CLAIMS

1. An activatable antibody that in an activated state binds Epidermal Growth Factor Receptor (EGFR) comprising:

an antibody or an antigen binding fragment thereof (AB) that specifically binds to EGFR, wherein the AB comprises (i) a heavy chain amino acid sequence selected from the group consisting of SEQ ID NO: 26, SEQ ID NO: 30 and SEQ ID NO: 34 and a light chain amino acid sequence comprising SEQ ID NO: 68, or (ii) a heavy chain amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 6 and SEQ ID NO: 10 and a light chain amino acid sequence comprising SEQ ID NO: 68;

a masking moiety (MM) that inhibits the binding of the AB of the activatable antibody in an uncleaved state to EGFR, wherein the masking moiety comprises the amino acid sequence CISPRGCPDGPYVMY (SEQ ID NO: 14); and

a cleavable moiety (CM) coupled to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease, and wherein the CM comprises the amino acid sequence LSGRSDNH (SEQ ID NO: 13),

wherein the activatable antibody in the uncleaved state has the structural arrangement from N-terminus to C-terminus as follows: MM-CM-AB or AB-CM-MM.

2. The activatable antibody of claim 1, wherein the antigen binding fragment thereof is selected from the group consisting of a Fab fragment, a $F(ab')_2$ fragment, a scFv, and a scAb.

3. The activatable antibody of claim 1, wherein the activatable antibody comprises a combination of heavy and light chains selected from the group consisting of:

(a) a heavy chain comprising amino acid sequence of SEQ ID NO: 26 and a light chain comprising the amino acid sequence of SEQ ID NO: 28;

(b) a heavy chain comprising amino acid sequence of SEQ ID NO: 2 and a light chain comprising the amino acid sequence of SEQ ID NO: 4;

(c) a heavy chain comprising amino acid sequence of SEQ ID NO: 6 and a light chain comprising the amino acid sequence of SEQ ID NO: 4;

(d) a heavy chain comprising amino acid sequence of SEQ ID NO 30 and a light chain comprising the amino acid sequence of SEQ ID NO: 28;

(e) a heavy chain comprising amino acid sequence of SEQ ID NO: 10 and a light chain comprising the amino acid sequence of SEQ ID NO: 4; and

(f) a heavy chain comprising amino acid sequence of SEQ ID NO: 34 and a light chain comprising the amino acid sequence of SEQ ID NO: 28.

4. The activatable antibody of claim 1, wherein the activatable antibody comprises a heavy chain comprising amino acid sequence of SEQ ID NO: 26 and a light chain comprising the amino acid sequence of SEQ ID NO: 28.

5. The activatable antibody of claim 1, wherein the activatable antibody comprises a heavy chain comprising amino acid sequence of SEQ ID NO: 30 and a light chain comprising the amino acid sequence of SEQ ID NO: 28.

6. The activatable antibody of claim 1, wherein the activatable antibody comprises a heavy chain comprising amino acid sequence of SEQ ID NO: 34 and a light chain comprising the amino acid sequence of SEQ ID NO: 28.

7. The activatable antibody of claim 1, wherein the AB has an equilibrium dissociation constant of about 100 nM or less for binding to EGFR.

8. The activatable antibody of claim 1, wherein the MM has an equilibrium dissociation constant for binding to the AB which is greater than the equilibrium dissociation constant of the AB to EGFR.

9. The activatable antibody of claim 1, wherein the MM does not interfere or compete with the AB of the activatable antibody in a cleaved state for binding to EGFR.

10. The activatable antibody of claim 1, wherein the MM is a polypeptide of no more than 40 amino acids in length.

11. The activatable antibody of claim 1, wherein the MM polypeptide sequence is different from that of EGFR and wherein the MM polypeptide sequence is no more than 50% identical to any natural binding partner of the AB.

12. The activatable antibody of claim 1, wherein the MM does not comprise more than 25% amino acid sequence identity to EGFR.

13. The activatable antibody of claim 1, wherein the MM does not comprise more than 10% amino acid sequence identity to EGFR.

