

WHAT IS CLAIMED IS:

1. An isolated antibody or antigen binding fragment thereof that specifically binds to human epidermal growth factor receptor (EGFR), wherein the antibody or antigen binding fragment thereof comprises:
 - a) an immunoglobulin heavy chain variable region (VH) comprising a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 2 or 4, and a CDR3 sequence of SEQ ID NO: 3 or 5; and
 - b) an immunoglobulin light chain variable region (VL) comprising a CDR1 sequence of SEQ ID NO: 13 or 14, a CDR2 sequence of SEQ ID NO: 11, and a CDR3 sequence of SEQ ID NO: 12.
2. The isolated antibody or antigen binding fragment thereof of claim 1, wherein said antibody does not inhibit more than 20% proliferation of keratinocytes or MCF-10A epithelial cells at 60 nM or lower.
3. The antibody or antigen binding fragment thereof of claim 2, wherein said antibody (a) inhibits at least 80% of EGF and TGF α binding to A431 cells at a concentration of 10 nM or higher, or b) causes at least 50% inhibition of H292 or HCC827 tumor cell proliferation at 30 nM or higher.
4. The antibody or antigen binding fragment thereof of claim 3, wherein said antibody (a) inhibits at least 80% of EGF and TGF α binding to A431 cells at a concentration of 10 nM or higher, and (b) causes at least 50% inhibition of H292 or HCC827 tumor cell proliferation at 30 nM or higher.
5. The isolated antibody or antigen binding fragment thereof of any one of claims 1-4, wherein said antibody or antigen binding fragment thereof comprises (a) a VH sequence at least 90%, at least 95%, at least 99%, or 100% identical to the reference VH sequence of SEQ ID NO: 21 and (b) a VL sequence at least 90%, at least 95%, at least 99%, or 100% identical to the reference VL sequence of SEQ ID NO: 26.
6. An immunoconjugate having the formula (A) - (L) - (C), wherein:
 - (A) is the antibody or antigen binding fragment thereof of any one of claims 1-5;
 - (L) is the linker N-succinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (SMCC); and
 - (C) is the cytotoxic agent N(2')-deacetyl-N(2')-(3-mercapto-1-oxopropyl)-maytansine (DM1);and

wherein the linker (L) links (A) to (C).

7. An antibody or antigen binding fragment thereof that specifically binds to human EGFR, wherein said antibody does not inhibit more than 20% proliferation of keratinocytes or MCF-10A epithelial cells at 60 nM or lower.
8. The antibody or antigen binding fragment thereof of claim 7, wherein said antibody (a) inhibits at least 80% of EGF and TGF α binding to A431 cells at a concentration of 10 nM or higher, or b) causes at least 50% inhibition of H292 or HCC827 tumor cell proliferation at 30 nM or higher.
9. The antibody or antigen binding fragment thereof of claim 7, wherein said antibody (a) inhibits at least 80% of EGF and TGF α binding to A431 cells at a concentration of 10 nM or higher, and (b) causes at least 50% inhibition of H292 or HCC827 tumor cell proliferation at 30 nM or higher.
10. The antibody or antigen binding fragment thereof of any of claims 7-9, wherein the antibody comprises (a) a VH sequence at least 90%, at least 95%, at least 99%, or 100% identical to a reference VH sequence selected from the group consisting of SEQ ID NOs:19-23, 69, and 71-73; and (b) a VL sequence at least 90%, at least 95%, at least 99%, or 100% identical to a reference VL sequence selected from the group consisting of SEQ ID NOs:24-30 and 70.
11. The antibody or antigen binding fragment thereof of claim 10, which comprises:
 - a) SEQ ID NO:19 and SEQ ID NO:24;
 - b) SEQ ID NO:20 and SEQ ID NO:25;
 - c) SEQ ID NO:21 and SEQ ID NO:26;
 - d) SEQ ID NO:21 and SEQ ID NO:27;
 - e) SEQ ID NO:22 and SEQ ID NO:28;
 - f) SEQ ID NO:23 and SEQ ID NO:29;
 - g) SEQ ID NO:23 and SEQ ID NO:30;
 - h) SEQ ID NO:69 and SEQ ID NO:70;
 - i) SEQ ID NO:71 and SEQ ID NO:26;
 - j) SEQ ID NO:71 and SEQ ID NO:27;

- k) SEQ ID NO:72 and SEQ ID NO:26;
- l) SEQ ID NO:72 and SEQ ID NO:27;
- m) SEQ ID NO:73 and SEQ ID NO:26; or
- n) SEQ ID NO:73 and SEQ ID NO:27.

12. An antibody or antigen binding fragment thereof that competitively inhibits binding of a second antibody to human EGFR, wherein said second antibody comprises the heavy chain variable region of SEQ ID NO:21 and the light chain variable region of SEQ ID NOs: 26 or 27, and wherein the first antibody or antigen binding fragment: (a) inhibits at least 80% of epidermal growth factor (EGF) and transforming growth factor alpha (TGF α) binding to A431 cells at a concentration of 10 nM or higher, (b) causes at least 50% inhibition of H292 or HCC827 tumor cell proliferation at 30 nM or higher, or (c) does not inhibit more than 20% proliferation of keratinocytes or MCF-10A epithelial cells at 60 nM or lower.

13. An antibody or antigen binding fragment thereof produced by hybridoma selected from the group consisting of ATCC Deposit Designation PTA-11331, deposited with the ATCC on October 6, 2010, ATCC Deposit Designation PTA-11332, deposited with the ATCC on October 6, 2010, and ATCC Deposit Designation PTA-11333, deposited with the ATCC on October 6, 2010.

