

## CLAIMS

### **What is claimed is:**

1. An isolated monoclonal antibody or antigen-binding fragment thereof that specifically binds to discoidin domain receptor 1 (DDR1) protein, comprising a light chain variable region having a LC-LC-CDR1, LC-CDR2 and LC-CDR3 within the light chain variable region selected from SEQ ID NOs:108-128, and a heavy variable region having a HC-CDR1, HC-CDR2, and HC-CDR3 within the heavy chain variable region selected from SEQ ID NOs:129-149, or variants thereof wherein one or more of the LC-CDRs and/or HC-CDRs has one, two, or three amino acid substitutions, additions, deletions, or combinations thereof.
2. The isolated monoclonal antibody or antigen-binding fragment thereof of **claim 1**, comprising a clone-paired LC-LC-CDR1, LC-CDR2 and LC-CDR3 selected from **Table 1** and a HC-CDR1, HC-CDR2, and HC-CDR3 selected from **Table 2**, or variants thereof wherein one or more of the LC-CDRs and/or HC-CDRs has one, two, or three amino acid substitutions, additions, deletions, or combinations thereof.
3. The isolated monoclonal antibody or antigen-binding fragment thereof of **claim 1**, comprising a light chain variable region having a LC-CDR1 comprising the amino acid sequence QSIGSV (SEQ ID NO:11), a LC-CDR2 comprising the amino acid sequence GVF, and a LC-CDR3 comprising the amino acid sequence QYIPYGSSP (SEQ ID NO:12), and a heavy chain variable region having a HC-CDR1 comprising the amino acid sequence GFSLNRYYY (SEQ ID NO:57), a HC-CDR2 comprising the amino acid sequence ISYGDTT (SEQ ID NO:58), and a HC-CDR3 comprising the amino acid sequence ARADTGDNGYLGLQL (SEQ ID NO:59) (DDR1-9), or variants thereof wherein one or more of the LC-CDRs and/or HC-CDRs has one, two, or three amino acid substitutions, additions, deletions or combinations of.
4. The isolated monoclonal antibody or antigen-binding fragment thereof of **claim 1**, comprising a light chain variable region having a LC-CDR1 comprising the amino acid sequence ESINSW (SEQ ID NO:41), a LC-CDR2 comprising the amino acid sequence DAS, and a LC-CDR3 comprising the amino acid sequence QSYIINRSNYGNS (SEQ ID NO:42), and a heavy chain variable region having a HC-CDR1 comprising the amino acid sequence GFSLSSYY (SEQ ID NO:102), a HC-CDR2 comprising the amino acid sequence ITTAGPL (SEQ ID NO:103), and a HC-CDR3 comprising the amino acid sequence ARGHAGSIYYSYFDL (SEQ ID NO:104) (DDR1-32), or variants thereof wherein one or more of the LC-CDRs and/or HC-CDRs has one, two, or three amino acid substitutions, additions, deletions, or combinations of.

5. The isolated monoclonal antibody or antigen-binding fragment thereof of **claim 1**, comprising a light chain variable region having an amino acid sequence selected from SEQ ID Nos: 108-128, and a heavy chain variable region having an amino acid sequence selected from SEQ ID NOs: 129-149.

6. The isolated monoclonal antibody or antigen-binding fragments thereof of **claim 1**, comprising:

(a) a light chain variable region having an amino acid sequence of SEQ ID NO: 108 (DDR1-1K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 129 (DDR1-1H);

(b) a light chain variable region having an amino acid sequence of SEQ ID NO: 109 (DDR1-3K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 130 (DDR1-3H);

(c) a light chain variable region having an amino acid sequence of SEQ ID NO: 110 (DDR1-5K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 131 (DDR1-5H);

(d) a light chain variable region having an amino acid sequence of SEQ ID NO: 111 (DDR1-6K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 132 (DDR1-6H);

(e) a light chain variable region having an amino acid sequence of SEQ ID NO: 112 (DDR1-9K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 133 (DDR1-9H);

(f) a light chain variable region having an amino acid sequence of SEQ ID NO: 113 (DDR1-11K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 134 (DDR1-11H);

(g) a light chain variable region having an amino acid sequence of SEQ ID NO: 114 (DDR1-12K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 135 (DDR1-12H);

(h) a light chain variable region having an amino acid sequence of SEQ ID NO: 115 (DDR1-13K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 136 (DDR1-13H);

