Claims

1. An isolated antibody or antigen binding fragment thereof that specifically binds a human folate receptor, wherein the isolated antibody or antigen binding fragment comprises:

(a) a heavy chain (HC) CDR1 comprising the amino acid sequence of GYTFTGYFMN (SEQ ID NO:132); a HC CDR2 comprising the amino acid sequence of RIHPYDGDTF (SEQ ID NO:131); and a HC CDR3 comprising YDGSRAMDY (SEQ ID NO:3); and

(b) a light chain (LC) CDR1 comprising the amino acid sequence of KASQSVSFAGTSLMH (SEQ ID NO:7); a LC CDR2 comprising the amino acid sequence of RASNLEA (SEQ ID NO:8); and a LC CDR3 comprising the amino acid sequence of QQSREYPYT (SEQ ID NO:9).

2. The isolated antibody or antigen binding fragment thereof of claim 1, wherein the isolated antibody or antigen binding fragment thereof comprises a HC variable domain comprising the amino acid sequence of SEQ ID NO:4.

3. The isolated antibody or antigen binding fragment thereof of claim 2, wherein the isolated antibody or antigen binding fragment thereof comprises a HC comprising the amino acid sequence of SEQ ID NO:6.

4. The isolated antibody or antigen binding fragment thereof of claim 1, wherein the isolated antibody or antigen binding fragment thereof comprises a LC variable domain comprising the amino acid sequence of SEQ ID NO:10 or SEQ ID NO:11.

5. The isolated antibody or antigen binding fragment thereof of claim 4, wherein the isolated antibody or antigen binding fragment thereof comprises a LC comprising the amino acid sequence of SEQ ID NO:12 or SEQ ID NO:13.

6. An isolated antibody or antigen binding fragment thereof that specifically binds a human folate receptor, wherein the isolated antibody or antigen binding fragment comprises:

(a) a heavy chain (HC) CDR1 comprising the amino acid sequence of GYTFTGYFMN (SEQ ID NO:132); a HC CDR2 comprising the amino acid sequence of RIHPYDGDTFYNQKFQG (SEQ ID NO:2); and a HC CDR3 comprising YDGSRAMDY (SEQ ID NO:3); and

(b) a light chain (LC) CDR1 comprising the amino acid sequence of KASQSVSFAGTSLMH (SEQ ID NO:7); a LC CDR2 comprising the amino acid sequence of RASNLEA (SEQ ID NO:8); and a LC CDR3 comprising the amino acid sequence of QQSREYPYT (SEQ ID NO:9).

7. The isolated antibody or antigen binding fragment thereof of claim 6, wherein the isolated antibody or antigen binding fragment thereof comprises a LC variable domain comprising the amino acid sequence of SEQ ID NO:10 or SEQ ID NO:11.

8. The isolated antibody or antigen binding fragment thereof of claim 7, wherein the isolated antibody or antigen binding fragment thereof comprises a LC comprising the amino acid sequence of SEQ ID NO:12 or SEQ ID NO:13.

9. The isolated antibody or antigen binding fragment thereof of any one of claims 1-8, which is a full length antibody.

10. The isolated antibody or antigen binding fragment thereof of any one of claims 1, 2, 4, 6, and 7, which is an antibody fragment.

11. The isolated antibody or antigen binding fragment thereof of claim 10, wherein the antigen binding fragment is a Fab, Fab', F(ab')2, scFv, disulfide linked Fv, intrabody, IgG-CH2, minibody, F(ab')3, tetrabody, triabody, diabody, DVD-Ig, mAb2, (scFv)2, or scFv-Fc.

12. The isolated antibody or antigen binding fragment thereof of any one of claims 1-8, wherein the isolated antibody or antigen binding fragment thereof binds to a human folate receptor 1 with a Kd of about 1.0 to about 10 nM, and wherein the binding affinity is measured by flow cytometry, Biacore, or radioimmunoassay.

13. The isolated antibody or antigen binding fragment thereof of any one of claims 1-8, wherein the isolated antibody or antigen binding fragment thereof binds to a human folate receptor 1 with a Kd of about 0.06 nM to about 1.0 nM, and wherein the binding affinity is measured by flow cytometry, Biacore, or radioimmunoassay.

14. A method of making the isolated antibody of any one of claims 1, 2, 4, 6, and 7, comprising (a) culturing a cell expressing the antibody; and (b) isolating the antibody from the cultured cell.

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

(A) is an isolated antibody or antigen binding fragment thereof that specifically binds a human folate receptor,

(L) is a linker, and

(C) is a cytotoxic agent;

wherein said linker (L) links (A) to (C); and

wherein the isolated antibody or antigen binding fragment thereof comprises:

(a) a HC CDR1 comprising the amino acid sequence of GYTFTGYFMN (SEQ ID NO:132), a HC CDR2 comprising the amino acid sequence of RIHPYDGDTF (SEQ ID NO:131), and a HC CDR3 comprising the amino acid sequence of YDGSRAMDY (SEQ ID NO:3), and

(b) a LC CDR1 comprising the amino acid sequence of KASQSVSFAGTSLMH (SEQ ID NO:7), a LC CDR2 comprising the amino acid sequence of RASNLEA (SEQ ID NO:8), and a LC CDR3 comprising the amino acid sequence of QQSREYPYT (SEQ ID NO:9).

16. The immunoconjugate of claim 15, wherein the isolated antibody or antigen binding fragment thereof comprises a HC variable domain comprising the amino acid sequence of SEQ ID NO:4.

17. The immunoconjugate of claim 16, wherein the isolated antibody or antigen binding fragment thereof comprises a HC comprising the amino acid sequence of SEQ ID NO:6.

