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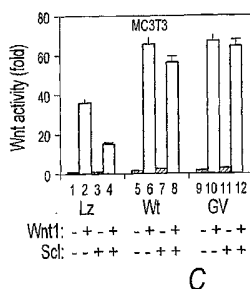
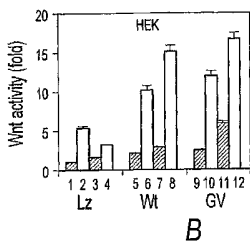
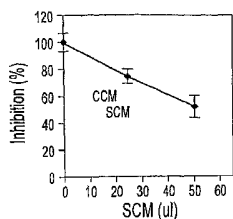
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(54) Title: SCLEROSTIN AND THE INHIBITION OF WNT SIGNALING AND BONE FORMATION



(57) Abstract: The loss of the SOST gene product sclerostin leads to sclerosteosis characterized by high bone mass (HBM). In this report, we found that sclerostin could antagonize canonical, Wnt signaling in human embryonic kidney A293 cells and mouse osteoblastic MC3T3 cells. This sclerostin-mediated antagonism could be reversed by over-expression of Wnt coreceptor LRP5. In addition, we found that sclerostin bound to LRP5 as well as LRP6 and identified the first two YWTD-EGF repeat domains of LRP5 as being responsible for the binding. Although these two repeat domains are required for transducing canonical Wnt signals, canonical Wnt did not appear to compete with sclerostin for binding to LRP5. Examination of the expression of sclerostin and Wnt7b, an autoocrine canonical Wnt, during primary calvarial osteoblast differentiation revealed that sclerostin is expressed at the late stages of osteoblast differentiation coinciding with the expression of osteogenic marker osteocalcin and trailing after the expression of Wnt7b. Given the plethora of evidence indicating that canonical Wnt signaling stimulates osteogenesis, we believe that the HBM phenotype associated with the loss of sclerostin may at least in part be attributed to an increase in canonical Wnt signaling resulting from the reduction in sclerostin-mediated Wnt antagonism.

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SCLEROSTIN AND THE INHIBITION OF WNT SIGNALING AND BONE FORMATIONREFERENCE TO RELATED PATENT APPLICATIONS

This application is a continuation-in-part of the patent application entitled "Compositions and Methods for Bone Formation and Remodeling," Application No. 10/849,067, filed on May 19, 2004. This application is also related to the patent application entitled "Compositions and Methods for the Stimulation or Enhancement of Bone Formation and the Self-Renewal of Cells," Application No. 10/849,643, filed on May 19, 2004, and its contents is hereby incorporated by reference, in its entirety.

FIELD OF THE INVENTION

The present invention relates to the protein sclerostin, an antagonist and/or inhibitor of Wnt proteins. Sclerostin inhibits Wnt signaling and thus the formation of bone when it binds to the LRP5 receptor or the LRP6 receptor (LRP5/6). The invention relates to the field of therapeutic methods, compositions and uses thereof, in the treatment of bone fractures, bone disease, bone injury, bone abnormality, tumors, or growths. More particularly, the compositions and methods are directed to compounds that block sclerostin, thereby allowing bone formation to occur. The compounds were identified from a National Cancer Institute (NCI) database through various screening methods and assays. These compounds could also be modified to create derivatives or analogues not found in the NCI database or in nature which also function effectively.

All patents, patent applications, patent publications, scientific articles, and the like, cited or identified in this application are hereby incorporated by reference in their entirety in order to describe more fully the state of the art to which the invention pertains.

BACKGROUND OF THE INVENTION

The Wnt family of secretory glycoproteins is one of the major families of developmentally important signaling molecules which play important roles in embryonic induction, generation of cell polarity, and specification of cell fate. Both genetic and biochemical studies indicate that frizzled (Fz) and LRP5/6 are co-receptors for transducing canonical Wnt signaling that eventually leads to the stabilization of β -catenin and regulation of gene transcription through transcription regulators including lymphoid enhancing factor-1 (LEF-1) and T cell factors (TCF). Wnt signaling is also regulated by a number of naturally occurring antagonists that include Dickkopf (Dkk) molecules. The first Dkk (*Xenopus* Dkk-1), was initially discovered as a Wnt antagonist that plays an important role in head formation. To date, four members of Dkk have been identified in mammals. However, only the first two members (Dkk1 and Dkk2) have been well documented to function as antagonists of canonical Wnt signaling. Both Dkk1 and Dkk2 antagonize canonical Wnt signaling by simultaneously binding to LRP5/6 and a single transmembrane protein called Kremen. It has been further demonstrated that the second, but not the first, Cys-rich domains of Dkk1 and Dkk2 inhibit canonical Wnt signaling.

A myriad of evidence demonstrates that an increase in LRP5/6-mediated canonical Wnt signaling leads to an increase in bone mass. Loss-of-function mutations in LRP5 are responsible for human osteoporosis-pseudoglioma syndrome (OPPG), an autosomal recessive disorder, while putative gain of function mutations, including the Gly171 to Val substitution, are associated with human high bone mass (HBM) phenotypes. In addition, mice in which the LRP5 gene was inactivated by gene targeting showed phenotypes similar to those of OPPG patients, and the transgenic expression of LRP5_{G171V} in mice resulted in HBM. Moreover, mouse primary osteoblasts showed reduced responsiveness to Wnt and low proliferation indices in the absence of LRP5, and canonical Wnts or activated β -catenin stimulated the canonical Wnt signaling activity and induced the production of an osteoblast marker alkaline phosphatase (AP) in osteoblast-like cells. The finding that inactivation of the Wnt antagonist sFRP1 enhances trabecular bone accrual further supports the idea that canonical Wnt signaling enhances bone formation. Dkk1 is expressed in differentiated osteoblast cells and osteocytes and the G171V

mutation in LRP5 may cause the HBM phenotype by attenuating the antagonistic effect of Dkk1 on canonical Wnt signaling.

Itasaki et al. described a new Wnt antagonist called WISE. WISE appears to be a context-dependent regulator of Wnt signaling; it may inhibit or stimulate Wnt signaling in different assays in *Xenopus*. WISE was also shown to bind to LRP6 and compete with Wnt8 for binding to LRP6. WISE shares 38% amino acid identity with sclerostin, the gene product of SOST. Loss of function mutations of SOST are responsible for an autosomal recessive sclerostin skeletal disorder. Previous studies have shown that sclerostin was highly expressed in osteocytes and that it might act as a bone morphogenetic protein (BMP) antagonist, but another study suggested that sclerostin might not be a functional BMP antagonist and speculated that it might modulate Wnt signaling. In this report, we now clearly demonstrate that sclerostin can bind to both LRP5 and LRP6 and act as a Wnt antagonist. Because sclerostin expression occurs after peak Wnt7b expression during the osteogenic differentiation, the reduction in sclerostin-mediated antagonism of Wnt signaling contributes to the increases in bone mass associated with SOST.

SUMMARY OF THE INVENTION

The present invention is directed to methods and compositions that address several problems related to bone remodeling, such as osteoporosis and other bone diseases. The invention also provides for the use of compositions to aid in the healing of fractures or other injuries or abnormalities of bone. In particular, the invention provides a process for promoting bone formation in a mammalian subject comprising administering to the subject an effective amount of compounds which prevent the binding of sclerostin.

The invention further provides for gene therapy methodologies for clinical conditions characterized by insufficient bone formation comprising administering an effective amount of a compound that prevents sclerostin binding, or by causing a decrease in the expression of sclerostin.

In other aspects of the invention, gene expression, detection and quantification of sclerostin or related proteins serve as potential diagnostic methods for a variety of bone diseases.

The present invention is also directed to methods and compositions that address tumors or other bone growths.

