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(71) Applicant (for all designated States except US): AMGEN INC. [US/US]; One Amgen Center Drive, Thousand Oaks, CA 91320-1799 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): FLORIO, Monica [US/US]; 3264 Casino Drive, Thousand Oaks, CA 91362 (US). ARORA, Taruna [US/US]; 5380 Via Pisa, Thousand Oaks, CA 91320 (US). PASZTY, Christopher, J., R. [US/US]; 1027 Westridge Drive, Ventura, CA 93003 (US). RICHARDS, William, G. [US/US]; 3079 Espana Lane, Thousand Oaks, CA 91362-4921 (US).

(74) Agent: PENN, Michael, G.; Amgen Inc., One Amgen Center Drive, MS 28-2-C, Thousand Oaks, CA 91320-1799 (US).

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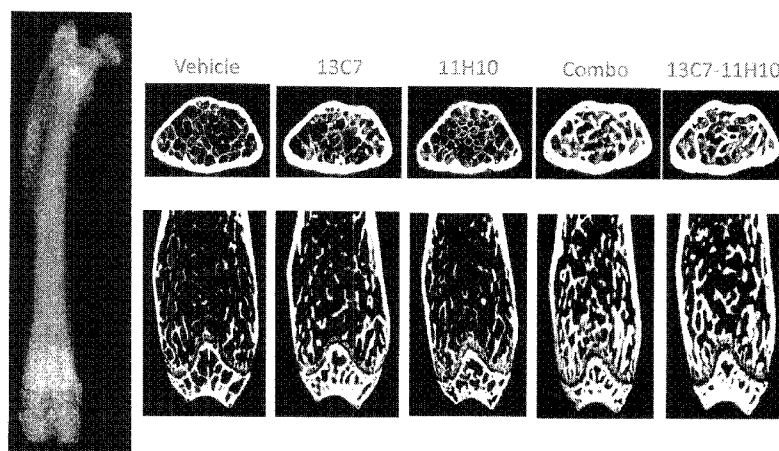
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[Continued on next page]

(54) Title: BISPECIFIC BINDING AGENTS

FIG. 11



(57) Abstract: The invention relates to bispecific anti-sclerostin/anti-DKK1 binding agents and combinations of anti-sclerostin and anti-DKK1 binding agents, and related methods of treatment.



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BISPECIFIC BINDING AGENTS**CROSS-REFERENCE TO RELATED APPLICATION**

- 5 This application claims the benefit of priority to U.S. provisional application No. 61/448,089 filed March 1, 2011, and to U.S. provisional application No. 61/482,979 filed May 5, 2011, each of which is hereby incorporated by reference herein.

10 This application contains an ASCII "txt" compliant sequence listing which serves as both the computer readable form (CRF) and the paper copy required by 37 C.F.R. Section 1.821(c) and 1.821(e), and is hereby incorporated by reference in its entirety. The name of the "txt" file created on February 29, 2012 is A-1598-US-NP_SequenceListing_022912_ST25_AddedSeq485-496.txt, and is 471 KB in size.

15 **BACKGROUND OF THE INVENTION**

Field of the Invention

The invention relates to bispecific anti-sclerostin/anti-DKK1 binding agents and combinations of anti-sclerostin and anti-DKK1 binding agents, and related methods of treatment.

20

Background of the Invention

Two or three distinct phases of changes to bone mass occur over the life of an individual (see Riggs, West J. Med. 154:63 77 (1991)). The first phase occurs in both men and women and proceeds to attainment of a peak bone mass. This first phase is achieved through
25 linear growth of the endochondral growth plates and radial growth due to a rate of periosteal apposition. The second phase begins around age 30 for trabecular bone (flat bones such as the vertebrae and pelvis) and about age 40 for cortical bone (e.g., long bones found in the limbs) and continues to old age. This phase is characterized by slow bone loss
30 and occurs in both men and women. In women, a third phase of bone loss also occurs, most likely due to postmenopausal estrogen deficiencies. During this phase alone, women

may lose additional bone mass from the cortical bone and from the trabecular compartment (see Riggs, supra).

Loss of bone mineral content can be caused by a wide variety of conditions and may result
5 in significant medical problems. For example, osteoporosis is a debilitating disease in humans and is characterized by marked decreases in skeletal bone mass and mineral density, structural deterioration of bone, including degradation of bone microarchitecture and corresponding increases in bone fragility (i.e., decreases in bone strength), and susceptibility to fracture in afflicted individuals. Osteoporosis in humans is generally
10 preceded by clinical osteopenia (bone mineral density that is greater than one standard deviation but less than 2.5 standard deviations below the mean value for young adult bone), a condition found in approximately 25 million people in the United States. Another 7.8 million patients in the United States have been diagnosed with clinical osteoporosis (defined as bone mineral content greater than 2.5 standard deviations below that of
15 mature young adult bone). The frequency of osteoporosis in the human population increases with age. Among Caucasians, osteoporosis is predominant in women who, in the United States, comprise 80% of the osteoporosis patient pool. The increased fragility and susceptibility to fracture of skeletal bone in the aged is aggravated by the greater risk of accidental falls in this population. Fractured hips, wrists, and vertebrae are among the
20 most common injuries associated with osteoporosis. Hip fractures in particular are extremely uncomfortable and expensive for the patient, and for women, correlate with high rates of mortality and morbidity.

Although osteoporosis has been regarded as an increase in the risk of fracture due to decreased bone mass, few of the presently available treatments for skeletal disorders can
25 increase the bone density of adults, and most of the presently available treatments work primarily by inhibiting further bone resorption rather than stimulating new bone formation. Estrogen is now being prescribed to retard bone loss. However, some controversy exists over whether patients gain any long term benefit and whether estrogen has any effect on patients over 75 years old. Moreover, use of estrogen is believed to increase the risk of
30 breast and endometrial cancer. Calcitonin, osteocalcin with vitamin K, or high doses of dietary calcium, with or without vitamin D, have also been suggested for postmenopausal women. High doses of calcium, however, often have undesired gastrointestinal side

effects, and serum and urinary calcium levels must be continuously monitored (e.g., Khosla and Riggs, Mayo Clin. Proc. 70:978982, 1995).

- Other current therapeutic approaches to osteoporosis include bisphosphonates (e.g., FosamaxTM, ActonelTM, BonvivaTM, ZometaTM, olpadronate, neridronate, skelid, bonefos), parathyroid hormone, calcilytics, calcimimetics (e.g., cinacalcet), statins, anabolic steroids, lanthanum and strontium salts, and sodium fluoride. Such therapeutics, however, are often associated with undesirable side effects (see Khosla and Riggs, supra).
- 10 Sclerostin, the product of the SOST gene, is absent in sclerosteosis, a skeletal disease illustrated by bone overgrowth and strong dense bones (Brunkow et al., Am. J. Hum. Genet., 68:577 589, 2001; Balemans et al., Hum. Mol. Genet., 10:537 543, 2001). Inhibitors of sclerostin have been shown to increase the rate of bone mineralization, and thus bone mineral density (Padhi et al., J Bone Miner Res. 2010 Jun; e-published ahead of print).
- 15 Likewise, Dkk-1 has been shown to be involved in the regulation of bone formation, particularly in bone fracture repair, and its role in various other diseases that are associated with bone loss (e.g., cancer and diabetes) (Komatsu et al., J. Orthop. Res. 2010 Jul;28(7):928-36; Gavriatopoulou et al., Expert Opin. Ther. Targets. 2009 Jul;13(7):839-48).
- 20 Dickkopf-1 (Dkk-1) is a secreted protein that participates in embryonic head induction and antagonizes Wnt (Glinka et al., Nature 391: 357-362 (1998)). The amino acid sequence of human Dkk-1 and nucleotides encoding it have been described (U.S. Pat. Nos. 6,344,541; 6,844,422; 7,057,017; Published Patent Application No. 20050069915; Krupnick et al., Gene 238: 301-313(1999)). Expression of Dkk-1 in human was thought to be restricted to
- 25 placenta, suggesting a role for Dkk-1 in embryonic development (Krupnick et al., supra). Allen and colleagues (U.S. Published Patent Application No. 20040038860) describe assays relating to the interaction between LRP5, HBM or LRP6 with Dkk-1. Antibodies that bind Dkk-1 have been described in the aforementioned patents and patent applications and in U.S. Published patent Application Nos. 20050079173 and 20060127393.
- 30 Human Dkk-1 is a member of a Dickkopf gene family which includes Dkk-1, Dkk-2, Dkk-3, and Dkk4 (Krupnick et al., supra). Although Dkk-1 and Dkk-4 have been shown to suppress

Wnt-induced secondary axis induction in *Xenopus* embryos, neither block axis induction triggered by *Xenopus* Dishevelled or Frizzled, suggesting that their Wnt inhibitory activity is upstream of Frizzled in the Wnt signaling pathway (Krupnick et al., supra). It has been suggested that Dkk-1 might have an inhibitory effect on bone formation, making them

5 potential targets for the prevention or treatment of osteoporosis (Patel and Karensky, N. Eng. J. Med. 346: 1572-1573 (2002); Boyden et al., N. Eng. J. Med. 346: 1513-1521 (2002)).

SUMMARY OF THE INVENTION

Provided herein are novel inhibitors that are effective in treating conditions requiring

10 increased bone building, for example, fracture repair or bone loss associated with pathological conditions, such as multiple myeloma. In addition, provided herein are multi-specific agents that increase bone anabolism including combinations of DKK-1 and sclerostin inhibitors. These combinations can be used for treatment of, for example, osteoporosis, accelerating healing of fractures, and any number of conditions requiring an

15 increase in the rate of bone building. In particular, the DKK-1 and sclerostin inhibitors can be two separate inhibitors, for example, an anti-sclerostin antibody and an anti-DKK-1 antibody. Alternatively, the DKK-1 and sclerostin inhibitors can be a single molecular entity. Nonlimiting examples include bispecific binding molecules such as DVD-Ig's, bispecific antibodies, and bispecific linker bodies.

20

In one aspect of this embodiment, the patient suitable for treatment with the molecules of the invention is one who suffers from cancer that metastasizes to bone, and in another aspect, the patient is one who suffers from multiple myeloma. In yet another aspect, the patient is selected from patients who have osteoporosis, osteopenia, Paget's disease,

25 periodontitis, rheumatoid arthritis, and bone loss due to immobilization. In yet other embodiments, the patient is selected from those who have bone damage that may or may not result from an underlying loss of bone mass such as that caused by osteoporosis or osteolytic lesions associated with cancer (e.g., multiple myeloma). Examples of such bone damage include but are not limited to orthopedic procedures, dental procedures, implant

30 surgery, joint replacement (e.g., hip replacement, knee replacement, etc.), bone grafting, bone cosmetic surgery and bone repair such as fracture healing, nonunion healing, delayed

union healing and facial reconstruction. One or more compositions may be administered before, during and/or after the procedure, replacement, graft, surgery or repair.

In one embodiment, provided is a binding molecule comprising a polypeptide chain,
5 wherein said polypeptide chain comprises VH1-(X1)_n-VH2-C-(X2)_n, wherein: VH1 is a first heavy chain variable domain obtained from a first parent antibody or antigen binding portion thereof; VH2 is a second heavy chain variable domain obtained from a second parent antibody or antigen binding portion thereof; C is a heavy chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n is an Fc region,
10 wherein said (X2)_n is either present or absent, wherein the binding molecule specifically binds both sclerostin and DKK-1.

In another embodiment, provided is a binding molecule comprising a polypeptide chain, wherein said polypeptide chain comprises VL1-(X1)_n-VL2-C-(X2)_n, wherein: VL1 is a first
15 light chain variable domain obtained from a first parent antibody or antigen binding portion thereof; VL2 is a second light chain variable domain obtained from a second parent antibody or antigen binding portion thereof; C is a light chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n is an Fc region, wherein said (X2)_n is either present or absent, wherein the binding molecule specifically binds both
20 sclerostin and DKK-1.

In a further embodiment, provided is a binding molecule comprising first and second polypeptide chains, wherein said first polypeptide chain comprises a VH1-(X1)_n-VH2-C-(X2)_n, wherein VH1 is a first heavy chain variable domain obtained from a first parent
25 antibody or antigen binding portion thereof; VH2 is a second heavy chain variable domain obtained from a second parent antibody or antigen binding portion thereof; C is a heavy chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n is an Fc region, wherein said (X2)_n is either present or absent; and wherein said second polypeptide chain comprises a VL1-(X1)_n-VL2-C-(X2)_n, wherein VL1 is a first light
30 chain variable domain obtained from a first parent antibody or antigen binding portion thereof; VL2 is a second light chain variable domain obtained from a second parent antibody or antigen binding portion thereof; C is a light chain constant domain; (X1)_n is a

linker, wherein said (X1)_n is either present or absent; and (X2)_n does not comprise an Fc region, wherein said (X2)_n is either present or absent, wherein the binding molecule specifically binds sclerostin and DKK-1.

- 5 In another embodiment, provided is a binding molecule that binds both sclerostin and DKK-1 comprising four polypeptide chains, wherein first and third polypeptide chains comprise VH1-(X1)_n-VH2-C-(X2)_n, wherein: VH1 is a first heavy chain variable domain; VH2 is a second heavy chain variable domain; C is a heavy chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n is an Fc region, wherein said (X2)_n
- 10 is either present or absent; and wherein second and fourth polypeptide chains comprise VL1-(X1)_n-VL2-C-(X2)_n, wherein VL1 is a first light chain variable domain; VL2 is a second light chain variable domain; C is a light chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n does not comprise an Fc region, wherein said (X2)_n is either present or absent, wherein the VH1 and VH2 heavy chain variable
- 15 domains comprise an amino acid sequence selected from the group consisting of sclerostin binders SEQ ID NOs: 95, 96, 104, 112, 120, 128, 136, 144, 152, 160, 168, 176, 184, 192, 200, 208, and 216, or DKK-1 binders SEQ ID NOs: 224, 232, 240, 248, 256, 264, 272, 280, 288, 296, 304, 312, 320, 328, 336, 344, 352, 360, 368, 376, 384, 392, 400, and 408, and wherein the VL1 and VL2 light chain variable domains comprise an amino acid sequence selected
- 20 from the group consisting of sclerostin binders SEQ ID NOs: 94, 103, 111, 119, 127, 135, 143, 151, 159, 167, 175, 183, 191, 199, 207, and 215, or DKK-1 binders SEQ ID NOs: 223, 231, 239, 247, 255, 263, 271, 279, 287, 295, 303, 311, 319, 327, 335, 343, 351, 359, 367, 375, 383, 391, 399, and 407.
- 25 In yet a further embodiment, provided is a binding molecule that binds both sclerostin and DKK-1 comprising four polypeptide chains, wherein first and third polypeptide chains comprise VH1-(X1)_n-VH2-C-(X2)_n, wherein: VH1 is a first heavy chain variable domain; VH2 is a second heavy chain variable domain; C is a heavy chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n is an Fc region, wherein
- 30 said (X2)_n is either present or absent; and wherein second and fourth polypeptide chains comprise VL1-(X1)_n-VL2-C-(X2)_n, wherein VL1 is a first light chain variable domain; VL2 is a second light chain variable domain; C is a light chain constant domain; (X1)_n is a linker,

wherein said (X1)_n is either present or absent; and (X2)_n does not comprise an Fc region, wherein said (X2)_n is either present or absent, wherein the binding molecule comprises VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairings selected from the group consisting of:

- 5 SEQ ID NOs: 18 and 20; 22 and 24; 26 and 28; 30 and 32; 34 and 36; 38 and 40; 42 and 44; 46 and 48; 50 and 52; 54 and 76; 56 and 72; 58 and 60; 62 and 64; 66 and 68; 70 and 72; 74 and 76; 78 and 80; 82 and 84; 86 and 88; and 90 and 92.

- In another embodiment, provided is a binding molecule comprising four polypeptide chains, wherein first and third polypeptide chains comprise VH1-(X1)_n-VH2-C-(X2)_n, wherein: VH1 is a first heavy chain variable domain; VH2 is a second heavy chain variable domain; C is a heavy chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n is an Fc region, wherein said (X2)_n is either present or absent; and wherein second and fourth polypeptide chains comprise VL1-(X1)_n-VL2-C-(X2)_n, wherein VL1 is a first light chain variable domain; VL2 is a second light chain variable domain; C is a light chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n does not comprise an Fc region, wherein said (X2)_n is either present or absent, wherein the binding molecule comprises 3 VH1 CDRs, 3 VH2 CDRs, 3 VL1 CDRs and 3 VL2 CDRs, wherein the paired VH1 and VL1 CDRs, and paired VH2 and VL2 CDRs, are selected from the group consisting of SEQ ID NOs:

- 97-102; 105-110; 113-118; 121-126; 129-134; 137-142; 145-150; 153-158; 161-166; 169-174; 177-182; 185-190; 193-198; 201-206; 209-214; 217-222,
or SEQ ID NOs:
225-230; 233-238; 241-246; 249-254; 257-262; 265-270; 273-278; 281-286;
289-294; 297-302; 305-310; 313-318; 321-326; 329-334; 337-342; 345-350;
353-358; 361-366; 369-374; 377-382; 385-390; 393-398; 401-406; 409-414.

- In another embodiment, provided is a method for generating a binding molecule that binds sclerostin and DKK-1 comprising the steps of: (a) obtaining a first parent antibody, or antigen binding portion thereof, that can bind sclerostin or DKK-1; (b) obtaining a second parent antibody, or antigen binding portion thereof, that can bind sclerostin or DKK-1; (c) constructing first and third polypeptide chains comprising VH1-(X1)_n-VH2-C-(X2)_n, wherein:

VH1 is a first heavy chain variable domain obtained from said first parent antibody or antigen binding portion thereof; VH2 is a second heavy chain variable domain obtained from said second parent antibody or antigen binding portion thereof; C is a heavy chain constant domain; (X1)_n is a linker with the proviso that it is not CH1, wherein said (X1)_n is
5 either present or absent; and (X2)_n is an Fc region, wherein said (X2)_n is either present or absent; (d) constructing second and fourth polypeptide chains comprising VL1-(X1)_n-VL2-C-(X2)_n, wherein: VL1 is a first light chain variable domain obtained from said first parent antibody or antigen binding portion thereof; VL2 is a second light chain variable domain obtained from said second parent antibody or antigen binding thereof; C is a light chain
10 constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n does not comprise an Fc region, wherein said (X2)_n is either present or absent; and (e) expressing said first, second, third and fourth polypeptide chains such that a binding molecule that binds sclerostin and DKK-1 is generated.

15 In another embodiment, pharmaceutical compositions comprising binding molecules of the invention are provided. In a further embodiment, binding molecules of the invention in combination with one or more of a pharmaceutically acceptable excipient, diluent or carrier are provided.

20 In one embodiment, provided is a method of treating a bone disorder comprising administering to a patient in need thereof a binding molecule of the invention. In another embodiment, provided is a method of accelerating bone fracture repair comprising administering to a patient in need thereof a binding molecule of the invention. In another embodiment, provided is a method of increasing bone density comprising administering to
25 a patient in need thereof a binding molecule of the invention. In a further embodiment, provided is a method of increasing bone strength comprising administering to a patient in need thereof a binding molecule of the invention.

These and other aspects of the present invention will become apparent upon reference to
30 the following detailed description and attached drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 summarizes ELISA analysis of bispecific huAbs binding to huDKK1 or huScl.

Figure 2 summarizes ELISA analysis of bispecific Rat-Abs binding to huDKK1 or huScl.

- 5 **Figure 3** summarizes ELISA analysis of bispecific Abs binding to huDKK1 and huScl at the same time.

Figure 4 summarizes in vitro bioassay results showing that rAB-4-11H10 has similar neutralizing activity to control Mabs when same molar ratio is used.

- 10 **Figure 5** summarizes the percent change in bone mass density (BMD) and bone mineral content (BMC) in lumbar vertebrae and whole leg data from an in vivo study using mice treated with vehicle, anti-sclerostin mAb, anti-DKK1 mAb, a combination of anti-sclerostin mAb and DKK1 mAb, and 13C7-11H10 bispecific.

Figure 6 summarizes the analysis of gene expression data after treatment with combination anti-sclerostin/anti-DKK-1 therapy.

- 15 **Figures 7 and 8** summarize the BMD percent change of the lumbar vertebrae and the femur-tibia in mice treated with vehicle, anti-sclerostin mAb, anti-DKK1 mAb, a combination of anti-sclerostin mAb and DKK1 mAb, and 13C7-11H10 bispecific.

- Figures 9 and 10** summarize the percent change in bone strength from mice treated with vehicle, anti-sclerostin mAb, anti-DKK1 mAb, a combination of anti-sclerostin mAb and
20 DKK1 mAb, and 13C7-11H10 bispecific.

Figure 11 contains cross section images of mouse femurs from mice treated with vehicle, anti-sclerostin mAb, anti-DKK1 mAb, a combination of anti-sclerostin mAb and DKK1 mAb, and 13C7-11H10 bispecific.

- Figure 12** summarizes percent change in bone strength in a torsional model from rats
25 treated with vehicle, anti-sclerostin mAb, anti-DKK1 mAb, and DKK1 mAb, and 13C7-11H10 bispecific.

Figures 13-14 summarize percent change in BMD in lumbar vertebrae and femur-tibia from rats treated with vehicle, 6.147-2x-Ab5 bispecific, 6.37-AbL-Ab23 bispecific, Ab5K-AbS-6.147 bispecific, 6.147-AbL-27H6 bispecific, and 8G2-AbL-6.37.5 bispecific.

- 30 **Figures 15-16** summarize the percent change in bone strength from mice treated with vehicle, anti-sclerostin mAb, anti-DKK1 mAb, and 13C7-11H10 bispecific.

Figure 17 summarizes the results of an osteoblast supertopflash competition assay showing rat 13C7-11H10 retains the neutralizing activity of parental antibodies in osteoblast MC3T3E1 cells treated with Wnt proteins.

Figure 18 summarizes the results of an osteoblast supertopflash competition assay showing rat and human DVD-Igs have potent neutralizing activity against both sclerostin and Dkk1 in osteoblast MC3T3E1STF cells treated with Wnt1 protein.

Figure 19 summarizes the results of an Alphascreen competition assay showing inhibition of Lrp6 binding to sclerostin or Dkk1 by DVD-Igs.

Figure 20 is a schematic of a representative bispecific binding molecule known as a DVD-Ig.

10

DETAILED DESCRIPTION OF THE INVENTION

The section headings herein are for organizational purposes only and are not to be construed as limiting the subject matter described therein. All references cited in this application are expressly incorporated by reference herein. Unless otherwise defined herein, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

20

Provided herein are novel bispecific molecules that are effective in treating conditions requiring increased bone building, for example, fracture repair or bone loss associated with pathological conditions, such as multiple myeloma. In addition, provided herein are combinations of agents that increase bone anabolism including combinations of DKK-1 and sclerostin inhibitors. These combinations can be used for treatment of, for example, osteoporosis, increase the rate of fracture healing, and any number of conditions requiring an increase in the rate of bone building. The combination therapeutic can take the form of two separate inhibitors, for example, an anti-sclerostin antibody and a bispecific molecule, or can be a single molecular entity, for example, a bispecific binding molecule.

30

Reports indicate that Dkk-1 expression is elevated in fracture models of non-unions (Bajada, et al., 2009 Bone; 45(4):726-35.). Likewise, healthy bone expresses lower levels of

Dkk-1 helping to explain the limited effect of Dkk-1 antibodies alone on BMD in intact bone. Thus, combinations of sclerostin and Dkk-1 inhibitors to treat fractures are particularly useful given the surprisingly strong healing response including the significant increase in the peak load in a relatively short period. A bispecific molecule comprising inhibitors of
5 both sclerostin and DKK-1 has been unexpectedly found to generate a greater biological response than either monotherapy alone.

As used herein, a bispecific molecule binds one antigen on one of its two binding regions, and binds a different antigen on its second binding region. Thus, for example, a bispecific
10 antibody may have two distinct antigen binding regions and be monovalent for each antigen it binds. A further nonlimiting example of a bispecific molecule is a DVD-Ig, which may have two distinct antigen binding regions on each of its two arms, thus being bivalent for both distinct antigens. Bispecific and bifunctional sclerostin and DKK-1 binding molecules provided herein can include one or more CDRs or one or more variable regions
15 as described herein. A bispecific or bifunctional antibody in some instances is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. These bispecific antibodies may be produced by a variety of methods including, but not limited to, fusion of hybridomas or linking of Fab' fragments. See, e.g., Songsivilai & Lachmann, 1990, Clin. Exp. Immunol. 79: 315-321; Kostelny et al., 1992, J. Immunol. 148:
20 1547-1553.

Bispecific molecules can also be created according to the invention by fusion. In one example, it can be linked (e.g., by expressing fused proteins, chemical linking, high affinity non-covalent association or the like) to one or more other binding molecules. Examples of
25 such binding molecules include but are not limited to another antibody, antibody fragment, peptide or binding mimetic, such that a bispecific molecule results.

Bispecific molecules can also be created by selecting for, and/or engineering, an antibody that specifically binds to two distinct antigens, such as DKK-1 and sclerostin. See, e.g.,
30 Bostrom et al., 2009, Science 323: 1610-1614.

Bispecific molecules can also comprise a first binding specificity for sclerostin and a second binding specificity for a second target. For example, the second target can be another epitope of sclerostin different from the first epitope. Another example is a bispecific molecule comprising at least one first binding specificity for sclerostin and a second binding specificity for an epitope within Dkk-1. Another example is a bispecific molecule comprising at least one first binding specificity for sclerostin and a second binding specificity for an epitope within LRP4. Additionally, for the invention in which the bispecific molecule is multi-specific, the molecule can further include a third binding specificity, in addition to the first and second target epitope.

10

Formats for Bispecific Binding Agents

In one aspect, the present invention features bispecific or multispecific molecules comprising an anti-sclerostin binding agent and an anti-DKK1 binding agent, or a fragment thereof. An antibody of the invention, or antigen-binding regions thereof, can be derivatized or linked to another functional molecule, e.g., another peptide or protein (e.g., another antibody or ligand for a receptor) to generate a bispecific molecule that binds to at least two different binding sites or target molecules. The antibody of the invention may in fact be derivatized or linked to more than one other functional molecule to generate multi-specific molecules that bind to more than two different binding sites and/or target molecules; such multi-specific molecules are also intended to be encompassed by the term "bispecific molecule" or "bispecific binding molecule" or "bispecific binding protein" as used herein.

25 To create a bispecific molecule of the invention, an antibody of the invention can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other binding molecules, such as another antibody, antibody fragment, peptide or binding mimetic, such that a bispecific molecule results.

30 Accordingly, the present invention includes bispecific molecules comprising at least one first binding specificity for sclerostin and a second binding specificity for a second target epitope. For example, the second target epitope is another epitope of sclerostin different

from the first target epitope. Another example is a bispecific molecule comprising at least one first binding specificity for sclerostin and a second binding specificity for an epitope within Dkk-1. Another example is a bispecific molecule comprising at least one first binding specificity for sclerostin and a second binding specificity for an epitope within LRP4.

- 5 Additionally, for the invention in which the bispecific molecule is multi-specific, the molecule can further include a third binding specificity, in addition to the first and second target epitope.

- 10 In certain embodiments, the bispecific format is a dual variable domain (DVD) Ig. In certain embodiments, the DVD-Ig format comprises two variable domains on each arm on an immunoglobulin, giving a total of four variable domains per molecule. In one embodiment the binding protein of the invention is a DVD-Ig capable of binding two antigens comprising four polypeptide chains, wherein, first and third polypeptide chains comprise VH1-(X1)n-VH2-C-(X2)n, wherein, VH1 is a first heavy chain variable domain obtained from a first parent antibody or antigen binding portion thereof; VH2 is a second heavy chain variable domain obtained from a second parent antibody or antigen binding portion thereof; C is a heavy chain constant domain; (X1)n is a linker, wherein said (X1)n is either present or absent; and (X2)n is an Fc region, wherein said (X2)n is either present or absent; and wherein second and fourth polypeptide chains comprise VL1-(X1)n-VL2-C-(X2)n, wherein
- 15 VL1 is a first light chain variable domain obtained from a first parent antibody or antigen binding portion thereof; VL2 is a second light chain variable domain obtained from a second parent antibody or antigen binding portion thereof; C is a light chain constant domain.
- 20 Nonlimiting examples of the combinations contemplated are provided herein in Table 1, SEQ ID NOs: 17-92, which describe nucleic acid and amino acid sequences of DVD-Ig heavy chains and light chains. However, any combination of antibodies, or fragments thereof, including CDRs, provided herein, is contemplated.

- Nonlimiting examples of DVD-Ig's can be found in U.S. Patent No. 7,612,181, U.S. Patent Appl. Publ. Nos. US20110008766A1, US20090311253A1, US20100047239A1,
- 30 US20090215992A1, US20070081996A1, US20070071675A1, US20070041905A1, US20100260668A1, US20100076178A1, US20090304693A1, US20090311253A1, and US20100233079A1. Additional nonlimiting examples of DVD-Ig's can be found in

International Patent Application Publ. Nos. WO2007024715A2, WO2008024188A2, WO2009134776A2, WO2009149185A2, WO2009149189A2, WO2010065882A1, WO2010127284A2, and WO2010127294A2.

- 5 The term "linker" is used to denote polypeptides comprising two or more amino acid residues joined by peptide bonds and are optionally used to link one or more antigen binding portions. Such linker polypeptides are well known in the art (see e.g., Holliger, P., et al. (1993) Proc. Natl. Acad. Sci. USA 90:6444-6448; Poljak, R. J., et al. (1994) Structure 2:1121-1123). For example, X1 of the DVD-Ig can be a linker selected from any of the linker
10 sequences set forth in Table 1 herein.

- In specific embodiments, the linkers can be mutated to make amino acid substitutions to change their properties. For example, O-glycosylation may be observed with DVD-Igs that comprise the AbL linker. To address this, one or more Ser or Thr residues (underlined
15 below) may be changed to glycine (Gly; G) or glutamine (Gln; Q) depending on which specific sites are O-glycosylated in each DVD-Ig as determined by peptide mapping.

ASTKGPSVFPLAP HC
TVAAPSVFIFPP LC
QPKAAPSVTLFPP LC

- 20 Sites may be substituted in either, or in both the heavy chain and light chain linkers.

In one embodiment, the binding protein does not comprise X2. In another embodiment, X1 is a linker with the proviso that it is not CH1.

- 25 In one embodiment, both the variable heavy and variable light chain comprise the same linker. In another embodiment, the variable heavy and variable light chain comprise different linkers. In another embodiment, both the variable heavy and variable light chain comprise a short (about 6 amino acids or shorter) linker. In another embodiment, both the variable heavy and variable light chain comprise a long (greater than 6 amino acids) linker.
30 In another embodiment, the variable heavy chain comprises a short linker and the variable light chain comprises a long linker. In another embodiment, the variable heavy chain comprises a long linker and the variable light chain comprises a short linker.

- In certain embodiments, the bispecific format is an immunoglobulin further comprising a monomer domain that binds to sclerostin or DKK-1. See, for example, U.S. Patent Nos. 7,503,907 and 7,820,790, and U.S. Patent Publ. Nos. 20040175756, 20050048512, 5 20050053973, and 20060223114. In one embodiment the bispecific molecule comprises multiple monomer domains, alternatively known as an avimer. Avimers comprise two or more peptide sequences of 30 to 35 amino acids each, connected by linker peptides. In certain embodiments, the individual sequences are derived from A domains of various membrane receptors and have a rigid structure, stabilized by disulfide bonds and calcium.
- 10 In some embodiments, each A domain can bind to a certain epitope of the target protein. The combination of domains binding to different epitopes of the same protein increases affinity to this protein, an effect known as avidity. In one embodiment, the monomer domain or the avimer is located within the Fc region of the immunoglobulin.
- 15 In certain embodiments, the bispecific format is a linkerbody. A "linkerbody" is a bivalent, bispecific antibody. The linkerbody is constructed by joining a VL of an antibody to its respective heavy chain using a linker. Two halves representing specificity for DKK and sclerostin respectively can be brought together by introducing opposite charge pair mutations in the Fc of each heavy chain. For example, the first Fc contains 392D and 409D
- 20 while the second Fc contains 356K and 359K (see, e.g., Kannan Gunasekhran et al, J. Biol Chem, June 2010).

- In certain embodiments, the bispecific format comprises a peptide binding region (e.g. a peptide mimetic). Mimetics (e.g., "peptide mimetics" or "peptidomimetics") based upon
- 25 the variable region domains and CDRs that are described herein are also provided. These analogs can be peptides, non-peptides or combinations of peptide and non-peptide regions. Fauchere, 1986, Adv. Drug Res. 15: 29; Veber and Freidinger, 1985, TINS p. 392; and Evans et al., 1987, J. Med. Chem. 30: 1229, which are incorporated herein by reference for any purpose. Peptide mimetics that are structurally similar to therapeutically useful
- 30 peptides may be used to produce a similar therapeutic or prophylactic effect. Such compounds are often developed with the aid of computerized molecular modeling. Generally, peptidomimetics of the invention are proteins that are structurally similar to an

antibody displaying a desired biological activity, such as here the ability to specifically bind Dkk-1 or sclerostin, but have one or more peptide linkages optionally replaced by a linkage selected from: --CH₂NH--, --CH₂S--, --CH₂--CH₂--, --CH--CH-(cis and trans), --COCH₂--, --CH(OH)CH₂--, and --CH₂SO--, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (e.g., D-lysine in place of L-lysine) may be used in certain embodiments of the invention to generate more stable proteins. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation may be generated by methods known in the art (Rizo and Gierasch, 1992, *Ann. Rev. Biochem.* 61: 387), incorporated herein by reference), for example, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

In certain embodiments, the bispecific binding molecule is a bispecific diabody. Bispecific diabodies (Db) utilize the diabody format for expression. Diabodies are produced from scFv fragments by reducing the length of the linker connecting the VH and VL domain to approximately 5 residues (see Peipp, M. and T. Valerius (2002) *Biochem. Soc. Trans.* 30(4): 507-11). This reduction of linker size facilitates dimerization of two polypeptide chains by crossover pairing of the VH and VL domains. Bispecific diabodies are produced by expressing, two polypeptide chains with, either the structure VHA-VLB and VHB-VLA (VH-VL configuration), or VLA-VHB and VLB-VHA (VL-VH configuration) within the same cell. A large variety of different bispecific diabodies have been produced in the past and most of them are expressed in soluble form in bacteria. However, a recent comparative study demonstrates that the orientation of the variable domains can influence expression and formation of active binding sites (see Mack, M. et al. (1995) *Proc. Natl. Acad. Sci. USA* 92(15): 7021-5). Nevertheless, soluble expression in bacteria represents an important advantage over tandem scFv molecules. However, since two different polypeptide chains are expressed within a single cell inactive homodimers can be produced together with active heterodimers. This necessitates the implementation of additional purification steps in order to obtain homogenous preparations of bispecific diabodies. One approach to force the generation of bispecific diabodies is the production of knob-into-hole diabodies (see Holliger, P., T. Prospero, and G. Winter (1993) *Proc. Natl. Acad. Sci. USA* 90(14): 6444-8.18). This approach was demonstrated for a bispecific diabody directed against HER2 and CD3. A

large knob was introduced in the VH domain by exchanging Va137 with Phe and Leu45 with Trp and a complementary hole was produced in the VL domain by mutating Phe98 to Met and Tyr87 to Ala, either in the anti-HER2 or the anti-CD3 variable domains. By using this approach the production of bispecific diabodies could be increased from 72% by the parental diabody to over 90% by the knob-into-hole diabody. Diabodies have also been fused to Fc to generate more Ig-like molecules, named di-diabodies (see Lu, D., et al. (2004) J. Biol. Chem. 279(4): 2856-65). In addition, multivalent antibody construct comprising two Fab repeats in the heavy chain of an IgG and capable of binding four antigen molecules has been described (see WO 0177342A1, and Miller, K., et al. (2003) J. Immunol. 170(9): 4854-61).

In certain embodiments, the bispecific binding molecule can be in the context of a multispecific binding molecule. A nonlimiting example of this format can be found in International Patent Application Publ. No. WO2009018386A1 and U.S. Patent Appl. Publ. No. US20090155275.

In certain embodiments, the bispecific format is a domain antibody. A "domain antibody" is an immunologically functional immunoglobulin fragment containing only the variable region of a heavy chain or the variable region of a light chain. In some instances, two or more VH regions are covalently joined with a peptide linker to create a bivalent domain antibody. The two VH regions of a bivalent domain antibody may target the same or different antigens. See for example, U.S. Patent Publ. Nos. 20100234570 and 20040219643A1.

In one embodiment, the bispecific molecules of the invention comprise as a binding specificity at least one antibody, or an antibody fragment thereof, including, e.g., an Fab, Fab', F(ab')₂, Fv, or a single chain Fv from a novel bispecific molecule sequence provided herein. It may also be a light chain or heavy chain dimer, or any minimal fragment such as a Fv or a single chain construct as described in Ladner et al. U.S. Patent No. 4,946,778.

Bispecific molecules can be prepared by chemically conjugating the binding portions using methods known in the art. When the binding portions are proteins or peptides, a variety of

coupling or cross-linking agents can be used for covalent conjugation. Examples include protein A, carbodiimide, N-succinimidyl-S-acetyl-thioacetate (SATA), 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB), o-phenylenedimaleimide (oPDM), N-succinimidyl-3-(2-pyridyl)dithiopropionate (SPDP), and sulfosuccinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate (sulfo-SMCC) (see e.g., Karpovsky et al., 1984 J. Exp. Med. 160:1686; Liu, MA et al., 1985 Proc. Natl. Acad. Sci. USA 82:8648). Other methods include those described in Paulus, 1985 Behring Ins. Mitt. No. 78,118-132; Brennan et al., 1985 Science 229:81-83, and Glennie et al., 1987 J. Immunol. 139: 2367-2375. Conjugating agents include SATA and sulfo-SMCC, both available from Pierce Chemical Co. (Rockford, IL). When the binding portions are antibodies, they can be conjugated by sulfhydryl bonding of the hinge regions of the two heavy chains. In one embodiment, the hinge region is modified to contain an odd number of sulfhydryl residues such that there is a free sulfhydryl group that has not formed a disulfide linkage with a corresponding heavy or light chain counterpart.

Bispecific molecules may comprise at least two single chain molecules. Non-limiting examples of methods for preparing bispecific molecules are described various patent publications including in U.S. Patent Number 5,260,203; U.S. Patent Number 5,455,030; U.S. Patent Number 4,881,175; U.S. Patent Number 5,132,405; U.S. Patent Number 5,091,513; U.S. Patent Number 5,476,786; U.S. Patent Number 5,013,653; U.S. Patent Number 5,258,498; U.S. Patent Number 5,482,858; and U.S. Patent Application No. 2010/0076178.

Alternatively, both binding moieties can be encoded in the same vector and expressed and assembled in the same host cell. This method is particularly useful where the bispecific molecule is a mAb x mAb, mAb x Fab, Fab x F(ab):₂ or ligand x Fab fusion protein. A bispecific molecule of the invention can be a single chain molecule comprising one single chain antibody and a binding determinant, or a single chain bispecific molecule comprising two binding determinants.

Nonlimiting examples of antibodies that bind to Sclerostin and DKK-1 are disclosed herein. It will be appreciated by one skilled in the art that the antibodies described herein can be employed in the context of the bispecific molecules of the invention.

- 5 Binding of the bispecific molecules to their specific targets can be confirmed by, for example, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (REA), FACS analysis, bioassay (e.g., growth inhibition), or Western Blot assay. Each of these assays generally detects the presence of protein-antibody complexes of particular interest by employing a labeled reagent (e.g., an antibody) specific for the complex of interest.

10

Sclerostin Binding Molecules

- The invention provides sclerostin binding molecules that can be used in the bispecific
15 molecules of the invention. In certain embodiments, the sclerostin binding molecules are antibodies, or fragments thereof. In certain embodiments, the bispecific molecule comprises the VH and/or the VL domain of an immunoglobulin described herein. In other embodiments, the bispecific molecule comprises at least one of light chain CDR1, CDR2, CDR3 and at least one heavy chain CDR1, CDR2, or CDR3. Nonlimiting examples of CDR
20 sequences of sclerostin binding molecules are provided in Table1 herein.

- The sclerostin binding component of the bispecific molecules that are provided can include one, two, three, four, five or six of the CDRs listed in Table 1. It is contemplated that the bispecific molecule can include two or more CDRs from a single antibody, or two or more
25 CDRs from any combination of the antibodies listed above. Some sclerostin binding components include both the light chain CDR3 and the heavy chain CDR3. Certain sclerostin binding components have variant forms of the CDRs listed in Table 1, with one or more (i.e., 2, 3, 4, 5 or 6) of the CDRs each having at least 80%, 85%, 90% or 95% sequence identity to a CDR sequence listed in Table 1. For example, the sclerostin binding
30 components can include both a light chain CDR3 and a heavy chain CDR3 that each have at least 80%, 85%, 90% or 95% sequence identity to the light chain CDR3 sequence and the

heavy chain CDR3, respectively, listed in Table 1. The CDR sequences of some of the sclerostin binding components that are provided may also differ from the CDR sequences listed in Table 1, such that the amino acid sequence for any given CDR differs from the sequence listed in Table 1 by no more than 1, 2, 3, 4 or 5 amino acid residues. Differences
5 from the listed sequences are typically, but not limited to, conservative substitutions.

It is further contemplated that each of the light chains described herein can be combined with any of the heavy chains described herein to form the sclerostin binding component of the bispecific molecule. Certain sclerostin binding components that are provided herein
10 comprise a light chain variable domain comprising a sequence of amino acids that differs from the sequence of a light chain variable domain provided herein at only 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acid residues, wherein each such sequence difference is independently either a deletion, insertion or substitution of one amino acid, or a combination thereof. The light chain variable region in certain sclerostin binding
15 components comprises a sequence of amino acids that has at least 70%, 75%, 80%, 85%, 90%, 95%, 97% or 99% sequence identity to the amino acid sequences of the light chain variable regions provided herein.

Certain sclerostin binding components that are provided herein comprise a heavy chain
20 variable domain comprising a sequence of amino acids that differs from the sequence of a heavy chain variable domain provided herein at only 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acid residues, wherein each such sequence difference is independently either a deletion, insertion or substitution of one amino acid, or a combination thereof. The heavy chain variable region in certain sclerostin binding components comprises a
25 sequence of amino acids that has at least 70%, 75%, 80%, 85%, 90%, 95%, 97% or 99% sequence identity to the amino acid sequences of the heavy chain variable regions provided herein.

In other embodiments, the portion of the bispecific molecule that binds to sclerostin is
30 selected from those sclerostin binding molecules disclosed in U.S. Patent No. 7,744,874, U.S. Patent No. 7,592,429, and U.S. Patent Appl. Publ. No. 2009/0130113. In a specific

embodiment, a DVD-Ig comprising a sclerostin binding VH and VL from the antibodies disclosed in the above patents and patent applications is contemplated.

DKK-1 Binding Agents

5

The invention provides DKK-1 binding molecules that can be used in the bispecific molecules of the invention. In certain embodiments, the DKK-1 binding molecules are antibodies, or fragments thereof. In certain embodiments, the bispecific molecule comprises the VH and/or the VL domain of an immunoglobulin described herein. In other
10 embodiments, the bispecific molecule comprises at least one of light chain CDR1, CDR2, CDR3 and heavy chain CDR1, CDR2, or CDR3. Nonlimiting examples of CDR sequences of DKK-1 binding molecules are provided in Table 1.

The DKK-1 binding component of the bispecific molecules that are provided can include
15 one, two, three, four, five or six of the CDRs listed in Table 1. It is contemplated that the bispecific molecule can include two or more CDRs from a single antibody, or two or more CDRs from any combination of the antibodies listed in Table 1. Some DKK-1 binding components include both the light chain CDR3 and the heavy chain CDR3. Certain DKK-1 binding components have variant forms of the CDRs listed in Table 1, with one or more (i.e.,
20 2, 3, 4, 5 or 6) of the CDRs each having at least 80%, 85%, 90% or 95% sequence identity to a CDR sequence listed in Table 1. For example, the DKK-1 binding components can include both a light chain CDR3 and a heavy chain CDR3 that each have at least 80%, 85%, 90% or 95% sequence identity to the light chain CDR3 sequence and the heavy chain CDR3, respectively, listed in Table 1. The CDR sequences of some of the DKK-1 binding
25 components that are provided may also differ from the CDR sequences listed in Table 1 such that the amino acid sequence for any given CDR differs from the sequence listed in Table 1 by no more than 1, 2, 3, 4 or 5 amino acid residues. Differences from the listed sequences are typically, but not limited to, conservative substitutions.

It is further contemplated that each of the light chains described herein can be combined with any of the heavy chains described herein to form the DKK-1 binding component of the bispecific molecule. Certain DKK-1 binding components that are provided herein comprise a light chain variable domain comprising a sequence of amino acids that differs from the
5 sequence of a light chain variable domain provided herein at only 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acid residues, wherein each such sequence difference is independently either a deletion, insertion or substitution of one amino acid, or a combination thereof. The light chain variable region in certain DKK-1 binding components comprises a sequence of amino acids that has at least 70%, 75%, 80%, 85%, 90%, 95%, 97%
10 or 99% sequence identity to the amino acid sequences of the light chain variable regions provided herein.

Certain DKK-1 binding components that are provided herein comprise a heavy chain variable domain comprising a sequence of amino acids that differs from the sequence of a
15 heavy chain variable domains provided herein at only 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acid residues, wherein each such sequence difference is independently either a deletion, insertion or substitution of one amino acid, or a combination thereof. The heavy chain variable region in certain DKK-1 binding components comprises a sequence of amino acids that has at least 70%, 75%, 80%, 85%, 90%, 95%, 97% or 99%
20 sequence identity to the amino acid sequences of the heavy chain variable regions provided herein.

In other embodiments, the portion of the bispecific molecule that binds to DKK-1 is selected from those DKK-1 binding molecules disclosed in U.S. Patent No. 7,709,611, U.S. Patent Publ. No. 2008/0193449, U.S. Patent No. 7,642,238, U.S. Patent No. 7,700,101, and
25 WO 2007/084344. In a specific embodiment, a DVD-Ig comprising a sclerostin binding VH and VL from the antibodies disclosed in the above patents and patent applications is contemplated.

30

Antibodies and Binding Epitopes

The bispecific binding molecules of the invention can comprise the anti-sclerostin and anti-DKK-1 antibodies and fragments thereof provided herein. The term "antibody" refers to an intact immunoglobulin of any isotype, or a fragment thereof that can compete with the intact antibody for specific binding to the target antigen, and includes, for instance,

5 chimeric, humanized, fully human, and bispecific antibodies. An "antibody" is a species of an antigen binding protein. An intact antibody will generally comprise at least two full-length heavy chains and two full-length light chains, but in some instances can include fewer chains such as antibodies naturally occurring in camelids which can comprise only heavy chains. Antibodies can be derived solely from a single source, or can be "chimeric,"

10 that is, different portions of the antibody can be derived from two different antibodies as described further below. The antigen binding proteins, antibodies, or binding fragments can be produced in hybridomas, by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact antibodies. Unless otherwise indicated, the term "antibody" includes, in addition to antibodies comprising two full-length heavy chains and two full-

15 length light chains, derivatives, variants, fragments, and muteins thereof. Furthermore, unless explicitly excluded, antibodies include monoclonal antibodies, bispecific antibodies, minibodies, domain antibodies, synthetic antibodies (sometimes referred to herein as "antibody mimetics"), chimeric antibodies, humanized antibodies, human antibodies, antibody fusions (sometimes referred to herein as "antibody conjugates"), and fragments

20 thereof, respectively.

Naturally occurring antibody structural units typically comprise a tetramer. Each such tetramer typically is composed of two identical pairs of polypeptide chains, each pair having one full-length "light" (in certain embodiments, about 25 kDa) and one full-length

25 "heavy" chain (in certain embodiments, about 50-70 kDa). The amino-terminal portion of each chain typically includes a variable region of about 100 to 10 or more amino acids that typically is responsible for antigen recognition. The carboxy-terminal portion of each chain typically defines a constant region that can be responsible for effector function. Human light chains are typically classified as kappa and lambda light chains. Heavy chains are

30 typically classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. IgG has several subclasses, including, but not limited to, IgG1, IgG2, IgG3, and IgG4. IgM has subclasses including, but not limited to, IgM1

and IgM2. IgA is similarly subdivided into subclasses including, but not limited to, IgA1 and IgA2. Within full-length light and heavy chains, typically, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. See, e.g., Fundamental Immunology, Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)) (incorporated by reference in its entirety for all purposes). The variable regions of each light/heavy chain pair typically form the antigen binding site.

The variable regions typically exhibit the same general structure of relatively conserved framework regions (FR) joined by three hyper variable regions, also called complementarity determining regions or CDRs. The CDRs from the two chains of each pair typically are aligned by the framework regions, which can enable binding to a specific epitope. From N-terminal to C-terminal, both light and heavy chain variable regions typically comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is typically in accordance with the definitions of Kabat Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md. (1987 and 1991)), or Chothia & Lesk, J. Mol. Biol., 196:901-917 (1987); Chothia et al., Nature, 342:878-883 (1989).

In certain embodiments, an antibody heavy chain binds to an antigen in the absence of an antibody light chain. In certain embodiments, an antibody light chain binds to an antigen in the absence of an antibody heavy chain. In certain embodiments, an antibody binding region binds to an antigen in the absence of an antibody light chain. In certain embodiments, an antibody binding region binds to an antigen in the absence of an antibody heavy chain. In certain embodiments, an individual variable region specifically binds to an antigen in the absence of other variable regions.

In certain embodiments, definitive delineation of a CDR and identification of residues comprising the binding site of an antibody is accomplished by solving the structure of the antibody and/or solving the structure of the antibody-ligand complex. In certain embodiments, that can be accomplished by any of a variety of techniques known to those skilled in the art, such as X-ray crystallography. In certain embodiments, various methods

of analysis can be employed to identify or approximate the CDR regions. Examples of such methods include, but are not limited to, the Kabat definition, the Chothia definition, the AbM definition and the contact definition.

- 5 The Kabat definition is a standard for numbering the residues in an antibody and is typically used to identify CDR regions. See, e.g., Johnson & Wu, *Nucleic Acids Res.*, 28: 214-8 (2000). The Chothia definition is similar to the Kabat definition, but the Chothia definition takes into account positions of certain structural loop regions. See, e.g., Chothia et al., *J. Mol. Biol.*, 196: 901-17 (1986); Chothia et al., *Nature*, 342: 877-83 (1989). The AbM definition
- 10 uses an integrated suite of computer programs produced by Oxford Molecular Group that model antibody structure. See, e.g., Martin et al., *Proc Natl Acad Sci (USA)*, 86:9268-9272 (1989); "AbM™, A Computer Program for Modeling Variable Regions of Antibodies," Oxford, UK; Oxford Molecular, Ltd. The AbM definition models the tertiary structure of an antibody from primary sequence using a combination of knowledge databases and ab initio
- 15 methods, such as those described by Samudrala et al., "Ab Initio Protein Structure Prediction Using a Combined Hierarchical Approach," in *PROTEINS, Structure, Function and Genetics Suppl.*, 3:194-198 (1999). The contact definition is based on an analysis of the available complex crystal structures. See, e.g., MacCallum et al., *J. Mol. Biol.*, 5:732-45 (1996).

20

By convention, the CDR regions in the heavy chain are typically referred to as H1, H2, and H3 and are numbered sequentially in the direction from the amino terminus to the carboxy terminus. The CDR regions in the light chain are typically referred to as L1, L2, and L3 and are numbered sequentially in the direction from the amino terminus to the carboxy

25 terminus.

- The term "light chain" includes a full-length light chain and fragments thereof having sufficient variable region sequence to confer binding specificity. A full-length light chain includes a variable region domain, VL, and a constant region domain, CL. The variable
- 30 region domain of the light chain is at the amino-terminus of the polypeptide. Light chains include kappa chains and lambda chains.

The term "heavy chain" includes a full-length heavy chain and fragments thereof having sufficient variable region sequence to confer binding specificity. A full-length heavy chain includes a variable region domain, VH, and three constant region domains, CH1, CH2, and CH3. The VH domain is at the amino-terminus of the polypeptide, and the CH domains are
5 at the carboxyl-terminus, with the CH3 being closest to the carboxy-terminus of the polypeptide. Heavy chains can be of any isotype, including IgG (including IgG1, IgG2, IgG3 and IgG4 subtypes), IgA (including IgA1 and IgA2 subtypes), IgM and IgE.

When an antibody is said to bind an epitope within specified residues, such as within Dkk-1,
10 for example, what is meant is that the antibody specifically binds to a polypeptide consisting of the specified residues (e.g., a specified segment of Dkk-1). Such an antibody does not necessarily contact every residue within Dkk-1. Nor does every single amino acid substitution or deletion within Dkk-1 necessarily significantly affect binding affinity. Epitope specificity of an antibody can be determined in variety of ways. One approach, for
15 example, involves testing a collection of overlapping peptides of about 15 amino acids spanning the sequence of Dkk-1 and differing in increments of a small number of amino acids (e.g., 3 amino acids). The peptides are immobilized within the wells of a microtiter dish. Immobilization can be effected by biotinylating one terminus of the peptides. Optionally, different samples of the same peptide can be biotinylated at the N and C
20 terminus and immobilized in separate wells for purposes of comparison. This is useful for identifying end-specific antibodies. Optionally, additional peptides can be included terminating at a particular amino acid of interest. This approach is useful for identifying end-specific antibodies to internal fragments of Dkk-1. An antibody or immunologically functional fragment is screened for specific binding to each of the various peptides. The
25 epitope is defined as occurring with a segment of amino acids that is common to all peptides to which the antibody shows specific binding.

Antibodies and functional fragments thereof that bind to a conformational epitope that is located in the carboxy-terminal portion of Dkk-1 are also provided to be used in the
30 bispecific molecules of the invention. The carboxy-terminus of Dkk-1 contains several cysteine residues that form a cluster of disulfide bonds which create several loops. The invention provides antibodies, for use in the bispecific molecules of the invention, that bind

to two of these loops, thereby neutralizing the ability of Dkk-1 to suppress Wnt activity. Exemplary antibodies, for use in the bispecific molecules of the invention, capable of binding to the aforementioned conformational epitope are the monoclonal antibodies 11H10 and 1F11, each of which comprises a light chain and a heavy chain. Further
5 examples for use in the bispecific molecules of the invention can be found in U.S. Patent Appl. No. 61/407,128, filed on October 27, 2010, and International Patent App. No. PCT/US2011/058025, filed on October 27, 2011. The epitope comprising these two loops is formed by disulfide bonds between cysteine residues 220 and 237 of SEQ ID NO: 190 and between cysteine residues 245 and 263 of SEQ ID NO: 190. The body of the two loops that
10 form the epitope thus includes amino acids 221-236 and 246-262 of SEQ ID NO: 190. Segments within this loop that are involved in binding include amino acids 221-229 of SEQ ID NO: 190 and amino acids 246-253 of SEQ ID NO: 190. Thus, certain antibodies and fragments that are provided herein, for use in the bispecific molecules of the invention, specifically bind to the foregoing region(s). Some of the antibodies and fragments, for
15 instance, bind to a peptide comprising or consisting of amino acids 221 to 262 of SEQ ID NO: 190.

Competing Antibodies

20 Antibodies and immunologically functional fragments thereof that are useful in the context of the bispecific binding molecules of the invention that compete with one of the exemplified antibodies or functional fragments for specific binding to Dkk-1 or sclerostin are also provided. Such antibodies and fragments may also bind to the same epitope as one of the exemplified antibodies. Antibodies and fragments that compete with or bind to
25 the same epitope as the exemplified antibody or fragment are expected to show similar functional properties. The exemplified antibodies and fragment include those described herein, including those with the heavy and light chains, variable region domains and CDRs listed herein. In specific embodiments, the invention encompasses bispecific binding molecules, such as the provided DVD-Igs (e.g., SEQ ID NOs 17-92 of the present invention),
30 that comprise the VH and VL of the provided antibodies, and binding molecules that compete for binding with these bispecific binding molecules. The binding competition can

be for DKK-1 and/or sclerostin. Competition assays, such as a Biacore assay, are well known in the art.

Each individual immunoglobulin chain is typically composed of several "immunoglobulin domains," each consisting of roughly 90 to 110 amino acids and having a characteristic folding pattern. These domains are the basic units of which antibody polypeptides are composed. In humans, the IgA and IgD isotypes contain four heavy chains and four light chains; the IgG and IgE isotypes contain two heavy chains and two light chains; and the IgM isotype contains five heavy chains and five light chains. The heavy chain C region typically comprises one or more domains that can be responsible for effector function. The number of heavy chain constant region domains will depend on the isotype. IgG heavy chains, for example, contain three C region domains known as CH1, CH2 and CH3. The antibodies that are provided for use in the bispecific molecules of the invention can have any of these isotypes and subtypes.

The term "variable region" or "variable domain" refers to a portion of the light and/or heavy chains of an antibody, typically including approximately the amino-terminal 120 to 130 amino acids in the heavy chain and about 100 to 110 amino terminal amino acids in the light chain. In certain embodiments, variable regions of different antibodies differ extensively in amino acid sequence even among antibodies of the same species. The variable region of an antibody typically determines specificity of a particular antibody for its target

The term "neutralizing antigen binding protein" or "neutralizing antibody" refers to an antigen binding protein or antibody, respectively, for use in the bispecific molecules of the invention, that binds to a ligand and prevents or reduces the biological effect of that ligand. This can be done, for example, by directly blocking a binding site on the ligand or by binding to the ligand and altering the ligand's ability to bind through indirect means (such as structural or energetic alterations in the ligand). In some embodiments, the term can also denote an antigen binding protein that prevents the protein to which it is bound from performing a biological function. In assessing the binding and/or specificity of an antigen binding protein, e.g., an antibody or immunologically functional fragment thereof, an

antibody or fragment can substantially inhibit binding of a ligand to its binding partner when an excess of antibody reduces the quantity of binding partner bound to the ligand by at least about 1-20, 20-30%, 30-40%, 40-50%, 50-60%, 60-70%, 70-80%, 80-85%, 85-90%, 90-95%, 95-97%, 97-98%, 98-99% or more (as measured in an in vitro competitive binding assay). In some embodiments, the neutralizing ability is characterized and/or described via a competition assay. In some embodiments, the neutralizing ability is described in terms of an IC_{50} or EC_{50} value.

