Appl. Pub. No. US 2012/0009181 which is herein incorporated by reference. The full-length amino acid (aa) and nucleotide (nt) sequences for FOLR1 are known in the art and also provided herein as represented by SEQ ID NOs: 1 and 2, respectively. A specifically useful antibody for detection of FOLR1 is the mouse monoclonal anti-huFOLR1 clone BN3.2 (Leica # NCL-L-FRalpha). An example of a therapeutically effective anti-FOLR1 antibody is huMov19 (M9346A). The polypeptides of SEQ ID NOs: 3-5 comprise the variable domain of the heavy chain of huMov19 (M9346A), and the variable domain light chain version 1.00, the variable domain light chain version 1.60 of huMov19, respectively. The huMov19 (M9346A) antibody comprises: (a) a heavy chain CDR1 comprising GYFMN (SEQ ID NO:6); a heavy chain CDR2 comprising RIHPYDGDTFYNQKFQG (SEQ ID NO:7); and a heavy chain CDR3 comprising YDGSRAMDY (SEQ ID NO:8); and (b) a light chain CDR1 comprising KASQSVSFAGTSLMH (SEQ ID NO:9); a light chain CDR2 comprising RASNLEA (SEQ ID NO:10); and a light chain CDR3 comprising QQSREYPYT (SEQ ID NO:11). In certain embodiments, the huMov19 (M9346A) antibody is encoded by the plasmids deposited with the American Type Culture Collection (ATCC), located at 10801 University Boulevard, Manassas, VA 20110 on April 7, 2010 under the terms of the Budapest Treaty and having ATCC deposit nos. PTA-10772 and PTA-10773 or 10774. Examples of FOLR1 immunoconjugates ~~userful~~useful in the therapeutic methods of the invention are provided below.

IX. FOLR1 Immunoconjugates

[0133] The present invention also includes methods for increasing the efficacy of conjugates (also referred to herein as immunoconjugates), comprising the anti-FOLR1 antibodies, antibody fragments, functional equivalents, improved antibodies and their aspects as disclosed herein, linked or conjugated to a cytotoxin (drug) or prodrug. Exemplary FOLR1 immunoconjugates can be found in US Appl. Pub. No. US 2012/0009181, which is herein incorporated by reference. A particularly effective therapeutic immunoconjugate of the invention comprises the huMov19 antibody described above.

[0134] Suitable drugs or prodrugs are known in the art. In certain embodiments, drugs or prodrugs are cytotoxic agents. The cytotoxic agent used in the cytotoxic conjugate of the present invention can be any compound that results in the death of a cell, or induces cell death, or in some manner decreases cell viability, and includes, for example, maytansinoids and maytansinoid analogs, benzodiazepines, taxoids, CC-1065 and CC-1065 analogs, duocarmycins and duocarmycin analogs, enediynes, such as calicheamicins, dolastatin and dolastatin analogs including auristatins, tomaymycin derivaties, leptomycin derivaties, methotrexate, cisplatin, carboplatin, daunorubicin, doxorubicin, vincristine, vinblastine,

SEQUENCES

SEQ ID NO:1 - human folate receptor 1
MAQRMTTQLLLLLVWVAVVGEAQTRIAWARTELLNVCMNAKHHKEKPGPEDKLHEQCR
PWRKNACCSTNTSQEAHKDVSYLYRFNWNHCGEMAPACKRHFIQDTCLYECSPNLGPWI
QQVDQSWRKERVLNVPLCKEDCEQWWEDCRTSYTCKSNWHKGWNWTSGFNKCAVGA
ACQPFHFYFPTPTVLCNEIWTHSYKVSNYSRGSGRCIQMWFDPAQGNPNEEVARFYAAAM
SGAGPWAAWPFLLSLALMLLWLLS

SEQ ID NO:2 - human folate receptor 1 nucleic acid sequence
atggctcagcggatgacaacacagctgctgctccttctagtgtgggtggctgtagtaggggaggctcagacaaggattgcatgggccaggact
gagcttctcaatgtctgcatgaacgccaagcaccacaaggaaaagccaggccccgaggacaagttgcatgagcagtgtcgaccctggagga
agaatgcctgctgttctaccaacaccagccaggaagcccataaggatgtttcctacctatatagattcaactggaaccactgtggagagatggca
cctgcctgcaaacggcatttcatccaggacacctgcctctacgagtgctccccccaacttggggccctggatccagcaggtggatcagagctgg
cgcaaagagcgggtactgaacgtgccccctgtgcaaagaggactgtgagcaatggtgggaagattgtcgcacctcctacacctgcaagagcaa
ctggcacaagggctggaactggacttcagggtttaacaagtgcgcagtgggagctgcctgccaacctttccatttctacttccccacacccactg
ttctgtgcaatgaaatctggactcactcctacaaggtcagcaactacagccgagggagtggccgctgcatccagatgtggttcgacccagccca
gggcaaccccaatgaggaggtggcgaggttctatgctgcagccatgagtggggctgggccctgggcagcctggctttcctgcttagcctgg
ccctaatgctgctgtggctgctcagc

