CLAIMS:

1. A modified anti-EGFR antibody, or antigen-binding fragment thereof, comprising the amino acid replacement Y104D in the variable heavy chain of the unmodified antibody, wherein:

the modified anti-EGFR antibody or antigen-binding fragment thereof comprises a variable heavy (VH) chain and a variable light (VL) chain, or a portion thereof that is sufficient to bind EGFR antigen, whereby one or both of the VH or VL is modified;

the portion thereof is sufficient to form an antigen binding site and contains the amino acid replacement;

the unmodified anti-EGFR antibody is selected from among:

i) cetuximab, or an antigen-binding fragment thereof, comprising a variable heavy chain set forth in SEQ ID NO:3 and a variable light chain set forth in SEQ ID NO:4 or 10;

ii) a variant of i) comprising a variable heavy chain having a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:3, and a variable light chain having a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:4 or 10, wherein the variant does not comprise the amino acid replacement and specifically binds to EGFR; and

iii) a humanized form of i) or ii).

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

the modified anti-EGFR antibody, or antigen-binding fragment thereof, exhibits a ratio of binding activity to human epidermal growth factor receptor (EGFR) or a soluble fragment thereof under conditions in a tumor environment compared to under conditions in a non-tumor environment of at least 2.0 or at least 3.0;

conditions in a tumor environment comprise one or both of pH between or about between 6.0 to 6.5 or lactate concentration between or about between 5 mM to 20 mM, and protein concentration of 10 mg/mL to 50 mg/mL;

conditions in a non-tumor environment comprise one or both of pH of about 7.4 or lactate concentration between or about between 0.5 mM to 5 mM, and protein concentration of 10 mg/mL to 50 mg/mL , whereby the anti-EGFR antibody or fragment thereof is conditionally active under conditions in a tumor microenvironment.

3. The anti-EGFR antibody, or antigen-binding fragment thereof, of claim 1 , wherein the anti-EGFR antibody, or antigen-binding fragment thereof, exhibits the ratio of activity under conditions that exist in a tumor microenvironment that comprise a pH of between or about between 6.0 to 6.5 compared to under conditions that exist in a non-tumor microenvironment that comprise a pH of about 7.4.

4. The anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-3, wherein the anti-EGFR antibody or, or antigen-binding fragment thereof, exhibits the ratio of activity under conditions of a tumor microenvironment that comprise pH of 6.0 to 6.5 and lactate concentration of 10 mM to 20 mM compared to under condition of a non-tumor microenvironment that comprise pH of 7.0 to 7.4, inclusive, and lactate concentration of 0.5 mM to 2 mM.

5. The anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-4 , wherein the protein concentration under conditions in a tumor microenvironment and under conditions in a non-tumor microenvironment is substantially the same or is the same.

6. The anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-5, comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NO:495, 1062, 1112, 1114-1117, 1124-1126, 1128-1130, 1134-1137, or 1146-1152, or a sequence of amino acids that exhibits at least 85% sequence identity to any of SEQ ID NOS: 495, 1062, 1112, 1114-1117, 1124-1126, 1128-1130, 1134-1137, or 1146-1152; and

b) a variable light (VL) chain comprising the sequence of amino acids set forth in SEQ ID NO:4, 10, 1138-1145, 1153-1159 or 1186, or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4, 10, 1138-1145, 1153-1159 or 1186.

7. The anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-6, selected from among an antibody comprising:

a) the variable heavy chain set forth in SEQ ID NO:495 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:495, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

b) the variable heavy chain set forth in SEQ ID NO:1062 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1062, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

c) the variable heavy chain set forth in SEQ ID NO:1112 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1112, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

d) the variable heavy chain set forth in SEQ ID NO:1114 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1114, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

e) the variable heavy chain set forth in SEQ ID NO:1115 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1115, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

f) the variable heavy chain set forth in SEQ ID NO:1116 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1116, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

g) the variable heavy chain set forth in SEQ ID NO:1117 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1117, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

h) the variable heavy chain set forth in SEQ ID NO:1124 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1124, and the variable light chain set forth

in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

i) the variable heavy chain set forth in SEQ ID NO:1125 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1125, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

j) the variable heavy chain set forth in SEQ ID NO:1126 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1126, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