In certain embodiments, the antibodies that are provided for use in the bispecific molecules of the invention have a binding affinity (K_a) for sclerostin or Dkk-1 of at least 10^4 or $10^5/M \times \text{seconds}$ as measured by techniques well known in the art (e.g. Biacore or KinExA). Other antibodies have a K_a of at least 10^6 , 10^7 , 10^8 or $10^9/M \times \text{seconds}$. Certain antibodies that are provided have a low disassociation rate. Some antibodies, for instance, have a K_{off} of $1 \times 10^{-4}s^{-1}$, $1 \times 10^{-5}s^{-1}$ or lower.

Monoclonal antibodies may be produced using any technique known in the art, e.g., by immortalizing spleen cells harvested from the transgenic animal after completion of the immunization schedule. The spleen cells can be immortalized using any technique known in the art, e.g., by fusing them with myeloma cells to produce hybridomas. Myeloma cells for use in hybridoma-producing fusion procedures preferably are non-antibody-producing, have high fusion efficiency, and enzyme deficiencies that render them incapable of growing in certain selective media which support the growth of only the desired fused cells (hybridomas). Examples of suitable cell lines for use in mouse fusions include Sp-20, P3-X63/Ag8, P3-X63-Ag8.653, NS1/1.Ag 4 1, Sp210-Ag14, FO, NSO/U, MPC-11, MPC11-X45-GTG 1.7 and S194/5XXO Bul; examples of cell lines used in rat fusions include R210.RCY3, Y3-Ag 1.2.3, IR983F and 4B210. Other cell lines useful for cell fusions are U-266, GM1500-GRG2, LICR-LON-HMy2 and UC729-6.

In some instances, a hybridoma cell line is produced by immunizing an animal (e.g., a transgenic animal having human immunoglobulin sequences) with a Dkk-1 immunogen; harvesting spleen cells from the immunized animal; fusing the harvested spleen cells to a myeloma cell line, thereby generating hybridoma cells; establishing hybridoma cell lines

from the hybridoma cells, and identifying a hybridoma cell line that produces an antibody that binds a Dkk-1 polypeptide. Such hybridoma cell lines, and anti-Dkk-1 monoclonal antibodies produced by them, are encompassed by the present invention.

- 5 Monoclonal antibodies secreted by a hybridoma cell line can be purified using any useful technique known in the antibody arts. Hybridomas or mAbs may be further screened to identify mAbs with particular properties, such as the ability to block a Wnt induced activity. Examples of such screens are provided in the examples below.
- 10 Chimeric and humanized antibodies based upon the foregoing sequences are also provided. Monoclonal antibodies for use as therapeutic agents may be modified in various ways prior to use. One example is a "chimeric" antibody, which is an antibody composed of protein segments from different antibodies that are covalently joined to produce functional immunoglobulin light or heavy chains or immunologically functional portions thereof.
- 15 Generally, a portion of the heavy chain and/or light chain is identical with or homologous to a corresponding sequence in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is/are identical with or homologous to a corresponding sequence in antibodies derived from another species or belonging to another antibody class or subclass. For methods relating to
- 20 chimeric antibodies, see, for example, U.S. Pat. No. 4,816,567; and Morrison et al., Proc. Natl. Acad. Sci. USA 81:6851-6855 (1985). CDR grafting is described, for example, in U.S. Pat. Nos. 6,180,370, 5,693,762, 5,693,761, 5,585,089, and 5,530,101.

- Generally, the goal of making a chimeric antibody is to create a chimera in which the
- 25 number of amino acids from the intended patient species is maximized. One example is the "CDR-grafted" antibody, in which the antibody comprises one or more complementarity determining regions (CDRs) from a particular species or belonging to a particular antibody class or subclass, while the remainder of the antibody chain(s) is/are identical with or homologous to a corresponding sequence in antibodies derived from
- 30 another species or belonging to another antibody class or subclass. For use in humans, the V region or selected CDRs from a rodent antibody often are grafted into a human antibody, replacing the naturally-occurring V regions or CDRs of the human antibody.

One useful type of chimeric antibody is a "humanized" antibody. Generally, a humanized antibody is produced from a monoclonal antibody raised initially in a non-human animal. Certain amino acid residues in this monoclonal antibody, typically from non-antigen
5 recognizing portions of the antibody, are modified to be homologous to corresponding residues in a human antibody of corresponding isotype. Humanization can be performed, for example, using various methods by substituting at least a portion of a rodent variable region for the corresponding regions of a human antibody (see, e.g., U.S. Pat. Nos. 5,585,089, and 5,693,762; Jones et al., 1986, *Nature* 321:522-25; Riechmann et al., 1988,
10 *Nature* 332:323-27; Verhoeyen et al., 1988, *Science* 239:1534-36). In certain embodiments, constant regions from species other than human can be used along with the human variable region(s) to produce hybrid antibodies.

Fully human antibodies are also provided. Methods are available for making fully human
15 antibodies specific for a given antigen without exposing human beings to the antigen ("fully human antibodies"). One means for implementing the production of fully human antibodies is the "humanization" of the mouse humoral immune system. Introduction of human immunoglobulin (Ig) loci into mice in which the endogenous Ig genes have been inactivated is one means of producing fully human monoclonal antibodies (MAbs) in
20 mouse, an animal that can be immunized with any desirable antigen. Using fully human antibodies can minimize the immunogenic and allergic responses that can sometimes be caused by administering mouse or mouse-derivatized Mabs to humans as therapeutic agents.

25 Fully human antibodies can be produced by immunizing transgenic animals (usually mice) that are capable of producing a repertoire of human antibodies in the absence of endogenous immunoglobulin production. Antigens for this purpose typically have six or more contiguous amino acids, and optionally are conjugated to a carrier, such as a hapten. See, for example, Jakobovits et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:2551-2555;
30 Jakobovits et al., 1993, *Nature* 362:255-258; and Bruggermann et al., 1993, *Year in Immunol.* 7:33. In one example of such a method, transgenic animals are produced by incapacitating the endogenous mouse immunoglobulin loci encoding the mouse heavy and

light immunoglobulin chains therein, and inserting into the mouse genome large fragments of human genome DNA containing loci that encode human heavy and light chain proteins. Partially modified animals, which have less than the full complement of human immunoglobulin loci, are then cross-bred to obtain an animal having all of the desired immune system modifications. When administered an immunogen, these transgenic animals produce antibodies that are immunospecific for the immunogen but have human rather than murine amino acid sequences, including the variable regions. For further details of such methods, see, for example, WO96/33735 and WO94/02602. Additional methods relating to transgenic mice for making human antibodies are described in U.S. Pat. Nos. 5,545,807; 6,713,610; 6,673,986; 6,162,963; 5,545,807; 6,300,129; 6,255,458; 5,877,397; 5,874,299 and 5,545,806; in PCT publications WO91/10741, WO90/04036, and in EP 546073B1 and EP 546073A1.

The transgenic mice described above, referred to herein as "HuMab" mice, contain a human immunoglobulin gene minilocus that encodes unrearranged human heavy (μ and γ) and kappa light chain immunoglobulin sequences, together with targeted mutations that inactivate the endogenous μ and κ chain loci (Lonberg et al., 1994, Nature 368: 856-859). Accordingly, the mice exhibit reduced expression of mouse IgM or κ and in response to immunization, and the introduced human heavy and light chain transgenes undergo class switching and somatic mutation to generate high affinity human IgG κ monoclonal antibodies (Lonberg et al., supra.; Lonberg and Huszar, 1995, Intern. Rev. Immunol., 13: 65-93; Harding and Lonberg, 1995, Ann. N.Y Acad. Sci 764: 536-546). The preparation of HuMab mice is described in detail in Taylor et al., 1992, Nucleic Acids Research, 20: 6287-6295; Chen et al., 1993, International Immunology 5: 647-656; Tuailon et al., 1994, J. Immunol. 152: 2912-2920; Lonberg et al., 1994, Nature 368: 856-859; Lonberg, 1994, Handbook of Exp. Pharmacology 113: 49-101; Taylor et al., 1994, International Immunology 6: 579-591; Lonberg and Huszar, 1995, Intern. Rev. Immunol. 13: 65-93; Harding and Lonberg, 1995, Ann. N.Y Acad. Sci. 764: 536-546; Fishwild et al., 1996, Nature Biotechnology 14: 845-851. See further U.S. Pat. Nos. 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,789,650; 5,877,397; 5,661,016; 5,814,318; 5,874,299; and 5,770,429; as well as U.S. Pat. No. 5,545,807; International Publication Nos. WO 93/1227; WO 92/22646; and WO 92/03918. Technologies utilized for producing human antibodies in

these transgenic mice are disclosed also in WO 98/24893, and Mendez et al., 1997, Nature Genetics 15: 146-156. For example, the HCO7 and HCO12 transgenic mice strains can be used to generate binding agents suitable for use herein.

- 5 Using hybridoma technology, antigen-specific human MAbs with the desired specificity can be produced and selected from the transgenic mice such as those described above. Such antibodies may be cloned and expressed using a suitable vector and host cell, or the antibodies can be harvested from cultured hybridoma cells.
- 10 Fully human antibodies can also be derived from phage-display libraries (as disclosed in Hoogenboom et al., 1991, J. Mol. Biol. 227:381; and Marks et al., 1991, J. Mol. Biol. 222:581). Phage display techniques mimic immune selection through the display of antibody repertoires on the surface of filamentous bacteriophage, and subsequent selection of phage by their binding to an antigen of choice. One such technique is described
- 15 in PCT Publication No. WO99/10494, which describes the isolation of high affinity and functional agonistic antibodies for MPL- and msk-receptors using such an approach.

- The bispecific molecules provided herein may also block or reduce binding between sclerostin and/or Dkk-1 and LRP5 and/or LRP6, thereby stimulating at least one activity
- 20 associated with Wnt signaling.

- Nucleic acids molecules, vectors, and host cells useful in the production of the antibodies and selective binding agents are also provided. Certain bispecific molecules or fragments include one, two, three, four, five or all six of the anti-sclerostin or anti-DKK-1 antibody
- 25 CDRs listed in Table 1, and in certain embodiments a bispecific binding molecule will comprise a total of twelve CDRs (6 from a VH and 6 from a VL).

- Pharmaceutical compositions that include any of the foregoing bispecific molecules and fragments are also provided. Such compositions typically also include a buffer, a
- 30 pharmaceutically acceptable diluent, a carrier, a solubilizer, an emulsifier or a preservative. The use of the foregoing antibodies and fragments in the preparation of a pharmaceutical composition or medicament is also provided.

Variants

Some of the antibodies or fragments that are provided for use in the bispecific molecules of the invention are variant forms of the antibodies and fragments disclosed above (e.g.,
5 those having the sequences listed in Table 1). For instance, some of the antibodies or fragments are ones having one or more conservative amino acid substitutions in one or more of the heavy or light chains, variable regions or CDRs listed in Table 1.

Naturally-occurring amino acids may be divided into classes based on common side chain
10 properties: 1) hydrophobic: norleucine, Met, Ala, Val, Leu, Ile; 2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln; 3) acidic: Asp, Glu; 4) basic: His, Lys, Arg; 5) residues that influence chain orientation: Gly, Pro; and 6) aromatic: Trp, Tyr, Phe. Conservative amino acid substitutions may involve exchange of a member of one of these classes with another member of the same class. Conservative amino acid substitutions may encompass non-naturally occurring
15 amino acid residues, which are typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems. These include peptidomimetics and other reversed or inverted forms of amino acid moieties.

Non-conservative substitutions may involve the exchange of a member of one of the above
20 classes for a member from another class. Such substituted residues may be introduced into regions that are homologous with human corresponding sequences, or into the non-homologous regions of the molecule.

In making such changes, according to certain embodiments, the hydropathic index of amino
25 acids may be considered. The hydropathic profile of a protein is calculated by assigning each amino acid a numerical value ("hydropathy index") and then repetitively averaging these values along the peptide chain. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics. They are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5);
30 methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

The importance of the hydropathic profile in conferring interactive biological function on a protein is understood in the art (see, for example, Kyte et al., 1982, J. Mol. Biol. 157:105-131). It is known that certain amino acids may be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. In making changes based upon the hydropathic index, in certain embodiments, the substitution of amino acids whose hydropathic indices are within ± 2 is included. In some aspects of the invention, those which are within ± 1 are included, and in other aspects of the invention, those within ± 0.5 are included.

10

It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity, particularly where the biologically functional protein or peptide thereby created is intended for use in immunological embodiments, as in the present case. In certain embodiments, the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with its immunogenicity and antigen-binding or immunogenicity, that is, with a biological property of the protein.

The following hydrophilicity values have been assigned to these amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 ± 1); glutamate (+3.0 ± 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5 ± 1); alanine (-0.5); histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5) and tryptophan (-3.4). In making changes based upon similar hydrophilicity values, in certain embodiments, the substitution of amino acids whose hydrophilicity values are within ± 2 is included, in other embodiments, those which are within ± 1 are included, and in still other embodiments, those within ± 0.5 are included. In some instances, one may also identify epitopes from primary amino acid sequences on the basis of hydrophilicity. These regions are also referred to as "epitopic core regions."

30

A skilled artisan will be able to determine suitable variants of polypeptides as set forth herein using well-known techniques. One skilled in the art may identify suitable areas of

the molecule that may be changed without destroying activity by targeting regions not believed to be important for activity. The skilled artisan also will be able to identify residues and portions of the molecules that are conserved among similar polypeptides. In further embodiments, even areas that may be important for biological activity or for structure may be subject to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the polypeptide structure.

Additionally, one skilled in the art can review structure-function studies identifying residues in similar polypeptides that are important for activity or structure. In view of such a comparison, one can predict the importance of amino acid residues in a protein that correspond to amino acid residues important for activity or structure in similar proteins. One skilled in the art may opt for chemically similar amino acid substitutions for such predicted important amino acid residues.

A number of scientific publications have been devoted to the prediction of secondary structure. See Moulton, 1996, Curr. Op. in Biotech. 7:422-427; Chou et al., 1974, Biochemistry 13:222-245; Chou et al., 1974, Biochemistry 113:211-222; Chou et al., 1978, Adv. Enzymol. Relat. Areas Mol. Biol. 47:45-148; Chou et al., 1979, Ann. Rev. Biochem. 47:251-276; and Chou et al., 1979, Biophys. J. 26:367-384. Moreover, computer programs are currently available to assist with predicting secondary structure. One method of predicting secondary structure is based upon homology modeling. For example, two polypeptides or proteins that have a sequence identity of greater than 30%, or similarity greater than 40% often have similar structural topologies. The recent growth of the protein structural database (PDB) has provided enhanced predictability of secondary structure, including the potential number of folds within a polypeptide's or protein's structure. See Holm et al., 1999, Nucl. Acid. Res. 27:244-247. It has been suggested (Brenner et al., 1997, Curr. Op. Struct. Biol. 7:369-376) that there are a limited number of folds in a given polypeptide or protein and that once a critical number of structures have been resolved, structural prediction will become dramatically more accurate.

Additional methods of predicting secondary structure include "threading" (Jones, 1997, Curr. Opin. Struct. Biol. 7:377-87; Sippl et al., 1996, Structure 4:15-19), "profile analysis"

(Bowie et al., 1991, Science 253:164-170; Gribskov et al., 1990, Meth. Enzym. 183:146-159; Gribskov et al., 1987, Proc. Nat. Acad. Sci. 84:4355-4358), and "evolutionary linkage" (See Holm, 1999, supra; and Brenner, 1997, supra).

- 5 In some embodiments of the invention, amino acid substitutions are made that: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter ligand or antigen binding affinities, and/or (4) confer or modify other physicochemical or functional properties on such polypeptides. For example, single or multiple amino acid substitutions (in certain embodiments, conservative
- 10 amino acid substitutions) may be made in the naturally-occurring sequence. Substitutions can be made in that portion of the antibody that lies outside the domain(s) forming intermolecular contacts). In such embodiments, conservative amino acid substitutions can be used that do not substantially change the structural characteristics of the parent sequence (e.g., one or more replacement amino acids that do not disrupt the secondary
- 15 structure that characterizes the parent or native antibody). Examples of art-recognized polypeptide secondary and tertiary structures are described in Proteins, Structures and Molecular Principles (Creighton, Ed.), 1984, W. H. New York: Freeman and Company; Introduction to Protein Structure (Branden and Tooze, eds.), 1991, New York: Garland Publishing; and Thornton et al., 1991, Nature 354: 105, which are each incorporated herein
- 20 by reference.

- The invention also encompasses glycosylation variants of the bispecific molecules of the invention wherein the number and/or type of glycosylation site(s) has been altered compared to the amino acid sequences of the parent polypeptide. In certain
- 25 embodiments, antibody protein variants comprise a greater or a lesser number of N-linked glycosylation sites than the native antibody. An N-linked glycosylation site is characterized by the sequence: Asn-X-Ser or Asn-X-Thr, wherein the amino acid residue designated as X may be any amino acid residue except proline. The substitution of amino acid residues to create this sequence provides a potential new site for the addition of an N-linked
- 30 carbohydrate chain. Alternatively, substitutions that eliminate or alter this sequence will prevent addition of an N-linked carbohydrate chain present in the native polypeptide. For example, the glycosylation can be reduced by the deletion of an Asn or by substituting the

Asn with a different amino acid. In other embodiments, one or more new N-linked sites are created. Antibodies typically have a N-linked glycosylation site in the Fc region.

Additional variants include cysteine variants wherein one or more cysteine residues in the parent or native amino acid sequence are deleted from or substituted with another amino acid (e.g., serine). Cysteine variants are useful, inter alia when antibodies must be refolded into a biologically active conformation. Cysteine variants may have fewer cysteine residues than the native antibody, and typically have an even number to minimize interactions resulting from unpaired cysteines.

Mimetics (e.g., peptide mimetics" or "peptidomimetics") based upon the variable region domains and CDRs that are described herein are also provided. These analogs can be peptides, non-peptides or combinations of peptide and non-peptide regions. Fauchere, 1986, Adv. Drug Res. 15: 29; Veber and Freidinger, 1985, TINS p. 392; and Evans et al., 1987, J. Med. Chem. 30: 1229, which are incorporated herein by reference for any purpose. Peptide mimetics that are structurally similar to therapeutically useful peptides may be used to produce a similar therapeutic or prophylactic effect. Such compounds are often developed with the aid of computerized molecular modeling. Generally, peptidomimetics of the invention are proteins that are structurally similar to an antibody displaying a desired biological activity, such as here the ability to specifically bind Dkk-1, but have one or more peptide linkages optionally replaced by a linkage selected from: --CH₂NH--, --CH₂S--, --CH₂--CH₂--, --CH--CH-(cis and trans), --COCH₂--, --CH(OH)CH₂--, and --CH₂SO--, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (e.g., D-lysine in place of L-lysine) may be used in certain embodiments of the invention to generate more stable proteins. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation may be generated by methods known in the art (Rizo and Gierasch, 1992, Ann. Rev. Biochem. 61: 387), incorporated herein by reference), for example, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

Derivatives of the antibodies and fragments for use in the bispecific molecules of the invention that are described herein are also provided. The derivatized antibody or fragment may comprise any molecule or substance that imparts a desired property to the antibody or fragment, such as increased half-life in a particular use. The derivatized antibody can

5 comprise, for example, a detectable (or labeling) moiety (e.g., a radioactive, colorimetric, antigenic or enzymatic molecule, a detectable bead (such as a magnetic or electrodeposited (e.g., gold) bead), or a molecule that binds to another molecule (e.g., biotin or streptavidin)), a therapeutic or diagnostic moiety (e.g., a radioactive, cytotoxic, or pharmaceutically active moiety), or a molecule that increases the suitability of the antibody

10 for a particular use (e.g., administration to a subject, such as a human subject, or other in vivo or in vitro uses). Examples of molecules that can be used to derivatize an antibody include albumin (e.g., human serum albumin) and polyethylene glycol (PEG). Albumin-linked and PEGylated derivatives of antibodies can be prepared using techniques well known in the art. In one embodiment, the antibody is conjugated or otherwise linked to

15 transthyretin (TTR) or a TTR variant. The TTR or TTR variant can be chemically modified with, for example, a chemical selected from the group consisting of dextran, poly(n-vinyl pyrrolidone), polyethylene glycols, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohols.

20 Other derivatives include covalent or aggregative conjugates of bispecific molecules, or fragments thereof, with other proteins or polypeptides, such as by expression of recombinant fusion proteins comprising heterologous polypeptides fused to the N-terminus or C-terminus of a bispecific molecule polypeptide. For example, the conjugated peptide may be a heterologous signal (or leader) polypeptide, e.g., the yeast alpha-factor

25 leader, or a peptide such as an epitope tag. Bispecific molecule-containing fusion proteins can comprise peptides added to facilitate purification or identification of the molecule (e.g., poly-His). A bispecific molecule polypeptide also can be linked to the FLAG peptide as described in Hopp et al., Bio/Technology 6:1204, 1988, and U.S. Pat. No. 5,011,912. The FLAG peptide is highly antigenic and provides an epitope reversibly bound by a specific

30 monoclonal antibody (mAb), enabling rapid assay and facile purification of expressed recombinant protein. Reagents useful for preparing fusion proteins in which the FLAG peptide is fused to a given polypeptide are commercially available (Sigma, St. Louis, Mo.).

The term "Fc polypeptide" as used herein includes native and mutein forms of polypeptides derived from the Fc region of an antibody. Truncated forms of such polypeptides containing the hinge region that promotes dimerization also are included. Fusion proteins comprising
5 Fc moieties (and oligomers formed therefrom) offer the advantage of facile purification by affinity chromatography over Protein A or Protein G columns.

One suitable Fc polypeptide, described in PCT application WO 93/10151 and U.S. Pat. Nos. 5,426,048 and 5,262,522 (each of which is hereby incorporated by reference), is a single
10 chain polypeptide extending from the N-terminal hinge region to the native C-terminus of the Fc region of a human IgG1 antibody. Another useful Fc polypeptide is the Fc mutein described in U.S. Pat. No. 5,457,035 and in Baum et al., 1994, EMBO J. 13:3992-4001. The amino acid sequence of this mutein is identical to that of the native Fc sequence presented in WO 93/10151, except that amino acid 19 has been changed from Leu to Ala, amino acid
15 20 has been changed from Leu to Glu, and amino acid 22 has been changed from Gly to Ala. The mutein exhibits reduced affinity for Fc receptors.

In other embodiments, the variable portion of the heavy and/or light chains of a bispecific molecule such as disclosed herein may be substituted for the variable portion of an
20 antibody heavy and/or light chain.

Alternatively, the oligomer is a fusion protein comprising multiple bispecific molecule polypeptides, with or without peptide linkers (spacer peptides). Among the suitable peptide linkers are those described in U.S. Pat. Nos. 4,751,180 and 4,935,233.

25

Another method for preparing oligomeric bispecific molecule derivatives involves use of a leucine zipper. Leucine zipper domains are peptides that promote oligomerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., 1988, Science 240:1759), and have since been found in
30 a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble oligomeric proteins are described in PCT application

- WO 94/10308, and the leucine zipper derived from lung surfactant protein D (SPD) described in Hoppe et al., 1994, FEBS Letters 344:191, hereby incorporated by reference. The use of a modified leucine zipper that allows for stable trimerization of a heterologous protein fused thereto is described in Fanslow et al., 1994, Semin. Immunol. 6:267-78. In
- 5 one approach, recombinant fusion proteins comprising a bispecific molecule fragment or derivative fused to a leucine zipper peptide are expressed in suitable host cells, and the soluble oligomeric bispecific molecule fragments or derivatives that form are recovered from the culture supernatant.
- 10 In another aspect, the present invention provides a bispecific molecule having a half-life of at least one day in vitro or in vivo (e.g., when administered to a human subject). In one embodiment, the antibody has a half-life of at least three days. In another embodiment, the antibody or portion thereof has a half-life of four days or longer. In another
- 15 embodiment, the antibody or portion thereof has a half-life of eight days or longer. In another embodiment, the antibody or antigen-binding portion thereof is derivatized or modified such that it has a longer half-life as compared to the underivatized or unmodified antibody. In another embodiment, the antibody contains point mutations to increase serum half life, such as described in WO 00/09560.
- 20 Nucleic acids that encode the polypeptide chains of a bispecific molecule of the invention, or a fragment, derivative, mutein, or variant thereof, polynucleotides sufficient for use as hybridization probes, PCR primers or sequencing primers for identifying, analyzing, mutating or amplifying a polynucleotide encoding a polypeptide, anti-sense nucleic acids for inhibiting expression of a polynucleotide, and complementary sequences of the
- 25 foregoing are also provided. The nucleic acids can be any length. They can be, for example, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 450, 500, 750, 1,000, 1,500, 3,000, 5,000 or more nucleotides in length, and/or can comprise one or more additional sequences, for example, regulatory sequences, and/or be part of a larger nucleic acid, for example, a vector. The nucleic acids can be single-stranded or
- 30 double-stranded and can comprise RNA and/or DNA nucleotides, and artificial variants thereof (e.g., peptide nucleic acids).

- DNA encoding antibody polypeptides (e.g., heavy or light chain, variable domain only, or full length) may be isolated from B-cells of mice that have been immunized with Dkk-1 or sclerostin or an immunogenic fragment thereof. The DNA may be isolated by conventional procedures such as polymerase chain reaction (PCR). Phage display is another example of a
- 5 known technique whereby derivatives of antibodies may be prepared. In one approach, polypeptides that are components of an antibody of interest are expressed in any suitable recombinant expression system, and the expressed polypeptides are allowed to assemble to form antibody molecules.
- 10 The invention further provides nucleic acids that hybridize to other nucleic acids under particular hybridization conditions. Methods for hybridizing nucleic acids are well-known in the art. See, e.g., Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. As defined herein, a moderately stringent hybridization condition uses a prewashing solution containing 5.times. sodium chloride/sodium citrate (SSC), 0.5% SDS,
- 15 1.0 mM EDTA (pH 8.0), hybridization buffer of about 50% formamide, 6x SSC, and a hybridization temperature of 55° C. (or other similar hybridization solutions, such as one containing about 50% formamide, with a hybridization temperature of 42° C.), and washing conditions of 60° C, in 0.5x SSC, 0.1% SDS. A stringent hybridization condition hybridizes in 6x SSC at 45° C, followed by one or more washes in 0.1x SSC, 0.2% SDS at 68° C.
- 20 Furthermore, one of skill in the art can manipulate the hybridization and/or washing conditions to increase or decrease the stringency of hybridization such that nucleic acids comprising nucleotide sequences that are at least 65, 70, 75, 80, 85, 90, 95, 98 or 99% identical to each other typically remain hybridized to each other.
- 25 The basic parameters affecting the choice of hybridization conditions and guidance for devising suitable conditions are set forth by, for example, Sambrook, Fritsch, and Maniatis (1989, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., chapters 9 and 11; and Current Protocols in Molecular Biology, 1995, Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4), and can be readily
- 30 determined by those having ordinary skill in the art based on, for example, the length and/or base composition of the DNA.

Changes can be introduced by mutation into a nucleic acid, thereby leading to changes in the amino acid sequence of a polypeptide that it encodes. Mutations can be introduced using any technique known in the art. In one embodiment, one or more particular amino acid residues are changed using, for example, a site-directed mutagenesis protocol. In
5 another embodiment, one or more randomly selected residue is changed using, for example, a random mutagenesis protocol. However it is made, a mutant polypeptide can be expressed and screened for a desired property.

Mutations can be introduced into a nucleic acid without significantly altering the biological
10 activity of a polypeptide that it encodes. For example, one can make nucleotide substitutions leading to amino acid substitutions at non-essential amino acid residues. Alternatively, one or more mutations can be introduced into a nucleic acid that selectively change the biological activity of a polypeptide that it encodes. For example, the mutation can quantitatively or qualitatively change the biological activity. Examples of quantitative
15 changes include increasing, reducing or eliminating the activity. Examples of qualitative changes include changing the antigen specificity of an antibody.

Conservative modifications may be made to the heavy and light chains described in (and corresponding modifications to the encoding nucleic acids) to produce a bispecific molecule
20 having functional and biochemical characteristics. Methods for achieving such modifications are described above.

The single chain antibodies that are contemplated for use with the bispecific molecules of the invention may be formed by linking heavy and light chain variable domain (Fv region)
25 fragments provided herein via an amino acid bridge (short peptide linker), resulting in a single polypeptide chain. Such single-chain Fvs (scFvs) may be prepared by fusing DNA encoding a peptide linker between DNAs encoding the two variable domain polypeptides (VL and VH). The resulting polypeptides can fold back on themselves to form antigen-binding monomers, or they can form multimers (e.g., dimers, trimers, or tetramers),
30 depending on the length of a flexible linker between the two variable domains (Kortt et al., 1997, Prot. Eng. 10:423; Kortt et al., 2001, Biomol. Eng. 18:95-108). By combining different VL and VH-comprising polypeptides, one can form multimeric scFvs that bind to different

epitopes (Kriangkum et al., 2001, *Biomol. Eng.* 18:31-40). Techniques developed for the production of single chain antibodies include those described in U.S. Pat. No. 4,946,778; Bird, 1988, *Science* 242:423; Huston et al., 1988, *Proc. Natl. Acad. Sci. USA* 85:5879; Ward et al., 1989, *Nature* 334:544; de Graaf et al., 2002, *Methods Mol Biol.* 178:379-87.

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Proteins and functional fragments thereof according to the invention may be further modified in various ways. For example, if they are to be used for therapeutic purposes, they may be conjugated with polyethylene glycol (pegylated) to prolong the serum half-life or to enhance protein delivery. Alternatively, the V region of the subject antibodies or fragments thereof may be fused with the Fc region of a different antibody molecule. The Fc region used for this purpose may be modified so that it does not bind complement, thus reducing the likelihood of inducing cell lysis in the patient when the fusion protein is used as a therapeutic agent. In addition, the subject antibodies or functional fragments thereof may be conjugated with human serum albumin to enhance the serum half-life of the antibody or fragment thereof. Another useful fusion partner for the inventive antibodies or fragments thereof is transthyretin (TTR). TTR has the capacity to form a tetramer, thus an antibody-TTR fusion protein can form a multivalent antibody which may increase its binding avidity.

Alternatively, substantial modifications in the functional and/or biochemical characteristics of the antibodies and fragments described herein may be achieved by creating substitutions in the amino acid sequence of the heavy and light chains that differ significantly in their effect on maintaining (a) the structure of the molecular backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulkiness of the side chain. A "conservative amino acid substitution" may involve a substitution of a native amino acid residue with a nonnative residue that has little or no effect on the polarity or charge of the amino acid residue at that position. Furthermore, any native residue in the polypeptide may also be substituted with alanine, as has been previously described for alanine scanning mutagenesis.

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Amino acid substitutions (whether conservative or non-conservative) of the subject antibodies can be implemented by those skilled in the art by applying routine techniques.

Amino acid substitutions can be used to identify important residues of the antibodies or bispecific molecules of the invention provided herein, or to increase or decrease the affinity of these antibodies or bispecific molecules of the invention for human Dkk-1 or sclerostin or for modifying the binding affinity of other bispecific molecules described herein.

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Expression

The bispecific molecules and functional fragments can be prepared by any of a number of conventional techniques to express the nucleic acid sequences provided in Table 1, or to express an nucleic acid sequence that encodes any of the amino acid sequences provided in

10 Table 1.

For example, bispecific molecules may be produced by recombinant expression systems, using any technique known in the art. See, for example, Monoclonal Antibodies, Hybridomas: A New Dimension in Biological Analyses, Kennet et al. (eds.) Plenum Press, New York (1980); and Antibodies: A Laboratory Manual, Harlow and Lane (eds.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1988).

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Bispecific molecules of the present invention can be expressed in hybridoma cell lines or in cell lines other than hybridomas. Expression constructs encoding the antibodies can be used to transform a mammalian, insect or microbial host cell. Transformation can be performed using any known method for introducing polynucleotides into a host cell, including, for example packaging the polynucleotide in a virus or bacteriophage and transducing a host cell with the construct by transfection procedures known in the art, as exemplified by U.S. Pat. Nos. 4,399,216, 4,912,040, 4,740,461, and 4,959,455. The optimal transformation procedure used will depend upon which type of host cell is being transformed. Methods for introduction of heterologous polynucleotides into mammalian cells are well known in the art and include, but are not limited to, dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, mixing nucleic acid with positively-charged lipids, and direct microinjection of the DNA into nuclei.

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Recombinant expression constructs of the invention typically comprise a nucleic acid molecule encoding a polypeptide comprising one or more of the following: a heavy chain constant region (e.g., CH1, CH2 and/or CH3); a heavy chain variable region, and optionally, at least two or more heavy chain variable regions; a light chain constant region; a light chain variable region, and optionally, at least two or more light chain variable regions; one or more CDRs of the light or heavy chain of the bispecific molecule; and optionally a linker sequence between multiple variable regions. These nucleic acid sequences are inserted into an appropriate expression vector using standard ligation techniques. In some embodiments, vectors are used that employ protein-fragment complementation assays using protein reporters, such as dihydrofolate reductase (see, for example, U.S. Pat. No. 6,270,964). Suitable expression vectors can be purchased, for example, from Invitrogen Life Technologies or BD Biosciences (formerly "Clontech"). Other useful vectors for cloning and expressing the antibodies and fragments of the invention include those described in Bianchi and McGrew, *Biotech Bioengineer* 84(4):439-44 (2003). Additional suitable expression vectors are discussed, for example, in *Methods Enzymol*, vol. 185 (D. V. Goeddel, ed.), 1990, New York: Academic Press, which is hereby incorporated by reference.

Typically, expression vectors used in any of the host cells contain sequences for plasmid or virus maintenance and for cloning and expression of exogenous nucleotide sequences. Such sequences, collectively referred to as "flanking sequences" typically include one or more of the following operatively linked nucleotide sequences: a promoter, one or more enhancer sequences, an origin of replication, a transcriptional termination sequence, a complete intron sequence containing a donor and acceptor splice site, a sequence encoding a leader sequence for polypeptide secretion, a ribosome binding site, a polyadenylation sequence, a polylinker region for inserting the nucleic acid encoding the polypeptide to be expressed, and a selectable marker element.

Optionally, the vector may contain a "tag"-encoding sequence, that is, an oligonucleotide molecule located at the 5' or 3' end of the coding sequence, the oligonucleotide sequence encoding polyHis (such as hexaHis), or another "tag" for which commercially available antibodies exist, such as FLAG®, HA (hemagglutinin from influenza virus), or myc. The tag is typically fused to the antibody protein upon expression, and can serve as a means for

affinity purification of the antibody from the host cell. Affinity purification can be accomplished, for example, by column chromatography using antibodies against the tag as an affinity matrix. Optionally, the tag can subsequently be removed from the purified antibody polypeptide by various means such as using certain peptidases for cleavage.

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Flanking sequences in the expression vector may be homologous (i.e., from the same species and/or strain as the host cell), heterologous (i.e., from a species other than the host cell species or strain), hybrid (i.e., a combination of flanking sequences from more than one source), synthetic or native. As such, the source of a flanking sequence may be any
10 prokaryotic or eukaryotic organism, any vertebrate or invertebrate organism, or any plant, provided that the flanking sequence is functional in, and can be activated by, the host cell machinery.

Flanking sequences useful in the vectors of this invention may be obtained by any of
15 several methods well known in the art. Typically, flanking sequences useful herein will have been previously identified by mapping and/or by restriction endonuclease digestion and can thus be isolated from the proper tissue source using the appropriate restriction endonucleases. In some cases, the full nucleotide sequence of a flanking sequence may be known. Here, the flanking sequence may be synthesized using the methods described
20 herein for nucleic acid synthesis or cloning.

Where all or only a portion of the flanking sequence is known, it may be obtained using PCR and/or by screening a genomic library with a suitable oligonucleotide and/or flanking sequence fragment from the same or another species. Where the flanking sequence is not
25 known, a fragment of DNA containing a flanking sequence may be isolated from a larger piece of DNA that may contain, for example, a coding sequence or even another gene or genes. Isolation may be accomplished by restriction endonuclease digestion to produce the proper DNA fragment followed by isolation using agarose gel purification, Qiagen.RTM. column chromatography (Chatsworth, Calif.), or other methods known to the skilled
30 artisan. The selection of suitable enzymes to accomplish this purpose will be readily apparent to those skilled in the art.

An origin of replication is typically a part of prokaryotic expression vectors, particularly those purchased commercially, and the origin aids in the amplification of the vector in a host cell. If the vector of choice does not contain an origin of replication site, one may be chemically synthesized based on a known sequence, and ligated into the vector. For
5 example, the origin of replication from the plasmid pBR322 (New England Biolabs, Beverly, Mass.) is suitable for most gram-negative bacteria and various origins (e.g., SV40, polyoma, adenovirus, vesicular stomatitis virus (VSV), or papillomaviruses such as HPV or BPV) are useful for cloning vectors in mammalian cells. Generally, a mammalian origin of replication is not needed for mammalian expression vectors (for example, the SV40 origin is often used
10 only because it contains the early promoter).

The expression and cloning vectors of the present invention will typically contain a promoter that is recognized by the host organism and operably linked to nucleic acid encoding the bispecific molecule or immunologically functional fragment thereof
15 Promoters are untranscribed sequences located upstream (i.e., 5') to the start codon of a structural gene (generally within about 100 to 1000 bp) that control transcription of the structural gene. Promoters are conventionally grouped into one of two classes: inducible promoters and constitutive promoters. Inducible promoters initiate increased levels of transcription from DNA under their control in response to some change in culture
20 conditions, such as the presence or absence of a nutrient or a change in temperature. Constitutive promoters, on the other hand, initiate continuous gene product production; that is, there is little or no experimental control over gene expression. A large number of promoters, recognized by a variety of potential host cells, are well known. A suitable promoter is operably linked to the DNA encoding bispecific molecule by removing the
25 promoter from the source DNA by restriction enzyme digestion or amplifying the promoter by polymerase chain reaction and inserting the desired promoter sequence into the vector.

Suitable promoters for use with yeast hosts are also well known in the art. Yeast enhancers are advantageously used with yeast promoters. Suitable promoters for use with
30 mammalian host cells are well known and include, but are not limited to, those obtained from the genomes of viruses such as polyoma virus, fowlpox virus, adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, retroviruses,

hepatitis-B virus and -most preferably Simian Virus 40 (SV40). Other suitable mammalian promoters include heterologous mammalian promoters, for example, heat-shock promoters and the actin promoter.

- 5 Particular promoters useful in the practice of the recombinant expression vectors of the invention include, but are not limited to: the SV40 early promoter region (Bemoist and Chambon, 1981, *Nature* 290: 304-10); the CMV promoter; the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto, et al., 1980, *Cell* 22: 787-97); the herpes thymidine kinase promoter (Wagner et al., 1981, *Proc. Natl. Acad. Sci. U.S.A.* 78: 10 1444-45); the regulatory sequences of the metallothionine gene (Brinster et al., 1982, *Nature* 296: 39-42); prokaryotic expression vectors such as the beta-lactamase promoter (Villa-Kamaroff et al., 1978, *Proc. Natl. Acad. Sci. U.S.A.*, 75: 3727-31); or the tac promoter (DeBoer et al., 1983, *Proc. Natl. Acad. Sci. U.S.A.* 80: 21-25). Also available for use are the following animal transcriptional control regions, which exhibit tissue specificity and have 15 been utilized in transgenic animals: the elastase I gene control region that is active in pancreatic acinar cells (Swift et al., 1984, *Cell* 38: 639-46; Ornitz et al., 1986, *Cold Spring Harbor Symp. Quant. Biol.* 50: 399-409; MacDonald, 1987, *Hepatology* 7: 425-515); the insulin gene control region that is active in pancreatic beta cells (Hanahan, 1985, *Nature* 315: 115-22); the mouse mammary tumor virus control region that is active in testicular, 20 breast, lymphoid and mast cells (Leder et al., 1986, *Cell* 45: 485-95); the albumin gene control region that is active in liver (Pinkert et al., 1987, *Genes and Devel.* 1: 268-76); the alpha-feto-protein gene control region that is active in liver (Krumlauf et al., 1985, *Mol. Cell. Biol.* 5: 1639-48; Hammer et al., 1987, *Science* 235: 53-58); the alpha 1-antitrypsin gene control region that is active in the liver (Kelsey et al., 1987, *Genes and Devel.* 1: 161- 25 71); the beta-globin gene control region that is active in myeloid cells (Mogam et al., 1985, *Nature* 315: 338-40; Kollias et al., 1986, *Cell* 46: 89-94); the myelin basic protein gene control region that is active in oligodendrocyte cells in the brain (Readhead et al., 1987, *Cell* 48: 703-12); the myosin light chain-2 gene control region that is active in skeletal muscle (Sani, 1985, *Nature* 314: 283-86); the gonadotropic releasing hormone gene control region 30 that is active in the hypothalamus (Mason et al., 1986, *Science* 234: 1372-78); and most particularly the immunoglobulin gene control region that is active in lymphoid cells

(Grosschedl et al., 1984, Cell 38: 647-58; Adames et al., 1985, Nature 318: 533-38; Alexander et al., 1987, Mol. Cell Biol. 7: 1436-44).

An enhancer sequence may be inserted into the vector to increase the transcription in
5 higher eukaryotes of a nucleic acid encoding a bispecific molecule or immunologically
functional fragment thereof of the present invention. Enhancers are cis-acting elements of
DNA, usually about 10-300 bp in length, that act on promoters to increase transcription.
Enhancers are relatively orientation and position independent. They have been found 5'
and 3' to the transcription unit. Several enhancer sequences available from mammalian
10 genes are known (e.g., globin, elastase, albumin, alpha-feto-protein and insulin). An
enhancer sequence from a virus also can be used. The SV40 enhancer, the cytomegalovirus
early promoter enhancer, the polyoma enhancer, and adenovirus enhancers are exemplary
enhancing elements for the activation of eukaryotic promoters. While an enhancer may be
spliced into the vector at a position 5' or 3' to a nucleic acid molecule, it is typically placed
15 at a site 5' to the promoter.

In expression vectors, a transcription termination sequence is typically located 3' of the end
of a polypeptide-coding region and serves to terminate transcription. A transcription
termination sequence used for expression in prokaryotic cells typically is a G-C rich
20 fragment followed by a poly-T sequence. While the sequence is easily cloned from a library
or even purchased commercially as part of a vector, it can also be readily synthesized using
methods for nucleic acid synthesis such as those described herein.

A selectable marker gene element encodes a protein necessary for the survival and growth
25 of a host cell grown in a selective culture medium. Typical selection marker genes used in
expression vectors encode proteins that (a) confer resistance to antibiotics or other toxins,
e.g., ampicillin, tetracycline, or kanamycin for prokaryotic host cells; (b) complement
auxotrophic deficiencies of the cell; or (c) supply critical nutrients not available from
complex media. Examples of selectable markers include the kanamycin resistance gene, the
30 ampicillin resistance gene and the tetracycline resistance gene. A bacterial neomycin
resistance gene can also be used for selection in both prokaryotic and eukaryotic host cells.

Other selection genes can be used to amplify the gene that will be expressed. Amplification is a process whereby genes that cannot in single copy be expressed at high enough levels to permit survival and growth of cells under certain selection conditions are reiterated in tandem within the chromosomes of successive generations of recombinant cells. Examples
5 of suitable amplifiable selectable markers for mammalian cells include dihydrofolate reductase (DHFR) and promoterless thymidine kinase. In the use of these markers mammalian cell transformants are placed under selection pressure wherein only the transformants are uniquely adapted to survive by virtue of the selection gene present in the vector. Selection pressure is imposed by culturing the transformed cells under
10 conditions in which the concentration of selection agent in the medium is successively increased, thereby permitting survival of only those cells in which the selection gene has been amplified. Under these circumstances, DNA adjacent to the selection gene, such as DNA encoding a bispecific molecule of the invention, is co-amplified with the selection gene.

15 A ribosome-binding site is usually necessary for translation initiation of mRNA and is characterized by a Shine-Dalgarno sequence (prokaryotes) or a Kozak sequence (eukaryotes). The element is typically located 3' to the promoter and 5' to the coding sequence of the polypeptide to be expressed.

20 In some cases, for example where glycosylation is desired in a eukaryotic host cell expression system, various presequences can be manipulated to improve glycosylation or yield. For example, the peptidase cleavage site of a particular signal peptide can be altered, or pro-sequences added, which also may affect glycosylation. The final protein product
25 may have, in the -1 position (relative to the first amino acid of the mature protein) one or more additional amino acids incident to expression, which may not have been totally removed. For example, the final protein product may have one or two amino acid residues found in the peptidase cleavage site, attached to the amino-terminus. Alternatively, use of some enzyme cleavage sites may result in a slightly truncated yet active form of the desired
30 polypeptide, if the enzyme cuts at such area within the mature polypeptide.

Where a commercially available expression vector lacks some of the desired flanking sequences as described above, the vector can be modified by individually ligating these sequences into the vector. After the vector has been chosen and modified as desired, a nucleic acid molecule encoding a bispecific molecule or immunologically functional
5 fragment thereof is inserted into the proper site of the vector.

The completed vector containing sequences encoding the inventive antibody or immunologically functional fragment thereof is inserted into a suitable host cell for amplification and/or polypeptide expression. The transformation of an expression vector
10 for a bispecific molecule immunologically functional fragment thereof into a selected host cell may be accomplished by well-known methods including methods such as transfection, infection, calcium chloride, electroporation, microinjection, lipofection, DEAE-dextran method, or other known techniques. The method selected will in part be a function of the type of host cell to be used. These methods and other suitable methods are well known to
15 the skilled artisan.

The transformed host cell, when cultured under appropriate conditions, synthesizes a bispecific molecule or functional fragment thereof that can subsequently be collected from the culture medium (if the host cell secretes it into the medium) or directly from the host
20 cell producing it (if it is not secreted). The selection of an appropriate host cell will depend upon various factors, such as desired expression levels, polypeptide modifications that are desirable or necessary for activity (such as glycosylation or phosphorylation) and ease of folding into a biologically active molecule.

25 Mammalian cell lines available as hosts for expression are well known in the art and include, but are not limited to, many immortalized cell lines available from the American Type Culture Collection (ATCC), such as Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g., Hep G2), and a number of other cell lines. In certain embodiments, the best cell
30 line for expressing a particular DNA construct may be selected by testing various cell lines to determine which ones have the highest levels of expression levels and produce antibodies with constitutive Dkk-1 binding properties.

Formulation

In certain embodiments, the invention also provides compositions comprising the subject bispecific molecules or fragments thereof together with one or more of the following: a pharmaceutically acceptable diluent; a carrier; a solubilizer; an emulsifier; a preservative; and/or an adjuvant. Such compositions may contain an effective amount of the bispecific molecule or immunologically functional fragment thereof. Thus, the use of the antibodies and fragments that are provided herein in the preparation of a pharmaceutical composition or medicament is also included. Such compositions can be used in the treatment of a variety of diseases such as listed below in the section on exemplary utilities.

Acceptable formulation components for pharmaceutical preparations are nontoxic to recipients at the dosages and concentrations employed. In addition to the bispecific molecules, the antibodies, and the fragments that are provided, compositions according to the invention may contain components for modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. Suitable materials for formulating pharmaceutical compositions include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as acetate, borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin); fillers; monosaccharides; disaccharides; and other carbohydrates (such as glucose, mannose or dextrans); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronics, PEG,

sorbitan esters, polysorbates such as polysorbate 20, polysorbate 80, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (such as sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical
5 adjuvants. (see Remington's Pharmaceutical Sciences, 18th Edition, (A. R. Gennaro, ed.), 1990, Mack Publishing Company), hereby incorporated by reference.

The primary vehicle or carrier in a pharmaceutical composition may be either aqueous or non-aqueous in nature. Suitable vehicles or carriers for such compositions include water for
10 injection, physiological saline solution or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Compositions comprising bispecific molecules or fragments thereof may be prepared for storage by mixing the selected composition having the desired degree of purity with
15 optional formulation agents in the form of a lyophilized cake or an aqueous solution. Further, the bispecific molecules or fragments thereof may be formulated as a lyophilizate using appropriate excipients such as sucrose.

Formulation components are present in concentrations that are acceptable to the site of
20 administration. Buffers are advantageously used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 4.0 to about 8.5, or alternatively, between about 5.0 to 8.0. Pharmaceutical compositions can comprise TRIS buffer of about pH 6.5-8.5, or acetate buffer of about pH 4.0-5.5, which may further include sorbitol or a suitable substitute therefor.

25 A pharmaceutical composition may involve an effective quantity of bispecific molecules or fragments thereof in a mixture with non-toxic excipients that are suitable for the manufacture of tablets. By dissolving the tablets in sterile water, or another appropriate vehicle, solutions may be prepared in unit-dose form. Suitable excipients include, but are
30 not limited to, inert materials, such as calcium carbonate, sodium carbonate or bicarbonate, lactose, or calcium phosphate; or binding agents, such as starch, gelatin, or acacia; or lubricating agents such as magnesium stearate, stearic acid, or talc.

Additional pharmaceutical compositions are in the form of sustained- or controlled-delivery formulations. Techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections can be used (see, for e.g., PCT/US93/00829, which describes the controlled release of porous polymeric microparticles for the delivery of pharmaceutical compositions). Sustained-release preparations may include semipermeable polymer matrices in the form of shaped articles, e.g. films, or microcapsules, polyesters, hydrogels, polylactides (U.S. Pat. No. 3,773,919 and EP 058,481), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman et al., 1983, Biopolymers 22: 547-556), poly (2-hydroxyethyl-methacrylate) (Langer et al., 1981, J Biomed Mater Res 15: 167-277) and Langer, 1982, Chem Tech 12: 98-105), ethylene vinyl acetate (Langer et al., *ibid.*) or poly-D(-)-3-hydroxybutyric acid (EP 133,988). Sustained release compositions may also include liposomes, which can be prepared by any of several methods known in the art. See e.g., Eppstein et al., 1985, Proc. Natl. Acad. Sci. USA 82: 3688-3692; EP 036,676; EP 088,046 and EP 143,949.

The pharmaceutical composition to be used for in vivo administration typically is sterile. Sterilization may be accomplished by filtration through sterile filtration membranes. If the composition is lyophilized, sterilization may be conducted either prior to or following lyophilization and reconstitution. The composition for parenteral administration may be stored in lyophilized form or in a solution. In certain embodiments, parenteral compositions are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle, or a sterile pre-filled syringe ready to use for injection.

Once the pharmaceutical composition of the invention has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or as a dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form or in a form (e.g., lyophilized) that is reconstituted prior to administration.

The components used to formulate the pharmaceutical compositions are preferably of high purity and are substantially free of potentially harmful contaminants (e.g., at least National Food (NF) grade, generally at least analytical grade, and more typically at least pharmaceutical grade). Moreover, compositions intended for in vivo use are usually sterile.

- 5 To the extent that a given compound must be synthesized prior to use, the resulting product is typically substantially free of any potentially toxic agents, particularly any endotoxins, which may be present during the synthesis or purification process. Compositions for parental administration are also sterile, substantially isotonic and made under GMP conditions.

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The present invention provides kits for producing a multi-dose or single-dose administration units. For example, kits according to the invention may each contain both a first container having a dried protein and a second container having an aqueous diluent, including for example single and multi-chambered pre-filled syringes (e.g., liquid syringes, lyosyringes or needle-free syringes).

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The pharmaceutical compositions of the invention can be delivered parenterally, typically by injection. Injections can be intraocular, intraperitoneal, intraportal, intramuscular, intravenous, intrathecal, intracerebral (intra-parenchymal), intracerebroventricular, intraarterial, intralesional, perilesional or subcutaneous. Eye drops can be used for intraocular administration. In some instances, injections may be localized to the vicinity of a particular bone or bones to which the treatment is targeted. For parenteral administration, the antibodies may be administered in a pyrogen-free, parenterally acceptable aqueous solution comprising the desired bispecific molecules or fragments thereof in a pharmaceutically acceptable vehicle. A particularly suitable vehicle for parenteral injection is sterile distilled water in which the bispecific molecules or fragments thereof are formulated as a sterile, isotonic solution, properly preserved.

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Pharmaceutical compositions comprising the subject bispecific molecules and functional fragments thereof may be administered by bolus injection or continuously by infusion, by implantation device, sustained release systems or other means for accomplishing prolonged release. The pharmaceutical composition also can be administered locally via

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implantation of a membrane, sponge or another appropriate material onto which the desired molecule has been absorbed or encapsulated. Where an implantation device is used, the device may be implanted into any suitable tissue or organ, and delivery of the desired molecule may be via diffusion, timed-release bolus, or continuous release. The preparation may be formulated with agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (such as polylactic acid; polyglycolic acid; or copoly (lactic/glycolic) acid (PLGA), beads or liposomes, that can provide controlled or sustained release of the product which may then be delivered via a depot injection. Formulation with hyaluronic acid has the effect of promoting sustained duration in the circulation.

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The subject compositions comprising a bispecific molecule or functional fragment thereof may be formulated for inhalation. In these embodiments, a bispecific molecule is formulated as a dry powder for inhalation, or bispecific molecule inhalation solutions may also be formulated with a propellant for aerosol delivery, such as by nebulization.

15 Pulmonary administration is further described in PCT/US94/001875, which describes pulmonary delivery of chemically modified proteins, and which is hereby incorporated by reference.

Certain pharmaceutical compositions of the invention can be delivered through the digestive tract, such as orally. The subject bispecific molecules or fragments thereof that are administered in this fashion may be formulated with or without those carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. A capsule may be designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. Additional agents can be included to facilitate absorption of the bispecific molecule or functional fragment thereof. For oral administration, modified amino acids may be used to confer resistance to digestive enzymes. Diluents, flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and binders may also be employed.

30

The subject compositions comprising bispecific molecules or fragments thereof also may be used ex vivo. In such instances, cells, tissues or organs that have been removed from the

patient are exposed to or cultured with the bispecific molecule. The cultured cells may then be implanted back into the patient or a different patient or used for other purposes.

In certain embodiments, bispecific molecules or fragments thereof can be delivered by
5 implanting certain cells that have been genetically engineered, using methods such as those described herein, to express and secrete the polypeptide. Such cells may be animal or human cells, and may be autologous, heterologous, or xenogenic, or may be immortalized. In order to decrease the chance of an immunological response, the cells may be encapsulated to avoid infiltration of surrounding tissues. Encapsulation materials are
10 typically biocompatible, semi-permeable polymeric enclosures or membranes that allow the release of the protein product(s) but prevent the destruction of the cells by the patient's immune system or by other detrimental factors from the surrounding tissues.

Dosage

15 The pharmaceutical compositions that are provided can be administered for prophylactic and/or therapeutic treatments. An "effective amount" refers generally to an amount that is a sufficient, but non-toxic, amount of the active ingredient (i.e., a bispecific molecule or immunologically functional fragment thereof) to achieve the desired effect, which is a reduction or elimination in the severity and/or frequency of symptoms and/or
20 improvement or remediation of damage. A "therapeutically effective amount" refers to an amount that is sufficient to remedy a disease state or symptoms, or otherwise prevent, hinder, retard or reverse the progression of a disease or any other undesirable symptom. A "prophylactically effective amount" refers to an amount that is effective to prevent, hinder or retard the onset of a disease state or symptom.

25

In general, toxicity and therapeutic efficacy of the antibody or fragment can be determined according to standard pharmaceutical procedures in cell cultures and/or experimental animals, including, for example, determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The
30 dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compositions that exhibit large therapeutic indices are preferred.

The data obtained from cell culture and/or animal studies can be used in formulating a range of dosages for humans. The dosage of the active ingredient typically lines within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized.

The effective amount of a pharmaceutical composition comprising bispecific molecules or fragments thereof to be employed therapeutically or prophylactically will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment, according to certain embodiments, will thus vary depending, in part, upon the molecule delivered, the indication for which the bispecific molecule is being used, the route of administration, and the size (body weight, body surface or organ size) and/or condition (the age and general health) of the patient. A clinician may titer the dosage and modify the route of administration to obtain the optimal therapeutic effect. Typical dosages range from about 0.1 $\mu\text{g/kg}$ to up to about 100 mg/kg or more, depending on the factors mentioned above. In certain embodiments, the dosage may range from 0.1 $\mu\text{g/kg}$ up to about 150 mg/kg ; or 1 $\mu\text{g/kg}$ up to about 100 mg/kg ; or 5 $\mu\text{g/kg}$ up to about 50 mg/kg . In certain embodiments, the dose is at least 0.1 $\mu\text{g/kg}$. In certain embodiments, the dose is at least 1 $\mu\text{g/kg}$. In certain embodiments, the dose is at least 5 $\mu\text{g/kg}$. In certain embodiments, the dose is at least 5 mg/kg . In certain embodiments, the dose is at least 10 mg/kg . In certain embodiments, the dose is at least 50 mg/kg . In certain embodiments, the dose is at least 100 mg/kg .

The dosing frequency will depend upon the pharmacokinetic parameters of the bispecific molecule or immunologically functional fragment thereof in the formulation. For example, a clinician will administer the composition until a dosage is reached that achieves the desired effect. The composition may therefore be administered as a single dose, or as two or more doses (which may or may not contain the same amount of the desired molecule) over time, or as a continuous infusion via an implantation device or catheter. Treatment may be continuous over time or intermittent. Further refinement of the appropriate dosage is routinely made by those of ordinary skill in the art and is within the ambit of tasks

routinely performed by them. Appropriate dosages may be ascertained through use of appropriate dose-response data.

To treat a medical disorder by targeting Sclerostin and/or Dkk-1, a composition comprising
5 the subject bispecific molecules or fragments thereof may be administered to the patient in
an amount and for a time sufficient to induce a sustained improvement in at least one
indicator that reflects the severity of the disorder. An improvement is considered
"sustained" if the patient exhibits the improvement on at least two occasions separated by
at least one to seven days, or in some instances one to six weeks. The appropriate interval
10 will depend to some extent on what disease condition is being treated; it is within the
purview of the skilled physician to determine the appropriate interval for determining
whether the improvement is sustained. The degree of improvement is determined based
on signs or symptoms, and may also employ questionnaires that are administered to the
patient, such as quality-of-life questionnaires.

15 Various indicators that reflect the extent of the patient's illness may be assessed for
determining whether the amount and time of the treatment is sufficient. The baseline
value for the chosen indicator or indicators is established by examination of the patient
prior to administration of the first dose of antibody. Preferably, the baseline examination is
20 done within about 60 days of administering the first dose. If the antibody is being
administered to treat acute symptoms, such as for example to treat a broken bone, the first
dose is administered as soon as practically possible after the injury has occurred.

Improvement is induced by administering the subject bispecific molecules or fragments
25 thereof until the patient manifests an improvement over baseline for the chosen indicator
or indicators. In treating chronic conditions, this degree of improvement is obtained by
repeatedly administering this medicament over a period of at least a month or more, e.g.,
for one, two, or three months or longer, or indefinitely. A period of one to six weeks, or
even a single dose, often is sufficient for treating acute conditions. For injuries or acute
30 conditions, a single dose may be sufficient.