SEQ ID NO:3 - huMov19 vHC
QVQLVQSGAEVVKPGASVKISCKASGYTFTGYFMNWVKQSPGQSLEWIGRIHPYDGDTFY
NQKFQGKATLTVDKSSNTAHMELLSLTSEDFAVYYCTRYDGSRAMDYWGQGTTVTVSS

SEQ ID NO:4 - huMov19 vLCv1.00
DIVLTQSPLSLAVSLGQPAIISCKASQSVSFAGTSLMHWYHQKPGQQPRLLIYRASNLEAGV
PDRFSGSGSKTDFTLNISPVEAEDAATYYCQQSREYPYTFGGGTKLEIKR

SEQ ID NO:5 - huMov19 vLCv1.60
DIVLTQSPLSLAVSLGQPAIISCKASQSVSFAGTSLMHWYHQKPGQQPRLLIYRASNLEAGV
PDRFSGSGSKTDFTLTISPVEAEDAATYYCQQSREYPYTFGGGTKLEIKR

WHAT IS CLAIMED IS:

1. An anti-Folate receptor 1 (FOLR1) antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate for use in cancer therapy in a subject, wherein an increased expression of FOLR1 gene or protein in the cancer sample from said subject has been detected using a detection method that distinguishes between staining intensity or staining uniformity in a FOLR1 expressing cancer sample as compared to staining intensity or staining uniformity in one or more reference sample, and wherein the efficacy of cancer therapy with an anti-FOLR1 antibody or anti-FOLR1 immunoconjugate has thereby been increased.

2. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of claim 1, wherein the detection method is immunohistochemistry (IHC).

3. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of claim 2, wherein the IHC can distinguish different levels of FOLR1 expression.

4. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of any of claims 1-3, wherein said detection method produces a range of staining intensity for samples having weak FOLR1 expression, moderate FOLR1 expression, or strong FOLR1 expression.

5. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of any of claims 1-4, wherein said detection method distinguishes between staining intensity and staining uniformity in a FOLR1 expressing cancer sample as compared to a reference sample.

6. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of any of claims 1-5, wherein the cancer sample has a staining intensity score of 1 or greater for FOLR1 expression by immunohistochemistry.

7. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of claim 6, wherein the cancer sample has a staining intensity score of 2 or greater for FOLR1 expression by immunohistochemistry.

8. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of any of claims 6-7, wherein the cancer sample has a staining intensity score of 2, 3, or 3+ for FOLR1 expression by immunohistochemistry.

9. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of any of claims 6-8, wherein the cancer sample has a staining uniformity for FOLR1 expression that is homogenous.

10. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of any of claims 6-8, wherein the cancer sample has a staining uniformity for FOLR1 expression that is heterogeneous.

11. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate for use in cancer therapy in a subject of any of claims 2-10, wherein the IHC is performed manually.

12. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of any of claims 2-10, wherein the IHC is performed using an automated system.

13. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of any of claims 1-12, wherein said reference sample is a positive reference sample or a negative reference sample.

14. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of any of claims 1-13, wherein the reference sample comprises cells, cell pellets, or tissue.

15. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of any of claims 1-14, wherein the detection method comprises detecting FOLR1 expression with an antibody or antigen binding fragment thereof that specifically binds FOLR1.

16. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of claim 15, wherein said antibody or antigen binding fragment thereof for detecting FOLR1 expression is the antibody huMov19 or BN3.2.

17. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of claim 15 or 16, wherein said antibody or antigen binding fragment thereof for detecting FOLR1 expression further comprises a detection reagent selected from the group consisting of: an enzyme, a fluorophore, a radioactive label, and a luminophore.

18. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of claim 17, wherein said detection reagent is selected from the group consisting of: biotin, digoxigenin, fluorescein, tritium, and rhodamine.

19. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of any of claims 15-18, wherein the concentration of said antibody or antigen binding fragment thereof for detecting FOLR1 expression is about 0.9 to about 3.8 μg/ml.

20. An article of manufacture comprising an anti-FOLR1 antibody, an antigen binding fragment thereof, or an anti-FOLR1 immunoconjugate; a container; and a package insert or label indicating that the antibody or immunoconjugate can be used to treat a cancer characterized by the expression of FOLR1 at a level of 1 or greater measured by IHC.

21. The article of manufacture of claim 20, wherein said IHC can distinguish different levels of FOLR1 intensity.

22. The article of manufacture of claim 20 or 21, wherein a cancer sample from said cancer has an IHC [[a]] staining intensity score of 1 or greater for FOLR1 expression and a staining uniformity that is heterogeneous or homogeneous.

