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Description

[0001] The present invention relates to human engineered antibodies against DKK-1 and their use in treating diseases in which pathogenesis is mediated by DKK-1.

[0002] Dickkopf-1 (Dkk-1) is a member of the dickkopf family of proteins that have been shown to be negative regulators of the canonical Wnt-signaling pathway. The pathway plays a central role in bone development and formation. Dkk-1 inhibits Wnt signaling through its interaction with the Wnt co-receptor LRP5 or LRP6 and the kremen proteins. Dkk-1 prevents members of the Wnt pathway from interacting with either LRP5 or LRP6, thus preventing Wnt-mediated signal transduction. DKK1 has also been shown to be involved in bone metastasizing cancers, including multiple myeloma, breast carcinoma, renal carcinoma and non-small cell lung cancer.

[0003] WO 2007/084344 teaches antibodies that bind to the protein Dickkopf (DKK-1) which are used to treat cells with osteolytic conditions and, in particular, to treat osteolytic lesions associated with cancer.

[0004] Antibodies that bind Dkk-1 have also been described (for example, see WO2006/015373), however, there is still a need for therapeutic human engineered DKK-1 antibodies that will inhibit the interaction of Dkk-1 with LRP5 and LRP6. In addition, in view of the involvement of Dkk-1 in the regulation of bone formation, there is a need for therapeutic human engineered anti-Dkk-1 antibodies for use in bone healing. In addition, given the involvement of Dkk-1 in cancers, there is a need for human engineered anti-Dkk-1 antibodies for treating cancers, including multiple myeloma, breast and non-small cell lung cancers.

[0005] Yaccoby Shmeul et al, Blood, American Society of Hematology, US LNKD_D01: 10.1182/BLOOD_2006_09_047712, Vol. 109, No. 5, 1 March 2007, pages 2106-2111, XP002485200 describes anti-DKK-1 stimulated osteoblast activity, reduced osteoclastogenesis and promotion of bone formation in myelomatous and nonmyelomatous bones.

[0006] The antibodies of the present invention are therapeutically useful DKK-1 antagonists possessing a number of desirable properties. The present human engineered antibodies exhibit high affinity (Kd) to human DKK-1, cynomolgus DKK-1, rat DKK-1, mouse DKK-1, and rabbit DKK-1. Antibodies of the present invention block DKK-1-mediated inhibition of alkaline phosphatase, a marker of osteoblast activity. Furthermore, antibodies of the present invention exhibit an increase in bone mass density at both anterior and posterior cortices in a cortical defect in vivo model and demonstrate significant growth inhibition of non-small cell lung xenografts in vivo.

[0007] According to a first aspect of the present invention, there is provided a human engineered DKK-1 antibody or antigen binding fragment thereof, comprising a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR comprises CDRs LCDR1, LCDR2, and LCDR3 and the HCVR comprises CDRs HCDR1, HCDR2, and HCDR3, wherein LCDR1 is SEQ ID NO: 5, LCDR2 is SEQ ID NO: 8, LCDR3 is SEQ ID NO: 7, HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2, and HCDR3 is SEQ ID NO: 4 for use in the treatment of cancer.

[0008] Preferably, the human engineered DKK-1 antibody or antigen-binding fragment thereof, according to the present invention is used in the treatment of cancer, wherein the cancer is selected from multiple myeloma, breast cancer, and non-small cell lung cancer.

[0009] Preferably, the human engineered DKK-1 antibody is for use according to the present invention and wherein the LCVR comprises the amino acid sequence of SEQ ID NO: 14 and the HCVR comprises the amino acid sequence of SEQ ID NO: 12.

[0010] More preferably, the human engineered DKK-1 antibody is for use according to the present invention and wherein the human engineered DKK-1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 18 and a light chain comprising the amino acid sequence of SEQ ID NO: 20.

[0011] The human engineered DKK-1 antibody is preferably for use according to the present invention and comprising two light chains wherein each light chain comprises the amino acid sequence of SEQ ID NO: 20, and two heavy chains wherein each heavy chain comprises the amino acid sequence of SEQ ID NO: 18.

[0012] According to a second aspect of the present invention, there is provided a pharmaceutical composition comprising the human engineered DKK-1 antibody or antigen-binding fragment thereof, comprising a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR comprises CDRs LCDR1, LCDR2, and LCDR3 and the HCVR comprises CDRs HCDR1, HCDR2, and HCDR3, wherein LCDR1 is SEQ ID NO: 5, LCDR2 is SEQ ID NO: 8, LCDR3 is SEQ ID NO: 7, HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2, and HCDR3 is SEQ ID NO: 4 together with a pharmaceutically acceptable carrier, diluent, or excipient for use in the treatment of cancer.

[0013] Preferably, the pharmaceutical composition is for use according to the present invention in the treatment of cancer, wherein the cancer is selected from multiple myeloma, breast cancer, and non-small cell lung cancer.

[0014] The pharmaceutical composition for use according to the present invention may further optionally comprise other therapeutic ingredients.

[0015] The present invention provides a human engineered DKK-1 antibody or antigen-binding fragment thereof that has a Kd at 37°C of less than 5.0×10^{-11} M for human DKK-1 (SEQ ID NO: 29), cynomolgus DKK-1 (SEQ ID NO: 30), rat Dkk-1 (SEQ ID NO: 31), mouse DKK-1 (SEQ ID NO: 33), and rabbit DKK-1 (SEQ ID NO: 32).

[0016] The present invention provides a human engineered DKK-1 antibody or a binding fragment thereof wherein

LCDR1 has the amino sequence of SEQ ID NO:5, LCDR2 has the amino sequence of SEQ ID NO:47, LCDR3 has the amino sequence of SEQ ID NO:49, HCDR1 has the amino sequence of SEQ ID NO:1, HCDR2 has the amino sequence of SEQ ID NO:2, and HCDR3 has the amino sequence of SEQ ID NO:44.

[0017] The present invention also provides a pharmaceutical composition comprising the human engineered DKK-1 antibody or antigen-binding fragment thereof of the present invention and a pharmaceutically acceptable carrier, diluent, or excipient.

[0018] The present invention provides a method of treating cancer comprising administering a human engineered DKK-1 antibody or antigen binding fragment thereof of the present invention, wherein the cancer is selected from the group consisting of multiple myeloma, breast cancer and non-small cell lung cancer.

[0019] The present invention provides a human engineered DKK-1 antibody or antigen-binding fragment thereof as described herein, wherein the antibody has a K_d of less than 1.5×10^{-11} M for human DKK-1 (SEQ ID NO: 29). More preferably, the present invention provides human engineered DKK-1 antibody or antigen-binding fragment thereof, wherein the antibody has a K_d of less than 1.0×10^{-11} M for human DKK-1 (SEQ ID NO: 29). Further preferred, the present invention provides human engineered DKK-1 antibody or antigen-binding fragment thereof, wherein the antibody has a K_d of less than 5.0×10^{-12} M for human DKK-1 (SEQ ID NO: 29). More preferably, the present invention provides human engineered DKK-1 antibody or antigen-binding fragment thereof, wherein the antibody has a K_d between 0.5×10^{-12} M and 1.5×10^{-11} M for human DKK-1 (SEQ ID NO: 29). Further preferred, the present invention provides human engineered DKK-1 antibody or antigen-binding fragment thereof, wherein the antibody has a K_d between 1.0×10^{-12} M and 1.0×10^{-11} M for human DKK-1 (SEQ ID NO: 29). The K_d values are established by a binding equilibrium at 37°C as described in Example 2.

[0020] The present invention also provides a human engineered DKK-1 antibody or antigen-binding fragment thereof as described herein, wherein the antibody has a K_d of less than 5.0×10^{-11} M for human DKK-1 (SEQ ID NO: 29), cynomolgus DKK-1 (SEQ ID NO: 30), rat Dkk-1 (SEQ ID NO: 31), mouse DKK-1 (SEQ ID NO: 33), and rabbit DKK-1 (SEQ ID NO: 32). More preferably, the present invention provides human engineered DKK-1 antibody or antigen-binding fragment thereof, wherein the antibody has a K_d of less than 3.0×10^{-11} M for human DKK-1 (SEQ ID NO: 29), cynomolgus DKK-1 (SEQ ID NO: 30), rat Dkk-1 (SEQ ID NO: 31), mouse DKK-1 (SEQ ID NO: 33), and rabbit DKK-1 (SEQ ID NO: 32). Further preferred, the present invention provides human engineered DKK-1 antibody or antigen-binding fragment thereof, wherein the antibody has a K_d of less than 2.0×10^{-11} M for human DKK-1 (SEQ ID NO: 29), rat Dkk-1 (SEQ ID NO: 31), and mouse DKK-1 (SEQ ID NO: 33). More preferably, the present invention provides human engineered DKK-1 antibody or antigen-binding fragment thereof, wherein the antibody has a K_d between 1.0×10^{-11} M and 5.0×10^{-11} M for human DKK-1 (SEQ ID NO: 29), cynomolgus DKK-1 (SEQ ID NO: 30), rat Dkk-1 (SEQ ID NO: 31), mouse DKK-1 (SEQ ID NO: 33), and rabbit DKK-1 (SEQ ID NO: 32). Further preferred, the present invention provides human engineered DKK-1 antibody or antigen-binding fragment thereof, wherein the antibody has a K_d between 1.5×10^{-11} M and 3.0×10^{-11} M for human DKK-1 (SEQ ID NO: 29), rat Dkk-1 (SEQ ID NO: 31), and mouse DKK-1 (SEQ ID NO: 33). The K_d values are established by a binding equilibrium at 37°C as described in Example 2.

[0021] More preferably, the present invention provides a human engineered DKK-1 antibody or antigen-binding fragment thereof comprising a LCVR comprising the amino acid sequence of SEQ ID NO: 14 and a HCVR comprising the amino acid sequence of SEQ ID NO: 12 and wherein the human engineered DKK-1 antibody or antigen-binding fragment thereof has a K_d of less than 3.0×10^{-11} M for human DKK-1 (SEQ ID NO: 29), cynomolgus DKK-1 (SEQ ID NO: 30), rat Dkk-1 (SEQ ID NO: 31), mouse DKK-1 (SEQ ID NO: 33), and rabbit DKK-1 (SEQ ID NO: 32). Further preferred, the present invention provides a human engineered DKK-1 antibody or antigen-binding fragment thereof comprising a LCVR comprising the amino acid sequence of SEQ ID NO: 14 and a HCVR comprising the amino acid sequence of SEQ ID NO:12 and wherein the human engineered DKK-1 antibody or antigen-binding fragment thereof has a K_d of less than 2.5×10^{-11} M for human DKK-1 (SEQ ID NO: 29), cynomolgus DKK-1 (SEQ ID NO: 30), rat Dkk-1 (SEQ ID NO: 31), mouse DKK-1 (SEQ ID NO: 33), and rabbit DKK-1 (SEQ ID NO: 32). More preferably, the present invention provides a human engineered DKK-1 antibody or antigen-binding fragment thereof comprising a LCVR comprising the amino acid sequence of SEQ ID NO:14 and a HCVR comprising the amino acid sequence of SEQ ID NO: 12 and wherein the human engineered DKK-1 antibody or antigen-binding fragment thereof has a K_d of less than 2.0×10^{-11} M for human DKK-1 (SEQ ID NO: 29), cynomolgus DKK-1 (SEQ ID NO: 30), rat Dkk-1 (SEQ ID NO: 31), mouse DKK-1 (SEQ ID NO: 33), and rabbit DKK-1 (SEQ ID NO: 32). Further preferred, the present invention provides a human engineered DKK-1 antibody or antigen-binding fragment thereof comprising a LCVR comprising the amino acid sequence of SEQ ID NO: 14 and a HCVR comprising the amino acid sequence of SEQ ID NO:12 and wherein the human engineered DKK-1 antibody or antigen-binding fragment thereof has a K_d between 0.5×10^{-12} M and 3.0×10^{-11} M for human DKK-1 (SEQ ID NO: 29), cynomolgus DKK-1 (SEQ ID NO: 30), rat Dkk-1 (SEQ ID NO: 31), mouse DKK-1 (SEQ ID NO: 33), and rabbit DKK-1 (SEQ ID NO: 32). More preferably, the present invention provides a human engineered DKK-1 antibody or antigen-binding fragment thereof comprising a LCVR comprising the amino acid sequence of SEQ ID NO:14 and a HCVR comprising the amino acid sequence of SEQ ID NO:12 and wherein the human engineered DKK-1 antibody or antigen-binding fragment thereof has a K_d between 1.0×10^{-12} M and 2.5×10^{-11} M for human DKK-1 (SEQ ID NO: 29).

29), cynomolgus DKK-1 (SEQ ID NO: 30), rat Dkk-1 (SEQ ID NO: 31), mouse DKK-1 (SEQ ID NO: 33), and rabbit DKK-1 (SEQ ID NO: 32). The K_d values are established by a binding equilibrium at 37°C as described in Example 2.

[0022] The present invention provides a human engineered DKK-1 antibody or a binding fragment thereof, comprising a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR comprises complementarity determining regions (CDRs) LCDR1, LCDR2, and LCDR3 and the HCVR comprises CDRs HCDR1, HCDR2 and HCDR3, wherein LCDR1 has the amino sequence of SEQ ID NO:5, HCDR1 has the amino sequence of SEQ ID NO:1, and HCDR2 has the amino sequence of SEQ ID NO:2.

[0023] The present invention provides a human engineered DKK-1 antibody or a binding fragment thereof wherein LCDR1 has the amino sequence of SEQ ID NO:46, LCDR2 has the amino sequence of SEQ ID NO:48, LCDR3 has the amino sequence of SEQ ID NO:50, HCDR1 has the amino sequence of SEQ ID NO:1, HCDR2 has the amino sequence of SEQ ID NO:43, and HCDR3 has the amino sequence of SEQ ID NO:45. The present invention preferably provides a human engineered DKK-1 antibody or a binding fragment thereof wherein LCDR1 has the amino sequence of SEQ ID NO:5, LCDR2 has the amino sequence of SEQ ID NO:47, LCDR3 has the amino sequence of SEQ ID NO:49, HCDR1 has the amino sequence of SEQ ID NO:1, HCDR2 has the amino sequence of SEQ ID NO:2, and HCDR3 has the amino sequence of SEQ ID NO:44.