The present invention has identified compounds which, when provided to a cell, bind to, interact with, or fit into sites or cavities found on the domains of the co-receptors involved in the stimulation, enhancement, inhibition or regulation of bone formation, or bone remodeling. These receptors include the LRP5 receptor, the LRP6 receptor, the frizzled receptor or any other receptor involved in the LRP5 or LRP6 (LRP5/6) receptor system.

The compounds were identified using screening methods described in Patent Application No. 10/849,067. These compounds were found to disrupt the sclerostin and LRP5/6 interaction. Other compounds inhibited Wnt signaling by inhibiting the binding of Wnt to LRP5/6. The compounds of the present invention are non-native, or exogenous compounds which are not present in the cell, but originate from an outside source. Specifically, the compounds identified as IIC3 (NCI8642) and IIC8 (NCI366218) were found to disrupt the

sclerostin and LRP5/6 interaction. As shown on Figure 5, the binding of sclerostin-AP (a fusion protein of sclerostin and alkaline phosphatase) to LRP5 decreased when either 111C3 or 11C8 was added. The compounds bind to LRP5/6, and therefore prevent sclerostin from binding, blocking Wnt and probably inhibiting bone formation.

DETAILED DESCRIPTION OF THE INVENTION

Because of the homology shared between WISE and sclerostin, experiments were carried out to determine whether sclerostin would exert an effect on canonical Wnt signaling. The effect of conditioned medium (CM) containing mouse sclerostin on Wnt3a-induced activation of canonical Wnt signaling was determined using the LEF-1-based reporter gene assay in human embryonic kidney (HEK) cells. Sclerostin-containing CM showed marked inhibition of Wnt3a activity in a dose-dependent manner (Fig. 1A). Because control CM started to show significant inhibition at 50 micro-liters, higher doses were not tested. To further confirm this effect of sclerostin, sclerostin and another canonical Wnt, Wnt1, were coexpressed in HEK cells, and sclerostin showed up to 60% inhibition of the activity of coexpressed Wnt-1 (Fig. 1B, bars 2&4). Interestingly, coexpression of LRP5 abolished the antagonistic effect of sclerostin on Wnt signaling, and a slight stimulation of Wnt1 signaling by sclerostin was even observed in the presence of coexpressed LRP5 (Fig. 1B, bars 6&8). The effect of sclerostin on Wnt signaling in an osteoblastic cell line MC3T3 was also examined. Expression of sclerostin also showed up to 70% inhibition of Wnt-1 activated reporter gene activity in MC3T3 cells (Fig. 1C, bars 2&4). Once again, expression of LRP5 reversed the inhibition (Fig. 1C, bars 6&8). However, there was no increase in Wnt1 activity in MC3T3 cells when sclerostin and LRP5 were expressed with Wnt (Fig. 1C). Nevertheless, all these results clearly demonstrate that sclerostin antagonizes canonical Wnt activity activated by canonical Wnts when LRP5 is expressed at endogenous levels.

To understand how sclerostin antagonizes canonical signaling, experiments were carried out to determine if sclerostin binds to LRP5/6 directly. The binding of sclerostin-alkaline phosphatase (AP) fusion protein to cells expressing exogenous LRP5 or LRP6 were measured, with the same methods used for Dkk1-AP. As shown in Fig. 2A, sclerostin-AP showed a LRP6-binding curve similar to Dkk1-AP, suggesting that sclerostin-AP has an affinity for LRP6 comparable to that of Dkk1-AP, which was previously determined to be sub-nanomolar. The binding of sclerostin-AP and Dkk1-AP to LRP5-expressing cells revealed that sclerostin-AP and Dkk1-AP also have similar affinities for LRP5 (Fig. 2B). To delineate which regions of LRP5 are responsible for the binding of sclerostin-AP, we measured the binding of sclerostin-AP to two LRP5 mutants that lack either the first or last two YWTD-EGF repeat domains. These

mutants are designated as LRP5R12 or LRP5R34, respectively (Fig. 2E). While Dkk1-AP was capable of binding to both LRP5 mutants (Fig. 2D), sclerostin-AP could only bind to LRP5R12, but not LRP5R34 (Fig. 2C).

We have previously shown that LRP5R12 was still able to transduce Wnt signaling, suggesting that this LRP5 mutant may still retain the Wnt-binding sequences. To determine if sclerostin and Wnt compete with each other for the binding to LRP5R12, the binding of sclerostin-AP to cells expressing LRP5R12 in the presence or absence of Wnt3a CM was measured. The presence of Wnt3a did not affect the binding of sclerostin-AP to LRP5R12 at all (Fig. 3A). In contrast, the presence of Dkk1 completely blocked the binding of sclerostin-AP to LRP5R12 (Fig. 3B). In an attempt to further delineate sclerostin binding sequences on LRP5, two additional LRP5 mutants were constructed, which lack the second to fourth YWTD-EGF repeat domains and the first, third, and fourth YWTD-EGF repeat domains, respectively. However, these two LRP5 mutants did not bind to either sclerostin-AP or Dkk1-AP, nor did they transduce Wnt signaling. These results suggest that, either both first and second YWTD-EGF repeat domains are required for the binding of sclerostin to LRP5 or these LRP5 mutants were incorrectly folded.

Several LRP5 mutations in the first YWTD-EGF repeat domain have been found to be associated with HBM. We have previously characterized one of the mutations, G171V, and found that this mutation interfered with the interaction of LRP5 with its chaperon Mesd, resulting in poor transportation of LRP5 to cell surfaces. Because this LRP5 mutant was still able to transduce signals intracellularly for autocrine Wnts, it was thought that the mutation may increase Wnt signaling by retaining the LRP5 receptor inside the cells from extracellular antagonists such as Dkk1 because Dkk1 is highly expressed in osteocytes. The finding of sclerostin as a new Wnt antagonist, which is known to be expressed in the bone and osteocytes, may provide alternative explanations for the effects of the G171V mutation, which is located in the first YWTD-EGF repeat domain and within the sclerostin-binding region. One of such explanations may be that the G171V mutation directly interferes with the binding of LRP5 to sclerostin. To test this possibility, we measured and compared the binding of sclerostin-AP to LRP5G171V with that of Dkk1-AP. As we have previously shown, cells expressing LRP5GV have a five-fold lower apparent binding to Dkk1-AP than cells expressing wildtype LRP5 (Fig.

3C) due to the interference of the chaperon's function by the mutation. Similarly, cells expressing LRP5GV also showed a reduction in the binding of sclerostin-AP to the same degree (Fig. 3B). As the G171V mutation does not directly interfere with the interaction between LRP5 and Dkk1, it is also unlikely that the mutation interferes with the interaction between LRP5 and sclerostin. The observation that LRP5GV could still reverse sclerostin-mediated inhibition of Wnt activity in the same dose range as the wildtype LRP5 (Fig. 1B,C) provides further support for the idea that the G171V mutation does not interfere with the interaction between LRP5, or LRP6 and Dkk1.