23. The article of manufacture of any of claims 20-22, wherein a cancer sample from said cancer has a staining intensity score of 2, 3, or 3+ for FOLR1 expression.

24. The article of manufacture of any of claim 20-23, wherein the immunohistochemistry is performed manually.

25. The article of manufacture of any of claims 20-23, wherein the immunohistochemistry is performed using an automated system.

26. The article of manufacture of any of claims 20-25, wherein said anti-FOLR1 immunoconjugate comprises an anti-FOLR1 antibody or antigen binding fragment thereof, a linker, and a cytotoxin.

27. The article of manufacture of claim 26, wherein said anti-FOLR1 antibody or antigen binding fragment thereof of said anti-FOLR1 immunoconjugate is huMovl9 (M9346A).

28. The article of manufacture of claims 26 or 27, 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.

29. The article of manufacture of claim 28, wherein said linker is selected from the group consisting: N-succinimidyl 4-(2-pyridyldithio)pentanoate (SPP) or N-succinimidyl 4-(2-pyridyldithio)-2-sulfopentanoate (sulfo-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).

30. The article of manufacture of claim 29, wherein said linker is N-succinimidyl 4-(2-pyridyldithio)-2-sulfobutanoate (sulfo-SPDB).

31. The article of manufacture of any one of claims 26-30, wherein said cytotoxic agent is selected from the group consisting of a maytansinoid, maytansinoid analog, 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 agent.

32. The article of manufacture of claim 31, wherein said cytotoxic agent is a maytansinoid.

33. The article of manufacture of claim 32, wherein said cytotoxic agent is N(2')-deacetyl-N(2')-(3-mercapto-1-oxopropyl)-maytansine or N(2')-deacetyl-N(2')-(4-mercapto-4-methyl-1-oxopentyl)-maytansine (DM4).

34. The article of manufacture of claim 33, wherein said cytotoxic agent is N(2')-deacetyl-N(2')-(4-mercapto-4-methyl-1-oxopentyl)-maytansine (DM4).

35. The article of manufacture of any of claims 26-34, wherein said anti-FOLR1 immunoconjugate comprises the antibody huMovl9 (M9346A), sulfo-SPDB, and DM4 (IMGN853).

36. A combination diagnostic and pharmaceutical kit comprising a murine anti-FOLR1 antibody for use in diagnosis and further comprising a humanized anti-FOLR1 antibody, an antigen binding fragment thereof, or an anti-FOLR1 immunoconjugate comprising a humanized anti-FOLR1 antibody for use in therapy.

37. The kit of claim 36, wherein the diagnostic antibody is able to detect FOLR1 expression by IHC.

38. The kit of claim 37, wherein said IHC can distinguish different levels of FOLR1 expression.

39. The kit of claim 38, wherein said IHC produces a range of staining intensity for samples having weak FOLR1 expression, moderate FOLR1 expression, or strong FOLR1 expression.

40. The kit of any of claims 37-39, wherein said IHC distinguishes between staining intensity and staining uniformity in a FOLR1 expressing cancer sample as compared to a reference sample.

41. The kit of any of claims 36-40, further comprising one or more reference samples.

42. The kit of claim 41, wherein said reference sample is a positive reference sample or a negative reference sample.

43. The kit of claim 41 or 42, wherein the reference sample comprises cells, cell pellets, or tissue.

44. The kit of any of claims 36-43, wherein said detection antibody further comprises a detection reagent selected from the group consisting of: an enzyme, a fluorophore, a radioactive label, and a luminophore.

45. The kit of claim 44, wherein said detection reagent is selected from the group consisting of: biotin, digoxigenin, fluorescein, tritium, and rhodamine.

46. The kit of any of claims 36-45, wherein the concentration of the detection antibody is about 0.9 to about 3.8 μg/ml.

47. The kit of any of claims 36-46, wherein the humanized anti-FOLR1 antibody is huMov19 (M9346A).

48. The kit of any of claims 36-46, wherein said anti-FOLR1 immunoconjugate comprises an anti-FOLR1 antibody or antigen binding fragment thereof, a linker, and a cytotoxin.

49. The kit of claim 48, wherein said anti-FOLR1 antibody or antigen binding fragment thereof of said anti-FOLR1 immunoconjugate is huMov19 (M9346A).

50. The kit of claims 48 or 49, 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.

51. The kit of claim 50, wherein said linker is selected from the group consisting: N-succinimidyl 4-(2-pyridyldithio)pentanoate (SPP) or N-succinimidyl 4-(2-pyridyldithio)-2-sulfopentanoate (sulfo-SPP); N-succinimidyl 4-(2-pyridyldithio)butanoate (SPDB) or N-succinimidyl 4-(2-pyridyidithio)-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).

