U.S.C. § 371 of International Patent Application No. PCT/US08/86864, filed on December 15, 2008, which claims priority to U.S. Provisional Patent Application No. 61/013,917, filed December 14, 2007.

BACKGROUND OF THE INVENTION

[0005] The development of bispecific antibodies as therapeutic agents for human diseases has great clinical potential. Bispecific antibodies can simultaneously recognize two different antigens, neutralize different pathogenic mediators, recruit different type of effector cells, and modulate signal pathways. However, production of bispecific antibodies has been very challenging. The broad application of bispecific antibodies has been hindered by the difficulties of developing a platform for producing bispecific antibodies that exhibit favorable half-life, high stability, lack of immunogenicity, and feasibilities for large scale manufacturing and purification. Promising bispecific antibodies formats such as DVD-Ig (Dual Variable Domain Ig) (Nature Biotechnology 25, 1290 - 1297 (2007)); Cross-over Ig [Schaefer W et al (2011) PNAS 108(27): 11187-11192]; Two-in-One Ig (Science 2009, 323, 1610); BiTE® antibodies [PNAS 92(15):7021-7025; 1995] allow the production of a bispecific antibody, but they do have different kinds of liabilities.

SUMMARY OF THE INVENTION

[0006] Described herein are methods of generating heterodimeric antibodies from two different preexisting antibodies.

[0006A] In one aspect, there is provided an antibody that binds to a region of sclerostin comprising amino acids 86-111 of SEQ ID NO: 1, wherein the antibody comprises a first heavy chain and a first light chain comprising a sclerostin-binding portion and a second heavy chain and a second light chain comprising a DKK1-binding portion, wherein the first heavy chain comprises amino acid substitutions at EU positions 183, 356 and 399, wherein the second heavy chain comprises amino acid substitutions at EU positions 183, 392 and 409, and wherein the first and second light chains comprise an amino acid substitution at EU position 176, wherein the amino acid substitutions introduce a charged amino acid at said positions; wherein the substitutions introduce charged amino acids that are electrostatically unfavorable to homodimer formation and electrostatically favorable to heterodimer formation, wherein the antibody comprises a set of six CDRs selected from the group consisting of a) CDR sequences of SEQ ID NOs:54, 55, and 56 and CDR sequences of SEQ ID NOs:51, 52, and 53; b) CDR sequences of SEQ ID NOs:60, 61, and 62 and CDR

sequences of SEQ ID NOs:57, 58, and 59; c) CDR sequences of SEQ ID NOs:48, 49, and 50 and CDR sequences of SEQ ID NOs: 45, 46, and 47; d) CDR sequences of SEQ ID NOs:42, 43, and 44 and CDR sequences of SEQ ID NOs:39, 40, and 41; e) CDR sequences of SEQ ID NOs:275, 276, and 277 and CDR sequences of SEQ ID NOs:287, 288, and 289; f) CDR sequences of SEQ ID NOs:278, 279, and 280 and CDR sequences of SEQ ID NOs:290, 291, and 292; g) CDR sequences of SEQ ID NOs:78, 79, and 80 and CDR sequences of SEQ ID NOs: 245, 246, and 247; h) CDR sequences of SEQ ID NOs:81, 99, and 100 and CDR sequences of SEQ ID NOs:248, 249, and 250; i) CDR sequences of SEQ ID NOs:101, 102, and 103 and CDR sequences of SEQ ID NOs:251, 252, and 253; j) CDR sequences of SEQ ID NOs:104, 105, and 106 and CDR sequences of SEQ ID NOs:254, 255, and 256; k) CDR sequences of SEQ ID NOs:107, 108, and 109 and CDR sequences of SEQ ID NOs:257, 258, and 259; l) CDR sequences of SEQ ID NOs:110, 111, and 112 and CDR sequences of SEQ ID NOs:260, 261, and 262; m) CDR sequences of SEQ ID NOs:281, 282, and 283 and CDR sequences of SEQ ID NOs:293, 294, and 295; n) CDR sequences of SEQ ID NOs:113, 114, and 115 and CDR sequences of SEQ ID NOs:263, 264, and 265; o) CDR sequences of SEQ ID NOs:284, 285, and 286 and CDR sequences of SEQ ID NOs:296, 297, and 298; p) CDR sequences of SEQ ID NOs:116, 237, and 238 and CDR sequences of SEQ ID NOs:266, 267, and 268; q) CDR sequences of SEQ ID NOs:239, 240, and 241 and CDR sequences of SEQ ID NOs:269, 270, and 271) CDR sequences of SEQ ID NOs:242, 243, and 244 and CDR sequences of SEQ ID NOs:272, 273, and 274; and s) CDR sequences of SEQ ID NOs:351, 352, and 353 and CDR sequences of SEQ ID NOs:358, 359, and 360.