k) the variable heavy chain set forth in SEQ ID NO:1128 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1128, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

l) the variable heavy chain set forth in SEQ ID NO:1129 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1129, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

m) the variable heavy chain set forth in SEQ ID NO:1130 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1130, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

n) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1138 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1138;

o) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1139 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1139;

p) the variable heavy chain set forth in SEQ ID NO:1135 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1135, and the variable light chain set forth in SEQ ID NO:1138 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1138;

q) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1140 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1140;

r) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1141 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1141;

s) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth

in SEQ ID NO:1142 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1142;

t) the variable heavy chain set forth in SEQ ID NO:1135 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1135, and the variable light chain set forth in SEQ ID NO:1142 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1142;

u) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1143 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1143;

v) the variable heavy chain set forth in SEQ ID NO:1136 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1136, and the variable light chain set forth in SEQ ID NO:1142 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1142;

w) the variable heavy chain set forth in SEQ ID NO:1137 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1137, and the variable light chain set forth in SEQ ID NO:1144 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1144;

x) the variable heavy chain set forth in SEQ ID NO:1136 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1136, and the variable light chain set forth in SEQ ID NO:1144 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1144;

y) the variable heavy chain set forth in SEQ ID NO:1137 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1137, and the variable light chain set forth in SEQ ID NO:1145 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1145;

z) the variable heavy chain set forth in SEQ ID NO:1136 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1136, and the variable light chain set forth in SEQ ID NO:1145 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1145;

aa) the variable heavy chain set forth in SEQ ID NO:1146 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1146, and the variable light chain set forth in SEQ ID NO:1153 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1153;

bb) the variable heavy chain set forth in SEQ ID NO:1147 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1147, and the variable light chain set forth in SEQ ID NO:1153 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1153;

cc) the variable heavy chain set forth in SEQ ID NO:1148 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1148, and the variable light chain set forth in SEQ ID NO:1154 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1154;

dd) the variable heavy chain set forth in SEQ ID NO:1149 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1149, and the variable light chain set forth

in SEQ ID NO:1154 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1154;

ee) the variable heavy chain set forth in SEQ ID NO:1150 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1150, and the variable light chain set forth in SEQ ID NO:1155 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1155;

ff) the variable heavy chain set forth in SEQ ID NO:1151 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1151, and the variable light chain set forth in SEQ ID NO:1156 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1156;

gg) the variable heavy chain set forth in SEQ ID NO:1146 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1146, and the variable light chain set forth in SEQ ID NO:1156 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1156;

hh) the variable heavy chain set forth in SEQ ID NO:1149 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1149, and the variable light chain set forth in SEQ ID NO:1156 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1156;

ii) the variable heavy chain set forth in SEQ ID NO:1150 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1150, and the variable light chain set forth in SEQ ID NO:1157 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1157;

jj) the variable heavy chain set forth in SEQ ID NO:1152 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1152, and the variable light chain set forth in SEQ ID NO:1157 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1157;

kk) the variable heavy chain set forth in SEQ ID NO:1148 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1148, and the variable light chain set forth in SEQ ID NO:1157 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1157;

ll) the variable heavy chain set forth in SEQ ID NO:1149 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1149, and the variable light chain set forth in SEQ ID NO:1157 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1157;

mm) the variable heavy chain set forth in SEQ ID NO:1150 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1150, and the variable light chain set forth in SEQ ID NO:1186 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1186;

nn) the variable heavy chain set forth in SEQ ID NO:1152 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1152, and the variable light chain set forth in SEQ ID NO:1186 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1186;

oo) the variable heavy chain set forth in SEQ ID NO:1148 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1148, and the variable light chain set forth

in SEQ ID NO:1186 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1186;

pp) the variable heavy chain set forth in SEQ ID NO:1149 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1149, and the variable light chain set forth in SEQ ID NO:1186 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1186;

qq) the variable heavy chain set forth in SEQ ID NO:1150 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1150, and the variable light chain set forth in SEQ ID NO:1158 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1158;

rr) the variable heavy chain set forth in SEQ ID NO:1152 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1152, and the variable light chain set forth in SEQ ID NO:1159 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1159;

ss) the variable heavy chain set forth in SEQ ID NO:1146 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1146, and the variable light chain set forth in SEQ ID NO:1159 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1159;

tt) the variable heavy chain set forth in SEQ ID NO:1146 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1146, and the variable light chain set forth in SEQ ID NO:1157 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1157;

uu) the variable heavy chain set forth in SEQ ID NO:1146 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1146, and the variable light chain set forth in SEQ ID NO:1186 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1186; and

vv) the variable heavy chain set forth in SEQ ID NO:1118 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1118, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10.

