What is claimed is:

1. A composition comprising an antigen-binding region that specifically binds an epitope in a DKK1 polypeptide (SEQ ID NO: 1) and/or in a DKK4 polypeptide (SEQ ID NO: 122), wherein the antibody or functional fragment thereof binds to at least one epitope in DKK1 or DKK4, or both.

2. The antibody according to claim 1, wherein binding to DKK1 or DKK4 is determined in at least one assay selected from: antagonism of Wnt-signaled transcription; electrochemiluminescence-based binding analysis; enzyme-linked immunosorbent assay binding; FMAT; SET; SPR; osteocalcin (OCN) serum concentration; osteoprotegrin (OPG) serum concentration; procollagen type 1 nitrogenous propeptide (P1NP) serum concentration, ALP production; TopFlash or ameliorating osteolysis.

3. An isolated amino acid sequence selected from the group of SEQ ID NOs: 2-20 and SEQ ID NOs: 40-72 and conservative or humaneered variants thereof.

4. The isolated amino acid sequences according to claim 3, wherein the amino acid sequences selected from:

a) the group of SEQ ID NOs: 2-20, 65-72, each comprising an antigen-binding region comprising an H-CDR3 region;

b) the group of SEQ ID NOs: 2-20, 57-64 each comprising an H-CDR2 region;

c) the group of SEQ ID NO: 40 comprising the sequence GISGSGSYTYYADSVKF, SEQ ID NO: 41 comprising the sequence GISYYGGNTYYADSVKF, and SEQ ID NO: 42 comprising the sequence GISYYGGSTYYADSVKF, each comprising a consensus H-CDR2 region;

d) the group of SEQ ID NOs: 2-5, 8-11, 20, 49-56 each comprises an H-CDR1 region; and,

e) the group of SEQ ID NO: 43 having amino acid sequence GFTFSSYGMT, SEQ ID NO: 44 having amino acid sequence GFTFNSYGMT, SEQ ID NO: 45 having amino acid sequence GFTFSNYGMT, SEQ ID NO: 46 having amino acid sequence GFTFSSYWMT, SEQ ID NO: 47 having amino acid sequence GFTFSSYAMTF, and SEQ ID NO: 48 having amino acid sequence GFTFSSYGMS of each comprises a consensus H-CDR1 region; or

f) SEQ ID NOs: 21-39 and 73-88; and

conservative or humaneered variants thereof.

5. The isolated antigen-binding region according to claim 4, wherein the amino acid sequences selected from the group of SEQ ID NOs: 21-39 each comprises an L-CDR3 region, the amino acid sequences selected from the group of SEQ ID NOs: 21-39, 73-80 each comprises an L-CDR1

region, the amino acid sequences selected from the group of SEQ ID NOs: 21-39, 81-88 each comprises an L-CDR2 region, the amino acid sequences selected from the group of SEQ ID NOs: 21-39 each comprises a variable region of a light chain.

6. An isolated nucleotide sequence selected from the group of SEQ ID NOs: 97-103.

7. An isolated amino acid sequence encoded by a nucleotide sequence according to claim 6, and conservative or humaneered variants of the amino acid sequence, wherein

a) each of SEQ ID NOs: 97-100 encodes an antigen binding light chain; and

b) each of SEQ ID NOs: 101-103 encodes an antigen binding heavy chain.

8. An isolated nucleotide sequence according to claim 6, wherein the nucleotide sequence is further optimized for expression and/or for clinical use.

9. An isolated nucleotide sequence selected from the group of SEQ ID NOs: 104-110.

10. An isolated amino acid sequence encoded by a nucleotide sequence according to claim 9, and conservative or humaneered variants of the amino acid sequence, wherein:

a) each of SEQ ID NOs: 104-107 encodes an antigen binding light chain, and

b) each of SEQ ID NOs: 108-110 encodes an antigen binding heavy chain.

11. A isolated nucleotide sequence according to claim 9, wherein the nucleotide sequence is optimized for expression and/or for clinical use.

12. An isolated amino acid sequence selected from the group of 111-117 and conservative or humaneered variants thereof, wherein

a) each of SEQ ID NOs: 111-114 encodes an antigen binding light chain, and

b) each of SEQ ID NOs: 115-117 encodes an antigen binding heavy chain.

