B
% signal reduction
-25
0
25
50
75
100
RII
RIII
RIV
RII Hammer
RIII Hug

Fig. 1

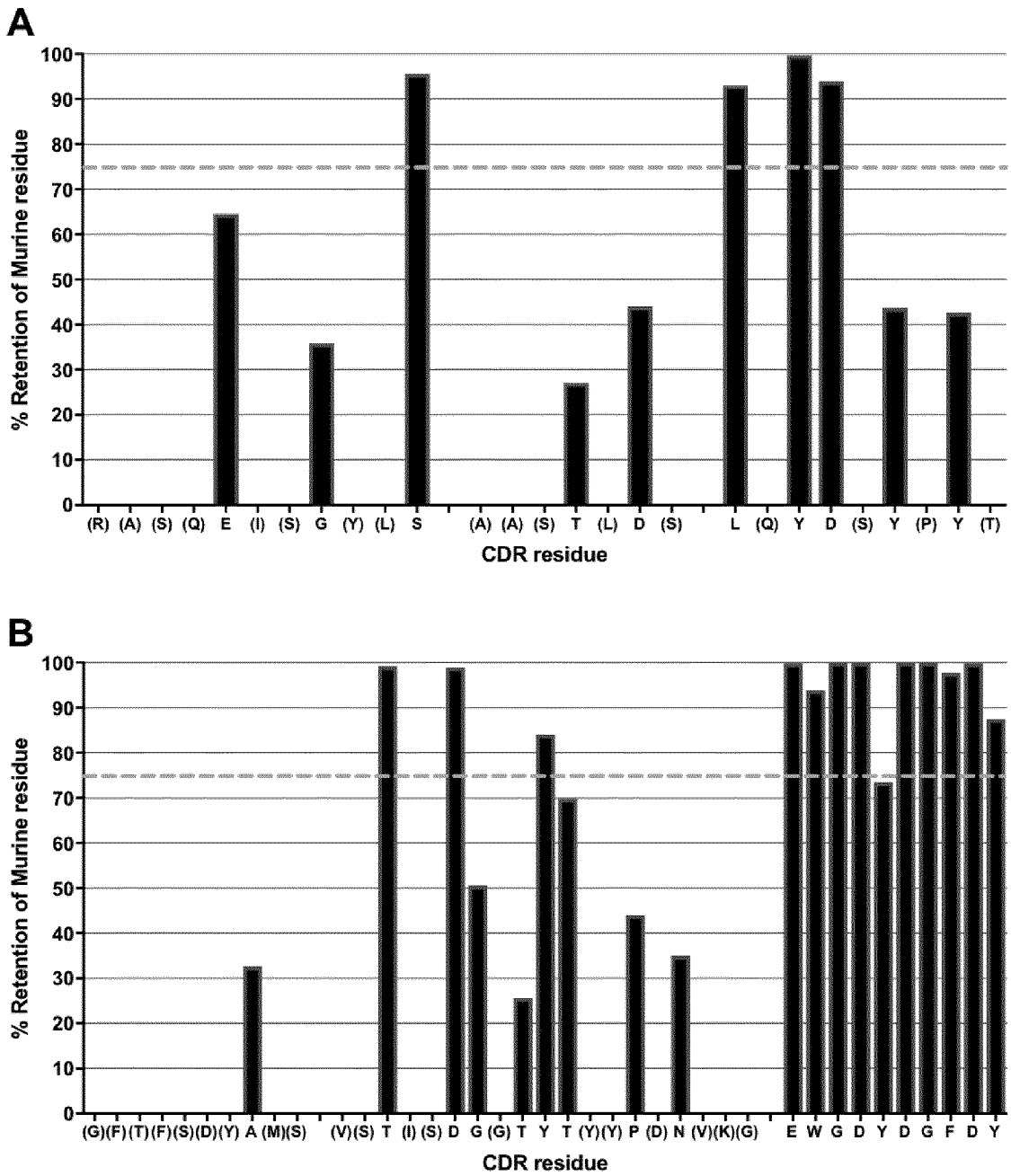

A
% Retention of Murine residue
100
90
80
70
60
50
40
30
20
10
0
(R) (A) (S) (Q) E (I) (S) G (Y) (L) S (A) (A) (S) T (L) D (S) L (Q) Y D (S) Y (P) Y (T)
CDR residue
B
% Retention of Murine residue
100
90
80
70
60
50
40
30
20
10
0
(G)(F)(T)(F)(S)(D)(Y) A (M)(S) (V)(S) T (I) (S) D G (G) T Y T (Y)(Y) P (D) N (V)(K)(G) E W G D Y D G F D Y
CDR residue

Fig. 2

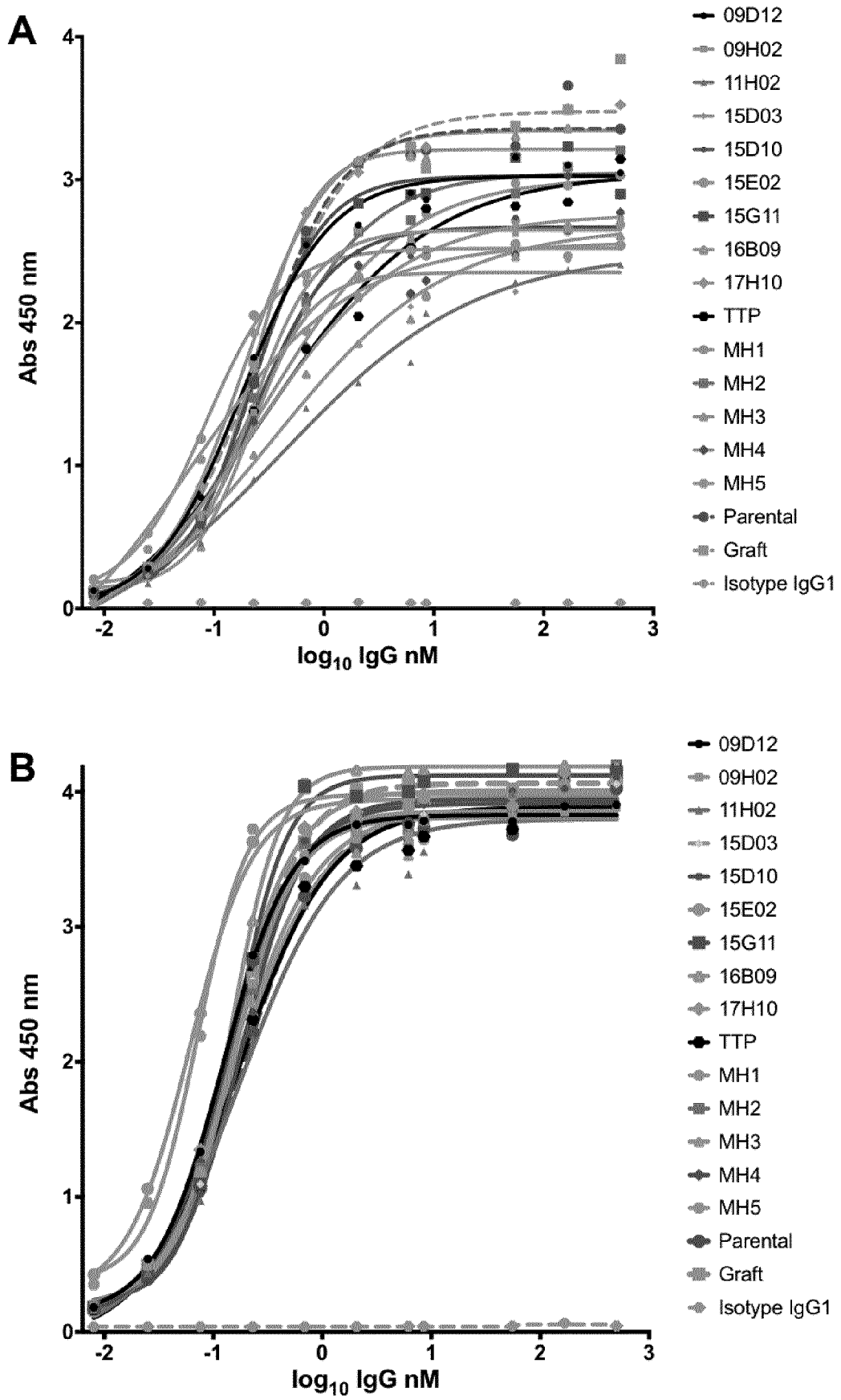

A
Abs 450 nm
log10 IgG nM
09D12
09H02
11H02
15D03
15D10
15E02
15G11
16B09
17H10
TTP
MH1
MH2
MH3
MH4
MH5
Parental
Graft
Isotype IgG1
B
Abs 450 nm
log10 IgG nM
09D12
09H02
11H02
15D03
15D10
15E02
15G11
16B09
17H10
TTP
MH1
MH2
MH3
MH4
MH5
Parental
Graft
Isotype IgG1