14. An antibody or antigen binding fragment thereof that specifically binds to the same EGFR epitope as an antibody selected from the group consisting of ATCC Deposit Designation PTA-11331, deposited with the ATCC on October 6, 2010, ATCC Deposit Designation PTA-11332, deposited with the ATCC on October 6, 2010, and ATCC Deposit Designation PTA-11333, deposited with the ATCC on October 6, 2010.

15. An antibody or antigen binding fragment thereof that competitively inhibits binding of a reference antibody to human EGFR, wherein said reference antibody is selected from the group consisting of ATCC Deposit Designation PTA-11331, deposited with the ATCC on October 6, 2010, ATCC Deposit Designation PTA-11332, deposited with the ATCC on October 6, 2010, and ATCC Deposit Designation PTA-11333, deposited with the ATCC on October 6, 2010, and wherein the antibody or antigen binding fragment: (a) inhibits at least 80% of epidermal growth factor (EGF) and transforming growth factor alpha (TGF α) binding to A431 cells at a concentration of 10 nM or higher, (b) causes at least 50% inhibition of H292 or HCC827 tumor cell proliferation at 30 nM or higher, or (c) does not inhibit more than 20% proliferation of keratinocytes or MCF-10A epithelial cells at 60 nM or lower.

16. An antibody or antigen binding fragment thereof that specifically binds to the same EGFR epitope as an antibody selected from the group consisting of:

- a) an antibody comprising the VH polypeptide of SEQ ID NO:19 and the VL polypeptide of SEQ ID NO:24;
- b) an antibody comprising the VH polypeptide of SEQ ID NO:20 and the VL polypeptide of SEQ ID NO:25;
- c) an antibody comprising the VH polypeptide of SEQ ID NO:21 and the VL polypeptide of SEQ ID NO:26;
- d) an antibody comprising the VH polypeptide of SEQ ID NO:21 and the VL polypeptide of SEQ ID NO:27;
- e) an antibody comprising the VH polypeptide of SEQ ID NO:22 and the VL polypeptide of SEQ ID NO:28;
- f) an antibody comprising the VH polypeptide of SEQ ID NO:23 and the VL polypeptide of SEQ ID NO:29;
- g) an antibody comprising the VH polypeptide of SEQ ID NO:23 and the VL polypeptide of SEQ ID NO:30;
- h) an antibody comprising the VH polypeptide of SEQ ID NO:69 and the VL polypeptide of SEQ ID NO:70;
- i) an antibody comprising the VH polypeptide of SEQ ID NO:71 and the VL polypeptide of SEQ ID NO:26;
- j) an antibody comprising the VH polypeptide of SEQ ID NO:71 and the VL polypeptide of SEQ ID NO:27;
- k) an antibody comprising the VH polypeptide of SEQ ID NO:72 and the VL polypeptide of SEQ ID NO:26;
- l) an antibody comprising the VH polypeptide of SEQ ID NO:72 and the VL polypeptide of SEQ ID NO:27;
- m) an antibody comprising the VH polypeptide of SEQ ID NO:73 and the VL polypeptide of SEQ ID NO:26; and

- n) an antibody comprising the VH polypeptide of SEQ ID NO:73 and the VL polypeptide of SEQ ID NO:27.

17. An antibody or antigen binding fragment thereof that competitively inhibits binding of a reference antibody to human EGFR, wherein said reference antibody is selected from the group consisting of:

- a) an antibody comprising the VH polypeptide of SEQ ID NO:19 and the VL polypeptide of SEQ ID NO:24;
- b) an antibody comprising the VH polypeptide of SEQ ID NO:20 and the VL polypeptide of SEQ ID NO:25;
- c) an antibody comprising the VH polypeptide of SEQ ID NO:21 and the VL polypeptide of SEQ ID NO:26;
- d) an antibody comprising the VH polypeptide of SEQ ID NO:21 and the VL polypeptide of SEQ ID NO:27;
- e) an antibody comprising the VH polypeptide of SEQ ID NO:22 and the VL polypeptide of SEQ ID NO:28;
- f) an antibody comprising the VH polypeptide of SEQ ID NO:23 and the VL polypeptide of SEQ ID NO:29;
- g) an antibody comprising the VH polypeptide of SEQ ID NO:23 and the VL polypeptide of SEQ ID NO:30;
- h) an antibody comprising the VH polypeptide of SEQ ID NO:69 and the VL polypeptide of SEQ ID NO:70;
- i) an antibody comprising the VH polypeptide of SEQ ID NO:71 and the VL polypeptide of SEQ ID NO:26;
- j) an antibody comprising the VH polypeptide of SEQ ID NO:71 and the VL polypeptide of SEQ ID NO:27;
- k) an antibody comprising the VH polypeptide of SEQ ID NO:72 and the VL polypeptide of SEQ ID NO:26;