[0024] The present invention provides a human engineered DKK-1 antibody or a binding fragment thereof wherein LCDR1 has the amino sequence of SEQ ID NO:5, LCDR2 has an amino sequence selected from the group consisting of SEQ ID NO:6, SEQ ID NO:8, and SEQ ID NO:10, LCDR3 has an amino sequence selected from the group consisting of SEQ ID NO:7 and SEQ ID NO:9, HCDR1 has the amino sequence of SEQ ID NO:1, HCDR2 has the amino sequence of SEQ ID NO:2, and HCDR3 has an amino sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:4.

[0025] The present invention preferably provides a human engineered DKK-1 antibody or antigen-binding fragment thereof wherein LCDR1, LCDR2, LCDR3, HCDR1, HCDR2 and HCDR3 have amino acid sequences selected from the group consisting of:

- (i) LCDR1 is SEQ ID NO: 5, LCDR2 is SEQ ID NO: 6, LCDR3 is SEQ ID NO: 7, HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2, and HCDR3 is SEQ ID NO: 3,
- (ii) LCDR1 is SEQ ID NO: 5, LCDR2 is SEQ ID NO: 8, LCDR3 is SEQ ID NO: 7, HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2, and HCDR3 is SEQ ID NO: 4,
- (iii) LCDR1 is SEQ ID NO: 5, LCDR2 is SEQ ID NO: 6, LCDR3 is SEQ ID NO: 9, HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2, and HCDR3 is SEQ ID NO: 3,
- (iv) LCDR1 is SEQ ID NO: 5, LCDR2 is SEQ ID NO: 10, LCDR3 is SEQ ID NO: 9, HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2, and HCDR3 is SEQ ID NO: 3

[0026] The present invention provides a human engineered DKK-1 antibody or antigen-binding fragment thereof wherein the LCVR comprises the amino acid sequence of SEQ ID NO: 52 and the HCVR comprises the amino acid sequence of SEQ ID NO: 51.

[0027] The present invention preferably provides a human engineered DKK-1 antibody or antigen-binding fragment thereof wherein the LCVR comprises an amino acid sequence selected from the group consisting of SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO: 15, and SEQ ID NO:16.

[0028] The present invention preferably provides a human engineered DKK-1 antibody or antigen-binding fragment thereof, wherein the HCVR comprises an amino acid sequence selected from the group consisting of SEQ ID NO:11 and SEQ ID NO: 12.

[0029] The present invention preferably provides a human engineered DKK-1 antibody or antigen-binding fragment thereof, wherein the LCVR and HCVR comprise amino acid sequences selected from the group consisting of:

- (i) a LCVR comprising the amino acid sequence of SEQ ID NO:13 and a HCVR comprising the amino acid sequence of SEQ ID NO: 11;
- (ii) a LCVR comprising the amino acid sequence of SEQ ID NO:14 and a HCVR comprising the amino acid sequence of SEQ ID NO:12;
- (iii) a LCVR comprising the amino acid sequence of SEQ ID NO:15 and a HCVR comprising the amino acid sequence of SEQ ID NO: 11;
- (iv) a LCVR comprising the amino acid sequence of SEQ ID NO:16 and a HCVR comprising the amino acid sequence of SEQ ID NO: 11.

[0030] The present invention preferably provides a human engineered DKK-1 antibody or antigen-binding fragment thereof comprising a LCVR comprising the amino acid sequence of SEQ ID NO:14 and a HCVR comprising the amino acid sequence of SEQ ID NO:12.

[0031] The present invention preferably provides a human engineered DKK-1 antibody wherein the human engineered DKK-1 antibody comprises a light chain wherein the light chain comprises an amino acid sequence selected from the group consisting of SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, and SEQ ID NO:22.

[0032] The present invention preferably provides a human engineered DKK-1 antibody, wherein the human engineered DKK-1 antibody comprises a heavy chain wherein the heavy chain comprises an amino acid sequence selected from the group consisting of SEQ ID NO:17 and SEQ ID NO:18.

[0033] More preferably, the present invention provides a human engineered DKK-1 antibody, wherein the human engineered DKK-1 antibody comprises a heavy chain and a light chain amino acid sequence selected from the group consisting of

(i) a heavy chain comprising the amino acid sequence of SEQ ID NO: 17 and light chain comprising the amino acid sequence of SEQ ID NO:19,

(ii) a heavy chain comprising the amino acid sequence of SEQ ID NO:18 and a light chain comprising the amino acid sequence of SEQ ID NO:20,

(iii) a heavy chain comprising the amino acid sequence of SEQ ID NO: 17 and a light chain comprising the amino acid sequence of SEQ ID NO:21, and

(iv) a heavy chain comprising the amino acid sequence of SEQ ID NO: 17 and a light chain comprising the amino acid sequence of SEQ ID NO: 22.

[0034] The present invention preferably provides a human engineered DKK-1 antibody comprising two light chains wherein each light chain comprises the amino acid sequence of SEQ ID NO: 19, and two heavy chains wherein each heavy chain comprises the amino acid sequence of SEQ ID NO: 17.

[0035] The present invention preferably provides a human engineered DKK-1 antibody comprising two light chains wherein each light chain comprises the amino acid sequence of SEQ ID NO: 21, and two heavy chains wherein each heavy chain comprises the amino acid sequence of SEQ ID NO: 17.

[0036] The present invention preferably provides a human engineered DKK-1 antibody comprising two light chains wherein each light chain comprises the amino acid sequence of SEQ ID NO:22, and two heavy chains wherein each heavy chain comprises the amino acid sequence of SEQ ID NO: 17.

[0037] The present invention preferably provides a human engineered DKK-1 antibody comprising two light chains wherein each light chain comprises the amino acid sequence of SEQ ID NO: 20, and two heavy chains wherein each heavy chain comprises the amino acid sequence of SEQ ID NO:18.

[0038] The present invention also provides an antibody or antigen-binding fragment thereof, which competes with the human engineered DKK-1 antibody or antigen-binding fragment thereof of the present invention for binding to human DKK-1 (SEQ ID NO: 29) as determined via an antibody competition assay.

[0039] The present invention also provides a pharmaceutical composition comprising the human engineered DKK-1 antibody or antigen-binding fragment thereof of the present invention and a pharmaceutically acceptable carrier, diluent, or excipient.

[0040] Furthermore, the present invention provides a pharmaceutical composition comprising the human engineered DKK-1 antibody or antigen-binding fragment thereof of the present invention together with a pharmaceutically acceptable carrier, diluent, or excipient and optionally other therapeutic ingredients.

[0041] The antibody of the present invention may be used in a method of healing bone comprising administering a human engineered DKK-1 antibody or antigen binding fragment thereof of the present invention.

[0042] In a further aspect, the present invention provides a method of treating cancer comprising administering a human engineered DKK-1 antibody or antigen binding fragment thereof of the present invention, wherein the cancer is preferably selected from the group consisting of multiple myeloma, breast cancer and non-small cell lung cancer.

[0043] Furthermore, the present invention provides a human engineered DKK-1 antibody or antigen binding fragment thereof of the present invention for use in therapy. Preferably, the present invention provides a human engineered DKK-1 antibody or antigen binding fragment thereof of the present invention for use in the treatment of cancer, wherein the cancer is preferably selected from the group consisting of multiple myeloma, breast cancer and non-small cell lung cancer.

[0044] Furthermore, the present invention also provides for the use of a human engineered DKK-1 antibody or antigen binding fragment thereof of the present invention in the manufacture of a medicament to treat cancer, wherein the cancer is preferably selected from the group consisting of multiple myeloma, breast cancer and non-small cell lung cancer.

Definitions

[0045] A full-length antibody as it exists naturally is an immunoglobulin molecule comprising 2 heavy (H) chains and 2 light (L) chains interconnected by disulfide bonds. The amino terminal portion of each chain includes a variable region of about 100-110 amino acids primarily responsible for antigen recognition via the complementarity determining regions

(CDRs) contained therein. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function.

[0046] The CDRs are interspersed with regions that are more conserved, termed framework regions ("FR"). Each light chain variable region (LCVR) and heavy chain variable region (HCVR) is composed of 3 CDRs and 4 FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The 3 CDRs of the light chain are referred to as "LCDR1, LCDR2, and LCDR3" and the 3 CDRs of the heavy chain are referred to as "HCDR1, HCDR2, and HCDR3." The CDRs contain most of the residues which form specific interactions with the antigen. The numbering and positioning of CDR amino acid residues within the LCVR and HCVR regions is in accordance with the well-known Kabat numbering convention.

[0047] Light chains are classified as kappa or lambda, and are characterized by a particular constant region as known in the art. Heavy chains are classified as gamma, mu, alpha, delta, or epsilon, and define the isotype of an antibody as IgG, IgM, IgA, IgD, or IgE, respectively. IgG antibodies can be further divided into subclasses, e.g., IgG1, IgG2, IgG3, IgG4. Each heavy chain type is characterized by a particular constant region with a sequence well known in the art.

[0048] As used herein, the term "monoclonal antibody" (Mab) refers to an antibody that is derived from a single copy or clone including, for example, any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced. Mabs of the present invention preferably exist in a homogeneous or substantially homogeneous population. Complete Mabs contain 2 heavy chains and 2 light chains. "Antigen-binding fragments" of such monoclonal antibodies include, for example, Fab fragments, Fab' fragments, F(ab')₂ fragments, and single chain Fv fragments. Monoclonal antibodies and antigen-binding fragments thereof of the present invention can be produced, for example, by recombinant technologies, phage display technologies, synthetic technologies, e.g., CDR-grafting, or combinations of such technologies, or other technologies known in the art. For example, mice can be immunized with human DKK-1 or fragments thereof, the resulting antibodies can be recovered and purified, and determination of whether they possess binding and functional properties similar to or the same as the antibody compounds disclosed herein can be assessed by the methods disclosed in Examples below. Antigen-binding fragments can also be prepared by conventional methods. Methods for producing and purifying antibodies and antigen-binding fragments are well known in the art and can be found, for example, in Harlow and Lane (1988) *Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, chapters 5-8 and 15, ISBN 0-87969-314-2.

[0049] The phrase "chimeric antibody" refers to an antibody containing domains from different species (generally 2 species). Antibody V is a chimeric antibody wherein the light chain and heavy chain variable domains contain residues from a murine antibody, whereas the constant region light chain domain contains residues comprising a rat kappa light chain and the constant region heavy chain domains contains residues comprising a rat IgG1 antibody. Antibody V is a murine/rat chimera and is used in studies to reduce the likelihood of immune response in long-term pre-clinical models.

[0050] The phrase "human engineered antibodies" refers to monoclonal antibodies that have binding and functional properties according to the invention, and that have framework regions that are substantially human or fully human surrounding CDRs derived from a non-human antibody. "Antigen-binding fragments" of such human engineered antibodies include, for example, Fab fragments, Fab' fragments, F(ab')₂ fragments, and single chain Fv fragments. "Framework region" or "framework sequence" refers to any one of framework regions 1 to 4. Human engineered antibodies and antigen-binding fragments thereof encompassed by the present invention include molecules wherein any one or more of framework regions 1 to 4 is substantially or fully human, i.e., wherein any of the possible combinations of individual substantially or fully human framework regions 1 to 4, is present. For example, this includes molecules in which framework region 1 and framework region 2, framework region 1 and framework region 3, framework region 1, 2, and 3, etc., are substantially or fully human. Substantially human frameworks are those that have at least about 80% sequence identity to a known human germline framework sequence. Preferably, the substantially human frameworks have at least about 85%, about 90%, about 95%, or about 99% sequence identity to a known human germline framework sequence.

[0051] Fully human frameworks are those that are identical to a known human germline framework sequence. Human framework germline sequences can be obtained from ImMunoGeneTics (IMGT) via their website <http://imgt.cines.fr>, or from *The Immunoglobulin FactsBook* by Marie-Paule Lefranc and Gerard Lefranc, Academic Press, 2001, ISBN 012441351. For example, germline light chain frameworks can be selected from the group consisting of: A11, A17, A18, A19, A20, A27, A30, LI, L11, L12, L2, L5, L15, L6, L8, 012, 02, and 08, and germline heavy chain framework regions can be selected from the group consisting of: VH2-5, VH2-26, VH2-70, VH3-20, VH3-72, VHI-46, VH3-9, VH3-66, VH3-74, VH4-31, VHI-18, VHI-69, VI-13-7, VH3-11, VH3-15, VH3-21, VH3-23, VH3-30, VH3-48, VH4-39, VH4-59, and VH5-51.

[0052] Human engineered antibodies in addition to those disclosed herein exhibiting similar functional properties according to the present invention can be generated using several different methods. The specific antibody compounds disclosed herein can be used as templates or parent antibody compounds to prepare additional antibody compounds. In one approach, the parent antibody compound CDRs are grafted into a human framework that has a high sequence identity with the parent antibody compound framework. The sequence identity of the new framework will generally be at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% identical to the

sequence of the corresponding framework in the parent antibody compound. This grafting may result in a reduction in binding affinity compared to that of the parent antibody. If this is the case, the framework can be back-mutated to the parent framework at certain positions based on specific criteria disclosed by Queen et al. (1991) Proc. Natl. Acad. Sci. USA 88:2869. Additional references describing methods useful in humanizing mouse antibodies include U.S. Patent Nos. 4,816,397; 5,225,539, and 5,693,761; computer programs ABMOD and ENCAD as described in Levitt (1983) J. Mol. Biol. 168:595-620; and the method of Winter and co-workers (Jones et al. (1986) Nature 321:522-525; Riechmann et al. (1988) Nature 332:323-327; and Verhoeven et al. (1988) Science 239:1534-1536.

[0053] The identification of residues to consider for back-mutation can be carried out as follows:

When an amino acid falls under the following category, the framework amino acid of the human germ-line sequence that is being used (the "acceptor framework") is replaced by a framework amino acid from a framework of the parent antibody compound (the "donor framework"):

- (a) the amino acid in the human framework region of the acceptor framework is unusual for human frameworks at that position, whereas the corresponding amino acid in the donor immunoglobulin is typical for human frameworks at that position;
- (b) the position of the amino acid is immediately adjacent to one of the CDRs; or
- (c) any side chain atom of a framework amino acid is within about 5-6 angstroms (center-to-center) of any atom of a CDR amino acid in a three dimensional immunoglobulin model.