18. The immunoconjugate of claim 15, wherein the isolated antibody or antigen binding fragment thereof comprises a LC variable domain comprising the amino acid sequence of SEQ ID NO:10 or SEQ ID NO:11.

19. The immunoconjugate of claim 18, wherein the isolated antibody or antigen binding fragment thereof comprises a LC comprising the amino acid sequence of SEQ ID NO:12 or SEQ ID NO:13.

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

(A) is an isolated antibody or antigen binding fragment thereof that specifically binds a human folate receptor,

(L) is a linker, and

(C) is a cytotoxic agent;

wherein said linker (L) links (A) to (C); and

wherein the isolated antibody or antigen binding fragment thereof comprises:

(a) a HC CDR1 comprising the amino acid sequence of GYTFTGYFMN (SEQ ID NO:132), a HC CDR2 comprising the amino acid sequence of RIHPYDGDTFYNQKFQG (SEQ ID NO:2), and a HC CDR3 comprising the amino acid sequence of YDGSRAMDY (SEQ ID NO:3), and

(b) a LC CDR1 comprising the amino acid sequence of KASQSVSFAGTSLMH (SEQ ID NO:7), a LC CDR2 comprising the amino acid sequence of RASNLEA (SEQ ID NO:8), and a LC CDR3 comprising the amino acid sequence of QQSREYPYT (SEQ ID NO:9).

21. The immunoconjugate of claim 20, wherein the isolated antibody or antigen binding fragment thereof comprises a LC variable domain comprising the amino acid sequence of SEQ ID NO:10 or SEQ ID NO:11.

22. The immunoconjugate of claim 21, wherein the isolated antibody or antigen binding fragment thereof comprises a LC comprising the amino acid sequence of SEQ ID NO:12 or SEQ ID NO:13.

23. The immunoconjugate of any one of claims 15-22, wherein the linker is selected from the group consisting of: a non-cleavable linker, a hydrophilic linker, and a dicarboxylic acid based linker.

24. The immunoconjugate of any one of claims 15-22, wherein the linker is a cleavable linker.

25. The immunoconjugate of any one of claims 15-22, wherein the linker is selected from the group consisting of: *N*-succinimidyl 4-(2-pyridyldithio)pentanoate (SPP); *N*-succinimidyl 4-(2-pyridyldithio)-2-sulfopentanoate (sulfo-SPP); *N*-succinimidyl 4-(2-pyridyldithio)butanoate (SPDB); *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).

26. The immunoconjugate of claim 25, wherein the linker is *N*-succinimidyl 4-(2-pyridyldithio)butanoate (SPDB) or *N*-succinimidyl 4-(2-pyridyldithio)-2-sulfobutanoate (sulfo-SPDB).

27. The immunoconjugate of any one of claims 15-22, wherein the 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 cytotoxic agent.

28. The immunoconjugate of claim 27, wherein the cytotoxic agent is a maytansinoid.

29. The immunoconjugate of claim 28, wherein the cytotoxic agent is N(2')-deacetyl-N(2')-(3-mercapto-l-oxopropyl)-maytansine (DM1) or N(2')-deacetyl-N(2')-(4-mercapto-4-methyl-1-oxopentyl)-maytansine (DM4).

30. The immunoconjugate of claim 15, wherein the linker (L) is *N*-succinimidyl 4-(2-pyridyldithio)-2-sulfobutanoate (sulfo-SPDB), and wherein the cytotoxic agent (C) is N(2')-deacetyl-N(2')-(4-mercapto-4-methyl-1-oxopentyl)-maytansine (DM4).

31. The immunoconjugate of claim 20, wherein the linker (L) is *N*-succinimidyl 4-(2-pyridyldithio)-2-sulfobutanoate (sulfo-SPDB), and wherein the cytotoxic agent (C) is N(2')-deacetyl-N(2')-(4-mercapto-4-methyl-1-oxopentyl)-maytansine (DM4).

32. The immunoconjugate of any one of claims 15-22, 30, and 31 comprising 2-6 (C) per (A).

33. A pharmaceutical composition comprising the isolated antibody or antigen binding fragment thereof of any one of claims 1-13 or the immunoconjugate of any one of claims 15-32 and a pharmaceutically acceptable carrier.

34. The pharmaceutical composition of claim 33, wherein the immunoconjugates have an average of about 3 to about 4 (C) per (A).

35. A diagnostic reagent comprising the isolated antibody or antigen binding fragment thereof of any one of claims 1-13 or the immunoconjugate of any one of claims 15-32.

36. The diagnostic reagent of claim 35, further comprising a label selected from the group consisting of: a radio label, a fluorophore, a chromophore, an imaging agent and a metal ion.

37. A kit comprising the isolated antibody or antigen binding fragment thereof of any one of claims 1-13 or the immunoconjugate of any one of claims 15-32.

38. A method of inhibiting tumor growth in a subject, comprising administering a therapeutically effective amount of the isolated antibody or antigen binding fragment thereof of any one of claims 1-13, the immunoconjugate of any one of claims 15-32, or the pharmaceutical composition of claim 33 or claim 34 to the subject.

39. The method of claim 38, wherein the tumor is selected from the group consisting of: ovarian tumor, brain tumor, breast tumor, uterine tumor, endometrial tumor, pancreatic tumor, renal tumor, peritoneal tumor, and lung tumor.

40. The method of claim 39, wherein the tumor is an ovarian tumor.

41. The method of claim 39, wherein the tumor is a lung tumor.

42. The method of claim 39, wherein the tumor is an endometrial tumor.

43. The method of claim 39, wherein the tumor is a peritoneal tumor.

44. The method of claim 39, wherein the tumor is a uterine tumor.

45. The method of any one of claims 38-44, wherein tumor growth is inhibited to treat cancer.

46. An isolated cell producing the isolated antibody of any one of claims 1-8.