- l) an antibody comprising the VH polypeptide of SEQ ID NO:72 and the VL polypeptide of SEQ ID NO:27;
 - m) an antibody comprising the VH polypeptide of SEQ ID NO:73 and the VL polypeptide of SEQ ID NO:26; and
 - n) an antibody comprising the VH polypeptide of SEQ ID NO:73 and the VL polypeptide of SEQ ID NO:27.
18. An antibody or antigen binding fragment thereof that specifically binds to human EGFR, wherein the antibody or antigen binding fragment thereof comprises:
- a) an immunoglobulin heavy chain variable region comprising CDR1, CDR2, and CDR3, which, with the exception of 1, 2, or 3 conservative amino acid substitutions, are respectively identical to the reference heavy chain CDR1 sequence of SEQ ID NO:1, the reference heavy chain CDR2 sequence of SEQ ID NO: 2, 4, 6, 63, or 64, and the reference heavy chain CDR3 sequence of SEQ ID NO: 3 or 5; and
 - b) an immunoglobulin a light chain variable region comprising CDR1, CDR2, and CDR3, which, with the exception of 1, 2, or 3 conservative amino acid substitutions, are respectively identical to the reference light chain CDR1 sequence of SEQ ID NO: 10, 13, or 14, the reference light chain sequence CDR2 of SEQ ID NO:11, and the reference light chain CDR3 sequence of SEQ ID NO: 12.
19. The antibody or antigen binding fragment thereof of claim 18, which comprises:
- a) an immunoglobulin heavy chain variable region comprising CDR1, CDR2, and CDR3, which are respectively identical to the reference heavy chain CDR1 sequence of SEQ ID NO:1, the reference heavy chain CDR2 sequence of SEQ ID NO: 2, 4, 6, 63, or 64, and the reference heavy chain CDR3 sequence of SEQ ID NO: 3 or 5; and
 - b) an immunoglobulin a light chain variable region comprising CDR1, CDR2, and CDR3, which are respectively identical to the reference light chain CDR1 sequence of SEQ ID NO: 10, 13, or 14, the reference light chain sequence CDR2 of SEQ ID NO:11, and the reference light chain CDR3 sequence of SEQ ID NO: 12.
20. An antibody or antigen binding fragment thereof that specifically binds to human EGFR, wherein the antibody or antigen binding fragment thereof comprises:

- a) an immunoglobulin heavy chain variable region comprising CDR1, CDR2, and CDR3, which, with the exception of 1, 2, or 3 conservative amino acid substitutions, are respectively identical to the reference heavy chain CDR1 sequence of SEQ ID NO:1, the reference heavy chain CDR2 sequence of SEQ ID NO: 7, 8, or 9, and the reference heavy chain CDR3 sequence of SEQ ID NO: 3; and
- b) an immunoglobulin a light chain variable region comprising CDR1, CDR2, and CDR3, which, with the exception of 1, 2, or 3 conservative amino acid substitutions, are respectively identical to the reference light chain CDR1 sequence of SEQ ID NO: 15 or 16, the reference light chain CDR2 sequence of SEQ ID NO:17, and the reference light chain CDR3 sequence of SEQ ID NO: 18.

21. The antibody or antigen binding fragment thereof of claim 20, which comprises:

- a) an immunoglobulin heavy chain variable region comprising CDR1, CDR2, and CDR3, which are respectively identical to the reference heavy chain CDR1 sequence of SEQ ID NO:1, the reference heavy chain CDR2 sequence of SEQ ID NO: 7, 8, or 9, and the reference heavy chain CDR3 sequence of SEQ ID NO: 3; and
- b) an immunoglobulin a light chain variable region comprising CDR1, CDR2, and CDR3, which are respectively identical to the reference light chain CDR1 sequence of SEQ ID NO: 15 or 16, the reference light chain CDR2 sequence of SEQ ID NO:17, and the reference light chain CDR3 sequence of SEQ ID NO: 18.

22. An antibody or antigen binding fragment thereof that specifically binds to human EGFR, wherein the antibody or antigen binding fragment thereof comprises:

- a) an immunoglobulin heavy chain variable region comprising CDR1, CDR2, and CDR3, which, with the exception of 1, 2, or 3 conservative amino acid substitutions, are respectively identical to the reference heavy chain CDR1 sequence of SEQ ID NO:1, the reference heavy chain CDR2 sequence of SEQ ID NO: 65, 66, or 67, and the reference heavy chain CDR3 sequence of SEQ ID NO: 3; and
- b) an immunoglobulin a light chain variable region comprising CDR1, CDR2, and CDR3, which, with the exception of 1, 2, or 3 conservative amino acid substitutions, are respectively identical to the reference light chain CDR1 sequence of SEQ ID NO: 68 or 13, the reference light chain sequence CDR2 of SEQ ID NO:11, and the reference light chain CDR3 sequence of SEQ ID NO: 12.

23. The antibody or antigen binding fragment thereof of claim 22, which comprises:
- a) an immunoglobulin heavy chain variable region comprising CDR1, CDR2, and CDR3, which are respectively identical to the reference heavy chain CDR1 sequence of SEQ ID NO:1, the reference heavy chain CDR2 sequence of SEQ ID NO: 65, 66, or 67, and the reference heavy chain CDR3 sequence of SEQ ID NO: 3; and
 - b) an immunoglobulin a light chain variable region comprising CDR1, CDR2, and CDR3, which are respectively identical to the reference light chain CDR1 sequence of SEQ ID NO: 68 or 13, the reference light chain sequence CDR2 of SEQ ID NO:11, and the reference light chain CDR3 sequence of SEQ ID NO: 12.
24. The antibody or antigen binding fragment thereof of any one of claims 1-5 and 7-23, wherein said antibody or antigen binding fragment thereof is murine, non-human, humanized, chimeric, resurfaced, or human.
25. The antibody or antigen binding fragment thereof of any one of claims 1-5 and 7-24, which is a full length antibody.
26. The antibody or antigen binding fragment thereof of any one of claims 1-5 and 7-24, which is an antigen binding fragment.
27. The antibody or antigen binding fragment thereof of any one of claims 1-5 and 7-24, wherein said antibody or antigen binding fragment thereof comprises a Fab, Fab', F(ab')₂, Fd, single chain Fv or scFv, disulfide linked Fv, V-NAR domain, IgNar, intrabody, IgGΔCH2, minibody, F(ab')₃, tetrabody, triabody, diabody, single-domain antibody, DVD-Ig, Fcab, mAb₂, (scFv)₂, or scFv-Fc.
28. A polypeptide comprising the VH and VL sequences of any of claims 1-5 and 7-27.
29. The antibody or polypeptide of any of claims 1-5 and 7-28, wherein the antibody or antigen binding fragment thereof bind both human and macaque EGFR with a substantially similar binding affinity.
30. The antibody or polypeptide of claim 28 or 29, which binds to human or macaque EGFR with a binding affinity of about 1.0 to about 10 nM K_d.
31. The antibody or polypeptide of claim 28 or 29, which binds to human or macaque EGFR with a binding affinity of about 1.0 nM K_d or better.