[0054] When each of the amino acids in the human framework region of the acceptor framework and a corresponding amino acid in the donor framework is generally unusual for human frameworks at that position, such amino acid can be replaced by an amino acid typical for human frameworks at that position. This back-mutation criterion enables one to recover the activity of the parent antibody compound.

[0055] Another approach to generating human engineered antibodies exhibiting similar functional properties to the antibody compounds disclosed herein involves randomly mutating amino acids within the grafted CDRs without changing the framework, and screening the resultant molecules for binding affinity and other functional properties that are as good as or better than those of the parent antibody compounds. Single mutations can also be introduced at each amino acid position within each CDR, followed by assessing the effects of such mutations on binding affinity and other functional properties. Single mutations producing improved properties can be combined to assess their effects in combination with one another.

[0056] Further, a combination of both of the foregoing approaches is possible. After CDR grafting, one can back-mutate specific framework regions in addition to introducing amino acid changes in the CDRs. This methodology is described in Wu et al. (1999) J. Mol. Biol. 294:151-162.

[0057] Applying the teachings of the present invention, a person skilled in the art can use common techniques, e.g., site-directed mutagenesis, to substitute amino acids within the presently disclosed CDR and framework sequences and thereby generate further variable region amino acid sequences derived from the present sequences. All alternative naturally occurring amino acids can be introduced at a specific substitution site. The methods disclosed herein can then be used to screen these additional variable region amino acid sequences to identify sequences having the indicated *in vivo* functions. In this way, further sequences suitable for preparing human engineered antibodies and antigen-binding portions thereof in accordance with the present invention can be identified. Preferably, amino acid substitution within the frameworks is restricted to one, two, or three positions within any one or more of the 4 light chain and/or heavy chain framework regions disclosed herein. Preferably, amino acid substitution within the CDRs is restricted to one, two, or three positions within any one or more of the 3 light chain and/or heavy chain CDRs. Combinations of the various changes within these framework regions and CDRs described above are also possible. Most preferably, these techniques are used to generate further variable region amino acid sequences using the variable heavy and light chain amino acid sequences describes in SEQ ID NO:12 and SEQ ID NO:14 respectively.

[0058] Human engineered antibodies or antigen-binding fragments thereof that "compete" with the molecules disclosed herein are those that bind human DKK-1 (SEQ ID NO:29) at site(s) that are identical to, or overlapping with, the site(s) at which the present molecules bind. Competing human engineered antibodies or antigen-binding fragments thereof can be identified, for example, via an antibody competition assay. For example, a sample of purified or partially purified human DKK-1 (SEQ ID NO:29) is bound to a solid support. An antibody disclosed herein and a test monoclonal antibody or antigen-binding fragment, with either the test or antibody of the present invention labeled, are then added. If the labeled antibody and the unlabeled antibody bind to separate and discrete sites on DKK-1, the labeled antibody will bind to the same level whether or not the suspected competing antibody is present. However, if the sites of interaction are identical or overlapping, the unlabeled antibody will compete, and the amount of labeled antibody bound to the antigen will be lowered. If the unlabeled antibody is present in excess, no labeled antibody will bind. For purposes of the present invention, competing human engineered antibodies or antigen-binding fragments thereof are those that decrease the

binding of the present antibodies to DKK-1 by about 50%, about 60%, about 70%, about 80%, about 85%, about 90%, about 95%, or about 99%. Details of procedures for carrying out such competition assays are well known in the art and can be found, for example, in Harlow and Lane (1988) *Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, pages 567-569, ISBN 0-87969-314-2. Such assays can be made quantitative by using purified antibodies. A standard curve is established by titrating one antibody against a labeled version of itself. The capacity of an unlabeled competing monoclonal antibody or antigen-binding fragment thereof to inhibit the binding of the labeled molecule to the plate is titrated. The results are plotted, and the concentrations necessary to achieve the desired degree of binding inhibition are compared. Whether monoclonal antibodies or antigen-binding fragments thereof that compete with human engineered antibodies or antigen-binding fragments thereof of the present invention in such competition assays possess the same or similar functional properties of the present human engineered antibodies can be determined via the methods disclosed in Examples herein.

[0059] The term "inhibit" means the ability to substantially antagonize, prohibit, prevent, restrain, slow, disrupt, eliminate, stop, reduce, or reverse the biological effects of DKK-1.

[0060] The term "treating" (or "treat" or "treatment") refers to processes involving a slowing, interrupting, arresting, controlling, stopping, reducing, or reversing the progression or severity of a symptom, disorder, condition, or disease, but does not necessarily involve a total elimination of all disease-related symptoms, conditions, or disorders associated with DKK-1 activity.

[0061] The term "preventing" (or "prevent" or "prevention") means prohibiting, restraining, or inhibiting the incidence or occurrence of a symptom, disorder, condition, or disease. Acute events and chronic conditions may be treated and prevented. In an acute event, an antibody or antigen-binding fragment thereof is administered at the onset of a symptom, disorder, condition, or disease, and is discontinued when the acute event ends. In contrast, a chronic symptom, disorder, condition, or disease is treated over a more protracted time frame.

[0062] The term "effective amount" refers to the amount or dose of an antibody compound of the present invention which, upon single or multiple dose administration to a patient, provides the desired treatment or prevention. Therapeutically effective amounts of the present antibody compounds can comprise an amount in the range of from about 0.1 mg/kg to about 20 mg/kg per single dose. A therapeutically effective amount for any individual patient can be determined by the health care provider by monitoring the effect of the antibody compounds on a biomarker.

[0063] The term "bone healing" refers to the stimulation of bone formation at sites of injury by blocking DKK-1. Examples of bone healing indications include, but are not limited to, fracture healing, implant fixation/retention, and dental implant fixation/retention.

[0064] The human engineered antibodies of the present invention can be used as medicaments in human medicine, administered by a variety of routes. Most preferably, such compositions are for parenteral administration. Such pharmaceutical compositions can be prepared by methods well known in the art (See, e.g., Remington: *The Science and Practice of Pharmacy*, 19th ed. (1995), A. Gennaro et al., Mack Publishing Co.) and comprise a human engineered antibody as disclosed herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

[0065] The results of the following assays demonstrate that the monoclonal antibodies and antigen-binding fragments thereof, of the present invention are useful as a DKK-1 inhibitor. The antibodies of the present invention possess a number of desirable properties. For example, Antibody II of the present invention has increased chemical and physical stability, and solubility. Accelerated studies are performed to assess the chemical stability of antibodies by incubating the antibodies of the present invention under different buffer conditions (pH and NaCl variation) and incubating at 4°C, 25°C, and 40°C for 4 weeks. Chemical modifications of the antibodies of the present invention are detected by cation-exchange ("CEX") chromatography to separate charge variants (eg., deamidation of asparagine to aspartic acid) and LC-MS analysis to identify specific sites of degradation. Antibody II has the least amount of degradation detected by CEX and this result is further confirmed by LC-MS data showing that all three asparagine residues in the CDRs had the least amount of deamidation compared to the other antibodies described herein after 4-week incubation at 40°C in pH 8 buffer. Solubility for Antibody II is more favorable compared to Antibody I when formulated at pH 6 + 150 mM NaCl. Furthermore, Antibody II maintained solubility of > 105 mg/mL when stored in 4°C, whereas solubility for Antibody I is only 48 mg/mL and precipitated under these same conditions. As used herein, "EC50" refers to the concentration of an agent which produces 50% of the maximal response possible for that agent. "Kd" refers to the equilibrium dissociation constant which can be calculated by the formula: $k_{off}/k_{on} = Kd$.

Example 1-Production of Antibodies

[0066] Antibodies I, II, III, and IV can be made and purified as follows. An appropriate host cell, such as HEK 293 EBNA or CHO, is either transiently or stably transfected with an expression system for secreting antibodies using an optimal predetermined HC:LC vector ratio or a single vector system encoding both HC, such as SEQ ID NO: 23, or SEQ ID NO: 24, and LC, such as SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, or SEQ ID NO: 28. Clarified media, into which the antibody has been secreted, is purified using any of many commonly-used techniques. For example, the

medium may be conveniently applied to a Protein A or G Sepharose FF column that has been equilibrated with a compatible buffer, such as phosphate buffered saline (pH 7.4). The column is washed to remove nonspecific binding components. The bound antibody is eluted, for example, by pH gradient (such as 0.1 M sodium phosphate buffer pH 6.8 to 0.1 M sodium citrate buffer pH 3.0). Antibody fractions are detected, such as by SDS-PAGE, and then are pooled. Further purification is optional, depending on the intended use. The antibody may be concentrated and/or sterile filtered using common techniques. Soluble aggregate and multimers may be effectively removed by common techniques, including size exclusion, hydrophobic interaction, ion exchange, or hydroxyapatite chromatography. The purity of the antibody after these chromatography steps is greater than 99%. The product may be immediately frozen at -70°C or may be lyophilized. The amino acid sequences for these antibodies are provided below.

SEQ ID NOs

[0067]

Antibody	Heavy Chain	Light Chain	HCVR	LCVR
I	17	19	11	13
II	18	20	12	14
III	17	21	11	15
IV	17	22	11	16
V	35	34	37	36

Antibody	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
I	1	2	3	5	6	7
II	1	2	4	5	8	7
III	1	2	3	5	6	9
IV	1	2	3	5	10	9
V	1	38	39	40	41	42

Example 2: Affinity (Kd) measurements for DKK-1 antibodies

[0068] To establish a binding equilibrium, a constant concentration of antibody is mixed with varying concentrations of His-tagged DKK-1 (SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, or SEQ ID NO:33) (1 nM - 1 pM range) in PBS (pH 7.4) + 1 mg/mL bovine serum albumin ("BSA") or buffer alone and incubated for several days at 37°C. Two sets of binding reactions are set up, one set at low concentration of antibody (3 pM) and one set at high concentration of antibody (30 or 50 pM).

[0069] After establishing equilibrium, a KinExA 3000 instrument (Sapidyne Inst. Inc.) is used to probe for the fraction of 'free' (unbound) antibody. Briefly, His-tagged DKK-1 is covalently coupled to NHS-activated Sepharose 4 Fast Flow beads (GE Healthcare) which are packed by the instrument to create a small column. The pre-equilibrated mixtures of antibody + His-tagged DKK-1 are passed over the beads to capture only free antibody. The amount of free antibody captured is proportional to the free concentration in the equilibrated samples, and is detected by injection of a fluorescently labeled secondary antibody. Data sets from low and high concentrations of antibody are fit globally using n-curve analysis in the KinExA software. This fitting returns a Kd value as well as the 95% confidence interval.

Table 1: Antibody II affinity to DKK-1 from various species

DKK-1 Species	Kd (pM)	95% Confidence Interval for Kd (pM)
Human	3.3	1.4 - 7.5
Cynomolgus	14	8.4 - 26
Rat	8.4	3.9 - 23

(continued)

DKK-1 Species	Kd (pM)	95% Confidence Interval for Kd (pM)
Murine	7.0	4.7 - 11
Rabbit	17	11 - 27

Example 3: Effect of Dkk-1 antibodies in C2C12 alkaline phosphatase assay

[0070] Canonical Wnt signaling is important for osteoblast differentiation and activity. Wnt-3a CM (Conditioned Media) combined with BMP-4 induces pluripotent mouse C2C12 cells to differentiate into osteoblasts with a measurable endpoint of alkaline phosphatase ("AP"), a marker of osteoblast activity. DKK-1, an inhibitor of canonical Wnt signaling, inhibits the differentiation and production of AP. Neutralizing DKK-1 antibodies prevent DKK-1-mediated inhibition of AP. Antibodies which block DKK-1 inhibitory activity prevent the loss of AP activity.

[0071] C2C12 cells are grown to 60% - 80% confluence in tissue culture flasks in growth medium (Dulbecco's Modified Eagle's Medium ("DMEM") containing L-glutamine, 10% heat-inactivated fetal bovine serum ("FBS"), 1x antibiotic/antimycotic, 1x sodium pyruvate). C2C12 cells are resuspended to a concentration of 30,000 cells/mL in growth medium and 100 μ L/well are added to a 96-well tissue culture plate and incubated overnight at 37°C, 95% humidity, 5% CO₂. Growth medium is replaced with 50 μ L assay medium (DMEM containing L-glutamine, 5% heat-inactivated FBS, 1x antibiotic/antimycotic, 1x sodium pyruvate). To stimulate differentiation (and thus induce AP production), 100 μ L assay medium plus 1.5x Wnt-3a CM + BMP-4 (R & D Systems catalogue #314-BP) are added. This yields a final concentration of 1x Wnt-3a CM and 25 ng/mL BMP-4. Negative controls contain only L-cell CM (no Wnt-3a or BMP-4). Cells are incubated at 37°C, 95% humidity, 5% CO₂ for 72 hours. Medium is removed, cells are washed with 200 μ L phosphate-buffered saline ("PBS"), and the PBS is removed. Cells are freeze-thawed 3 times. 100 μ L One-step pNPP substrate (Thermo Scientific catalogue #37621) is added per well, and the plate is incubated at room temperature. Absorbance is read at 405 nm. To determine the concentration of DKK-1 required to inhibit differentiation, Dkk-1 molecules from various species are titrated to identify the minimal concentration required to fully inhibit AP induction.

[0072] The minimal concentration of DKK-1 from each species which fully inhibits AP induction is as follows: human DKK-1=38 nM, cynomolgus DKK-1=11.4 nM, rat DKK-1=5.8 nM, and rabbit DKK-1= 25.0 nM.

[0073] Having determined the concentration of DKK-1 which fully inhibits AP induction, increasing concentrations of an anti-DKK-1 antibody are pre-incubated in assay medium with an inhibitory concentration of Dkk-1 for 30 minutes at room temperature. AP induction is determined as described above. Results are reported as an EC50 (nM $\pm$ standard error).

[0074] Antibody II blocks Dkk-1-mediated inhibition of C2C12 AP. For the DKK-1 of various species, the EC50's (given as nM $\pm$ standard error) are as follows: human = 9.8 $\pm$ 0.41, cynomolgus = 6.4 $\pm$ 0.25, rat= 2.9 $\pm$ 0.25, and rabbit = 6.0 $\pm$ 0.32.

