Summary of the Invention

In one aspect, there is provided an isolated antibody comprising six hypervariable region (HVR) sequences comprising:

(i) HVR-L1 comprising the sequence NIAKTISGY (SEQ ID NO:1),

(ii) HVR-L2 comprising the sequence WGSFLY (SEQ ID NO:2), and

(iii) HVR-L3 comprising the sequence HYSSPP (SEQ ID NO:3); and

(a) further comprising HVR sequences comprising:

(iv) HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4),

(v) HVR-H2 comprising the sequence RIYPTNGYTR (SEQ ID NO:5), and

(vi) HVR-H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6); or

(b) further comprising HVR sequences comprising:

(iv) HVR-H1 comprising the sequence NISGTY (SEQ ID NO:7),

(v) HVR-H2 comprising the sequence RIYPSEGYTR (SEQ ID NO:8), and

(vi) HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO:9);

wherein said antibody specifically binds human epidermal growth factor receptor 2 (HER2) and vascular endothelial growth factor (VEGF).

Also disclosed is ~~The present invention provides~~ an isolated antibody comprising a hypervariable region (HVR) L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1), where the antibody specifically binds human epidermal growth factor receptor 2 (HER2) and vascular endothelial growth factor (VEGF). In one ~~embodiment~~example, the antibody further comprises an HVR-L2 comprising the sequence WGSFLY (SEQ ID NO: 2) and/or an HVR-L3 comprising the sequence HYSSPP (SEQ ID NO: 3). In another ~~embodiment~~example, the antibody further comprises, one, two, or three HVR sequences selected from (i) HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4); (ii) HVR-H2 comprising the sequence RIYPTNGYTR (SEQ ID NO:5); and (iii) HVR-H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6). In another ~~embodiment~~example, the antibody further comprises, one, two, or three HVR sequences selected from (i) HVR-H1 comprising the sequence NISGTY (SEQ ID NO:7); (ii) HVR-H2 comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and (iii) HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO:9).

Also disclosed is~~In another aspect, the invention features~~ an isolated antibody comprising an HVR-L1 sequence comprising the sequence $X_1I\ X_3X_4X_5X_6X_7X_8X_9Y$ (SEQ ID NO: 83), wherein X_1 is any amino acid except aspartic acid, X_3 is any amino acid except proline, X_4 is any amino acid except arginine, and X_5 is any amino acid except serine, where the antibody specifically binds HER2 and VEGF. In one ~~embodiment~~example, an antibody comprising the sequence $X_1I\ X_3X_4X_5X_6X_7X_8X_9Y$ (SEQ ID NO: 83) has an asparagine at X_1, an alanine at X_3, a lysine at X_4, a threonine at X_5, a serine at X_7, and/or a glycine at X_8, or any combination thereof. In various ~~embodiments~~examples of ~~this aspect of the invention~~the present disclosure, any of the HVR-L1 residues shown in Figure 57 to have an F value of greater than 1, 5, or 10 are residues that are preferably maintained as the same residue found in the same position of the HVR-L1 of bH1-44 or bH1-81 (SEQ ID NO: 1). In additional ~~embodiments~~examples, any of the HVR-L1 residues shown in Table 14 to have $\Delta\Delta G$ values greater than 1 are residues that are preferably maintained as the same residue found in the same position of the HVR-L1 of bH1-44 or bH1-81 (SEQ ID NO: 1). In one ~~embodiment~~example, the antibody comprises an HVR-H2 sequence comprising the sequence $RX_2X_3X_4X_5X_6X_7X_8X_9R$ (SEQ ID NO: 84). In one ~~embodiment~~example, the antibody further comprises an HVR-L2 comprising the sequence WGSFLY (SEQ ID NO: 2) and/or an HVR-L3 comprising the sequence HYSSPP (SEQ ID NO: 3). In another ~~embodiment~~example, the antibody further comprises, one, two, or three HVR sequences selected from (i) HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4); (ii) HVR-H2 comprising the sequence RIYPTNGYTR (SEQ ID NO:5); and (iii) HVR-H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6). In another ~~embodiment~~example, the antibody further comprises, one, two, or three HVR sequences selected from (i) HVR-H1 comprising the sequence

NISGTY (SEQ ID NO:7); (ii) HVR-H2 comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and (iii) HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO:9).

Also disclosed is~~In another aspect, the invention features~~ an isolated antibody comprising an HVR-H2 sequence comprising the sequence $RX_2X_3X_4X_5X_6X_7X_8X_9R$ (SEQ ID NO: 85), wherein X_5 is any amino acid except threonine and X_6 is any amino acid except asparagine and where the antibody specifically binds HER2 and VEGF. In another ~~embodiment~~example, an antibody comprising the sequence RX_2X_3 $X_4X_5X_6X_7X_8X_9R$ (SEQ ID NO: 84) has a tyrosine at X_8. In one ~~embodiment~~example, an antibody comprising the sequence $RX_2X_3X_4X_5X_6X_7X_8X_9R$ (SEQ ID NO: 84) has a serine at X_5 and/or a glutamic acid at X_6. In another ~~embodiment~~example ~~of this aspect~~, the antibodies further comprise one, two, or three HVR sequences selected from the group of a HVR-L1 comprising the sequence NIAKTISGY (SEQ ID NO: 1), a HVR-L2 comprising the sequence WGSFLY (SEQ ID NO: 2), and/or a HVR-L3 comprising the sequence HYSSPP (SEQ ID NO: 3). In any of the ~~embodiments~~examples described herein, the antibodies further comprise, one or two HVR sequences selected from (i) HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4) and (ii) HVR-H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6). In an additional ~~embodiment~~example, the antibodies further comprise, one or two HVR sequences selected from (i) HVR-H1 comprising the sequence NISGTY (SEQ ID NO:7) and (ii) HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO:9).

In various ~~embodiments~~examples ~~of this aspect of the invention~~, any of the HVR-H2 residues shown in Figure 57 to have an F value of greater than 1, 5, or 10 are residues that are preferably maintained as the same residue found in the same position of the HVR-H2 of bH1-44 or bH1-81 (SEQ ID NOS: 8 and 5, respectively). In additional ~~embodiments~~examples, any of the HVR-H2 residues shown in Table 14 to have $\Delta\Delta G$ values greater than 1 are residues that are preferably maintained as the same residue found in the same position of the HVR-H2 of bH1-44 or bH1-81 (SEQ ID NOS: 8 and 5, respectively).

In particular ~~embodiments~~examples, the antibody comprises an HVR-L1 sequence comprising NIAKTISGY (SEQ ID NO:1); an HVR-L2 sequence comprising WGSFLY (SEQ ID NO:2); an HVR-L3 sequence comprising HYSSPP (SEQ ID NO:3); an HVR-H1 sequence comprising NIKDTY (SEQ ID NO:4); an HVR-H2 sequence comprising RIYPTNGYTR (SEQ ID NO:5); and an HVR-H3 sequence comprising WGGDGFYAMD (SEQ ID NO:6) or comprises an HVR-L1 sequence comprising NIAKTISGY (SEQ ID NO:1); an HVR-L2 sequence comprising WGSFLY (SEQ ID NO:2); an HVR-L3 sequence comprising HYSSPP (SEQ ID NO:3); an HVR-H1 sequence comprising NISGTY (SEQ ID NO:7); an HVR-H2 sequence comprising RIYPSEGYTR (SEQ ID NO:8); and/or an HVR-H3 sequence comprising WVGVGFYAMD (SEQ ID NO:9).

In a further particular ~~embodiment~~example the isolated antibody comprises HVR-L1, HVR-L2, HVR-L3, HVR-H1, HVR-H2, and HVR-H3, wherein each, in order, comprises the sequence NIAKTISGY (SEQ ID NO:1); WGSFLY (SEQ ID NO:2); HYSSPP (SEQ ID NO:3); NIKDTY (SEQ ID NO:4); RIYPTNGYTR (SEQ ID NO:5); and WGGDGFYAMD (SEQ ID NO:6) and specifically binds HER2 and VEGF. In another particular ~~embodiment~~example, the antibody comprises HVR-L1, HVR-L2, HVR-L3, HVR-H1, HVR-H2, and HVR-H3, wherein each, in order, comprises the sequence NIAKTISGY (SEQ ID NO:1); WGSFLY (SEQ ID NO:2); HYSSPP (SEQ ID NO:3); NISGTY (SEQ ID NO:7); RIYPSEGYTR (SEQ ID NO:8); and WVGVGFYAMD (SEQ ID NO:9) and specifically binds HER2 and VEGF.

