(2004) Cancer Res. 64, 3395-3405; Schaefer *et al.* (2006) Neoplasia 8, 612-622). Accordingly, therapies that effectively interfere with HER3 phosphorylation are desirable.

[0010] In addition, HER3 has been found to be overexpressed and/or overactivated in several types of cancers such as breast cancer, ovarian cancer, prostate cancer, liver cancer, kidney and urinary bladder cancers, pancreatic cancers, brain cancers, hematopoietic neoplasms, retinoblastomas, melanomas, colorectal cancers, gastric cancers, head and neck cancers, lung cancer, etc. (see, *e.g.*, Sithanandam & Anderson (2008) Cancer Gene Ther. 15, 413-448). In general, HER3 is frequently activated in EGFR, HER2, C-Met, and FGFRII-expressing cancers.

[0011] A correlation between the expression of HER2/HER3 and the progression from a non-invasive to an invasive stage has been shown (Alimandi *et al.*, Oncogene 10, 1813-1821; DeFazio *et al.*, Cancer 87, 487-498; Naidu *et al.*, Br. J. Cancer 78, 1385-1390). Thus, HER3 can be used as a diagnostic marker for increased tumor aggressiveness and poor survival. Sustained HER3 activation of PI3K/AKT has been repetitively shown to account for tumor resistance to EGFR/HER2 inhibitors.

[0012] Although the role of HER3 in the development and progression of cancer has been explored (see, *e.g.*, Horst et al. (2005) Int. J. Cancer 115, 519-527; Xue *et al.* (2006) Cancer Res. 66, 1418-1426), HER3 remains largely unappreciated as a target for clinical intervention. Most current immunotherapies primarily focus on inhibiting the action of HER2 and, in particular, heterodimerization of HER2/HER3 complexes (see, *e.g.*, Sliwkowski *et al.* (1994) J. Biol. Chem. 269, 14661-14665). Thus, it is an object of the present invention to provide improved immunotherapeutic agents that effectively inhibit HER3-mediated cell signaling that can be used for diagnosis, prognosis prediction, and treatment of a variety of cancers.

BRIEF SUMMARY

[0013] In a first aspect, the present invention refers to a monoclonal antibody or an antigen-binding fragment thereof, which specifically binds to HER3, comprising an antibody variable light chain region (VL) and an antibody variable heavy chain region (VH), wherein the VL comprises the amino acid sequence: [FW1]SGSLSNIGLNYVS(SEQ ID NO:19)[FW2]RNNQRPS(SEQ ID NO:21)[FW3]AAWDDSPPGEA(SEQ ID NO:23)[FW4], wherein [FW1], [FW2], [FW3] and [FW4] represent VL framework regions, and wherein the VH comprises the amino acid sequence: [FW5]YYYMQ(SEQ ID

NO:31)[FW6]YIGSSGGVTNYADSVKG(SEQ ID NO:32) [FW7]VGLGDAFDI(SEQ ID NO:35)[FW8], wherein [FW5], [FW6], [FW7] and [FW8] represent VH framework regions. In another aspect, the present invention refers to a composition comprising the monoclonal antibody of the present invention, and a pharmaceutically acceptable carrier. In another aspect, the present invention refers to a nucleic acid comprising a sequence encoding the monoclonal antibody or antigen-binding fragment according to the present invention. In another aspect, the present invention refers to a vector comprising a nucleic acid according to the present invention. In another aspect, the present invention refers to an *in vitro* or *ex vivo* host cell comprising a nucleic acid sequence according to the present invention. In another aspect, the present invention refers to a method of making the monoclonal antibody or antigen-binding fragment thereof, comprising (a) culturing a cell comprising the nucleic acid of the present inventon; and (b) isolating the monoclonal antibody or antigen-binding fragment thereof. In another aspect, the present invention refers to the use of the monoclonal antibody or antigen-binding fragment thereof of the present invention in the manufacture of a medicament for inhibiting the proliferation of a cell expressing HER3. In another aspect, the present invention refers to the use of the monoclonal antibody or antigen-binding fragment thereof of the present invention in the manufacture of a medicament for reducing tumor volume of a HER3-expressing tumor in a subject. In another aspect, the present invention refers to the use of the monoclonal antibody or antigen-binding fragment thereof of the present invention in the manufacture of a medicament for treating cancer in a subject. In another aspect, the present invention refers to the use of the monoclonal antibody or antigen-binding fragment thereof of the present invention in the manufacture of a medicament for treating cancer in a subject, said treating comprising administration of the monoclonal antibody or antigen binding fragment to the subject with an additional therapy. In another aspect, the present invention refers to a kit comprising the monoclonal antibody or antigen-binding fragment thereof of the present invention. In another aspect, the present invention refers to a method of diagnosing a HER3-expressing cancer in a patient, wherein the method comprises the steps of: (a) contacting a biological sample from the patient with the monoclonal antibody or antigen-binding fragment of the present invention; (b) detecting binding of the monoclonal antibody or antigen-binding fragment to HER3 to determine a HER3 protein level in the biological sample from the patient; and (c) comparing the HER3 protein level with a standard HER3 protein level. In another aspect, the present invention refers to a method of monitoring the HER3 protein level during treatment of a HER3-expressing cancer in a patient, wherein the method comprises the steps of: (a) contacting a