52. The kit of claim 51, wherein said linker is N-succinimidyl 4-(2-pyridyldithio)-2-sulfobutanoate (sulfo-SPDB).

53. The kit of any one of claims 48-52, wherein the cytotoxin is selected from the group consisting of a maytansinoid, maytansinoid analog, 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 agent.

54. The kit of claim 53, wherein said cytotoxic agent is a maytansinoid.

55. The kit of claim 54, wherein said cytotoxic agent is N(2')-deacetyl-N(2')-(3-mercapto-1-oxopropyl)-maytansine or N(2')-deacetyl-N(2')-(4-mercapto-4-methyl-1-oxopentyl)-maytansine (DM4).

56. The kit of claim 55, wherein said cytotoxic agent is N(2')-deacetyl-N(2')-(4-mercapto-4-methyl-1-oxopentyl)-maytansine (DM4).

57. The kit of any of claims 48-56, wherein said anti-FOLR1 immunoconjugate comprises the antibody huMov19 (M9346A), sulfo-SPDB, and DM4 (IMGN853).

58. A diagnostic kit comprising an anti-FOLR1 antibody that specifically binds to cell surface FOLR1, a reagent for immunohistochemistry, and one or more standardized controls for reference, wherein said standardized controls comprise cells, cell pellets, or formalin fixed paraffin embedded tissue samples, and wherein said one or more standardized controls are from

non-FOLR1 expressing, weak-FOLR1 expressing, moderate-FOLR1 expressing, or strong-FOLR1 expressing cells, cell pellets, or tissues.

59. The kit of claim 58, wherein the weak-FOLR1 expressing control is selected from the group consisting of: salivary gland tissue, lung tissue, OVCAR3 cells, and T47D cells.

60. The kit of claim 58, wherein the strong-FOLR1 expressing control is selected form the group consisting of: pancreas tissue, KB cells, IGROV1 cells, and a cell line stably or transiently transfected with Folate Receptor 1.

61. The kit of claim 60, wherein said cell line stable or transiently transfected with Folate receptor 1 is 300.19/FR1.

62. A method for identifying a cancer likely to respond to an anti-FOLR1 antibody, an antigen binding fragment thereof, or anti-FOLR1 immunoconjugate, said method comprising:

(a) contacting a biological sample taken from said cancer with an antibody or antigen binding fragment thereof that specifically binds FOLR1;

(b) detecting binding of said antibody or antigen binding fragment thereof that specifically binds FOLR1 of said biological sample of (a) using a detection method;

(c) assigning a score to said binding of step (b), wherein said score is assigned based on comparison to one or more reference samples; and

(d) comparing said score in step (c) to the score of a reference tissue or cell, wherein a score for said cancer FOLR1 level that is greater than the score for a low FOLR1 expressing reference sample or a score for said cancer FOLR1 level that is equal to or greater than the score for a high FOLR1 expressing reference sample identifies said cancer as likely to respond to an anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate.

63. The method of claim 62, wherein said cancer is ovarian, endometrial, or non-small cell lung cancer.

64. A method of identifying a tumor sensitive to treatment with an anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate, said method comprising:

(a) measuring the level of FOLR1 expression in a tumor tissue sample taken from said tumor, wherein said measuring comprises the use of a detection method that distinguishes between staining intensity or staining uniformity in a FOLR1 expressing cancer sample as compared to staining intensity or staining uniformity in one or more reference samples;

(b) determining a FOLR1 staining intensity score for said tumor tissue sample; and

(c) comparing the FOLR1 staining intensity score determined in step (b) to a reference value determined by measuring FOLR1 protein expression in at least one reference sample, wherein

said at least one reference sample is a tissue, cell, or cell pellet sample which is not sensitive to treatment with an anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate, and wherein a FOLR1 staining intensity score for said sample determined in step (b) that is higher than said reference value identifies said tumor as being sensitive to treatment with an anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate, wherein said anti-FOLR1 antibody for treatment comprises the heavy chain variable domain of SEQ ID NO:3 and the light chain variable domain of SEQ ID NO:4 or 5, and wherein said anti-FOLR1 immunoconjugate for treatment comprises an anti-FOLR1 antibody or antigen binding fragment thereof comprising the heavy chain variable domain of SEQ ID NO:3 and the light chain variable domain of SEQ ID NO:4 or 5.

65. The method of any of claims 62-64, wherein said detection method is performed manually or using an automated system.

66. The method of claim 65, wherein said detection method is automated.

67. The method of any of claims 62-66, wherein the detection method is IHC.

68. The method of claim 67, wherein said IHC is calibrated IHC that can distinguish different levels of FOLR1 expression.

69. The method of any of claims 62-68, wherein said detection method produces a range of staining intensity for samples having weak FOLR1 expression, moderate FOLR1 expression, or strong FOLR1 expression.