In various ~~embodiments~~examples ~~of any of the aspects described herein~~, the antibody binds human and murine VEGF with a Kd of 150 nM or stronger and HER2 with a Kd of 7 nM or stronger. In additional ~~embodiments~~examples, the antibody inhibits VEGF-induced cell proliferation and proliferation of a HER2 expressing cell relative to a control. In a particular ~~embodiment~~example, the antibody binds human and murine VEGF with a Kd of 36 nM or stronger and HER2 with a Kd of 1 nM or stronger. In an additional ~~embodiment~~example, the antibody inhibits VEGF binding to VEGFR2.

Also disclosed is~~In another aspect, the invention features~~ an isolated antibody that binds human and murine VEGF with a Kd of 150 nM or stronger and HER2 with a Kd of 7 nM or stronger and wherein the antibody inhibits VEGF-induced cell proliferation and proliferation of a HER2 expressing cell relative to a control. In one ~~embodiment~~example, the antibody binds human and murine VEGF with a Kd of 36 nM or stronger and HER2 with a Kd of 1 nM or stronger.

In another aspect, there is provided an isolated antibody fragment of the antibody as defined herein, wherein said antibody fragment binds human VEGF with a Kd of 33 nM or stronger and HER2 with a Kd of 0.7 nM or stronger, and wherein said antibody fragment inhibits VEGF-induced cell proliferation and proliferation of a HER2 expressing cell relative to a control.

Also disclosed is~~In yet another aspect the invention provides~~ an isolated antibody fragment that binds human VEGF with a Kd of 58 nM or stronger and HER2 with a Kd of 6 nM or stronger, and/or inhibits VEGF-induced cell proliferation and proliferation of a HER2 expressing cell relative to a control. In a particular ~~embodiment~~example, the antibody fragment binds human and murine VEGF with a Kd of 33 nM or stronger and HER2 with a Kd of 0.7 nM or stronger. In another particular ~~embodiment~~example, the fragment is a Fab fragment or a single chain variable fragment (scFv).

In any of the above-described ~~aspects~~examples, the antibody may be a monoclonal antibody. In another ~~embodiment~~example of all the above aspects, the antibody may be an IgG antibody. In additional ~~embodiments~~examples of all the above aspects, at least a portion of the framework sequence of the antibody may be a human consensus framework sequence.

In yet another aspect, there is provided an antibody fragment of the antibody as defined herein, wherein said antibody fragment specifically binds HER2 and VEGF.

Also disclosed is~~In another aspect, the invention features~~ a fragment of an antibody any of the antibodies described herein. One ~~embodiment~~example of an antibody fragment is a fragment comprising a HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1) that specifically binds HER2 and VEGF. In another ~~embodiment~~example, the antibody fragment further

comprises one or two HVR sequences selected from (i) HVR-L2 comprising the sequence WGSFLY (SEQ ID NO:2); and (ii) HVR-L3 comprising the sequence HYSSPP (SEQ ID NO:3). In another ~~embodiment~~example, the antibody fragment further comprises, one, two, or three HVR sequences selected from (i) HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4); (ii) HVR-H2 comprising the sequence RIYPTNGYTR (SEQ ID NO:5); and (iii) HVR-H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6). In an additional ~~embodiment~~example, the antibody fragment further comprises, one, two, or three HVR sequences selected from (i) HVR-H1 comprising the sequence NISGTY (SEQ ID NO:7); (ii) HVR-H2 comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and (iii) HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO:9). In particular ~~embodiments~~examples, the antibody fragment comprises an HVR-L1 sequence comprising NIAKTISGY (SEQ ID NO:1); an HVR-L2 sequence comprising WGSFLY (SEQ ID NO:2); an HVR-L3 sequence comprising HYSSPP (SEQ ID NO:3); an HVR-H1 sequence comprising NIKDTY (SEQ ID NO:4); an HVR-H2 sequence comprising RIYPTNGYTR (SEQ ID NO:5); and an HVR-H3 sequence comprising WGGDGFYAMD (SEQ ID NO:6) or comprises an HVR-L1 sequence comprising NIAKTISGY (SEQ ID NO:1); an HVR-L2 sequence comprising WGSFLY (SEQ ID NO:2); an HVR-L3 sequence comprising HYSSPP (SEQ ID NO:3); an HVR-H1 sequence comprising NISGTY (SEQ ID NO:7); an HVR-H2 sequence comprising RIYPSEGYTR (SEQ ID NO:8); and an HVR-H3 sequence comprising WVGVGFYAMD (SEQ ID NO:9). In one ~~embodiment~~example, the fragment is a Fab fragment or a single chain variable fragment (scFv). In additional ~~embodiments~~examples of all the above aspects, at least a portion of the framework sequence of the antibody may be a human consensus framework sequence.

In yet another aspect, there is provided a polynucleotide encoding the antibody as defined herein, or the antibody fragment as defined herein.

In yet another aspect, there is provided a vector or an expression vector comprising the polynucleotide as defined herein.

In yet another aspect, there is provided a host cell comprising a vector as defined herein.

Also disclosed are~~In further aspects, the invention features~~ polynucleotides encoding any antibody or antibody fragment described herein, as well as a vector comprising such a polynucleotide. In particular ~~embodiments~~examples, the encoded antibody comprises an HVR-L1 sequence comprising NIAKTISGY (SEQ ID NO:1). Optionally or additionally, the polynucleotide encodes an antibody that also comprises an HVR-L2 sequence comprising WGSFLY (SEQ ID NO:2); and/or an HVR-L3 sequence comprising HYSSPP (SEQ ID NO:3), or any combination thereof. T~~In an additional aspect, t~~he polynucleotide may further encode an antibody comprising one, two, or three of an HVR-H1 sequence comprising NIKDTY (SEQ ID NO:4); an HVR-H2 sequence comprising RIYPTNGYTR (SEQ ID NO:5); and an HVR-H3 sequence comprising WGGDGFYAMD (SEQ ID NO:6); or an antibody comprising one, two, or three of an HVR-H1 comprising NISGTY (SEQ ID NO:7); an HVR-H2 comprising RIYPSEGYTR (SEQ ID NO:8); and/or an HVR-H3 sequence comprising WVGVGFYAMD (SEQ ID NO:9).

In ~~additional aspects of the invention~~some examples, the polynucleotide encodes an HVR-H1 sequence comprising the sequence of NISGTY (SEQ ID NO: 7), an HVR-H2 comprising the

sequence of RIYPSEGYTR (SEQ ID NO: 8), or an HVR-H3 comprising the sequence of WVGVGFYAMD (SEQ ID NO: 9), or any combination thereof.

Also disclosed is~~In other aspects, the invention features~~ an isolated polynucleotide encoding an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1) and, optionally, the polynucleotide further encodes one, two, or three HVR sequences selected from (i) an HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4); (ii) an HVR-H2 comprising the sequence RIYPTNGYTR (SEQ ID NO:5); and (iii) an HVR-H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6). In additional ~~aspects~~examples, the ~~invention~~present disclosure features an isolated polynucleotide encoding an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1); and (i) an HVR-L2 sequence comprising the sequence WGSFLY (SEQ ID NO:2) or (ii) an HVR-L3 sequence comprising the sequence HYSSPP (SEQ ID NO:3), or both, and, optionally, the polynucleotide further encodes one, two, or three HVR sequences selected from (i) an HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4); (ii) an HVR-H2 comprising the sequence RIYPTNGYTR (SEQ ID NO:5); and (iii) an HVR-H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6).