8. The anti-EGFR antibody, or antigen-binding fragment thereof, of claim 6 or claim 7, wherein sequence identity is at least 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 98%, 99% or more.

9. The modified anti-EGFR antibody or fragment thereof of claim 1, wherein:

a) the variable heavy chain, or portion thereof, of the modified anti-EGFR antibody contains an amino acid replacement corresponding to an amino acid replacement selected from among V24E, V24I, V24L, S25C, S25H, S25R, S25A, S25D, S25G, S25M, S25Q, S25V, S25L, S28C, L29H, N31H, G54D, G54S, F63R, F63C, F63M, F63P, F63S, T64V, L67G, D72L, D72P, D72W, N73Q, K75H, K75G, K75P, K75W, S76I, S76V, Q77E, T100P, Y104S, Y104V, Q111I and Q111V, with reference to amino acid positions set forth in SEQ ID NO:3, wherein:

corresponding amino acid positions are identified by alignment of the VH chain of the antibody with the VH chain set forth in SEQ ID NO:3; and

the portion thereof is sufficient to form an antigen binding site and contains the amino acid replacement; and/or

b) the variable light chain, or portion thereof, of the modified anti-EGFR antibody contains an amino acid replacement corresponding to an amino acid replacement selected from among L4F, L4V, T5P and R24G, with reference to amino acid positions set forth in SEQ ID NO:4, wherein:

corresponding amino acid positions are identified by alignment of the VL chain of the antibody with the VL chain set forth in SEQ ID NO:4; and

the portion thereof is sufficient to form an antigen binding site and contains the amino acid replacement.

10. The modified anti-EGFR antibody of claim 9, wherein:

the variable heavy chain, or portion thereof, of the modified anti-EGFR antibody contains a further amino acid replacement selected from among V24E, S25C, S25V, F27R, T30F, S53G, D72L, R97H, Y104D and Q111P.

11. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-10, wherein the unmodified cetuximab antibody, antigen-binding fragment thereof or variant thereof comprises:

a heavy chain having a sequence of amino acids set forth in SEQ ID NO:1 or a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:1 and a light chain having a sequence of amino acids set forth SEQ ID NO:2 or a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:2; or

a heavy chain having a having a sequence of amino acids set forth in SEQ ID NO: 8 or a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:8 and a light chain having a sequence of amino acids set forth SEQ ID NO:9 or a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:9.

12. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-11, wherein the unmodified anti-EGFR antibody is humanized.

13. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 12 wherein the unmodified anti-EGFR antibody comprises the variable heavy chain set forth in SEQ ID NO:28 and the variable light chain set forth in SEQ ID NO:29.

14. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-13, wherein:

the unmodified anti-EGFR antibody is an antigen-binding fragment; and

the antigen-binding fragment is selected from among a Fab, Fab', $F(ab')_2$, single-chain Fv (scFv), Fv, dsFv, diabody, Fd and Fd' fragments.

15. The modified anti-EGFR antibody or antigen binding fragment of any of claims 1-14 that is a full-length IgG antibody or is an antigen-binding fragment selected from among a Fab, Fab', $F(ab')_2$, single-chain Fv (scFv), Fv, dsFv, diabody, Fd and Fd' fragments.

16. A conjugate, comprising a modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-15 linked directly or indirectly to a targeted agent.

17. The conjugate of claim 16, wherein the targeted agent is a therapeutic moiety.

18. The conjugate of claim 17, wherein the therapeutic moiety is a cytotoxic moiety, a radioisotope, a chemotherapeutic agent, a lytic peptide or a cytokine.