70. The method of any of claims 62-69, wherein said detection method distinguishes between staining intensity and staining uniformity in a FOLR1 expressing cancer sample as compared to a reference sample.

71. The method of any of claims 62-70, wherein the sample has a staining intensity score of 1 or greater for FOLR1 expression by immunohistochemistry.

72. The method of claim 71, wherein the sample has a staining intensity score of 2 or greater for FOLR1 expression by immunohistochemistry.

73. The method of claim 71 or 72, wherein the sample has a staining intensity score of 2, 3, or 3+ for FOLR1 expression by immunohistochemistry.

74. The method of any of claims 62-73, wherein the sample has a staining uniformity for FOLR1 expression that is heterogeneous or homogenous.

75. The method of any of claims 62-74, wherein the sample has a staining uniformity for FOLR1 expression that is homogenous.

76. The method of claim 64, wherein the level of FOLR1 expression is measured using an antibody or antigen binding fragment thereof that specifically binds FOLR1.

77. The method of any of claims 62, 63, and 65-76, wherein said antibody or antigen binding fragment thereof for measuring or detecting FOLR1 is the antibody huMov19 (M9346A).

78. The method of any of claims 62, 63, and 65-77, wherein said antibody or antigen binding fragment thereof for measuring or detecting FOLR1 further comprises a detection reagent selected from the group consisting of: an enzyme, a fluorophore, a radioactive label, and a luminophore.

79. The method of claim 78, wherein said detection reagent is selected from the group consisting of: biotin, digoxigenin, fluorescein, tritium, and rhodamine.

80. The method of any of claims 76-79, wherein the concentration of said antibody or antigen binding fragment thereof for measuring or detecting FOLR1 is about 0.9 to about 3.8 μg/ml.

81. A method of optimizing a therapeutic regimen with an anti-FOLR1 antibody, an antigen binding fragment thereof, or an anti-FOLR1 immunoconjugate for a subject having lung or ovarian cancer, said method comprising:

(a) contacting a tumor tissue sample taken from said subject with an antibody or antigen binding fragment thereof that specifically binds FOLR1;

(b) measuring the binding of said antibody or antigen binding fragment thereof in (a) to FOLR1 in said sample using a detection method that can distinguish between staining intensity or staining uniformity in a FOLR1 expressing cancer sample as compared to staining intensity or staining uniformity in one or more reference samples and assigning a staining score to said sample;

wherein a score in step (b) is equal to or greater than the score for a low FOLR1 expressing reference sample identifies said lung or ovarian cancer as likely to respond to an anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate.

82. A method of detecting the expression of FOLR1 in a tumor tissue sample from a subject, said method comprising:

(a) obtaining a tumor tissue sample from a subject, wherein said tumor tissue sample is formalin-fixed paraffin embedded;

(b) contacting said tumor tissue sample with an antibody or antigen binding fragment thereof that specifically binds FOLR1;

(c) measuring the binding of said antibody or antigen binding fragment thereof in (b) to FOLR1 in said tumor tissue sample using a detection method that can distinguish between staining intensity or staining uniformity in a FOLR1 expressing cancer sample as compared to staining intensity or staining uniformity in one or more reference samples; and

(d) assigning a FOLR1 expression score to said tumor tissue sample after comparing the level of FOLR1 staining intensity or staining uniformity in said tumor tissue sample to one or more reference samples.

83. A method of identifying a subject having a lung or ovarian cancer as likely to respond to an anti-FOLR1 antibody, an antigen binding fragment thereof, or anti-FOLR1 immunoconjugate treatment regimen, said method comprising:

(a) contacting a biological sample taken from a subject comprising cells from said ovarian or lung cancer with an agent that specifically binds FOLR1;

(b) detecting binding of said agent to said biological sample of (a);

(c) assigning a score to said binding of step (b), wherein said score is assigned based on comparison to one or more reference samples; and

(d) comparing said score in step (c) to the score of a reference tissue or cell, wherein a score for said ovarian or lung cancer FOLR1 level that is greater than the score for a low FOLR1 expressing reference sample or a score for said ovarian or lung cancer FOLR1 level that is equal to or greater than the score for a high FOLR1 expressing reference sample identifies said ovarian or lung cancer as likely to respond to an anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate.

84. The method of claim 82, wherein said cancer is ovarian, endometrial, or non-small cell lung cancer.

85. The method of any of claims 81-84, wherein the detection method produces a range of staining intensity for samples having weak FOLR1 expression, moderate FOLR1 expression, or strong FOLR1 expression.

86. The method of any of claims 81-84, wherein the sample has a staining intensity score of 1 or greater for FOLR1 expression, and wherein the sample has a staining uniformity for FOLR1 expression that is homogeneous or heterogeneous.

