Also provided herein is conjugate, comprising an anti-EGFR antibody, or antigen-binding fragment thereof, as described above linked directly or indirectly to a therapeutic moiety.

Also provided herein is a modified anti-EGFR antibody or antigen-binding fragment thereof, comprising an amino acid replacement(s) in a variable heavy chain (VH) of an unmodified anti-EGFR antibody or antigen-binding fragment thereof, wherein the replacement is replacement with glutamic acid (E) at a position corresponding to position 104 (Y104E), with reference to amino acid positions set forth in SEQ ID NO: 2 or 7, wherein:

corresponding amino acid positions are identified by alignment of the variable heavy chain of the antibody with the variable heavy chain set forth in SEQ ID NO: 2 or 7;

the modified anti-EGFR antibody, or antigen-binding fragment thereof, specifically binds epidermal growth factor receptor (EGFR) or a soluble fragment thereof and the modification(s) is/are only the replacement Y104E or the replacement Y104E and up to 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 additional amino acid replacements in the unmodified antibody or antigen-binding fragment thereof;

the modified anti-EGFR antibody, or antigen-binding fragment thereof, exhibits a ratio of binding activity for EGFR of greater than 1.0 in the presence of a pH that is pH 6.0 to 6.5, inclusive compared to in the presence of pH 7.4, when measured under the same conditions except for the difference in pH; and

the unmodified anti-EGFR antibody or antigen-binding fragment thereof is selected from among:

i) cetuximab or an antigen-binding fragment thereof comprising a variable heavy chain set forth in SEQ ID NO:2 or 7 and a variable light chain set forth in SEQ ID NOS: 4, 9 or 11;

ii) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:1 and the light chain sequence set forth in SEQ ID NO:3, or an antigen-binding fragment thereof

iii) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:5 and the light chain sequence set forth in SEQ ID NO:3, or an antigen-binding fragment thereof;

iv) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:12 and the light chain sequence set forth in SEQ ID NO:13, or an antigen-binding fragment thereof;

v) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:6 and the light chain sequence set forth in SEQ ID NO:8, or an antigen-binding fragment thereof;

vi) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:6 and the light chain sequence set forth in SEQ ID NO:10, or an antigen-binding fragment thereof; and

vii) a humanized form of any of i)-vi).

Also provided herein is a conjugate, comprising the modified anti-EGFR antibody, or antigen-binding fragment thereof, as described herein linked directly or indirectly via a chemical or physical bond to a targeted agent, wherein the targeted agent is for delivery to a tumor that expresses EGFR.

Also provided herein is a conjugate, comprising the modified anti-EGFR antibody, or antigen-binding fragment thereof, as described herein linked directly or indirectly via a linker (L) to a targeted agent, wherein the targeted agent is for delivery to a tumor that expresses EGFR.

Also provided herein is a nucleic acid molecule(s), comprising a sequence of nucleotides encoding a modified anti-EGFR antibody, or antigen-binding fragment thereof, as described herein; or

comprising a sequence of nucleotides encoding the heavy chain of the modified anti-EGFR antibody, or antigen-binding fragment thereof, as described herein.

Also provided herein is a method of making a modified anti-EGFR antibody, or antigen-binding fragment thereof, comprising expressing the heavy chain or light chain encoded from a vector or vectors as described herein encoding the heavy chain and the light chain in a suitable host cell to produce the antibody; and, optionally, recovering the antibody.

Also provided herein is a pharmaceutical composition comprising:

the modified anti-EGFR antibody or antigen-binding fragment as described herein, or conjugate as described herein; and

a pharmaceutically acceptable carrier or excipient.

Also provided herein is use of a pharmaceutical composition as described herein, for formulation of a medicament for treating a condition responsive to treatment with an anti-EGFR antibody in a subject, wherein the condition is a tumor that expresses EGFR.

Also provided herein is a pharmaceutical composition as described herein for use in treating a condition responsive to treatment with an anti-EGFR antibody in a subject, wherein the condition is a tumor that expresses EGFR.

Also provided herein is use of the modified anti-EGFR antibody as described herein or conjugate as described herein for formulation of a medicament for treating a condition responsive to treatment with an anti-EGFR antibody in a subject, wherein the condition is a tumor that expresses EGFR.

