

Anti-HER2 Antibodies

This application claims priority from SG10201801219V filed 13 February 2018, the contents and elements of which are herein incorporated by reference for all purposes.

Field of the Invention

The present invention relates to antibodies that bind to the HER2 protein.

Background to the Invention

Breast cancer is the most common cause of cancer deaths in females with more than 400,000 deaths per year globally. In Singapore, it is the most frequent cancer in women; affecting more than 8,000 women in Singapore from 2007-2011, representing about 30% of cancer cases in Singaporean females and being the leading cause of cancer deaths in Singaporean women (Singapore Cancer Registry, Interim Annual Registry Report, Trends in Cancer Incidence in Singapore).

A turning point in breast cancer treatment has been reached with the introduction of the monoclonal antibody, trastuzumab (Herceptin®) targeting the Epidermal Growth Factor Receptor 2 (HER2/HER-2) positive cancers, i.e. ~20-30% of breast cancers and the most aggressive ones. HER2 is a member of the epidermal growth factor receptor family including epidermal growth factor receptor (EGFR/HER1), HER3 and HER4. Either homo- or hetero-dimerization of these receptor tyrosine kinases results in the phosphorylation of intracellular domain residues, triggering a downstream signalling cascade including the RAS/Raf and Akt pathways. Dimerization of HER2 is known to result in increased cell survival, proliferation and resistance to apoptosis.

Trastuzumab is a humanised antibody approved for the treatment of HER2-positive breast cancer by FDA in 1998. Trastuzumab binds to domain IV of HER2, and while the mechanism of action of the antibody is still not well understood, several effects had been observed, including cell cycle arrest, immune-mediated cytotoxicity and inhibition of angiogenesis. However, response rates to trastuzumab treatment are still low, ranging from 15-30%. While the use of trastuzumab in combination with chemotherapy prolongs response duration, a majority of responders develop resistance within a year.

The mechanism of resistance has been studied intensively, but has not been validated clinically. Possible causes of resistance include reduced trastuzumab binding, e.g., the masking of trastuzumab binding sites by MUC4 glycoprotein upon association with HER2, signalling through alternative HER2 independent pathways, e.g., Insulin-like growth factor-I receptor (IGF-IR), and constitutive HER2 signalling as a result of mutations in downstream signalling molecules such as PTEN and PI3K.

In addition, there is evidence for an important role of HER3/HER2 heterodimers in breast cancer development, and the inability of trastuzumab to inhibit such heterodimer formation could be a contributing factor in the resistance to treatment.

To address this, pertuzumab (Perjeta®), a second generation HER2 humanised monoclonal antibody was developed. It binds to HER2 domain II, an epitope which hinders the receptor's dimerization. A phase III clinical study comparing the use of pertuzumab in combination with trastuzumab, and an anti-mitotic drug docetaxel (Taxotere®) in HER2-positive patients, showed significant improvements in overall survival with the new regimen, prompting the FDA to approve the combination therapy for treatment of HER2-positive metastatic breast cancer patients in 2012.

The prevalence of HER2-related cancers and the high risk of resistance to current therapies highlights the importance of developing new therapeutics to treat such cancers.

Summary

The present disclosure is concerned with antibodies, or antigen binding fragments, that bind to HER2. Heavy and light chain polypeptides are also disclosed. The antibodies, antigen binding fragments and polypeptides may be provided in isolated and/or purified form and may be formulated into compositions suitable for use in research, therapy and diagnosis.

In one aspect, the present disclosure refers to an antibody or antigen binding fragment which is capable of binding to HER2, optionally isolated, wherein the antibody or antigen binding fragment comprises: (i) a light chain variable region incorporating the following CDRs:

LC-CDR1: GLSSGSVSTGHYAS (SEQ ID NO:15)
 LC-CDR2: NTNTRSS (SEQ ID NO:16)
 LC-CDR3: VLYVGDGIWV (SEQ ID NO:17); and a heavy chain variable region

incorporating the following CDRs:

HC-CDR1: SYYIH (SEQ ID NO:18)
 HC-CDR2: IINPGNGDTNYAQRFGG (SEQ ID NO:19)

HC-CDR3: EIASYSGSYDY (SEQ ID NO:20).

5 In another aspect, the present disclosure refers to a chimeric antigen receptor (CAR) comprising an antibody or antigen binding fragment as disclosed.

In another aspect, the present disclosure refers to an *in vitro* complex, optionally isolated, comprising an antibody or antigen binding fragment as disclosed, or a CAR according as disclosed, bound to HER2.

10 In another aspect, the present disclosure refers to a nucleic acid, optionally isolated, encoding an antibody or antigen binding fragment as disclosed, or a CAR as disclosed.

In another aspect, the present disclosure refers to a vector comprising the nucleic acid as disclosed.

15 In another aspect, the present disclosure refers to a cell comprising the nucleic acid as disclosed, or the vector as disclosed.

20 In another aspect, the present disclosure refers to a method for making an antibody or antigen binding fragment as disclosed herein, or a CAR as disclosed herein, comprising culturing a cell as disclosed under conditions suitable for the expression of the antibody, antigen binding fragment or CAR from the nucleic acid or vector.

In another aspect, the present disclosure refers to a composition comprising an antibody or antigen binding fragment as disclosed, or a cell as disclosed herein, and at least one pharmaceutically-acceptable carrier.

5 In another aspect, the present disclosure refers to an antibody or antigen binding fragment as disclosed herein, a cell as disclosed herein, or a composition as disclosed, for use in therapy, or in a method of medical treatment, wherein the cell as disclosed herein is a CAR T cell or a CAR NK cell.

10 In another aspect, the present disclosure refers to a use of an antibody or antigen binding fragment as disclosed, a cell as disclosed or a composition as disclosed herein, in the manufacture of a medicament for treating a HER2-positive cancer, wherein the cell as disclosed herein is a CAR T cell or a CAR NK cell.

15 In another aspect, the present disclosure refers to a method comprising contacting, *in vitro*, a sample containing, or suspected to contain, HER2 with an antibody or antigen binding fragment as disclosed herein, and detecting the formation of a complex comprising the antibody or antigen binding fragment and HER2.
In yet another aspect, the present disclosure refers to a method of diagnosing a HER2-positive cancer in a subject, the method comprising contacting, *in vitro*, a sample from the subject with an antibody or antigen binding

fragment as disclosed, and detecting the formation of a complex comprising the antibody or antigen binding fragment and HER2.

In one example of the present disclosure an antibody, or antigen binding fragment, is provided, the amino acid sequence of the antibody or antigen binding fragment may comprise the amino acid sequences i) to iii), or the amino acid sequences iv) to vi), or preferably the amino acid sequences i) to vi):

- i) LC-CDR1: GLSSGSVSTX₁X₂YX₃S (SEQ ID NO:9);
- ii) LC-CDR2: X₄TNX₅RSS (SEQ ID NO:10);
- iii) LC-CDR3: X₆LYX₇GX₈GIX₉V (SEQ ID NO:11);
- iv) HC-CDR1: X₁₀X₁₁X₁₂X₁₃X₁₄X₁₅X₁₆ (SEQ ID NO:12);
- v) HC-CDR2: X₁₇X₁₈X₁₉X₂₀X₂₁X₂₂GX₂₃TX₂₄YX₂₅X₂₆X₂₇X₂₈X₂₉X₃₀ (SEQ ID NO:13);
- vi) HC-CDR3: X₃₁X₃₂X₃₃X₃₄X₃₅SX₃₆X₃₇YX₃₈X₃₉X₄₀X₄₁X₄₂X₄₃ (SEQ ID NO:14);

or a variant thereof in which one or two or three amino acids in one or more of the sequences (i) to (vi) are replaced with another amino acid, where X₁ = G or S; X₂ = H or Y; X₃ = A or P; X₄ = N, S or T; X₅ = T, S or I; X₆ = V or M; X₇ = V or M; X₈ = D or S; X₉ = W or S; X₁₀ = S or absent; X₁₁ = S or absent; X₁₂ = S or G; X₁₃ = Y or N; X₁₄ = Y or W; X₁₅ = I or W; X₁₆ = H, G or S; X₁₇ = I or absent; X₁₈ = I, S or E; X₁₉ = N or I; X₂₀ = P, Y or N; X₂₁ = G, Y or H; X₂₂ = N or S; X₂₃ = D or S; X₂₄ = N or Y; X₂₅ = A or N; X₂₆ = Q or P; X₂₇ = R or S; X₂₈ = F or L; X₂₉ = Q or K; X₃₀ = G or S; X₃₁ = E or absent; X₃₂ = I, Y or M; X₃₃ = A or G; X₃₄ = S, P, I or A; X₃₅ = Y, D or N; X₃₆ = G or S; X₃₇ = G or S; X₃₈ = L or absent; X₃₉ = V or Y; X₄₀ = A, D or G; X₄₁ = F, M or Y; X₄₂ = D or absent; and X₄₃ = I, V or absent.

In some examples LC-CDR1 is one of GLSSGSVSTGHYAS (SEQ ID NO:15), GLSSGSVSTGYYP (SEQ ID NO:21), or GLSSGSVSTSYYP (SEQ ID NO:27).

5 In some examples LC-CDR2 is one of NTNTRSS (SEQ ID NO:16), STNSRSS (SEQ ID NO:22), TTNIRSS (SEQ ID NO:28), or STNTRSS (SEQ ID NO:33).

In some examples LC-CDR3 is one of VLYVGDGIWV (SEQ ID NO:17), VLYMGSGISV (SEQ ID NO:23); MLYMGSGIWV (SEQ ID NO:29), or VLYMGSGIWV (SEQ ID NO:34).

10 In some examples HC-CDR1 is one of SYYIH (SEQ ID NO:18), SSSYYWG (SEQ ID NO:24), GYYWS (SEQ ID NO:30), or SSNWWS (SEQ ID NO:35).

In some examples HC-CDR2 is one of IINPGNGDTNYAQRFG (SEQ ID NO:19), SIYYSGSTYYNPSLKS (SEQ ID NO:25), EINHSGSTNYNPSLKS (SEQ ID NO:31), or EIYHSGSTNYNPSLKS (SEQ ID NO:36).

In some examples HC-CDR3 is one of EIASYSGSYDY (SEQ ID NO:20), YAPDSSGYLVAFDI (SEQ ID NO:26), MGINSGGYLYGMDV (SEQ ID NO:32), or MGANSGGYLYGMDV (SEQ ID NO:37).

5 In some examples the antibody, or antigen binding fragment, may comprise at least one light chain variable region incorporating the following CDRs:

LC-CDR1: GLSSGSVSTX₁X₂YX₃S (SEQ ID NO:9);

LC-CDR2: X₄TNX₅RSS (SEQ ID NO:10);

LC-CDR3: X₆LYX₇GX₈GIX₉V (SEQ ID NO:11);

where X₁ = G or S; X₂ = H or Y; X₃ = A or P; X₄ = N, S or T; X₅ = T, S or I; X₆ = V or M; X₇ = V or M;
X₈ = D or S; and X₉ = W or S.

In some examples the antibody, or antigen binding fragment, may comprise at least one light chain variable region incorporating the following CDRs:

LC-CDR1: GLSSGSVSTGHHYAS (SEQ ID NO:15)

LC-CDR2: NTNTRSS (SEQ ID NO:16)

LC-CDR3: VLYVGDGIWV (SEQ ID NO:17).

In some examples the antibody, or antigen binding fragment, may comprise at least one light chain variable region incorporating the following CDRs:

LC-CDR1: GLSSGSVSTGYYPSS (SEQ ID NO:21)

LC-CDR2: STNSRSS (SEQ ID NO:22)

LC-CDR3: VLYMGSGISV (SEQ ID NO:23).

In some examples the antibody, or antigen binding fragment, may comprise at least one light chain variable region incorporating the following CDRs:

LC-CDR1: GLSSGSVSTSYYPSS (SEQ ID NO:27)

LC-CDR2: TTNIRSS (SEQ ID NO:28)

LC-CDR3: MLYMGSGIWV (SEQ ID NO:29).

In some examples the antibody, or antigen binding fragment, may comprise at least one light chain variable region incorporating the following CDRs:

LC-CDR1: GLSSGSVSTSYYPSS (SEQ ID NO:27)

LC-CDR2: STNTRSS (SEQ ID NO:33)

LC-CDR3: VLYMGSGIWV (SEQ ID NO:34).

In some examples the antibody, or antigen binding fragment, may comprise at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: X₁₀X₁₁X₁₂X₁₃X₁₄X₁₅X₁₆ (SEQ ID NO:12);

HC-CDR2: X₁₇X₁₈X₁₉X₂₀X₂₁X₂₂GX₂₃TX₂₄YX₂₅X₂₆X₂₇X₂₈X₂₉X₃₀ (SEQ ID NO:13);

HC-CDR3: X₃₁X₃₂X₃₃X₃₄X₃₅SX₃₆X₃₇YX₃₈X₃₉X₄₀X₄₁X₄₂X₄₃ (SEQ ID NO:14);

where X₁₀ = S or absent; X₁₁ = S or absent; X₁₂ = S or G; X₁₃ = Y or N; X₁₄ = Y or W; X₁₅ = I or W;
X₁₆ = H, G or S; X₁₇ = I or absent; X₁₈ = I, S or E; X₁₉ = N or I; X₂₀ = P, Y or N; X₂₁ = G, Y or H; X₂₂ = N or S;
X₂₃ = D or S; X₂₄ = N or Y; X₂₅ = A or N; X₂₆ = Q or P, X₂₇ = R or S, X₂₈ = F or L; X₂₉ = Q or K; X₃₀ = G or S;
X₃₁ = E or absent; X₃₂ = I, Y or M; X₃₃ = A or G; X₃₄ = S, P, I or A, X₃₅ = Y, D or N; X₃₆ = G or S; X₃₇ = G or

S; X₃₈ = L or absent; X₃₉ = V or Y; X₄₀ = A, D or G; X₄₁ = F, M or Y; X₄₂ = D or absent; and X₄₃ = I, V or absent.

In some examples the antibody, or antigen binding fragment, may comprise at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: SYYIH (SEQ ID NO:18)
 HC-CDR2: IINPGNGDTNYAQRFG (SEQ ID NO:19)
 HC-CDR3: EIASYSGSYDY (SEQ ID NO:20).

In some examples the antibody, or antigen binding fragment, may comprise at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: SSSYYWG (SEQ ID NO:24)
 HC-CDR2: SIYYSGSTYYNPSLKS (SEQ ID NO:25)
 HC-CDR3: YAPDSSGYLVAFDI (SEQ ID NO:26).

In some examples the antibody, or antigen binding fragment, may comprise at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: GYYWS (SEQ ID NO:30)
 HC-CDR2: EINHSGSTNYNPSLKS (SEQ ID NO:31)
 HC-CDR3: MGINSGGYLYGMDV (SEQ ID NO:32).

In some examples the antibody, or antigen binding fragment, may comprise at least one heavy chain variable region incorporating the following CDRs:

HC-CDR1: SSNWWS (SEQ ID NO:35)
 HC-CDR2: EIYHSGSTNYNPSLKS (SEQ ID NO:36)
 HC-CDR3: MGANSGGYLYGMDV (SEQ ID NO:37).

The antibody may comprise at least one light chain variable region (V_L) comprising the amino acid sequence of one of SEQ ID NOs 1, 15, 16, 17; or 2, 21, 22, 23; or 3, 27, 28, 29; or 4, 33, 34, 35, or an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to SEQ ID NOs 1, 15, 16, 17; or 2, 21, 22, 23; or 3, 27, 28, 29; or 4, 33, 34, 35.

The antibody may comprise at least one heavy chain variable region (V_H) comprising the amino acid sequence of one of SEQ ID NOs 5, 18, 19, 20; or 6, 24, 25, 26; or 7, 30, 31, 32; or 8, 36, 37, 38, or an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to SEQ ID NOs 5, 18, 19, 20; or 6, 24, 25, 26; or 7, 30, 31, 32; or 8, 36, 37, 38.

The antibody may comprise at least one light chain variable region (V_L) comprising the amino acid sequence of one of SEQ ID NOs 1, 15, 16, 17; or 2, 21, 22, 23; or 3, 27, 28, 29; or 4, 33, 34, 35, or an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to SEQ ID NOs 1, 15, 16, 17; or 2, 21, 22, 23; or 3, 27, 28, 29; or 4, 33, 34, 35, and at least one heavy chain variable region (V_H) comprising the amino acid sequence of one of SEQ ID NOs 5, 18, 19, 20; or 6, 24, 25, 26; or 7, 30, 31, 32; or 8, 36, 37, 38, or an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to SEQ ID NOs 5, 18, 19, 20; or 6, 24, 25, 26; or 7, 30, 31, 32; or 8, 36, 37, 38.

An antibody, antigen binding fragment or polypeptide provided herein, may optionally bind HER2, optionally human or murine HER2. The antibody, antigen binding fragment, polypeptide may bind specifically to human, rhesus macaque and/or murine HER2. The antibody, antigen binding fragment or polypeptide may optionally have amino acid sequence components as described above. The antibody, antigen binding fragment or polypeptide may be an IgG or derived from an IgG. The antibody, antigen binding fragment or polypeptide may have a molecular weight of about 140 to 160kDa, preferably about 150kDa. In one example an *in vitro* complex, optionally isolated, comprising an antibody, antigen binding fragment, or polypeptide as described herein, bound to HER2 is provided.

In one example of the present disclosure an isolated light chain variable region polypeptide is provided, the light chain variable region polypeptide comprising the following CDRs:

LC-CDR1: GLSSGSVSTX₁X₂YX₃S (SEQ ID NO:9)

LC-CDR2: X₄TNX₅RSS (SEQ ID NO:10)

LC-CDR3: X₆LYX₇GX₈GIX₉V (SEQ ID NO:11);

where X₁ = G or S; X₂ = H or Y; X₃ = A or P; X₄ = N, S or T; X₅ = T, S or I; X₆ = V or M; X₇ = V or M; X₈ = D or S; and X₉ = W or S.

In some examples the isolated light chain variable region polypeptide is provided in combination with a heavy chain variable region polypeptide as described herein.

In some examples LC-CDR1 is one of GLSSGSVSTGHYAS (SEQ ID NO:15), GLSSGSVSTGYYP (SEQ ID NO:21), or GLSSGSVSTSYYP (SEQ ID NO:27),. In some examples LC-CDR2 is one of NTNTRSS (SEQ ID NO:16), STNSRSS (SEQ ID NO:22), TTNIRSS (SEQ ID NO:28), or STNTRSS (SEQ ID NO:33). In some examples LC-CDR3 is one of VLYVGDGIWV (SEQ ID NO:17), VLYMGSGISV (SEQ ID NO:23), MLYMGSGIWV (SEQ ID NO:29), or VLYMGSGIWV (SEQ ID NO:34). In some examples the isolated light chain variable region polypeptide is capable of binding to HER2.

In one example of the present disclosure an light chain variable region polypeptide is provided, comprising an amino acid sequence having at least 85% sequence identity to the light chain sequence: SEQ ID NO:1,

2, 3, or 4 (Figure 1A to 1D). In some examples the isolated light chain variable region polypeptide is capable of binding to HER2.

In one example of the present disclosure an isolated heavy chain variable region polypeptide is provided, the heavy chain variable region polypeptide comprising the following CDRs:

HC-CDR1: X₁₀X₁₁X₁₂X₁₃X₁₄X₁₅X₁₆ (SEQ ID NO:12);

HC-CDR2: X₁₇X₁₈X₁₉X₂₀X₂₁X₂₂GX₂₃TX₂₄YX₂₅X₂₆X₂₇X₂₈X₂₉X₃₀ (SEQ ID NO:13);

HC-CDR3: X₃₁X₃₂X₃₃X₃₄X₃₅SX₃₆X₃₇YX₃₈X₃₉X₄₀X₄₁X₄₂X₄₃ (SEQ ID NO:14);

where X₁₀ = S or absent; X₁₁ = S or absent; X₁₂ = S or G; X₁₃ = Y or N; X₁₄ = Y or W; X₁₅ = I or W; X₁₆ = H, G or S; X₁₇ = I or absent; X₁₈ = I, S or E; X₁₉ = N or I; X₂₀ = P, Y or N; X₂₁ = G, Y or H; X₂₂ = N or S; X₂₃ = D or S; X₂₄ = N or Y; X₂₅ = A or N; X₂₆ = Q or P, X₂₇ = R or S, X₂₈ = F or L; X₂₉ = Q or K; X₃₀ = G or S; X₃₁ = E or absent; X₃₂ = I, Y or M; X₃₃ = A or G; X₃₄ = S, P, I or A, X₃₅ = Y, D or N; X₃₆ = G or S; X₃₇ = G or S; X₃₈ = L or absent; X₃₉ = V or Y; X₄₀ = A, D or G; X₄₁ = F, M or Y; X₄₂ = D or absent; and X₄₃ = I, V or absent.

In some examples the isolated heavy chain variable region polypeptide is provided in combination with a light chain variable region polypeptide as described herein.

In some examples HC-CDR1 is one of SYIYH (SEQ ID NO:18), SSSYYWG (SEQ ID NO:24), GYYWS (SEQ ID NO:30), or SSNWWWS (SEQ ID NO:35). In some examples HC-CDR2 is one of IINPGNGDTNYAQRFGQ (SEQ ID NO:19), SIYYSGSTYYNPSLKS (SEQ ID NO:25), EINHSGSTNYNPSLKS (SEQ ID NO:31), or EIYHSGSTNYNPSLKS (SEQ ID NO:36). In some examples HC-CDR3 is one of EIASYSGSYDY (SEQ ID NO:20), YAPDSSGYLVAFDI (SEQ ID NO:26), MGINSGGYLYGMDV (SEQ ID NO:32), or MGANSGGYLYGMDV (SEQ ID NO:37). In some examples the isolated heavy chain variable region polypeptide is capable of binding to HER2.

In one example of the present disclosure an isolated heavy chain variable region polypeptide is provided, comprising an amino acid sequence having at least 85% sequence identity to the heavy chain sequence of SEQ ID NO:5, 6, 7, or 8 (Figure 2A to 2D). In some examples the isolated heavy chain variable region polypeptide is capable of binding to HER2.

In one example of the present disclosure an antibody, or antigen binding fragment, is provided, the antibody, or antigen binding fragment, comprising a heavy chain and a light chain variable region sequence, wherein:

the light chain comprises a LC-CDR1, LC-CDR2, LC-CDR3, having at least 85% overall sequence identity to LC-CDR1: one of GLSSGSVSTX₁X₂YX₃S (SEQ ID NO:9), GLSSGSVSTGHYAS (SEQ ID NO:15), GLSSGSVSTGYYP (SEQ ID NO:21), or GLSSGSVSTSYYP (SEQ ID NO:27), LC-CDR2: one of X₄TX₅RSS (SEQ ID NO:10), NTNTRSS (SEQ ID NO:16), STNSRSS (SEQ ID NO:22), TTNIRSS (SEQ ID NO:28), or STNTRSS (SEQ ID NO:33), and LC-CDR3: one of X₆LYX₇GX₈GIX₉V (SEQ ID NO:11), VLYVGDGIWV (SEQ ID NO:17), VLYMGSGISV (SEQ ID NO:23); MLYMGSGIWW (SEQ ID NO:29), or

VLYMGSGIWV (SEQ ID NO:34), respectively, where $X_1 = G$ or S ; $X_2 = H$ or Y ; $X_3 = A$ or P ; $X_4 = N$, S or T ; $X_5 = T$, S or I ; $X_6 = V$ or M ; $X_7 = V$ or M ; $X_8 = D$ or S ; and $X_9 = W$ or S , and;

the heavy chain comprises a HC-CDR1, HC-CDR2, HC-CDR3, having at least 85% overall sequence identity to HC-CDR1: one of $X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_{16}$ (SEQ ID NO:12), SYIYH (SEQ ID NO:18), SSSYYWG (SEQ ID NO:24), GYYWS (SEQ ID NO:30), or SSNNWS (SEQ ID NO:35), HC-CDR2: one of $X_{17}X_{18}X_{19}X_{20}X_{21}X_{22}GX_{23}TX_{24}YX_{25}X_{26}X_{27}X_{28}X_{29}X_{30}$ (SEQ ID NO:13), IINPGNGDTNYAQRFG (SEQ ID NO:19), SIYYSGSTYYNPSLKS (SEQ ID NO:25), EINHSGSTNYNPSLKS (SEQ ID NO:31), or EIYHSGSTNYNPSLKS (SEQ ID NO:36), and HC-CDR3: one of

$X_{31}X_{32}X_{33}X_{34}X_{35}SX_{36}X_{37}YX_{38}X_{39}X_{40}X_{41}X_{42}X_{43}$ (SEQ ID NO:14), EIASYSGSYDY (SEQ ID NO:20), YAPDSSGYLVAFDI (SEQ ID NO:26), MGINSGGYLYGMDV (SEQ ID NO:32), or MGANSGGYLYGMDV (SEQ ID NO:37), respectively, where $X_{10} = S$ or absent; $X_{11} = S$ or absent; $X_{12} = S$ or G ; $X_{13} = Y$ or N ; $X_{14} = Y$ or W ; $X_{15} = I$ or W ; $X_{16} = H$, G or S ; $X_{17} = I$ or absent; $X_{18} = I$, S or E ; $X_{19} = N$ or I ; $X_{20} = P$, Y or N ; $X_{21} = G$, Y or H ; $X_{22} = N$ or S ; $X_{23} = D$ or S ; $X_{24} = N$ or Y ; $X_{25} = A$ or N ; $X_{26} = Q$ or P ; $X_{27} = R$ or S ; $X_{28} = F$ or L ; $X_{29} = Q$ or K ; $X_{30} = G$ or S ; $X_{31} = E$ or absent; $X_{32} = I$, Y or M ; $X_{33} = A$ or G ; $X_{34} = S$, P , I or A ; $X_{35} = Y$, D or N ; $X_{36} = G$ or S ; $X_{37} = G$ or S ; $X_{38} = L$ or absent; $X_{39} = V$ or Y ; $X_{40} = A$, D or G ; $X_{41} = F$, M or Y ; $X_{42} = D$ or absent; and $X_{43} = I$, V or absent.

In some examples the degree of sequence identity may be one of 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%.

In another example of the present disclosure an antibody or antigen binding fragment which is capable of binding to HER2, optionally isolated, is provided comprising a heavy chain and a light chain variable region sequence, wherein:

the light chain sequence has at least 85% sequence identity to the light chain sequence of SEQ ID NO:1, 2, 3, or 4 (Figure 1A to 1D), and;

the heavy chain sequence has at least 85% sequence identity to the heavy chain sequence of SEQ ID NO:5, 6, 7, or 8 (Figure 2A to 2D).

In some examples the degree of sequence identity may be one of 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%.

In another example of the present disclosure an antibody, antigen binding fragment or polypeptide which is capable of binding to HER2, optionally isolated, is provided having the amino acid sequences i) to iii), or the amino acid sequences iv) to vi), or preferably the amino acid sequences i) to vi):

i) LC-CDR1: one of RSSQSLHSDGNKYLD (SEQ ID NO:74), RSSQSLHSDGNKYLD (SEQ ID NO:84), RSSQSLVYSDGNTYLN (SEQ ID NO:93), RSSQSLHSDGNKYLD (SEQ ID NO:102), RSSQSLHSDGNTYLD (SEQ ID NO:110), RASQSVRNLA (SEQ ID NO:120), GSTTGAVTSGHYPS (SEQ ID NO:138), RASQSVSSSYLA (SEQ ID NO:161), RSSQSLQHSNGYQYLD (SEQ ID NO:170), TGRSANIGGFVDQ (SEQ ID NO:186), ALTSGSVSTSYPS (SEQ ID NO:194), TSSQSLVYSDGNTYLN (SEQ ID NO:211), RSSQSLRSDGYNFVD (SEQ ID NO:217), RASQGISSWLA (SEQ ID NO:226),

RASRSVGKYLA (SEQ ID NO:247), GLSSGSVSTTYPS (SEQ ID NO:255), TLRSGINVGTYRIY (SEQ ID NO:261), RASQSVSSYLA (SEQ ID NO:270), GLTSGAVSSSYPS (SEQ ID NO:279), TGNNNNVGFAGAA (SEQ ID NO:287);

ii) LC-CDR2: one of LGSNRAS (SEQ ID NO:75), KVSNRDS (SEQ ID NO:94), SGSNRAS (SEQ ID NO:111); YASTRAT (SEQ ID NO:121), STSNKHS (SEQ ID NO:139), LGSHRAS (SEQ ID NO:146), LGSNRAP (SEQ ID NO:155), GASSRAT (SEQ ID NO:162), LGSFRAS (SEQ ID NO:171), DNSNRPS (SEQ ID NO:187), STNLRSS (SEQ ID NO:195), KVSDRDS (SEQ ID NO:204), KVSKRDS (SEQ ID NO:212), LGSDRAS (SEQ ID NO:218), AASSLQS (SEQ ID NO:227), YKSDSDKQQGS (SEQ ID NO:262), DASTRAS (SEQ ID NO:248), STNTRSS (SEQ ID NO:33), DASNRAT (SEQ ID NO:271), NTDIRFS (SEQ ID NO:280), RNNDRPS (SEQ ID NO:288);

iii) LC-CDR3: one of MQGLQTPYT (SEQ ID NO:76), MLGTHWPPMYI (SEQ ID NO:85), MQGTHWPLT (SEQ ID NO:95), MQALQTPWT (SEQ ID NO:103), MQGTHWPPT (SEQ ID NO:112), QHYGSSRT (SEQ ID NO:122), MAGLQTPRLT (SEQ ID NO:130), LLYYGGARV (SEQ ID NO:140), MQALQTPLT (SEQ ID NO:147), QQYGSSPRT (SEQ ID NO:163), MHALSTPPWT (SEQ ID NO:172), MQGTHWPGT (SEQ ID NO:180), GTWDSYLNIVV (SEQ ID NO:188), ELYMGSGISV (SEQ ID NO:196), MQGTHWPQT (SEQ ID NO:205), MQALQTPRT (SEQ ID NO:219), QQANSFPPT (SEQ ID NO:228), QQYGSSSA (SEQ ID NO:233), MIWHSSAWV (SEQ ID NO:263), QHYGTSPFI (SEQ ID NO:249), VLYMGNGISV (SEQ ID NO:256), QQRSNWPLT (SEQ ID NO:272), VLYMGSGISV (SEQ ID NO:23), SAWDSSLKVQV (SEQ ID NO:289);

iv) HC-CDR1: one of SYGMH (SEQ ID NO:77), SAAAAWN (SEQ ID NO:86), SYAMH (SEQ ID NO:96), SFAMN (SEQ ID NO:113), SYGIS (SEQ ID NO:123), SYAMS (SEQ ID NO:131), SYAIS (SEQ ID NO:148), TYTMH (SEQ ID NO:173), GYYWS (SEQ ID NO:30), SYWIG (SEQ ID NO:197), NYGMH (SEQ ID NO:234), SYAIH (SEQ ID NO:241), SSSYYWG (SEQ ID NO:24), DYYIH (SEQ ID NO:281);

v) HC-CDR2: one of VISYDGSNKYYADSVKG (SEQ ID NO:78), RTYYRSKWYSEYAVSVKS (SEQ ID NO:87), WINAGNGNTKYSQKFQG (SEQ ID NO:104), TIGGSGDSTFYADPVKG (SEQ ID NO:114), WISAYNGNTNYAQKLQG (SEQ ID NO:124), AISGSGGSTYYADSVKG (SEQ ID NO:132), GIPIFGTANYAQKFQG (SEQ ID NO:149), GINWNGGSTGYADSVKG (SEQ ID NO:164), WITPGNGNTHYSQNFQG (SEQ ID NO:174), EINHSGSTNYNPSLKS (SEQ ID NO:31), IIPGDS DTRYSPSFQG (SEQ ID NO:198), AISSNGGSTYYADSVKG (SEQ ID NO:206), VISYDESNKYYADSVKG (SEQ ID NO:220), FISYDGTNKYYADSVKG (SEQ ID NO:235), SIYYSGSTYYNPSLKS (SEQ ID NO:25), VIWYDGSNKYYADSVKG (SEQ ID NO:264), SSSSSSYIYYADSVKG (SEQ ID NO:273), WVSAYNGDTNYAQKFQG (SEQ ID NO:282);

vi) HC-CDR3: one of DLFAVVGYYYYYGMDV (SEQ ID NO:79), GSIFDV (SEQ ID NO:88), SRGYYGMDV (SEQ ID NO:97), GGYLVGY (SEQ ID NO:105), AYGSGGHYFFAY (SEQ ID NO:115), DWGSSWSDY (SEQ ID NO:125), TYYDFWSGRVGAFDI (SEQ ID NO:133), DRGYYGMDV (SEQ ID NO:141), GRGSGYPDTWFWFDP (SEQ ID NO:150), SYGSGSYRSHAFDI (SEQ ID NO:156), GLVPAASMDV (SEQ ID NO:165), SRVGALDY (SEQ ID NO:175), SRGYSGYDN (SEQ ID NO:181), GLPYYYFDY (SEQ ID NO:189), LGYGVPLPEYFDL (SEQ ID NO:199), EPSGWSYLYYYYYYGMDV (SEQ ID NO:221), HYGDYYYYYGMDV (SEQ ID NO:236), VYGYGLHYYGMDV (SEQ ID NO:242),

SYDSSGYYYFDY (SEQ ID NO:250), YAPDSSGYLVAFDI (SEQ ID NO:26), MTTEDY (SEQ ID NO:265), DGSAWSRPY (SEQ ID NO:274), EIASYSGSYDY (SEQ ID NO:20), GADWNSDY (SEQ ID NO:290);

or a variant thereof in which one or two or three amino acids in one or more of the sequences (i) to (vi) are replaced with another amino acid.

5

In another example of the present disclosure an antibody, antigen binding fragment, or polypeptide which is capable of binding to HER2, optionally isolated, is provided comprising a heavy chain and a light chain variable region sequence, wherein:

the light chain comprises a LC-CDR1, LC-CDR2, LC-CDR3, having at least 85% overall sequence identity to LC-CDR1: one of RSSQSLHSDGNKYLD (SEQ ID NO:74), RSSQSLHSDGNKYLD (SEQ ID NO:84), RSSQSLVYSDGNTYLN (SEQ ID NO:93), RSSQSLHSDNGYNYLD (SEQ ID NO:102), RSSQSLHSDNGNTYLD (SEQ ID NO:110), RASQSVRNLA (SEQ ID NO:120), GSTTGAVTSGHYPS (SEQ ID NO:138), RASQSVSSSYLA (SEQ ID NO:161), RSSQSLQHSNGYQYLD (SEQ ID NO:170), TGRSANIGGFVDQ (SEQ ID NO:186), ALTSGSVSTSYPS (SEQ ID NO:194), TSSQSLVYSDGNTYLN (SEQ ID NO:211), RSSQSLRSDGYNFVD (SEQ ID NO:217), RASQGISSWLA (SEQ ID NO:226), RASRSVGKYLA (SEQ ID NO:247), GLSSGSVSTTYPS (SEQ ID NO:255), TLRSGINVGTYRIY (SEQ ID NO:261), RASQSVSSSYLA (SEQ ID NO:270), GLTSGAVSSSYPS (SEQ ID NO:279), TGNNNNVGFAGAA (SEQ ID NO:287);

LC-CDR2: one of LGSNRAS (SEQ ID NO:75), KVSNRDS (SEQ ID NO:94), SGSNRAS (SEQ ID NO:111); YASTRAT (SEQ ID NO:121), STSNKHS (SEQ ID NO:139), LGSHRAS (SEQ ID NO:146), LGSNRAP (SEQ ID NO:155), GASSRAT (SEQ ID NO:162), LGSFRAS (SEQ ID NO:171), DNSNRPS (SEQ ID NO:187), STNLRSS (SEQ ID NO:195), KVSDRDS (SEQ ID NO:204), KVSKRDS (SEQ ID NO:212), LGSDRAS (SEQ ID NO:218), AASSLQS (SEQ ID NO:227), YKSDSDKQQGS (SEQ ID NO:262), DASTRAS (SEQ ID NO:248), STNTRSS (SEQ ID NO:33), DASNRAT (SEQ ID NO:271), NTDIRFS (SEQ ID NO:280), RNNDRPS (SEQ ID NO:288);

LC-CDR3: one of MQGLQTPYT (SEQ ID NO:76), MLGTHWPPMYI (SEQ ID NO:85), MQGTHWPLT (SEQ ID NO:95), MQALQTPWT (SEQ ID NO:103), MQGTHWPPT (SEQ ID NO:112), QHYGSSRT (SEQ ID NO:122), MAGLQTPRLT (SEQ ID NO:130), LLYYGGARV (SEQ ID NO:140), MQALQTPLT (SEQ ID NO:147), QQYGSSPRT (SEQ ID NO:163), MHALSTPPWT (SEQ ID NO:172), MQGTHWPGT (SEQ ID NO:180), GTWDSYLNWV (SEQ ID NO:188), ELYMGSGISV (SEQ ID NO:196), MQGTHWPQT (SEQ ID NO:205), MQALQTPRT (SEQ ID NO:219), QQANSFPPT (SEQ ID NO:228), QQYGSSSA (SEQ ID NO:233), MIWHSSAWV (SEQ ID NO:263), QHYGTSPFPI (SEQ ID NO:249), VLYMGNGISV (SEQ ID NO:256), QQRSNWPLT (SEQ ID NO:272), VLYMGSGISV (SEQ ID NO:23), SAWDSSLKVQV (SEQ ID NO:289), and;

the heavy chain comprises a HC-CDR1, HC-CDR2, HC-CDR3, having at least 85% overall sequence identity to HC-CDR1: one of SYGMH (SEQ ID NO:77), SAAAAWN (SEQ ID NO:86), SYAMH (SEQ ID NO:96), SFAMN (SEQ ID NO:113), SYGIS (SEQ ID NO:123), SYAMS (SEQ ID NO:131), SYAIS (SEQ ID NO:148), TYTMH (SEQ ID NO:173), GYYWS (SEQ ID NO:30), SYWIG (SEQ ID NO:197), NYGMH (SEQ ID NO:234), SYAIH (SEQ ID NO:241), SSSYYWG (SEQ ID NO:24), DYYIH (SEQ ID NO:281);

40

HC-CDR2: one of VISYDGSNKYYADSVKG (SEQ ID NO:78), RTYYRSKWYSEYAVSVKS (SEQ ID NO:87), WINAGNGNTKYSQKFQG (SEQ ID NO:104), TIGSGDSTFYADPVKG (SEQ ID NO:114), WISAYNGNTNYAQKLQG (SEQ ID NO:124), AISGSGGSTYYADSVKG (SEQ ID NO:132), GIPIFGTANYAQKFQG (SEQ ID NO:149), GINWNGGSTGYADSVKG (SEQ ID NO:164), WITPGNGNTHYSQNFQG (SEQ ID NO:174), EINHSGSTNYPNPSLKS (SEQ ID NO:31), IIPGSDSTRYSPSFQG (SEQ ID NO:198), AISSNGGSTYYADSVKG (SEQ ID NO:206), VISYDESNKYYADSVKG (SEQ ID NO:220), FISYDGTNKYYADSVKG (SEQ ID NO:235), SIYSGSTYYNPSLKS (SEQ ID NO:25), VIWYDGSNKYYADSVKG (SEQ ID NO:264), SSSSSSYIYYADSVKG (SEQ ID NO:273), WVSAYNGDTNYAQKFQG (SEQ ID NO:282);

HC-CDR3: one of DLFAVVGYYYYYGMDV (SEQ ID NO:79), GSIFDV (SEQ ID NO:88), SRGYGMDV (SEQ ID NO:97), GGYLVGY (SEQ ID NO:105), AYGSGGHYFFAY (SEQ ID NO:115), DWGSSWSDY (SEQ ID NO:125), TYYDFWSGRVGAFDI (SEQ ID NO:133), DRGYGMDV (SEQ ID NO:141), GRGSGYPDTWFWFDP (SEQ ID NO:150), SYGSGSYRSHAFDI (SEQ ID NO:156), GLVPAASMDV (SEQ ID NO:165), SRVGALDY (SEQ ID NO:175), SRGYSGYDN (SEQ ID NO:181), GLPYFFDY (SEQ ID NO:189), LGYGVPLPEYFDL (SEQ ID NO:199), EPSGSWSYLYYYYYGMDV (SEQ ID NO:221), HYGDYYYYYGMDV (SEQ ID NO:236), VYGYGLHYGMDV (SEQ ID NO:242), SYDSSGYFFDY (SEQ ID NO:250), YAPDSSGYLVAFDI (SEQ ID NO:26), MTTEDY (SEQ ID NO:265), DGSAWSRPY (SEQ ID NO:274), EIASYSGSYDY (SEQ ID NO:20), GADWNSDY (SEQ ID NO:290).