19. The conjugate of claim 18, wherein the therapeutic moiety is selected from among taxol; cytochalasin B; gramicidin D; ethidium bromide; emetine; mitomycin; etoposide; tenoposide; vincristine; vinblastine; colchicin; doxorubicin; daunorubicin; dihydroxy anthracin dione; maytansine or an analog or derivative thereof; an auristatin or a functional peptide analog or derivative thereof; dolastatin 10 or 15 or an analogue thereof; irinotecan or an analogue thereof; mitoxantrone; mithramycin; actinomycin D; 1-dehydrotestosterone; a glucocorticoid; procaine; tetracaine; lidocaine; propranolol; puromycin; calicheamicin or an analog or derivative thereof; an antimetabolite; an alkylating agent; a platinum derivative; duocarmycin A, duocarmycin SA, rachelmycin (CC-1065), or an analog or derivative thereof; an antibiotic; pyrrolo[2,l-c][l, 4]-benzodiazepines (PDB); a toxin; ribonuclease (RNase); DNase I, Staphylococcal enterotoxin A; and pokeweed antiviral protein.

20. The conjugate of claim 18 or claim 19, wherein the therapeutic moiety is a maytansine derivative that is a maytansinoids selected from among ansamitocin or mertansine (DM1) or is an auristatin or a functional peptide analog or derivative thereof that is monomethyl auristatin E (MMAE) or F (MMAF); or isis an antimetabolite selected from among methotrexate, 6 mercaptopurine, 6 thioguanine, cytarabine, fludarabin, 5 fluorouracil, decarbazine, hydroxyurea, asparaginase, gemcitabine, and cladribine; or is

an alkylating agent selected from among mechlorethamine, thioepa, chlorambucil, melphalan, carmustine (BSNU), lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, dacarbazine (DTIC), procarbazine and mitomycin C; or is a platinum derivative that is cisplatin or carboplatin or is an antibiotic selected from among dactinomycin, bleomycin, daunorubicin, doxorubicin, idarubicin, mithramycin, mitomycin, mitoxantrone, plicamycin and anthramycin (AMC); or is a toxin selected from among a diphtheria toxin and active fragments thereof and hybrid molecules, a ricin toxin, cholera toxin, a Shiga-like toxin, LT toxin, C3 toxin, Shiga toxin, pertussis toxin, tetanus toxin, soybean Bowman-Birk protease inhibitor, Pseudomonas exotoxin, alorin, saporin, modeccin, gelanin, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolacca americana proteins, momordica charantia inhibitor, curcin, crotin, , gelonin, mitogellin, restrictocin, phenomycin, and enomycin toxins.

21. A nucleic acid molecule, comprising a sequence of nucleotides encoding the heavy chain of any of the anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-15; and/or

a nucleic acid molecule, comprising a sequence of nucleotides encoding the light chain of any of the anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-15.

22. A vector, comprising the nucleic acid molecule(s) of claim 21.

23. A cell, comprising a vector or vectors of claim 22.

24. 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 22 encoding the heavy chain and the light chain in a suitable host cells and recovering the antibody.

25. A pharmaceutical composition comprising:

a modified anti-EGFR antibody or antigen-binding fragment of any of claims 1-15 or a conjugate of any of claims 16-20; and

a pharmaceutically acceptable carrier or excipient.

26. The pharmaceutical composition claim 25 for treating a tumor, cancer or metastasis.

27. Use of a modified anti-EGFR antibody or antigen-binding fragment of any of claims 1-15 or a conjugate of any of claims 16-20 for preparation of a medicament for treating a tumor, cancer or metastasis.

CLAIMS:

1. A modified anti-EGFR antibody, or antigen-binding fragment thereof, comprising replacement with aspartic acid at a position corresponding to position 104 (Y104D) in the variable heavy chain of the unmodified antibody, wherein:

the modified anti-EGFR antibody or antigen-binding fragment thereof comprises a variable heavy (VH) chain and a variable light (VL) chain, or a portion thereof that is sufficient to bind EGFR antigen, whereby the VH alone or both the VH and VL is modified;

the portion thereof is sufficient to form an antigen binding site and contains the Y104D amino acid replacement;

corresponding amino acid positions are identified by alignment of the VH chain of the antibody with the VH chain set forth in SEQ ID NO:3;

the modified anti-EGFR antibody, or antigen-binding fragment thereof, specifically binds to epidermal growth factor receptor (EGFR) or a soluble fragment thereof, and contains up to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11 amino acid replacements, including Y104D, in the unmodified antibody or antigen-binding fragment;