Anti-EGFR antibodies are employed as anti-tumor therapeutics because they bind to EGFR receptors and inhibit ligand binding, thereby preventing EGFR-mediated activities that occur upon ligand binding. As a result, such antibodies can inhibit or treat tumors. Because tissues, other than tumors, such as tissues in the skin, also express EGFRs, the anti-EGFR antibodies also inhibit activities of these receptors, thereby causing undesirable side-effects. The antibodies provided herein exhibit pH-selective binding activity, such that EGFR binding activity is reduced at neutral pH (*e.g.*, pH 7.0 to 7.4) compared to antibodies that do not exhibit pH-selective binding activity and/or compared to EGFR binding activity under acidic pH conditions. By virtue of the pH-selective activity, the anti-EGFR antibodies provided produce fewer or lesser undesirable side-effects and/or exhibit improved efficacy in a treated subject by virtue of the ability to administer higher doses.

For example, provided herein are modified anti-EGFR antibodies, and antigen-binding fragments thereof, that contain an amino acid replacement(s) in a variable heavy chain of an unmodified anti-EGFR antibody, or antigen-binding fragment thereof, corresponding to replacement with glutamic acid (E) at a position corresponding to position 104 with reference to amino acid positions set forth in SEQ ID NO: 2 or 7, as long as the modified anti-EGFR antibody specifically binds epidermal growth factor receptor (EGFR) or a soluble fragment thereof; the unmodified anti-EGFR antibody is cetuximab, an antigen-binding fragment thereof or a variant thereof, specifically binds to EGFR and does not already contain the amino acid replacement; and corresponding amino acid positions are identified by alignment of the variable heavy chain of the antibody with the variable heavy chain set forth in SEQ ID NO: 2 or 7.

In any of such examples of the modified anti-EGFR antibodies provided herein, the unmodified anti-EGFR antibody, or antigen-binding fragment thereof, to which the amino acid replacement is made contains a variable heavy chain set forth in SEQ ID NO: 2 or 7, or a sequence of amino acids that exhibits at least 70% sequence identity to SEQ ID NO: 2 or 7; and a variable light chain set forth in SEQ ID NO: 4, 9 or 11 or a sequence of amino acids that exhibits at least 70% sequence identity to SEQ ID NO: 4, 9 or 11. For example, the unmodified anti-EGFR antibody, or antigen-binding fragment thereof, contains a variable heavy chain that exhibits at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 2 or 7; and/or a variable light chain that exhibits at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%,

CLAIMS:

1. A modified anti-EGFR antibody or antigen-binding fragment thereof, comprising an amino acid replacement(s) in a variable heavy chain (VH) of an unmodified anti-EGFR antibody or antigen-binding fragment thereof, wherein the replacement is replacement with glutamic acid (E) at a position corresponding to position 104 (Y104E), with reference to amino acid positions set forth in SEQ ID NO: 2 or 7, wherein:

corresponding amino acid positions are identified by alignment of the variable heavy chain of the antibody with the variable heavy chain set forth in SEQ ID NO: 2 or 7;

the modified anti-EGFR antibody, or antigen-binding fragment thereof, specifically binds epidermal growth factor receptor (EGFR) or a soluble fragment thereof and the modification(s) is/are only the replacement Y104E or the replacement Y104E and up to 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 additional amino acid replacements in the unmodified antibody or antigen-binding fragment thereof;

the modified anti-EGFR antibody, or antigen-binding fragment thereof, exhibits a ratio of binding activity for EGFR of greater than 1.0 in the presence of a pH that is pH 6.0 to 6.5, inclusive compared to in the presence of pH 7.4, when measured under the same conditions except for the difference in pH; and

the unmodified anti-EGFR antibody or antigen-binding fragment thereof is selected from among:

i) cetuximab or an antigen-binding fragment thereof comprising a variable heavy chain set forth in SEQ ID NO:2 or 7 and a variable light chain set forth in SEQ ID NOS: 4, 9 or 11;

ii) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:1 and the light chain sequence set forth in SEQ ID NO:3, or an antigen-binding fragment thereof

iii) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:5 and the light chain sequence set forth in SEQ ID NO:3, or an antigen-binding fragment thereof;

iv) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:12 and the light chain sequence set forth in SEQ ID NO:13, or an antigen-binding fragment thereof;

v) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:6 and the light chain sequence set forth in SEQ ID NO:8, or an antigen-binding fragment thereof;

vi) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:6 and the light chain sequence set forth in SEQ ID NO:10, or an antigen-binding fragment thereof; and

vii) a humanized form of any of i)-vi).

