

Claims:

1. An antibody that binds to FOLR1, comprising a first heavy chain variable region comprising:
 - (a) a CDR1 sequence having two or fewer substitutions in any of the amino acid sequences of SEQ ID NOs: 1-5; and~~or~~
 - (b) a CDR2 sequence having two or fewer substitutions in any of the amino acid sequences of SEQ ID NOs: 6-17; and~~or~~
 - (c) a CDR3 sequence having two or fewer substitutions in any of the amino acid sequences of SEQ ID NOs: 18-22.
2. The antibody of claim 1, further comprising a second heavy chain variable region comprising:
 - (a) a CDR1 sequence having two or fewer substitutions in any of the amino acid sequences of SEQ ID NOs: 1-5; and~~or~~
 - (b) a CDR2 sequence having two or fewer substitutions in any of the amino acid sequences of SEQ ID NOs: 6-17; and~~or~~
 - (c) a CDR3 sequence having two or fewer substitutions in any of the amino acid sequences of SEQ ID NOs: 18-22.
3. The antibody of ~~any one of claims 1 or 2~~claim 1 or claim 2, wherein said CDR1, CDR2, and CDR3 sequences are present in a human framework.
4. The antibody of any one of claims 1 to 3, further comprising a heavy chain constant region sequence in the absence of a CH1 sequence.
5. The antibody of any one of claims 1 to 4, wherein the first heavy chain variable region comprises:
 - (a) a CDR1 sequence selected from the group consisting of SEQ ID NOs: 1-5; and~~or~~
 - (b) a CDR2 sequence selected from the group consisting of SEQ ID NOs: 6-17; and~~or~~
 - (c) a CDR3 sequence selected from the group consisting of SEQ ID NOs: 18-22.
6. The antibody of claim 5, wherein the first heavy chain variable region comprises:
 - (a) a CDR1 sequence selected from the group consisting of SEQ ID NOs: 1-5; and
 - (b) a CDR2 sequence selected from the group consisting of SEQ ID NOs: 6-11; and
 - (c) a CDR3 sequence selected from the group consisting of SEQ ID NOs: 18-19.

7. The antibody of claim 5, wherein the first heavy chain variable region comprises:

- (a) a CDR1 sequence of SEQ ID NO: 2 or SEQ ID NO: 4; and
- (b) a CDR2 sequence selected from the group consisting of SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, and SEQ ID NO: 17; and
- (c) a CDR3 sequence selected from the group consisting of SEQ ID NOs: 20-22.

~~6~~8. The antibody of any one of claims 2 to ~~5~~7, wherein the second heavy chain variable region comprises:

- ~~(a) a CDR1 sequence selected from the group consisting of SEQ ID NOs: 1-5; and~~(a) a CDR1 sequence selected from the group consisting of SEQ ID NOs: 1-5; and
- ~~(b) a CDR2 sequence selected from the group consisting of SEQ ID NOs: 6-17; and~~(b) a CDR2 sequence selected from the group consisting of SEQ ID NOs: 6-17; and
- ~~(c) a CDR3 sequence selected from the group consisting of SEQ ID NOs: 18-22.~~

9. The antibody of claim 8, wherein the second heavy chain variable region comprises:

- (a) a CDR1 sequence selected from the group consisting of SEQ ID NOs: 1-5; and
- (b) a CDR2 sequence selected from the group consisting of SEQ ID NOs: 6-11; and
- (c) a CDR3 sequence selected from the group consisting of SEQ ID NOs: 18-19.

10. The antibody of claim 8, wherein the second heavy chain variable region comprises:

- (a) a CDR1 sequence of SEQ ID NO: 2 or SEQ ID NO: 4; and
- (b) a CDR2 sequence selected from the group consisting of SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, and SEQ ID NO: 17; and
- (c) a CDR3 sequence selected from the group consisting of SEQ ID NOs: 20-22.