the unmodified anti-EGFR antibody is selected from among:

i) cetuximab, comprising (a) a variable heavy chain set forth in SEQ ID NO:3 and a variable light chain set forth in SEQ ID NO:4 or 10, or (b) a heavy chain set forth in SEQ ID NO:1 and a light chain set forth in SEQ ID NO:2, or an antigen-binding fragment thereof;

ii) an antibody comprising a heavy chain set forth in SEQ ID NO:8 and a light chain set forth in SEQ ID NO:9, or an antigen-binding fragment thereof;

iii) a Fab fragment comprising a heavy chain set forth in SEQ ID NO:5 and a light chain set forth in SEQ ID NO:2, or an antigen-binding fragment thereof; and

iv) a humanized form of i), ii) or iii) ; and

the modified anti-EGFR antibody, or antigen-binding fragment thereof, is conditionally active in a tumor environment and exhibits a ratio of binding activity to human epidermal growth factor receptor (EGFR) or a soluble fragment thereof under conditions in a tumor environment compared to under conditions in a non-tumor environment of at least 1.7, wherein;

conditions in a tumor environment comprise one or both of pH between 6.0 to 6.5 or lactate concentration between 5 mM to 20 mM, and protein concentration of 10 mg/mL to 50 mg/mL; and

conditions in a non-tumor environment comprise one or both of pH between 7.0 to 7.8 or lactate concentration between 0.5 mM to 5 mM, and protein concentration of 10 mg/mL to 50 mg/mL.

2. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 1, wherein the ratio of binding activity is at least 2.0 or at least 3.0.

3. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 1, wherein the anti-EGFR antibody, or antigen-binding fragment thereof, exhibits the ratio of activity under conditions that exist in a tumor microenvironment that comprise a pH of between or about between 6.0 to 6.5 compared to under conditions that exist in a non-tumor microenvironment that comprise a pH of about 7.4.

4. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-3, wherein the anti-EGFR antibody or, or antigen-binding fragment thereof, exhibits the ratio of activity under conditions of a tumor microenvironment that comprise pH of 6.0 to 6.5 and lactate concentration of 10 mM to 20 mM compared to under condition of a non-tumor microenvironment that comprise pH of 7.0 to 7.4, inclusive, and lactate concentration of 0.5 mM to 2 mM.

5. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-4, wherein the protein concentration under conditions in a tumor microenvironment and under conditions in a non-tumor microenvironment is substantially the same or is the same.

6. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-5, selected from among:

i) an antibody, comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NO:495, 1062, 1112, 1114-1117, 1124-1126 or 1128-1130; and

b) a variable light (VL) chain comprising the sequence of amino acids set forth in SEQ ID NO:4 or 10,

ii) antigen-binding fragments of the antibody of i); and

iii) humanized variants of i) or ii).

7. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 1, selected from among an antibody comprising:

a) the variable heavy chain set forth in SEQ ID NO:495 and the variable light chain set forth in SEQ ID NO:4 or 10 ;

b) the variable heavy chain set forth in SEQ ID NO:1062 and the variable light chain set forth in SEQ ID NO:4 or 10 ;

c) the variable heavy chain set forth in SEQ ID NO:1112 and the variable light chain set forth in SEQ ID NO:4 or 10 ;

d) the variable heavy chain set forth in SEQ ID NO:1114 and the variable light chain set forth in SEQ ID NO:4 or 10 ;

e) the variable heavy chain set forth in SEQ ID NO:1115 and the variable light chain set forth in SEQ ID NO:4 or 10 ;

f) the variable heavy chain set forth in SEQ ID NO:1116 and the variable light chain set forth in SEQ ID NO:4 or 10 ;

g) the variable heavy chain set forth in SEQ ID NO:1117 and the variable light chain set forth in SEQ ID NO:4 or 10 ;

h) the variable heavy chain set forth in SEQ ID NO:1124 and the variable light chain set forth in SEQ ID NO:4 or 10 ;

i) the variable heavy chain set forth in SEQ ID NO:1125 and the variable light chain set forth in SEQ ID NO:4 or 10 ;

j) the variable heavy chain set forth in SEQ ID NO:1126 and the variable light chain set forth in SEQ ID NO:4 or 10 ;

k) the variable heavy chain set forth in SEQ ID NO:1128 and the variable light chain set forth in SEQ ID NO:4 or 10 ;

l) the variable heavy chain set forth in SEQ ID NO:1129 and the variable light chain set forth in SEQ ID NO:4 or 10 ;

m) the variable heavy chain set forth in SEQ ID NO:1130 and the variable light chain set forth in SEQ ID NO:4 or 10 ; and

n) the variable heavy chain set forth in SEQ ID NO:1118 and the variable light chain set forth in SEQ ID NO:4 or 10 .