Example 4: Cortical defect (CD) in vivo assay

[0075] Six month old female Sprague-Dawley rats are ovariectomized and allowed to lose bone for two months. 2 mm diameter defects are introduced into the left and right femurs with an electric drill with a 2 mm dental bit. This hole extends through both the anterior and posterior cortices. Healing of bone is monitored longitudinally by assessing bone mass density ("BMD") through the use of quantitative computed tomography ("qCT") for 35 days after surgery. At the end of the experiment, animals are sacrificed and whole femora are subjected to loaded-to-failure determinations to ascertain biomechanical strength of the whole diaphysis. Antibodies are administered subcutaneously at doses and intervals as indicated.

[0076] Antibody II is dosed as follows: 5 mg/kg once every two weeks starting one day after surgery (Group 1), 1 mg/kg (Group 2), 5 mg/kg (Group 3), or 15 mg/kg (Group 4) is administered once every two weeks starting nine days after surgery. BMD is assessed by qCT at day 35. Group 1 showed a statistically significant increase in BMD at both the anterior and posterior cortices. Group 4 showed a statistically significant increase in BMD at both cortices, although Groups 2 and 3 showed a non-significant increase in BMD.

Example 5: Cancer in vivo efficacy assay

[0077] Mice (female C.B-17 mice, Fox Chase severe combined immunodeficient model # CB17SC-M) are acclimated for one week in an animal facility prior to experiment initiation. After acclimation, mice are randomized into groups of 10 per treatment. Cultured human A549 non-small cell lung carcinoma cells are implanted subcutaneously in the rear flank

of the mice and tumor are allowed to reach a mean tumor volume ~ 100 mm³. Antibody II (1 mg/kg and 5 mg/kg), control IgG antibody (1 mg/kg and 5 mg/kg), or vehicle (citrate buffered saline supplemented with 0.02% Tween 80) is administered via subcutaneous injection. Animals receive 2 treatments separated by 7 days.

[0078] The tumors are measured 2 times per week by electronic calipers to plot growth curves. Animals are also monitored twice a week for fluctuations in body weight and signs of toxicity. Tumor volume measurements shown in table 3 are taken on day 29.

[0079] As shown in Table 2, treatment groups receiving Antibody II, demonstrated significant growth inhibition of human A549 non-small cell lung xenografts in vivo.

Table 2: Efficacy of Antibody II in A549 human non-small cell lung carcinoma xenograft model

Treatment Group	Tumor Volume $\pm$ Standard Error (mm ³)	p-Value (relative to vehicle control group)
Citrate vehicle	402 $\pm$ 36	-
IgG control (1 mg/kg)	372 $\pm$ 45	-
IgG control (5 mg/kg)	492 $\pm$ 72	-
Antibody II (1 mg/kg)	279 $\pm$ 32	0.01 - 0.05
Antibody II (5 mg/kg)	202 $\pm$ 21	< 0.001

Example 6: Angiogenic re-normalization in vivo xenograft assay

[0080] To understand the mechanism of the anti-tumor efficacy, high content imaging analysis is carried out on A549 tumors treated with Antibody II or IgG control. Several phenotypic-based markers are analyzed both quantitatively and qualitatively to assess the cancer-relevant biological processes of angiogenesis (CD31 and smooth muscle actin, SMA), hypoxia induction (Glucose transporter 1, GLUT1), cell proliferation (Ki67), and apoptosis (Terminal UDP Nick-End Labeling, TUNEL).

[0081] Female C.B-17 (Fox Chase SCID) model # CB17SC-M mice age 7 to 8 weeks old are acclimated for one week and allowed to feed *ad libitum* on a normal low fat (4.5%) diet, which is continued for the duration of the study.

[0082] A549 cells from ATCC origin are grown and divided in F-12 Kaighn's media (Invitrogen #21127) supplemented with 10% FBS (Invitrogen #0, and 100x dilutions of sodium pyruvate, non-essential amino acids and pen-strep (Invitrogen #11360, #11140 and #15140 respectively). They are detached and prepared at a final concentration of 50x10⁶ cells/ml in PBS at passage 19 with 95% viability.

[0083] 5x10⁶ A549 human lung carcinoma cells are injected subcutaneously in the flank of subject mice in a 1:1 mixture of PBS and Matrigel (Becton Dickinson, Bedford, MA). Tumor and body weight measurements are performed twice weekly. Prior to treatment, mice are randomized based on tumor size using a randomization algorithm.

[0084] Starting when tumors reached 200 mm³, the randomized mice are separated into 2 groups of 10 animals and dosed subcutaneously on day 1 and again on day 8 with 5 mg/kg of either Antibody II or the IgG4 control. The study is terminated 10 days after administration of the first dose of antibody.

[0085] Antibody II is prepared in Citrate Buffered Saline (CBS) (10 mM citrate pH6, 150 mM NaCl and 0.2% polysorbate). IgG4 control is provided at 6.0 mg/ml in Phosphate Buffered Saline (PBS).

[0086] Xenograft tumors are excised from mice after 17 days of dosing and placed into Zinc-Tris fixative (BD Pharmingen). Fixed tumors are processed, blocked in paraffin, and sectioned as 3 μ M slices onto standard microscope slides. Slides are baked at 60°F for 1 hour and then deparaffinized in xylene (4 treatments, 10 minutes each). Slides are rehydrated through a series of ethanol/water immersions with final washes in Tris-buffered saline/Tween (TBST). Slides are then blocked with Protein Block (DAKO) for 30 minutes. For the Tumor Health Panel, slides are stained with a combination of Hoechst 33324 (Invitrogen), rat anti-human CD31 (Pharmingen)/anti-rat Alexa-488 (Invitrogen), rabbit anti-Ki67 (NeoMarkers)/anti-rabbit Alexa 647 (Invitrogen), and TUNEL-TMR red (diluted 1:5 in TUNEL dilution buffer; Roche). For the Angiogenesis Panel, slides are stained with a combination of Hoechst 33324 (Invitrogen), rat anti-human CD31 (Pharmingen)/anti-rat Alexa-488 (Invitrogen), rabbit anti-GLUT1 (Chemicon)/anti-rabbit Alexa 647 (Invitrogen), and mouse anti-Smooth Muscle Actin/Cy3 (Sigma). Slides are imaged using an iCys Laser Scanning Cytometer (CompuCyte) and a Marianas Digital Imaging Workstation configured with a Zeiss Axiovert 200M inverted fluorescence microscope (Intelligent Imaging Innovations). Quantitative data comparisons of treatment groups are performed using the Dunnet's analysis in JMP statistics software (SAS).

[0087] As shown in Table 3, A549 xenografts from control IgG-treated animals are modestly vascularized, have moderate levels of myofibroblasts and many focalized areas of hypoxia. Control IgG-treated tumors have an extended network

of vessels consisting of both neoangiogenic vascular sprouts and mature vessels that are poorly covered by pericytes. Control IgG-treated tumors have hypoxic areas (marked by GLUT1) that are clearly demarcated zones some distance from perfused vessels and necrotic areas that are even further from vessels. Treatment with Antibody II results in decreased vessel area, decreased pericyte area, and decreased pericyte coverage of vessels. However, this treatment did not result in a significant difference in tumor hypoxia. Qualitatively, the Antibody II-treated tumor vasculature appears to consist of smaller, less-networked vessels and with less pericyte coverage compared with the control IgG-treated group. [0088] As shown in Table 3, IgG-treated tumors have proliferating tumor cells evenly distributed throughout, but also frequently display one or more large areas of necrosis that are avascular. Treatment with Antibody II results in no change in apoptosis and only a slight, non-significant decrease in total proliferation area. However, there is a profound decrease in the percentage of area of high-intensity Ki67 cells in the Antibody II-treated tumors, which could indicate a decreased amount of cells in the G2 cell cycle phase.

Table 3: Antibody II in angiogenic re-normalization in vivo xenograft assay

Phenotypic Panel	Biological Parameter	Control IgG Value : Antibody II Treatment Value	Statistical Significance (Dunnet's p-value)
Tumor Angiogenesis Panel	% Total Vessel Area	10.26 : 7.88	0.001
Tumor Angiogenesis Panel	% Functional Vessel Area	9.84 : 7.59	0.0009
Tumor Angiogenesis Panel	% Non-Functional Vessel Area	0.42 : 0.30	0.1341
Tumor Angiogenesis Panel	% Pericyte Covered Vessels	42.44 : 30.88	0.0234
Tumor Angiogenesis Panel	% Tumor Hypoxic Area	14.90 : 11.77	0.3615
Tumor Proliferation Panel	% Tumor Proliferation Area	12.16 : 9.68	0.1739
Tumor Proliferation Panel	% High Ki67 Area	0.66 : 0.19	0.0012
Tumor Proliferation Panel	% Cycling Tumor Cells with High Ki67	5.24 : 1.68	<0.0001
Tumor Apoptosis Panel	% Tumor Apoptosis Area	8.63 : 8.24	0.7466
% Total Vessel Area - Percentage of tumor tissue area covered by all vessels regardless of their functional status.			
% Functional Vessel Area - Percentage of tumor tissue area covered by vessels in non-hypoxic regions.			
% Non-Functional Vessel Area - Percentage of tumor tissue area covered by vessels in hypoxic regions.			
% Pericyte Covered Vessels - Percentage of all tumor vessels that are associated with smooth muscle actin (SMA)-expressing cells.			
% Tumor Hypoxic Area - Percentage of tumor tissue area covered by cells expressing GLUT1, a surrogate marker for hypoxia.			
% Tumor Proliferation Area - Percentage of tumor tissue area that is positive for Ki67, a nuclear protein routinely used as a marker of actively proliferating cells.			
% High Ki67 Area - Percentage of tumor tissue area that stains intensely for Ki67. Cells expressing high levels of Ki67 are in later phases of cell cycle than those that express lower levels of Ki67.			
% Cycling Tumor cells with High Ki67 - Percentage of all Ki67 positive cells that are designated as having a high level of Ki67 expression. Cells expressing high levels of Ki67 are in later phases of cell cycle than those that express lower levels of Ki67.			
% Tumor Apoptosis Area - Percentage of tumor tissue area with high TUNEL staining. TUNEL is a routinely used method to detect double-stranded DNA breakages which is indicative of terminal apoptosis.			

Example 7: Bone in vivo efficacy assay

[0089] To evaluate the ability of Antibody V (Light chain SEQ ID NO:34 and Heavy chain SEQ ID NO:35) accelerating the peri-implant bone formation and regenerating bone tissue, four months old male Sprague-Dawley rats (Harlan Sprague Dawley Inc) weighting around 425gram are utilized. Rats are surgically implanted with titanium screw (2 mm

x 4mm) into the both legs of the media lateral side right above the tibial - fibular junction. Rats then are randomly divided into 2 groups according the body weight and receive either Antibody V 10mg/kg or IgG control 10mg/kg subcutaneously injection once weekly starting the same day of the surgery for 21 days. Quantitative computed tomography (Aloka LaTheta LTC-100 model CT scanner) is used to *ex vivo* scan and quantify the newly formed bone with a 60- μ m voxel size. Volume of interest (VOI) is defined as 28 slices at 0.1mm interval over the previous implant site. Group differences are assessed with JMP version 5.1. software (Cary, North Carolina), comparison against IgG-control using Dunnett's Method with a significance level of $P < 0.05$. Qualitatively evaluation by *ex vivo* faxitron x-ray images indicates that Antibody V treated rats have more new bone or callus around the implant. Quantitative CT analyses reveal a statistically significant increase cortical peri-implant bone mineral content (14%), new bone area (16%), cortical thickness (7%) and bone marrow cancellous peri-implant new bone mineral content (18%), and bone area (16%) in Antibody V treated rats when compared to IgG control. The data demonstrate that Antibody V stimulates new bone formation and accelerate regenerating bone tissue in titanium implanted rats.

Table 4: Micro-CT analyses of Peri-implant New Bone Formation

Group	n	Bone Marrow Peri-implant Analyses		Cortical Peri-implant Analyses		
		Bone mineral Content (mg)	Bone Area (cm ²)	Bone mineral Content (mg)	Bone Area (cm ²)	Cortical thickness (cm)
IgG control	10	0.84 ± 0.04	0.034 ± 0.001	6.70 ± 0.07	0.064 ± 0.001	0.054 ± 0.001
Antibody V	10	1.00 $\pm 0.04^*$	0.039 $\pm 0.002^*$	7.61 $\pm 0.06^*$	0.074 $\pm 0.001^*$	0.057 $\pm 0.001^*$

Data are presented as Mean $\pm$ SE. *, $p < 0.05$, vs IgG control, JMP Dunnett's test.