biological sample from the patient with the monoclonal antibody or antigen-binding fragment according to the present invention; (b) detecting binding of the monoclonal antibody or antigen-binding fragment to HER3 to determine a HER3 protein level in the biological sample from the patient; and (c) comparing the HER3 protein level with a standard HER3 protein level. In another aspect, the present invention refers to a method of monitoring HER3 protein activity level during treatment of cancer in a patient being administered the monoclonal antibody or antigen-binding fragment of the present invention, wherein the method comprises the steps of: (a) contacting a biological sample from the patient with an monoclonal antibody or antigen-binding fragment that specifically binds to phosphorylated HER3; (b) detecting binding of the monoclonal antibody or antigen-binding fragment to phosphorylated HER3 to determine a HER3 protein activity level in the biological sample from the patient; and (c) comparing the HER3 protein activity level with a standard HER3 protein activity level. The disclosure provides anti-HER3 binding molecules, *e.g.*, antibodies or antigen-binding fragments thereof, *e.g.*, monoclonal antibodies capable of suppressing HER3 activity in both ligand-dependent and independent settings. In contrast, other anti-HER3

WHAT IS CLAIMED IS:

1. A monoclonal antibody or an antigen-binding fragment thereof, which specifically binds to HER3, comprising an antibody variable light chain region (VL) and an antibody variable heavy chain region (VH), wherein the VL comprises the amino acid sequence:
[FW1]SGSLSNIGLNYVS(SEQ ID NO:19)[FW2]RNNQRPS(SEQ ID NO:21)[FW3]AAWDDSPPGEA(SEQ ID NO:23)[FW4]
wherein [FW1], [FW2], [FW3] and [FW4] represent VL framework regions, and
wherein the VH comprises the amino acid sequence:
[FW5]YYYMQ(SEQ ID NO:31)[FW6]YIGSSGGVTNYADSVKG(SEQ ID NO:32)[FW7]VGLGDAFDI(SEQ ID NO:35)[FW8]
wherein [FW5], [FW6], [FW7] and [FW8] represent VH framework regions.

2. The monoclonal antibody or antigen-binding fragment of claim 1, wherein the VL comprises an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 3, and wherein the VH comprises an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 2.

3. The monoclonal antibody or antigen-binding fragment of claim 1, wherein the VL comprises an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 3, and wherein the VH comprises an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 2.

4. The monoclonal antibody or antigen-binding fragment of claim 1, wherein the VL comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 3, and wherein the VH comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 2.

5. The monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein FW1 comprises SEQ ID NO: 40 or 44, FW2 comprises SEQ ID NO: 41, FW3 comprises SEQ ID NO: 42, FW4 comprises SEQ ID NO: 43, FW5 comprises SEQ ID NO: 36, FW6 comprises SEQ ID NO: 37, FW7 comprises SEQ ID NO: 38 and FW8 comprises SEQ ID NO: 39.

6. The monoclonal antibody or antigen-binding fragment thereof of claim 1, which comprises a VL comprising SEQ ID NO: 3 and a VH comprising SEQ ID NO: 2.

7. The monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-6, which comprises a heavy chain constant region.

8. The monoclonal antibody or antigen-binding fragment thereof of claim 7, wherein the heavy chain constant region is a human IgG constant region.

9. The monoclonal antibody or antigen-binding fragment thereof of claim 8, wherein the human IgG constant region is an IgG1 constant region.