[0007] Disclosed herein is a heterodimeric antibody or fragment thereof comprising one or more substitutions in each of the following domains: a first CH_3-domain, a second CH_3-domain, a CH_1-domain, a C_L-domain, a V_H-domain and a V_L-domain, wherein the one or more substitutions introduce charged amino acids that are electrostatically unfavorable to homodimer formation and electrostatically favorable to heterodimer formation.

[0008] In some variations, the first CH3-domain or the second CH3-domain comprises an amino acid sequence differing from wild-type IgG amino acid sequence such that one or more positive-charged amino acids (e.g., lysine, histidine and arginine) in the wild-type human IgG amino acid sequence are replaced with one or more negative-charged amino acids (e.g., aspartic acid and glutamic acid) at the corresponding position(s) in the CH3 domain. Alternatively, the first CH3-domain or the second CH3-domain comprises an amino acid sequence differing from wild-type IgG amino acid sequence such that one or more negative-

charged amino acids in the wild-type human IgG amino acid sequence are replaced with one or more positive-charged amino acids at the corresponding position(s) in the CH3 domain.

[0009] In some variations, the CH1-domain or the CL-domain comprises an amino acid sequence differing from wild-type IgG amino acid sequence such that one or more positive-charged amino acids in wild-type IgG amino acid sequence are replaced with one or more negative-charged amino acids. Alternatively, the CH1-domain or the CL-domain comprises an amino acid sequence differing from wild-type IgG amino acid sequence such that one or more negative-charged amino acids in wild-type IgG amino acid sequence are replaced with one or more positive-charged amino acids.

[0010] The VH-domain or the VL-domain of a heterodimeric antibody described herein comprises, in some variations, an amino acid sequence differing from wild-type IgG amino acid sequence such that one or more positive-charged amino acids in wild-type IgG amino acid sequence are replaced with one or more negative-charged amino acids. Alternatively, the VH-domain or the VL-domain comprises an amino acid sequence differing from wild-type IgG amino acid sequence such that one or more negative-charged amino acids in wild-type IgG amino acid sequence are replaced with one or more positive-charged amino acids.

[0011] In another example, described herein is a heterodimeric antibody or fragment thereof comprising a heavy chain comprising (a) a first amino acid substitution at an AHo position selected from the group consisting of AHo positions 42-50 that introduces a charged amino acid at said position, (b) a second amino acid substitution at a position selected from the group consisting of positions 126-213 (EU numbering) that introduces a charged amino acid at said position, (c) a third amino acid substitution at a position selected from the group consisting of positions 352-360 (EU numbering) that introduces a charged amino acid at said position, and (d) a fourth amino acid substitution at a position selected from the group consisting of positions 395-403 (EU numbering) that introduces a charged amino acid, wherein the charged amino acid of (a) has the same charge as the charged amino acid of (b), and wherein the charged amino acids of (c) and (d) have an opposite charge of the charged amino acids of (a) and (b).

[0012] In some examples, the first amino acid substitution is at AHo position 46, the second amino acid substitution is at EU position 183, the third amino acid substitution is at EU position 356 and the fourth amino acid substitution is at EU position 399. In some embodiments, glutamine at AHo position 46 is replaced with glutamic acid, serine at EU

position 183 is replaced with glutamic acid, glutamic acid at EU position 356 is replaced with lysine, and aspartic acid at EU position 399 is replaced with lysine.