Although the extent of the patient's illness after treatment may appear improved according to one or more indicators, treatment may be continued indefinitely at the same level or at a reduced dose or frequency. Once treatment has been reduced or discontinued, it later may be resumed at the original level if symptoms should reappear.

5

The subject bispecific molecules and fragments thereof can be used to detect sclerostin and/or Dkk-1 in biological samples. Such uses allow the identification of cells or tissues that produce the protein or serve as a diagnostic for detecting pathological conditions in which sclerostin and/or Dkk-1 is overproduced or underproduced. The antibodies and fragments
10 that are provided can also be used in methods to screen for a molecule that binds to sclerostin and/or Dkk-1. A variety of competitive screening methods, for example, can be used. In some methods, a sclerostin and/or Dkk-1 molecule or fragment thereof to which a bispecific molecule binds, is contacted with an antibody or fragment disclosed herein together with another molecule (i.e., a candidate molecule). A reduction in binding
15 between the bispecific molecule or fragment and sclerostin and/or Dkk-1 is an indication that the molecule binds the target. Binding of the bispecific molecule or fragment can be detected using a variety of methods, e.g., an ELISA. Detection of binding between the bispecific molecule or fragment to the target can be simplified by detectably labeling the antibody. In some methods, a molecule that exhibits binding in the initial screen is further
20 analyzed to determine whether it inhibits a sclerostin and/or Dkk-1 activity (e.g., whether the molecule activates Wnt signaling).

Methods of Treatment and Uses

In another aspect, the use of the foregoing antibodies or fragments in the treatment of a
25 variety of diseases is disclosed. Certain methods, for instance, involve administering to a patient in need thereof an effective amount of a bispecific molecules of the invention or fragment as described herein to treat arthritis, diseases responsive to stem cell renewal, inflammatory diseases, neurological diseases, ocular diseases, renal diseases, pulmonary diseases, and skin diseases. Some treatment methods involve treating rheumatoid arthritis,
30 psoriatic arthritis or osteoarthritis. Certain antibodies and fragments are used to treat a disease that: (a) is responsive to stem cell renewal and is selected from the group consisting of diabetes, chronic heart failure and diseases of the muscle; (b) is an

inflammatory disease selected from the group consisting of Crohn's disease, colitis, and inflammatory bowel disease; (c) is a neurological disease selected from the group consisting of Alzheimer's disease, Parkinson's disease, and Huntington's disease; (d) is an ocular disease selected from the group consisting of macular degeneration and
5 retinopathies; (e) is a renal disease selected from the group consisting of end stage renal disease, chronic renal disease, glomerulonephritis, tubulointerstitial nephritis, and IgA nephropathy; (f) is a pulmonary disease selected from the group consisting of chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and cystic fibrosis; or (g) is a skin disease resulting from chemotherapy-induced damage to the intestinal epithelium.

10

Further provided herein are methods of treating or preventing loss of bone mass comprising administering to a patient in need thereof a therapeutically effective amount of a bispecific molecule of the invention. In one embodiment, the bispecific molecule of the invention comprises a variable region selected from an antibody described in any of US
15 7,744,874, US 2009/0130113, US 7,592,429, US 2008/0193449, US 7,642,238 and US 7,700,101, or immunologically functional fragment thereof as described herein. In one aspect of this embodiment, the patient is one who suffers from cancer that metastasizes to bone, and in another aspect, the patient is one who suffers from multiple myeloma.

20 Particular conditions which may be treated by the compositions of the present invention include dysplasias, wherein growth or development of bone is abnormal. Representative examples of such conditions include achondroplasia, cleidocranial dysostosis, enchondromatosis, fibrous dysplasia, Gaucher's Disease, hypophosphatemic rickets, Marfan's syndrome, multiple hereditary exotoses, neurofibromatosis, osteogenesis
25 imperfecta, osteopetrosis, osteopoikilosis, sclerotic lesions, pseudoarthrosis, and pyogenic osteomyelitis.

Other conditions that may be treated or prevented include a wide variety of causes of osteopenia, osteoporosis and bone loss. Representative examples of such conditions
30 include periodontal disease, anti-epileptic drug induced bone loss, primary and secondary hyperparathyroidism, familial hyperparathyroidism syndromes, weightlessness induced bone loss, osteoporosis in men, postmenopausal bone loss, osteoarthritis, renal

osteodystrophy, infiltrative disorders of bone, oral bone loss, osteonecrosis of the jaw, juvenile Paget's disease, melorheostosis, metabolic bone diseases, mastocytosis, sickle cell disease, ischemic bone disease (such as Legg-Calve-Perthes disease, regional migratory osteoporosis), anemic states, conditions caused by steroids, glucocorticoid-induced bone loss, heparin-induced bone loss, bone marrow disorders, scurvy, malnutrition, calcium deficiency, idiopathic osteopenia or osteoporosis, congenital osteopenia or osteoporosis, alcoholism, chronic liver disease, postmenopausal state, chronic inflammatory conditions, rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, inflammatory colitis, Crohn's disease, oligomenorrhea, amenorrhea, pregnancy, diabetes mellitus, hyperthyroidism, thyroid disorders, parathyroid disorders, Cushing's disease, acromegaly, hypogonadism, immobilization or disuse, reflex sympathetic dystrophy syndrome, regional osteoporosis, osteomalacia, bone loss associated with joint replacement, HIV associated bone loss, bone loss associated with loss of growth hormone, bone loss associated with cystic fibrosis, fibrous dysplasia, chemotherapy associated bone loss, tumor induced bone loss, cancer-related bone loss, hormone ablative bone loss, multiple myeloma, drug-induced bone loss, anorexia nervosa, disease associated facial bone loss, disease associated cranial bone loss, disease associated bone loss of the jaw, disease associated bone loss of the skull, and bone loss associated with space travel. Further conditions relate to bone loss associated with aging, including facial bone loss associated with aging, cranial bone loss associated with aging, jaw bone loss associated with aging, and skull bone loss associated with aging.

Compositions of the present invention may also be useful for improving outcomes in orthopedic procedures, dental procedures, implant surgery, joint replacement (e.g., hip or knee), bone grafting, bone cosmetic surgery and bone repair such as fracture healing, nonunion healing, delayed union healing and facial reconstruction. One or more compositions may be administered before, during and/or after the procedure, replacement, graft, surgery or repair.

In certain embodiments, local delivery of the binding molecules of the invention is envisioned, such as, but not limited to, fracture sites, spinal fusion or dentistry related indications. In one embodiment, the binding molecule is delivered via a local injection to

the site of therapy. In another embodiment, an additional binding sequence is added to the binding molecules of the invention to direct the binding molecules against proteins restricted to the bone extracellular matrix, which can improve retention time at the therapeutic site and the PK of the binding molecule, thereby improving efficacy.

5 Nonlimiting examples of these proteins include, but are not limited to, type 1 collagen, bone sialoprotein, and dentin matrix protein. In certain embodiments, the additional binding sequence is a binding peptide or an avimer sequence that binds the proteins restricted to the bone extracellular matrix.

10 The following is a nonlimiting list of specific embodiments contemplated by the present invention:

It is contemplated that when a VH1, or CDRs from a VH1, is selected from the sclerostin binders, the VH2, or CDRs from a VH2, is selected from the DKK-1 binders. Conversely,

15 when a VH1, or CDRs from a VH1, is selected from DKK-1 binders, the VH2, or CDRs from a VH2, is selected from sclerostin binders. It is further contemplated that when a VL1, or CDRs from a VL1, is selected from the sclerostin binders, the VL2, or CDRs from a VL2, is selected from the DKK-1 binders. Conversely, when a VL1, or CDRs from a VL1, is selected from DKK-1 binders, the VL2, or CDRs from a VL2, is selected from sclerostin binders.

20

1. A binding molecule comprising a polypeptide chain, wherein said polypeptide chain comprises VH1-(X1)_n-VH2-C-(X2)_n, wherein: VH1 is a first heavy chain variable domain obtained from a first parent antibody or antigen binding portion thereof; VH2 is a second heavy chain variable domain obtained from a second parent antibody or antigen binding portion thereof; C is a heavy chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n is an Fc region, wherein said (X2)_n is either present or absent, wherein the binding molecule specifically binds both sclerostin and DKK-1.

25

2. The binding molecule of embodiment 1, wherein VH1 and VH2 comprise an amino acid sequence selected from the group consisting of sclerostin binders SEQ ID NOs: 95, 96, 104, 112, 120, 128, 136, 144, 152, 160, 168, 176, 184, 192, 200, 208, and 216, or DKK-1 binders

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SEQ ID NOs: 224, 232, 240, 248, 256, 264, 272, 280, 288, 296, 304, 312, 320, 328, 336, 344, 352, 360, 368, 376, 384, 392, 400, and 408.

3. A binding molecule comprising a polypeptide chain, wherein said polypeptide chain
5 comprises VL1-(X1)_n-VL2-C-(X2)_n, wherein: VL1 is a first light chain variable domain
obtained from a first parent antibody or antigen binding portion thereof; VL2 is a second
light chain variable domain obtained from a second parent antibody or antigen binding
portion thereof; C is a light chain constant domain; (X1)_n is a linker, wherein said (X1)_n is
either present or absent; and (X2)_n is an Fc region, wherein said (X2)_n is either present or
10 absent, wherein the binding molecule specifically binds both sclerostin and DKK-1.
4. The binding molecule of embodiment 3, wherein VL1 and VL2 comprise an amino acid
sequence selected from the group consisting of sclerostin binders SEQ ID NOs: 94, 103, 111,
119, 127, 135, 143, 151, 159, 167, 175, 183, 191, 199, 207, and 215, or DKK-1 binders SEQ
15 ID NOs: 223, 231, 239, 247, 255, 263, 271, 279, 287, 295, 303, 311, 319, 327, 335, 343, 351,
359, 367, 375, 383, 391, 399, and 407.
5. The binding molecule of embodiment 1 or 3, wherein (X2)_n is absent.
- 20 6. A binding molecule comprising first and second polypeptide chains, wherein said first
polypeptide chain comprises a VH1-(X1)_n-VH2-C-(X2)_n, wherein VH1 is a first heavy chain
variable domain obtained from a first parent antibody or antigen binding portion thereof;
VH2 is a second heavy chain variable domain obtained from a second parent antibody or
antigen binding portion thereof; C is a heavy chain constant domain; (X1)_n is a linker,
25 wherein said (X1)_n is either present or absent; and (X2)_n is an Fc region, wherein said (X2)_n
is either present or absent; and wherein said second polypeptide chain comprises a VL1-
(X1)_n-VL2-C-(X2)_n, wherein VL1 is a first light chain variable domain obtained from a first
parent antibody or antigen binding portion thereof; VL2 is a second light chain variable
domain obtained from a second parent antibody or antigen binding portion thereof; C is a
30 light chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent;
and (X2)_n does not comprise an Fc region, wherein said (X2)_n is either present or absent,
wherein the binding molecule specifically binds sclerostin and DKK-1.

7. The binding molecule of embodiment 6, wherein the VH1 and VH2 heavy chain variable domains comprise an amino acid sequence selected from the group consisting of sclerostin binders SEQ ID NOs: 95, 96, 104, 112, 120, 128, 136, 144, 152, 160, 168, 176, 184, 192, 200, 208, and 216, or DKK-1 binders SEQ ID NOs: 224, 232, 240, 248, 256, 264, 272, 280, 288, 296, 304, 312, 320, 328, 336, 344, 352, 360, 368, 376, 384, 392, 400, and 408, and wherein the VL1 and VL2 light chain variable domains comprise an amino acid sequence selected from the group consisting of sclerostin binders SEQ ID NOs: 94, 103, 111, 119, 127, 135, 143, 151, 159, 167, 175, 183, 191, 199, 207, and 215, or DKK-1 binders SEQ ID NOs: 223, 231, 239, 247, 255, 263, 271, 279, 287, 295, 303, 311, 319, 327, 335, 343, 351, 359, 367, 375, 383, 391, 399, and 407.
8. The binding molecule of embodiment 1, 3, or 6, wherein (X1)_n is an amino acid sequence selected from the group consisting of SEQ ID NOs: 415-482.
9. The binding molecule of embodiments 6, wherein the binding molecule comprises two first polypeptide chains and two second polypeptide chains.
10. The binding molecule of embodiment 1, 3, or 6, wherein the Fc region is selected from the group consisting of native sequence Fc region and a variant sequence Fc region.
11. The binding molecule of embodiment 10, wherein the Fc region is selected from the group consisting of an Fc region from an IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgE, and IgD.
12. The binding molecule of embodiment 1, 3, or 6, wherein said VH1 of the first polypeptide chain and said VL1 of the second polypeptide chain are obtained from the same parent antibody or antigen binding portion thereof.
13. The binding molecule of embodiment 1, 3, or 6, wherein said VH1 of the first polypeptide chain and said VL1 of the second polypeptide chain are obtained from different parent antibody or antigen binding portion thereof.

14. The binding molecule of embodiment 1, 3, or 6, wherein said VH2 of the first polypeptide chain and said VL2 of the second polypeptide chain are obtained from the same parent antibody or antigen binding portion thereof.
- 5 15. The binding molecule of embodiment 1, 3, or 6, wherein said VH2 of the first polypeptide chain and said VL2 of the second polypeptide chain are obtained from different parent antibody or antigen binding portion thereof.
16. The binding molecule of embodiment 1, 3, or 6 with the proviso that said linker (X1)_n is
10 not CH1.
17. The binding molecule of embodiment 1, 3, or 6, wherein said first parent antibody, or antigen binding portion thereof, binds said first antigen with a potency different from the potency with which said second parent antibody, or antigen binding portion thereof, binds
15 said second antigen.
18. The binding molecule of embodiment 1, 3, or 6, wherein said first parent antibody, or antigen binding portion thereof, binds said first antigen with an affinity different from the affinity with which said second parent antibody, or antigen binding portion thereof, binds
20 said second antigen.
19. The binding molecule of embodiment 1, 3, or 6, wherein said first parent antibody, or antigen binding portion thereof, and said second parent antibody, or antigen binding portion thereof, are selected from the group consisting of a human antibody, a CDR grafted
25 antibody, and a humanized antibody.
20. The binding molecule of embodiment 1, 3, or 6, wherein said first parent antibody, or antigen binding portion thereof, and said second parent antibody, or antigen binding portion thereof, are selected from the group consisting of a Fab fragment; a F(ab')₂
30 fragment; a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the VH and CH1 domains; a Fv fragment

consisting of the VL and VH domains of a single arm of an antibody; a dAb fragment; an isolated complementarity determining region (CDR); a single chain antibody; and a diabody.

21. The binding molecule of embodiment 1, 3, or 6, wherein said binding molecule
5 possesses at least one desired property exhibited by said first parent antibody, or antigen binding portion thereof, or said second parent antibody, or antigen binding portion thereof.

22. The binding molecule of embodiment 21, wherein said desired property is selected from one or more antibody parameters.

10

23. The binding molecule of embodiment 21, wherein said antibody parameters are selected from the group consisting of antigen specificity, affinity to antigen, potency, biological function, epitope recognition, stability, solubility, production efficiency, immunogenicity, pharmacokinetics, bioavailability, tissue cross reactivity, and orthologous
15 antigen binding.

24. A binding molecule that binds both sclerostin and DKK-1 comprising four polypeptide chains, wherein first and third polypeptide chains comprise VH1-(X1)_n-VH2-C-(X2)_n, wherein: VH1 is a first heavy chain variable domain; VH2 is a second heavy chain variable
20 domain; C is a heavy chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n is an Fc region, wherein said (X2)_n is either present or absent; and wherein second and fourth polypeptide chains comprise VL1-(X1)_n-VL2-C-(X2)_n, wherein VL1 is a first light chain variable domain; VL2 is a second light chain variable domain; C is a light chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either
25 present or absent; and (X2)_n does not comprise an Fc region, wherein said (X2)_n is either present or absent, wherein the VH1 and VH2 heavy chain variable domains comprise an amino acid sequence selected from the group consisting of sclerostin binders SEQ ID NOs: 95, 96, 104, 112, 120, 128, 136, 144, 152, 160, 168, 176, 184, 192, 200, 208, and 216, or DKK-1 binders SEQ ID NOs: 224, 232, 240, 248, 256, 264, 272, 280, 288, 296, 304, 312, 320,
30 328, 336, 344, 352, 360, 368, 376, 384, 392, 400, and 408, and wherein the VL1 and VL2 light chain variable domains comprise an amino acid sequence selected from the group consisting of sclerostin binders SEQ ID NOs: 94, 103, 111, 119, 127, 135, 143, 151, 159, 167,

175, 183, 191, 199, 207, and 215, or DKK-1 binders SEQ ID NOs: 223, 231, 239, 247, 255, 263, 271, 279, 287, 295, 303, 311, 319, 327, 335, 343, 351, 359, 367, 375, 383, 391, 399, and 407.

5 25. The binding molecule of embodiment 24 with the proviso that said linker (X1)_n is not CH1.

26. A binding molecule that binds both sclerostin and DKK-1 comprising four polypeptide chains, wherein first and third polypeptide chains comprise VH1-(X1)_n-VH2-C-(X2)_n,
10 wherein: VH1 is a first heavy chain variable domain; VH2 is a second heavy chain variable domain; C is a heavy chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n is an Fc region, wherein said (X2)_n is either present or absent; and wherein second and fourth polypeptide chains comprise VL1-(X1)_n-VL2-C-(X2)_n,
15 wherein VL1 is a first light chain variable domain; VL2 is a second light chain variable domain; C is a light chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n does not comprise an Fc region, wherein said (X2)_n is either present or absent, wherein the binding molecule comprises VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairings selected from the group consisting of:

20 SEQ ID NOs: 18 and 20; 22 and 24; 26 and 28; 30 and 32; 34 and 36; 38 and 40; 42 and 44; 46 and 48; 50 and 52; 54 and 56; 58 and 60; 62 and 64; 66 and 68; 70 and 72; 74 and 76; 78 and 80; 82 and 84; 86 and 88; 90 and 92; 486 and 488; 490 and 492; and 494 and 496.

27. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 18 and 20.

28. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 22 and 24.

30 29. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 26 and 28.

30. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 30 and 32.
31. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-
5 (X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 34 and 36.
32. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 38 and 40.
- 10 33. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 42 and 44.
34. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 46 and 48.
- 15 35. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 50 and 52.
36. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-
20 (X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 54 and 76.
37. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 56 and 72.
- 25 38. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 58 and 60.
39. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 62 and 64.
- 30 40. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 66 and 68.

41. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 70 and 72.
- 5 42. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 74 and 76.
43. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 78 and 80.
- 10 44. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 82 and 84.
45. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-
- 15 (X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 86 and 88.
46. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 90 and 92.
- 20 47. The binding molecule of embodiments 1, 3 and 6, wherein the sclerostin binder VH comprises 3 CDRs selected from the group consisting of SEQ ID NOs, where each group member has 3 CDRs (CDR1, CDR2, CDR3):
- 100, 101, 102; 108, 109, 110; 116, 117, 118; 124, 125, 126; 132, 133, 134; 140, 141, 142; 148, 149, 150; 156, 157, 158; 164, 165, 166; 172, 173, 174; 180, 181, 182; 188, 189, 190; 196, 197, 198; 204, 205, 206; 212, 213, 214; and 220, 221, 222,
- 25
- and wherein the DKK1 binder VH comprises 3 CDRs selected from the group consisting of SEQ ID NOs where each group member has 3 CDRs (CDR1, CDR2, CDR3):
- 30 228, 229, 230; 236, 237, 238; 244, 245, 246; 252, 253, 254; 260, 261, 262; 268, 269, 270; 276, 277, 278; 284, 285, 286; 292, 293, 294; 300, 301, 302; 308, 309, 310; 316, 317, 318; 324, 325, 326; 332, 333, 334; 340, 341, 342; 348, 349, 350;

356, 357, 358; 364, 365, 366; 372, 373, 374; 380, 381, 382; 388, 389, 390; 396,
397, 398; 404, 405, 406; and 412, 413, 414.

48. The binding molecule of embodiments 1, 3 and 6, wherein the sclerostin binder VL
5 comprises 3 CDRs selected from the group consisting of SEQ ID NOs where each group
member has 3 CDRs (CDR1, CDR2, CDR3):

97, 98, 99; 105, 106, 107; 113, 114, 115; 121, 122, 123; 129, 130, 131; 137, 138,
139; 145, 146, 147; 153, 154, 155; 161, 162, 163; 169, 170, 171; 177, 178, 179;
185, 186, 187; 193, 194, 195; 201, 202, 203; 209, 210, 211; and 217, 218, 219,

10

and wherein the DKK1 binder VL comprises 3 CDRs selected from the group consisting of
SEQ ID NOs where each group member has 3 CDRs (CDR1, CDR2, CDR3):

a) 225, 226, 227; 233, 234, 235; 241, 242, 243; 249, 250, 251; 257, 258, 259;
265, 266, 267; 273, 274, 275; 281, 282, 283; 289, 290, 291; 297, 298, 299;
15 305, 306, 307; 313, 314, 315; 321, 322, 323; 329, 330, 331; 337, 338, 339;
345, 346, 347; 353, 354, 355; 361, 362, 363; 369, 370, 371; 377, 378, 379;
385, 386, 387; 393, 394, 395; 401, 402, 403; and 409, 410, 411.

49. The binding molecule of embodiments 1, 3, and 6, wherein the sclerostin binder VH
20 comprises 3 CDRs selected from the group consisting of SEQ ID NOs where each group
member has 3 CDRs (CDR1, CDR2, CDR3):

100, 101, 102; 108, 109, 110; 116, 117, 118; 124, 125, 126; 132, 133, 134; 140,
141, 142; 148, 149, 150; 156, 157, 158; 164, 165, 166; 172, 173, 174; 180, 181,
182; 188, 189, 190; 196, 197, 198; 204, 205, 206; 212, 213, 214; and 220, 221,
25 222,

and wherein the DKK1 binder VH comprises 3 CDRs selected from the group consisting of
SEQ ID NOs where each group member has 3 CDRs (CDR1, CDR2, CDR3):

228, 229, 230; 236, 237, 238; 244, 245, 246; 252, 253, 254; 260, 261, 262; 268,
30 269, 270; 276, 277, 278; 284, 285, 286; 292, 293, 294; 300, 301, 302; 308, 309,
310; 316, 317, 318; 324, 325, 326; 332, 333, 334; 340, 341, 342; 348, 349, 350;

356, 357, 358; 364, 365, 366; 372, 373, 374; 380, 381, 382; 388, 389, 390; 396, 397, 398; 404, 405, 406; and 412, 413, 414.

and wherein the sclerostin binder VL comprises 3 CDRs selected from the group consisting of SEQ ID NOs where each group member has 3 CDRs (CDR1, CDR2, CDR3):

97, 98, 99; 105, 106, 107; 113, 114, 115; 121, 122, 123; 129, 130, 131; 137, 138, 139; 145, 146, 147; 153, 154, 155; 161, 162, 163; 169, 170, 171; 177, 178, 179; 185, 186, 187; 193, 194, 195; 201, 202, 203; 209, 210, 211; and 217, 218, 219,

10 and wherein the DKK1 binder VL comprises 3 CDRs selected from the group consisting of SEQ ID NOs where each group member has 3 CDRs (CDR1, CDR2, CDR3):

225, 226, 227; 233, 234, 235; 241, 242, 243; 249, 250, 251; 257, 258, 259; 265, 266, 267; 273, 274, 275; 281, 282, 283; 289, 290, 291; 297, 298, 299; 305, 306, 307; 313, 314, 315; 321, 322, 323; 329, 330, 331; 337, 338, 339; 345, 346, 347; 15 353, 354, 355; 361, 362, 363; 369, 370, 371; 377, 378, 379; 385, 386, 387; 393, 394, 395; 401, 402, 403; and 409, 410, 411.

50. A binding molecule comprising four polypeptide chains, wherein first and third polypeptide chains comprise VH1-(X1)_n-VH2-C-(X2)_n, wherein: VH1 is a first heavy chain variable domain; VH2 is a second heavy chain variable domain; C is a heavy chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n is an Fc region, wherein said (X2)_n is either present or absent; and wherein second and fourth polypeptide chains comprise VL1-(X1)_n-VL2-C-(X2)_n, wherein VL1 is a first light chain variable domain; VL2 is a second light chain variable domain; C is a light chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n does not 25 comprise an Fc region, wherein said (X2)_n is either present or absent, wherein the binding molecule comprises 3 VH1 CDRs, 3 VH2 CDRs, 3 VL1 CDRs and 3 VL2 CDRs, wherein the paired VH1 and VL1 CDRs, and paired VH2 and VL2 CDRs, are selected from the group consisting of SEQ ID NOs:

30 97-102; 105-110; 113-118; 121-126; 129-134; 137-142; 145-150; 153-158; 161-166; 169-174; 177-182; 185-190; 193-198; 201-206; 209-214; 217-222,

or SEQ ID NOs:

- a) 225-230; 233-238; 241-246; 249-254; 257-262; 265-270; 273-278; 281-286;
289-294; 297-302; 305-310; 313-318; 321-326; 329-334; 337-342; 345-350;
353-358; 361-366; 369-374; 377-382; 385-390; 393-398; 401-406; 409-414.

5

51. The binding molecule of embodiment 50, wherein said VL1 CDRs are SEQ ID NOs: 161-163, said VH1 CDRs are SEQ ID NOs: 164-166, said VL2 CDRs are SEQ ID NOs: 385-387, and said VH2 CDRs are SEQ ID NOs: 388-390.

- 10 52. The binding molecule of embodiment 50, wherein said VL1 CDRs are SEQ ID NOs: 385-387, said VH1 CDRs are SEQ ID NOs: 388-390, said VL2 CDRs are SEQ ID NOs: 161-163, and said VH2 CDRs are SEQ ID NOs: 164-166.

53. The binding molecule of embodiment 50, wherein said VL1 CDRs are SEQ ID NOs: 153-155, said VH1 CDRs are SEQ ID NOs: 156-158, said VL2 CDRs are SEQ ID NOs: 385-387, and said VH2 CDRs are SEQ ID NOs: 388-390.

54. The binding molecule of embodiment 50, wherein said VL1 CDRs are SEQ ID NOs: 385-387, said VH1 CDRs are SEQ ID NOs: 388-390, said VL2 CDRs are SEQ ID NOs: 153-155, and said VH2 CDRs are SEQ ID NOs: 156-158.

55. The binding molecule of embodiment 50, wherein said VL1 CDRs are SEQ ID NOs: 409-411, said VH1 CDRs are SEQ ID NOs: 412-414, said VL2 CDRs are SEQ ID NOs: 121-123, and said VH2 CDRs are SEQ ID NOs: 124-126.

25

56. The binding molecule of embodiment 50, wherein said VL1 CDRs are SEQ ID NOs: 409-411, said VH1 CDRs are SEQ ID NOs: 412-414, said VL2 CDRs are SEQ ID NOs: 177-179, and said VH2 CDRs are SEQ ID NOs: 180-182.

- 30 57. The binding molecule of embodiment 50, wherein said VL1 CDRs are SEQ ID NOs: 409-411, said VH1 CDRs are SEQ ID NOs: 412-414, said VL2 CDRs are SEQ ID NOs: 97-99, and said VH2 CDRs are SEQ ID NOs: 100-102.

58. The binding molecule of embodiment 50, wherein said VL1 CDRs are SEQ ID NOs: 385-387, said VH1 CDRs are SEQ ID NOs: 388-390, said VL2 CDRs are SEQ ID NOs: 105-107, and said VH2 CDRs are SEQ ID NOs: 108-110.
- 5
59. The binding molecule of embodiment 50, wherein said VL1 CDRs are SEQ ID NOs: 97-99, said VH1 CDRs are SEQ ID NOs: 100-102, said VL2 CDRs are SEQ ID NOs: 409-411, and said VH2 CDRs are SEQ ID NOs: 412-414.
- 10
60. The binding molecule of embodiment 50, wherein said VL1 CDRs are SEQ ID NOs: 385-387, said VH1 CDRs are SEQ ID NOs: 388-390, said VL2 CDRs are SEQ ID NOs: 105-107, and said VH2 CDRs are SEQ ID NOs: 108-110.
61. The binding molecule of embodiment 50, wherein said VL1 CDRs are SEQ ID NOs: 409-411, said VH1 CDRs are SEQ ID NOs: 412-414, said VL2 CDRs are SEQ ID NOs: 105-107, and said VH2 CDRs are SEQ ID NOs: 108-110.
- 15
62. The binding molecule of embodiment 50, wherein said VL1 CDRs are SEQ ID NOs: 105-107, said VH1 CDRs are SEQ ID NOs: 108-110, said VL2 CDRs are SEQ ID NOs: 385-387, and said VH2 CDRs are SEQ ID NOs: 388-390.
- 20
63. The binding molecule of embodiment 50, wherein said VL1 CDRs are SEQ ID NOs: 105-107, said VH1 CDRs are SEQ ID NOs: 108-110, said VL2 CDRs are SEQ ID NOs: 409-411, and said VH2 CDRs are SEQ ID NOs: 412-414.
- 25
64. The binding molecule of embodiment 50, wherein said VL1 CDRs are SEQ ID NOs: 369-371, said VH1 CDRs are SEQ ID NOs: 372-374, said VL2 CDRs are SEQ ID NOs: 105-107, and said VH2 CDRs are SEQ ID NOs: 108-110.
- 30
65. The binding molecule of embodiments 50-64, wherein said (X1)_n is selected from the group consisting of SEQ ID NOs: 415-484.

66. The binding molecule of embodiments 50-64, wherein said (X1)_n is selected from the group consisting of SEQ ID NOs: 440, 441, 437, 438, 431, 432, 483, and 484.
67. The binding molecule of embodiments 50-64, wherein said (X1)_n of the VH1-(X1)_n-VH2-
5 C-(X2)_n chain is SEQ ID NO: 440.
68. The binding molecule of embodiments 50-64, wherein said (X1)_n of the VH1-(X1)_n-VH2-
C-(X2)_n chain is SEQ ID NO: 441.
69. The binding molecule of embodiments 50-64, wherein said (X1)_n of the VH1-(X1)_n-VH2-
10 C-(X2)_n chain is SEQ ID NO: 437.
70. The binding molecule of embodiments 50-64, wherein said (X1)_n of the VH1-(X1)_n-VH2-
C-(X2)_n chain is SEQ ID NO: 438.
71. The binding molecule of embodiments 50-64, wherein said (X1)_n of the VL1-(X1)_n-VL2-
15 C-(X2)_n is SEQ ID NO: 440.
72. The binding molecule of embodiments 50-64, wherein said (X1)_n of the VL1-(X1)_n-VL2-
20 C-(X2)_n is SEQ ID NO: 441.
73. The binding molecule of embodiments 50-64, wherein said (X1)_n of the VL1-(X1)_n-VL2-
C-(X2)_n is SEQ ID NO: 483.
74. The binding molecule of embodiments 50-64, wherein said (X1)_n of the VL1-(X1)_n-VL2-
25 C-(X2)_n is SEQ ID NO: 484.
75. The binding molecule of embodiments 50-64, wherein said (X1)_n of the VL1-(X1)_n-VL2-
C-(X2)_n is SEQ ID NO: 431.
76. The binding molecule of embodiments 50-64, wherein said (X1)_n of the VL1-(X1)_n-VL2-
30 C-(X2)_n is SEQ ID NO: 432.

77. The binding molecule of embodiments 1, 3, 6, 24, 26 and 50, wherein said (X1)_n is the different on the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n chains.

5 78. A method for generating a binding molecule that binds sclerostin and DKK-1 comprising the steps of: (a) obtaining a first parent antibody, or antigen binding portion thereof, that can bind sclerostin or DKK-1; (b) obtaining a second parent antibody, or antigen binding portion thereof, that can bind sclerostin or DKK-1; (c) constructing first and third polypeptide chains comprising VH1-(X1)_n-VH2-C-(X2)_n, wherein: VH1 is a first heavy chain
10 variable domain obtained from said first parent antibody or antigen binding portion thereof; VH2 is a second heavy chain variable domain obtained from said second parent antibody or antigen binding portion thereof; C is a heavy chain constant domain; (X1)_n is a linker with the proviso that it is not CH1, wherein said (X1)_n is either present or absent; and (X2)_n is an Fc region, wherein said (X2)_n is either present or absent; (d) constructing second
15 and fourth polypeptide chains comprising VL1-(X1)_n-VL2-C-(X2)_n, wherein: VL1 is a first light chain variable domain obtained from said first parent antibody or antigen binding portion thereof; VL2 is a second light chain variable domain obtained from said second parent antibody or antigen binding thereof; C is a light chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n does not comprise an Fc
20 region, wherein said (X2)_n is either present or absent; and (e) expressing said first, second, third and fourth polypeptide chains such that a binding molecule that binds sclerostin and DKK-1 is generated.

79. The method of embodiment 78, wherein the VH1 and VH2 heavy chain variable
25 domains comprise an amino acid sequence selected from the group consisting of sclerostin binders SEQ ID NOs: 95, 96, 104, 112, 120, 128, 136, 144, 152, 160, 168, 176, 184, 192, 200, 208, and 216, or DKK-1 binders SEQ ID NOs: 224, 232, 240, 248, 256, 264, 272, 280, 288, 296, 304, 312, 320, 328, 336, 344, 352, 360, 368, 376, 384, 392, 400, and 408, and wherein the VL1 and VL2 light chain variable domains comprise an amino acid sequence selected
30 from the group consisting of sclerostin binders SEQ ID NOs: 94, 103, 111, 119, 127, 135, 143, 151, 159, 167, 175, 183, 191, 199, 207, and 215, or DKK-1 binders SEQ ID NOs: 223,

231, 239, 247, 255, 263, 271, 279, 287, 295, 303, 311, 319, 327, 335, 343, 351, 359, 367, 375, 383, 391, 399, and 407.

80. The method of embodiment 78, wherein each of said first parent antibody, or antigen
5 binding portion thereof, and each of said second parent antibody, or antigen binding
portion thereof, are separately selected from the group consisting of a human antibody, a
CDR grafted antibody, and a humanized antibody.

81. The method of embodiment 78, wherein each of said first parent antibody, or antigen
10 binding portion thereof, and each of said second parent antibody, or antigen binding
portion thereof, are separately selected from the group consisting of a Fab fragment, a
F(ab')₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide
bridge at the hinge region; a Fd fragment consisting of the VH and CH1 domains; a Fv
fragment consisting of the VL and VH domains of a single arm of an antibody, a dAb
15 fragment, an isolated complementarity determining region (CDR), a single chain antibody,
and diabodies.

82. The method of embodiment 78, wherein said first parent antibody, or antigen binding
portion thereof, possesses at least one desired property exhibited by the binding molecule.
20

83. The method of embodiment 78, wherein said second parent antibody, or antigen
binding portion thereof, possesses at least one desired property exhibited by the binding
molecule.

25 84. The method of embodiment 78, wherein the Fc region is selected from the group
consisting of a native sequence Fc region and a variant sequence Fc region.

85. The method of embodiment 78, wherein the Fc region is selected from the group
consisting of an Fc region from an IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgE, and IgD.
30

86. The method of embodiment 78, wherein said desired property is selected from one or
more antibody parameters.

87. The method of embodiment 78, wherein said desired property is selected from one or more antibody parameters.
- 5 88. The method of embodiment 78, wherein said antibody parameters are selected from the group consisting of antigen specificity, affinity to antigen, potency, biological function, epitope recognition, stability, solubility, production efficiency, immunogenicity, pharmacokinetics, bioavailability, tissue cross reactivity, and orthologous antigen binding.
- 10 89. The method of embodiment 78, wherein said antibody parameters are selected from the group consisting of antigen specificity, affinity to antigen, potency, biological function, epitope recognition, stability, solubility, production efficiency, immunogenicity, pharmacokinetics, bioavailability, tissue cross reactivity, and orthologous antigen binding.
- 15 90. The method of embodiment 78, wherein said first parent antibody, or antigen binding portion thereof, binds said first antigen with a different affinity than the affinity with which said second parent antibody, or antigen binding portion thereof, binds said second antigen.
- 20 91. The method of embodiment 78, wherein said first parent antibody, or antigen binding portion thereof, binds said first antigen with a different potency than the potency with which said second parent antibody, or antigen binding portion thereof, binds said second antigen.
- 25 92. The method of embodiment 78, with the proviso that said linker is not CH1.
93. A pharmaceutical composition comprising the binding molecule of any of embodiments 1-77.
- 30 94. The binding molecule of any of embodiments 1-77 in combination with one or more of a pharmaceutically acceptable excipient, diluent or carrier.

95. A method of treating a bone disorder comprising administering to a patient in need thereof the binding molecule of any of embodiments 1-77.
96. A method of accelerating bone fracture repair comprising administering to a patient in need thereof the binding molecule of any of embodiments 1-77.
97. A method of increasing bone density comprising administering to a patient in need thereof the binding molecule of any of embodiments 1-77.
98. A method of increasing bone strength comprising administering to a patient in need thereof the binding molecule of any of embodiments 1-77.
99. The method of embodiments 96-98, wherein BMC is increased by at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, or 200 percent as compared to an untreated patient.
100. The method of embodiments 96-98, wherein BMD is increased by at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, or 200 percent as compared to an untreated patient.
101. A polynucleotide encoding the binding molecule of any of embodiments 1-77.
102. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 486 and 488.
103. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 490 and 492.
104. The binding molecule of embodiment 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 494 and 496.

105. The binding molecule of embodiment 50, wherein said VL1 CDRs are SEQ ID NOs: 225-227, said VH1 CDRs are SEQ ID NOs: 228-230, said VL2 CDRs are SEQ ID NOs: 105-107, and said VH2 CDRs are SEQ ID NOs: 108-110.

5

As permitted in certain national jurisdictions, all references disclosed herein are hereby incorporated by reference in their entireties as if each was incorporated individually, for any purpose including enabling and describing the invention. The following examples are provided solely to illustrate certain aspects of the antibodies, fragments and compositions

10 that are provided herein and thus should not be construed to limit the scope of the claimed invention.

15

TABLE 1

SEQ ID NO:	DESCRIPTION	SEQUENCE
Target Protein Sequences		
1	Human DKK-1 NA	ATGATGGCTCTGGGCGCAGCGGGAGCTACCCGGGTCTTTGTCGCGATG GTAGCGGCGGCTCTCGGCGGCCACCCTCTGCTGGGAGTGAGCGCCAC CTTGAACCTCGGTTCTCAATTCCAACGCTATCAAGAACCTGCCCCCACC GCTGGGCGGCGCTGCGGGGCACCCAGGCTCTGCAGTCAGCGCCGCGC CGGGAATCCTGTACCCGGGCGGGAATAAGTACCAGACCATTGACAAC TACCAGCCGTACCCGTGCGCAGAGGACGAGGAGTGCGGCACTGATGA GTACTGCGCTAGTCCCACCCGCGGAGGGGACGCAGGCGTGCAAATCT GTCTCGCCTGCAGGAAGCGCCGAAAACGCTGCATGCGTCACGTCATGT GCTGCCCCGGGAATTACTGCAAAAATGGAATATGTGTGTCTTCTGATC AAAATCATTTCCGAGGAGAAATTGAGGAAACCATCACTGAAAGCTTT GGTAATGATCATAGCACCTTGGATGGGTATTCCAGAAGAACCACCTTG TCTTCAAAAATGTATCACACCAAAGGACAAGAAGGTTCTGTTTGTCTC AGGTCATCAGACTGTGCCTCAGGATTGTGTTGTGATAGACACTTCTGG TCCAAGATCTGTAAACCTGTCCTGAAAGAAGGTCAAGTGTGTACCAAG CATAGGAGAAAAGGCTCTCATGGACTAGAAATATTCCAGCGTTGTTAC TGTGGAGAAGGTCTGTCTTGCCGGATACAGAAAGATCACCATCAAGC CAGTAATTCTTCTAGGCTTCACACTTGTGAGAGACAC
2	Human DKK-1 AA	MMALGAAGATRVFVAMVAAALGGHPLLGVSATLNSVLNSNAIKNLPPP LGGAAGHPGSAVSAAPGILYPGGNKYQTIDNYQPYPCAEDEECGTDEYC ASPTRGGDAGVQICLACRKRRCMRHAMCCPGNYCKNGICVSSDQNH FRGEIETITESFGNDHSTLDGYSRRTTLLSSKMYHTKGQEGSVCLRSDCA SGLCCDRHFWSKICKPVLKEGQVCTKHRRKGSHGLEIFQRCYCGEGLSCR IQKDHQASNSSRLHTCQRH
3	Mouse DKK-1 NA	ATGATGGTTGTGTGTGCAGCGGCAGCTGTCCGGTTCTTGCGCGTGT ACAATGATGGCTCTCTGCAGCCTCCCTCTGCTAGGAGCCAGTGCCACC TTGAACCTCAGTTCTCATCAATTCCAACGCGATCAAGAACCTGCCCCCA CCGCTGGGTGGTGTCTGGGGGGCAGCCGGGCTCTGCTGTCACTGTGGCG CCGGGAGTTCTCTATGAGGGCGGGAACAAGTACCAGACTCTTGACAA CTACCAGCCCTACCCTTGCGCTGAAGATGAGGAGTGCGGCTCTGACGA GTACTGCTCCAGCCCCAGCCGCGGGGCAGCCGGCGTCTCGGAGGTGTAC AGATCTGTCTGGCTTGCCGAAAGCGCAGGAAGCGCTGCATGAGGCAC GCTATGTGCTGCCCCGGGAACCTACTGCAAAAATGGAATATGCATGCC TCTGACCACAGCCATTTTCTCGAGGGGAGATTGAGGAAAGCATCATT GAAAACCTTGGTAATGACCACAACGCCGCCGCGGGGGATGGATATCC CAGAAGAACCACACTGACTTCAAAAATATATCACACCAAAGGACAAG AAGGCTCCGTCTGCCTCCGATCATCAGACTGTGCCGAGGGCTGTGTT GTGCAAGACACTTCTGGTCCAAGATCTGTAAACCTGTCCTTAAAGAAG GTCAGGTGTGCACCAAGCACAAACGGAAAGGCTCCACGGGCTGGAG ATATTCCAGCGCTGTTACTGCGGGGAAGGCTGGCTTGCAGGATACAG AAAGATCACCATCAAGCCAGCAATTCTTCTAGGCTCCACACCTGCCAG AGACAC
4	Mouse DKK-1 AA	MMVVCAAAAVRFLAVFTMMALCSLPLLGASATLNSVLINSNAIKNLPPP LGAGGQPGSAVSVAPGVLYEGGNKYQTLIDNYQPYPCAEDEECGSDEY CSSPSRGAAGVGGVQICLACRKRRCMRHAMCCPGNYCKNGICMPSD HSHFPRGEIEESIENLGNDHNAAAGDGYPRRTTLLSKIYHTKGQEGSVCL RSSDCAAGLCCARHFWSKICKPVLKEGQVCTKHRRKGSHGLEIFQRCYC GEGLACRIQKDHQASNSSRLHTCQRH

SEQ ID NO:	DESCRIPTION	SEQUENCE
5	Rat DKK-1 NA	ATGACGGTTGTGCGTGCAGTGGCAGCTGTCCGGTTCTTGGTCTGTGCTT ACAACGATGGCTCTCTGCAGCCTCCCTCCGCTCGGAGTCAGCGCCACT TTGAACTCAGTTCTCATCAATTCCAACGCGATCAAGAACCTGCCCCCA CCGCTGGGTGGTGTGCTGGGGGGCAGCCGGGCTCTGCTGTGAGCGTGGC GCCCCGAGTCCTCTATGAGGGCGGGAACAAGTACCAGACTCTTGACA ACTACCAGCCCTACCCTTGC GCGGAGGATGAGGAGTGC GGCAGT GAC GAGTACTGCTCCAGTCCCAGCCGCGGGGCAGCCGGCGTGGGAGGTGT ACAAATCTGCCTGGCTTGCCGAAAGCGCAGGAAACGCTGCATGAGGC ACGCTATGTGCTGCCCCGGGAATTACTGCAAAAACGGAATATGCATGC CCTCTGACCACAGCCATTTACCTCGAGGGGAAATCGAGGAAGGCATC ATTGAAAACCTTGCCAATGACCACGGTGCCGGGATGGATATCCCAG AAGAACCACACTGACTTCAAAAATATATCACACCAAAGGGCAAGAAG GCTCTGTCTGCCTCCGATCATCAGACTGCGCCACAGGGCTGTGTTGTG CAAGACATTTCTGGTCCAAGATCTGTAAACCTGCTCTTAAAGAAGGTC AGGTATGCACCAAGCACAGAAGGAAAGGCTCCCACGGGCTGGAGATA TTCCAGCGCTGTTACTGTGGGGAAGGTCTGGCTTG CAGGATACAGAAA GATCACCATCAAACCAGCAATTCTTCCAGGCTCCACACCTGCCAGAGA CAC
6	Rat DKK-1 AA	MTVVRAVA AVRFLVVLTTMALCSLPLGVSATLNSVLINSNAIKNLPPPL GGAGGQPGSAVSVAPGVLYEGGNKYQTL DNYQPYPCAEDEECGTDEYC SSPSRGAAGVGGVQICLACRKRRCMRHAMCCPGNYCKNGICMPSDH SHLPRGEIEEGHIENLGNDHGAGDGYPRRTTLTSKIYHTKGQEGSVCLRSS DCATGLCCARHFWSKICKPVLKEGQVCTKHRRKGSHGLEIFQRCYCGEG LACRIQKDDHHQTSNSSRLHTCQRH
7	Cyno DKK-1 NA	ATGATGGCTCTGGGCGCAGCAGGAGCTGCCCGGGTCTTGGTCTGCGCTG GTAGCGGCGGCTCTTGGCGGCCACCCTCTGCTGGGAGTGAGCGCCACC TTGAACTCGGTTCTCAATTCCAACGCGATCAAGAACCTGCCCCACCG CTGGGCGGCGCTGCGGGGCACCCAGGCTCTGCAGTCAGCGCCGCGCC AGGAATTCTGTACCCGGGCGGGAATAAGTACCAGACCATTGACAACT ACCAGCCGTACCCTTGCGCAGAGGATGAGGAGTGC GGCAGT GATGAG TACTGCGCTAGTCCCACCCGCGGAGGGGACGCGGGCGTGCAAACTCTG TCTCGCCTGCAGGAAGCGCCGAAAACGCTGCATGCGTACGCTATGTG CTGCCCCGGAATTACTGCAAAAATGGAATATGTGTGTCTTCTGATCA AAATAATTTCCGAGGGGAAATTGAGGAAACCATTACTGAAAAGCTTTG GTAATGATCATAGCACTTTGGATGGGTATTCCAGAAGAACAACATTGT CTTCAAAAATGTATCACAGCAAAGGACAAGAAGGTTCTGTGTGTCTCC GGTCATCAGACTGTGCCACAGGACTGTGTTGTGCTAGACACTTCTGGT CCAAGATCTGTAAACCTGTCCTCAAAGAAGGTCAAGTGTGTACCAAGC ATAGAAGAAAAGGCTCTCATGGGCTAGAAATATTCCAGCGTTGTTACT GCGGAGAAGGTCTGTCTTGCCGGATACAGAAAGATCACCATCAAGCC AGTAATTCTTCTAGGCTTCACACTTGT CAGAGACAC
8	Cyno DKK-1 AA	MMALGAAGAARVLVALVAAALGGHPLLGV SATLNSVLINSNAIKNLPPPL GGAAGHPGSAVSAAPGILYPGNKYQTIDNYQPYPCAEDEECGTDEYCA SPTRGGDAGVQICLACRKRRCMRHAMCCPGNYCKNGICVSSDQNNF RGEIETITESFGNDHSTLDGYSRRTTLSSKMYHSGQEGSVCLRSSDCAT GLCCARHFWSKICKPVLKEGQVCTKHRRKGSHGLEIFQRCYCGEGLSCRI QKDDHHQASNSSRLHTCQRH

SEQ ID NO:	DESCRIPTION	SEQUENCE
9	Human Sclerostin NA	ATGCAGCTCCCACTGGCCCTGTGTCTCGTCTGCCTGCTGGTACACACA GCCTTCCGTGTAGTGGAGGGCCAGGGGTGGCAGGCGTTCAAGAATGA TGCCACGGAAATCATCCCCGAGCTCGGAGAGTACCCCGAGCCTCCAC CGGAGCTGGAGAACAACAAGACCATGAACCGGGCGGAGAACGGAGG GCGGCCTCCCCACCACCCCTTTGAGACCAAAGACGTGTCCGAGTACAG CTGCCGCGAGCTGCACTTACCCGCTACGTGACCGATGGGCCGTGCCG CAGCGCCAAGCCGGTCACCGAGCTGGTGTGCTCCGGCCAGTGCGGCC CGGCGCGCCTGCTGCCAACGCCATCGGCCGCGGCAAGTGGTGGCGA CCTAGTGGGCCCCACTTCCGCTGCATCCCCGACCGCTACCGCGCGCAG CGCGTGCAGCTGCTGTGTCCCGGTGGTGAGGCGCCGCGCGCGCGCA GGTGCCTGGTGGCCTCGTGCAAGTGCAAGCGCCTACCCGCTTCCA CAACCAGTCGGAGCTCAAGGACTTCGGGACCGAGGCGCTCGGCCGC AGAAGGGCCGGAAGCCGCGGCCCGCGCCCGGAGCGCCAAAGCCAA CCAGGCCGAGCTGGAGAACGCCTACTAG
10	Human Sclerostin AA (signal peptide underlined)	<u>MQLPLALCLVCLLVHTAFRVVEG</u> QGWQAFKNDAT ~~EH~~ PELGEY ~~PE~~ PPPEL ENNKT ~~M~~ NRAENGGRPPHHPF ETKDVSEYSCRELHFTRYVTDGPCRSAPVTEL ~~V~~ CSGQC ~~G~~ PARLLPNAIG RGKWWRPSGPDFRCIPDRYR AQRVQLLCPGGEAPRARKVRLVASCKCKRLTRFHNQSELKDFGTEAARP QKGRKPRPRARSAKANQAELE NAY
11	Mouse Sclerostin NA	ATGCAGCCCTCACTAGCCCCGTGCCTCATCTGCCTACTTGTGCACGCT GCCTTCTGTGCTGTGGAGGGCCAGGGGTGGCAAGCCTTCAGGAATGAT GCCACAGAGGTCATCCCAGGGCTTGGAGAGTACCCCGAGCCTCCTCCT GAGAACAACCAGACCATGAACCGGGCGGAGAATGGAGGCAGACCTC CCCACCATCCCTATGACGCCAAAGATGTGTCCGAGTACAGCTGCCGCG AGCTGCACTACACCCGCTTCTGACAGACGGCCCATGCCGCGAGCGCCA AGCCGGTCACCGAGTTGGTGTGCTCCGGCCAGTGCGGCCCGCGCGG CTGCTGCCCAACGCCATCGGGCGCGTGAAGTGGTGGCGCCCGAACGG ACCGGATTTCCGCTGCATCCCGGATCGCTACCGCGCGCAGCGGGTGCA GCTGCTGTGCCCCGGGGCGCGCGCCGCGCTCGCGCAAGGTGCCGT TGGTGGCCTCGTGCAAGTGCAAGCGCCTACCCGCTTCCACAACAGT CGGAGCTCAAGGACTTCGGGCCGAGACCGCGCGGCCGAGAAAGGT CGCAAGCCGCGGCCCGCGGCCCGGGAGCCAAAGCCAACAGGCGG AGCTGGAGAACGCCTACTAG
12	Mouse Sclerostin AA (signal peptide underlined)	<u>MQPSLAPCLICLLVHA</u> AFC ~~AVE~~ GQGWQAFRNDAT ~~EV~~ IPGLGEY ~~PE~~ PPPEN NQTMNRAENGGRPPHHPYDAKDVSEYSCRELHYTRFLT ~~D~~ GPCRSAPVT ELVCSGQC ~~G~~ PARLLPNAIGRVKWWRPNGPDFRCIPDRYRAQRVQLLCPG GAAPRSRKVRLVASCKCKRLTRFHNQSELKDFGPETARPQKGRKPRPGA RGAKANQAELENAY
13	Rat Sclerostin NA	ATGCAGCTCTCACTAGCCCCCTTGCCTTGCCTGCCTGCTTGTACATGCAG CCTTCGTTGCTGTGGAGAGCCAGGGGTGGCAAGCCTTCAAGAATGATG CCACAGAAATCATCCCGGGACTCAGAGAGTACCCAGAGCCTCCTCAG GAACTAGAGAACAACCAGACCATGAACCGGGCCGAGAACGGAGGCA GACCCCCCACCATCCTTATGACACCAAAGACGTGTCCGAGTACAGCT GCCGCGAGCTGCACTACACCCGCTTCTGTACCGACGGCCCGTGCCGCA GTGCCAAGCCGGTCACCGAGTTGGTGTGCTCGGGCCAGTGCGGCCCC GCGCGGCTGCTGCCAACGCCATCGGGCGCGTGAAGTGGTGGCGCCC GAACGGACCCGACTTCCGCTGCATCCCGGATCGCTACCGCGCGCAGC GGGTGCAGCTGCTGTGCCCCGGCGCGCGCGCGCGCTCGCGCAAG GTGCGTCTGGTGGCCTCGTGCAAGTGCAAGCGCCTACCCGCTTCCAC AACCAGTCGGAGCTCAAGGACTTCGGACCTGAGACCGCGCGGCCGCA GAAGGGTCGCAAGCCGCGGCCCGCGCCCGGGGAGCCAAAGCCAACC AGGCGGAGCTGGAGAACGCCTACTAG

SEQ ID NO:	DESCRIPTION	SEQUENCE
14	Rat Sclerostin AA (signal peptide underlined)	<u>MQLSLAPCLACLLVHAA</u> FVAVESQGWQAFKNDAT EII PGLREY PEPPQEL ENNQTMNRAENGGRPPHHPYDTKDVSEYSCRELHYTRFVTDGPCRSAKP VTELVCSGQCGPARLLPNAIGRVKWWRPNGPDFRCIPDRYRAQRVQLLC PGGAAPRSRKVRLVASCKCKRLTRFHNQSELKDFGPETARPQKGRKPRP RARGAKANQAELENAY
15	Cyno Sclerostin NA	ATGCAGCTCCCACTAGCCCTGTGTCTTGTCTGCCTGCTGGTACACGCA GCCTTCCGTGTAGTGGAGGGCCAGGGGTGGCAGGCCTTCAAGAATGA TGCCACGGAAATCATCCCCGAGCTCGGAGAGTACCCCGAGCCTCCAC CGGAGCTGGAGAACAAACAAGACCATGAACCGGGCGGAGAACGGAGG GCGGCCTCCCCACCACCCCTTTGAGACCAAAGACGTGTCCGAGTACAG CTGCCGAGAGCTGCACCTTACCCCGCTACGTGACCGACGGGCAGTGCC GCAGCGCCAAGCCAGTCACCGAGTTGGTGTGCTCCGGCCAGTGCGGC CCGGCACGCTGCTGCCCAACGCCATCGGCCGCGGCAAGTGGTGGCG CCCGAGTGGGCCCCGACTTTCGCTGCATCCCCGACCGCTACCGCGCGCA GCGTGTGCAGCTGCTGTGTCCCGGTGGTGCCGCGCCGCGCGCGCAA GGTGCGCCTGGTGGCCTCGTGCAAGTGCAAGCGCCTCACCCGCTTCCA CAACCAGTCGGAGCTCAAGGACTTCGGTCCCGAGGCCGCTCGGCCGC AGAAGGGCCGGAAGCCGCGGCCCGCGCCCGGGGGGCCAAAGCCAA TCAGGCTGAGCTGGAGAACGCCTACTAG
16	Cyno Sclerostin AA (signal peptide underlined)	<u>MQLPLALCLVCLLVHAA</u> FRVVEGQGWQAFKNDAT EII PELGEY PEPPPEL ENNKTMNRAENGGRPPHHPFETKDVSEYSCRELHFTRYVTDGQCRSAKP VTELVCSGQCGPARLLPNAIGRGKWWRPSPDFRCIPDRYRAQRVQLLC PGGAAPRARKVRLVASCKCKRLTRFHNQSELKDFGPEAAPRPQKGRKPRP RARGAKANQAELENAY
DVD-Ig Sequences		

SEQ ID NO:	DESCRIPTION	SEQUENCE
17	19D11-6.37 G2 NA	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGCTGCTGTGG CT GAGAGGTGCGCGCTGTGAGGTGCAGCTGGTGGAGTCTGGGGGAGGCT TGG TACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCA CC TTCAGTAGCTACGACATGCACTGGGTCCGCCAAGCTACAGGAAAAGG TCT GGAGTGGGTCTCAGCTATTGGTACTGCTGGTGACACATACTATGCAGG CT CCGTGAAGGGCCGATTACCATCTCCAGAGAAAATGCCAAGAACTCC TTG TATCTTCAAATGAACAGCCTGAGAGTCGGGGACACGGCTGTGTATTAC TG TGCAAGGTCCTGGGGAGAGGGGAATTACTACTTCTACTACGGTATGGA CG TCTGGGGCCAAGGGACCACGGTCACCGTCTCTAGTGCCTCCACCAAGG GC CCATCGGTCTTCCCCCTGGCGCCCCAGGTGCAGCTGGTGGAGTCTGGG GG AGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTC TG GATTCACCTTCAGTGGCTATGGCATGCACTGGGTCCGCCAGGCTCCAG GC AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAATGATAA ATA CTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATGC CA AGAACACGCTGTATCTGCAAATGAACAGCCTGAGAGCTGAGGACACG GCT GTGTATTACTGTGCGAGAGAGCTACGGGTCTCTGGGGCCAGGGAAC CCT GGTCACCGTCTCTAGTGCCTCCACCAAGGGCCCATCGGTCTTCCCCCT GG CGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGC CTG GTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCAGGC GC TCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCTACAGTCCTCAGG AC TCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCA CC CAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGT GGA CAAGACAGTTGAGCGCAAATGTTGTGTGAGTGGCCACCGTGCCACG AC CACCTGTGGCAGGACCGTCAGTCTTCTCTTCCCCCAAAACCCAAGG AC ACCCTCATGATCTCCCGGACCCCTGAGGTACGTGCGTGGTGGTGGAC GT GAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCG TGG AGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGC ACG TTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGAAC GG CAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCA TCG AGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTG TAC ACCCTGCCCCCATCTCGGGAGGAGATGACCAAGAACCAGGTCAGCCT GAC CTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGA GA GCAATGGGCAGCCGGAGAACAACACTACAAGACCACACCTCCCATGCTG