32. The antibody or polypeptide of any of claims 29-31, wherein the binding affinity is measured by flow cytometry, Biacore, or radioimmunoassay.
33. An isolated cell producing the antibody or antigen binding fragment thereof, or polypeptide of any one of claims 1-5 and 7-32.
34. A method of making the antibody or antigen-binding fragment thereof, or polypeptide of any one of claims 1-5 and 7-32, comprising (a) culturing the cell of claim 33; and (b) isolating said antibody, antigen-binding fragment thereof, or polypeptide from said cultured cell.
35. The method of claim 34, wherein said cell is a eukaryotic cell.
36. An immunoconjugate having the formula (A) - (L) - (C), wherein:
- (A) is an antibody or antigen binding fragment thereof, or polypeptide of any one of claims 1-5 and 7-32;
- (L) is a linker; and
- (C) is a cytotoxic agent; and
- wherein said linker (L) links (A) to (C).
37. The immunoconjugate of claim 36, wherein said linker is selected from the group consisting of a cleavable linker, a non-cleavable linker, a hydrophilic linker, and a dicarboxylic acid based linker.
38. The immunoconjugate of claim 37, wherein said linker is a non-cleavable linker.
39. The immunoconjugate of claim 37, wherein said linker is selected from the group consisting: N-succinimidyl 4-(2-pyridyldithio)pentanoate (SPP); N-succinimidyl 4-(2-pyridyldithio)butanoate (SPDB) or N-succinimidyl 4-(2-pyridyldithio)-2-sulfobutanoate (sulfo-SPDB); N-succinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (SMCC); N-sulfosuccinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (sulfoSMCC); N-succinimidyl-4-(iodoacetyl)-aminobenzoate (SIAB); and N-succinimidyl-[(N-maleimidopropionamido)-tetraethyleneglycol] ester (NHS-PEG4-maleimide).
40. The immunoconjugate of claim 39, wherein said linker is N-succinimidyl-[(N-maleimidopropionamido)-tetraethyleneglycol] ester (NHS-PEG4-maleimide).
41. The immunoconjugate of any one of claims 36-40, wherein said cytotoxic agent is selected from the group consisting of a maytansinoid, maytansinoid analog, doxorubicin, a modified doxorubicin, benzodiazepine, taxoid, CC-1065, CC-1065 analog, duocarmycin, duocarmycin analog,

calicheamicin, dolastatin, dolastatin analog, aristatin, tomaymycin derivative, and leptomycin derivative or a prodrug of the agent.

42. The immunoconjugate of claim 41, wherein said cytotoxic agent is a maytansinoid.

43. The immunoconjugate of claim 42, wherein said cytotoxic agent is N(2')-deacetyl-N(2')-(3-mercapto-1-oxopropyl)-maytansine (DM1) or N(2')-deacetyl-N2-(4-mercapto-4-methyl-1-oxopentyl)-maytansine (DM4).

44. A pharmaceutical composition comprising the antibody or antigen binding fragment thereof, or polypeptide of any one of claims 1-5 and 7-32, or the immunoconjugate of any one of claims 6 and 36-43 and a pharmaceutically acceptable carrier.

45. The pharmaceutical composition of claim 44, further comprising a second anti-cancer agent.

46. A diagnostic reagent comprising the antibody or antigen binding fragment thereof, or polypeptide of any one of claims 1-5 and 7-32, or the immunoconjugate of any one of claims 6 and 36-43.

47. The diagnostic reagent of claim 46, further comprising a label selected from the group consisting of a radiolabel, a fluorophore, a chromophore, an imaging agent and a metal ion.

48. A kit comprising the antibody or antigen binding fragment thereof, or polypeptide of any one of claims 1-5 and 7-32, or the immunoconjugate of any one of claims 6 and 36-43.

49. The antibody or antigen binding fragment thereof, or polypeptide of any one of claims 1-5 and 7-32, the immunoconjugate of any one of claims 6 and 36-43, or the pharmaceutical composition of claim 44 or 45 for use in a method for inhibiting the growth of a cell expressing EGFR comprising contacting the cell with the antibody or antigen binding fragment thereof, or polypeptide of any one of claims 1-5 and 7-32, the immunoconjugate of any one of claims 6 and 36-43, or the pharmaceutical composition of claim 44 or 45.

50. The use of claim 49, wherein said cell is a tumor cell.

51. The antibody or antigen binding fragment thereof, or polypeptide of any one of claims 1-5 and 7-32, the immunoconjugate of any one of claims 6 and 36-43, or the pharmaceutical composition of claim 44 or 45 for use in treating a patient having cancer.

