

WE CLAIM:

1. An antibody, an antibody-based binding protein or an antibody fragment that specifically binds to the extracellular domain of human receptor tyrosine kinase-like orphan receptor 1 (ROR1) with the same binding specificity as that of a second antibody, wherein the second antibody comprises a heavy chain variable region sequence and a light chain variable region sequence respectively shown in (1) SEQ ID NO:1 and SEQ ID NO:14; (2) SEQ ID NO:2 and SEQ ID NO:15; (3) SEQ ID NO:3 and SEQ ID NO:16; (4) SEQ ID NO:4 and SEQ ID NO:17; (5) SEQ ID NO:5 and SEQ ID NO:18; (6) SEQ ID NO:6 and SEQ ID NO:19; (7) SEQ ID NO:7 and SEQ ID NO:20; (8) SEQ ID NO:8 and SEQ ID NO:21; (9) SEQ ID NO:9 and SEQ ID NO:22; (10) SEQ ID NO:10 and SEQ ID NO:23; (11) SEQ ID NO:11 and SEQ ID NO:24; (12) SEQ ID NO:12 and SEQ ID NO:25; (13) SEQ ID NO:13 and SEQ ID NO:26; (14) SEQ ID NO:130 and SEQ ID NO:136; (15) SEQ ID NO:131 and SEQ ID NO:137; (16) SEQ ID NO:132 and SEQ ID NO:138; (17) SEQ ID NO:133 and SEQ ID NO:139; (18) SEQ ID NO:134 and SEQ ID NO:140; or (19) SEQ ID NO:135 and SEQ ID NO:141.

2. The antibody, antibody-based binding protein or antibody fragment of claim 1, comprising a heavy chain variable region sequence and a light chain variable region sequence, one or both of which are at least 90% or at least 95% identical to a heavy chain variable region sequence and a light chain variable region sequence respectively shown in (1) SEQ ID NO:1 and SEQ ID NO:14; (2) SEQ ID NO:2 and SEQ ID NO:15; (3) SEQ ID NO:3 and SEQ ID NO:16; (4) SEQ ID NO:4 and SEQ ID NO:17; (5) SEQ ID NO:5 and SEQ ID NO:18; (6) SEQ ID NO:6 and SEQ ID NO:19; (7) SEQ ID NO:7 and SEQ ID NO:20; (8) SEQ ID NO:8 and SEQ ID NO:21; (9) SEQ ID NO:9 and SEQ ID NO:22; (10) SEQ ID NO:10 and SEQ ID NO:23; (11) SEQ ID NO:11 and SEQ ID NO:24; (12) SEQ ID NO:12 and SEQ ID NO:25; (13) SEQ ID NO:13 and SEQ ID NO:26; (14) SEQ ID NO:130 and SEQ ID NO:136; (15) SEQ ID NO:131 and SEQ ID NO:137; (16) SEQ ID NO:132 and SEQ ID NO:138; (17) SEQ ID NO:133 and SEQ ID NO:139; (18) SEQ ID NO:134 and SEQ ID NO:140; or (19) SEQ ID NO:135 and SEQ ID NO:141.

3. The antibody, antibody-based binding protein or antibody fragment of claim 1, comprising a heavy chain variable region sequence and a light chain variable region sequence, one or both of which are identical to a heavy chain variable region sequence and a light chain variable region sequence respectively shown in (1) SEQ ID NO:1 and SEQ ID NO:14; (2) SEQ ID NO:2 and SEQ ID NO:15; (3) SEQ ID NO:3 and SEQ ID NO:16; (4) SEQ ID NO:4 and SEQ ID NO:17; (5) SEQ ID NO:5 and SEQ ID NO:18; (6) SEQ ID NO:6 and SEQ ID NO:19; (7) SEQ ID NO:7 and SEQ ID NO:20; (8) SEQ ID NO:8 and SEQ ID NO:21; (9) SEQ ID NO:9 and SEQ ID NO:22; (10) SEQ ID NO:10 and SEQ ID NO:23; (11) SEQ ID NO:11 and SEQ ID NO:24; (12) SEQ ID NO:12 and SEQ ID NO:25; (13) SEQ ID NO:13 and SEQ ID NO:26; (14) SEQ ID NO:130 and SEQ ID NO:136; (15) SEQ ID NO:131 and SEQ ID NO:137; (16) SEQ ID NO:132 and SEQ ID NO:138; (17) SEQ ID NO:133 and SEQ ID NO:139; (18) SEQ ID NO:134 and SEQ ID NO:140; or (19) SEQ ID NO:135 and SEQ ID NO:141.