SEQ ID Listing

Heavy Chain CDRs

[0090]

SEQ ID NO:1 GFTFSSYTMS
 SEQ ID NO:2 TISGGGFGTYYPDSVKG
 SEQ ID NO:3 PGYHNYFFDI
 SEQ ID NO:4 PGYNNYFFDI

Light Chain CDRs

[0091]

SEQ ID NO:5 HASDSISNSLH
 SEQ ID NO:6 YGRQSIQ
 SEQ ID NO:7 QQSESWPLH
 SEQ ID NO:8 YARQSIQ
 SEQ ID NO:9 QQSASWPLH
 SEQ ID NO:10 YARQSEQ

Heavy Chain Variable Regions

[0092]

SEQ ID NO:11

5 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYTMSWVRQAPGKGLEWVATISGG
GFGTYYPDSVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCARPGYHNYYFDI
WGQGTTVTVSS

SEQ ID NO: 12

10 EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYTMSWVRQAPGKGLEWVATISGG
GFGTYYPDSVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCARPGYNNYYFDI
WGQGTTVTVSS

15 **Light Chain Variable Regions**

[0093]

SEQ ID NO:13

20 EIVLTQSPATLSLSPGERATLSCHASDSISNSLHWYQQKPGQAPRLLIYYGRQSIQG
IPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQSESWPLHFGGGKVEIK

25 SEQ ID NO:14

EIVLTQSPATLSLSPGERATLSCHASDSISNSLHWYQQKPGQAPRLLIYYARQSIQG
IPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQSESWPLHFGGGKVEIK

30 SEQ ID NO:15

EIVLTQSPATLSLSPGERATLSCHASDSISNSLHWYQQKPGQAPRLLIYYGRQSIQG
35 IPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQSASWPLHFGGGKVEIK

SEQ ID NO:16

40 EIVLTQSPATLSLSPGERATLSCHASDSISNSLHWYQQKPGQAPRLLIYYARQSEQ
GIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQSASWPLHFGGGKVEIK

Complete Heavy Chains

45 **[0094]**

SEQ ID NO:17

50

55

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYTMSWVRQAPGKGLEWVATISGG
 GFGTYYPDSVKGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCARPGYHNYYFDI
 WGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG
 5 ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDPHKPSNTKVDKRVE
 SKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQF
 NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWES
 10 NGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT
 QKSLSLSLG

SEQ ID NO:18

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYTMSWVRQAPGKGLEWVATISGG
 GFGTYYPDSVKGRFTISRDNANKNSLYLQMNSLRAEDTAVYYCARPGYNNYYFDI
 WGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG
 15 ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDPHKPSNTKVDKRVE
 SKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVDSQEDPEVQF
 20 NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWES
 NGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYT
 25 QKSLSLSLG

Complete Light Chains

[0095]

SEQ ID NO:19

EIVLTQSPATLSLSPGERATLSCHASDSISNSLHWYQQKPGQAPRLLIYYGRQSIQG
 35 IPARFSGSGSGTDFTLTISSELPEDFAVYYCQQSESWPLHFGGGGTKVEIKRTVAAPS
 VFIFPPSDEQLKSGTASVVCLLNNFYPRKAKVQWKVDNALQSGNSQESVTEQDS
 KDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC

SEQ ID NO:20

EIVLTQSPATLSLSPGERATLSCHASDSISNSLHWYQQKPGQAPRLLIYYARQSIQG
 45 IPARFSGSGSGTDFTLTISSELPEDFAVYYCQQSESWPLHFGGGGTKVEIKRTVAAPS
 VFIFPPSDEQLKSGTASVVCLLNNFYPRKAKVQWKVDNALQSGNSQESVTEQDS
 KDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC

SEQ ID NO:21

EIVLTQSPATLSLSPGERATLSCHASDSISNSLHWYQQKPGQAPRLLIYYGRQSIQG
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 55 SVFIFPPSDEQLKSGTASVVCLLNNFYPRKAKVQWKVDNALQSGNSQESVTEQDS
 KDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC

SEQ ID NO:22

EIVLTQSPATLSLSPGERATLSCHASDSISNSLHWYQQKPGQAPRLLIYYARQSEQ
 GIPARFSGSGSGTDFLTLSISLEPEDFAVYYCQQSASWPLHFGGGTKVEIKRTVAA
 PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD
 SKDSTYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Nucleotide Sequences - Heavy Chain Variable Regions

[0096]

SEQ ID NO:23

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 TGGTGGTTTCGGCACATACTATCCCGACAGTGTGAAGGGTTCGATTACCATCT
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 TTGACATCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGCCTCCACCAA
 GGGCCCATCGGTCTTCCCGCTAGCGCCCTGCTCCAGGAGCACCTCCGAGAGC
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 CAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAAC
 ACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCACCCCT
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 ACCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTG
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 GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACA
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 GGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCG
 AGAAAACCATCTCCAAGGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACA
 CCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTG
 CCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAAAGCAAT
 GGGCAGCCGGAGAACAATAAGACCACGCCTCCCGTGCTGGACTCCGACG
 GCTCCTTCTTCTCTACAGCAGGCTAACCGTGGACAAGAGCAGGTGGCAGGA
 GGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACA
 CACAGAAGAGCCTCTCCCTGTCTCTGGGT

SEQ ID NO:24

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 GGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCACCATTTCGGG
 TGGTGGTTTCGGCACATACTATCCCGACAGTGTGAAGGGTTCGATTACCATCT
 CCAGAGACAACGCCAAGAAGTCACTGTATCTGCAAATGAACAGCCTGAGAGC
 CGAGGACACGGCTGTGTATTACTGTGCGAGACCTGGATATAATAACTACTACT

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 5 TGTCGTGGAACCTCAGGCGCCCTGACCAGCGGCGTGACACCTTCCCGGCTGTC
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 10 GCCCAGCACCTGAGGCGCGCGGGGACCATCAGTCTTCCCTGTTCCCCCCTAAA
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 15 GCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAAC
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 20 CCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAAAGCAAT
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 GCTCCTTCTTCTCTACAGCAGGCTAACCGTGGACAAGAGCAGGTGGCAGGA
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 25 CACAGAAGAGCCTCTCCCTGTCTCTGGGT

Nucleotide Sequences - Light Chain Variable Regions

[0097]

SEQ ID NO:25

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 35 ACCAACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATTATGGCAGACA
 GTCCATCCAGGGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGACAGAC
 TTCACTCTCACCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTG
 TCAACAGAGTGAGAGCTGGCCGCTCCACTTCGGCGGAGGGACCAAGGTGGAG
 40 ATCAAACGAACCTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGA
 GCAGTTGAAATCTGGAACCTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATC
 CCAGAGAGGGCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAA
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 45 AGCAGCACCCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTAC
 GCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCA
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SEQ ID NO:26

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GTCCATCCAGGGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGACAGAC
TTCACCTCTCACCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTG
TCAACAGAGTGAGAGCTGGCCGCTCCACTTCGGCGGAGGGACCAAGGTGGAG
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AGCAGCACCCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTAC
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SEQ ID NO:27

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ACCAACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATTATGGCAGACA
GTCCATCCAGGGCATCCCAGCCAGGTTTCAGTGGCAGTGGGTCTGGGACAGAC
TTCACCTCTCACCATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTG
TCAACAGAGTGCCAGCTGGCCGCTCCACTTCGGCGGAGGGACCAAGGTGGAG
ATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGA
GCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATC
CCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAA
CTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC
AGCAGCACCCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTAC
GCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCA
ACAGGGGAGAGTGC

SEQ ID NO:28

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AGCCACCCTCTCCTGCCACGCCAGCGACAGTATTAGCAACAGCCTACACTGGT
ACCAACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATTATGCTAGACA
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GCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATC
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CTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTC
AGCAGCACCCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTAC
GCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCA
ACAGGGGAGAGTGC

Human DKK-1**[0098]**

5 SEQ ID NO:29

10 TLNSVLNSNAIKNLPPPLGGAAGHPGSAVSAAPGILYPGGNKYQTIDNYQPYP
 EDEECGTDEYCASPTRGGDAGVQICLACRKRRKRCMRHAMCCPGNYCKNGICV
 SSDQNHFRGEIEETITESFGNDHSTLDGYSRRTTLSSKMYHTKGQEGSVCLRSSDC
 ASGLCCARHFWSKICKPVLKEGQVCTKHRRKGSHGLEIFQRCYCGEGLScriQKD
 HHQASNSSRLHTCQRH

15 **Cynomolgus DKK-1****[0099]**

20 SEQ ID NO:30

25 TLNSVLNSNAIKNLPPPLGGAAGHPGSAVSAAPGILYPGGNKYQTIDNYQPYP
 EDEECGTDEYCASPTRGGDAGVQICLACRKRRKRCMRHAMCCPGNYCKNGICV
 SSDQNNFRGEIEETITESFGNDHSTLDGYSRRTTLSSKMYHSGQEGSVCLRSSDC
 ATGLCCARHFWSKICKPVLKEGQVCTKHRRKGSHGLEIFQRCYCGEGLScriQKD
 HHQASNSSRLHTCQR

Rat DKK-1

30

[0100]

SEQ ID NO:31

35 TLNSVLINSNAIKNLPPPLGGAGGQPGSAVSVAPGVLYEGGNKYQTLDNYQPYP
 AEDEECGTDEYCSSPSRGAAGVGGVQICLACRKRRKRCMRHAMCCPGNYCKNG
 ICMPSDHS LPRGEIEEGIIENLGNDHGAGDGYPRRTTLTSKIYHTKGQEGSVCLR
 SSDCATGLCCARHFWSKICKPVLKEGQVCTKHRRKGSHGLEIFQRCYCGEGLAC
 40 RIQKDHHQTSNSSRLHTCQRHAFIDYKDDDDKHV

Rabbit DKK-145 **[0101]**

SEQ ID NO:32

50 TLNSVLVNSNAIKNLPPPLGGANGHPGSAVSATPGILYEGGNKYLPDNYQPYP
 TEDEECGTDEYCASPARGGGAGVQICLACRKRRKRCMRHAMCCPGNYCKNGIC
 MPSDHNHFHFRGEIEETIVESFGNDHSTSDGYSRRTTLSSKMYHAKGQEGSVCLRS
 SDCATGLCCARHFWSKICKPVLKEGQVCTKHRRKGSHGLEIFQRCYCGDGLSCR
 55 LQNDQHEASNSSRLHTCQR

Mouse DKK-1**[0102]**

5 SEQ ID NO:33

10 TLNSVLINSNAIKNLPPPLGGAGGQPGSAVSVAPGVLYEGGNKYQTLDNYQPYP
 AEDEECGSDEYCSPSRGAAGVGGVQICLACRKRRCMTHAMCCPGNYCKNG
 ICMPSDHSFPRGEIEESIIENLGNDHNAAAGDGYPRRTTLTSKIYHTKGQEGSVC
 LRSSDCAAGLCCARHFWKICKPVLKEGQVCTKHKRKGSHGLEIFQRCCYCGEGL
 ACRIQKDDHHQASNSSRLHTCQRH

15 **Antibody V - Complete Light Chain****[0103]**

20 SEQ ID NO:34

25 DILLTQSPATLSVTPGDSVSLSCRASDSISGSLHWYQQKSHESPRLLIKYASQSIGI
 PSRFSGSGSGTDFTLINSVETEDFGMYFCQQSNSWPLNFGAGTKLELKRADAAP
 TVSIFPPSTEQLATGGASVVCLMNNFYPRDISVKWKIDGTERRDGVLDSVTDQDS
 KDSTYSMSSTLSLSKADYESHNLYTCEVVHKTSSSPVVKSFNRNEC

30 **Antibody V - Complete Heavy Chain****[0104]**

35 SEQ ID NO:35

40 EVQLVESGGGLVKPGGSLKLSCAASGFTFSSYTMSWVRQTPEKRLEWVATISGG
 GGNTYYPDSVKGRFTISRDNKNTLYLQLSSLRSEDTALYYCARPGYNNYYFDY
 WGQGTTLTVSSAKTTPPSVYPLAPGTALKSNSMVTLGCLVKGYFPEPVTVTWNS
 GALSSGVHTFPAVLQSGLYTLTSSVTVPSSWPSQTVTCNVVHPASSTKVDKKIV
 PRNCGGDCCKPCICTGSEVSSVFIFPPKPKDVLITITLTPKVTCTVVDISQDDPEVHFS
 WFDVDDVEVHTAQTRPPEEQFNSTFRSVSELPILHQQDWLNGRTRCKVTSAAFPSP
 EKTISKPEGRTQVPHVYTMSPTKEEMTQNEVSITCMVKGFPDIYVEWQMNGQ
 PQENYKNTPTMDTDGSYFLYSKLVKKEKWQQGNTFTCSVLHEGLNHHTK
 45 SLSHSPGK

Antibody V - Light Chain Variable Region**[0105]**

50 SEQ ID NO:36

55 DILLTQSPATLSVTPGDSVSLSCRASDSISGSLHWYQQKSHESPRLLIKYASQSIGI
 PSRFSGSGSGTDFTLINSVETEDFGMYFCQQSNSWPLNFGAGTKLELK

Antibody V - Heavy Chain Variable Region**[0106]**

5 SEQ ID NO:37

EVQLVESGGGLVKPGGSLKLSAASGFTFSSYTMSWVRQTPEKRLEWVATISGG
 GGNTYYPDSVKGRFTISRDNAKNTLYLQLSSLRSEDTALYYCARPGYNYYFDY
 10 WGQGTTTLTVSS

Antibody V - Heavy Chain CDRs**[0107]**

15

SEQ ID NO:38 TISGGGGNTYYPDSVKG
 SEQ ID NO:39 PGYNYYFDY

20 **Antibody V - Light Chain CDRs****[0108]**

25

SEQ ID NO:40 RASDSISGSLH
 SEQ ID NO:41 YASQIS
 SEQ ID NO:42 QQSNSWPLN

Consensus Heavy Chain CDRs

30

[0109]

35

SEQ ID NO:43 TISGGG**X**₁**X**₂TYYPDSVKG
X₁ is F, G
X₂ is G, N

SEQ ID NO:44 PGY**X**₃NYFFDI
X₃ is H, N

40

SEQ ID NO:45 PGY**X**₄NYFFD**X**₅
X₄ is H, N
X₅ is I, Y

45 **Consensus Light Chain CDRs****[0110]**

50

SEQ ID NO:46 **X**₆ASDSIS**X**₇SLH
X₆ is H, R
X₇ is N, G

55

SEQ ID NO:47 Y**X**₈RQS**X**₉Q
X₈ is G, A
X₉ is I, E

SEQ ID NO:48 Y**X**₁₀**X**₁₁QS**X**₁₂**X**₁₃

(continued)

 X_{10} is G, A X_{11} is R, S X_{12} is I, E X_{13} is Q, SSEQ ID NO:49 QQS X_{14} SWPLH X_{14} is E, ASEQ ID NO:50 QQS X_{15} SWPL X_{16} X_{15} is E, A, N X_{16} is H, N**Consensus Heavy Chain Variable Region****[0111]**

SEQ ID NO:51

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYTMSWVRQAPGKGLEWVATISGG
 GFGTYYPDSVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCARPGY X_{17} NYFF
 DI WGQGTTVTVSS

 X_{17} is H, N**Consensus Light Chain Variable Region****[0112]**

SEQ ID NO:52

EIVLTQSPATLSLSPGERATLSCHASDSISNSLHWYQQKPGQAPRLLIYY X_{18} RQS
 X_{19} QGIPARFSGSGSGTDFTLTISSELPEDFAVYYC QQS X_{20} SWPLHFGGGGTKVEIK

 X_{18} is G, A X_{19} is I, E X_{20} is E, A**SEQUENCE LISTING****[0113]**

<110> Eli Lilly and Company

<120> DKK-1 Antibodies

<130> X-18097

<150> 61/168411

<151> 2009-04-10

<160> 52

<170> PatentIn version 3.5

<210> 1

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<211> 10

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<210> 5

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 50 Tyr Ala Arg Gln Ser Ile Gln
 1 5
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EP 2 417 158 B9