14. The activatable antibody of claim 1, wherein the CM is a polypeptide of up to 15 amino acids in length.

15. The activatable antibody of claim 1, wherein the protease is co-localized with EGFR in a tissue, and wherein the protease cleaves the CM in the activatable antibody when the activatable antibody is exposed to the protease.

16. The activatable antibody of claim 1, wherein the activatable antibody comprises a linking peptide between the MM and the CM.

17. The activatable antibody of claim 1, wherein the activatable antibody comprises a linking peptide between the CM and the AB.

18. The activatable antibody of claim 1, wherein the activatable antibody comprises a first linking peptide (LP1) and a second linking peptide (LP2), and wherein the activatable antibody in an uncleaved state has the structural arrangement from N-terminus to C-terminus as follows: MM-LP1-CM-LP2-AB or AB-LP2-CM-LP1-MM.

19. The activatable antibody of claim 18, wherein the two linking peptides need not be identical to each other.

20. The activatable antibody of claim 18, wherein at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of $(GS)_n$, $(GGS)_n$, $(GSGGS)_n$ (SEQ ID NO: 15) and $(GGGS)_n$ (SEQ ID NO: 16), where n is an integer of at least one.

21. The activatable antibody of claim 18, wherein at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of GGSG (SEQ ID NO: 17), GGSGG (SEQ ID NO: 18), GSGSG (SEQ ID NO: 19), GSGGG (SEQ ID NO: 20), GGGSG (SEQ ID NO: 21), and GSSSG (SEQ ID NO: 22).

22. The activatable antibody of claim 18, wherein LP1 comprises the amino acid sequence GSSGGSGGSGGSG (SEQ ID NO: 23).

23. The activatable antibody of claim 18, wherein LP2 comprises the amino acid sequence GSSGT (SEQ ID NO: 24) or GSSG (SEQ ID NO: 37).

24. The activatable antibody of claim 1, wherein the activatable antibody in an uncleaved state comprises a spacer, wherein the spacer is joined directly to the MM and has the structural arrangement from N-terminus to C-terminus of spacer-MM-CM-AB.

25. The activatable antibody of claim 24, wherein the spacer comprises the amino acid sequence QGQSGQ (SEQ ID NO: 38).

26. The activatable antibody of claim 24, wherein the spacer and MM comprises the amino acid sequence QGQSGQCISPRGCPDGPYVMY (SEQ ID NO: 59).

27. The activatable antibody of claim 1, wherein the AB is conjugated to an agent.

28. The activatable antibody of claim 27, wherein the agent is a toxin or fragment thereof.

29. The activatable antibody of claim 27, wherein the agent is a dolastatin.

30. The activatable antibody of claim 27, wherein the agent is an auristatin or derivative thereof.

31. The activatable antibody of claim 27, wherein the agent is auristatin E or a derivative thereof.

32. The activatable antibody of claim 27, wherein the agent is monomethyl auristatin E (MMAE).

33. The activatable antibody of claim 27, wherein the agent is a maytansinoid or a derivative thereof.

34. The activatable antibody of claim 27, wherein the agent is DM1 or DM4.

35. The activatable antibody of claim 27, wherein the agent is a duocarmycin or derivative thereof.

36. The activatable antibody of claim 27, wherein the agent is a calicheamicin or derivative thereof.

37. The activatable antibody of claim 27, wherein the agent is conjugated to the AB via a linker.

38. The activatable antibody of claim 37, wherein the linker is a cleavable linker.

39. The activatable antibody of claim 1 comprising a detectable moiety.

40. The activatable antibody of claim 39, wherein the detectable moiety is a diagnostic agent.

41. An isolated nucleic acid molecule encoding the activatable antibody of claim 1.

42. The isolated nucleic acid molecule of claim 41, wherein the nucleic acid encoding the activatable antibody comprises a nucleic acid encoding a signal peptide.

43. The isolated nucleic acid molecule of claim 42, wherein the nucleic acid encoding the signal peptide is operably linked to the nucleic acid encoding the activatable antibody via a nucleic acid encoding a spacer.