(i) a light chain variable region having an amino acid sequence of SEQ ID NO: 116 (DDR1-14K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 137 (DDR1-14H);

(j) a light chain variable region having an amino acid sequence of SEQ ID NO: 117 (DDR1-15K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 138 (DDR1-15H);

(k) a light chain variable region having an amino acid sequence of SEQ ID NO: 118 (DDR1-17K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 139 (DDR1-17H);

(l) a light chain variable region having an amino acid sequence of SEQ ID NO: 119 (DDR1-20K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 140 (DDR1-20H);

(m) a light chain variable region having an amino acid sequence of SEQ ID NO: 120 (DDR1-21K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 141 (DDR1-21H);

(n) a light chain variable region having an amino acid sequence of SEQ ID NO: 121 (DDR1-22K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 142 (DDR1-22H);

(o) a light chain variable region having an amino acid sequence of SEQ ID NO: 122 (DDR1-23K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 143 (DDR1-23H);

(p) a light chain variable region having an amino acid sequence of SEQ ID NO: 123 (DDR1-26K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 144 (DDR1-26H);

(q) a light chain variable region having an amino acid sequence of SEQ ID NO: 124 (DDR1-28K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 145 (DDR1-28H);

(r) a light chain variable region having an amino acid sequence of SEQ ID NO: 125 (DDR1-29K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 146 (DDR1-29H);

(s) a light chain variable region having an amino acid sequence of SEQ ID NO: 126 (DDR1-32K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 147 (DDR1-32H);

(t) a light chain variable region having an amino acid sequence of SEQ ID NO: 127 (DDR1-33K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 148 (DDR1-33H); or

(u) a light chain variable region having an amino acid sequence of SEQ ID NO: 128 (DDR1-34K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 149 (DDR1-34H); or

a variant thereof, wherein the light chain variable region has 80% or more amino acid sequence identity to the parent light chain variable region amino acid sequence, and the heavy chain variable region has 80% or more sequence identity to the parent heavy chain variable region amino acid sequence, wherein the variant specifically binds to DDR1 protein.

7. The isolated monoclonal antibody or antigen-binding fragment thereof of **claim 1**, comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 112 (DDR1-9K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 133 (DDR1-9H).
8. The isolated monoclonal antibody or antigen-binding fragment thereof of **claim 1**, comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 126 (DDR1-32K) and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 147 (DDR1-32H).
9. The isolated monoclonal antibody or an antigen binding fragment thereof of **claim 1 or 2**, wherein the isolated monoclonal antibody is a murine, a rodent, a rabbit, a chimeric, humanized, or human antibody.
10. The isolated monoclonal antibody or an antigen-binding fragment thereof of **claim 9**, wherein the isolated monoclonal antibody is a rabbit or a chimeric antibody.
11. The isolated monoclonal antibody or an antigen-binding fragment thereof of **claim 9**, wherein the isolated monoclonal antibody is a rabbit or a chimeric antibody.
12. The isolated monoclonal antibody or an antigen-binding fragment thereof of any one of **claims 1-4**, wherein the isolated monoclonal antibody is a humanized antibody.
13. The isolated monoclonal antibody or an antigen-binding fragment thereof of **claim 1**, comprising a light chain variable region having an amino acid sequence of SEQ ID NO: 150 or 151 (DDR1-9hu\_Lv1 or DDR1-9hu\_Lc2), and a heavy chain variable region having an amino acid sequence of SEQ ID NO: 152 (DDR1-9hu\_Hv); or variants thereof, wherein the light chain variable region has 80% or more amino acid sequence identity to the parent light chain variable region amino acid sequence, and the heavy chain variable region has 80% or more sequence identity to the parent heavy chain variable region amino acid sequence, wherein the variant specifically binds to DDR1 protein.
14. The isolated monoclonal antibody or an antigen-binding fragment thereof of any one of **claims 1-13**, wherein the antigen-binding fragment is a ScFv (single chain fragment variable) antibody, Fab fragment, F(ab')<sub>2</sub> fragment, or Fv fragment.
15. An isolated monoclonal antibody or an antigen-binding fragment thereof, which binds specifically to all or portion of the epitope or the same epitope specifically bound by the isolated monoclonal antibody or an antigen-binding fragment thereof of any one of **claims 1-14**.