4. The antibody, antibody-based binding protein or antibody fragment of claim 1, comprising a heavy chain variable region sequence and a light chain variable region sequence respectively shown in (1) SEQ ID NO:1 and SEQ ID NO:14; (2) SEQ ID NO:2 and SEQ ID NO:15; (3) SEQ ID NO:3 and SEQ ID NO:16; (4) SEQ ID NO:4 and SEQ ID NO:17; (5) SEQ ID NO:5 and SEQ ID NO:18; (6) SEQ ID NO:6 and SEQ ID NO:19; (7) SEQ ID NO:7 and SEQ ID NO:20; (8) SEQ ID NO:8 and SEQ ID NO:21; (9) SEQ ID NO:9 and SEQ ID NO:22; (10) SEQ ID NO:10 and SEQ ID NO:23; (11) SEQ ID NO:11 and SEQ ID NO:24; (12) SEQ ID NO:12 and SEQ ID NO:25; (13) SEQ ID NO:13 and SEQ ID NO:26; (14) SEQ ID NO:130 and SEQ ID NO:136; (15) SEQ ID NO:131 and SEQ ID NO:137; (16) SEQ ID NO:132 and SEQ ID NO:138; (17) SEQ ID NO:133 and SEQ ID NO:139; (18) SEQ ID NO:134 and SEQ ID NO:140; or (19) SEQ ID NO:135 and SEQ ID NO:141.

5. The antibody, antibody-based binding protein or antibody fragment of claim 1, comprising heavy chain CDR sequences and light chain CDR sequences that are at least 90% or at least 95% identical, respectively, to (1) SEQ ID NOs:27-29 and SEQ ID NOs:66-68, (2) SEQ ID NOs:30-32 and SEQ ID NOs:69-71, (3) SEQ ID NOs:33-35 and SEQ ID NOs:72-74, (4) SEQ ID NOs:36-38 and SEQ ID NOs:75-77, (5) SEQ ID NOs:39-

41 and SEQ ID NOs:78-80, (6) SEQ ID NOs:42-44 and SEQ ID NOs:81-83, (7) SEQ ID NOs:45-47 and SEQ ID NOs:84-86, (8) SEQ ID NOs:48-50 and SEQ ID NOs:87-89, (9) SEQ ID NOs:51-53 and SEQ ID NOs:90-92, (10) SEQ ID NOs:54-56 and SEQ ID NOs:93-95, (11) SEQ ID NOs:57-59 and SEQ ID NOs:96-98, (12) SEQ ID NOs:60-62 and SEQ ID NOs:99-101, or (13) SEQ ID NOs:63-65 and SEQ ID NOs:102-104.

6. The antibody, antibody-based binding protein or antibody fragment of claim 1, comprising a heavy chain CDR sequence selected from the group consisting of SEQ ID NOs:27-65.

7. The antibody, antibody-based binding protein or antibody fragment of claim 6, further comprising a light chain CDR sequence selected from the group consisting of SEQ ID NOs:66-104.

8. The antibody, antibody-based binding protein or antibody fragment of claim 6, comprising heavy chain CDR1, CDR2, and CDR3 sequences that are respectively identical to SEQ ID NOs:27-29, SEQ ID NOs:30-32, SEQ ID NOs:33-35, SEQ ID NO:36-38, SEQ ID NOs:39-41, SEQ ID NOs:42-44, SEQ ID NOs:45-47, SEQ ID NOs:48-50, SEQ ID NOs:51-53, SEQ ID NOs:54-56, SEQ ID NOs:57-59, SEQ ID NOs:60-62, or SEQ ID NOs:63-65.

9. The antibody, antibody-based binding protein or antibody fragment of claim 8, comprising heavy chain CDR1, CDR2 and CDR3 sequences and light chain CDR1, CDR2 and CDR3 sequences respectively shown in (1) SEQ ID NOs:27-29 and SEQ ID NOs:66-68, (2) SEQ ID NOs:30-32 and SEQ ID NOs:69-71, (3) SEQ ID NOs:33-35 and SEQ ID NOs:72-74, (4) SEQ ID NOs:36-38 and SEQ ID NOs:75-77, (5) SEQ ID NOs:39-41 and SEQ ID NOs:78-80, (6) SEQ ID NOs:42-44 and SEQ ID NOs:81-83, (7) SEQ ID NOs:45-47 and SEQ ID NOs:84-86, (8) SEQ ID NOs:48-50 and SEQ ID NOs:87-89, (9) SEQ ID NOs:51-53 and SEQ ID NOs:90-92, (10) SEQ ID NOs:54-56 and SEQ ID NOs:93-95, (11) SEQ ID NOs:57-59 and SEQ ID NOs:96-98, (12) SEQ ID NOs:60-62 and SEQ ID NOs:99-101, or (13) SEQ ID NOs:63-65 and SEQ ID NOs:102-104.