~~7.~~ The antibody of any one of claims 5 to 6, comprising:

- ~~(a) a CDR1 sequence selected from the group consisting of SEQ ID NOs: 1-5; and~~
- ~~(b) a CDR2 sequence selected from the group consisting of SEQ ID NOs: 6-17; and~~
- ~~(c) a CDR3 sequence selected from the group consisting of SEQ ID NOs: 18-22.~~

~~8.~~ The antibody of any one of claims 5 to 7, wherein the second heavy chain variable region comprises:

- ~~(a) a CDR1 sequence selected from the group consisting of SEQ ID NOs: 1-5; and~~
- ~~(b) a CDR2 sequence selected from the group consisting of SEQ ID NOs: 6-17; and~~
- ~~(c) a CDR3 sequence selected from the group consisting of SEQ ID NOs: 18-22.~~

~~9~~11. The antibody of any one of claims 1 to ~~8~~4, comprising:

- (a) a CDR1 sequence of SEQ ID NO: 2, a CDR2 sequence of SEQ ID NO: 6, and a CDR3 sequence of SEQ ID NO: 19; or
- (b) a CDR1 sequence of SEQ ID NO: 4, a CDR2 sequence of SEQ ID NO: 16, and a CDR3 sequence of SEQ ID NO: 20.

~~10~~12. The antibody of any one of claims 1 to ~~9~~4, comprising a heavy chain variable region sequence having at least 95% sequence identity to any one of the sequences of SEQ ID NOs: 23-74.

13. The antibody of claim 12, comprising a heavy chain variable region sequence having at least 95% sequence identity to any one of the sequences of SEQ ID NOs: 23-49 and 52-72.

~~11~~14. The antibody of any one of claims 1 to ~~10~~4, comprising a heavy chain variable region sequence selected from the group consisting of SEQ ID NOs: 23-74.

15. The antibody of claim 14, comprising a heavy chain variable region sequence selected from the group consisting of SEQ ID NOs: 23-49 and 52-72.

~~12~~6. The antibody of claim ~~11~~14, wherein the heavy chain variable region sequence is selected from the group consisting of: SEQ ID NO: 26, SEQ ID NO: 49, SEQ ID NO: 61, and SEQ ID NO: 72.

~~13~~17. An antibody that binds to FOLR1, comprising a first heavy chain variable region comprising:

- (a) a CDR1 sequence of the formula:

G F X1 F X2 S X3 X4 (SEQ ID NO: 75)

where: X1 is N, T, I, or S;
X2 is R or S;
X3 is F or Y; and
X4 is G, S, or T; and

- (b) a CDR2 sequence of the formula:

I S S X1 S X2 X3 I (SEQ ID NO: 76)

where: X1 is G or S;
X2 is S or T; and
X3 is Y, D, T, or S; and

- (c) a CDR3 sequence of the formula:

A R D V T S G I A A A G X1 A F N I (SEQ ID NO: 77)

where: X1 is A or S,

in a monovalent or bivalent format.

1418. An antibody that binds to FOLR1, comprising a first heavy chain variable region comprising:

(a) a CDR1 sequence of the formula:

G F X1 F S S Y S (SEQ ID NO: 78)

where: X1 is S or T; and

(b) a CDR2 sequence of the formula:

I X1 X2 S S X3 X4 I (SEQ ID NO: 79)

where: X1 is S, T, or D;

X2 is S, R, or G;

X3 is D or S; and

X4 is T or I; and

(c) a CDR3 sequence of the formula:

A X1 V G L X2 F D Y (SEQ ID NO: 80)

where: X1 is S or T; and

X2 is D or E,

in a monovalent or bivalent format.