16. An isolated monoclonal antibody or an antigen-binding fragment thereof, which competes for the same epitope with the isolated monoclonal antibody or an antigen-binding fragment thereof of any one of **claims 1-14**.
17. An antibody-drug conjugate, comprising the isolated monoclonal antibody or antigen-binding fragment thereof of any one of **claims 1-16**, and an anti-tumor drug, wherein the anti-tumor drug is linked to the antibody or antigen-binding fragment thereof.
18. The antibody-drug conjugate of **claim 17**, wherein the antitumor drug is linked to the antibody through a photolabile linker or an enzymatically cleavable linker.
19. The antibody-drug conjugate of **claim 17** or **18**, wherein said antitumor drug is a toxin, a radioisotope, a cytokine, or an enzyme.
20. A pharmaceutical composition comprising the isolated monoclonal antibody or an antigen-binding fragment thereof of any one of **claims 1-14**, and a pharmaceutically acceptable carrier.
21. An isolated polynucleotide that encodes the isolated monoclonal antibody or antigen-binding fragment thereof of any one of **claims 1-14**.
22. A vector comprising the isolated nucleic acid of **claim 21**.
23. The vector of **claim 22**, comprising an expression vector capable of expressing the encoded antibody or antigen-binding fragment thereof.
24. A host cell comprising the polynucleotide of **claim 21** or vector of **claim 22** or **23**.
25. The host cell of **claim 24**, wherein the host cell is a mammalian cell.
26. The host cell of **claim 25**, wherein the host cell is a CHO cell.
27. A hybridoma or engineered cell encoding and/or producing the isolated monoclonal antibody according to any of **claims 1-14**.
28. A process of producing an antibody, comprising culturing the host cell of any one of **claims 24-26**, wherein the host cell is capable of expressing the monoclonal antibody or antigen fragment thereof, comprising culturing the host cell under conditions suitable for expressing the antibody or antigen-binding fragment thereof, and isolating the antibody or antigen binding fragment thereof.

29. A chimeric antigen receptor (CAR) protein comprising an antibody or antigen-binding fragment thereof of any one of **claims 1-14**.
30. An isolated nucleic acid that encodes a CAR protein of **claim 29**.
31. A vector comprising the isolated nucleic acid of **claim 30**.
32. The vector of **claim 31**, wherein the vector is capable of expressing the CAR protein.
33. An engineered cell comprising the isolated nucleic acid of **claim 30** or the vector of **claim 32**.
34. The engineered cell of **claim 33**, wherein the cell is a T cell, NK cell, or macrophage.
35. A method of treating or ameliorating the effect of a cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of the antibody or an antigen-binding fragment thereof of any one of **claims 1-14**, or the engineered cell of **claim 33** or **34**.
36. The method of **claim 35**, wherein the method reduces or eradicates the tumor burden in the subject.
37. The method of **claim 36**, wherein the method reduces the number of tumor cells or reduces tumor size.
38. The method of **claim 35**, wherein the cancer is a solid cancer or tumor.
39. The method of **claim 38**, wherein the cancer is selected from pancreatic cancer; lung cancer, including small cell lung cancer and non-small cell lung cancer; colon and colorectal cancer; head and neck cancer; stomach (gastric) cancer; ovarian cancer; breast cancer; kidney cancer; liver cancer; prostate cancer, cervical cancer, brain cancer; skin cancer, including melanoma; and bone cancer.
40. The method of **claim 38**, wherein the cancer is breast cancer.
41. The method of **claim 40**, wherein the breast cancer is a breast cancer subtype selected from (a) luminal A (ER+ and/or PR+, HER2-); (b) luminal B (ER+ and/or PR+, HER2+); (c) triple-negative (ER-, PR-, HER2-); (d) HER2+/ER- (ER-, PR-, and HER2+); and (e) unclassified (ER-, PR-, HER2-, cytokeratin 5/6-, and HER1-).

42. The method of any one of **claims 35-41**, wherein the cancer cells of the cancer are identified as expressing or determined to express secreted DDR1 protein and/or DDR1 protein on the cancer cell surface.

43. The method of any one of **claims 35-42**, wherein the antibody or an antigen-binding fragment thereof is administered intravenously, intra-arterially, intra-tumorally, or subcutaneously.