Sclerostin has been previously shown to be primarily expressed in osteocytes. We examined sclerostin expression in relation to Wnt7B expression during primary calvarial osteoblast differentiation. We previously identified Wnt7b, a canonical Wnt that can stabilize β -catenin, as the only Wnt that showed drastic changes in its expression levels during primary bone marrow osteoblast differentiation. Similarly, the expression levels of Wnt7b showed drastic changes during calvarial osteoblast differentiation; the expression of Wnt 7b peaks at Day 8 and then receded to lower levels, preceding the expression of osteogenic marker osteocalcin and another Wnt antagonist Dkk1 (Fig. 4A). *In situ* hybridization further confirms the conclusion on Wnt 7b expression in that Wnt7b mRNA was detected primarily in early undifferentiated osteoblasts in a mouse long bone (Fig. 4B). The expression of sclerostin showed a similar time course to that of osteocalcin and only occurred at the late stages of the differentiation when presumably osteocytes are forming in the mineralized matrix (Fig. 4A). This pattern of sclerostin expression is consistent with previous *in vivo* observations that sclerostin is expressed in osteocytes buried in the bone matrix and may play a role in mechanical loading. On the basis of the expression patterns of sclerostin and Wnt7b, we postulate that sclerostin contributes to the G171V-associated HBM phenotype even though sclerostin may not directly interfere with Wnt binding or the mutation does not affect sclerostin binding to LRP5. As suggested by our hypothesis that the G171V mutation may hide the receptor from paracrine antagonists without diminishing the signaling ability of the mutant receptor for autocrine Wnt, sclerostin, which is only produced by well differentiated osteoblasts or osteocytes, would be one of such paracrine antagonists that conceivably has less access to LRP5G171V than the wildtype LRP5. Thus, the G171V mutation may increase Wnt activity by attenuating the antagonism of canonical Wnt signaling by not only Dkk1, but also sclerostin and potentially other paracrine Wnt antagonists

present in the bone.

In previous studies, sclerostin was shown to act as a BMP antagonist. It is convincing that sclerostin has a reasonably high affinity for BMP6 and BMP7. However, the biological effects of sclerostin on BMP was merely determined by measuring BMP-induced alkaline phosphatase (AP) activity 3-6 days post ligand addition in osteoblastic cells. This AP activity readout is not specific for BMP activity. In fact, canonical Wnts can also stimulate AP activity in these types of cells. In contrast, our Wnt reporter gene assay is specific for canonical Wnt and cannot be activated by BMP in HEK cells (data not shown). In addition, in the assay using CM, we measured the effect of sclerostin in 6 hours (Fig. 1A). Given the recent observations that sclerostin failed to inhibit early responses elicited by BMP, we believe that it is more likely that sclerostin is biologically a canonical Wnt antagonist and that its effects on bone mass is probably primarily attributed to its antagonistic effect on canonical Wnt signaling.

As shown in Fig. 2, sclerostin binds to the first two YWTD-EGF repeat domains of LRP5, which are also required for transducing Wnt signals. However, our evidence suggests that the antagonistic effect of sclerostin is unlikely due to direct competition with Wnt for LRP binding, because 1) Wnt3a failed to inhibit the binding of sclerostin-AP to LRP5; and 2) LRP5 could reverse the inhibitory effect of sclerostin on canonical Wnt signaling. The latter observation is reminiscent of the effect of Dkk1 on Wnt signaling as Dkk1 suppression of Wnt signaling can also be reversed by exogenous expression of LRP5/6. The reason for the ability of LRP5/6 molecules to reverse Dkk's effects is because Dkk-mediated antagonism requires another protein Kremen. When Kremen is coexpressed with LRP5/6, Dkk-mediated inhibition could be restored. Although Kremen had no effect on sclerostin-mediated antagonism, we suspect that a similar mechanism may be used by sclerostin to inhibit Wnt signaling. In other words, there may be accessory proteins like Kremen that may be required for sclerostin to function efficiently as an antagonist. Recently, noggin has been shown to directly interact with sclerostin and inhibit noggin's capacity to inhibit BMP signaling. Thus, noggin, once bound to sclerostin, might inhibit sclerostin capacity to modulate Wnt signaling. In addition, the observation that sclerostin showed slight stimulation of the LEF-1 reporter gene activity in the presence of exogenous LRP5 or LRP5GV suggests that sclerostin may be a partial agonist under certain circumstances, even in mammalian systems.

The present invention provides methods for promoting or regulating bone formation or bone remodeling comprising administering at least one non-native compound, a fragment of a non-native compound, or any combination thereof. A non-native compound is defined as a compound that is not naturally found in a mammalian subject, a human body in particular. A non-native compound may also comprise an artificially manufactured compound that is identical to a compound that is naturally found in the human body. When the non-native compound or compounds bind to a receptor or co-receptor involved in bone formation or bone remodeling, the binding of sclerostin is prevented, thereby allowing bone to form.

Two or more non-native compounds may join together directly through cross-linking, for example, or indirectly through a linker arm. Each of these linked compounds may dock in different locations on the same binding site, protein or receptor. Each of these linked compounds may also dock in different locations on different binding sites, proteins or receptors.

The compounds or fragments of compounds may be a small molecule, protein, peptide, polypeptide, cyclic molecule, heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein or chemical. The compounds or fragments may also be agonists, antagonists, partial agonists, or any combination of the aforesaid.

The compound may be administered by inhalation, orally, intravenously, intraperitoneally, intramuscularly, parenterally, transdermally, intravaginally, intranasally, mucosally, sublingually, topically, rectally or subcutaneously.

The present invention also provides a method for identifying a compound or drug candidate that will bind to a signal peptide or protein involved in protein-protein interactions, to inhibit or promote the occurrence of subsequent events. Specifically, the compound or drug candidate will bind to the receptor protein to inhibit or promote bone formation or bone remodeling. The first step involves determining the virtual or computational structure of the receptor protein through the use of various methods such as amino acid sequencing, X-ray crystallography, NMR, analogs or derivatives of the receptor protein, or any combination of the

aforesaid methods. In a preferred embodiment, the protein is non-soluble or membrane-bound.

The next step involves identifying a particular binding cavity site or domain on the receptor protein through the use of experiments based on biological function comprising mutational analysis, chemical modifications (of amino acids, for example), co-crystallography, NMR or any combination of the aforesaid methods. Using the results obtained from these experiments, such as mutations and chemical modifications, a specific binding site or domain is identified within the binding cavity to which the compound or drug candidate will bind. The entire binding cavity or a specific binding site within the cavity may be used to screen for a compound that fits and binds. The screening is conducted using the UNITY™ program. The docking of the compound into the cavity is carried out through the use of the Flexx™ program. The compound with the highest binding affinity or the lowest binding energy using the Cscore™ program is then selected. The ultimate goal is to select a compound or drug candidate with the best fit.

A preferred embodiment of the invention is a method for preventing or blocking bone formation in a mammalian subject by administering sclerostin.

Another preferred embodiment of the present invention is a method for the treatment of abnormal bone growth comprising administering an antibody for sclerostin, or any other compound or fragment of a compound which decreases or eliminates sclerostin, or decreases or eliminates the affinity of sclerostin to a receptor or co-receptor involved in bone formation or bone remodeling.

MATERIALS AND METHODS

Cell culture, transfection, preparation of CM, and luciferase assay.

Human embryonic kidney cell (HEK) line A293T and mouse osteoblastic cell line MC3T3 were maintained and transfected as previously described. For luciferase assays, cells in 24-well plates were seeded at 5×10^4 cells/well and transfected with 0.5 μg DNA/well using Lipofectamine Plus (Invitrogen, CA), as suggested by the manufacturer. The LacZ plasmid was usually used to make DNA concentrations equal for each transfection. Cell extracts were collected 24 hr after transfection. Luciferase assays were performed as previously described. Luminescence intensity was normalized against fluorescence intensity of GFP. For preparation of DKK1-AP and sclerostin-AP containing CM, HEK cells were seeded in 6 well-plates at 4×10^5 cells/well and transfected with 1 μg DNA/well. CMs were collected 48 hr after transfection.

Construction of expression plasmids and mutagenesis.

The wild-type and mutant forms of human LRP5, LRP6, mouse Wnt1, DKK1, sclerostin, and DKK-2 were generated by PCR using the high fidelity thermostable DNA polymerase *Pfu Ultra* (Stratagene, CA). nucleotide sequences were verified by DNA sequencing. HA or Flag epitope tags were introduced to the C-termini of the full-length and mutant molecules. The expression of these molecules was driven by a CMV promoter. The LEF-1 reporter gene constructs were kindly provided by Dr. Grosschedl.