44. The isolated nucleic acid molecule of claim 43, wherein the nucleic acid encoding the spacer encodes an amino acid sequence that comprises QGQSGQ (SEQ ID NO: 38).

45. A vector comprising the isolated nucleic acid molecule of any one of claims 41 to 44.

46. A method of producing an activatable antibody by culturing a cell under conditions that lead to expression of the activatable antibody, wherein the cell comprises the vector of claim 45.

47. A method of manufacturing an activatable antibody that in an activated state binds Epidermal Growth Factor Receptor (EGFR), the method comprising:

(a) culturing a cell comprising a nucleic acid construct that encodes the activatable antibody of claim 1 under conditions that lead to expression of the activatable antibody, and

(b) recovering the activatable antibody.

48. Use of the activatable antibody of claim 1 or claim 27 in the manufacture of a medicament for treating or delaying the progression of an EGFR-related disorder in a subject.

49. The use of claim 48, wherein the EGFR-related disorder is a cancer.

50. The use of claim 49, wherein the cancer is breast cancer, colorectal cancer, gastric cancer, glioblastoma, head and neck cancer, lung cancer, ovarian cancer, endometrial cancer, pancreatic cancer, prostate cancer, renal cancer, sarcoma, or skin cancer.

51. The use of claim 48, wherein the EGFR-related disorder is psoriasis.

52. Use of the activatable antibody of claim 1 or claim 27 in the manufacture of a medicament for inhibiting angiogenesis in a subject.

53. A method of detecting presence or absence of a cleaving agent and Epidermal Growth Factor Receptor (EGFR) in a subject or a sample, the method comprising:

(a) contacting a subject or sample with the anti-EGFR activatable antibody of claim 1 or the anti-EGFR activatable antibody of claim 24, and

(b) measuring a level of activated anti-EGFR activatable antibody in the subject or sample,

wherein a detectable level of activated anti-EGFR activatable antibody in the subject or sample indicates that the cleaving agent and EGFR are present in the subject or sample, and wherein no detectable level of activated anti-EGFR activatable antibody in the subject or sample indicates that the cleaving agent, EGFR or both the cleaving agent and EGFR are absent in the subject or sample.

54. The method of claim 53, wherein the anti-EGFR activatable antibody comprises a detectable label.

55. The method of claim 54, wherein the detectable label comprises an imaging agent, a contrasting agent, an enzyme, a fluorescent label, a chromophore, a dye, one or more metal ions, or a ligand-based label.

56. The method of claim 53, wherein the method is an *in vivo* method, an *in situ* method, an *ex vivo* method or *in vitro* method.

57. A method of identifying or refining a patient population for treatment of an EGFR-related disorder, the method comprising (i) contacting a sample from a subject with an anti-EGFR activatable antibody according to claim 1 or claim 27; (ii) measuring a level of activated anti-EGFR activatable antibody in the sample, wherein a detectable level of activated anti-EGFR

activatable antibody in the sample indicates that the sample is positive for the presence of EGFR and a cleaving agent that cleaves the substrate in the cleavable moiety (CM) of the activatable antibody according to claim 1 or claim 27; (iii) identifying and selecting one or more subjects that test positive for the presence of EGFR and the cleaving agent thereby identifying or refining a patient population; and (iv) administering a therapeutically effective amount of the activatable antibody according to claim 1 or claim 27 to the one or more subjects in the patient population that test positive for the presence of EGFR and the cleaving agent.

58. The method of claim 57, wherein the anti-EGFR activatable antibody comprises a detectable label.

59. The method of claim 58, wherein the detectable label comprises an imaging agent, a contrasting agent, an enzyme, a fluorescent label, a chromophore, a dye, one or more metal ions, or a ligand-based label.

60. The method of claim 57, wherein the EGFR-related disorder is cancer.

61. The method of claim 60, wherein the cancer is breast cancer, colorectal cancer, gastric cancer, glioblastoma, head and neck cancer, lung cancer, ovarian cancer, endometrial cancer, pancreatic cancer, prostate cancer, renal cancer, sarcoma, or skin cancer.