[0013] In another example, described herein is an antibody or fragment thereof comprising a heavy chain comprising (a) a first amino acid substitution at an AHo position selected from the group consisting of AHo positions 35-43 that introduces a charged amino acid at said position, (b) a second amino acid substitution at a position selected from the group consisting of positions 126-213 (EU numbering) that introduces a charged amino acid at said position, (c) a third amino acid substitution at a position selected from the group consisting of positions 388-398 (EU numbering) that introduces a charged amino acid at said position, and (d) a fourth amino acid substitution at a position selected from the group consisting of positions 404-413 (EU numbering) that introduces a charged amino acid, wherein the charged amino acids of (c) and (d) have an opposite charge of the charged amino acids of (a) and (b). In some examples, the glutamine at AHo position 46 is replaced with lysine, serine at EU position 183 is replaced with lysine, lysine at EU position 392 is replaced with aspartic acid and lysine at EU position 409 is replaced with aspartic acid.

[0014] In yet another example, described herein is an antibody or fragment comprising a light chain comprising (a) a first amino acid substitution at an AHo position selected from the group consisting of AHo positions 42-50 that introduces a charged amino acid at said position, and (b) a second amino acid substitution at a position selected from the group consisting of positions 126-213 (EU numbering) that introduces a charged amino acid at said position. In some examples, glutamine at AHo position 46 is replaced with glutamic acid and serine at EU position 176 is replaced with glutamic acid.

[0015] In another example, described herein is an antibody comprising a heavy chain comprising (a) a first amino acid substitution at an AHo position selected from the group consisting of AHo positions 42-50 that introduces a charged amino acid at said position, (b) a second amino acid substitution at a position selected from the group consisting of positions 126-213 (EU numbering) that introduces a charged amino acid at said position, (c) a third amino acid substitution at a position selected from the group consisting of positions 352-360 (EU numbering) that introduces a charged amino acid at said position, and (d) a fourth amino acid substitution at a position selected from the group consisting of positions 395-403 (EU numbering) that introduces a charged amino acid, wherein the charged amino acids of (a) and (b) have a negative-charge and the charged amino acids of (c) and (d) have a positive charge. In some examples, the first amino acid substitution is at position AHo 46, the second

amino acid substitution is at EU position 183, the third amino acid substitution is at EU position 356 and the fourth amino acid substitution is at EU position 399. In some examples, the antibody comprises a light chain comprising positive-charged amino acids at AHo position 46 and EU position 176.

[0016] In still another example, described herein is a heterodimeric antibody comprising a first heavy chain and a second heavy chain and a first light chain and a second light chain, wherein the first heavy chain comprises amino acid substitutions at AHo position 46 and EU positions 183, 356 and 399, wherein the second heavy chain comprises amino acid substitutions at AHo position 46 and EU positions 183, 392 and 409, and wherein the first and second light chains comprise an amino acid substitution at AHo position 46 and EU position176, wherein the amino acid substitutions introduce a charged amino acid at said positions. In some examples, the glutamine at position AHo 46 of the first heavy chain is replaced with glutamic acid, the glutamine at position AHo 46 of the second heavy chain is replaced with lysine, the glutamine at position AHo 46 of the first light chain is replaced with lysine, the glutamine at position AHo 46 of the second light chain is replaced with glutamic acid, the serine at EU position 183 of the first heavy chain is replaced with glutamic acid, the glutamic acid at EU position 356 of the first heavy chain is replaced with lysine, the glutamic acid at EU position 399 of the first heavy chain is replaced with lysine, the serine at EU position 183 of the second heavy chain is replaced with lysine, the lysine at EU position 392 of the second heavy chain is replaced with aspartic acid, and the lysine at EU position 409 of the second heavy chain is replaced with aspartic acid.

[0017] In some or any of the examples described herein, the antibody binds to a region of sclerostin comprising amino acids 86-111 of SEQ ID NO: 1.