87. The method of claim 86, wherein the sample has a staining uniformity for FOLR1 expression that is homogenous.

88. The method of any of claims 86-87, wherein the sample has a staining intensity score of 2, 3, or 3+ for FOLR1 expression.

89. The method of any of claims 81-88, wherein the detection method is performed manually.

90. The method of any of claims 81-88, wherein the detection method is performed using an automated system.

91. The method of any of claims 81-90, wherein said reference sample is a positive reference sample or a negative reference sample.

92. The method of any of claims 81-91, wherein the reference sample comprises cells, cell pellets, or tissue.

93. The method of any of claims 81-92, wherein said agent or antibody or antigen binding fragment thereof that specifically binds FOLR1 further comprises a detection reagent selected from the group consisting of: an enzyme, a fluorophore, a radioactive label, and a luminophore.

94. The method of claim 93, wherein said detection reagent is selected from the group consisting of: biotin, digoxigenin, fluorescein, tritium, and rhodamine.

95. The method of any of claims 81-94, wherein the concentration of said agent or antibody or antigen binding fragment thereof that specifically binds FOLR1 is at a concentration of about 0.9 to about 3.8 μg/ml.

96. The method of an of claims 81-95, wherein said agent or antibody or antigen binding fragment thereof that specifically binds FOLR1 comprises the heavy chain variable domain of SEQ ID NO:3 and the light chain variable domain of SEQ ID NO:4 or 5.

97. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of any of claims 15-19, wherein said antibody or antigen binding fragment thereof for detecting FOLR1 expression comprises the heavy chain variable domain of SEQ ID NO:3 and the light chain variable domain of SEQ ID NO:4 or 5.

98. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of any of claims 1-19, wherein said anti-FOLR1 antibody for use in cancer therapy comprises the heavy chain variable domain of SEQ ID NO:3 and the light chain variable domain of SEQ ID NO:4 or 5.

99. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of any of claims 1-19, wherein said anti-FOLR1 immunoconjugate comprises an anti-FOLR1 antibody or antigen binding fragment thereof, a linker, and a cytotoxin.

100. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of claim 99, wherein said anti-FOLR1 antibody or antigen binding fragment thereof of said anti-FOLR1 immunoconjugate is huMov19 (M9346A).

101. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of claim 99, wherein said anti-FOLR1 antibody or antigen binding fragment thereof of said anti-FOLR1 immunoconjugate comprises the heavy chain variable domain of SEQ ID NO:3 and the light chain variable domain of SEQ ID NO:4 or 5.

102. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of any of claims 99-101, 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.

103. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of claim 102, wherein said linker is selected from the group consisting: N-succinimidyl 4-(2-pyridyldithio)pentanoate (SPP) or N-succinimidyl 4-(2-pyridyldithio)-2-sulfopentanoate (sulfo-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).

104. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of claim 103, wherein said linker is N-succinimidyl 4-(2-pyridyldithio)-2-sulfobutanoate (sulfo-SPDB).

105. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of any of claims 99-104, wherein said cytotoxic agent is selected from the group consisting of a maytansinoid, maytansinoid analog, 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 agent.

106. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of claim 105, wherein said cytotoxic agent is a maytansinoid.

107. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of claim 106, wherein said cytotoxic agent is N(2')-deacetyl-N(2')-(3-mercapto-1-oxopropyl)-maytansine or N(2')-deacetyl-N(2')-(4-mercapto-4-methyl-1-oxopentyl)-maytansine (DM4).

108. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of claim 107, wherein said cytotoxic agent is N(2')-deacetyl-N(2')-(4-mercapto-4-methyl-1-oxopentyl)-maytansine (DM4).

109. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of any of claims 99-108, wherein said anti-FOLR1 immunoconjugate comprises the antibody huMovl9 (M9346A), sulfo-SPDB, and DM4 (IMGN853).

110. The anti-FOLR1 antibody, antigen binding fragment thereof, or anti-FOLR1 immunoconjugate of any of claims 99-108, wherein said anti-FOLR1 antibody or antigen binding fragment thereof of said anti-FOLR1 immunoconjugate comprises the heavy chain variable domain of SEQ ID NO:3 and the light chain variable domain of SEQ ID NO:4 or 5, and wherein said anti-FOLR1 immunoconjugate comprises the linker sulfo-SPDB and the cytotoxin DM4.

111. The article of manufacture of any of claims 20-25, wherein said anti-FOLR1 antibody or antigen binding fragment thereof comprises the heavy chain variable domain of SEQ ID NO:3 and the light chain variable domain of SEQ ID NO:4 or 5.