44. The method of **claim 35**, further comprising administering to the subject one or more drugs selected from the group consisting of a topoisomerase inhibitor, an anthracycline topoisomerase inhibitor, an anthracycline, a daunorubicin, a nucleoside metabolic inhibitor, a cytarabine, a hypomethylating agent, a low dose cytarabine (LDAC), a combination of daunorubicin and cytarabine, a daunorubicin and cytarabine liposome for injection, Vyxeos®, an azacytidine, Vidaza®, a decitabine, an all-trans-retinoic acid (ATRA), an arsenic, an arsenic trioxide, a histamine dihydrochloride, Ceplene®, an interleukin-2, an aldesleukin, Proleukin®, a gemtuzumab ozogamicin, Mylotarg®, an FLT-3 inhibitor, a midostaurin, Rydapt®, a clofarabine, a farnesyl transferase inhibitor, a decitabine, an IDH1 inhibitor, an ivosidenib, Tibsovo®, an IDH2 inhibitor, an enasidenib, Idhifa®, a smoothened (SMO) inhibitor, a glasdegib, an arginase inhibitor, an IDO inhibitor, an epacadostat, a BCL-2 inhibitor, a venetoclax, Venclexta®, a platinum complex derivative, oxaliplatin, a kinase inhibitor, a tyrosine kinase inhibitor, a PI3 kinase inhibitor, a BTK inhibitor, an ibrutinib, IMBRUVICA®, an acalabrutinib, CALQUENCE®, a zanubrutinib, a PD-1 antibody, a PD-L1 antibody, a CTLA-4 antibody, a LAG3 antibody, an ICOS antibody, a TIGIT antibody, a TIM3 antibody, a CD40 antibody, a 4-1BB antibody, a CD47 antibody, a SIRP1 $\alpha$  antibody or fusions protein, an antagonist of E-selectin, an antibody binding to a tumor antigen, an antibody binding to a T-cell surface marker, an antibody binding to a myeloid cell or NK cell surface marker, an alkylating agent, a nitrosourea agent, an antimetabolite, an antitumor antibiotic, an alkaloid derived from a plant, a hormone therapy medicine, a hormone antagonist, an aromatase inhibitor, and a P-glycoprotein inhibitor.

45. The method according to any of **claims 35-44**, wherein the isolated monoclonal antibody or an antigen binding fragment thereof further comprises an antitumor drug linked thereto.

46. The method of **claim 45**, wherein the antitumor drug is a toxin, a radioisotope, a cytokine, or an enzyme.

47. A method of treating or ameliorating the effect of fibrosis in a subject, the method comprising administering to the subject a therapeutically effective amount of the antibody or an antigen-binding fragment thereof according to any of **claims 1-14** or the engineered cell of **claim 33 or 34**.

48. The method of **claim 47**, wherein the subject has organ fibrosis.
49. The method of **claim 48**, wherein the subject has fibrosis of the kidney, liver, lung, or heart.
50. The method of **claim 49**, wherein the subject has fibrosis of the lung.
51. The method of **claim 50**, wherein the subject has interstitial lung disease.
52. The method of **claim 50**, wherein the subject has Idiopathic Pulmonary Fibrosis (IPF) or lung scarring.
53. A method of detecting a cancer cell or cancer stem cell in a sample or subject comprising:
- (a) contacting a subject or a sample from the subject with the antibody or an antigen-binding fragment thereof according to any of **claims 1-14**; and
  - (b) detecting binding of said antibody to a cancer cell or cancer stem cell in said subject or sample.
54. The method of **claim 53**, wherein the sample is a body fluid or biopsy.
55. The method of **claim 54**, wherein the sample is blood, bone marrow, sputum, tears, saliva, mucous, serum, urine or feces
56. The method of any one of **claims 53-55**, wherein detection comprises immunohistochemistry, flow cytometry, FACS, ELISA, RIA or Western blot.
57. The method of **claim 53**, further comprising performing steps (a) and (b) a second time and determining a change in detection levels as compared to the first time.
58. The method of any one of **claims 53-57** wherein said isolated monoclonal antibody or an antigen binding fragment thereof further comprises a label.
59. The method of **claim 58** wherein said label is a peptide tag, an enzyme, a magnetic particle, a chromophore, a fluorescent molecule, a chemo-luminescent molecule, or a dye.
60. The method according to any of **claims 35-59**, wherein said isolated monoclonal antibody or an antigen binding fragment thereof is conjugated to a liposome or nanoparticle.