[0018] Also described herein is a heterodimeric antibody that binds to a region of sclerostin comprising amino acids 86-111 of SEQ ID NO: 1, wherein the antibody comprises a first heavy chain and a first light chain comprising a sclerostin-binding portion and a second heavy chain and a second light chain comprising a DKK1-binding portion, wherein the first heavy chain comprises amino acid substitutions at AHo position 46 and EU positions 183, 356 and 399, wherein the second heavy chain comprises amino acid substitutions at AHo position 46 and EU positions 183, 392 and 409, wherein the first and second light chains comprise an amino acid substitution at AHo position 46 and EU position 176, and wherein the amino acid substitutions introduce a charged amino acid at said positions.

[0028] In some embodiments, the heterodimeric antibody that binds sclerostin and DKK1 comprises a first heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1048; a second heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1042; a first light chain comprising the amino acid sequence set forth in SEQ ID NO: 1049 and a second light chain comprising the amino acid sequence set forth in SEQ ID NO: 1043.

[0029] In some embodiments, the heterodimeric antibody that binds sclerostin and DKK1 comprises a first heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1048; a second heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1044; a first light chain comprising the amino acid sequence set forth in SEQ ID NO: 1049 and a second light chain comprising the amino acid sequence set forth in SEQ ID NO: 1045.

[0030] The invention also contemplates a heterodimeric antibody comprising a heavy chain that comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 1038, SEQ ID NO: 1046, SEQ ID NO: 1040 and SEQ ID NO: 1048. In some embodiments, the heterodimeric antibody optionally comprises a light chain amino acid sequence selected from the group consisting of SEQ ID NO: 1039, SEQ ID NO: 1047, SEQ ID NO: 1041 and SEQ ID NO: 1049.

[0031] The invention also contemplates a heterodimeric antibody comprising a heavy chain that comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 1034, SEQ ID NO: 1042, SEQ ID NO: 1036 and SEQ ID NO: 1044. In some embodiments, the heterodimeric antibody optionally comprises a light chain amino acid sequence selected from the group consisting of SEQ ID NO: 1035, SEQ ID NO: 1043, SEQ ID NO: 1037 and SEQ ID NO: 1045.

[0032] In another examples, described herein is an antibody that binds to a region of sclerostin comprising amino acids 86-111 of SEQ ID NO: 1, wherein the antibody comprises substitutions in each of the following domains: a first CH3-domain, a second CH3-domain, a CH1-domain, and a CL-domain, wherein the one or more substitutions introduce charged amino acids that are electrostatically unfavorable to homodimer formation and electrostatically favorable to heterodimer formation.

[0033] Also described herein is an antibody that binds to a region of sclerostin comprising amino acids 86-111 of SEQ ID NO: 1, wherein the antibody comprises a heavy chain having a CH3 domain comprising one or more amino acid substitutions, wherein the one or more substitutions introduce charged amino acids that are electrostatically unfavorable to

homodimer formation and electrostatically favorable to heterodimer formation. In some embodiments, a negative charged amino acid in the CH3 domain (e.g., at EU position D399, E356 or E357) is substituted with a positive charged amino acid. In some embodiments, amino acids at EU positions D399, E356 and E357 are substituted with a positive charged amino acid (e.g., lysine).

[0034] In alternative embodiments, a positive charged amino acid in the CH3 domain (e.g., at EU position K370, K392 or K409) is substituted with a negative charged amino acid. In some embodiments, amino acids as EU positions K370, K392 and K409 are substituted with a negative charged amino acid (e.g., aspartic acid).

[0035] The heterodimeric antibody is, in some embodiments, an antibody, a bispecific antibody, a monospecific monovalent antibody, a bispecific maxibody, a monobody, a peptibody, a bispecific peptibody, a monovalent peptibody or a receptor fusion protein.

[0036] Nucleic acids comprising a nucleotide sequence encoding any of the heterodimeric antibodies described herein are also provided, as well as vectors and host cells comprising the nucleic acid (or vector).

[0036A] In one aspect, there is provided a nucleic acid comprising a nucleotide sequence encoding the heterodimeric antibody as described herein.

[0036B] In another aspect, there is provided a vector comprising the nucleotide sequence as described herein.

[0036C] In yet another aspect, there is provided an isolated host cell comprising the nucleic acid as described herein.