10. The monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-9, which comprises a light chain constant region selected from the group consisting of a human kappa constant region and a human lambda constant region.

11. The monoclonal antibody or antigen-binding fragment thereof of claim 10, which comprises a human lambda constant region.

12. The monoclonal antibody or antigen-binding fragment of claim 8,
(i) wherein the human IgG constant region comprises amino acid substitutions relative to a wild-type human IgG constant domain at positions 252, 254, and 256, wherein the numbering is according to the EU index as set forth in Kabat, and wherein
(a) the amino acid at position 252 (Methionine) is substituted with Tyrosine (Y),
(b) the amino acid at position 254 (Serine) is substituted with Threonine (T), and
(c) the amino acid at position 256 (Threonine) is substituted with Glutamic acid (E).

13. The monoclonal antibody or antigen-binding fragment of any one of claim 1-6, wherein the monoclonal antibody is a human antibody, a humanized antibody, a chimeric antibody, a recombinant antibody, a multispecific antibody, or an antigen-binding fragment thereof; wherein the antigen-binding fragment is an Fv, Fab, F(ab')2, Fab', dsFv, scFv, or sc(Fv)2; or wherein the monoclonal antibody or antigen-binding fragment thereof is conjugated to at least one heterologous agent.

14. The monoclonal antibody or antigen-binding fragment thereof of claim 1, comprising (i) an antibody light chain comprising an antibody VL comprising SEQ ID NO: 3 and a human lambda light chain constant region, and (ii) an antibody heavy chain comprising an antibody VH comprising SEQ ID NO: 2 and a human IgG1 heavy chain constant region, wherein the human IgG1 constant region comprises amino acid substitutions relative to a wild-type human IgG1 constant domain at positions 252, 254, and 256, wherein the numbering is according to the EU index as set forth in Kabat, and wherein

(a) the amino acid at position 252 (Methionine) is substituted with Tyrosine (Y),

(b) the amino acid at position 254 (Serine) is substituted with Threonine (T), and

(c) the amino acid at position 256 (Threonine) is substituted with Glutamic acid (E).

15. The monoclonal antibody of any one of claims 1-14, wherein the monoclonal antibody is a human antibody.

16. A composition comprising the monoclonal antibody of any one of claims 1-15, and a pharmaceutically acceptable carrier.

17. The composition of claim 16, wherein the composition is refrigerator stable, wherein the monoclonal antibody or antigen-binding fragment thereof is at a concentration of 25-100 mg/mL, and wherein the composition further comprises 25 mM histidine/histidine HCl, 205 mM sucrose, and 0.02% polysorbate 80 at pH 6.0.

18. A nucleic acid comprising a sequence encoding the monoclonal antibody or antigen-binding fragment according to any one of claims 1-15.

19. A vector comprising a nucleic acid according to claim 18.

20. An *in vitro* or *ex vivo* host cell comprising a nucleic acid sequence according to claim 18.

21. A method of making the monoclonal antibody or antigen-binding fragment thereof, comprising (a) culturing a cell comprising the nucleic acid of claim 18; and (b) isolating the monoclonal antibody or antigen-binding fragment thereof.

22. Use of the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-15 in the manufacture of a medicament for inhibiting the proliferation of a cell expressing HER3.

23. The use of claim 22, wherein said cell is a human head and neck tumor cell, a human non-small cell lung cancer cell, a human colorectal tumor cell, a human prostate tumor cell, or a human breast cancer cell.

24. Use of the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-15 in the manufacture of a medicament for reducing tumor volume of a HER3-expressing tumor in a subject.

25. The use of claim 24, wherein said tumor is a human head and neck tumor, a human non-small cell lung cancer tumor, a human colorectal tumor, a human prostate tumor, or a human breast cancer tumor.

26. Use of the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-15 in the manufacture of a medicament for treating cancer in a subject.

27. The use of claim 26, wherein the cancer is a carcinoma.

28. The use of claim 26, wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, gastric cancer, breast cancer, head and neck cancer, prostate cancer, pancreatic cancer, thyroid cancer, melanoma, esophageal cancer, ovarian cancer, kidney cancer, and bladder cancer.