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

a) the variable heavy chain, or portion thereof, of the modified anti-EGFR antibody further contains an amino acid replacement corresponding to an amino acid replacement selected from among V24E, V24I, V24L, S25C, S25H, S25R, S25A, S25D, S25G, S25M, S25Q, S25V, S25L, F27R, L29H, T30F, N31H, S53G, G54D, G54S F63R, F63C, F63M, F63S, T64V, D72L, D72W, N73Q, K75H, K75W, Q77E, R97H, T100P, Q111P and Q111V, with reference to amino acid positions set forth in SEQ ID NO:3, wherein:

corresponding amino acid positions are identified by alignment of the VH chain of the antibody with the VH chain set forth in SEQ ID NO:3; and

the portion thereof is sufficient to form an antigen binding site and contains the amino acid replacement; and/or

b) the variable light chain, or portion thereof, of the modified anti-EGFR antibody contains an amino acid replacement corresponding to an amino acid replacement selected from among L4C, L4F, L4V, T5P, R24G and I29S, with reference to amino acid positions set forth in SEQ ID NO:4, wherein:

corresponding amino acid positions are identified by alignment of the VL chain of the antibody with the VL chain set forth in SEQ ID NO:4; and

the portion thereof is sufficient to form an antigen binding site and contains the amino acid replacement.

9. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-8, comprising up to 5 amino acid replacements, including Y104D.

10. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 9, wherein the amino acid replacements are HC-Y104D; HC-Y104D/ HC-Q111P; HC-S25C/ HC-Y104D; HC-Y104D/LC-I29S; HC-S53G/HC-Y104D; HC-S53G/HC-Y104D/HC-Q111P; HC-S25V/HC-Y104D; HC-S25V/HC-Y104D/HC-Q111P; HC-S25V/HC-S53G/HC-Y104D; HC-S25V/HC-S53G/HC-Y104D/HC-Q111P; HC-T30F/HC-Y104D; HC-T30F/HC-Y104D/HC-Q111P; HC-T30F/HC-S53G/HC-Y104D; HC-T30F/HC-S53G/HC-Y104D/HC-Q111P; HC-D72L/HC-Y104D; HC-D72L/HC-Y104D/HC-Q111P; HC-S53G/ HC-D72L/HC-Y104D or HC-S53G/HC-D72L/HC-Y104D/HC-Q111P.

11. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-10, wherein the unmodified cetuximab antibody, antigen-binding fragment thereof or variant thereof comprises:

a heavy chain having a sequence of amino acids set forth in SEQ ID NO:1 and a light chain having a sequence of amino acids set forth SEQ ID NO:2 ; or

a heavy chain having a having a sequence of amino acids set forth in SEQ ID NO: 8 and a light chain having a sequence of amino acids set forth SEQ ID NO:9 .

12. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-11, wherein the unmodified anti-EGFR antibody is a humanized form of i), ii) or iii).

13. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 12, wherein the unmodified anti-EGFR antibody comprises the variable heavy chain set forth in SEQ ID NO:28 and the variable light chain set forth in SEQ ID NO:29.

14. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-13, wherein:

the unmodified anti-EGFR antibody is an antigen-binding fragment; and

the antigen-binding fragment is selected from among a Fab, Fab', $F(ab')_2$, single-chain Fv (scFv), Fv, dsFv, diabody, Fd and Fd' fragments.

15. The modified anti-EGFR antibody, or antigen binding fragment thereof, of any of claims 1-14 that is a full-length IgG antibody or is an antigen-binding fragment selected from among a Fab, Fab', $F(ab')_2$, single-chain Fv (scFv), Fv, dsFv, diabody, Fd and Fd' fragments.

16. A conjugate, comprising a modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-15 linked directly or indirectly to a targeted agent.