DKK1-AP and sclerostin-AP binding assay.

HEK cells in 24-well plates were transfected with LRP5 and its mutants. One day later, cells were washed with cold washing buffer (HBBS containing BSA and NaN_3) and incubated with mouse DKK1-AP or sclerostin-AP CM on ice for two hours. Then, cells were washed three times with the washing buffer and lysed. The lysates were heated at 65°C for 10 min, and its AP activity was determined using a Tropix luminescence AP assay kit. The immunoprecipitation assays were carried out essentially as previously described.

Primary calvarial osteoblast culture.

Mouse calvarial osteoblast cultures from 5 day old mice were generated as previously described and were induced to undergo osteogenic differentiation in the presence of 8mM β -Glycerophosphate, and 50ug/ml ascorbic acid. Media were changed every two days.

Quantitative PCR analysis.

Total RNA was isolated using the TRIzol reagent (Invitrogen) according to manufacturer's instructions. For QPCR analysis, RNA was reverse-transcribed by SuperScriptTM First-Strand Synthesis System for RT-PCR (Invitrogen). QPCR was carried out using QuantiTectTM SYBR Green PCR kit (Qiagen) on a DNA Engine OPTICONTM (MJ Research Inc.) instrument. B-actin was used as an internal reference for each sample. Using a formula previously described, the relative change in mRNA levels was normalized against the β -actin mRNA levels.

***In situ* hybridization.**

The full-length coding region of Wnt7b was used to synthesize anti-sense and sense probes. The probes were labeled with Digoxigenin using an RNA Labeling Kit (Roche, Indianapolis, IN, USA). Sections of the tibia from a 3-weeks old mouse were dewaxed, rehydrated and fixed again with 4% paraformaldehyde. Then the sections were treated with 2% glycine and Proteinase-K and acetylated using an acetic anhydride/TEA solution, followed by hybridization with a digoxigenin-labelled probe. After washing the sections with 50% formamide, 5XSSC, 5% SDS for 30 minutes at 70 °C twice and 50% formamide, 2XSSC for 30 minutes at 65 °C, the sections were incubated with anti-digoxigenin-alkaline phosphatase antibody followed by Nitro Blue etrazolium/4-bromo-5-chloro indolylphosphate, which yields a purple blue color. The sections were also counterstained with methyl green (nuclei) and orange G (cytoplasm).

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Sclerostin antagonizes canonical Wnt signaling.

A) Effects of sclerostin CM on Wnt3a CM. Wnt3a CM (25 ul) were mixed with varying amounts of Sclerostin CM (SCM) or control CM (CCM) and added to HEK cells transfected with the LEF-1 reporter gene. Six hours later, cells were lysed, and luciferase activity was determined. The activity in the absence of SCM is taken as 100%. Wnt3a CM increased reporter gene activity by 5 folds. Expression of Flag tagged sclerostin was detected by an anti-Flag antibody (insert). B,C) Effects of coexpressed sclerostin on Wnt1 signaling in HEK (B) and MC3T3 (C) cells. Cells were transfected with cDNAs encoding Wnt1, Sclerostin (Scl), wildtype LRP5 (Wt), or G171V LRP5 (GV) as indicated in the figure and the LEF-1 reporter gene and a GFP expression plasmid. One day later, cells were lysed, and the GFP levels and luciferase activities were determined and normalized against GFP levels.

Figure 2. Binding of sclerostin-AP to LRP5 and its mutants.

A,B) Binding of Dkk1-AP and sclerostin-AP to full length LRP6, LRP5 or LacZ. HEK cells were transfected with the full-length LRP6 (A) or LRP5 (B). Binding of Dkk1-AP or sclerostin-AP (Scl) was determined as described in the Method. Binding to cells transfected with control plasmid LacZ was subtracted as non-specific binding. Specific binding is presented in the charts. B,C) Binding of Dkk1-AP and sclerostin-AP to LRP5 mutants. HEK cells were transfected with LacZ or LRP5 mutants as indicated. Binding of sclerostin-AP (C) and Dkk1-AP (D) was determined. (E) Schematic representation of LRP5 mutants.

Figure 3. Effects of Wnt3a, Dkk1, and LRP5 mutation on sclerostin binding.

A) HEK cells were transfected with LRP5. Binding of sclerostin-AP (5 ul) was determined in the presence of control CM (CCM) or Wnt3a CM (WCM, 100 ul). B) HEK cells were transfected with LRP5R12. Binding of sclerostin-AP (50 ul) was determined in the presence of buffer or recombinant Dkk1 (10 nM). C) HEK cells were transfected with LRP5 (black bars) or LRP5G171V (white bars). Binding of Dkk1-AP (Dkk) or Sclerostin-AP (Scl) was determined. In all these binding assays, binding to cells transfected with control plasmid LacZ was subtracted

as non-specific binding. Specific binding is presented in the charts.

Figure 4. Expression of Wnt7b, sclerostin, Dkk1, and osteocalcin.

A) Primary calvarial osteoblast cultures were established from 5 days old mice. Differentiation inducers were added on day 5. Relative expression levels of Wnt7b, sclerostin (scl), osteocalcin (OC), and Dkk1 were determined by QRT-PCR as described in the Methods. B) Expression of Wnt7b in a mouse long was examined using *in situ* hybridization. Wnt7b (dark stain) is primarily detected in osteoblasts. Nuclei are counterstained in green.

Figure 5. Effect of IIC3 and IIC8 on the binding of sclerostin-AP to LRP5.

A) The inhibition of bone formation was inversely related to the amount of IIC3 present. The greater the amount of IIC3 added, the lower the percentage of the inhibition of bone formation. B) The greater the amount of IIC8 added, the lower the percentage of the inhibition of bone formation.

CLAIMS

1. A method for promoting bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that prevents the binding of sclerostin to a receptor or co-receptor involved in bone formation or bone remodeling.
2. A method for promoting bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that prevents the binding of sclerostin to the LRP5 or LRP6 receptor.
3. A method for promoting bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that prevents the binding of sclerostin to a homologue of the LRP5 or LRP6 receptor.
4. A method for promoting bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that prevents the binding of sclerostin to at least one domain of the LRP5 or LRP6 receptor.
5. A method for promoting bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that prevents the binding of sclerostin to the first or second domain of the LRP5 or LRP6 receptor.
6. The method of claims 1 to 5 wherein said compound or said fragment of a compound comprises IIC3 or IIC8.
7. The method of claims 1 to 5 wherein said compound or said fragment of a compound comprises IIC3, IIC8, or any derivative or analog thereof.
8. The method of claims 6 or 7 wherein said two or more compounds, or said fragments of compounds are directly linked together with cross-linking, or indirectly linked together with a linker arm.
9. The method of claim 8 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on the same binding site, receptor or protein.
10. The method of claim 8 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on different binding sites, receptors or proteins.
11. The method of claims 1 to 5 wherein said compounds, or said fragments of a compound, are linked together with a linker arm or cross-linking.