[0036D] In another aspect, there is provided use of heterodimeric antibody as described herein in the manufacture of a medicament for increasing bone mineral density in a mammalian subject in need of increased bone mineral density.

[0036E] In yet another aspect, there is provided a composition comprising the antibody as described herein and a pharmaceutically acceptable carrier, diluent or adjuvant.

[0037] Also disclosed is method of increasing bone mineral density in a mammalian subject comprising administering a heterodimeric antibody described herein to the subject in an amount effective to increase bone mineral density in the subject. The invention also includes methods of using heterodimeric antibodies described herein for increasing bone

mineral density. Methods of using as described herein can alternatively be characterized as uses of the heterodimeric antibodies for increasing bone mineral density.

[0038] The disclosure also includes compositions comprising a heterodimeric antibody described herein and a pharmaceutically acceptable carrier, diluent or adjuvant. In some embodiments, less than 5% (or less than 4%, or less than 3%, or less than 2% or less than 1% or less) of the antibody in the composition is in aggregate form after two weeks of storage at about 4°C. The amount of antibody aggregation in the composition can be determined, for example, by Size Seclusion Chromatography (SEC) or Dynamic Light Scattering (DLS).

[0039] In another example, described herein is a composition comprising a heterodimeric antibody or fragment thereof and a pharmaceutically acceptable carrier, diluent or adjuvant, the heterodimeric antibody or fragment thereof comprising one or more substitutions in each of the following domains: a first CH_3-domain, a second CH_3-domain, a CH_1-domain, a C_L-domain, a V_H-domain and a V_L-domain, wherein the one or more substitutions introduce

What is claimed is:

1. An antibody that binds to a region of sclerostin comprising amino acids 86-111 of SEQ ID NO: 1,

wherein the antibody comprises a first heavy chain and a first light chain comprising a sclerostin-binding portion and a second heavy chain and a second light chain comprising a DKK1-binding portion, wherein the first heavy chain comprises amino acid substitutions at EU positions 183, 356 and 399, wherein the second heavy chain comprises amino acid substitutions at EU positions 183, 392 and 409, and wherein the first and second light chains comprise an amino acid substitution at EU position 176, wherein the amino acid substitutions introduce a charged amino acid at said positions; wherein the substitutions introduce charged amino acids that are electrostatically unfavorable to homodimer formation and electrostatically favorable to heterodimer formation,

wherein the antibody comprises a set of six CDRs selected from the group consisting of a) CDR sequences of SEQ ID NOs:54, 55, and 56 and CDR sequences of SEQ ID NOs:51, 52, and 53; b) CDR sequences of SEQ ID NOs:60, 61, and 62 and CDR sequences of SEQ ID NOs:57, 58, and 59; c) CDR sequences of SEQ ID NOs:48, 49, and 50 and CDR sequences of SEQ ID NOs: 45, 46, and 47; d) CDR sequences of SEQ ID NOs:42, 43, and 44 and CDR sequences of SEQ ID NOs:39, 40, and 41; e) CDR sequences of SEQ ID NOs:275, 276, and 277 and CDR sequences of SEQ ID NOs:287, 288, and 289; f) CDR sequences of SEQ ID NOs:278, 279, and 280 and CDR sequences of SEQ ID NOs:290, 291, and 292; g) CDR sequences of SEQ ID NOs:78, 79, and 80 and CDR sequences of SEQ ID NOs: 245, 246, and 247; h) CDR sequences of SEQ ID NOs:81, 99, and 100 and CDR sequences of SEQ ID NOs:248, 249, and 250; i) CDR sequences of SEQ ID NOs:101, 102, and 103 and CDR sequences of SEQ ID NOs:251, 252, and 253; j) CDR sequences of SEQ ID NOs:104, 105, and 106 and CDR sequences of SEQ ID NOs:254, 255, and 256; k) CDR sequences of SEQ ID NOs:107, 108, and 109 and CDR sequences of SEQ ID NOs:257, 258, and 259; l) CDR sequences of SEQ ID NOs:110, 111, and 112 and CDR sequences of SEQ ID NOs:260, 261, and 262; m) CDR sequences of SEQ ID NOs:281, 282, and 283 and CDR sequences of SEQ ID NOs:293, 294, and 295; n) CDR sequences of SEQ ID NOs:113, 114, and 115 and CDR sequences of SEQ ID NOs:263, 264, and 265; o) CDR sequences of SEQ ID NOs:284, 285, and 286 and CDR sequences of SEQ ID NOs:296, 297, and 298; p) CDR sequences of SEQ ID NOs:116, 237, and 238 and CDR sequences of SEQ ID NOs:266, 267, and 268; q) CDR sequences of SEQ ID NOs:239, 240, and 241 and CDR sequences of SEQ ID NOs:269, 270,