Also disclosed is~~In a further aspect, the invention features~~ an isolated polynucleotide encoding an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1); an HVR-H1 comprising the sequence NISGTY (SEQ ID NO:7); an HVR-H2 comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and an HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO:9). Also disclosed is~~In yet another aspect, the invention features~~ an isolated polynucleotide encoding an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1); an HVR-L2 sequence comprising the sequence WGSFLY (SEQ ID NO:2); an HVR-L3 sequence comprising the sequence HYSSPP (SEQ ID NO:3); an HVR-H1 comprising the sequence NISGTY (SEQ ID NO:7); an HVR-H2 comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and an HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO:9).

Also disclosed is~~In other aspects, the invention features~~ an isolated polynucleotide *encoding an HVR-H1 sequence comprising the sequence* NISGTY (SEQ ID NO:7), *an* isolated polynucleotide encoding an HVR-H2 sequence comprising the sequence RIYPSEGYTR (SEQ ID NO:8), and an isolated polynucleotide encoding an HVR-H3 sequence comprising the sequence WVGVGFYAMD (SEQ ID NO:9). Also disclosed is~~In another aspect, the invention features~~ an isolated polynucleotide encoding an polypeptide comprising an HVR-H1 sequence comprising the sequence NISGTY (SEQ ID NO:7); an HVR-H2 sequence comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and an HVR-H3 sequence comprising the sequence WVGVGFYAMD (SEQ ID NO:9).

In an additional ~~embodiment~~example of the ~~invention~~present disclosure, the isolated polynucleotide encodes an HVR-L1 sequence comprising the sequence X_1I $X_3X_4X_5X_6X_7X_8X_9Y$ (SEQ ID NO: 83),

wherein X_1 is any amino acid except aspartic acid, X_3 is any amino acid except proline, X_4 is any amino acid except arginine, and X_5 is any amino acid except serine. In another ~~embodiment~~example ~~of the invention~~, the polynucleotide encodes an HVR-L1 sequence comprising the sequence X_1I $X_3X_4X_5X_6X_7X_8X_9$Y (SEQ ID NO: 83), wherein X_1 is any amino acid except Asp, X_3 is any amino acid except proline, X_4 is any amino acid except arginine, and X_5 is any amino acid except serine; and a HVR-L2 sequence comprising the sequence WGSFLY (SEQ ID NO: 2) and/or an HVR-L3 sequence comprising the sequence HYSSPP (SEQ ID NO: 3). In additional ~~embodiments~~examples ~~of this aspect of the invention~~, the polynucleotide encodes an antibody comprising the sequence X_1I $X_3X_4X_5X_6X_7X_8X_9$Y (SEQ ID NO: 83) that has an asparagine at X_1, an alanine at X_3, a lysine at X_4, a threonine at X_5, a serine at X_7, and/or a glycine at X_8, or any combination thereof. In various ~~embodiments~~examples ~~of this aspect of the invention~~, any of the HVR-L1 residues shown in Figure 57 to have an F value of greater than 1, 5, or 10 are residues that are preferably maintained as the same residue found in the same position of the HVR-L1 of bH1-44 or bH1-81 (SEQ ID NO: 1). In additional ~~embodiments~~examples, any of the HVR-L1 residues shown in Table 14 to have ΔΔG values greater than 1 are residues that are preferably maintained as the same residue found in the same position of the HVR-L1 of bH1-44 or bH1-81 (SEQ ID NO: 1).

In an additional ~~embodiment~~example ~~of the invention~~, the polynucleotide encodes an HVR-H2 sequence comprising the sequence R$X_2X_3X_4X_5X_6X_7X_8X_9$R (SEQ ID NO: 85), wherein X_5 is any amino acid except threonine and X_6 is any amino acid except asparagine. In another ~~aspect~~example, the ~~invention~~present disclosure provides a polynucleotide encoding an HVR-H1 sequence comprising the sequence NISGTY (SEQ ID NO: 7); an HVR-H2 sequence comprising the sequence R$X_2X_3X_4X_5X_6X_7X_8X_9$R (SEQ ID NO: 85), wherein wherein X_5 is any amino acid except threonine and X_6 is any amino acid except asparagine; and an HVR-H3 sequence comprising the sequence WVGVGFYAMD (SEQ ID NO: 9). In an additional ~~embodiments~~examples ~~of the invention~~, the polynucleotide encodes an HVR-H2 sequence comprising the sequence R$X_2X_3X_4X_5X_6X_7X_8X_9$R (SEQ ID NO: 84) that has a serine at X_5, a glutamic acid at X_6, and/or a tyrosine at X_8, or any combination thereof. In various ~~embodiments~~examples ~~of this aspect of the invention~~, any of the HVR-H2 residues shown in Figure 57 to have an F value of greater than 1, 5, or 10 are residues that are preferably maintained as the same residue found in the same position of the HVR-H2 of bH1-44 or bH1-81 (SEQ ID NOS: 8 and 5, respectively). In additional ~~embodiments~~examples, any of the HVR-H2 residues shown in Table 14 to have ΔΔG values greater than 1 are residues that are preferably maintained as the same residue found in the same position of the HVR-H2 of bH1-44 or bH1-81 (SEQ ID NOS: 8 and 5, respectively).

Also disclosed is~~In further aspects, the invention features~~ an isolated polypeptide comprising an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1) or an isolated

polypeptide comprising an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1); an HVR-L2 sequence comprising the sequence WGSFLY (SEQ ID NO:2); and/or an HVR-L3 sequence comprising the sequence HYSSPP (SEQ ID NO:3). Also disclosed is~~In another aspect, the invention provides~~ a polypeptide comprising an HVR-L1 sequence comprising the sequence $X_1IX_3X_4X_5X_6X_7X_8X_9Y$ (SEQ ID NO: 83), wherein X_1 is any amino acid except aspartic acid, X_3 is any amino acid except proline, X_4 is any amino acid except arginine, and X_5 is any amino acid except serine. In another ~~embodiment~~example ~~of this aspect~~, the polypeptide comprises the HVR-L1 sequence $X_1I\ X_3X_4X_5X_6X_7X_8X_9Y$ (SEQ ID NO: 83), wherein X_1 is any amino acid except aspartic acid, X_3 is any amino acid except proline, X_4 is any amino acid except arginine, and X_5 is any amino acid except serine. Optionally, the polypeptide further comprises an HVR-L2 sequence comprising the sequence WGSFLY (SEQ ID NO: 2) and/or an HVR-L3 sequence comprising the sequence HYSSPP (SEQ ID NO: 3). In particular ~~embodiments~~examples ~~of any of the above aspects~~ that comprise a polypeptide that comprises the sequence $X_1IX_3X_4X_5X_6X_7X_8X_9Y$ (SEQ ID NO: 83), there is an asparagine at X_1, an alanine at X_3, a lysine at X_4, a threonine at X_5, a serine at X_7, and/or a glycine at X_8, or any combination thereof. In various ~~embodiments~~examples ~~of this aspect of the invention~~, any of the HVR-L1 residues shown in Figure 57 to have an F value of greater than 1, 5, or 10 are residues that are preferably maintained as the same residue found in the same position of the HVR-L1 of bH1-44 or bH1-81 (SEQ ID NO: 1). In additional ~~embodiments~~examples, any of the HVR-L1 residues shown in Table 14 to have $\Delta\Delta G$ values greater than 1 are residues that are preferably maintained as the same residue found in the same position of the HVR-L1 of bH1-44 or bH1-81 (SEQ ID NO: 1).