SEQ ID NO:	DESCRIPTION	SEQUENCE
18	19D11-6.37 G2 AA	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYDMHWVRQATGKGLEWV SA IGTAGDTYYAGSVKGRFTISRENAKNSLYLQMNSLRVGD TAVYYCARSW G EGNYFYFYGM DVWGQGTTVT VSSASTKGPSVFPLAPQVQLVESGGGVV QP GRSLRLSCAASGFTFSGYGMHWVRQAPGKGLEWVAVISYDGNDKYYAD SV KGRFTISRDN AKNTLYLQMNSLRAEDTAVYYCARELRVLWGQGT LVT V SS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT VSWNSGALTSGV HTFPAVLQSSGLYSLSSVTV PSSNFGTQTYTCNV DHKPSNTKVDKTV R KCCVECP PCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVS VLT VVH QDWLNGKEY KC KVS NKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTTPPMLDS DGSFFLYSKLTVDKSRWQQG N VFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
19	19D11-6.37 LC NA	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGCTGCTGTGG CT GAGAGGTGCGCGCTGTTCTATGTGCTGACTCAGCCACCCTCGGTGTC AG TGGCCCCAGGACAGACGGCCAGGATTACCTGTGGGGGAGACAACATT GGA AGTATAAGTGTGCATTGGTACCAGCAGAAGCCAGGCCAGGCCCCCTGT GCT GGTCGTCTATGATGATAGCGACCGGCCCTCAGGGATCCCTGAGCGATT CT CTGGCTCCAACCTCTGGGAACACGGCCACCCTGACCATCAGCTGGGTCTG AA GCCGGGGATGAGGCCGACTATTACTGTCAGGTGTGGGATAGTAGTATT GA TCATCCTGTGTTATTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCA GC CCAAGGCTGCCCCCTCGGTCACTCTGTTTCGATATTGTGATGACCCAGA CT CCACTCTCTCTGTCCGTCACCCCTGGACAGCCGGCCTCCATCTCCTGCA A GTCTGGTCAGAGCCTCCTGCATAGTGATGGAAAGACCTATTTGTATTG GT ACCTGCAGAAGCCAGGCCAGCCTCCACAGTTCCTGATCTATGAAGTTT CC AACCGGTTCTCTAGAGTGCCAGATAGGTTTCAGTGGCAGCGGGTCAGG GAC AGATTTCACTGAGAATCAGCCGGGTGGAGGCTGAGGATGTTGGAA TTT ATTACTGCATGCAAAGTATACAGCTTCCGTGGACGTTTCGGCCAAGGGA CC CAGGTGGAAATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTC CC GCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCT GC TGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAAGGTGGAT AAC GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAG CAA GGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAG ACT ACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTG AGC TCGCCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT
20	19D11-6.37 LC AA	SYVLTQPPSVSVAPGQTARITCGGDNIGSISVHWYQQKPGQAPVLVYDD SDRPSGIPERFSGSNSGNTATLTISWVEAGDEADYYCQVWDSSIDHPVLF GGGTKLTVLGQPKAAPSVTLFDIVMTQTPLSLSVTPGQPASISCKSGQSL LHSDGKTYLYWYLQKPGQPPQFLIYEVSNRFSRVPDRFSGSGSGTDFTLR ISRVEAEDVGIYYCMQSIQLPWTFGQGTQVEIKRTVAAPSVFIFPPSDEQ LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDST YS LSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:	DESCRIPTION	SEQUENCE
21	6.37.5-19D11 G2 NA	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGCTGCTGTGG CT GAGAGGTGCGCGCTGTCAGGTGCAGCTGGTGGAGTCTGGGGGAGGCG TGG TCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCA CC TTCAGTGGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGG GCT GGAGTGGGTGGCAGTTATATCATATGATGGAAATGATAAATACTATGC AG ACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATGCCAAGAAC ACG CTGTATCTGCAAATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTAT TA CTGTGCGAGAGAGCTACGGGTCCTCTGGGGCCAGGGAACCTGGTCA CCG TCTCTAGTGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCG AG GTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTC CCT GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTAGCTACGACAT GC ACTGGGTCCGCCAAGCTACAGGAAAAGGTCTGGAGTGGGTCTCAGCT ATT GGTACTGCTGGTGACACATACTATGCAGGCTCCGTGAAGGGCCGATTC AC CATCTCCAGAGAAAATGCCAAGAACTCCTTGTATCTTCAAATGAACAG CC TGAGAGTCGGGGACACGGCTGTGTATTACTGTGCAAGGTCTCTGGGGA GAG GGGAATTACTACTTCTACTACGGTATGGACGTCTGGGGCCAAGGGACC AC GGTCACCGTCTCTAGTGCCTCCACCAAGGGCCCATCGGTCTTCCCCCT GG CGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGC CTG GTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGGAACCTCAGGC GC TCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGG AC TCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCA CC CAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGT GGA CAAGACAGTTGAGCGCAAATGTTGTGTGTCAGGTGCCACCGTGCCACG AC CACCTGTGGCAGGACCGTCAGTCTTCTCTTCCCCCAAAACCCAAGG AC ACCCTCATGATCTCCCGGACCCCTGAGGTACGTGCGTGGTGGTGGAC GT GAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCG TGG AGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGC ACG TTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCTGAAC GG CAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCA TCG AGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTG TAC ACCCTGCCCCCATCT ⁸⁹ GGGAGGAGATGACCAAGAACCAGGTCAGCCT GAC CTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGA GA GCAATGGGCAGCCGGAGAACAACACTACAAGACCACACCTCCCATGCTG

SEQ ID NO:	DESCRIPTION	SEQUENCE
22	6.37.5-19D11 G2 AA	QVQLVESGGGVVQPGRSLRLSCAASGFTFSGYGMHWVRQAPGKGLEWV AV ISYDGNDKYYADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCARE L RVLWGQGTLLTVSSASTKGPSVFPLAPEVQLVESGGGLVQPGGSLRLSCA ASGFTFSSYDMHWVRQATGKGLEWVSAIGTAGDTYYAGSVKGRFTISRE N AKNSLYLQMNSLRVGD TAVYYCARSWGEGNYYFYYGMDVWGQGTTV TVSS ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNV DHKPSNTKVDKTVR KCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVS VLT TVVHQDWLNGKEY KC KVS NKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG FYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSRWQQG N VFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
23	6.37.5-19D11 LC NA	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGCTGCTGTGG CT GAGAGGTGCGCGCTGTGATATTGTGATGACCCAGACTCCACTCTCTCT GT CCGTCACCCCTGGACAGCCGGCCTCCATCTCCTGCAAGTCTGGTCAGA GC CTCCTGCATAGTGATGGAAGACCTATTTGTATTGGTACCTGCAGAAG CC AGGCCAGCCTCCACAGTTCCTGATCTATGAAGTTTCCAACCGGTTCTC TA GAGTGCCAGATAGGTTTCAGTGGCAGCGGGTCAGGGACAGATTTACACA CTG AGAATCAGCCGGGTGGAGGCTGAGGATGTTGGAATTTATTACTGCATG CA AAGTATACAGCTTCCGTGGACGTTCCGGCCAAGGGACCCAGGTGAAAA TCA AACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCGTCCTATGTGCT G ACTCAGCCACCCTCGGTGTCAGTGGCCCCAGGACAGACGGCCAGGAT TAC CTGTGGGGGAGACAACATTGGAAGTATAAGTGTGCATTGGTACCAGC AGA AGCCAGGCCAGGCCCTGTGCTGGTCGTCTATGATGATAGCGACCGGCC CC TCAGGGATCCCTGAGCGATTCTCTGGCTCCAACTCTGGGAACACGGCC AC CCTGACCATCAGCTGGGTCTGAAGCCGGGGATGAGGCCGACTATTACT GTC AGGTGTGGGATAGTAGTATTGATCATCCTGTGTTATTCGGCGGAGGGA CC AAGCTGACCGTCCTAGGTCAGCCAAGGCCAACCCCACTGTCACTCTG TT CCCGCCCTCCTCTGAGGAGCTCCAAGCCAACAAGGCCACACTAGTGTG TC TGATCAGTGACTTCTACCCGGGAGCTGTGACAGTGGCCTGGAAGGCA GAT GGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCAAACCCTCCAAACA GAG CAACAACAAGTACGCGGCCAGCAGCTACCTGAGCCTGACGCCCCGAGC AGT GGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGC ACC GTGGAGAAGACAGTGGCCCCCTACAGAATGTTCA
24	6.37.5-19D11 LC AA	DIVMTQTPLSLSVTPGQPASISCKSGQSLHSDGKTYLYWYLQKPGQPPQ FLIYEVSNRFSRVPDRFSGSGTDFTLRISRVEAEDVGIYYCMQSIQLP WTFGQGTQVEIKRTVAAPSVFIFPSYVLTQPPSVSVAPGQTARITCGGDN IGSISVHWYQQKPGQAPVLVYDDSDRPSGIPERFSGSNSGNTATLTISW VEAGDEADYYCQVWDSSIDHPVLFGGGKLTVLGQPKANPTVTLFPPSSE ELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNKY A ASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

SEQ ID NO:	DESCRIPTION	SEQUENCE
25	8G2-6.37 G2 NA	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGCTGCTGTGG CT GAGAGGTGCGCGCTGTCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGG TGA AGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATACA CC TTCACCAGTTATGATATCAACTGGGTGCGACAGGCCACTGGACAAGG GCT TGAGTGGATGGGATGGATGAACCCTAACAGTGGTAAACAGGGTATG CAC AGAAGTTCCAGGGCAGAGTCACCATGACCAGGGACACCTCCATAAGC ACA GCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTA TTA CTGTGCGAGAGAGGAGGAATACTATGAATCGGGGAGCCTCTTCTACT ACT ACGGTTTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCTAGTG CC TCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCCAGGTGCAGCTG GT GGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCT CCT GTGCAGCCTCTGGATTACCTTCAGTGGCTATGGCATGCACTGGGTCC GC CAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATCATATGA TGG AAATGATAAATACTATGCAGACTCCGTGAAGGGCCGATTACCATCTC CA GAGACAATGCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGA GCT GAGGACACGGCTGTGTATTACTGTGCGAGAGAGCTACGGGTCTCTGG GG CCAGGGAACCCTGGTCACCGTCTCTAGTGCCTCCACCAAGGGGCCATC GG TCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGG CC CTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTG TG GAACTCAGGCGCTCTGACCAGCGGCGTGACACACCTTCCCAGCTGTCT AC AGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GC AACTTCGGCACCCAGACCTACACCTGCAACGTAGATCACAAGCCCAG CAA CACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTCGAGTGCC CAC CGTGCCAGCACCACTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCC CA AAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGC GT GGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGT ACG TGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAG CAG TTCAACAGCACGTTCCGTGTGGTCAGCGTCCTACCGTTGTGCACCAG GA CTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCC TCC CAGCCCCCATCGAGAAAACCATCTCCAAAACCAAGGGCAGCCCCGA GAA CCACAGGTGTACAC ⁹² CTGCCCCCATCCCGGGAGGAGATGACCAAGAA CCA GGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGC CG TGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCAC

SEQ ID NO:	DESCRIPTION	SEQUENCE
26	8G2-6.37 G2 AA	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQATGQGLEWM GW MNPNSGKTGYAQKFQGRVTMTRDTSISTAYMELSSLRSED TAVYYCARE E EYYESGSLFYFYYGLDVWGQGT TTVTVSSASTKGPSVFPLAPQVQLVESGG G VVQPGRSLRLSCAASGFTFSGYGMHWVRQAPGKGLEWVAVISYDGNDK YY ADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCARELRVLWGQGT LV TVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNV DHPKPSNTKVDK TVERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVS VLT TVVHQDWLN GK EYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSR W QQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
27	8G2-6.37 LC NA	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGCTGCTGTGG CT GAGAGGTGCGCGCTGTGACATCCAGATGACCCAGTCTCCATCTTCCGT GT CTGCGTCTGTAGGAGACAGAGTCACCATCACTTGTCTGGGCGAGTCAGG AT ATTAGCAACTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGTCCC CAA GCTCCTGATCTATGCTGCGTCCTATTTACAAAGTGGGGTCCCATCAAG GT TCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCC TG CAGCCTGAAGATTTTGCAACTTACTCTTGTC AACAGGCTAACAGTTTC CC ATTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAACGTA CTGTGGC TG CACCATCTGTCTTCATCTTCCCGCCAGATATTGTGATGACCCAGACTCC A CTCTCTCTGTCCGTCACCCCTGGACAGCCGGCCTCCATCTCCTGCAAGT C TGGTCAGAGCCTCCTGCATAGTGATGGAAAGACCTATTTGTATTGGTA CC TGCAGAAGCCAGGCCAGCCTCCACAGTTCCTGATCTATGAAGTTTCCA AC CGGTTCTCTAGAGTGCCAGATAGGTTCA GTGGCAGCGGGTCAGGGAC AGA TTTCACACTGAGAATCAGCCGGGTGGAGGCTGAGGATGTTGGAATTTA TT ACTGCATGCAAAGTATACAGCTTCCGTGGACGTTCTGGCCAAGGGACCC AG GTGGAAATCAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCG CC ATCTGATGAGCAGTTGAAATCTGGA ACTGCCTCTGTTGTGTGCCTGCT GA ATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC GCC CTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAA GGA CAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAGACT ACG AGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGC TCG CCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT
28	8G2-6.37 LC AA	DIQMTQSPSSVSASVGDRTITCRASQDISNWLAWYQQKPGKVPKLLIYA ASYLQSGVPSRFSGSGSDFTLTISLQPEDFATYSCQQANSFPFTFGP GTKVDIKRTVAAPSVFIFPPDIVMTQTPLSLSVTPGQPASISCKSGQSLL HSDGKTYLYWYLQKPGQPPQFLIYEVSNRFSRVPDRFSGSGSDFTLRI SRVEAEDVGIYYCMQSIQLPWTFGQGTQVEIKRTVAAPSVFIFPPSDEQL KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSTYS L SSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:	DESCRIPTION	SEQUENCE
29	6.37-8G2 G2 NA	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGCTGCTGTGG CT GAGAGGTGCGCGCTGTCAGGTGCAGCTGGTGGAGTCTGGGGGAGGGC TGG TCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCA CC TTCAGTGGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGCAAGGG GCT GGAGTGGGTGGCAGTTATATCATATGATGGAAATGATAAATACTATGC AG ACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAATGCCAAGAAC ACG CTGTATCTGCAAATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTAT TA CTGTGCGAGAGAGCTACGGGTCCTCTGGGGCCAGGGAACCTGGTCA CCG TCTCTAGTGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCC AG GTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC AGT GAAGGTCTCCTGCAAGGCTTCTGGATACACCTTACCAGTTATGATAT CA ACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGATGG ATG AACCCTAACAGTGGTAAAACAGGGTATGCACAGAAGTTCCAGGGCAG AGT CACCATGACCAGGGACACCTCCATAAGCACAGCCTACATGGAGCTGA GCA GCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGAGGAG GAA TACTATGAATCGGGGAGCCTCTTCTACTACTACGGTTTGGACGTCTGG GG CCAAGGGACCACGGTCACCGTCTCTAGTGCCTCCACCAAGGGCCCATC GG TCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGG CC CTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTG TG GAACTCAGGCGCTCTGACCAGCGGCGTGACACACCTTCCCAGCTGTCTT AC AGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GC AACTTCGGCACCCAGACCTACACCTGCAACGTAGATCACAAGCCCAG CAA CACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTGCGAGTGCC CAC CGTGCCAGCACACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCC CA AAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGC GT GGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGT ACG TGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAG CAG TTCAACAGCACGTTCCGTGTGGTCAGCGTCCTACCGTTGTGCACCAG GA CTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCC TCC CAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGA GAA CCACAGGTGTACAC ⁹⁵ CTGCCCCCATCCCGGGAGGAGATGACCAAGAA CCA GGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGC CG TGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCAC

SEQ ID NO:	DESCRIPTION	SEQUENCE
30	6.37-8G2 G2 AA	QVQLVESGGGVVQPGRSRLSCAASGFTFSGYGMHWVRQAPGKGLEWV AV ISYDGNDKYYADSVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCARE L RVLWGQGTLLTVSSASTKGPSVFPLAPQVQLVQSGAEVKKPGASVKVSC K ASGYTFTSYDINWVRQATGQGLEWMGWMNPNSGKTGYAQKFQGRVTM TRD TSISTAYMELSSLRSED TAVYYCAREEEYYESGSLFYYYGLDVWGQGT V TVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDPKPSNTKVDK TVERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVS VLT VVHQDWLN GK EYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLT LVKGFYPSDIAVEWESNGQPENNYKTTTPMLDSDGSFFLYSKLTVDKSR W QQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
31	6.37-8G2 LC NA	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGCTGCTGTGG CT GAGAGGTGCGCGCTGTGATATTGTGATGACCCAGACTCCACTCTCTCT GT CCGTCACCCCTGGACAGCCGGCCTCCATCTCCTGCAAGTCTGGTCAGA GC CTCCTGCATAGTGATGGAAGACCTATTTGTATTGGTACCTGCAGAAG CC AGGCCAGCCTCCACAGTTCCTGATCTATGAAGTTTCCAACCGGTTCTC TA GAGTGCCAGATAGGTTTCAGTGGCAGCGGGTCAGGGACAGATTTACACA CTG AGAATCAGCCGGGTGGAGGCTGAGGATGTTGGAATTTATTACTGCATG CA AAGTATACAGCTTCCGTGGACGTTTCGGCCAAGGGACCCAGGTGAAAA TCA AACGAACGGTGGCTGCACCATCTGTCTTCATCTTCCCGGACATCCAGA TG ACCCAGTCTCCATCTTCCGTGTCTGCGTCTGTAGGAGACAGAGTCACC AT CACTTGTCGGGCGAGTCAGGATATTAGCAACTGGTTAGCCTGGTATCA GC AGAAACCAGGGAAAGTCCCCAAGCTCCTGATCTATGCTGCGTCCTATT TA CAAAGTGGGGTCCCATCAAGGTTTCAGCGGCAGTGGATCTGGGACAGA TTT CACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTACTC TT GTCAACAGGCTAACAGTTTCCCATTCACCTTTCGGCCCTGGGACCAAAG TG GATATCAAACGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCA TC TGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAA TA ACTTCTATCCCAGAGAGGGCCAAAGTACAGTGGAAGGTGGATAACGCC CTC CAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGA CAG CACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAGACTACG AGA AACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCG CCC GTCACAAAGAGCTTCAACAGGGGAGAGTGT
32	6.37-8G2 LC AA	DIVMTQTPLSLSVTPGQPASISCKSGQSLHSDGKTYLYWYLQKPGQPPQ FLIYEVSNRFSRVPDRFSGSGSGTDFTLRISRVEAEDVGIYYCMQSIQLP WTFGQGTQVEIKRTVAAPSVFIFPDIQMTQSPSSVSASVGDRVTITCRAS QDISNWLAWYQQKPGKVPKLLIYAASYLQSGVPSRFSGSGSGTDFTLTIS SLQPEDFATYSCQANSFPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQLK SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSL S STLTLSKADYEHKVKYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:	DESCRIPTION	SEQUENCE
33	6.147-AbL-20C3.1 G2 NA	CAGGTGCAGCTTGTCTGAGAGCGGTGGAGGGGTGGTACAACCCGGAAG ATCACTCCGGCTTTCATGCGCAGCATCCGGTTTTACATTTTCGCGGTAT GACATGCACTGGGTGAGACAGGCACCAGGAAAAGGGCTGGAGTGGGT GGCCATCATCTTCTATGATGGGTCCAATAAGTACTACGCCGACCCGGT AAAAGGGAGGTTCACTATTAGCCGCGACAACCTCGAAGAATACGCTGT ACCTGCAGATGAACTCGTTGCGAGCCGAAGATACCGCGGTCTACTATT GTGCGACGCTCGCGGCTGCGTTCGATTACTGGGGCCAAGGAACATTGG TCACGGTCTCCTCAGCGTCAACGAAAGGACCGTCGGTGTTCCCCTTGG CCCCTCAGGTCCAAGTCAAGAGTCAGGACCCGGCCTTGTGAAACCTT CGGAAACTCTTAGCTTGACGTGTACTGTGTCTGGGAGGATCAATCTCGT CATACTATTGGTCGTGGATTCTGGCAGCCGCTGGTAAAGGCTTGGAGT GGATTGGGTATATCTCCGACTCCGGGTCCACGAATTACAACCCCTCCC TCAAGTCGAGAATTCCGATCAGCGTGGATACCTCGAAGAACCAGTTTA GCCTCAAGCTGTCGTGAGTACAGCGGCCGACACCGCCGTCTATTACT GCGCACGCTGGCAGCTCGCTCACGATGCGTTCGACATCTGGGGTCAGG GGACAATGGTAACCGTCTTAGTGCCTCCACCAAGGGCCCATCGGTCT TCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCC TGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGT GGAACCTCAGGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCC TACAGTCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCT CCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGATCACAAAG CCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAAATGTTGTGT CGAGTGCCCAACCGTGCCAGCACCACTGTGGCAGGACCGTCAGTCTT CCTCTTCCCCCAAAACCAAGGACACCCTCATGATCTCCCGGACCCC TGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGG TCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAG ACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAG CGTCCTCACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACA AGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCATCGAGAAAACC ATCTCCAAAACCAAGGGCAGCCCCGAGAACCACAGGTGTACACCCT GCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTGACGCTGACCT GCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAG AGCAATGGGCAGCCGGAGAACAACCTACAAGACCACACCTCCCATGCT GGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAA GAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATG AGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG GTAAA
34	6.147-AbL-20C3.1 G2 AA	QVQLVESGGGVVQPGRSRLRLSCAASGFTFSRYDMHWVRQAPGKGLEW VAHFFYDGSNKYYADPVKGRFTISRDNKNTLYLQMNSLR AEDTAVYYC ATLAAAFDYWGQGLTVTVSSASTKGPSVFPLAPQVQLQESGPGLVKPS E TLSTCTVSGGSISYYWSWIRQPPGKLEWIGYISDSGSTINYNPSLKSR I PISVDTSKNQFSLKLSSVTAADTAVYYCARWQLAHDAFDIWGQGMVT VSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPTVSWNSGALTS GVHTFPAVLQSSGLYSLSVTVTPSSNFGTQTYTCNVDPKPSNTKVDKTV ERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGK EYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSRW QQGNVVFSCSVMEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
35	6.147-AbL-20C3.1 LC NA	TCATACGTGCTCACTCAGCCGCCAGCGTATCGGTGGCTCCCGGACAG ACGGCGCGAATCACGTGCGGTGGGAACAATATCGGCTCCAAGTCAGT CCATTGGTATCAACAGAAACCTGGTCAGGCACCAGTCTGGTGGTATA CGATGACTCGGACAGGCCCTCGGAGATTCCGGAACGCTTCTCCGGATC GAATTCGGGGAACACAGCGACCTTGACGATCAGCAGAGTGGAGGCCG GAGATGAAGCCGACTACTATTGTCAGGTGTGGGATTCCAGCTCCGACC ACGTCGTATTTGGAGGTGGGACACGGCTTACCGTCTCGGGCAGCCCA AGGCTGCGCCATCGGTCACTCTGTTCCACCTCAGAGCGCCCTGACCC AACC GGCGTCCGTGTCCGGTTCACCAGGCCAGTCAATCACTATTTTCAT GTACGGGGACGTCTGCCGACGTGGGAGGGTACAAC TACGTATCATGG TATCAACAGCACCCCGGTAAAGCGCCGAAGCTGATGATCTACGAGGT CAGCTATAGGCCTTCGGAGGTGTCAAATCGGTTCTCCGGTTCGAAATC GGGTTTCGACGGCATCGTTGACAATCAGCGGGCTCCAGCCCGAAGATG AGGCCGACTACTATTGCTCCTCGTATGCGATTTCCAGCACTCTTGTCTT TGGCGGAGGAACAAAGATGACCGTCCTAGGTCAGCCCAAGGCCAACC CCACTGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTCCAAGCCAACA AGGCCACACTAGTGTGTCTGATCAGTGACTTCTACCCGGGAGCTGTGA CAGTGGCCTGGAAGGCAGATGGCAGCCCCGTCAAGGCGGGAGTGGAG ACCACCAAACCCTCCAAACAGAGCAACAACAAGTACGCGGCCAGCAG CTACCTGAGCCTGACGCCCCGAGCAGTGGAAGTCCCACAGAAGCTACA GCTGCCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCC CCTACAGAATGTTCA
36	6.147-AbL-20C3.1 LC AA	SYVLTQPPSVSVAPGQTARITCGC NNIGSKSVHWYQQKPGQAPVLVVD DSDRPSEIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVV GGGTRLTVLGQPKAAPSVTLFPPQSALTQPASVSGSPGQSITISCTGTSSD VGGYNYYSWYQQHPGKAPKLMIEVSYPKGVSNRFGSGSKSGSTASLTI SGLQPEDEADYYCSSYAISSITLVFGGGTKMTVLGQPKANPTVTLFPPSSE ELQANKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYA ASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

SEQ ID NO:	DESCRIPTION	SEQUENCE
37	6.147-AbL-27H6 G2 NA	CAGGTGCAGCTTGTCTGAGAGCGGTGGAGGGGTGGTACAACCCGGAAG ATCACTCCGGCTTTCATGCGCAGCATCCGGTTTTACATTTTCGCGGTAT GACATGCACTGGGTGAGACAGGCACCAGGAAAAGGGCTGGAGTGGGT GGCCATCATCTTCTATGATGGGTCCAATAAGTACTACGCCGACCCGGT AAAAGGGAGGTTCACTATTAGCCGCGACAACCTCGAAGAATACGCTGT ACCTGCAGATGAACTCGTTGCGAGCCGAAGATACCGCGGTCTACTATT GTGCGACGCTCGCGGTGCGTTCGATTACTGGGGCCAAGGAACATTGG TCACGGTCTCCTCAGCGTCAACGAAAGGACCGTCGGTGTTCCCCTTGG CCCCTGAGGTGCAGCTCGTCGAAAGCGGAGGAGGCCTGGTCCAACCT GGTGGTTCCCTCCGACTGTCATGTGCCGCATCCGGTTTACGTTTTCAT CGTACTCGATGAACTGGGTCCGCCAGGCACCGGGGAAAGGGTTGGAA TGGGTATCCTACATTTTCGTCCAGCGGGTCAAGCATCTACTATGCGGAT AGCGTAAAGGGCCGGTTCACGATCTCGAGAGACAACGCGAAGAATTC GTTGTATCTTCAGATGAATTCGCTCAGGGATGAGGACACAGCGGTGTA TTACTGCGCTCGCGAAAGATACTATGGAGACACCCCCCTTTGATTACTG GGGACAGGGAACCTCTTGTGACCGTCTCTAGTGCTCCACCAAGGGCCC ATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCAC AGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGAC GGTGTCTGGAAGTCAAGGCGCTCTGACCAGCGGCGTGACACCTTCCC AGCTGTCTACAGTCTCAGGACTCTACTCCCTCAGCAGCGTGGTGAC CGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGA TCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAAT GTTGTGTCGAGTGCCACCGTGCCAGCACCACTGTGGCAGGACCGT CAGTCTTCTCTTCCCCCAAAACCAAGGACACCTCATGATCTCCC GGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGAC CCCGAGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAA TGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTG TGGTCAGCGTCTCACC GTTGTGCACCAGGACTGGCTGAACGGCAAGG AGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCAGCCCCATCGAG AAAACCATCTCCAAAACCAAGGGCAGCCCCGAGAACCACAGGTGTA CACCTGCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTGACCC TGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGT GGGAGAGCAATGGGCAGCCGGAGAACAATAACAAGACCACACCTCCC ATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTG GACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGAT GCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTC TCCGGGTAAA
38	6.147-AbL-27H6 G2 AA	QVQLVESGGGVVQPGRLRLSCAASGFTFSRYDMHWVRQAPGKGLEW VAHFDGSNKYYADPVKGRFTISRDN SKNTLYLQMNSLR AEDTAVYYC ATLAAAFDYWGQGLTVTVSSASTKGPSVFPLAPEVQLVESGGGLVQPGG SLRLSCAASGFTFSYSMNWVRQAPGKGLEWVSYISSGSSIIYADSVK GRFTISRDN AKNSLYLQMNSLRDEDTAVYYCARERYYGDPEDYWGQG TLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPTVSWNSG ALTSGVHTFPAVLQSSGLYSLSVTVTPSSNFGTQTYTCNV DHKPSNTKV DKTVERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVS VLT VVHQDW LNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFPYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTV D KSRWQQGNV FSCSV MHEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
39	6.147-AbL-27H6 LC NA	TCATACGTGCTCACTCAGCCGCCAGCGTATCGGTGGCTCCCGGACAG ACGGCGCGAATCACGTGCGGTGGGAACAATATCGGCTCCAAGTCAGT CCATTGGTATCAACAGAAACCTGGTCAGGCACCAGTCTGGTGGTATA CGATGACTCGGACAGGCCCTCGGAGATTCCGGAACGCTTCTCCGGATC GAATTCGGGGAACACAGCGACCTTGACGATCAGCAGAGTGGAGGCCG GAGATGAAGCCGACTACTATTGTCAGGTGTGGGATTCCAGCTCCGACC ACGTCGTATTTGGAGGTGGGACACGGCTTACCGTCTCGGGCAGCCCA AGGCTGCGCCATCGGTCACTCTGTTCCACCTGATATCGTAATGACAC AGACACCCCTCTCCCTCCCCGTGACCCAGGGGAGCCTGCATCAATCT CCTGCCGCTCATCGCAGTCGCTTCTGAATTCGGTGGACGGATCGACTA ACCTTGACTGGTATTTGCAAAAACCGGGACAGTCACCTCAACTCCTGA TCTACACTCTGAGCTATCGGGCGTCAGGCGTCCCCGACAGGTTTAGCG GTTCCGGGTCCGGCACGGATTTACGCTTAAGATTTTCGCGAGTCGAGG CCGAAGATGTGGGTGTATACTACTGTATGCAGAGAATCGAATTCCCGT TGACATTTGGGGGAGGGACCAAAGTGGAGATTAAGCGTACGGTGGCT GCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTG GAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGG CCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCC CAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCT CAGCAGCACCCGTACGCTGAGCAAAGCAGACTACGAGAAACACAAAG TCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAA AGAGCTTCAACAGGGGAGAGTGT
40	6.147-AbL-27H6 LC AA	SYVLTQPPSVSVAPGQTARITCGCENNIGSKSVHWYQOKPGQAPVLVVYD DSDRPSEIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVVF GGGTRLTVLGQPKAAPSVTLFPPDIVMTQTPLSLPVTPGEPASISCRSSQSI LNSVDGSTNLDWYLQKPGQSPQLLIYILSYRASGVDPDRFSGSGSGTDFTL KISRVEAEDVGVYYCMQRITFPLTFGGGTKVEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS YLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:	DESCRIPTION	SEQUENCE
41	6.147-AbL- Ab5K G2 NA	CAGGTGCAGCTTGTCTGAGAGCGGTGGAGGGGTGGTACAACCCGGAAG ATCACTCCGGCTTTCATGCGCAGCATCCGGTTTTACATTTTCGCGGTAT GACATGCACTGGGTGAGACAGGCACCAGGAAAAGGGCTGGAGTGGGT GGCCATCATCTTCTATGATGGGTCCAATAAGTACTACGCCGACCCGGT AAAAGGGAGGTTCACTATTAGCCGCGACAACCTCGAAGAATACGCTGT ACCTGCAGATGAACTCGTTGCGAGCCGAAGATACCGCGGTCTACTATT GTGCGACGCTCGCGGCTGCGTTCGATTACTGGGGCCAAGGAACATTGG TCACGGTCTCCTCAGCGTCAACGAAAGGACCGTCGGTGTTCCCCTTGG CCCCTGAGGTGCAGCTCGTGCAGTCCGGAGCCGAGGTGGTGCAGCCT GGGGCATCCGTCAAAGTCTCGTGCGCCGCGTCAGGGTACACATTCACC GACTATAACATGCATTGGGTCCGGCAGGCTCCCGGTGAGGGGTGAGG GTGGATGGGGGAAATCAATCCGAACCTCCGAGGGGCGAGGATACAATC AAAAGTTTAAGGGACGCGTAACGATGACCACTGACACGTCAACCTCC ACGGCGTATATGGAGCTCAGAAGCCTCCGAAGCGACGACACTGCTGT CTATTACTGTGCGAGACTGGGATATGATGATATCTACGACGATTGGTA CTTCGATGTATGGGGACAAGGGACGACGGTCACCGTCTCTAGTGCCTC CACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCAC CTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCC CGAACCGGTGACGGTGTCTGTGGAACCTCAGGCGCTCTGACCAGCGGCG TGCACACCTTCCCAGCTGTCCTACAGTCTCAGGACTCTACTCCCTCA GCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCAGCCAGACCTACA CCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAAGACA GTTGAGCGCAAATGTTGTGTGCGAGTGCCCAACCGTGCCAGCACCACCT GTGGCAGGACCGTCAGTCTTCTCTTCCCCCCTTCCCAAGGACACC CTCATGATCTCCCGGACCCCTGAGGTACAGTGCCTGGTGGTGGACGTG AGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCGT GGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACA GCACGTTCCGTGTGGTCAAGCTCCTCACCCTGTGACACAGGACTGGC TGAACGGCAAGGAGTACAAGTGAAGGTCTCCAACAAAGGCCTCCCA GCCCCCATCGAGAAAACCATCTCCAAAACCAAGGGCAGCCCCGAGA ACCACAGGTGTACACCCTGCCCCCATCCCGGAGGAGATGACCAAGA ACCAGGTACGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCGAGCGACA TCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAG ACCACACCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGC AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTC ATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGA GCCTCTCCCTGTCTCCGGGTAAA
42	6.147-AbL- Ab5K G2 AA	QVQLVESGGGVVQPGRSRLRLSCAASGFTFSRYDMHWVRQAPGKGLEW VAHFFYDGSNKYYADPVKGRFTISRDNLSKNTLYLQMNSLRAEDTAVYYC ATLAAAFDYWGQGLTVTVSSASTKGPSVFPLAPEVQLVQSGAEVVPQA SVKVS CAASGYTFTDYNMHWVRQAPGQGLEWMGEINPNSGGAGYNQ KFKGRVTMTTDTSTAYMELRSLRSDDTAVYYCARLGYDDIYDDWYF DYWGQGLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDH KPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLT VVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSGGSFLL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
43	6.147-AbL- Ab5 LC NA	TCATACGTGCTCACTCAGCCGCCAGCGTATCGGTGGCTCCCGGACAG ACGGCGCGAATCACGTGCGGTGGGAACAATATCGGCTCCAAGTCAGT CCATTGGTATCAACAGAAACCTGGTCAGGCACCAGTCCTGGTGGTATA CGATGACTCGGACAGGCCCTCGGAGATTCCGGAACGCTTCTCCGGATC GAATTCGGGGAACACAGCGACCTTGACGATCAGCAGAGTGGAGGCCG GAGATGAAGCCGACTACTATTGTCAGGTGTGGGATTCCAGCTCCGACC ACGTCGTATTTGGAGGTGGGACACGGCTTACCGTCTCGGGCAGCCCA AGGCTGCGCCATCGGTCACTCTGTTCCACCTGACATTCAGATGACTC AGTCGCCTTCGTCATTGAGCGCGTCGGTGGGAGATCGGGTCACGATTA CTTGTCGGGCATCGCAAGACATCTCGAACTATTTGAATTGGTACCAGC AAAAGCCTGGTAAAGCGCCCAAACCTTCTTATCTACTATACGTCCCGCC TCCTCTCGGGCGTCCCGTCAAGGTTTAGCGGATCGGGAAGCGGGACG GATTTCACTGACGATTTCACTTCAGCCCCAAGATTTCCGCCACC TATTACTGTCAGCAAGGAGACACCCTGCCATACACTTTTGGCGGTGGG ACAAAGGTCGAAATCAAGCGTACGGTGGCTGCACCATCTGTCTTCATC TTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTG TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAAGTACAGTGGAA GGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAG AGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACG CTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGT CACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGG GAGAGTGT
44	6.147-AbL- Ab5 LC AA	SYVLTQPPSVSVAPGQTARITCGCENNIGSKSVHWYQOKPGQAPVLVVYD DSDRPSEIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVV GGGTRLTVLGQPKAAPSVTLFPPDIQMTQSPSSLSASVGDRVITICRASQD ISNYLNWYQOKPGKAPKLLIYYTSRIISGVPSRFSGSGSGTDFTLTISLQ PEDFATYYCQQGDTLPYTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSSTL TLISKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:	DESCRIPTION	SEQUENCE
45	6.147-AbS- Ab5K G2 NA	CAGGTGCAGCTTGTCTGAGAGCGGTGGAGGGGTGGTACAACCCGGAAG ATCACTCCGGCTTTCATGCGCAGCATCCGGTTTTACATTTTCGCGGTAT GACATGCACTGGGTGAGACAGGCACCAGGAAAAGGGCTGGAGTGGGT GGCCATCATCTTCTATGATGGGTCCAATAAGTACTACGCCGACCCGGT AAAAGGGAGGTTCACTATTAGCCGCGACAACCTCGAAGAATACGCTGT ACCTGCAGATGAACTCGTTGCGAGCCGAAGATACCGCGGTCTACTATT GTGCGACGCTCGCGGTGCGTTCGATTACTGGGGCCAAGGAACATTGG TCACGGTCTCCTCAGCGTCAACGAAAGGACCGGAGGTGCAGCTCGTG CAGTCCGGAGCCGAGGTGGTGCAGCCTGGGGCATCCGTCAAAGTCTC GTGCGCCGCGTCAGGGTACACATTACCGACTATAAATGCATTGGGT CCGGCAGGCTCCCGGTGAGGGGTGGAGTGGATGGGGGAAATCAATC CGAACTCCGGAGGGGCAGGATACAATCAAAAGTTTAAAGGACGCGTA ACGATGACCACTGACACGTCAACCTCCACGGCGTATATGGAGCTCAG AAGCCTCCGAAGCGACGACACTGCTGTCTATTACTGTGCGAGACTGGG ATATGATGATATCTACGACGATTGGTACTTCGATGTATGGGGACAAGG GACGACGGTCACCGTCTCTAGTGCCTCCACCAAGGGCCCATCGGTCTT CCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCT GGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGT GAACTCAGGCGCTCTGACCAGCGGCGTGACACCTTCCCAGCTGTCTC ACAGTCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTC CAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGATCACAAGC CCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTC GAGTGCCACCGTGCCAGCACCACCTGTGGCAGGACCGTCAGTCTTC CTCTTCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCT GAGGTACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGT CCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGA CAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTACAGC GTCCTCACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAA GTGCAAGGTCTCCAACAAAGGCCTCCAGCCCCCATCGAGAAAACCA TCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCTG CCCCCATCCCGGAGGAGATGACCAAGAACCAGGTGACGCTGACCTG CCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGA GCAATGGGCAGCCGAGAACAACTACAAGACCACACCTCCCATGCTG GACTCCGACGGTCTCTTCTCTCTACAGCAAGCTCACCGTGGACAAG AGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGA GGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG TAAA
46	6.147-AbS- Ab5K G2 AA	QVQLVESGGGVVQPGRSRLRLSCAASGFTFSRYDMHWVRQAPGKGLEW VAHFFYDGSNKYYADPVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYC ATLAAAFDYWGQGLTVTVSSASTKGPEVQLVQSGAEVVP GASVKVSC AASGYTFTDYNMHWVRQAPGQGLEWMGEINPNSGGAGYNQKFKGRV TMTTDTSTSTAYMELRSLRSDDTAVYYCARLGYDDIYDDWYFDVWGQ GTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVTVPSNFNGTQTYTCNVDHKPSNTK VDKTVERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQD WLNKGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
47	6.147-Abs- Ab5 LC NA	TCATACGTGCTCACTCAGCCGCCAGCGTATCGGTGGCTCCCGGACAG ACGGCGCGAATCACGTGCGGTGGGAACAATATCGGCTCCAAGTCAGT CCATTGGTATCAACAGAAACCTGGTCAGGCACCAGTCTGGTGGTATA CGATGACTCGGACAGGCCCTCGGAGATTCCGGAACGCTTCTCCGGATC GAATTCGGGGAACACAGCGACCTTGACGATCAGCAGAGTGGAGGCCG GAGATGAAGCCGACTACTATTGTCAGGTGTGGGATTCCAGCTCCGACC ACGTCGTATTTGGAGGTGGGACACGGCTTACCGTCTCGGGCAGCCCA AGGCTGCGCCAGACATTCAGATGACTCAGTCGCCTTCGTCAATTGAGCG CGTCGGTGGGAGATCGGGTCACGATTACTTGTCTGGGCATCGCAAGAC ATCTCGAACTATTTGAATTGGTACCAGCAAAAGCCTGGTAAAGCGCCC AAACTTCTTATCTACTATACGTCCCGCTCCTCTCGGGCGTCCCGTCAA GGTTTAGCGGATCGGGAAGCGGGACGGATTTACACTGACGATTTTCAT CACTTCAGCCCGAAGATTTGCGCCACCTATTACTGTCAGCAAGGAGACA CCCTGCCATACACTTTTGGCGGTGGGACAAAGGTCGAAATCAAGCGTA CGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTT GAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCC AGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGG TAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCT ACAGCCTCAGCAGCACCTTGACGCTGAGCAAAGCAGACTACGAGAAA CACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCC GTCACAAAGAGCTTCAACAGGGGAGAGTGT
48	6.147-Abs- Ab5 LC AA	SYVLTQPPSVSVAPGQTARITC GGNNIGSKSVH WYQOKPGQAPVLVVYD DSDRP SEIPERFSGSNSGNTATLTISRVEAGDEADYYC QVWDSSSDHVV F GGGTRLTVLG QPKA APDIQMTQSPSSLSASVGDRVTTIT CRASQDISNYLN WYQOKPGKAPKLLIY YTSRL LSGVPSRFSGSGSGTDFTLTISSLQPEDFAT YYC QQGDTLPYT FGGGTKVEIKR TVAAPSVFIFPPSDEQLKSGTASVVCL LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:	DESCRIPTION	SEQUENCE
49	6.37-AbL- Ab23 G2 NA	CAGGTACAACCTGGTCGAGTCAGGTGGAGGCGTGGTCCAGCCCGGACG GTCGCTCAGGCTCAGCTGTGCTGCGTCAGGGTTACCTTTTCGGGGTA TGGGATGCACTGGGTGCGCCAAGCACCGGGAAAAGGGCTTGAATGGG TCGCGGTCAATTTCTACGACGGGAACGACAAATACTACGCGGACTCCG TAAAGGGAAGGTTACAATCAGCCGGGATAACGCCAAGAATACGTTG TATCTCCAGATGAATTTCGTTGCGAGCAGAAGATACGGCCGTGTACTAT TGCGCGAGAGAGCTTCGCGTGTGTGGGGACAGGGTACTCTGGTGAC GGTCTCCTCAGCGTCAACGAAAGGACCGTCGGTGTTCCTTGGCCCC TGAGGTGCAGCTCGTACAGTCGGGTGCGGAAGTAAAGAAACCCGGCT CATCCGTGAAAGTCTCGTGTAAGCCTCCGGGTTCACCTTCACAGACT ACATTATGCACTGGGTGCGGCAGGCCCTGGGCAGGGCCTTGAATGG ATGGGGTATATCAACCCCTACAATGATGACACGAGTAAAGCAAAAA GTTTAAGGGAAGGGTGACAATCACGGCGGATAAGAGCACCAGCACTG CATACATGGAGCTCTCGTCATTGCGCTCGGAGGACACTGCAGTCTACT ATTGCGCGAGATCCATCTACTATTACGATGCGCCGTTTGCTTATTGGG GACAAGGAACGCTGGTCACCGTCTCTAGTGCCTCCACCAAGGGCCCAT CGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAG CGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGG TGTCGTGGAACCTCAGGCGCTCTGACCAGCGGCGTGACACCTTCCCAG CTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCG TGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGATAGTC ACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGT TGTGTCGAGTGCCCAACCGTGCCAGCACCACTGTGGCAGGACCGTCA GTCTTCCTCTTCCCCCAAAAACCCAAGGACACCCTCATGATCTCCCGG ACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCC CGAGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATG CCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTG GTCAGCGTCTCACC GTTGTGCACCAGGACTGGCTGAACGGCAAGGA GTACAAGTGCAAGGTCTCCAACAAAGGCCTCCAGCCCCCATCGAGA AAACCATCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTAC ACCCTGCCCCCATCCCGGAGGAGATGACCAAGAACCAGCTGACCT GACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTG GGAGAGCAATGGGCAGCCGAGACAACACTACAAGACCACACCTCCCA TGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGG ACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATG CATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCT CCGGGTAAA
50	6.37-AbL- Ab23 G2 AA	QVQLVESGGGVVQPGRSRLRLSCAASGFTFSGYGMHWVRQAPGKGLEW VAVISYDGNDKYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYY CARELRVLEWGQGLTVTVSSASTKGPSVFPLAPEVQLVQSGAEVKKPGSS VKVSCKASGFTFTDYIMHWVRQAPGQGLEWMGYINPYNDITEYNEKE KGRVTITADKSTSTAYMELSSLRSEDTAVYYCARSIYYDAPEAYWGQ TLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSVTVTPSSNFGTQTYTCNVDPKPSNTKV DKTVERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDW LNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPMLDSDGSFFLYSKLTVD KSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
51	6.37-AbL- Ab23 LC NA	GATATTGTGATGACCCAGACGCCGTTGTCACTGAGCGTCACACCCGGA CAGCCCGCGTCGATTAGCTGCAAATCGGGACAATCGCTTCTCCACTCG GACGGGAAAACGTATCTTTACTGGTATTTGCAAAAAGCCAGGGCAGCCT CCCCAGTTTCTTATCTACGAAGTGTGGAACAGGTTTTCCAGAGTACCT GACCGATTCTCCGGATCAGGTAGCGGAACGGACTTCACTCTGCGCATC TCACGGGTCGAAGCCGAGGATGTGGGCATCTACTACTGTATGCAGTCA ATTCAGCTCCCGTGGACATTCGGTCAGGGGACCCAAGTAGAGATCAA GCGCACAGTGGCTGCTCCATCCGTCTTTATCTTCCCTCCAGACATTCAA ATGACACAGTCGCCCTCCTCGCTCTCGGCGTCAGTCGGGGATCGCGTG ACAATCACGTGTCTGGGCCAGCCAGGACATTTTCGAGCTACCTCAACTGG TATCAGCAGAAACCGGGGAAAGCGCCGAAGCTGCTTATCTACTCCAC CTCAAGGTTGAATTCCGGAGTACCCTCAAGATTTTCGGGTAGCGGATC AGGAACCGACTTCACACTTACGATCTCGTCGTTGCAGCCAGAAGATTT CGCAACGTACTATTGCCAGCAAGATATCAAGCACCCCTACGTTTGGTCA GGGCACTAAAGTGGAGATTAAGCGTACGGTGGCTGCACCATCTGTCTT CATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGT TGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTG GAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCA CAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTG ACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGA AGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACA GGGGAGAGTGT
52	6.37-AbL- Ab23 LC AA	DIVMTQTPLSLSVTPGQPASISCKSGQSLLHSDGKTYLYWYLOKPGOPP QFLIYEVSNRFSRVPDRFSGSGSGTDFTLRISRVEAEDVGIYYCMQSIQLP WTFGQGTQVEIKRTVAAPSVFIFPPDIQMTQSPSSLSASVGDRVTITCRAS QDISSYLNWYQQKPGKAPKLLIYSTSRINSGVPSRFSGSGSGTDFTLTIS LQPEDFATYYCQQDIKHPTEFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSG TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:	DESCRIPTION	SEQUENCE
53	Ab5K-AbL-6.147 G2 NA	GAGGTGCAGCTCGTGCAGTCCGGAGCCGAGGTGGTGCAGCCTGGGGC ATCCGTCAAAGTCTCGTGCGCCGCGTCAGGGTACACATTCACCGACTA TAACATGCATTGGGTCCGGCAGGCTCCCGGTACAGGGGCTGGAGTGGA TGGGGGAAATCAATCCGAACTCCGGAGGGGCAGGATACAATCAAAAG TTTAAGGGACGCGTAACGATGACCACTGACACGTCAACCTCCACGGC GTATATGGAGCTCAGAAGCCTCCGAAGCGACGACACTGCTGTCTATTA CTGTGCGAGACTGGGATATGATGATATCTACGACGATTGGTACTTCGA TGTATGGGGACAAGGGACGACGGTCACGGTCTCCTCAGCGTCAACGA AAGGACCGTCGGTGTTCCCCTTGCCCCCTCAGGTGCAGCTTGTGCGAGA GCGGTGGAGGGGTGGTACAACCCGGAAGATCACTCCGGCTTTCATGC GCAGCATCCGGTTTTACATTTTCGCGGTATGACATGCACCTGGTGAGA CAGGCACCAAGGAAAAGGGCTGGAGTGGGTGGCCATCATCTTCTATGA TGGGTCCAATAAGTACTACGCCGACCCGGTAAAAGGGAGGTTCACTA TTAGCCGCGACAACCTCGAAGAATACGCTGTACCTGCAGATGAACCTCGT TGCGAGCCGAAGATACCGCGGTCTACTATTGTGCGACGCTCGCGGCTG CGTTCGATTACTGGGGCCAAGGAACATTGGTCACCGTCTCTAGTGCCT CCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCA CCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCC CCGAACCGGTGACGGTGTCTGTGGAACCTCAGGCGCTCTGACCAGCGGC GTGCACACCTTCCCAGCTGTCTACAGTCCTCAGGACTCTACTCCCTC AGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTAC ACCTGCAACGTAGATCACAAGCCAGCAACACCAAGGTGGACAAGAC AGTTGAGCGCAAATGTTGTGTCGAGTGCCCAACCGTGCCACGACCACC TGTGGCAGGACCGTCAGTCTTCTCTTCCCCCAAACCCAAAGGACAC CCTCATGATCTCCCGGACCCCTGAGGTACGTCGTGGTGGTGGACGT GAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCG TGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAAC AGCACGTTCCGTGTGGTCAGCGTCCTCACC GTTGTGCACCAGGACTGG CTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCC AGCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAG AACCACAGGTGTACACCTGCCCCCATCCGGGAGGAGATGACCAAG AACCAGGTACGCTGACCTGCCTGGTCAAAGGTCTTACCCACGCGAC ATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACCTACAA GACCACACCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAG CAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCT CATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAG AGCCTCTCCCTGTCTCCGGGTAAA
54	Ab5K-AbL-6.147 G2 AA	EVQLVQSGAEVVPQASVKVSCAASGYTFTDYNMHWVRQAPGQGLEW MGEINPNSGGAGYNQKFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYY CARLGYDDIYDDWYFDVWGQGTITVTVSSASTKGPSVFPLAPQVQLVES GGGVVQGRSLRLSCAASGFTFSRYDMHWVRQAPGKGLEWVAIFYDG SNKYYADPVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCATLAAAF DYWGQGTITVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDH KPSNTKVDKTVRKCCVECPPCPAPPVAGPSVFLPPKPKDTLMISRTPE VTCVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLT VVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSGDSFLL YSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
55	Ab5K-AbS-6.147 G2 NA	GAGGTGCAGCTCGTGCAGTCCGGAGCCGAGGTGGTGCAGCCTGGGGC ATCCGTCAAAGTCTCGTGCGCCGCGTCAGGGTACACATTCACCGACTA TAACATGCATTGGGTCCGGCAGGCTCCCGGTACAGGGGCTGGAGTGGA TGGGGGAAATCAATCCGAACTCCGGAGGGGCAGGATACAATCAAAAG TTTAAGGGACGCGTAACGATGACCACTGACACGTCAACCTCCACGGC GTATATGGAGCTCAGAAGCCTCCGAAGCGACGACACTGCTGTCTATTA CTGTGCGAGACTGGGATATGATGATATCTACGACGATTGGTACTTCGA TGTATGGGGACAAGGGACGACGGTCACGGTCTCCTCAGCGTCAACGA AAGGACCGCAGGTGCAGCTTGTTCGAGAGCGGTGGAGGGGTGGTACAA CCCGGAAGATCACTCCGGCTTTCATGCGCAGCATCCGGTTTTACATTTT CGCGGTATGACATGCACTGGGTGAGACAGGCACCAAGGAAAAGGGCTG GAGTGGGTGGCCATCATCTTCTATGATGGGTCCAATAAGTACTACGCC GACCCGGTAAAAGGGAGGTTCACTATTAGCCGCGACAACCTCGAAGAA TACGCTGTACCTGCAGATGAACTCGTTGCGAGCCGAAGATACCGCGGT CTACTATTGTGCGACGCTCGCGGCTGCGTTCGATTACTGGGGCCAAGG AACATTGGTCACCGTCTCTAGTGCCTCCACCAAGGGCCCATCGGTCTT CCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCT GGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTG GAACTCAGGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCTT ACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTC CAGCAACTTCGGCACCAGACCTACACCTGCAACGTAGATCACAAGC CCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTC GAGTGCCCAACCGTGCCAGCACCACTGTGGCAGGACCGTCAGTCTTC CTCTTCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCT GAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGT CCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGA CAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTACAGC GTCCTCACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAA GTGCAAGGTCTCCAACAAAGGCCTCCAGCCCCCATCGAGAAAACCA TCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCTG CCCCCATCCCGGAGGAGATGACCAAGAACCAGGTGACGCTGACCTG CCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGA GCAATGGGCAGCCGAGACAACACTACAAGACCACACCTCCCATGCTG GACTCCGACGGCTCCTTCTCCTCTACAGCAAGCTCACCGTGGACAAG AGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGA GGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG TAAA
56	Ab5K-AbS-6.147 G2 AA	EVQLVQSGAEVVPQASVKVSCAASGYTFTDYNMHFWVRQAPGQGLEW MGEINPNSGGAGYNQKFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYY CARLGYDDIYDDWYFDVWGQGTITVTVSSASTKGIPQVQLVESGGGVVQP GRSLRLSCAASGFTFSRYDMHFWVRQAPGKGLEWVAHFYDGSNKYYAD PVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCATLAAAFDYWGQGT LTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPSNTKVD KTVRKCCVECPPCPAPPVAGPSVFLPPKPKDTLMISRTPEVTCVVVDV SHEDPEVFQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWL NGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
57	6.37-3x- Ab23 G2 NA	CAGGTACAAC TGGTCGAGTCAGGTGGAGGCGTGGTCCAGCCCGGACG GTCGCTCAGGCTCAGCTGTGCTGCGTCAGGGTTACCTTTTCGGGGTA TGGGATGCACTGGGTGCGCCAAGCACCGGGAAAAGGGCTTGAATGGG TCGCGGTCAATTTCTACGACGGGAACGACAAATACTACGCGGACTCCG TAAAGGGAAGGTTACAATCAGCCGGGATAACGCCAAGAATACGTTG TATCTCCAGATGAATTGCTTGCAGCAGAAGATACGGCCGTGTACTAT TGCGCGAGAGAGCTTCGCGTGTGTGGGGACAGGGTACTCTGGTGAC AGTGAGCTCAGGGGGTGGCGGTTCCGGGCGGTGGAGGCTCGGGAGGTG GTGGATCCGAGGTGCAGCTCGTACAGTCGGGTGCGGAAGTAAAGAAA CCCGGCTCATCCGTGAAAGTCTCGTGTAAGCCTCCGGGTTACCTTC ACAGACTACATTATGCAGTGGGTGCGGCAGGCCCTGGGCAGGGCCTT GAATGGATGGGGTATATCAACCCCTACAATGATGACACGGAGTATAA CGAAAAGTTTAAGGGAAGGGTGACAATCACGGCGGATAAGAGACCA GCACTGCATACATGGAGCTCTCGTCATTGCGCTCGGAGGACACTGCAG TCTACTATTGCGCGAGATCCATCTACTATTACGATGCGCCGTTTGCTTA TTGGGGACAAGGAACGCTGGTCACCGTCTCTAGTGCCTCCACCAAGGG CCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAG CACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGT GACGGTGTCTGTGGAACCTCAGGCGCTCTGACCAGCGGCGTGCACACCTT CCCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGT GACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGT AGATCACAAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCA AATGTTGTGTCGAGTGCCCACCGTGCCCAGCACCACTGTGGCAGGAC CGTCAGTCTTCTCTTCCCCCAAAACCAAGGACACCTCATGATCT CCCGGACCCCTGAGGTACGTGCGTGGTGGTGGACGTGAGCCACGAA GACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCA TAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCC GTGTGGTCAGCGTCCTCACC GTTGTGCACCAGGACTGGCTGAACGGCA AGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCATC GAGAAAACCATCTCCAAAACCAAGGGCAGCCCCGAGAACCACAGGT GTACACCTGCCCCCATCCCCGGGAGGAGATGACCAAGAACCAGGTCA GCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGCATCGCCGTGG AGTGGGAGAGCAATGGGCAGCCGAGAAACAATAAGACCACACCT CCCATGCTGGACTCCGACGGCTCCTTCTCTCTACAGCAAGCTCACC GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCT GTCTCCGGGTAAA
58	6.37-3x- Ab23 G2 AA	QVQLVESGGGVVQPGRSRLRLSCAASGFTFSGYGMHWVRQAPGKGLEW VAVISYDGNDKYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYY CARELRVLEWGQGLVTVSSGGGGSGGGSGGGGSEVQLVQSGAEVKKP GSSVKVSCKASGFTFTDYIMHWVRQAPGQGLEWMGYINPYNDITEYN EKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCARSIYYDAPFAYW GQGLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVTVPSNFQTQYTCNVDHKPSNT KVDKTVKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQ DWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLT VDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
59	6.37-3x- Ab23 LC NA	GATATTGTGATGACCCAGACGCCGTTGTCACTGAGCGTCACACCCGGA CAGCCCGCGTCGATTAGCTGCAAATCGGGACAAATCGCTTCTCCACTCG GACGGGAAAACGTATCTTTACTGGTATTTGCAAAAAGCCAGGGCAGCCT CCCCAGTTTCTTATCTACGAAGTGTGGAACAGGTTTTCCAGAGTACCT GACCGATTCTCCGGATCAGGTAGCGGAACGGACTTCACTCTGCGCATC TCACGGGTGCAAGCCGAGGATGTGGGCATCTACTACTGTATGCAGTCA ATTCAGCTCCCGTGGACATTTCGGTCAGGGGACCCAAGTAGAGATCAA GGGGGGTGGCGGTTCCGGGCGGTGGAGGCTCGGGAGGTGGTGGATCCG ACATTCAAATGACACAGTCGCCCTCCTCGCTCTCGGCGTCAGTCGGGG ATCGCGTGACAATCACGTGTGCGGGCCAGCCAGGACATTTTCAGCTACC TCAACTGGTATCAGCAGAAACCGGGGAAAGCGCGGAAGCTGCTTATC TACTCCACCTCAAGGTTGAATTCCGGAGTACCCTCAAGATTTTCGGGT AGCGGATCAGGAACCGACTTCACACTTACGATCTCGTCGTTGCAGCCA GAAGATTTTCGCAACGTACTATTGCCAGCAAGATATCAAGCACCTACG TTTGGTCAGGGCACTAAAGTGGAGATTAAGCGTACGGTGGCTGCACC ATCTGTCTTCATCTTCCC GCCATCTGATGAGCAGTTGAAATCTGGAAC GCCTCTGTTGTGTGCTGCTGAATAACTTCTATCCCAGAGAGGCCAAA GTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGA GAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCA GCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTAC GCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAG CTTCAACAGGGGAGAGTGT
60	6.37-3x- Ab23 LC AA	DIVMTQTPLSLSVTPGQPASISCKSGQSLLHSDGKTYLYWYLOKPGOPP QFLIYEVSNRFSRVPDRFSGSGSGTDFTLRISRVEAEDVGIYYCMQSIQLP WTFGQGTQVEIKGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTIT CRASQDISSYLNWYQOKPGKAPKLLIYSTRINSVPSRFSGSGSGTDFT LTISSLQPEDFATYYCQQDIKHPITFGQGTKVEIKRTVAAPSVFIFPPSDEQ LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC

SEQ ID NO:	DESCRIPTION	SEQUENCE
61	6.147-2x- Ab5 G2 NA	CAGGTGCAGCTTGTCTGAGAGCGGTGGAGGGGTGGTACAACCCGGAAG ATCACTCCGGCTTTCATGCGCAGCATCCGGTTTTACATTTTCGCGGTAT GACATGCACTGGGTGAGACAGGCACCAGGAAAAGGGCTGGAGTGGGT GGCCATCATCTTCTATGATGGGTCCAATAAGTACTACGCCGACCCGGT AAAAGGGAGGTTCACTATTAGCCGCGACAACCTCGAAGAATACGCTGT ACCTGCAGATGAACTCGTTGCGAGCCGAAGATACCGCGGTCTACTATT GTGCGACGCTCGCGGTGCGTTCGATTACTGGGGCCAAGGAACATTGG TCACAGTGAGCTCAGGCGGTGGAGGCTCGGGAGGTGGTGGATCCGAG GTGCAGCTCGTGCACTCCGGAGCCGAGGTGAAGAAGCCTGGGGCATC CGTCAAAGTCTCGTGCAAGGCGTCAGGGTACACATTACCGACTATAA CATGCATTGGGTCCGGCAGGCTCCCGGTACAGGGGTGGAGTGGATGG GGGAAATCAATCCGAACCTCCGGAGGGGCAGGATACAATCAAAAGTTT AAGGGACGCGTAACGATGACCACTGACACGTCAACCTCCACGGCGTA TATGGAGCTCAGAAGCCTCCGAAGCGACGACACTGCTGTCTATTACTG TGCGAGACTGGGATATGATGATATCTACGACGATTGGTACTTTCGATGT ATGGGGACAAGGGACGACGGTCACCGTCTCTAGTGCCTCCACCAAGG GCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGA GCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCG GTGACGGTGTCTGTGGAACCTCAGGCGCTCTGACCAGCGGCGTGCACAC CTTCCCAGCTGTCTACAGTCTCAGGACTCTACTCCCTCAGCAGCGT GGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAA CGTAGATCACAAGCCAGCAACACCAAGGTGGAGAACAGACAGTTGAGC GCAAATGTTGTGTCGAGTGCCACCGTGCCAGCACCACCTGTGGCAG GACCGTCAGTCTTCTCTTCCCCCAAAACCAAGGACACCCTCATGA TCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACG AAGACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTG CATAATGCCAAGACAAAAGCCACGGGAGGAGCAGTTCAACAGCACGTT CCGTGTGGTCAGCGTCTCACC GTTGTGCACCAGGACTGGCTGAACGG CAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCA TCGAGAAAACCATCTCCAAAACCAAGGGCAGCCCCGAGAACACAG GTGTACACCCTGCCCCCATCCCGGAGGAGATGACCAAGAACACAGT CAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGT GGAGTGGGAGAGCAATGGGCAGCCGGAGAACTACAAGACCACA CCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTC ACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTC CGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCT CCCTGTCTCCGGGTAAA
62	6.147-2x- Ab5 G2 AA	QVQLVESGGGVVQPGRSRLRLSCAASGFTFSRYDMHWVRQAPGKGLEW VAHFFYDGSNKYYADPVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC ATLAAAFDYWGQGLTVTVSSGGGGSGGGGSEVQLVQSGAEVKKPGASV KVSCKASGYTFTDYNMHWVRQAPGQGLEWMGEINPNSGGAGYNQKF KGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARLGYDDIYDDWYFDV WGQGTITVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPS NTKVDKTKVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVV HQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDSGFFLYSK LTVDKSRWQQGNVFCVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
63	6.147-2x- Ab5 LC NA	TCATACGTGCTCACTCAGCCGCCAGCGTATCGGTGGCTCCCGGACAG ACGGCGCGAATCACGTGCGGTGGGAACAATATCGGCTCCAAGTCAGT CCATTGGTATCAACAGAAACCTGGTCAGGCACCAGTCTGGTGGTATA CGATGACTCGGACAGGCCCTCGGAGATTCCGGAACGCTTCTCCGGATC GAATTCGGGGAACACAGCGACCTTGACGATCAGCAGAGTGGAGGCCG GAGATGAAGCCGACTACTATTGTCAGGTGTGGGATTCCAGCTCCGACC ACGTCGTATTTGGAGGTGGGACACGGCTTACCGTCTTGGGCGGTGGAG GCTCGGGAGGTGGTGGATCCGACATTCAGATGACTCAGTCGCCTTCGT CATTGAGCGCGTTCGGTGGGAGATCGGGTCACGATTACTTGTCCGGCAT CGCAAGACATCTCGAACTATTTGAATTGGTACCAGCAAAAGCCTGGTA AAGCGCCCAAACCTTCTTATCTACTATACGTCCCGCCTCCTCTCGGGCG TCCCGTCAAGGTTTAGCGGATCGGGAAGCGGGACGGATTTACACTG ACGATTTTCATCACTTCAGCCCCGAAGATTTGCCACCTATTACTGTCAG CAAGGAGACACCCTGCCATACACTTTTGGCGGTGGGACAAAGGTCGA AATCAAGCGTACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCT GATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAAT AACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAACGC CCTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCA AGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCA GACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGG CCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT
64	6.147-2x- Ab5 LC AA	SYVLTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQOKPGQAPVLVVYD DSDRPSEIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVV GGGTRLTVLGGGGSGGGSDIQMTQSPSSLASVGDRTITCRASQDISN YLNWYQOKPGKAPKLLIYYTSRLSGVPSRFSGSGSGTDFTLTISLQPED FATYYCQQGDILPYTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYLSSTLTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:	DESCRIPTION	SEQUENCE
65	6.147-AbL- Ab23 G2 NA	CAGGTGCAGCTTGTCTGAGAGCGGTGGAGGGGTGGTACAACCCGGAAG ATCACTCCGGCTTTTCATGCGCAGCATCCGGTTTTACATTTTCGCGGTAT GACATGCACTGGGTGAGACAGGCACCAGGAAAAGGGCTGGAGTGGGT GGCCATCATCTTCTATGATGGGTCCAATAAGTACTACGCCGACCCGGT AAAAGGGAGGTTCACTATTAGCCGCGACAACCTCGAAGAATACGCTGT ACCTGCAGATGAACTCGTTGCGAGCCGAAGATACCGCGGTCTACTATT GTGCGACGCTCGCGGCTGCGTTCGATTACTGGGGCCAAGGAACATTGG TCACGGTCTCCTCAGCGTCAACGAAAGGACCGTCGGTGTTCCCCTTGG CCCCTGAGGTGCAGCTCGTACAGTCGGGTGCGGAAGTAAAGAAACCC GGCTCATCCGTGAAAGTCTCGTGTAAGCCTCCGGGTTCACCTTCACA GACTACATTATGCACTGGGTGCGGCAGGCCCTGGGCGAGGCTTGA ATGGATGGGGTATATCAACCCCTACAATGATGACACGGAGTATAACG AAAAGTTTAAGGGAAGGGTGACAATCACGGCGGATAAGAGCACCAGC ACTGCATACATGGAGCTCTCGTCATTGCGCTCGGAGGACACTGCAGTC TACTATTGCGCGAGATCCATCTACTATTACGATGCGCCGTTTGCTTATT GGGGACAAGGAACGCTGGTCACCGTCTCTAGTGCCTCCACCAAGGGC CCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGC ACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTG ACGGTGTCGTGGAACCTCAGGCGCTCTGACCAGCGGCGTGACACCTTC CCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTG ACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTA GATCAAAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAA ATGTTGTGTGAGTGCCCAACCGTGCCCGAGCACCACTGTGGCAGGACC GTCAGTCTTCTCTTCCCCCAAAACCCAAGGACACCTCATGATCTC CCGGACCCCTGAGGTACGTGCGTGGTGGTGGACGTGAGCCACGAAG ACCCCGAGGTCCAGTTCAACTGGTACGTGGACGCGCTGGAGGTGCAT AATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCG TGTGGTCAGCGTCTCACCAGTGTGCAACCAGGACTGGCTGAACGGCAA GGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCAGCCCCCATCG AGAAAACCATCTCCAAAACCAAGGGCAGCCCCGAGAACCACAGGTG TACACCCTGCCCCATCCCGGGAGGAGATGACCAAGAACAGGTGAGT CCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGA GTGGGAGAGCAATGGGCAGCCGGAGAACAACCTACAAGACCACACCTC CCATGCTGGACTCCGACGGCTCCTTCTCCTCTACAGCAAGCTCACCG TGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTG ATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTG TCTCCGGGTAAA
66	6.147-AbL- Ab23 G2 AA	QVQLVESGGGVVQPGRSRLRLSCAASGFTFSRYDMHWVRQAPGKGLEW VAHFDGSNKYYADPVKGRFTISRDNLSKNTLYLQMNSLRLEDTAIVYYC ATLAAAFDYWGQGLTVTVSSASTKGPSVFPLAPEVQLVQSGAEVKKPGS SVKVSCKASGFTFTDYIMHWVRQAPGQGLEWMGYINPYNDDTEYNEK FKGRVTITADKSTSTAYMELSSLRSEDTAIVYYCARSIYYDAPEAYWGQ GTLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPSNTK VDKTVRKKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQD WLNKGKEYCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSGDSFFLYSKLTV DKSRWQQGNVFSCSVMEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
67	6.147-AbL- Ab23 LC NA	TCATACGTGCTCACTCAGCCGCCAGCGTATCGGTGGCTCCCGGACAG ACGGCGCGAATCACGTGCGGTGGGAACAATATCGGCTCCAAGTCAGT CCATTGGTATCAACAGAAACCTGGTCAGGCACCAGTCCTGGTGGTATA CGATGACTCGGACAGGCCCTCGGAGATTCCGGAACGCTTCTCCGGATC GAATTCGGGGAACACAGCGACCTTGACGATCAGCAGAGTGGAGGCCG GAGATGAAGCCGACTACTATTGTCAGGTGTGGGATTCCAGCTCCGACC ACGTCGTATTTGGAGGTGGGACACGGCTTACCGTCCTCGGGCAGCCCA AGGCTGCGCCATCGGTCACTCTGTTCCACCTGACATTCAAATGACAC AGTCGCCCTCCTCGCTCTCGGCGTCAGTCGGGGATCGCGTGACAATCA CGTGTCGGGCCAGCCAGGACATTTTCGAGCTACCTCAACTGGTATCAGC AGAAACCGGGGAAAGCGCCGAAGCTGCTTATCTACTCCACCTCAAGG TTGAATTCGGGAGTACCCTCAAGATTTTCGGGTAGCGGATCAGGAACC GACTTCACACTTACGATCTCGTCGTTGCAGCCAGAAGATTTTCGCAACG TACTATTGCCAGCAAGATATCAAGCACCTACGTTTGGTCAGGGCACT AAAGTGGAGATTAAGCGTACGGTGGCTGCACCATCTGTCTTCATCTTC CCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGC CTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAAGGT GGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGC AGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTG AGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCAC CCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAG AGTGT
68	6.147-AbL- Ab23 LC AA	SYVLTQPPSVSVAPGQTARITCGCENNIGSKSVHWYQOKPGQAPVLVVYD DSDRPSEIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVV GGGTRLTVLGQPKAAPSVTLFPPDIQMTQSPSSLSASVGDRTITCRASQD ISSYLNWYQOKPGKAPKLLIYTSRLNSGVPSRFSGSGSGTDFLTISLQP EDFATYYCQQDIKHPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLSSTLTL SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:	DESCRIPTION	SEQUENCE
69	Ab5-AbS- 6.147 G2 NA	GAGGTGCAGCTCGTGCAGTCCGGAGCCGAGGTGAAGAAGCCTGGGGC ATCCGTCAAAGTCTCGTGCAAGGCGTCAGGGTACACATTCACCGACTA TAACATGCATTGGGTCCGGCAGGCTCCCGGTCAGGGGCTGGAGTGGA TGGGGGAAATCAATCCGAACTCCGGAGGGGCAGGATACAATCAAAAG TTTAAGGGACGCGTAACGATGACCACTGACACGTCAACCTCCACGGC GTATATGGAGCTCAGAAGCCTCCGAAGCGACGACACTGCTGTCTATTA CTGTGCGAGACTGGGATATGATGATATCTACGACGATTGGTACTTCGA TGTATGGGGACAAGGGACGACGGTCACGGTCTCCTCAGCGTCAACGA AAGGACCGCAGGTGCAGCTTGTTCGAGAGCGGTGGAGGGGTGGTACAA CCCGGAAGATCACTCCGGCTTTCATGCGCAGCATCCGGTTTTACATTTT CGCGGTATGACATGCACTGGGTGAGACAGGCACCAAGGAAAAGGGCTG GAGTGGGTGGCCATCATCTTCTATGATGGGTCCAATAAGTACTACGCC GACCCGGTAAAAGGGAGGTTCACTATTAGCCGCGACAACCTCGAAGAA TACGCTGTACCTGCAGATGAACTCGTTGCGAGCCGAAGATACCGCGGT CTACTATTGTGCGACGCTCGCGGCTGCGTTAGATTACTGGGGCCAAGG AACATTGGTCACCGTCTCTAGTGCCTCCACCAAGGGCCCATCGGTCTT CCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCT GGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTG GAACTCAGGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCTT ACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTC CAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGATCACAAGC CCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTC GAGTGCCACCGTGCCAGCACCACTGTGGCAGGACCGTCAGTCTTC CTCTTCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCT GAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGT CCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGA CAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGC GTCCTCACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAA GTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCCATCGAGAAAACCA TCTCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTG CCCCCATCCCGGAGGAGATGACCAAGAACCAGGTGACGCTGACCTG CCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGA GCAATGGGCAGCCGAGAACAACTACAAGACCACACCTCCCATGCTG GACTCCGACGGCTCCTTCTCCTCTACAGCAAGCTCACCGTGGACAAG AGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGA GGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG TAAA
70	Ab5-AbS- 6.147 G2 AA	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDYNMHFWVRQAPGQGLEW MGEINPNSGGAGYNQKFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYY CARLGYDDIYDDWYFDVWGQGTITVTVSSASTKGPPQVQLVESGGGVVQP GRSLRLSCAASGFTFSRYDMHFWVRQAPGKGLEWVAHFYDGSNKYYAD PVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCATLAAAFDYWGQGT LTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPSNTKVD KTVRKCCVECPPCPAPPVAGPSVFLPPKPKDTLMISRTPEVTCVVVDV SHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWL NGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
71	Ab5-AbS- 6.147 LC NA	GACATTCAGATGACTCAGTCGCCTTCGTCATTGAGCGCGTCGGTGGGA GATCGGGTCACGATTACTTGTCGGGCATCGCAAGACATCTCGAACTAT TTGAATTGGTACCAGCAAAAGCCTGGTAAAGCGCCCAAACCTTCTTATC TACTATACGTCCCGCCTCCTCTCGGGCGTCCCGTCAAGGTTTAGCGGA TCGGGAAGCGGGACGGATTTCACACTGACGATTTCATCACTTCAGCCC GAAGATTCGCCACCTATTACTGTCAGCAAGGAGACACCCTGCCATAC ACTTTTGGCGGTGGGACAAAGGTTCGAAATCAAGCGCACAGTGGCTGC TCCATCATACGTGCTCACTCAGCCGCCAGCGTATCGGTGGCTCCCGG ACAGACGGCGCAATCACGTGCGGTGGGAACAATATCGGCTCCAAGT CAGTCCATTGGTATCAACAGAAACCTGGTCAGGCACCAGTCTCTGGTGG TATACGATGACTCGGACAGGCCCTCGGAGATTCCGGAACGCTTCTCCG GATCGAATTCGGGGAACACAGCGACCTTGACGATCAGCAGAGTGGAG GCCGGAGATGAAGCCGACTACTATTGTCAGGTGTGGGATTCCAGCTCC GACCACGTCGTATTTGGAGGTGGGACACGGCTTACCGTCCTAGGTCAG CCCAAGGCCAACCCCACTGTCACTCTGTTCCCGCCCTCCTCTGAGGAG CTCCAAGCCAACAAGGCCACACTAGTGTGTCTGATCAGTGACTTCTAC CCGGGAGCTGTGACAGTGGCCTGGAAGGCAGATGGCAGCCCCGTCAA GGCGGGAGTGGAGACCACCAAACCTCCAAACAGAGCAACAACAAGT ACGCGGCCAGCAGCTACCTGAGCCTGACGCCCAGCAGTGGAAAGTCC CACAGAAGCTACAGCTGCCAGGTCACGCATGAAGGGAGCACCGTGGA GAAGACAGTGGCCCTACAGAATGTTCA
72	Ab5-AbS- 6.147 LC AA	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQOKPGKAPKLLIYY TSRLISGVPSRFRSGSGSGTDFLTISLQPEDFATYYCQQGDILPYIFGG GTKVEIKRTVAAPSYVLTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQ QKPGQAPVLVVYDDSDRPSIPIPERFSGSNSGNTATLTISRVEAGDEADYY CQVWDSSSDHYVFGGGTRLTVLGQPKANPTVTLFPPSSEELQANKATLV CLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLTPE QWKSHRSYSYSCQVTHEGSTVEKTVAPTECS

SEQ ID NO:	DESCRIPTION	SEQUENCE
73	Ab5-AbL- 6.147 G2 NA	GAGGTGCAGCTCGTGCAGTCCGGAGCCGAGGTGAAGAAGCCTGGGGC ATCCGTCAAAGTCTCGTGCAAGGCGTCAGGGTACACATTCACCGACTA TAACATGCATTGGGTCCGGCAGGCTCCCGGTCAGGGGCTGGAGTGGA TGGGGGAAATCAATCCGAACTCCGGAGGGGCAGGATACAATCAAAAG TTTAAGGGACGCGTAACGATGACCACTGACACGTCAACCTCCACGGC GTATATGGAGCTCAGAAGCCTCCGAAGCGACGACACTGCTGTCTATTA CTGTGCGAGACTGGGATATGATGATATCTACGACGATTGGTACTTCGA TGTATGGGGACAAGGGACGACGGTCACGGTCTCCTCAGCGTCAACGA AAGGACCGTCGGTGTTCCCCTTGCCCCCTCAGGTGCAGCTTGTGCGAGA GCGGTGGAGGGGTGGTACAACCCGGAAGATCACTCCGGCTTTCATGC GCAGCATCCGGTTTTACATTTTCGCGGTATGACATGCACCTGGTGAGA CAGGCACCAGGAAAAGGGCTGGAGTGGGTGGCCATCATCTTCTATGA TGGGTCCAATAAGTACTACGCCGACCCGGTAAAAGGGAGGTTCACTA TTAGCCGCGACAACCTCGAAGAATACGCTGTACCTGCAGATGAACTCGT TGCGAGCCGAAGATACCGCGGTCTACTATTGTGCGACGCTCGCGGCTG CGTTCGATTACTGGGGCCAAGGAACATTGGTCACCGTCTCTAGTGCCT CCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCA CCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCC CCGAACCGGTGACGGTGTCTGTGGAACCTCAGGCGCTCTGACCAGCGGC GTGCACACCTTCCCAGCTGTCTACAGTCCTCAGGACTCTACTCCCTC AGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTAC ACCTGCAACGTAGATCAACAAGCCAGCAACACCAAGGTGGACAAGAC AGTTGAGCGCAAATGTTGTGTCGAGTGCCCAACCGTGCCAGCACCACC TGTGGCAGGACCGTCAGTCTTCTCTTCCCCCAAACCCAAAGGACAC CCTCATGATCTCCCGGACCCCTGAGGTACGTCGTGGTGGTGGACGT GAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCG TGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAAC AGCACGTTCCGTGTGGTCAGCGTCCTCACC GTTGTGCACCAGGACTGG CTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCC AGCCCCATCGAGAAAACCATCTCCAAAACCAAAGGGCAGCCCCGAG AACCACAGGTGTACACCTGCCCCCATCCGGGAGGAGATGACCAAG AACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGAC ATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACCTACAA GACCACACCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAG CAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCT CATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAG AGCCTCTCCCTGTCTCCGGGTAAA
74	Ab5-AbL- 6.147 G2 AA	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDYNMHWVRQAPGQGLEW MGEINPNSGGAGYNQKFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYY CARLGYDDIYDDWYFDVWGQGTITVTVSSASTKGPSVFPLAPQVQLVES GGGVVQPGRLRLSCLASGFTFSRYDMHWVRQAPGKGLEWVAIFDYDG SNKYYADPVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCATLAAAF DYWGQGTITVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDH KPSNTKVDKTVRKCCVECPPCPAPPVAGPSVFLPPKPKDTLMISRTPE VTCVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLT VVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSGDSFLL YSKLTVDKSRWQQGNVVFCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
75	Ab5-AbL-6.147 LC NA	GACATTCAGATGACTCAGTCGCCTTCGTCATTGAGCGCGTCGGTGGA GATCGGGTCACGATTACTTGTCGGGCATCGCAAGACATCTCGAACTAT TTGAATTGGTACCAGCAAAAGCCTGGTAAAGCGCCCAAACCTTCTTATC TACTATACGTCCCGCCTCCTCTCGGGCGTCCCGTCAAGGTTTAGCGGA TCGGGAAGCGGGACGGATTTCACACTGACGATTTTCATCACTTCAGCCC GAAGATTCGCCACCTATTACTGTCAGCAAGGAGACACCCTGCCATAC ACTTTTGGCGGTGGGACAAAGGTTCGAAATCAAGCGCACAGTGGCTGC TCCATCCGTCTTTATCTTCCCTCCATCATACGTGCTCACTCAGCCGCC AGCGTATCGGTGGCTCCCGGACAGACGGCGCAATCACGTGCGGTGG GAACAATATCGGCTCCAAGTCAGTCCATTGGTATCAACAGAAACCTGG TCAGGCACCAGTCCCTGGTGATACGATGACTCGGACAGGCCCTCGGA GATTCCGGAACGCTTCTCCGGATCGAATTCGGGGAACACAGCGACCTT GACGATCAGCAGAGTGAGGCGCGGAGATGAAGCCGACTACTATTGTC AGGTGTGGGATTCCAGCTCCGACCACGTCGTATTTGGAGGTGGGACAC GGCTTACCGTCCTAGGTGAGCCCAAGGCCAACCCCACTGTCACTCTGT TCCCGCCCTCCTCTGAGGAGCTCCAAGCCAACAAGGCCACACTAGTGT GTCTGATCAGTGACTTCTACCCGGGAGCTGTGACAGTGGCCTGGAAGG CAGATGGCAGCCCCGTCAAGGCGGGAGTGAGAGACCACCAAACCCTCC AAACAGAGCAACAACAAGTACGCGGCCAGCAGCTACCTGAGCCTGAC GCCCCGAGCAGTGGAAGTCCACAGAAGCTACAGCTGCCAGGTCACGC ATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCA
76	Ab5-AbL-6.147 LC AA	DIQMTQSPSSLSASVGDRVITTCRASQDISNYLNWYQOKPGKAPKLLIYY TSRLLSGVPSRFSGSGSGTDFLTISLQPEDFATYYCQQGDILPYTFGG GTKVEIKRTVAAPSVFIFPPSYVLTQPPSVSVAPGQTARITCGGNNIGSKS VHWYQOKPGQAPVLVYVDDSDRPFSEIPERFSGSNSGNTATLTISRVEAGD EADYYCQYWDSSSDHYVFGGGTRLTVLGQPKANPTVTLFPPSSEELQAN KATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYL SLTPEQWKSHRSYSQVTHEGSTVEKTVAPTECS

SEQ ID NO:	DESCRIPTION	SEQUENCE
77	Ab23-2x- 6.37 G2 NA	GAGGTGCAGCTCGTACAGTCGGGTGCGGAAGTAAAGAAACCCGGCTC ATCCGTGAAAAGTCTCGTGTAAGCCTCCGGGTTCACCTTCACAGACTA CATTATGCACTGGGTGCGGCAGGCCCTGGGCAGGGCCTTGAATGGAT GGGGTATATCAACCCCTACAATGATGACACGGAGTATAACGAAAAGT TTAAGGGAAGGGTGACAATCACGGCGGATAAGAGCACCAGCACTGCA TACATGGAGCTCTCGTCATTGCGCTCGGAGGACACTGCAGTCTACTAT TGCGCGAGATCCATCTACTATTACGATGCGCCGTTTGTATTGGGGA CAAGGAACGCTGGTCACAGTGAGCTCAGGCGGTGGAGGCTCGGGAGG TGGTGGATCCCAGGTACAACCTGGTCGAGTCAGGTGGAGGCGTGGTCC AGCCCGGACGGTCGCTCAGGCTCAGCTGTGCTGCGTCAGGGTTCACCT TTTCGGGGTATGGGATGCAGCTGGGTGCGCCAAGCAGCGAAAAGGG CTTGAATGGGTGCGGGTCATTTCTACGACGGGAACGAGAAATACTAC GCGGACTCCGTAAAGGGAAGGTTTACAATCAGCCGGGATAACGCCAA GAATACGTTGTATCTCCAGATGAATTCGTTGCGAGCAGAAGATACGGC CGTGTACTATTGCGCGAGAGAGCTTCGCGTGTTGTGGGGACAGGGTAC TCTGGTGACCGTCTCTAGTGCCTCCACCAAGGGCCCATCGGTCTTCCC CCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGG GCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCTGTGA ACTCAGGCGCTCTGACCAGCGGCGTGACACCTTCCCAGCTGTCTCTAC AGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCA GCAACTTCGGCACCCAGACCTACACCTGCAACGTGATACACAAGCCC AGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGTGTCTGA GTGCCCACCGTGCCCAGCACCACTGTGGCAGGACCGTCAGTCTTCTCT CTTCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGACCCCTGA GGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCC AGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACA AAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGT CCTCACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGT GCAAGGTCTCCAACAAAGGCCTCCCAGCCCCATCGAGAAAACCATC TCCAAAACCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCC CCCATCCCGGGAGGAGATGACCAAGAACCAGGTGACGCTGACCTGCC TGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGAGAGC AATGGGCAGCCGGAGAACAATACTACAAGACCACACCTCCCATGCTGGA CTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGACAAGAG CAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGC TCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAA A
78	Ab23-2x- 6.37 G2 AA	EVQLVQSGAEVKKPGSSVKVSKASGFTFTDYMHWVRQAPGQGLEWM GYINPYNDDIEYNEKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCA RSIYYDAPIAYWGQGLVTVSSGGGSGGGGSQVQLVESGGGVVQPG RSLRLSCAASGFTFSGYGMHWVRQAPGKLEWVAISYDGNKYAD SVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARELRVTVWGQGLV TVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPSNTKVDKT VERKCCVECPPCPAPPVAGPSVFLPPKPKDTLMISRTPEVTCVVVDVSH EDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNG KEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
79	Ab23-2x- 6.37 LC NA	GACATTCAAATGACACAGTCGCCCTCCTCGCTCTCGGCGTCAGTCGGG GATCGCGTGACAATCACGTGTCTGGGCCAGCCAGGACATTTTCGAGCTAC CTCAACTGGTATCAGCAGAAACCGGGGAAAGCGCCGAAGCTGCTTAT CTACTCCACCTCAAGGTTGAATTCCGGAGTACCCTCAAGATTTTCGGG TAGCGGATCAGGAACCGACTTCACACTTACGATCTCGTCGTTGCAGCC AGAAGATTTTCGCAACGTACTATTGCCAGCAAGATATCAAGCACCTAC GTTTGGTTCAGGGCACTAAAGTGGAGATTAAGGGCGGTGGAGGCTCGG GAGGTGGTGGATCCGATATTGTGATGACCCAGACGCCGTTGTACTGA GCGTCACACCCGGACAGCCCGCTCGATTAGCTGCAAATCGGGACAA TCGCTTCTCCACTCGGACGGGAAAACGTATCTTTACTGGTATTTGCAA AAGCCAGGGCAGCCTCCCCAGTTTCTTATCTACGAAGTGTCGAACAGG TTTTCCAGAGTACCTGACCGATTCTCCGGATCAGGTAGCGGAACGGAC TTCACTCTGCGCATCTCACGGGTCGAAGCCGAGGATGTGGGCATCTAC TACTGTATGCAGTCAATTCAGCTCCCGTGGACATTCGGTCAGGGGACC CAAGTAGAGATCAAGCGTACGGTGGCTGCACCATCTGTCTTCATCTTC CCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGCCTCTGTTGTGTGC CTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGT GGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGC AGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTG AGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCAC CCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAG AGTGT
80	Ab23-2x- 6.37 LC AA	DIQMTQSPSSLSASVGDRTITCRASQDISSYLNWYQQKPGKAPKLLIYS TSRLNSGVPSRFRSGSGSGTDFTLTISLQPEDFATYYCQODIKHPTEFGQGT KVEIKGGGSGGGGSDIVMTQTPLSLSVTPGPASISCKSGQSLLHSDGK TYLYWYLQKPGQPPQFLIYFVSNRFRSRVPDRFSGSGSGTDFTLRISRVEAE DVGIIYCMQSIQLPWTFEGQGTQVEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYLSSTLT SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:	DESCRIPTION	SEQUENCE
81	Ab23-AbL-6.147 G2 NA	GAGGTGCAGCTCGTACAGTCGGGTGCGGAAGTAAAGAAACCCGGCTC ATCCGTGAAAGTCTCGTGTAAGCCTCCGGGTTACCTTCACAGACTA CATTATGCACTGGGTGCGGCAGGCCCTGGGCAGGGCCTTGAATGGAT GGGGTATATCAACCCCTACAATGATGACACGGAGTATAACGAAAAGT TTAAGGGAAGGGTGACAATCACGGCGGATAAGAGCACCAGCACTGCA TACATGGAGCTCTCGTCATTGCGCTCGGAGGACACTGCAGTCTACTAT TGCGCGAGATCCATCTACTATTACGATGCGCCGTTTGCTTATTGGGA CAAGGAACGCTGGTCACGGTCTCCTCAGCGTCAACGAAAGGACCGTC GGTGTTCCTTGGCCCCCTCAGGTGCAGCTTGTGAGAGCGGTGGAGG GGTGGTACAACCCGGAAGATCACTCCGGCTTTCATGCGCAGCATCCGG TTTACATTTTCGCGGTATGACATGCACTGGGTGAGACAGGCACAGG AAAAGGGCTGGAGTGGGTGGCCATCATCTTCTATGATGGGTCCAATAA GTACTACGCCGACCCGGTAAAAGGGAGGTTCACTATTAGCCGCGACA ACTCGAAGAATACGCTGTACCTGCAGATGAACTCGTTGCGAGCCGAA GATACCGCGGTCTACTATTGTGCGACGCTCGCGGCTGCGTTCGATTAC TGGGGCCAAGGAACATTGGTCAACGCTCTCTAGTGCCTCCACCAAGGGC CCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAGC ACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTG ACGGTGTCTGGAAGTCAAGGCGCTCTGACCAGCGGCGTGCACACCTTC CCAGCTGTCTACAGTCTCAGGACTCTACTCCCTCAGCAGCGTGGTG ACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAA ATGTTGTGTGAGTGCCCAACCGTGCCCGAGCACCACTGTGGCAGGACC GTCAGTCTTCTCTTCCCCCAAAACCCAAGGACACCTCATGATCTC CCGACCCCTGAGGTACGTGCGTGGTGGTGGACGTGAGCCACGAAG ACCCGAGGTCCAGTTCAACTGGTACGTGGACGCGCTGGAGGTGCAT AATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCG TGTGGTCAGCGTCTCACCCTGTGCAACGAGGACTGGCTGAACGGCAA GGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCAGCCCCCATCG AGAAAACCATCTCCAAAACCAAGGGCAGCCCCGAGAACCACAGGTG TACACCCTGCCCCATCCCGGAGGAGATGACCAAGAACAGGTGAGT CCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGA GTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACACCTC CCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCG TGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTG ATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTG TCTCCGGGTA
82	Ab23-AbL-6.147 G2 AA	EVQLVQSGAEVKKPGSSVKVSKASGFTFTDYIMHWVRQAPGQGLEWM GYINPYNDDIEYNEKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCA RSIYYDAPIAYWGQGLTVTVSSASTKGPSVFPLAPQVQLVESGGGVVQ PGRSLRLSCAASGFTFSRYDMHWVRQAPGKLEWVAIFDYDSNKYYA DPVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCATLAAAFDYWGQ TLTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSVTVTPSSNFGTQTYTCNVDPKPSNTKV DKTVERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVD VSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSIVLVVHQQDW LNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQV SLTCLVKGFPYSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
83	Ab23-AbL-6.147 LC NA	GACATTCAAATGACACAGTCGCCCTCCTCGCTCTCGGCGTCAGTCGGG GATCGCGTGACAATCACGTGTCGGGCCAGCCAGGACATTTTCGAGCTAC CTCAACTGGTATCAGCAGAAAACCGGGGAAAGCGCCGAAGCTGCTTAT CTACTCCACCTCAAGGTTGAATTCCGGAGTACCCTCAAGATTTTCGGG TAGCGGATCAGGAACCGACTTCACACTTACGATCTCGTCGTTGCAGCC AGAAGATTTTCGCAACGTACTATTGCCAGCAAGATATCAAGCACCTAC GTTTGGTCAGGGCACTAAAGTGGAGATTAAGCGCACAGTGGCTGCTCC ATCCGTCTTTATCTTCCCTCCATCATACTGCTCACTCAGCCGCCAGC GTATCGGTGGCTCCCGGACAGACGGCGCGAATCACGTGCGGTGGGAA CAATATCGGCTCCAAGTCAGTCCATTGGTATCAACAGAAAACCTGGTCA GGCACCAGTCCTGGTGGTATACGATGACTCGGACAGGCCCTCGGAGA TTCCGGAACGCTTCTCCGGATCGAATTCGGGGAACACAGCGACCTTGA CGATCAGCAGAGTGGAGGCCGAGATGAAGCCGACTACTATTGTCAG GTGTGGGATTCCAGCTCCGACCACGTCGTATTTGGAGGTGGGACACGG CTTACCGTCCTAGGTCAGCCCAAGGCCAACCCCACTGTCACTCTGTTC CCGCCCTCCTCTGAGGAGCTCCAAGCCAACAAGGCCACACTAGTGTGT CTGATCAGTGACTTCTACCCGGGAGCTGTGACAGTGGCCTGGAAGGCA GATGGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCAAAACCTCCAA ACAGAGCAACAACAAGTACGCGGCCAGCAGCTACCTGAGCCTGACGC CCGAGCAGTGGAAAGTCCACAGAAGCTACAGCTGCCAGGTCACGCAT GAAGGGAGCACCGTGGAGAAGACAGTGGCCCCCTACAGAATGTTCA
84	Ab23-AbL-6.147 LC AA	DIQMTQSPSSLSASVGDRVTITCRASQDISSYLNWYQQKPGKAPKLLIYS TSRLNSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQDIKHPTEFGQT KVEIKRTVAAPSVFIEPPSYVLTQPPSVSVAPGQTARITCGGNNIGSKSVH WYQQKPGQAPVLRVYDDSDRPSFSEIPERFSGSNSGNTATLTISRVEAGDEA DYYCQYWDSSSDHYVFGGGTRLTVLGQPKANPTVTLFPPSSEELQANKA TLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSYLSLT PEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

SEQ ID NO:	DESCRIPTION	SEQUENCE
85	5.80-AbL- Ab23 G2 NA	GAGGTGCAGCTGGTGCAGTCTGGAGCAGAGGTGAAAAAGCCCCGGGA GTCTCTGAAGATCTCCTGTAAGGGTTCTGGATACAGCTTTACCAGCTA CTGGATCGGCTGGGTGCGCCAGATGCCCCGGGAAAGGCCTGGAGTGGA TGGGGATCATCTATCCTGGTGA CTCTGATACCAGATACAGCCCGTCT TCCAAGGCCAGGTCACCATCTCAGCCGACAAGTCCATCAGCACCGCCT ACCTGCAGTGGAGCAGCCTGACGGCCTCGGACACCGCCATGTATTACT GTGCGAGACAGGGAGAGAGCTTTGACTACTGGGGCCAGGGAACCCTG GTCACGGTCTCCTCAGCGTCAACGAAAGGACCGTCGGTGTTCCTTG GCCCCGTGAGGTGCAGCTCGTACAGTCGGGTGCGGAAGTAAAGAAACC CGGCTCATCCGTGAAAGTCTCGTGTAAGCCTCCGGGTTACCTTCAC AGACTACATTATGCACTGGGTGCGGCAGGCCCTGGGCGAGGGCCTTG AATGGATGGGGTATATCAACCCCTACAATGATGACACGGAGGATAAC GAAAAGTTTAAGGGAAGGGTGACAATCACGGCGGATAAGAGCACCAG CACTGCATACATGGAGCTCTCGTCATTGCGCTCGGAGGACACTGCAGT CTACTATTGCGGAGATCCATCTACTATTACGATGCGCCGTTTGCTTAT TGGGGACAAGGAACGCTGGTCACCGTCTCTAGTGCCTCCACCAAGGG CCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAG CACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGT GACGGTGTCTGTGGA ACTCAGGCGCTCTGACCAGCGGCGTGCACACCTT CCCAGCTGTCCTACAGTCTCAGGACTCTACTCCCTCAGCAGCGTGGT GACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGT AGATCACAAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCA AATGTTGTGTCGAGTGCCCAACCGTGCCAGCACCACCTGTGGCAGGAC CGTCAGTCTTCTCTTCCCCCAAAACCAAGGACACCCTCATGATCT CCCGGACCCCTGAGGTACGTGCGTGGTGGTGGACGTGAGCCACGAA GACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCA TAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCC GTGTGGTCAGCGTCTCACC GTTGTGCACCAGGACTGGCTGAACGGCA AGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCCCATC GAGAAAACCATCTCCAAAACCAAGGGCAGCCCCGAGAACCACAGGT GTACACCCTGCCCCCATCCC GGGAGGAGATGACCAAGAACCAGGTCA GCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGG AGTGGGAGAGCAATGGGCAGCCGAGAAACA ACTACAAGACCACACCT CCCATGCTGGACTCCGACGGCTCCTTCTCTCTACAGCAAGCTCACC GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCT GTCTCCGGGTAAA
86	5.80-AbL- Ab23 G2 AA	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWM GHYPGDS ~~SD~~ TRYSP ~~SI~~ QGV ~~Q~~ VTISADKSISTAYLQWSSLTASDTAMY ~~Y~~ CAR QGES ~~FD~~ YWGQGLVTVSSASTKGPSVFPLAPEVQLVQSGAEVKKPGSSV KVSCKASGFTFTDYIM ~~HW~~ VRQAPQG ~~LE~~ WMGYINPYND ~~DT~~ EYNEK ~~FK~~ GRVTITADKSTSTAYMELSSLRSEDTAVYYCAR ~~SI~~ YYDA ~~PF~~ AYWGQGT LTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNV ~~DH~~ KPSNTKVD K ~~TV~~ ERKCCVECP ~~PC~~ PAPPVAGPSVFLPPKPKDTLMISRTPEVTCVVVDV SHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVS ~~VL~~ TVVH ~~QD~~ WL NGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVY ~~TL~~ PPSREEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYK ~~TP~~ MLDS ~~DS~~ GFFLYSKLTV ~~DK~~ SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
87	5.80-AbL- Ab23 LC NA	CAGTCAGTGCTGACGCAGCCGCCCTCAGTGTCTGGGGCCCCAGGGCA GAGGGTCACCATCTCCTGCACTGGGAGCAGCTCCAACATCGGGGCAG ATTATGATGTACACTGGTACCAGCAGCTTCCAGGAACAGCCCCAAAC TCCTCATCTATGATTACAGCAATCGGCCCTCAGGGGTCCCTGACCGAT TCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCACTGGGC TCCAGGCTGAGGATGAGGCTGATTATTACTGCCAGTCCTATGACAACA GCCTGAGTGGTTATGTGGTATTTCGGCGGAGGGACCAAGCTGACCGTCC TCGGGCAGCCCAAGGCTGCGCCATCGGTCACTCTGTTCCCACCTGACA TTCAAATGACACAGTCGCCCTCCTCGCTCTCGGCGTCAGTCGGGGATC GCGTGACAATCACGTGTCTGGGCCAGCCAGGACATTTTCGAGCTACCTCA ACTGGTATCAGCAGAAACCGGGGAAAGCGCCGAAGCTGCTTATCTAC TCCACCTCAAGGTTGAATTCCGGAGTACCCTCAAGATTTTCGGGTAGC GGATCAGGAACCGACTTCACACTTACGATCTCGTCGTTGCAGCCAGAA GATTTTCGAACGTACTATTGCCAGCAAGATATCAAGCACCTACGTTT GGTCAGGGCACTAAAGTGGAGATTAAGCGTACGGTGGCTGCACCATC TGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAGTGC CTCTGTTGTGTGCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGT ACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGA GTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGC ACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGC CTGCGAAGTCACCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTT CAACAGGGGAGAGTGT
88	5.80-AbL- Ab23 LC AA	QSVLTQPPSVSGAPGQRTVISC TGSSSNIGADYDVH HWYQQLPGTAPKLLI YDYSNRPS GVPDRFSGSKSGTSASLAITGLQAEDEADYYC QSYDNSLSG YVVFGGGTKLTVLG QPKAAPSVTLFPPDIQMTQSPSSLSASVGDRTITCR ASQDISSYLN WYQOKPGKAPKLLIY STSRINSGVPSRFS SGSGSGTDFTLTI SSLQPEDFATYYC QQDIKHPT FGQGTKVEIKR TVAAPSVFIFPPSDEQLKS GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSS TLTSLKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO:	DESCRIPTION	SEQUENCE
89	Ab23-AbL- 5.80 G2 NA	GAGGTGCAGCTCGTACAGTCGGGTGCGGAAGTAAAGAAACCCGGCTC ATCCGTGAAAGTCTCGTGTAAGCCTCCGGGTTACCTTCACAGACTA CATTATGCACTGGGTGCGGCAGGCCCTGGGCAGGGCCTTGAATGGAT GGGGTATATCAACCCCTACAATGATGACACGGAGTATAACGAAAAGT TTAAGGGAAGGGTGACAATCACGGCGGATAAGAGCACCAGCACTGCA TACATGGAGCTCTCGTCATTGCGCTCGGAGGACACTGCAGTCTACTAT TGCGCGAGATCCATCTACTATTACGATGCGCCGTTTGCTTATTGGGGA CAAGGAACGCTGGTCACGGTCTCCTCAGCGTCAACGAAAGGACCGTC GGTGTTCCTTGGCCCCCTGAGGTGCAGCTGGTGCAGTCTGGAGCAGA GGTGAAAAAGCCCCGGGAGTCTCTGAAGATCTCCTGTAAGGGTTCTG GATACAGCTTTACCAGCTACTGGATCGGCTGGGTGCGCCAGATGCCCG GGAAAGGCCTGGAGTGGATGGGGATCATCTATCTCTGGTGACTGTGATA CCAGATACAGCCCGTCTTCCAAGGCCAGGTACCATCTCAGCCGACA AGTCCATCAGCACC GCCTACCTGCAGTGGAGCAGCCTGACGGCCTCG GACACCGCCATGTATTACTGTGCGAGACAGGGAGAGAGCTTTGACTA CTGGGGCCAGGGAACCTGGTCACCGTCTCTAGTGCCTCCACCAAGGG CCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGAGAG CACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGT GACGGTGTCTGTGGAAGTCAAGCGCTCTGACCAGCGGCGTGCACACCTT CCCAGCTGTCCTACAGTCTCAGGACTCTACTCCCTCAGCAGCGTGGT GACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGT AGATCACAAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCA AATGTTGTGTCGAGTGCCCAACCGTGCCAGCACCACCTGTGGCAGGAC CGTCAGTCTTCTCTTCCCCCAAAACCAAGGACACCCTCATGATCT CCCGGACCCCTGAGGTACGTGCGTGGTGGTGGACGTGAGCCACGAA GACCCCGAGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCA TAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCC GTGTGGTCAGCGTCTCACC GTTGTGCACCAGGACTGGCTGAACGGCA AGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCAGCCCCATC GAGAAAACCATCTCCAAAACCAAGGGCAGCCCCGAGAACCACAGGT GTACACCCTGCCCCCATCCC GGGAGGAGATGACCAAGAACCAGGTCA GCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGG AGTGGGAGAGCAATGGGCAGCCGAGAAACAATAAGACCACACCT CCCATGCTGGACTCCGACGGCTCCTTCTCTCTACAGCAAGCTCACC GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGT GATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCT GTCTCCGGGTAAA
90	Ab23-AbL- 5.80 G2 AA	EVQLVQSGAEVKKPGSSVKVSKASGFTFTDYIMHWVRQAPGQGLEWM GYINPYNDDEYNEKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCA RSIYYDAPIAYWGQGLVTVSSASTKGPSVFPLAPEVQLVQSGAEVKK PGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGHYPGDSDIRYSP SFQGGQVTISADKSISTAYLQWSSLTASDTAMYYCARQGSEFDYWGQGL VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPTVSWNSGAL TSGVHTFPAVLQSSGLYSLSVVTVPSSNFGTQTYTCNVDPKPSNTKVDK TVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVDVS HEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSIVLVVHVDWLN GKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
91	Ab23-AbL-5.80 LC NA	GACATTCAAATGACACAGTCGCCCTCCTCGCTCTCGGCGTCAGTCGGG GATCGCGTGACAATCACGTGTCGGGCCAGCCAGGACATTTTCGAGCTAC CTCAACTGGTATCAGCAGAAACCGGGGAAAGCGCCGAAGCTGCTTAT CTACTCCACCTCAAGGTTGAATTCCGGAGTACCCTCAAGATTTTCGGG TAGCGGATCAGGAACCGACTTCACACTTACGATCTCGTCGTTGCAGCC AGAAGATTTTCGCAACGTACTATTGCCAGCAAGATATCAAGCACCTAC GTTTGGTCAGGGCACTAAAGTGGAGATTAAGCGCACAGTGGCTGCTCC ATCCGTCTTTATCTTCCCTCCACAGTCAGTGCTGACGCAGCCGCCCTCA GTGTCTGGGGCCCCAGGGCAGAGGGTCACCATCTCCTGCACTGGGAG CAGCTCCAACATCGGGGCAGATTATGATGTACACTGGTACCAGCAGCT TCCAGGAACAGCCCCAACTCCTCATCTATGATTACAGCAATCGGCC CTCAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGC CTCCCTGGCCATCACTGGGCTCCAGGCTGAGGATGAGGCTGATTATTA CTGCCAGTCCTATGACAACAGCCTGAGTGGTTATGTGGTATTCGGCGG AGGGACCAAGCTGACCGTCCTAGGTACAGCCAAGGCCAACCCCACTG TCACTCTGTTCCCGCCCTCCTCTGAGGAGCTCCAAGCCAACAAGGCCA CACTAGTGTGTCTGATCAGTGACTTCTACCCGGGAGCTGTGACAGTGG CCTGGAAGGCAGATGGCAGCCCCGTCAAGGCGGGAGTGGAGACCACC AAACCTCCAAACAGAGCAACAACAAGTACGCGGCCAGCAGCTACCT GAGCCTGACGCCCAGCAGTGGAAGTCCACAGAAGCTACAGCTGCC AGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCCTACA GAATGTTCA
92	Ab23-AbL-5.80 LC AA	DIQMTQSPSSLSASVGDRVTITCRASQDISSYLNWYQQKPGKAPKLLIY TSRLNSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQDIKHPTFGQGT KVEIKRTVAAPSVFIFPPQSIVLTQPPSVSGAPGQRVTISCTGSSSNIGADYD VHWYQQLPGTAPKLLIYDYSNRPSPGVDRFSGSKSGTSASLAITGLQAED EADYYCQSYDNSLSGYVYFGGGLTLVLGQPKANPTVTLFPPSSEELQA NKATLVCLISDFYPGAVTVAWKADGSPVKAGVETTKPSKQSNNKYAASSY LSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
93	vK1 leader sequence	MDMRVPAQLLGLLLLWLRGARC
Sclerostin mAbs AA sequences		
94	Ab5 and Ab5K VL	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKAPKLLIYY TSRLNSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQGDTLPYTFGGG TKVEIK
95	Ab5 VH	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDYNMHVWRQAPGQGLEW MGEINPNSGGAGYNQKFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYY CARLGYDDIYDDWYFDVWVGQGTITVTVSS
96	Ab5K VH	EVQLVQSGAEVVPQASVKVSCAASGYTFTDYNMHVWRQAPGQGLEW MGEINPNSGGAGYNQKFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYY CARLGYDDIYDDWYFDVWVGQGTITVTVSS
97	Ab5 and Ab5K VL CDR1	RASQDISNYLN
98	Ab5 and Ab5K VL CDR2	YTSRLLS
99	Ab5 and Ab5K VL CDR3	QQGDTLPYT
100	Ab5 and Ab5K VH CDR1	DYNMH
101	Ab5 and Ab5K VH CDR2	EINPNSGGAGYNQKFKG
102	Ab5 and Ab5K VH CDR3	LGYYDDIYDDWYFDV
103	Ab23 VL	DIQMTQSPSSLSASVGDRVTITCRASQDISSYLNWYQQKPGKAPKLLIYST SRLNSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQDIKHPTFGQGTK VEIK

SEQ ID NO:	DESCRIPTION	SEQUENCE
104	Ab23 VH	EVQLVQSGAEVKKPGSSVKVSKASGFTFTDYIMHWVRQAPGQGLEWM GYINPYNDDTEYNEKFKGRVTITADKSTSTAYMELSSLRSEDTAVYYCAR SIYYDAPFAYWGQGLTVTVSS
105	Ab23VL CDR1	RASQDISSYLN
106	Ab23VL CDR2	STSRLNS
107	Ab23VL CDR3	QQDIKHPT
108	Ab23VH CDR1	DYIMH
109	Ab23VH CDR2	YINPYNDDTEYNEKFKG
110	Ab23VH CDR3	SIYYDAPFAY
111	13F3 VL	DIQMTQSPSSVSASVGDRTITCRASQGISNWLAWYQQKPGTAPKLLIYA ASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPFTFGPGT KVDIK
112	13F3 VH	QVQLVQSGTEVKKPGASMKVSKASGYTFTSYMHVVRQAPGQGLEW MGIINPSGDSTSYAQKFQGRVTMTRDTSTNTVYMELSSLRSEDTAMYYC ARDVEVRGISHFDYWGQGLTVTVSS
113	13F3 VL CDR1	RASQGISNWL
114	13F3 VL CDR2	AASSLQS
115	13F3 VL CDR3	QQANSFPFT
116	13F3 VH CDR1	SYMH
117	13F3 VH CDR2	IINPSGDSTSYAQKFQ
118	13F3 VH CDR3	DVEVRGISHFDY
119	20C3.1 VL	QSALTQPASVSGSPQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLM YEVSYPSPGVSNRFSGSGSGTASLTISGLQPEDEADYYCSSYAISSTLVFG GGTKMTVLG
120	20C3.1 VH	QVQLQESGPGLVKPSSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYI SDSGSTNYPNPSLKSRIPIVDTSKNQFSLKLSVTAADTAVYYCARWQLA HDAFDIWGQGMVTVSS
121	20C3.1 VL CDR1	TGTSSDVGGYNYVS
122	20C3.1 VL CDR2	EVSYRPS
123	20C3.1 VL CDR3	SSYAISSTLV
124	20C3.1 VH CDR1	SYYS
125	20C3.1 VH CDR2	YISDSGSTNYPNPSLKS
126	20C3.1 VH CDR3	WQLAHDAFDI
127	38B12.1 VL	DIQMTQSPSSLSASVGDRTITCRASQTISNYLNWYQQKPGKAPNLLIYA ASGLQSGVPSRFSGSGSGTDFTLTISSLQPEDFGTYCQQSFSTPITFGQGT RLEIK
128	38B12.1 VH	QVQLVQSGAEVKKPGASVKVSKASGYTFTNYYMYWVRQAPGQGLEW MGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCA REDTAMAYFDYWGQGLTVTVSS
129	38B12.1 VL CDR1	RASQTISNYLN
130	38B12.1 VL CDR2	AASGLQS
131	38B12.1 VL CDR3	QQSFSTPIT
132	38B12.1 VH CDR1	NYYMY
133	38B12.1 VH CDR2	IINPSGGSTSYAQKFQ
134	38B12.1 VH CDR3	EDTAMAYFDY

SEQ ID NO:	DESCRIPTION	SEQUENCE
135	46H1 VL	DIQMTQSPASVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYN TFSLESGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQANSFPFTFGPGT KVDMMK
136	46H1 VH	QVQLQESGPGLVKPSSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYI YYSGSTSYNPSLKSRVTISIDTSKNQFSLKLSSVTAADTAVYYCARDLELE AFDIWGQGTMTVTVSS
137	46H1 VL CDR1	RASQGISSWLA
138	46H1 VL CDR2	NTFSLES
139	46H1 VL CDR3	QQANSFPFT
140	46H1 VH CDR1	SYYWS
141	46H1 VH CDR2	YIYYSGSTSYNPSLKS
142	46H1 VH CDR3	DLELEAFDI
143	2B8.1 VL	NFMLTQPHSVSESPGKTVAISCTRNSGSIASNSVQWYQQRPGSSPTTVIFE DNQRPSGVPDRFSGSIDSSNSASLTISGLKTEDEADYYCQSYDSNNWVF GGGTKLTVL
144	2B8.1 VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYVMHWVRQAPGKGLEWV AVIWYDGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYC AREGYDYGEDY YYYGMDVWGQGTITVTVSS
145	2B8.1 VL CDR1	TRNSGSIASNSVQ
146	2B8.1 VL CDR2	EDNQRPS
147	2B8.1 VL CDR3	QSYDSNNWV
148	2B8.1 VH CDR1	SYVMH
149	2B8.1 VH CDR2	VIWYDGSNKYYADSVKG
150	2B8.1 VH CDR3	EGYDYGEDY YYYGMDV
151	8G2.1 VL	DIQMTQSPSSVSASVGDRVTITCRASQDISNWLAWYQQKPGKVPKLLIYA ASYLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYSCQQANSFPFTFGPGT KVDIK
152	8G2.1 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQATGQGLEWM GWMNPNSGKTGYAQKFQGRVTMTRDTSISTAYMELSSLRSED TAVYYC AREEEYYESGSLFY YYYGLDVWGQGTITVTVSS
153	8G2.1 VL CDR1	RASQDISNWLA
154	8G2.1 VL CDR2	AASYLQS
155	8G2.1 VL CDR3	QQANSFPFT
156	8G2.1 VH CDR1	SYDIN
157	8G2.1 VH CDR2	WMNPNSGKTGYAQKFQG
158	8G2.1 VH CDR3	EEEEEYESGSLFY YYYGLDV
159	19D11.1 VL	SYVLTQPPSVSVAPGQTARITCGGDNIGSISVHWYQQKPGQAPVLVYDD SDRPSGIPERFSGSNSGNTATLTISWVEAGDEADYYCQVWDSSIDHPVLF GGGTKLTVL

SEQ ID NO:	DESCRIPTION	SEQUENCE
160	19D11.1 VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYDMHWVRQATGKGLEWV SAIGTAGDTYYAGSVKGRFTISRENAKNSLYLQMNSLRVGD TAVYYCAR SWGEGNYFFYYGMDVWGQGTTTVTVSS
161	19D11.1 VL CDR1	GGDNIGSISVH
162	19D11.1 VL CDR2	DDSDRPS
163	19D11.1 VL CDR3	QVWDSSIDHPVL
164	19D11.1 VH CDR1	SYDMH
165	19D11.1 VH CDR2	AIGTAGDTYYAGSVKG
166	19D11.1 VH CDR3	SWGEGNYFFYYGMDV
167	34H3.1 VL	DIQMTQSPSSVSASVGDRVTITCRASQGINTWLAWYQQKPGKAPKLLIYV ASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQSDSFPWTFGP GT KVEIT
168	34H3.1 VH	QVQLVQSGAEVKKPGASVKVSCKVSGYTLTELSMHWVRQAPGKGLEW MGGFDPEDGETIYVQKFQGRVTMTEDTSTD TAYMELSSLRSED TAVYYC ATDLGYGSGNSYYYYSGMDVWGQGTTTVTVSS
169	34H3.1 VL CDR1	RASQGINTWLA
170	34H3.1 VL CDR2	VASSLQS
171	34H3.1 VL CDR3	QQSDSFPWT
172	34H3.1 VH CDR1	ELSMH
173	34H3.1 VH CDR2	GFDPEDGETIYVQKFQG
174	34H3.1 VH CDR3	DLGYGSGNSYYYYSGMDV
175	27H6.1 VL	DIVMTQTPLSLPVTGPGEPAISCRSSQSLNSVDGSTNLDWYLQKPGQSPQ LLIYTLNYSRASGVDPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQRIEFPL TFGGGT KVEIK
176	27H6.1 VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVS YISSGSSIIYADSVKGRFTISRDN AKNSLYLQMNSLRDED TAVYYCARE RYYGDTPFDYWGQGLTLTVTVSS
177	27H6.1 VL CDR1	RSSQSLNSVDGSTNLD
178	27H6.1 VL CDR2	TLNYSRAS
179	27H6.1 VL CDR3	MQRIEFPLT
180	27H6.1 VH CDR1	SYSMN
181	27H6.1 VH CDR2	YISSGSSIIYADSVKG
182	27H6.1 VH CDR3	ERYYGDTFPDY
183	42F4HZ VL	DIQLTQSPSFLSASVGDRVTITCRASSVTSSYLNWYQQKPGKAPKLLIYS TSNLASGVPSRFSGSGSGTEFTLTISLQPEDFATYYCQQYDFFPSTFGGGT KVEIK
184	42F4HZ VH	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDYYMNWVRQAPGQRLEW MGDINPYND DTTYNHKFKGRVTITRDT SASTAYMELSSLRSED TAVYYC ARETAVITTNAMDYWGQGTTTVTVSS