29. The use of claim 28, wherein the cancer is a squamous cell carcinoma of the head and neck.

30. The use of claim 26, wherein the cancer comprises cells comprising a KRAS mutation.

31. The use of claim 26, wherein the cancer comprises cells expressing heregulin.

32. Use of the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-15 in the manufacture of a medicament for treating cancer in a subject, said treating comprising administration of the monoclonal antibody or antigen binding fragment to the subject with an additional therapy.

33. The use of claim 32, wherein the additional therapy is surgery.

34. The use of claim 32, wherein the additional therapy is radiation therapy.

35. The use of claim 32, wherein the additional therapy is a therapeutically effective amount of a second agent, wherein the second agent is an anti-cancer agent other than the monoclonal antibody or antigen-binding fragment thereof.

36. The use of claim 35, wherein the second agent is an EGFR inhibitor, a HER2 inhibitor, a HER3 inhibitor, or a MEK inhibitor.

37. The use of claim 35, wherein the second agent is cetuximab, panitumumab, matuzumab, nimotuzumab, MM-151, or Sym004.

38. The use of claim 35, wherein the second agent is trastuzumab, trastuzumab emtansine, or pertuzumab.

39. The use of claim 35, wherein the second agent is a kinase inhibitor.

40. The use of claim 35, wherein the second agent is gefitinib, canertinib, lapatinib, erlotinib, afatinib, neratinib, selumetinib, WX-554 , trametinib, refametinib, E-6201, MEK-162, or MEHD-7945 A.

41. The use of claim 35, wherein the cancer comprises cells comprising a BRAF mutation.

42. The use of claim 41, wherein the second agent is a MEK inhibitor.

43. The use of claim 35, wherein the cancer comprises cells comprising a KRAS mutation.

44. The use of claim 43, wherein the second agent is a MEK inhibitor.

45. The use of claim 35, wherein the cancer is a head and neck cancer.

46. The use of claim 35, wherein the cancer is a squamous cell carcinoma of the head and neck.

47. The use of claim 35, wherein the cancer is a squamous cell carcinoma of the head and neck, and wherein the second agent is cetuximab.

48. The use of claim 35, wherein the cancer is a non-small cell lung cancer.

49. The use of claim 48, wherein the non-small cell lung cancer cells comprise a KRAS mutation, and wherein the second agent is a MEK inhibitor.

50. The use of claim 35, wherein the cancer is a thyroid cancer.

51. The use of claim 50, wherein the thyroid cancer comprises cells copmrising a BRAF mutation.

52. The use of claim 51, wherein the second agent is a MEK inhibitor.

53. The use of claim 35, wherein the cancer is colorectal cancer.

54. The use of claim 35, wherein the cancer is breast cancer.

55. The use of claim 35, wherein the cancer is a HER2-amplified cancer.

56. The use of claim 35, wherein the cancer is melanoma.

57. The use of claim 56, wherein the second agent is a MEK inhibitor.

58. The use of claim 35, wherein the cancer is gastric cancer.

59. The use of claim 35, wherein the cancer is prostrate cancer.

60. A kit comprising the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1-15.

61. A method of diagnosing a HER3-expressing cancer in a patient, wherein the method comprises the steps of:
(a) contacting a biological sample from the patient with the monoclonal antibody or antigen-binding fragment of any one of claims 1-15;
(b) detecting binding of the monoclonal antibody or antigen-binding fragment to HER3 to determine a HER3 protein level in the biological sample from the patient; and
(c) comparing the HER3 protein level with a standard HER3 protein level.

62. A method of monitoring the HER3 protein level during treatment of a HER3-expressing cancer in a patient, wherein the method comprises the steps of:
(a) contacting a biological sample from the patient with the monoclonal antibody or antigen-binding fragment according to any one of claims 1-15;
(b) detecting binding of the monoclonal antibody or antigen-binding fragment to HER3 to determine a HER3 protein level in the biological sample from the patient; and
(c) comparing the HER3 protein level with a standard HER3 protein level.

63. A method of monitoring HER3 protein activity level during treatment of cancer in a patient being administered the monoclonal antibody or antigen-binding fragment of any one of claims 1-15, wherein the method comprises the steps of:
(a) contacting a biological sample from the patient with the monoclonal antibody or antigen-binding fragment that specifically binds to phosphorylated HER3;
(b) detecting binding of the monoclonal antibody or antigen-binding fragment to phosphorylated HER3 to determine a HER3 protein activity level in the biological sample from the patient; and
(c) comparing the HER3 protein activity level with a standard HER3 protein activity level.