10. The antibody, antibody-based binding protein or antibody fragment of claim 1, comprising a light chain CDR sequence selected from the group consisting of SEQ ID NOs:66-104.

11. The antibody, antibody-based binding protein or antibody fragment of claim 10, further comprising a heavy chain CDR sequence selected from the group consisting of SEQ ID NOs:27-65.

12. The antibody, antibody-based binding protein or antibody fragment of claim 10, comprising light chain CDR1, CDR2, and CDR3 sequences that are respectively identical to SEQ ID NOs:66-68, SEQ ID NOs:69-71, SEQ ID NOs:72-74, SEQ ID NO:75-77, SEQ ID NOs:78-80, SEQ ID NOs:81-83, SEQ ID NOs:84-86, SEQ ID NOs:87-89, SEQ ID NOs:90-92, SEQ ID NOs:93-95, SEQ ID NOs:96-98, SEQ ID NOs:99-101, or SEQ ID NOs:102-104.

13. The antibody, antibody-based binding protein or antibody fragment of claim 1, comprising a chimeric antibody or humanized antibody.

14. The antibody, antibody-based binding protein or antibody fragment of claim 1, comprising (1) an immunoglobulin heavy chain variable region sequence that is at least 90% identical to a sequence selected from SEQ ID NOs:130-135 and/or (2) an immunoglobulin light chain variable region sequence that is at least 90% identical to a sequence selected from SEQ ID NOs:136-141.

15. The antibody, antibody-based binding protein or antibody fragment of claim 14, comprising (1) an immunoglobulin heavy chain variable region sequence that is identical to a sequence selected from SEQ ID NOs:130-135 and/or (2) an immunoglobulin light chain variable region sequence that is identical to a sequence selected from SEQ ID NOs:136-141.

16. The antibody, antibody-based binding protein or antibody fragment of claim 14 comprising a heavy chain variable region sequence and a light chain variable region sequence that are identical to a heavy chain variable region sequence and a light chain variable region sequence respectively shown in (1) SEQ ID NO:130 and SEQ ID NO:136;

(2) SEQ ID NO:131 and SEQ ID NO:137; (3) SEQ ID NO:132 and SEQ ID NO:138; (4) SEQ ID NO:133 and SEQ ID NO:139; (5) SEQ ID NO:134 and SEQ ID NO:140; or (6) SEQ ID NO:135 and SEQ ID NO:141.

17. The antibody, antibody-based binding protein or antibody fragment of claim 1, which is IgA1, IgA2, IgD, IgE, IgG1, IgG2, IgG3, IgG4, synthetic IgG, IgM, F(ab)₂, Fv, scFv, IgGACH2, F(ab')₂, scFv2CH3, Fab, VL, VH, scFv4, scFv3, scFv2, dsFv, Fv, scFv-Fc, (scFv)₂, a non-depleting IgG, a diabody, and a bivalent antibody.

18. The antibody, antibody-based binding protein or antibody fragment of claim 1, which is conjugated to a synthetic molecule.

19. The antibody, antibody-based binding protein or antibody fragment of claim 18, wherein the synthetic molecule is a label, a cytotoxic agent, a therapeutic radioisotope, or a liposome.

20. The antibody, antibody-based binding protein or antibody fragment of claim 19, wherein the cytotoxic agent is a small molecule weight toxin, or a peptide toxin, or a protein toxin.

21. An antibody drug conjugate (ADC), comprising the antibody or antibody fragment of claim 1 and at least one cytotoxic agent.

22. The antibody drug conjugate of claim 21, wherein the cytotoxic agent is a small molecular weight toxin, a peptide toxin, or a protein toxin.

23. The antibody drug conjugate of claim 21, wherein the antibody or antibody fragment is conjugated to the cytotoxic agent via sortase enzyme mediated antibody conjugation (SMAC).

24. The antibody drug conjugate of claim 21, wherein the cytotoxic agent is anthracycline (PNU) toxin derivative Gly_(n)-EDA-PNU, where n is any number from 1 to 21.

25. The antibody drug conjugate of claim 21, wherein the antibody or antibody fragment is chimeric or humanized.

26. The antibody drug conjugate of claim 21, wherein the antibody or antibody fragment comprises heavy chain CDR1, CDR2 and CDR3 sequences and light chain CDR1, CDR2 and CDR3 sequences respectively shown in (1) SEQ ID NOs:27-29 and SEQ ID NOs:66-68, (2) SEQ ID NOs:39-41 and SEQ ID NOs:78-80 or (3) SEQ ID NOs:60-62 and SEQ ID NOs:99-101.