and 271) CDR sequences of SEQ ID NOs:242, 243, and 244 and CDR sequences of SEQ ID NOs:272, 273, and 274; and s) CDR sequences of SEQ ID NOs:351, 352, and 353 and CDR sequences of SEQ ID NOs:358, 359, and 360..

2. The antibody of claim 1 that comprises a light chain comprising a variable region amino acid sequence selected from the group consisting of SEQ ID NO: 364, SEQ ID NO: 376, SEQ ID NO: 75, SEQ ID NO: 384, SEQ ID NO: 388, SEQ ID NO: 380, SEQ ID NO: 299, SEQ ID NO: 303, SEQ ID NO: 314, SEQ ID NO: 311, SEQ ID NO: 315 and SEQ ID NO: 368.

3. The antibody of any of the preceding claims that comprises a heavy chain comprising a variable region amino acid sequence selected from the group consisting of SEQ ID NO: 366, SEQ ID NO: 378, SEQ ID NO: 77, SEQ ID NO: 386, SEQ ID NO: 390, SEQ ID NO: 382, SEQ ID NO: 301, SEQ ID NO: 305, SEQ ID NO: 327, SEQ ID NO: 313, SEQ ID NO: 317 and SEQ ID NO: 370.

4. The antibody according to claim 1, wherein the antibody comprises

a first heavy chain and a first light chain comprising a sclerostin-binding portion and a second heavy chain and a second light chain comprising a DKK1-binding portion, wherein the first heavy chain comprises amino acid substitutions at AHo position 46 and EU positions 183, 356 and 399, wherein the second heavy chain comprises amino acid substitutions at AHo position 46 and EU positions 183, 392 and 409, wherein the first and second light chains comprise an amino acid substitution at AHo position 46 and EU position 176, and wherein the amino acid substitutions introduce a charged amino acid at said positions.

5. The heterodimeric antibody of claim 1, wherein the sclerostin-binding portion comprises a set of six CDRs selected from the group consisting of a) CDR-L1 of SEQ ID NO: 284, CDR-L2 of SEQ ID NO: 285, CDR-L3 of SEQ ID NO: 286, CDR-H1 of SEQ ID NO: 296, CDR-H2 of SEQ ID NO: 297, and CDR-H3 of SEQ ID NO: 298; b) CDR-L1 of SEQ ID NO: 48, CDR-L2 of SEQ ID NO: 49, CDR-L3 of SEQ ID NO: 50, CDR-H1 of SEQ ID NO: 45, CDR-H2 of SEQ ID NO: 46, and CDR-H3 of SEQ ID NO: 47; and c) CDR-L1 of SEQ ID NO: 42, CDR-L2 of SEQ ID NO: 43, CDR-L3 of SEQ ID NO: 44, CDR-H1 of SEQ ID NO: 39, CDR-H2 of SEQ ID NO: 40, and CDR-H3 of SEQ ID NO: 41.

6. The heterodimeric antibody of claim 1, wherein the sclerostin-binding portion comprises a heavy chain and a light chain comprising CDR-H1 of SEQ ID NO: 269, CDR-

H2 of SEQ ID NO: 270, CDR-H3 of SEQ ID NO: 271, CDR-L1 of SEQ ID NO: 239, CDR-L2 of SEQ ID NO: 240 and CDR-L3 of SEQ ID NO: 241.