Fig. 3

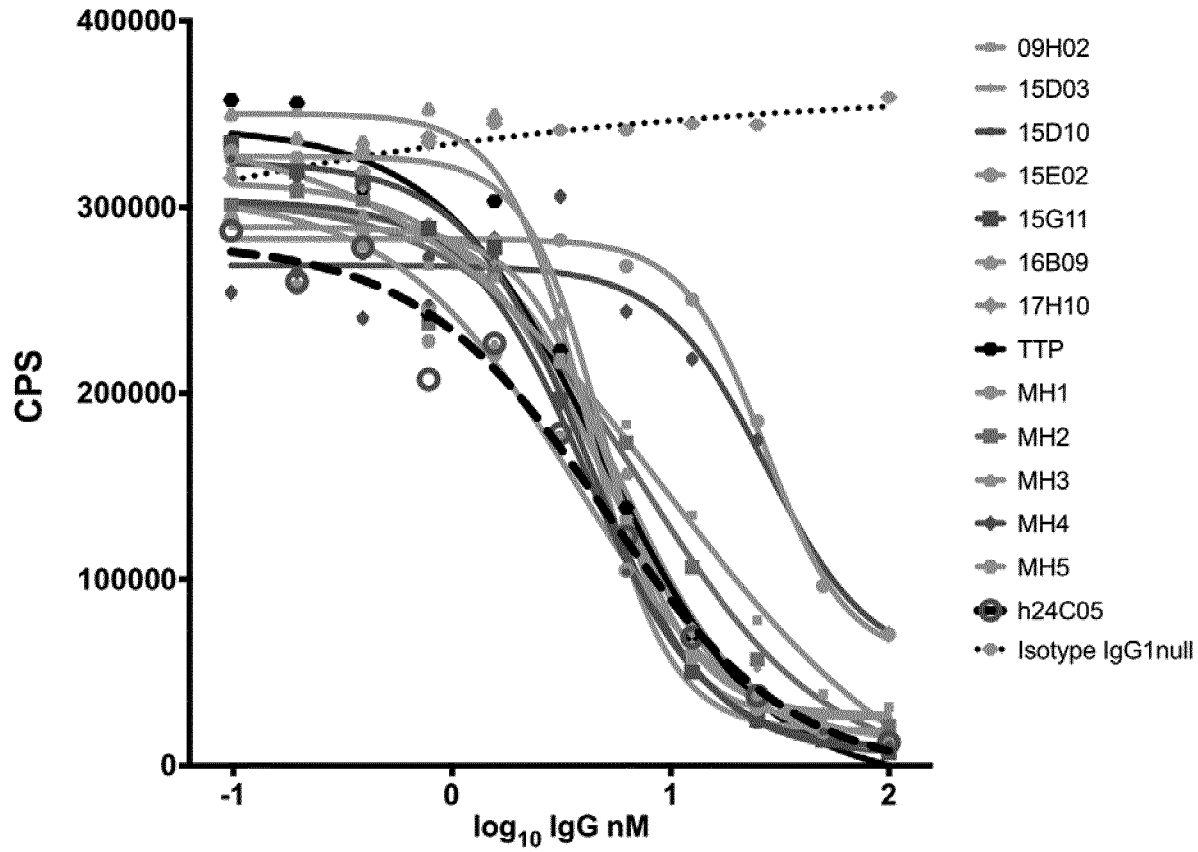

400000
300000
200000
100000
0
CPS
-1
0
1
2
log10 IgG nM
09H02
15D03
15D10
15E02
15G11
16B09
17H10
TTP
MH1
MH2
MH3
MH4
MH5
h24C05
Isotype IgG1null

Fig. 4

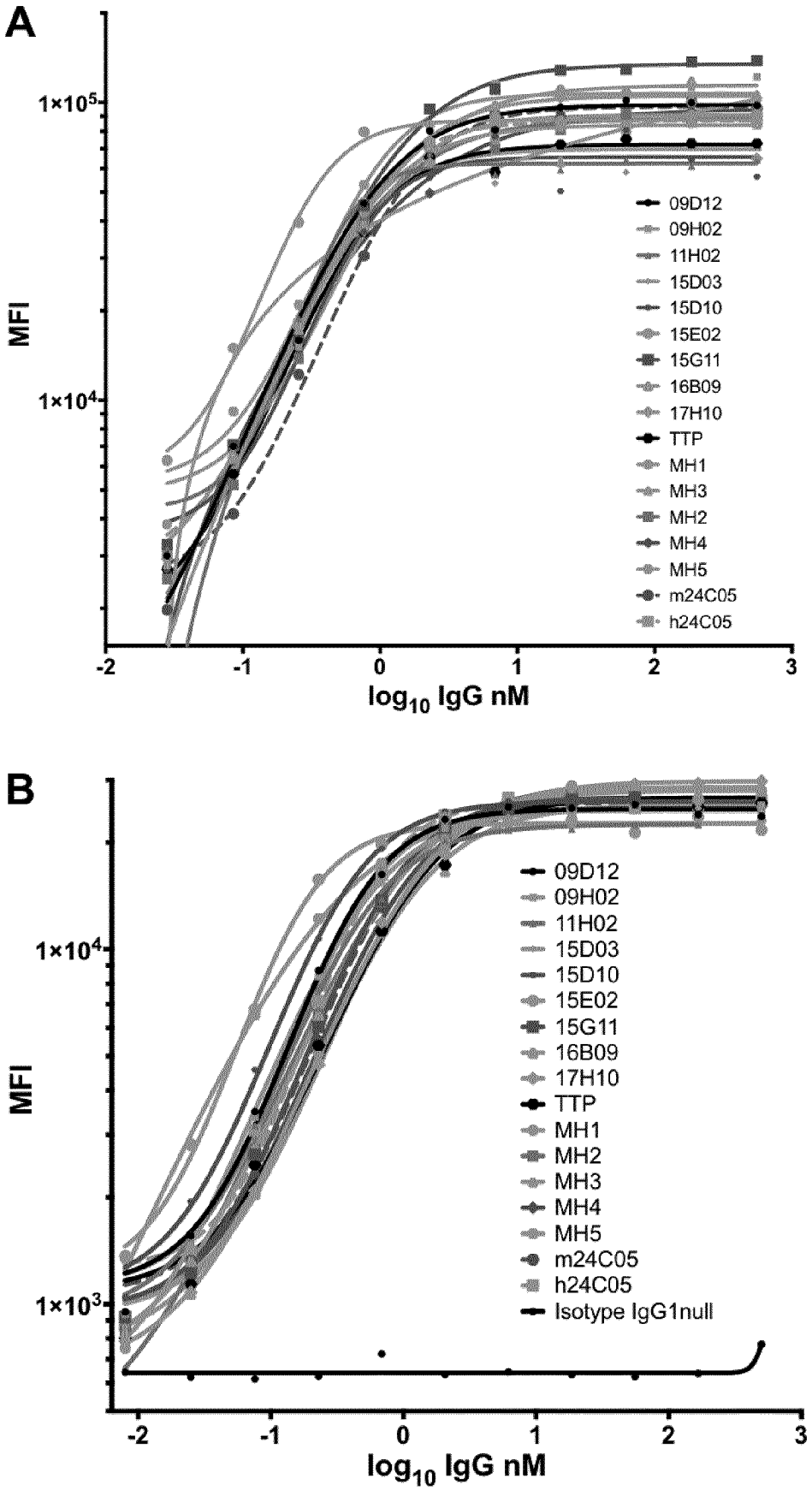

A
1×10^5
1×10^4
MFI
-2
-1
0
1
2
3
log10 IgG nM
09D12
09H02
11H02
15D03
15D10
15E02
15G11
16B09
17H10
TTP
MH1
MH3
MH2
MH4
MH5
m24C05
h24C05
B
1×10^4
1×10^3
MFI
-2
-1
0
1
2
3
log10 IgG nM
09D12
09H02
11H02
15D03
15D10
15E02
15G11
16B09
17H10
TTP
MH1
MH2
MH3
MH4
MH5
m24C05
h24C05
Isotype IgG1null