The ~~invention~~present disclosure also provides a polypeptide comprising an HVR-H2 sequence comprising the sequence $RX_2X_3X_4X_5X_6X_7X_8X_9R$ (SEQ ID NO: 85), wherein X_5 is any amino acid except threonine and X_6 is any amino acid except asparagine. Also disclosed is~~In another aspect of the invention,~~ the polypeptide that comprises the HVR-H2 sequence $RX_2X_3X_4X_5X_6X_7X_8X_9R$ (SEQ ID NO: 85), wherein X_5 is any amino acid except threonine and X_6 is any amino acid except asparagine, a HVR-H1 sequence comprising the sequence NISGTY (SEQ ID NO: 7), and an HVR-H3 sequence comprising the sequence WVGVGFYAMD (SEQ ID NO: 9). In different ~~embodiments~~examples ~~of the above aspects~~, the polypeptide comprising the HVR-H2 sequence comprising the sequence $RX_2X_3X_4X_5X_6X_7X_8X_9R$ (SEQ ID NO: 84) has a serine at X_5, a glutamic acid at X_6, and/or a tyrosine at X_8, or any combination thereof. In various ~~embodiments~~examples ~~of this aspect~~ of the ~~invention~~present disclosure, any of the HVR-H2 residues shown in Figure 57 to have an F value of greater than 1, 5, or 10 are residues that are preferably maintained as the same residue found in the same position of the HVR-H2 of bH1-44 or bH1-81 (SEQ ID NOS: 8 and 5, respectively). In additional ~~embodiments~~examples, any of the HVR-H2 residues shown in

Table 14 to have ΔΔG values greater than 1 are residues that are preferably maintained as the same residue found in the same position of the HVR-H2 of bH1-44 or bH1-81 (SEQ ID NOS: 8 and 5, respectively).

The ~~invention~~present disclosure also provides a polypeptide comprising one, two, or three of an HVR-H1 sequence comprising the sequence NISGTY (SEQ ID NO: 7), a HVR-H2 sequence comprising the sequence RIYPSEGYTR (SEQ ID NO: 8), and/or an HVR-H3 sequence comprising the sequence WVGVGFYAMD (SEQ ID NO: 9), or any combination thereof.

In any of the above ~~aspects~~examples, the isolated polypeptide may further comprise one, two, or three of an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1); an HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4); an HVR-H2 comprising the sequence RIYPTNGYTR (SEQ ID NO:5); and/or an HVR-H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6), or any combination thereof.

In any of the above ~~aspects~~examples, the isolated polypeptide may further comprise one, two, or three of an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1); an HVR-L2 sequence comprising the sequence WGSFLY (SEQ ID NO:2); and/or an HVR-L3 sequence comprising the sequence HYSSPP (SEQ ID NO:3), or any combination thereof.

In any of the above ~~aspects~~examples, the isolated polypeptide may further comprise an HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4); an HVR-H2 comprising the sequence RIYPTNGYTR (SEQ ID NO:5); and/or an HVR-H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6), or any combination thereof.

In any of the above ~~aspects~~examples, the isolated polypeptide may further comprise one, two, or three HVR sequences selected from an HVR-H1 comprising the sequence NISGTY (SEQ ID NO: 7); an HVR-H2 sequence comprising the sequence RIYPSEGYTR (SEQ ID NO: 8); and/or an HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO: 9), or any combination thereof.

In additional ~~aspects~~examples, the ~~invention~~present disclosure features ~~features~~ an isolated polypeptide comprising an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1) and (i) an HVR-L2 sequence comprising the sequence WGSFLY (SEQ ID NO:2) or (ii) an HVR-L3 sequence comprising the sequence HYSSPP (SEQ ID NO:3), or both; and one, two, of three HVR sequences selected from (i) an HVR-H1 comprising the sequence NISGTY (SEQ ID NO:7); (ii) an HVR-H2 comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and/or (iii) an HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO:9), or any combination thereof.

In additional ~~aspects~~examples, the ~~invention~~present disclosure features ~~features~~ an isolated polypeptide comprising an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1) and (i) an HVR-L2 sequence comprising the sequence WGSFLY (SEQ ID NO:2) or (ii) an HVR-

L3 sequence comprising the sequence HYSSPP (SEQ ID NO:3), or both; and one, two, of three HVR sequences selected from (i) an HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4); (ii) an HVR-H2 comprising the sequence RIYPTNGYTR (SEQ ID NO:5); and/or (iii) an HVR-H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6), or any combination thereof.

Also disclosed is~~In further aspects, the invention features~~ an isolated polypeptide comprising an HVR-H1 sequence comprising the sequence NISGTY (SEQ ID NO:7), an isolated polypeptide comprising an HVR-H2 sequence comprising the sequence RIYPSEGYTR (SEQ ID NO:8), and an isolated polypeptide comprising an HVR-H3 sequence comprising the sequence WVGVGFYAMD (SEQ ID NO:9). Also disclosed is~~In yet a further aspect, the invention features~~ an isolated polypeptide comprising an HVR-H1 sequence comprising the sequence NISGTY (SEQ ID NO:7); an HVR-H2 sequence comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and an HVR-H3 sequence comprising the sequence WVGVGFYAMD (SEQ ID NO:9).

In one ~~embodiment~~example, the ~~invention~~present disclosure provides a vector comprising any of the above described polynucleotides of the ~~invention~~present disclosure. In another ~~aspect~~example, the ~~invention~~present disclosure features a host cell comprising any of the vectors of the ~~invention~~present disclosure. In one ~~embodiment~~example, the host cell is prokaryotic. In another ~~embodiment~~example, the host cell is eukaryotic, for example, a mammalian cell.

In another aspect, the invention features a method of producing the antibody as defined herein, or the antibody fragment as defined herein, said method comprising culturing a host cell that comprises a vector comprising the polynucleotide as defined herein and recovering said antibody or antibody fragment. Also disclosed is a method of producing any of the antibodies or antibody fragments described above. This method comprises culturing a host cell that comprises a vector comprising a polynucleotide encoding the antibody and recovering the antibody. In certain ~~embodiments~~examples, the polynucleotide encodes an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1) and, optionally, the polynucleotide further encodes an HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4); an HVR-H2 comprising the sequence RIYPTNGYTR (SEQ ID NO:5); and an HVR-H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6). In other ~~embodiments~~examples, the polynucleotide encodes an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1); an HVR-L2 sequence comprising the sequence WGSFLY (SEQ ID NO:2); and an HVR-L3 sequence comprising the sequence HYSSPP (SEQ ID NO:3) and, optionally, the polynucleotide further encodes an HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4); an HVR-H2 comprising the sequence RIYPTNGYTR (SEQ ID NO:5); and an HVR-

H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6). In another ~~embodiment~~example, the polynucleotide encodes an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1); an HVR-H1 comprising the sequence NISGTY (SEQ ID NO:7); an HVR-H2 comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and an HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO:9). In yet another ~~embodiment~~example, the polynucleotide

encodes an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1); an HVR-L2 sequence comprising the sequence WGSFLY (SEQ ID NO:2); an HVR-L3 sequence comprising the sequence HYSSPP (SEQ ID NO:3); an HVR-H1 comprising the sequence NISGTY (SEQ ID NO:7); an HVR-H2 comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and an HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO:9).

In further ~~embodiments~~examples, the polynucleotide encodes an HVR-H1 sequence comprising the sequence NISGTY (SEQ ID NO:7), an HVR-H2 sequence comprising the sequence RIYPSEGYTR (SEQ ID NO:8), or an HVR-H3 sequence comprising the sequence WVGVGFYAMD (SEQ ID NO:9). In yet a further ~~embodiment~~example, the polynucleotide encodes a polypeptide comprising an HVR-H1 sequence comprising the sequence NISGTY (SEQ ID NO:7); an HVR-H2 sequence comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and an HVR-H3 sequence comprising the sequence WVGVGFYAMD (SEQ ID NO:9).

In one ~~embodiment~~example, the host cell is prokaryotic and in another ~~embodiment~~example, the host cell is eukaryotic, such as a mammalian cell.

In another aspect, there is provided an antibody as defined herein, or an antibody fragment as defined herein for use in the treatment or prevention of a tumor.

In another aspect, there is provided an antibody as defined herein, or an antibody fragment as defined herein for use in the treatment or prevention of an autoimmune disease in a subject.

