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 aspect, 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).

[0011a] In another aspect, there is provided 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.

[0011b] In yet another aspect, there is provided a heterodimeric antibody that binds to a region of sclerostin comprising amino acids 86-111 of SEQ ID NO: 1, the antibody comprising 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.

[0012] In some ~~embodiments~~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

[0019] ~~In yet another aspect, described herein~~Also disclosed is a heterodimeric antibody that binds to a region of sclerostin comprising amino acids 86-111 of SEQ ID NO: 1, the antibody comprising 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.

[0020] ~~Another aspect of the invention relates to a~~Also disclosed is a heterodimeric antibody that binds sclerostin and DKK-1, comprising a first heavy chain comprising a heavy chain variable region amino acid sequence of any one of the sclerostin antibodies described herein and comprising amino acid substitutions at EU positions 183, 356 and 399 of the first heavy chain, a second heavy chain comprising a heavy chain variable region amino acid sequence of any one of the DKK-1 antibodies described herein and comprising amino acid substitutions at EU positions 183, 392 and 409 of the second heavy chain, a first light chain comprising a light chain variable region amino acid sequence of any one of the sclerostin antibodies described herein and comprising an amino acid substitution at EU position 176 of the first light chain, and a second light chain comprising a light chain variable region amino acid sequence of any of the DKK-1 antibodies described herein 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.

[0021] Another aspect of the invention relates to 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 974 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

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).

[0033a] Thus, in another aspects, 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 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.

[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 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.

[0037] ~~Another aspect of the invention relates to~~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 invention 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 aspect, 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

71. The heterodimeric antibody of any one of claims 1-70, that is an IgG immunoglobulin.

72. A nucleic acid comprising a nucleotide sequence encoding the heterodimeric antibody according to any one of claims 1-71.

73. A vector comprising the nucleotide sequence of claim 72.

74. An isolated host cell comprising the nucleic acid of claim 72 or the vector of claim 73.

75. ~~A method of increasing bone mineral density in a mammalian subject comprising administering the~~ Use of heterodimeric antibody of any one of claims 1-71 in the manufacture of a medicament for increasing bone mineral density in a mammalian subject. ~~to the subject in an amount effective to increase bone mineral density in the subject.~~

76. A composition comprising the antibody of any one of claims 1-71 and a pharmaceutically acceptable carrier, diluent or adjuvant.

77. The composition according to claim 76, wherein less than 5% of the antibody in the composition is in aggregate form after two weeks of storage at about 4°C.

78. The composition according to claim 76, wherein less than 1% of the antibody in the composition is in aggregate form after two weeks of storage at about 4°C.

79. The composition according to claim 77 or claim 78, wherein an amount of antibody in the composition present in aggregate form in determined by Size Exclusion Chromatography.

88. 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 charged amino acids that are electrostatically unfavorable to homodimer formation and electrostatically favorable to heterodimer formation;

wherein less than 5% of the antibody or fragment in the composition is in aggregate form after two weeks of storage at about 4°C.