SEQ ID NO:	DESCRIPTION	SEQUENCE
185	42F4HZ VL CDR1	RASSSVTSSYLN
186	42F4HZ VL CDR2	STSNLAS
187	42F4HZ VL CDR3	QQYDFFPST
188	42F4HZ VH CDR1	DYYMN
189	42F4HZ VH CDR2	DINPYNDDTTYNHKFKG
190	42F4HZ VH CDR3	ETAVITTNAMDY
191	42F4MU VL	QIVLTQSPAIMASAPGEKVTMTCRASSSVTSSYLNWYQQKPGSSPKLWIY STSNLASGVPARFSGSGSGTSLTISSVEAEDAATYYCQQYDFFPSTFGG GTKLEIK
192	42F4MU VH	EVQLQQSGPELVKPGASVKMSCKASGYTFTDYMNWVKQSHGESLEWI GDINPYNDDTTYNHKFKGKATLTVDKSSNTAYMQLNSLTSEDSAVYYCA RETAVITTNAMDYWGQGSVTVSS
193	42F4MU VL CDR1	RASSSVTSSYLN
194	42F4MU VL CDR2	STSNLAS
195	42F4MU VL CDR3	QQYDFFPST
196	42F4MU VH CDR1	DYYMN
197	42F4MU VH CDR2	DINPYNDDTTYNHKFKG
198	42F4MU VH CDR3	ETAVITTNAMDY
199	13C7MU VL	DIQMTQITSSLSASLGDRVSISCRASQDISNYLNWYQQKPDGTFKLLIFYTS RLLSGVPSRFSGSGSGTDYSLTIYNLEQEDFATYFCQQGDTLPYTFGGGK LEIK
200	13C7MU VH	EVQLQQSGPELMKPGASVKMSCKASGYTFTDYNMHWVKQNQGKTLEW IGEINPNSGGAGYNQKFKGKATLTVDKSSTTAYMELRSLTSEDSAVYYCA RLGYDDIYDDWYFDVWGAGTTVTVSS
201	13C7MU VL CDR1	RASQDISNYLN
202	13C7MU VL CDR2	YTSRLLS
203	13C7MU VL CDR3	QQGDTLPYT
204	13C7MU VH CDR1	DYNMH
205	13C7MU VH CDR2	EINPNSGGAGYNQKFKG
206	13C7MU VH CDR3	LGYYDDIYDDWYFDV
207	13C7Rat VL	DIQMTQSPSSLSASLGDRVTITCRASQDISNYLNWYQQKPDGTVKRLIYY TSRLLSGVPSRFSGSGSGTDYSLSISSLESEDFAMYYCQQGDTLPYTFGGG TKLELK
208	13C7Rat VH	EVQLQQSGPELQRPASVKLSCKASGYTFTDYNMHWVKQSHGKSLEWI GEINPNSGGAGYNQKFKGKATLTADKSSNTAYMELRSLTSEDSAVYYCA RLGYDDIYDDWYFDVWGQGTITVTVSS
209	13C7Rat VL CDR1	RASQDISNYLN

SEQ ID NO:	DESCRIPTION	SEQUENCE
210	13C7Rat VL CDR2	YTSRLLS
211	13C7Rat VL CDR3	QQGDTLPYT
212	13C7Rat VH CDR1	DYNMH
213	13C7Rat VH CDR2	EINPNSGGAGYNQKFKG
214	13C7Rat VH CDR3	LGYDDIYDDWYFDV
215	13C7Hu VL	DIQMTQSPSSLSASVGDRVTITCRASQDISNYLNWYQQKPGKAPK LLIY YTSRLLSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQGD TLPYTFGGGTKVEIK
216	13C7Hu VH	EVQLVQSGAEVKKPGASVKVSCKASGYTFTDYNMHFWVRQAPGQGLEW MGEINPNSGGAGYNQKFKGRVTMTTDTSTSTAYMELRSLRSDDTAVYY CARLGYYDDIYDDWYFDVWGQGTTVTVSS
217	13C7Hu VL CDR1	RASQDISNYLN
218	13C7Hu VL CDR2	YTSRLLS
219	13C7Hu VL CDR3	QQGDTLPYT
220	13C7Hu VH CDR1	DYNMH
221	13C7Hu VH CDR2	EINPNSGGAGYNQKFKG
222	13C7Hu VH CDR3	LGYDDIYDDWYFDV
DKK-1 mAbs AA Sequences		
223	11H10Hu VL	EIVLTQSPATLSLSPGERATLSCRASQWVSSYLAWYQQKPGQAPRLLIYD ASNRATGIPARFSGSGSGTDFTLTISLQPEDFAVYYCAWQEFFGQGTKLE IK
224	11H10Hu VH	EVQLVQSGGGLVQPGGSLRLSCTASGFTFSNHWIHWVRQAPGKGLEWVS GINWNSGSRGYSDSVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCAR ERPVATGAFDIWGQGTTVTVSS
225	11H10Hu VL CDR1	RASQWVSSYLA
226	11H10Hu VL CDR2	DASNRAT
227	11H10Hu VL CDR3	AWQEF
228	11H10Hu VH CDR1	NHWIH
229	11H10Hu VH CDR2	GINWNSGSRGYSDSVKG
230	11H10Hu VH CDR3	ERPVATGAFDI
231	11H10Rat VL	DIRMTQSPASLSASLGETVNIETCLASEDIYSDLAWYQQKPGKSPQLLIYNA NSLQNGVPSRFSGSGSGTQYSLKINSLSQSEDVATYFCQQYNNYPPTFGGG TKLELK
232	11H10Rat VH	EVQLVESGGGLVQPANSLKLSCAASGFTFSDYAMAWVRQSPKKGLEWV ATIIYDGSSTYYRDSVKGRFTISRDNKSTLYLQMDSLRSEDATATYYCAT GLGIATDYFDYWGQGVLTVTSS
233	11H10Rat VL CDR1	LASEDIYSDLA
234	11H10Rat VL CDR2	NANSLQN

SEQ ID NO:	DESCRIPTION	SEQUENCE
235	11H10Rat VL CDR3	QQYNNYPPT
236	11H10Rat VH CDR1	DYAMA
237	11H10Rat VH CDR2	THYDGSSTYYRDSVKG
238	11H10Rat VH CDR3	GLGIATDYFDY
239	2.4.1 VL	DIQMTQSPSSLSASVGDRVTITCRASQGIRDDLGFQKPGKAPKRLIYA ASSLQSGVPSRFSGSGSGTEFTLTISLQPEDFATYYCLQHNSYPCSFQGT KLEFK
240	2.4.1 VH	QVQLMQSGAEVKKPGASVKVSCASGYTFTSYGISWVRQAPGQGLEWM GWISADNGHTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYC ARDGELLNYYYYYGMDEVWGQGTTLTVSS
241	2.4.1 VL CDR1	RASQGIRDDL
242	2.4.1 VL CDR2	AASSLQS
243	2.4.1 VL CDR3	LQHNSYPCS
244	2.4.1 VH CDR1	SYGIS
245	2.4.1 VH CDR2	WISADNGHTNYAQKLQG
246	2.4.1 VH CDR3	DGELLNYYYYYGMDEV
247	2.20.1 VL	DIVMTQTPLSLSVIPGPASISCKSSQSLHSDGKTYLYWYLQRPQGPPQL LIYEVSNRFSGVPHRLSGSGSGTDFTLKISRVEAEDVGYYCMQSIQVPW TFGQGTKVEIK
248	2.20.1 VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWV AVISYDGSDKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCA RDQWGGSPAGPWGQGTTLTVSS
249	2.20.1 VL CDR1	KSSQSLHSDGKTYLY
250	2.20.1 VL CDR2	EVSNRFS
251	2.20.1 VL CDR3	MQSIQVPWT
252	2.20.1 VH CDR1	SYGMH
253	2.20.1 VH CDR2	VISYDGSDKYYADSVKG
254	2.20.1 VH CDR3	DQWGGSPAGP
255	2.37.1 VL	EIVLTQSPGTLSPGERATLSCRASQSVSSNYLAWYQQKPGQAPRLIYG ASSRATGIPDRFSGSGSGTDFTLISRLEPEDFAVYYCQQYGSSPITFGQGT RLEIK
256	2.37.1 VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWV AVISYDGSDKYYADSVKGRFTFSRDNSKNTLYLQMNSLRAEDTAVYYCA RELGIAASFDYWGQGTTLTVSS
257	2.37.1 VL CDR1	RASQSVSSNYLA
258	2.37.1 VL CDR2	GASSRAT
259	2.37.1 VL CDR3	QQYGSSPIT
260	2.37.1 VH CDR1	SYGMH
261	2.37.1 VH CDR2	VISYDGSDKYYADSVKG
262	2.37.1 VH CDR3	ELGIAASFDY

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SEQ ID NO:	DESCRIPTION	SEQUENCE
288	5.17.1 VH	QVQLQESGPGGLVKPSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYI YYSGNTNYNPSLKSRTISVDTSKNQFSLKLRSVTAADTAVYYCARYNW NNDLFDYWGQGTLLTVSS
289	5.17.1 VL CDR1	QASQDINNYLN
290	5.17.1 VL CDR2	DASNLET
291	5.17.1 VL CDR3	QQYDDFPLT
292	5.17.1 VH CDR1	SYYWS
293	5.17.1 VH CDR2	YIYYSGNTNYNPSLKS
294	5.17.1 VH CDR3	YNWNNDLFDY
295	5.23.1 VL	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYD ASNLETGVPSRFSGSGSGTDFTFTISLQPEDATYYCQQYDNLPLTFGGG TKVEIK
296	5.23.1 VH	QVQLVESGGGVVQPGSRRLSCAASGFTFSSYGMHWVRQAPGKGLEWV AVIWCDSNKKYYADSVKGRFTISRDSKNTLYLQMNSLRAEDTAVYYCA RGGYGSGSYEDYYYGMDVWGQGTITVTVSS
297	5.23.1 VL CDR1	QASQDISNYLN
298	5.23.1 VL CDR2	DASNLET
299	5.23.1 VL CDR3	QQYDNLPLT
300	5.23.1 VH CDR1	SYGMH
301	5.23.1 VH CDR2	VIWCDSNKKYYADSVKG
302	5.23.1 VH CDR3	GGYGSGSYEDYYYGMDV
303	5.25.1 VL	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPRLIYD ASNLETGVPSRFSGSGSGTDFTFTISLQPEDATFYCQQYDHLPIAFGQGT RLEIK
304	5.25.1 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQATGQGLEWM GWMDPNSGNTGYAQKFQGRVTMTRNTSISTAFMELSSLRSEDATVYYC ARTDYFYFGMDVWGQGTITVTVSS
305	5.25.1 VL CDR1	QASQDISKDLN
306	5.25.1 VL CDR2	DASNLET
307	5.25.1 VL CDR3	QQYDNLPLT
308	5.25.1 VH CDR1	SYGMH
309	5.25.1 VH CDR2	WMDPNSGNTGYAQKFQG
310	VH CDR3	TDYFYFGMDV
311	5.31.1 VL	DIQVTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKFLIYD ASNLEAGVPSRFSGSGSGTDFTFTISLQPEDATYYCQQYDNLPLTFGGG TKVEIK
312	5.31.1 VH	QVQLVESGGGVVQPGSRRLSCAASGFTFSSYGMHWVRQAPGKGLEWV AVIWDGRNKKYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYC ARGGGAVADYNYYYGMDVWGQGTITVTVSS

SEQ ID NO:	DESCRIPTION	SEQUENCE
313	5.31.1 VL CDR1	QASQDISNYLN
314	5.31.1 VL CDR2	DASNLEA
315	5.31.1 VL CDR3	QQYDNLPLT
316	5.31.1 VH CDR1	SYGMH
317	5.31.1 VH CDR2	VIWYDGRNKYYADSVKG
318	5.31.1 VH CDR3	GGGAVADYNYYYGMDV
319	5.32.1 VL	DIQMTQSPSSLSASVGDRVITTCQASQDISKDLNHWYQQKPGKAPKLLIYD ASNLETGVPSRFSGSGSGTDFTFTISLQPEDATYYCQQYDDLPTFGQGT RLEIK
320	5.32.1 VH	QVQLVQSGAEVKKPGASVKVSCKASGFTFTSYDISWVRQATGLGLEWM GWMNPSSGYTGQAQNFQGRVTMTWNTSISTVYMELSSLRSEDVAVYYC ARTDYYYYGMDVWGRGTTVTVSS
321	5.32.1 VL CDR1	QASQDISKDLN
322	5.32.1 VL CDR2	DASNLET
323	5.32.1 VL CDR3	QQYDDLPT
324	5.32.1 VH CDR1	SYDIS
325	5.32.1 VH CDR2	WMNPSSGYTGQAQNFQG
326	5.32.1 VH CDR3	TDYYYYGMDV
327	5.40.1 VL	DIRLTQSPSSLSASVGDRVITTCQASQDISNYLNHWYQQEPGKAPKLLIYDA SNLETGVPSRFSGSGSGTDFTFTISLQPEDATYYCQQYDNFPLTFGGGTK VEIK
328	5.40.1 VH	QVLLQESGPGLVKPSLTLCTVSGGSISSYYWSWIRQTPGKGLEWIGY VYYSGSTSYNPSLKSRTISMYSKTEFSLKLSVTAADTAVYYCARYNW NNDLFDYWGQGLVTVSS
329	5.40.1 VL CDR1	QASQDISNYLN
330	5.40.1 VL CDR2	DASNLET
331	5.40.1 VL CDR3	QQYDNFPLT
332	5.40.1 VH CDR1	SYVWS
333	5.40.1 VH CDR2	YVYYSGSTSYNPSLKS
334	5.40.1 VH CDR3	YNWNNDLFDY
335	5.65.1 VL	SYVLTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVYD DSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVLDSSSDHVF GGTKLTVL
336	5.65.1 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTSGNYAMSWVRQAPGKGLEWV SAISGGGGTYYADSVEGRFTISRDN SKNTLYQLNSLRAEDTAVYYCAK EFGELEPRFDYWGQGLVTVSS
337	5.65.1 VL CDR1	GGNNIGSKSVH

SEQ ID NO:	DESCRIPTION	SEQUENCE
338	5.65.1 VL CDR2	DDSDRPS
339	5.65.1 VL CDR3	QVLDSSSDHVI
340	5.65.1 VH CDR1	NYAMS
341	5.65.1 VH CDR2	AISGGGGTTYADSV
342	5.65.1 VH CDR3	EFGELEPRFDY
343	5.76.1 VL	SYVLTQPPSVSVAPGQTARITCGGNNIGSESVHWYQQKPGQAPVLVVD DSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSNDHVV FGGTKLTVL
344	5.76.1 VH	QLQLQESGPGPLVKPSETLSLTCTVSGGSISSSNYYWGWIRQPPGKGLEWIG TIYYSGSTYYTPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARERA IAAIAIVFFDYWGQGTLLTVSS
345	5.76.1 VL CDR1	GGNNIGSESVH
346	5.76.1 VL CDR2	DDSDRPS
347	5.76.1 VL CDR3	QVWDSSNDHVV
348	5.76.1 VH CDR1	SSNYYWG
349	5.76.1 VH CDR2	TIYYSGSTYYTPSLKS
350	5.76.1 VH CDR3	ERAAIAAIVFFDY
351	5.77.1 VL	QSPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVVD DSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVV FGGTKLTVL
352	5.77.1 VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQATGQGLEWM GWMNLNSDNTGYAQKFQGRVTMTRNTSISTAYMELSSRLSEDTAVYYC ASIAARRDYNYYGMDVWGQGTLLTVSS
353	5.77.1 VL CDR1	GGNNIGSKSVH
354	5.77.1 VL CDR2	DDSDRPS
355	5.77.1 VL CDR3	QVWDSSSDHWV
356	5.77.1 VH CDR1	SYDIN
357	5.77.1 VH CDR2	WMNLNSDNTGYAQKFQG
358	5.77.1 VH CDR3	IAARRDYNYYGMDV
359	5.78.1 VL	EIVLTQSPGTLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLIYG ASGRATGIPDRFSGSGSGTDILTISRLEPEDFAVYYCQQYGSSFTFGGGTK VEIK
360	5.78.1 VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWV AVILYDGSNYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCA REGIAVAGDY YYGMDVWGQGTLLTVSS
361	5.78.1 VL CDR1	RASQSVSSSYLA
362	5.78.1 VL CDR2	GASGRAT

SEQ ID NO:	DESCRIPTION	SEQUENCE
363	5.78.1 VL CDR3	QQYGSSFT
364	5.78.1 VH CDR1	SYGMH
365	5.78.1 VH CDR2	VILYDGSDNYYADSVKG
366	5.78.1 VH CDR3	EGIAVAGDYYYYGMDV
367	5.80.1 VL	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGADYDVHWYQQLPGTAPKLLIYDYSNRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDNSLSGYVVFGGGTCLTVL
368	5.80.1 VH	EVQLVQSGAEVKKPAGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIHYPGDS DTRYSPSFQGGQVTISADKSISTAYLQWSSLTASDTAMYYCARQGESFDYWGQGTCLTVSS
369	5.80.1 VL CDR1	TGSSSNIGADYDVH
370	5.80.1 VL CDR2	DYSNRPS
371	5.80.1 VL CDR3	QSYDNSLSGYVV
372	5.80.1 VH CDR1	SYWIG
373	5.80.1 VH CDR2	IIYPGDS DTRYSPSFQG
374	5.80.1 VH CDR3	QGESFDY
375	5.85.1 VL	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPRTAPKLLIYGNSNRPSGVPDRFSDSKSGTSASLAITGLQAEDEADYYCQSYDSSLVIFGGGTCLTVL
376	5.85.1 VH	EVQLVQSGAEVKKPAGESLKISCKVSGYSFTTYWIGWVRQMPGKGLDWMGIHYPGDS DTRYSPSFQGGQVTISADKSISTAYLQWSSLKASDTAMYYCARQGIAFDYWGQGTCLTVSS
377	5.85.1 VL CDR1	TGSSSNIGAGYDVH
378	5.85.1 VL CDR2	GNSNRPS
379	5.85.1 VL CDR3	QSYDSSLVI
380	5.85.1 VH CDR1	TYWIG
381	5.85.1 VH CDR2	IIYPGDS DTRYSPSFQG
382	5.85.1 VH CDR3	QGIAFDY
383	6.37.5 VL	DIVMTQTPLSLSVTPGQPASISCKSGQSLHSDGKTYLYWYLQKPGQPPQFLIYEVSNRFSRVPDRFSGSGGTDFTLRISRVEAEDVGIYYCMQSIQLPWTFGQGTQVEIK
384	6.37.5 VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSGYGMHWVRQAPGKGLEWVAVISYDGN DKYYADSVKGRFTISRDN AKNTLYLQMNSLRAEDTAVYYCARELRVLWGQGTCLTVSS
385	6.37.5 VL CDR1	KSGQSLHSDGKTYLY
386	6.37.5 VL CDR2	EVS NRFS
387	6.37.5 VL CDR3	MQSIQLPWT

SEQ ID NO:	DESCRIPTION	SEQUENCE
388	6.37.5 VH CDR1	GYGMH
389	6.37.5 VH CDR2	VISYDGNDKYYADSVKG
390	6.37.5 VH CDR3	ELRVL
391	6.116.6 VL	DIVMTQTPLSLSVTPGQPASISCKSGQSLLHNDGKTYLYWYLQKPGQPPQ FLIYEVSNRFSRVPDRFSGSGSGTDFTLKISRVEAEDVGIYYCMQSIQLPW TFGQGTQVEIK
392	6.116.6 VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSGYGMHWVRQAPGKGLEWV AVISYDGNDKYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYC ARELRVLWGQGTLLTVSS
393	6.116.6 VL CDR1	KSGQSLLHNDGKTYLY
394	6.116.6 VL CDR2	EVSNRFS
395	6.116.6 VL CDR3	MQSIQLPWT
396	6.116.6 VH CDR1	GYGMH
397	6.116.6 VH CDR2	VISYDGNDKYYADSVKG
398	6.116.6 VH CDR3	ELRVL
399	6.139.5 VL	DIVMTQTPLSLSVTPRQPASISCKSSQSLLHSDGKTYLYWYLQKPGQPPQF LIYEVSNRFSRVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQSIQLPWT FGQGTKVEIK
400	6.139.5 VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWV AVISYDGGDQYYADSVKGRFTISRDNKNTLYLQMNSLRTEDTAEYYCA RELRLVLWGQGTLLTVSS
401	6.139.5 VL CDR1	AASGFTFSRYDMH
402	6.139.5 VL CDR2	IFYDGSNKYYAD
403	6.139.5 VL CDR3	ATLAAAFDY
404	6.139.5 VH CDR1	SYGMH
405	6.139.5 VH CDR2	VISYDGGDQYYADSVKG
406	6.139.5 VH CDR3	ELRVL
407	6.147.4 VL	YVLTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVYYDD SDRPSEIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVVFG GGTRLTVL
408	6.147.4 VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSRYDMHWVRQAPGKGLEWV AIFYDGSNKYYADPVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAT LAAAFDYWGQGTLLTVSS
409	6.147.4 VL CDR1	GGNNIGSKSVH
410	6.147.4 VL CDR2	DDSDRPS
411	6.147.4 VL CDR3	QVWDSSSDHVV
412	6.147.4 VH CDR1	RYDMH

SEQ ID NO:	DESCRIPTION	SEQUENCE
413	6.147.4 VH CDR2	IIFYDGSNKYYADPVKG
414	6.147.4 VH CDR3	LAAAFDY
Linkers		
415	linker	AKTTPKLEEGEFSEAR
416	linker	AKTTPKLEEGEFSEARV
417	linker	AKTTPKLGG
418	linker	SAKTTPKLGG
419	linker	SAKTTP
420	linker	RADAAP
421	linker	RADAAPTVS
422	linker	RADAAAAGGPGS
423	linker	RADAAAA(G ₄ S) ₄
424	linker	SAKTTPKLEEGEFSEARV
425	linker	ADAAP
426	linker	ADAAPTVSIFPP
427	linker	TVAA
428	linker	TVAAP
429	linker	TVAAPSVFIFP
430	linker	TVAAPSVFIFPP
431	linker	QPKAAP (lambda "AbS")
432	linker	QPKAAPSVTLFPP (lambda "AbL")
433	linker	AKTTPP
434	linker	AKTTPPSVTPLAP
435	linker	AKTTAP
436	linker	AKTTAPSVYPLAP
437	linker	ASTKGP (gamma "AbS")
438	linker	ASTKGPSVFPLAP (gamma "AbL")
439	linker	GGGGS ("1X")
440	linker	GGGSGGGGS ("2X")
441	linker	GGGSGGGSGGGGS ("3X")
442	linker	GENKVEYAPALMALS
443	linker	GPAKELTPLKEAKVS
444	linker	GHEAAAVMQVQYPAS
445	linker	GGGGGGGP
446	linker	GGGGGGGGP
447	linker	PAPNLLGGP
448	linker	PNLLGGP

SEQ ID NO:	DESCRIPTION	SEQUENCE
449	linker	GGGGGGP
450	linker	PAPELLGGP
451	linker	PTISPAPNLLGGP
452	linker	TVAADDDDKSVFIVPP
453	linker	TVDDDDKAAP
454	linker	LVPRGSAAP
455	linker	ASDDDDKGGP
456	linker	ALVPRGSGP
457	linker	ASTDDDDKSVFPLAP
458	linker	TVALVPRGSVFIFPP
459	linker	ASTLVPRGSVFPLAP
460	linker	TVAADDDDKSVFIVPP
461	linker	ASTDDDKSVFPLAP
462	linker	LEVLFQGP
463	linker	TVAALEVLFQGPAP
464	linker	ASTLEVLFQGPLAP
465	linker	PAPLEVLFQGP
466	linker	TAENLYFQGAP
467	linker	AENLYFQGA
468	linker	PGPFGRSAGGP
469	linker	PGPFGRSAGG
470	linker	PQRGRSAG
471	linker	PHYGRSGG
472	linker	GPFGRSAGP
473	linker	GDDDDKGGP
474	linker	AGDDDDKGGP
475	linker	GGDDDDKGGP
476	linker	AS
477	linker	TVA
478	linker	ASTK
479	linker	ASTKGPSV
480	linker	ASTKGPSVFP
481	linker	TVAAPSV
482	linker	TVAAPSVFI
483	linker	RTVAAP (kappa "AbS")
484	linker	RTVAAPSVFIFPP (kappa "AbL")
Additional DVD-Ig Sequences		

SEQ ID NO:	DESCRIPTION	SEQUENCE
485	6.147-AbL-Ab5 G2 NA	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGCTGCTGTGGCTGAGA GGTGCGCGCTGTTCAGGTGCAGCTTGTGAGAGCGGTGGAGGGGTGGTACAACCC GGAAGATCACTCCGGCTTTTCATGCGCAGCATCCGGTTTTACATTTTCGCGGTAT GACATGCACTGGGTGAGACAGGCACCAGGAAAAGGGCTGGAGTGGGTGGCCATC ATCTTCTATGATGGGTCCAATAAGTACTACGCCGACCCGGTAAAAGGGAGGTTT ACTATTAGCCGCGACAACTCGAAGAATACGCTGTACCTGCAGATGAACTCGTTG CGAGCCGAAGATACCGCGGTCTACTATTGTGCGACGCTCGCGGCTGCGTTTCGAT TACTGGGGCCAAGGAACATTGGTACAGGTCTCCTCAGCGTCAACGAAAGGACCG TCGGTGTTCCTTGGCCCCTGAGGTGCAGCTCGTGCAGTCCGGAGCCGAGGTG AAGAAGCCTGGGGCATCCGTCAAAGTCTCGTGCAAGGCGTCAGGGTACACATT ACCGACTATAACATGCATTGGGTCCGGCAGGCTCCCGGTTCAGGGCTGGAGTGG ATGGGGGAAATCAATCCGAACCTCCGAGGGGCAGGATACAATCAAAAAGTTTAA GGACGCGTAACGATGACCACTGACACGTCAACCTCCACGGCGTATATGGAGCTC AGAAGCCTCCGAAGCGACGACACTGCTGTCTATTACTGTGCGAGACTGGGATAT GATGATATCTACGACGATTGGTACTTCGATGTATGGGGACAAGGGACGACGGTC ACCGTCTCTAGTGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGC TCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTAC TTCCCCGAACCGGTGACGGTGTCTGTGAAGTCAAGGCGCTCTGACGAGCGCGTG CACACCTTCCCAGCTGTCTACAGTCTCAGGACTCTACTCCCTCAGCAGCGTG GTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGAT CACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAAATGTTGTGTC GAGTGCCACCGTGCCAGCACCACTGTGGCAGGACCGTCAGTCTTCTCTTC CCCCAAAACCCAAGGACACCTCATGATCTCCCGACCCCTGAGGTACAGTGC GTGGTGGTGAGCGTACGACGACGAGACCCCGAGGTCCAGTTCACTGGTACGTG GACGGCGTGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAAC AGCAGTTCCTGTGGTTCAGCGTCTCACCCTGTGTGCACAGGACTGGCTGAAC GGCAAGGAGTACAAGTGAAGTCTCCAACAAAGGCCCTCCAGCCCCATCGAG AAAACCATCTCCAAAACCAAGGGCAGCCCCGAGAACCACAGGTGTACACCTG CCCCATCCCGGGAGGAGATGACCAAGAACCAGGTACAGCTGACCTGCCTGGTC AAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG GAGAACAACATAAGACCACACCTCCCATGCTGGACTCCGACGGCTCCTTCTTC CTCTACAGCAAGCTACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTC TCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTC TCCCTGTCTCCGGGTAA
486	6.147-AbL-Ab5 G2 AA	QVQLVESGGGVVQPGRSRLRSCAASGFTFSRYDMHWVRQAPGKGLEWVAITFYD GSNKYYADPVTKGRFTISRDN SKNTLYLQMNSLR AEDTAVYYCATLAAAFDYWGQ GTLVTVSSASTKGPSVFPLAPEVQLVQSGAEVKKPGASVKVSCKASGYTFDYN MHWVRQAPGQGLEWMGEINPNISGGAGYNQKFKGRVTMTTDTSTSTAYMELRSLR SDDTAVYYCARLGYYDDIYDDWYFDVWGQGTITVTVSS ASTKGPSVFPLAPCSRST SESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSNFGTQTYTCNVDHKPSNTKVDKVERKCCVECPPCPAPPVAGPSVLEFPKPK KDTLMI SRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFR VVSVLTVVHQDNLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSR EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPMLDSGGSFFLYSK LTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
487	6.147-AbL- Ab5 LC NA	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGCTGCTGTGGCTGAGA GGTGCGCGCTGTTTCATACGTGCTCACTCAGCCGCCCAGCGTATCGGTGGCTCCC GGACAGACGGCGCGAATCAGTGCGGTGGGAACAATATCGGCTCCAAGTCAGTC CATTGGTATCAACAGAAACCTGGTCAGGCACCAAGTCCTGGTGGTATACGATGAC TCGGACAGGCCCTCGGAGATTCCGGAACGCTTCTCCGGATCGAATTCGGGGAAC ACAGCGACCTTGACGATCAGCAGAGTGGAGGCCGGAGATGAAGCCGACTACTAT TGTCAGGTGTGGGATTCCAGCTCCGACCACGTCGTATTTGGAGGTGGGACACGG CTTACCGTCCTCGGGCAGCCCAAGGCTGCGCCATCGGTCACTCTGTTCCACCT GACATTCAGATGACTCAGTCGCCTTCGTCATTGAGCGCGTCGGTGGGAGATCGG GTCACGATTACTTGTGCGGCATCGCAAGACATCTCGAATATTGAATTGGTAC CAGCAAAAGCCTGGTAAAGCGCCAAACTTCTTATCTACTATACGTCCCGCCTC CTCTCGGGCGTCCCGTCAAGGTTTAGCGGATCGGGAAGCGGGACGGATTTCACA CTGACGATTTCACTTCACTTCAGCCCGAAGATTTGCCACCTATTACTGTCAGCAA GGAGACACCCTGCCATACACTTTTGGCGGTGGGACAAAGGTCGAAATCAAGCGT ACGGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAA TCTGGAAGTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCC AAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGT GTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGACCCCTGACG CTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCAT CAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT
488	6.147-AbL- Ab5 LC AA	SYVLTQPPSVSVAPGQTARITC ~~GGNNIGSKSVHWYQOKPGQAPVLVVYDSDRE~~ ~~SEIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVVF~~ GGGTRLTVL GQPKAAPSVTLFPPDIQMTQSPSSLSASVGDRTITC ~~PASQDISNYLIHWYQOKP~~ GKAPKLLIYYTSRLLSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC ~~QQGDTL~~ ~~PYTF~~ GGGTKVEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW KVDNALQSGNSQESVTEQDSKDSYSTLSSTLTLSKADYEKHKVYACEVTHQGLS SPVTKSFNRGEC

SEQ ID NO:	DESCRIPTION	SEQUENCE
489	6.147-3x- Ab5 G2 NA	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGCTGCTGTGGCTGAGA GGTGC GCGCTGT CAGGTGCAGCTTGTGAGAGCGGTGGAGGGGTGGTACAACCC GGAAGATCACTCCGGCTTTTCATGCGCAGCATCCGGTTTTACATTTTCGCGGTAT GACATGCACTGGGTGAGACAGGCACCAGGAAAAGGGCTGGAGTGGGTGGCCATC ATCTTCTATGATGGGTCCAATAAGTACTACGCCGACCCGGTAAAAGGGAGGTTT ACTATTAGCCGCGACAACTCGAAGAATACGCTGTACCTGCAGATGAACTCGTTG CGAGCCGAAGATACCGCGGTCTACTATTGTGCGACGCTCGCGGCTGCGTTTCGAT TACTGGGGCCAAGGAACATTGGTCACAGTGAGCTCAGGGGGTGCGGTTTCGGGC GGTGGAGGCTCGGGAGGTGGTGGATCCGAGGTGCAGCTCGTGCAGTCCGGAGCC GAGGTGAAGAAGCCTGGGGCATCCGTCAAAGTCTCGTGCAAGGCGTCAGGGTAC ACATTCAACCGACTATAACATGCATTGGGTCCGGCAGGCTCCCGGTCAGGGGCTG GAGTGGATGGGGGAAATCAATCCGAACTCCGAGGGGCAGGATACAATCAAAAG TTTAAGGGACGCGTAACGATGACCACTGACACGTCAACCTCCACGGCGTATATG GAGCTCAGAAGCCTCCGAAGCGACGACACTGCTGTCTATTACTGTGCGAGACTG GGATATGATGATATCTACGACGATTGGTACTTCGATGTATGGGGACAAGGGACG ACGGTCACCGTCTCTAGTGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCG CCCTGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCTGGTCAAG GACTACTTCCCCGAACCGGTGACGGTGTCTGGAAGTCAAGCGCTCTGACCAGC GGCGTGACACACTTCCAGCTGTCTACAGTCTCAGGACTCTACTCCCTCAGC AGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAAC GTAGATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAATGT TGTGTCGAGTGCCACCGTGCCAGCACCACTGTGGCAGGACCGTCAGTCTTC CTCTTCCCCCAAAACCAAGGACACCTCATGATCTCCCGGACCCCTGAGGTC ACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGG TACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAG TTCAACAGCACGTTCCGTGTGGTCAGCGTCTCACC GTTGTGCACCAGGACTGG CTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAGGCCCTCCAGCCCCC ATCGAGAAAACCATCTCCAAAACCAAGGGCAGCCCCGAGAACCACAGGTGTAC ACCTTGCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTGACCTGACCTGC CTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGG CAGCCGGAGAACAATAACAAGACCACCTCCCATGCTGGACTCCGACGGCTCC TTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAAC GTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAG AGCCTCTCCCTGTCTCCGGGTAAA
490	6.147-3x- Ab5 G2 AA	QVQLVESGGGVVQPGRSRLSCAASGFTFSRYDMHWVRQAPGKGLEWVAITFYD GSKYYADEFTGRFTISRDN SKNTLYLQMNSLR AEDTAVYYCATLAAAFDYWGQ GTLVTVSSGGGGSGGGSGGGSEVQLVQSGAEVKKPGASVKV SCKASGYTFD YIMHWVRQAPGQGLEWMGEINPNSGGAGYHOKFKGRVTMTTDTSTSTAYMELRS LRSDDTAVYYCARLGYDDIYDDWYFDYWGQTTVTVSS ASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSNFGTQTYTCNV DHKPSNTKVDKVERKCCVECP P PAPPVAGPSVFLFPP KPKDTLMI SRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNST FRVVSVLT VVHQDWLNGKEYKCKVSNKGLPAPI EKTISKTKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT P PMLDSDGSFFLY SKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
491	6.147-3x- Ab5 LC NA	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGCTGCTGTGGCTGAGA GGTGCGCGCTGTTTCATACGTGCTCACTCAGCCGCCAGCGTATCGGTGGCTCCC GGACAGACGGCGCGAATCAGTGCCTGGGAACAATATCGGCTCCAAGTCAGTC CATTGGTATCAACAGAAACCTGGTCAGGCACCAAGTCCTGGTGGTATACGATGAC TCGGACAGGCCCTCGGAGATTCCGGAACGCTTCTCCGGATCGAATTCGGGGAAC ACAGCGACCTTGACGATCAGCAGAGTGGAGGCCGAGATGAAGCCGACTACTAT TGTCAGGTGTGGGATTCCAGCTCCGACCACGTCGTATTTGGAGGTGGGACACGG CTTGGGGGTGGCGGTTCTGGGCGGTGGAGGCTCGGGAGGTGGTGATCCGACATT CAGATGACTCAGTCGCCTTCGTCATTGAGCGCGTCGGTGGGAGATCGGGTCACG ATTACTTGTCGGGCATCGCAAGACATCTCGAACTATTTGAATTGGTACCAGCAA AAGCCTGGTAAAGCGCCCAAACCTTCTTATCTACTATACGTCCCGCCTCCTCTCG GCGTCCCGTCAAGGTTTAGCGGATCGGGAAGCGGGACGGATTTCACACTGACG ATTTCACTACTTCAGCCCGAAGATTCGCCACCTATTACTGTCAGCAAGGAGAC ACCCTGCCATACACTTTTGGCGGTGGGACAAAGGTCGAAATCAAGCGTACGGTG GCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTA CAGTGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACA GAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGC AAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGC CTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGT
492	6.147-3x- Ab5 LC AA	SYVLTQPPSVSVAPGQTARITC ~~GGNNIGSKSVHWYQOKPGQAPVLVVYDDSDRE~~ ~~SEIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVV~~ FGGGTRLGGG GSGGGSGGGGSDIQMTQSPSSLSASVGDRVITITCRASQDISHYLIHWYQOKPGK APKLLIYYTSRLLSGVPSRFSGSGSGTDFTLTIISSLQPEDFATYYCQQGDTLPY ~~TFGGG~~ TKVEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV DNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC

SEQ ID NO:	DESCRIPTION	SEQUENCE
493	11H10-AbL- Ab23 G2 NA	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGCTGCTGTGGCTGAGA GGTGC GCGCTGTGAAGTGCA GTTGGTACAGTCGGGTGGGGGACTGGTGCAGCCA GGGGGTTCGCTTAGGTTGTCGTGCACAGCGTCGGGGTTTACATTCTCAAACAC TGGATTCACTGGGTGAGACAAGCCCCCTGGTAAAGGGCTGGAATGGGTGAGCGGG ATCAATTGGAATTCAGGCAGCCGGGGATATTTCGATTCCGTAAAAGGAAGGTTT ACTATCTCGAGGGATAACGCAAAGAACTCCCTCTATTTGCAGATGAACAGCCTT CGGGCGGAGGACACGGCAGTCTACTACTGTGCCCCGAGAAAGACCCGTGGCCACA GGCGCGTTTGACATTTGGGGTCAGGGCACGACAGTAACGGTCTCCTCAGCGTCA ACGAAAGGACCGTCGGTGTTCCTTGGCCCCGTGAGGTGCAGTCGTACAGTCG GGTGCGGAAGTAAAGAAACCCGGCTCATCCGTGAAAGTCTCGTGTAAAGCCTCC GGGTTCACCTTCACAGACTACATTATGCACTGGGTGCGGCAGGCCCTGGGCAG GGCCTTGAATGGATGGGGTATATCAACCCCTACAATGATGACACGGAGTATAAC GAAAAGTTTAAGGGAAGGGTGACAATCACGGCGGATAAGAGCACCAGCACTGCA TACATGGAGCTCTCGTCATTGCGCTCGGAGGACACTGCAGTCTACTATTGCGCG AGATCCATCTACTATTACGATGCGCCGTTTGCTTATTGGGGACAGGAACGCTG GTCACCGTCTCTAGTGCCCTCCACCAAGGGGCCATCGGTCTTCCCCCTGGCGCCC TGCTCCAGGAGCACCTCCGAGAGCACAGCGGCCCTGGGCTGCCGTGGTCAAGGAC TACTTCCCCGAACCGGTGACGGTGTGCTGGAACCTCAGGCGCTCTGACCAGCGGC GTGCACACCTTCCAGCTGTCTTACAGTCCTCAGGACTCTACTCCCTCAGCAGC GTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTA GATCACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGAGCGCAAATGTTGT GTCGAGTGCCCAACCGTGCCAGCACCACTGTGGCAGGACCGTCAGTCTTCCCTC TTCCCCCAAAACCAAGGACACCTCATGATCTCCCGGACCCCTGAGGTCACG TGCGTGGTGGTGACGTGAGCCACGAAGACCCGAGGTCCAGTTCAACTGGTAC GTGGACGGCGTGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTC AACAGCACGTTCCGTGTGGTCAGCGTCTCACC GTTGTGCACCAGGACTGGCTG AACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAGGCCTCCAGCCCCATC GAGAAAACCATCTCCAAAACCAAGGGCAGCCCCGAGAACCACAGGTGTACACC CTGCCCCCATCCCGGAGGAGATGACCAAGAACCAGGTGACCTGACCTGCCTG GTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG CCGGAGAACAAC TACAAGACCACACCTCCCATGCTGGACTCCGACGGCTCCTTC TTCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTC TTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACC ACTACACGCAGAAGAGC CTCTCCCTGTCTCCGGGTAAA
494	11H10-AbL- Ab23 G2 AA	EVQLVQSGGGLVQPGGSLRLSCTASGFTFSNHWIHWVRQAPGKGLEWVSGIHWI SGSRGYSDSVFGRTISRDNAKNSLYLQMNSLRAEDTAVYYCARERPVATGAFD IWQGTITVTVSSASTKGPSVFPLAPEVQLVQSGAEVKKPGSSVKVSKASGFTF TDYIMHWVRQAPGQGLEWMGYINPYNDDTEYMEKFKGRVTITADKSTSTAYMEL SSLRSED TAVYYCARSIYYDAPFAIWQGTITVTVSSASTKGPSVFPLAPCSRS TSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTV PSSNFGTQTYTCNV DHPKPSNTKVDKTV ERKCCVECP PAPPVAGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTF RVVSVLTVVHQDNLNGKEYKCKVSNKGLPAP IEKTI SKTKGQPREPQVYTLPPS REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPMLDS DGSFFLYS KLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGK

SEQ ID NO:	DESCRIPTION	SEQUENCE
495	11H10-AbL- Ab23 LC NA	ATGGACATGAGGGTGCCCGCTCAGCTCCTGGGGCTCCTGCTGCTGCTGGCTGAGA GGTGCGCGCTGTGAGATTGTATTGACTCAGTCACCGGCCACGCTCTCGCTGTCA CCCGGCCGAAAGAGCAACACTGAGCTGTGCGGGCGTCGCAGTGGGTGTCGTCGTAT TTGGCCTGGTATCAACAAAAGCCTGGACAGGCGCCCAGGCTGCTCATCTACGAC GCGTCCAACCGCGCCACCGGTATCCCGGCACGATTCTCCGGTTCGGGGTCGGGA ACAGACTTCACGTTGACGATTAGCTCCCTTGAGCCAGAAGATTTGCGGTCTAC TACTGCGCTTGGCAGGAGTTCCTTGGGCAGGGGACCAAGCTTGAAATCAAACGC ACAGTGGCTGCTCCATCCGTCTTTATCTTCCCTCCAGACATTCAAATGACACAG TCGCCCTCCTCGCTCTCGGCGTCAGTCGGGGATCGCGTGACAATCAGTGTCTCG GCCAGCCAGGACATTTTCGAGCTACCTCAACTGGTATCAGCAGAAACCGGGAAA GCGCCGAAGCTGCTTATCTACTCCACCTCAAGGTTGAATTCGGAGTACCCTCA AGATTTTCGGGTAGCGGATCAGGAACCGACTTCACACTTACGATCTCGTCGTTG CAGCCAGAAGATTTTCGCAACGTACTATTGCCAGCAAGATATCAAGCACCTACG TTTGGTGAGGGCACTAAAGTGGAGATTAAGCGTACGGTGGCTGCACCATCTGTC TTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACCTGCCTCTGTTGTG TGCTGCTGAATAACTTCTATCCAGAGAGGCCAAAGTACAGTGGAAGGTGGAT AACGCCCTCCAATCGGGTAACCTCCAGGAGAGTGTACAGAGCAGGACAGCAAG GACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAGACTACGAG AAACACAAAAGTCTACGCCGTCGGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTC ACAAAGAGCTTCAACAGGGGAGAGTGT
496	11H10-AbL- Ab23 LC AA	EIVLTQSPATLSLSPGERATLSCFASQWYSSYLAWYQQKPGQAPRLLIYDASNR ATGIPARFSGSGSGTDFTLTISSELEPEDFAVYYCAWQEFFGQGTKLEIKRTVAA PSVFIFPPDIQMTQSPSSLSASVGRVTITCRASQDISSYLNWYQQKPGKAPKL LIYSTSRINSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQODIKHPTFGQG TKVEIKR <i>TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ SGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF NRGEC</i>

*Note that the CDRs are bold/highlighted and the heavy chain constant region is bold/italic for SEQ ID NOs 17-92 and 485-496.

EXAMPLES

EXAMPLE 1

5 Engineering of Bi-specific Dual Variable Domain Ig Molecules: Anti-Sclerostin and Anti-DKK1

Antibodies directed against human Sclerostin and DKK1 were used for construction of several sets of dual variable domain (DVD) Ig molecules. The DNAs for light chain and heavy chain genes were obtained from mouse, rat or xenomouse hybridomas. To construct the dual domain light chain light,
10 the VL domain of anti-human sclerostin antibody was fused in tandem by a linker (the first 12 amino acids of the CL1 domain of light chains) to the N-terminus of the variable domain of anti-hu DKK1 antibody light chain followed by CL to form the full length DVD-Ig light chain.

Similarly, the variable domain of heavy chain (VH) of anti-hu sclerostin antibody was fused in tandem
15 by a linker (the first 13 or 12 amino acids of CH1 on heavy chain) to N-terminus of VH of anti-hu DKK1 antibody followed by full constant region of heavy chain. The other version of DVD is VH/VL of anti-DKK1 on the N-terminus of heavy/light chain of anti-Sclerostin with respective linkers.

The linker between two variable domains of light chain was derived from CL1 region while the linker
20 between two variable domains of heavy chain was derived from CH1 region of constant region of heavy chain. All DNA constructs were cloned into pTT5 vector through unique restriction sites.

One example of the DVD-Ig molecules generated is the rat chimeric DVD AB-4-11H10 where VL/VH of a mouse anti-hu Sclerostin antibody AB-4 were joined to the N-terminus of the light/heavy chain
25 of rat anti-hu DKK1 11H10 antibody and contains rat IgG2a constant region. DVD's with reversed orientation of variable domains were also made, where the variable domains (VL/VH) of rat anti-hu DKK1 11H10 were fused to the N-terminus of the light/heavy chain of mouse anti-SclerostinAB-4.

Rat constant domain derived linkers were selected to provide structural stability as well as make the
30 construct more rat like. This type of ratized bispecific antibody should have less risk of potential immunogenicity when used in short and long term rat models.

EXAMPLE 2

Expression of Sclerostin-DKK1 DVD-Ig

Large scale production of the sclerostin-DKK1 DVD-Ig was performed in a Wave bioreactor (25 L) as follows:

3L flasks were inoculated with 1L each of 293-6E cells at 3E5 viable cells per ml (VC/ml). F17
5 expression medium was used and supplemented with 1.1 mg/ml Pluronic, 6 mM L-Glutamine and 25
ug/ml Geneticin. After 48 hrs, cell counts were performed and viability ranging between 99.1% to
99.9% was observed. A 1:2 dilution of the culture was obtained by mixing 11.25 liters of 293-6E
culture in a 50L Wave bag with 11.25 liters of fresh F17 medium. Another cell count was performed
24 hrs later and 98.5% viability was determined. A 1:10 dilution in F17 media was then carried out
10 and 0.5mg of total plasmid DNA/L of culture(or 12.5 mg) was added with 3ml PEI Max/mg DNA.
Equal amounts of DNA for each of the antibody chains was added (6.25 mg). Twenty four hours post
transfection, 625 mls (25ml/L of culture) of feed (consisting of 20% Tryptone N1 in F17 with 0.1%
Pluronic) were added to the culture followed by a five day incubation. Subsequently, cell counts
were performed and 82.9% cell viability was observed. The conditioned media (CM) was then
15 harvested by centrifugation at 4000 rpm for 45 minutes and the CM was filtered with a 0.2 um filter.
An aliquot of the antibody was analyzed by SDS-PAGE under reducing and non-reducing conditions.

EXAMPLE 3

Purification and Formulation of Sclerostin-DKK1 DVD-Ig for *In Vivo* Studies

20 Sclerostin-DKK1 DVD-Ig was purified from transient cell culture. The purification scheme used
affinity chromatography followed by hydrophobic interaction chromatography (HIC).

Cell Culture Fluid Concentration

25 Concentration of the cell culture fluid was performed at 4°C using a TFF (tangential flow filtration)
device. PES 10kD MWCO (5 x 1 sq. ft.) membranes were used to concentrate the product
approximately ten-fold. Cross flow was 0.7 L/sq. ft/min, and the TMP was 25-30 psi.

30 Protein G chromatography

Protein G chromatography was performed at room temperature, although the cell culture fluid
remained cold during loading. The flow rate remained constant at 0.2 column volumes per minute.

20 liters of clarified cell culture fluid was concentrated ten-fold, diluted with a half volume of 1.2 M sodium citrate, 75 mM Tris pH 9, and then loaded onto a 230 mL Protein G Sepharose Fast Flow column (XK50, 19.6 cm² x 12.5 cm) equilibrated in 0.4 M sodium citrate, 25 mM Tris, pH 9. After loading the cell culture fluid, the column was washed with 0.4 M sodium citrate, 25 mM Tris, pH 9 until the absorbance at 280 nm returned to baseline. Following the wash, the antibody was eluted from the column with 0.1 M acetic acid pH 3 and the entire elution peak was collected. The elution pool contained 2.197 grams of product. Following elution the Protein G pool was immediately adjusted to pH 7 with 1M Tris Base.

10 Phenyl HP chromatography

Phenyl HP chromatography was performed at room temperature, binding at approximately 7 mg of protein per mL of resin. The flow rate remained constant at 0.2 column volumes per minute.

15 The Protein G pool was conditioned for binding onto Phenyl HP by adding 20 mM sodium phosphate, 3M ammonium sulfate pH 7 to a final concentration of 0.6 M ammonium sulfate. 115 mL (245 mg) of the conditioned Protein G pool was loaded onto a 35 mL Phenyl HP column (XK 26, 5.3 cm² x 6.6 cm) equilibrated in 20 mM sodium phosphate, 0.6 M ammonium sulfate pH 7. After loading, the column was washed with 20 mM sodium phosphate, 0.6 M ammonium sulfate pH 7 until the absorbance at 280 nm of the flow-through returned to baseline. A 20 column volume linear gradient of decreasing ammonium sulfate (0.6-0M) in 20 mM sodium phosphate at pH 7 was used to elute the product from the Phenyl HP column. 0.5 column volume fractions were collected and assayed by size exclusion HPLC to determine purity. Fractions were pooled based on % main peak to form a product pool. 86% of the product was recovered, yielding 210 mg.

25

Formulation: Buffer Exchange and Concentration

Buffer exchange was performed at 4°C using regenerated cellulose 10kD MWCO dialysis cassettes. Concentration was performed at 4°C using a PES 10kD MWCO centrifugal device. Recovery was 85%.

30

80 mL (80 mg) of Phenyl HP pool was buffer exchanged into 10 mM Tris, 250 mM L-Proline pH 7.5. Dialysis was performed by dialyzing three times against 3 liters of 10 mM Tris, 250 mM L-Proline pH 7.5. The volume of the post-dialysis product pool was 113 mL at a protein concentration of 0.674 mg/mL. Following dialysis the product pool was concentrated down to 18.5 mL using a centrifugal

concentration device. The product pool was then sterile filtered (0.22 micron). The concentration of the filtered pure bulk measured 3.65 mg/mL. Overall recovery was 73%, or 67.6 mg. The endotoxin level of the filtered pure bulk measured less than 0.07 EU/mg. The filtered pure bulk product was stored at 4°C.

5

EXAMPLE 4Sclerostin and DKK1 ELISA

The ability of various bispecific antibodies to specifically bind Sclerostin and Dkk1 simultaneously was determined by an ELISA capture assay. Plates were coated with 20 ml/well of 1 mg/ml of mouse anti-huScl MAb 56H2 in coating buffer (0.015M Na₂CO₃, 0.035M NaHCO₃, pH9.6) in 96-well half-area plate (Costar, cat#3694) and incubated at RT for one hour or 4°C overnight. The plates were washed once with 100 ml/well of washing solution (PBS containing 0.2% Tween20, BIO-RAD) and subsequently 100 ml/well of blocking solution (PBS containing 1% BSA, 1% goat serum and 0.5% Tween20) was added for one hour at RT. Human Sclerostin protein was added (20 ml/well of a 10ng/ml stock solution diluted in blocking solution) and incubated at room temperature for one hour followed by washing as described above. 20 ml/well of various diluted bispecific Abs (0, 0.008, 0.04, 0.2, 1, 5, 25, 125, 625 nM), parental Abs (positive control) and non-DKK1/Scl related IgG (human or rat IgG, negative control) were added in blocking solution and plates were incubated at room temperature for one hour. Following incubation in washing solution, 20 ml/well of huDKK1-biotin (10ng/ml) diluted in blocking solution was added to the plates for 1 hour at room temperature and then in washing solution. Neutravidin-HRP dilution (Pierce, cat#31001) diluted in blocking solution was added at a 1:50,000 dilution to the wells (20 ml/well), followed by incubation at RT for one hour and subsequent washing three times with 100 ml/well of washing solution. As a final step 20 ml/well of a SuperSignal ELISA Femto (Thermo, cat#37074) working solution was added to the plates and the signal was read using a luminometer at 425 nm. The data, as summarized in Figures 1-3, indicate that all bispecifics tested are capable of binding both targets simultaneously and hence the linker sequences joining the variable regions of the antibodies nor the binding of each variable domain to one ligand pose significant steric constraints on binding of the second ligand.

30 **EXAMPLE 5**Sclerostin and DKK1 Biacore Assay

To further demonstrate that the bispecific antibodies can bind both targets, tetravalent dual specific binding activity was assessed by Biacore analysis. Briefly, goat anti-huIgG, Fc fragment specific antibody was immobilized to all four flowcells of a CM5 chip at a high surface density (>3,500 RU

immobilized). The bispecific antibodies were diluted to 20nM in 25mM Tris, pH 8.5, 250mM NaCl, 0.005% P-20, 0.1mg/mL BSA and captured on individual flowcells. Ligands (human Dkk-1 and human Sclerostin) were diluted to 100nM in the same buffer and were injected sequentially over the captured bispecific Ig.

5

The sensograms show that when the bispecific antibody was saturated with the first antigen (either human Dkk1 or human Sclerostin) and the second antigen was injected, a second binding signal was observed. This observation was similar when the antigen injection sequence was reversed. The observation of two separate binding events indicate that the bispecific antibody can bind both

10 ligands simultaneously.

EXAMPLE 6

Osteoblast Wnt Activation Bioassay

Engineered bispecific antibodies are capable of neutralizing the ability of both targets to block canonical Wnt signaling as demonstrated in an osteoblast Wnt activation assay. MC3T3-E1 cells were transfected with a Super-TOPFlash reporter construct, and the stable cell lines were selected and evaluated. Clone C10 was identified as the best clone and it has been well characterized under various conditions and shown to have decreased reporter activity following incubation with either purified Sclerostin or Dkk1 proteins due to inhibition of Wnt pathway activation. Cells were cultured in Expansion Medium (Alpha-MEM medium containing 10%FBS, 1X Pen-Strep-Glu and 1.0ug/ml of puromycin) . When the cells reached 80% confluence, the medium was switched to Differentiation Medium (Expansion Medium, 50 ug/ml ascorbic acid and 10 mM beta-glycerophosphate) for 4 days. Following differentiation, this cell line produces an endogenous protein (s) that triggers canonical Wnt activation in an autocrine manner. Media was aspirated and 100uLs of fresh DM containing various concentrations of monospecific or bispecific antibodies (preincubated for 4hrs with Dkk1 and/or Sclerostin for 45-60 min at 37C) was added to the wells for 24 hrs. Luciferase activity was measured following manufacturer's instructions (Promega's Luciferase Assay System, Cat No: E4530).

30 Various rat and human bispecific antibodies tested were capable of dose-dependently activating the osteoblast canonical Wnt pathway in the presence of both Sclerostin and Dkk1 further demonstrating that the antibodies can simultaneously neutralize the Wnt inhibitory function of both soluble proteins.

EXAMPLE 7Wnt Induced Luciferase Bioassay

The engineered bispecific antibodies were capable of neutralizing Dkk1 and blocking Wnt1 induced

5 TCF/LEF luciferase activity as determined in an osteoblast cell based assay. The osteoblast MC3T3E1/TetON-Wnt1/STF-Luc#5 cell line was engineered by lentiviral transduction with a T-Cell Factor (TCF)-responsive luciferase construct, a Tet repressor construct and a doxycycline inducible Wnt1 construct. In this assay, addition of doxycycline (10ng/ml) to the culture medium for 22-26hr induced expression of Wnt1 and signal transduction via the binding of Wnt1 to cell surface LRP5/6

10 and Frizzled receptors, resulting in the expression of the luciferase reporter gene. MC3T3E1/TetON-Wnt1/STF-luc#5 cells were incubated in the presence of Sclerostin and /or Dkk1 and Wnt signaling was inhibited due to competitive binding of Sclerostin and Dkk1 to LRP5/6. Human Dkk1 protein (0.1ug/ml) or human Sclerostin protein (1 g/ml) were premixed with control PBS or a serial dilution of the bispecific antibodies. 24hrs later the luciferase signal was determined as described above and

15 the data were plotted by using PRISM software. As summarized in Figure 4 and 18, the bispecific antibodies dose-dependently inhibited Sclerostin and Dkk1 and restored Wnt signaling induced by Wnt1.

EXAMPLE 820 Screening Method for Binders of Sclerostin and/or DKK1

A method for screening the ability of bispecific abs, peptibodies and avimers to block Sclerostin or Dkk1 binding to Lrp6 was established using purified biotin-labeled Dkk1 and Sclerostin proteins and purified His-tagged Lrp6 or Lrp5. The ability of the bispecifics/peptides/avimers to block Scl or Dkk1 binding to Lrp6/Lrp5 was determined using an AlphaScreen assay. 5μl of biotin-Scl (or biotin-Dkk1)

25 and 5μl of Lrp6-His were incubated for 1 hour at room temperature first, and then 5μl of bispecific agent was added for additional 1 hour followed by addition of 10ul of a donor /acceptor beads mixture. The reaction was incubated for 1 more hour before the AlphaScreen signal was read on an EnVision apparatus at 520-620nm. The loss of signal in the bispecific agent treated wells indicated that the bispecifics block the binding of Dkk1 and Sclerostin to Lrp5/Lrp6 and may thereby allow

30 canonical signaling to be triggered by various Wnt proteins. Figure 19 summarizes data from one such screening experiment.