17. The conjugate of claim 16, wherein the targeted agent is a therapeutic moiety.18. The conjugate of claim 17, wherein the therapeutic moiety is a cytotoxic moiety, a radioisotope, a chemotherapeutic agent, a lytic peptide or a cytokine.

19. The conjugate of claim 18, wherein the therapeutic moiety is selected from among taxol; cytochalasin B; gramicidin D; ethidium bromide; emetine; mitomycin; etoposide; tenoposide; vincristine; vinblastine; colchicin; doxorubicin; daunorubicin; dihydroxy anthracin dione; maytansine or an analog or derivative thereof; an auristatin or a functional peptide analog or derivative thereof; dolastatin 10 or 15 or an analogue thereof; irinotecan or an analogue thereof; mitoxantrone; mithramycin; actinomycin D; 1-dehydrotestosterone; a glucocorticoid; procaine; tetracaine; lidocaine; propranolol; puromycin; calicheamicin or an analog or derivative thereof; an antimetabolite; an alkylating agent; a platinum derivative; duocarmycin A, duocarmycin SA, rachelmycin (CC-1065), or an analog or derivative thereof; an antibiotic; pyrrolo[2,1-c][1, 4]-benzodiazepines (PDB); a toxin; ribonuclease (RNase); DNase I, Staphylococcal enterotoxin A; and pokeweed antiviral protein.

20. The conjugate of claim 18 or claim 19, wherein the therapeutic moiety is a maytansine derivative that is a maytansinoid selected from among ansamitocin or mertansine (DM1); or is

an auristatin or a functional peptide analog or derivative thereof that is monomethyl auristatin E (MMAE) or F (MMAF); or is

an antimetabolite selected from among methotrexate, 6 mercaptopurine, 6 thioguanine, cytarabine, fludarabin, 5 fluorouracil, decarbazine, hydroxyurea, asparaginase, gemcitabine, and cladribine; or is

an alkylating agent selected from among mechlorethamine, thioepa, chlorambucil, melphalan, carmustine (BSNU), lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, dacarbazine (DTIC), procarbazine and mitomycin C; or is

a platinum derivative that is cisplatin or carboplatin; or is

an antibiotic selected from among dactinomycin, bleomycin, daunorubicin, doxorubicin, idarubicin, mithramycin, mitomycin, mitoxantrone, plicamycin and anthramycin (AMC); or is

a toxin selected from among a diphtheria toxin and active fragments thereof and hybrid molecules, a ricin toxin, cholera toxin, a Shiga-like toxin, LT toxin, C3 toxin, Shiga toxin, pertussis toxin, tetanus toxin, soybean Bowman-Birk protease inhibitor, Pseudomonas exotoxin, alorin, saporin, modeccin, gelanin, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolacca americana proteins, momordica charantia inhibitor, curcin, crotin,, gelonin, mitogellin, restrictocin, phenomycin, and enomycin toxins.

21. A nucleic acid molecule, selected from among one or more of:

a nucleic acid molecule, comprising a sequence of nucleotides encoding the heavy chain of the modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-15;

a nucleic acid molecule, comprising a sequence of nucleotides encoding the light chain of the modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-5 and 8-15 that comprises at least one amino acid replacement corresponding to an amino acid replacement selected from among L4F, L4V, T5P, R24G and I29S; and/or

a nucleic acid molecule, comprising a sequence of nucleotides encoding the modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-15.

22. A vector, comprising the nucleic acid molecule(s) of claim 21.

23. A cell, comprising a vector or vectors of claim 22.

24. A method of making a modified anti-EGFR antibody, or antigen-binding fragment thereof, comprising expressing the heavy chain, light chain or antibody encoded from a vector or vectors of claim 22 in a suitable host cell and recovering the antibody.

25. A pharmaceutical composition comprising:

a modified anti-EGFR antibody or antigen-binding fragment of any of claims 1-15 or a conjugate of any of claims 16-20; and

a pharmaceutically acceptable carrier or excipient.

26. The pharmaceutical composition claim 25 for use in treating a tumor, cancer or metastasis.

27. Use of a modified anti-EGFR antibody or antigen-binding fragment of any of claims 1-15 or a conjugate of any of claims 16-20 in the manufacture of a medicament for treating a tumor, cancer or metastasis.