62. The method of claim 57, wherein the EGFR-related disorder is psoriasis.

63. A kit for identifying or refining a patient population for treatment of an EGFR-related disorder, the kit comprising (i) an anti-EGFR activatable antibody according to claim 1 or claim 27; (ii) means for measuring a level of activated anti-EGFR activatable antibody in a sample from a subject, wherein a detectable level of activated anti-EGFR activatable antibody in the sample indicates that the sample is positive for the presence of EGFR and a cleaving agent that cleaves the substrate in the cleavable moiety (CM) of the activatable antibody according to claim 1 or claim 27; (iii) means for identifying and selecting one or more subjects that test positive for the presence of EGFR and the cleaving agent thereby identifying or refining a patient population;

and (iv) instructions for administering a therapeutically effective amount of the activatable antibody according to claim 1 or claim 27 to the one or more subjects in the patient population that test positive for the presence of EGFR and the cleaving agent.

64. The kit of claim 63, wherein the anti-EGFR activatable antibody comprises a detectable label.

65. The kit of claim 64, wherein the detectable label comprises an imaging agent, a contrasting agent, an enzyme, a fluorescent label, a chromophore, a dye, one or more metal ions, or a ligand-based label.

66. The kit of claim 63, wherein the EGFR-related disorder is cancer.

67. The kit of claim 66, wherein the cancer is breast cancer, colorectal cancer, gastric cancer, glioblastoma, head and neck cancer, lung cancer, ovarian cancer, endometrial cancer, pancreatic cancer, prostate cancer, renal cancer, sarcoma, or skin cancer.

68. The kit of claim 63, wherein the EGFR-related disorder is psoriasis.

CLAIMS

1. An activatable antibody that in an activated state binds Epidermal Growth Factor Receptor (EGFR) comprising:

an antibody or an antigen binding fragment thereof (AB) that specifically binds to EGFR, wherein the AB comprises (i) a heavy chain amino acid sequence selected from the group consisting of SEQ ID NO: 26, SEQ ID NO: 30 and SEQ ID NO: 34 and a light chain amino acid sequence comprising SEQ ID NO: 68, or (ii) a heavy chain amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 6 and SEQ ID NO: 10 and a light chain amino acid sequence comprising SEQ ID NO: 68;

a masking moiety (MM) that inhibits the binding of the AB of the activatable antibody in an uncleaved state to EGFR, wherein the masking moiety comprises the amino acid sequence CISPRGCPDGPYVMY (SEQ ID NO: 14); and

a cleavable moiety (CM) coupled to the AB, wherein the CM is a polypeptide that functions as a substrate for a protease, and wherein the CM comprises the amino acid sequence LSGRSDNH (SEQ ID NO: 13), wherein the activatable antibody in the uncleaved state has the structural arrangement from N-terminus to C-terminus as follows: MM-CM-AB or AB-CM-MM.

2. The activatable antibody of claim 1, wherein the antigen binding fragment thereof is selected from the group consisting of a Fab fragment, a $F(ab')_2$ fragment, a scFv, and a scAb.

3. The activatable antibody of claim 1, wherein the activatable antibody comprises a combination of heavy and light chains selected from the group consisting of:

(a) a heavy chain comprising amino acid sequence of SEQ ID NO: 26 and a light chain comprising the amino acid sequence of SEQ ID NO: 28;

(b) a heavy chain comprising amino acid sequence of SEQ ID NO: 2 and a light chain comprising the amino acid sequence of SEQ ID NO: 4;

(c) a heavy chain comprising amino acid sequence of SEQ ID NO: 6 and a light chain comprising the amino acid sequence of SEQ ID NO: 4;

d) a heavy chain comprising amino acid sequence of SEQ ID NO 30 and a light chain comprising the amino acid sequence of SEQ ID NO: 28;

(e) a heavy chain comprising amino acid sequence of SEQ ID NO: 10 and a light chain comprising the amino acid sequence of SEQ ID NO: 4; and

(f) a heavy chain comprising amino acid sequence of SEQ ID NO: 34 and a light chain comprising the amino acid sequence of SEQ ID NO: 28.