12. The method of claims 1 to 11 wherein said compound or said fragment of a compound comprises a small molecule, protein, peptide, polypeptide, cyclic molecule, heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, chemical, or a fragment of a compound that comprises a heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, or chemical.
13. The method of claims 1 to 5 wherein said administering step comprises administration by inhalation, oral, intravenous, intraperitoneal, intramuscular, parenteral, transdermal, intravaginal, intranasal, mucosal, sublingual, topical, rectal, or subcutaneous administration, or any combination thereof.
14. The method of claims 1 to 12 wherein said compound or said fragment of a compound comprises at least one agonist, antagonist, partial agonist, or any combination thereof.
15. The method of claims 1 to 14 wherein said compound is identified using a method comprising:
 - a. screening for a compound that fits into the cavity on the receptor using the UNITY™ program;
 - b. docking said compound into the cavity using the Flexx™ program; and
 - c. obtaining the compound with the highest binding affinity using the Cscore™ program.
16. A method for the treatment of a bone fracture, bone disease, bone injury, or bone abnormality in a mammalian subject comprising administering at least one non-native compound, at least one fragment of a non-native compound or any combination thereof, that prevents the binding of sclerostin to a receptor or co-receptor involved in bone formation or bone remodeling.
17. A method for the treatment of a bone fracture, bone disease, bone injury, or bone abnormality in a mammalian subject comprising administering at least one non-native compound, at least one fragment of a non-native compound or any combination thereof, that prevents the binding of sclerostin to the LRP5 or LRP6 receptor.
18. A method for the treatment of a bone fracture, bone disease, bone injury, or bone abnormality in a mammalian subject comprising administering at least one non-native compound, at least one fragment of a non-native compound or any combination thereof, that prevents the binding of sclerostin to a homologue of the LRP5 or LRP6 receptor.
19. The method of claims 16 to 18 wherein said compound comprises IIC3 or IIC8.
20. The method of claims 16 to 18 wherein said compound or said fragment of a compound comprises IIC3 or IIC8
21. The method of claims 19 or 20 wherein said two or more compounds or said fragments of compounds are directly linked together with cross-linking, or indirectly linked together with a linker arm.

22. The method of claim 21 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on the same binding site, receptor or protein.
23. The method of claim 21 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on different binding sites, receptors or proteins.
24. The method of claims 16 to 18 wherein said compounds, or said fragments of a compound, are linked together with a linker arm or cross-linking.
25. The method of claims 16 to 24 wherein said compound or said fragment of a compound comprises a small molecule, protein, peptide, polypeptide, cyclic molecule, heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, chemical, or a fragment of a compound that comprises a heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, or chemical.
26. The method of claims 16 to 18 wherein said administering step comprises administration by inhalation, oral, intravenous, intraperitoneal, intramuscular, parenteral, transdermal, intravaginal, intranasal, mucosal, sublingual, topical, rectal, or subcutaneous administration, or any combination thereof.
27. The method of claims 16 to 25 wherein said compound or said fragment of a compound comprises at least one agonist, antagonist, partial agonist, or any combination thereof.
28. The method of claims 16 to 27 wherein said compound is identified using a method comprising:
 - a. screening for a compound that fits into the cavity on the receptor using the UNITYTM program;
 - b. docking said compound into the cavity using the FlexxTM program; and
 - c. obtaining the compound with the highest binding affinity using the CscoreTM program.
29. A therapeutic composition for the treatment of a bone fracture, bone disease, bone injury or bone abnormality in a mammalian subject comprising at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that prevents the binding of sclerostin to a receptor or co-receptor in bone formation or bone remodeling.
30. A therapeutic composition for the treatment of a bone fracture, bone disease, bone injury or bone abnormality in a mammalian subject comprising at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that prevents the binding of sclerostin to the LRP5 or LRP6 receptor.
31. A therapeutic composition for the treatment of a bone fracture, bone disease, bone injury

- or bone abnormality in a mammalian subject comprising at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that prevents the binding of sclerostin to a homologue of the LRP5 or LRP6 receptor.
32. The composition of claims 29 to 30 wherein said compound or said fragment of a compound comprises IIC3 or IIC8 .
 33. The composition of claims 29 to 31 wherein said compound or said fragment of a compound comprises IIC3 or IIC8, or any derivative or analog thereof.
 34. The composition of claim 32 or 33 wherein said two or more compounds or fragments of compounds are directly linked together with cross-linking, or indirectly linked together with a linker arm.
 35. The method of claim 34 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on the same binding site, receptor or protein.
 36. The composition of claim 34 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on different binding sites receptors or proteins.
 37. The composition of claims 29 to 31 wherein said compounds, or said fragments of a compound, are linked together with a linker arm or cross-linking.
 38. The composition of claims 29 to 37 wherein said compound or said fragment of a compound comprises a small molecule, protein, peptide, polypeptide, cyclic molecule, heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, chemical, or a fragment of a compound that comprises a heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, or chemical.
 39. The composition of claims 29 to 31 wherein said administering step comprises administration by inhalation, oral, intravenous, intraperitoneal, intramuscular, parenteral, transdermal, intravaginal, intranasal, mucosal, sublingual, topical, rectal, or subcutaneous administration, or any combination thereof.
 40. The composition of claims 29 to 38 wherein said compound or said fragment of a compound comprises at least one agonist, antagonist, partial agonist, or any combination thereof.
 41. The composition of claims 29 to 40 wherein said non-native compound is identified using a method comprising:
 - a. screening for a compound that fits into the cavity on the receptor using the UNITYTM program;
 - b. docking said compound into the cavity using the FlexxTM program; and
 - c. obtaining the compound with the highest binding affinity using the CscoreTM

program.

42. The composition of claims 29 to 41 wherein said composition further comprises a pharmaceutically acceptable carrier.
43. The composition of claims 29 to 41 wherein said composition is formulated as a tablet, pill, dragee, liquid, gel, capsule, syrup, slurry or suspension.
44. A method for the regulation of bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound or any combination thereof, that disrupts the interaction of sclerostin with a receptor or co-receptor involved in bone formation or bone remodeling.
45. A method for the regulation of bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that disrupts the interaction of sclerostin with the LRP5 or LRP6 receptor.
46. A method for the regulation of bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that disrupts the interaction of sclerostin with a homologue of the LRP5 or LRP6 receptor.
47. A method for the regulation of bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that disrupts the interaction of sclerostin with at least one domain of the LRP5 or LRP6 receptor.
48. A method for the regulation of bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that disrupts the interaction of sclerostin with the first or second domain of the LRP5 or LRP6 receptor.
49. The method of claims 44 to 48 wherein said compound or said fragment of a compound comprises IIC3 or IIC8.
50. The method of claims 44 to 48 wherein said compound or said fragment of a compound comprises IIC3, or IIC8, or any derivative or analog thereof.
51. The method of claims 49 or 50 wherein said two or more compounds or said fragments of compounds are directly linked together with cross-linking, or indirectly linked together with a linker arm.
52. The method of claim 51 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on the same binding site, receptor or protein.
53. The method of claim 51 wherein said compounds, said fragments of a compound, or any

- combination thereof, dock in a first location and a second location on different binding sites, receptors or proteins.
54. The method of claims 44 to 48 wherein said compounds, or said fragments of a compound, are linked together with a linker arm or cross-linking.
 55. The method of claims 44 to 54 wherein said compound or said fragment of a compound comprises a small molecule, protein, peptide, polypeptide, cyclic molecule, heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, chemical, or a fragment of a compound that comprises a heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, or chemical.
 56. The method of claims 44 to 48 wherein said administering step comprises administration by inhalation, oral, intravenous, intraperitoneal, intramuscular, parenteral, transdermal, intravaginal, intranasal, mucosal, sublingual, topical, rectal, or subcutaneous administration, or any combination thereof.
 57. The method of claims 44 to 55 wherein said compound or said fragment of a compound comprises at least one agonist, antagonist, partial agonist, or any combination thereof.
 58. The method of claims 44 to 57 wherein said non-native compound is identified using a method comprising:
 - a. screening for a compound that fits into the cavity on the receptor using the UNITYTM program;
 - b. docking said compound into the cavity using the FlexxTM program; and
 - c. obtaining the compound with the highest binding affinity using the CscoreTM program.
 59. A method for the treatment of a bone fracture, bone disease, bone injury, or bone abnormality in a mammalian subject comprising administering at least one non-native compound, at least one fragment of a non-native compound or any combination thereof, that disrupts the interaction of sclerostin with a receptor or co-receptor involved in bone formation or bone remodeling.
 60. A method for the treatment of a bone fracture, bone disease, bone injury, or bone abnormality in a mammalian subject comprising administering at least one non-native compound, at least one fragment of a non-native compound or any combination thereof, that disrupts the interaction of sclerostin with the LRP5 or LRP6 receptor.
 61. A method for the treatment of a bone fracture, bone disease, bone injury, or bone abnormality in a mammalian subject comprising administering at least one non-native compound, at least one fraction of a non-native compound, or any combination thereof, that disrupts the interaction of sclerostin with a homologue of the LRP5 or LRP6 receptor.
 62. A method for the treatment of a bone fracture, bone disease, bone injury, or bone abnormality in a mammalian subject comprising administering at least one non-native