Fig. 5

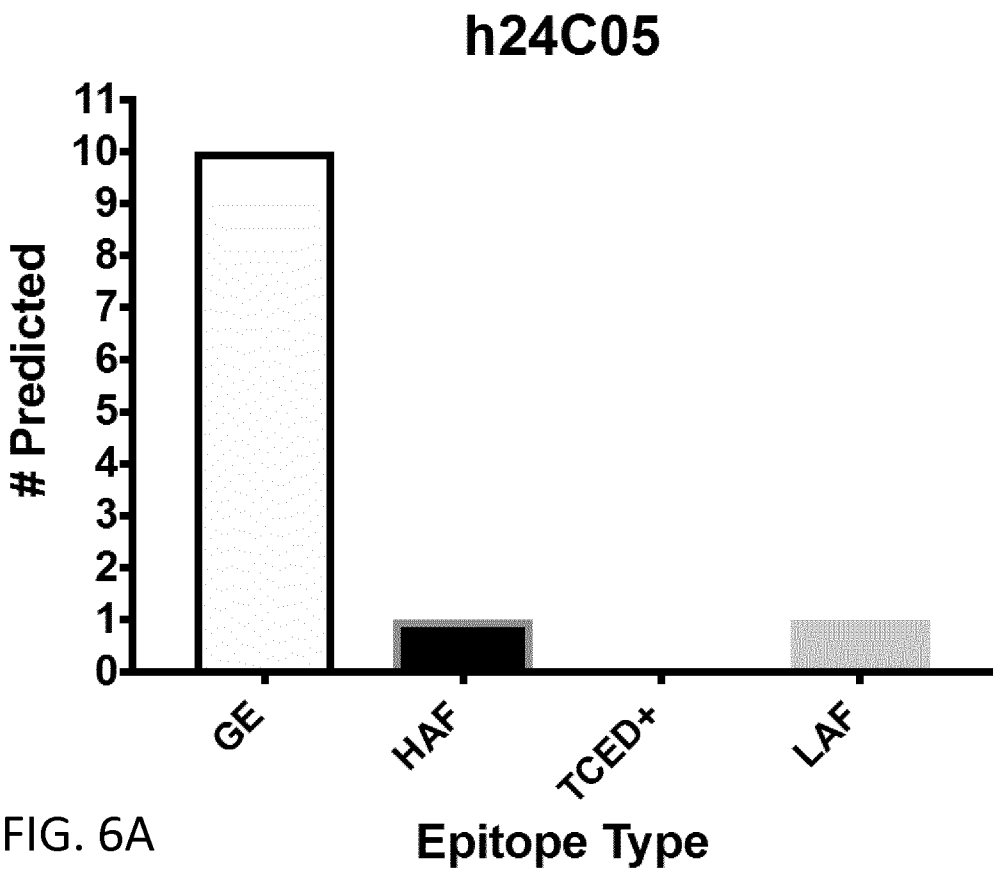

h24C05
Predicted
11
10
9
8
7
6
5
4
3
2
1
0
GE
HAF
TCED+
LAF
Epitope Type

FIG. 6A

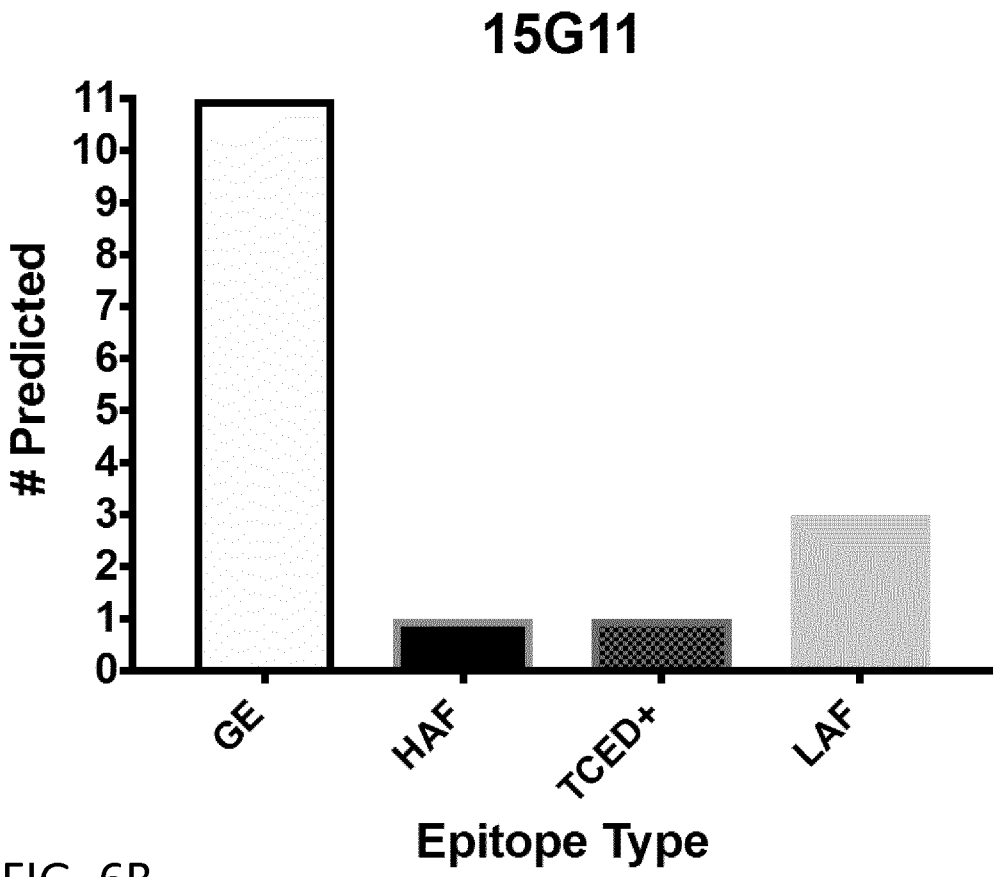

15G11
Predicted
11
10
9
8
7
6
5
4
3
2
1
0
GE
HAF
TCED+
LAF
Epitope Type

FIG. 6B

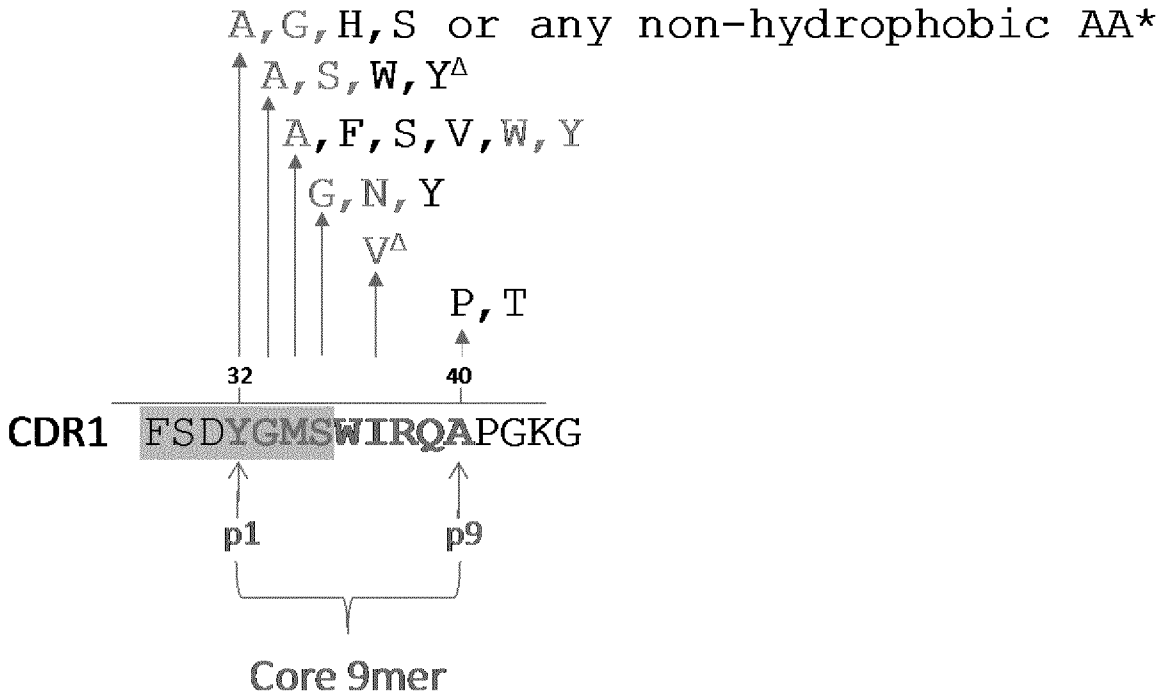

A,G,H,S or any non-hydrophobic AA*
A,S,W,Y^Δ
A,F,S,V,W,Y
G,N,Y
V^Δ
P,T
32
40
CDR1
FSDYGMSWIRQAPGKG
p1
p9
Core 9mer

Fig. 7A

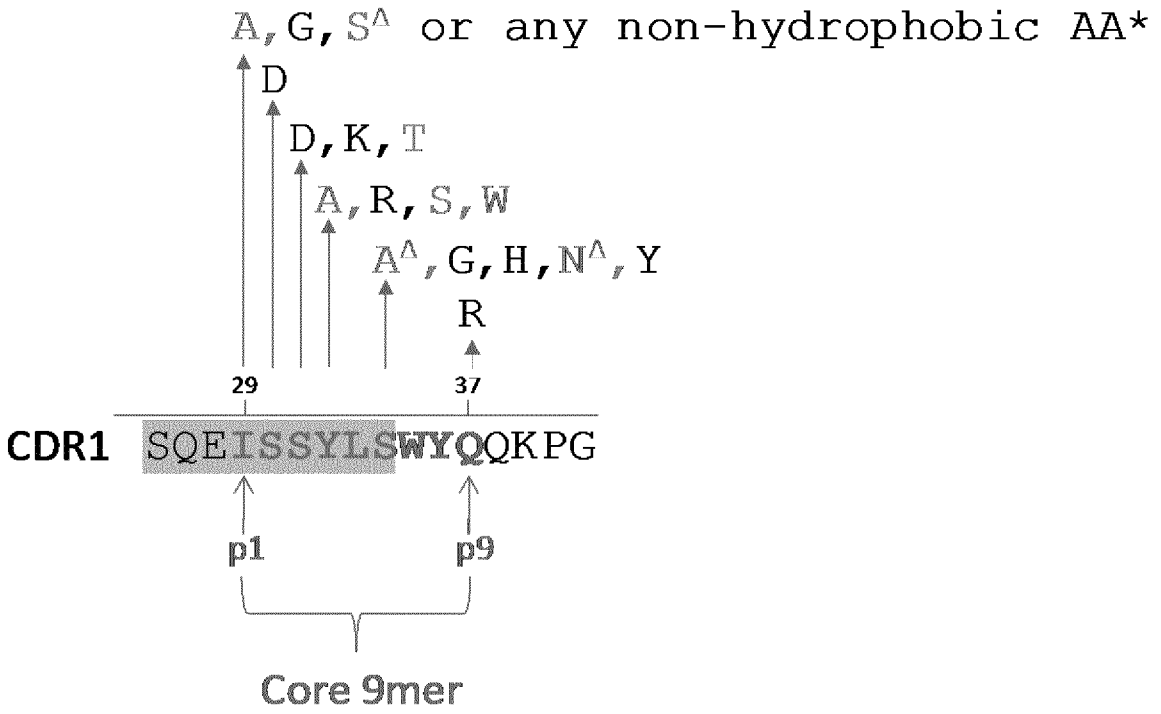

A,G,S^ or any non-hydrophobic AA*
D
D,K,T
A,R,S,W
A^,G,H,N^,Y
R
29
37
CDR1
SQEISSYLSWYQQKPG
p1
p9
Core 9mer

Fig. 7B

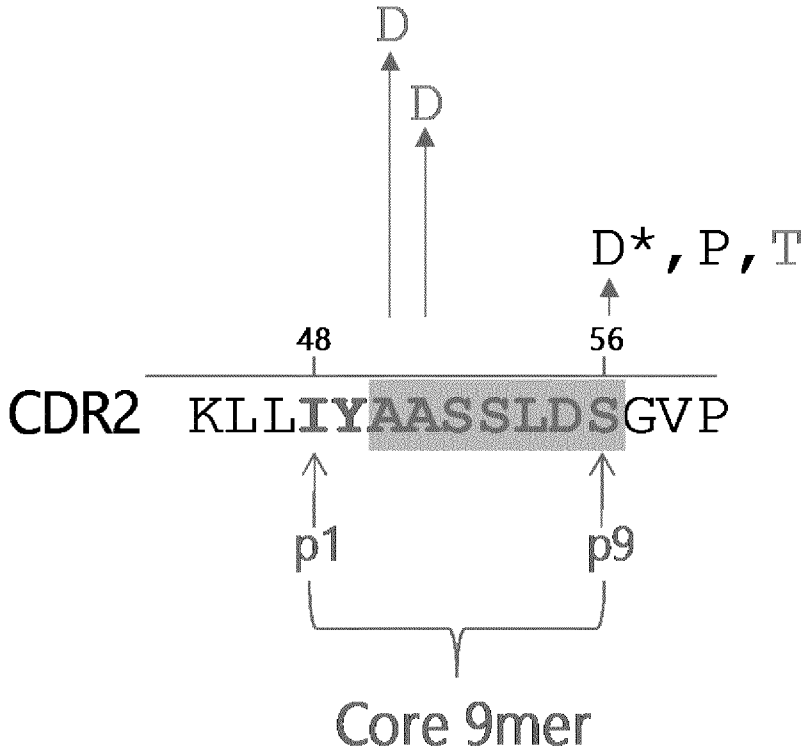


Fig. 7C

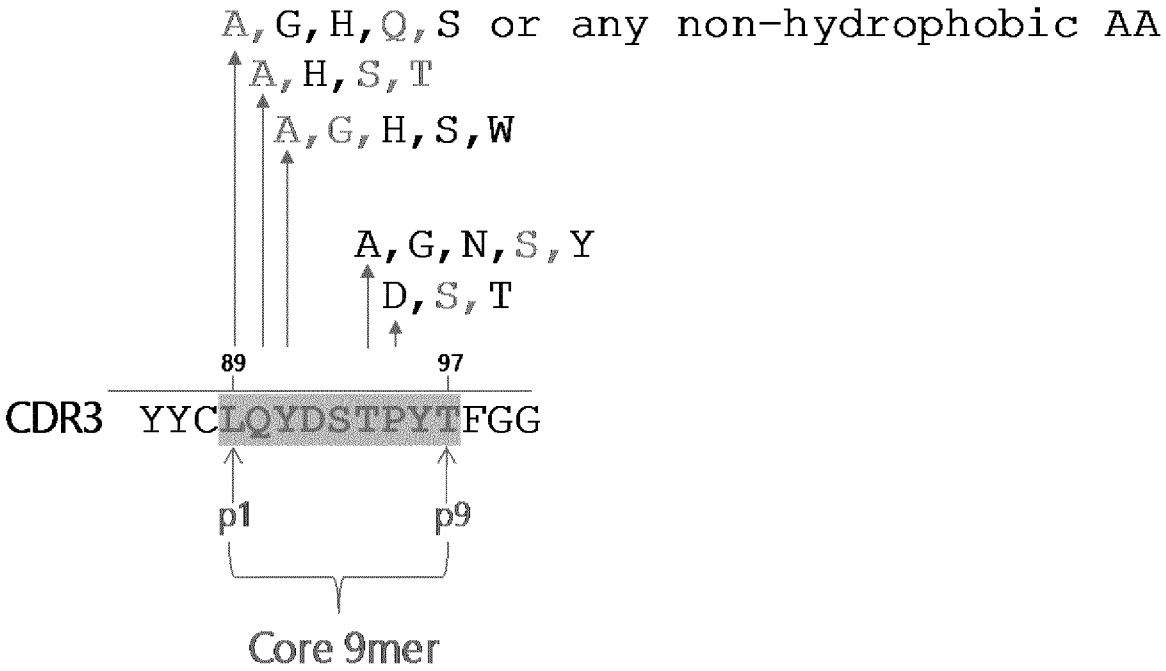

A,G,H,Q,S or any non-hydrophobic AA
A,H,S,T
A,G,H,S,W
A,G,N,S,Y
D,S,T
89
97
CDR3 YYCLQYDSTPYTFGG
p1
p9
Core 9mer