112. The article of manufacture of any of claims 26-34, wherein said anti-FOLR1 antibody or antigen binding fragment thereof of said anti-FOLR1 immunoconjugate comprises the heavy chain variable domain of SEQ ID NO:3 and the light chain variable domain of SEQ ID NO:4 or 5, and wherein said anti-FOLR1 immunoconjugate comprises the linker sulfo-SPDB and the cytotoxin DM4.

113. The kit of any of claims 36-47, wherein said humanized anti-FOLR1 antibody comprises the heavy chain variable domain of SEQ ID NO:3 and the light chain variable domain of SEQ ID NO:4 or 5.

114. The kit of any of claims 48-56, wherein said anti-FOLR1 antibody or antigen binding fragment thereof of said anti-FOLR1 immunoconjugate comprises the heavy chain variable domain of SEQ ID NO:3 and the light chain variable domain of SEQ ID NO:4 or 5, and wherein said anti-FOLR1 immunoconjugate comprises the linker sulfo-SPDB and the cytotoxin DM4.

115. The method of any of claims 76-80, wherein said antibody or antigen binding fragment thereof for measuring or detecting FOLR1 comprises the heavy chain variable domain of SEQ ID NO:3 and the light chain variable domain of SEQ ID NO:4 or 5.

SEQUENCE LISTING

<110> Immunogen, Inc.
CARRIGAN, Christina N.
WHITEMAN, Kathleen R.
PAYNE, Gillian
LADD, Sharron

<120> METHODS FOR INCREASING EFFICACY OF FOLR1 CANCER THERAPY

<130> 2921.015PC01

<140> PCT/US2012/031544
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<151> 2011-04-01

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<170> PatentIn version 3.5

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Lys Arg His Phe Ile Gln Asp Thr Cys Leu Tyr Glu Cys Ser Pro Asn
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Leu Gly Pro Trp Ile Gln Gln Val Asp Gln Ser Trp Arg Lys Glu Arg
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Trp Thr His Ser Tyr Lys Val Ser Asn Tyr Ser Arg Gly Ser Gly Arg
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Arg Phe Ser Gly Ser Gly Ser Lys Thr Asp Phe Thr Leu Thr Ile Ser
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WHAT IS CLAIMED IS:

1. An anti-Folate receptor 1 (FOLR1) immunoconjugate for use in cancer therapy in a subject,

wherein a tumor sample from said subject exhibits increased expression of FOLR1 using a detection method that distinguishes between staining intensity or staining uniformity in a FOLR1 expressing cancer sample as compared to staining intensity or staining uniformity in one or more reference sample,

wherein the anti-FOLR1 immunoconjugate has the formula (A) – (L) – (C), wherein:

(A) comprises an anti-FOLR1 antibody or antigen binding fragment thereof comprising: (a) a heavy chain CDR1 comprising GYFMN (SEQ ID NO:6); a heavy chain CDR2 comprising RIHPYDGDTFYNQKFQG (SEQ ID NO:7); and a heavy chain CDR3 comprising YDGSRAMDY (SEQ ID NO:8); and (b) a light chain CDR1 comprising KASQSVSFAGTSLMH (SEQ ID NO:9); a light chain CDR2 comprising RASNLEA (SEQ ID NO:10); and a light chain CDR3 comprising QQSREYPYT (SEQ ID NO:11),

(L) comprises a cleavable linker, and

(C) comprises a maytansinoid or analog thereof, and

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

2. The anti-FOLR1 immunoconjugate of claim 1, wherein said anti-FOLR1 antibody or antigen binding fragment thereof comprises the heavy chain variable domain of SEQ ID NO:3 and the light chain variable domain of SEQ ID NO:4 or 5.

3. The anti-FOLR1 immunoconjugate of claim 1 or 2, wherein the detection method is immunohistochemistry (IHC).

4. The anti-FOLR1 immunoconjugate of claim 3, wherein the IHC can distinguish different levels of FOLR1 expression.

5. The anti-FOLR1 immunoconjugate of any of claims 1-4, wherein said detection method produces a range of staining intensity for samples having weak FOLR1 expression, moderate FOLR1 expression, or strong FOLR1 expression.

6. The anti-FOLR1 immunoconjugate of any of claims 1-5, wherein said detection method distinguishes between staining intensity and staining uniformity in a FOLR1 expressing cancer sample as compared to a reference sample.

7. The anti-FOLR1 immunoconjugate of any of claims 1-6, wherein the cancer sample has a staining intensity score of 1 or greater for FOLR1 expression by IHC.

8. The anti-FOLR1 immunoconjugate of claim 7, wherein the cancer sample has a staining intensity score of 2 or greater for FOLR1 expression by IHC.

9. The anti-FOLR1 immunoconjugate of claim 7 or 8, wherein the cancer sample has a staining intensity score of 2, 3, or 3+ for FOLR1 expression by IHC.

10. The anti-FOLR1 immunoconjugate of any of claims 7-9, wherein the cancer sample has a staining uniformity for FOLR1 expression that is homogenous.