52. The use of claim 51, wherein said cancer is selected from the group consisting of: non-small cell lung cancer, breast cancer, colorectal cancer, head and neck cancer, and prostate cancer.

53. The use of claim 51 or 52, further comprising administering a second anti-cancer agent to the subject
54. The use of claim 53, wherein said second anti-cancer agent is a chemotherapeutic agent.
55. The antibody or antigen binding fragment thereof, or polypeptide of any one of claims 1-5 and 7-32, the immunoconjugate of any one of claims 6 and 36-43, or the pharmaceutical composition of claim 44 or 45 for use in treating a cell proliferative disorder.
56. The use of claim 55, wherein said cell proliferative disorder is selected from the group consisting of: adrenal cortex hyperplasia (Cushing's disease), congenital adrenal hyperplasia, endometrial hyperplasia, benign prostatic hyperplasia, breast hyperplasia, intimal hyperplasia, focal epithelial hyperplasia (Heck's disease), sebaceous hyperplasia, compensatory liver hyperplasia, and any other cell proliferation disease, besides neoplasia.
57. An isolated polynucleotide comprising a sequence that encodes a polypeptide at least 90%, at least 95%, or at least 99%, identical to a sequence selected from the group consisting of SEQ ID NOs: 39-43, 77-80, and 82-84.
58. An isolated polynucleotide which comprises a sequence that is at least 90%, at least 95%, or at least 99%, identical to SEQ ID NOs: 44-50 and 81.
59. An isolated polynucleotide comprising a sequence selected from the group consisting of SEQ ID NOs: 39-58 and 77-84.
60. A vector comprising the polynucleotide of any one of claims 57-59.
61. A host cell comprising the vector of claim 60.
62. The immunoconjugate of claim 36, wherein said immunoconjugate can eliminate EGFR positive tumor cells, but only inhibit 40% or less the growth of human primary keratinocytes at concentration of 3.3 nM.
63. An immunoconjugate having the formula (A) - (L) - (C), wherein:
- (A) is an antibody or antigen binding fragment thereof comprising the heavy chain variable region of SEQ ID NO:21 and the light chain variable region of SEQ ID NOs: 26 or 27;
- (L) is a N-succinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (SMCC) linker; and
- (C) is the cytotoxic agent N(2')-deacetyl-N(2')-(3-mercapto-1-oxopropyl)-maytansine (DM1).

WHAT IS CLAIMED IS:

1. An isolated antibody or antigen binding fragment thereof that specifically binds to human epidermal growth factor receptor (EGFR), wherein the isolated antibody or antigen binding fragment thereof comprises:

- a) an immunoglobulin heavy chain variable region (VH) comprising a CDR1 sequence of SEQ ID NO: 1, a CDR2 sequence of SEQ ID NO: 2 or 4, and a CDR3 sequence of SEQ ID NO: 3 or 5; and
- b) an immunoglobulin light chain variable region (VL) comprising a CDR1 sequence of SEQ ID NO: 10, 13 or 14, a CDR2 sequence of SEQ ID NO: 11, and a CDR3 sequence of SEQ ID NO: 12.

2. The isolated antibody or antigen binding fragment thereof of claim 1, wherein the isolated antibody or antigen binding fragment thereof comprises:

- a) a VH sequence at least 90%, at least 95%, or at least 99% identical to the reference VH sequence of SEQ ID NO:19 and a VL sequence at least 90%, at least 95%, or at least 99% identical to the reference VL sequence of SEQ ID NO:24;
- b) a VH sequence at least 90%, at least 95%, or at least 99% identical to the reference VH sequence of SEQ ID NO:21 and a VL sequence at least 90%, at least 95%, or at least 99% identical to the reference VL sequence of SEQ ID NO:26;
- c) a VH sequence at least 90%, at least 95%, or at least 99% identical to the reference VH sequence of SEQ ID NO:21 and a VL sequence at least 90%, at least 95%, or at least 99% identical to the reference VL sequence of SEQ ID NO:27;
- d) a VH sequence at least 90%, at least 95%, or at least 99% identical to the reference VH sequence of SEQ ID NO:22 and a VL sequence at least 90%, at least 95%, or at least 99% identical to the reference VL sequence of SEQ ID NO:28;
- e) a VH sequence at least 90%, at least 95%, or at least 99% identical to the reference VH sequence of SEQ ID NO:73 and a VL sequence at least 90%, at

least 95%, or at least 99% identical to the reference VL sequence of SEQ ID NO:26; or

- f) a VH sequence at least 90%, at least 95%, or at least 99% identical to the reference VH sequence of SEQ ID NO:73 and a VL sequence at least 90%, at least 95%, or at least 99% identical to the reference VL sequence of SEQ ID NO:27.

3. The isolated antibody or antigen binding fragment thereof of claim 1, wherein the isolated antibody or antigen binding fragment thereof comprises:

- a) the VH sequence of SEQ ID NO:19 and the VL sequence of SEQ ID NO:24;
- b) the VH sequence of SEQ ID NO:21 and the VL sequence of SEQ ID NO:26;
- c) the VH sequence of SEQ ID NO:21 and the VL sequence of SEQ ID NO:27;
- d) the VH sequence of SEQ ID NO:22 and the VL sequence of SEQ ID NO:28;
- e) the VH sequence of SEQ ID NO:73 and the VL sequence of SEQ ID NO:26; or
- f) the VH sequence of SEQ ID NO:73 and the VL sequence of SEQ ID NO:27.