1519. An antibody that binds to FOLR1, comprising:

a first heavy chain variable region comprising:

(a) a CDR1 sequence of the formula:

G F X1 F X2 S X3 X4 (SEQ ID NO: 75)

where: X1 is N, T, I, or S;

X2 is R or S;

X3 is F or Y; and

X4 is G, S, or T; and

(b) a CDR2 sequence of the formula:

I S S X1 S X2 X3 I (SEQ ID NO: 76)

where: X1 is G or S;

X2 is S or T; and

X3 is Y, D, T, or S; and

(c) a CDR3 sequence of the formula:

A R D V T S G I A A A G X1 A F N I (SEQ ID NO: 77)

where: X1 is A or S; and

a second heavy chain variable region comprising:

(a) a CDR1 sequence of the formula:

G F X1 F S S Y S (SEQ ID NO: 78)

where: X1 is S or T; and

(b) a CDR2 sequence of the formula:

I X1 X2 S S X3 X4 I (SEQ ID NO: 79)

where: X1 is S, T, or D;

X2 is S, R, or G;

X3 is D or S; and

X4 is T or I; and

(c) a CDR3 sequence of the formula:

A X1 V G L X2 F D Y (SEQ ID NO: 80)

where: X1 is S or T; and

X2 is D or E.

~~16. The antibody of claim 15, wherein the first heavy chain variable region is located nearer to the N-terminus relative to the second heavy chain variable region.~~

~~17. The antibody of claim 15, wherein the first heavy chain variable region is located nearer to the C-terminus relative to the second heavy chain variable region.~~

~~18. An antibody that binds to FOLR1, comprising a heavy chain variable region comprising CDR1, CDR2 and CDR3 sequences in a human VH framework, wherein the CDR sequences comprise a sequence having two or fewer substitutions in a CDR sequence selected from the group consisting of SEQ ID NOs: 1-22.~~

~~19. The antibody of claim 18, comprising a heavy chain variable region comprising CDR1, CDR2 and CDR3 sequences in a human VH framework, wherein the CDR sequences are selected from the group consisting of SEQ ID NOs: 1-22.~~

20. An antibody that binds to FOLR1, comprising:

(a) a heavy chain variable region comprising a CDR1 sequence of SEQ ID NO: 2, a CDR2 sequence of SEQ ID NO: 6, and a CDR3 sequence of SEQ ID NO: 19 in a human VH framework; or

(b) a heavy chain variable region comprising a CDR1 sequence of SEQ ID NO: 4, a CDR2 sequence of SEQ ID NO: 16, and a CDR3 sequence of SEQ ID NO: 20 in a human VH framework.

21. An antibody that binds to FOLR1, comprising:

(a) a heavy chain variable region comprising a CDR1 sequence of SEQ ID NO: 2, a CDR2 sequence of SEQ ID NO: 6, and a CDR3 sequence of SEQ ID NO: 19 in a human VH framework, in a monovalent or bivalent configuration; or

(b) a heavy chain variable region comprising a CDR1 sequence of SEQ ID NO: 4, a CDR2 sequence of SEQ ID NO: 16, and a CDR3 sequence of SEQ ID NO: 20 in a human VH framework, in a monovalent or bivalent configuration.

~~22. An antibody that binds to FOLR1, comprising:~~

~~a heavy chain variable region comprising a CDR1 sequence of SEQ ID NO: 4, a CDR2 sequence of SEQ ID NO: 16, and a CDR3 sequence of SEQ ID NO: 20 in a human VH framework.~~

~~23. An antibody that binds to FOLR1, comprising:~~

~~a heavy chain variable region comprising a CDR1 sequence of SEQ ID NO: 4, a CDR2 sequence of SEQ ID NO: 16, and a CDR3 sequence of SEQ ID NO: 20 in a human VH framework, in a monovalent or bivalent configuration.~~

~~24~~22. An antibody that binds to FOLR1, comprising:

a first heavy chain variable region comprising:

a CDR1 sequence of SEQ ID NO: 2, a CDR2 sequence of SEQ ID NO: 6, and a CDR3 sequence of SEQ ID NO: 19, in a human VH framework; and

a second heavy chain variable region comprising:

a CDR1 sequence of SEQ ID NO: 4, a CDR2 sequence of SEQ ID NO: 16, and a CDR3 sequence of SEQ ID NO: 20, in a human VH framework.