13. The isolated amino acid sequence according to claim 12, wherein the amino acid sequence is optimized for expression and/or for clinical use.

14. An isolated nucleotide sequence selected from the group of SEQ ID NOs: 120-121.

15. An isolated amino acid sequence encoded by a nucleotide sequence according to claim 14, and conservative or humaneered variants of the amino acid sequence, wherein

a) SEQ ID NO: 120 encodes an antigen binding variable region of a light chain, and

b) SEQ ID NO: 121 encodes an antigen binding variable region of a heavy chain.

16. An isolated nucleotide sequence according to claim 14, wherein the nucleotide sequence is optimized for expression and/or for clinical use.

17. An isolated antigen-binding region comprising a variable region of a light chain encoded by a nucleotide sequence selected from the group of SEQ ID NO: 120, and a variable region of a heavy chain encoded by a nucleotide sequence selected from the group of SEQ ID NO: 121.

18. An isolated amino acid sequence selected from the group of 118-119 and conservative or humaneered variants thereof.

19. The isolated amino acid sequence according to claim 18, wherein SEQ ID NO: 118 depicts an antigen binding variable region of a light chain.

20. The isolated amino acid sequence according to claim 18, wherein SEQ ID NO: 119 depicts an antigen binding variable region of a heavy chain.

21. The isolated amino acid sequence according to claim 18, wherein the amino acid sequence is optimized for expression and/or for clinical use.

22. An isolated amino acid sequence having at least 95 percent identity with at least one CDR region selected from the regions depicted in SEQ ID NOs: 2-121.

23. An isolated amino acid sequence having a consensus sequence of the CDR regions as shown in Tables 11A and 11B.

24. The isolated antibody according to claim 1, which comprises a scaffold selected from an IgM and an IgG, wherein the IgG is selected from an IgG1, an IgG2, and IgG3 or an IgG4.

25. The isolated antibody according to claim 24, wherein the IgM or the IgG is selected from a polyclonal or monoclonal.

26. An isolated antibody or functional fragment thereof, comprising an antigen-binding region that is specific for an epitope of DKK1, wherein the antibody or functional fragment binds to DKK1 or DKK4, and prevents or ameliorates development of a DKK1-associated disease or a DKK4-associated disease.

27. An isolated antigen-binding region of an antibody or functional fragment thereof according to claim 26.

28. An isolated antibody or functional fragment thereof comprising an antigen-binding region that is specific for an epitope of target DKK1 or DKK4 or both, wherein the epitope comprises at least six or more amino acid residues of a CYS2 domain of target DKK1 or DKK4.

29. The isolated antibody or functional fragment according to any of the preceding claims 1-28, which is selected from a whole immunoglobulin or Fab fragment or scFv antibody fragment thereof; a heavy chain antibody, and an antigen-binding region therof on a non-immunoglobulin scaffold.

30. The isolated antibody or functional fragment thereof according to claim 29 wherein the epitope is a conformational epitope.

31. A pharmaceutical composition comprising at least one antibody or functional fragment according to claim 29 and a pharmaceutically acceptable carrier or excipient therefor.

32. A transgenic animal carrying a gene encoding an antibody or functional fragment thereof according to any of claim 29

33. A method for treating a disorder or condition associated with the presence of DKK1 or DKK4, comprising administering to a subject in need thereof an effective amount of the pharmaceutical composition according to claim 31.

34. The method according to claim 33, wherein the disorder or condition is selected from osteolytic lesions - especially osteolytic lesions associated with a myeloma, especially a multiple myeloma, or with cancers of the bone, breast, colon, melanocytes, hepatocytes, epithelium, esophagus, brain, lung, prostate or pancreas or metastasis thereof; bone loss associated with transplantation; or is an osteosarcoma, prostate cancer, hepatocellular carcinoma (HCC), myeloma including multiple myeloma, diabetes, obesity, muscle wasting, Alzheimers disease, osteoporosis, osteopenia, rheumatism, colitis and/or unwanted hair loss.