In some examples the degree of sequence identity may be one of 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%.

In some examples the antibody, antigen binding fragment or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLLHSNGFNLYD (SEQ ID NO:74), LC-CDR2: LGSNRAS (SEQ ID NO:75), LC-CDR3: MQGLQTPYT (SEQ ID NO:76). In some examples the antibody, antigen binding fragment or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYGMH (SEQ ID NO:77), HC-CDR2: VISYDGSNKYYADSVKG (SEQ ID NO:78), HC-CDR3: DLFAVVGYYYYYGMDV (SEQ ID NO:79). In some examples the antibody, antigen binding fragment or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLLHSNGFNLYD (SEQ ID NO:74), LC-CDR2: LGSNRAS (SEQ ID NO:75), LC-CDR3: MQGLQTPYT (SEQ ID NO:76), and at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYGMH (SEQ ID NO:77), HC-CDR2: VISYDGSNKYYADSVKG (SEQ ID NO:78), HC-CDR3: DLFAVVGYYYYYGMDV (SEQ ID NO:79).

In some examples the antibody, antigen binding fragment or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLLHSDGNKYLD (SEQ ID NO:84), LC-CDR2: LGSNRAS (SEQ ID NO:75), LC-CDR3: MLGTHWPPMYI (SEQ ID NO:85). In some examples the antibody, antigen binding fragment or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SAAAAWN (SEQ ID NO:86), HC-CDR2: RTYYRSKWYSEYAVSVKS (SEQ ID NO:87), HC-CDR3: GSIFDV (SEQ ID NO:88). In some examples the

antibody, antigen binding fragment or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLHSDGNKYLD (SEQ ID NO:84), LC-CDR2: LGSNRAS (SEQ ID NO:75), LC-CDR3: MLGTHWPPMYI (SEQ ID NO:85), and at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SAAAAWN (SEQ ID NO:86), HC-CDR2: RTYYRSKWYSEYAVSVKS (SEQ ID NO:87), HC-CDR3: GSIFDV (SEQ ID NO:88).

In some examples the antibody, antigen binding fragment or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLVYSDGNTYLN (SEQ ID NO:93), LC-CDR2: KVSNRDS (SEQ ID NO:94), LC-CDR3: MQGTHWPLT (SEQ ID NO:95). In some examples the antibody, antigen binding fragment or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMH (SEQ ID NO:96), HC-CDR2: VISYDGSNKYYADSVKG (SEQ ID NO:78), HC-CDR3: SRGYGMDV (SEQ ID NO:97). In some examples the antibody, antigen binding fragment or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLVYSDGNTYLN (SEQ ID NO:93), LC-CDR2: KVSNRDS (SEQ ID NO:94), LC-CDR3: MQGTHWPLT (SEQ ID NO:95), and at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMH (SEQ ID NO:96), HC-CDR2: VISYDGSNKYYADSVKG (SEQ ID NO:78), HC-CDR3: SRGYGMDV (SEQ ID NO:97).

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLHSDGNYLYD (SEQ ID NO:102), LC-CDR2: LGSNRAS (SEQ ID NO:75), LC-CDR3: MQALQTPWT (SEQ ID NO:103). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMH (SEQ ID NO:96), HC-CDR2: WINAGNGNTKYSQKFQG (SEQ ID NO:104), HC-CDR3: GGYLVGY (SEQ ID NO:105). In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLHSDGNYLYD (SEQ ID NO:102), LC-CDR2: LGSNRAS (SEQ ID NO:75), LC-CDR3: MQALQTPWT (SEQ ID NO:103), and at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMH (SEQ ID NO:96), HC-CDR2: WINAGNGNTKYSQKFQG (SEQ ID NO:104), HC-CDR3: GGYLVGY (SEQ ID NO:105).

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLHSDGNTYLYD (SEQ ID NO:110), LC-CDR2: SGSNRAS (SEQ ID NO:111), LC-CDR3: MQGTHWPPT (SEQ ID NO:112). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SFAMN (SEQ ID NO:113), HC-CDR2: TIGGSGDSTFYADPVKG (SEQ ID NO:114), HC-CDR3: AYGSGGHYFFAY (SEQ ID NO:115). In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLHSDGNTYLYD (SEQ ID NO:110), LC-CDR2: SGSNRAS (SEQ ID NO:111), LC-CDR3: MQGTHWPPT (SEQ ID NO:112), and at least one heavy chain

variable region incorporating the following CDRs: HC-CDR1: SFAMN (SEQ ID NO:113), HC-CDR2: TIGGSGDSTFYADPVKG (SEQ ID NO:114), HC-CDR3: AYGSGGHYFFAY (SEQ ID NO:115).

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RASQSVRNLA (SEQ ID NO:120), LC-CDR2: YASTRAT (SEQ ID NO:121), LC-CDR3: QHYGSSRT (SEQ ID NO:122). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYGIS (SEQ ID NO:123), HC-CDR2:

WISAYNGNTNYAQLQG (SEQ ID NO:124), HC-CDR3: DWGSSWSDY (SEQ ID NO:125). In some

examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RASQSVRNLA (SEQ ID NO:120), LC-CDR2: YASTRAT (SEQ ID NO:121), LC-CDR3: QHYGSSRT (SEQ ID NO:122), and at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYGIS (SEQ ID NO:123), HC-CDR2: WISAYNGNTNYAQLQG (SEQ ID NO:124), HC-CDR3: DWGSSWSDY (SEQ ID NO:125).

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLHNSNGYNYLD (SEQ ID NO:102), LC-CDR2: LGSNRAS (SEQ ID NO:75), LC-CDR3: MAGLQTPRLT (SEQ ID NO:130). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMS (SEQ ID NO:131), HC-CDR2:

AISGSGGSTYYADSVKG (SEQ ID NO:132), HC-CDR3: TYYDFWSGRVGAFDI (SEQ ID NO:133). In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLHNSNGYNYLD (SEQ ID NO:102), LC-CDR2:

LGSNRAS (SEQ ID NO:75), LC-CDR3: MAGLQTPRLT (SEQ ID NO:130), and at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMS (SEQ ID NO:131), HC-CDR2:

AISGSGGSTYYADSVKG (SEQ ID NO:132), HC-CDR3: TYYDFWSGRVGAFDI (SEQ ID NO:133).

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: GSTTGAVTSGHYPS (SEQ ID NO:138), LC-CDR2: STSNKHS (SEQ ID NO:139), LC-CDR3: LLYYGGARV (SEQ ID NO:140). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYGMH (SEQ ID NO:77), HC-CDR2:

VISYDGSNKYYADSVKG (SEQ ID NO:78), HC-CDR3: DRGYGMDV (SEQ ID NO:141). In some

examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: GSTTGAVTSGHYPS (SEQ ID NO:138), LC-CDR2: STSNKHS (SEQ ID NO:139), LC-CDR3: LLYYGGARV (SEQ ID NO:140), and at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYGMH (SEQ ID NO:77), HC-CDR2: VISYDGSNKYYADSVKG (SEQ ID NO:78), HC-CDR3: DRGYGMDV (SEQ ID NO:141).

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLLHSNGYNYLD (SEQ ID NO:102), LC-CDR2: LGSHRAS (SEQ ID NO:146), LC-CDR3: MQALQTPLT (SEQ ID NO:147). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAIS (SEQ ID NO:148), HC-CDR2: GIIPFGTANYAQKFQG (SEQ ID NO:149), HC-CDR3: GRGSGYPDTWFWFDP (SEQ ID NO:150). In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLLHSNGYNYLD (SEQ ID NO:102), LC-CDR2: LGSHRAS (SEQ ID NO:146), LC-CDR3: MQALQTPLT (SEQ ID NO:147), and at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAIS (SEQ ID NO:148), HC-CDR2: GIIPFGTANYAQKFQG (SEQ ID NO:149), HC-CDR3: GRGSGYPDTWFWFDP (SEQ ID NO:150).

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLLHSNGYNYLD (SEQ ID NO:102), LC-CDR2: LGSNRAP (SEQ ID NO:155), LC-CDR3: MQGTHWPLT (SEQ ID NO:95). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMH (SEQ ID NO:96), HC-CDR2: VISYDGSNKYYADSVKG (SEQ ID NO:78), HC-CDR3: SYGSGSYRSHAFDI (SEQ ID NO:156). In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLLHSNGYNYLD (SEQ ID NO:102), LC-CDR2: LGSNRAP (SEQ ID NO:155), LC-CDR3: MQGTHWPLT (SEQ ID NO:95), and has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMH (SEQ ID NO:96), HC-CDR2: VISYDGSNKYYADSVKG (SEQ ID NO:78), HC-CDR3: SYGSGSYRSHAFDI (SEQ ID NO:156).

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RASQSVSSSYLA (SEQ ID NO:161), LC-CDR2: GASSRAT (SEQ ID NO:162), LC-CDR3: QQYGSSPRT (SEQ ID NO:163). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMS (SEQ ID NO:131), HC-CDR2: GINWNGGSTGYADSVKG (SEQ ID NO:164), HC-CDR3: GLVPAASMDV (SEQ ID NO:165). In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RASQSVSSSYLA (SEQ ID NO:161), LC-CDR2: GASSRAT (SEQ ID NO:162), LC-CDR3: QQYGSSPRT (SEQ ID NO:163), and has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMS (SEQ ID NO:131), HC-CDR2: GINWNGGSTGYADSVKG (SEQ ID NO:164), HC-CDR3: GLVPAASMDV (SEQ ID NO:165).

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLQHSNGYQYLD (SEQ ID NO:170), LC-CDR2: LGSFRAS (SEQ ID NO:171), LC-CDR3: MHALSTPPWT (SEQ ID NO:172). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region

incorporating the following CDRs: HC-CDR1: TYTMH (SEQ ID NO:173), HC-CDR2: WITPGNGNTHYSQNFQG (SEQ ID NO:174), HC-CDR3: SRVGALDY (SEQ ID NO:175). In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLQHSHNGYQYLD (SEQ ID NO:170), LC-CDR2: LGSFRAS (SEQ ID NO:171), LC-CDR3: MHALSTPPWT (SEQ ID NO:172), and has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: TYTMH (SEQ ID NO:173), HC-CDR2: WITPGNGNTHYSQNFQG (SEQ ID NO:174), HC-CDR3: SRVGALDY (SEQ ID NO:175).

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLVYSDGNTYLN (SEQ ID NO:93), LC-CDR2: KVSNRDS (SEQ ID NO:94), LC-CDR3: MQGTHWPGT (SEQ ID NO:180). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYGMH (SEQ ID NO:77), HC-CDR2: VISYDGSNKYYADSVKG (SEQ ID NO:78), HC-CDR3: SRGYSGYDN (SEQ ID NO:181). In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLVYSDGNTYLN (SEQ ID NO:93), LC-CDR2: KVSNRDS (SEQ ID NO:94), LC-CDR3: MQGTHWPGT (SEQ ID NO:180), and has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYGMH (SEQ ID NO:77), HC-CDR2: VISYDGSNKYYADSVKG (SEQ ID NO:78), HC-CDR3: SRGYSGYDN (SEQ ID NO:181).

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: TGRSANIGGFQDVQ (SEQ ID NO:186), LC-CDR2: DNSNRPS (SEQ ID NO:187), LC-CDR3: GTWDSYLNIVV (SEQ ID NO:188). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: GYYWS (SEQ ID NO:30), HC-CDR2: EINHSGSTNYPNLSLKS (SEQ ID NO:31), HC-CDR3: GLPYYYFDY (SEQ ID NO:189). In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: TGRSANIGGFQDVQ (SEQ ID NO:186), LC-CDR2: DNSNRPS (SEQ ID NO:187), LC-CDR3: GTWDSYLNIVV (SEQ ID NO:188), and has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: GYYWS (SEQ ID NO:30), HC-CDR2: EINHSGSTNYPNLSLKS (SEQ ID NO:31), HC-CDR3: GLPYYYFDY (SEQ ID NO:189).

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: ALTSGSVSTSYYPYPS (SEQ ID NO:194), LC-CDR2: STNLRSS (SEQ ID NO:195), LC-CDR3: ELYMGSGISV (SEQ ID NO:196). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYWIG (SEQ ID NO:197), HC-CDR2: IYPGDSSTRYSPSFQG (SEQ ID NO:198), HC-CDR3: LYGVPPLPEYFDL (SEQ ID NO:199). In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: ALTSGSVSTSYYPYPS (SEQ ID NO:194), LC-CDR2: STNLRSS

(SEQ ID NO:195), LC-CDR3: ELYMGSGISV (SEQ ID NO:196), and at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYWIG (SEQ ID NO:197), HC-CDR2: ILYPGDSDTRYSPSFQG (SEQ ID NO:198), HC-CDR3: LGYGVPLPEYFDL (SEQ ID NO:199).

5 In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLVYSDGNTYLN (SEQ ID NO:93), LC-CDR2: KVSDRDS (SEQ ID NO:204), LC-CDR3: MQGTHWPQT (SEQ ID NO:205). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMH (SEQ ID NO:96), HC-CDR2:
10 AISSNGGSTYYADSVKG (SEQ ID NO:206), HC-CDR3: SRGYYGMDV (SEQ ID NO:97). In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLVYSDGNTYLN (SEQ ID NO:93), LC-CDR2: KVSDRDS (SEQ ID NO:204), LC-CDR3: MQGTHWPQT (SEQ ID NO:205), and has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMH (SEQ ID NO:96), HC-CDR2:
15 AISSNGGSTYYADSVKG (SEQ ID NO:206), HC-CDR3: SRGYYGMDV (SEQ ID NO:97).

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: TSSQSLVYSDGNTYLN (SEQ ID NO:211), LC-CDR2: KVSKRDS (SEQ ID NO:212), LC-CDR3: MQGTHWPLT (SEQ ID NO:95). In some examples
20 the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMH (SEQ ID NO:96), HC-CDR2: VISYDGSNKYYADSVKG (SEQ ID NO:78), HC-CDR3: SRGYYGMDV (SEQ ID NO:97). In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: TSSQSLVYSDGNTYLN (SEQ ID NO:211), LC-CDR2:
25 KVSKRDS (SEQ ID NO:212), LC-CDR3: MQGTHWPLT (SEQ ID NO:95), and has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMH (SEQ ID NO:96), HC-CDR2: VISYDGSNKYYADSVKG (SEQ ID NO:78), HC-CDR3: SRGYYGMDV (SEQ ID NO:97).

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLLRSDGYNFVD (SEQ ID NO:217), LC-CDR2: LGSDRAS (SEQ ID NO:218), LC-CDR3: MQALQTPRT (SEQ ID NO:219). In some examples
30 the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMH (SEQ ID NO:96), HC-CDR2: VISYDESNKYADSVKG (SEQ ID NO:220), HC-CDR3: EPSGSWSYLYYYYYGMDV (SEQ ID NO:221). In
35 some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLLRSDGYNFVD (SEQ ID NO:217), LC-CDR2: LGSDRAS (SEQ ID NO:218), LC-CDR3: MQALQTPRT (SEQ ID NO:219), and has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMH (SEQ ID NO:96), HC-CDR2: VISYDESNKYADSVKG (SEQ ID NO:220), HC-CDR3: EPSGSWSYLYYYYYGMDV (SEQ ID NO:221).

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RASQGISSWLA (SEQ ID NO:226), LC-CDR2: AASSLQS (SEQ ID NO:227), LC-CDR3: QQANSFPPT (SEQ ID NO:228). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMH (SEQ ID NO:96), HC-CDR2: VISYDGSNKYYADSVKG (SEQ ID NO:78), HC-CDR3: SRGYYGMDV (SEQ ID NO:97). In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RASQGISSWLA (SEQ ID NO:226), LC-CDR2: AASSLQS (SEQ ID NO:227), LC-CDR3: QQANSFPPT (SEQ ID NO:228), and has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMH (SEQ ID NO:96), HC-CDR2: VISYDGSNKYYADSVKG (SEQ ID NO:78), HC-CDR3: SRGYYGMDV (SEQ ID NO:97).

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RASQSVSSSYLA (SEQ ID NO:161), LC-CDR2: GASSRAT (SEQ ID NO:162), LC-CDR3: QQYGSSSA (SEQ ID NO:233). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: NYGMH (SEQ ID NO:234), HC-CDR2: FISYDGTNKYYADSVKG (SEQ ID NO:235), HC-CDR3: HYGDYYYYYGMDV (SEQ ID NO:236). In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RASQSVSSSYLA (SEQ ID NO:161), LC-CDR2: GASSRAT (SEQ ID NO:162), LC-CDR3: QQYGSSSA (SEQ ID NO:233), and has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: NYGMH (SEQ ID NO:234), HC-CDR2: FISYDGTNKYYADSVKG (SEQ ID NO:235), HC-CDR3: HYGDYYYYYGMDV (SEQ ID NO:236).

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLLHSNGYNYLD (SEQ ID NO:102), LC-CDR2: LGSNRAS (SEQ ID NO:75), LC-CDR3: MQGTHWPGT (SEQ ID NO:180). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAIH (SEQ ID NO:241), HC-CDR2: AISSNGGSTYYADSVKG (SEQ ID NO:206), HC-CDR3: VYGYGLHYYGMDV (SEQ ID NO:242). In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLLHSNGYNYLD (SEQ ID NO:102), LC-CDR2: LGSNRAS (SEQ ID NO:75), LC-CDR3: MQGTHWPGT (SEQ ID NO:180), and has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAIH (SEQ ID NO:241), HC-CDR2: AISSNGGSTYYADSVKG (SEQ ID NO:206), HC-CDR3: VYGYGLHYYGMDV (SEQ ID NO:242).

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RASRSVGKYLA (SEQ ID NO:247), LC-CDR2: DASTRAS (SEQ ID NO:248), LC-CDR3: QHYGTSPPI (SEQ ID NO:249). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region

incorporating the following CDRs: HC-CDR1: SYAIS (SEQ ID NO:148), HC-CDR2: GIPIFGTANYAQKFQG (SEQ ID NO:149), HC-CDR3: SYDSSGYYYFDY (SEQ ID NO:250). In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RASRSVGKYLE (SEQ ID NO:247), LC-CDR2: DASTRAS (SEQ ID NO:248),
 5 LC-CDR3: QHYGTSPFFI (SEQ ID NO:249), and has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAIS (SEQ ID NO:148), HC-CDR2: GIPIFGTANYAQKFQG (SEQ ID NO:149), HC-CDR3: SYDSSGYYYFDY (SEQ ID NO:250).

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: GLSSGSVSTTYPS (SEQ ID NO:255), LC-CDR2: STNTRSS (SEQ ID NO:33), LC-CDR3: VLYMGNGISV (SEQ ID NO:256). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SSSYYWG (SEQ ID NO:24), HC-CDR2: SIYYSGSTYYNPSLKS (SEQ ID NO:25), HC-CDR3: YAPDSSGYLVAFDI (SEQ ID NO:26). In some
 10 examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: GLSSGSVSTTYPS (SEQ ID NO:255), LC-CDR2: STNTRSS (SEQ ID NO:33), LC-CDR3: VLYMGNGISV (SEQ ID NO:256), and has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SSSYYWG (SEQ ID NO:24), HC-CDR2: SIYYSGSTYYNPSLKS (SEQ ID NO:25), HC-CDR3: YAPDSSGYLVAFDI (SEQ ID NO:26).
 15

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: TLRSGINVGTYRIY (SEQ ID NO:261), LC-CDR2: YKSDSDKQQGS (SEQ ID NO:262), LC-CDR3: MIWHSSAWV (SEQ ID NO:263). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable
 20 region incorporating the following CDRs: HC-CDR1: SYGMH (SEQ ID NO:77), HC-CDR2: VIWYDGSNKYYADSVKG (SEQ ID NO:264), HC-CDR3: MTTEDY (SEQ ID NO:265). In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: LC-CDR1: TLRSGINVGTYRIY (SEQ ID NO:261), LC-CDR2: YKSDSDKQQGS (SEQ ID NO:262), LC-CDR3: MIWHSSAWV (SEQ ID NO:263), and has at least one
 25 heavy chain variable region incorporating the following CDRs: HC-CDR1: SYGMH (SEQ ID NO:77), HC-CDR2: VIWYDGSNKYYADSVKG (SEQ ID NO:264), HC-CDR3: MTTEDY (SEQ ID NO:265).
 30

In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RASQSVSSYLA (SEQ ID NO:270), LC-CDR2: DASNRAT (SEQ ID NO:271), LC-CDR3: QQRSNWPLT (SEQ ID NO:272). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMS (SEQ ID NO:131), HC-CDR2: SISSSSSYIYADSVKG (SEQ ID NO:273), HC-CDR3: DGSAWSRPY (SEQ ID NO:274). In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-
 35 CDR1: RASQSVSSYLA (SEQ ID NO:270), LC-CDR2: DASNRAT (SEQ ID NO:271), LC-CDR3:
 40

QQRSNWPLT (SEQ ID NO:272), and has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMS (SEQ ID NO:131), HC-CDR2: SISSSSSYIYYADSVKG (SEQ ID NO:273), HC-CDR3: DGSAWSRPY (SEQ ID NO:274).

- 5 In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: GLTSGAVSSSYPS (SEQ ID NO:279), LC-CDR2: NTDIRFS (SEQ ID NO:280), LC-CDR3: VLYMGSGISV (SEQ ID NO:23). In some examples the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: DYYIH (SEQ ID NO:281), HC-CDR2:
- 10 WVSAYNGDTNYAQKFQG (SEQ ID NO:282), HC-CDR3: EIASYSGSYDY (SEQ ID NO:20). In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: GLTSGAVSSSYPS (SEQ ID NO:279), LC-CDR2: NTDIRFS (SEQ ID NO:280), LC-CDR3: VLYMGSGISV (SEQ ID NO:23), and has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: DYYIH (SEQ ID NO:281), HC-CDR2:
- 15 WVSAYNGDTNYAQKFQG (SEQ ID NO:282), HC-CDR3: EIASYSGSYDY (SEQ ID NO:20).

- In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: TGNNNNVGFAGAA (SEQ ID NO:287), LC-CDR2: RNNDRPS (SEQ ID NO:288), LC-CDR3: SAWDSSLKVQV (SEQ ID NO:289). In some examples
- 20 the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAIS (SEQ ID NO:148), HC-CDR2: GIPIFGTANYAQKFQG (SEQ ID NO:149), HC-CDR3: GADWNSDY (SEQ ID NO:290). In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: TGNNNNVGFAGAA (SEQ ID NO:287), LC-CDR2: RNNDRPS (SEQ ID NO:288), LC-
- 25 CDR3: SAWDSSLKVQV (SEQ ID NO:289), and has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAIS (SEQ ID NO:148), HC-CDR2: GIPIFGTANYAQKFQG (SEQ ID NO:149), HC-CDR3: GADWNSDY (SEQ ID NO:290).

- In some examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLHSHNGYNYLD (SEQ ID NO:102), LC-CDR2: LGSNRAP (SEQ ID NO:155), LC-CDR3: MQGTHWPLT (SEQ ID NO:95). In some examples
- 30 the antibody, antigen binding fragment, or polypeptide has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMH (SEQ ID NO:96), HC-CDR2: VISYDGSNKYYADSVKG (SEQ ID NO:78), HC-CDR3: SYGSGSYRSHAFDI (SEQ ID NO:156). In some
- 35 examples the antibody, antigen binding fragment, or polypeptide has at least one light chain variable region incorporating the following CDRs: LC-CDR1: RSSQSLHSHNGYNYLD (SEQ ID NO:102), LC-CDR2: LGSNRAP (SEQ ID NO:155), LC-CDR3: MQGTHWPLT (SEQ ID NO:95), and has at least one heavy chain variable region incorporating the following CDRs: HC-CDR1: SYAMH (SEQ ID NO:96), HC-CDR2: VISYDGSNKYYADSVKG (SEQ ID NO:78), HC-CDR3: SYGSGSYRSHAFDI (SEQ ID NO:156).

In another example of the present disclosure an antibody, antigen binding fragment, or polypeptide which is capable of binding to HER2, optionally isolated, is provided comprising a heavy chain and a light chain variable region sequence, wherein:

the light chain sequence has at least 85% sequence identity to the light chain sequence of SEQ ID NO: 72, 82, 91, 100, 108, 118, 128, 136, 144, 153, 159, 168, 178, 184, 192, 202, 209, 215, 224, 231, 239, 245, 253, 259, 268, 277, 285, or 293, and;

the heavy chain sequence has at least 85% sequence identity to the heavy chain sequence of SEQ ID NO:73, 83, 92, 101, 109, 119, 129, 137, 145, 154, 160, 169, 179, 185, 193, 203, 210, 216, 225, 232, 240, 246, 254, 260, 269, 278, 286, or 294.

In some examples the degree of sequence identity may be one of 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%.

In some examples an isolated light chain variable region polypeptide is provided comprising the following CDRs:

LC-CDR1: one of RSSQSLHSDGNKYLD (SEQ ID NO:74), RSSQSLHSDGNKYLD (SEQ ID NO:84), RSSQSLVSDGNTYLN (SEQ ID NO:93), RSSQSLHSDGNYNYLD (SEQ ID NO:102), RSSQSLHSDGNTYLD (SEQ ID NO:110), RASQSVRNLA (SEQ ID NO:120), GSTTGAVTSGHYPS (SEQ ID NO:138), RASQSVSSSYLA (SEQ ID NO:161), RSSQSLQHSNGYQYLD (SEQ ID NO:170), TGRSANIGGFVDVQ (SEQ ID NO:186), ALTSGSVSTSYYP (SEQ ID NO:194), TSSQSLVSDGNTYLN (SEQ ID NO:211), RSSQSLRSDGYNFVD (SEQ ID NO:217), RASQGISSWLA (SEQ ID NO:226), RASRSVGKYLA (SEQ ID NO:247), GLSSGSVSTTYYP (SEQ ID NO:255), TLRSGINVGTYRIY (SEQ ID NO:261), RASQSVSSSYLA (SEQ ID NO:270), GLTSGAVSSSYYP (SEQ ID NO:279), or TGNNNNVGFAGAA (SEQ ID NO:287);

LC-CDR2: one of LGSNRAS (SEQ ID NO:75), KVSNRDS (SEQ ID NO:94), SGSNRAS (SEQ ID NO:111); YASTRAT (SEQ ID NO:121), STSNKHS (SEQ ID NO:139), LGSHRAS (SEQ ID NO:146), LGSNRAP (SEQ ID NO:155), GASSRAT (SEQ ID NO:162), LGSFRAS (SEQ ID NO:171), DNSNRPS (SEQ ID NO:187), STNLRSS (SEQ ID NO:195), KVSDRDS (SEQ ID NO:204), KVSKRDS (SEQ ID NO:212), LGSDRAS (SEQ ID NO:218), AASSLQS (SEQ ID NO:227), YKSDSDKQQGS (SEQ ID NO:262), DASTRAS (SEQ ID NO:248), STNTRSS (SEQ ID NO:33), DASNRAT (SEQ ID NO:271), NTDIRFS (SEQ ID NO:280), or RNNDRPS (SEQ ID NO:288);

LC-CDR3: one of MQGLQTPYT (SEQ ID NO:76), MLGTHWPPMYI (SEQ ID NO:85), MQGTHWPLT (SEQ ID NO:95), MQALQTPWT (SEQ ID NO:103), MQGTHWPPT (SEQ ID NO:112), QHYGSSRT (SEQ ID NO:122), MAGLQTPRLT (SEQ ID NO:130), LLYYGGARV (SEQ ID NO:140), MQALQTPLT (SEQ ID NO:147), QQYGSSPRT (SEQ ID NO:163), MHALSTPPWT (SEQ ID NO:172), MQGTHWPGT (SEQ ID NO:180), GTWDSYLNIVV (SEQ ID NO:188), ELYMGSGISV (SEQ ID NO:196), MQGTHWPQT (SEQ ID NO:205), MQALQTPRT (SEQ ID NO:219), QQANSFPPT (SEQ ID NO:228), QQYGSSSA (SEQ ID NO:233), MIWHSSAWV (SEQ ID NO:263), QHYGTSPPI (SEQ ID NO:249), VLYMGNGISV (SEQ ID NO:256), QQRSNWPLT (SEQ ID NO:272), VLYMGSGISV (SEQ ID NO:23), or SAWDSSLKVQV (SEQ ID NO:289).

In some examples an isolated heavy chain variable region polypeptide is provided comprising the following CDRs:

HC-CDR1: one of SYGMH (SEQ ID NO:77), SAAAAWN (SEQ ID NO:86), SYAMH (SEQ ID NO:96),
 5 SFAMN (SEQ ID NO:113), SYGIS (SEQ ID NO:123), SYAMS (SEQ ID NO:131), SYAIS (SEQ ID NO:148),
 TYTMH (SEQ ID NO:173), GYYWS (SEQ ID NO:30), SYWIG (SEQ ID NO:197), NYGMH (SEQ ID
 NO:234), SYAIH (SEQ ID NO:241), SSSYYWG (SEQ ID NO:24), or DYYIH (SEQ ID NO:281);
 one of VISYDGSNKYYADSVKG (SEQ ID NO:78), RTYYRSKWYSEYAVSVKS (SEQ ID NO:87),
 10 WINAGNGNTKYSQKFQG (SEQ ID NO:104), TIGSGDSTFYADPVKG (SEQ ID NO:114),
 WISAYNGNTNYAQKLQG (SEQ ID NO:124), AISGSGGSTYYADSVKG (SEQ ID NO:132),
 GIPIFGTANYAQKFQG (SEQ ID NO:149), GINWNGGSTGYADSVKG (SEQ ID NO:164),
 WITPGNGNTHYSQNFQG (SEQ ID NO:174), EINHSGSTNYPNPSLKS (SEQ ID NO:31),
 IIPGSDSTRYSPSFQG (SEQ ID NO:198), AISSNGGSTYYADSVKG (SEQ ID NO:206),
 15 VISYDESNKYYADSVKG (SEQ ID NO:220), FISYDGTNKYYADSVKG (SEQ ID NO:235),
 SIYYSGSTYYNPSLKS (SEQ ID NO:25), VIWYDGSNKYYADSVKG (SEQ ID NO:264),
 SSSSSSYIYYADSVKG (SEQ ID NO:273), or WVSAYNGDTNYAQKFQG (SEQ ID NO:282);
 HC-CDR3: one of DLFAVVGYYYYYGMDV (SEQ ID NO:79), GSIFDV (SEQ ID NO:88),
 SRGYYGMDV (SEQ ID NO:97), GGYLVGY (SEQ ID NO:105), AYGSGGHYFFAY (SEQ ID NO:115),
 DWGSSWSDY (SEQ ID NO:125), TYYDFWSGRVGAFDI (SEQ ID NO:133), DRGYYGMDV (SEQ ID
 20 NO:141), GRGSGYPDTWFWFDP (SEQ ID NO:150), SYGSGSYRSHAFDI (SEQ ID NO:156),
 GLVPAASMDV (SEQ ID NO:165), SRVGALDY (SEQ ID NO:175), SRGYSGYDN (SEQ ID NO:181),
 GLPYYYFDY (SEQ ID NO:189), LGYGVPLPEYFDL (SEQ ID NO:199), EPSGSWSYLYYYYYGMDV (SEQ
 ID NO:221), HYGDYYYYYGMDV (SEQ ID NO:236), VYGYGLHYYGMDV (SEQ ID NO:242),
 SYDSSGYYYFDY (SEQ ID NO:250), YAPDSSGYLVAFDI (SEQ ID NO:26), MTTEDY (SEQ ID NO:265),
 25 DGSAWSRPY (SEQ ID NO:274), EIASYSGSYDY (SEQ ID NO:20), or GADWNSDY (SEQ ID NO:290).

In some examples an antibody, antigen binding fragment or polypeptide of the present disclosure
 comprises any 6 of the CDR sequences described herein. In some examples an antibody, antigen-binding
 fragment or polypeptide comprises any 3 light chain ('LC') CDR sequences described herein, and/or any 3
 30 heavy chain ('HC') CDR sequences described herein.

In some examples the antibody, antigen binding fragment, or polypeptide further comprises variable region
 light chain framework sequences between the CDRs according to the formula: LCFR1-CDR1-LCFR2-
 CDR2-LCFR3-CDR3-LCFR4. The framework sequences may be derived from human consensus
 35 framework sequences.

In some examples the antibody, antigen binding fragment, or polypeptide further comprises variable region
 heavy chain framework sequences between the CDRs according to the formula: HCFR1-CDR1-HCFR2-
 CDR2-HCFR3-CDR3-HCFR4. The framework sequences may be derived from human consensus
 40 framework sequences.

In some examples, the antibody, antibody binding fragment, or polypeptide, may further comprise a human constant region. For example selected from one of IgG1, IgG2, IgG3 and IgG4.

5 In some examples, the antibody, antibody binding fragment, or polypeptide, may further comprise a murine constant region. For example, selected from one of IgG1, IgG2A, IgG2B and IgG3.

10 In another example of the present disclosure, an antibody, antigen binding fragment, or polypeptide conjugated to a drug moiety or a detectable moiety is provided. The drug moiety may be an anti-cancer drug moiety.

15 In another example of the present disclosure a composition is provided. The composition may be, for example, a pharmaceutical composition or medicament. The composition may comprise an antibody, antigen binding fragment, or polypeptide as described herein. The composition may comprise an antibody, antigen binding fragment, or polypeptide as described herein and at least one pharmaceutically-acceptable carrier, excipient, adjuvant or diluent. The composition may comprise an antibody, antigen binding fragment, or polypeptide as described herein and at least one anti-cancer agent, optionally with at least one pharmaceutically-acceptable carrier, excipient, adjuvant or diluent.

20 In another example of the present disclosure, an *in vitro* complex is provided comprising an antibody, or antigen binding fragment, or polypeptide as described herein bound to HER2. The *in vitro* complex may be isolated.

25 In any example of the present disclosure an antibody, antigen binding fragment, or polypeptide as described herein may induce cell death via cell membrane disruption. In any example of the present disclosure an antibody, antigen binding fragment, or polypeptide as described herein may induce cell death by apoptosis. The apoptotic process may proceed through the caspase 3/7 pathway, and optionally involve PARP cleavage. The antibody, antigen binding fragment, or polypeptide as described herein may induce the activation of caspase 3/7 and trigger PARP cleavage. Cell death caused by cell membrane disruption or apoptosis may be induced by an antibody, antigen binding fragment, or polypeptide as described herein binding to HER2.

35 In another example of the present disclosure a nucleic acid, optionally isolated, encoding an antibody, antigen binding fragment, or polypeptide as described herein is provided. The nucleic acid may comprise a sequence of one or more of SEQ ID NOs 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, or 69 or a coding sequence which is degenerate as a result of the genetic code, or may have a nucleotide sequence having at least 70% identity thereto, optionally one of 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%. The nucleic acid may comprise a sequence of one or more of SEQ ID NOs 70, 71, 80, 40 81, 89, 90, 98, 99, 106, 107, 116, 117, 126, 127, 134, 135, 142, 143, 151, 152, 157, 158, 166, 167, 176,

177, 182, 183, 190, 191, 200, 201, 207, 208, 213, 214, 222, 223, 229, 230, 237, 238, 243, 244, 251, 252, 257, 258, 266, 267, 275, 276, 283, 284, 291, or 292, or a coding sequence which is degenerate as a result of the genetic code, or may have a nucleotide sequence having at least 70% identity thereto, optionally one of 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%. A coding sequence which is degenerate as a result of the genetic code refers to a coding sequence which encodes an equivalent polypeptide sequence via redundancy of the genetic code.

In one example of the present disclosure there is provided a vector comprising a nucleic acid described herein. In another example of the present disclosure, there is provided a cell comprising the vector. For example, the cell may be eukaryotic, or mammalian, e.g. Chinese Hamster Ovary (CHO), human or non-human, or may be a prokaryotic cell, e.g. *E. coli*.

In one example of the present disclosure a method for making an antibody, or antigen binding fragment or polypeptide as described herein is provided, the method comprising culturing a cell as described herein under conditions suitable for the expression of an antibody, or antigen binding fragment or polypeptide from a nucleic acid or vector described herein.

In another example of the present disclosure an antibody, antigen binding fragment, polypeptide, conjugate, nucleic acid, vector, cell or composition as described herein is provided for use in therapy, or in a method of medical treatment. An antibody, antigen binding fragment, polypeptide, conjugate, nucleic acid, vector, cell or composition as described herein may be used in a method of medical treatment or prophylaxis.

In another example of the present disclosure an antibody, antigen binding fragment, polypeptide, conjugate, nucleic acid, vector, cell or composition as described herein is provided for use in the treatment of cancer, e.g. is provided for use in a method of treating or preventing cancer. In some examples the cancer is a HER2-positive (HER2+) cancer. In some examples the cancer comprises a HER2-positive tumour cell. In some examples the cancer comprises a HER2-positive tumour. In some examples the treatment comprises administering the antibody, antigen binding fragment, polypeptide or composition in combination with a therapeutic agent. In some examples the therapeutic agent is an anti-cancer agent. In some examples the therapeutic agent is an anti-HER2 antibody. In some examples the therapeutic agent may be trastuzumab or pertuzumab.

In another example of the present disclosure, the use of an antibody, antigen binding fragment, polypeptide or composition as described herein in the manufacture of a medicament for use in the treatment of cancer is provided. In some examples the cancer is a HER2-positive (HER2+) cancer. In some examples the cancer comprises a HER2-positive tumour cell. In some examples the cancer comprises a HER2-positive tumour.

In another example of the present disclosure a method of treating cancer is provided, the method comprising administering an antibody, antigen binding fragment, polypeptide or composition as described

herein to a patient suffering from cancer. In some examples the cancer is a HER2-positive (HER2+) cancer. In some examples the cancer comprises a HER2-positive tumour cell. In some examples the cancer comprises a HER2-positive tumour. In some examples the method comprises administering the antibody, antigen binding fragment, polypeptide or composition in combination with a therapeutic agent. In some examples the therapeutic agent is an anti-cancer agent. In some examples the therapeutic agent is an agent which targets HER2. In some examples the therapeutic agent is an anti-HER2 antibody. In some examples the therapeutic agent may be trastuzumab or pertuzumab.

In another example of the present disclosure a method of inhibiting growth of a tumour cell is provided, comprising administering to the cell an antibody, antigen binding fragment, polypeptide, or composition as described herein. The method may be *in vitro* or *in vivo*. In some examples a method of inhibiting growth of a tumour cell in a subject is provided, the method comprising administering to the subject a therapeutically effective amount of an antibody, antigen binding fragment, polypeptide, or composition as described herein. Also provided is an antibody, antigen binding fragment, polypeptide, or composition as described herein for use in a method of inhibiting growth of a tumour cell in a subject. In some examples the method of inhibiting growth of a tumour cell comprises administering the antibody, antigen binding fragment, polypeptide or composition in combination with a therapeutic agent as described herein.

Also provided is a method of killing a tumour cell, the method comprising administering to the cell an antibody, antigen binding fragment, polypeptide, or composition as described herein. The method may be performed *in vitro* or *in vivo*. In some examples a method of killing a tumour cell in a subject is provided, the method comprising administering to the subject a therapeutically effective amount of an antibody, antigen binding fragment, polypeptide, or composition as described herein. In some examples the method of killing a tumour cell comprises administering the antibody, antigen binding fragment, polypeptide or composition in combination with a therapeutic agent as described herein. Killing of a tumour cell may, for example, be as a result of membrane disruption, cell lysis, induction of apoptosis, antibody dependent cell-mediated cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), or through the action of a drug conjugated to the antibody, antigen binding fragment or polypeptide.

Also provided is an antibody, antigen binding fragment, polypeptide, or composition as described herein for use in a method of killing a tumour cell, e.g. in a subject, as described herein.

In another example of the present disclosure a method is provided comprising contacting a sample containing, or suspected to contain, HER2 with an antibody, antigen binding fragment, or polypeptide as described herein and detecting the formation of a complex of antibody, antigen binding fragment, or polypeptide, and HER2.

In another example of the present disclosure a method of diagnosing a disease or condition in a subject is provided, the method comprising contacting, *in vitro*, a sample from the subject with an antibody, antigen binding fragment, or polypeptide as described herein and detecting the formation of a complex of antibody, antigen binding fragment, or polypeptide, and HER2.

In another example of the present disclosure a method of selecting or stratifying a subject for treatment with HER2 targeted agents is provided, the method comprising contacting, *in vitro*, a sample from the subject with an antibody, antigen binding fragment, or polypeptide as described herein and detecting the formation of a complex of antibody, or antigen binding fragment, and HER2.

In a further example of the present disclosure a use of an antibody, antigen binding fragment, or polypeptide as described herein for the detection of HER2 *in vitro* is provided. In another example of the present disclosure a use of an antibody, antigen binding fragment, or polypeptide as described herein as an *in vitro* diagnostic agent is provided.