4. The isolated antibody or antigen binding fragment thereof of claim 3, wherein the isolated antibody or antigen binding fragment thereof comprises the VH sequence of SEQ ID NO: 21 and the VL sequence of SEQ ID NO: 26.

5. The isolated antibody or antigen binding fragment thereof of claim 1, wherein the isolated antibody is produced by a hybridoma having ATCC Deposit Designation PTA-11332, deposited with the ATCC on October 6, 2010.

6. The isolated antibody or antigen binding fragment thereof of claim 1, wherein the isolated antibody or antigen binding fragment thereof comprises:

- a) a VH comprising a CDR1 sequence of SEQ ID NO:1, a CDR2 sequence of SEQ ID NO: 65, and a CDR3 sequence of SEQ ID NO: 3; and
- b) a VL comprising a CDR1 sequence of SEQ ID NO: 68 or 13, a CDR2 sequence of SEQ ID NO:11, and a CDR3 sequence of SEQ ID NO: 12.

7. The isolated antibody or antigen binding fragment thereof of claim 6, wherein the isolated antibody or antigen binding fragment thereof comprises:

- a) a VH sequence at least 90%, at least 95%, or at least 99% identical to the reference VH sequence of SEQ ID NO:69 and a VL sequence at least 90%, at least 95%, or at least 99% identical to the reference VL sequence of SEQ ID NO:70;
- b) a VH sequence at least 90%, at least 95%, or at least 99% identical to the reference VH sequence of SEQ ID NO:71 and a VL sequence at least 90%, at least 95%, or at least 99% identical to the reference VL sequence of SEQ ID NO:26;
- c) a VH sequence at least 90%, at least 95%, or at least 99% identical to the reference VH sequence of SEQ ID NO:71 and a VL sequence at least 90%, at least 95%, or at least 99% identical to the reference VL sequence of SEQ ID NO:27;
- d) a VH sequence at least 90%, at least 95%, or at least 99% identical to the reference VH sequence of SEQ ID NO:72 and a VL sequence at least 90%, at least 95%, or at least 99% identical to the reference VL sequence of SEQ ID NO:26; or
- e) a VH sequence at least 90%, at least 95%, or at least 99% identical to the reference VH sequence of SEQ ID NO:72 and a VL sequence at least 90%, at least 95%, or at least 99% identical to the reference VL sequence of SEQ ID NO:27.

8. The isolated antibody or antigen binding fragment thereof of claim 6, wherein the isolated antibody or antigen binding fragment thereof comprises:

- a) the VH sequence of SEQ ID NO:69 and the VL sequence of SEQ ID NO:70;
- b) the VH sequence of SEQ ID NO:71 and the VL sequence of SEQ ID NO:26;
- c) the VH sequence of SEQ ID NO:71 and the VL sequence of SEQ ID NO:27;
- d) the VH sequence of SEQ ID NO:72 and the VL sequence of SEQ ID NO:26; or
- e) the VH sequence of SEQ ID NO:72 and the VL sequence of SEQ ID NO:27.

9. The isolated antibody or antigen binding fragment thereof of claim 6, wherein the isolated antibody is produced by a hybridoma having ATCC Deposit Designation PTA-11331, deposited with the ATCC on October 6, 2010.

10. An isolated antibody or antigen binding fragment thereof that specifically binds to human EGFR, wherein the isolated antibody or antigen binding fragment thereof comprises:

- a) a VH comprising a CDR1 sequence of SEQ ID NO:1, a CDR2 sequence of SEQ ID NO: 7, and a CDR3 sequence of SEQ ID NO: 3; and
- b) a VL comprising a CDR1 sequence of SEQ ID NO: 15 or 16, a CDR2 sequence of SEQ ID NO:17, and a CDR3 sequence of SEQ ID NO: 18.

11. The isolated antibody or antigen binding fragment thereof of claim 10, wherein the isolated antibody or antigen binding fragment thereof comprises:

- a) a VH sequence at least 90%, at least 95%, or at least 99% identical to the reference VH sequence of SEQ ID NO:20 and a VL sequence at least 90%, at least 95%, or at least 99% identical to the reference VL sequence of SEQ ID NO:25;
- b) a VH sequence at least 90%, at least 95%, or at least 99% identical to the reference VH sequence of SEQ ID NO:23 and a VL sequence at least 90%, at least 95%, or at least 99% identical to the reference VL sequence of SEQ ID NO:29; or
- c) a VH sequence at least 90%, at least 95%, or at least 99% identical to the reference VH sequence of SEQ ID NO:23 and a VL sequence at least 90%, at least 95%, or at least 99% identical to the reference VL sequence of SEQ ID NO:30.

12. The isolated antibody or antigen binding fragment thereof of claim 10, wherein the isolated antibody or antigen binding fragment thereof comprises:

- a) the VH sequence of SEQ ID NO:20 and the VL sequence of SEQ ID NO:25;
- b) the VH sequence of SEQ ID NO:23 and the VL sequence of SEQ ID NO:29; or
- c) the VH sequence of SEQ ID NO:23 and the VL sequence of SEQ ID NO:30.

13. The isolated antibody or antigen binding fragment thereof of claim 10, wherein the isolated antibody is produced by a hybridoma having ATCC Deposit Designation PTA-11333, deposited with the ATCC on October 6, 2010.

14. The isolated antibody or antigen binding fragment thereof of any one of claims 1-13, wherein said isolated antibody or antigen binding fragment thereof does not inhibit more than 20% proliferation of keratinocytes or MCF-10A epithelial cells at 60 nM or lower.