<400> 9

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<212> PRT

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<400> 10

Tyr Ala Arg Gln Ser Glu Gln
1 5

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<213> Artificial Sequence

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<223> Synthetic Construct

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Gly Gly Gly Phe Gly Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Pro Gly Tyr His Asn Tyr Tyr Phe Asp Ile Trp Gly Gln Gly
100 105 110

Thr Thr Val Thr Val Ser Ser
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<212> PRT

<213> Artificial Sequence

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<223> Synthetic Construct

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10      Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
      1          5          10          15

      Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
      20          25          30

15      Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
      35          40          45

20      Ala Thr Ile Ser Gly Gly Gly Phe Gly Thr Tyr Tyr Pro Asp Ser Val
      50          55          60

      Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
25      65          70          75          80

      Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
      85          90          95

30      Ala Arg Pro Gly Tyr Asn Asn Tyr Tyr Phe Asp Ile Trp Gly Gln Gly
      100          105          110

35      Thr Thr Val Thr Val Ser Ser
      115

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<210> 13

<211> 107

<212> PRT

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50      Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
      1          5          10          15

      Glu Arg Ala Thr Leu Ser Cys His Ala Ser Asp Ser Ile Ser Asn Ser
      20          25          30

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	Leu	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu	Ile
			35					40					45			
5	Tyr	Tyr	Gly	Arg	Gln	Ser	Ile	Gln	Gly	Ile	Pro	Ala	Arg	Phe	Ser	Gly
			50				55					60				
10	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Glu	Pro
	65					70					75				80	
15	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	Gln	Ser	Glu	Ser	Trp	Pro	Leu
				85						90					95	
20	His	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys					
				100					105							
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30	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Leu	Ser	Pro	Gly
	1				5					10					15	
35	Glu	Arg	Ala	Thr	Leu	Ser	Cys	His	Ala	Ser	Asp	Ser	Ile	Ser	Asn	Ser
				20					25					30		
40	Leu	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu	Ile
			35					40					45			
45	Tyr	Tyr	Ala	Arg	Gln	Ser	Ile	Gln	Gly	Ile	Pro	Ala	Arg	Phe	Ser	Gly
			50				55					60				
50	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Glu	Pro
	65					70					75				80	
55	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	Gln	Ser	Glu	Ser	Trp	Pro	Leu
				85						90					95	
	His	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys					
				100					105							
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<220>

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Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

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Glu Arg Ala Thr Leu Ser Cys His Ala Ser Asp Ser Ile Ser Asn Ser
20 25 30

15

Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Tyr Gly Arg Gln Ser Ile Gln Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

20

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

25

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Ala Ser Trp Pro Leu
85 90 95

His Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

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<211> 107

<212> PRT

<213> Artificial Sequence

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<400> 16

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Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

5 Glu Arg Ala Thr Leu Ser Cys His Ala Ser Asp Ser Ile Ser Asn Ser
20 25 30

10 Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

15 Tyr Tyr Ala Arg Gln Ser Glu Gln Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

20 Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Ala Ser Trp Pro Leu
85 90 95

His Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

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	Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	
	1				5					10					15		
5	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr	
				20					25					30			
	Thr	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
10			35					40					45				
	Ala	Thr	Ile	Ser	Gly	Gly	Gly	Phe	Gly	Thr	Tyr	Tyr	Pro	Asp	Ser	Val	
		50					55					60					
15	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Ser	Leu	Tyr	
	65					70					75					80	
	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
20				85						90					95		
	Ala	Arg	Pro	Gly	Tyr	His	Asn	Tyr	Tyr	Phe	Asp	Ile	Trp	Gly	Gln	Gly	
				100					105					110			
25	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	
			115					120					125				
30	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	
		130					135					140					
	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	
35	145					150					155					160	
	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	
					165					170					175		
40	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	
				180					185					190			
45	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	
			195					200					205				

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	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	
	210						215					220					
5	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser	Val	Phe	
	225					230					235					240	
10	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	
					245					250					255		
15	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	
				260					265					270			
20	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	
			275					280					285				
25	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	
		290						295				300					
30	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	
	305					310					315					320	
35	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	
					325					330					335		
40	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	
				340					345					350			
45	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	
			355					360					365				
50	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	
		370					375					380					
55	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	
	385					390					395					400	
60	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	
					405					410					415		
65	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	
				420					425					430			
70	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly				
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	Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly	
	1				5					10					15		
5	Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr	
				20					25					30			
	Thr	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	
10			35					40					45				
	Ala	Thr	Ile	Ser	Gly	Gly	Gly	Phe	Gly	Thr	Tyr	Tyr	Pro	Asp	Ser	Val	
		50					55					60					
15	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ala	Lys	Asn	Ser	Leu	Tyr	
	65					70					75					80	
	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
20				85						90					95		
	Ala	Arg	Pro	Gly	Tyr	Asn	Asn	Tyr	Tyr	Phe	Asp	Ile	Trp	Gly	Gln	Gly	
				100					105					110			
25	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	
			115					120					125				
	Pro	Leu	Ala	Pro	Cys	Ser	Arg	Ser	Thr	Ser	Glu	Ser	Thr	Ala	Ala	Leu	
30			130				135					140					
	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	
35	145					150				155						160	
	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	
				165					170						175		
40	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	
				180					185					190			
	Ser	Ser	Leu	Gly	Thr	Lys	Thr	Tyr	Thr	Cys	Asn	Val	Asp	His	Lys	Pro	
45			195				200						205				
	Ser	Asn	Thr	Lys	Val	Asp	Lys	Arg	Val	Glu	Ser	Lys	Tyr	Gly	Pro	Pro	
50		210					215					220					
	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Ala	Ala	Gly	Gly	Pro	Ser	Val	Phe	
	225					230					235					240	

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EP 2 417 158 B9

	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	
					245					250					255		
5	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	Gln	Glu	Asp	Pro	Glu	Val	
				260					265					270			
10	Gln	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	
			275					280					285				
15	Lys	Pro	Arg	Glu	Glu	Gln	Phe	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	
		290					295					300					
20	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	
	305					310					315					320	
25	Lys	Val	Ser	Asn	Lys	Gly	Leu	Pro	Ser	Ser	Ile	Glu	Lys	Thr	Ile	Ser	
				325					330						335		
30	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	
			340						345					350			
35	Ser	Gln	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	
		355						360					365				
40	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	
		370					375					380					
45	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	
	385					390					395					400	
50	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	
				405						410					415		
55	Gln	Glu	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	
			420						425					430			
60	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Leu	Gly				
			435					440					445				

<210> 19

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<400> 19

EP 2 417 158 B9

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly

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1 5 10 15

Glu Arg Ala Thr Leu Ser Cys His Ala Ser Asp Ser Ile Ser Asn Ser
20 25 30

10

Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

15

Tyr Tyr Gly Arg Gln Ser Ile Gln Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

20

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Glu Ser Trp Pro Leu
85 90 95

25

His Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

30

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

35

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

40

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

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Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

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Phe Asn Arg Gly Glu Cys
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EP 2 417 158 B9

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Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

10

Glu Arg Ala Thr Leu Ser Cys His Ala Ser Asp Ser Ile Ser Asn Ser
20 25 30

15

Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Tyr Ala Arg Gln Ser Ile Gln Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

20

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

25

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Glu Ser Trp Pro Leu
85 90 95

30

His Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

35

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

40

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

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Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

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Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

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Phe Asn Arg Gly Glu Cys
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<210> 21

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EP 2 417 158 B9

<212> PRT

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	Glu	Arg	Ala	Thr	Leu	Ser	Cys	His	Ala	Ser	Asp	Ser	Ile	Ser	Asn	Ser	
15				20					25					30			
	Leu	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu	Ile	
			35					40					45				
20	Tyr	Tyr	Gly	Arg	Gln	Ser	Ile	Gln	Gly	Ile	Pro	Ala	Arg	Phe	Ser	Gly	
	50						55					60					
	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Glu	Pro	
25	65					70					75					80	
	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	Gln	Ser	Ala	Ser	Trp	Pro	Leu	
					85					90					95		
30	His	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala	
				100					105					110			
	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly	
35			115					120					125				
	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala	
40		130					135					140					
	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln	
	145					150					155					160	
45	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser	
					165					170					175		
	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr	
50				180					185					190			
	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser	
			195					200					205				
55	Phe	Asn	Arg	Gly	Glu	Cys											
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EP 2 417 158 B9

	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Leu	Ser	Pro	Gly	
	1				5					10					15		
5	Glu	Arg	Ala	Thr	Leu	Ser	Cys	His	Ala	Ser	Asp	Ser	Ile	Ser	Asn	Ser	
				20					25					30			
	Leu	His	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln	Ala	Pro	Arg	Leu	Leu	Ile	
10			35					40					45				
	Tyr	Tyr	Ala	Arg	Gln	Ser	Glu	Gln	Gly	Ile	Pro	Ala	Arg	Phe	Ser	Gly	
		50					55					60					
15	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Glu	Pro	
	65					70					75					80	
	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln	Gln	Ser	Ala	Ser	Trp	Pro	Leu	
20					85					90					95		
	His	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala	
25				100					105					110			
	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly	
			115					120					125				
30	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala	
		130					135					140					
	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln	
35		145				150					155					160	
	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser	
					165					170					175		
40	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr	
				180					185					190			
	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser	
45			195					200					205				
	Phe	Asn	Arg	Gly	Glu	Cys											
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<212> DNA

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	ccaggggaagg ggctggagtg ggtggccacc atttccggtg gtggtttcgg cacatactat	180
10	cccgacagtg tgaagggtcg attcaccatc tccagagaca acgccaagaa ctcaactgtat	240
	ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagacctgga	300
	tatcacaact actactttga catctggggc caagggacca cggtcaccgt ctccctcagcc	360
15	tccaccaagg gcccatcggc cttcccgtc gcgccctgct ccaggagcac ctccgagagc	420
	acagccgccc tgggctgcct ggtcaaggac tacttccccg aaccggtgac ggtgtcgtgg	480
	aactcaggcg ccctgaccag cggcgtgcac accttccccg ctgtcctaca gtcctcagga	540
20	ctctactccc tcagcagcgt ggtgaccgtg ccctccagca gcttgggcac gaagacctac	600
	acctgcaacg tagatcacia gccagcaac accaagggtg acaagagagt tgagtccaaa	660
	tatggtcccc catgcccacc ctgcccagca cctgaggccg ccgggggacc atcagtcttc	720
25	ctgttcccc caaaacccaa ggacactctc atgatctccc ggaccctga ggtcacgtgc	780
	gtggtggtgg acgtgagcca ggaagacccc gaggtccagt tcaactggta cgtggatggc	840
	gtggaggtgc ataatgcaa gacaaagccg cgggaggagc agttcaacag cacgtaccgt	900
30	gtggtcagcg tcctcaccgt cctgcaccag gactggctga acggcaagga gtacaagtgc	960
	aaggtctcca acaaaggcct cccgtcctcc atcgagaaaa ccatctccaa agccaaaggg	1020
35	cagccccgag agccacaggt gtacaccctg ccccatccc aggaggagat gaccaagaac	1080
	caggtcagcc tgacctgctt ggtcaaaggc ttctaccca gcgacatcgc cgtggagtgg	1140
	gaaagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac	1200
40	ggctccttct tcctctacag caggctaacc gtggacaaga gcaggtggca ggaggggaat	1260
	gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacaca gaagagcctc	1320
	tcctgtctc tgggt	1335

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<210> 24

<211> 1335

<212> DNA

<213> Artificial Sequence

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<220>

<223> Synthetic Construct

55

<400> 24

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	gaggtgcagc tgggtggagtc tggggggaggc ttggtccagc ctgggggggtc cctgagactc	60
	tcctgtgcag cctctggatt cactttcagt agctatacca tgtcttgggt ccgccaggct	120
5	ccaggggaagg ggctggagtg ggtggccacc atttccggtg gtggtttcgg cacatactat	180
	cccgcagtg tgaagggtcg attcaccatc tccagagaca acgccaagaa ctcaactgtat	240
10	ctgcaaataga acagcctgag agccgaggac acggctgtgt attactgtgc gagacctgga	300
	tataataact actactttga catctggggc caagggacca cggtcaccgt ctccctcagcc	360
	tccaccaagg gcccatcggc cttcccgtc gcgccctgct ccaggagcac ctccgagagc	420
15	acagccgccc tgggctgcct ggtcaaggac tacttcccc aaccgggtgac ggtgtcgtgg	480
	aactcaggcg ccctgaccag cggcgtgcac accttccccg ctgtcctaca gtcctcagga	540
	ctctactccc tcagcagcgt ggtgaccgtg ccctccagca gcttggggcac gaagacctac	600
20	acctgcaacg tagatcacia gccagcaac accaaggtgg acaagagagt tgagtccaaa	660
	tatggtcccc catgccacc ctgccagca cctgaggccg ccggggggacc atcagtcctc	720
	ctgttcccc caaaacccaa ggacactctc atgatctccc ggacccctga ggtcacgtgc	780
25	gtggtggtgg acgtgagcca ggaagacccc gaggtccagt tcaactggta cgtggatggc	840
	gtggaggtgc ataatgcaa gacaaagccg cgggaggagc agttcaacag cacgtaccgt	900
30	gtggtcagcg tcctcaccgt cctgcaccag gactggctga acggcaagga gtacaagtgc	960
	aaggctcca acaaaggcct ccgctcctcc atcgagaaaa ccatctccaa agccaaaggg	1020
	cagccccgag agccacaggt gtacaccctg ccccatccc aggaggagat gaccaagaac	1080
35	caggtcagcc tgacctgcct ggtcaaaggc ttctaccca gcgacatcgc cgtggagtgg	1140
	gaaagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac	1200
	ggctccttct tcctctacag caggctaacc gtggacaaga gcagggtggca ggaggggaat	1260
40	gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacaca gaagagcctc	1320
	tcctgtctc tgggt	1335

<210> 25

<211> 642

<212> DNA

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 25

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	gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc	60
	ctctcctgcc acgccagcga cagtattagc aacagcctac actggtacca acagaaacct	120
5	ggccaggctc ccaggctcct catctattat ggcagacagt ccatccaggg catcccagcc	180
	aggttcagtg gcagtgggtc tgggacagac ttactctca ccatcagcag cctagagcct	240
	gaagattttg cagtttatta ctgtcaacag agtgagagct ggccgctcca cttcggcgga	300
10	gggaccaagg tggagatcaa acgaactgtg gctgcaccat ctgtcttcat cttcccgcc	360
	tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat	420
	cccagagagg ccaaagtaca gtggaagggtg gataacgccc tccaatcggg taactcccag	480
15		
	gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg	540
	ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc	600
20	ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gc	642