27. The antibody drug conjugate of claim 21, wherein the antibody or antibody fragment comprises a heavy chain variable region sequence and a light chain variable region sequence respectively shown in (1) SEQ ID NO:130 and SEQ ID NO:136; (2) SEQ ID NO:131 and SEQ ID NO:137; (3) SEQ ID NO:132 and SEQ ID NO:138; (4) SEQ ID NO:133 and SEQ ID NO:139; (5) SEQ ID NO:134 and SEQ ID NO:140; (6) SEQ ID NO:135 and SEQ ID NO:141; (7) SEQ ID NO:1 and SEQ ID NO:14; (8) SEQ ID NO:5 and SEQ ID NO:18; or (9) SEQ ID NO:12 and SEQ ID NO:25.

28. A chimeric antigen receptor (CAR), comprising the antibody or antibody fragment of claim 1 that is fused to a transmembrane region and an intracellular T-cell receptor (TCR) signaling domain.

29. The chimeric antigen receptor of claim 28, wherein the antibody or antibody fragment is chimeric or humanized.

30. The chimeric antigen receptor of claim 28, wherein the antibody or antibody fragment comprises heavy chain CDR1, CDR2 and CDR3 sequences and light chain CDR1, CDR2 and CDR3 sequences respectively shown in (1) SEQ ID NOs:27-29 and SEQ ID NOs:66-68.

31. The chimeric antigen receptor of claim 28, wherein the antibody or antibody fragment comprises a heavy chain variable region sequence and a light chain variable region sequence respectively shown in (1) SEQ ID NO:130 and SEQ ID NO:136; (2) SEQ ID NO:131 and SEQ ID NO:137; (3) SEQ ID NO:132 and SEQ ID NO:138; (4) SEQ ID NO:133 and SEQ ID NO:139; (5) SEQ ID NO:134 and SEQ ID NO:140; (6) SEQ ID NO:135 and SEQ ID NO:141; or (7) SEQ ID NO:1 and SEQ ID NO:14.

32. A pharmaceutical composition comprising (1) a therapeutically effective amount of (a) an antibody, antibody-based binding protein or antibody fragment of claim 1 or (b) an antibody drug conjugate (ADC) of claim 21, and (2) a pharmaceutically acceptable carrier.
33. A kit comprising (1) an antibody, antibody-based binding protein or antibody fragment of claim 1 or (2) an antibody drug conjugate (ADC) of claim 21.
34. A polynucleotide encoding the variable region of the heavy chain or light chain of the antibody, antibody-based binding protein or antibody fragment of claim 1.
35. A vector harboring the polynucleotide of claim 34.
36. A method of killing or inhibiting the growth of a cell expressing ROR1 in a subject, comprising administering a pharmaceutical composition of claim 32 to a subject in need thereof, thereby killing or inhibiting the growth of the cell expressing ROR1 in the subject.
37. The method of claim 36, wherein the cell is a tumor cell.
38. The method of claim 36, wherein the pharmaceutical composition comprises an antibody drug conjugate (ADC) comprising an antibody, antibody-based binding protein or antibody fragment of claim 1 that is conjugated to a cytotoxic agent.
39. The method of claim 38, wherein the cytotoxic agent is a small molecular weight toxin, a peptide toxin, or a protein toxin.
40. A method of treating a disease or condition associated with elevated expression of ROR1 in a subject, comprising administering a pharmaceutical composition of claim 32 to a subject having a disease or condition associated with elevated expression of ROR1, thereby treating the disease or condition associated with elevated expression of ROR1 in the subject.
41. The method of claim 40, wherein the disease or condition is a cancer.

42. The method of claim 40 wherein the disease or condition is selected from the group consisting of chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), mantle cell lymphoma, neuroblastoma, sarcoma, renal cell carcinoma, breast cancer, lung cancer, colon cancer, head and neck cancer, and melanoma.

43. The method of claim 40, wherein the pharmaceutical composition comprises an antibody drug conjugate (ADC) comprising an antibody, antibody-based binding protein or antibody fragment of claim 1 that is conjugated to a cytotoxic agent.

44. The method of claim 43, wherein the cytotoxic agent is a small molecular weight toxin, a peptide toxin, or a protein toxin.

45. The method of claim 40, wherein the antibody or antibody fragment is fused to a transmembrane region and an intracellular T-cell receptor (TCR) signaling domain to form a chimeric antigen receptor (CAR).