CLAIMS

WHAT IS CLAIMED IS:

1. An antibody or antibody fragment that binds to dickkopf-1 (DKK1) comprising a VHH domain, wherein the VHH domain comprises:

(a) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 66, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 164, and a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 262;

(b) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 69, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 167, and a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 265;

(c) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 94, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 192, and a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 290;

(d) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 98, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 196, and a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 294;

(e) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 977, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 1391, and a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 1805;

(f) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 1305, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 1719, and a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 2133;

(g) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 10, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 108, and a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 206;

(h) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 37, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 135, and a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 233;

(i) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 919, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 1333, and a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 1747;

(j) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 923, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 1337, and a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 1751;

(k) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 948, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 1362, and a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 1776;

(l) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 951, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 1365, and a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 1779; or

(m) a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 1290, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 1704, and a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 2118.

2. The antibody or antibody fragment of claim 1 wherein the VHH domain comprises an amino acid sequence at least about 90% identical to the amino acid sequence of any one of SEQ ID NOs: 360, 363, 388, 392, 452, 2231, 304, 331, 394, 398, 423, 426, and 2216.

3. The antibody or antibody fragment of claim 1 or 2, wherein the VHH domain comprises the amino acid sequence of any one of SEQ ID NOs: 360, 363, 388, 392, 452, 2231, 304, 331, 394, 398, 423, 426, and 2216.

4. An antibody or antibody fragment that binds to dickkopf-1 (DKK1) comprising a variable domain heavy chain region (VH), wherein the VH comprises complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein (a) an amino acid sequence of CDRH1 is as set forth in any one of SEQ ID NOs: 1-98, 919-1031, and 1238-1332; (b) an amino acid sequence of CDRH2 is as set forth in any one of SEQ ID NOs: 99-196, 1333-1445, and 1652-1746; and (c) an amino acid sequence of CDRH3 is as set forth in any one of SEQ ID NOs: 197-294, 1747-1859, and 2066-2160.

5. The antibody or antibody fragment of claim 4, wherein the VH comprises an amino acid sequence at least about 90% identical to a sequence as set forth in any one of SEQ ID NOs: 295-392, 394-506, and 2164-2258.

6. The antibody or antibody fragment of claim 4 or 5, wherein the VH comprises the amino acid sequence as set forth in any one of SEQ ID NOs: 295-392, 394-506, and 2164-2258.

7. An antibody or antibody fragment that binds to dickkopf-1 (DKK1) comprising a variable domain light chain region (VH), wherein the VH comprises complementarity determining regions CDRH1, CDRH2, and CDRH3, and wherein (a) an amino acid sequence of CDRH1is as set forth in any one of SEQ ID NOs: 1032-1237; (b) an amino acid sequence of CDRH2 is as set forth in any one of SEQ ID NOs: 1446-1651; and (c) an amino acid sequence of CDRH3 is as set forth in any one of SEQ ID NOs: 1860-2065; and a variable domain light chain region (VL), wherein the VL comprises complementarity determining regions CDRL1, CDRL2, and CDRL3, and wherein (a) an amino acid sequence of CDRL1 is as set forth in any one of SEQ ID NOs: 2259-2464; (b) an amino acid sequence of CDRL2 is as set forth in any one of SEQ ID NOs: 2465-2521; and (c) an amino acid sequence of CDRL3 is as set forth in any one of SEQ ID NOs: 2522-2727.

8. The antibody or antibody fragment of claim 7, wherein the VH comprises an amino acid sequence at least about 90% identical to a sequence as set forth in any one of SEQ ID NOs: 507-712; and the VL comprises an amino acid sequence at least about 90% identical to a sequence as set forth in any one of SEQ ID NOs: 713-918.

9. The antibody or antibody fragment of claim 7 or 8, wherein the VH comprises the amino acid sequence as set forth in any one of SEQ ID NOs: 507-712; and the VL comprises the amino acid sequence as set forth in any one of SEQ ID NOs: 713-918.

10. The antibody or antibody fragment of any one of claims 1-9, wherein the antibody is a monoclonal antibody, a bi-specific antibody, a multispecific antibody, a grafted antibody, a humanized antibody, a synthetic antibody, a chimeric antibody, a single-domain antibody, an intrabody, or an antigen-binding fragments thereof.

11. The antibody or antibody fragment of any one of claims 1-10, wherein the antibody is a single domain antibody.

12. The antibody or antibody fragment of any one of claims 1-11, wherein the antibody or antibody fragment comprises a Fc region.

13. The antibody or antibody fragment of claim 12, wherein the Fc region is an IgG2 Fc region.

14. The antibody or antibody fragment of any one of claims 1-13, wherein the antibody or antibody fragment comprises a K_D of less than 50 nM, 25 nM, 10 nM, or 5 nM.

15. A pharmaceutical composition, comprising the antibody or antibody fragment of any one of claims 1-14.

16. An isolated nucleic acid that encodes the antibody or antibody fragment of any one of claims 1-14.

17. An expression vector comprising the nucleic acid of claim 16.

18. An isolated cell comprising the nucleic acid of claim 16 or the expression vector of claim 17.

19. Use of the antibody or antibody fragment of any one of claims 1-14 or the pharmaceutical composition of claim 15 in the manufacture of a medicament for treating a disease or disorder a subject in need, wherein the disease or disorder is a cancer, an inflammatory disease or disorder, a metabolic disease or disorder, a cardiovascular disease or disorder, a respiratory disease or disorder, pain, a digestive disease or disorder, a reproductive disease or disorder, an endocrine disease or disorder, or a neurological disease or disorder.

20. The use of claim 19, wherein the cancer is a gastro-esophageal cancer, an endometrial cancer, an ovarian cancer, a prostate cancer, or a liver cancer.

21. The use of claim 19, wherein the metabolic disease or disorder or endocrine disease or disorder is weight gain, obesity, Type II diabetes, hypoglycemia, or hyperinsulinism.

22. Use of the antibody or antibody fragment of any one of claims 1-14 or the pharmaceutical composition of claim 15 in the manufacture of a medicament for activating an immune cell.

23. The use of claim 22, wherein the immune cell is a natural killer (NK) cell.

24. Use of the antibody or antibody fragment of any one of claims 1-14 or the pharmaceutical composition of claim 15 in the manufacture of a medicament for increasing interferon-γ (IFNγ) expression in an immune cell.

25. Use of the antibody or antibody fragment of any one of claims 1-14 or the pharmaceutical composition of claim 15 in the manufacture of a medicament for increasing granulocyte macrophage colony-stimulating factor (GM-CSF) expression in an immune cell.

26. The antibody or antibody fragment of any one of claims 1-14 or the pharmaceutical composition of claim 15 for use in therapy.