Also disclosed is~~In a further aspect, the invention features~~ a method of treating a tumor in a subject. This method comprises administering to the subject an antibody or antibody fragment described herein, where the administering is for a time and in an amount sufficient to treat or prevent the tumor in the subject. In one ~~embodiment~~example, the tumor is a colorectal tumor, a breast cancer, a lung cancer, a renal cell carcinoma, a glioma, a glioblastoma, or an ovarian cancer. In another ~~embodiment~~example, the antibody comprises an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1) and specifically binds HER2 and VEGF. According to one ~~embodiment~~example, the antibody further comprises one or two HVR sequences selected from (i) HVR-L2 comprising the sequence WGSFLY (SEQ ID NO:2); and (ii) HVR-L3 comprising the sequence HYSSPP (SEQ ID NO:3). In another ~~embodiment~~example, the antibody comprises, one, two, or three HVR sequences selected from (i) HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4); (ii) HVR-H2 comprising the sequence RIYPTNGYTR (SEQ ID NO:5); and (iii) HVR-H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6). In an additional ~~embodiment~~example, the antibody comprises, one, two, or three HVR sequences selected from (i) HVR-H1 comprising the sequence NISGTY (SEQ ID NO:7); (ii)

HVR-H2 comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and (iii) HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO:9). In particular ~~embodiments~~examples, the antibody comprises an HVR-L1 sequence comprising NIAKTISGY (SEQ ID NO:1); an HVR-L2 sequence comprising WGSFLY (SEQ ID NO:2); an HVR-L3 sequence comprising HYSSPP (SEQ ID NO:3); an HVR-H1 sequence comprising NIKDTY (SEQ ID NO:4); an HVR-H2 sequence comprising RIYPTNGYTR (SEQ ID NO:5); and an HVR-H3 sequence comprising WGGDGFYAMD (SEQ ID NO:6) and specifically binds HER2 and VEGF. In

another ~~embodiment~~example, the antibody comprises an HVR-L1 sequence comprising NIAKTISGY (SEQ ID NO:1); an HVR-L2 sequence comprising WGSFLY (SEQ ID NO:2); an HVR-L3 sequence comprising HYSSPP (SEQ ID NO:3); an HVR-H1 sequence comprising NISGTY (SEQ ID NO:7); an HVR-H2 sequence comprising RIYPSEGYTR (SEQ ID NO:8); and an HVR-H3 sequence comprising WVGVGFYAMD (SEQ ID NO:9) and specifically binds HER2 and VEGF.

In an ~~embodiment~~example, the method further comprises administering to the subject an additional anti-cancer therapy. In another ~~embodiment~~example, the additional anti-cancer therapy comprises another antibody, a chemotherapeutic agent, a cytotoxic agent, an anti-angiogenic agent, an immunosuppressive agent, a prodrug, a cytokine, a cytokine antagonist, cytotoxic radiotherapy, a corticosteroid, an anti-emetic, a cancer vaccine, an analgesic, or a growth-inhibitory agent.

In an additional ~~embodiment~~example, the additional anti-cancer therapy is administered prior to or subsequent to the administration of an antibody. In a further ~~embodiment~~example, the additional anti-cancer therapy is administered concurrently with an antibody.

Also disclosed is~~In a further aspect, the invention features~~ a method of treating an autoimmune disease in a subject. This method comprises administering to the subject an antibody or antibody fragment described herein, where the administering is for a time and in an amount sufficient to treat or prevent the autoimmune disease in the subject. In one ~~embodiment~~example, the antibody comprises an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1) and specifically binds HER2 and VEGF. According to one ~~embodiment~~example, the antibody comprises one or two HVR sequences selected from (i) HVR-L2 comprising the sequence WGSFLY (SEQ ID NO:2); and (ii) HVR-L3 comprising the sequence HYSSPP (SEQ ID NO:3). In another ~~embodiment~~example, the antibody comprises, one, two, or three HVR sequences selected from (i) HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4); (ii) HVR-H2 comprising the sequence RIYPTNGYTR (SEQ ID NO:5); and (iii) HVR-H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6). In an additional ~~embodiment~~example, the antibody comprises, one, two, or three HVR sequences selected from (i) HVR-H1 comprising the sequence NISGTY (SEQ ID NO:7); (ii) HVR-H2 comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and (iii). HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO:9). In particular ~~embodiments~~examples, the antibody comprises an HVR-L1 sequence comprising NIAKTISGY (SEQ ID NO:1); an HVR-L2 sequence comprising WGSFLY (SEQ ID NO:2); an HVR-L3 sequence comprising HYSSPP (SEQ ID NO:3); an HVR-H1 sequence comprising NIKDTY (SEQ ID NO:4); an HVR-H2 sequence comprising RIYPTNGYTR (SEQ ID NO:5); and an HVR-H3 sequence comprising WGGDGFYAMD (SEQ ID NO:6) and specifically binds HER2 and VEGF or the antibody comprises an HVR-L1 sequence

comprising NIAKTISGY (SEQ ID NO:1); an HVR-L2 sequence comprising WGSFLY (SEQ ID NO:2); an HVR-L3 sequence comprising HYSSPP (SEQ ID NO:3); an HVR-H1 sequence comprising NISGTY (SEQ ID NO:7); an HVR-H2 sequence comprising RIYPSEGYTR (SEQ ID NO:8); and an HVR-H3 sequence comprising WVGVGFYAMD (SEQ ID NO:9) and specifically binds HER2 and VEGF.

Also disclosed is~~In yet another aspect, the invention features~~ a method of treating a non-malignant disease involving abnormal activation of HER2 in a subject. This method comprises administering to the subject an antibody or antibody fragment described herein, where the administering is for a time and in an amount sufficient to treat or prevent the non-malignant disease in the subject. In one ~~embodiment~~example, the antibody comprises an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1) and specifically binds HER2 and VEGF. According to one ~~embodiment~~example, the antibody comprises one or two HVR sequences selected from (i) HVR-L2 comprising the sequence WGSFLY (SEQ ID NO:2); and (ii) HVR-L3 comprising the sequence HYSSPP (SEQ ID NO:3). In another ~~embodiment~~example, the antibody further comprises, one, two, or three HVR sequences selected from (i) HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4); (ii) HVR-H2 comprising the sequence RIYPTNGYTR (SEQ ID NO:5); and (iii) HVR-H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6). In an additional ~~embodiment~~example, the antibody comprises, one, two, or three HVR sequences selected from (i) HVR-H1 comprising the sequence NISGTY (SEQ ID NO:7); (ii) HVR-H2 comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and (iii) HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO:9). In particular ~~embodiments~~examples, the antibody comprises an HVR-L1 sequence comprising NIAKTISGY (SEQ ID NO:1); an HVR-L2 sequence comprising WGSFLY (SEQ ID NO:2); an HVR-L3 sequence comprising HYSSPP (SEQ ID NO:3); an HVR-H1 sequence comprising NIKDTY (SEQ ID NO:4); an HVR-H2 sequence comprising RIYPTNGYTR (SEQ ID NO:5); and an HVR-H3 sequence comprising WGGDGFYAMD (SEQ ID NO:6) and specifically binds HER2 and VEGF or the antibody comprises an HVR-L1 sequence comprising NIAKTISGY (SEQ ID NO:1); an HVR-L2 sequence comprising WGSFLY (SEQ ID NO:2); an HVR-L3 sequence comprising HYSSPP (SEQ ID NO:3); an HVR-H1 sequence comprising NISGTY (SEQ ID NO:7); an HVR-H2 sequence comprising RIYPSEGYTR (SEQ ID NO:8); and an HVR-H3 sequence comprising WVGVGFYAMD (SEQ ID NO:9) and specifically binds HER2 and VEGF.