Fig. 7D

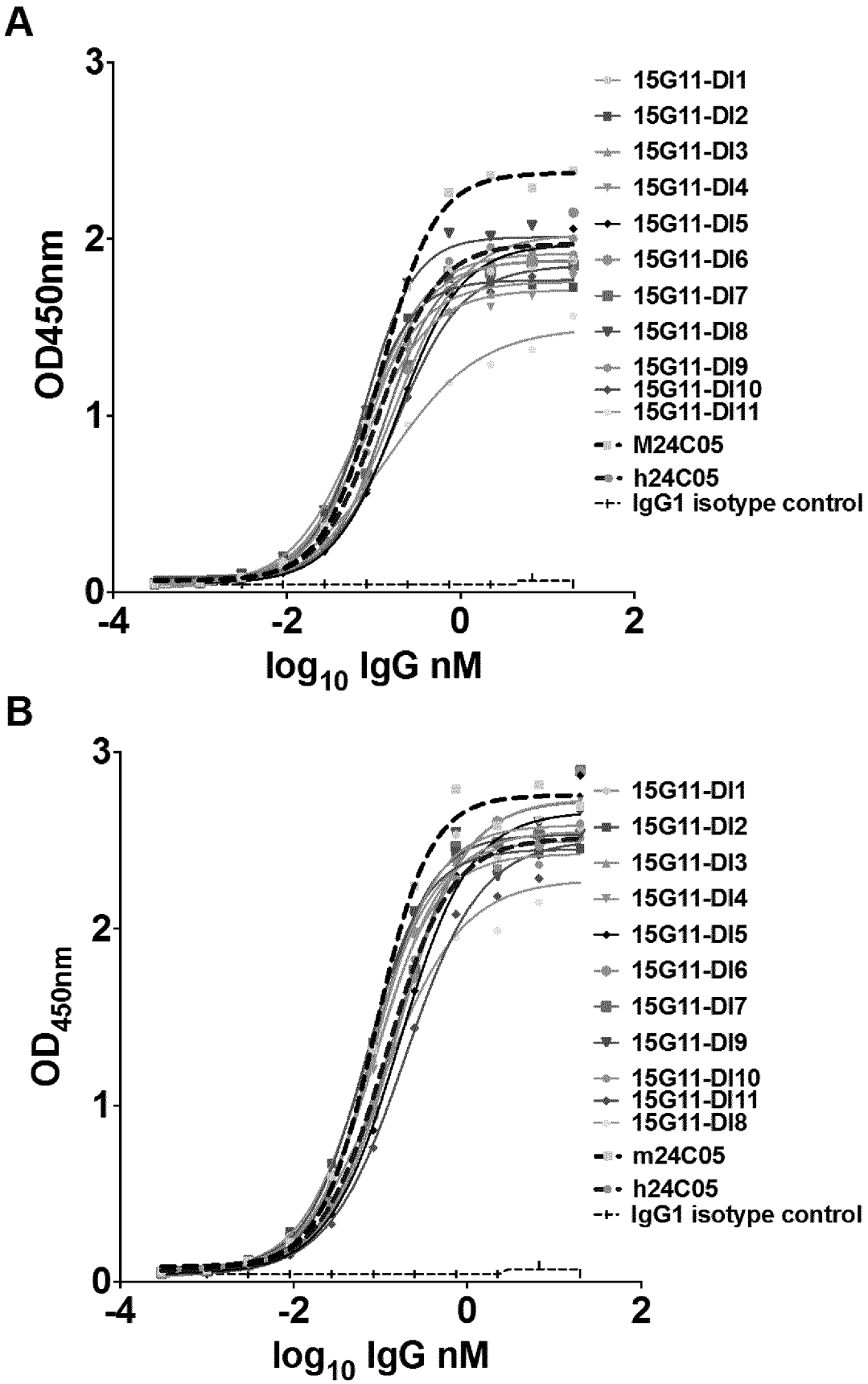

A
OD450nm
log10 IgG nM
15G11-DI1
15G11-DI2
15G11-DI3
15G11-DI4
15G11-DI5
15G11-DI6
15G11-DI7
15G11-DI8
15G11-DI9
15G11-DI10
15G11-DI11
M24C05
h24C05
IgG1 isotype control
B
OD450nm
log10 IgG nM
15G11-DI1
15G11-DI2
15G11-DI3
15G11-DI4
15G11-DI5
15G11-DI6
15G11-DI7
15G11-DI9
15G11-DI10
15G11-DI11
15G11-DI8
m24C05
h24C05
IgG1 isotype control

Fig. 8

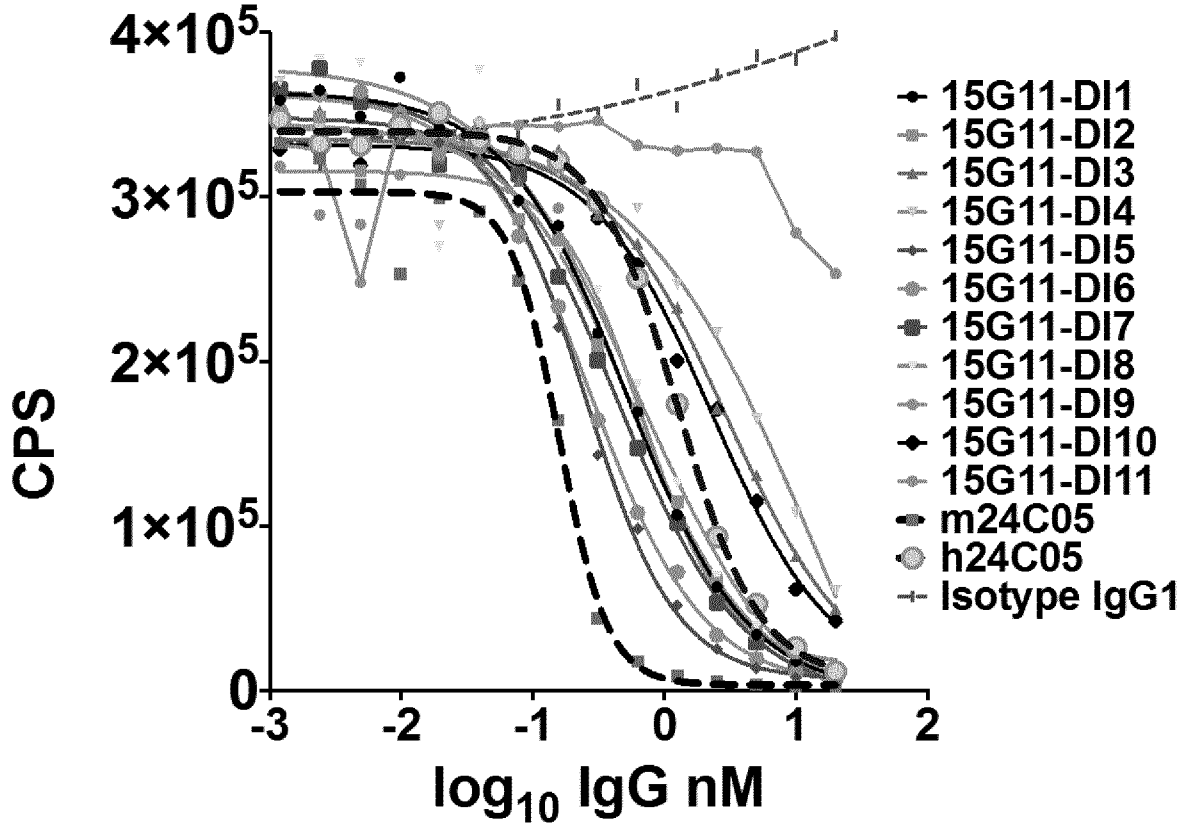

4×10^5
3×10^5
2×10^5
1×10^5
0
CPS
-3
-2
-1
0
1
2
log10 IgG nM
15G11-DI1
15G11-DI2
15G11-DI3
15G11-DI4
15G11-DI5
15G11-DI6
15G11-DI7
15G11-DI8
15G11-DI9
15G11-DI10
15G11-DI11
m24C05
h24C05
Isotype IgG1