EXAMPLE 9In Vivo Mouse Bone Mass and Bone Strength Model

These studies and results are summarized in Figure 5. Study Design: Total of 45 male 10 weeks old B6D2F1 mice were used in this study. At the beginning of the study, animals were divided into 5 groups (n=9/group), balancing by both body weight and BMD at the femur-tibia region by in vivo DXA. Mice were subcutaneously injected with either vehicle (proline) or sclerostin-Ab (Scl-Ab), or DKK1-Ab or combination of Scl-Ab and DKK1-Ab (Combination) or bispecific antibody (Bisp-Ab) twice per week for 3 weeks. Due to the differences in molecular weight, the antibodies were dosed at equal molarity ($1.82 \times 10^{-5}M$), with 18.2 mg/kg Scl-Ab, 18.07 mg/kg DKK1-Ab, 18.2 mg/kg Scl-Ab + 18.07 mg/kg DKK1-Ab in the Combination group, and 25 mg/kg Bisp-Ab. Animals were scanned weekly by in vivo DXA to monitor the bone anabolic effects of the drug treatments at lumbar vertebral and femur-tibia regions; then euthanized at the end of study. Femurs were collected for ex vivo densitometry by μ CT and bone strength analysis.

In vivo densitometry: animals were scanned by DXA (GE Lunar PIXImus II) at the regions of tibia-fibula junction to femur neck (femur-tibia) and lumbar vertebrae (LV1-5) to determine areal BMD at these sites.

Ex vivo densitometry: femurs were scanned using a desktop micro-CT system (eXplore Locus SP, GE Healthcare, London, Ontario, Canada) and reconstructed to a resolution of 13 μ m. The regions spanning 10% of the femur height at the cortical midshaft (threshold 800 mg/cc) for cortical bone and 10% of the trabecular distal femur (threshold 500 mg/cc for vehicle and DKK1-Ab; 550 mg/cc for Scl-Ab, and 600 mg/cc for Combination and Bisp-Ab) were examined. Cortical bone area (Ct.Ar) and cross-sectional moment of inertia (CSMI) were measured at the midshaft region. Cancellous bone volume fraction (BV/TV), trabecular number (Tb.N), trabecular thickness (Tb.Th), and trabecular BMD (Tb.BMD) were assessed at the distal femur.

Biomechanics: Femurs were tested in 3-point bending to failure at the midshaft, and bone strength parameters maximum load and stiffness were assessed (MTS 858 Mini Bionix II; span length = 6 mm; displacement rate = 6 mm/min).

Statistical analyses: GraphPad Prism (v. 5.01) was used to perform the statistical analyses. The comparison was conducted using the one way Anova, with a Tukey Kramer post-hoc test. Data reported as Mean + SEM, and $p < 0.05$ considered as significance.

RESULTS:

In vivo BMD: Significant increases in BMC and BMD were noted at both lumbar vertebrae (LV1-5) and femur-tibia regions for the Combination and Bisp-Ab groups as early as one week after treatment, and the response continued to increase at the level greater than Scl-Ab and DKK1-Ab alone over the treatment period. The data shown in Figure X represent the percent change in BMC from baseline at tibia-femur at the end of the study (3-weeks). All treatments resulted in significantly increased BMC compared to the vehicle treated group, which decreased only -3.5% compared to baseline. Animals treated with Scl-Ab increased BMC by 27%, Dkk1-Ab increased BMC by 13%, Combination increased BMC by 51% and Bisp-Ab increased BMC by 48% compared to baseline. The increases in BMC and BMD at both the lumbar vertebrae and femur-tibia induced by Combination or Bisp-Ab treatments were significantly greater than either Scl-Ab or Dkk1-Ab alone.

Bone Mass and Bone Strength: DKK1-Ab significantly increased distal femur BV/TV (+47%), Tb.N (+30%), and Tb.vBMD (+23%), but not Tb.Th (+13%) compared to vehicle. DKK1-Ab did not significantly affect diaphyseal Ct.Ar (+3%) and CSMI (+1%) compared to vehicle. Femoral shaft bending strength was not affected by DKK1-Ab treatment.

Scl-Ab significantly increased distal femur BV/TV (+76%), Tb.N (+21%), Tb.Th (+71%), and Tb.vBMD (+47%) compared with vehicle. Scl-Ab significantly increased diaphyseal Ct.Ar (+24%) but not CSMI (+22%) compared to vehicle. Scl-Ab significantly increased femur shaft maximum load (+29%) and stiffness (+24%) compared to vehicle.

Combination significantly increased distal femur BV/TV (+278%), Tb.N (+64%), Tb.Th (+175%), and Tb.vBMD (+149%) compared to vehicle. Combination significantly increased diaphyseal Ct.Ar (+37%) and CSMI (+44%) compared to vehicle. Combination significantly increased femur shaft maximum load (+47%) and stiffness (+46%) compared to vehicle. The mean values of all of these parameters in Combination were significantly greater than those observed for the Scl-Ab (except for CSMI) and DKK1-Ab alone groups.

Similar to Combination, Bisp-Ab significantly increased distal femur BV/TV (+228%), Tb.N (+57%), Tb.Th (+152%), and Tb.vBMD (129%) compared to vehicle. Bisp-Ab significantly increased diaphyseal Ct.Ar (+35%) and CSMI (+39%) compared with vehicle. Bisp-Ab significantly increased femur shaft maximum load (+45%) and stiffness (+44%) compared to vehicle. The mean values of all of these

parameters in Bisp-Ab were significantly greater than those observed for the Scl-Ab (except for CSMI) and DKK1-Ab alone groups.

Summary: Both Combination and Bisp-Ab treatments resulted in greater increases in bone mass and bone strength compared to the either monotherapy. These results clearly indicated both Combination and Bisp-Ab treatments have an unexpected synergistic effect on enhancing bone mass and bone strength in this mouse model.

Conclusion: Bispecific-Ab, a molecule containing inhibitory effects towards both sclerostin and Dkk1 appears to have stronger therapeutic activity than Scl-Ab or DKK1-Ab alone in conditions associated with low bone mass and bone repair.

Example 10

Sost-Ab and Dkk1-Ab Combination Therapy Increase PTHR1 expression

To better understand the molecular mechanism underlying the synergistic impact of Sost- and Dkk1-antibody combination treatment on bone formation the expression of bone anabolic pathway members was studied. Male 7-9 month old Sprague Dawley rats were treated with vehicle (Veh), Dkk1-Ab (10 mg/kg 2x/wk), Sost-Ab (10 mg/kg 2x/wk), combination (combo 5 mg/kg or 10 mg/kg 2x/wk) for two-weeks. Animals were sacrificed at day 14 and the rat femur was removed and cleaned of all muscle. The epiphyses and cartilage were removed and the femur was flushed with ice-cold PBS to remove the bone marrow. The bone was then flash frozen in liquid nitrogen and pulverized. Bone RNA was purified using PureLink™ Pro 96 total RNA Purification Kit (Invitrogen; Carlsbad, CA). Gene expression was analyzed with the Affymetrix QuantiGene-Plex 2.0 Panel 331140 (Affymetrix; Santa Clara, CA).

Treatment with combination therapy increased the expression of a large number of genes associated with bone anabolism to a much greater extent than either therapy alone. These genes included markers of osteocyte (DMP1), canonical Wnt-signaling pathway (Axin2), osteogenic (Col1A1) and osteoblast transcription (Osterix) biology. Unexpectedly, a synergistic increase in the parathyroid hormone (PTH) signaling pathway component PTH receptor 1 (PTHR1) was also observed (figure XX below). These data, as summarized in Figure 6, suggest that the synergistic action of Sost-Ab and Dkk1-Ab combination treatment on bone anabolism may in part be due to an unexpected increase in PTH signaling arising from combination treatment.

Example 11

High Throughput (HT) expression of binding molecules

Sclerostin/DKK1 pairings of the following were generated:

Sclerostin	DKK1
13F3	6.37.5
13F3	6.147
20C3	6.37.5
20C3	6.147
46H1	6.37.5
46H1	6.147
38B12	6.37.5
38B12	6.147
13C7	6.37.5
13C7	6.147
Ab23	6.37.5
Ab23	6.147
Ab23	PD17
13F3	PD17
20C3	PD17
46H1	PD17
38B12	PD17
13C7	PD17
19D11	6.37.5

Two different orientations and 5 different linkers (GGGS, GGGGSGGGGS, GGGGSGGGGSGGGGS, 1st 6 amino acids of CL/CH1, 1st 13 amino acids of CL/CH1) per orientation were tested for each pair.

- 5 Binding molecules were transiently expressed in adherence-adapted 293 6E cells in 96-well plates. Adherent 293 6E cells were seeded in Poly-D-Lysine coated 96-well tissue culture plates at 5E4 cells per well in Freestyle 293 Expression medium (Gibco # 12338) supplemented with 0.01% Pluronic F68, G418 at 25 µg/ml, and 5% FBS 24 hours prior to the transfection and incubated overnight at 37 °C in 5% CO₂.

10

On the day of transfection, 100 ng (40 ng/µl) each of the corresponding HC and LC DNA of the binding molecules were mixed together. 25 µl/well of premixed Freestyle Media : EugeneHD (Roche, cat# 04-709-713-001) (24 : 1) was added to the DNA mixtures. After incubation at room temperature for 15-30 min, the entire transfection mixtures were added to the culture plates

- 15 seeded the day before and mixed with gentle rocking motions. The culture plates were put back into the 37 °C, 5% CO₂ incubator overnight. The next day media and transfection mixtures were

aspirated out and replaced with 130 µl of serum free media containing 0.5% Tryptone. The plates were incubated for another 6 days. Conditioned media (CM) were harvested on day 7 after transfection. The plates were spun at 1000 rpm for 5 min to pellet any cell debris. Supernatants were carefully transferred into sterile polypropylene blocks.

5

Concentrations of binding molecules in the CM were measured on ForteBio QK using Protein A biosensors (ForteBio, Cat# 18-5010). Protein A biosensors were soaked for 10 min in Sample buffer before the run. At the start of the run, the prewet biosensors were dipped in two-fold diluted CM samples for 2 min and captured molecules were recorded. Sample Concentrations were calculated with Data Analysis 6.3 software using the preloaded IgG1 concentration standard curve.

10

ELISA screening was performed as described in Example 4 herein. The WNT assays were performed as described in Example 6 and 7 herein.

15 Conclusion: The HT screen led to identification of several fully human DVD-Ig candidates with potent dual neutralizing activity against Sclerostin and Dkk1. Of the 157 candidates screened 35% showed good transient expression in the HT expression screen, with several candidates yielding expression levels of greater than 10 µg/ml.

20 **Example 12**

Stimulating bone formation and increasing bone strength in intact young growing mouse model.

Study Design: Total of 45 male 10 weeks old B6D2F1 mice were used in this study. At the beginning of the study, animals were divided into 5 groups (n=9/group), balancing by both body weight and BMD at the femur-tibia region by in vivo DXA. Mice were subcutaneously injected with either vehicle (proline) or sclerostin-Ab (Scl-Ab), or DKK1-Ab or combination of Scl-Ab and DKK1-Ab (Combination) or 13C7-11H10 twice per week for 3 weeks. Due to the differences in molecular weight, the antibodies were dosed at equal molarity ($1.82 \times 10^{-5}M$), with 18.2 mg/kg Scl-Ab, 18.07 mg/kg DKK1-Ab, 18.2 mg/kg Scl-Ab + 18.07 mg/kg DKK1-Ab in the Combination group, and 25 mg/kg 13C7-11H10. Animals were scanned weekly by in vivo DXA to monitor the bone anabolic effects of the drug treatments at lumbar vertebral and femur-tibia regions; then euthanized at the end of study. Femurs were collected for ex vivo densitometry by µCT and bone strength analysis.

25

30

In vivo densitometry: animals were scanned by DXA (GE Lunar PIXImus II) at the regions of tibia-fibula junction to femur neck (femur-tibia) and lumbar vertebrae (LV1-5) to determine areal BMD at these sites.

- 5 Ex vivo densitometry: femurs were scanned using a desktop micro-CT system (eXplore Locus SP, GE Healthcare, London, Ontario, Canada) and reconstructed to a resolution of 13 μ m. The regions spanning 10% of the femur height at the cortical midshaft (threshold 800 mg/cc) for cortical bone and 10% of the trabecular distal femur (threshold 500 mg/cc for vehicle and DKK1-Ab; 550 mg/cc for Scl-Ab, and 600 mg/cc for Combination and Bisp-Ab) were examined. Cortical bone area (Ct.Ar) and
10 cross-sectional moment of inertia (CSMI) were measured at the midshaft region. Cancellous bone volume fraction (BV/TV), trabecular number (Tb.N), trabecular thickness (Tb.Th), and trabecular BMD (Tb.BMD) were assessed at the distal femur.

- Biomechanics: Femurs were tested in 3-point bending to failure at the midshaft, and bone strength
15 parameters maximum load and stiffness were assessed (MTS 858 Mini Bionix II; span length = 6 mm; displacement rate = 6 mm/min).

- Statistical analyses: GraphPad Prism (v. 5.01) was used to perform the statistical analyses. The comparison was conducted using the one way Anova, with a Tukey Kramer post-hoc test. Data
20 reported as Mean + SEM, and $p < 0.05$ considered as significance.

RESULTS:

- In vivo BMD:* Significant increases in BMC and BMD were noted at both lumbar vertebrae (LV1-5)
25 and femur-tibia regions for the Combination and 13C7-11H10 groups as early as one week after treatment, and the response continued to increase at the level greater than Scl-Ab and DKK1-Ab alone over the treatment period. The data shown represents the percent change in BMC from baseline at tibia-femur at the end of the study (3-weeks). All treatments resulted in significantly increased BMC compared to the vehicle treated group, which decreased only -3.5% compared to
30 baseline. Animals treated with Scl-Ab increased BMC by 27%, Dkk1-Ab increased BMC by 13%, Combination increased BMC by 51% and 13C7-11H10 increased BMC by 48% compared to baseline. The increases in BMC and BMD at both the lumbar vertebrae and femur-tibia induced by Combination or Bisp-Ab treatments were significantly greater than either Scl-Ab or Dkk1-Ab alone.

Bone Mass and Bone Strength:

DKK1-Ab significantly increased distal femur BV/TV (+47%), Tb.N (+30%), and Tb.vBMD (+23%), but not Tb.Th (+13%) compared to vehicle. DKK1-Ab did not significantly affect diaphyseal Ct.Ar (+3%) and CSMI (+1%) compared to vehicle. Femoral shaft bending strength was not affected by DKK1-Ab treatment.

Scl-Ab significantly increased distal femur BV/TV (+76%), Tb.N (+21%), Tb.Th (+71%), and Tb.vBMD (+47%) compared with vehicle. Scl-Ab significantly increased diaphyseal Ct.Ar (+24%) but not CSMI (+22%) compared to vehicle. Scl-Ab significantly increased femur shaft maximum load (+29%) and stiffness (+24%) compared to vehicle.

Combination significantly increased distal femur BV/TV (+278%), Tb.N (+64%), Tb.Th (+175%), and Tb.vBMD (+149%) compared to vehicle. Combination significantly increased diaphyseal Ct.Ar (+37%) and CSMI (+44%) compared to vehicle. Combination significantly increased femur shaft maximum load (+47%) and stiffness (+46%) compared to vehicle. The mean values of all of these parameters in Combination were significantly greater than those observed for the Scl-Ab (except for CSMI) and DKK1-Ab alone groups.

Similar to Combination, 13C7-11H10 significantly increased distal femur BV/TV (+228%), Tb.N (+57%), Tb.Th (+152%), and Tb.vBMD (129%) compared to vehicle. 13C7-11H10 significantly increased diaphyseal Ct.Ar (+35%) and CSMI (+39%) compared with vehicle. 13C7-11H10 significantly increased femur shaft maximum load (+45%) and stiffness (+44%) compared to vehicle. The mean values of all of these parameters in 13C7-11H10 were significantly greater than those observed for the Scl-Ab (except for CSMI) and DKK1-Ab alone groups.

The results from this Example are summarized in Figures 7-11. Both Combination and 13C7-11H10 treatments resulted in greater increases in bone mass and bone strength compared to the either monotherapy. These results clearly indicated both Combination and 13C7-11H10 treatments have a synergistic effect on enhancing bone mass and bone strength in an intact mouse model.

Example 13

Stimulating bone formation and increasing bone strength of the fractured femur in a rat closed femoral fracture model.

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Study Design: 12-week old male Sprague-Dawley (SD) rats (mean body weight 428 g) underwent unilateral closed femoral mid-diaphyseal fracture as reported previously (Bonnarens F, et al. J Orthop Res 1984; 2: 97-101). Briefly, an 18 gauge syringe needle was inserted into the medullary canal through the femoral condyles, and served as an internal fixation. The femur then underwent transverse fracture via blunt impact loading at the anterior (lateral) aspect of the thigh. One day after fracture, animals (n=18/group) were subcutaneously injected with either saline vehicle, Scl-Ab (25 mg/kg), DKK1-Ab (25 mg/kg), or the DVD-Igs 13C7-11H10, 6.147-2x-Ab5, 6.37-AbL-Ab23, Ab5K-AbS-6.147, 6.147-AbL-27H6 or 8G2-AbL-6.37.5 (indicated on each figure) (34.37 mg/kg) twice per week. At 5 weeks post-fracture, animals were euthanized; the fractured and non-fractured contralateral (CL) femurs were collected for densitometry and biomechanics. This study was approved by Amgen's Institution Animal Care and Use Committee.

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Densitometry by DXA: The intramedullary pins were removed from the fractured femurs prior to the densitometric analysis. Femurs were scanned ex vivo by dual energy x-ray absorptiometry (DXA; GE Lunar PIXImus II); analyses were performed at the central 30% of the fractured femur or the entire contralateral intact femur to determine areal bone mineral content (BMC).

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Densitometry by pQCT: Both femurs were also scanned by peripheral quantitative computed tomography (pQCT; Stratec XCT research SA+; Germany), at a resolution of 100 μ m. Analyses were performed for three 0.5-mm slices at the center of the fractured femur callus and the mid-point of contralateral femur (BMC).

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Biomechanics: The proximal and distal ends of each femur were embedded in Slow Set Lab Plaster (Heraeus-Kulzer) to isolate a 14-16mm long central region. These fractured and CL femurs were tested in torsion to failure at an angular displacement rate of 2.0 deg/sec (MTS 858 Mini Bionix II, MTS Corp., Minneapolis, USA). Bone strength parameters including maximum torque (N-mm), energy to failure (N-mm.deg) and torsional stiffness (N/mm) were assessed.

Statistical analyses: GraphPad Prism (v. 5.01) was used to determine statistical differences between groups by unpaired 2-sided t-tests, with $p < 0.05$ considered significant.

RESULTS: Fractured femurs: Both Scl-Ab and DKK1-Ab showed similar improvements in bone mass and bone strength at the fractured callus, as demonstrated by significant increases in BMC by DXA (+17 to 21%) and by pQCT (+13 to 22%) compared with vehicle controls. These increases in bone mass were associated with 42-44% greater maximum torque in the fractured femur, compared with vehicle controls.

The DVD-Igs greatly enhanced bone mass and bone strength at the fractured callus to levels greater than either Scl-Ab or DKK1-Ab alone. Compared with vehicle, fracture callus BMC was 44% greater by DXA and 32% greater by pQCT in the DVD-Ig group. This enhancement of bone mass was associated with an 85% increase in maximum torque in the DVD-Ig group as compared with vehicle. In addition, DXA BMC was significantly higher in the DVD-Ig group compared with Scl-Ab alone or DKK1-Ab alone groups.

Non-fractured contralateral femurs: DKK1-Ab did not significantly affect diaphyseal bone mass and bone strength in non-fractured contralateral femurs. However, Scl-Ab significantly increased mid-diaphyseal cortical thickness and maximum torque by 13% and 22% respectively, compared with vehicle. The DVD-Igs significantly increased contralateral femoral cortical bone thickness and maximum torque by 13% and 20% respectively, compared with vehicle, changes which were similar to those in the Scl-Ab group. Data expressed as Mean $\pm$ SE, * $p < 0.05$ vs. vehicle.

The results from this Example are summarized in figures 12-16.

Example 14

Lrp6/Sclerostin and Lrp6/Dkk1 alpha screen assays

The AlphaScreen competition assay was performed essentially as described in Silverman et.al 2005 Nature Biotech 23(12):1556-1561. Dose-response curves were generated by serially diluting parental and DVD-Ig proteins in assay buffer (40 mM HEPES pH 7.5, 100 mM NaCl, 1 mM CaCl_2 , 0.1% BSA, 0.05% Tween-20) in a 384-well Greiner microtiter plate. A tracer amount of in-house purified and chemically biotinylated recombinant human or rat Sclerostin (up to 1.5 nM) was added to the

- microtiter plate followed by the addition of a mixture containing either mouse LRP6-his or rhLRP6-Fc (R&D Systems) (up to 6- 12 nM) and AlphaScreen 'donor' streptavidin and 'acceptor' protein A beads (10 mg/ml each) (PerkinElmer). The microtiter plate was then sealed and incubated overnight at room temperature. Inhibition of complex formation was measured as a reduction in
- 5 chemiluminescent signal as measured on the Fusion Plate Reader (PerkinElmer) using excitation at 680 nm and emission at 520–620 nm. The results are summarized in Figure 19.

What is claimed is:

1. A binding molecule comprising a polypeptide chain, wherein said polypeptide chain comprises VH1-(X1)_n-VH2-C-(X2)_n, wherein: VH1 is a first heavy chain variable domain obtained from a first parent antibody or antigen binding portion thereof; VH2 is a second heavy chain variable domain obtained from a second parent antibody or antigen binding portion thereof; C is a heavy chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n is an Fc region, wherein said (X2)_n is either present or absent, wherein the binding molecule specifically binds both sclerostin and DKK-1.
2. The binding molecule of claim 1, wherein VH1 and VH2 comprise an amino acid sequence selected from the group consisting of sclerostin binders SEQ ID NOs: 95, 96, 104, 112, 120, 128, 136, 144, 152, 160, 168, 176, 184, 192, 200, 208, and 216, or DKK-1 binders SEQ ID NOs: 224, 232, 240, 248, 256, 264, 272, 280, 288, 296, 304, 312, 320, 328, 336, 344, 352, 360, 368, 376, 384, 392, 400, and 408.
3. A binding molecule comprising a polypeptide chain, wherein said polypeptide chain comprises VL1-(X1)_n-VL2-C-(X2)_n, wherein: VL1 is a first light chain variable domain obtained from a first parent antibody or antigen binding portion thereof; VL2 is a second light chain variable domain obtained from a second parent antibody or antigen binding portion thereof; C is a light chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n is an Fc region, wherein said (X2)_n is either present or absent, wherein the binding molecule specifically binds both sclerostin and DKK-1.
4. The binding molecule of claim 3, wherein VL1 and VL2 comprise an amino acid sequence selected from the group consisting of sclerostin binders SEQ ID NOs: 94, 103, 111, 119, 127, 135, 143, 151, 159, 167, 175, 183, 191, 199, 207, and 215, or DKK-1 binders SEQ ID NOs: 223, 231, 239, 247, 255, 263, 271, 279, 287, 295, 303, 311, 319, 327, 335, 343, 351, 359, 367, 375, 383, 391, 399, and 407.
5. The binding molecule of claim 1 or 3, wherein (X2)_n is absent.
6. A binding molecule comprising first and second polypeptide chains, wherein said first polypeptide chain comprises a VH1-(X1)_n-VH2-C-(X2)_n, wherein VH1 is a first heavy chain variable domain obtained from a first parent antibody or antigen binding portion thereof; VH2 is a second heavy

chain variable domain obtained from a second parent antibody or antigen binding portion thereof; C is a heavy chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n is an Fc region, wherein said (X2)_n is either present or absent; and wherein said second polypeptide chain comprises a VL1-(X1)_n-VL2-C-(X2)_n, wherein VL1 is a first light chain variable domain obtained from a first parent antibody or antigen binding portion thereof; VL2 is a second light chain variable domain obtained from a second parent antibody or antigen binding portion thereof; C is a light chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n does not comprise an Fc region, wherein said (X2)_n is either present or absent, wherein the binding molecule specifically binds sclerostin and DKK-1.

7. The binding molecule of claim 6, wherein the VH1 and VH2 heavy chain variable domains comprise an amino acid sequence selected from the group consisting of sclerostin binders SEQ ID NOs: 95, 96, 104, 112, 120, 128, 136, 144, 152, 160, 168, 176, 184, 192, 200, 208, and 216, or DKK-1 binders SEQ ID NOs: 224, 232, 240, 248, 256, 264, 272, 280, 288, 296, 304, 312, 320, 328, 336, 344, 352, 360, 368, 376, 384, 392, 400, and 408, and wherein the VL1 and VL2 light chain variable domains comprise an amino acid sequence selected from the group consisting of sclerostin binders SEQ ID NOs: 94, 103, 111, 119, 127, 135, 143, 151, 159, 167, 175, 183, 191, 199, 207, and 215, or DKK-1 binders SEQ ID NOs: 223, 231, 239, 247, 255, 263, 271, 279, 287, 295, 303, 311, 319, 327, 335, 343, 351, 359, 367, 375, 383, 391, 399, and 407.

8. The binding molecule of claim 1, 3, or 6, wherein (X1)_n is an amino acid sequence selected from the group consisting of SEQ ID NOs: 415-482.

9. The binding molecule of claims 6, wherein the binding molecule comprises two first polypeptide chains and two second polypeptide chains.

10. The binding molecule of claim 1, 3, or 6, wherein the Fc region is selected from the group consisting of native sequence Fc region and a variant sequence Fc region.

11. The binding molecule of claim 10, wherein the Fc region is selected from the group consisting of an Fc region from an IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgE, and IgD.

12. The binding molecule of claim 1, 3, or 6, wherein said VH1 of the first polypeptide chain and said VL1 of the second polypeptide chain are obtained from the same parent antibody or antigen binding portion thereof.

13. The binding molecule of claim 1, 3, or 6, wherein said VH1 of the first polypeptide chain and said VL1 of the second polypeptide chain are obtained from different parent antibody or antigen binding portion thereof.

14. The binding molecule of claim 1, 3, or 6, wherein said VH2 of the first polypeptide chain and said VL2 of the second polypeptide chain are obtained from the same parent antibody or antigen binding portion thereof.

15. The binding molecule of claim 1, 3, or 6, wherein said VH2 of the first polypeptide chain and said VL2 of the second polypeptide chain are obtained from different parent antibody or antigen binding portion thereof.

16. The binding molecule of claim 1, 3, or 6 with the proviso that said linker is not CH1.

17. The binding molecule of claim 1, 3, or 6, wherein said first parent antibody, or antigen binding portion thereof, binds said first antigen with a potency different from the potency with which said second parent antibody, or antigen binding portion thereof, binds said second antigen.

18. The binding molecule of claim 1, 3, or 6, wherein said first parent antibody, or antigen binding portion thereof, binds said first antigen with an affinity different from the affinity with which said second parent antibody, or antigen binding portion thereof, binds said second antigen.

19. The binding molecule of claim 1, 3, or 6, wherein said first parent antibody, or antigen binding portion thereof, and said second parent antibody, or antigen binding portion thereof, are selected from the group consisting of a human antibody, a CDR grafted antibody, and a humanized antibody.

20. The binding molecule of claim 1, 3, or 6, wherein said first parent antibody, or antigen binding portion thereof, and said second parent antibody, or antigen binding portion thereof, are selected from the group consisting of a Fab fragment; a F(ab')₂ fragment; a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the VH

and CH1 domains; a Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a dAb fragment; an isolated complementarity determining region (CDR); a single chain antibody; and a diabody.

21. The binding molecule of claim 1, 3, or 6, wherein said binding molecule possesses at least one desired property exhibited by said first parent antibody, or antigen binding portion thereof, or said second parent antibody, or antigen binding portion thereof.

22. The binding molecule of claim 21, wherein said desired property is selected from one or more antibody parameters.

23. The binding molecule of claim 21, wherein said antibody parameters are selected from the group consisting of antigen specificity, affinity to antigen, potency, biological function, epitope recognition, stability, solubility, production efficiency, immunogenicity, pharmacokinetics, bioavailability, tissue cross reactivity, and orthologous antigen binding.

24. A binding molecule that binds both sclerostin and DKK-1 comprising four polypeptide chains, wherein first and third polypeptide chains comprise VH1-(X1)_n-VH2-C-(X2)_n, wherein: VH1 is a first heavy chain variable domain; VH2 is a second heavy chain variable domain; C is a heavy chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n is an Fc region, wherein said (X2)_n is either present or absent; and wherein second and fourth polypeptide chains comprise VL1-(X1)_n-VL2-C-(X2)_n, wherein VL1 is a first light chain variable domain; VL2 is a second light chain variable domain; C is a light chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n does not comprise an Fc region, wherein said (X2)_n is either present or absent, wherein the VH1 and VH2 heavy chain variable domains comprise an amino acid sequence selected from the group consisting of sclerostin binders SEQ ID NOs: 95, 96, 104, 112, 120, 128, 136, 144, 152, 160, 168, 176, 184, 192, 200, 208, and 216, or DKK-1 binders SEQ ID NOs: 224, 232, 240, 248, 256, 264, 272, 280, 288, 296, 304, 312, 320, 328, 336, 344, 352, 360, 368, 376, 384, 392, 400, and 408, and wherein the VL1 and VL2 light chain variable domains comprise an amino acid sequence selected from the group consisting of sclerostin binders SEQ ID NOs: 94, 103, 111, 119, 127, 135, 143, 151, 159, 167, 175, 183, 191, 199, 207, and 215, or DKK-1 binders SEQ ID NOs: 223, 231, 239, 247, 255, 263, 271, 279, 287, 295, 303, 311, 319, 327, 335, 343, 351, 359, 367, 375, 383, 391, 399, and 407.

25. The binding molecule of claim 24 with the proviso that said linker is not CH1.

26. A binding molecule that binds both sclerostin and DKK-1 comprising four polypeptide chains, wherein first and third polypeptide chains comprise VH1-(X1)_n-VH2-C-(X2)_n, wherein: VH1 is a first heavy chain variable domain; VH2 is a second heavy chain variable domain; C is a heavy chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n is an Fc region, wherein said (X2)_n is either present or absent; and wherein second and fourth polypeptide chains comprise VL1-(X1)_n-VL2-C-(X2)_n, wherein VL1 is a first light chain variable domain; VL2 is a second light chain variable domain; C is a light chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n does not comprise an Fc region, wherein said (X2)_n is either present or absent, wherein the binding molecule comprises VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairings selected from the group consisting of:

SEQ ID NOs: 18 and 20; 22 and 24; 26 and 28; 30 and 32; 34 and 36; 38 and 40; 42 and 44; 46 and 48; 50 and 52; 54 and 76; 56 and 72; 58 and 60; 62 and 64; 66 and 68; 70 and 72; 74 and 76; 78 and 80; 82 and 84; 86 and 88; 90 and 92; 486 and 488; 490 and 492; and 494 and 496.

27. The binding molecule of claim 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 18 and 20.

28. The binding molecule of claim 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 22 and 24.

29. The binding molecule of claim 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 26 and 28.

30. The binding molecule of claim 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 30 and 32.

31. The binding molecule of claim 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 34 and 36.

32. The binding molecule of claim 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 38 and 40.

33. The binding molecule of claim 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 42 and 44.

34. The binding molecule of claim 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 46 and 48.

35. The binding molecule of claim 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 50 and 52.

36. The binding molecule of claim 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 54 and 76.

37. The binding molecule of claim 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 56 and 72.

38. The binding molecule of claim 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 58 and 60.

39. The binding molecule of claim 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 62 and 64.

40. The binding molecule of claim 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 66 and 68.

41. The binding molecule of claim 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 70 and 72.

42. The binding molecule of claim 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 74 and 76.

43. The binding molecule of claim 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 78 and 80.

44. The binding molecule of claim 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 82 and 84.

45. The binding molecule of claim 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 86 and 88.

46. The binding molecule of claim 26, wherein the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n pairing is SEQ ID NOs: 90 and 92.

47. The binding molecule of claims 1, 3, and 6, wherein the sclerostin binder VH comprises 3 CDRs selected from the group consisting of SEQ ID NOs:

- a) 100, 101, 102;
- b) 108, 109, 110;
- c) 116, 117, 118;
- d) 124, 125, 126;
- e) 132, 133, 134;
- f) 140, 141, 142;
- g) 148, 149, 150;
- h) 156, 157, 158;
- i) 164, 165, 166;
- j) 172, 173, 174;
- k) 180, 181, 182;
- l) 188, 189, 190;
- m) 196, 197, 198;
- n) 204, 205, 206;
- o) 212, 213, 214; and
- p) 220, 221, 222,

and wherein the DKK1 binder VH comprises 3 CDRs selected from the group consisting of SEQ ID NOs:

- a) 228, 229, 230;
- b) 236, 237, 238;
- c) 244, 245, 246;
- d) 252, 253, 254;

- e) 260, 261, 262;
- f) 268, 269, 270;
- g) 276, 277, 278;
- h) 284, 285, 286;
- i) 292, 293, 294;
- j) 300, 301, 302;
- k) 308, 309, 310;
- l) 316, 317, 318;
- m) 324, 325, 326;
- n) 332, 333, 334;
- o) 340, 341, 342;
- p) 348, 349, 350;
- q) 356, 357, 358;
- r) 364, 365, 366;
- s) 372, 373, 374;
- t) 380, 381, 382;
- u) 388, 389, 390;
- v) 396, 397, 398;
- w) 404, 405, 406; and
- x) 412, 413, 414.

48. The binding molecule of claims 1, 3 and 6, wherein the sclerostin binder VL comprises 3 CDRs selected from the group consisting of SEQ ID NOs:

- a) 97, 98, 99;
- b) 105, 106, 107;
- c) 113, 114, 115;
- d) 121, 122, 123;
- e) 129, 130, 131;
- f) 137, 138, 139;
- g) 145, 146, 147;
- h) 153, 154, 155;
- i) 161, 162, 163;
- j) 169, 170, 171;
- k) 177, 178, 179;

- l) 185, 186, 187;
- m) 193, 194, 195;
- n) 201, 202, 203;
- o) 209, 210, 211; and
- p) 217, 218, 219,

and wherein the DKK1 binder VL comprises 3 CDRs selected from the group consisting of SEQ ID NOs:

- b) 225, 226, 227;
- c) 233, 234, 235;
- d) 241, 242, 243;
- e) 249, 250, 251;
- f) 257, 258, 259;
- g) 265, 266, 267;
- h) 273, 274, 275;
- i) 281, 282, 283;
- j) 289, 290, 291;
- k) 297, 298, 299;
- l) 305, 306, 307;
- m) 313, 314, 315;
- n) 321, 322, 323;
- o) 329, 330, 331;
- p) 337, 338, 339;
- q) 345, 346, 347;
- r) 353, 354, 355;
- s) 361, 362, 363;
- t) 369, 370, 371;
- u) 377, 378, 379;
- v) 385, 386, 387;
- w) 393, 394, 395;
- x) 401, 402, 403; and
- y) 409, 410, 411.

49. The binding molecule of claims 1, 3, and 6, wherein the sclerostin binder VH comprises 3 CDRs selected from the group consisting of SEQ ID NOs:

- a) 100, 101, 102;
- b) 108, 109, 110;
- c) 116, 117, 118;
- d) 124, 125, 126;
- e) 132, 133, 134;
- f) 140, 141, 142;
- g) 148, 149, 150;
- h) 156, 157, 158;
- i) 164, 165, 166;
- j) 172, 173, 174;
- k) 180, 181, 182;
- l) 188, 189, 190;
- m) 196, 197, 198;
- n) 204, 205, 206;
- o) 212, 213, 214; and
- p) 220, 221, 222,

and wherein the DKK1 binder VH comprises 3 CDRs selected from the group consisting of SEQ ID NOs:

- a) 228, 229, 230;
- b) 236, 237, 238;
- c) 244, 245, 246;
- d) 252, 253, 254;
- e) 260, 261, 262;
- f) 268, 269, 270;
- g) 276, 277, 278;
- h) 284, 285, 286;
- i) 292, 293, 294;
- j) 300, 301, 302;
- k) 308, 309, 310;
- l) 316, 317, 318;
- m) 324, 325, 326;

- n) 332, 333, 334;
- o) 340, 341, 342;
- p) 348, 349, 350;
- q) 356, 357, 358;
- r) 364, 365, 366;
- s) 372, 373, 374;
- t) 380, 381, 382;
- u) 388, 389, 390;
- v) 396, 397, 398;
- w) 404, 405, 406; and
- x) 412, 413, 414.

and wherein the sclerostin binder VL comprises 3 CDRs selected from the group consisting of SEQ ID NOs:

- a) 97, 98, 99;
- b) 105, 106, 107;
- c) 113, 114, 115;
- d) 121, 122, 123;
- e) 129, 130, 131;
- f) 137, 138, 139;
- g) 145, 146, 147;
- h) 153, 154, 155;
- i) 161, 162, 163;
- j) 169, 170, 171;
- k) 177, 178, 179;
- l) 185, 186, 187;
- m) 193, 194, 195;
- n) 201, 202, 203;
- o) 209, 210, 211; and
- p) 217, 218, 219,

and wherein the DKK1 binder VL comprises 3 CDRs selected from the group consisting of SEQ ID NOs:

- a) 225, 226, 227;

- b) 233, 234, 235;
- c) 241, 242, 243;
- d) 249, 250, 251;
- e) 257, 258, 259;
- f) 265, 266, 267;
- g) 273, 274, 275;
- h) 281, 282, 283;
- i) 289, 290, 291;
- j) 297, 298, 299;
- k) 305, 306, 307;
- l) 313, 314, 315;
- m) 321, 322, 323;
- n) 329, 330, 331;
- o) 337, 338, 339;
- p) 345, 346, 347;
- q) 353, 354, 355;
- r) 361, 362, 363;
- s) 369, 370, 371;
- t) 377, 378, 379;
- u) 385, 386, 387;
- v) 393, 394, 395;
- w) 401, 402, 403; and
- x) 409, 410, 411.

50. A binding molecule comprising four polypeptide chains, wherein first and third polypeptide chains comprise VH1-(X1)_n-VH2-C-(X2)_n, wherein: VH1 is a first heavy chain variable domain; VH2 is a second heavy chain variable domain; C is a heavy chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n is an Fc region, wherein said (X2)_n is either present or absent; and wherein second and fourth polypeptide chains comprise VL1-(X1)_n-VL2-C-(X2)_n, wherein VL1 is a first light chain variable domain; VL2 is a second light chain variable domain; C is a light chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n does not comprise an Fc region, wherein said (X2)_n is either present or absent, wherein the binding molecule comprises 3 VH1 CDRs, 3 VH2 CDRs, 3 VL1 CDRs and 3 VL2 CDRs, wherein the

paired VH1 and VL1 CDRs, and paired VH2 and VL2 CDRs, are selected from the group consisting of SEQ ID NOs:

- a) 97-102;
- b) 105-110;
- c) 113-118;
- d) 121-126;
- e) 129-134;
- f) 137-142;
- g) 145-150;
- h) 153-158;
- i) 161-166;
- j) 169-174;
- k) 177-182;
- l) 185-190;
- m) 193-198;
- n) 201-206;
- o) 209-214;
- p) 217-222,

or SEQ ID NOs:

- b) 225-230;
- c) 233-238;
- d) 241-246;
- e) 249-254;
- f) 257-262;
- g) 265-270;
- h) 273-278;
- i) 281-286;
- j) 289-294;
- k) 297-302;
- l) 305-310;
- m) 313-318;
- n) 321-326;
- o) 329-334;

- p) 337-342;
- q) 345-350;
- r) 353-358;
- s) 361-366;
- t) 369-374;
- u) 377-382;
- v) 385-390;
- w) 393-398;
- x) 401-406;
- y) 409-414.

51. The binding molecule of claim 50, wherein said VL1 CDRs are SEQ ID NOs: 161-163, said VH1 CDRs are SEQ ID NOs: 164-166, said VL2 CDRs are SEQ ID NOs: 385-387, and said VH2 CDRs are SEQ ID NOs: 388-390.

52. The binding molecule of claim 50, wherein said VL1 CDRs are SEQ ID NOs: 385-387, said VH1 CDRs are SEQ ID NOs: 388-390, said VL2 CDRs are SEQ ID NOs: 161-163, and said VH2 CDRs are SEQ ID NOs: 164-166.

53. The binding molecule of claim 50, wherein said VL1 CDRs are SEQ ID NOs: 153-155, said VH1 CDRs are SEQ ID NOs: 156-158, said VL2 CDRs are SEQ ID NOs: 385-387, and said VH2 CDRs are SEQ ID NOs: 388-390.

54. The binding molecule of claim 50, wherein said VL1 CDRs are SEQ ID NOs: 385-387, said VH1 CDRs are SEQ ID NOs: 388-390, said VL2 CDRs are SEQ ID NOs: 153-155, and said VH2 CDRs are SEQ ID NOs: 156-158.

55. The binding molecule of claim 50, wherein said VL1 CDRs are SEQ ID NOs: 409-411, said VH1 CDRs are SEQ ID NOs: 412-414, said VL2 CDRs are SEQ ID NOs: 121-123, and said VH2 CDRs are SEQ ID NOs: 124-126.

56. The binding molecule of claim 50, wherein said VL1 CDRs are SEQ ID NOs: 409-411, said VH1 CDRs are SEQ ID NOs: 412-414, said VL2 CDRs are SEQ ID NOs: 177-179, and said VH2 CDRs are SEQ ID NOs: 180-182.

57. The binding molecule of claim 50, wherein said VL1 CDRs are SEQ ID NOs: 409-411, said VH1 CDRs are SEQ ID NOs: 412-414, said VL2 CDRs are SEQ ID NOs: 97-99, and said VH2 CDRs are SEQ ID NOs: 100-102.

58. The binding molecule of claim 50, wherein said VL1 CDRs are SEQ ID NOs: 385-387, said VH1 CDRs are SEQ ID NOs: 388-390, said VL2 CDRs are SEQ ID NOs: 105-107, and said VH2 CDRs are SEQ ID NOs: 108-110.

59. The binding molecule of claim 50, wherein said VL1 CDRs are SEQ ID NOs: 97-99, said VH1 CDRs are SEQ ID NOs: 100-102, said VL2 CDRs are SEQ ID NOs: 409-411, and said VH2 CDRs are SEQ ID NOs: 412-414.

60. The binding molecule of claim 50, wherein said VL1 CDRs are SEQ ID NOs: 385-387, said VH1 CDRs are SEQ ID NOs: 388-390, said VL2 CDRs are SEQ ID NOs: 105-107, and said VH2 CDRs are SEQ ID NOs: 108-110.

61. The binding molecule of claim 50, wherein said VL1 CDRs are SEQ ID NOs: 409-411, said VH1 CDRs are SEQ ID NOs: 412-414, said VL2 CDRs are SEQ ID NOs: 105-107, and said VH2 CDRs are SEQ ID NOs: 108-110.

62. The binding molecule of claim 50, wherein said VL1 CDRs are SEQ ID NOs: 105-107, said VH1 CDRs are SEQ ID NOs: 108-110, said VL2 CDRs are SEQ ID NOs: 385-387, and said VH2 CDRs are SEQ ID NOs: 388-390.

63. The binding molecule of claim 50, wherein said VL1 CDRs are SEQ ID NOs: 105-107, said VH1 CDRs are SEQ ID NOs: 108-110, said VL2 CDRs are SEQ ID NOs: 409-411, and said VH2 CDRs are SEQ ID NOs: 412-414.

64. The binding molecule of claim 50, wherein said VL1 CDRs are SEQ ID NOs: 369-371, said VH1 CDRs are SEQ ID NOs: 372-374, said VL2 CDRs are SEQ ID NOs: 105-107, and said VH2 CDRs are SEQ ID NOs: 108-110.

65. The binding molecule of claims 50-64, wherein said (X1)_n is selected from the group consisting of SEQ ID NOs: 415-484.

66. The binding molecule of claims 50-64, wherein said (X1)_n is selected from the group consisting of SEQ ID NOs: 440, 441, 437, 438, 431, 432, 483, and 484.

67. The binding molecule of claims 50-64, wherein said (X1)_n of the VH1-(X1)_n-VH2-C-(X2)_n chain is SEQ ID NO: 440.

68. The binding molecule of claims 50-64, wherein said (X1)_n of the VH1-(X1)_n-VH2-C-(X2)_n chain is SEQ ID NO: 441.

69. The binding molecule of claims 50-64, wherein said (X1)_n of the VH1-(X1)_n-VH2-C-(X2)_n chain is SEQ ID NO: 437.

70. The binding molecule of claims 50-64, wherein said (X1)_n of the VH1-(X1)_n-VH2-C-(X2)_n chain is SEQ ID NO: 438.

71. The binding molecule of claims 50-64, wherein said (X1)_n of the VL1-(X1)_n-VL2-C-(X2)_n is SEQ ID NO: 440.

72. The binding molecule of claims 50-64, wherein said (X1)_n of the VL1-(X1)_n-VL2-C-(X2)_n is SEQ ID NO: 441.

73. The binding molecule of claims 50-64, wherein said (X1)_n of the VL1-(X1)_n-VL2-C-(X2)_n is SEQ ID NO: 483.

74. The binding molecule of claims 50-64, wherein said (X1)_n of the VL1-(X1)_n-VL2-C-(X2)_n is SEQ ID NO: 484.

75. The binding molecule of claims 50-64, wherein said (X1)_n of the VL1-(X1)_n-VL2-C-(X2)_n is SEQ ID NO: 431.

76. The binding molecule of claims 50-64, wherein said (X1)_n of the VL1-(X1)_n-VL2-C-(X2)_n is SEQ ID NO: 432.

77. The binding molecule of claims 1, 3, 6, 24, 26 and 50, wherein said (X1)_n is the different on the VH1-(X1)_n-VH2-C-(X2)_n and VL1-(X1)_n-VL2-C-(X2)_n chains.

78. A method for generating a binding molecule that binds sclerostin and DKK-1 comprising the steps of: (a) obtaining a first parent antibody, or antigen binding portion thereof, that can bind sclerostin or DKK-1; (b) obtaining a second parent antibody, or antigen binding portion thereof, that can bind sclerostin or DKK-1; (c) constructing first and third polypeptide chains comprising VH1-(X1)_n-VH2-C-(X2)_n, wherein: VH1 is a first heavy chain variable domain obtained from said first parent antibody or antigen binding portion thereof; VH2 is a second heavy chain variable domain obtained from said second parent antibody or antigen binding portion thereof; C is a heavy chain constant domain; (X1)_n is a linker with the proviso that it is not CH1, wherein said (X1)_n is either present or absent; and (X2)_n is an Fc region, wherein said (X2)_n is either present or absent; (d) constructing second and fourth polypeptide chains comprising VL1-(X1)_n-VL2-C-(X2)_n, wherein: VL1 is a first light chain variable domain obtained from said first parent antibody or antigen binding portion thereof; VL2 is a second light chain variable domain obtained from said second parent antibody or antigen binding portion thereof; C is a light chain constant domain; (X1)_n is a linker, wherein said (X1)_n is either present or absent; and (X2)_n does not comprise an Fc region, wherein said (X2)_n is either present or absent; and (e) expressing said first, second, third and fourth polypeptide chains such that a binding molecule that binds sclerostin and DKK-1 is generated.

79. The method of claim 78, wherein the VH1 and VH2 heavy chain variable domains comprise an amino acid sequence selected from the group consisting of sclerostin binders SEQ ID NOs: 95, 96, 104, 112, 120, 128, 136, 144, 152, 160, 168, 176, 184, 192, 200, 208, and 216, or DKK-1 binders SEQ ID NOs: 224, 232, 240, 248, 256, 264, 272, 280, 288, 296, 304, 312, 320, 328, 336, 344, 352, 360, 368, 376, 384, 392, 400, and 408, and wherein the VL1 and VL2 light chain variable domains comprise an amino acid sequence selected from the group consisting of sclerostin binders SEQ ID NOs: 94, 103, 111, 119, 127, 135, 143, 151, 159, 167, 175, 183, 191, 199, 207, and 215, or DKK-1 binders SEQ ID NOs: 223, 231, 239, 247, 255, 263, 271, 279, 287, 295, 303, 311, 319, 327, 335, 343, 351, 359, 367, 375, 383, 391, 399, and 407.

80. The method of claim 78, wherein each of said first parent antibody, or antigen binding portion thereof, and each of said second parent antibody, or antigen binding portion thereof, are separately selected from the group consisting of a human antibody, a CDR grafted antibody, and a humanized antibody.

81. The method of claim 78, wherein each of said first parent antibody, or antigen binding portion thereof, and each of said second parent antibody, or antigen binding portion thereof, are separately selected from the group consisting of a Fab fragment, a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the VH and CH1 domains; a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, a dAb fragment, an isolated complementarity determining region (CDR), a single chain antibody, and diabodies.

82. The method of claim 78, wherein said first parent antibody, or antigen binding portion thereof, possesses at least one desired property exhibited by the binding molecule.

83. The method of claim 78, wherein said second parent antibody, or antigen binding portion thereof, possesses at least one desired property exhibited by the binding molecule.

84. The method of claim 78, wherein the Fc region is selected from the group consisting of a native sequence Fc region and a variant sequence Fc region.

85. The method of claim 78, wherein the Fc region is selected from the group consisting of an Fc region from an IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgE, and IgD.

86. The method of claim 78, wherein said desired property is selected from one or more antibody parameters.

87. The method of claim 78, wherein said desired property is selected from one or more antibody parameters.

88. The method of claim 78, wherein said antibody parameters are selected from the group consisting of antigen specificity, affinity to antigen, potency, biological function, epitope recognition,

stability, solubility, production efficiency, immunogenicity, pharmacokinetics, bioavailability, tissue cross reactivity, and orthologous antigen binding.

89. The method of claim 78, wherein said antibody parameters are selected from the group consisting of antigen specificity, affinity to antigen, potency, biological function, epitope recognition, stability, solubility, production efficiency, immunogenicity, pharmacokinetics, bioavailability, tissue cross reactivity, and orthologous antigen binding.

90. The method of claim 78, wherein said first parent antibody, or antigen binding portion thereof, binds said first antigen with a different affinity than the affinity with which said second parent antibody, or antigen binding portion thereof, binds said second antigen.

91. The method of claim 78, wherein said first parent antibody, or antigen binding portion thereof, binds said first antigen with a different potency than the potency with which said second parent antibody, or antigen binding portion thereof, binds said second antigen.

92. The method of claim 78, with the proviso that said linker is not CH1.

93. A pharmaceutical composition comprising the binding molecule of any of claims 1-77.

94. The binding molecule of any of claims 1-77 in combination with one or more of a pharmaceutically acceptable excipient, diluent or carrier.

95. A method of treating a bone disorder comprising administering to a patient in need thereof the binding molecule of any of claims 1-77.

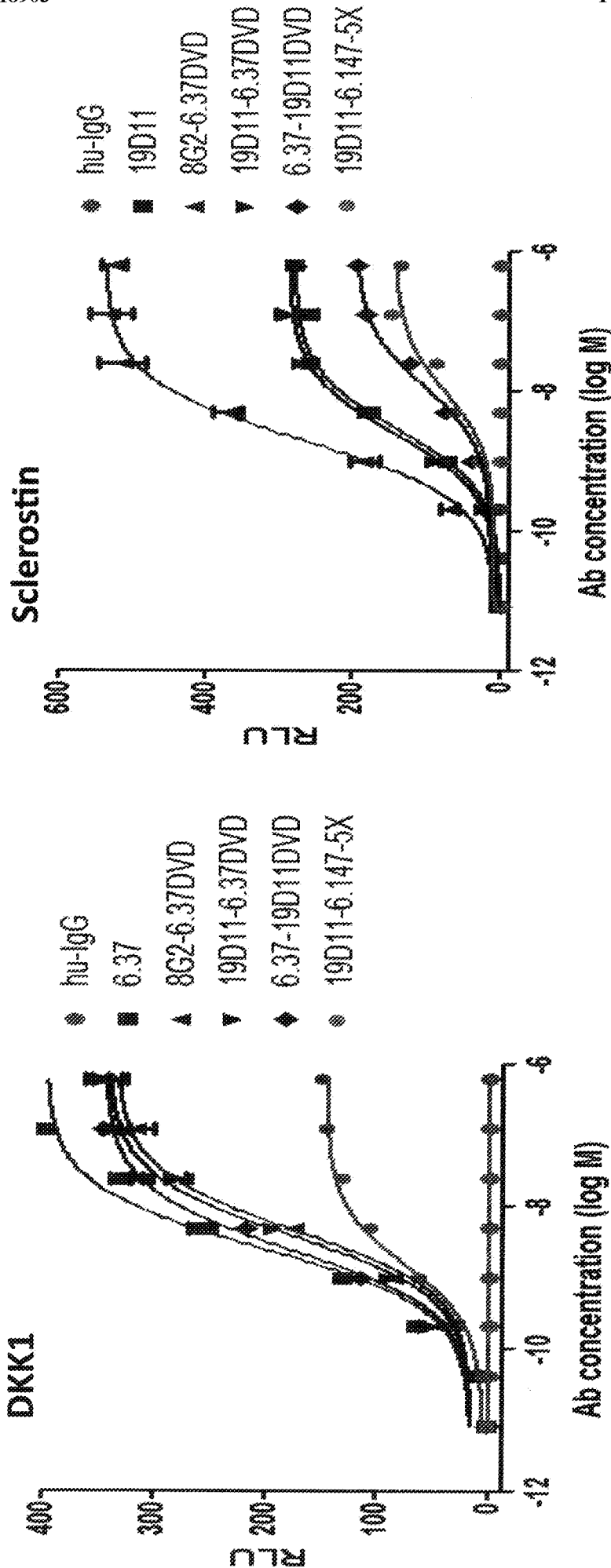
96. A method of accelerating bone fracture repair comprising administering to a patient in need thereof the binding molecule of any of claims 1-77.

97. A method of increasing bone density comprising administering to a patient in need thereof the binding molecule of any of claims 1-77.

98. A method of increasing bone strength comprising administering to a patient in need thereof the binding molecule of any of claims 1-77.