35. The method according to claim 33, wherein the method further comprises administering a second therapeutic agent.

36. The method according to claim 35, wherein the chemotherapeutic agent is Zometa.

37. The pharmaceutical composition according to claim 35, wherein the additional therapeutic agent is selected from the group consisting of an anti-cancer agent; an antimetabolic agent, an anti-diabetic agent, an anti-osteoporotic agent; an antibiotic; an anti-inflammatory agent; a growth factor; and a cytokine.

38. An isolated antibody comprising a first amino acid sequence which is a heavy chain selected from the group consisting of SEQ ID NOs: 2-20, and a sequence having at least 95 percent sequence identity in the CDR regions with the CDR regions depicted in SEQ ID NOs: 2-20; and a second amino acid sequence which is a light chain selected from the group consisting of SEQ ID NOs: 21-39, and a sequence having at least 95 percent sequence identity in the CDR regions with the CDR regions depicted in SEQ ID NOs: 21-39.

39. An immunoconjugate comprising a first component which is an antibody or fragment thereof according to any of the preceding claims.

40. A kit comprising an antibody or fragment thereof according to any of the preceding claims.

41. The kit according to claim 40, further comprising a pharmaceutically acceptable carrier or excipient therefore.

42. The kit according to claim 40, wherein the antibody is present in a unit dose.

43. The kit according to claim 40, further comprising instructions for use in administering to a subject.

44. A composition comprising a neutralizing anti-DKK1/4 antibody.

45. The antibody of claim 0, wherein the antibody binds to DKK1 with a K_{on} of less than 100 nM, 50 nM, 10nM, 1.0 nM, 500 pM or 100 pM; and has an off-rate for DKK1 of less than 10^{-2} per sec, 10^{-3} per sec, 10^{-4} per sec, or 10^{-5} per sec.

46. The antibody of claim 0, wherein the antibody has10^{2} - 10^{6} higher affinity to DKK1 or DKK4 compared to DKK2 or DKK3.

47. The antibody of claim 0, wherein the antibody competes against a neutralizing anti-DKK1/4 for binding to DKK1 or DKK4.

48. A method of treating diseases with a composition comprising at least a polypeptide sequence of SEQ ID NO:118 and a polypeptide sequence of SEQ ID NO:119, or conservative or humaneered changes thereof; wherein the composition is a neutralizing anti- DKK1/DKK4 antibody.

49. A method of preventing or treating proliferative diseases or diseases, such as a cancer, in a mammal, particularly a human, with a combination of pharmaceutical agents which comprises

(a) a neutralizing anti-DKK1/4 composition; and

(b) one or more pharmaceutically active agents.

The invention further relates to pharmaceutical compositions comprising:

(a) a neutralizing anti-DKK1/4 composition;

(b) a pharmaceutically active agent; and

(c) a pharmaceutically acceptable carrier.

The present invention further relates to a commercial package or product comprising:

(a) a pharmaceutical formulation of a neutralizing anti-DKK1/4 composition; and

(b) a pharmaceutical formulation of a pharmaceutically active agent for simultaneous, concurrent, separate or sequential use.

50. The method of claim 49, wherein the pharmaceutically active agent is meant especially any pharmaceutically active agent other than a neutralizing anti-DKK1/4 composition or a derivative thereof, which agent is selected from:

i. an aromatase inhibitor;

ii. an anti-estrogen, an anti-androgen or a gonadorelin agonist;

iii. a topoisomerase I inhibitor or a topoisomerase II inhibitor;

iv a microtubule active agent, an alkylating agent, an anti-neoplastic anti-metabolite or a platin compound;

v. a compound targeting/decreasing a protein or lipid kinase activity or a protein or lipid phosphatase activity, a further anti-angiogenic compound or a compound which induces cell differentiation processes;

vi. monoclonal antibodies;

vii. a cyclooxygenase inhibitor, a bisphosphonate, a heparanase inhibitor, a biological response modifier;

viii. an inhibitor of Ras oncogenic isoforms;

ix. a telomerase inhibitor;

x. a protease inhibitor, a matrix metalloproteinase inhibitor, a methionine aminopeptidase inhibitor, or a proteasome inhibitor;

xi. agents used in the treatment of hematologic malignancies or compounds which target, decrease or inhibit the activity of Flt-3;

xii. an HSP90 inhibitor;

xiii. antiproliferative antibodies;