~~25. The antibody of claim 24, wherein the first heavy chain variable region is located nearer to the N-terminus relative to the second heavy chain variable region.~~

~~26. The antibody of claim 24, wherein the first heavy chain variable region is located nearer to the C-terminus relative to the second heavy chain variable region.~~

~~27. The antibody of any one of claims 1-14 and 18-23, which is monospecific.~~

~~28~~23. The antibody of any one of claims 1 to ~~26~~22, which is multi-specific.

~~29~~24. The antibody of claim ~~28~~23, which is bispecific.

~~30~~25. The antibody of claim ~~28-23~~ or ~~29~~claim 24, which has binding affinity to a CD3 protein and an FOLR1 protein.

~~31. The antibody of claim 28 or 29, which has binding affinity to two different epitopes on the same FOLR1 protein.~~

~~32. The antibody of claim 28 or 29, having binding affinity to an effector cell.~~

~~33. The antibody of claim 32, having binding affinity to a T-cell antigen.~~

~~34. The antibody of claim 33, having binding affinity to CD3.~~

~~35~~26. A chimeric antigen receptor comprising ~~The-an~~ antibody of any one of claims 1 to ~~34~~24, which is in a CAR-T format.

27. An antibody that binds to FOLR1, comprising:

(a) a heavy chain variable region comprising a CDR1 sequence of SEQ ID NO: 2, a CDR2 sequence of SEQ ID NO: 6, and a CDR3 sequence of SEQ ID NO: 19 in a human VH framework, in a monovalent or bivalent configuration, or

(b) a heavy chain variable region comprising a CDR1 sequence of SEQ ID NO: 4, a CDR2 sequence of SEQ ID NO: 16, and a CDR3 sequence of SEQ ID NO: 20 in a human VH framework, in a monovalent or bivalent configuration, or

(c) a first heavy chain variable region comprising a CDR1 sequence of SEQ ID NO: 2, a CDR2 sequence of SEQ ID NO: 6, and a CDR3 sequence of SEQ ID NO: 19, in a human VH framework; and a second heavy chain variable region comprising a CDR1 sequence of SEQ ID NO: 4, a CDR2 sequence of SEQ ID NO: 16, and a CDR3 sequence of SEQ ID NO: 20, in a human VH framework,

wherein the antibody is multi-specific and has binding affinity to CD3.

~~3628.~~ A bispecific antibody comprising:

(i) a heavy chain variable region having binding affinity to CD3, comprising a CDR1 sequence of SEQ ID NO: 83, a CDR2 sequence of SEQ ID NO: 84, and CDR3 sequence of SEQ ID NO: 85, in a human VH framework;

(ii) a light chain variable region comprising a CDR1 sequence of SEQ ID NO: 86, a CDR2 sequence of SEQ ID NO: 87, and CDR3 sequences of SEQ ID NO: 88, in a human VL framework;
and

(iii) an antigen-binding domain of an anti-FOLR1 heavy chain antibody, comprising:

(A) a CDR1 sequence of SEQ ID NO: 2, a CDR2 sequence of SEQ ID NO: 6, and a CDR3 sequence of SEQ ID NO: 19, in a human VH framework; or

(B) a CDR1 sequence of SEQ ID NO: 4, a CDR2 sequence of SEQ ID NO: 16, and a CDR3 sequence of SEQ ID NO: 20, in a human VH framework.