In methods of the present disclosure the antibody, antigen binding fragment or polypeptide may be provided as a composition as described herein.

The present disclosure also provides a chimeric antigen receptor (CAR) comprising an antibody, antigen binding fragment or polypeptide according to the present disclosure.

The present disclosure also provides an *in vitro* complex, optionally isolated, comprising a CAR according to the present disclosure bound to HER2.

The present disclosure also provides a nucleic acid, optionally isolated, encoding a CAR according to the present disclosure.

The present disclosure also provides an expression vector comprising a nucleic acid according to the present disclosure.

The present disclosure also provides a cell comprising a CAR, a nucleic acid, or an expression vector according to the present disclosure.

The present disclosure also provides a composition comprising a CAR, a nucleic acid, an expression vector or a cell according to the present disclosure.

The present disclosure also provides a CAR, a nucleic acid, an expression vector, a cell or a composition according to the present disclosure for use in a method of medical treatment or prophylaxis. The present disclosure also provides a CAR, a nucleic acid, an expression vector, a cell or a composition according to the present disclosure for use in a method of treating or preventing cancer.

In any example the antibody may be clone P1A3, P1C5, P1E4, or P1F1 as described herein. In any example the antibody may be clone PFA4, PFB4, PFB5, PFC3, PFD4, PFE1, PFF5, or PFG3 as described

herein. In any example the antibody may be clone PFA1, PFA2, PFA5, PFB1, PFB2, PFB3, PFC2, PFC4, PFD1, PFD2, PFD3, PFE2, PFE5, PFF2, PFF3, PFF4, PFG1, PFG2, PFG4, or PFG5 as described herein.

5 Description

Antibodies and antigen-binding molecules

The present invention provides antibodies and antigen-binding molecules capable of binding to HER2.

10 Antibodies according to the present invention preferably bind to HER2 (the antigen), preferably human or murine HER2, optionally with a K_D in the range 4 to 23 nM.

Antibodies according to the present invention may be provided in isolated form. The antibodies may be provided in substantially purified form.

15 Antibodies according to the present invention may exhibit least one of the following properties:

- a) Binds to human HER2 with a K_D of 1 μ M or less, preferably one of ≤ 100 nM, ≤ 75 nM, ≤ 50 nM, ≤ 40 nM, ≤ 30 nM, ≤ 20 nM, ≤ 15 nM, ≤ 12.5 nM, ≤ 10 nM, ≤ 9 nM, ≤ 8 nM, ≤ 7 nM, ≤ 6 nM, ≤ 5 nM, ≤ 4 nM ≤ 3 nM, ≤ 2 nM, ≤ 1 nM, ≤ 500 pM (e.g. as determined by SPR);
- b) Binds to HER2-overexpressing or HER2-expressing cells, optionally does not bind to HER2-negative cells;
- c) Binds to an epitope of HER2, optionally human HER2, which is different to the epitope of HER2 to which trastuzumab (Herceptin®) binds;
- d) Induces cell death of HER2-expressing cells, optionally by disruption of cell membranes;

20

- e) Induces cell death of HER2-expressing cells by apoptosis, optionally via caspase 3/7 pathway activation and cleaved PARP activation;
- f) Induces cell death of HER2-expressing cells within 40 minutes of application;
- g) Inhibits tumour growth, optionally *in vivo*;
- h) Shows a synergistic effect on inhibition of tumour growth, optionally *in vivo*, optionally when used in combination with trastuzumab or pertuzumab.

By "antibody" we include a fragment or derivative thereof, or a synthetic antibody or synthetic antibody fragment. Fragments and derivatives thereof may be referred to as "antigen-binding molecules" or "antigen-binding fragments".

An "antibody" or "antigen-binding molecule" refers to a molecule which is capable of binding to a target antigen, and encompasses monoclonal antibodies, polyclonal antibodies, monospecific and multispecific antibodies (e.g., bispecific antibodies), and antibody fragments (e.g. Fv, scFv, Fab, scFab, F(ab')₂, Fab₂, diabodies, triabodies, scFv-Fc, minibodies, single domain antibodies (e.g. VhH), etc.), as long as they display binding to the relevant target molecule(s). The antibody/antigen-binding molecule of the present invention comprises a moiety capable of binding to a target antigen(s). In some embodiments, the moiety capable of binding to a target antigen comprises an antibody heavy chain variable region (VH) and an antibody light chain variable region (VL) of an antibody capable of specific binding to the target antigen. In some embodiments, the moiety capable of binding to a target antigen comprises or consists of an aptamer capable of binding to the target antigen, e.g. a nucleic acid aptamer (reviewed, for example, in Zhou and Rossi Nat Rev Drug Discov. 2017 16(3):181-202). In some embodiments, the moiety capable of binding to a target antigen comprises or consists of a antigen-binding peptide/polypeptide, e.g. a peptide aptamer, thioredoxin, monobody, anticalin, Kunitz domain, avimer, knottin, fynomer, atrimer, DARPin, affibody, nanobody (i.e. a single-domain antibody (sdAb)) affilin, armadillo repeat protein (ArmRP), OBody or fibronectin – reviewed e.g. in Reverdatto et al., Curr Top Med Chem. 2015; 15(12): 1082–1101, which is hereby incorporated by reference in its entirety (see also e.g. Boersma et al., J Biol Chem (2011) 286:41273-85 and Emanuel et al., Mabs (2011) 3:38-48).

In view of today's techniques in relation to monoclonal antibody technology, antibodies can be prepared to most antigens. The antigen-binding portion may be a part of an antibody (for example a Fab fragment) or a synthetic antibody fragment (for example a single chain Fv fragment [ScFv]). Suitable monoclonal antibodies to selected antigens may be prepared by known techniques, for example those disclosed in "Monoclonal Antibodies: A manual of techniques ", H Zola (CRC Press, 1988) and in "Monoclonal Hybridoma Antibodies: Techniques and Applications ", J G R Hurrell (CRC Press, 1982). Chimeric antibodies are discussed by Neuberger et al (1988, 8th International Biotechnology Symposium Part 2, 792-799).

Monoclonal antibodies (mAbs) are useful in the methods of the invention and are a homogenous population of antibodies specifically targeting a single epitope on an antigen.

Polyclonal antibodies are useful in the methods of the invention. Monospecific polyclonal antibodies are preferred. Suitable polyclonal antibodies can be prepared using methods well known in the art.

5 Antigen binding fragments of antibodies such as Fab and Fab₂ fragments may also be used and/or provided, as can genetically engineered antibodies and antibody fragments. The variable heavy (V_H) and variable light (V_L) domains of the antibody are involved in antigen recognition, a fact first recognised by early protease digestion experiments. Further confirmation was found by "humanisation" of rodent
10 antibodies. Variable domains of rodent origin may be fused to constant domains of human origin such that the resultant antibody retains the antigenic specificity of the rodent parented antibody (Morrison et al (1984) Proc. Natl. Acad. Sci. USA 81, 6851-6855).

That antigenic specificity is conferred by variable domains and is independent of the constant domains is known from experiments involving the bacterial expression of antibody fragments, all containing one or
15 more variable domains. These molecules include Fab-like molecules (Better et al (1988) Science 240, 1041); Fv molecules (Skerra et al (1988) Science 240, 1038); single-chain Fv (ScFv) molecules where the V_H and V_L partner domains are linked via a flexible oligopeptide (Bird et al (1988) Science 242, 423; Huston et al (1988) Proc. Natl. Acad. Sci. USA 85, 5879) and single domain antibodies (dAbs) comprising isolated V domains (Ward et al (1989) Nature 341, 544). A general review of the techniques involved in the
20 synthesis of antibody fragments which retain their specific binding sites is to be found in Winter & Milstein (1991) Nature 349, 293- 299.

By "ScFv molecules" we mean molecules wherein the V_H and V_L partner domains are covalently linked, e.g. by a flexible oligopeptide.

25 Fab, Fv, ScFv and dAb antibody fragments can all be expressed in and secreted from E. coli, thus allowing the facile production of large amounts of the said fragments. Synthetic antibodies which bind to HER2 may also be made using phage display technology as is well known in the art.

30 Antibodies generally comprise six complementarity-determining regions CDRs; three in the heavy chain variable (V_H) region: HC-CDR1, HC-CDR2 and HC-CDR3, and three in the light chain variable (V_L) region: LC-CDR1, LC-CDR2, and LC-CDR3. The six CDRs together define the paratope of the antibody, which is the part of the antibody which binds to the target antigen.

35 The V_H region and V_L region comprise framework regions (FRs) either side of each CDR, which provide a scaffold for the CDRs. From N-terminus to C-terminus, V_H regions comprise the following structure: N term-[HC-FR1]-[HC-CDR1]-[HC-FR2]-[HC-CDR2]-[HC-FR3]-[HC-CDR3]-[HC-FR4]-C term; and V_L regions comprise the following structure: N term-[LC-FR1]-[LC-CDR1]-[LC-FR2]-[LC-CDR2]-[LC-FR3]-[LC-CDR3]-[LC-FR4]-C term.

There are several different conventions for defining antibody CDRs and FRs, such as those described in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (1991), Chothia et al., J. Mol. Biol. 196:901-917 (1987), VBASE2, as described in Retter et al., Nucl. Acids Res. (2005) 33 (suppl 1): D671-D674, and the international IMGT (ImMunoGeneTics) information system (LeFranc et al., Nucleic Acids Res. (2015) 43 (Database issue):D413-22), which uses the IMGT V-DOMAIN numbering rules as described in Lefranc et al., Dev. Comp. Immunol. (2003) 27:55-77.

In some embodiments, the antibody/antigen-binding molecule comprises the CDRs of an antigen-binding molecule which is capable of binding to HER2. In some embodiments, the antibody/antigen-binding molecule comprises the FRs of an antigen-binding molecule which is capable of binding to HER2. In some embodiments, the antigen-binding molecule comprises the CDRs and the FRs of an antigen-binding molecule which is capable of binding to HER2. That is, in some embodiments the antigen-binding molecule comprises the VH region and the VL region of an antigen-binding molecule which is capable of binding to HER2.

Antibodies may be produced by a process of affinity maturation in which a modified antibody is generated that has an improvement in the affinity of the antibody for antigen, compared to an unmodified parent antibody. Affinity-matured antibodies may be produced by procedures known in the art, e.g., Marks *et al.*, *Rio/Technology* 10:779-783 (1992); Barbas *et al.* *Proc Nat. Acad. Sci. USA* 91:3809-3813 (1994); Schier *et al.* *Gene* 169:147-155 (1995); Yelton *et al.* *J. Immunol.* 155:1994-2004 (1995); Jackson *et al.*, *J. Immunol.* 154(7):331 0-15 9 (1995); and Hawkins *et al.*, *J. Mol. Biol.* 226:889-896 (1992). The antibodies, antigen binding fragments or polypeptides according to the present invention may undergo affinity maturation.

Antibodies, antigen binding fragments or polypeptides according to the present invention preferably exhibit specific binding to HER2. An antibody, antigen binding fragment or polypeptide that specifically binds to a target molecule preferably binds the target with greater affinity, and/or with greater duration than it binds to other targets.

Binding of an antibody, antigen binding fragment or polypeptide according to the present invention to a given molecule can be measured by techniques well known to the person skilled in the art, including ELISA, Surface Plasmon Resonance (SPR; see e.g. Hearty et al., *Methods Mol Biol* (2012) 907:411-442), Bio-Layer Interferometry (see e.g. Lad et al., (2015) *J Biomol Screen* 20(4): 498-507), flow cytometry or by a radioimmunoassay (RIA) enzyme-linked immunosorbent assay. Through such analysis binding to a given target can be measured and quantified. In some embodiments, the binding may be the response detected in a given assay. Binding affinity of an antibody for its target is often described in terms of its dissociation constant (K_D).

The extent of binding of an antibody to an unrelated target may be less than about 10% of the binding of the antibody to the target as measured, e.g., by ELISA, SPR, Bio-Layer Interferometry or by RIA.

Alternatively, the binding specificity may be reflected in terms of binding affinity where the anti-HER2 antibody of the present invention binds to HER2 with a K_D that is at least 0.1 order of magnitude (i.e. 0.1×10^n , where n is an integer representing the order of magnitude) greater than the K_D of the antibody towards another target molecule. This may optionally be one of at least 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5, or 2.0.

Antibodies, antigen binding fragments or polypeptides according to the present invention preferably have a dissociation constant (K_D) of one of $\leq 25\text{nM}$, $\leq 20\text{nM}$, $\leq 15\text{nM}$, $\leq 10\text{nM}$, $\leq 5\text{nM}$, $\leq 3\text{nM}$, $\leq 2\text{nM}$, $\leq 1.5\text{nM}$, $\leq 1.4\text{nM}$, $\leq 1.3\text{nM}$, $\leq 1.25\text{nM}$, $\leq 1.24\text{nM}$, $\leq 1.23\text{nM}$, $\leq 1.22\text{nM}$, $\leq 1.21\text{nM}$, $\leq 1.2\text{nM}$, $\leq 1.15\text{nM}$, $\leq 1.1\text{nM}$, $\leq 1.05\text{nM}$, $\leq 1\text{nM}$, $\leq 900\text{pM}$, $\leq 800\text{pM}$, $\leq 700\text{pM}$, $\leq 600\text{pM}$, or $\leq 500\text{pM}$ as determined by analysis according to SPR, Bio-Layer Interferometry or by RIA. The K_D may be in the range about 0.1 to about 3nM. The K_D may be in the range about 0.1 to about 10 nM. The K_D may be in the range about 0.1 to about 15 nM. The K_D may be in the range about 0.1 to about 25 nM. The K_D may be in the range about 1 to about 100 nM. The K_D may be in the range about 50 to about 500 nM.

The antibodies, antigen-binding fragments or polypeptides according to the present invention may exhibit high binding affinity for HER2. In some embodiments the antibodies, antigen-binding fragments or polypeptides according to the present invention have a dissociation constant (K_D) of 4 to 25 nM. The antibodies, antigen-binding fragments or polypeptides according to the present invention may exhibit intermediate or low binding affinity for HER2. In some embodiments the antibodies, antigen-binding fragments or polypeptides according to the present invention have a dissociation constant (K_D) of 12 to 350 nM. In some embodiments the antibodies, antigen-binding fragments or polypeptides according to the present invention have a dissociation constant (K_D) of 14 to 310 nM. In some embodiments the antibodies, antigen-binding fragments or polypeptides according to the present invention have a dissociation constant (K_D) of 25 to 310 nM. In some embodiments the antibodies, antigen-binding fragments or polypeptides according to the present invention have a dissociation constant (K_D) of 150 to 310 nM.

Antibodies, antigen binding fragments, or polypeptides of the present invention preferably bind to HER2-overexpressing or HER2-expressing cells. Antibodies, antigen binding fragments, or polypeptides may preferably bind to HER2-overexpressing cells. Preferably, antibodies, antigen binding fragments, or polypeptides as described herein do not bind to HER2-negative cells, i.e. cells that do not express HER2.

Antibodies, antigen binding fragments, or polypeptides of the present invention preferably bind to a HER2 epitope different to that bound by trastuzumab (Herceptin®). Trastuzumab is reported to bind at the C-terminal portion of subdomain IV of the HER2 extracellular domain (Cho et al., (2003) Nature 421: 756-760). Epitope binding assays can be performed by methods known in the art, such as by SPR as described herein (see e.g. Hearty et al., Methods Mol Biol (2012) 907:411-442). Briefly, the antibody of interest is immobilised on the SPR microchip, a flow of recombinant HER-2 is applied to bind to the immobilised

antibody, then the other antibodies of interest are flown and their binding measured. Dendrogram traces can identify whether antibodies of interest share a common epitopes with trastuzumab (similar binding profile), or bind to different epitopes (different binding profile), as described herein. In some embodiments antibodies, antigen binding fragments, or polypeptides of the present invention preferably bind to a HER2 epitope different to that bound by pertuzumab (Perjeta).

Antibodies, antigen binding fragments, or polypeptides of the present invention preferably induce cell death of HER2-expressing cells. In some embodiments the antibodies, antigen binding fragments, or polypeptides of the present invention induce cell death by disrupting the cell membrane. Cell death can be measured using methods well known in the art and described herein, such as by staining with propidium iodide. Insertion of propidium iodide into a cell indicates cell lysis.

In some embodiments the antibodies, antigen binding fragments, or polypeptides of the present invention induce cell death of HER2-expressing cells by apoptosis. Apoptosis can be measured using methods well known in the art and described herein, such as by staining with Annexin-V and propidium iodide. Cells stained with Annexin-V are apoptotic.

The caspase 3/7 pathway is involved in the apoptotic process. After activation caspase 3/7 activates cleaved PARP in the nucleus which in its turn can trigger the release of pro-apoptotic factors by mitochondria and can block the processes of DNA repair. In some embodiments the antibodies, antigen binding fragments, or polypeptides of the present invention induce cell death of HER2-expressing cells by apoptosis via caspase 3/7 pathway activation and cleaved PARP activation. Caspase 3/7 pathway activation and cleaved PARP activation can be measured using methods well known in the art.

In some embodiments the antibodies, antigen binding fragments, or polypeptides of the present invention induce cell death of HER2-expressing cells within 40 minutes of application. Induced cell death may be measured by propidium iodide uptake.

Antibodies, antigen binding fragments, or polypeptides of the present invention preferably inhibit tumour growth. In some embodiments the inhibition of tumour growth is *in vivo*. Tumour growth may be measured by methods well known in the art and as described herein, for example using a cell proliferation assay. In some embodiments the antibodies, antigen binding fragments, or polypeptides of the present invention show a synergistic effect on inhibition of tumour growth. In some embodiments the antibodies, antigen binding fragments, or polypeptides of the present invention show a synergistic effect on inhibition of tumour growth when used in combination with trastuzumab and/or pertuzumab. In some embodiments the antibodies, antigen binding fragments, or polypeptides of the present invention are capable of inducing death of HER2-expressing cells at a similar efficiency to that induced by trastuzumab and/or pertuzumab. In some embodiments the antibodies, antigen binding fragments, or polypeptides of the present invention are capable of inducing death of HER2-expressing cells at an increased efficiency to that induced by trastuzumab and/or pertuzumab. In some embodiments the antibodies, antigen binding fragments, or

polypeptides of the present invention are capable of inducing antibody dependent cell-mediated cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC), measured for example by LDH release by Promega Cytotox 96 non-radioactive cytotoxicity assay kit.

5 In some embodiments the antibodies, antigen binding fragments, or polypeptides of the present invention are capable of reducing tumour size e.g. compared to the size of a tumour not treated with an antibody, antigen binding fragment, or polypeptide of the present invention.

10 In some embodiments the antibodies, antigen binding fragments, or polypeptides of the present invention are capable of conferring long-term protection against cancer, cancer cells, tumours and/or tumour cells after administration of the antibodies, antigen binding fragments, or polypeptides ends. The protection conferred may be longer than other HER2 therapies known in the art, e.g. trastuzumab or pertuzumab. The present invention provides antigen-binding polypeptides. In aspects of the present invention the antigen-binding polypeptides are capable of binding to HER2. The polypeptides may be provided in
15 isolated or substantially purified form.

An "antigen-binding polypeptide" refers to a polypeptide which is capable of binding to a target molecule, and encompasses monoclonal antibodies, polyclonal antibodies, monospecific and multispecific antibodies (e.g., bispecific antibodies), and antibody fragments, as long as they display binding to the relevant target
20 molecule(s). An antigen-binding polypeptide as used herein also refers to a non-covalent or covalent complex of more than one polypeptide (e.g. 2, 3, 4, 6, or 8 polypeptides), e.g. a bispecific antigen-binding polypeptide comprising two heavy chain polypeptides and two light chain polypeptides.

25 The antigen-binding polypeptides described herein preferably display specific binding to the relevant target (e.g. HER2). As used herein, "specific binding" refers to binding which is selective for the antigen, and which can be discriminated from non-specific binding to non-target antigen. An antigen-binding polypeptide that specifically binds to a target molecule preferably binds the target with greater affinity, and/or with greater duration than it binds to other, non-target molecules.

30 In some embodiments, the antigen-binding polypeptide binds to the same or an overlapping epitope of the target molecule as a reference antigen-binding polypeptide which is capable of binding to the target molecule (i.e. HER2). In some embodiments, the antigen-binding polypeptide displays competitive binding with a reference antigen-binding polypeptide which is capable of binding to the target molecule. Whether a given antigen-binding polypeptide displays such competitive binding can be determined by various
35 methods known to the skilled person, including competition ELISA.

In some embodiments, the antigen-binding polypeptide comprises the complementarity-determining regions (CDRs) of an antigen-binding polypeptide which is capable of binding to the target molecule (i.e. HER2). Antibodies generally comprise six CDRs; three in the light chain variable region (VL): LC-CDR1,
40 LC-CDR2, LC-CDR3, and three in the heavy chain variable region (VH): HC-CDR1, HC-CDR2 and HC-

CDR3. The six CDRs together define the paratope of the antibody, which is the part of the antibody which binds to the target molecule. There are several different conventions for defining antibody CDRs, such as those described in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (1991), Chothia et al., J. Mol. Biol. 196:901-917 (1987), and VBASE2, as described in Retter et al., Nucl. Acids Res. (2005) 33 (suppl 1): D671-D674. Unless otherwise specified, CDRs of the antigen-binding polypeptides described herein are defined according to Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (1991).

In the present specification where a polypeptide comprises more than one domain or region, it will be appreciated that the plural domains/regions are preferably present in the same polypeptide chain. That is, the polypeptide comprises more than one domain or region is a fusion polypeptide comprising the domains/regions.

The antigen-binding polypeptide may be designed and prepared using the sequences of monoclonal antibodies (mAbs) capable of binding to HER2. Antigen-binding regions of antibodies, such as single chain variable fragment (scFv), Fab and Fab2 fragments may also be used/provided. An 'antigen-binding region' is any fragment of an antibody which is capable of binding to the target for which the given antibody is specific.

In some embodiments, the antigen-binding polypeptide of the present invention is a HER2-binding polypeptide. In some embodiments, the antigen-binding polypeptide comprises or consists of a HER2-binding polypeptide. In some embodiments the antigen-binding polypeptide comprises a heavy chain variable (VH) region comprising HC-CDR1, HC-CDR2 and HC-CDR3 of a HER2-binding antibody clone described herein, or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, HC-CDR3 are substituted with another amino acid. In some embodiments the antigen-binding polypeptide comprises a light chain variable (VL) region comprising LC-CDR1, LC-CDR2 and LC-CDR3 of a HER2-binding antibody clone described herein, or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, LC-CDR3 are substituted with another amino acid. In some embodiments the antigen-binding polypeptide comprises a VH region comprising HC-CDR1, HC-CDR2 and HC-CDR3 and a VL region comprising LC-CDR1, LC-CDR2 and LC-CDR3 of a HER2-binding antibody clone described herein, or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, HC-CDR3, LC-CDR1, LC-CDR2 or LC-CDR3 are substituted with another amino acid.

In some embodiments the antigen-binding polypeptide comprises a VH region which comprises or consists of an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to VH region of a HER2-binding antibody clone described herein. In some embodiments the antigen-binding polypeptide comprises a VL region which comprises or consists of an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%,

95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to VL region of a HER2-binding antibody clone described herein. In some embodiments the antigen-binding polypeptide comprises a VH region which comprises or consists of an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to VH region of a HER2-binding antibody clone described herein and a VL region which comprises or consists of an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to VL region of a HER2-binding antibody clone described herein.

In some embodiments, the antigen-binding polypeptide may comprise a variant of a reference VL/VH region, e.g. comprising 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 substitutions with respect to the amino acid sequence of the reference VL/VH region(s). In some embodiments the substitution(s) are not in the CDRs. In some embodiments the substitution(s) are in the framework region(s) – i.e. the amino acid sequences of the VL/VH region(s) other than the CDRs.

In some embodiments, the substitutions are conservative substitutions, for example according to the following Table. In some embodiments, amino acids in the same block in the middle column are substituted. In some embodiments, amino acids in the same line in the rightmost column are substituted:

ALIPHATIC	Non-polar	G A P
		I L V
	Polar - uncharged	C S T M
		N Q
	Polar - charged	D E
		K R
AROMATIC		H F W Y

In some embodiments the HER2-binding antigen-binding polypeptide according to the invention comprises or consists of an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to one of SEQ ID NOs:1 to 4. In some embodiments the HER2-binding antigen-binding polypeptide according to the invention comprises or consists of an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to one of SEQ ID NOs:5 to 8.

In some embodiments the HER2-binding antigen-binding polypeptide according to the invention comprises or consists of an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to one of SEQ ID NOs: 72, 82, 91, 100, 108, 118, 128, 136, 144, 153, 159, 168, 178, 184, 192, 202, 209, 215, 224, 231, 239, 245, 253, 259, 268, 277, 285, or 293. In some embodiments the HER2-binding antigen-binding polypeptide according to the invention comprises or consists of an amino acid sequence

having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to one of SEQ ID NOs: 73, 83, 92, 101, 109, 119, 129, 137, 145, 154, 160, 169, 179, 185, 193, 203, 210, 216, 225, 232, 240, 246, 254, 260, 269, 278, 286, or 294.

5

In some embodiments the HER2-binding antigen-binding polypeptide according to the present invention lacks HC-CDR1, HC-CDR2, HC-CDR3, LC-CDR1, LC-CDR2, and LC-CDR3 of one or more of the following clones: P1A3, P1C5, P1E4, and P1F1. In some embodiments the HER2-binding antigen-binding polypeptide according to the present invention lacks the VL domain sequence and/or the VH domain sequence of one or more of said clones.

10

The VL and VH region of an antigen-binding region of an antibody together constitute the Fv region. In some embodiments, the antigen-binding polypeptide according to the present invention comprises, or consists of, an Fv region which binds to HER2.

15

In some embodiments, the polypeptide additionally comprises one or more antibody heavy chain constant regions (CH). In some embodiments, the polypeptide additionally comprises one or more antibody light chain constant regions (CL). In some embodiments, the polypeptide comprises a CH1, CH2 region and/or a CH3 region of an immunoglobulin (Ig).

20

The VL and light chain constant (CL) region, and the VH region and heavy chain constant 1 (CH1) region of an antigen-binding region of an antibody together constitute the Fab region. In some embodiments, the antigen-binding polypeptide of the antigen-binding polypeptide described herein comprises, or consists of, a Fab region which binds to HER2.

25

In some embodiments the polypeptide comprises one or more regions of an immunoglobulin heavy chain constant sequence. In some embodiments the polypeptide comprises a CH1 region as described herein. In some embodiments the polypeptide comprises a CH1-CH2 hinge region as described herein. In some embodiments the polypeptide comprises a CH2 region as described herein. In some embodiments the polypeptide comprises a CH3 region as described herein.

30

In some embodiments the polypeptide lacks one or more regions of an immunoglobulin heavy chain constant sequence. In some embodiments the polypeptide lacks a CH2 region. In some embodiments the polypeptide lacks a CH3 region. In some embodiments the polypeptide lacks a CH2 region and also lacks a CH3 region.

35

In some embodiments, the polypeptide according to the present invention comprises a structure from N- to C-terminus according to one of the following:

40

(i) VH

- (ii) VL
- (iii) VH-CH1
- (iv) VL-CL
- (v) VL-CH1
- (vi) VH-CL
- (vii) VH-CH1-CH2-CH3
- (viii) VL-CL-CH2-CH3
- (ix) VL-CH1-CH2-CH3
- (x) VH-CL-CH2-CH3

Also provided by the present invention are antibodies and antigen-binding molecules composed of the polypeptides of the present invention. In some embodiments, the antibody/antigen-binding molecule of the present invention comprises one of the following combinations of polypeptides:

- (A) VH + VL
- (B) VH-CH1 + VL-CL
- (C) VL-CH1 + VH-CL
- (D) VH-CH1-CH2-CH3 + VL-CL
- (E) VH-CL-CH2-CH3 + VL-CH1
- (F) VL-CH1-CH2-CH3 + VH-CL
- (G) VL-CL-CH2-CH3 + VH-CH1
- (H) VH-CH1-CH2-CH3 + VL-CL-CH2-CH3
- (I) VH-CL-CH2-CH3 + VL-CH1-CH2-CH3

In some embodiments the antigen-binding molecule comprises more than one of a polypeptide of the combinations shown in (A) to (I) above. By way of example, with reference to (D) above, in some embodiments the antigen-binding molecule comprises two polypeptides comprising the structure VH-CH1-CH2-CH3, and two polypeptides comprising the structure VL-CL.

In some embodiments, the antigen-binding polypeptide described herein comprises, or consists of, a whole antibody which binds to HER2. As used herein, "whole antibody" refers to an antibody having a structure which is substantially similar to the structure of an immunoglobulin (Ig). Different kinds of immunoglobulins and their structures are described e.g. in Schroeder and Cavacini J Allergy Clin Immunol. (2010) 125(202): S41-S52, which is hereby incorporated by reference in its entirety.

Immunoglobulins of type G (i.e. IgG) are ~150 kDa glycoproteins comprising two heavy chains and two light chains. From N- to C-terminus, the heavy chains comprise a VH followed by a heavy chain constant region comprising three constant domains (CH1, CH2, and CH3), and similarly the light chain comprise a VL followed by a CL. Depending on the heavy chain, immunoglobulins may be classed as IgG (e.g. IgG1, IgG2, IgG3, IgG4), IgA (e.g. IgA1, IgA2), IgD, IgE, or IgM. The light chain may be kappa (κ) or lambda (λ).

In some embodiments, the antigen-binding polypeptide described herein comprises, or consists of, an IgG (e.g. IgG1, IgG2, IgG3, IgG4), IgA (e.g. IgA1, IgA2), IgD, IgE, or IgM which binds to HER2.

5 The antigen binding polypeptides according to the present invention may be provided in any suitable format.

In some aspects, the antibody is clone P1A3, or a variant of P1A3. P1A3 comprises the following CDR sequences:

10 Light chain:

LC-CDR1:	GLSSGSVSTGHYAS	(SEQ ID NO:15)
LC-CDR2:	NTNTRSS	(SEQ ID NO:16)
LC-CDR3:	VLYVGDIWW	(SEQ ID NO:17)

Heavy chain:

15 HC-CDR1:	SYIHH	(SEQ ID NO:18)
HC-CDR2:	IINPGNGDTNYAQRFGG	(SEQ ID NO:19)
HC-CDR3:	EIASYSGSYDDY	(SEQ ID NO:20)

20 Unless otherwise specified, CDRs of the antigen-binding polypeptides described herein are defined according to Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (1991)

In some aspects, the antibody is clone P1C5, or a variant of P1C5. P1C5 comprises the following CDR sequences:

25 Light chain:

LC-CDR1:	GLSSGSVSTGYGPS	(SEQ ID NO:21)
LC-CDR2:	STNSRSS	(SEQ ID NO:22)
LC-CDR3:	VLYMGSGISV	(SEQ ID NO:23)

Heavy chain:

30 HC-CDR1:	SSSYWGG	(SEQ ID NO:24)
HC-CDR2:	SIYSGSTYYNPSLKS	(SEQ ID NO:25)
HC-CDR3:	YAPDSSGYLVAFDI	(SEQ ID NO:26).

35 In some aspects, the antibody is clone P1E4, or a variant of P1E4. P1E4 comprises the following CDR sequences:

Light chain:

LC-CDR1:	GLSSGSVSTSYGPS	(SEQ ID NO:27)
LC-CDR2:	TTNIRSS	(SEQ ID NO:28)
40 LC-CDR3:	MLYMGSGIWW	(SEQ ID NO:29)

Heavy chain:

HC-CDR1:	GYYWS	(SEQ ID NO:30)
HC-CDR2:	EINHSGSTNYNPSLKS	(SEQ ID NO:31)
HC-CDR3:	MGINSGGYLYGMDV	(SEQ ID NO:32).

5

In some aspects, the antibody is clone P1F1, or a variant of P1F1. P1F1 comprises the following CDR sequences:

Light chain:

10	LC-CDR1:	GLSSGSVSTSYPS	(SEQ ID NO:27)
	LC-CDR2:	STNTRSS	(SEQ ID NO:33)
	LC-CDR3:	VLYMGSGIWW	(SEQ ID NO:34)

Heavy chain:

	HC-CDR1:	SSNWWWS	(SEQ ID NO:35)
15	HC-CDR2:	EIYHSGSTNYNPSLKS	(SEQ ID NO:36)
	HC-CDR3:	MGANSGGYLYGMDV	(SEQ ID NO:37).

20 Antibodies according to the present invention may comprise the CDRs of P1A3, P1C5, P1E4 or P1F1 or one of SEQ ID NOs 1 and 5; 2 and 6; 3 and 7; or 4 and 8. In an antibody according to the present invention one or two or three or four of the six CDR sequences may vary. A variant may have one or two amino acid substitutions in one or two of the six CDR sequences.

25 The amino acid sequences of the V_L and V_H chains of P1A3 (SEQ ID NO:1 and 5), P1C5 (SEQ ID NO:2 and 6), P1E4 (SEQ ID NO:3 and 7) and P1F1 (SEQ ID NO:4 and 8) have been determined as shown in Figures 1A-1D (V_L) and 2A-2D (V_H). The encoding nucleotide sequences are shown in SEQ ID NOs:39 and 43 (P1A3), 40 and 44 (P1C5), 41 and 45 (P1E4), 42 and 46 (P1F1), and in Figures 16 and 17.

30 In some aspects, antibodies according to the present invention may comprise one or more of the amino acid sequences described herein. Antibodies according to the present invention may be encoded by one or more of the nucleotide sequences described herein. In some aspects the antibody is clone A1, A2, A4, A5, B1, B2, B3, B4, B5, C2, C3, C4, D1, D2, D3, D4, E1, E2, E5, F2, F3, F4, F5, G1, G2, G3, G4, or G5, as described herein, or a variant of said clones.

35 In some aspects and embodiments, an antibody, antigen binding fragment or polypeptide comprises at least one VL region according to one of (1) to (31) below:

(1) (P1A3) a VL region incorporating the following CDRs:

	LC-CDR1 having the amino acid sequence of SEQ ID NO:15
	LC-CDR2 having the amino acid sequence of SEQ ID NO:16
40	LC-CDR3 having the amino acid sequence of SEQ ID NO:17,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(2) (P1C5) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:21

LC-CDR2 having the amino acid sequence of SEQ ID NO:22

LC-CDR3 having the amino acid sequence of SEQ ID NO:23,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(3) (P1E4) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:27

LC-CDR2 having the amino acid sequence of SEQ ID NO:28

LC-CDR3 having the amino acid sequence of SEQ ID NO:29,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(4) (P1F1) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:27

LC-CDR2 having the amino acid sequence of SEQ ID NO:33

LC-CDR3 having the amino acid sequence of SEQ ID NO:34,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(5) (PFA1) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:74

LC-CDR2 having the amino acid sequence of SEQ ID NO:75

LC-CDR3 having the amino acid sequence of SEQ ID NO:76,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(6) (PFA2) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:84

LC-CDR2 having the amino acid sequence of SEQ ID NO:75

LC-CDR3 having the amino acid sequence of SEQ ID NO:85,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(7) (PFA4) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:93

LC-CDR2 having the amino acid sequence of SEQ ID NO:94

LC-CDR3 having the amino acid sequence of SEQ ID NO:95,
or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

5 (8) (PFA5) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:102

LC-CDR2 having the amino acid sequence of SEQ ID NO:75

LC-CDR3 having the amino acid sequence of SEQ ID NO:103,

10 or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(9) (PFB1) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:110

LC-CDR2 having the amino acid sequence of SEQ ID NO:111

15 LC-CDR3 having the amino acid sequence of SEQ ID NO:112,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(10) (PFB2) a VL region incorporating the following CDRs:

20 LC-CDR1 having the amino acid sequence of SEQ ID NO:120

LC-CDR2 having the amino acid sequence of SEQ ID NO:121

LC-CDR3 having the amino acid sequence of SEQ ID NO:122,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

25

(11) (PFB3) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:102

LC-CDR2 having the amino acid sequence of SEQ ID NO:75

LC-CDR3 having the amino acid sequence of SEQ ID NO:130,

30 or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(12) (PFB4) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:138

35 LC-CDR2 having the amino acid sequence of SEQ ID NO:139

LC-CDR3 having the amino acid sequence of SEQ ID NO:140,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

40 (13) (PFB5) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:102

LC-CDR2 having the amino acid sequence of SEQ ID NO:146

LC-CDR3 having the amino acid sequence of SEQ ID NO:147,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(14) (PFC2; PFG5) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:102

LC-CDR2 having the amino acid sequence of SEQ ID NO:155

LC-CDR3 having the amino acid sequence of SEQ ID NO:95,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(15) (PFC3) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:161

LC-CDR2 having the amino acid sequence of SEQ ID NO:162

LC-CDR3 having the amino acid sequence of SEQ ID NO:163,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(16) (PFC4) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:170

LC-CDR2 having the amino acid sequence of SEQ ID NO:171

LC-CDR3 having the amino acid sequence of SEQ ID NO:172,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(17) (PFD1) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:93

LC-CDR2 having the amino acid sequence of SEQ ID NO:94

LC-CDR3 having the amino acid sequence of SEQ ID NO:180,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(18) (PFD2) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:186

LC-CDR2 having the amino acid sequence of SEQ ID NO:187

LC-CDR3 having the amino acid sequence of SEQ ID NO:188,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(19) (PFD3) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:194

LC-CDR2 having the amino acid sequence of SEQ ID NO:195

LC-CDR3 having the amino acid sequence of SEQ ID NO:196,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(20) (PFD4) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:93

LC-CDR2 having the amino acid sequence of SEQ ID NO:204

LC-CDR3 having the amino acid sequence of SEQ ID NO:205,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(21) (PFE1) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:211

LC-CDR2 having the amino acid sequence of SEQ ID NO:212

LC-CDR3 having the amino acid sequence of SEQ ID NO:95,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(22) (PFE2) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:217

LC-CDR2 having the amino acid sequence of SEQ ID NO:218

LC-CDR3 having the amino acid sequence of SEQ ID NO:219,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(23) (PFE5) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:226

LC-CDR2 having the amino acid sequence of SEQ ID NO:227

LC-CDR3 having the amino acid sequence of SEQ ID NO:228,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(24) (PFF2) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:161

LC-CDR2 having the amino acid sequence of SEQ ID NO:162

LC-CDR3 having the amino acid sequence of SEQ ID NO:233,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(25) (PFF3) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:102

LC-CDR2 having the amino acid sequence of SEQ ID NO:75

LC-CDR3 having the amino acid sequence of SEQ ID NO:180,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(26) (PFF4) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:247

LC-CDR2 having the amino acid sequence of SEQ ID NO:248

LC-CDR3 having the amino acid sequence of SEQ ID NO:249,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(27) (PFF5) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:255

LC-CDR2 having the amino acid sequence of SEQ ID NO:33

LC-CDR3 having the amino acid sequence of SEQ ID NO:256,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(28) (PFG1) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:261

LC-CDR2 having the amino acid sequence of SEQ ID NO:262

LC-CDR3 having the amino acid sequence of SEQ ID NO:263,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(29) (PFG2) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:270

LC-CDR2 having the amino acid sequence of SEQ ID NO:271

LC-CDR3 having the amino acid sequence of SEQ ID NO:272,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

(30) (PFG3) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:279

LC-CDR2 having the amino acid sequence of SEQ ID NO:280

LC-CDR3 having the amino acid sequence of SEQ ID NO:23,

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

5

(31) (PFG4) a VL region incorporating the following CDRs:

LC-CDR1 having the amino acid sequence of SEQ ID NO:287

LC-CDR2 having the amino acid sequence of SEQ ID NO:288

LC-CDR3 having the amino acid sequence of SEQ ID NO:289,

10

or a variant thereof in which one or two or three amino acids in one or more of LC-CDR1, LC-CDR2, or LC-CDR3 are substituted with another amino acid.

In some aspects and embodiments, an antibody, antigen binding fragment or polypeptide comprises at least one VL region according to one of (32) to (63) below:

15

(32) (P1A3) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:1.

20

(33) (P1C5) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:2.

25

(34) (P1E4) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:3.

30

(35) (P1F1) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:4.

35

(36) (PFA1) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:72.

(37) (PFA2) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:82.

(38) (PFA4) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:91.

5 (39) (PFA5) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:100.

10 (40) (PFB1) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:108.

15 (41) (PFB2) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:118.

20 (42) (PFB3) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:128.

(43) (PFB4) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:136.

25 (44) (PFB5) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:144.

30 (45) (PFC2) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:153.

35 (46) (PFC3) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:159.

(47) (PFC4) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:168.

(48) (PFD1) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:178.

5 (49) (PFD2) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:184.

10 (50) (PFD3) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:192.

15 (51) (PFD4) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:202.

20 (52) (PFE1) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:209.

(53) (PFE2) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:215.