15. The isolated antibody or antigen binding fragment thereof of claim 14, wherein said isolated antibody or antigen binding fragment thereof (a) inhibits at least 80% of EGF and TGF α binding to A431 cells at a concentration of 10 nM or higher, or (b) causes at least 50% inhibition of H292 or HCC827 tumor cell proliferation at 30 nM or higher.
16. The isolated antibody or antigen binding fragment thereof of claim 15, wherein said isolated antibody or antigen binding fragment thereof (a) inhibits at least 80% of EGF and TGF α binding to A431 cells at a concentration of 10 nM or higher, and (b) causes at least 50% inhibition of H292 or HCC827 tumor cell proliferation at 30 nM or higher.
17. The isolated antibody or antigen binding fragment thereof of any one of claims 1-16, wherein said isolated antibody or antigen binding fragment thereof is murine, non-human, humanized, or human.
18. The isolated antibody or antigen binding fragment thereof of claim 17, wherein said isolated humanized antibody or antigen binding fragment thereof is chimeric or resurfaced.
19. The isolated antibody or antigen binding fragment thereof of any one of claims 1-18, which is a full length antibody.
20. The isolated antibody or antigen binding fragment thereof of any one of claims 1-4, 6-8, 10-12, and 14-18, which is an antigen binding fragment.
21. The isolated antibody or antigen binding fragment thereof of claim 20, wherein said antigen binding fragment comprises a Fab, Fab', F(ab')₂, Fd, single chain Fv or scFv, disulfide linked Fv, intrabody, IgG Δ CH₂, minibody, F(ab')₃, tetrabody, triabody, diabody, DVD-Ig, mAb₂, (scFv)₂, or scFv-Fc.
22. A polypeptide comprising the VH and VL sequences of any one of claims 3, 4, 8, and 12.
23. The isolated antibody or antigen binding fragment thereof or polypeptide of any one of claims 1-22, wherein the isolated antibody or antigen binding fragment thereof or polypeptide bind both human and macaque EGFR with a substantially similar binding affinity.

24. The isolated antibody or antigen binding fragment thereof or polypeptide of claim 23, which binds to human or macaque EGFR with a binding affinity of 1.0 nM to 10 nM Kd.
25. The isolated antibody or antigen binding fragment thereof or polypeptide of claim 23, which binds to human EGFR with a binding affinity of 0.4 nM to 1.0 nM Kd.
26. The isolated antibody or antigen binding fragment thereof or polypeptide of any of claims 23-25, wherein the binding affinity is measured by flow cytometry, Biacore, or radioimmunoassay.
27. An isolated cell producing the antibody or antigen binding fragment thereof, or polypeptide of any one of claims 1-26.
28. A method of making the antibody or antigen binding fragment thereof, or polypeptide of any one of claims 1-26, comprising (a) culturing the cell of claim 27; and (b) isolating said antibody, antigen binding fragment thereof, or polypeptide from said cultured cell.
29. The method of claim 28, wherein said cell is a eukaryotic cell.
30. An immunoconjugate having the formula (A) - (L) - (C), wherein:
(A) is an antibody or antigen binding fragment thereof, or polypeptide of any one of claims 1-26;
(L) is a linker; and
(C) is a cytotoxic agent; and
wherein said linker (L) links (A) to (C).
31. An immunoconjugate having the formula (A) - (L) - (C), wherein:
(A) is an antibody or antigen binding fragment thereof that specifically binds to human EGFR, wherein the antibody or antigen binding fragment thereof comprises:
 - a) a VH comprising a CDR1 sequence of SEQ ID NO:1, a CDR2 sequence of SEQ ID NO: 2 or 4, and a CDR3 sequence of SEQ ID NO: 3 or 5, and
 - b) a VL comprising a CDR1 sequence of SEQ ID NO: 10, 13, or 14, a CDR2 sequence of SEQ ID NO:11, and a CDR3 sequence of SEQ ID NO: 12;
(L) is a linker; and

(C) is a cytotoxic agent; and
wherein said linker (L) links (A) to (C).

32. The immunoconjugate of claim 31, wherein the VH sequence of SEQ ID NO:21 and the VL sequence of SEQ ID NO:26.

33. The immunoconjugate of any one of claims 30-32, wherein said linker is selected from the group consisting of: a cleavable linker, a non-cleavable linker, a hydrophilic linker, and a dicarboxylic acid based linker.

34. The immunoconjugate of claim 33, wherein said linker is a non-cleavable linker.

35. The immunoconjugate of claim 33, wherein said linker is selected from the group consisting of: N-succinimidyl 4-(2-pyridyldithio)pentanoate (SPP); N-succinimidyl 4-(2-pyridyldithio)butanoate (SPDB); [[or]] N-succinimidyl 4-(2-pyridyldithio)-2-sulfobutanoate (sulfo-SPDB); N-succinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (SMCC); N-sulfosuccinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (sulfoSMCC); N-succinimidyl-4-(iodoacetyl)-aminobenzoate (SIAB); and N-succinimidyl-[(N-maleimidopropionamido)-tetraethyleneglycol] ester (NHS-PEG4-maleimide).

36. The immunoconjugate of claim 35, wherein said linker is N-succinimidyl-[(N-maleimidopropionamido)-tetraethyleneglycol] ester (NHS-PEG4-maleimide).

37. The immunoconjugate of claim 35, wherein said linker is N-succinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (SMCC).