FIG. 1

ELISA analysis of bispecific huAbs binding to huDKK1 or huScl

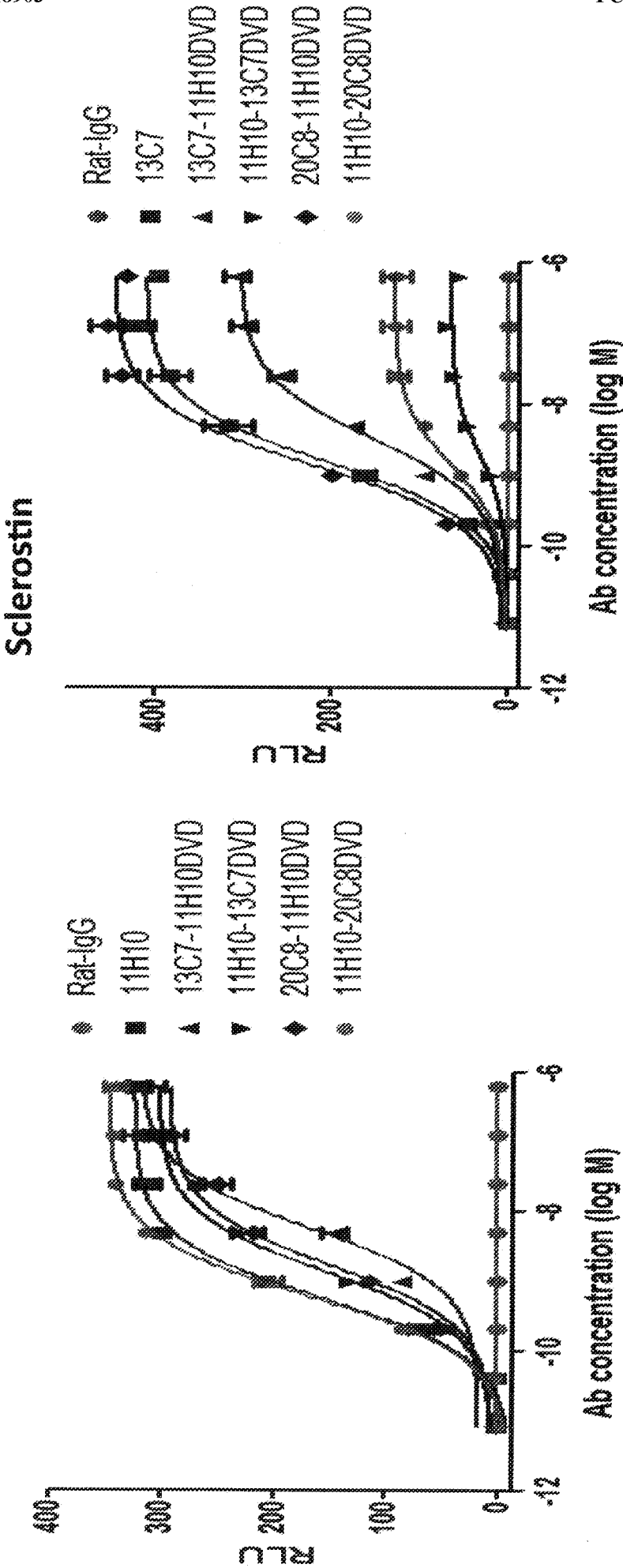


EC50 (nM)	6.37	19D11	8G2-6.37DVD	19D11-6.37DVD	6.37-19D11DVD	19D11-6.147-5X
DKK1	2.663		4.664	3.994	2.521	1.467
Sclerostin		2.745	1.987	2.417	11.32	9.434

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FIG. 2

ELISA analysis of bispecific Rat-Abs binding to huDKK1 or huScl

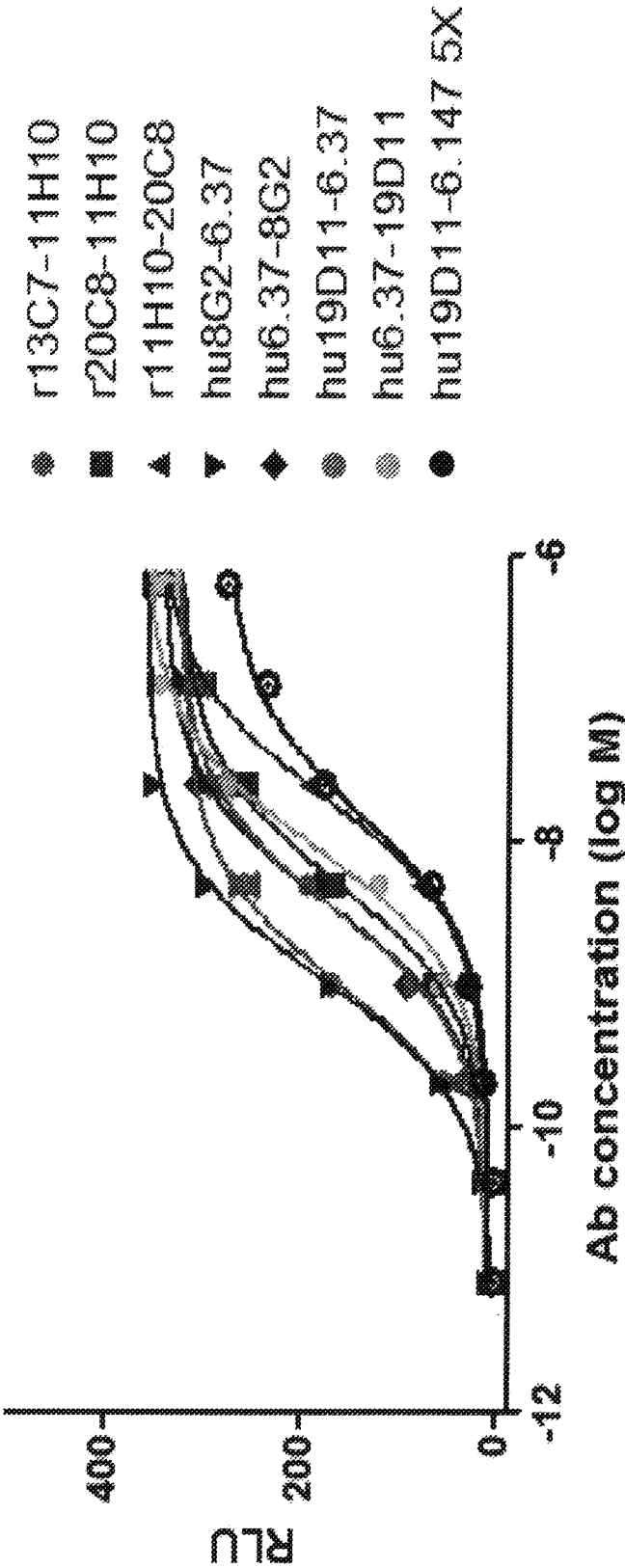


EC50 (nM)	r11H10	rAB-4	AB-4-11H10	11H10-AB-4	20C8-11H10	11H10-20C8
DKK1	0.566		5.778	1.368	1.67	0.604
Sclerostin		1.487	3.305	1.932	1.396	1.401

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FIG. 3

ELISA analysis of bispecific Abs binding to huDKK1 and huScl at the same time



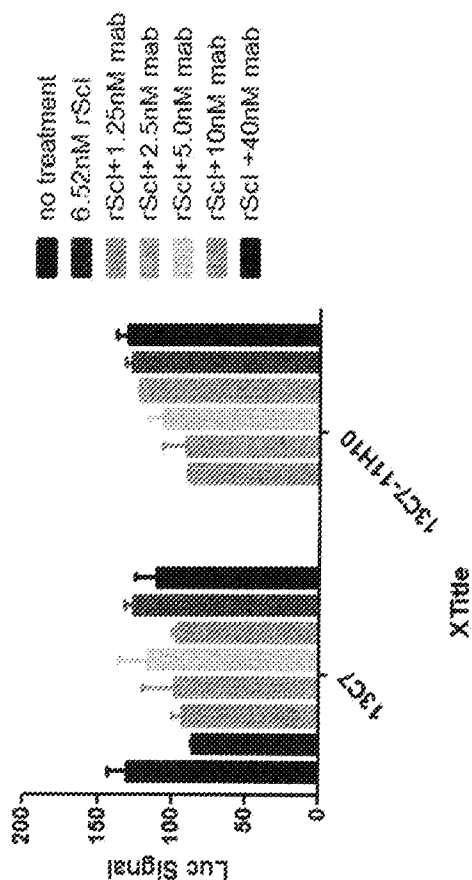
Human BiAbs	8G2-6.37	6.37-8G2	19D11-6.37	6.37-19D11	19D11-6.147-5X
EC50 (nM)	1.08	3.63	3.38	8.78	15.68
Rat BiAbs	AB-4-11H10	20C8-11H10	11H10-20C8		
EC50 (nM)	0.99	5.17	20.37		

rAB-4-11H10 has similar Neutralizing Activity to Control Mabs When Same Molar Ratio was used

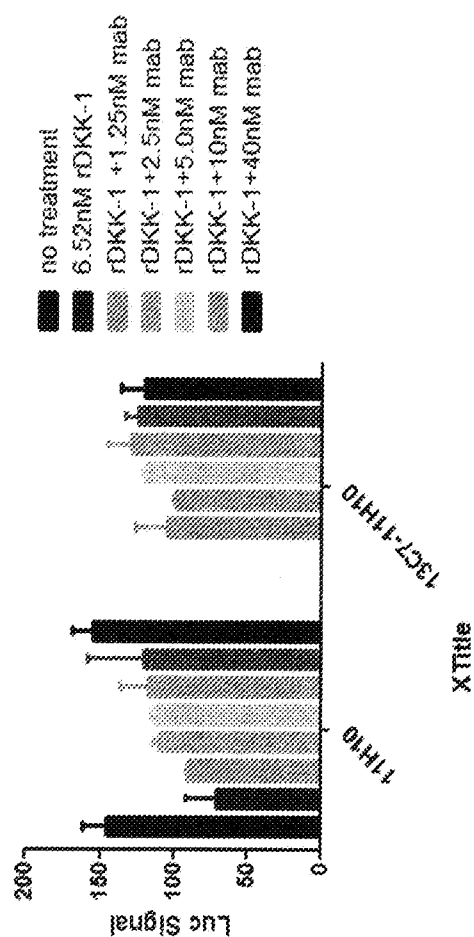
WO 2012/118903

PCT/US2012/027154

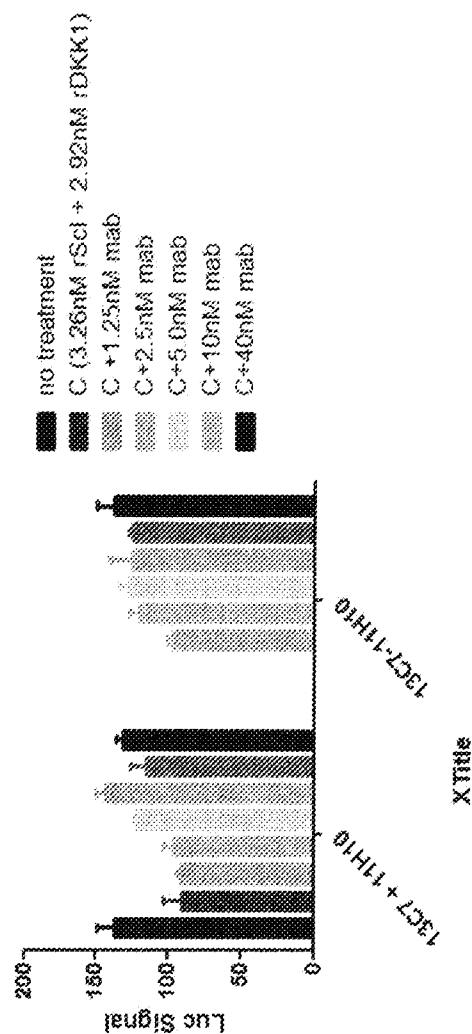
r13C7-11H10 VS. 13C7
(Against rScl, 071510)



r13C7-11H10 VS. 11H10
(Against rDKK-1, 071510)



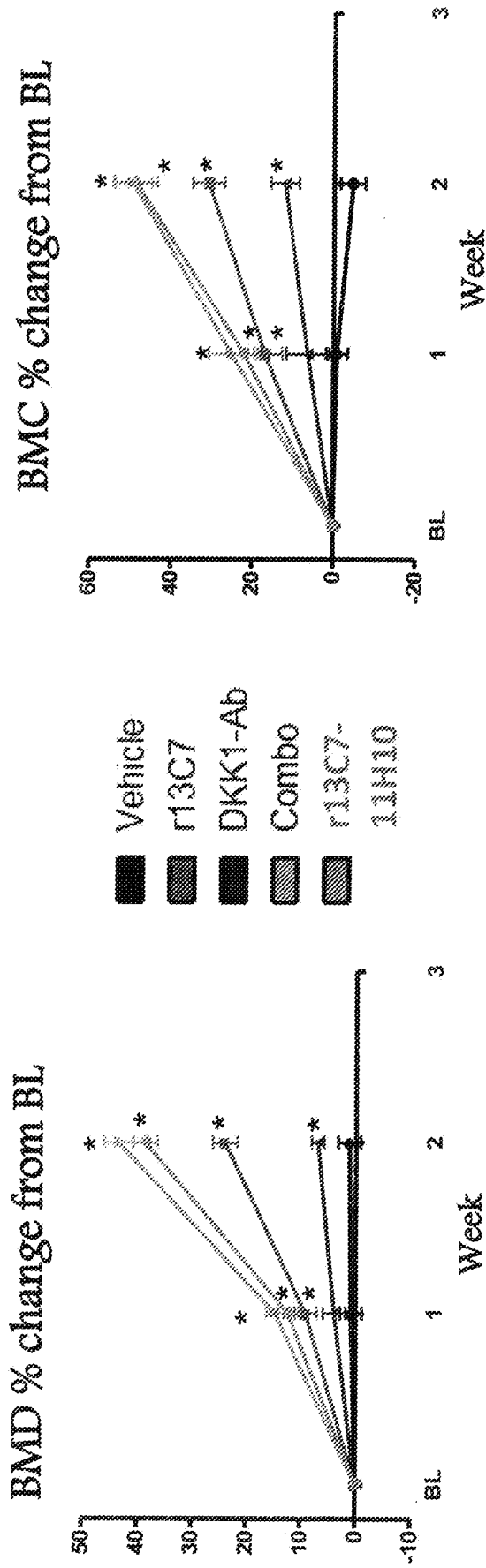
r13C7-11H10 VS. 13C7+11H10
(Against rScl / rDKK-1, 071510)



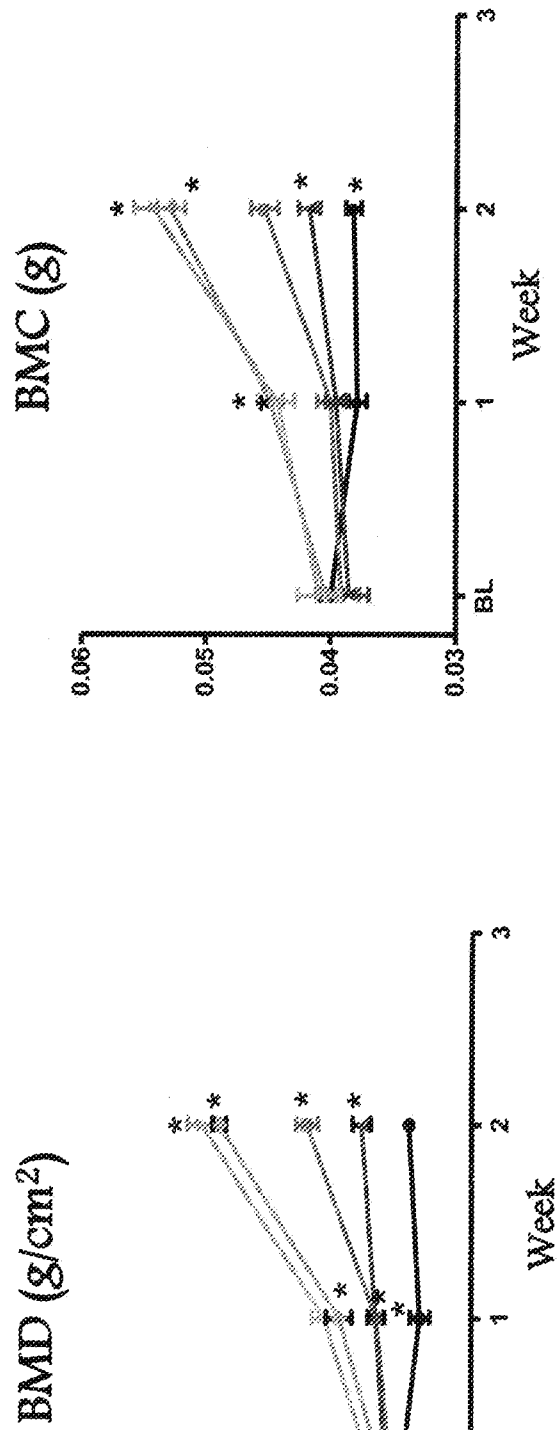
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FIG. 5

Lumbar Vertebrae



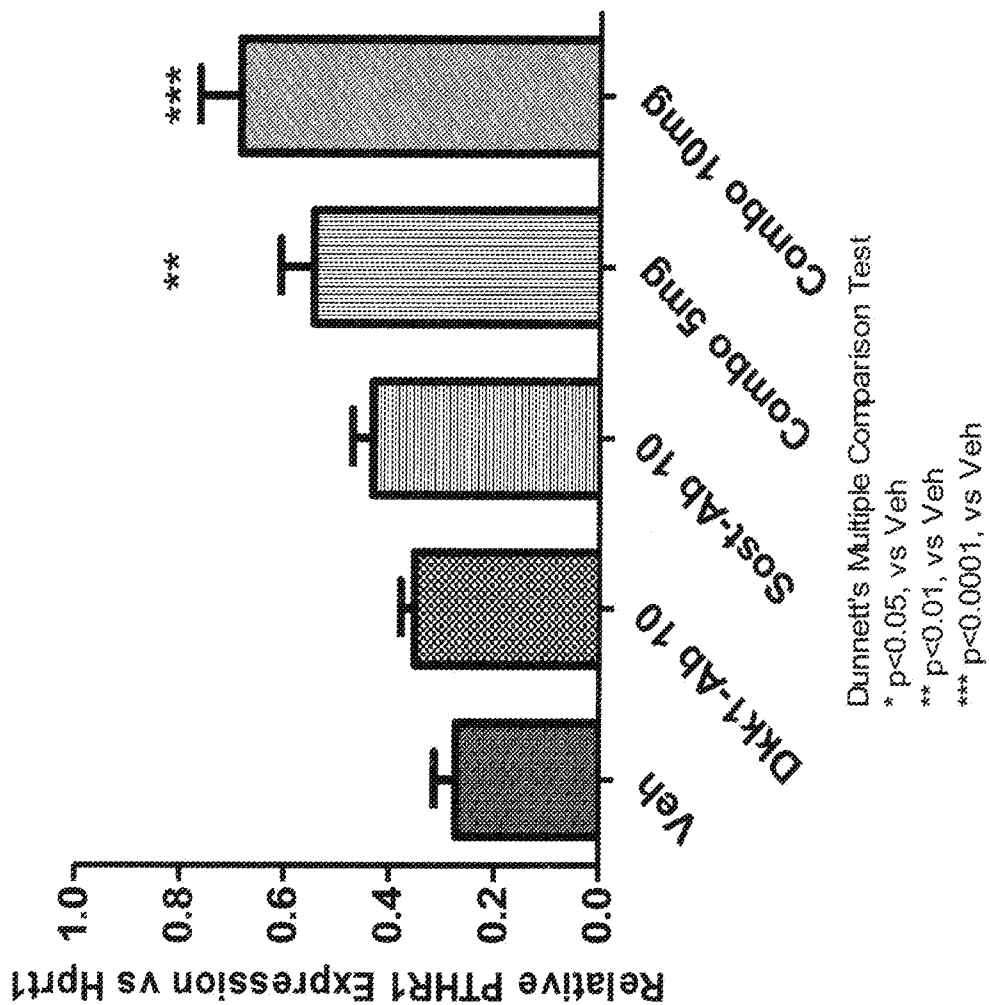
Whole Leg



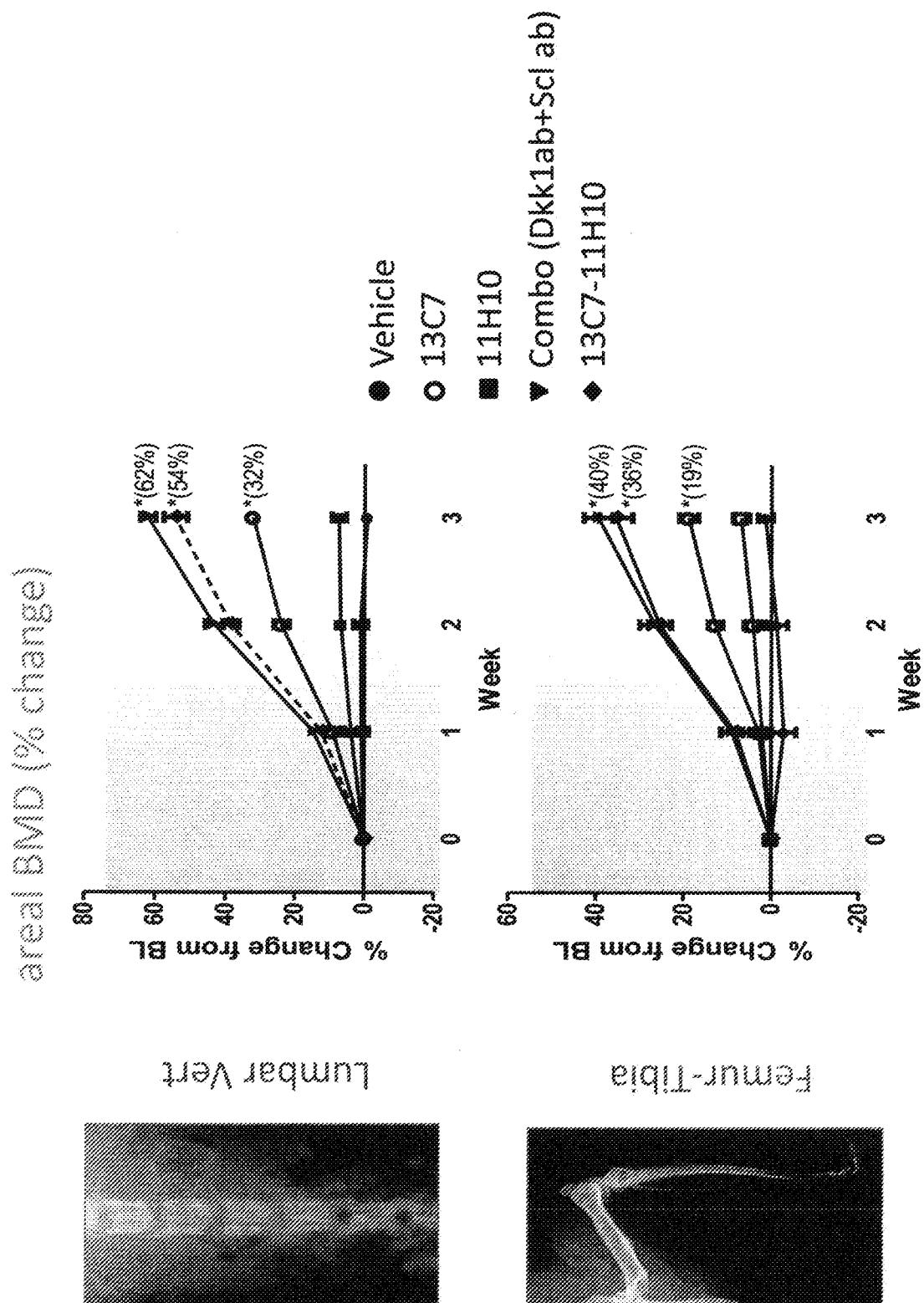
* P<0.05 vs. Vehicle group

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Sost-Ab and Dkk1-Ab Combination Therapy Increase PTHR1 expression

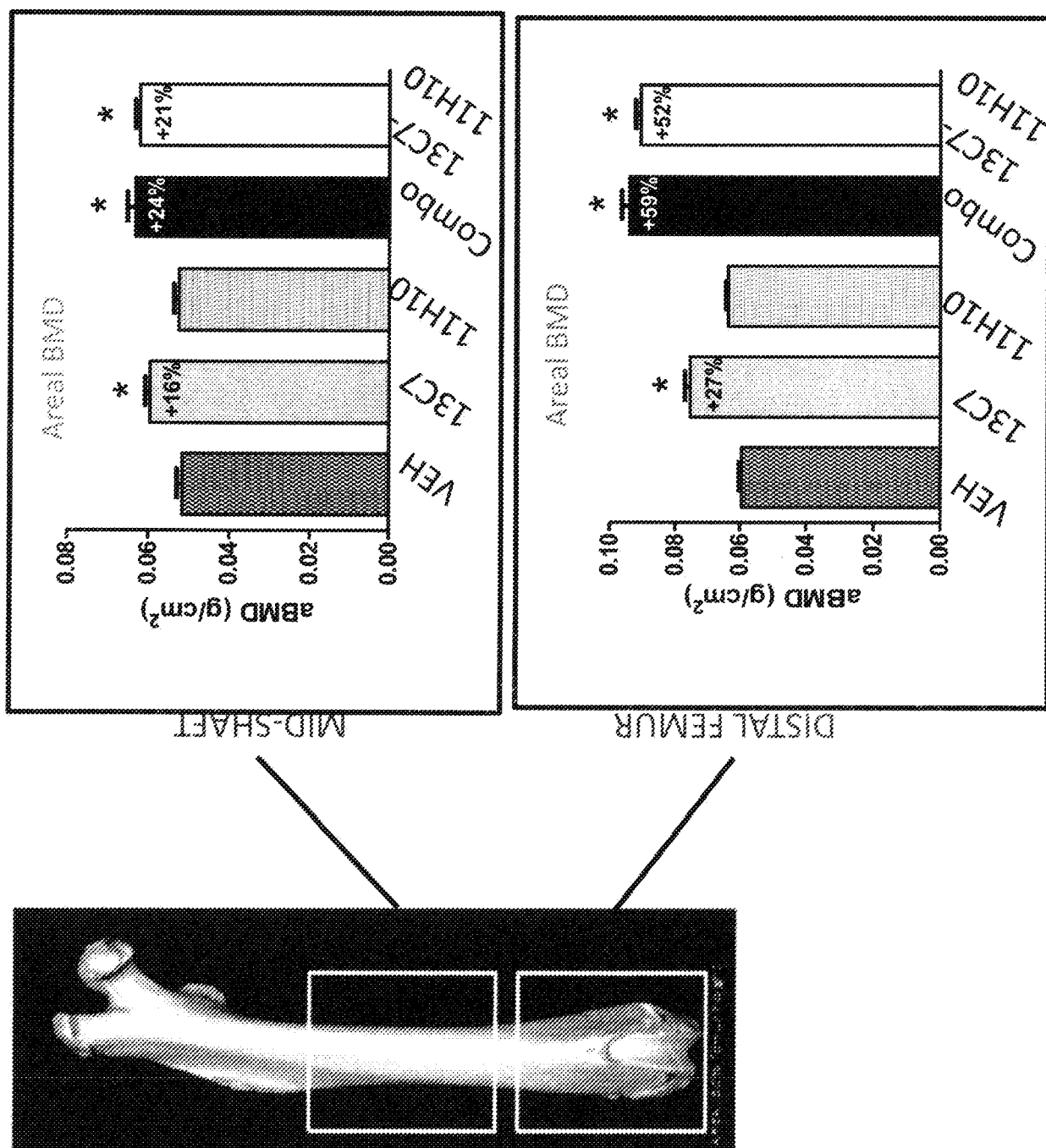


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FIG. 7



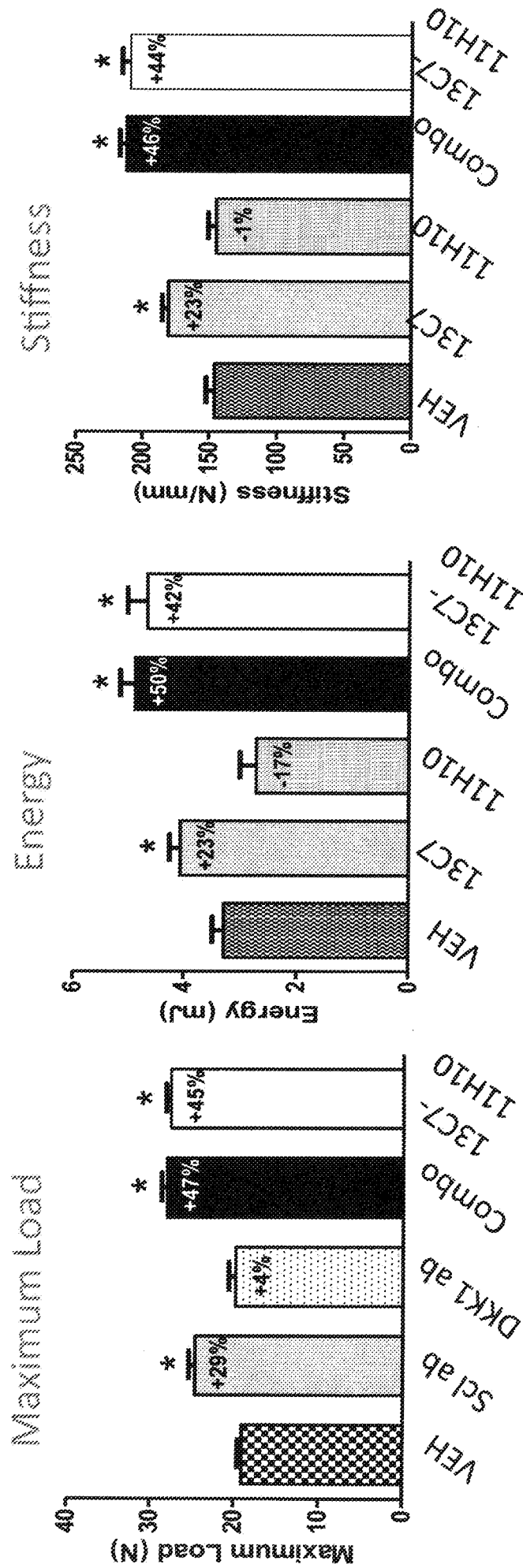
* Significantly different from Vehicle, $p < 0.05$, 1-wayANOVA, Tukey-Kramer Post Test.

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FIG. 8



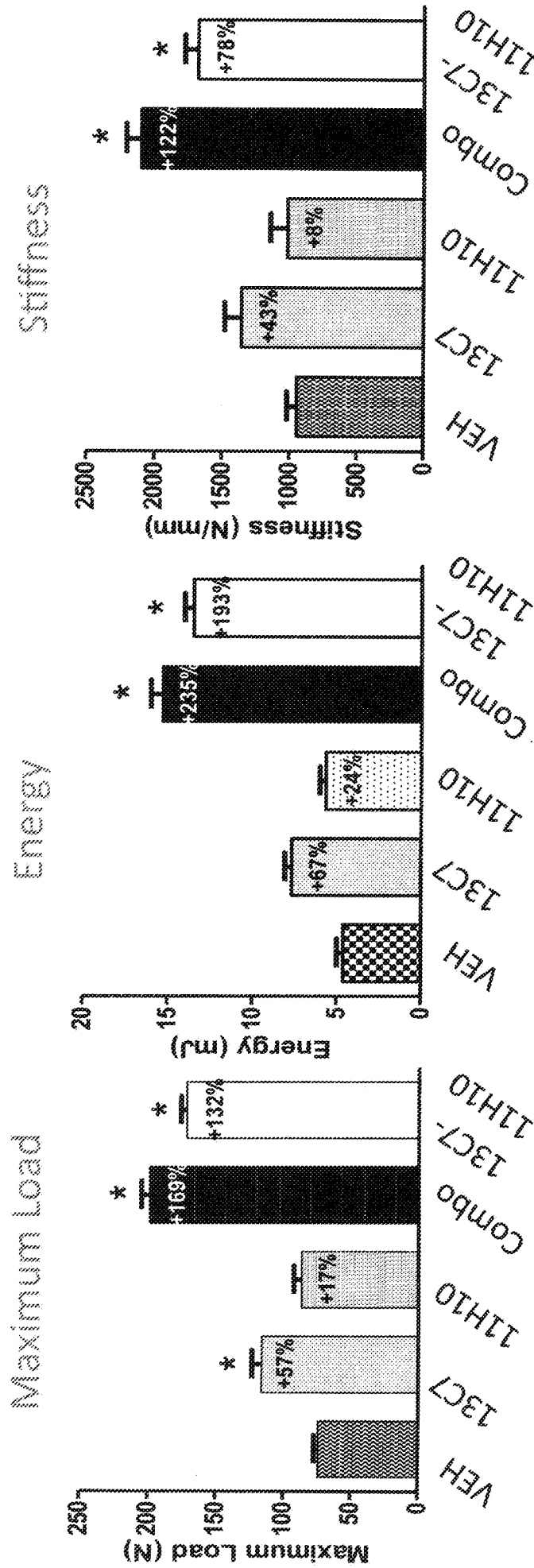
* Significantly different from Vehicle, $p < 0.05$, 1-wayANOVA, Tukey-Kramer Post Test.

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FIG. 9



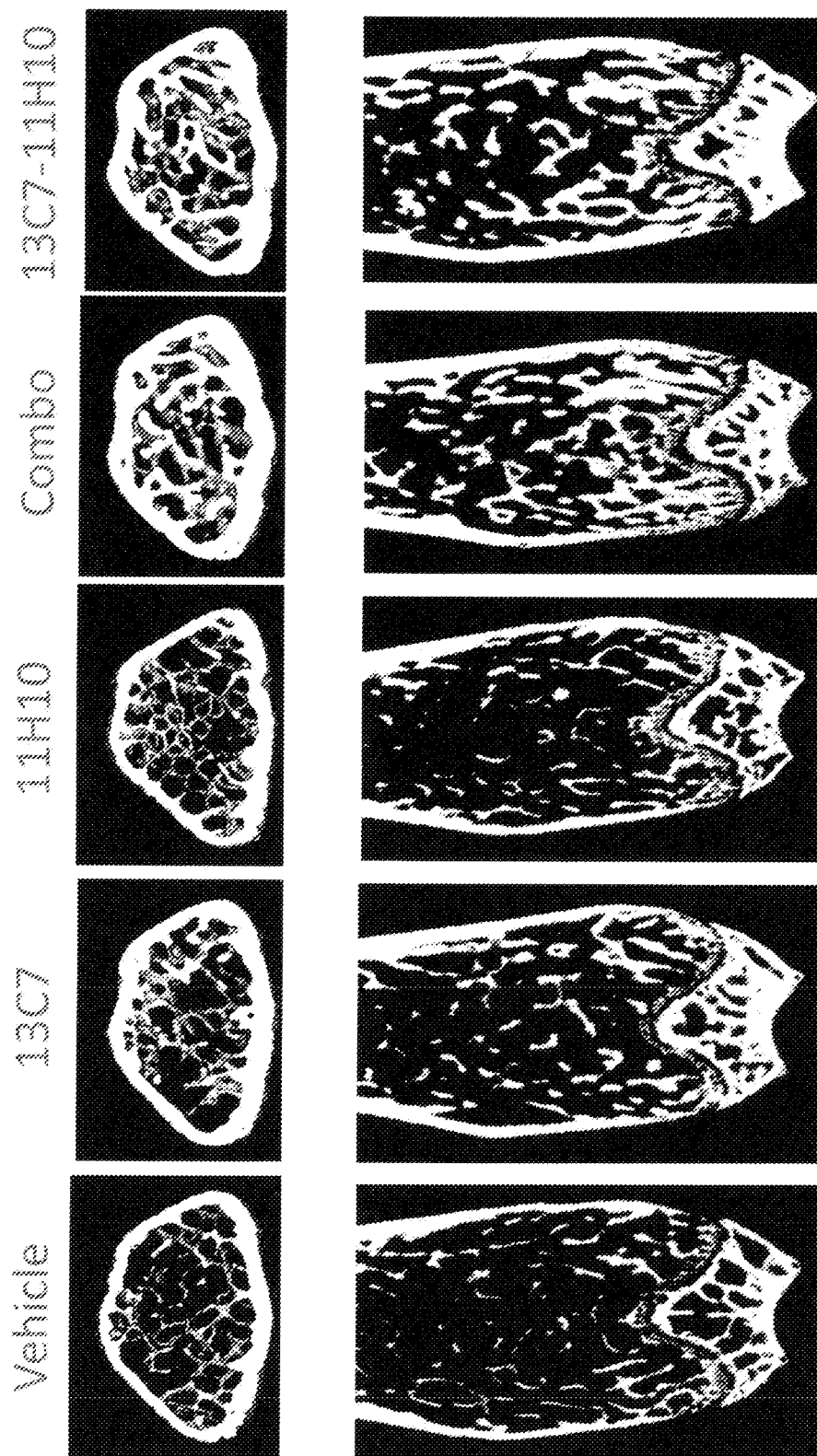
* Significantly different from Vehicle, p < 0.05, 1-wayANOVA, Tukey-Kramer Post Test.

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FIG. 10



* Significantly different from Vehicle, $p < 0.05$, 1-wayANOVA, Tukey-Kramer Post Test.

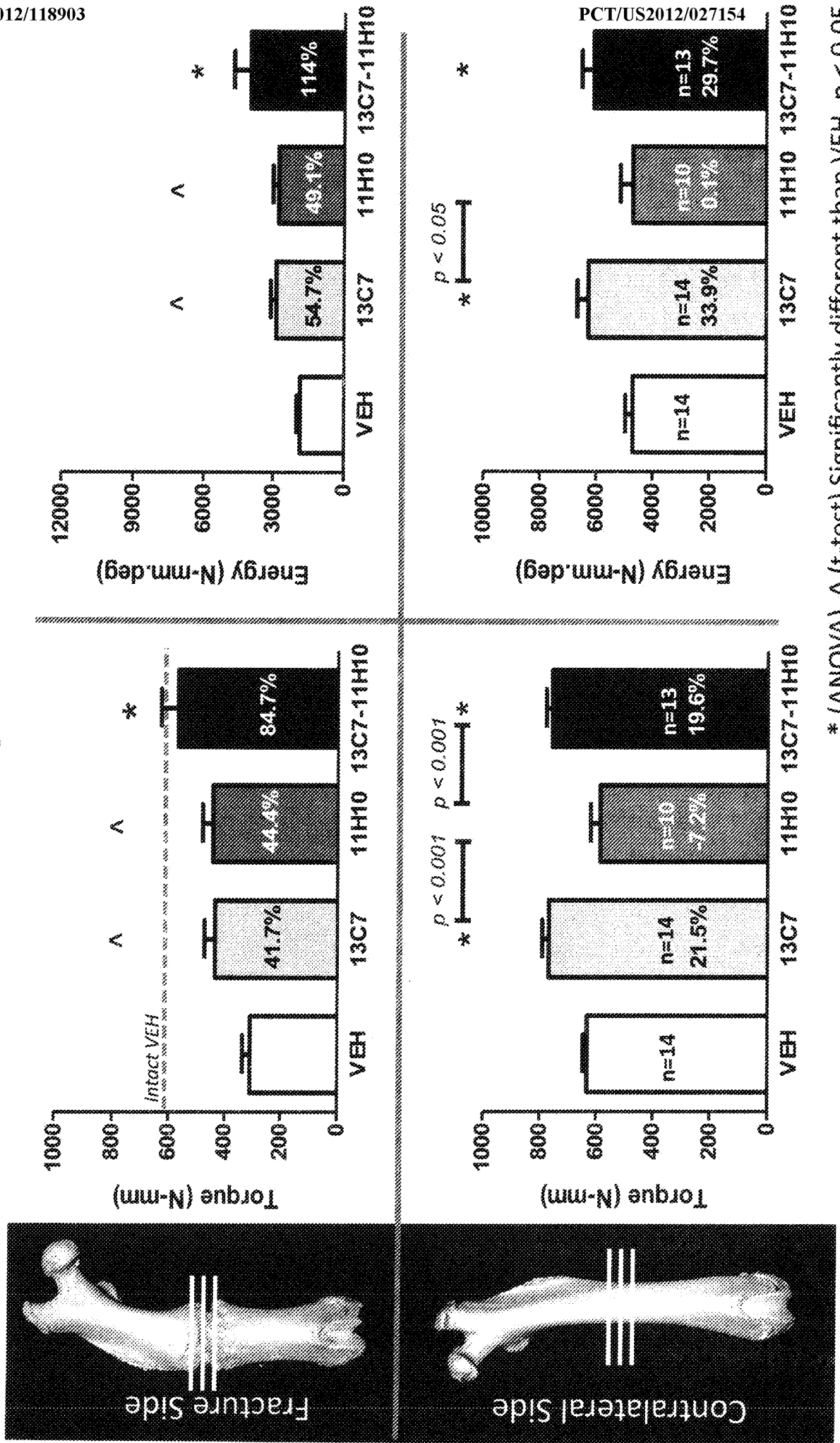
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FIG. 11



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FIG. 12

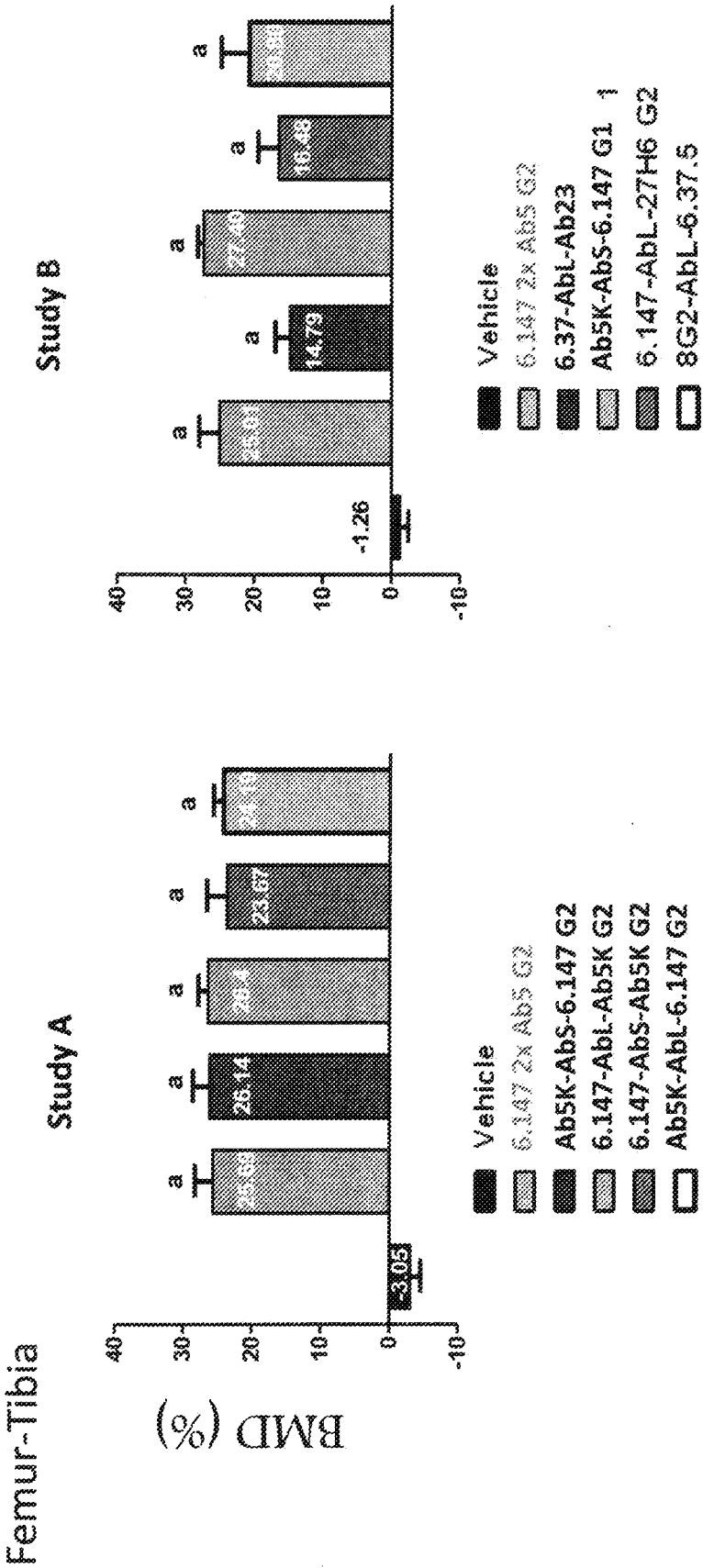
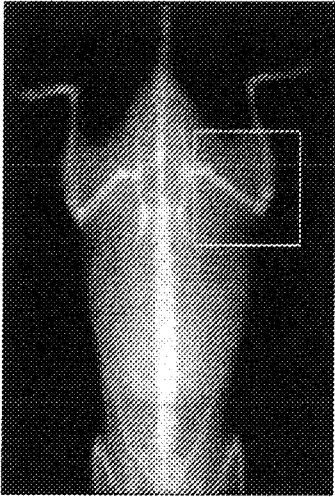
Bone Strength – Rat Close Fracture



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FIG. 14

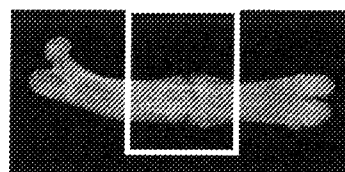
huDVD Ig Increased BMD in Femur-Tibia
(In vivo Analysis – at week2)



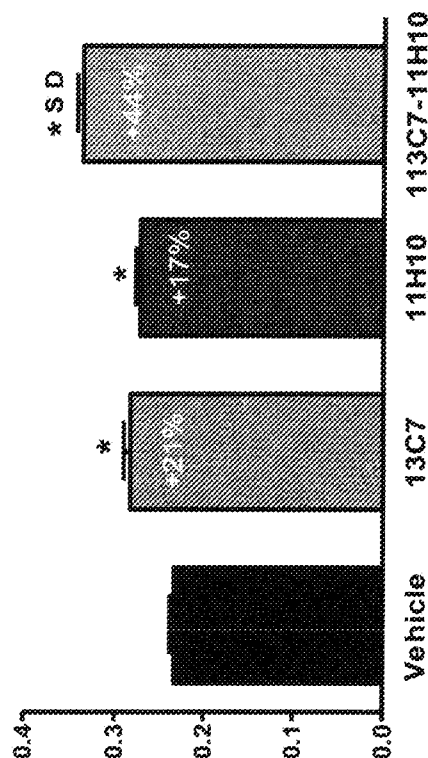
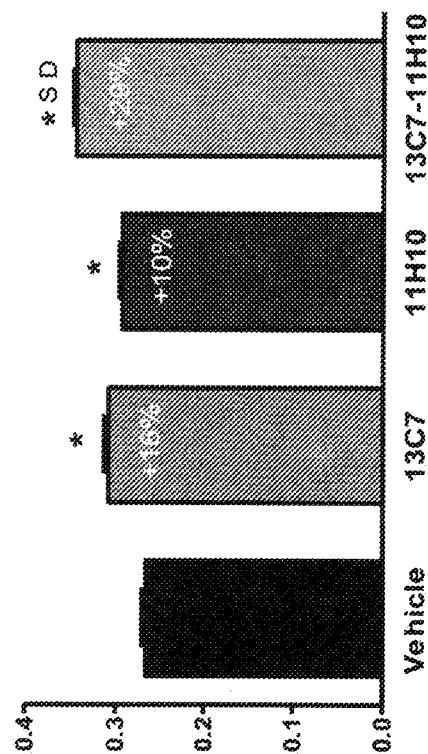
a p<0.05 vs. Vehicle by One-way ANOVA

DVD Ig had a greater effect in increasing bone mass in both fractured and intact bone (DXA)

DXA



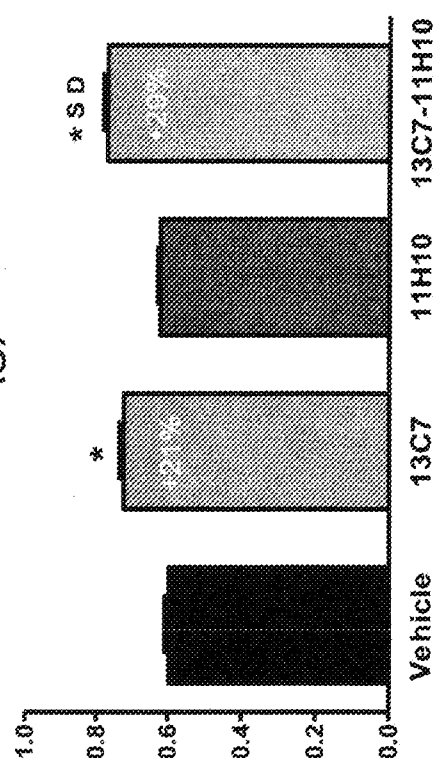
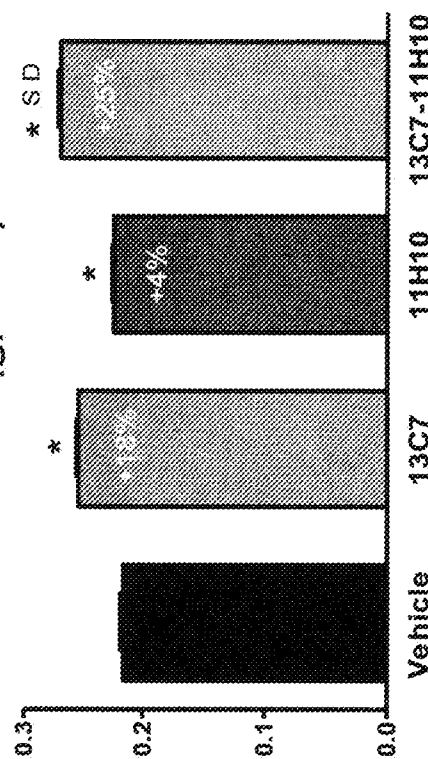
BMC (g)

BMD (g/cm²)

DXA



BMC (g)

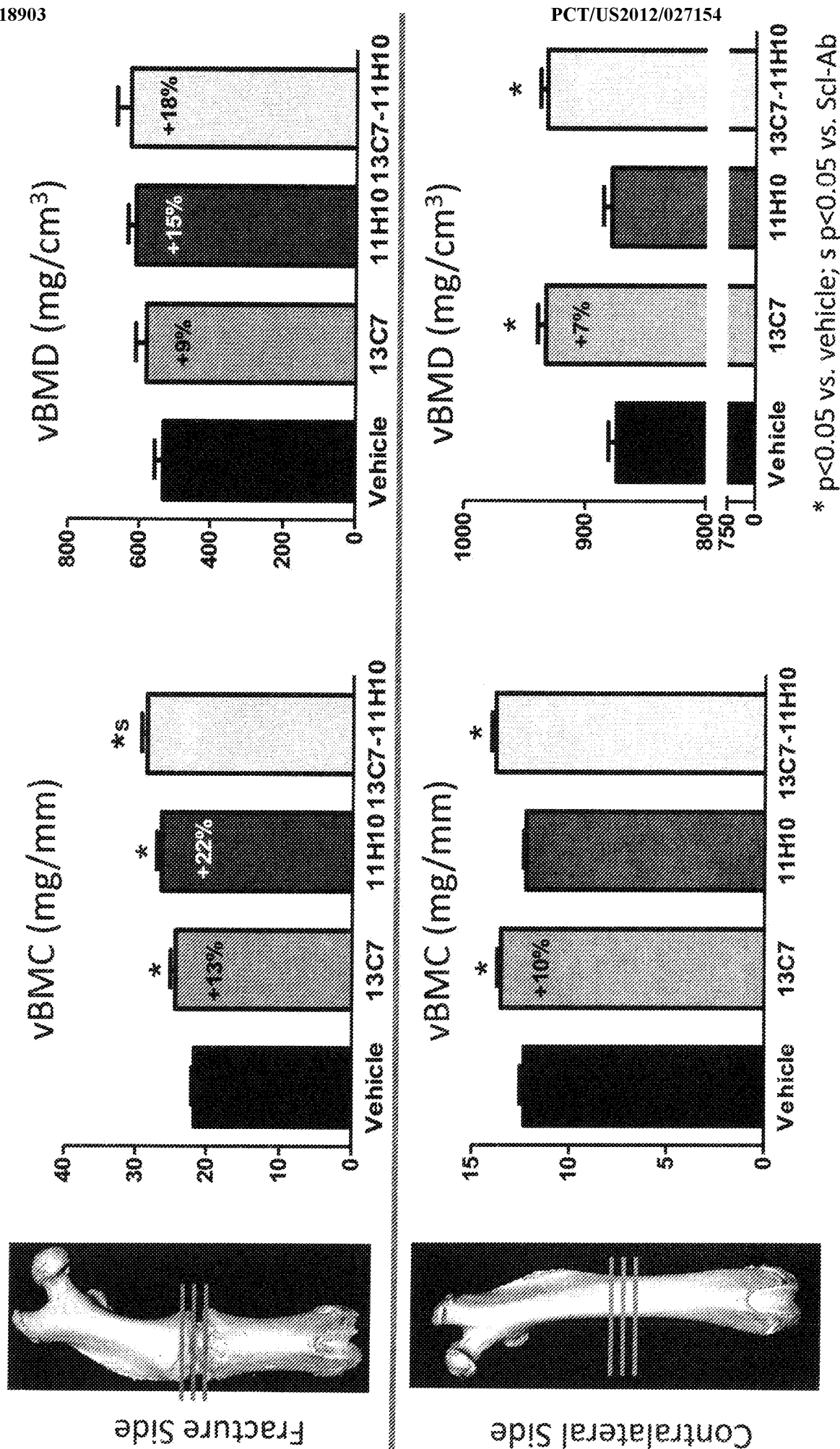
BMD (g/cm²)

* p<0.05 vs. vehicle; s p<0.05 vs. Scl-Ab; D p<0.05 vs. DKK1-Ab

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FIG. 16

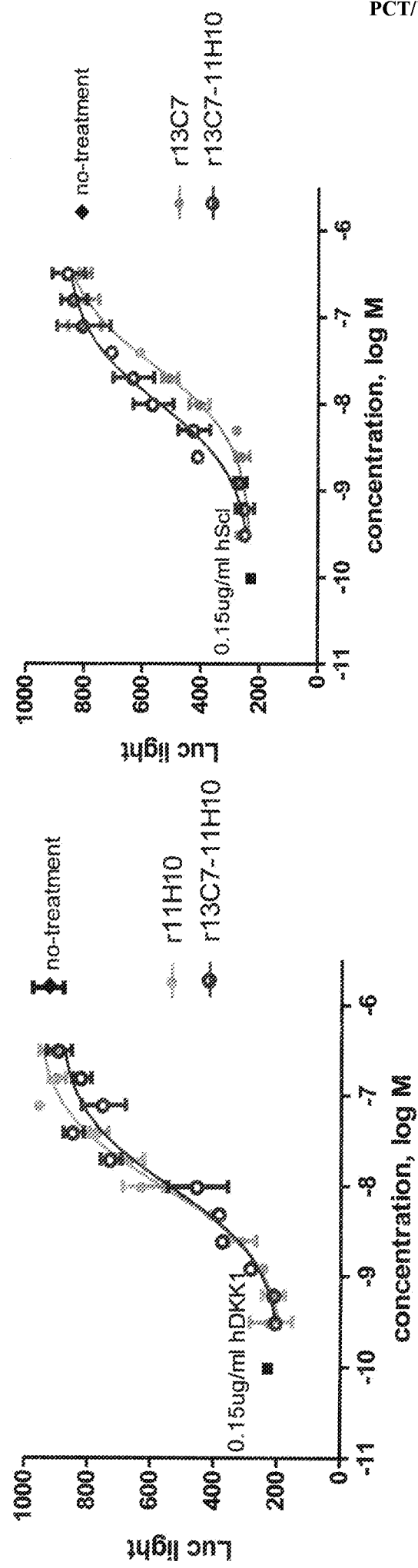
DVD Ig had a greater effect in increasing bone mass in both fractured and intact bone (pQCT)



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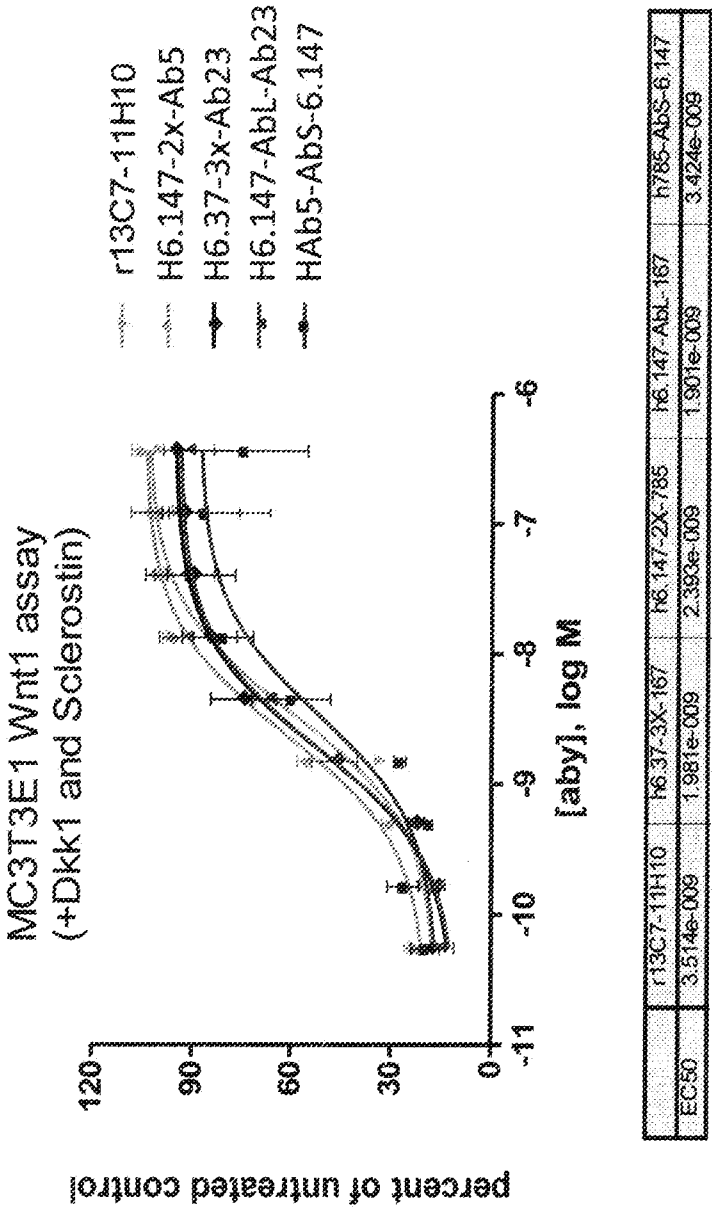
FIG. 17

Rat 13C7-11H10 retains the neutralizing activity of parental antibodies in osteoblast MC3T3E1 cells treated with Wnt proteins.



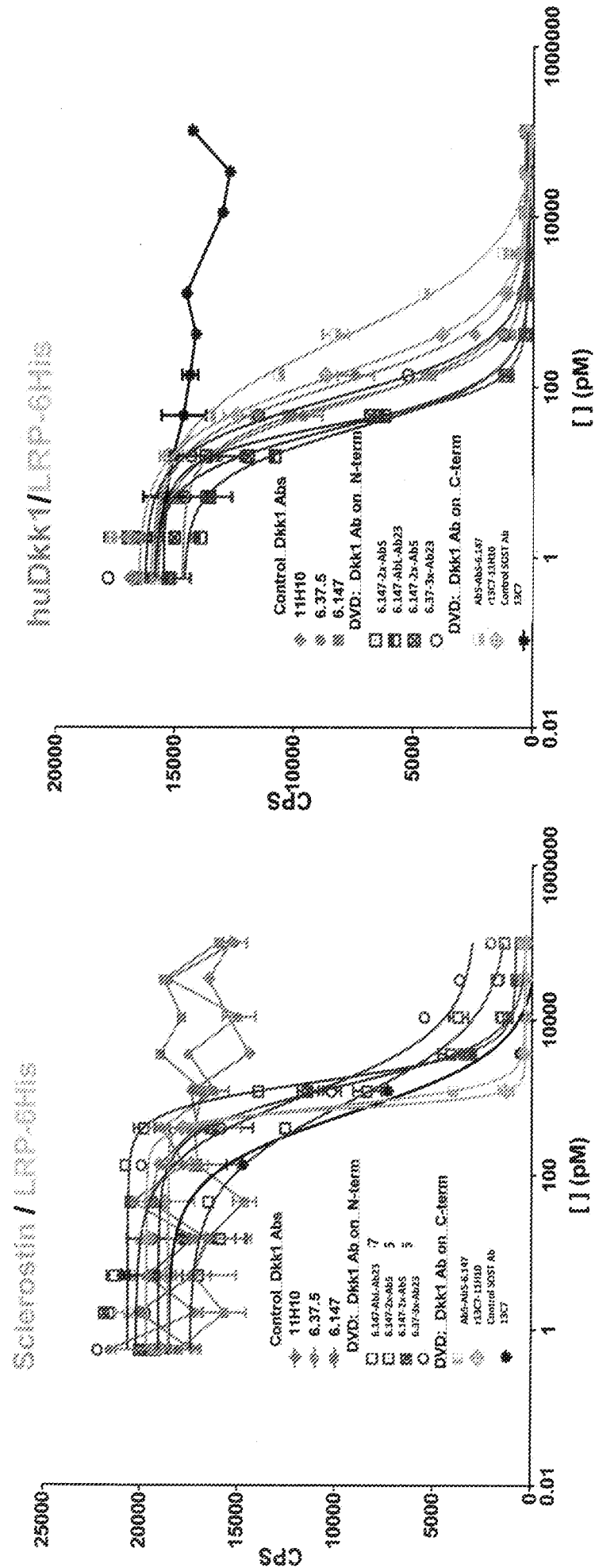
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FIG. 18

Rat and human DVD-Igs have potent neutralizing activity against both Sclerostin and Dkk1 in osteoblast MC3T3E1STF cells treated with Wnt1 protein



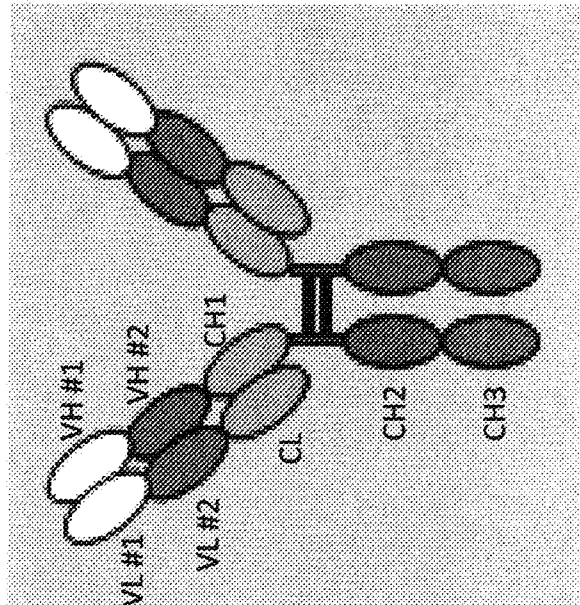
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FIG. 19

Inhibition of Lrp6 binding to Sclerostin or Dkk1 by DVD-Igs



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FIG. 20

DVD-Ig Structure



2 tandem variable domains to
encourage dual target binding

Linkers are inserted between
the 2 variable domains