25 (54) (PFE5) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:224.

30 (55) (PFF2) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:231.

35 (56) (PFF3) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:239.

(57) (PFF4) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:245.

(58) (PFF5) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:253.

5 (59) (PFG1) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:259.

10 (60) (PFG2) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:268.

15 (61) (PFG3) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:277.

20 (62) (PFG4) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:285.

(63) (PFG5) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:293.

25 In some aspects and embodiments, an antibody, antigen binding fragment or polypeptide comprises at least one VH region according to one of (64) to (92) below:

(64) (P1A3) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:18

HC-CDR2 having the amino acid sequence of SEQ ID NO:19

30 HC-CDR3 having the amino acid sequence of SEQ ID NO:20,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(65) (P1C5; PFF5) a VH region incorporating the following CDRs:

35 HC-CDR1 having the amino acid sequence of SEQ ID NO:24

HC-CDR2 having the amino acid sequence of SEQ ID NO:25

HC-CDR3 having the amino acid sequence of SEQ ID NO:26,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

40

(66) (P1E4) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:30

HC-CDR2 having the amino acid sequence of SEQ ID NO:31

HC-CDR3 having the amino acid sequence of SEQ ID NO:32,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(67) (P1F1) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:35

HC-CDR2 having the amino acid sequence of SEQ ID NO:36

HC-CDR3 having the amino acid sequence of SEQ ID NO:37,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(68) (PFA1) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:77

HC-CDR2 having the amino acid sequence of SEQ ID NO:78

HC-CDR3 having the amino acid sequence of SEQ ID NO:79,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(69) (PFA2) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:86

HC-CDR2 having the amino acid sequence of SEQ ID NO:87

HC-CDR3 having the amino acid sequence of SEQ ID NO:88,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(70) (PFA4) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:96

HC-CDR2 having the amino acid sequence of SEQ ID NO:78

HC-CDR3 having the amino acid sequence of SEQ ID NO:97,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(71) (PFA5) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:96

HC-CDR2 having the amino acid sequence of SEQ ID NO:104

HC-CDR3 having the amino acid sequence of SEQ ID NO:105,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(72) (PFB1) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:113

HC-CDR2 having the amino acid sequence of SEQ ID NO:114

HC-CDR3 having the amino acid sequence of SEQ ID NO:115,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(73) (PFB2) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:123

HC-CDR2 having the amino acid sequence of SEQ ID NO:124

HC-CDR3 having the amino acid sequence of SEQ ID NO:125,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(74) (PFB3) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:131

HC-CDR2 having the amino acid sequence of SEQ ID NO:132

HC-CDR3 having the amino acid sequence of SEQ ID NO:133,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(75) (PFB4) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:77

HC-CDR2 having the amino acid sequence of SEQ ID NO:78

HC-CDR3 having the amino acid sequence of SEQ ID NO:141,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(76) (PFB5) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:148

HC-CDR2 having the amino acid sequence of SEQ ID NO:149

HC-CDR3 having the amino acid sequence of SEQ ID NO:150,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(77) (PFC2; PFG5) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:96

HC-CDR2 having the amino acid sequence of SEQ ID NO:78

HC-CDR3 having the amino acid sequence of SEQ ID NO:156,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(78) (PFC3) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:131

HC-CDR2 having the amino acid sequence of SEQ ID NO:164

HC-CDR3 having the amino acid sequence of SEQ ID NO:165,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(79) (PFC4) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:173

HC-CDR2 having the amino acid sequence of SEQ ID NO:174

HC-CDR3 having the amino acid sequence of SEQ ID NO:175,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(80) (PFD1) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:77

HC-CDR2 having the amino acid sequence of SEQ ID NO:78

HC-CDR3 having the amino acid sequence of SEQ ID NO:181,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(81) (PFD2) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:30

HC-CDR2 having the amino acid sequence of SEQ ID NO:31

HC-CDR3 having the amino acid sequence of SEQ ID NO:189,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(82) (PFD3) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:197

HC-CDR2 having the amino acid sequence of SEQ ID NO:198

HC-CDR3 having the amino acid sequence of SEQ ID NO:199,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(83) (PFD4) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:96

HC-CDR2 having the amino acid sequence of SEQ ID NO:206
HC-CDR3 having the amino acid sequence of SEQ ID NO:97,
or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-
CDR2, or HC-CDR3 are substituted with another amino acid.

5

(84) (PFE1; PFE5) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:96

HC-CDR2 having the amino acid sequence of SEQ ID NO:78

HC-CDR3 having the amino acid sequence of SEQ ID NO:97,

10 or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-
CDR2, or HC-CDR3 are substituted with another amino acid.

(85) (PFE2) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:96

15 HC-CDR2 having the amino acid sequence of SEQ ID NO:220

HC-CDR3 having the amino acid sequence of SEQ ID NO:221,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-
CDR2, or HC-CDR3 are substituted with another amino acid.

20 (86) (PFF2) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:234

HC-CDR2 having the amino acid sequence of SEQ ID NO:235

HC-CDR3 having the amino acid sequence of SEQ ID NO:236,

25 or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-
CDR2, or HC-CDR3 are substituted with another amino acid.

(87) (PFF3) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:241

HC-CDR2 having the amino acid sequence of SEQ ID NO:206

30 HC-CDR3 having the amino acid sequence of SEQ ID NO:242,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-
CDR2, or HC-CDR3 are substituted with another amino acid.

(88) (PFF4) a VH region incorporating the following CDRs:

35 HC-CDR1 having the amino acid sequence of SEQ ID NO:148

HC-CDR2 having the amino acid sequence of SEQ ID NO:149

HC-CDR3 having the amino acid sequence of SEQ ID NO:250,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-
CDR2, or HC-CDR3 are substituted with another amino acid.

40

(89) (PFG1) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:77

HC-CDR2 having the amino acid sequence of SEQ ID NO:264

HC-CDR3 having the amino acid sequence of SEQ ID NO:265,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(90) (PFG2) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:131

HC-CDR2 having the amino acid sequence of SEQ ID NO:273

HC-CDR3 having the amino acid sequence of SEQ ID NO:274,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(91) (PFG3) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:281

HC-CDR2 having the amino acid sequence of SEQ ID NO:282

HC-CDR3 having the amino acid sequence of SEQ ID NO:20,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

(92) (PFG4) a VH region incorporating the following CDRs:

HC-CDR1 having the amino acid sequence of SEQ ID NO:148

HC-CDR2 having the amino acid sequence of SEQ ID NO:149

HC-CDR3 having the amino acid sequence of SEQ ID NO:290,

or a variant thereof in which one or two or three amino acids in one or more of HC-CDR1, HC-CDR2, or HC-CDR3 are substituted with another amino acid.

In some aspects and embodiments, an antibody, antigen binding fragment or polypeptide comprises at least one VH region according to one of (93) to (124) below:

(93) (P1A3) a VH region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:5.

(94) (P1C5) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:6.

(95) (P1E4) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:7.

5 (96) (P1F1) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:8.

10 (97) (PFA1) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:73.

15 (98) (PFA2) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:83.

20 (99) (PFA4) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:92.

(100) (PFA5) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:101.

25 (101) (PFB1) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:109.

30 (102) (PFB2) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:119.

35 (103) (PFB3) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:129.

(104) (PFB4) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:137.

40

(105) (PFB5) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:145.

5 (106) (PFC2) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:154.

10 (107) (PFC3) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:160.

15 (108) (PFC4) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:169.

20 (109) (PFD1) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:179.

(110) (PFD2) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:185.

25 (111) (PFD3) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:193.

30 (112) (PFD4) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:203.

35 (113) (PFE1) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:210.

(114) (PFE2) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:216.

(115) (PFE5) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:225.

5 (116) (PFF2) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:232.

10 (117) (PFF3) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:240.

15 (118) (PFF4) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:246.

20 (119) (PFF5) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:254.

(120) (PFG1) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:260.

25 (121) (PFG2) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:269.

30 (122) (PFG3) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:278.

35 (123) (PFG4) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:286.

(124) (PFG5) a VL region comprising an amino acid sequence having at least 70% sequence identity more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the amino acid sequence of SEQ ID NO:294.

In some embodiments the antigen-binding molecule comprises at least one VL region according to any one of (1) to (63) above, and at least one VH region according to any one of (64) to (124) above.

The light and heavy chain CDRs may also be particularly useful in conjunction with a number of different framework regions. Accordingly, light and/or heavy chains having LC-CDR1-3 or HC-CDR1-3 may possess an alternative framework region. Suitable framework regions are well known in the art and are described for example in M. Lefranc & G. Lefranc (2001) "The Immunoglobulin FactsBook", Academic Press, incorporated herein by reference.

In this specification, antibodies may have VL and/or VH chains comprising an amino acid sequence that has a high percentage sequence identity to one or more of the VL and/or VH amino acid sequences of SEQ ID NOs 1 and 5; 2 and 6; 3 and 7; or 4 and 8, or to one of the amino acid sequences shown in Figures 1 and 2.

For example, antibodies according to the present invention include antibodies that bind HER2 and have a VL or VH chain that comprises an amino acid sequence having at least 70%, more preferably one of at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, sequence identity to the VL or VH chain amino acid sequence of one of SEQ ID NOs 1 to 8, or to one of the amino acid sequences shown in Figures 1 and 2.

In some embodiments, an antibody, antigen-binding molecule or polypeptide provided herein comprises the CDRs, VL and/or VH chains of PFA4, PFB4, PFB5, PFC3, PFD4, PFE1, PFF5, or PFG3. In some embodiments, an antibody, antigen-binding molecule or polypeptide provided herein comprises the CDRs, VL and/or VH chains of PFA4, PFB4, PFC3, PFD4, PFE1, PFF5, or PFG3. In some embodiments, an antibody, antigen-binding molecule or polypeptide provided herein comprises the CDRs, VL and/or VH chains of PFB4, PFC3, PFD4, PFE1, PFF5, or PFG3. In some embodiments, an antibody, antigen-binding molecule or polypeptide provided herein comprises the CDRs, VL and/or VH chains of PFB4, PFC3, PFE1, PFF5, or PFG3. In some embodiments, an antibody, antigen-binding molecule or polypeptide provided herein comprises the CDRs, VL and/or VH chains of PFB4, PFC3, PFE1, PFF5, or PFG3.

In some embodiments, an antibody, antigen-binding molecule or polypeptide provided herein comprises the CDRs, VL and/or VH chains of P1A3, P1C5, P1E4, P1F1, PFA4, PFB4, PFC3, PFD4 or PFE1.

Multivalent antibodies

Whole antibodies, and F(ab')₂ fragments are "bivalent". By "bivalent" we mean that the said antibodies and F(ab')₂ fragments have two antigen combining sites. In contrast, Fab, Fv, ScFv and dAb fragments are monovalent, having only one antigen combining site.

The present application also provides an antibody or antigen binding fragment which is capable of binding to HER2, and which is a bispecific antibody or a bispecific antigen binding fragment. In some embodiments

the bispecific antibody or bispecific antigen binding fragment may be isolated. The term "bispecific" means that the antigen-binding molecule is able to bind specifically to at least two distinct antigenic determinants.

In some embodiments the bispecific antibodies and bispecific antigen binding fragment comprise an antigen binding fragment or a polypeptide according to the present invention. In some embodiments, the bispecific antibodies and bispecific antigen binding fragments comprise an antigen binding fragment capable of binding to HER2, wherein the antigen binding fragment which is capable of binding to HER2 comprises or consists of an antigen binding fragment or a polypeptide according to the present invention.

In some embodiments the bispecific antibodies and bispecific antigen binding fragments comprise an antigen binding fragment capable of binding to HER2, and an antigen binding fragment capable of binding to another target protein. In some embodiments the bispecific antibodies/antigen binding fragments comprise an antigen binding molecule capable of binding to HER2 and an antigen binding molecule capable of binding to an antigen other than HER2. In some embodiments the antigen other than HER2 is an immune cell surface molecule. In some embodiments the antigen other than HER2 is a cancer cell antigen. In some embodiments the antigen other than HER2 is a receptor molecule, e.g. a cell surface receptor.

A cancer cell antigen is an antigen which is expressed or over-expressed by a cancer cell. A cancer cell antigen may be any peptide/polypeptide, glycoprotein, lipoprotein, glycan, glycolipid, lipid, or fragment thereof. A cancer cell antigen's expression may be associated with a cancer. A cancer cell antigen may be abnormally expressed by a cancer cell (e.g. the cancer cell antigen may be expressed with abnormal localisation), or may be expressed with an abnormal structure by a cancer cell. A cancer cell antigen may be capable of eliciting an immune response. In some embodiments, the antigen is expressed at the cell surface of the cancer cell (i.e. the cancer cell antigen is a cancer cell surface antigen). In some embodiments, the part of the antigen which is bound by the antigen-binding molecule described herein is displayed on the external surface of the cancer cell (i.e. is extracellular). The cancer cell antigen may be a cancer-associated antigen. In some embodiments the cancer cell antigen is an antigen whose expression is associated with the development, progression or severity of symptoms of a cancer. The cancer-associated antigen may be associated with the cause or pathology of the cancer, or may be expressed abnormally as a consequence of the cancer. In some embodiments, the cancer cell antigen is an antigen whose expression is upregulated (e.g. at the RNA and/or protein level) by cells of a cancer, e.g. as compared to the level of expression of by comparable non-cancerous cells (e.g. non-cancerous cells derived from the same tissue/cell type). In some embodiments, the cancer-associated antigen may be preferentially expressed by cancerous cells, and not expressed by comparable non-cancerous cells (e.g. non-cancerous cells derived from the same tissue/cell type). In some embodiments, the cancer-associated antigen may be the product of a mutated oncogene or mutated tumor suppressor gene. In some embodiments, the cancer-associated antigen may be the product of an overexpressed cellular protein, a cancer antigen produced by an oncogenic virus, an oncofetal antigen, or a cell surface glycolipid or glycoprotein.

An immune cell surface molecule may be any peptide/polypeptide, glycoprotein, lipoprotein, glycan, glycolipid, lipid, or fragment thereof expressed at or on the cell surface of an immune cell. In some embodiments, the part of the immune cell surface molecule which is bound by the antigen-binding molecule of the present invention is on the external surface of the immune cell (i.e. is extracellular). The immune cell surface molecule may be expressed at the cell surface of any immune cell. In some embodiments, the immune cell may be a cell of hematopoietic origin, e.g. a neutrophil, eosinophil, basophil, dendritic cell, lymphocyte, or monocyte. The lymphocyte may be e.g. a T cell, B cell, natural killer (NK) cell, NKT cell or innate lymphoid cell (ILC), or a precursor thereof (e.g. a thymocyte or pre-B cell). In some embodiments the immune cell surface molecule may be a costimulatory molecule (e.g. CD28, OX40, 4-1BB, ICOS or CD27) or a ligand thereof. In some embodiments the immune cell surface molecule may be a checkpoint inhibitor (e.g. PD-1, CTLA-4, LAG-3, TIM-3, TIGIT or BTLA) or a ligand thereof.

In some embodiments the bispecific antibodies/antigen binding fragments comprise an antigen binding fragment/molecule as provided herein and an antigen binding fragment/molecule capable of binding to HER2. In some embodiments the bispecific antibodies/antigen binding fragments comprise an antigen binding fragment/molecule capable of binding HER2 at a first epitope and an antigen binding fragment/molecule capable of binding to HER2 at a second epitope. For example, the bispecific antibodies/antigen binding fragments comprise an antigen binding fragment/molecule as provided herein and an antigen binding fragment/molecule derived from trastuzumab and/or pertuzumab.

The antigen binding fragment capable of binding to another target protein may be capable of binding to another protein other than HER2.

The antibodies and antigen binding polypeptides as described herein may be multispecific. Multispecific antibodies and antigen binding polypeptides may be provided in any suitable format, such as those formats described in Kontermann MAb 2012, 4(2): 182-197, which is hereby incorporated by reference in its entirety. For example, an antigen-binding polypeptide may be a bispecific antibody conjugate (e.g. an IgG2, F(ab')₂ or CovX-Body), a bispecific IgG or IgG-like molecule (e.g. an IgG, scFv4-Ig, IgG-scFv, scFv-IgG, DVD-Ig, IgG-sVD, sVD-IgG, 2 in 1-IgG, mAb2, or Tandemab common LC), an asymmetric bispecific IgG or IgG-like molecule (e.g. a kih IgG, kih IgG common LC, CrossMab, kih IgG-scFab, mAb-Fv, charge pair or SEED-body), a small bispecific antibody molecule (e.g. a Diabody (Db), dsDb, DART, scDb, tandAbs, tandem scFv (taFv), tandem dAb/VHH, triple body, triple head, Fab-scFv, or F(ab')₂-scFv2), a bispecific Fc and CH3 fusion protein (e.g. a taFv-Fc, Di-diabody, scDb-CH3, scFv-Fc-scFv, HCAb-VHH, scFv-kih-Fc, or scFv-kih-CH3), or a bispecific fusion protein (e.g. a scFv2-albumin, scDb-albumin, taFv-toxin, DNL-Fab3, DNL-Fab4-IgG, DNL-Fab4-IgG-cytokine2). See in particular Figure 2 of Kontermann MAb 2012, 4(2): 182-19. By "multispecific" it is meant that the antigen-binding molecule displays specific binding to more than one target.

The skilled person is able to design and prepare bispecific antibodies. Methods for producing bispecific antibodies include chemically crosslinking of antibodies or antibody fragments, e.g. with reducible disulphide or non-reducible thioether bonds, for example as described in Segal and Bast, 2001. Production of Bispecific Antibodies. Current Protocols in Immunology. 14:IV:2.13:2.13.1–2.13.16, which is hereby incorporated by reference in its entirety. For example, N-succinimidyl-3-(2-pyridyldithio)-propionate (SPDP) can be used to chemically crosslink e.g. Fab fragments via hinge region SH- groups, to create disulfide-linked bispecific F(ab)₂ heterodimers. Other methods for producing bispecific antibodies include fusing antibody-producing hybridomas e.g. with polyethylene glycol, to produce a quadroma cell capable of secreting bispecific antibody, for example as described in D. M. and Bast, B. J. 2001. Production of Bispecific Antibodies. Current Protocols in Immunology. 14:IV:2.13:2.13.1–2.13.16.

Bispecific antibodies can also be produced recombinantly, by expression from e.g. a nucleic acid construct encoding polypeptides for the antigen binding molecules, for example as described in Antibody Engineering: Methods and Protocols, Second Edition (Humana Press, 2012), at Chapter 40: Production of Bispecific Antibodies: Diabodies and Tandem scFv (Hornig and Färber-Schwarz), or French, How to make bispecific antibodies, Methods Mol. Med. 2000; 40:333-339, the entire contents of both of which are hereby incorporated by reference. For example, a DNA construct encoding the light and heavy chain variable domains for the two antigen-binding fragments (i.e. the light and heavy chain variable domains for the antigen-binding fragment capable of binding HER2, and the light and heavy chain variable domains for the antigen-binding fragment capable of binding to another target protein/to another epitope on HER2), and including sequences encoding a suitable linker or dimerization domain between the antigen-binding fragments can be prepared by molecular cloning techniques. Recombinant bispecific antibody can thereafter be produced by expression (e.g. in vitro) of the construct in a suitable host cell (e.g. a mammalian host cell), and expressed recombinant bispecific antibody can then optionally be purified.

Antibody conjugates

The present invention also provides antibody conjugates, comprising an antibody, antigen binding fragment or polypeptide according to the invention conjugated to a chemical moiety.

In some embodiments, the chemical moiety may be a moiety for providing a therapeutic effect. In some embodiments, the chemical moiety may be a drug moiety (e.g. a cytotoxic or cytostatic agent). A cytotoxic agent is an agent that kills cells. A cytostatic agent is an agent that inhibits growth of cells.

The use of an antibody-drug conjugate targets delivery of the drug moiety to cancer cells expressing HER2 and may promote intracellular accumulation therein.

In some embodiments, the chemical moiety may be at least one anti-cancer agent. "At least one anti-cancer agent" refers to one, or two, or three, or four, or more agents that are effective in the treatment of malignant, or cancerous, disease such as the cancers described herein. An anti-cancer agent may also be described herein as a therapeutic agent, additional agent, or an additional therapeutic agent.

In some embodiments, the drug moiety may be a chemotherapeutic drug as described hereinbelow. In some embodiments the drug moiety may be a hormone capable of controlling tumour growth, such as ethinyloestradiol, medroxyprogesterone, norethisterone, megestrol, diethylstilboestrol, or fosfestrol. In some embodiments the drug moiety may be a hormone antagonist such as tamoxifen, toremifene, aminoglutethimide, anastrozole, letrozole, exemestane, trilostane, goserelin, buserelin, goserelin, leuporelin, triptorelin, cyproterone acetate, flutamide, or bicalutamide.

In some embodiments the chemical moiety may be a detectable moiety. Suitable moieties and means for their detection are well known to those in the art and include the radioactive isotope or non-isotopic entities described hereinabove.

The antibody conjugate may comprise a linker which may be cleaved so as to release the drug at the target location.

Chimeric antigen receptors

An antibody, antigen binding fragment or polypeptide according to the present invention may be incorporated into a chimeric antigen receptor (CAR) capable of binding to HER2. Thus, the present invention also provides CARs comprising the antibodies, antigen-binding molecules or polypeptides of the present invention.

Chimeric Antigen Receptors (CARs) are recombinant receptors that provide both antigen-binding and T cell activating functions. CAR structure and engineering is reviewed, for example, in Dotti et al., Immunol Rev (2014) 257(1), hereby incorporated by reference in its entirety. CARs comprise an antigen-binding region linked to a cell membrane anchor region and a signalling region. An optional hinge region may provide separation between the antigen-binding region and cell membrane anchor region, and may act as a flexible linker.

An antibody, antigen binding fragment or polypeptide according to the present invention may be used as the antigen binding domain of a chimeric antigen receptor (CAR). In some embodiments, the CAR comprises a V_L domain and a V_H domain according to any embodiment of an antibody, antigen binding fragment or polypeptide described herein. Accordingly, the antigen bound by the CAR according to the present invention is HER2.

Also provided is an *in vitro* complex, optionally isolated, comprising the CAR bound to HER2.

CARs may be combined with costimulatory ligands, chimeric costimulatory receptors or cytokines to further enhance T cell potency, specificity and safety (Sadelain et al., The basic principles of chimeric antigen receptor (CAR) design. Cancer Discov. 2013 April; 3(4): 388–398. doi:10.1158/2159-8290.CD-12-0548, specifically incorporated herein by reference).

The present invention provides a nucleic acid, optionally isolated, encoding a CAR as described herein. Also provided is an expression vector comprising the nucleic acid. The present invention also provides a cell comprising a CAR, nucleic acid, or an expression vector as described herein. Compositions comprising a CAR, nucleic acid, expression vector or cell as described herein are also provided. The CAR may be used to generate tumour-targeted T cells e.g. T cells targeted to tumour cells expressing or overexpressing HER2, for which the CAR is specific.

The cells may be immune cells e.g. T cells, antigen-specific T cells (e.g. virus-specific T cells), antigen-specific CD4 T cells, antigen-specific CD8 T cells, effector memory CD4 T cells, effector memory CD8 T cells, central memory CD4 T cells, central memory CD8 T cells, cytotoxic CD8+ T cells (i.e. CTLs) NK cells or antigen-specific NK cells.

Engineering of CARs into cells may be performed during culture, in vitro, for transduction and expansion, such as happens during expansion of T cells for adoptive T cell therapy. The transduction may utilize a variety of methods, but stable gene transfer is required to enable sustained CAR expression in clonally expanding and persisting T cells.

In addition to the HER2 specificity determining elements described herein, CAR molecules may be further engineered to express co-stimulatory endodomains such as those derived from CD28 and tumor necrosis factor receptor superfamily member 9 (TNFRSF9; 4-1BB) to promote T cell proliferation and persistence upon encountering tumor cells (Nishio and Dotti., *OncImmunology* 4:2, e988098; February 2015).

A CAR typically combines an antigen binding domain with an intracellular domain of the CD3- zeta chain or FcγRI protein in a single chimeric protein. The structural features of a CAR are described by Sjouke et al., (The pharmacology of second-generation chimeric antigen receptors. *Nature Reviews Drug Discovery*, 14, 499 509 (2015) doi:10.1038/nrd4597). A CAR typically has an extracellular antigen-binding domain linked to a transmembrane domain and endodomain. An optional hinge or spacer domain may provide separation between the binding moiety and transmembrane domain and may act as a flexible linker.

In accordance with the present invention, the antigen recognition domain of the CAR may be, or may be derived from, an antibody, antigen binding fragment or polypeptide which is capable of binding to HER2, as described herein. The antigen-binding region of the CAR of the present invention may be provided with any suitable format, e.g. scFv, scFab, etc.

In some embodiments the antigen recognition domain of the CAR may be, or may be derived from, clone P1A3, P1C5, P1E4, or P1F1 as described herein.

In some embodiments the CAR may comprise an antibody, antigen binding fragment or polypeptide described herein which exhibits intermediate or lower binding to HER2, as described herein. Intermediate

and/or lower affinity antigen-binding regions may be capable of discriminating cancer cells overexpressing a target protein from normal cells expressing physiological target levels, as described in e.g. Liu et al., Cancer Res. 2015; (75) (17) 3596-3607. This approach may spare non-cancer cells whilst specifically targeting cancer cells and reduce off-target toxicity. In some embodiments the antigen recognition domain of the CAR may be, or may be derived from, clone PFA4, PFB4, PFB5, PFC3, PFD4, PFE1, PFF5, or PFG3 as described herein. In some embodiments the antigen recognition domain of the CAR may be, or may be derived from, clone PFA4, PFB4, PFC3, PFD4, PFE1, PFF5, or PFG3 as described herein.

Hinge or spacer regions may be flexible domains allowing the binding moiety to orient in different directions. Hinge or spacer regions may be derived from IgG1, IgH or the CH₂CH₃ region of immunoglobulin.

Transmembrane domains may be hydrophobic alpha helix that spans the cell membrane. The transmembrane domain associated with the endodomain is commonly used. The transmembrane region may be termed the cell membrane anchor region. In some embodiments, the CAR comprises a cell membrane anchor region comprising or consisting of an amino acid sequence which comprises, consists of, or is derived from, the transmembrane region amino acid sequence for one of CD3-ζ, CD4, CD8 or CD28. As used herein, a region which is 'derived from' a reference amino acid sequence comprises an amino acid sequence having at least 60%, e.g. one of at least 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to the reference sequence.

The endodomain is responsible for receptor clustering/dimerization after antigen binding and for initiation of signal transduction to the cell. One commonly used transmembrane domain is the CD3-zeta transmembrane and endodomain. Intracellular domains from one or more co-stimulatory protein receptors, such as CD28 4-1BB, OX40, ICOS, may optionally be incorporated into the cytoplasmic tail of the CAR to provide additional co-stimulatory signaling, which may be beneficial in terms of anti-tumor activity.

A CAR described herein may comprise an extracellular domain having an antigen recognition domain, a transmembrane domain, and a cytoplasmic domain. A transmembrane domain that is naturally associated with one of the domains in the CAR may be used or the transmembrane domain can be selected or modified by amino acid substitution to avoid binding of such domains to the transmembrane domains of the same or different surface membrane proteins to minimize interactions with other members of the receptor complex. The cytoplasmic domain may be designed to comprise the CD28 and/or 4-1BB signaling domain by itself or be combined with any other desired cytoplasmic domain(s). The cytoplasmic domain may be designed to further comprise the signaling domain of CD3-zeta. For example, the cytoplasmic domain of the CAR can include but is not limited to CD3-zeta, 4-1BB and CD28 signaling modules and combinations thereof.

Also provided herein are CAR T cells comprising as a CAR an antigen binding fragment capable of binding to HER2, as described herein.

CAR T cells as described herein can be generated by introducing a lentiviral vector *in vitro* comprising a desired CAR, for example a CAR comprising anti-HER2, CD8a hinge and transmembrane domain, and human 4-1BB and CD3zeta signaling domains, into the cells. CAR T cells as described herein can also be generated by electroporation of mRNA encoding a desired CAR. The CAR T cells of the invention are able to replicate *in vivo* resulting in long-term persistence that can lead to sustained tumor control.

In some embodiments a CAR T cell according to the present invention promotes cytolysis of cells, e.g. cancer or tumour cells.

The present invention provides a CAR, nucleic acid, expression vector, cell, or composition as described herein for use in a method of medical treatment or prophylaxis. Also described herein is the administration of a genetically modified T cell expressing a CAR, nucleic acid or expression vector as described herein for use in a method of medical treatment or prophylaxis. In some embodiments a CAR or T cell as described herein is used for the treatment of a patient having cancer or at risk of having cancer. In some embodiments the cancer to be treated is a cancer described herein. In some embodiments the cancer is a cancer of the breast. In some embodiments the cancer to be treated is a cancer of the ovary, uterus, lung, e.g. adenocarcinoma of the lung, or the gastrointestinal tract e.g. stomach, salivary duct.

Administration may be by lymphocyte infusion. Preferably, autologous lymphocyte infusion is used in the treatment, i.e. the lymphocytes are derived from the patient to which they are introduced. Autologous PBMCs (peripheral blood mononuclear cells) are collected from a patient in need of treatment and T cells are activated and expanded using methods known in the art and then infused back into the patient. The generation, activation and expansion of cells may be performed *in vitro* or *ex vivo*. In some cases the cells may be obtained from an individual who is not the patient and introduced into the patient i.e. allogenic cell therapy.

Adoptive T cell transfer is described, for example, in Chia WK et al., Molecular Therapy (2014), 22(1): 132-139, Kalos and June 2013, Immunity 39(1): 49-60 and Cobbold et al., (2005) J. Exp. Med. 202: 379-386, which are hereby incorporated by reference in their entirety. Accordingly, the skilled person is able to determine appropriate reagents and procedures for adoptive transfer of immune cells described herein.

Methods of detection

Antibodies, antigen binding fragments, polypeptides, conjugates, CARs or cells as described herein may be detectably labelled or, at least, capable of detection. For example, the antibody may be labelled with a radioactive atom or a coloured molecule or a fluorescent molecule or a molecule which can be readily detected in any other way. Suitable detectable molecules include fluorescent proteins, luciferase, enzyme substrates, and radiolabels. The binding moiety may be directly labelled with a detectable label or it may be indirectly labelled. For example, the binding moiety may be an unlabelled antibody which can be detected

by another antibody which is itself labelled. Alternatively, the second antibody may have bound to it biotin and binding of labelled streptavidin to the biotin is used to indirectly label the first antibody.

Antibodies, antigen binding fragments, polypeptides, conjugates, CARs or cells described herein may be used in methods that involve the binding of the antibody or antigen binding fragment to HER2. Such methods may involve detection of the bound complex of antibody, antigen binding fragment, polypeptide, conjugate, CAR or cell, and HER2. As such, in one embodiment a method is provided, the method comprising contacting a sample containing, or suspected to contain, HER2 with an antibody, antigen binding fragment, polypeptide, conjugate, CAR or cell as described herein and detecting the formation of a complex of antibody, antigen binding fragment, polypeptide, conjugate, CAR or cell, and HER2.

Suitable method formats are well known in the art, including immunoassays such as sandwich assays, e.g. ELISA. The method may involve labelling the antibody, antigen binding fragment, polypeptide, conjugate, CAR or cell, or HER2, or both, with a detectable label, e.g. fluorescent, luminescent or radio- label. HER2 expression may be measured by immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH), for example in a tissue sample obtained by biopsy.

Methods of this kind may provide the basis of a method of diagnosis of a disease or condition requiring detection and or quantitation of HER2. Such methods may be performed *in vitro* on a patient sample, or following processing of a patient sample. Once the sample is collected, the patient is not required to be present for the *in vitro* method of diagnosis to be performed and therefore the method may be one which is not practised on the human or animal body.

The methods may involve determining the amount of HER2 present in a patient sample. The methods may further comprise comparing the determined amount against a standard or reference value as part of the process of reaching a diagnosis. Other diagnostic tests may be used in conjunction with those described here to enhance the accuracy of the diagnosis or prognosis or to confirm a result obtained by using the tests described here.

The level of HER2 present in a patient sample may be indicative that a patient may respond to treatment with an anti-HER2 antibody, antigen binding fragment, polypeptide, conjugate, CAR or cell. The presence of a high level of HER2 in a sample may be used to select a patient for treatment with an anti-HER2 antibody, antigen binding fragment, polypeptide, conjugate, CAR or cell. The antibodies, antigen binding fragments, polypeptides, conjugates, CARs or cells of the present invention may therefore be used to select a patient for treatment with anti-HER2 therapy.

Detection of HER2 in a sample may be used for the purpose of diagnosis of a cancerous condition in the patient, diagnosis of a predisposition to a cancerous condition or for providing a prognosis (prognosticating) of a cancerous condition. The diagnosis or prognosis may relate to an existing (previously diagnosed)

cancerous condition, which may be benign or malignant, may relate to a suspected cancerous condition or may relate to the screening for cancerous conditions in the patient (which may be previously undiagnosed).

A sample may be taken from any tissue or bodily fluid. The sample may comprise or may be derived from:
a quantity of blood; a quantity of serum derived from the individual's blood which may comprise the fluid portion of the blood obtained after removal of the fibrin clot and blood cells; a tissue sample or biopsy; or cells isolated from said individual.

Methods according to the present invention are preferably performed *in vitro*. The term "*in vitro*" is intended to encompass experiments with cells in culture whereas the term "*in vivo*" is intended to encompass experiments with intact multi-cellular organisms.

An antibody, antigen binding fragment, polypeptide, conjugate, CAR or cell as described herein may be used in methods for detecting, localizing or imaging a cancer (e.g. a tumour), e.g. *in vivo*.

An antibody, antigen binding fragment, polypeptide, conjugate, CAR or cell may be suitably labeled directly or indirectly with a detectable label (e.g. a signal-generating label), such as a radioactive isotope or non-isotopic entity, for detection. Radioisotopes include Iodine123, Iodine125, Iodine126, Iodine131, Iodine133, Bromine77, Technetium99m, Indium111, Indium113m, Gallium67, Gallium68, Ruthenium95, Ruthenium97, Ruthenium103, Ruthenium105, Mercury207, Mercury203, Rhenium99m, Rhenium101, Rhenium105, Scandium47, Tellurium121m, Tellurium122m, Tellurium125m, Thulium165, Thulium167, Thulium168, Copper67, Fluorine18, Yttrium90, Palladium100, Bismuth217 and Antimony211. Nonisotopic entities may be selected from enzymes (e.g. peroxidase, alkaline phosphatase, glucose oxidase, beta-galactosidase, luciferase), dyes, haptens, luminescent agents such as radioluminescent, chemiluminescent (e.g. acridinium ester, luminol, isoluminol), bioluminescent, fluorescent (e.g. fluorescein, rhodamine, eosine and NDB, green fluorescent protein (GFP) chelates of rare earths such as europium (Eu), terbium (Tb) and samarium (Sm), tetramethyl rhodamine, Texas Red, 4-methyl umbelliferone, 7-amino-4-methyl coumarin, Cy3, Cy5) or phosphorescent agents, antibodies, receptors and ligands such as biotin, avidin, streptavidin or digoxigenin.

Detection techniques are well known to those of skill in the art and can be selected to correspond with the labelling agent. Suitable techniques include PCR amplification of oligonucleotide tags, mass spectrometry, detection of fluorescence or colour, e.g. upon enzymatic conversion of a substrate by a reporter protein, or detection of radioactivity.

In some embodiments, the methods comprise administering the antibody, antibody fragment, polypeptide, conjugate, CAR or cell to a subject, e.g. a patient diagnosed with or suspected of having a cancer and detecting the antibody, antigen binding fragment, polypeptide, conjugate, CAR or cell. In some embodiments, the methods comprise detecting signal from the antibody, antigen binding fragment,

polypeptide, conjugate, CAR or cell. In some embodiments the method comprises conversion of the signal to an image.

5 The present invention also provides methods for selecting/ stratifying a subject for treatment with a HER2-targeted agent using the antibody, antigen binding fragment, polypeptide, conjugate, CAR, or cell according to the invention. In some embodiments the method comprises contacting a sample from the subject with an antibody, antigen binding fragment, polypeptide, conjugate, CAR or cell. In some embodiments the sample is contacted *in vitro*. In some embodiments, a subject is selected for treatment in accordance with the invention, or is identified as a subject which would benefit from such treatment, based on detection of the
10 the presence of HER2, or nucleic acid encoding HER2, e.g. in a sample obtained from the individual.

Therapeutic applications

15 Antibodies, antigen binding fragments, polypeptides, conjugates, nucleic acids, vectors, CARs and cells according to the present invention and compositions comprising such agents may be provided for use in methods of medical treatment. Treatment may be provided to subjects having a disease or condition in need of treatment. The disease or condition may be a cancer. The disease or condition may be a cancer in which HER2 is overexpressed.

20 The present invention provides an antibody, antigen binding fragment, polypeptide, conjugate, nucleic acid, vector, CAR or cell according to the present invention for use in a method of medical treatment or prophylaxis. The present invention also provides the use of an antibody, antigen binding fragment, polypeptide, conjugate, nucleic acid, vector, CAR or cell according to the present invention in the manufacture of a medicament for treating or preventing a disease or condition. The present invention also provides a method of treating or preventing a disease or condition, comprising administering to a subject a
25 therapeutically or prophylactically effective amount of an antibody, antigen binding fragment, polypeptide, conjugate, nucleic acid, vector, CAR or cell according to the present invention.

30 HER2 is a member of the epidermal growth factor receptor family and functions as a preferential heterodimerization-signalling partner with other members of the EGFR family (EGFR/HER1, HER3, and HER4), playing an important role in all stages of cell development including cellular proliferation and differentiation (Karunagaran et al., (1996) EMBO J. 15: 254-264; Klapper et al., (1999) PNAS 96: 4995-5000). As a key gene for cell survival, HER2 gene amplification and protein overexpression lead to malignant transformation (Neve et al., (2001) Ann Oncol. 12 Suppl 1():S9-13).

35 HER2 is expressed in a number of cancers, including breast, ovarian, gastric endometrium, bladder, lung, colon, prostate, and head and neck cancers. Overexpression of HER2 is directly associated with poor clinical outcomes. HER2 overexpression occurs in approximately 15-30% of breast cancers and 10-30% of gastric cancers (Iqbal & Iqbal (2014) Molecular Biology International, vol. 2014, Article ID 852748).

In some embodiments the cancer may comprise cells overexpressing HER2. In some embodiments the cancer may comprise cells expressing HER2 for which the antibody, antigen binding fragment, or polypeptide is specific.

5 Antibodies, antigen binding fragments, polypeptides, conjugates, nucleic acids, vectors, compositions, CARs or cells according to the present invention may be provided for use to treat cancers which express or overexpress HER2. For example, tumour cells overexpressing HER2 may be killed directly by treatment with antibodies, antigen binding fragments, polypeptides, conjugates, CARs or cells according to the present invention, e.g. by cell lysis or apoptosis, by antibody dependent cell-mediated cytotoxicity (ADCC),
10 complement dependent cytotoxicity (CDC), or using anti-HER2 antibody-drug conjugates.

'Treatment' may, for example, be reduction in the development or progression of a disease/condition, alleviation of the symptoms of a disease/condition or reduction in the pathology of a disease/condition. Treatment or alleviation of a disease/condition may be effective to prevent progression of the
15 disease/condition, e.g. to prevent worsening of the condition or to slow the rate of development. In some embodiments treatment or alleviation may lead to an improvement in the disease/condition, e.g. a reduction in the symptoms of the disease/condition or reduction in some other correlate of the severity/activity of the disease/condition. Prevention/prophylaxis of a disease/condition may refer to prevention of a worsening of the condition or prevention of the development of the disease/condition, e.g. preventing an early stage
20 disease/condition developing to a later, chronic, stage.

The treatment may be aimed at prevention of the development or progression of a cancer. As such, the antibodies, antigen binding fragments, polypeptides, conjugates, nucleic acids, vectors, compositions, CARs or cells may be used to formulate pharmaceutical compositions or medicaments and subjects may
25 be prophylactically treated against development of a disease state. This may take place before the onset of symptoms of the disease state, and/or may be given to subjects considered to be at greater risk of development or progression of cancer.

The treatment may be aimed at reducing the number of HER2-expressing cells; inducing cell death of
30 HER2-expressing cells; reducing tumour size; or inhibiting/preventing tumour growth.

In some embodiments a cancer, cell, tumour or subject to be treated has been determined, optionally *in vitro*, to be HER2-positive (HER2+). In some embodiments a method of treatment or prevention described herein comprises determining, optionally *in vitro*, whether HER2 is expressed by a cancer, cell, or tumour
35 of the subject to be treated. The determination may be performed in a sample obtained from the subject.