<210> 26

<211> 642

<212> DNA

25 <213> Artificial Sequence

<220>

<223> Synthetic Construct

30 <400> 26

	gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc	60
	ctctcctgcc acgccagcga cagtattagc aacagcctac actggtacca acagaaacct	120
35	ggccaggctc ccaggctcct catctattat gctagacagt ccatccaggg catcccagcc	180
	aggttcagtg gcagtgggtc tgggacagac ttactctca ccatcagcag cctagagcct	240
	gaagattttg cagtttatta ctgtcaacag agtgagagct ggccgctcca cttcggcgga	300
40	gggaccaagg tggagatcaa acgaactgtg gctgcaccat ctgtcttcat cttcccgcc	360
	tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat	420
	cccagagagg ccaaagtaca gtggaagggtg gataacgccc tccaatcggg taactcccag	480
45		
	gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg	540
	ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc	600
50	ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gc	642

<210> 27

<211> 642

55 <212> DNA

<213> Artificial Sequence

<220>

EP 2 417 158 B9

<223> Synthetic Construct

<400> 27

5	gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc	60
	ctctcctgcc acgccagcga cagtattagc aacagcctac actggtacca acagaaacct	120
	ggccaggctc ccaggctcct catctattat ggcagacagt ccatccaggg catcccagcc	180
10	aggttcagtg gcagtgggtc tgggacagac ttactctca ccatcagcag cctagagcct	240
	gaagattttg cagtttatta ctgtcaacag agtgccagct ggccgctcca cttcggcgga	300
	gggaccaagg tggagatcaa acgaactgtg gctgcaccat ctgtcttcat cttcccgcc	360
15	tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat	420
	cccagagagg ccaaagtaca gtggaagggtg gataacgccc tccaatcggg taactcccag	480
20	gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg	540
	ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc	600
	ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gc	642

25

<210> 28

<211> 642

<212> DNA

<213> Artificial Sequence

30

<220>

<223> Synthetic Construct

<400> 28

35

40

45

50

55

	gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc	60
	ctctcctgcc acgccagcga cagtattagc aacagcctac actggtacca acagaaacct	120
	ggccaggctc ccaggctcct catctattat gctagacagt ccgagcaggg catcccagcc	180
	aggttcagtg gcagtgggtc tgggacagac ttactctca ccatcagcag cctagagcct	240
	gaagattttg cagtttatta ctgtcaacag agtgccagct ggccgctcca cttcggcgga	300
	gggaccaagg tggagatcaa acgaactgtg gctgcaccat ctgtcttcat cttcccgcc	360
	tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat	420
	cccagagagg ccaaagtaca gtggaagggtg gataacgccc tccaatcggg taactcccag	480
	gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg	540
	ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc	600
	ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gc	642

<210> 29

<211> 235

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<212> PRT

<213> Homo sapiens

<400> 29

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Thr Leu Asn Ser Val Leu Asn Ser Asn Ala Ile Lys Asn Leu Pro Pro
1 5 10 15

10

Pro Leu Gly Gly Ala Ala Gly His Pro Gly Ser Ala Val Ser Ala Ala
20 25 30

15

Pro Gly Ile Leu Tyr Pro Gly Gly Asn Lys Tyr Gln Thr Ile Asp Asn
35 40 45

Tyr Gln Pro Tyr Pro Cys Ala Glu Asp Glu Glu Cys Gly Thr Asp Glu
50 55 60

20

Tyr Cys Ala Ser Pro Thr Arg Gly Gly Asp Ala Gly Val Gln Ile Cys
65 70 75 80

25

Leu Ala Cys Arg Lys Arg Arg Lys Arg Cys Met Arg His Ala Met Cys
85 90 95

Cys Pro Gly Asn Tyr Cys Lys Asn Gly Ile Cys Val Ser Ser Asp Gln
100 105 110

30

Asn His Phe Arg Gly Glu Ile Glu Glu Thr Ile Thr Glu Ser Phe Gly
115 120 125

35

Asn Asp His Ser Thr Leu Asp Gly Tyr Ser Arg Arg Thr Thr Leu Ser
130 135 140

40

Ser Lys Met Tyr His Thr Lys Gly Gln Glu Gly Ser Val Cys Leu Arg
145 150 155 160

Ser Ser Asp Cys Ala Ser Gly Leu Cys Cys Ala Arg His Phe Trp Ser
165 170 175

45

Lys Ile Cys Lys Pro Val Leu Lys Glu Gly Gln Val Cys Thr Lys His
180 185 190

50

Arg Arg Lys Gly Ser His Gly Leu Glu Ile Phe Gln Arg Cys Tyr Cys
195 200 205

Gly Glu Gly Leu Ser Cys Arg Ile Gln Lys Asp His His Gln Ala Ser
210 215 220

55

Asn Ser Ser Arg Leu His Thr Cys Gln Arg His
225 230 235

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<210> 30
 <211> 234
 <212> PRT
 <213> Cebus albifrons

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<400> 30

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Thr Leu Asn Ser Val Leu Asn Ser Asn Ala Ile Lys Asn Leu Pro Pro
 1 5 10 15

15

Pro Leu Gly Gly Ala Ala Gly His Pro Gly Ser Ala Val Ser Ala Ala
 20 25 30

Pro Gly Ile Leu Tyr Pro Gly Gly Asn Lys Tyr Gln Thr Ile Asp Asn
 35 40 45

20

Tyr Gln Pro Tyr Pro Cys Ala Glu Asp Glu Glu Cys Gly Thr Asp Glu
 50 55 60

25

Tyr Cys Ala Ser Pro Thr Arg Gly Gly Asp Ala Gly Val Gln Ile Cys
 65 70 75 80

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	Leu	Ala	Cys	Arg	Lys	Arg	Arg	Lys	Arg	Cys	Met	Arg	His	Ala	Met	Cys	
					85					90					95		
5	Cys	Pro	Gly	Asn	Tyr	Cys	Lys	Asn	Gly	Ile	Cys	Val	Ser	Ser	Asp	Gln	
				100					105					110			
10	Asn	Asn	Phe	Arg	Gly	Glu	Ile	Glu	Glu	Thr	Ile	Thr	Glu	Ser	Phe	Gly	
			115					120					125				
15	Asn	Asp	His	Ser	Thr	Leu	Asp	Gly	Tyr	Ser	Arg	Arg	Thr	Thr	Leu	Ser	
		130					135					140					
20	Ser	Lys	Met	Tyr	His	Ser	Lys	Gly	Gln	Glu	Gly	Ser	Val	Cys	Leu	Arg	
	145					150					155					160	
25	Ser	Ser	Asp	Cys	Ala	Thr	Gly	Leu	Cys	Cys	Ala	Arg	His	Phe	Trp	Ser	
					165					170					175		
30	Lys	Ile	Cys	Lys	Pro	Val	Leu	Lys	Glu	Gly	Gln	Val	Cys	Thr	Lys	His	
				180					185					190			
35	Arg	Arg	Lys	Gly	Ser	His	Gly	Leu	Glu	Ile	Phe	Gln	Arg	Cys	Tyr	Cys	
			195					200					205				
40	Gly	Glu	Gly	Leu	Ser	Cys	Arg	Ile	Gln	Lys	Asp	His	His	Gln	Ala	Ser	
		210					215					220					
45	Asn	Ser	Ser	Arg	Leu	His	Thr	Cys	Gln	Arg							
	225					230											
	<210> 31																
	<211> 252																
	<212> PRT																
	<213> Rattus rattus																
	<400> 31																
50	Thr	Leu	Asn	Ser	Val	Leu	Ile	Asn	Ser	Asn	Ala	Ile	Lys	Asn	Leu	Pro	
	1				5					10				15			
55	Pro	Pro	Leu	Gly	Gly	Ala	Gly	Gly	Gln	Pro	Gly	Ser	Ala	Val	Ser	Val	
				20					25					30			
60	Ala	Pro	Gly	Val	Leu	Tyr	Glu	Gly	Gly	Asn	Lys	Tyr	Gln	Thr	Leu	Asp	
			35					40					45				
65	Asn	Tyr	Gln	Pro	Tyr	Pro	Cys	Ala	Glu	Asp	Glu	Glu	Cys	Gly	Thr	Asp	
		50					55					60					

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	Glu	Tyr	Cys	Ser	Ser	Pro	Ser	Arg	Gly	Ala	Ala	Gly	Val	Gly	Gly	Val	
	65					70					75					80	
5	Gln	Ile	Cys	Leu	Ala	Cys	Arg	Lys	Arg	Arg	Lys	Arg	Cys	Met	Arg	His	
				85						90					95		
10	Ala	Met	Cys	Cys	Pro	Gly	Asn	Tyr	Cys	Lys	Asn	Gly	Ile	Cys	Met	Pro	
				100					105					110			
15	Ser	Asp	His	Ser	His	Leu	Pro	Arg	Gly	Glu	Ile	Glu	Glu	Gly	Ile	Ile	
			115					120					125				
20	Glu	Asn	Leu	Gly	Asn	Asp	His	Gly	Ala	Gly	Asp	Gly	Tyr	Pro	Arg	Arg	
		130					135					140					
25	Thr	Thr	Leu	Thr	Ser	Lys	Ile	Tyr	His	Thr	Lys	Gly	Gln	Glu	Gly	Ser	
	145					150					155					160	
30	Val	Cys	Leu	Arg	Ser	Ser	Asp	Cys	Ala	Thr	Gly	Leu	Cys	Cys	Ala	Arg	
					165					170					175		
35	His	Phe	Trp	Ser	Lys	Ile	Cys	Lys	Pro	Val	Leu	Lys	Glu	Gly	Gln	Val	
				180					185					190			
40	Cys	Thr	Lys	His	Arg	Arg	Lys	Gly	Ser	His	Gly	Leu	Glu	Ile	Phe	Gln	
			195					200					205				
45	Arg	Cys	Tyr	Cys	Gly	Glu	Gly	Leu	Ala	Cys	Arg	Ile	Gln	Lys	Asp	His	
		210					215					220					
50	His	Gln	Thr	Ser	Asn	Ser	Ser	Arg	Leu	His	Thr	Cys	Gln	Arg	His	Ala	
	225					230					235					240	
55	Phe	Ile	Asp	Tyr	Lys	Asp	Asp	Asp	Asp	Lys	His	Val					
					245					250							

<210> 32

<211> 236

<212> PRT

<213> Lepus americanus

<400> 32

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	Thr	Leu	Asn	Ser	Val	Leu	Val	Asn	Ser	Asn	Ala	Ile	Lys	Asn	Leu	Pro	
	1				5					10					15		
5	Pro	Pro	Leu	Gly	Gly	Ala	Asn	Gly	His	Pro	Gly	Ser	Ala	Val	Ser	Ala	
				20					25					30			
	Thr	Pro	Gly	Ile	Leu	Tyr	Glu	Gly	Gly	Asn	Lys	Tyr	Leu	Pro	Leu	Asp	
10			35					40					45				
	Asn	Tyr	Gln	Pro	Tyr	Pro	Cys	Thr	Glu	Asp	Glu	Glu	Cys	Gly	Thr	Asp	
		50					55					60					
15	Glu	Tyr	Cys	Ala	Ser	Pro	Ala	Arg	Gly	Gly	Gly	Ala	Gly	Val	Gln	Ile	
	65					70					75					80	
	Cys	Leu	Ala	Cys	Arg	Lys	Arg	Arg	Lys	Arg	Cys	Met	Arg	His	Ala	Met	
20					85					90					95		
	Cys	Cys	Pro	Gly	Asn	Tyr	Cys	Lys	Asn	Gly	Ile	Cys	Met	Pro	Ser	Asp	
				100					105					110			
25	His	Asn	His	Phe	His	Arg	Gly	Glu	Ile	Glu	Glu	Thr	Ile	Val	Glu	Ser	
			115					120					125				
30	Phe	Gly	Asn	Asp	His	Ser	Thr	Ser	Asp	Gly	Tyr	Ser	Arg	Arg	Thr	Thr	
		130					135					140					
	Leu	Ser	Ser	Lys	Met	Tyr	His	Ala	Lys	Gly	Gln	Glu	Gly	Ser	Val	Cys	
35	145					150					155					160	
	Leu	Arg	Ser	Ser	Asp	Cys	Ala	Thr	Gly	Leu	Cys	Cys	Ala	Arg	His	Phe	
					165					170					175		
40	Trp	Ser	Lys	Ile	Cys	Lys	Pro	Val	Leu	Lys	Glu	Gly	Gln	Val	Cys	Thr	
				180					185					190			
	Lys	His	Arg	Arg	Lys	Gly	Ser	His	Gly	Leu	Glu	Ile	Phe	Gln	Arg	Cys	
45			195					200					205				
	Tyr	Cys	Gly	Asp	Gly	Leu	Ser	Cys	Arg	Leu	Gln	Asn	Asp	Gln	His	Glu	
50		210					215					220					
	Ala	Ser	Asn	Ser	Ser	Arg	Leu	His	Thr	Cys	Gln	Arg					
	225					230					235						