Also disclosed is~~Additional aspects of the invention feature~~ the use of the antibodies and antibody fragments described herein in the treatment of a tumor, an autoimmune disease, or a non-malignant disease involving abnormal activation of HER2 in a subject, as well as use in the manufacture of a medicament for the treatment of a tumor, an autoimmune disease, or a non-

malignant disease involving abnormal activation of HER2 in a subject. In one ~~embodiment~~example of these uses, the antibody comprises an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1) and specifically binds HER2 and VEGF. According to one ~~embodiment~~example, the antibody further comprises one or two HVR sequences selected from (i) HVR-L2 comprising the sequence WGSFLY (SEQ ID NO:2); and (ii) HVR-L3 comprising the sequence HYSSPP (SEQ ID NO:3). In another ~~embodiment~~example, the antibody comprises, one, two, or three HVR sequences selected from (i) HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4); (ii) HVR-H2 comprising the sequence RIYPTNGYTR (SEQ ID NO:5); and (iii) HVR-H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6). In an additional ~~embodiment~~example, the antibody comprises, one, two, or three HVR sequences selected from (i) HVR-H1 comprising the sequence NISGTY (SEQ ID NO:7); (ii) HVR-H2 comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and (iii) HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO:9). In particular ~~embodiments~~examples, the antibody comprises an HVR-L1 sequence comprising NIAKTISGY (SEQ ID NO:1); an HVR-L2 sequence comprising WGSFLY (SEQ ID NO:2); an HVR-L3 sequence comprising HYSSPP (SEQ ID NO:3); an HVR-H1 sequence comprising NIKDTY (SEQ ID NO:4); an HVR-H2 sequence comprising RIYPTNGYTR (SEQ ID NO:5); and an HVR-H3 sequence comprising WGGDGFYAMD (SEQ ID NO:6) and specifically binds HER2 and VEGF or the antibody comprises an HVR-L1 sequence comprising NIAKTISGY (SEQ ID NO:1); an HVR-L2 sequence comprising WGSFLY (SEQ ID NO:2); an HVR-L3 sequence comprising HYSSPP (SEQ ID NO:3); an HVR-H1 sequence comprising NISGTY (SEQ ID NO:7); an HVR-H2 sequence comprising RIYPSEGYTR (SEQ ID NO:8); and an HVR-H3 sequence comprising WVGVGFYAMD (SEQ ID NO:9) and specifically binds HER2 and VEGF.

In an ~~embodiment~~example of the methods of treating a tumor, an autoimmune disease, or a non-malignant disease involving abnormal activation of HER2 described herein, the subject is a human.

Also, contemplated are kits, compositions, and articles of manufacture comprising the antibodies and antibody fragments described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the designed diversity in various LC libraries.

Figure 2 shows a summary of four light chain libraries used to alter anti-VEGF antibodies or anti-Her2 antibodies to bind to an additional target. The italicized NNK and XYZ refer to codon sets. Ys, Ds, Ts and Ss refer to soft randomizations by having tyrosine, aspartic acid,

CLAIMS

1. An isolated antibody comprising a hypervariable region (HVR) L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1), wherein said antibody specifically binds human epidermal growth factor receptor 2 (HER2) and vascular endothelial growth factor (VEGF).

2. The antibody of claim 1, wherein said antibody further comprises one or two HVR sequences selected from the group consisting of:

(i) HVR-L2 comprising the sequence WGSFLY (SEQ ID NO:2); and

(ii) HVR-L3 comprising the sequence HYSSPP (SEQ ID NO:3).

3. The antibody of claim 1, wherein said antibody further comprises, one, two, or three HVR sequences selected from the group consisting of:

(i) HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4);

(ii) HVR-H2 comprising the sequence RIYPTNGYTR (SEQ ID NO:5); and

(iii) HVR-H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6).

4. The antibody of claim 1, wherein said antibody further comprises, one, two, or three HVR sequences selected from the group consisting of:

(i) HVR-H1 comprising the sequence NISGTY (SEQ ID NO:7);

(ii) HVR-H2 comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and

(iii) HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO:9).

5. The antibody of claim 1, wherein said antibody binds human and murine VEGF with a Kd of 150 nM or stronger and HER2 with a Kd of 7 nM or stronger.

6. The antibody of claim 1, wherein said antibody inhibits VEGF-induced cell proliferation and proliferation of a HER2 expressing cell relative to a control.

7. The antibody of claim 1, wherein said antibody inhibits VEGF binding to VEGF receptor 2 (VEGFR2).

8. An isolated antibody, wherein said antibody binds human and murine VEGF with a Kd of 150 nM or stronger and HER2 with a Kd of 7 nM or stronger, and wherein said

antibody inhibits VEGF-induced cell proliferation and proliferation of a HER2 expressing cell relative to a control.

9. The antibody of claim 8, wherein said antibody binds human and murine VEGF with a Kd of 36 nM or stronger and HER2 with a Kd of 1 nM or stronger.

10. An isolated antibody fragment, wherein said antibody fragment binds human VEGF with a Kd of 58 nM or stronger and HER2 with a Kd of 6 nM or stronger, and wherein said antibody fragment inhibits VEGF-induced cell proliferation and proliferation of a HER2 expressing cell relative to a control.

11. The antibody fragment of claim 10, wherein said antibody fragment binds human and murine VEGF with a Kd of 33 nM or stronger and HER2 with a Kd of 0.7 nM or stronger.

12. The antibody fragment of claim 10 or 11, wherein said fragment is an Fab fragment.

13. An isolated antibody, wherein said antibody comprises HVR-L1, HVR-L2, HVR-L3, HVR-H1, HVR-H2, and HVR-H3, wherein each, in order, comprises the sequence of SEQ ID NO:1, 2, 3, 4, 5, and 6, and wherein said antibody specifically binds HER2 and VEGF.

14. An isolated antibody, wherein said antibody comprises HVR-L1, HVR-L2, HVR-L3, HVR-H1, HVR-H2, and HVR-H3, wherein each, in order, comprises the sequence of SEQ ID NO:1, 2, 3, 7, 8, and 9, and wherein said antibody specifically binds HER2 and VEGF.

15. An isolated antibody comprising an HVR L1 sequence comprising the sequence $X_1IX_3X_4X_5X_6X_7X_8X_9Y$ (SEQ ID NO:83), wherein X_1 is any amino acid except Asp, X_3 is any amino acid except Pro, X_4 is any amino acid except Arg, X_5 is any amino acid except Ser, and wherein said antibody specifically binds HER2 and VEGF.

16. The isolated antibody of claim 15, wherein X_1 is Asn, X_3 is Ala, X_4 is Lys, X_5 is Thr, or any combination thereof.

17. The isolated antibody of claim 15 or 16, wherein X_5 is Thr, X_7 is Ser, and X_8 is Gly.

18. The isolated antibody of any one of claims 15-17, wherein said antibody further comprises one or two HVR sequences selected from the group consisting of:

(i) HVR-L2 comprising the sequence WGSFLY (SEQ ID NO:2); and

(ii) HVR-L3 comprising the sequence HYSSPP (SEQ ID NO:3).

19. The isolated antibody of any one of claims 15-17, wherein said antibody further comprises one, two, or three HVR sequences selected from the group consisting of:

(i) HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4);

(ii) HVR-H2 comprising the sequence RIYPTNGYTR (SEQ ID NO:5); and

(iii) HVR-H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6).

20. The isolated antibody of any one of claims 15-17, wherein said antibody further comprises one, two, or three HVR sequences selected from the group consisting of:

(i) HVR-H1 comprising the sequence NISGTY (SEQ ID NO:7);

(ii) HVR-H2 comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and

(iii) HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO:9).

21. The isolated antibody of any one of claims 15-17, wherein said antibody binds human and murine VEGF with a Kd of 150 nM or stronger and HER2 with a Kd of 7 nM or stronger.

22. The isolated antibody of any one of claims 15-17, wherein sad antibody inhibits VEGF-induced cell proliferation and proliferation of a HER2 expressing cell relative to a control.

23. The isolated antibody of any one of claims 15-17, wherein said antibody inhibits VEGF binding to VEGFR2.

24. The isolated antibody of any one of claims 15-17, wherein said antibody further comprises an HVR H2 sequence comprising the sequence $RX_2X_3X_4X_5X_6X_7X_8X_9R$ (SEQ ID NO:84), and wherein said antibody specifically binds HER2 and VEGF.

25. An isolated antibody comprising an HVR-H2 sequence comprising the sequence $RX_2X_3X_4X_5X_6X_7X_8X_9R$ (SEQ ID NO:85), wherein X_5 is any amino acid except Thr and X_6 is any amino acid except Asn, and wherein said antibody specifically binds HER2 and VEGF.

26. The isolated antibody of claim 25, wherein X_5 is Ser, X_6 is Glu, or X_5 is Ser and X_6 is Glu.

27. The isolated antibody of claim 25 or 26, wherein X_8 is Tyr.

28. The isolated antibody of any one of claims 25-27, wherein said antibody further comprises one or two HVR sequences selected from the group consisting of:

(i) HVR-H1 comprising the sequence NISGTY (SEQ ID NO:7);

(ii) HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO:9).