11. The anti-FOLR1 immunoconjugate of any of claims 7-9, wherein the cancer sample has a staining uniformity for FOLR1 expression that is heterogeneous.

12. The anti-FOLR1 immunoconjugate for use in cancer therapy in a subject of any of claims 3-11, wherein the IHC is performed manually.

13. The anti-FOLR1 immunoconjugate of any of claims 3-11, wherein the IHC is performed using an automated system.

14. The anti-FOLR1 immunoconjugate of any of claims 1-13, wherein said reference sample is a positive reference sample or a negative reference sample.

15. The anti-FOLR1 immunoconjugate of any of claims 1-14, wherein the reference sample comprises cells, cell pellets, or tissue.

16. The anti-FOLR1 immunoconjugate of any of claims 1-15, wherein the detection method comprises detecting FOLR1 expression with a detection antibody or antigen binding fragment thereof that specifically binds FOLR1.

17. The anti-FOLR1 immunoconjugate of claim 16, wherein said detection antibody or antigen binding fragment thereof is the antibody huMov19 or BN3.2.

18. The anti-FOLR1 immunoconjugate of claim 16 or 17, wherein said detection antibody or antigen binding fragment thereof further comprises a detection reagent selected from the group consisting of: an enzyme, a fluorophore, a radioactive label, and a luminophore.

19. The anti-FOLR1 immunoconjugate of claim 18, wherein said detection reagent is selected from the group consisting of: biotin, digoxigenin, fluorescein, tritium, and rhodamine.

20. The anti-FOLR1 immunoconjugate of any of claims 16-19, wherein the concentration of said detection antibody or antigen binding fragment thereof is about 0.9 to about 3.8 μg/ml.

21. The anti-FOLR1 immunoconjugate of any of claims 16-20, wherein said detection antibody or antigen binding fragment thereof comprises: (a) a heavy chain CDR1 comprising GYFMN (SEQ ID NO:6); a heavy chain CDR2 comprising RIHPYDGDTFYNQKFQG (SEQ ID NO:7); and a heavy chain CDR3 comprising YDGSRAMDY (SEQ ID NO:8); and (b) a light chain CDR1 comprising KASQSVSFAGTSLMH (SEQ ID NO:9); a light chain CDR2 comprising RASNLEA (SEQ ID NO:10); and a light chain CDR3 comprising QQSREYPYT (SEQ ID NO:11).

22. The anti-FOLR1 immunoconjugate of claim 21, wherein said detection antibody or antigen binding fragment thereof comprises the heavy chain variable domain of SEQ ID NO:3 and the light chain variable domain of SEQ ID NO:4 or 5.

23. The anti-FOLR1 immunoconjugate of any of claims 1-22, wherein said anti-FOLR1 antibody or antigen binding fragment thereof is huMov19 (M9346A).

24. The anti-FOLR1 immunoconjugate of any of claims 1-23, wherein said cleavable linker is selected from the group consisting: N-succinimidyl 4-(2-pyridyldithio)pentanoate (SPP); [[or]] N-succinimidyl 4-(2-pyridyldithio)-2-sulfopentanoate (sulfo-SPP); N-succinimidyl 4-(2-pyridyldithio)butanoate (SPDB); and [[or]] N-succinimidyl 4-(2-pyridyldithio)-2-sulfobutanoate (sulfo-SPDB).

25. The anti-FOLR1 immunoconjugate of claim 24, wherein said cleavable linker is N-succinimidyl 4-(2-pyridyldithio)-2-sulfobutanoate (sulfo-SPDB).

26. The anti-FOLR1 immunoconjugate of any of claims 1-25, wherein said maytansinoid or analog thereof 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).

27. The anti-FOLR1 immunoconjugate of claim 26, wherein said maytansinoid or analog thereof is N(2')-deacetyl-N(2')-(4-mercapto-4-methyl-l-oxopentyl)-maytansine (DM4).

28. The anti-FOLR1 immunoconjugate of any of claims 1-27, wherein said cleavable linker is sulfo-SPDB, and wherein said maytansinoid or analog thereof is DM4.

29. The anti-FOLR1 immunoconjugate of any of claims 1-27, wherein said anti-FOLR1 antibody or antigen binding fragment thereof comprises the heavy chain variable domain of SEQ ID NO:3 and the light chain variable domain of SEQ ID NO:4 or 5, wherein said cleavable linker is sulfo-SPDB, and wherein said maytansinoid or analog thereof is DM4.

30. The anti-FOLR1 immunoconjugate of any of claims 1-27, wherein said anti-FOLR antibody or antigen binding fragment thereof is huMov19 (M9346A), wherein said cleavable linker is sulfo-SPDB, and wherein said maytansinoid or analog thereof is DM4.