4. The activatable antibody of claim 1, wherein the activatable antibody comprises a heavy chain comprising amino acid sequence of SEQ ID NO: 26 and a light chain comprising the amino acid sequence of SEQ ID NO: 28.

5. The activatable antibody of claim 1, wherein the activatable antibody comprises a heavy chain comprising amino acid sequence of SEQ ID NO: 30 and a light chain comprising the amino acid sequence of SEQ ID NO: 28.

6. The activatable antibody of claim 1, wherein the activatable antibody comprises a heavy chain comprising amino acid sequence of SEQ ID NO: 34 and a light chain comprising the amino acid sequence of SEQ ID NO: 28.

7. The activatable antibody of any one of claims 1 to 6, wherein the AB has an equilibrium dissociation constant of about 100 nM or less for binding to EGFR.

8. The activatable antibody of any one of claims 1 to 7, wherein the MM has an equilibrium dissociation constant for binding to the AB which is greater than the equilibrium dissociation constant of the AB to EGFR.

9. The activatable antibody of any one of claims 1 to 8, wherein the MM does not interfere or compete with the AB of the activatable antibody in a cleaved state for binding to EGFR.

10. The activatable antibody of any one of claims 1 to 9, wherein the MM is a polypeptide of no more than 40 amino acids in length.

11. The activatable antibody of any one of claims 1 to 10, wherein the MM polypeptide sequence is different from that of EGFR and wherein the MM polypeptide sequence is no more than 50% identical to any natural binding partner of the AB.

12. The activatable antibody of any one of claims 1 to 10, wherein the MM does not comprise more than 25% amino acid sequence identity to EGFR.

13. The activatable antibody of any one of claims 1 to 10, wherein the MM does not comprise more than 10% amino acid sequence identity to EGFR.

14. The activatable antibody of any one of claims 1 to 13, wherein the CM is a polypeptide of up to 15 amino acids in length.

15. The activatable antibody of any one of claims 1 to 14, wherein the protease is co-localized with EGFR in a tissue, and wherein the protease cleaves the CM in the activatable antibody when the activatable antibody is exposed to the protease.

16. The activatable antibody of any one of claims 1 to 15, wherein the activatable antibody comprises a linking peptide between the MM and the CM.

17. The activatable antibody of any one of claims 1 to 16, wherein the activatable antibody comprises a linking peptide between the CM and the AB.

18. The activatable antibody of any one of claims 1 to 15, wherein the activatable antibody comprises a first linking peptide (LP1) and a second linking peptide (LP2), and wherein the activatable antibody in an uncleaved state has the structural arrangement from N-terminus to C-terminus as follows: MM-LP1-CM-LP2-AB or AB-LP2-CM-LP1-MM.

19. The activatable antibody of claim 18, wherein the two linking peptides need not be identical to each other.

20. The activatable antibody of claim 18, wherein at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of $(GS)_n$, $(GGS)_n$, $(GSGGS)_n$ (SEQ ID NO: 15) and $(GGGS)_n$ (SEQ ID NO: 16), where n is an integer of at least one.

21. The activatable antibody of claim 18, wherein at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of GGSG (SEQ ID NO: 17), GGSGG (SEQ ID NO: 18), GSGSG (SEQ ID NO: 19), GSGGG (SEQ ID NO: 20), GGGSG (SEQ ID NO: 21), and GSSSG (SEQ ID NO: 22).

22. The activatable antibody of claim 18, wherein LP1 comprises the amino acid sequence GSSGGSGGSGGSG (SEQ ID NO: 23).

23. The activatable antibody of claim 18, wherein LP2 comprises the amino acid sequence GSSGT (SEQ ID NO: 24) or GSSG (SEQ ID NO: 37).

24. The activatable antibody of any one of claims 1 to 23, wherein the activatable antibody in an uncleaved state comprises a spacer, wherein the spacer is joined directly to the MM and has the structural arrangement from N-terminus to C- terminus of spacer-MM-CM-AB.

25. The activatable antibody of claim 24, wherein the spacer comprises the amino acid sequence QGQSGQ (SEQ ID NO: 38).

26. The activatable antibody of claim 24, wherein the spacer and MM comprises the amino acid sequence QGQSGQCISPRGCPDGPYVMY (SEQ ID NO: 59).