29. The isolated antibody of any one of claims 25-27, wherein said antibody further comprises one, two, or three HVR sequences selected from the group consisting of:

(i) HVR-L1 comprising the sequence NIAKTISGY (SEQ ID NO:1);

(ii) HVR-L2 comprising the sequence WGSFLY (SEQ ID NO:2);

(iii) HVR-L3 comprising the sequence HYSSPP (SEQ ID NO:3).

30. The isolated antibody of any one of claims 25-27, wherein said antibody binds human and murine VEGF with a Kd of 150 nM or stronger and HER2 with a Kd of 7 nM or stronger.

31. The isolated antibody of any one of claims 25-27, wherein said antibody inhibits VEGF-induced cell proliferation and proliferation of a HER2 expressing cell relative to a control.

32. The isolated antibody of any one of claims 25-27, wherein said antibody inhibits VEGF binding to VEGFR2.

33. The antibody of any one of claims 1-9 or 13-32, wherein said antibody is a monoclonal antibody.

34. The antibody of any one of claims 1-9 or 13-32, wherein said antibody is an IgG antibody.

35. A fragment of the antibody of any one of claims 1-9 or 13-32, wherein said fragment specifically binds HER2 and VEGF.

36. The fragment of claim 35, wherein said fragment is a Fab fragment or a single chain variable fragment (scFv).

37. The antibody or antibody fragment of any of claims 1-36, wherein at least a portion of the framework sequence is a human consensus framework sequence.

38. A polynucleotide encoding an antibody or antibody fragment of any of claims 1-37.

39. A polynucleotide encoding an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1).

40. A polynucleotide encoding an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1), and (i) an HVR-L2 sequence comprising the sequence WGSFLY (SEQ ID NO:2), or (ii) an HVR-L3 sequence comprising the sequence HYSSPP (SEQ ID NO:3), or both (i) and (ii).

41. The polynucleotide of claim 39 or 40, wherein said polynucleotide further encodes one, two, or three HVR sequences selected from the group consisting of:

(i) an HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4);

(ii) an HVR-H2 comprising the sequence RIYPTNGYTR (SEQ ID NO:5); and

(iii) an HVR-H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6).

42. The polynucleotide of claim 39 or 40, wherein said polynucleotide further encodes one, two, or three HVR sequences selected from the group consisting of:

(i) an HVR-H1 comprising the sequence NISGTY (SEQ ID NO:7);

(ii) an HVR-H2 comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and

(iii) an HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO:9).

43. A polynucleotide encoding an HVR-H1 sequence comprising the sequence NISGTY (SEQ ID NO:7).

44. A polynucleotide encoding an HVR-H2 sequence comprising the sequence RIYPSEGYTR (SEQ ID NO:8).

45. A polynucleotide encoding an HVR-H3 sequence comprising the sequence WVGVGFYAMD (SEQ ID NO:9).

46. A polynucleotide encoding an HVR-H1 sequence comprising the sequence NISGTY (SEQ ID NO:7); an HVR-H2 sequence comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and an HVR-H3 sequence comprising the sequence WVGVGFYAMD (SEQ ID NO:9).

47. A polynucleotide encoding an HVR-L1 sequence comprising the sequence $X_1IX_3X_4X_5X_6X_7X_8X_9Y$ (SEQ ID NO:83), wherein X_1 is any amino acid except Asp, X_3 is any amino acid except Pro, X_4 is any amino acid except Arg, X_5 is any amino acid except Ser.

48. A polynucleotide encoding an HVR-L1 sequence comprising the sequence $X_1IX_3X_4X_5X_6X_7X_8X_9Y$ (SEQ ID NO:83), wherein X_1 is any amino acid except Asp, X_3 is any amino acid except Pro, X_4 is any amino acid except Arg, X_5 is any amino acid except Ser and (i) an HVR-L2 sequence comprising the sequence WGSFLY (SEQ ID NO:2), or (ii) an HVR-L3 sequence comprising the sequence HYSSPP (SEQ ID NO:3), or both (i) and (ii).

49. The polynucleotide of claims 47 or 48, wherein X_1 is Asn, X_3 is Ala, X_4 is Lys, X_5 is Thr, X_7 is Ser, X_8 is Gly, or any combination thereof.

50. A polynucleotide encoding an HVR-H2 sequence comprising the sequence $RX_2X_3X_4X_5X_6X_7X_8X_9R$ (SEQ ID NO:85), wherein X_5 is any amino acid except Thr and X_6 is any amino acid except Asn.

51. A polynucleotide encoding an HVR-H1 sequence comprising the sequence NISGTY (SEQ ID NO:7); an HVR-H2 sequence comprising the sequence $RX_2X_3X_4X_5X_6X_7X_8X_9R$ (SEQ ID NO:85), wherein X_5 is any amino acid except Thr and X_6 is any amino acid except Asn; and an HVR-H3 sequence comprising the sequence WVGVGFYAMD (SEQ ID NO:9).

52. The polynucleotide of claims 50 or 51, wherein X_5 is Ser, X_6 is Glu, X_8 is Tyr, or any combination thereof.

53. A polypeptide comprising an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1).

54. A polypeptide comprising an HVR-L1 sequence comprising the sequence $X_1IX_3X_4X_5X_6X_7X_8X_9Y$ (SEQ ID NO:83), wherein X_1 is any amino acid except Asp, X_3 is any amino acid except Pro, X_4 is any amino acid except Arg, X_5 is any amino acid except Ser.

55. A polypeptide comprising an HVR-L1 sequence comprising the sequence NIAKTISGY (SEQ ID NO:1), and (i) an HVR-L2 sequence comprising the sequence WGSFLY (SEQ ID NO:2), or (ii) an HVR-L3 sequence comprising the sequence HYSSPP (SEQ ID NO:3), or both (i) and (ii).

56. A polypeptide comprising an HVR-L1 sequence comprising the sequence $X_1IX_3X_4X_5X_6X_7X_8X_9Y$ (SEQ ID NO:83), wherein X_1 is any amino acid except Asp, X_3 is any amino acid except Pro, X_4 is any amino acid except Arg, X_5 is any amino acid except Ser , and (i) an HVR-L2 sequence comprising the sequence WGSFLY (SEQ ID NO:2), or (ii) an HVR-L3 sequence comprising the sequence HYSSPP (SEQ ID NO:3), or both (i) and (ii).

57. The polypeptide of claims 54 or 56, wherein X_1 is Asn, X_3 is Ala, X_4 is Lys, X_5 is Thr, X_7 is Ser, X_8 is Gly, or any combination thereof.

58. The polypeptide of claim 54, 55, 56, or 57, wherein said polypeptide further comprises one, two, or three HVR sequences selected from the group consisting of:

(i) an HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4);

(ii) an HVR-H2 comprising the sequence RIYPTNGYTR (SEQ ID NO:5); and

(iii) an HVR-H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6).

59. The polypeptide of claim 54, 55, 56, or 57, wherein said polypeptide further comprises one, two, or three HVR sequences selected from the group consisting of:

(i) an HVR-H1 comprising the sequence NISGTY (SEQ ID NO:7);

(ii) an HVR-H2 comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and

(iii) an HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO:9).

60. A polypeptide comprising an HVR-H1 sequence comprising the sequence NISGTY (SEQ ID NO:7).

61. A polypeptide comprising an HVR-H2 sequence comprising the sequence RIYPSEGYTR (SEQ ID NO:8).

62. A polypeptide comprising an HVR-H3 sequence comprising the sequence WVGVGFYAMD (SEQ ID NO:9).

63. A polypeptide comprising an HVR-H2 sequence comprising the sequence $RX_2X_3X_4X_5X_6X_7X_8X_9R$ (SEQ ID NO:85), wherein X_5 is any amino acid except Thr and X_6 is any amino acid except Asn.

64. A polypeptide comprising an HVR-H1 sequence comprising the sequence NISGTY (SEQ ID NO:7); an HVR-H2 sequence comprising the sequence RIYPSEGYTR (SEQ ID NO:8); and an HVR-H3 sequence comprising the sequence WVGVGFYAMD (SEQ ID NO:9).