xiv. a histone deacetylase (HDAC) inhibitor;

xv. a compound which targets, decreases or inhibits the activity/function of serine/threonine mTOR kinase;

xvi. a somatostatin receptor antagonist;

xvii. an anti-leukemic compound;

xviii. tumor cell damaging approaches;

xix. an EDG binder;

xx. a ribonucleotide reductase inhibitor;

xxi. an S-adenosylmethionine decarboxylase inhibitor;

xxii. a monoclonal antibody of VEGF or VEGFR;

xxiii. photodynamic therapy;

xxiv. an angiostatic steroid;

xxv. an implant containing corticosteroids;

xxvi. an AT1 receptor antagonist; and

xxvii. an ACE inhibitor.

51. An antibody that binds to DKK-1 with an affinity of (KD) or 10^{-8} or less and competes with any of the antibodies of claim 1.

52. The antibody according to claim 51 that does not detectably bind to DKK2 or DKK3.

53. The antibody of claim 52, wherein the antibody binds DKK1 or DKK4 with a (KD) of 10^{-3} or higher.

What is claimed is:

1. A composition comprising an isolated antibody or a functional fragment thereof comprising:

(a) CDR sequences of a variable heavy chain comprising: CDR1 with a sequence comprising amino acids 26 to 35 of SEQ ID NO: 11, CDR2 with a sequence comprising amino acids 47 to 66 of SEQ ID NO: 11, and CDR3 with a sequence comprising amino acids 99 to 105 of SEQ ID NO: 11, and

(b) CDR sequences of a variable light chain comprising: CDR1 with a sequence comprising amino acids 23 to 36 of SEQ ID NO: 30, CDR2 with a sequence comprising amino acids 48 to 58 of SEQ ID NO: 30, and CDR3 with a sequence comprising amino acids 91 to 100 of SEQ ID NO: 30,

wherein the antibody or functional fragment thereof specifically binds to human DKK1 and/or human DKK4.

2. The composition according to claim **1**, wherein binding to DKK1 or DKK4 is determined in at least one assay selected from: antagonism of Wnt-signaled transcription; electrochemiluminescence-based binding analysis; enzyme-linked immunosorbent assay binding; FMAT; SET; SPR; osteocalcin (OCN) serum concentration; osteoprotegrin (OPG) serum concentration; procollagen type 1 nitrogenous propeptide (P1 NP) serum concentration, ALP production; TopFlash or ameliorating osteolysis.

3. The composition according to claim **1**, which comprises a scaffold selected from an IgM and an IgG, wherein the IgG is selected from an IgG1, an IgG2, and IgG3 or an IgG4.

4. The composition according to claim **3**, wherein the IgM or the IgG is selected from a polyclonal or monoclonal.

5. The composition according to claim **1**, which is selected from a whole immunoglobulin or Fab fragment or scFv anti-

body fragment thereof, a heavy chain antibody, and an antigen-binding region thereof on a non-immunoglobulin scaffold.

6. A pharmaceutical composition comprising a composition of claim **1** and a pharmaceutically acceptable carrier or excipient.

7. An immunoconjugate comprising a first component which is an antibody or functional fragment thereof comprising:

(a) CDR sequences of a variable heavy chain comprising: CDR1 with a sequence comprising amino acids 26 to 35 of SEQ ID NO: 11, CDR2 with a sequence comprising amino acids 47 to 66 of SEQ ID NO: 11, and CDR3 with a sequence comprising amino acids 99 to 105 of SEQ ID NO: 11, and

(b) CDR sequences of a variable light chain comprising: CDR1 with a sequence comprising amino acids 23 to 36 of SEQ ID NO: 30, CDR2 with a sequence comprising amino acids 48 to 58 of SEQ ID NO: 30, and CDR3 with a sequence comprising amino acids 91 to 100 of SEQ ID NO: 30,

wherein the antibody or functional fragment thereof specifically binds to human DKK1 and/or human DKK4.

8. A kit comprising composition according to claim **1**.

9. The kit according to claim **8**, further comprising a pharmaceutically acceptable carrier or excipient therefore.

10. The kit according to claim **8**, wherein the antibody is present in a unit dose.

11. The kit according to claim **8**, further comprising instructions for use in administering to a subject.