~~3729.~~ A bispecific antibody comprising:

(i) a heavy chain variable region having binding affinity to CD3, comprising a CDR1 sequence of SEQ ID NO: 83, a CDR2 sequence of SEQ ID NO: 84, and CDR3 sequence of SEQ ID NO: 85, in a human VH framework;

(ii) a light chain variable region comprising a CDR1 sequence of SEQ ID NO: 86, a CDR2 sequence of SEQ ID NO: 87, and a CDR3 sequence of SEQ ID NO: 88, in a human VL framework;
and

(iii) an antigen-binding domain of an anti-FOLR1 heavy chain antibody, comprising:

(A) a CDR1 sequence of SEQ ID NO: 2, a CDR2 sequence of SEQ ID NO: 6, and a CDR3 sequence of SEQ ID NO: 19, in a human VH framework, in a monovalent or bivalent configuration; or

(B) a CDR1 sequence of SEQ ID NO: 4, a CDR2 sequence of SEQ ID NO: 16, and a CDR3 sequence of SEQ ID NO: 20, in a human VH framework, in a monovalent or bivalent configuration.

~~38.~~ A bispecific antibody comprising:

~~(i) a heavy chain variable region having binding affinity to CD3, comprising a CDR1 sequence of SEQ ID NO: 83, a CDR2 sequence of SEQ ID NO: 84, and CDR3 sequence of SEQ ID NO: 85, in a human VH framework;~~

~~(ii) a light chain variable region comprising a CDR1 sequence of SEQ ID NO: 86, a CDR2 sequence of SEQ ID NO: 87, and CDR3 sequences of SEQ ID NO: 88, in a human VL framework;
and~~

~~_____ (iii) an antigen binding domain of an anti FOLR1 heavy chain antibody, comprising a CDR1 sequence of SEQ ID NO: 4, a CDR2 sequence of SEQ ID NO: 16, and a CDR3 sequence of SEQ ID NO: 20, in a human VH framework.~~

39. ~~_____ A bispecific antibody comprising:~~

~~_____ (i) a heavy chain variable region having binding affinity to CD3, comprising a CDR1 sequence of SEQ ID NO: 83, a CDR2 sequence of SEQ ID NO: 84, and CDR3 sequence of SEQ ID NO: 85, in a human VH framework;~~

~~_____ (ii) a light chain variable region comprising a CDR1 sequence of SEQ ID NO: 86, a CDR2 sequence of SEQ ID NO: 87, and CDR3 sequences of SEQ ID NO: 88, in a human VL framework;~~
~~and~~

~~_____ (iii) an antigen binding domain of an anti FOLR1 heavy chain antibody, comprising a CDR1 sequence of SEQ ID NO: 4, a CDR2 sequence of SEQ ID NO: 16, and a CDR3 sequence of SEQ ID NO: 20, in a human VH framework, in a monovalent or bivalent configuration.~~

30. The bispecific antibody of claim 28 or claim 29, wherein the heavy chain variable region having binding affinity to CD3 comprises a sequence having at least 95% sequence identity to SEQ ID NO: 89.

31. The bispecific antibody of claim 30, wherein the heavy chain variable region having binding affinity to CD3 comprises SEQ ID NO: 89.

32. The bispecific antibody of any one of claims 28 to 31, wherein the light chain variable region comprises a sequence having at least 95% sequence identity to SEQ ID NO: 90.

33. The bispecific antibody of claim 32, wherein the light chain variable region comprises SEQ ID NO: 90.

34. The bispecific antibody of claim 29, wherein the antigen-binding domain of the anti-FOLR1 heavy chain antibody is in a bivalent configuration and comprises a linker comprising SEQ ID NO: 81 or SEQ ID NO: 82.

35. A bispecific antibody that binds to FOLR1 and CD3, comprising:

_____ (a) a first polypeptide comprising SEQ ID NO: 102;

_____ (b) a second polypeptide comprising SEQ ID NO: 103; and

(c) a third polypeptide comprising SEQ ID NO: 104, 105, 106, 107, 108 or 109.