65. A polypeptide comprising an HVR-H1 sequence comprising the sequence NISGTY (SEQ ID NO:7); an HVR-H2 sequence comprising the sequence $RX_2X_3X_4X_5X_6X_7X_8X_9R$ (SEQ ID NO:85), wherein X_5 is any amino acid except Thr and X_6 is any amino acid except Asn; and an HVR-H3 sequence comprising the sequence WVGVGFYAMD (SEQ ID NO:9).

66. The polypeptide of claims 63 or 65, wherein X_5 is Ser, X_6 is Glu, X_8 is Tyr, or any combination thereof.

67. A vector comprising the polynucleotide of any one of claims 38-52.

68. The vector of claim 67, wherein the vector is an expression vector.

69. A host cell comprising a vector of claim 67 or 68.

70. The host cell of claim 69, wherein the host cell is prokaryotic.

71. The host cell of claim 69, wherein the host cell is eukaryotic.

72. The host cell of claim 71, wherein the host cell is mammalian.

73. A method of producing the antibody or antibody fragment of any one of claims 1-37, said method comprising culturing a host cell that comprises a vector comprising the polynucleotide of any one of claims 38-52 and recovering said antibody.

74. The method of claim 73, wherein the host cell is prokaryotic.

75. The method of claim 73, wherein the host cell is eukaryotic.

76. The method of claim 75, wherein the host cell is mammalian.

77. A method of treating a tumor in a subject, said method comprising administering to said subject the antibody or antibody fragment of any one of claims 1-37, wherein said administering is for a time and in an amount sufficient to treat or prevent said tumor in said subject.

78. The method of claim 77, wherein said tumor is a colorectal tumor, a breast cancer, a lung cancer, a renal cell carcinoma, a glioma, a glioblastoma, or an ovarian cancer.

79. The method of claim 77, further comprising administering to said subject an additional anti-cancer therapy.

80. The method of claim 79, wherein said additional anti-cancer therapy comprises another antibody or antibody fragment, a chemotherapeutic agent, a cytotoxic agent, an anti-angiogenic agent, an immunosuppressive agent, a prodrug, a cytokine, a cytokine antagonist, cytotoxic radiotherapy, a corticosteroid, an anti-emetic, a cancer vaccine, an analgesic, or a growth-inhibitory agent.

81. The method of claim 79, wherein said additional anti-cancer therapy is administered prior to or subsequent to the administration of the antibody or antibody fragment of any one of claims 1-37.

82. The method of claim 79, wherein said additional anti-cancer therapy is administered concurrently with the antibody or antibody fragment of any one of claims 1-37.

83. A method of treating an autoimmune disease in a subject, said method comprising administering to said subject the antibody or antibody fragment of any one of

claims 1-37, wherein said administering is for a time and in an amount sufficient to treat or prevent said autoimmune disease in said subject.

84. A method of treating a non-malignant disease involving abnormal activation of HER2 in a subject, said method comprising administering to said subject the antibody or antibody fragment of any one of claims 1-37, wherein said administering is for a time and in an amount sufficient to treat or prevent said non-malignant disease in said subject.

85. The method of claim 77, 83, or 84, wherein the subject is a human.

CLAIMS

1. An isolated antibody comprising six hypervariable region (HVR) sequences comprising:

(i) HVR-L1 comprising the sequence NIAKTISGY (SEQ ID NO:1),

(ii) HVR-L2 comprising the sequence WGSFLY (SEQ ID NO:2), and

(iii) HVR-L3 comprising the sequence HYSSPP (SEQ ID NO:3); and

(a) further comprising HVR sequences comprising:

(iv) HVR-H1 comprising the sequence NIKDTY (SEQ ID NO:4),

(v) HVR-H2 comprising the sequence RIYPTNGYTR (SEQ ID NO:5), and

(vi) HVR-H3 comprising the sequence WGGDGFYAMD (SEQ ID NO:6); or

(b) further comprising HVR sequences comprising:

(iv) HVR-H1 comprising the sequence NISGTY (SEQ ID NO:7),

(v) HVR-H2 comprising the sequence RIYPSEGYTR (SEQ ID NO:8), and

(vi) HVR-H3 comprising the sequence WVGVGFYAMD (SEQ ID NO:9);

wherein said antibody specifically binds human epidermal growth factor receptor 2 (HER2) and vascular endothelial growth factor (VEGF).

2. The antibody of claim 1, wherein said antibody binds human and murine VEGF with a Kd of 150 nM or stronger and HER2 with a Kd of 7 nM or stronger.

3. The antibody of claim 1, wherein said antibody inhibits VEGF-induced cell proliferation and proliferation of a HER2 expressing cell relative to a control.

4. The antibody of claim 1, wherein said antibody inhibits VEGF binding to VEGF receptor 2 (VEGFR2).

5. The antibody of claim 1, wherein said antibody binds human and murine VEGF with a Kd of 150 nM or stronger and HER2 with a Kd of 7 nM or stronger, and wherein said antibody inhibits VEGF-induced cell proliferation and proliferation of a HER2 expressing cell relative to a control.

6. The antibody of claim 2 or 5, wherein said antibody binds human and murine VEGF with a Kd of 36 nM or stronger and HER2 with a Kd of 1 nM or stronger.

7. An isolated antibody fragment of the antibody of claim 1, wherein said antibody fragment binds human VEGF with a Kd of 33 nM or stronger and HER2 with a Kd of 0.7 nM or stronger, and wherein said antibody fragment inhibits VEGF-induced cell proliferation and proliferation of a HER2 expressing cell relative to a control.

8. The antibody of any one of claims 1 to 6, wherein said antibody is a monoclonal antibody or an IgG antibody.

9. An antibody fragment of the antibody of any one of claims 1 to 6 or 8, wherein said antibody fragment specifically binds HER2 and VEGF.

10. The antibody fragment of claim 9, wherein said antibody fragment is a Fab fragment or a single chain variable fragment (scFv).

11. The antibody of any one of claims 1 to 6 or 8, or an antibody fragment of any of claims 7, 9 or 10, wherein at least a portion of the framework sequence is a human consensus framework sequence.

12. A polynucleotide encoding the antibody of any one of claims 1 to 6 or 8, or the antibody fragment of any one of claims 7, 9 or 10.

13. A vector or an expression vector comprising the polynucleotide of claim 12.

14. A host cell comprising a vector of claim 13.

15. A method of producing the antibody of any one of claims 1 to 6 or 8, or the antibody fragment of any one of claims 7, 9 or 10, said method comprising culturing a host cell that comprises a vector comprising the polynucleotide of claim 12 and recovering said antibody or antibody fragment.

16. An antibody of any one of claims 1 to 6 or 8, or an antibody fragment of any one of claims 7, 9 or 10 for use in the treatment or prevention of a tumor.

17. The antibody for use according to claim 16, wherein said tumor is a colorectal tumor, a breast cancer, a lung cancer, a renal cell carcinoma, a glioma, a glioblastoma, or an ovarian cancer.

18. The antibody for use according to claim 16, further comprising an additional anti-cancer therapeutic.

19. The antibody for use according to claim 18, wherein said additional anti-cancer therapeutic comprises another antibody or antibody fragment, a chemotherapeutic agent, a cytotoxic agent, an anti-angiogenic agent, an immunosuppressive agent, a prodrug, a cytokine, a cytokine antagonist, cytotoxic radiotherapy, a corticosteroid, an anti-emetic, a cancer vaccine, an analgesic, or a growth-inhibitory agent.

20. The antibody for use according to claim 18, wherein said additional anti-cancer therapeutic is to be administered prior to or subsequent to the administration of the said antibody or antibody fragment.

21. The antibody for use according to claim 18, wherein said additional anti-cancer therapeutic is to be administered concurrently with said antibody or antibody fragment.

22. An antibody of any one of claims 1 to 6 or 8, or an antibody fragment of any one of claims 7, 9 or 10 for use in the treatment or prevention of an autoimmune disease in a subject.