In some embodiments a cancer, cell, tumour or subject to be treated is one that cannot receive or does not respond to other therapies directed at HER2+ cancer. In some embodiments, a subject to be treated cannot receive and/or has been determined that they cannot receive/be treated with trastuzumab and/or

pertuzumab. For example, trastuzumab has been associated with cardiotoxic effects (Murray, CMAJ. 2006; 174(1): 36–37).

In some embodiments a cancer, cell, tumour or subject to be treated is one that has already been treated with another therapy directed at HER2+ cancer. In some embodiments, a subject to be treated has already been administered and/or treated with trastuzumab and/or pertuzumab.

Cancer

A cancer may be any unwanted cell proliferation (or any disease manifesting itself by unwanted cell proliferation), neoplasm or tumour or increased risk of or predisposition to the unwanted cell proliferation, neoplasm or tumour. The cancer may be benign or malignant and may be primary or secondary (metastatic). A neoplasm or tumour may be any abnormal growth or proliferation of cells and may be located in any tissue. Examples of tissues include the adrenal gland, adrenal medulla, anus, appendix, bladder, blood, bone, bone marrow, brain, breast, cecum, central nervous system (including or excluding the brain) cerebellum, cervix, colon, duodenum, endometrium, epithelial cells (e.g. renal epithelia), gallbladder, oesophagus, glial cells, heart, ileum, jejunum, kidney, lacrimal gland, larynx, liver, lung, lymph, lymph node, lymphoblast, maxilla, mediastinum, mesentery, myometrium, nasopharynx, omentum, oral cavity, ovary, pancreas, parotid gland, peripheral nervous system, peritoneum, pleura, prostate, salivary gland, sigmoid colon, skin, small intestine, soft tissues, spleen, stomach, testis, thymus, thyroid gland, tongue, tonsil, trachea, uterus, vulva, white blood cells.

In some embodiments the cancer to be treated is a cancer of the breast. In some embodiments the cancer to be treated is a cancer of the ovary, uterus, lung, e.g. adenocarcinoma of the lung, or the gastrointestinal tract e.g. stomach, salivary duct.

Tumours to be treated may be nervous or non-nervous system tumours. Nervous system tumours may originate either in the central or peripheral nervous system, e.g. glioma, medulloblastoma, meningioma, neurofibroma, ependymoma, Schwannoma, neurofibrosarcoma, astrocytoma and oligodendroglioma. Non-nervous system cancers/tumors may originate in any other non-nervous tissue, examples include melanoma, mesothelioma, lymphoma, myeloma, leukemia, Non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma, chronic myelogenous leukemia (CML), acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), cutaneous T-cell lymphoma (CTCL), chronic lymphocytic leukemia (CLL), hepatoma, epidermoid carcinoma, prostate carcinoma, breast cancer, lung cancer, colon cancer, ovarian cancer, pancreatic cancer, thymic carcinoma, NSCLC, haematologic cancer and sarcoma.

In some embodiments the cancer is a cancer encoding or expressing HER2. In some embodiments the cancer is a cancer overexpressing HER2. As used herein, a "HER2-positive cancer" or "HER2+ cancer" is a cancer expressing or overexpressing the HER2 gene and/or protein.

As used herein, "a cancer encoding or expressing HER2" or "a cancer overexpressing HER2" includes any cell encoding or expressing HER2. In some embodiments, the cell may be a cell of a tumour. Such cells may be identified as HER2-positive cells or HER2-positive tumour cells. As used herein, "a tumour cell" includes one or more tumour cells.

A cancer or cell expressing or overexpressing HER2 may be identified by methods including immunohistochemistry (IHC), fluorescence in situ hybridisation (FISH), chromogenic in situ hybridization (CISH) and silver enhanced in situ hybridization (SISH), as well as other methods known in the art (Wolff et al., Arch Pathol Lab Med. 2007;131(1):18-43, hereby incorporated by reference in its entirety). Other methods include the HERmark ® test, an assay using the VeraTag system to measure total HER2 as well as HER2 homodimers and heterodimers to predict efficacy of anti-HER2 therapies (Shi et al. (2009) Diagn Mol Pathol. Mar;18(1):11-21, hereby incorporated by reference in its entirety).

HER2 testing results by IHC fall into three categories: positive, equivocal and negative. A positive status is given a score of 3+ and indicates a uniform intense membrane staining of >30% of invasive tumour cells. An equivocal status is given a score of 2+ and indicates complete membrane staining, non-uniform or weak in intensity in at least 10% of the cells or intense complete membrane staining in ≤30% of tumour cells. A negative status is given a score of 1+ or 0 and indicates that there is weak or incomplete membrane staining in any proportion of tumour cells, or no staining, respectively (Wolff et al., *supra*). In the context of the present invention, a score of 3+ or 2+ is considered to be "HER2-positive".

Fluorescent (FISH) or chromogenic (CISH) in situ hybridization for HER2 gene amplification has become an integral part of the diagnostic work up for patients with breast cancer. The principles of in situ hybridization are simple: DNA probes complementary to genomic sequences of interest are generated, labeled and then hybridized to the target tissue. FISH/CISH methods can be applied to a wide range of samples: cell lines, frozen tissue, paraffin embedded tissue and micro-tissue arrays. FISH utilizes fluorescence microscopy while CISH employs light microscopy (Gutierrez and Schiff (2011) Arch Pathol Lab Med. 135(1): 55–62). CISH has some advantages in the detection of gene amplification over FISH: 1) permanent staining, samples can be archived; 2) use of bright field microscopy; 3) easy identification of the target cells; 4) tumor heterogeneity is easily assessed, but CISH does not permit a determination of the actual gene copy number (Lambros et al., Hum Pathol. 2007 Aug; 38(8):1105-22).

HER2 FISH positive is defined as an average of >6 HER2 gene copies/nucleus for test systems without an internal control probe or HER2/CEP 17 ratio of more than 2.2, where CEP17 is a centromeric probe for chromosome 17 on which the HER2 gene resides. The equivocal range for HER2 FISH assays is defined as HER/CEP ratios from 1.8 to 2.2 or average gene copy number between 4.0 and 6.0 for those systems without an internal control. Negative HER2 FISH amplification is defined as HER2/CEP17 ratio of less than 1.8 or an average of fewer than four copies of HER2 gene per nucleus for systems without an internal control probe (Wolff et al. *supra*). In the context of the present invention, a FISH status of positive or equivocal is considered to be "HER2-positive".

Formulating pharmaceutically useful compositions and medicaments

Antibodies, antigen binding fragments, polypeptides, conjugates, nucleic acids, vectors, CARs and cells according to the present invention may be formulated as pharmaceutical compositions for clinical use and may comprise a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.

In accordance with the present invention methods are also provided for the production of pharmaceutically useful compositions, such methods of production may comprise one or more steps selected from: isolating an antibody, antigen binding fragment, polypeptide, conjugate, nucleic acid, vector, CAR, or cell as described herein; and/or mixing an isolated antibody, antigen binding fragment, polypeptide, conjugate, nucleic acid, vector, CAR, or cell as described herein with a pharmaceutically acceptable carrier, adjuvant, excipient or diluent.

For example, a further aspect of the present invention relates to a method of formulating or producing a medicament or pharmaceutical composition for use in the treatment of a cancer, the method comprising formulating a pharmaceutical composition or medicament by mixing an antibody, antigen binding fragment, polypeptide, conjugate, conjugate, nucleic acid, vector, CAR, or cell as described herein with a pharmaceutically acceptable carrier, adjuvant, excipient or diluent.

Antibodies, antigen binding fragments, polypeptides, conjugates, nucleic acids, vectors, CARs, cells, medicaments and pharmaceutical compositions according to aspects of the present invention may be formulated for administration by a number of routes, including but not limited to, parenteral, intravenous, intra-arterial, intramuscular, intratumoural, oral and nasal. The medicaments and compositions may be formulated for injection or formulated in solid form. Antibodies, antigen binding fragments, polypeptides, conjugates, nucleic acids, vectors, CARs, cells and therapeutic agents may be formulated in fluid or solid form. Fluid formulations may be formulated for administration by injection to a selected region of the human or animal body.

Administration of an antibody, antigen binding fragment, polypeptide, conjugate, nucleic acid, vector, composition, CAR or cell is preferably in a "therapeutically effective amount", this being sufficient to show benefit to the individual. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of the disease being treated. Prescription of treatment, e.g. decisions on dosage etc., is within the responsibility of general practitioners and other medical doctors, and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners. Examples of the techniques and protocols mentioned above can be found in Remington's Pharmaceutical Sciences, 20th Edition, 2000, pub. Lippincott, Williams & Wilkins, incorporated herein by reference.

Antibodies, antigen binding fragments, polypeptides, conjugates, nucleic acids, vectors, CARs, cells, medicaments and pharmaceutical compositions may be administered alone or in combination with other

treatments, either simultaneously or sequentially dependent upon the condition to be treated. The other treatment may be one or more therapeutic agents.

In this specification an antibody, antigen binding fragment, polypeptide, conjugate, nucleic acid, vector, CAR, cell or composition of the present invention and a therapeutic agent may be administered simultaneously or sequentially. The therapeutic agent may be a chemotherapeutic agent.

In some embodiments, treatment with an antibody, antigen binding fragment, polypeptide, conjugate, nucleic acid, vector, composition, CAR, or cell of the present invention may be accompanied by chemotherapy.

In some embodiments, treatment with an antibody, antigen binding fragment, polypeptide, conjugate, nucleic acid, vector, composition, CAR, or cell of the present invention may be accompanied by at least one anti-cancer agent. "At least one anti-cancer agent" refers to one, or two, or three, or four, or more agents that are effective in the treatment of malignant, or cancerous, disease such as the cancers described herein.

Simultaneous administration refers to administration of the antibody, antigen binding fragment, polypeptide, conjugate, nucleic acid, vector, composition, CAR, or cell together with the therapeutic or anti-cancer agent, for example as a pharmaceutical composition containing both agents (combined preparation), or immediately after each other and optionally via the same route of administration, e.g. to the same artery, vein or other blood vessel.

Sequential administration refers to administration of one of the antibody, antigen binding fragment, polypeptide, conjugate, nucleic acid, vector, composition, CAR, or cell or therapeutic agent/anti-cancer agent followed after a given time interval by separate administration of the other agent. It is not required that the two agents are administered by the same route, although this is the case in some embodiments. The time interval may be any time interval.

A therapeutic agent or anti-cancer agent as described herein may be an anti-HER2 antibody or an agent which targets HER2. In some embodiments a therapeutic agent or anti-cancer agent as described herein is one or more of trastuzumab (Herceptin®), trastuzumab emtansine (Kadcyla®), lapatinib (Tyverb®), and/or pertuzumab (Perjeta®). In some embodiments an antibody, antigen-binding molecule or polypeptide as described herein is administered in combination, e.g. simultaneously or sequentially, with one or more of the above agents, such as trastuzumab (Herceptin®) and/or pertuzumab (Perjeta®).

A therapeutic agent or anti-cancer agent as described herein may be formulated so as to be suitable for injection or infusion to a tumour or to the blood.

Chemotherapy/radiotherapy

Chemotherapy and radiotherapy respectively refer to treatment of a cancer with a drug or with ionising radiation (e.g. radiotherapy using X-rays or γ -rays).

5 The drug may be a chemical entity, e.g. small molecule pharmaceutical, antibiotic, DNA intercalator, protein inhibitor (e.g. kinase inhibitor), or a biological agent, e.g. antibody, antibody fragment, nucleic acid or peptide aptamer, nucleic acid (e.g. DNA, RNA), peptide, polypeptide, or protein. The drug may be formulated as a pharmaceutical composition or medicament. The formulation may comprise one or more drugs (e.g. one or more active agents) together with one or more pharmaceutically acceptable diluents,
10 excipients or carriers.

A treatment may involve administration of more than one drug. A drug may be administered alone or in combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated. For example, the chemotherapy may be a co-therapy involving administration of two drugs, one
15 or more of which may be intended to treat the cancer.

The chemotherapy may be administered by one or more routes of administration, e.g. parenteral, intravenous injection, oral, subcutaneous, intradermal or intratumoral.

20 The chemotherapy may be administered according to a treatment regime. The treatment regime may be a pre-determined timetable, plan, scheme or schedule of chemotherapy administration which may be prepared by a physician or medical practitioner and may be tailored to suit the patient requiring treatment.

The treatment regime may indicate one or more of: the type of chemotherapy to administer to the patient;
25 the dose of each drug or radiation; the time interval between administrations; the length of each treatment; the number and nature of any treatment holidays, if any etc. For a co-therapy a single treatment regime may be provided which indicates how each drug is to be administered.

Chemotherapeutic drugs and biologics may be selected from: alkylating agents such as cisplatin, carboplatin, mechlorethamine, cyclophosphamide, chlorambucil, ifosfamide; purine or pyrimidine anti-metabolites such as azathiopurine or mercaptopurine; alkaloids and terpenoids, such as vinca alkaloids (e.g. vincristine, vinblastine, vinorelbine, vindesine), podophyllotoxin, etoposide, teniposide, taxanes such as paclitaxel (TaxolTM), docetaxel; topoisomerase inhibitors such as the type I topoisomerase inhibitors camptothecins irinotecan and topotecan, or the type II topoisomerase inhibitors amsacrine, etoposide,
30 etoposide phosphate, teniposide; antitumor antibiotics (e.g. anthracycline antibiotics) such as dactinomycin, doxorubicin (AdriamycinTM), epirubicin, bleomycin, rapamycin; antibody based agents, such as anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-TIM-3 antibodies, anti-CTLA-4, anti-4-1BB, anti-GITR, anti-CD27, anti-BLTA, anti-OX43, anti-VEGF, anti-TNF α , anti-IL-2, antiGpIIb/IIIa, anti-CD-52, anti-CD20, anti-RSV, anti-HER2/neu(erbB2), anti-TNF receptor, anti-EGFR antibodies, monoclonal antibodies or antibody
35 fragments, examples include: cetuximab, panitumumab, infliximab, basiliximab, bevacizumab (Avastin[®]),
40

abciximab, daclizumab, gemtuzumab, alemtuzumab, rituximab (Mabthera®), palivizumab, trastuzumab, etanercept, adalimumab, nimotuzumab; EGFR inhibitors such as erlotinib, cetuximab and gefitinib; anti-angiogenic agents such as bevacizumab (Avastin®); cancer vaccines such as Sipuleucel-T (Provenge®).

- 5 Further chemotherapeutic drugs may be selected from: 13-cis-Retinoic Acid, 2-Chlorodeoxyadenosine, 5-Azacitidine, 5-Fluorouracil, 6-Mercaptopurine, 6-Thioguanine, Abraxane, Accutane®, Actinomycin-D Adriamycin®, Atracuril®, Afinitor®, Agrylin®, Ala-Cort®, Aldesleukin, Alemtuzumab, ALIMTA, Alitretinoin, Alkaban-AQ®, Alkeran®, All-transretinoic Acid, Alpha Interferon, Altretamine, Amethopterin, Amifostine, Aminoglutethimide, Anagrelide, Anandron®, Anastrozole, Arabinosylcytosine, Aranesp®, Aredia®,
- 10 Arimidex®, Aromasin®, Arranon®, Arsenic Trioxide, Asparaginase, ATRA Avastin®, Azacitidine, BCG, BCNU, Bendamustine, Bevacizumab, Bexarotene, BEXXAR®, Bicalutamide, BiCNU, Bleomycin, Bortezomib, Busulfan, Busulfex®, Calcium Leucovorin, Campath®, Camptosar®, Camptothecin-11, Capecitabine, Carac™, Carboplatin, Carmustine, Casodex®, CC-5013, CCI-779, CCNU, CDDP, CeeNU, Cerubidine®, Cetuximab, Chlorambucil, Cisplatin, Citrovorum Factor, Cladribine,
- 15 Cortisone, Cosmegen®, CPT-11, Cyclophosphamide, Cytadren®, Cytarabine Cytosar-U®, Cytoxan®, Dacogen, Dactinomycin, Darbepoetin Alfa, Dasatinib, Daunomycin, Daunorubicin, Daunorubicin Hydrochloride, Daunorubicin Liposomal, DaunoXome®, Decadron, Decitabine, Delta-Cortef®, Deltasone®, Denileukin, Diflucan, DepoCyt™, Dexamethasone, Dexamethasone Acetate, Dexamethasone Sodium Phosphate, Dexasone, Dexrazoxane, DHAD, DIC, Diodes, Docetaxel, Doxil®, Doxorubicin, Doxorubicin
- 20 Liposomal, Droxia™, DTIC, DTIC-Dome®, Duralone®, Eligard™, Ellence™, Eloxatin™, Elspar®, Emcyte®, Epirubicin, Epoetin Alfa, Erbitux, Erlotinib, Erwinia L-asparaginase, Estramustine, Ethiol Etopophos®, Etoposide, Etoposide Phosphate, Eulexin®, Everolimus, Evista®, Exemestane, Faslodex®, Femara®, Filgrastim, Floxuridine, Fludara®, Fludarabine, Fluoroplex®, Fluorouracil, Fluoxymesterone, Flutamide, Folinic Acid, FUDR®, Fulvestrant, Gefitinib, Gemcitabine, Gemtuzumab ozogamicin, Gleevec™, Gliadel®
- 25 Wafer, Goserelin, Granulocyte - Colony Stimulating Factor, Granulocyte Macrophage Colony Stimulating Factor, Herceptin®, Hexadrol, Hexalen®, Hexamethylmelamine, HMM, Hycamtin®, Hydrea®, Hydrocort Acetate®, Hydrocortisone, Hydrocortisone Sodium Phosphate, Hydrocortisone Sodium Succinate, Hydrocortone Phosphate, Hydroxyurea, Ibritumomab, Ibritumomab Tiuxetan, Idamycin®, Idarubicin, Ifex®, IFN-alpha, Ifosfamide, IL-11, IL-2, Imatinib mesylate, Imidazole Carboxamide, Interferon alfa, Interferon
- 30 Alfa-2b (PEG Conjugate), Interleukin - 2, Interleukin-11, Intron A® (interferon alfa-2b), Iressa®, Irinotecan, Isotretinoin, Ixabepilone, Ixempra™, Kidrolase, Lanacort®, Lapatinib, L-asparaginase, LCR, Lenalidomide, Letrozole, Leucovorin, Leukeran, Leukine™, Leuprolide, Leurocristine, Leustatin™, Liposomal Ara-C, Liquid Pred®, Lomustine, L-PAM, L-Sarcosine, Lupron®, Lupron Depot®, Matulane®, Maxidex, Mechlorethamine, Mechlorethamine Hydrochloride, Medrolone®, Medrol®, Megace®, Megestrol, Megestrol
- 35 Acetate, Melphalan, Mercaptopurine, Mesna, Mesnex™, Methotrexate, Methotrexate Sodium, Methylprednisolone, Meticorten®, Mitomycin, Mitomycin-C, Mitoxantrone, M-Prednisol®, MTC, MTX, Mustargen®, Mustine, Mutamycin®, Myleran®, Mylocel™, Mylotarg®, Navelbine®, Nelarabine, Neosar®, Neulasta™, Neumega®, Neupogen®, Nexavar®, Nilandron®, Nilutamide, Nipent®, Nitrogen Mustard, Novaldex®, Novantrone®, Octreotide, Octreotide acetate, Oncospar®, Oncovin®, Ontak®, Onxal™,
- 40 Oprevelkin, Orapred®, Orasone®, Oxaliplatin, Paclitaxel, Paclitaxel Protein-bound, Pamidronate,

- Panitumumab, Panretin®, Paraplatin®, Pediapred®, PEG Interferon, Pegaspargase, Pegfilgrastim, PEG-
 INTRON™, PEG-L-asparaginase, PEMETREXED, Pentostatin, Phenylalanine Mustard, Platinol®, Platinol-
 AQ®, Prednisolone, Prednisone, Prelone®, Procarbazine, PROCRT®, Proleukin®, Prolifeprospan 20 with
 Carmustine Implant Purinethol®, Raloxifene, Revlimid®, Rheumatex®, Rituxan®, Rituximab, Roferon-A®
 5 (Interferon Alfa-2a), Rubex®, Rubidomycin hydrochloride, Sandostatin® Sandostatin LAR®, Sargramostim,
 Solu-Cortef®, Solu-Medrol®, Sorafenib, SPRYCEL™, STI-571, Streptozocin, SU11248, Sunitinib, Sutent®,
 Tamoxifen, Tarceva®, Targretin®, Taxol®, Taxotere®, Temodar®, Temozolomide, Temsirolimus,
 Teniposide, TESPAs, Thalidomide, Thalomid®, TheraCys®, Thioguanine, Thioguanine Tabloid®,
 Thiophosphoamide, Thioplex®, Thiotepa, TICE®, Toposar®, Topotecan, Toremifene, Torisel®,
 10 Tositumomab, Trastuzumab, Treanda®, Tretinoin, Trexall™, Trisenox®, TSPA, TYKERB®, VCR,
 Vectibix™, Velban®, Velcade®, VePesid®, Vesanoid®, Viadur™, Vidaza®, Vinblastine, Vinblastine
 Sulfate, Vincasar Pfs®, Vincristine, Vinorelbine, Vinorelbine tartrate, VLB, VM-26, Vorinostat, VP-16,
 Vumon®, Xeloda®, Zanosar®, Zevalin™, Zinecard®, Zoladex®, Zoledronic acid, Zolinza, Zometa®.
- 15 In some embodiments the antibody/antigen binding fragment according to the present invention is
 administered in combination with one or more of doxorubicin, epirubicin, paclitaxel, docetaxel, fluorouracil,
 cyclophosphamide, methotrexate and capecitabine.

Dosage regimes

- 20 Multiple doses of the antibody, antigen binding fragment, polypeptide, conjugate, nucleic acid, vector, CAR
 or cell may be provided. One or more, or each, of the doses may be accompanied by simultaneous or
 sequential administration of another therapeutic agent.

- 25 Multiple doses may be separated by a predetermined time interval, which may be selected to be one of 1,
 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or 31
 days, or 1, 2, 3, 4, 5, or 6 months. By way of example, doses may be given once every 7, 14, 21 or 28 days
 (plus or minus 3, 2, or 1 days).

Kits

- 30 In some aspects of the present invention a kit of parts is provided. In some embodiments the kit may have
 at least one container having a predetermined quantity of the antibody, antigen binding fragment,
 polypeptide, conjugate, nucleic acid, vector, CAR or cell according to the invention. The kit may provide the
 antibody, antigen binding fragment, polypeptide, conjugate, nucleic acid, vector, CAR or cell in the form of
 a medicament or pharmaceutical composition, and may be provided together with instructions for
 35 administration to a patient in order to treat a specified disease or condition. The antibody, antigen binding
 fragment or polypeptide may be formulated so as to be suitable for injection or infusion to a tumour or to
 the blood.

In some embodiments the kit may further comprise at least one container having a predetermined quantity of another therapeutic agent (e.g. chemotherapeutic agent or anti-cancer agent). In such embodiments, the kit may also comprise a second medicament or pharmaceutical composition such that the two medicaments or pharmaceutical compositions may be administered simultaneously or separately such that they provide a combined treatment for the specific disease or condition. The therapeutic agent or anti-cancer agent may also be formulated so as to be suitable for injection or infusion to a tumour or to the blood.

Subjects

The subject to be treated with an antibody, antigen binding fragment, polypeptide, conjugate, nucleic acid, vector, CAR or cell according to the invention may be any animal or human. The subject is preferably mammalian, more preferably human. The subject may be a non-human mammal, but is more preferably human. The subject may be male or female. The subject may be a patient. A subject may have been diagnosed with a disease or condition requiring treatment, or be suspected of having such a disease or condition.

Sequence Identity

Percentage (%) sequence identity is defined as the percentage of amino acid residues in a candidate sequence that are identical with residues in the given listed sequence (referred to by the SEQ ID NO) after aligning the sequences and introducing gaps if necessary, to achieve the maximum sequence identity, and not considering any conservative substitutions as part of the sequence identity. Sequence identity is preferably calculated over the entire length of the respective sequences.

Where the aligned sequences are of different length, sequence identity of the shorter comparison sequence may be determined over the entire length of the longer given sequence or, where the comparison sequence is longer than the given sequence, sequence identity of the comparison sequence may be determined over the entire length of the shorter given sequence.

Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways known to a person of skill in the art, for instance, using publicly available computer software such as ClustalW 1.82., ClustalO, T-coffee or Megalign (DNASTAR) software. When using such software, the default parameters, e.g. for gap penalty and extension penalty, are preferably used. The default parameters of ClustalW 1.82 are: Protein Gap Open Penalty = 10.0, Protein Gap Extension Penalty = 0.2, Protein matrix = Gonnet, Protein/DNA ENDGAP = -1, Protein/DNA GAPDIST = 4. The default parameters of ClustalO are described in Söding, J. (2005) 'Protein homology detection by HMM–HMM comparison'. *Bioinformatics* 21, 951-960.

Recombinant production

The immunogens, antibodies, fragments, polypeptides, conjugates and CARs according to the invention may be produced by recombinant expression. Molecular biology techniques suitable for recombinant production

are well known in the art, such as those set out in Green and Sambrook, *Molecular Cloning: A Laboratory Manual* (4th Edition), Cold Spring Harbor Press, 2012, which is hereby incorporated by reference in its entirety.

5 In some embodiments, a nucleic acid described herein is purified or isolated, e.g. from other nucleic acid, or naturally-occurring biological material. In some embodiments the nucleic acid(s) comprise or consist of DNA and/or RNA.

10 Expression may be from a nucleotide sequence. The nucleotide sequence may be contained in a vector. A “vector” as used herein is an oligonucleotide molecule (DNA or RNA) used as a vehicle to transfer foreign genetic material into a cell. The vector may be an expression vector for expression of the foreign genetic material in the cell. Such vectors may include a promoter sequence operably linked to the nucleotide sequence encoding the sequence to be expressed. A vector may also include a termination codon and expression enhancers. Any suitable vectors, promoters, enhancers and termination codons known in the art may be used to express a peptide or polypeptide from a vector according to the invention. In some 15 embodiments, the vector may be a plasmid, MAC, virus, etc. In some embodiments, the vector may be a eukaryotic expression vector, e.g. a vector comprising the elements necessary for expression of protein from the vector in a eukaryotic cell. In some embodiments, the vector may be a mammalian expression vector, e.g. comprising a cytomegalovirus (CMV) or SV40 promoter to drive protein expression.

20 The term “operably linked” may include the situation where a selected nucleotide sequence and regulatory nucleotide sequence (e.g. promoter and/or enhancer) are covalently linked in such a way as to place the expression of the nucleotide sequence under the influence or control of the regulatory sequence (thereby forming an expression cassette). Thus a regulatory sequence is operably linked to the selected nucleotide sequence if the regulatory sequence is capable of effecting transcription of the nucleotide sequence. The 25 resulting transcript may then be translated into a desired peptide or polypeptide.

30 For recombinant production according to the invention, any cell suitable for the expression of polypeptides may be used. The cell may be a prokaryote or eukaryote. In some embodiments the cell is a prokaryotic cell, such as a cell of archaea or bacteria. In some embodiments the bacteria may be Gram-negative bacteria such as bacteria of the family Enterobacteriaceae, for example *Escherichia coli*.

35 In some embodiments, the cell is a eukaryotic cell such as a yeast cell, a plant cell, insect cell or a mammalian cell, e.g. CHO, HEK, HeLa or COS cells. In some embodiments the host cell is a non-human cell, e.g. a non-human mammalian cell.

40 In some cases the cell is not a prokaryotic cell because some prokaryotic cells do not allow for the same folding or post-translational modifications as eukaryotic cells. In addition, very high expression levels are possible in eukaryotes and proteins can be easier to purify from eukaryotes using appropriate tags. Specific plasmids may also be utilised which enhance secretion of the protein into the media.

Production may involve culture or fermentation of a eukaryotic cell modified to express the peptide or polypeptide. The culture or fermentation may be performed in a bioreactor provided with an appropriate supply of nutrients, air/oxygen and/or growth factors. Secreted proteins can be collected by partitioning culture media/fermentation broth from the cells, extracting the protein content, and separating individual proteins to isolate secreted peptide or polypeptide. Culture, fermentation and separation techniques are well known to those of skill in the art, and are described, for example, in Green and Sambrook, *Molecular Cloning: A Laboratory Manual* (4th Edition; incorporated by reference herein above).

Bioreactors include one or more vessels in which cells may be cultured. Culture in the bioreactor may occur continuously, with a continuous flow of reactants into, and a continuous flow of cultured cells from, the reactor. Alternatively, the culture may occur in batches. The bioreactor monitors and controls environmental conditions such as pH, oxygen, flow rates into and out of, and agitation within the vessel such that optimum conditions are provided for the cells being cultured.

Following culture of cells that express the immunogen, antibody, fragment, polypeptide, conjugate or CAR, the peptide/polypeptide of interest is preferably isolated. Any suitable method for separating proteins from cell culture known in the art may be used. In order to isolate the peptide/polypeptide from a culture, it may be necessary to first separate the cultured cells from media containing the peptide/polypeptide of interest. If the peptide/polypeptide of interest is secreted from the cells, the cells may be separated from the culture media that contains the secreted peptide/polypeptide of interest by centrifugation. If the peptide/polypeptide of interest collects within the cell it will be necessary to disrupt the cells prior to centrifugation, for example using sonification, rapid freeze-thaw or osmotic lysis. Centrifugation will produce a pellet containing the cultured cells, or cell debris of the cultured cells, and a supernatant containing culture medium and the peptide/polypeptide of interest.

It may then be desirable to isolate the peptide/polypeptide of interest from the supernatant or culture medium, which may contain other protein and non-protein components. A common approach to separating protein components from a supernatant or culture medium is by precipitation. Proteins of different solubilities are precipitated at different concentrations of precipitating agent such as ammonium sulfate. For example, at low concentrations of precipitating agent, water soluble proteins are extracted. Thus, by adding different increasing concentrations of precipitating agent, proteins of different solubilities may be distinguished. Dialysis may be subsequently used to remove ammonium sulfate from the separated proteins.

Other methods for distinguishing different proteins are known in the art, for example ion exchange chromatography and size chromatography. These may be used as an alternative to precipitation, or may be performed subsequently to precipitation.

Once the peptide/polypeptide of interest has been isolated from culture it may be desired or necessary to concentrate the peptide or polypeptide. A number of methods for concentrating proteins are known in the art, such as ultrafiltration or lyophilisation.

5 Sequences

SEQ ID NO:	Description	Sequence
1	P1A3 (lambda) (light chain VD) (Fig 1A)	QAVVTQEPSL SVSPGGTVTL TCGLSSGSVS TGHYASWYQQ TPGQAPRTLF YNTNTRSSGV PDRFSGSIVG NKAALTITGA QAEDDESYYC VLYVGDGIWV FGGGTKLTVL GQPKAAPSVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV AWKADSSPVK AGVETTTPSK QSNNKYAASS YLSLTPEQWK SHKSYSCQVT HEGSTVEKTV APTECS
2	P1C5 (lambda) (light chain VD) (Fig 1B)	QTVVTQEPSF SVSPGGTVTL TCGLSSGSVS TGYYPWYQQ TPGQAPRTLI YSTNSRSSGV PDRFSGSILG NKAALTITGA QAEDDESYYC VLYMGSGISV FGGGTKLTVL GQPKAAPSVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV AWKADSSPVK AGVETTTPSK QSNNKYAASS YLSLTPEQWK SHKSYSCQVT HEGSTVEKTV APTECS
3	P1E4 (lambda) (light chain VD) (Fig 1C)	QTVVTQEPSF SVSPGGTVTL TCGLSSGSVS TSYYPWYQQ IPGQAPRTLI YTTNIRSSGV PDRFSGSILG NKAALTITGA QAEDDESYYC MLYMGSGIIV FGGGTKLTVL GQPKAAPSVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV AWKADSSPVK AGVETTTPSK QSNNKYAASS YLSLTPEQWK SHKSYSCQVT HEGSTVEKTV APAECS
4	P1F1 (lambda) (light chain VD) (Fig 1D)	QTVVTQEPSF SVSPGGTVTL TCGLSSGSVS TSYYPWYQQ TPGQAPRTLI YSTNTRSSGV PDRFSGSILG NKAALTITGA QAEDDESYYC VLYMGSGIIV FGGGTKLTVL GQPKAAPSVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV AWKADSSPVK AGVETTTPSK QSNNKYAASS YLSLTPEQWK SHKSYSCQVT HEGSTVEKTV APTECS
5	P1A3 (heavy chain VD; Fig 2A)	EVQLVQSGTE VKKPGASVRV SCKSSGYTFT SYIIHWVRQA PGQGLEWMAI INPGNGDTNY AQRFGQVRITM TRDTSTSTVY MELRSLRSDT TAVYFCAREI ASYSGSYDYD WGQGTLLTVTS S
6	P1C5 (heavy chain VD; Fig 2B)	QVQLQESGPG LVKPSSETLSL TCTVSGGSIS SSSYYWGWRP QPPGKLEWII GSIYSGSTY YNPSLKSRTV ISVDTSKNQF SLKLSSVTAA DTAVYYCARY APDSSGYLVA FDIWGQGTMTV TVSS
7	P1E4 (heavy chain VD; Fig 2C)	QVQLQQWGAG LLKPSSETLSL TCAVYGGSF S GYYWSWIRQP PGKGLEWIGE INHSGSTNYN PSLKSRTVITIS VDTSKNQFSL KLSSVTADT AVYYCARMGI NSGGYLYGMD VWGQGTITVTV SS
8	P1F1 (heavy chain VD; Fig 2D)	QVQLVESGPG LVKPSGTLSSL TCAVSGGSIS SSNWSWVRQ PPGKLEWIG EIIYHSGSTNY NPSLKSRTVIT SVDTSKNQFS LKLSSVTAA TAVYYCARMG ANSGGYLYGM DVWGQGTITVT VSS
9	LC-CDR1 consensus	GLSSGSVSTX ₁ X ₂ YX ₃ S
10	LC-CDR2 consensus	X ₄ TNX ₅ RSS
11	LC-CDR3 consensus	X ₆ LYX ₇ GX ₈ GIX ₉ V
12	HC-CDR1 consensus	X ₁₀ X ₁₁ X ₁₂ X ₁₃ X ₁₄ X ₁₅ X ₁₆
13	HC-CDR2 consensus	X ₁₇ X ₁₈ X ₁₉ X ₂₀ X ₂₁ X ₂₂ GX ₂₃ TX ₂₄ YX ₂₅ X ₂₆ X ₂₇ X ₂₈ X ₂₉ X ₃₀
14	HC-CDR3 consensus	X ₃₁ X ₃₂ X ₃₃ X ₃₄ X ₃₅ SX ₃₆ X ₃₇ YX ₃₈ X ₃₉ X ₄₀ X ₄₁ X ₄₂ X ₄₃
15	P1A3 LC-CDR1	GLSSGSVSTGHYAS
16	P1A3 LC-CDR2	NTNTRSS
17	P1A3 LC-CDR3	VLYVGDGIWV
18	P1A3 HC-CDR1	SYIIH
19	P1A3 HC-CDR2	IINPGNGDTNYAQRFGQ
20	P1A3 HC-CDR3 PFG3 HC-CDR3	EIASYSGSYDYD
21	P1C5 LC-CDR1	GLSSGSVSTGYIPS
22	P1C5 LC-CDR2	STNSRSS
23	P1C5 LC-CDR3 PFG3 LC-CDR3	VLYMGSGISV
24	P1C5 HC-CDR1 PFF5 HC-CDR1	SSSYYWG
25	P1C5 HC-CDR2 PFF5 HC-CDR2	SIYYSYSTYYNPSLKS
26	P1C5 HC-CDR3 PFF5 HC-CDR3	YAPDSSGYLVAFDI
27	P1E4 LC-CDR1 P1F1 LC-CDR1	GLSSGSVSTSYIPS
28	P1E4 LC-CDR2	TTNIRSS
29	P1E4 LC-CDR3	MLYMGSGIIV
30	P1E4 HC-CDR1 P1D2 HC-CDR1	GYYWS