27. The activatable antibody of any one of claims 1 to 26, wherein the AB is conjugated to an agent.

28. The activatable antibody of claim 27, wherein the agent is a toxin or fragment thereof.

29. The activatable antibody of claim 27, wherein the agent is a dolastatin or a derivative thereof.

30. The activatable antibody of claim 27, wherein the agent is an auristatin or derivative thereof.

31. The activatable antibody of claim 27, wherein the agent is auristatin E or a derivative thereof.

32. The activatable antibody of claim 27, wherein the agent is monomethyl auristatin E (MMAE).

33. The activatable antibody of claim 27, wherein the agent is a maytansinoid or a derivative thereof.

34. The activatable antibody of claim 27, wherein the agent is DM1 or DM4.

35. The activatable antibody of claim 27, wherein the agent is a duocarmycin or derivative thereof.

36. The activatable antibody of claim 27, wherein the agent is a calicheamicin or derivative thereof.

37. The activatable antibody of any one of claims 27 to 36, wherein the agent is conjugated to the AB via a linker.

38. The activatable antibody of claim 37, wherein the linker is a cleavable linker.

39. The activatable antibody of any one of claims 1 to 38 comprising a detectable moiety.

40. The activatable antibody of claim 39, wherein the detectable moiety is a diagnostic agent.

41. An isolated nucleic acid molecule encoding the activatable antibody of any one of claims 1 to 26.

42. The isolated nucleic acid molecule of claim 41, wherein the nucleic acid encoding the activatable antibody comprises a nucleic acid encoding a signal peptide.

43. The isolated nucleic acid molecule of claim 42, wherein the nucleic acid encoding the signal peptide is operably linked to the nucleic acid encoding the activatable antibody via a nucleic acid encoding a spacer.

44. The isolated nucleic acid molecule of claim 43, wherein the nucleic acid encoding the spacer encodes an amino acid sequence that comprises QGQSGQ (SEQ ID NO: 38).

45. A vector comprising the isolated nucleic acid molecule of anyone of claims 41 to 44.

46. A method of producing an activatable antibody by culturing a cell under conditions that lead to expression of the activatable antibody, wherein the cell comprises the vector of claim 45.

47. A method of manufacturing an activatable antibody that in an activated state binds Epidermal Growth Factor Receptor (EGFR), the method comprising:

(a) culturing a cell comprising a nucleic acid construct that encodes the activatable antibody of any one of claims 1 to 26 under conditions that lead to expression of the activatable antibody, and

(b) recovering the activatable antibody.

48. Use of the activatable antibody of any one of claims 1 to 40 in the manufacture of a medicament for treating or delaying the progression of an inflammatory disorder and/or an autoimmune disease in a subject.

49. Use of the activatable antibody of any one of claims 1 to 40 in the manufacture of a medicament for treating or delaying the progression of a cancer in a subject.

50. The use of claim 49, wherein the cancer is breast cancer, colorectal cancer, gastric cancer, glioblastoma, head and neck cancer, lung cancer, ovarian cancer, endometrial cancer, pancreatic cancer, prostate cancer, renal cancer, sarcoma, or skin cancer.

51. The use of claim 48, wherein the EGFR-related disorder is psoriasis.

52. Use of the activatable antibody of any one of claims 1 to 40 in the manufacture of a medicament for inhibiting angiogenesis in a subject.

53. A method of detecting presence or absence of a cleaving agent and Epidermal Growth Factor Receptor (EGFR) in a subject or a sample, the method comprising:

(a) contacting a subject or sample with the anti-EGFR activatable antibody of any one of claims 1 to 40, and

(b) measuring a level of activated anti-EGFR activatable antibody in the subject or sample,

wherein a detectable level of activated anti-EGFR activatable antibody in the subject or sample indicates that the cleaving agent and EGFR are present in the subject or sample, and wherein no detectable level of activated anti-EGFR activatable antibody in the subject or sample indicates that the cleaving agent, EGFR or both the cleaving agent and EGFR are absent in the subject or sample.