36. The bispecific antibody of claim 35, wherein the third polypeptide subunit comprises SEQ ID NO: 107.

37. The bispecific antibody of claim 45 or claim 46, which is a bispecific three-chain antibody like molecule.

~~40~~38. A multi-specific antibody comprising:

(i) a heavy chain variable region having binding affinity to CD3, comprising a CDR1 sequence of SEQ ID NO: 83, a CDR2 sequence of SEQ ID NO: 84, and CDR3 sequence of SEQ ID NO: 85, in a human VH framework;

(ii) a light chain variable region comprising a CDR1 sequence of SEQ ID NO: 86, a CDR2 sequence of SEQ ID NO: 87, and CDR3 sequences of SEQ ID NO: 88, in a human VL framework; and

(iii) an antigen-binding domain of an anti-FOLR1 heavy chain antibody, wherein the antigen-binding domain comprises a first and a second antigen-binding region, in a bivalent configuration, wherein:

the first antigen-binding region comprises a CDR1 sequence of SEQ ID NO: 2, a CDR2 sequence of SEQ ID NO: 6, and a CDR3 sequence of SEQ ID NO: 19, in a human VH framework; and

the second antigen-binding region comprises a CDR1 sequence of SEQ ID NO: 4, a CDR2 sequence of SEQ ID NO: 16, and a CDR3 sequence of SEQ ID NO: 20, in a human VH framework.

~~41. The multi-specific antibody of claim 40, wherein the first antigen-binding region is located nearer to the N-terminus relative to the second antigen-binding region.~~

~~42. The multi-specific antibody of claim 40, wherein the first antigen-binding region is located nearer to the C-terminus relative to the second antigen-binding region.~~

~~43~~39. The multi-specific ~~or bispecific~~ antibody of ~~any one of claims 36 to 42~~claim 38, wherein the first and second antigen-binding regions of the antigen-binding domain of the anti-FOLR1 heavy chain antibody are connected by a polypeptide linker.

~~44. The multi-specific or bispecific antibody of claim 43, wherein the polypeptide linker is a GS linker.~~

~~45. The multi-specific or bispecific antibody of claim 44, wherein the GS linker consists of the sequence of SEQ ID NO: 81 or SEQ ID NO: 82.~~

~~46~~40. A pharmaceutical composition comprising the antibody of any one of claims 1 to 25 or 27 to 45~~39~~.

~~47. A method for the treatment of a disorder characterized by expression of FOLR1, comprising administering to a subject with said disorder an antibody of any one of claims 1 to 45, or the pharmaceutical composition of claim 46.~~

~~48~~41. Use of an antibody of any one of claims 1 to 25 or 27 to 45~~39~~, in the preparation of a medicament for the treatment of a disorder characterized by expression of FOLR1.

~~49~~42. An antibody of any one of claims 1 to 25 or 27 to 45, for use~~39 in the treatment of a disorder characterized by expression of FOLR1~~for use in therapy.

~~50~~43. The ~~method, use, or antibody use~~ of ~~any one of claims 47 to 49~~claim 41 or claim 42, wherein the disorder is selected from the group consisting of: ovarian cancer, uterine cancers, lung cancer, renal cancer, colorectal cancer, breast cancer, and brain cancer.

~~51~~44. A polynucleotide encoding an antibody of any one of claims 1 to 25 or 27 to 39~~45~~.

~~52~~45. A vector comprising the polynucleotide of claim ~~51~~44.

~~53~~46. A cell comprising the vector of claim ~~52~~45.

~~54. A method of producing an antibody of any one of claims 1 to 45, comprising growing a cell according to claim 53 under conditions permissive for expression of the antibody, and isolating the antibody from the cell.~~

~~55. A method of making an antibody of any one of claims 1 to 45, comprising immunizing a UniRat animal with an FOLR1 protein and identifying FOLR1 binding antibody sequences.~~

56. —A method of treatment, comprising administering to an individual in need an effective dose of the antibody of any one of claims 1 to 45, or the pharmaceutical composition of claim 46.