2. The modified anti-EGFR antibody of claim 1, wherein the ratio of binding activity is at least 2.0.

3. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 1 or claim 2, wherein the unmodified anti-EGFR antibody comprises:

a variable heavy chain set forth in SEQ ID NO:2 and a variable light chain set forth in SEQ ID NO: 4; or

a variable heavy chain set forth in SEQ ID NO: 7 and a variable light chain set forth in SEQ ID NO: 9 or 11.

4. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 1 or claim 2, comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NO:74 or 75; and

b) a variable light (VL) chain comprising the sequence of amino acids set forth in SEQ ID NO:4, 9 or 11.

5. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 4, comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NO: 74; and

b) a variable light (VL) chain containing the sequence of amino acids set forth in SEQ ID NO: 9.

6. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 1 or claim 2 that is a full-length IgG antibody, wherein the modified anti-EGFR antibody comprises:

a) a heavy chain comprising the sequence of amino acids set forth in SEQ ID NO:72 ; and

b) a light chain comprising the sequence of amino acids set forth in any of SEQ ID NOS: 3, 8, 10 or 13.

7. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 1 or claim 2, wherein:

the modified antibody comprises up to 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid replacements in the variable heavy chain set forth in SEQ ID NO: 74 or 75 and/or in the variable light chain set forth in SEQ ID NO: 4, 9 or 11, other than replacement with E at a position corresponding to position 104 in the heavy chain; or

the modified antibody comprises up to 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid replacements in the heavy chain set forth in SEQ ID NO:72 and/or in the light chain set forth in any of SEQ ID NOS:3, 8, 10 or 13, other than replacement with E at a position corresponding to position 104 in the heavy chain.

8. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-7, comprising an additional amino acid replacement(s) in a variable heavy chain of the unmodified antibody, wherein:

the additional amino acid replacement(s) is/are at a position corresponding to a position selected from among positions 24, 25, 27, 53, 72, 97 and 111, with reference to amino acid positions set forth in SEQ ID NO: 2 or 7; and

the amino acid replacement(s) is/are selected from among V24E, S25C, S25V, F27R, S53G, D72L, R97H, and Q111P in addition to the replacement corresponding to Y104E.

9. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-8, comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NOS: 77, 78, 80, 81, 83, 84, 86, 87, 89, 90, 92, 93, 95, 96, 98, 99, 101, 102, 104, 105, 107, 108, 110, 111, 113, 114, 116, 117, 119, 120, 122, or 123; and

b) a variable light (VL) chain comprising the sequence of amino acids set forth in SEQ ID NO:4, 9 or 11.

10. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-9,

comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NO:74, 77 or 104; and

b) a variable light (VL) chain comprising the sequence of amino acids set forth in SEQ ID NO:4, 9 or 11; or

comprising:

a) a heavy chain region set forth in any of SEQ ID NOS: 76, 79, 82, 85, 88, 91, 94, 97, 100, 103, 106, 109, 112, 115, 118, or 121; and

b) a light chain region set forth in any of SEQ ID NOS: 3, 8, 10 or 13; or

comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NO:74, 75, 77, 78, 80, 81, 83, 84, 86, 87, 89, 90, 92, 93, 95, 96, 98, 99, 101, 102, 104, 105, 107, 108, 110, 111, 113, 114, 116, 117, 119, 120, 122, or 123; and

b) a variable light (VL) chain comprising the sequence of amino acids set forth in SEQ ID NO:125, 126 or 127; or

comprising:

a) a heavy chain comprising the sequence of amino acids set forth in any of SEQ ID NOS:72, 76, 79, 82, 85, 88, 91, 94, 97, 100, 103, 106, 109, 112, 115, 118, or 121; and

b) a light chain comprising the sequence of amino acids set forth in SEQ ID NO: 124.