- compound, at least one fragment of a non-native compound, or any combination thereof, that disrupts the interaction of sclerostin with at least one domain of the LRP5 or LRP6 receptor.
63. A method for the treatment of a bone fracture, bone disease, bone injury, or bone abnormality in a mammalian subject comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that disrupts the interaction of sclerostin with the first or second domain of the LRP5 or LRP6 receptor.
 64. The method of claims 59 to 63 wherein said compound or said fragment of a compound comprises IIC3 or IIC8.
 65. The method of claims 59 to 63 wherein said compound or said fragment of a compound comprises IIC3, IIC8 or any derivative or analog thereof.
 66. The method of claim 64 or 65 wherein said two or more compounds or said fragments of compounds are directly linked together with cross-linking, or indirectly linked together with a linker arm.
 67. The method of claim 66 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on the same binding site, receptor or protein.
 68. The method of claim 66 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on different binding sites, receptors or proteins.
 69. The method of claims 59 to 63 wherein said compounds, or said fragments of a compound, are linked together with a linker arm or cross-linking.
 70. The method of claims 59 to 69 wherein said compound or said fragment of a compound comprises a small molecule, protein, peptide, polypeptide, cyclic molecule, heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, chemical, or a fragment of a compound that comprises a heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, or chemical.
 71. The method of claims 59 to 63 wherein said administering step comprises administration by inhalation, oral, intravenous, intraperitoneal, intramuscular, parenteral, transdermal, intravaginal, intranasal, mucosal, sublingual, topical, rectal, or subcutaneous administration, or any combination thereof.
 72. The method of claims 59 to 69 wherein said compound or said fragment of a compound comprises at least one agonist, antagonist, partial agonist, or any combination thereof.
 73. The method of claims 59 to 72 wherein said non-native compound is identified using a

method comprising:

- a. screening for a compound that fits into the cavity on the receptor using the UNITY™ program;
 - b. docking said compound into the cavity using the Flexx™ program; and
 - c. obtaining the compound with the highest binding affinity using the Cscore™ program.
74. A therapeutic composition for the treatment of a bone fracture, bone disease, bone injury or bone abnormality in a mammalian subject comprising at least one non-native compound, at least one fragment of a compound, or any combination thereof, that disrupts the interaction of sclerostin with a receptor or co-receptor involved in bone formation or bone remodeling.
75. A therapeutic composition for the treatment of a bone fracture, bone disease, bone injury or bone abnormality in a mammalian subject comprising at least one non-native compound, at least one fragment of a compound, or any combination thereof, that disrupts the interaction of sclerostin with the LRP5 or LRP6 receptor.
76. A therapeutic composition for the treatment of a bone fracture, bone disease, bone injury or bone abnormality in a mammalian subject comprising at least one non-native compound, at least one fragment of a compound, or any combination thereof, that disrupts the interaction of sclerostin with a homologue of the LRP5 or LRP6 receptor.
77. A therapeutic composition for the treatment of a bone fracture, bone disease, bone injury or bone abnormality in a mammalian subject comprising at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that disrupts the interaction of sclerostin with at least one domain of the LRP5 or LRP6 receptor.
78. A therapeutic composition for the treatment of a bone fracture, bone disease, bone injury or bone abnormality in a mammalian subject comprising at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that disrupts the interaction of sclerostin with the first or second domain of the LRP5 or LRP6 receptor.
79. The composition of claims 74 to 78 wherein said compound comprises IIC3 or IIC8.
80. The composition of claims 74 to 78 wherein said compound comprises IIC3, IIC8 or any derivative or analog thereof.
81. The composition of claim 79 or 80 wherein said two or more compounds or said fragments of compounds are directly linked together with cross-linking, or indirectly linked together with a linker arm.
82. The method of claim 81 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on the same binding

- site, receptor or protein.
83. The method of claim 81 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on different binding sites, receptors or proteins.
 84. The method of claims 74 to 78 wherein said compounds, or said fragments of a compound, are linked together with a linker arm or cross-linking.
 85. The composition of claims 74 to 84 wherein said compound or said fragment of a compound comprises a small molecule, protein, peptide, polypeptide, cyclic molecule, heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, chemical, or a fragment of a compound that comprises a heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, or chemical.
 86. The composition of claims 74 to 78 wherein said administering step comprises administration by inhalation, oral, intravenous, intraperitoneal, intramuscular, parenteral, transdermal, intravaginal, intranasal, mucosal, sublingual, topical, rectal, or subcutaneous administration, or any combination thereof.
 87. The composition of claims 74 to 86 wherein said non-native compound is identified using a method comprising:
 - a. screening for a compound that fits into the cavity on the receptor using the UNITYTM program;
 - b. docking said compound into the cavity using the FlexxTM program; and
 - c. obtaining the compound with the highest binding affinity using the CscoreTM program.
 88. The composition of claims 74 to 87 further comprising a pharmaceutically acceptable carrier.
 89. The composition of claims 74 to 87 wherein said composition is formulated as a tablet, pill, dragee, liquid, gel, capsule, syrup, slurry or suspension.
 90. A method for preventing or blocking bone formation in a mammalian subject by administering sclerostin.
 91. A method for the treatment of abnormal bone growth in a mammalian subject comprising administering an antibody for sclerostin, or any other non-native compound or fragment of a compound which decreases or eliminates sclerostin.
 92. The method of claim 91 wherein said compound or said fragment of a compound comprises a small molecule, protein, peptide, polypeptide, cyclic molecule, heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein or chemical.

93. The method of claim 91 or 92 wherein said administering step comprises administration by inhalation, oral, intravenous, intraperitoneal, intramuscular, parenteral, transdermal, intravaginal, intranasal, mucosal, sublingual, topical, rectal, or subcutaneous administration, or any combination thereof.
94. The method of claims 90 to 92 wherein said sclerostin comprises a related protein, an unrelated protein with analogous functions, or any homologue or derivative of sclerostin.
95. A therapeutic composition for preventing or blocking bone formation in a mammalian subject comprising sclerostin.
96. A therapeutic composition for preventing or blocking bone formation in a mammalian subject comprising a sclerostin antibody or any other non-native compound or fragment of a compound which decreases or eliminates sclerostin.
97. The method or composition of claims 91 to 96 wherein said non-native compound is identified using a method comprising:
 - a. screening for a compound that fits into the cavity on the receptor using the UNITYTM program;
 - b. docking said compound into the cavity using the FlexxTM program; and
 - c. obtaining the compound with the highest binding affinity using the CscoreTM program.
98. A method for identifying a drug candidate or compound which promotes or inhibits a protein-protein interaction comprising:
 - a. determining the virtual structure of a receptor protein;
 - b. identifying a particular binding cavity on said receptor protein;
 - c. identifying a specific site within said binding cavity; and
 - d. screening for a compound that fits into said specific site.
99. The method of claim 98 further comprising the step of identifying the compound with the highest binding affinity using the CscoreTM program.
100. The method of claim 98 wherein said step of identifying a particular binding cavity comprises conducting experiments based on the biological functions of the compounds.
101. The method of claim 100 wherein said experiments comprise mutational analyses.
102. The method of claim 98 wherein said receptor protein is non-soluble or membrane bound.
103. A method for identifying a drug candidate or compound which promotes or inhibits a protein-protein interaction comprising:
 - a. determining the virtual structure of a receptor protein;
 - b. identifying a particular binding cavity on said receptor protein;
 - c. identifying a specific site within said binding cavity;
 - d. screening for a compound that fits into said specific site using the UNITYTM program;