Fig. 9

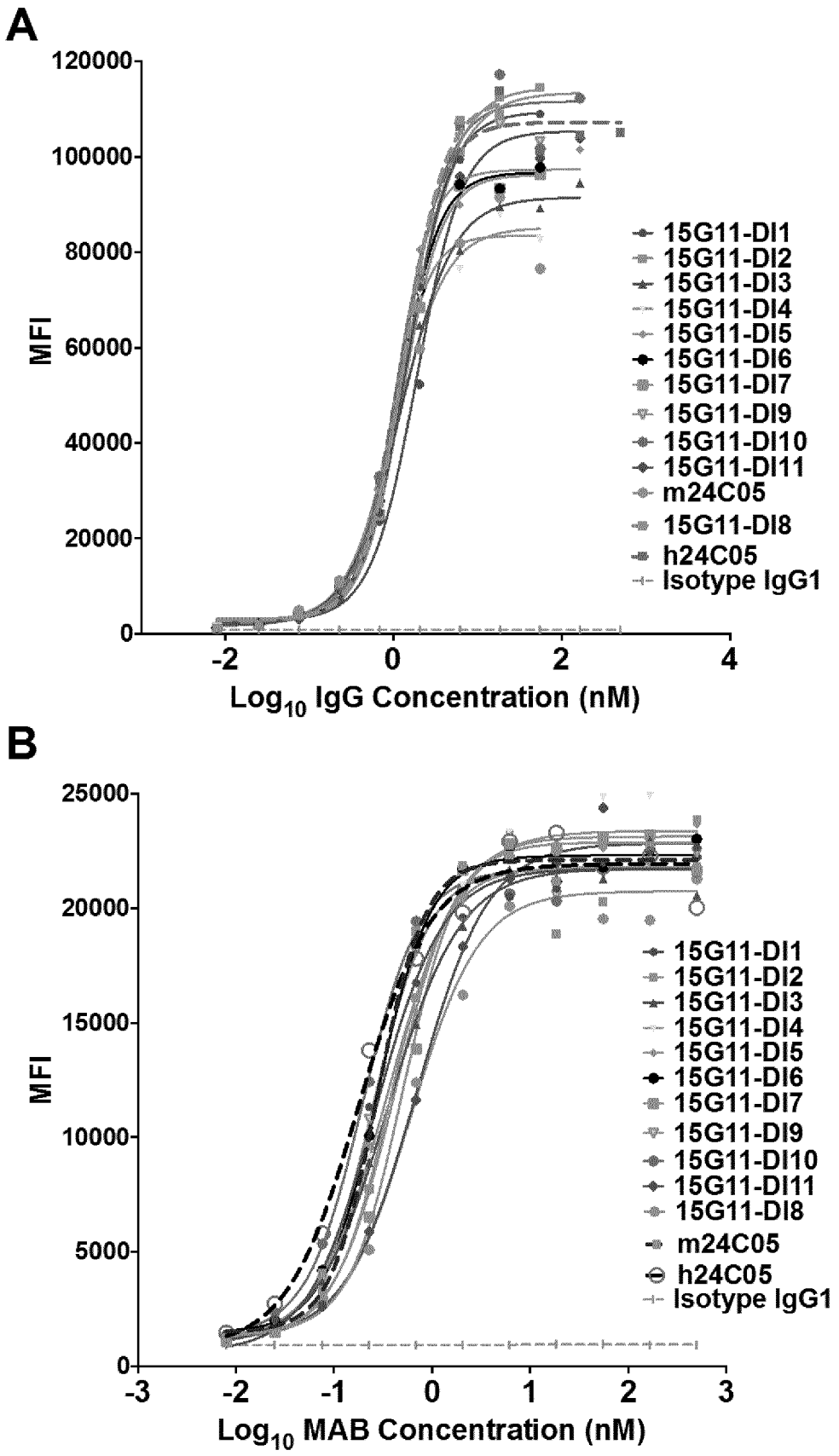

A
120000
100000
80000
60000
40000
20000
0
MFI
-2
0
2
4
Log10 IgG Concentration (nM)
15G11-DI1
15G11-DI2
15G11-DI3
15G11-DI4
15G11-DI5
15G11-DI6
15G11-DI7
15G11-DI9
15G11-DI10
15G11-DI11
m24C05
15G11-DI8
h24C05
Isotype IgG1
B
25000
20000
15000
10000
5000
0
MFI
-3
-2
-1
0
1
2
3
Log10 MAB Concentration (nM)
15G11-DI1
15G11-DI2
15G11-DI3
15G11-DI4
15G11-DI5
15G11-DI6
15G11-DI7
15G11-DI9
15G11-DI10
15G11-DI11
15G11-DI8
m24C05
h24C05
Isotype IgG1

Fig. 10

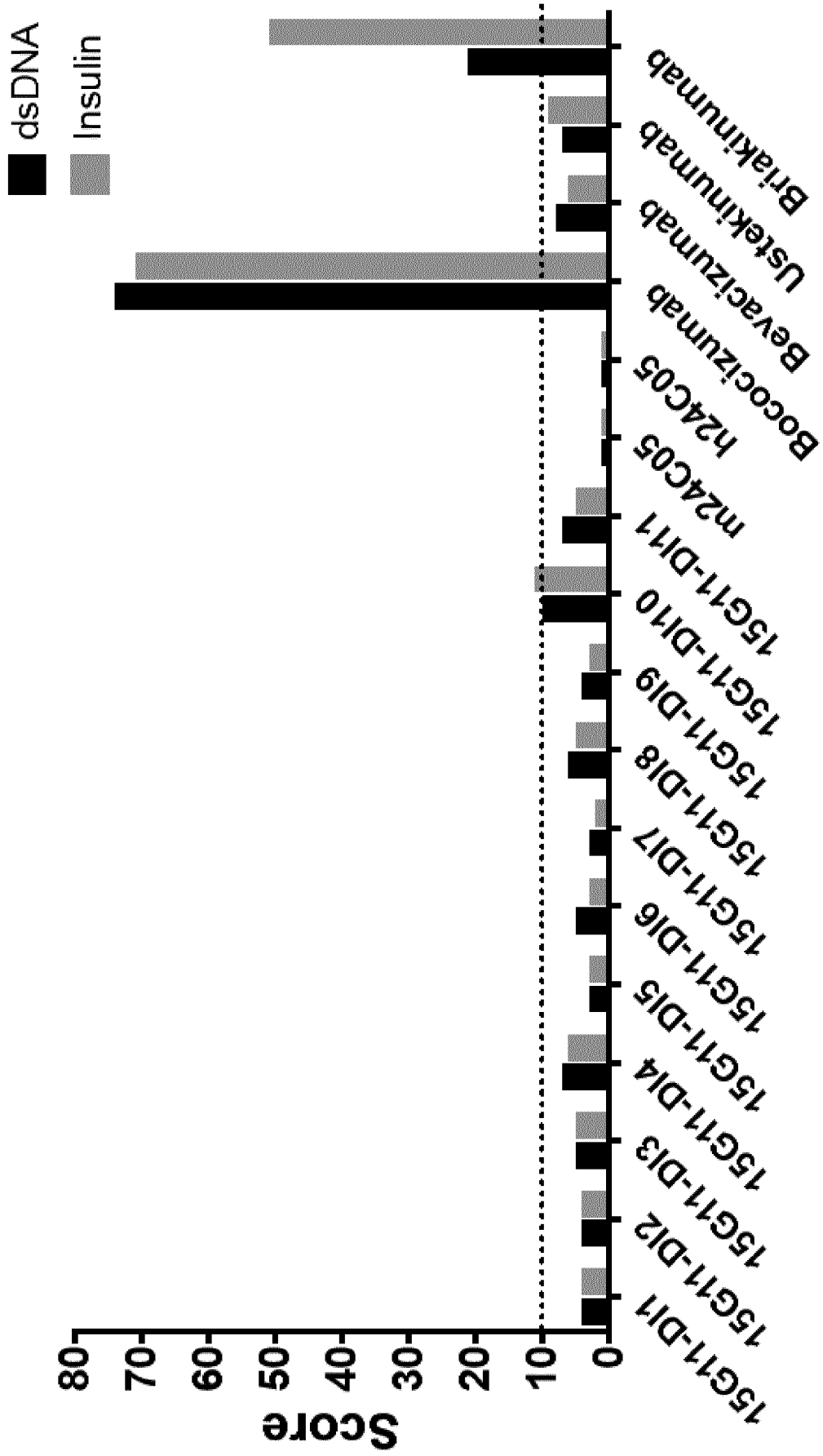

dsDNA
Insulin
Score
0
10
20
30
40
50
60
70
80
15G11-DI1
15G11-DI2
15G11-DI3
15G11-DI4
15G11-DI5
15G11-DI6
15G11-DI7
15G11-DI8
15G11-DI9
15G11-DI10
15G11-DI11
m24C05
h24C05
Bococizumab
Bevacizumab
Ustekinumab
Briakinumab

Fig. 11

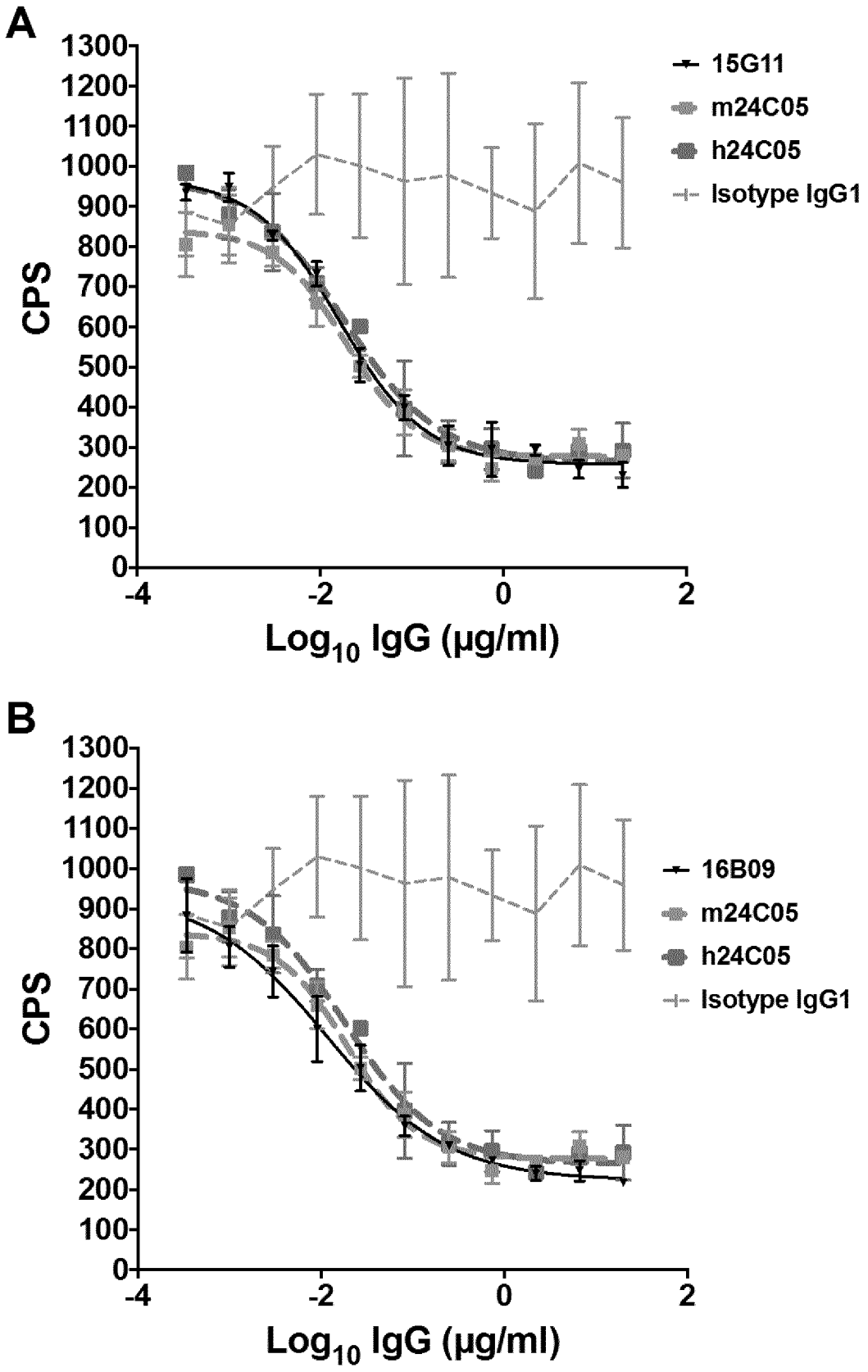
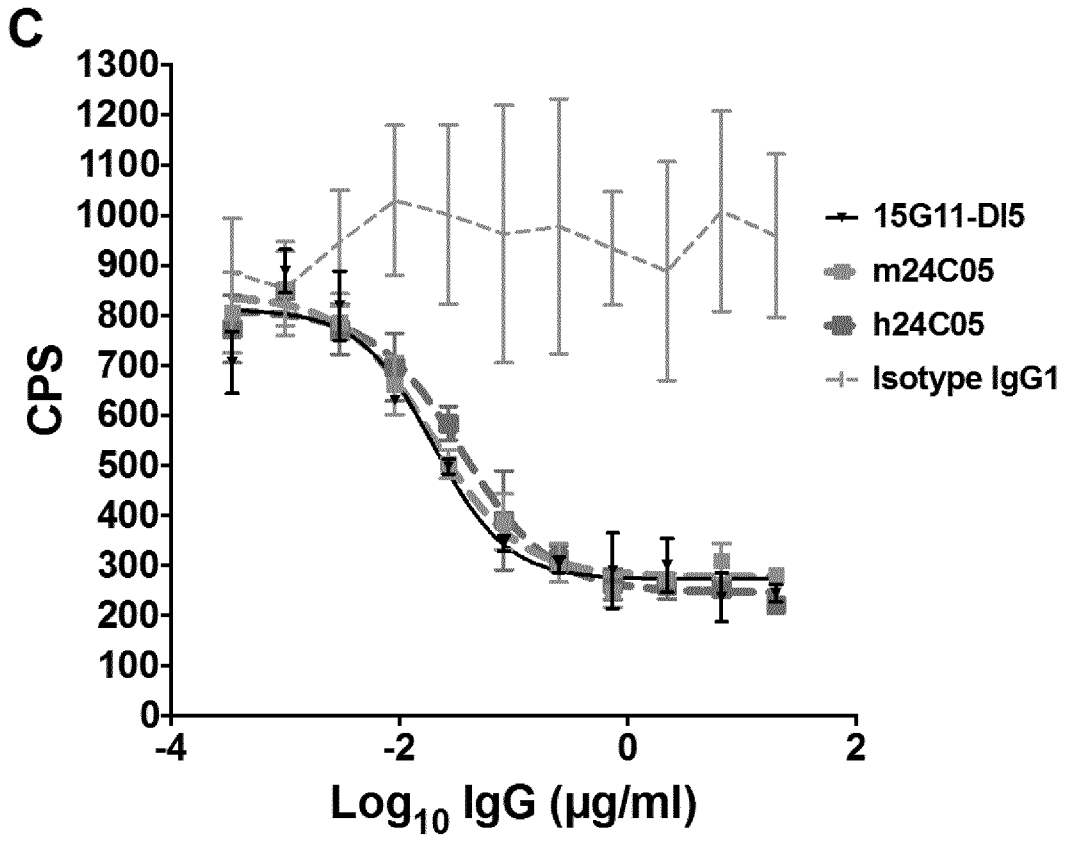