11. The modified anti-EGFR antibody or antigen-binding fragment thereof, of claim 1 or claim 2 that has only the amino acid replacement Y104E in the variable heavy chain of an unmodified anti-EGFR antibody or antigen-binding fragment thereof, wherein:

the unmodified anti-EGFR antibody or antigen-binding fragment thereof is selected from among:

i) cetuximab or an antigen-binding fragment thereof comprising a variable heavy chain set forth in SEQ ID NO:2 or 7 and a variable light chain set forth in SEQ ID NOS: 4, 9 or 11;

ii) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:1 and the light chain sequence set forth in SEQ ID NO:3, or an antigen-binding fragment thereof

iii) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:5 and the light chain sequence set forth in SEQ ID NO:3, or an antigen-binding fragment thereof;

iv) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:12 and the light chain sequence set forth in SEQ ID NO:13, or an antigen-binding fragment thereof;

v) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:6 and the light chain sequence set forth in SEQ ID NO:8, or an antigen-binding fragment thereof;

vi) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:6 and the light chain sequence set forth in SEQ ID NO:10, or an antigen-binding fragment thereof; and

vii) a humanized form of any of i)-vi).

12. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-11 that comprises up to 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid replacements in the variable heavy chain set forth in SEQ ID NO: 61 or 63 and/or in the variable light chain set forth in SEQ ID NO: 183, 184 or 186, in addition to replacement with E at a position corresponding to position 104 in the heavy chain.

13. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-12, wherein the amino acid replacements are HC-Y104E/ HC-Q111P; HC-S25C/ HC-Y104E; HC-Y104E/LC-I29S; HC-Y104E/HC-Q111P/LC-I29S; HC-S53G/HC-Y104E; HC-S53G/HC-Y104E/HC-Q111P; HC-S25V/HC-Y104E; HC-S25V/HC-Y104E/HC-Q111P; HC-S25V/HC-S53G/HC-Y104E; HC-S25V/HC-S53G/HC-Y104E/HC-Q111P; HC-T30F/HC-Y104E; HC-T30F/HC-Y104E/HC-Q111P; HC-T30F/HC-S53G/HC-Y104E; HC-T30F/HC-S53G/HC-Y104E/HC-Q111P; HC-D72L/HC-Y104E; HC-D72L/HC-Y104E/HC-Q111P; HC-S53G/ HC-D72L/HC-Y104E; or HC-S53G/HC-D72L/HC-Y104E/HC-Q111P.

14 A modified anti-EGFR antibody, or antigen-binding fragment thereof of claim 1, comprising the heavy chain whose sequence is set forth in SEQ ID NO: 59 , and the light chain whose sequence is set forth in SEQ ID NO: 181, or is an antigen-binding fragment thereof.

15. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claim 1 or claim 2, comprising a sequence of amino acids selected from among:

s) the variable heavy chain set forth in SEQ ID NO: 241 or 243 , and the variable light chain set forth in SEQ ID NO: 274, 275 or 277 ;

t) the variable heavy chain set forth in SEQ ID NO: 223 or 225 , and the variable light chain set forth in SEQ ID NO: 274, 275 or 277 ;

u) the variable heavy chain set forth in SEQ ID NO: 229 or 231 , and the variable light chain set forth in SEQ ID NO: 274, 275 or 277 ;

v) the variable heavy chain set forth in SEQ ID NO: 235 or 237 , and the variable light chain set forth in SEQ ID NO: 281, 282 or 284 ;

w) the variable heavy chain set forth in SEQ ID NO: 247 or 249 , and the variable light chain set forth in SEQ ID NO: 281, 282 or 284 ;

x) the variable heavy chain set forth in SEQ ID NO: 223 or 225 , and the variable light chain set forth in SEQ ID NO: 281, 282 or 284 ;

y) the variable heavy chain set forth in SEQ ID NO: 229 or 231 , and the variable light chain set forth in SEQ ID NO: 281, 282 or 284 ;

z) the variable heavy chain set forth in SEQ ID NO: 235 or 237 , and the variable light chain set forth in SEQ ID NO: 288, 289 or 291 ;

aa) the variable heavy chain set forth in SEQ ID NO: 247 or 249 , and the variable light chain set forth in SEQ ID NO: 288, 289 or 291 ;

bb) the variable heavy chain set forth in SEQ ID NO: 223 or 225 , and the variable light chain set forth in SEQ ID NO: 288, 289 or 291 ;

cc) the variable heavy chain set forth in SEQ ID NO: 229 or 231 , and the variable light chain set forth in SEQ ID NO: 288, 289 or 291 ;

dd) the variable heavy chain set forth in SEQ ID NO: 235 or 237 , and the variable light chain set forth in SEQ ID NO: 295, 296 or 298 ;

ee) the variable heavy chain set forth in SEQ ID NO: 247 or 249 , and the variable light chain set forth in SEQ ID NO: 302, 303 or 305 ;

ff) the variable heavy chain set forth in SEQ ID NO: 211 or 213 , and the variable light chain set forth in SEQ ID NO: 302, 303 or 305 ;

gg) the variable heavy chain set forth in SEQ ID NO: 211 or 213 , and the variable light chain set forth in SEQ ID NO: 281, 282 or 284 ; and

hh) the variable heavy chain set forth in SEQ ID NO: 211 or 213 , and the variable light chain set forth in SEQ ID NO: 288, 289 or 291.

16. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 15, comprising the variable heavy chain set forth in SEQ ID NO: 137 and the variable light chain set forth in SEQ ID NO: 183.

17. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 1 or claim 2, that is a full-length antibody, wherein the antibody comprises a sequence of amino acids selected from among:

a) the heavy chain set forth in SEQ ID NO: 129 , and the light chain set forth in SEQ ID NO: 153 ;

b) the heavy chain set forth in SEQ ID NO: 129 , and the light chain set forth in SEQ ID NO: 160 ;

c) the heavy chain set forth in SEQ ID NO: 135 , and the light chain set forth in SEQ ID NO: 153 ;

d) the heavy chain set forth in SEQ ID NO: 129 , and the light chain set forth in SEQ ID NO: 167 ;

e) the heavy chain set forth in SEQ ID NO: 129 , and the light chain set forth in SEQ ID NO: 174 ;

f) the heavy chain set forth in SEQ ID NO: 129 , and the light chain set forth in SEQ ID NO: 181 ;

g) the heavy chain set forth in SEQ ID NO: 135 , and the light chain set forth in SEQ ID NO: 181 ;

h) the heavy chain set forth in SEQ ID NO: 129 , and the light chain set forth in SEQ ID NO: 188 ;

i) the heavy chain set forth in SEQ ID NO: 141 , and the light chain set forth in SEQ ID NO: 181 ;

j) the heavy chain set forth in SEQ ID NO: 147 , and the light chain set forth in SEQ ID NO: 195 ;

k) the heavy chain set forth in SEQ ID NO: 141 , and the light chain set forth in SEQ ID NO: 195 ;

l) the heavy chain set forth in SEQ ID NO: 147 , and the light chain set forth in SEQ ID NO: 202 ;

m) the heavy chain set forth in SEQ ID NO: 141 , and the light chain set forth in SEQ ID NO: 202 ;

n) the heavy chain set forth in SEQ ID NO: 209 , and the light chain set forth in SEQ ID NO: 251 ;

o) the heavy chain set forth in SEQ ID NO: 215 , and the light chain set forth in SEQ ID NO: 251 ;

p) the heavy chain set forth in SEQ ID NO: 221 , and the light chain set forth in SEQ ID NO: 258 ;

q) the heavy chain set forth in SEQ ID NO: 227 , and the light chain set forth in SEQ ID NO: 258 ;

18. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 6, wherein the modified anti-EGFR antibody comprises:

a) a heavy chain comprising the sequence of amino acids set forth in SEQ ID NO:72; and

b) a light chain comprising the sequence of amino acids set forth in SEQ ID NO:8.

19. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 1 or claim 2, comprising a sequence of amino acids containing the variable heavy chain set forth in SEQ ID NO: 61 and the variable light chain set forth in SEQ ID NO: 183.

20. The modified anti-EGFR antibody, or antigen-binding fragment thereof of any of claims 1-19, wherein the unmodified antibody or antigen-binding fragment thereof is humanized.

21. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 20, wherein the humanized unmodified anti-EGFR antibody or antigen-binding fragment thereof comprises:

a variable heavy chain set forth in SEQ ID NO: 14 and variable light chain set forth in SEQ ID NO: 15; or

a variable heavy chain set forth in SEQ ID NO: 16 and a variable light chain set forth in SEQ ID NO: 17.

22. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-21 that is a full-length antibody.

23. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-21 that is an antigen-binding fragment selected from among Fab, Fab', $F(ab')_2$, single-chain Fv (scFv), Fv, dsFv, diabody, Fd and Fd' fragments.

24. A conjugate, comprising the modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-23 linked directly or indirectly via a chemical or physical bond to a targeted agent, wherein the targeted agent is for delivery to a tumor that expresses EGFR.