7. The heterodimeric antibody of claim 1, wherein the first light chain comprises a variable region amino acid sequence selected from the group consisting of SEQ ID NO: 364, SEQ ID NO: 376, SEQ ID NO: 75, SEQ ID NO: 384, SEQ ID NO: 388, SEQ ID NO: 380, SEQ ID NO: 299, SEQ ID NO: 303, SEQ ID NO: 314, SEQ ID NO: 311, SEQ ID NO: 315 and SEQ ID NO: 368.

8. The heterodimeric antibody of claim 1, wherein the first heavy chain comprises a variable region amino acid sequence selected from the group consisting of SEQ ID NO: 366, SEQ ID NO: 378, SEQ ID NO: 77, SEQ ID NO: 386, SEQ ID NO: 390, SEQ ID NO: 382, SEQ ID NO: 301, SEQ ID NO: 305, SEQ ID NO: 327, SEQ ID NO: 313, SEQ ID NO: 317 and SEQ ID NO: 370.

9. The heterodimeric antibody of claim 1, wherein the DKK1-binding portion comprises a set of six CDRs selected from the group consisting of (a) SEQ ID NOs: 820-825, (b) SEQ ID NOs: 828-833, (c) SEQ ID NOs: 836-841, (d) SEQ ID NOs: 844-849, (e) SEQ ID NOs: 852-857, (f) SEQ ID NOs: 860-865, (g) SEQ ID NOs: 868-873, (h) SEQ ID NOs: 876-881, (i) SEQ ID NOs: 884-889, (j) SEQ ID NOs: 892-897, (k) SEQ ID NOs: 900-905, (l) SEQ ID NOs: 908-913, (m) SEQ ID NOs: 916-921, (n) SEQ ID NOs: 924-929, (o) SEQ ID NOs: 932-937, (p) SEQ ID NOs: 940-945, (q) SEQ ID NOs: 948-953, (r) SEQ ID NOs: 956-961, (s) SEQ ID NOs: 964-969, (t) SEQ ID NOs: 972-977, (u) SEQ ID NOs: 980-985, (v) SEQ ID NOs: 988-993, (w) SEQ ID NOs: 996-1001, and (x) SEQ ID NOs: 1004-1009.

10. The heterodimeric antibody of claim 1, wherein the DKK1-binding portion comprises a set of six CDRs selected from the group consisting of SEQ ID NOs: 980-985 and SEQ ID NOs: 1004-1009.

11. The heterodimeric antibody of claim 1, wherein the second light chain comprises a variable region amino acid sequence selected from the group consisting of SEQ ID NO: 818, SEQ ID NO: 826, SEQ ID NO: 834, SEQ ID NO: 842, SEQ ID NO: 850, SEQ ID NO: 866, SEQ ID NO: 874, SEQ ID NO: 882, SEQ ID NO: 890, SEQ ID NO: 898, SEQ ID NO: 906, SEQ ID NO: 814, SEQ ID NO: 822, SEQ ID NO: 830, SEQ ID NO: 938, SEQ ID NO: 946, SEQ ID NO: 954, SEQ ID NO: 962, SEQ ID NO: 970, SEQ ID NO: 978, SEQ ID NO: 988, SEQ ID NO: 994 and SEQ ID NO: 1002.

12. The heterodimeric antibody of claim 1, wherein the second heavy chain comprises a variable region amino acid sequence selected from the group consisting of SEQ ID NO: 819, SEQ ID NO: 827, SEQ ID NO: 835, SEQ ID NO: 843, SEQ ID NO: 851, SEQ ID NO: 859, SEQ ID NO: 867, SEQ ID NO: 875, SEQ ID NO: 883, SEQ ID NO: 891, SEQ ID NO: 899, SEQ ID NO: 907, SEQ ID NO: 915, SEQ ID NO: 923, SEQ ID NO: 931, SEQ ID NO: 939, SEQ ID NO: 947, SEQ ID NO: 955, SEQ ID NO: 963, SEQ ID NO: 971, SEQ ID NO: 979, SEQ ID NO: 987, SEQ ID NO: 995 and SEQ ID NO: 1003.