54. The method of claim 53, wherein the anti-EGFR activatable antibody comprises a detectable label.

55. The method of claim 54, wherein the detectable label comprises an imaging agent, a contrasting agent, an enzyme, a fluorescent label, a chromophore, a dye, one or more metal ions, or a ligand-based label.

56. The method of claim 53, wherein the method is an *in vivo* method, an *in situ* method, an *ex vivo* method or *in vitro* method.

57. A method of identifying or refining a patient population, the method comprising (i) contacting a sample from a subject in the patient population with an anti-EGFR activatable antibody according to any one of claims 1 to 40; (ii) measuring a level of activated anti-EGFR activatable antibody in the sample, wherein a detectable level of activated anti-EGFR activatable antibody in the sample indicates that the sample is positive for the presence of EGFR and a cleaving agent that cleaves the substrate in the cleavable moiety (CM) of the activatable antibody; and (iii) identifying and selecting one or more samples that test positive for the presence of EGFR and the cleaving agent thereby identifying or refining a patient population.

58. The method of claim 57, wherein the anti-EGFR activatable antibody comprises a detectable label.

59. The method of claim 58, wherein the detectable label comprises an imaging agent, a contrasting agent, an enzyme, a fluorescent label, a chromophore, a dye, one or more metal ions, or a ligand-based label.

60. The method of claim 57, wherein the identifying or the refining of the patient population comprises identifying or refining the patient population for treatment of an EGFR-related disorder, and wherein the EGFR-related disorder is cancer.

61. The method of claim 60, wherein the cancer is breast cancer, colorectal cancer, gastric cancer, glioblastoma, head and neck cancer, lung cancer, ovarian cancer, endometrial cancer, pancreatic cancer, prostate cancer, renal cancer, sarcoma, or skin cancer.

62. The method of claim 60, wherein the EGFR-related disorder is an inflammatory disorder and/or an autoimmune disease, and optionally wherein the EGFR-related disorder is psoriasis.

63. A kit for identifying or refining a patient population for treatment of an EGFR-related disorder, the kit comprising (i) an anti-EGFR activatable antibody according to any one of claims 1 to 40; (ii) means for measuring a level of activated anti-EGFR activatable antibody in a sample from a subject, wherein a detectable level of activated anti-EGFR activatable

antibody in the sample indicates that the sample is positive for the presence of EGFR and a cleaving agent that cleaves the substrate in the cleavable moiety (CM) of the activatable antibody; (iii) means for identifying and selecting one or more subjects that test positive for the presence of EGFR and the cleaving agent thereby identifying or refining a patient population; and (iv) instructions for administering a therapeutically effective amount of an activatable antibody according to any one of claims 1 to 40 to the one or more subjects in the patient population that test positive for the presence of EGFR and the cleaving agent.

64. The kit of claim 63, wherein the anti-EGFR activatable antibody comprises a detectable label.

65. The kit of claim 64, wherein the detectable label comprises an imaging agent, a contrasting agent, an enzyme, a fluorescent label, a chromophore, a dye, one or more metal ions, or a ligand-based label.

66. The kit of claim 63, wherein the EGFR-related disorder is cancer.

67. The kit of claim 66, wherein the cancer is breast cancer, colorectal cancer, gastric cancer, glioblastoma, head and neck cancer, lung cancer, ovarian cancer, endometrial cancer, pancreatic cancer, prostate cancer, renal cancer, sarcoma, or skin cancer.

68. The kit of claim 63, wherein the EGFR-related disorder is an inflammatory disorder and/or an autoimmune disease, and optionally wherein the EGFR-related disorder is psoriasis.

69. Use of the activatable antibody of any one of claims 1 to 40 in the manufacture of a medicament for treating or delaying the progression of a disorder associated with aberrant expression and/or activity of EGFR in a subject.

70. The method of claim 60, wherein the EGFR-related disorder is a disorder associated with aberrant expression and/or activity of EGFR in a subject.

71. The kit of claim 63, wherein the EGFR-related disorder is a disorder associated with aberrant expression and/or activity of EGFR in a subject.