31	P1E4 HC-CDR2 P1D2 HC-CDR2	EINHSGSTNYPNPSLKS
32	P1E4 HC-CDR3	MGINSGGYLYGMDV
33	P1F1 LC-CDR2 PFF5 LC-CDR2	STNTRSS
34	P1F1 LC-CDR3	VLYMGSGIWW
35	P1F1 HC-CDR1	SSNWWS
36	P1F1 HC-CDR2	EIYHSGSTNYPNPSLKS
37	P1F1 HC-CDR3	MGANSGGYLYGMDV
38	P1A3 (lambda) LC Nucleotide sequence	CAG GCT GTG GTG ACT CAG GAG CCA TCG TTG TCA GTG TCC CCT GGA GGG ACA GTC ACA CTC ACT TGT GGC TTG AGC TCT GGC TCA GTC TCT ACT GGT CAC TAC GCC AGC TGG TAC CAG CAG ACC CCA GGC CAG GCT CCA CGC ACG CTC TTC TAC AAC ACA AAC ACT CGC TCT TCT GGG GTG CCT GAT CGC TTC TCT GGC TCC ATC GTT GGG AAC AAA GCT GCC CTC ACC ATC ACG GGG GCC CAG GCA GAT GAT GAA TCT GAC TAT TAC TGT GTG CTG TAT GTG GGT GAT GGC ATT TGG GGT TTC GGC GGA GGG ACC AAG CTG ACC GTC CTA GGT CAG CCC AAG GGT GCC CCC TCG GTC ACT CTG TTC CCA CCC TCC TCT GAG GAG CTT CAA GCC AAC AAG GCC ACA CTG GTG TGT CTC ATA AGT GAC TTC TAC CCG GGA GCC GTG ACA GTG GCC TGG AAG GCA GAT AGC AGC CCC GTC AAG GCG GGA GTG GAG ACC ACC ACA CCC TCC AAA CAA AGC AAC AAC AAG TAC GCG GCC AGC AGC TAC CTG AGC CTG ACG CCT GAG CAG TGG AAG TCC CAC AAA AGC TAC AGC TGC CAG GTC AGC CAT GAA GGG AGC ACC GTG GAG AAG ACA GTG GCC CCT ACA GAA TGT TCA
39	P1C5 (lambda) LC Nucleotide sequence	CAG ACT GTG GTG ACT CAG GAG CCA TCG TTC TCA GTG TCC CCT GGA GGG ACA GTC ACA CTC ACT TGT GGC TTG AGC TCT GGC TCA GTC TCT ACT GGT TAC TAC CCC AGC TGG TAC CAG CAG ACC CCA GGC CAG GCT CCA CGC ACG CTC ATC TAC AGC ACA AAC AGT CGC TCT TCT GGG GTG CCT GAT CGC TTC TCT GGC TCC ATC CTT GGG AAC AAA GCT GCC CTC ACC ATC ACG GGG GCC CAG GCA GAA GAT GAA TCT GAT TAT TAC TGT GTG CTG TAT ATG GGT AGT GGC ATT TCG GTG TTC GGC GGA GGG ACC AAG CTG ACC GTC CTA GGT CAG CCC AAG GCT GCC CCC TCG GTC ACT CTG TTC CCA CCC TCC TCT GAG GAG CTT CAA GCC AAC AAG GCC ACA CTG GTG TGT CTC ATA AGT GAC TTC TAC CCG GGA GCC GTG ACA GTG GCC TGG AAG GCA GAT AGC AGC CCC GTC AAG GCG GGA GTG GAG ACC ACC ACA CCC TCC AAA CAA AGC AAC AAC AAG TAC GCG GCC AGC AGC TAC CTG AGC CTG ACG CCT GAG CAG TGG AAG TCC CAC AAA AGC TAC AGC TGC CAG GTC ACG CAT GAA GGG AGC ACC GTG GAG AAG ACA GTG GCC CCT ACA GAA TGT TCA
40	P1E4 (lambda) LC Nucleotide sequence	CAG ACT GTG GTG ACT CAG GAG CCA TCG TTC TCA GTG TCC CCT GGA GGG ACC GTC ACA CTC ACT TGT GGC CTG AGC TCT GGC TCA GTC TCT ACT AGT TAC TAC CCC AGC TGG TAC CAA CAG ATT CCA GGC CAG GCT CCA CGC ACG CTC ATT TAC ACC ACA AAC ATT CGC TCT TCT GGG GTG CCT GAT CGC TTC GGT GGC TCC ATC CTT GGG AAC AAA GCT GCC CTC ACC ATC ACG GGG GCC CAG GCA GAA GAT GAA TCT GAT TAC TAC TGT ATG CTC TAT ATG GGG AGT GGC ATT TGG GTG TTC GGC GGA GGG ACC AAA CTG ACC GTC CTA GGT CAG CCC AAG ACT GCC CCC TCG GTC ACT CTG TTC CCA CCC TCC TCT GAG GAG CTT CAA GCC AAC AAG GCC ACA CTG GTG TGT CTC ATA AGT GAC TTC TAC CCG GGA GCC GTG ACA GTG GCC TGG AAG GCA GAT AGC AGC CCC GTC AAG GCG GGA GTG GAG ACC ACC ACA CCC TCC AAA CAA AGC AAC AAC AAG TAC GCG GCC AGC AGC TAC CTG AGC CTG ACG CCT GAG CAG TGG AAG TCC CAC AAA AGC TAC AGC TGC CAG GTC ACG CAT GAA GGG AGC ACC GTG GAG AAG ACA GTG GCC CCT ACA GAA TGT TCA
41	P1F1 (lambda) LC VD Nucleotide sequence	CAG ACT GTG GTG ACT CAG GAG CCA TCG TTC TCA GTG TCC CCT GGA GGG ACA GTC ACA CTC ACT TGT GGC TTG AGC TCT GGC TCA GTC TCT ACT AGT TAC TAC CCC AGC TGG TAC CAG CAG ACC CCA GGC CAG GCT CCA CGC ACG CTC ATC TAC AGC ACA AAC ACT CGC TCT TCT GGG GTG CCT GAT CGC TTC TCT GGC TCC ATC CTT GGG AAC AAA GCT GCC CTC ACC ATC ACG GGG GCC CAG GCA GAT GAT GAA TCT GAT TAT TAC TGT GTG CTG TAT ATG GGT AGT GGC ATT TGG GTG TTC GGC GGA GGG ACC AAG CTG ACC GTC CTA GGT CAG CCC AAG GGT GCC CCC TCG GTC ACT CTG TTC CCA CCC TCC TCT GAG GAG CTT CAA GCC AAC AAG GCC ACA CTG GTG TGT CTC ATA AGT GAC TTC TAC CCG GGA GCC GTG ACA GTG GCC TGG AAG GCA GAT AGC AGC CCC GTC AAG GCG GGA GTG GAG ACC ACC ACA CCC TCC AAA CAA AGC AAC AAC AAG TAC GCG GCC AGC AGC TAC CTG AGC CTG ACG CCT GAG CAG TGG AAG TCC CAC AAA AGC TAC AGC TGC CAG GTC ACG CAT GAA GGG AGC ACC GTG GAG AAG ACA GTG GCC CCT ACA GAA TGT TCA
42	P1A3 HC VD nucleotide sequence	GAG GTC CAG CTG GTG CAG TCT GGG ACT GAG GTG AAG CCA CCT GGG GCC TCA GTG AGG GTT TCC TGC AAG TCA TCT GGA TAC ACC TTC AGC TAC TAT ATA CAC TGG GTG CGA CAG GCC CCT GGA CAA GGA CTT GAG TGG ATG GCA ATA ATC AAC CCT GGT AAT GGT GAC ACA AAC TAC GCA CAG AGG TTC CAG GGC AGA GTC ACC ATG ACC AGG GAC ACG TCC ACG AGC ACA GTC TAC ATG GAG CTG AGG AGC CTG AGA TCT GAC GAC ACG GCC GTC TAT TTC TGT GCG AGA GAG ATT GCC TCC TAT AGT GGG AGC TAC TAC GAC TAC TGG GGC CAG GGA ACC CTG GTC ACC GTC TCA AGC
43	P1C5 HC VD nucleotide sequence	CAG GTG CAG CTG CAG GAG TCG GGC CCA GGA CTG GTG AAG CCT TCG GAG ACC CTG TCC CTC ACC TGC ACT GTC TCT GGT GGC TCC ATC AGC AGT AGT AGT TAC TAC TGG GGC TGG ATC CGC CAG CCC CCA GGG AAG GGG CTG GAG TGG ATT GGG AGT ATC TAT TAT AGT GGG AGC ACC TAC TAC AAC CCG TCC CTC AAG AGT CGA GTC ACC ATA TCC GTA GAC ACG TCC AAG AAC CAG TTC TCC CTG AAG CTG AGC TCT GTG ACC GCC GCA GAC ACG GCT GTG TAT TAC TGT GCG AGA TAC GCG CCT GAT AGT AGT GGT TAC TTG GTG GCT TTT GAT ATC TGG GGC CAA GGG ACA ATG GTC ACC GTC TCA AGC
44	P1E4 HC VD nucleotide sequence	CAG GTG CAG CTA CAG CAG TGG GGC GCA GGA CTG TTG AAG CCT TCG GAG ACC CTG TCC CTC ACC TGC GCT GTC TAT GGT GGG TCC TTC AGT GGT TAC TAC TGG AGC TGG ATC CGC CAG CCC CCA GGG AAG GGG CTG GAG TGG ATT GGG GAA ATC AAT CAT AGT GGA AGC ACC AAC TAC AAC CCG TCC CTC AAG AGT GCA ACC ATA TCA GTA GAC ACG TCC AAG AAC CAG TTC TCC CTG AAG CTG AGC TCT GTG ACC ACT GCG GAC ACG GCC GTG TAT TAC TGT GCG AGG ATG GGA ATA AAT AGT GGT GGT TAT CTC TAC GGT ATG GAC GTC TGG GGC CAA GGG ACC ACG GTC ACC GTC TCA AGC

45	P1F1 HC VD nucleotide sequence	CAG GTG CAG CTG GTG GAG TCT GGC CCA GGA CTG GTG AAG CCT TCG GGG ACC CTG TCC CTC ACC TGC GCT GTC TCT GGT GGC TCC ATC AGC AGT AGT AAC TGG TGG AGT TGG GTC CGC CAG CCC CCA GGG AAG GGG CTG GAG TGG ATT GGG GAA ATC TAT CAT AGT GGG AGC ACC AAC TAC AAC CCG TCC CTC AAG AGT CGA GTC ACC ATA TCA GTA GAC ACG TCC AAG AAC CAG TTC TCC CTG AAG CTG AGC TCT GTG ACC GCT GCG GAC ACG GCC GTG TAT TAC TGT GCG AGG ATG GGA GCA AAT AGT GGT GGG TAT CTC TAC GGT ATG GAC GTC TGG GGC CAA GGG ACC ACG GTC ACC GTC TCA AGC
46	P1A3 (lambda) LC-CDR1 Nucleotide sequence	GGC TTG AGC TCT GGC TCA GTC TCT ACT GGT CAC TAC GCC AGC
47	P1A3 (lambda) LC-CDR2 Nucleotide sequence	AAC ACA AAC ACT CGC TCT TCT
48	P1A3 (lambda) LC-CDR3 Nucleotide sequence	GTG CTG TAT GTG GGT GAT GGC ATT TGG GTT
49	P1A3 HC-CDR1 nucleotide sequence	AGC TAC TAT ATA CAC
50	P1A3 HC-CDR2 nucleotide sequence	ATA ATC AAC CCT GGT AAT GGT GAC ACA AAC TAC GCA CAG AGG TTC CAG GGC
51	P1A3 HC-CDR3 nucleotide sequence	GAG ATT GCC TCC TAT AGT GGG AGC TAC TAC GAC TAC
52	P1C5 (lambda) LC-CDR1 Nucleotide sequence	GGC TTG AGC TCT GGC TCA GTC TCT ACT GGT TAC TAC CCC AGC
53	P1C5 (lambda) LC-CDR2 Nucleotide sequence	AGC ACA AAC AGT CGC TCT TCT
54	P1C5 (lambda) LC-CDR3 Nucleotide sequence	GTG CTG TAT ATG GGT AGT GGC ATT TCG GTG
55	P1C5 HC-CDR1 nucleotide sequence	AGT AGT AGT TAC TAC TGG GGC
56	P1C5 HC-CDR2 nucleotide sequence	AGT ATC TAT TAT AGT GGG AGC ACC TAC TAC AAC CCG TCC CTC AAG AGT
57	P1C5 HC-CDR3 nucleotide sequence	TAC GCG CCT GAT AGT AGT GGT TAC TTG GTG GCT TTT GAT ATC
58	P1E4 (lambda) LC-CDR1 Nucleotide sequence	GGC CTG AGC TCT GGC TCA GTC TCT ACT AGT TAC TAC CCC AGC
59	P1E4 (lambda) LC-CDR2 Nucleotide sequence	ACC ACA AAC ATT CGC TCT TCT
60	P1E4 (lambda) LC-CDR3 Nucleotide sequence	ATG CTC TAT ATG GGG AGT GGC ATT TGG GTG
61	P1E4 HC-CDR1 nucleotide sequence	GGT TAC TAC TGG AGC
62	P1E4 HC-CDR2 nucleotide sequence	GAA ATC AAT CAT AGT GGA AGC ACC AAC TAC AAC CCG TCC CTC AAG AGT
63	P1E4 HC-CDR3 nucleotide sequence	ATG GGA ATA AAT AGT GGT GGT TAT CTC TAC GGT ATG GAC GTC
64	P1F1 (lambda)	GGC TTG AGC TCT GGC TCA GTC TCT ACT AGT TAC TAC CCC AGC

	LC-CDR1 Nucleotide sequence	
65	P1F1 (lambda) LC-CDR2 Nucleotide sequence	AGC ACA AAC ACT CGC TCT TCT
66	P1F1 (lambda) LC-CDR3 Nucleotide sequence	GTG CTG TAT ATG GGT AGT GGC ATT TGG GTG
67	P1F1 HC-CDR1 nucleotide sequence	AGT AGT AAC TGG TGG AGT
68	P1F1 HC-CDR2 nucleotide sequence	GAA ATC TAT CAT AGT GGG AGC ACC AAC TAC AAC CCG TCC CTC AAG AGT
69	P1F1 HC-CDR3 nucleotide sequence	ATG GGA GCA AAT AGT GGT GGG TAT CTC TAC GGT ATG GAC GTC
70	PFA1 Light chain nucleotide sequence	GAAATTGTGCTGACTCAGTCTCCATTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCCATCTCCTGCA AGGTCTAGTCAGAGCCTCCTGCATAGTAATGGATTCAACTATTTGGATTGGTACCTGCAGAAGCCAGGG CAGTCTCCACAACCTCCTGATCTATTTGGGTTCTAATCGGGCCTCCGGGGTCCCTGACAGGTTCACTGGC AGTGGATCAGGCACAGATTTTACACTGAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTAC TGCATGCAAGGTCTACAGACTCCGTACACTTTTGGCCAGGGGACCAAGCTGGAGATCAAACGAACGTG GCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTG TGCCTGCTGAATAACTTCTATCCAGAGAGGCCAAAGTACAGTGAAGGTGGATAACGCCCTCCAATCG GGTAACCTCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTG ACGCTGAGCAAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGC TCGCCCCGCACAAAGAGCTTCAACAGGGGAGAGTGT
71	PFA1 Heavy chain nucleotide sequence	GAGGTCCAGCTGGTACAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCA GCGTCTGGATTACCTTCAGTAGCTATGGCATGCAGTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAG TGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGCCGATTACACC ATCTCCAGAGACAATTCCAAGAACACCCCTGTTTCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCT GTGTATTACTGTGCGAGAGATCTCTTTGCGGTGGTAGGCTACTACTACTACGATGACGCTCTGG GGCCAAGGGACCACGGTCAACGCTCTCAAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACC TCCTCCAAGAGCACCTCTGGGGGACAGCGGCCCTGGGCTGCCTGCTCAGGACTACTTCCCGAACC GTGACGGTGTCTGGAAGTCAAGCGCCCTGACCAGCGCGCTCCACACCTTCCCGCTGTCTACAGTCC TCAGGACTCTACTCCCTCAGCAGCGTAGTGACCGTGCCTCCAGCAGCTGGGCAACCCAGACCTACATC TGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAATCTTGT
72	PFA1 Light chain VD	EIVLTQSPFSLPVTPEPASISCRSSQSLHNSGFNYLDWYLQKPGQSPQLLIYLGSNRASGVDPDRFSG SGSGTDFTLKISRVEAEDVGVIYMQGLQTPYTFQGKLEIKRTVAAPSVFIFPPSDEQLKSGTASV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTLSSTLTLSKADYERHKVYACEVTHQGLS SPVTKSFNRGEC
73	PFA1 Heavy chain VD	EVQLVQSGGQVQPGRLRLSCAASGFTFSSYGMHWVRQAPGKLEWVAVISYDGSNKYYADSVKCRFT ISRDNSKNTLFLQMNSLRAEDTAVYYCARDLFAVVGYYGGMDVWVGQGTITVTVSSASTKGPSVFPLAP SSKSTSGGTAAALGLVKDYFPEPVTWSNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSLGLTQTYI CNVNHKPSNTKVDKKEPKSC
74	PFA1 LC-CDR1	RSSQSLHNSGFNYLD
75	PFA1 LC-CDR2 PFA2 LC-CDR2 PFA5 LC-CDR2 PFB3 LC- CDR2PFF3 LC- CDR2	LGSNRAS
76	PFA1 LC-CDR3	MQGLQTPYT
77	PFA1 HC-CDR1 PFB4 HC-CDR1 PFD1 HC-CDR1 PFG1 HC-CDR1	SYGMH
78	PFA1 HC-CDR2 PFA4 HC-CDR2 PFB4 HC-CDR2 PFC2 HC-CDR2 PFD1 HC-CDR2 PFE1 HC-CDR2 PFE5 HC-CDR2 PFG5 HC-CDR2	VISYDGSNKYYADSVKG
79	PFA1 HC-CDR3	DLFAVVGYYGGMDV
80	PFA2 Light chain nucleotide sequence	GAAATTGTGTTGACGAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCCATCTCCTGCA AGGTCTAGTCAGAGTCTCCTGCACAGTATGGGAACAAATATTTGGATTGGTACCTGCAGAAGCCAGGG CAGTCTCCACAGCTCCTGATCTATTTGGGTTCTAATCGGGCCTCCGGGGTCCCTGAGAGGTTCACTGGC AGTGGATCAGGCACAGATTTTACACTGAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTAC TGCATGCTAGGTACACACTGGCCTCCGATGTACATTTTGGCCAGGGGACCAAGCTGGAGATCAAACGA ACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCT

		GTTGTGTGCTGCTGAATAAATTCTATCCCAGAGAGGCCAAAGTACAGTGAAGGTGGATAACGCCCTC CAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGC ACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCCTGCGAAGTACCCATCAGGGC CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT
81	PFA2 Heavy chain nucleotide sequence	CAGGTACAGCTGCAGCAGTCAGGTCCAGGACTGGTGAAGCCCTCGCAGACCCTCTCGCTCACCTGTGCC ATCTCCGGGGAAAGCGTCTCTAGCGCCGCTGCTGCTTGGAACTGGATCAGGCAGTCCCCATCGAGAGGC CTTGAGTGGCTGGGAAGGACATACACTACAGGTCCAAGTGGTATAGTGAATATGCAGTATCTGTGAAAAGT CGAATAACCATCAACGGAGACACATCCAAGAACCAGGTCTCCCTGCACCTGAACGCTGTGACTCCCGAG GACACGGCTATATATTACTGTGTAAAGGGCAGTATTTTTGATGTGTGGGGCCAAAGGACAAATGGTCACC GTCTCAAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGG GGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGAACTCA GGCGCCCTGACCAGCGCGTCCACACCTTCCCGGCTGTCTACAGTCTCTCAGGACTCTACTCCCTCAGC AGCGTAGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCC AGCAACACCAAGGTGGACAAGAAAGTTGAGCCCCAAATCTTGT
82	PFA2 Light chain VD	EIVLTQSPFLSLPVTIPGEPASISCRSSQSLHSDGNKYLDWYLQKPGQSPQLLIYLGSNRASGVPERFSG SGSGTDFTLKISRVEAEDVGVIYCMGLTHWPPMYIFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
83	PFA2 Heavy chain VD	QVQLQQSGPGLVKPSQTLSTLCAISGESVSSAAAWNWIRQSPSRGLEWLGRTYYSKWKYSEYAVSVKS RITINGDTSKNQVSLHLNAVTPEDTAIYYCVRGSIQFVWQGTMTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSC
84	PFA2 LC-CDR1	RSSQSLHSDGNKYLD
85	PFA2 LC-CDR3	MLGTHWPPMYI
86	PFA2 HC-CDR1	SAAAWN
87	PFA2 HC-CDR2	RTYYSKWKYSEYAVSVKS
88	PFA2 HC-CDR3	GSIFDV
89	PFA4 Light chain nucleotide sequence	GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTACCCTTGGACAGCGCGCCTCCATCTCTCTGC AGGTCTAGTCAAAGCCTCGTATACAGTGTGGAACACCTACTTGAATTGGTTTCAGCAGAGGCCAGGC CAATCTCCAAGCGCCTAATTTATAAGGTTTCTAACCGGACTCTGGGGTCCCACAGATTACAGCGGC AGTGGGTGAGGCACTGATTTCACACTGAAATACAGCAGGTGGAGGCTGAGGATGTTGGGGTTTATTAC TGCATGCAAGGTACACACTGGCCTCTCACTTTTGGCCAGGGGACCAAGCTGGAGATCAACGAAGTGTG GCTGCACCATCTGTCTTTCATCTTCCCGCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTGTGTG TGCTGTGTAATAAATTCTATCCCAGAGAGGCCAAAGTACAGTGAAGGTGGATAACGCCCTCCAATCG GGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTCG ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGC TCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT
90	PFA4 Heavy chain nucleotide sequence	GAGGTCCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCTGTGCA GCCTCTGATTACCTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAG TGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTACGAGACTCCGTGAAGGGCCGATTACACC ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCTGAGGACACGGCT GTGTATTACTGTGCGAGGAGTCGAGGCTACTACGGTATGGACGCTCTGGGGCCAAAGGACACCGTCACC GTCTCAAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGG GGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAAGTCA GGCGCCCTGACCAGCGCGCTCCACACCTTCCCGGCTGTCTACAGTCTCTCAGGACTCTACTCCCTCAGC AGCGTAGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCC AGCAACACCAAGGTGGACAAGAAAGTTGAGCCCCAAATCTTGT
91	PFA4 Light chain VD	DVMTQSPFLSLPVTILGQPASISCRSSQSLVYSDGNTYLNWFQQRPGQSPRRLIYKVSNRDSGVPRDFSG SGSGTDFTLKISRVEAEDVGVIYCMGLTHWPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTLSSTLTLSKADYEKHKVYACEVTHQGLS SPVTIKSFNRGEC
92	PFA4 Heavy chain VD	EVQLVQSGGQVVPGRSLRLSCAASGFTFSYAMHWVRQAPGKLEWVAIVSYDGSNKYYADSVKGRFT ISRDNKNTLYLQMNLSRAEDTAVYYCARSGYGMVWQGTITVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSC
93	PFA4 LC-CDR1 PFD1 LC-CDR1 PFD4 LC-CDR1	RSSQSLVYSDGNTYLN
94	PFA4 LC-CDR2 PFD1 LC-CDR2	KVSNRDS
95	PFA4 LC-CDR3 PFC2 LC-CDR3 PFE1 LC-CDR3 PFG5 LC-CDR3	MQGTHWPLT
96	PFA4 HC-CDR1 PFA5 HC- CDR1PFC2 HC- CDR1 PFD4 HC-CDR1 PFE1 HC-CDR1 PFE2 HC-CDR1 PFE5 HC-CDR1 PFG5 HC-CDR1	SYAMH
97	PFA4 HC-CDR3 PFD4 HC-CDR3	SRGYYGMDV

	PFE1 HC-CDR3 PFE5 HC-CDR3	
98	PFA5 Light chain nucleotide sequence	GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTACCCCTGGAGAGCCGGCCTCCATCTCCTGC AGGTCTAGTCAGAGCCTCCTGCATAGTAATGGATACAACATATTTGGATTGGTACCTGCAGAAGCCAGGG CAGTCTCCACAGCTCCTGATCTATTTGGGTTCTAATCGGGCCTCCGGGCTCCCTGACAGTTTCACTGGC AGTGGATCAGGCACAGATTTTACACTGAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTAC TGCATGCAAGCTCTACAACTCCGTGGACGTTCCGCCAAGGGACCAAGGTGGAATCAAACGAACGTGTG GCTGCACCATCTGTCTTCTATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTG TGCCTGCTGAATAACTTCTATCCAGAGAGGCCAAAGTACAGTGAAGGTGGATAACGCCCTCCAATCG GGTAACCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTG ACGCTGAGCAAAGCAGACTACGAGAAACAAACTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGC TCGCCCCGTACAAAGAGCTTCAACAGGGGAGAGTGT
99	PFA5 Heavy chain nucleotide sequence	CAGGTGCAGCTGGTGCAATCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTTTCTGCAAG GCTTCTGGATACACCTTCACTAGCTATGCTATGCATTGGGTGCGCCAGGCCCCCGGACAAAGGCTTGAG TGGATGGGATGGATCAACGCTGGCAATGGTAACACAAAATATTACAGAAGTTCCAGGGCAGAGTCACC ATTACCAGGGACACATCCGCGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAAGACACGGCT GTGTATTACTGTGCGAGAGGAGGATACCTCGTAGGCTACTGGGGCCAGGGCACCCTGGTCACCGTCTCA AGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGGGCACA CGCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAAGTCAAGCGCC CTGACCAGCGCGCTCCACACCTTCCCGGCTGTCTACAGTCTCAGGACTCTACTCCCTCAGCAGCGTA GTACCGTGGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCAAGCCACGCAAC ACCAAGGTGGACAAGAAAGTTAGCCCCAAATCTTGT
100	PFA5 Light chain VD	DVVMTQSPSLPVPPEPASISCRSSQSLHNSNGYNYLDWYLQKPGQSPQLLIYLSNRRASGVPDRFSG SGSGTDFTLKISRVEAEDVGVIYCMQALQTPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYSLSSTLTLSKADYEHKLYACEVTHQGLS SPVTKSFNRGEC
101	PFA5 Heavy chain VD	QVQLVQSGAEVKKFGASVKVSKASGYFTFSYAMHWVRQAPGQRLEWMGWINAGNNTKYSQKFQGRVT ITRDTASASTAYMELSSLRSEDTAVYYCARGGYLVGYWGQGLTLTVSSASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSC
102	PFA5 LC-CDR1 PFB3 LC-CDR1 PFB5 LC-CDR1 PFC2 LC-CDR1 PFF3 LC-CDR1 PFG5 LC-CDR1	RSSQSLHNSNGYNYLD
103	PFA5 LC-CDR3	MQALQTPWT
104	PFA5 HC-CDR2	WINAGNNTKYSQKFQG
105	PFA5 HC-CDR3	GGYLVGY
106	PFB1 Light chain nucleotide sequence	GATGTTGTGATGACTCAGTCTCCACTCTCCCTCCCCGTCACTCCTGGAGAGCCGGCCTCCATCTCCTGT AGGTCTAGTCAGAGCCTCCTGCATAGTAATGGGAACACCTATTTGGATTGGTACCTGCAGAAGCCAGGG CAGTCTCCACAGGCTCCTGATCTATTTGGGTTCTAATCGGGCCTCTGGAGTCCCAGACAGTTTCACTGGC AGTGGGTGAGGACTGATTTACACTGAAATCAGCAGGCTGGAGGCTGAGGATGTTGGGGTTTATTAC TGCATGCAAGGTACACACTGGCCTCCGACGTTCCGCCAAGGGACCAAGGTGGAATCAAACGAACGTGTG GCTGCACCATCTGTCTTCTATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTG TGCCTGCTGAATAACTTCTATCCAGAGAGGCCAAAGTACAGTGAAGGTGGATAACGCCCTCCAATCG GGTAACCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTG ACGCTGAGCAAAGCAGACTACGAGAAACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGC TCGCCCCGTACAAAGAGCTTCAACAGGGGAGAGTGT
107	PFB1 Heavy chain nucleotide sequence	CAGGTGCAGCTGCAGGAGTCCGGGGGAGGCTTGGTACAGCCTGGGGGCTCCCTGAGACTCTCCTGTGCA GCCTCTGGATTACCTTTAGCAGCTTTGCCATGAACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAG TGGGTCTCAACTATTGGTGGTAGTGGTGATAGCACATTCTACGACAGCCCCGTGAAGGGCCGGTTACAC GTCTCCAGAGACAATTCCAAGAACACTGTGATCTGCAATGAACAGCTGAGAGCCGAGGACACGGCC GTATATTACTGTGCGCAAGCCTATGGTTTCGGGGGCTCATTATTTCTTTGCTACTGGGGCCAGGGAAC CTGGTCACCGTCTCAAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGC ACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTG TGAAGTCAAGCGCCCTGACCAGCGGCTCCACACCTTCCCGGCTGCTTACAGTCTCAGGACTCTAC TCCCTCAGCAGCTAGTGACCGTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAAT CACAAGCCAGCAACACCAAGGTGGACAAGAAAGTTAGCCCCAAATCTTGT
108	PFB1 Light chain VD	DVVMTQSPSLPVPPEPASISCRSSQSLHNSNGYNYLDWYLQKPGQSPQVLIYSGSNRRASGVPDRFSG SGSGTDFTLKISRVEAEDVGVIYCMQGTHWPPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYSLSSTLTLSKADYEHKLYACEVTHQGLS SPVTKSFNRGEC
109	PFB1 Heavy chain VD	QVQLQESGGGLVQPGGSLRLSCAASGFTFSFAMNHWVRQAPGKLEWVSTIGSGDSTFYADPVKGRFT VSRDNSKNTLYLQMNSLAEDTAVYYCAQAYGSGGHYFFAYWGQGLTLTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSC
110	PFB1 LC-CDR1	RSSQSLHNSNGYNYLD
111	PFB1 LC-CDR2	SGSNRRAS
112	PFB1 LC-CDR3	MQGTHWPPT
113	PFB1 HC-CDR1	SFAMN
114	PFB1 HC-CDR2	TIGSGDSTFYADPVKG
115	PFB1 HC-CDR3	AYGSGGHYFFAY
116	PFB2	GAAACGACACTCAGCAGTCTCCAGCCACCTGTCTCTGCTCTCCGGGGGAAAGAGCCACCTCTCCTGC AGGGCCAGTCAGAGTGTAGGAACAACCTAGCCTGGTACCAGCATAAAGCTGGCCAGGCTCCAGGCTC

	Light chain nucleotide sequence	CTCATCTATTATGCATCCACCAGGGCCACTGGCATCCCAGACAGGTTTCAGTGGCAGTGGGCTCTGGGACA GACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCACTGTATTACTGTGCAGCATATGGT AGCTCCCCGGACGTTCCGGCCAAAGGACCAAGGTGAAATCAAACGAAGCTGGGCTCCACCATCTGTCTTC ATCTTCCCAGCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTC TATCCCAGAGAGGCCAAAGTACAGTGGAAAGTGGATAACGCCCTCCAATCAGGTAAGTCCAGGAGAGT GTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGACCCCTGACGCTGAGCAAAGCAGAC TACGAGAAACACAAAGTCTACGCCTGCGAAGTACCCATCAGGGCTGAGCTCGCCCGTCACAAAGAGC TTCAACAGGGGAGAGTGT
117	PFB2 Heavy chain nucleotide sequence	GAGGTCCAGCTGGTGACGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAG GCTTCTGGTTACACCTTTACCAGCTATGGTATCAGCTGGGTGCGACAGGCCCCCTGGAGAAGGGCTTGAG TGGATGGGATGGATCAGCGCTTACAACTAACACAAACTATGCACAGAAGCTCCAGGGCAGAGTCACC ATGACCACAGACACATCCACGAGCAGCCTACATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCC GTGTATTACTGTGCGAGAGATTGGGGCAGCAGCTGGTCCGACTACTGGGGCCAGGGCACCTTGGTCACC GTCTCAAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGG GGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCGAACCGGTGACGGTGTCTGTGGAAGTCA GGCGCCCTGACCAGCGCGCTCCACACCTTCCCGGCTGTCTACAGTCTCAGGACTCTACTCCCTCAGC AGCGTAGTGACCGTGCCTCCAGCAGCTTGGGCAACCCAGACCTACATCTGCAACGTGAATCACAAGCCC AGCAACACCAAGGTGGACAAGAAAGTTGAGCCCCAAATCTTGT
118	PFB2 Light chain VD	ETTLTQSPATLSLSPGERATLSCRASQSVRNRLAWYQHKPGQAPRLLIYYASTRATGIPDRFSGSGSGT DFTLTISRLEPEDFALYYCQHYGSSRTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF YPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC
119	PFB2 Heavy chain VD	EVQLVQSGAEVKKPGASVKVSCKASGYFTSYGISWVRQAPGEGLEWMGWISAYNGNTNYAQKLQGRVT MTTDTSTSTAYMELRSLRSDDTAVYYCARDWGSSWSWDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSCALTSKVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPK SNTKVDKKVEPKSC
120	PFB2 LC-CDR1	RASQSVRNRLA
121	PFB2 LC-CDR2	YASTRAT
122	PFB2 LC-CDR3	QHYGSSRT
123	PFB2 HC-CDR1	SYGIS
124	PFB2 HC-CDR2	WISAYNGNTNYAQKLQG
125	PFB2 HC-CDR3	DWGSSWSDY
126	PFB3 Light chain nucleotide sequence	GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTACCCCTGGAGAGCCGGCCTCCATCTCTGTC AGGTCTAGTCAGAGCCTCCTGCATAGTAATGGATACAATATTTGGATTGTTACCTGCAGAAGCCAGGG CAGTCTCCACAGCTCCTGATCTATTTGGGCTCTAATCGGGCCTCCGGGGTCCCTGACAGGTTTCAGTGGT AGTGGATCAGGCACAGATTTTACACTGAAATCACCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTAC TGCATGGCAGGTCTACAACTCCTCGGCTACCTTCCGGCCTGGGACCAAGTGGATATCAGACGAAGT GTGGCTGCACCATCTGTCTTCTATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTT GTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAAGTGGATAACGCCCTCCAA TCGGGTAAGTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACC CTGACGCTGAGCAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTACCCATCAGGGCCTG AGCTCGCCCGTCAAAAGAGCTTCAACAGGGGAGAGTGT
127	PFB3 Heavy chain nucleotide sequence	CAGGTGCAGCTGCAGGAGTCCGGGGGAGGCTTGGTACAGCCTGGGGGTCCTGAGACTCTCCTGTGCA GCCTCTGGATTACCTTTAGCAGCTATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAG TGGGTCTCAGCTATTAGTGGTAGTGGTGGTAGCACATACTACGACAGCTCCGTGAAGGCCGATTACACC ATCTCCAGAGACAATTCCAAGAACACAGTATATCTGCAAATGAACAGCCTGAGAGCTGAGGACACGGCT GTTTATTACTGTGCGAGGACGTATTACGATTTTGGAGTGGCAGGGTTGGGGCTTTTGATATCTGGGGC CAAGGGACACGGCTACCGTCTCAAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCC TCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTGAAGGCTGAGGACAGCGGTG ACGGTGTCTGTGGAAGTCAAGCGCCCTGACCAGCGGCTCCACACCTTCCCGGCTGTCTACAGTCTCA GGACTCTACTCCCTCAGCAGCGTAGTGACCGTGCCTCCAGCAGCTTGGGCAACCCAGACCTACATCTGC AACGTGAATCACAAGCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCCAAATCTTGT
128	PFB3 Light chain VD	DVVMTQSPPLSLPVPGEPAISCRSSQSLHNSGYNLYDWYLQKPGQSPQLLIYLGNSNRASGVPDRFSG SGSGTDFTLKITRVEAEVDGVYYCMAGLQTPRLTFPGPTKVDIRRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC
129	PFB3 Heavy chain VD	QVQLQESGGGLVQPGGSLRLSCAASGFTFSSYAMSWSVRQAPGKLEWVSAISGSGGSTYYADSVKGRFT ISRDNKNTVYLGQMSLRAEDTAVYYCARTYYDFWSSGRVGAFDIWGQGTITVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSKVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYIC NVNHKPKSNTKVDKKVEPKSC
130	PFB3 LC-CDR3	MAGLQTPRLT
131	PFB3 HC-CDR1 PFC3 HC-CDR1 PFG2 HC-CDR1	SYAMS
132	PFB3 HC-CDR2	AISGSGGSTYYADSVKG
133	PFB3 HC-CDR3	TYDFWSSGRVGAFDI
134	PFB4 Light chain nucleotide sequence	CAGGCTGTGGTGATCCAGGAGCCCTCACTGACTGTGTCCCCAGGAGGGACAGTCACTCTCACCTGTGGC TCCACCACTGGAGCTGTACCAGTGGCCATTATCCCTCCTGGTTCCAGCAGAAGCCTGGCCAAGCACCC AGGGCACTGATTTATAGTACAAGCAACAACACTCCTTGACCCCTGCCCCGTTCTCAGGCTCCCTCCTT GGGGGCAAGGCTGCCCTGACACTGTCAAGTGTGACGCTGAGGACGAGGCTGAGTATTACTGCCTGCTC TACTATGTGTGCTCGAGTGTTCGGCGGAGGGACCAAGCTGACCGTCCCTAGTTCAGCCCAAGGCTGCC CCCTCGGTCACTCTGTTCCACCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGTCTC ATAAGTGAATCTTACCCGGGAGCCGTGACAGTGGCTTGAAGGCAGATAGCAGCCCCGTCAAGGCGGGA GTGGAGACCACCACCCCTCCAACAACAAGCAACAAGTACGCGGCCAGCAGCTACCTGAGCCTGACG CCTGAGCAGTGGAAAGTCCACAGAAGCTACAGTCCAGGTACGCATGAAGGGAGCACCGTGGAGAAG ACAGTGGCCCTGCAGAATGCTCT

135	PFB4 Heavy chain nucleotide sequence	GAGGTCCAGCTGGTACAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCA GCCTCTGGATTACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAG TGGGTGGCAGTTATATCATATGATGGAATATAAATACTATGCAGACTCCGTGAAGGGCCGATTACAC ATCTCCAGAGACGATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCTGAGGACACGGCT GTGTATTACTGTGCGAAAGATCGCGGTTACTACGGTATGGACGCTCTGGGGCCAAAGGGACACGGTACAC GTCTCAAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGG GGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCA GGCGCCCTGACCAGCGGCGTCCACACCTTCCCGGCTGTCTACAGTCTCTCAGGACTCTACTCCCTCAGC AGCGTAGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCC AGCAACACCAAGGTGGACAAGAAAGTTGAGCCCCAAATCTTGT
136	PFB4 Light chain VD	QAVVIQEPSTLTVSPGGTVTLTCGSTTGAVTSGHYPSWFOQKPGQAPRALIYSTSNKHSWTPARFSGSL GGKAALTLSGVQPEDEAEYYCLLYGGARVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCL ISDFYPGAVTVAWKADSSFPVKAGVETTTFSKQSNKNYAASSYLSLTPEQWKSRSYSCQVTHEGSTVEK TVAPAEC
137	PFB4 Heavy chain VD	EVQLVQSGGGVQVPGSRSLRLSCAASGFTFSSYGMHWVRQAPGKLEWVAIVSYDGSNKYYADSVKGRFT ISRDDSKNTLYLQMNSLRAEDTAVYYCAKDRGYGMDVWVGQGTITVSSASTKGPSVFPPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQYIICNVNHKP SNTKVDKKVEPKSC
138	PFB4 LC-CDR1	GSTTGAVTSGHYPS
139	PFB4 LC-CDR2	STSNKHS
140	PFB4 LC-CDR3	LLYYGGARV
141	PFB4 HC-CDR3	DRGYYGMDV
142	PFB5 Light chain nucleotide sequence	GAAATTGTGCTGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCCATCTCCTGC AGGTCTAGTCAGAGCCTCTGCATAGTAATGGATACAACATTTTGGACTGGTACCTGCAGAAGCCAGGG CAGTCTCCACAGCTCCTGATCTATTTGGGTTCTCATCGGCCCTCCGGGGTCCCTGACAGGTTCACTGGC AGTGGATCAGGCACAGATTTTACACTGAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTAC TGCATGCAAGCTCTACAACTCCTCTCACTTTCCGGCGGAGGGACCAAGGTGGAGATCAACGAAGTGTG GCTGCACCATCTGTCTTCACTCTTCCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTGTG TGCTGTGTAATAACTTCTATCCAGAGAGGCCAAAGTACAGTGAAGGTGGATAACGCCCTCCAATCG GGTAAGTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTCG ACGCTGAGCAAAGCAGACTACGAGAAACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGC TCGCCCCGTACAAAGAGCTTCAACAGGGGAGAGTGT
143	PFB5 Heavy chain nucleotide sequence	GAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCTCGGTGAAGGTCTCCTGCAAG GCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAGGCCCTGGACAAGGGCTTGAG TGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAAATACGCACAGAAGTTCAGGGCAGAGTCACG ATTACCGCGGACGAATCCACGAGCAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCC GTGTATTACTGTGCGAGAGGCCGAGGGAGCGGCTATCCCGATACGTGGTCTGGTTCGACCCCTGGGGC CAGGGCACCTTGGTCACCGTCTCAAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCTCC TCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCGAACCAGGTG ACGGTGTCTGTGGAAGTCAAGCGCCCTGACCAGCGGCGTCCACACCTTCCCGGCTGTCTACAGTCTCTCA GGACTCTACTCCCTCAGCAGCGTAGTGACCGTGCCTTCCAGCAGCTTGGGCACCCAGACCTACATCTGC AACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCCAAATCTTGT
144	PFB5 Light chain VD	EIVLTQSPFLSLPVPPEPASISCRSSQSLHNSGYNLYLDWYLQKPGQSPQLLIYLGSHRASGVPDRFSG SGSGTDFTLKISRVEAEDVGVYYCMQALQPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV CLLNNFYPREAKVQWVKVDNALQSGNSQESVTEQDSKDYSLSSLTTLTKADYKHKVYACEVTHQGLS SPVTKSFNRGEC
145	PFB5 Heavy chain VD	EVQLVQSGAEVKKPGSSSVKVSCKASGFTFSSYAISWVRQAPGQGLEWMGGIIPFGTANYAQKFQGRVT ITADESTSTAYMELSSLRSEDTAVYYCARGRGSYPDTWFWFDPWGQGLTVTVSSASTKGPSVFPPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQYIIC NVNHKPSNTKVDKKVEPKSC
146	PFB5 LC-CDR2	LGSHRAS
147	PFB5 LC-CDR3	MQALQPLT
148	PFB5 HC-CDR1 PFB4 HC-CDR1 PFB4 HC-CDR1	SYAIS
149	PFB5 HC-CDR2 PFB4 HC-CDR2 PFB4 HC-CDR2	GIIPFGTANYAQKFQG
150	PFB5 HC-CDR3	GRGSGYPDTWFWFDP
151	PFC2 Light chain nucleotide sequence	GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCCATCTCCTGC AGGTCTAGTCAGAGCCTCTGCATAGTAATGGATACAACATTTTGGATTGGTACCTGCAGAAGCCAGGG CAGTCTCCACAGCTCCTGATCTACTTGGGTTCTAATCGGGCCCCCGGGTCCCTGACAGGTTCACTGGC AGTGGATCAGGCACAGATTTTACACTGAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTAC TGCATGCAAGGTACACACTGGCCTCTCACTTTCCGGCGGAGGGACCAAGGTGGAGATCAACGAAGTGTG GCTGCACCATTTGTCTTCTATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTGTG TGCTGTGTAATAACTTCTATCCAGAGAGGCCAAAGTACAGTGAAGGTGGATAACGCCCTCCAATCG GGTAAGTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTGAGCAGCACCTCG ACGCTGAGCAAAGCAGACTACGAGAAACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGC TCGCCCCGTACAAAGAGCTTCAACAGGGGAGAGTGT
152	PFC2 Heavy chain nucleotide sequence	GAAGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCA GCCTCTCGATTACCTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAG TGGGTGGCAGTTATATCATATGATGGAAGCAATAAATACTACGCAGACTCCGTGAAGGGCCGATTACAC ATCTCCAGAGACAATCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCTGAGGACACGGCT GTGTATTACTGTGCGAGATCGTATGGTTCGGGGAGTTATAGGTCCCAGTCTTTTGATATCTGGGGCCAA GGACAATGGTACCGTCTCAAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCGTGGCACCTCTCC AAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCGAACCAGGTGACG

		GTGTCGTGGAACCTCAGGCGCCCTGACCAGCGGCGTCCACACCTTCCCGGCTGTCTACAGTCTCTCAGGA CTCTACTCCCTCAGCAGCTAGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAAC GTGAATCACAAGCCAGCAACACCAAGGTGGACAAAGAAAGTTGAGCCCAATCTTGT
153	PFC2 Light chain VD	DVVMTQSPSLPVPFGEPAISICRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRAPGVPDFRSG SGSGTDFTLKISRVEAEDVGVIYCMQGTWHPLTFGGGTKEIKRTVAAPFVFIFPPSDEQLKSGTASV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSLTLLSKADYEKHKVYACEVTHQGLS SPVTKSFNRGEC
154	PFC2 Heavy chain VD	EVQLVQSGGGVVPGRSLRLSCAASGFTFSSYAMHWVRQAPGKLEWVAIVSYDGSNKYYADSVKGRFT ISRDN SKNTLYLQMNLSRAEDTAVYYCARSYSGSYRSHAFDIWGQGTMTVSSASTKGPSVFPLAPSS KSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSC
155	PFC2 LC-CDR2 PFG5 LC-CDR2	LGSNRAP
156	PFC2 HC-CDR3 PFG5 HC-CDR3	SYGSGSYRSHAFDI
157	PFC3 Light chain nucleotide sequence	GAAACGACACTCAGCAGTCTCCAGGCACCTGTCTTTGTCTCCAGGGGAAAGACCCCTCTCTGCG AGGGCCAGTCAGAGTGTAGCAGCAGTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGG CTCCTCATCTATGCTGCATCCAGCAGGGCCACTGGCATCCAGACAGGTTCACTGGCAGTGGGTCTGGG ACAGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTAT GGTAGCTCACCTCGGACGTTTCGGCCAAAGGACCAAGGTGAAATCAAACGAACCTGGCTGCACCATCT GTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACCTGCCTCTGTTGTGTGCTGTGAAT AACTTCTATCCAGAGAGGCCAAAGTACAGTGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCAG GAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAA GCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCAACCATCAGGGCCTGAGCTCGCCCGTCACA AAGAGCTTCAACAGGGGAGAGTGT
158	PFC3 Heavy chain nucleotide sequence	CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGCTCCCTGAGACTCTCTGTGCA GCCTCTGGATTACCTTTAGCAGCTATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAG TGGGTCTCTGGTATTAATTGGAATGGTGGTAGCACAGGTATGACAGACTCTGTGAAGGGCCGATTACAC ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAATAGCCTGAGAGCCGAGGACACGGCC GTATATTACTGTGCGAAAGGGCTAGTACCGCTGCGAGTATGGAGCTCTGGGGCCAAAGGACACGGTC ACCGTCTCAAGCGCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCTCTCCAAGAGCACCTCT GGGGGCACAGCGGCCCTGGGCTGCTGGTCAAGGACTACTTCCCGAACCGGTGACGGTGTCTGTGAAC TCAGGCGCCCTGACCAGCGGCTCCACACCTTCCCGGCTGTCTACAGTCTCAGGACTCTACTCCCTC AGCAGCGTAGTGACCGTGCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAG CCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAATCTTGT
159	PFC3 Light chain VD	ETTLTQSPGTLSPGERATLSRASQSVSSSYLAWYQKPGQAPRLLIYGASSRATGIPDRFSGSGSG TDFTLTI SRLEPEDFAVYYCQYQSSPRTFQGQTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVCLLN NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSLTLLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC
160	PFC3 Heavy chain VD	QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVSGINWNGGSTGYADSVKGRFT ISRDN SKNTLYLQMNLSRAEDTAVYYCARGLVPAASMDVWGQGTMTVTVSSASTKGPSVFPLAPSSKST SGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSC
161	PFC3 LC-CDR1 PFF2 LC-CDR1	RASQSVSSSYLA
162	PFC3 LC-CDR2 PFF2 LC-CDR2	GASSRAT
163	PFC3 LC-CDR3	QYQSSPRT
164	PFC3 HC-CDR2	GINWNGSGTYADSVKG
165	PFC3 HC-CDR3	GLVPAASMDV
166	PFC4 Light chain nucleotide sequence	GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTACCCCTGGACAGCGGCGCTCCATCTCTGCG AGGTCTAGTCAGAGCCTCCAACATAGCAACGGATACAGTACTTGGACTGGTACGTGCAGAAGCCAGGG CAGTCTCCACAACCTCTGATCTATTTGGGTTCTTTTCGGGCTCCGGGGTCCCCGCCAGGTTCACTGGC AGCGGATCAGGCACAGATTCTCACTAGAAATCAACAAGTGGAGCTGAGGACCTTGGGTTTGGGTTTACT TGATGACAGCTCTAAGTACTCTCCGTGGACGTTTCGGCCAGGGGACAGGGTGAAGTCAAACGAACT GTGGCTGCACCATCTGTCTTCATCTTCCCGCATCTGATGAGCAGTTGAAATCTGGAACCTGCTGTGTT GTGTGCTGTGTAATACTTCTATCCAGAGAGGCCAAAGTACAGTGAAGGTGGATAACGCCCTCCAA TCGGGTAACTCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCTCAGCAGCACC CTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCAACCATCAGGGCCTG AGCTCGCCCGTCAAAAGAGCTTCAACAGGGGAGAGTGT
167	PFC4 Heavy chain nucleotide sequence	GAGGTCCAGCTGGTGCAGTCTGGAGCTGAGGTGAGGAAGCCTGGGGCTCAGTGAAGGTCTCTGCAAG GCTTCTGGATACACCTTCACTACTATGATTGGGTGCGCCAGGCCCCGGACAGAGTCTTGAG TGGATGGCATGGATACCCCTGGCAATGGTAATACACATTATTACAGAACTTCCAGGGCAGAGTCACC ATTACAGGGACACATCCACGAGCACAGCTACATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCC GTGATTACTGTGCGAGTCTAGGTTGGGAGCCCTTACTACTGGGGCCAGGGAAACCTGGTCACCGCT TCAAGCGCTCCACCAAGGGCCATCGGTCTTCCCCCTGGCACCCCTCTCCAAGAGCACCTCTGGGGC ACAGCGGCCCTGGGCTGCTGGTCAAGGACTACTTCCCGAACCGGTGACGGTGTCTGTGAAGTCAAGC GCCCTGACCAGCGGCTCCACACCTTCCCGGCTGTCTACAGTCTCAGGACTCTACTCCCTCAGCAGC GTAGTGACCGTGCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGC AACACCAAGGTGGACAAGAAAGTTGAGCCCAATCTTGT
168	PFC4 Light chain VD	DVVMTQSPSLPVPFGEPAISICRSSQSLLHSNGYQYLDWYVQKPGQSPQLLIYLGSRASGVPARFSG SGSGTDFTLRINKVEPEDVGVIYCMHALSTPPWTFQGQTRVELKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSLTLLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC
169	PFC4 Heavy chain VD	EVQLVQSGAEVRKPGASVKVSKASGYFTFTYTMHWVRQAPGQSLLEWMAWITPGNGNTHYSQNFGQGRVT ITRDTSTSTAYMELRSLRSDDTAVYYCARSRVGLDYWGQGTITLVTVSSASTKGPSVFPLAPSSKSTSGG

		TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSC
170	PFC4 LC-CDR1	RSSQSLQHSNGYQYLD
171	PFC4 LC-CDR2	LGSFRAS
172	PFC4 LC-CDR3	MHALSTPPWT
173	PFC4 HC-CDR1	TYTMH
174	PFC4 HC-CDR2	WITPGNGNTHYSQNFQG
175	PFC4 HC-CDR3	SRVGALDY
176	PFD1 Light chain nucleotide sequence	GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCTTGGACAGCCGGCCTCCATCTCCTGC AGGTCTAGTCAAAGCCTCGTATACAGTGTGAAACACCTACTTGAATTGGTTTCAGCAGAGGCCAGGC CAATCTCCAAGCGCCTGTTTTATAAGGTTTCTAACCGGACTCTGGGGTCCCAGACAGATTACAGCGGC AGTGGGTCAAGGCACTGATTTCACACTGAAATCAGCAGGTGGAGGCTAGGATGTTGGGTTTTATTAC TGCATGCAAGGTACACACTGGCCGGGCACTTTTGGCCAGGGGACCAAGCTGGAGATCAAACGAAGTGTG GCTGCACCATCTGTCTTCTATCTTCCCGCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTGTGTG TGCTGTGTAATAACTTCTATCCAGAGAGGCCAAAGTACAGTGAAGGTGGATAACGCCCTCCAATCG GGTAACCTCCAGAGAGTGTACAGAGCAGGACGGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTG ACGCTGAGCAAAGCAGACTACGAGAAACAAAGTCTACGCCTGCGAAGTCACCATCAGGGCCTGAGC TCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT
177	PFD1 Heavy chain nucleotide sequence	GAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCA GCCTCTGGATTACCTTCAGTAGCTATGGCATGCACTGGGTCCGGCAGGTCCAGGCAAGGGGCTGGAG TGGGTGGCAGTTATATCATATGATGGAAGTAATAATACTATGCAGACTCCGTGAAGGGCCGATTACAC ATCTCCAGAGACAATGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCT GTATATTACTGTGCGAGATCAGCTGGATATAGTGGCTACGACAACTGGGGCCAGGGCACCTGGTCAAC GTCTCAAGCGCCTCCACCAAGGGCCATCGGTCTTCCCCCTGGCACCTCTCTCAAGAGCACCTCTGGG GGCAGAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAAACCGGTGACCGGTCTCGTGGAATCA GGCGCCCTGACCAGCGGCTCCACACCTTCCCGGCTGTCTACAGTCTCTAGGACTCTACTCCCTCAGC AGCGTAGTGACCGTGCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCC AGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAATCTTGT
178	PFD1 Light chain VD	DVVMTQSPSLPVLTLGQPASISCRSSQSLVYSNGNTYLNWFQQRPGQSPRRLFYKVSNRDSGVPDRFSG SGSGTDFTLKISRVEAEDVGVIYCMQGTGHPGTFGQGTLEIKRTVAAPSVFIFPPSDEQLKSGTASV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDQKDSYLSSTLTLSKADYEKHKVYACEVTHQGLS SPVTKSFNRGEC
179	PFD1 Heavy chain VD	EVQLVQSGGGLVQPGPGRSLRLSCAASGFTSSYGMHWVRQAPGKLEWVAIVSYDGSNKYYADSVKGRFT ISRDNANKNSLYLQMNSLRAEDTAVYYCARSGYSGYDNWGQGLTVTVSSASTKGPSVFPPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS SNTKVDKKVEPKSC
180	PFD1 LC-CDR3 PFD1 LC-CDR3	MQGTHWPGT
181	PFD1 HC-CDR3	SRGYSYDN
182	PFD2 Light chain nucleotide sequence	CAGTCTGTGCTGACGACGCGCCCTCAGTGTCTGGGGCCCCCGGCAGAGGGTACCATCTCCTGCACT GGGAGAAGCGCCAAATATCGGGGTTTTGATGTACAGTGGTACCGACAACCTCCAGGAACAGCCCCCAA CTCCTCATATATGACAACAGCAATCGGGCCCTCAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGC ACCTCAGCCACCCTGGCCATCAGCGGACTTCAGACTGGCGACGAGGCCGATTATTACTGCGGAACATGG GATTCTCTACCTCAATATTGGGTGTTCCGGCGAGGGACCAAGCTGACCGTCTTAGTCAGCCCAAGGCT GCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGT CTCATAAGTGACTTCTACCGGGAGCCGTGACAGTGGCTTGAAGGCGAGATAGCAGCCCGCTCAAGGCG GGAGTGGAGACCACACACCTCCAAACAAGCAACAAGTACGCGGCCAGCAGCTACCTGAGCCTG ACGCTGAGCAGTGAAGTCCCAACAAAGCTACAGCTGCCAGGTACGCATGAAGGGAGACCGGTGGAG AAGACAGTGGCCCTACAGAATGTTCA
183	PFD2 Heavy chain nucleotide sequence	CAGGTGCAGCTACAGCAGTGGGGCGCAGGACTGTGAAGCCTTCGGAGACCCTGTCCCTACCTGCGCT GTCTATGGTGGTCTTCACTGTTACTACTGGAGCTGGATCCGCCAGCCCCAGGGAAGGGGCTGGAG TGGATTGGGGAAATCAATCATAGTGAAGCACCACCTACAACCCGTCCCTCAAGAGTCCAGTACCCATA TCAGTAGACAGTCCAAGAACCAGTCTTCCCTGAAGCTGAGCTCTGTGACCGCCCGGACACGGCTGTG TATTACTGTGCGAGAGCCTTCCGTATTACTTGTACTGCTGAGTGGGCGACCTGGTCAACGCTCAGCGC TCAAGCGCCTCCACCAAGGGCCATCGGTCTTCCCCCTGGCACCTCTCTCAAGAGCACCTCTGGGGG ACAGCGGCCCTGGGCTGCTGTTCAAGGACTACTTCCCCGAACCGGTGACGGTGTGCTGGAAGTCAAGG GCCCTGACCAGCGGCTCCACACCTTCCCGGCTGTCTACAGTCTCTAGGACTCTACTCCCTCAGCAGC GTAGTGACCGTGCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGC AACACCAAGGTGGACAAGAAAGTTGAGCCCAATCTTGT
184	PFD2 Light chain VD	QSVVTQPPSVSGAPGQRTVTSCTGRSANIGGFVQWYRQLPGTAPQLLIYDNSNRPVSGVPDRFSGSKSG TSATLAISGLQTGDEADYYCGTWDSYLNIVWFGGGTKLTVLSQPKAAPSVTLFPPSSEELQANKATLV LISDFYPGAVTVAWKADSSPVKAGVETTPSKQSNKYAASSYLSLTPEQWQSHKSYSCQVTHEGSTVE KTVAPTECS
185	PFD2 Heavy chain VD	QVQLQQWAGALLKPSSETLSLTCAVYGGSGFYYSWIRQPPGKLEWIGEINHSSTNYPNPSLKSRTVI SVDTSKNQFSLKLSSVTAADTAVYYCARGLPYFYFDYWGQGLTVTVSSASTKGPSVFPPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSC
186	PFD2 LC-CDR1	TGRSANIGGFVQ
187	PFD2 LC-CDR2	DNSNRPS
188	PFD2 LC-CDR3	GTWDSYLNIVW
189	PFD2 HC-CDR3	GLPYFYFDY
190	PFD3 Light chain nucleotide sequence	CAGGCTGTGGTGATCCAGGAGCCATCGTTCTCAGTGTCCCTGGAGGGACAGTACACTCACTTGTGCC TTGACCTCTGGCTCAGTCTCTACTAGTTACTACCCAGCTGGTACCAGCAGACCCAGGCCAGCCTCCA CGCAGCTCATTTACAGCACAACCTTCCCTCTTCTGGGTCCCTGATCGCTTCTTGGCTCCATCCTT GGGAACAAGGCTGCCCTACCATCAGGGGGGCCAGCGGATGATGAATCTGATTATTACTGTGAGTTG

		TATATGGGTAGTGGCATTTCGGTGTTCGGCGGAGGGACCAAGGTGACCGTCCTAGGTTCAGCCCAAGGCT GCCCCCTCGGTCACTCTGTTCCCAACCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGT CTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTGGAAGGCAGATAGCAGCCCGTCAAGGCG GGAGTGGAGACCACCACACCTTCCAAACAAGCAACAACAAGTACGCGGCCAGCAGCTACCTGAGCCTG ACGCCTGAGCAGTGAAGTCCACAAAGCTACAGCTGCCAGGTACGCATGAAGGGAGACCCGTGGAG AAGACAGTGGCCCTACACAATGTTCA
191	PFD3 Heavy chain nucleotide sequence	GAGGTCCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCGGGAGTCTCTGAAGATCTCCTGTAAG GGTCTGGATACAGCTTTACCAGTACTGGATCGGCTGGGTGCGCCAGATGCCCCGGAAGGCCCTGGAG TGGATGGGGATCATCTATCCTGGTGAAGTCTGATACCAGATACAGCCCGTCTTCCAAGGCCAGGTACACC ATCTCAGCCGACAAGTCCATCAGCACCAGCTACCTGCAGTGGAGCAGCTGAAGGCCTCGGACACCCGCC ATGTATTACTGTGCGAGACTGGGCTACGGTGTCCCCCTGCCTGAGTACTCGATCTCTGGGGCCGTGGA ACCCCTGGTCAACGCTCTCAAGCGCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCTTCCAAG AGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTG TCGTGGAAGTACAGCGCCCTGACCAGCGGCGTCCACACCTTCCCCGCTGTCTACAGTCTCTAGGACTC TACTCCCTCAGCAGCGTAGTGACCGTGCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTG AATCACAAGCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAATCTTGT
192	PFD3 Light chain VD	QAVVIQEPSFSVSPGGTVTLTCAITSGSVSTSYSPSWYQQTGQPPRTLIYSTNLRSSGVPDRFSGSIL GNKAALITITGAQADDES DYCELYMGSGISVFGGGTKVTVLGGPKAAPSVTLFPPSSEELQANKATLV LISDFYPGAVTVAWKADSSPVKAGVETTPSKQSNKNYAASSYLSLTPEQWKS HSYSCQVTHEGSTVE KTVAPTECS
193	PFD3 Heavy chain VD	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKLEWMGI IYPGDS DTRYSPSFQGV ISADKSI STAYLQWSSSLKASDTAMYYCARLG YGVPLPEYFDLWGRGLTVTVSSASTKGPSVFPLAPSSK STSGGTAAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFPPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSC
194	PFD3 LC-CDR1	ALTSGSVSTSYSPS
195	PFD3 LC-CDR2	STNLRSS
196	PFD3 LC-CDR3	ELYMGSGISV
197	PFD3 HC-CDR1	SYWIG
198	PFD3 HC-CDR2	I IYPGDS DTRYSPSFQGV
199	PFD3 HC-CDR3	LG YGVPLPEYFDL
200	PFD4 Light chain nucleotide sequence	GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTACCCCTGGACAGCCGGCCTCCATCTCTGTC AGGTCTAGTCAAAGCCTCGTATACAGTGATGAAACACCTACTTGAATTGGTTTCAGCAGAGGCCAGGC CAATCTCCAAGGCGCCTAATTTATAAGTTTCTGACCGGACTCTGGGGTCCCAGACAGATTACAGCGGC AGTGGGTCAAGGCACTGATTTACACTGAAATCAGCAGGGTGGAGGCTGAGGATGTTGGGGTTTATTAC TGCATGCAAGGCACACACTGGCCTCAGACTTTTGGCCAGGGGACCAAGTGGAGATCAAACGAACCTGTG GCTGCACCATCTGTCTTCACTTCCCCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTG TGCCTGCTGAATAACTTCTATCCAGAGAGGCCAAAGTACAGTGAAGGTGGATAAGCCCTCCCAATCG GGTAAGTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTG ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGC TCGCCCCGTTACAAAGAGCTTCAACAGGGGAGAGTGT
201	PFD4 Heavy chain nucleotide sequence	CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGTCCCTGAGACTCTCCTGTTCA GCCTCTGGATTACCTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCCAGGGAAGGGACTGGAA TATGTTTCAGCTATTAGTAGTAATGGGGGTAGCACAATACTACGAGACTCCGTGAAGGGCAGATTACACC ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTTCAAATGAGCAGTCTGAGAGCTGAGGACACGGCT GTGTATTACTGTGCGAAGTATAGGGCTACTACGGTATGAGCAGTCTGGGGTCCAGGACCAAGCCCTCCGTCACC GTCTCAAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGG GGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAAGTCA GGCGCCCTGACCAGCGGCTCCACACCTTCCCCGCTGTCTACAGTCTCTCAGGACTCTACTCCCTCAGC AGCGTAGTGACCGTGCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCC AGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAATCTTGT
202	PFD4 Light chain VD	DVVMTQSPSLPVLTLGQPASISCRSSQSLVYSDGNTYLNWFQQRPGQSPRRLIYKVSDRDSGVPDRFSG SGSGTDFTLKISRVEAEDVGVIYCMQGT HWPQT FQGQTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV CLNNFYPREAKVQWKVDNALQCSNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLS SPVTKSFNRGEC
203	PFD4 Heavy chain VD	QVQLVQSGGGLVQPGGSLRLSCSASGFTFSSYAMHWVRQAPGKLEYVSAISSNGGSTYYADSVKGRFT ISRDN SKNTLYLQMSLRAEDTAVYYCARSRGYGMDVWQGT TVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFPPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSC
204	PFD4 LC-CDR2	KVSDRDS
205	PFD4 LC-CDR3	MQGTHWPQT
206	PFD4 HC-CDR2 PFD3 HC-CDR2	AISSNGGSTYYADSVKGV
207	PFE1 Light chain nucleotide sequence	GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTACCCCTGGACAGCCGGCCTCCATCTCTGTC ACGTCTAGTCAAAGCCTCGTATACAGTGATGAAACACCTACTTGAATTGGTTTCAGCAGAGGCCAGGC CAATCTCCAAGGCGCCTAATTTATAAGTTTCTAAGCGGACTCTGGGGTCCCAGACAGATTACAGCGGC AGTGGGTCAAGGCACTGATTTACACTGAAATAAGCAGGGTGGAGGCTGAGGATGTTGCGATTTATTAC TGCATGCAAGGTACACACTGGCCTCTCACTTTCCGCGGAGGGACCAAGGTGGAGATCAAACGAAGTGTG GCTGCACCATCTGTCTTCACTTCCCCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTG TGCCTGCTGAATAACTTCTATCCAGAGAGGCCAAAGTACAGTGAAGGTGGATAACGCCCTCCCAATCG GGTAAGTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTG ACGCTGAGCAAAGCAGACTACGAGAAACACAAACTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGC TCGCCCCGTACAAAGAGCTTCAACAGGGGAGAGTGT
208	PFE1 Heavy chain nucleotide	GAGGTCCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCA GCCTCTGGATTACCTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAG TGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTACGAGACTCCGTGAAGGGCCGATTACACC ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAATGAACAGCCTGAGAGCTGAGGACACGGCT

	sequence	GTGTATTACTGTGCGAGGAGTCGAGGCTACTACGGTATGGACGCTCTGGGGCCAAGGGACCACGGTCACC GTCTCAAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCTCCCAAGAGCACCTCTGGG GGCACAGCGGCCCTGGGCTGCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAATCTCA GGCGCCCTGACCAGCGGCTCCACACCTTCCCGGCTGTCTACAGTCTCTAGGACTCTACTCCCTCAGC AGCGTAGTGACCGTGCCCTCCAGCAGCTTGGGCAACCCAGACCTACATCTGCAACGTGAATCACAAGCCC AGCAACACCAAGGTGGACAAGAAAGTTGAGCCCCAAATCTTGT
209	PFE1 Light chain VD	DVVMTQSPSLSPVTLGQFPASISCTSSQSLVYSDGNTYLNWFQQRPGQSPRRLLIYKVKRDSGVPDRFSG SGSGTDFTLKISRVEAEDVAIYYCMQGTWHPLTFGGGKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKLYACEVTHQGLS SPVTKSFNRGEC
210	PFE1 Heavy chain VD	EVQLVQSGGGVVPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAIVSYDGSNKYYADSVKGRFT ISRDN SKNTLYLQMNLSRAEDTAVYYCARSRGYYGMDVWGQGTITVTVSSASTKGPSVFPLAPSSKSTSG GTAAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSC
211	PFE1 LC-CDR1	TSSQSLVYSDGNTYLN
212	PFE1 LC-CDR2	KVKRDS
213	PFE2 Light chain nucleotide sequence	GTGAAAAAATTATTATTCGCAATTCCTTTAGTTGTTCTTCTATTCTCACAGTGCACCTTGATGTTGTG ATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCCATCTCCTGCAGGCTAGT CAGAGCCTCCTGCCAGTATGATGATACTTTTGTGGATTGGTACCTGCAGAAGGCAGGGCAGTCTCCA CAGCTCCTGATCCATTGTGGTTCTGATCGGGCCTCCGGGCTCCCTGACAGCCTTCAATGCGGATGATCA GGCACAGATTTTACACTGAGAATCAGCAGAGTGGAGGCTGAGGATGTTGGAGTTTATTACTGCATGCAA GCTCTACAACTCCTCGGACGTTCTGGCCCAAGGGACCAAGGTGGAATCAACGAACTGTGGCTGCACCA TCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACGCTCTGTGTGTGCTGCTG AATAACTTCTATCCAGAGAGGCCAAAGTACAGTGGAAAGGTGGATGACAGCCTCAATCGGGTAATCC CAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGC AAAGCAGACTACGAGAAACACAAGTCTACGCCCTGCGAAGTACCCATCAGGGCCTGAGCTCGCCCGT ACAAAGAGCTTCAACAGGGGAGAGTGT
214	PFE2 Heavy chain nucleotide sequence	GAGGTCCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCA GCCTCTGGATTACCTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAG TGGGTGGCAGTTATATCATATGATGAAAGCAATAAATACTACGCAGACTCCGTGAAGGGCCGATTACAC ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCTGAGGACACGGCT GTGTATTACTGTGCGAGGAGGCCAAGCGGCAGCTGGTCTGACCTTACTACTACTACTACGCTATGAGC GTCTGGGGCCAAGGGACCAAGGTCACCGTCTCAAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTG GCACCCTCCTCCAGAGACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCC GAACCGGTGACGGTGTCTGGAACCTCAGCGCCCTGACCAGCGGCTCCACACCTTCCCGGCTGTCTTA CAGTCTCAGGACTCTACTCCCTCAGCAGCGTAGTGACCGTGCCCTCAGCAGCCTTGGGCACCCAGACC TACATCTGCAACGTGAATCACAAGCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAATCTTGT
215	PFE2 Light chain VD	DVVMTQSPSLSPVTPGEPASISCRSSQSLRLSDGYNFVDWYLQKAGQSPQLLIHLGSDRASGVPDRFSG SGSGTDFTLRISRVEAEDVGVIYCMQALQTPRTFQGGTVEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLS SPVTKSFNRGEC
216	PFE2 Heavy chain VD	EVQLVQSGGGVVPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAIVSYDES NKYYADSVKGRFT ISRDN SKNTLYLQMNLSRAEDTAVYYCAREPSGSWSYLYYYYGMDVWGQGTITVTVSSASTKGPSVFPL APSSKSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQT YICNVNHKPSNTKVDKKVEPKSC
217	PFE2 LC-CDR1	RSSQSLRLSDGYNFVD
218	PFE2 LC-CDR2	LGSDRAS
219	PFE2 LC-CDR3	MQALQTPRT
220	PFE2 HC-CDR2	VISYDES NKYYADSVKG
221	PFE2 HC-CDR3	EPSCGSWSYLYYYYGMDV
222	PFE5 Light chain nucleotide sequence	GACATCCAGATGACCCAGTCTCCATCCTCCTGTCTGCATCTGTAGGAGACAGAGTACCATCACTTGT CGGGCAGTCAAGGTATTAGCAGCTGGTGTAGCCTGGTATCAGCAGAAACAGGGAAAGCCCTAAGCTC CTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTACAGCGGACGTGGATCTGGGACA GATTTCACCTCTCACCATCAGCAGCCTGACGCTGAAGATTTTGCAACTTACTATGTCAACAGGCTAAC AGTTTCCCTCCCACTTTTCGGCCCTGGGACCAAGTGGATATCAACGAACTGTGGCTGCACCATCTGTC TTCTATCTCCCGCATCTGATGAGCAGTTGAAATCTGGAACCTGCTCTGTGTGTGCTGCTGAATAAC TTCTATCCAGAGAGGCCAAAGTACAGTGGAAAGTGGATAACGCCCTCCAATCGGGTAACCTCCAGGAG AGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCA GACTACGAGAAACACAAGTCTACGCCTGCGAAGTACCCATCAGGGCCTGAGCTCGCCCGTCACAAAG AGCTTCAACAGGGGAGAGTGT
223	PFE5 Heavy chain nucleotide sequence	GAGGTCCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCA GCCTCTGGATTACCTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAG TGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTACGCAGACTCCGTGAAGGGCCGATTACAC ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCTGAGGACACGGCT GTGTATTACTGTGCGAGGAGTCGAGGCTACTACGGTATGGACGCTCTGGGGCCAAGGGACCAAGGTCACC GTCTCAAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCTCCCTGAGGCTGCTGGG GGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGGAACCTCA GGCGCCCTGACCAGCGGCTCCACACCTTCCCGGCTGTCTACAGTCTCAGGACTCTACTCCCTCAGC AGCGTAGTGACCGTGCCCTCCAGCAGCTTGGGCAACCCAGACCTACATCTGCAACGTGAATCACAAGCCC AGCAACACCAAGGTGGACAAGAAAGTTGAGCCCCAAATCTTGT
224	PFE5 Light chain VD	DIQMTQSPSSLSASVGRVITITCRASQGISWLAWYQQKPGKAPKLLIYAASLSQGVPSRFSGSGSGT DFTLTISLQPEDFATYYCQANSPPTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC
225	PFE5 Heavy chain VD	EVQLVQSGGGVVPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAIVSYDGSNKYYADSVKGRFT ISRDN SKNTLYLQMNLSRAEDTAVYYCARSRGYYGMDVWGQGTITVTVSSASTKGPSVFPLAPSSKSTSG

		GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLGTQTYICNVNHPK SNTKVDKKVEPKSC
226	PFE5 LC-CDR1	RASQGISSWLA
227	PFE5 LC-CDR2	AASSLQS
228	PFE5 LC-CDR3	QQANSFPPT
229	PFF2 Light chain nucleotide sequence	GAAATTGTGTTGACGCAGTCTCCAGGCACCCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCCTCTCTGCG AGGGCCAGTCAGAGTGTAGCAGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCAGG CTCCTCATCTATGGTGCCATCCAGCAGGGCCACTGGCATCCAGACAGGTTCACTGGCAGTGGGTCTGGG ACAGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTAT GGTAGCTCCTCCGCTTTTCGGCCCTGGGACCAAAGTGGATATCAACGAACCTGTGGCTGCACCATCTGTC TTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACCTGCCTCTGTTGTGTGCCTGCTGAATAAC TTCTATCCCAAGAGAGGCCAAAGTACAGTGAAGGTGGATAACGCCCTCAATACCGTCTGGGCCAAGGAG AGTGTACACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCAAAGCA GACTACGAGAAACACAAAGTCTACGCCTCGGAAGTACCCATCAGGGCCTGAGCTCGCCCGTCACAAAG AGCTTCAACAGGGGAGAGTGT
230	PFF2 Heavy chain nucleotide sequence	CAGATGCAGCTGGTGCGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCACTGAGACTCTCCTGTGCA GCCTCTGGATTCACTTTCAAAAATTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAG TGGGTGGCATTATCTCATATGATGGAACATAATAATATGATGAGACTCCGTGAAGGGCCGATTACACC ATCTCCAGAGACAATTTCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCC GTATATTACTGTGCGAAGCAGTACGCTGCTACTACTACTACGCTTGGAGCTTGGGCCAAGGAG ACCACGGTCACCGTCTCAAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCTTCCAAG AGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTG TCGTGGAACCTCAGGCGCCCTGACCAGCGGCGTCCACACCTTCCCGGCTGTCTACAGTCTCTCAGGACTC TACTCCCTCAGCAGCGTAGTGACCGTGCCCTCCAGCAGCTTGGGACCCAGACCTACATCTGCAACGTG AATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGT
231	PFF2 Light chain VD	EIVLTQSPGTLISLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLIYGAASSRATGIPDRFSGSGSG TDFLTISRLEPEDFAVYYCQQYGSSSAFPGPTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK SFNRGEC
232	PFF2 Heavy chain VD	QMQLVQSGGGVVQPGSRSLRLSCAASGFSFKNYGMHWVRQAPGKLEWVAFISYDGTNKYYADSVKGRFT ISRDNKNTLYLQMNSLRAEDTAVYYCAKHYGDIYGYGMDVWGQGTITVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLGTQTYICNV NHPKSNKVDKKVEPKSC
233	PFF2 LC-CDR3	QQYGSSSA
234	PFF2 HC-CDR1	NYGMH
235	PFF2 HC-CDR2	FISYDGTNKYYADSVKG
236	PFF2 HC-CDR3	HYGDYYYYYGMVDV
237	PFF3 Light chain nucleotide sequence	GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCACCCCTGGAGAGCCGGCCTCCATCTCTGCG AGGTCTAGTCAGAGCCTCTGTCATAGTAATGGATACAATATTTGGATTGGTACCTGCAGAAGCCAGGG CAGTCTCCACAGCTCCTGATCTACTTGGGTCTTAATCGGGCCTCCGGGGTCCCTGACAGGCTCAGTGGC AGTGGATCAGGCACAGATTTTACACTGAAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTAC TGCATGCCAAGGTACACACTGGCCAGGGACGCTTCGGCCAAAGGACCAAGGTGGAATCAACAGCACTGTG GCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACCTGCCTCTGTTGTG TGCTGTGTAATAACTTCTATCCAGAGAGGCCAAAGTACAGTGAAGGTGGATAACGCCCTCCAAATCG GGTAACCTCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGACCCCTG ACGCTGAGCAAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCAACCATCAGGGCCTGAGC TCGCCCCGTACAAAAGAGCTTCAACAGGGGAGAGTGT
238	PFF3 Heavy chain nucleotide sequence	CAGGTCCAGCTGGTACAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTTCA GCCTCTGGATTACCTTTCAGTAGCTATGCTATCCACTGGGTCCGCCAGGCTCCAGGGAAGGGACTGGAA TATGTTTCAGCTATTAGTAGTAATGGGGGTAGCACATACTACGACAGACTCCGTGAAGGGCAGATTACAC ATCTCCAGAGACAATTTCAAGAACACGCTGTATCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCT GTGTATTACTGTGCGAGACTCTATGGATATGGTCTCCACTACTACGGTATGGACCTCTGGGGCCAAAGG ACCACGGTCACCGTCTCAAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCTTCCAAG AGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTG TCGTGGAACCTCAGGCGCCCTGACCAGCGGCGTCCACACCTTCCCGGCTGTCTACAGTCTCTCAGGACTC TACTCCCTCAGCAGCGTAGTGACCGTGCCCTCCAGCAGCTTGGGACCCAGACCTACATCTGCAACGTG AATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGT
239	PFF3 Light chain VD	DVVMTQSPSLPVPTEPASIISCRSSQSLLSNGYNYLDWYLQKPGQSPQLLIYLSNRRASGVPDRLSG SGSGTDFTLKISRVEAEDVGVYYCMQGTHWPGTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLS SPVTKSFNRGEC
240	PFF3 Heavy chain VD	QVQLVQSGGGLVQPGGSLRLSCSASGFTSSYAIHWVRQAPGKLEYVSAISSNGGSTYYADSVKGRFT ISRDNKNTLYLQMNSLRAEDTAVYYCARVYGYGLHYGMDVWGQGTITVTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVFSSSLGTQTYICNV NHPKSNKVDKKVEPKSC
241	PFF3 HC-CDR1	SYAIH
242	PFF3 HC-CDR3	VYGYGLHYGMDV
243	PFF4 Light chain nucleotide sequence	GAAACGACACTCAGCAGTCTCCAGGCACGCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCCTCTCTGCG AGGGCCAGTCGGAGTGTGGCAAGTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCACCTTA GTCATTTATGATGCATCAACCAGGGCCTCCGGCATTCCAGACAGGTTCACTGCCAGTGGCTCTGGGACT GACTTCACTCTCACCATCAGCAGTCTGGAGCCTGAAGATTTTGCAGTGTATTCTGTGACACTATGGT ACCTCACCTCCGTTTCAATTTTGGCCAAGGGACAGACTGGAGATTAAACGAACCTGTGGCTGCACCATCT GTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACCTGCCTCTGTTGTGTGCTGTGTAAT AACTTCTATCCAGAGAGGCCAAAGTACAGTGAAGGTGGATAACGCCCTCCAAATCGGGTAACTCCAG GAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCAAA GCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCAACCATCAGGGCCTGAGCTCGCCCGTCACA

		AAGAGCTTCAACAGGGGAGAGTGT
244	PFF4 Heavy chain nucleotide sequence	GAAGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCTCGGTGAAGGTCTCCTGCAAG GCTTCTGGAGGCACTTCAGCAGCTATGCTATCAGCTGGGTGCGACAGGCCCTGGACAAGGGCTTGAG TGGATGGGAGGGATCATCCCTATCTTTGGTACGGGCAAACTACGCACAGAAGTTCAGGGCAGAGTCACG ATTACCGCGGACGAATCCACGAGCAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCC GTGTATTACTGTGCGAGATCCTATGATAGTAGTGGTTATTACTACTTTGACTACTGGGGCCAGGGAACC CTGGTCACCGTCTCAAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGC ACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTG TGGAACTCAGGCGCCCTGACCAGCGCGCTCCACACCTTCCCGGCTGTCTACAGTCTCAGGACTCTAC TCCCTCAGCAGCGTAGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAAT CACAAGCCCAAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAATCTTGT
245	PFF4 Light chain VD	ETTLTQSPGTLSSLSPGERATLSCRASRSVGKYLAWYQQKPGQAPTLVIYDASTRASGIPDRFSASGSGT DFTLTISLLEPEDFAVYFCQHYGTSPFFIFGQGTRLKIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN NFYFPREKQVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC
246	PFF4 Heavy chain VD	EVQLVQSGAEVKKPKSSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPFGTANYAQKFGQGRVT ITADESTSTAYMELSSLSRSEDYAVYYCARSYDSSGYYFYDYWGQGTLLVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSC
247	PFF4 LC-CDR1	RASRSVGKYLA
248	PFF4 LC-CDR2	DASTRAS
249	PFF4 LC-CDR3	QHYGTSPFFI
250	PFF4 HC-CDR3	SYDSSGYYFYDY
251	PFF5 Light chain nucleotide sequence	CAGGCTGTGGTGATCCAGGAGCCATCGTTCTCAGTGTCCCTGGAGGGACAGTCACACTCACTTGTGGC TTGAGCTCTGGCTCAGTCTCTACTACTTACTACCCAGCTGGTACCAGCAGACCCAGGCCAGGCTCCA CGCAGCTCATCTACGACAAACTCGCTCTTCTGGGGTCCCTGATCGCTTCTCTGGCTCCATCCTT GGGAACAAAGCTGCCCTCACCATCAGGGGGGCCAGGCAGATGATGAATCTGATTATTACTGTGTGCTG TATATGGGTAATGGCATTTCGGTGTTCGGCGGAGGGACCAAGCTGACCGTCTAGGTACGCCCAAGGCT GCCCTCTCGGTCACTGTTCCTCCGCCCTCCTCTGAGGAGCTTCAAGCCACAAGGCCACACTGGTGTGT CTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCG GGAGTGGAGACCACACCCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCTACCTGAGCCTG ACGCCTGAGCAGTGGAAAGTCCCAAAAGCTACAGCTGCCAGGTACGCATGAAGGGAGCACCGTGGAG AAGACAGTGGCCCTGCAGAATGCTCT
252	PFF5 Heavy chain nucleotide sequence	CAGGTGCAGCTGCAGGAGTCCGGGCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCTTCACTGCACT GTCTCTGGTGGCTCCATCAGCAGTAGTAGTTACTACTGGGGCTGGATCCGCCAGCCCCAGGGAAGGGG CTGGAGTGGATTGGGAGTATCTATTATACTGGGAGCACCTACTACAACCCGTCCTCAAGAGTCGAGTC ACCATATCCGTAGACAGCTCCAAGAACCAAGTTCCTCCCTGAGGCTGAGCTGTGAGCGCCGACAGCAG GCCGTGTATTACTGTGCGAGATACGCGCCTGATAGTAGTGGTTACCTGGTGGCTTTTGATATCTGGGGC CAAGGGACAATGGTCACCGTCTCAAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCTCC TCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTG ACGGTGTCTGGAACTCAGGCGCCCTGACCAGCGCCCTCCACACCTTCCCGGCTGCTCTACAGTCTCA GGACTCTACTCCCTCAGCAGCGTAGTGACCGTGGCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGC AACGTGAATCACAGCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAATCTTGT
253	PFF5 Light chain VD	QAVVIQEPSFSVSPGGTTLTCLSSGSVSTTYPSWYQQTPGQAPRTLIYSTNTRSSGVDPDRFSGSIL GNKAALTIITGAQADDESYYICVLYMNGISVFGGKTLTVLGPKAAPSVTLFPSSSEELQANKATLVC LISDFYPGAVTVAWKADSSPVKAGVETTPSKQSNKNKYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVE KTVAPAEC
254	PFF5 Heavy chain VD	QVQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIQPPGKLEWIGSIYYSGSTYYNPSLKSRV TISVDTSKNQFSLRSSVAADTAVYYCARYAPDSSGYLVAFDIWGQGTMTVTVSSASTKGPSVFPLAPS SKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSC
255	PFF5 LC-CDR1	GLSSGSVSTTYPS
256	PFF5 LC-CDR3	VLYMNGISV
257	PFG1 Light chain nucleotide sequence	CAGGCTGTGCTGACTACGCGCTTCCCTCTCTGCATCTCCTGGAGCATCAGCCAGTCTCACCTGCACC TTGCGCAGTGGCATCAATGTTGGTACCTACAGGATATACTGGTACCAGCAGAAGCCAGGGAGTCTCTCC CAGTATCTCCTGAGGTACAATCAGACTCAGATAAGCAGCAGGGCTCTGGAGTCCCCAGCCGCTCTCT GGATCCAAAGATGCTTCGGCCAATGCAGGGATTCTTACTCATCTCTGGGCTCCAGTCTGAGGATGAGGCT GACTATTACTGTATGATTGGCACAGCAGCGCTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGCTCA GGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCACCCCTCCTCTGAGGAGCTTCAAGCCAACAAG GCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGCAGATAGC AGCCCCGTCAAGGCGGGAGTGGAGACCACACCCCTCCAAACAAAGCAACAACAAGTACGCGGCCAGC AGCTACCTGAGCCTGACGCTGAGCAGTGGAAAGTCCCAAAAGCTACAGCTGCCAGGTACGCATGAA GGGAGCACCGTGGAGAAGCAGTGGCCCTGCAGAATGCTCT
258	PFG1 Heavy chain nucleotide sequence	GAGGTCCAGCTGTGACAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCA GCGTCTGGATTACCTTCAGTAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAG TGGGTGGCAGTTATATGTTAGTGAAGTAATAACTATGCAAGTCCGTGTAAGGGCCAGTACC ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAATGAACAGCCTGAGAGCTGAGGACACGGCT GTATATTACTGTGCCAATGACTACTGAGGACTACTGGGGCCAGGGCACCCCTGGTCACCGTCTCAAGC GCCTCCACCAAGGGCCATCGGTCTTCCCCCTGGCACCCCTCCTCCAAGAGCACCTCTGGGGGCACAGCG CCCTGGGCTGCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTACCTGAGGAACTCAGGCGCCTG ACCAGCGCGCTCCACACCTTCCCGGCTGTCTACAGTCTCAGGACTCTACTCCCTCAGCAGCGTAGTG ACCGTGGCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCAGCAACACC AAGGTGGACAAGAAAGTTGAGCCCAATCTTGT
259	PFG1 Light chain VD	QAVLTQPSLSASFGASASLTCLRSINVGTYIRIYWYQQKPGSPPPQYLLRYKSDSDKQQGSGVPSRFS GSKDASANAGILLISGLQSEDEADYYCMTWSSAWVFGGKTLTVLGPKAAPSVTLFPSSSEELQANK ATLVCLISDFYPGAVTVAWKADSSPVKAGVETTPSKQSNKNKYAASSYLSLTPEQWKSHKSYSCQVTHE