55 <210> 33
 <211> 241
 <212> PRT
 <213> Mus musculus

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<400> 33

5	Thr	Leu	Asn	Ser	Val	Leu	Ile	Asn	Ser	Asn	Ala	Ile	Lys	Asn	Leu	Pro	1	5	10	15
	Pro	Pro	Leu	Gly	Gly	Ala	Gly	Gly	Gln	Pro	Gly	Ser	Ala	Val	Ser	Val	20	25	30	
10	Ala	Pro	Gly	Val	Leu	Tyr	Glu	Gly	Gly	Asn	Lys	Tyr	Gln	Thr	Leu	Asp	35	40	45	
15	Asn	Tyr	Gln	Pro	Tyr	Pro	Cys	Ala	Glu	Asp	Glu	Glu	Cys	Gly	Ser	Asp	50	55	60	
20	Glu	Tyr	Cys	Ser	Ser	Pro	Ser	Arg	Gly	Ala	Ala	Gly	Val	Gly	Gly	Val	65	70	75	80
	Gln	Ile	Cys	Leu	Ala	Cys	Arg	Lys	Arg	Arg	Lys	Arg	Cys	Met	Thr	His	85	90	95	
25	Ala	Met	Cys	Cys	Pro	Gly	Asn	Tyr	Cys	Lys	Asn	Gly	Ile	Cys	Met	Pro	100	105	110	
30	Ser	Asp	His	Ser	His	Phe	Pro	Arg	Gly	Glu	Ile	Glu	Glu	Ser	Ile	Ile	115	120	125	
	Glu	Asn	Leu	Gly	Asn	Asp	His	Asn	Ala	Ala	Ala	Gly	Asp	Gly	Tyr	Pro	130	135	140	
35	Arg	Arg	Thr	Thr	Leu	Thr	Ser	Lys	Ile	Tyr	His	Thr	Lys	Gly	Gln	Glu	145	150	155	160
40	Gly	Ser	Val	Cys	Leu	Arg	Ser	Ser	Asp	Cys	Ala	Ala	Gly	Leu	Cys	Cys	165	170	175	
45	Ala	Arg	His	Phe	Trp	Ser	Lys	Ile	Cys	Lys	Pro	Val	Leu	Lys	Glu	Gly	180	185	190	
	Gln	Val	Cys	Thr	Lys	His	Lys	Arg	Lys	Gly	Ser	His	Gly	Leu	Glu	Ile	195	200	205	
50	Phe	Gln	Arg	Cys	Tyr	Cys	Gly	Glu	Gly	Leu	Ala	Cys	Arg	Ile	Gln	Lys	210	215	220	
55	Asp	His	His	Gln	Ala	Ser	Asn	Ser	Ser	Arg	Leu	His	Thr	Cys	Gln	Arg	225	230	235	240
	His																			

<210> 34
<211> 214
<212> PRT
<213> Artificial Sequence

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<220>
<223> Synthetic Construct

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1	Asp	Ile	Leu	Leu	Thr	Gln	Ser	Pro	Ala	Thr	Leu	Ser	Val	Thr	Pro	Gly		
					5					10					15			
5	Asp	Ser	Val	Ser	Leu	Ser	Cys	Arg	Ala	Ser	Asp	Ser	Ile	Ser	Gly	Ser		
					20				25					30				
10	Leu	His	Trp	Tyr	Gln	Gln	Lys	Ser	His	Glu	Ser	Pro	Arg	Leu	Leu	Ile		
					35			40					45					
15	Lys	Tyr	Ala	Ser	Gln	Ser	Ile	Ser	Gly	Ile	Pro	Ser	Arg	Phe	Ser	Gly		
					50		55					60						
20	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Ser	Ile	Asn	Ser	Val	Glu	Thr		
					65		70				75				80			
25	Glu	Asp	Phe	Gly	Met	Tyr	Phe	Cys	Gln	Gln	Ser	Asn	Ser	Trp	Pro	Leu		
					85				90						95			
30	Asn	Phe	Gly	Ala	Gly	Thr	Lys	Leu	Glu	Leu	Lys	Arg	Ala	Asp	Ala	Ala		
					100				105					110				
35	Pro	Thr	Val	Ser	Ile	Phe	Pro	Pro	Ser	Thr	Glu	Gln	Leu	Ala	Thr	Gly		
					115			120					125					
40	Gly	Ala	Ser	Val	Val	Cys	Leu	Met	Asn	Asn	Phe	Tyr	Pro	Arg	Asp	Ile		
					130		135					140						
45	Ser	Val	Lys	Trp	Lys	Ile	Asp	Gly	Thr	Glu	Arg	Arg	Asp	Gly	Val	Leu		
					145		150				155					160		
50	Asp	Ser	Val	Thr	Asp	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Met	Ser		
					165				170						175			
55	Ser	Thr	Leu	Ser	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Ser	His	Asn	Leu	Tyr		
					180			185						190				
60	Thr	Cys	Glu	Val	Val	His	Lys	Thr	Ser	Ser	Ser	Pro	Val	Val	Lys	Ser		
					195			200					205					
65	Phe	Asn	Arg	Asn	Glu	Cys												
					210													

<210> 35

<211> 445

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Construct

<400> 35

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	Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly	Leu	Val	Lys	Pro	Gly	Gly	
	1				5					10					15		
5	Ser	Leu	Lys	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr	
				20					25					30			
10	Thr	Met	Ser	Trp	Val	Arg	Gln	Thr	Pro	Glu	Lys	Arg	Leu	Glu	Trp	Val	
			35					40					45				
15	Ala	Thr	Ile	Ser	Gly	Gly	Gly	Gly	Asn	Thr	Tyr	Tyr	Pro	Asp	Ser	Val	
		50					55					60					
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45	Gly	Cys	Leu	Val	Lys	Gly	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Thr	Trp	
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55	Gln	Ser	Gly	Leu	Tyr	Thr	Leu	Thr	Ser	Ser	Val	Thr	Val	Pro	Ser	Ser	
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60	Thr	Trp	Pro	Ser	Gln	Thr	Val	Thr	Cys	Asn	Val	Ala	His	Pro	Ala	Ser	
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70	Cys	Lys	Pro	Cys	Ile	Cys	Thr	Gly	Ser	Glu	Val	Ser	Ser	Val	Phe	Ile	
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

15

Thr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

20

Ala Thr Ile Ser Gly Gly Gly Phe Gly Thr Tyr Tyr Pro Asp Ser Val
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25

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
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Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45

Tyr Tyr Xaa Arg Gln Ser Xaa Gln Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
 65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser Xaa Ser Trp Pro Leu
 85 90 95

His Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105

Claims

1. A human engineered DKK-1 antibody or antigen binding fragment thereof, comprising a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR comprises CDRs LCDR1, LCDR2, and LCDR3 and the HCVR comprises CDRs HCDR1, HCDR2, and HCDR3, wherein LCDR1 is SEQ ID NO: 5, LCDR2 is SEQ ID NO: 8, LCDR3 is SEQ ID NO: 7, HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2, and HCDR3 is SEQ ID NO: 4 for use in the treatment of cancer.
2. A human engineered DKK-1 antibody or antigen-binding fragment thereof, for use according to claim 1 wherein the cancer is selected from multiple myeloma, breast cancer, and non-small cell lung cancer.
3. A human engineered DKK-1 antibody for use according to claim 1 or claim 2, wherein the LCVR comprises the amino acid sequence of SEQ ID NO: 14 and the HCVR comprises the amino acid sequence of SEQ ID NO: 12.
4. A human engineered DKK-1 antibody for use according to any one of claims 1 to 3, wherein the human engineered DKK-1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 18 and a light chain comprising the amino acid sequence of SEQ ID NO: 20.
5. A human engineered DKK-1 antibody for use according to any one of claims 1 to 4, comprising two light chains wherein each light chain comprises the amino acid sequence of SEQ ID NO: 20, and two heavy chains wherein each heavy chain comprises the amino acid sequence of SEQ ID NO: 18.
6. A pharmaceutical composition comprising the human engineered DKK-1 antibody or antigen-binding fragment thereof, comprising a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR comprises CDRs LCDR1, LCDR2, and LCDR3 and the HCVR comprises CDRs HCDR1, HCDR2, and HCDR3, wherein LCDR1 is SEQ ID NO: 5, LCDR2 is SEQ ID NO: 8, LCDR3 is SEQ ID NO: 7, HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2, and HCDR3 is SEQ ID NO: 4 together with a pharmaceutically acceptable carrier, diluent, or excipient for use in the treatment of cancer.
7. A pharmaceutical composition for use according to claim 6 in the treatment of cancer, wherein the cancer is selected

from multiple myeloma, breast cancer, and non-small cell lung cancer.

8. A pharmaceutical composition for use according to claim 6 and claim 7 further optionally comprising other therapeutic ingredients.

Patentansprüche

1. Humaner konstruierter DKK-1-Antikörper oder antigenbindendes Fragment davon, der bzw. das eine variable Region der leichten Kette (LCVR) und eine variable Region der schweren Kette (HCVR) umfasst, wobei die LCVR CDR LCDR1, LCDR2 und LCDR3 umfasst und die HCVR CDR HCDR1, HCDR2 und HCDR3 umfasst, wobei LCDR1 SEQ ID NO: 5 ist, LCDR2 SEQ ID NO: 8 ist, LCDR3 SEQ ID NO: 7 ist, HCDR1 SEQ ID NO: 1 ist, HCDR2 SEQ ID NO: 2 ist und HCDR3 SEQ ID NO: 4 ist, zur Verwendung bei der Behandlung einer Krebserkrankung.
2. Humaner konstruierter DKK-1-Antikörper oder antigenbindendes Fragment davon zur Verwendung nach Anspruch 1, wobei die Krebserkrankung aus multiplem Myelom, Brustkrebs und nichtkleinzelligem Lungenkrebs ausgewählt ist.
3. Humaner konstruierter DKK-1-Antikörper zur Verwendung nach Anspruch 1 oder 2, wobei die LCVR die Aminosäuresequenz von SEQ ID NO: 14 umfasst und die HCVR die Aminosäuresequenz von SEQ ID NO: 12 umfasst.
4. Humaner konstruierter DKK-1-Antikörper zur Verwendung nach einem der Ansprüche 1 bis 3, wobei der humane konstruierte DKK-1-Antikörper eine schwere Kette, die die Aminosäuresequenz von SEQ ID NO: 18 umfasst, und eine leichte Kette, die die Aminosäuresequenz von SEQ ID NO: 20 umfasst, umfasst.
5. Humaner konstruierter DKK-1-Antikörper zur Verwendung nach einem der Ansprüche 1 bis 4, wobei der humane konstruierte DKK-1-Antikörper zwei leichte Ketten, wobei jede leichte Kette die Aminosäuresequenz von SEQ ID NO: 20 umfasst, und zwei schwere Ketten, wobei jede schwere Kette die Aminosäuresequenz von SEQ ID NO: 18 umfasst, umfasst.
6. Pharmazeutische Zusammensetzung, die den humanen konstruierten DKK-1-Antikörper oder das antigenbindende Fragment davon, der bzw. das eine variable Region der leichten Kette (LCVR) und eine variable Region der schweren Kette (HCVR) umfasst, wobei die LCVR CDR LCDR1, LCDR2 und LCDR3 umfasst und die HCVR CDR HCDR1, HCDR2 und HCDR3 umfasst, wobei LCDR1 SEQ ID NO: 5 ist, LCDR2 SEQ ID NO: 8 ist, LCDR3 SEQ ID NO: 7 ist, HCDR1 SEQ ID NO: 1 ist, HCDR2 SEQ ID NO: 2 ist und HCDR3 SEQ ID NO: 4 ist, zusammen mit einem pharmazeutisch akzeptablen Trägerstoff, Verdünnungsmittel oder Hilfsstoff umfasst, zur Verwendung bei der Behandlung einer Krebserkrankung.
7. Pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 6, wobei die Krebserkrankung aus multiplem Myelom, Brustkrebs und nichtkleinzelligem Lungenkrebs ausgewählt ist.
8. Pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 6 und 7, die weiterhin gegebenenfalls andere therapeutische Inhaltsstoffe umfasst.

Revendications

1. Anticorps anti-DKK-1 humain manipulé ou fragment de liaison à l'antigène correspondant, comprenant une région variable à chaîne légère (LCVR) et une région variable à chaîne lourde (HCVR), la LCVR comprenant les CDR LCDR1, LCDR2 et LCDR3 et la HCVR comprenant les CDR HCDR1, HCDR2 et HCDR3, LCDR1 présentant la séquence SEQ ID NO : 5, LCDR2 présentant la séquence SEQ ID NO : 8, LCDR3 présentant la séquence SEQ ID NO : 7, HCDR1 présentant la SEQ ID NO : 1, HCDR2 présentant la séquence SEQ ID NO : 2 et HCDR3 présentant la séquence SEQ ID NO : 4, pour une utilisation dans le traitement du cancer.
2. Anticorps anti DKK-1 humain manipulé ou fragment de liaison à l'antigène correspondant pour une utilisation selon la revendication 1, le cancer étant choisi parmi le myélome multiple, le cancer du sein et cancer du poumon non à petites cellules.
3. Anticorps anti-DKK-1 humain manipulé pour une utilisation selon la revendication 1 ou la revendication 2, la LCVR

comprenant la séquence d'acides aminés SEQ ID NO : 14 et la HCVR comprenant la séquence d'acides aminés SEQ ID NO : 12.

4. Anticorps anti-DKK-1 humain manipulé pour une utilisation selon l'une quelconque des revendications 1 à 3, l'anticorps anti-DKK-1 humain manipulé comprenant une chaîne lourde comprenant la séquence d'acides aminés SEQ ID NO : 18 et une chaîne légère comprenant la séquence d'acides aminés SEQ ID NO : 20.
5. Anticorps anti-DKK-1 humain manipulé pour une utilisation selon l'une quelconque des revendications 1 à 4, comprenant deux chaînes légères, chaque chaîne légère comprenant la séquence d'acides aminés SEQ ID NO : 20, et deux chaînes lourdes, chaque chaîne lourde comprenant la séquence d'acides aminés SEQ ID NO : 18.
6. Composition pharmaceutique comprenant l'anticorps anti-DKK-1 humain manipulé ou un fragment de liaison à l'antigène correspondant, comprenant une région variable à chaîne légère (LCVR) et une région variable à chaîne lourde (HCVR), la LCVR comprenant les CDR LCDR1, LCDR2 et LCDR3 et la HCVR comprenant les CDR HCDR1, HCDR2 et HCDR3, LCDR1 présentant la séquence SEQ ID NO : 5, LCDR2 présentant la séquence SEQ ID NO : 8, LCDR3 présentant la séquence SEQ ID NO : 7, HCDR1 présentant la SEQ ID NO : 1, HCDR2 présentant la séquence SEQ ID NO : 2 et HCDR3 présentant la séquence SEQ ID NO : 4, conjointement avec un support, un diluant ou un excipient pharmaceutiquement acceptable pour une utilisation dans le traitement du cancer.
7. Composition pharmaceutique pour une utilisation selon la revendication 6 dans le traitement du cancer, le cancer étant choisi parmi le myélome multiple, le cancer du sein et cancer du poumon non à petites cellules.
8. Composition pharmaceutique pour une utilisation selon la revendication 6 et la revendication 7, comprenant en outre éventuellement d'autres ingrédients thérapeutiques.

REFERENCES CITED IN THE DESCRIPTION

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