A
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
CPS
-4
-2
0
2
Log10 IgG (µg/ml)
15G11
m24C05
h24C05
Isotype IgG1
B
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
CPS
-4
-2
0
2
Log10 IgG (µg/ml)
16B09
m24C05
h24C05
Isotype IgG1

Fig. 12


C
CPS
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-4
-2
0
2
Log10 IgG (µg/ml)
15G11-DI5
m24C05
h24C05
Isotype IgG1

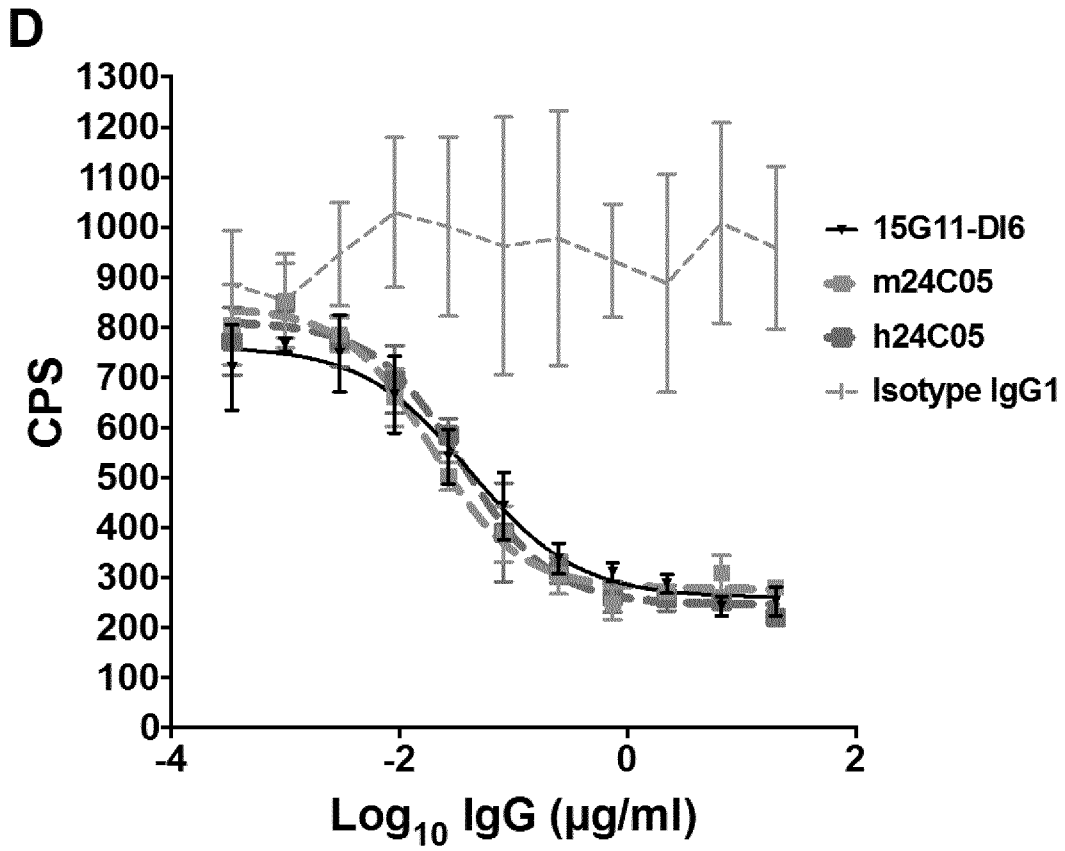
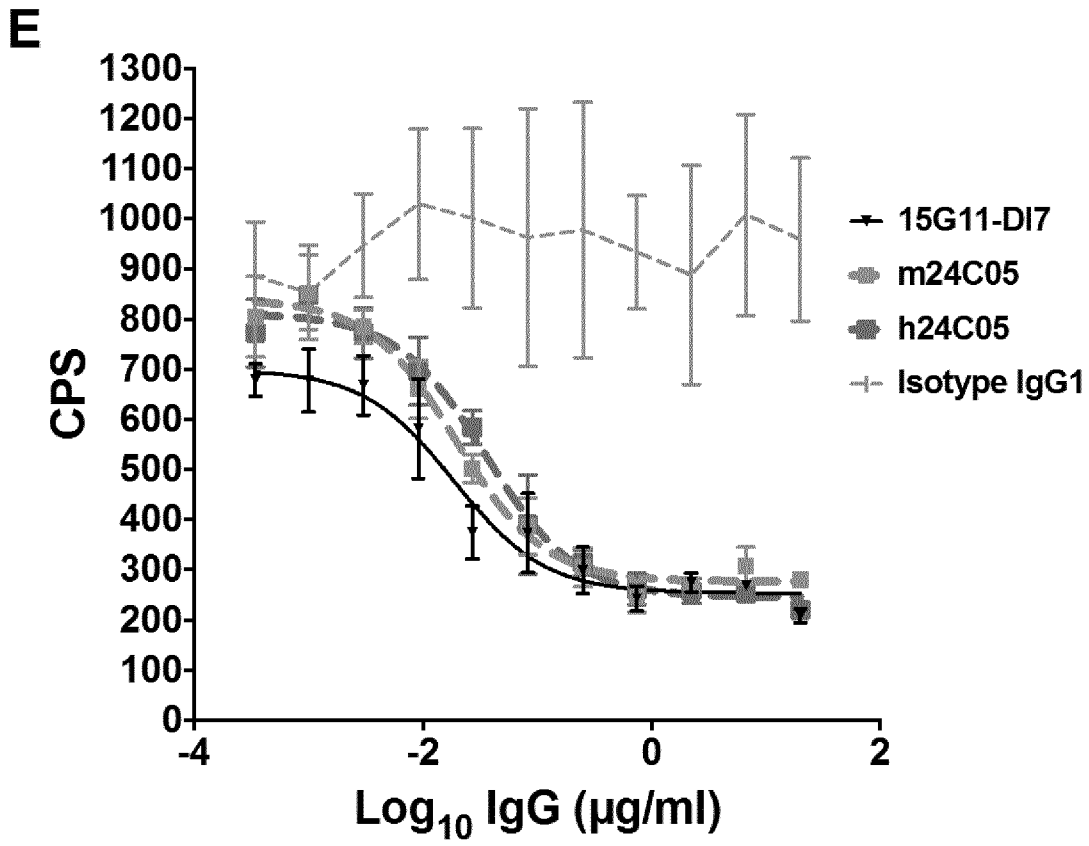

D
CPS
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-4
-2
0
2
Log10 IgG (µg/ml)
15G11-DI6
m24C05
h24C05
Isotype IgG1

Fig. 12


E
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
CPS
-4
-2
0
2
Log10 IgG (µg/ml)
15G11-DI7
m24C05
h24C05
Isotype IgG1