13. A heterodimeric antibody that binds sclerostin and DKK-1, comprising

a first heavy chain comprising a variable region amino acid sequence selected from the group consisting of SEQ ID NOs: 378 and 366 and comprising amino acid substitutions at EU positions 183, 356 and 399 of the first heavy chain,

a second heavy chain comprising a variable region amino acid sequence selected from the group consisting of SEQ ID NOs: 1003 and 979 and comprising amino acid substitutions at EU positions 183, 392 and 409 of the second heavy chain,

a first light chain comprising a variable region amino acid sequence selected from the group consisting of SEQ ID NOs: 376 and 364 and comprising an amino acid substitution at EU position 176 of the first light chain, and

a second light chain comprising a variable region amino acid sequence selected from the group consisting of SEQ ID NOs: 1002 and 978 and comprising an amino acid substitution at EU position 176 of the second light chain;

wherein the amino acid substitutions introduce a charged amino acid at said positions.

14. A heterodimeric antibody that binds sclerostin and DKK-1, comprising

(a) a first heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1038; a second heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1034; a first light chain comprising the amino acid sequence set forth in SEQ ID NO: 1039 and a second light chain comprising the amino acid sequence set forth in SEQ ID NO: 1035;

(b) a first heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1038; a second heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1036; a first light chain comprising the amino acid sequence set forth in SEQ ID NO: 1039 and a second light chain comprising the amino acid sequence set forth in SEQ ID NO: 1037;

(c) a first heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1040; a second heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1034; a first light chain comprising the amino acid sequence set forth in SEQ ID NO: 1041 and a second light chain comprising the amino acid sequence set forth in SEQ ID NO: 1035;

(d) a first heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1040; a second heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1036; a first light chain comprising the amino acid sequence set forth in SEQ ID NO: 1041 and a second light chain comprising the amino acid sequence set forth in SEQ ID NO: 1037;

(e) a first heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1046; a second heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1042; a first light chain comprising the amino acid sequence set forth in SEQ ID NO: 1047 and a second light chain comprising the amino acid sequence set forth in SEQ ID NO: 1043;

(f) a first heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1046; a second heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1044; a first light chain comprising the amino acid sequence set forth in SEQ ID NO: 1047 and a second light chain comprising the amino acid sequence set forth in SEQ ID NO: 1045;

(g) a first heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1048; a second heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1042; a first light chain comprising the amino acid sequence set forth in SEQ ID NO: 1049 and a second light chain comprising the amino acid sequence set forth in SEQ ID NO: 1043; or

(h) a first heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1048; a second heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 1044; a first light chain comprising the amino acid sequence set forth in SEQ ID NO: 1049 and a second light chain comprising the amino acid sequence set forth in SEQ ID NO: 1045.

15. A heterodimeric antibody that binds sclerostin and DKK-1, comprising:

(a) a heavy chain that comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 1038, SEQ ID NO: 1046, SEQ ID NO: 1040 and SEQ ID NO: 1048, and a light chain amino acid sequence selected from the group consisting of SEQ ID NO: 1039, SEQ ID NO: 1047, SEQ ID NO: 1041 and SEQ ID NO: 1049; or

(b) a heavy chain that comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 1034, SEQ ID NO: 1042, SEQ ID NO: 1036 and SEQ ID NO: 1044, and a light chain amino acid sequence selected from the group consisting of SEQ ID NO: 1035, SEQ ID NO: 1043, SEQ ID NO: 1037 and SEQ ID NO: 1045.

16. The heterodimeric antibody of claim 1, that is an IgG immunoglobulin.

17. A nucleic acid comprising a nucleotide sequence encoding the heterodimeric antibody according to claim 1.

18. A vector comprising the nucleotide sequence of claim 17.

19. An isolated host cell comprising the nucleic acid of claim 17.

20. Use of heterodimeric antibody of any one of claim 1 and claims 4-15in the manufacture of a medicament for increasing bone mineral density in a mammalian subject in need of increased bone mineral density.

21. A composition comprising the antibody of any one of claims 4-15 and a pharmaceutically acceptable carrier, diluent or adjuvant.