- e. docking said compound into the cavity using the Flexx™ program; and
 - f. obtaining the compound with the highest binding affinity using the Cscore™ program.
104. The method of claim 103 wherein said step of identifying a particular binding cavity comprises conducting experiments based on the biological functions of the compounds.
105. The method of claim 104 wherein said experiments comprise mutational analyses.
106. The method of claim 103 wherein said receptor protein is non-soluble or membrane-bound.
107. A method for identifying a drug candidate compound which binds to a receptor protein involved in bone formation or bone remodeling comprising:
- a. determining the virtual or computational structure of a non-soluble receptor protein comprising the use of amino acid sequencing, X-ray crystallography, NMR, analogs or derivatives of said receptor protein, or any combination thereof;
 - b. identifying a particular binding cavity on said receptor protein through the use of experiments based on biological function comprising mutational analysis, chemical modification of amino acids, co-crystallography, NMR, or any combination thereof;
 - c. identifying a specific binding site within said binding cavity based on mutations or chemical modifications;
 - d. screening for a compound that fits into said specific site using the UNITY™ program.; and
 - e. identifying the compound with the highest binding affinity or the lowest energy using the Cscore™ program to find the compound with the best fit.
108. A method for identifying a drug candidate compound which binds to a receptor protein involved in bone formation or bone remodeling comprising:
- a. determining the virtual or computational structure of a signal peptide comprising the use of amino acid sequencing, X-ray crystallography, NMR, analogs or derivatives of said signal peptide, or any combination thereof;
 - b. identifying a particular binding cavity on said receptor protein through the use of experiments based on biological function comprising mutational analysis, chemical modification, co-crystallography, NMR or any combination thereof;
 - c. identifying a specific binding site within said binding cavity based on the results obtained from said experiments;
 - d. screening for a compound that fits into said binding cavity or said specific site in said binding cavity using the UNITY™ program;
 - e. docking said compound into said binding cavity or said specific site in said binding cavity using the Flexx™ program; and
 - f. identifying the compound with the highest binding affinity or the lowest energy using the Cscore™ program.
109. A method for identifying a drug candidate or compound which binds to a protein involved in a signal transduction system comprising:

- a. providing or determining the virtual or computational structure of said protein comprising the use of amino acid sequencing, X-ray crystallography, NMR, analogs or derivatives of said receptor protein, or any combination thereof;
 - b. identifying a particular binding cavity, site or domain on said protein using various experiments comprising mutational analysis, chemical modification of amino acids, co-crystallography, NMR, or any combination thereof;
 - c. identifying a specific binding site within said binding cavity, site or domain based on the results of said experiments; and
 - d. screening a library of drug candidate compounds to identify the drug candidate or compound having the best fit with said specific binding site or said binding cavity, site or domain.
110. A method for identifying a drug candidate or compound which binds to a nonsoluble or membrane-bound protein involved in a signal transduction system comprising:
- a. providing or determining the virtual or computational structure of said protein comprising the use of amino acid sequencing, X-ray crystallography, NMR, analogs or derivatives of said receptor protein, or any combination thereof;
 - b. identifying a particular binding cavity, site or domain or said protein using various experiments comprising mutational analysis, chemical modification of amino acids, co-crystallography, NMR, or any combination thereof;
 - c. identifying a specific binding site within said binding cavity, site or domain based on the results of said experiments; and
 - d. screening a library of drug candidate compounds to identify the drug candidate or compound having the best fit with said specific binding site or said binding cavity, site or domain.
111. A method for identifying a drug candidate or compound which binds to a protein involved in a Wnt signaling pathway comprising:
- a. providing or determining the virtual or computational structure of said protein comprising the use of amino acid sequencing, X-ray crystallography, NMR, analogs or derivatives of said receptor protein, or any combination thereof;
 - b. identifying a particular binding cavity, site or domain or said protein using various experiments comprising mutational analysis, chemical modification of amino acids, co-crystallography, NMR, or any combination thereof;
 - c. identifying a specific binding site within said binding cavity, site or domain based on the results of said experiments; and
 - d. screening a library of drug candidate compounds to identify the drug candidate or compound having the best fit with said specific binding site or said binding cavity, site or domain.
112. A method for identifying a drug candidate or compound which binds to a protein involved in a signal transduction system for promoting or inhibiting bone growth comprising:
- a. providing or determining the virtual or computational structure of said protein comprising the use of amino acid sequencing, X-ray crystallography, NMR, analogs or derivatives of said receptor protein, or any combination thereof;
 - b. identifying a particular binding cavity, site or domain or said protein using

- various experiments comprising mutational analysis, chemical modification of amino acids, co-crystallography, NMR, or any combination thereof;
- c. identifying a specific binding site within said binding cavity, site or domain based on the results of said experiments; and
 - d. screening a library of drug candidate compounds to identify the drug candidate or compound having the best fit with said specific binding site or said binding cavity, site or domain.
113. A method for the regulation of bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that decreases or eliminates the affinity of sclerostin to a receptor or co-receptor involved in bone formation or bone remodeling.

CLAIMS

1. A method for promoting bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that prevents the binding of sclerostin to a receptor or co-receptor involved in bone formation or bone remodeling.
2. A method for promoting bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that prevents the binding of sclerostin to the LRP5 or LRP6 receptor.
3. A method for promoting bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that prevents the binding of sclerostin to a homologue of the LRP5 or LRP6 receptor.
4. A method for promoting bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that prevents the binding of sclerostin to at least one domain of the LRP5 or LRP6 receptor.
5. A method for promoting bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that prevents the binding of sclerostin to the first or second domain of the LRP5 or LRP6 receptor.
6. The method of claims 1 to 5 wherein said compound or said fragment of a compound comprises IIC3 or IIC8.
7. The method of claims 1 to 5 wherein said compound or said fragment of a compound comprises IIC3, IIC8, or any derivative or analog thereof.

8. The method of claims 6 or 7 wherein said two or more compounds, or said fragments of compounds are directly linked together with cross-linking, or indirectly linked together with a linker arm.
9. The method of claim 8 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on the same binding site, receptor or protein.
10. The method of claim 8 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on different binding sites, receptors or proteins.
11. The method of claims 1 to 5 wherein said compounds, or said fragments of a compound, are linked together with a linker arm or cross-linking.
12. The method of claims 1 to 11 wherein said compound or said fragment of a compound comprises a small molecule, protein, peptide, polypeptide, cyclic molecule, heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, chemical, or a fragment of a compound that comprises a heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, or chemical.
13. The method of claims 1 to 5 wherein said administering step comprises administration by inhalation, oral, intravenous, intraperitoneal, intramuscular, parenteral, transdermal, intravaginal, intranasal, mucosal, sublingual, topical, rectal, or subcutaneous administration, or any combination thereof.
14. The method of claims 1 to 12 wherein said compound or said fragment of a compound comprises at least one agonist, antagonist, partial agonist, or any combination thereof.