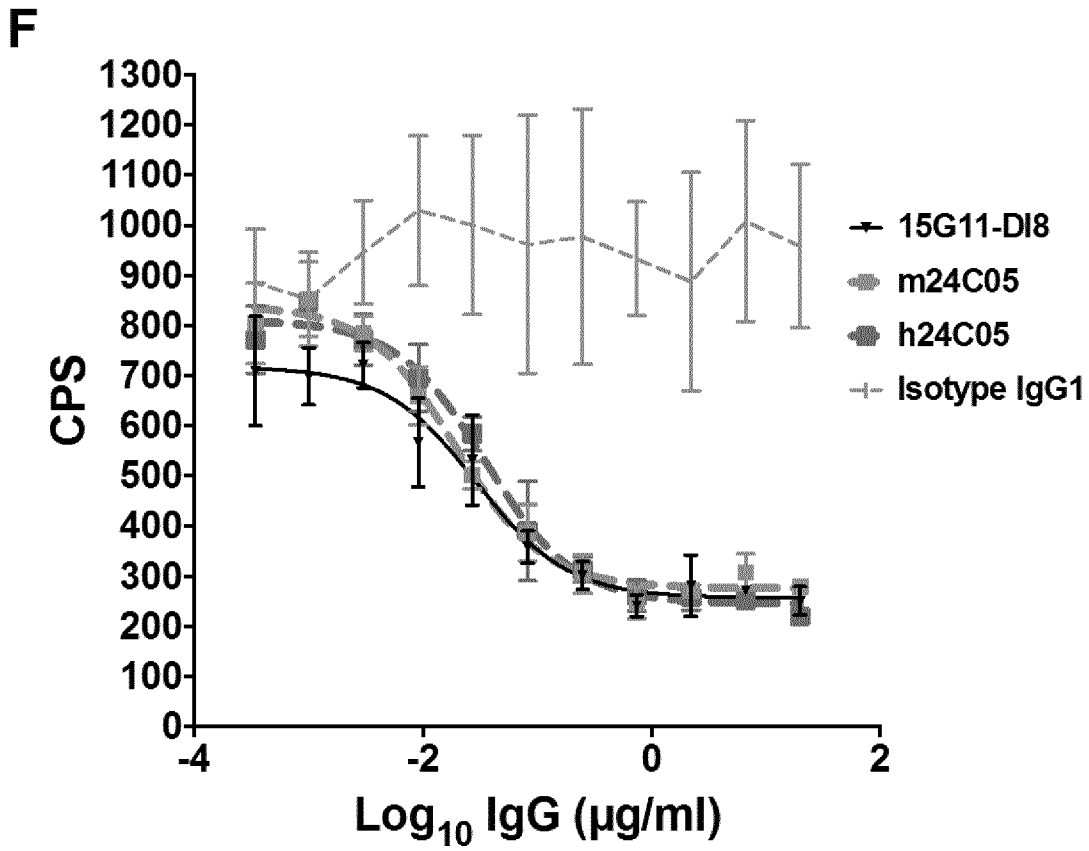

F
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
CPS
-4
-2
0
2
Log10 IgG (µg/ml)
15G11-DI8
m24C05
h24C05
Isotype IgG1

Fig. 12

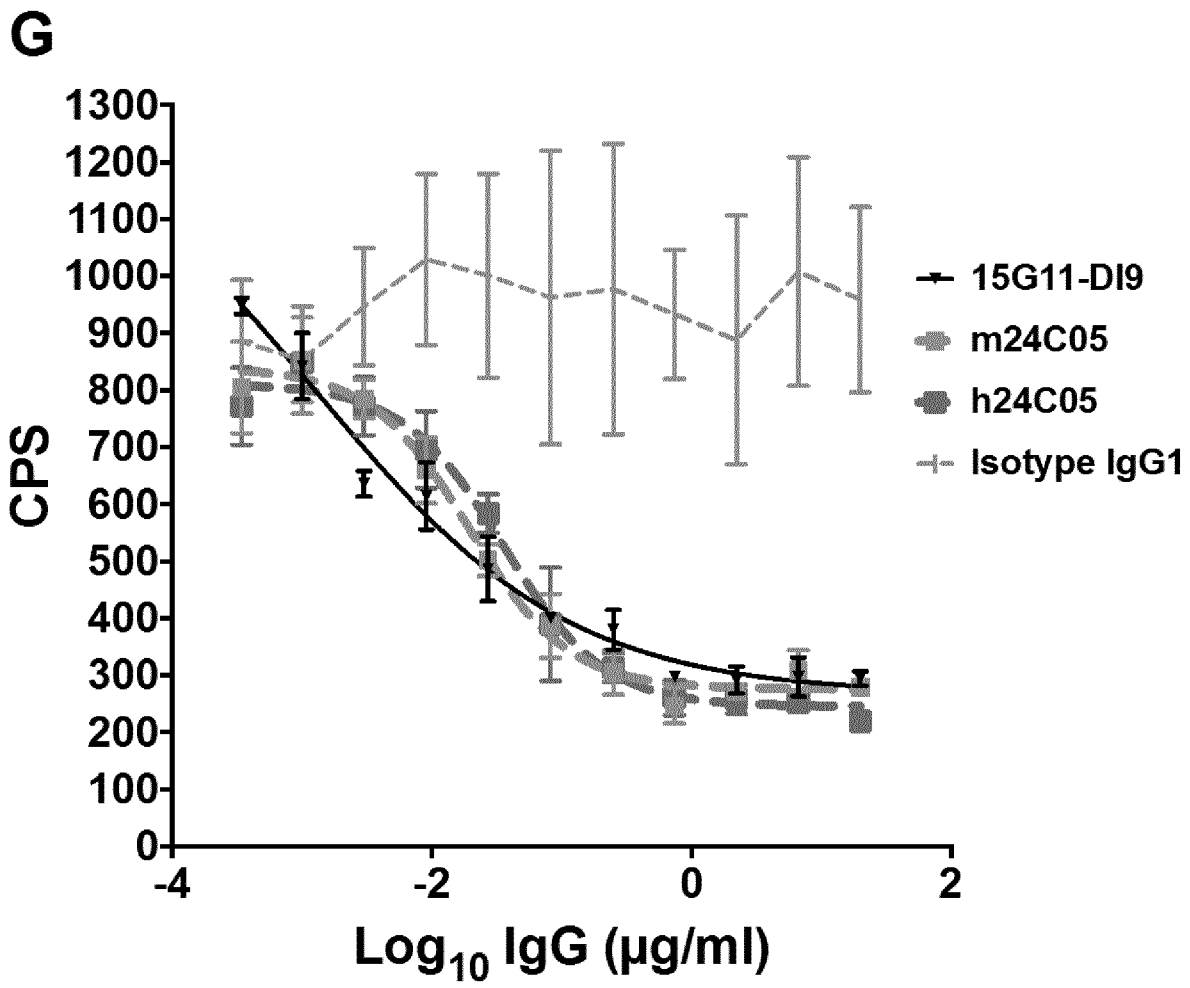

G
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
CPS
-4
-2
0
2
Log10 IgG (µg/ml)
15G11-DI9
m24C05
h24C05
Isotype IgG1

Fig. 12

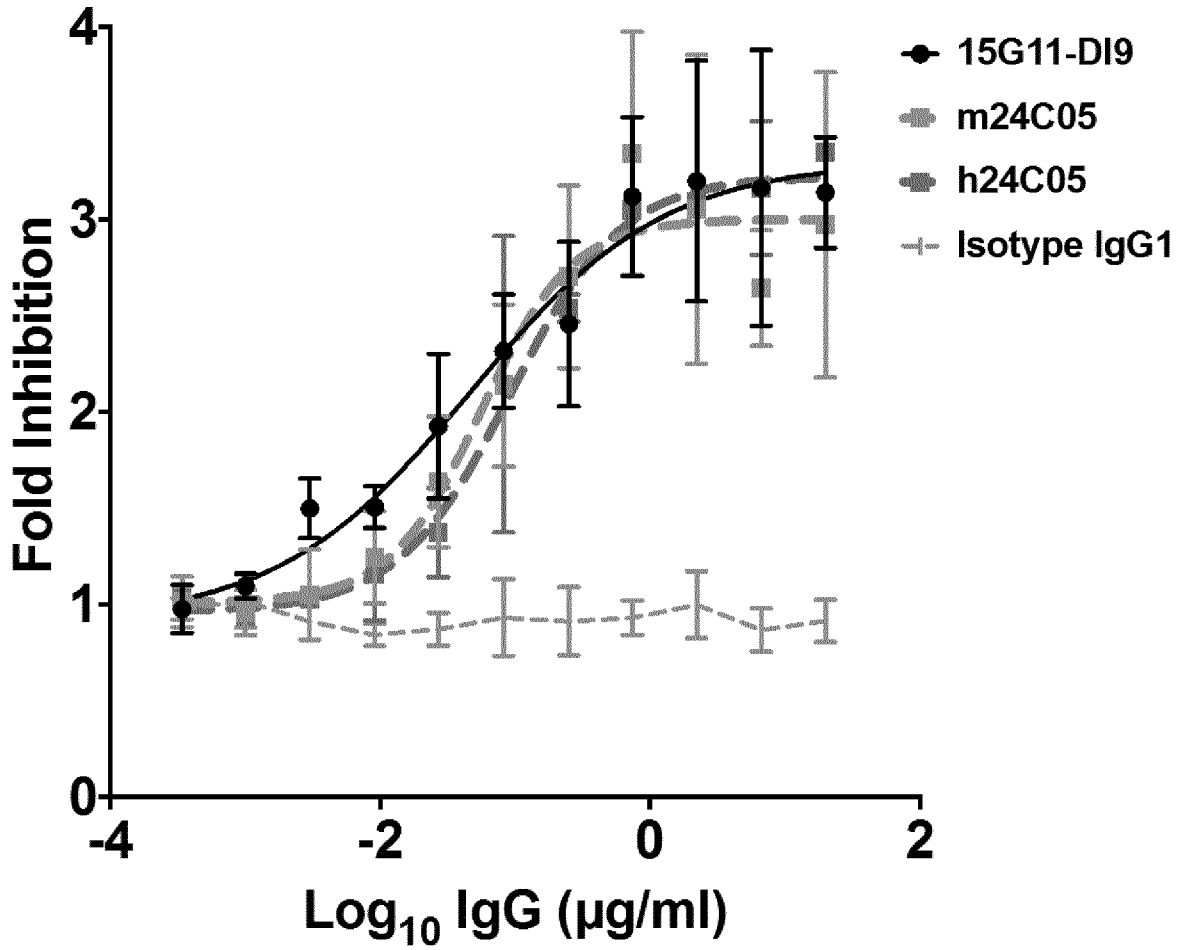

Fold Inhibition
4
3
2
1
0
-4
-2
0
2
Log10 IgG (µg/ml)
15G11-DI9
m24C05
h24C05
Isotype IgG1