38. The immunoconjugate of any one of claims 30-37, wherein said cytotoxic agent is selected from the group consisting of: a maytansinoid, maytansinoid analog, doxorubicin, a modified doxorubicin, benzodiazepine, taxoid, CC-1065, CC-1065 analog, duocarmycin, duocarmycin analog, calicheamicin, dolastatin, dolastatin analog, auristatin, tomaymycin derivative, and leptomycin derivative or a prodrug of the cytotoxic agent.

39. The immunoconjugate of claim 38, wherein said cytotoxic agent is a maytansinoid.

40. The immunoconjugate of claim 39, wherein said cytotoxic agent is N(2')-deacetyl-N(2')-(3-mercapto-1-oxopropyl)-maytansine (DM1) or N(2')-deacetyl-N(2')-(4-mercapto-4-methyl-1-oxopentyl)-maytansine (DM4).

41. An immunoconjugate having the formula (A) - (L) - (C), wherein:

(A) is an antibody or antigen binding fragment thereof that specifically binds to human EGFR, wherein the antibody or antigen binding fragment thereof comprises the VH sequence of SEQ ID NO:21 and the VH sequence of SEQ ID NO:26;

(L) is a N-succinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (SMCC) linker; and

(C) is the N(2')-deacetyl-N(2')-(3-mercapto-1-oxopropyl)-maytansine (DM1) cytotoxic agent; and

wherein said linker (L) links (A) to (C).

42. The immunoconjugate of any one of claims 30-41, wherein said immunoconjugate comprises 2-5 (C).

43. The immunoconjugate of any one of claims 30-41, wherein said immunoconjugate comprises 2-10 (C).

44. A pharmaceutical composition comprising the antibody or antigen binding fragment thereof, or polypeptide of any one of claims 1-26, or the immunoconjugate of any one of claims 30-43 and a pharmaceutically acceptable carrier.

45. A diagnostic reagent comprising the antibody or antigen binding fragment thereof, or polypeptide of any one of claims 1-26, or the immunoconjugate of any one of claims 30-43.

46. The diagnostic reagent of claim 45, further comprising a label selected from the group consisting of: a radiolabel, a fluorophore, a chromophore, an imaging agent and a metal ion.

47. A kit comprising the antibody or antigen binding fragment thereof, or polypeptide of any one of claims 1-26, or the immunoconjugate of any one of claims 30-43.

48. The isolated antibody or antigen binding fragment thereof, or polypeptide of any one of claims 1-26, the immunoconjugate of any one of claims 30-43, or the pharmaceutical

composition of claim 44 for use in a method for inhibiting the growth of a cell expressing EGFR comprising contacting the cell with the isolated antibody or antigen binding fragment thereof, or polypeptide of any one of claims 1-26, the immunoconjugate of any one of claims 30-43 or the pharmaceutical composition of claim 44.

49. The isolated antibody or antigen binding fragment thereof, or polypeptide of claim 48, wherein said cell is a tumor cell.

50. The isolated antibody or antigen binding fragment thereof, or polypeptide of any one of claims 1-26, the immunoconjugate of any one of claims 30-43, or the pharmaceutical composition of claim 44 for use in treating a patient having cancer.

51. The isolated antibody or antigen binding fragment thereof, or polypeptide of claim 50, wherein said cancer is selected from the group consisting of: non-small cell lung cancer, breast cancer, colorectal cancer, head and neck cancer, bladder cancer, brain cancer, pancreatic cancer, ovarian cancer, skin cancer, kidney cancer, cancer of the peritoneum, endometrial cancer, and prostate cancer.

52. The isolated antibody or antigen binding fragment thereof, or polypeptide of claim 51, wherein said cancer is breast cancer.

53. The isolated antibody or antigen binding fragment thereof, or polypeptide of claim 51, wherein said cancer is colorectal cancer.

54. The isolated antibody or antigen binding fragment thereof, or polypeptide of claim 51, wherein said cancer is head and neck cancer.

55. The isolated antibody or antigen binding fragment thereof, or polypeptide of claim 51, wherein said cancer is prostate cancer.

56. The isolated antibody or antigen binding fragment thereof, or polypeptide of claim 51, wherein said cancer is non-small cell lung cancer.

57. The isolated antibody or antigen binding fragment thereof, or polypeptide of claim 51, wherein said cancer is cancer of the peritoneum.

58. The isolated antibody or antigen binding fragment thereof, or polypeptide of claim 51, wherein said cancer is endometrial cancer.

59. The isolated antibody or antigen binding fragment thereof, or polypeptide of any one of claims 1-26, the immunoconjugate of any one of claims 30-43, or the pharmaceutical composition of claim 44 for use in treating a cell proliferative disorder.

60. The isolated antibody or antigen binding fragment thereof, or polypeptide of claim 59, wherein said cell proliferative disorder is selected from the group consisting of: adrenal cortex hyperplasia (Cushing's disease), congenital adrenal hyperplasia, endometrial hyperplasia, benign prostatic hyperplasia, breast hyperplasia, intimal hyperplasia, focal epithelial hyperplasia (Heck's disease), sebaceous hyperplasia, compensatory liver hyperplasia, and any other cell proliferation disease, besides neoplasia.

61. An isolated polynucleotide comprising a sequence selected from the group consisting of SEQ ID NOs: 39, 41, 42, 44, 46-48, 51-55, and 84.

62. An isolated polynucleotide comprising a sequence selected from the group consisting of SEQ ID NOs: 77-79 and 81-83.

63. An isolated polynucleotide comprising a sequence selected from the group consisting of SEQ ID NOs: 40, 43, 45, 49, 50, and 56-58.

64. A vector comprising the polynucleotide of any one of claims 61-63.

65. A host cell comprising the vector of claim 64.