		GSTVEKTVAPAECS
260	PFG1 Heavy chain VD	EVQLVQSGGGVVPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWDGNSNKYYADSVKGRFT ISRDN SKNTLYLQMNSLRAEDTAVYYCATMTTEDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNT KVDKKVEPKSC
261	PFG1 LC-CDR1	TLRSGINVGTYRIY
262	PFG1 LC-CDR2	YKSDSDKQQGS
263	PFG1 LC-CDR3	MIWHSSAWV
264	PFG1 HC-CDR2	VIWYDGSNKYYADSVKG
265	PFG1 HC-CDR3	MTTEDY
266	PFG2 Light chain nucleotide sequence	GAAATTGTGTTGACGCAGTCTCCAGCCACCTGTCTTTGTCTCCAGGGGAAAGAGCCACCTCTCTCTGC AGGGCCAGTCAGAGTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCCAGGCTC CTCATCTATGATGCGTCCAACAGGGCCACTGGCATCCCAGCCAGGTTCACTGGCAGTGGGTCTGGGACA GACTTCACTCTCACCATCAGCAGCTAGAGCCTGAAGATTTTGAGTTTATTACTGTACAGCAGCGTAGC AACTGGCCGCTCACTTTCCGGCGGAGGGACCAAGGTGGAGATCAAACGAAGTGTGGCTGCACCATCTGTCT TTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTGTGTGCCTGTGAATAAC TTCTATCCCAGAGAGGCCAAAGTACAGTGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAG AGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCA GACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAG AGCTTCAACAGGGGAGAGTGT
267	PFG2 Heavy chain nucleotide sequence	GAAGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCA GCCTCTGGATTACCTTTAGCAGCTATGCGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAG TGGGTCTCATCCATTAGTAGTAGTAGTGTACATATACTACGCAGACTCGGTGAAGGGCCGATTACACC ATCTCCAGAGACAACGCCAAGAATTCAGTATCTGCAAAATGAACAGCTGAGGGCCGAGGACAGCGCT GTCTATTACTGTGCGAGAGATGGCAGTGGTGGTACGACCCCTACTGGGGCCAGGGAACTGGTCAACC GTCTCAAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCTCTCTCAAGAGCACTCTGGG GGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGAAGTCA GGCGCCCTGACCAGCGCGCTCCACACCTTCCCGGCTGTCTACAGTCTCAGGACTCTACTCCCTCAGC AGCGTAGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCC AGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAATCTTGT
268	PFG2 Light chain VD	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRTGIPARFSGSGSGT DFTLTISLEPEDFAVYYCQQRNWPFLFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLNN FYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEHKHYACEVTHQGLSSPVT SFNRGEC
269	PFG2 Heavy chain VD	EVQLVQSGGGLVPPGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSISSSSSYIYYADSVKGRFT ISRDNKNSLYLQMNSLRAEDTAVYYCARDGSAWSRPYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSC
270	PFG2 LC-CDR1	RAQSVSSYLA
271	PFG2 LC-CDR2	DASNRT
272	PFG2 LC-CDR3	QQRNWPFLT
273	PFG2 HC-CDR2	SISSSSSYIYYADSVKG
274	PFG2 HC-CDR3	DGSAWSRPY
275	PFG3 Light chain nucleotide sequence	CAGGCTGTGGTGTCTCAGGAGCCATCGTTCTCAGTGTCCCTGGAGGGACAGTCACACTCACTTGTGGC TTGACCTCTGGCGCAGTCTCCAGTTCTTACTACCCAGCTGGTACCAGCAGACCCAGGCCAGGCTCCT CGCACTCTCATTATATAACACAGACATTCCGCTTTTCTGGGTCCCTGATCGCTTCTTGGCTCCATCCTT GGGAACAAAGCTGCCCTCACCATCAGGGGGGCCAGGCAGATGATGAATCTGATTATTACTGTGTACTA TATATGGGTAGTGGCATTTCGGTGTTCGGCGGAGGGACCAAAGTACCGTCTAGGTACAGCCCAAGGCT GCCCCCTCGGTCACTCTGTTCCCAACCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGT CTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCTGGAAGGCATGACGACCCGCTCAAGCGG GGAGTGGAGACCACACACCTCCAAACAAAGCAACAACAAGTACGCGGCAGCAGCTACCTGAGCCTG ACGCCTGAGCAGTGAAGTCCACAAAAGCTACAGCTGCCAGGTACGCATGAAGGGAGACCGTGGAG AAAACAGTGGCCCTGCGAATGCTCT
276	PFG3 Heavy chain nucleotide sequence	GAAGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGACCTCAGTGACAGTCTCCTGCAGG GCTTCTGGATTACCTTACGCACTACTATATACACTGGGTGCGACAGGCCCTGGACAAGGGCTTGAG TGGATGGGATGGGTACGCGCTTACAATGGTGACACAACTATGCGCAGAAGTTCAGGGCAGAGTACC GTGACCACAGACACATCCAGGACACAGCTACATGGAGCTGAGGAGCTGAGATCTGACGACACGGCC GTGTATTCTGTGCGAGAGATTGCCTCCTATAGTGGGAGCTACTACGACTACTGGGGCCAGGGCACC CTGGTCAACGCTCTCAAGCGCTCCACCAAGGGCCATCGGTCTTCCCCCTGGCACCTCTCTCAAGAGC ACCTCTGGGGGCACAGCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTG TGAAGTCAAGCGCCCTGACAGCGCGCTCCACACCTTCCCGGCTGTCTACAGTCTCAGGACTCTAC TCCCTCAGCAGCGTAGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAAT CACAAGCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAATCTTGT
277	PFG3 Light chain VD	QAVVLQEPFSFVSPPGTVTLTCLGTSAGVSSSYPSWYQQTPGQAPRTLIYNTDIRFSGVPDRFSGSIL GNKAALTIITGAQADDESYYCVLYMGSGISVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLV LISDFYPGAVTVAWKADSSPVKAGVETTPSKQSNKNYAASSYLSLTPEQWKSHKSYSCQVTHEGSTVE KTVAPAECS
278	PFG3 Heavy chain VD	EVQLVQSGAEVKKPGTSTVTVSCRASGFTFSDYYIHVVRQAPGQGLEWMGWVSAYNGDTNYAQKFQGRVT VTTDTSTSTAYMELRSLRSDDTAVYFCAREIASYSGSYDYWGQGLTVTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSC
279	PFG3 LC-CDR1	GLTSGAVSSSYPS
280	PFG3 LC-CDR2	NTDIRFS
281	PFG3 HC-CDR1	DYYIH
282	PFG3 HC-CDR2	WVSAYNGDTNYAQKFQG

283	PFG4 Light chain nucleotide sequence	CAGTCTGTGCTGACTCAGCCACCCTCGGTGTCCAAGGCCTTGAGACAGACCGCCACCCTCACCTGCACG GGGAACAACAACATGTTGGCTTCGCAGGAGCAGCTTGGTTTCTGCAGCACCAGGGCCACCCTCCCAAG CTCCTGGCCTACAGGAATAACGACCGGCCCTCAGGGATCTCAGAGAGATTTTCTGCTTCCAGGTCAGGC AATACTGCCTCCCTGACCATTACTGGACTCCAGCCTGAGGACGAGGCTGATTATTACTGCTCAGCATGG GACAGCAGTCTCAAAGTTCAGGTGTTTCGGCGGAGGGACCAAGCTGACCGTCTAGGTCAGCCCAAGGCT GCCCCCTCGGTCACTCTGTTCCCAACCCTCCTCTGAGGAGCTTCAAGCCAACAAGGCCACACTGGTGTGT CTCATAAGTGACTTCTACCCGGGAGCGGTGACAGTGGCTTGAAGGCAGATAGCAGCCCGTCAAGCGG GGACTGGACACCACCACACCCTCCAAACAAGCAACAACAAGTACGCGGCCAGCAGCTACCTGAGCCTG ACGCCTGAGCAGTGAAGTCCCAACAAGCTACAGCTGCCAGGTACGCATGAAGGGAGACCCGTGGAG AAGACAGTGGCCCTACAGAATGTTCA
284	PFG4 Heavy chain nucleotide sequence	CAGGTACAGCTGCAGCAGTCAGGGGCTGAGGTGAAGAAGCCTGGGTCTCGGTGAAGGTCTCCTGCAAG GCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAGGCCCCCTGGACAAGGGCTTGAG TGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCAGGGCAGAGTCACG ATTACCGCGGACAAATCCACGAGCAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCC GTGTATTACTGTGCGAGAGGTGCCGACTGGAACAGTGAAGTACTGAGGCGCAGGAGCCCGTCAAGCGT TCAAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCCTCAAGAGCACCTCTGGGGG ACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAAGTCAAGG GCCCTGACCAGCGGCGTCCACACCTTCCCGGCTGTCTACAGTCTCTCAGGACTCTACTCCCTCAGCAGC GTAGTGACCGTGCCTTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCAAGAAGCCAGC AACACCAAGGTGGACAAGAAGTTGAGCCCAATCTTGT
285	PFG4 Light chain VD	QSVLTQPPSVSKALRQTATLTCTGNNNNVGFAGAAWFLQHGHPPKLLAYRNNDRPSGISERFSASRSG NTASLTITGLQPEDEADYYCSAWDSSLKVQVFGGGTKLTVLQGPKAAPSVTLFPPSSSEELQANKATLVC LISDFYPGAVTVAWKADSSPVKAGVETTPSKQSNKNYAASSYLSLTPEQWQSHKSYSCQVTHEGSTVE KTVAPTECS
286	PFG4 Heavy chain VD	QVQLQQSGAEVKKPGSSSVKVSCKASGGTSSYAIISWVRQAPQGLEWMGGIIPFIFTANYAQKFQGRVT ITADKSTSTAYMELSSLSRSEDYAVYYCARGADWNSDYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGG TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPS NTKVDKKVEPKSC
287	PFG4 LC-CDR1	TGNNNNVGFAGAA
288	PFG4 LC-CDR2	RNNDRPS
289	PFG4 LC-CDR3	SAWDSSLKVQV
290	PFG4 HC-CDR3	GADWNSDY
291	PFG5 Light chain nucleotide sequence	GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTACCCCTGGAGAGCCGGCCTCCATCTCCTGC AGGTCTAGTCAGAGCCTCCTGCATAGTAATGGATACAACATATTTGGATTGGTACCTGCAGAAGCCAGGG CAGTCTCCACAGCTCCTGATCTACTTGGGTCTTAATCGGGCCCCGGGGTCCCTGACAGGTTCACTGGC AGTGGATCAGGCACAGATTTTACACTGAAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTAC TGCATGCAAGGTACACACTGGCCTCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAGCAACTGTG GCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTG TGCCTGTGAATAACTTCTATCCAGAGAGGCCAAAGTACAGTGAAGGTGGATAACGCCCTCCAAATCG GGTAATCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTG ACGCTGAGCAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTACCCATCAGGGCCTGAGC TCGCCCCGTACAAAGAGCTTCAACAGGGGAGAGTGT
292	PFG5 Heavy chain nucleotide sequence	GAAGTGACGCTGGTGACGCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCA GCCTCTGGATTACCTTCAGTAGCTATGCTATGCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAG TGGGTGGCAGTTATATCATATGATGGAAGCAATAAATACTACGCAGACTCCGTGAAGGCCGATTACAC ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCTGAGGACACGGCT GTGTATTACTGTGCGAGATCGTATGGTTTCGGGGAGTTATAGGTCCCATGCTTTTGATATCTGGGGCCAA GGGACAAATGGTCACCGTCTCAAGCGCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCACCCCTCCTCC AAGAGCACCTCTGGGGGACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACG GTGTCGTGGAAGTCAAGCGCCCTGACCAGCGGCTCCACACCTTCCCGGCTGTCTACAGTCTCTCAGGA CTCTACTCCCTCAGCAGCGTAGTGACCGTGCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAAC GTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAAAGTTGAGCCCAATCTTGT
293	PFG5 Light chain VD	DVVMTQSPSLPVPFGEPAISICRSSQSLHNSGYNLDWYLQKPGQSPQLLIYLGSRNAPGVPDRFSG SGSGTDFTLKISRVEAEDVGVYYCMQGTHWPLTFGGGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSLSTLTLSKADYEKHKVYACEVTHQGLS SPVTKSFNRGEC
294	PFG5 Heavy chain VD	EVQLVQSGGGVQFGRSLRLSCAASGFTSSYAMHWVRQAPGKLEWVAIVSYDGSNKKYADSVKGRFT ISRDNKNTLYLQMNSLRADYAVYYCARSYSGSYRSYHAFDIWGQMTVTVSSASTKGPSVFPLAPSS KSTSGGTAAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSC

The invention includes the combination of the aspects and preferred features described except where such a combination is clearly impermissible or expressly avoided.

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

Aspects and embodiments of the present invention will now be illustrated, by way of example, with reference to the accompanying figures. Further aspects and embodiments will be apparent to those skilled in the art. All documents mentioned in this text are incorporated herein by reference.

Throughout this specification, including the claims which follow, unless the context requires otherwise, the word "comprise," and variations such as "comprises" and "comprising," will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Ranges may be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by the use of the antecedent "about," it will be understood that the particular value forms another embodiment.

Brief Description of the Figures

Embodiments and experiments illustrating the principles of the invention will now be discussed with reference to the accompanying figures in which:

Figure 1. Light chain variable domain amino acid sequences for anti-HER2 antibody clones (A) P1A3, (B) P1C5, (C) P1E4, and (D) P1F1. CDRs are underlined.

Figure 2. Heavy chain variable domain amino acid sequences for anti-HER2 antibody clones (A) P1A3, (B) P1C5, (C) P1E4, and (D) P1F1. CDRs are underlined.

Figure 3. Binding to immobilized HER2 protein by bacteria-produced crude Fabs selected from antibody phage display library.

Figure 4. Binding of P1A3, P1C5, P1E4 and P1F1 to HER-2, EGFR, and HER-3 immobilised on microchip in SPR assay. Trastuzumab was used as a HER-2 positive binder control.

Figure 5. Binding of P1A3, P1C5, P1E4 and P1F1 to HER-2 overexpressing cells (A), low-expressing cells (B) or non-expressing cells (C). Trastuzumab was used as a positive binder control and the secondary antibody alone as a negative control.

Figure 6. Dose effect binding of P1A3, P1C5, P1E4 and P1F1 to HER-2 overexpressing cells SK-BR-3 or lower expressing BT-20 and MCF-7 cell. Shown are mean fluorescence intensities (MFIs) after

incubation of the cells in the presence of various concentrations of antibodies, binding was revealed with the use of a fluoro-labelled secondary antibody, Trastuzumab was used as a positive binding control.

Figure 7. Binding of trastuzumab, P1A3, P1C5, P1E4 and P1F1 to HER-2 bound to immobilised antibody. P1A3, P1C5, P1E4 and P1F1 bind to HER-2 bound onto trastuzumab (1st panel). Trastuzumab binds to HER-2 bound to any of SIgN's antibody (all other panels).

Figure 8. Staining with propidium iodide on BT-474 cells after incubation in the presence of lysis buffer (lysis positive control), trastuzumab, an isotype control or, P1A3, P1C5, P1E4 or P1F1. Staining with propidium iodide is the proof of cell lysis.

Figure 9. P1E4-induced apoptosis. Staining with propidium iodide and Annexin-V of BT-474 cells (A) and SK-BR-3 cells (B) after incubation in the presence of P1E4 or trastuzumab.

Figure 10. Triggering of apoptosis via caspase 3/7 and cleaved PARP by P1E4. (A) Uptake of propidium iodide after incubation of BT-474 cells in the presence of trastuzumab, pertuzumab or P1E4. (B) Activation of caspase 3/7 after incubation of BT-474 cells in the presence of trastuzumab, pertuzumab or P1E4. (C) Levels of cleaved PARP in BT-474 cells after incubation with trastuzumab, pertuzumab or P1E4.

Figure 11. Kinetic of cell lysis after incubation of BT-474 cells in the presence of P1E4 or trastuzumab. Shown is the mean proportion of propidium iodide positive cells $\pm$ SD.

Figure 12. Cytostatic effect of P1E4, trastuzumab and pertuzumab on B-474 tumour cell growth after incubation with 1 μ g/mL, 5 μ g/mL or 25 μ g/mL of antibody. MDA-MB-468 cells growth was used as a negative control. Shown is the mean cellular growth $\pm$ SD compared to the growth of BT-474 cells in the absence of any treatment.

Figure 13. Cytostatic effect of the combination P1E4, trastuzumab and pertuzumab compared to single antibodies on BT-474 tumour cell growth after incubation with 1 μ g/mL, 5 μ g/mL or 25 μ g/mL of antibodies (A). MDA-MB-468 (HER-2 negative cells) cells growth was used as a negative control (B). Shown is the mean cellular growth $\pm$ SD compared to the growth of BT-474 cells in the absence of any treatment.

Figure 14. ADCC induced by P1A3, P1C5, P1E4 and P1F1 in BT-474 cells compared to trastuzumab. Cells were incubated at an effector to target ratio 10:1 in the presence of various concentrations of antibodies. Shown is the mean cell death $\pm$ SD.

Figure 15. Tumour control and regression by P1E4 and trastuzumab in Nude mice injected with BT-474 cells and treated with various doses of antibodies. Shown are mean tumour volumes in 5 mice per group $\pm$ SEM. The black line represents the tumour size at the beginning of antibody treatment.

Figure 16. Long-term effective tumour control using combinations of anti-HER2 antibodies. Nude mice injected with HER-2+ BT-474 cells were treated with combinations of P1E4, trastuzumab or pertuzumab antibodies at 10 mg/kg of antibodies. Shown are mean tumour volumes in 5 mice per group $\pm$ SEM. The black dotted line represents the tumour size at the beginning of antibody treatment.

Figure 17. Schematic representation of the construction of anti-HER2 CAR showing signal peptide (sp), anti-HER2 scFv, IgH hinge, CD28 transmembrane domain, and 4-1BB and CD3 ζ domain signalling tail.

Figures 18A and 18B. Graphs showing characteristics of anti-HER2 CAR T cells comprising clones A4, B4, B5, D4, E1, F5 and G3. **(18A)** Percentage cytolysis of BT474 human breast cancer cells by CAR T cells. **(18B)** Cytokine (IFN γ and IL-2) production by CAR T cells.

Figure 19. Schematic representation of an anti-HER2 CAR mRNA.

Figures 20A and 20B. Graphs showing characteristics of anti-HER2 CAR T cells comprising clone C3. **(20A)** Percentage cytolysis of BT474 human breast cancer cells by CAR T cells. **(20B)** Cytokine (IFN γ and IL-2) production by CAR T cells.

Examples

Example 1: Discovery

Anti-human HER-2 binding antibodies were isolated from a human Fabs library by phage display, in 3 rounds of biopanning. Binding of isolated Fabs from the human Fabs library and immobilised HER-2 protein was measured by ELISA (Figure 3). The dissociation rate (K_d) from HER-2 of each clone was measured by Surface Plasmon Resonance (SPR). The results are shown in Table 1.

Table 1. Dissociation rate (k_d) measured on immobilized HER2 protein by SPR

Clone	k_d (1/s)
A1	4.15×10^{-3}
A2	2.18×10^{-3}
A3	4.16×10^{-3}
A4	1.96×10^{-2}
A5	3.26×10^{-3}
B1	5.65×10^{-3}
B2	1.77×10^{-4}
B3	1.02×10^{-2}
B4	3.22×10^{-2}
B5	1.70×10^{-2}

C3	5.28×10^{-2}
C5	4.48×10^{-3}
D1	7.14×10^{-2}
D2	4.86×10^{-3}
D3	2.72×10^{-2}
D4	3.42×10^{-2}
E1	1.30×10^{-2}
E2	1.87×10^{-2}
E4	1.81×10^{-3}
E5	1.52×10^{-3}
F1	5.02×10^{-3}
F2	4.70×10^{-3}
F3	3.24×10^{-3}
F5	1.41×10^{-2}
G1	3.24×10^{-4}
G2	4.99×10^{-4}
G3	1.58×10^{-2}
G4	6.30×10^{-4}

Four clones were selected initially for further characterisation: P1A3, P1C5, P1E4 and P1F1. Clones A4, B4, B5, C3, D4, E1, F5 and G3 were also selected for characterisation and investigation into utility in CARs.

5

Example 2: Specific binding to HER-2

Binding onto HER-2

Interaction between the four antibody clones (P1A3, P1C5, P1E4 and P1F1) and HER-2 was tested by SPR using soluble HER-2 bound onto microchip and flowing the antibodies. In order to assess the specificity of the binding, molecules closely related to HER-2 were also used as bound antigens, namely EGFR and HER-3. The humanised anti-HER-2 antibody trastuzumab was used as a positive control.

10

The four antibodies showed specific binding to human HER-2 and no kinds of interaction with HER-3 or EGFR (Figure 4).

15

Binding onto HER-2 expressing cells

To further characterise the binding of the antibodies to HER-2, antibodies were incubated with cells constitutively overexpressing HER-2, BT-474 and SK-BR-3, cells expressing, but not over-expressing HER-2, BT-20 and MCF-7, or with a triple negative cancer cell line, MDA-MB-468, not expressing the antigen. Both BT-474 and SK-BR-3 cell lines are classified 3+ for HER-2 expression, i.e. overexpressing. BT-20 cell line is classified as basal HER-2 cell line with an expression score of 0/1+; MCF-7 presents the same score and is classified as a luminal tumour cell line. MDA-MB-468 has a HER-2 expression score of 0 (Subik K et al. 2010, Breast Cancer (Auckl), 4:35-41).

20

After incubation, a secondary antibody was added to detect binding to the cells via flow cytometry. In all assays, trastuzumab was used as a positive control.

The four anti-HER-2 antibodies bound to HER-2 overexpressing (Figure 5A) and expressing (Figure 5B) cells in a similar way as trastuzumab, while no binding was observed on HER-2-negative cells (Figure 5C).

Antibodies were then incubated with HER-2 expressing cells at various concentrations to study the dose effect binding profile. In such an assay, E4 showed the closest binding profile to trastuzumab (Figure 6).

Example 3: Binding to a different epitope than trastuzumab

To assess whether the four anti-HER-2 antibodies P1A3, P1C5, P1E4 and P1F1 were binding the same epitope as trastuzumab, binding assays were conducted by SPR. Briefly, the antibody of interest was immobilised on the SPR microchip, a flow of recombinant HER-2 was then applied to bind to the immobilised antibody. Later on, all other antibodies were flown and their binding measured.

All four antibodies showed similar dendrograms suggesting that they share a common epitopes or bind to very close epitopes. However, trastuzumab showed a different binding profile, demonstrating that the four antibodies do not share trastuzumab's epitope (Figure 7).

The binding epitopes of clones A4, B4, B5, C3, D4, E1, F5 and G3 are assessed by SPR as above. The binding profiles are compared to that of trastuzumab and clones A4, B4, B5, C3, D4, E1, F5 and G3 are found to bind a different epitope to trastuzumab.

Example 4: Affinity for human HER-2

Affinity was measured by SPR. E4 showed the highest affinity for HER-2 amongst the four clones (Table 2).

Table 2: affinity of antibodies P1A3, P1C5, P1E4 and P1F1 for HER-2.

Antibody	Affinity (K_D in nM)
Trastuzumab	0.17
P1A3	21.4
P1C5	12.7
P1E4	5.3
P1F1	11.6

The binding characteristics of clones A4, B4, B5, C3, D4, E1, F5 and G3 were also determined by SPR. Rate constants of association, dissociation (k_a , k_d) and the equilibrium dissociation constants (K_D) were determined for anti-HER2 Fab molecules. Human HER2 protein (50 $\mu\text{g/mL}$) was immobilised on the SPR

sensor chip and was exposed to five different concentrations of each Fab in 2- or 3-fold dilutions over the flow cells. 1:1 Langmuir model was used to derive the constants.

The results are shown in Table 3.

Table 3: affinity of the A4, B4, B5, C3, D4, E1, F5 and G3 Fab for HER-2.

anti-HER2 clones			
	k_a	k_d	K_D
	[M ⁻¹ s ⁻¹]	[s ⁻¹]	[nM]
A4	2.03E+06	0.042	20.5
B4	4.41E+06	0.078	17.6
B5	1.76E+05	0.020	112
C3	4.11E+06	0.063	15.3
D4	1.99E+06	0.028	14.3
E1	1.59E+06	0.026	16.5
F5	4.45E+04	0.014	305
G3	1.08E+05	0.019	183

Example 5: Mechanism of action

Disruption of membranes

HER2 overexpressing BT-474 cells were incubated in the presence of P1A3, P1C5, P1E4 or P1F1 and propidium iodide. Unlike trastuzumab, the 4 antibodies induced disruption of membrane, allowing propidium iodide insertion, and proving the induction of cell death (Figure 8).

Induction of apoptosis

HER2 overexpressing cell lines BT-474 and SK-BR-3 were incubated in the presence of P1E4 or trastuzumab and stained with Annexin-V and propidium iodide to measure apoptosis and death.

Cells incubated with P1E4 and showing propidium iodide staining, i.e. dying/dead cells, also showed staining with Annexin-V, showing that P1E4 induces cell death by apoptosis (Figure 9).

To further confirm the induction of apoptosis, BT-474 cells were incubated in the presence of P1E4, trastuzumab or pertuzumab (another anti-HER-2 antibody) for subsequent measurement of propidium intake, caspase 3/7 pathway activation and cleaved PARP activation. Caspase 3/7 pathway is involved in the apoptotic process. After activation caspase 3/7 activates cleaved PARP in the nucleus which in its turn can trigger the release of pro-apoptotic factors by mitochondria and can block the processes of DNA repair.

As previously shown, incubation in the presence of P1E4 resulted in uptake of propidium iodide (Figure 10A). P1E4 induced the activation of caspase 3/7 (Figure 10B) and triggered cleaved PARP (Figure 10C). Neither trastuzumab nor pertuzumab showed this pathway triggering in the assay, suggesting a different mechanism of action.

The kinetic of P1E4-induced cell death was analysed. Briefly, BT-474 and SK-BR-3 cells were incubated at 37°C with 10µg/mL of E4 or trastuzumab. Cells were harvested at 10, 20, 30, 40, 50 and 60 minutes after addition of antibodies and induced cell death was analysed by propidium iodide uptake.

As soon as 10-20 minutes after addition of P1E4, cells started to die, while cells incubated with trastuzumab did not show any signs of lysis (Figure 11).

Clones A3, C5, F1, A4, B4, B5, C3, D4, E1, F5 and G3 are assessed for their mechanism of action and are found to induce cell death, e.g. by apoptosis.

Example 6: Efficacy

In vitro anti-tumour activity

To assess the activity of antibodies on tumour growth, BT-474 cells were incubated in the presence of various concentrations of P1E4 for 72 hours. Trastuzumab and pertuzumab were used as positive controls able to restrain tumour growth. Some cells were left growing without antibodies to serve as a growth reference. MDA-MB-468 cell line, a cell line not expressing HER-2, was used as a negative control. After 72 hours, cell numbers were measured using Promega's Celltiter 96 Aqueous One Solution cell proliferation assay (MTS).

P1E4 showed a cytostatic effect on B-474 tumour growth that was comparable to that of trastuzumab or pertuzumab (Figure 12).

A similar assay was conducted to assess the potential synergistic effect of P1E4 and trastuzumab. The combination of P1E4 and trastuzumab showed a higher cytostatic effect than either antibody alone suggesting a synergistic effect (Figure 13).

The antibody-dependent cellular cytotoxicity of P1A3, P1C5, P1E4 or P1F1 was also measured and compared to that of trastuzumab. BT-474 cells were plated with antibodies at various concentrations and PBMCs at the effector to target (E:T) ratio of 10:1. After 16 hours of incubation at 37°C, supernatants were harvested and assessed for LDH release by Promega Cytotox 96 non-radioactive cytotoxicity assay kit.

All four antibodies were able to induce ADCC, with P1E4 showing the strongest ADCC effect. At high concentrations, P1E4 was able to trigger cell toxicity in a similar proportion as trastuzumab, it was however less effective at low doses (Figure 14).

Clones A4, B4, B5, C3, D4, E1, F5 and G3 are assessed for their effect on tumour growth and are found to have a cytotoxic effect.

In vivo anti-tumour efficacy

P1E4 was tested for its ability to control tumour growth *in vivo*. Briefly, BT-474 cells were injected in Nude mice. When tumours reached $\sim 125 \text{ mm}^3$, i.e. when palpable, antibodies were injected intravenously every 4 days between days 1 and 17 at 10 mg/kg for trastuzumab and at 3.3, 10, 20 or 30 mg/kg for P1E4. One control group only received vehicle 10 mL/kg/injection. Tumour growth was then monitored every 3 to 4 days until day 31.

While doses up to 20 mg/kg seemed to control tumour growth the during administration period, they did not confer a long-term protection and tumours started to grow at the end of the treatment. At the highest dose, P1E4 not only allowed a sensible regression of tumour size but also conferred a long-term protection with regressed tumours not growing back after administration ended (Figure 15).

Combination treatments with P1E4, trastuzumab or pertuzumab were tested for synergistic effects on tumour growth control *in vivo*. Similarly as described above, nude mice harbouring BT-474 xenografts were treated with combinations of either 2 antibodies at 10 mg/kg of trastuzumab, pertuzumab or P1E4 every 4 days between days 1 and 17; tumour growth was monitored up to day 39.

P1E4 in combination with either trastuzumab or pertuzumab is as effective as the combination of trastuzumab and pertuzumab in controlling tumour growth (Figure 16). Furthermore, combining P1E4 at 10 mg/kg with either trastuzumab or pertuzumab (at 10 mg/kg too) was found to be as effective in conferring a long-term protection (Fig.16) as 30 mg/kg of P1E4 alone (Fig.15) and much more effective than trastuzumab alone (Fig.15).

Example 7: Generation and activity of Chimeric Antigen Receptor (CAR) T cells

Figure 17 shows a schematic representation of the construction of anti-HER2 CAR. The CAR consists of a signal peptide, anti-HER2 scFv, IgH hinge, the transmembrane domain of CD28 followed by a second generation CAR signalling tail composed of the 4-1BB and CD3 ζ signalling domains.

Anti-HER2 CARs comprising clones A4, B4, B5, C3, D4, E1, F5 and G3 were constructed and assessed for anti-tumour activity.

Lentiviral-based construction

T cells from healthy donors were activated by TransAct™ (CD3/CD28 agonists) and maintained at a density of 1 to 2×10^6 cells/mL in TexMACS™ medium supplemented with 50 ng/mL IL2 for 48 hours. Upon stimulation, cells were transduced with lentivirus encoding anti-HER2 CARs comprising one of the clones A4, B4, B5, D4, E1, F5 and G3.

72hr post-transduction, anti-tumour activity (% cytotoxicity) were analysed in real-time manner by an electrical impedance-based tumour cell culture system (xCELLigence). BT474 cells (human breast cancer cells) were seeded at a density of 10,000 cells per well in electrode-coated 96-well plates (e-plates) in triplicates. 24 hours later, CAR T cells (the Effector cells) were added at a ratio of 3 effector cells for each target cell (BT474).

Cytokines (IFN- γ and IL-2) secreted to the medium following 48-hour co-cultures were measured by ELISA. Data in triplicates are presented as mean $\pm$ SEM

The results are shown in Figures 18A and 18B. CAR T cells comprising each one of the seven anti-HER2 CARs demonstrated cytotoxicity of tumour cells, i.e. anti-tumour activity, (18A) and increased IFN- γ and IL-2 secretion, i.e. T cell activation (18B).

Electroporation construction

Figure 19 shows a schematic representation of an anti-HER2 CAR mRNA.

CAR T cells were generated by mRNA electroporation. T cells from healthy donors were isolated, activated and cultured for 48 hours, as described above. Activated T cells were electroporated with CAR mRNA (2 μ g per 1×10^6 T cells) comprising clone C3 and were assessed for their cytotoxic activity (%) 20 hours post-electroporation by the xCELLigence system. Cytokines (IFN- γ and IL-2) secreted to the medium following 48-hour co-cultures were measured by ELISA. Data in triplicates are presented as mean $\pm$ SEM

The results are shown in Figures 20A and 20B. CAR T cells comprising anti-HER2 CAR (C3) demonstrated cytotoxicity of tumour cells, i.e. anti-tumour activity, (20A) and increased IFN- γ and IL-2 secretion, i.e. T cell activation (20B).

Selectivity for tumour cells

Anti-HER2 CAR T cells according to the present invention are assessed for their ability to discriminate between cells overexpressing HER2 and cells with lower or physiological levels of HER2. CAR T cells having lower or intermediate affinity for HER2 may be capable of discriminating between cells expressing HER2 at high and low levels (e.g. as described in Liu et al Cancer Res. 2015; (75) (17) 3596-3607).

Anti-HER2 CAR T cells of the present invention are stimulated with HER2-overexpressing tumour cell lines, e.g. SK-BR3 (breast cancer), SK-OV3 (ovarian cancer) and/or BT-474 (breast cancer), or tumour cell lines that express HER2 at a low or undetectable level, e.g. MCF7 (breast cancer), 293T (embryonic kidney), A549 (lung cancer), 624Mel (melanoma), PC3 (prostate cancer), MDA231 (breast cancer) and/or MDA468 (breast cancer). CAR T cell activation is assessed after 24 or 48 hours by upregulation of CD137 (4-1BB), secretion of IFN γ and IL2, and/or induction of surface CD107a expression. T cells expressing a CAR comprising the antigen-binding domains of trastuzumab (a high-affinity CAR) and T cells expressing a non-

HER2-specific CAR are used as controls. CD137 and CD107a expression is measured by flow cytometry (e.g. CD3+ gated), cytokine secretion in culture supernatants is measured by ELISA.

5 CAR-T cells comprising the antigen-binding molecules of the present invention are found to be strongly reactive to tumour cells with high HER2 expression, but are found to have low or no reactivity to tumour cell lines with low or no expression of HER2. The anti-HER2 CAR T cells are also found to secrete higher levels of cytokines when exposed to cells expressing high levels of HER2, indicating a higher degree of T cell activation compared to that seen with cells expressing low levels of, or no, HER2.

10 To assess if the anti-HER2 CAR T cells can discriminate between tumour cells and non-tumour cells, the T cells are contacted with tumour cells overexpressing HER2 (e.g. BT-474) and cells expressing HER2 at a physiological level e.g. primary organ cell lines. T cells expressing a non-HER2-specific CAR and cell lines that express HER2 at a high or low level are used as controls. CAR T cells are stimulated with the HER2-expressing cells for 4 hours. CAR T cell recognition and activation is evaluated by monitoring CD107a upregulation and analysed by flow cytometry by gating on CD3+ cells.

15 CAR-T cells comprising the antigen-binding molecules of the present invention are found to be selective for HER2-overexpressing cells. The cells are found to show strong reactivity to HER2-overexpressing cells whilst demonstrating no or weak activation when contacted with the organ cell lines.

20

Claims:

1. An antibody or antigen binding fragment which is capable of binding to HER2, optionally isolated, wherein the antibody or antigen binding fragment comprises:
 - a light chain variable region incorporating the following CDRs:
 - LC-CDR1: GLSSGSVSTGHYAS (SEQ ID NO:15)
 - LC-CDR2: NTNTRSS (SEQ ID NO:16)
 - LC-CDR3: VLYVGDGIWV (SEQ ID NO:17); and
 - a heavy chain variable region incorporating the following CDRs:
 - HC-CDR1: SYYIH (SEQ ID NO:18)
 - HC-CDR2: IINPGNGDTNYAQRFGG (SEQ ID NO:19)
 - HC-CDR3: EIASYSGSYDY (SEQ ID NO:20).
2. The antibody or antigen binding fragment according to claim 1, wherein the antibody or antigen binding fragment comprises:
 - a light chain variable region having at least 85% sequence identity to the light chain variable region sequence of SEQ ID NO:1; and
 - a heavy chain variable region having at least 85% sequence identity to the heavy chain variable region sequence of SEQ ID NO:5.
3. The antibody or antigen binding fragment according to claim 1 or claim 2, wherein the antibody or antigen binding fragment binds specifically to human, rhesus macaque or murine HER2.
4. The antibody or antigen binding fragment according to any one of claim 1 to 3, conjugated to a drug moiety or a detectable moiety.
5. The antibody or antigen binding fragment according to claim 4, wherein the drug moiety comprises an anti-cancer drug moiety.
6. A chimeric antigen receptor (CAR) comprising an antibody or antigen binding fragment according to any one of claims 1 to 3.
7. An *in vitro* complex, optionally isolated, comprising an antibody or antigen binding fragment according to any one of claims 1 to 5, or a CAR according to claim 6, bound to HER2.
8. A nucleic acid, optionally isolated, encoding an antibody or antigen binding fragment according to any one of claims 1 to 5, or a CAR according to claim 6.
9. A vector comprising the nucleic acid according to claim 8.

10. A cell comprising the nucleic acid according to claim 8, or the vector according to claim 9.
11. A method for making an antibody or antigen binding fragment according to any one of claims 1 to 5, or a CAR according to claim 6, comprising culturing a cell according to claim 10 under conditions suitable for the expression of the antibody, antigen binding fragment or CAR from the nucleic acid or vector.
12. A composition comprising an antibody or antigen binding fragment according to any one of claims 1 to 5, or a cell according to claim 10, and at least one pharmaceutically-acceptable carrier.
13. An antibody or antigen binding fragment according to any one of claims 1 to 5, a cell according to claim 10, or a composition according to claim 12, for use in therapy, or in a method of medical treatment, wherein the cell according to claim 10 is a CAR T cell or a CAR NK cell.
14. Use of an antibody or antigen binding fragment according to any one of claims 1 to 5, a cell according to claim 10, or a composition according to claim 12, in the manufacture of a medicament for treating a HER2-positive cancer, wherein the cell according to claim 10 is a CAR T cell or a CAR NK cell.
15. The use according to claim 14, wherein the cancer comprises a HER2-positive tumour cell.
16. A method comprising contacting, *in vitro*, a sample containing, or suspected to contain, HER2 with an antibody or antigen binding fragment according to any one of claims 1 to 5, and detecting the formation of a complex comprising the antibody or antigen binding fragment and HER2.
17. A method of diagnosing a HER2-positive cancer in a subject, the method comprising contacting, *in vitro*, a sample from the subject with an antibody or antigen binding fragment according to any one of claims 1 to 5, and detecting the formation of a complex comprising the antibody or antigen binding fragment and HER2.