Fig. 13

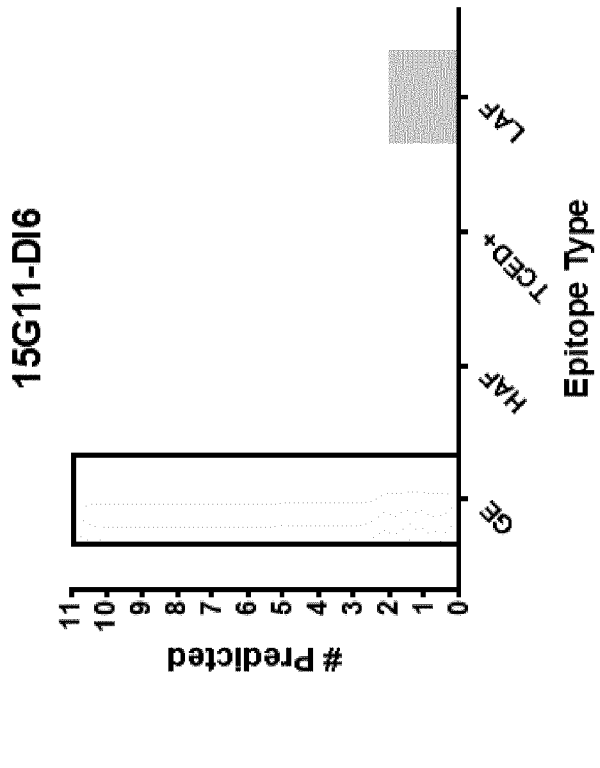


FIG. 14B

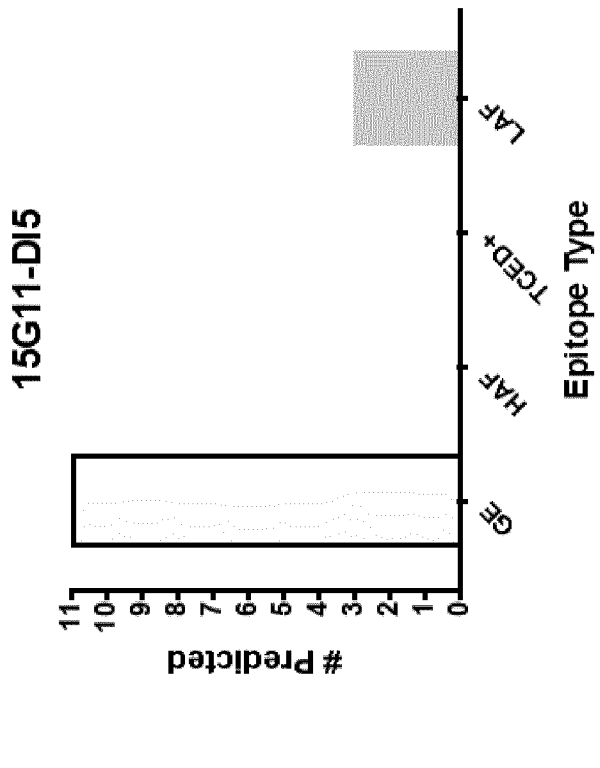


FIG. 14A

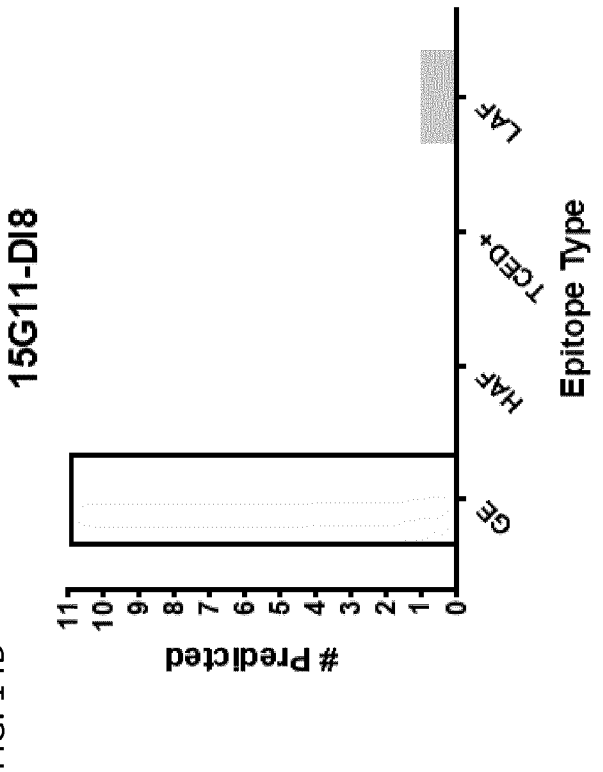


FIG. 14D

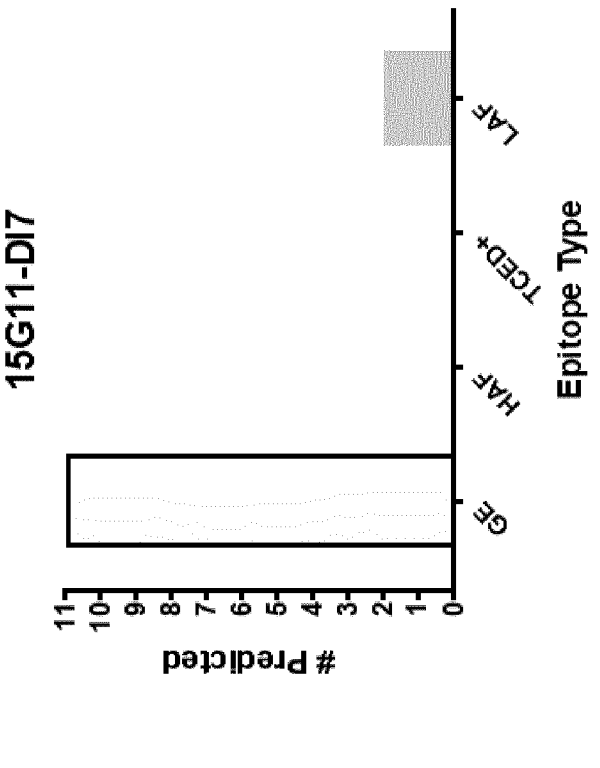
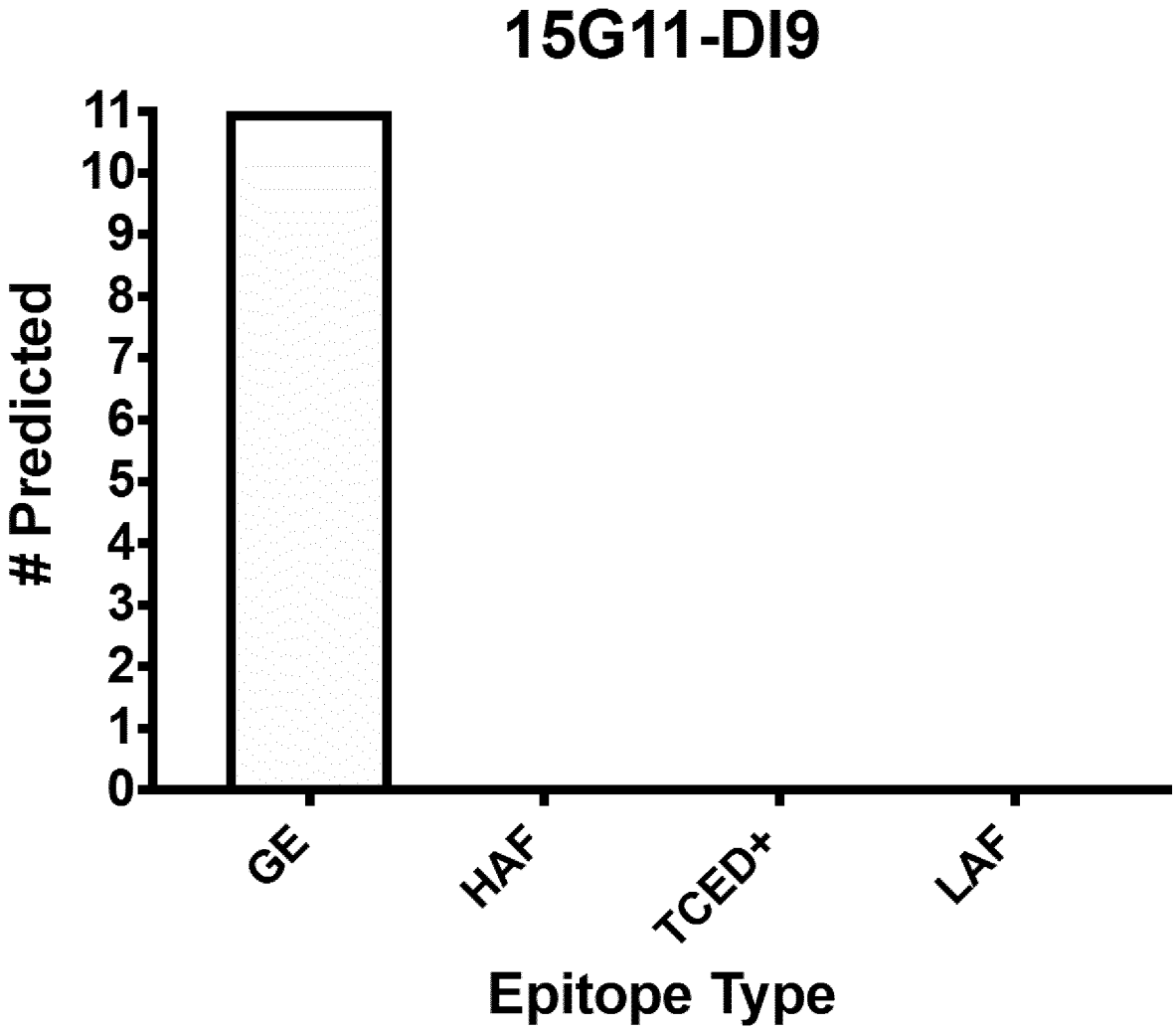


FIG. 14C

FIG. 14E


15G11-DI9
Predicted
11
10
9
8
7
6
5
4
3
2
1
0
GE
HAF
TCED+
LAF
Epitope Type

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/056506

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P35/00 C07K16/32
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/136911 A2 (AVEO PHARMACEUTICALS INC [US]; VINCENT SYLVIE [US] ET AL.) 3 November 2011 (2011-11-03) cited in the application examples 12-18 paragraph [0101] -----	1-39
X	WO 2014/159915 A1 (UNIV TEXAS [US]) 2 October 2014 (2014-10-02) example 9 paragraphs [0007], [0016] claim 33 -----	1-39

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
3 June 2019	12/06/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Covone-van Hees, M

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	GRISWOLD KARL E ET AL: "Design and engineering of deimmunized biotherapeutics", CURRENT OPINION IN STRUCTURAL BIOLOGY, ELSEVIER LTD, GB, vol. 39, 17 June 2016 (2016-06-17), pages 79-88, XP029764641, ISSN: 0959-440X, DOI: 10.1016/J.SBI.2016.06.003 the whole document	1-39
A	SUE TOWNSEND ET AL: "Augmented Binary Substitution: Single-pass CDR germ-lining and stabilization of therapeutic antibodies", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 112, no. 50, 30 November 2015 (2015-11-30), pages 15354-15359, XP55513906, US ISSN: 0027-8424, DOI: 10.1073/pnas.1510944112 cited in the application the whole document	1-39

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2019/056506

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