25. A conjugate, comprising the modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 19 linked directly or indirectly via a linker (L) to a targeted agent, wherein the targeted agent is for delivery to a tumor that expresses EGFR.

26. The conjugate of claim 24 or claim 25, comprising the following components: (Ab), $(L)_q$, and $(\text{targeted agent})_m$, wherein:

the conjugate has the following formula: $Ab - [(L)_q - (\text{targeted agent})_m]$;

Ab is the modified anti-EGFR antibody or antigen-binding fragment thereof that binds to EGFR;

L is a linker links the Ab to the targeted agent;

m is an integer that is at least 1;

q is 0 to 8;

the resulting conjugate binds to the EGFR.

27. The conjugate of claim 26, wherein m is 1 to 8 and q is 0 to 4.

28. The conjugate of any of claims 24-27, wherein the targeted agent is a protein, peptide, nucleic acid or small molecule.

29. The conjugate of any of claims 24-27, wherein the targeted agent is a cytotoxic moiety, a radioisotope, a chemotherapeutic agent, a lytic peptide or a cytokine.

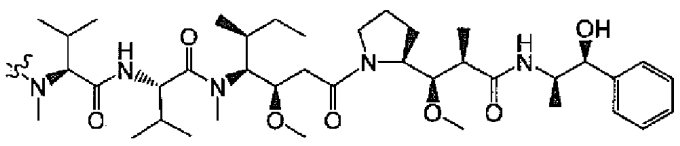
30. The conjugate of any of claims 24-29, wherein the targeted agent is an auristatin.

31. The conjugate of any of claims 24-30, wherein the linker L is selected from among N-succinimidyl-4(2-pyridylthio)propanoate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate(SMCC) and N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP).

32. The conjugate of any of claims 24-31, wherein the targeted agent is an auristatin or a functional peptide analog or derivative thereof that is monomethyl auristatin E (MMAE) or F (MMAF).

33. The conjugate of claim 32, wherein the therapeutic moiety is MMAE; and

MMAE has the structure:



or a pharmaceutically acceptable salt form thereof.

34. A nucleic acid molecule(s), comprising a sequence of nucleotides encoding a modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-23; or

comprising a sequence of nucleotides encoding the heavy chain of the modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-23.

35. A vector, comprising the nucleic acid molecule(s) of claim 34.

36. A cell, comprising a vector of claim 35.

37. A method of making a modified anti-EGFR antibody, or antigen-binding fragment thereof, comprising expressing the heavy chain or light chain encoded from a vector or vectors of claim 35 encoding the heavy chain and the light chain in a suitable host cell to produce the antibody; and, optionally, recovering the antibody.

38. A pharmaceutical composition comprising:

the modified anti-EGFR antibody or antigen-binding fragment of any of claims 1-23, or conjugate of any of claims 24-33; and

a pharmaceutically acceptable carrier or excipient.

39. Use of a pharmaceutical composition of claim 38, for formulation of a medicament for treating a condition responsive to treatment with an anti-EGFR antibody in a subject, wherein the condition is a tumor that expresses EGFR.

40. A pharmaceutical composition of claim 38 for use in treating a condition responsive to treatment with an anti-EGFR antibody in a subject, wherein the condition is a tumor that expresses EGFR.

41. Use of the modified anti-EGFR antibody of any of claims 1-23 or conjugate of any of claims 24-33 for formulation of a medicament for treating a condition responsive to treatment with an anti-EGFR antibody in a subject, wherein the condition is a tumor that expresses EGFR.

42. The use of claim 39 or claim 41, or the pharmaceutical composition of claim 40, wherein the condition responsive to treatment with an anti-EGFR antibody is head and neck cancer, non-small cell lung cancer or colorectal cancer.

43. The use of claim 39 or claim 41, or the pharmaceutical composition of claim 40, wherein the condition responsive to treatment with an anti-EGFR antibody is breast cancer.

44. The anti-EGFR antibody, or antigen-binding fragment thereof, of claim 15, comprising the variable heavy chain set forth in SEQ ID NO: 137 and the variable light chain set forth in SEQ ID NO: 183.

45. A conjugate, comprising an anti-EGFR antibody, or antigen-binding fragment thereof, of claim 44 linked directly or indirectly to a therapeutic moiety.

46. The conjugate of claim 45, wherein the therapeutic moiety is an auristatin.

47. The conjugate of claim 46, wherein the auristatin is monomethyl auristatin E (MMAE).