15. The method of claims 1 to 14 wherein said compound is identified using a method comprising:
 - a. screening for a compound that fits into the cavity on the receptor using the UNITYTM program;
 - b. docking said compound into the cavity using the FlexxTM program; and
 - c. obtaining the compound with the highest binding affinity using the CscoreTM program.
16. A method for the treatment of a bone fracture, bone disease, bone injury, or bone abnormality in a mammalian subject comprising administering at least one non-native compound, at least one fragment of a non-native compound or any combination thereof, that prevents the binding of sclerostin to a receptor or co-receptor involved in bone formation or bone remodeling.
17. A method for the treatment of a bone fracture, bone disease, bone injury, or bone abnormality in a mammalian subject comprising administering at least one non-native compound, at least one fragment of a non-native compound or any combination thereof, that prevents the binding of sclerostin to the LRP5 or LRP6 receptor.
18. A method for the treatment of a bone fracture, bone disease, bone injury, or bone abnormality in a mammalian subject comprising administering at least one non-native compound, at least one fragment of a non-native compound or any combination thereof, that prevents the binding of sclerostin to a homologue of the LRP5 or LRP6 receptor.
19. The method of claims 16 to 18 wherein said compound comprises IIC3 or IIC8.
20. The method of claims 16 to 18 wherein said compound or said fragment of a compound comprises IIC3 or IIC8.

21. The method of claims 19 or 20 wherein said two or more compounds or said fragments of compounds are directly linked together with cross-linking, or indirectly linked together with a linker arm.
22. The method of claim 21 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on the same binding site, receptor or protein.
23. The method of claim 21 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on different binding sites, receptors or proteins.
24. The method of claims 16 to 18 wherein said compounds, or said fragments of a compound, are linked together with a linker arm or cross-linking.
25. The method of claims 16 to 24 wherein said compound or said fragment of a compound comprises a small molecule, protein, peptide, polypeptide, cyclic molecule, heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, chemical, or a fragment of a compound that comprises a heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, or chemical.
26. The method of claims 16 to 18 wherein said administering step comprises administration by inhalation, oral, intravenous, intraperitoneal, intramuscular, parenteral, transdermal, intravaginal, intranasal, mucosal, sublingual, topical, rectal, or subcutaneous administration, or any combination thereof.
27. The method of claims 16 to 25 wherein said compound or said fragment of a compound comprises at least one agonist, antagonist, partial agonist, or any combination thereof.

28. The method of claims 16 to 27 wherein said compound is identified using a method comprising:
- screening for a compound that fits into the cavity on the receptor using the UNITY™ program;
 - docking said compound into the cavity using the Flexx™ program; and
 - obtaining the compound with the highest binding affinity using the Cscore™ program.
29. A therapeutic composition for the treatment of a bone fracture, bone disease, bone injury or bone abnormality in a mammalian subject comprising at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that prevents the binding of sclerostin to a receptor or co-receptor in bone formation or bone remodeling.
30. A therapeutic composition for the treatment of a bone fracture, bone disease, bone injury or bone abnormality in a mammalian subject comprising at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that prevents the binding of sclerostin to the LRP5 or LRP6 receptor.
31. A therapeutic composition for the treatment of a bone fracture, bone disease, bone injury or bone abnormality in a mammalian subject comprising at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that prevents the binding of sclerostin to a homologue of the LRP5 or LRP6 receptor.
32. The composition of claims 29 to 30 wherein said compound or said fragment of a compound comprises IIC3 or IIC8.
33. The composition of claims 29 to 31 wherein said compound or said fragment of a compound comprises IIC3 or IIC8, or any derivative or analog thereof.

34. The composition of claim 32 or 33 wherein said two or more compounds or fragments of compounds are directly linked together with cross-linking, or indirectly linked together with a linker arm.
35. The method of claim 34 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on the same binding site, receptor or protein.
36. The composition of claim 34 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on different binding sites receptors or proteins.
37. The composition of claims 29 to 31 wherein said compounds, or said fragments of a compound, are linked together with a linker arm or cross-linking.
38. The composition of claims 29 to 37 wherein said compound or said fragment of a compound comprises a small molecule, protein, peptide, polypeptide, cyclic molecule, heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, chemical, or a fragment of a compound that comprises a heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, or chemical.
39. The composition of claims 29 to 31 wherein said administering step comprises administration by inhalation, oral, intravenous, intraperitoneal, intramuscular, parenteral, transdermal, intravaginal, intranasal, mucosal, sublingual, topical, rectal, or subcutaneous administration, or any combination thereof.
40. The composition of claims 29 to 38 wherein said compound or said fragment of a compound comprises at least one agonist, antagonist, partial agonist, or any combination thereof.

41. The composition of claims 29 to 40 wherein said non-native compound is identified using a method comprising:
 - a. screening for a compound that fits into the cavity on the receptor using the UNITYTM program;
 - b. docking said compound into the cavity using the FlexxTM program; and
 - c. obtaining the compound with the highest binding affinity using the CscoreTM program.
42. The composition of claims 29 to 41 wherein said composition further comprises a pharmaceutically acceptable carrier.
43. The composition of claims 29 to 41 wherein said composition is formulated as a tablet, pill, dragee, liquid, gel, capsule, syrup, slurry or suspension.
44. A method for the regulation of bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound or any combination thereof, that disrupts the interaction of sclerostin with a receptor or co-receptor involved in bone formation or bone remodeling.
45. A method for the regulation of bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that disrupts the interaction of sclerostin with the LRP5 or LRP6 receptor.
46. A method for the regulation of bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that disrupts the interaction of sclerostin with a homologue of the LRP5 or LRP6 receptor.
47. A method for the regulation of bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native

compound, or any combination thereof, that disrupts the interaction of sclerostin with at least one domain of the LRP5 or LRP6 receptor.

48. A method for the regulation of bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that disrupts the interaction of sclerostin with the first or second domain of the LRP5 or LRP6 receptor.
49. The method of claims 44 to 48 wherein said compound or said fragment of a compound comprises IIC3 or IIC8.
50. The method of claims 44 to 48 wherein said compound or said fragment of a compound comprises IIC3, or IIC8, or any derivative or analog thereof.
51. The method of claims 49 or 50 wherein said two or more compounds or said fragments of compounds are directly linked together with cross-linking, or indirectly linked together with a linker arm.
52. The method of claim 51 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on the same binding site, receptor or protein.
53. The method of claim 51 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on different binding sites, receptors or proteins.
54. The method of claims 44 to 48 wherein said compounds, or said fragments of a compound, are linked together with a linker arm or cross-linking.
55. The method of claims 44 to 54 wherein said compound or said fragment of a compound comprises a small molecule, protein, peptide, polypeptide, cyclic molecule, heterocyclic

organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, chemical, or a fragment of a compound that comprises a heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, or chemical.

56. The method of claims 44 to 48 wherein said administering step comprises administration by inhalation, oral, intravenous, intraperitoneal, intramuscular, parenteral, transdermal, intravaginal, intranasal, mucosal, sublingual, topical, rectal, or subcutaneous administration, or any combination thereof.
57. The method of claims 44 to 55 wherein said compound or said fragment of a compound comprises at least one agonist, antagonist, partial agonist, or any combination thereof.
58. The method of claims 44 to 57 wherein said non-native compound is identified using a method comprising:
- a. screening for a compound that fits into the cavity on the receptor using the UNITYTM program;
 - b. docking said compound into the cavity using the FlexxTM program; and
 - c. obtaining the compound with the highest binding affinity using the CscoreTM program.
59. A method for the treatment of a bone fracture, bone disease, bone injury, or bone abnormality in a mammalian subject comprising administering at least one non-native compound, at least one fragment of a non-native compound or any combination thereof, that disrupts the interaction of sclerostin with a receptor or co-receptor involved in bone formation or bone remodeling.
60. A method for the treatment of a bone fracture, bone disease, bone injury, or bone abnormality in a mammalian subject comprising administering at least one non-native compound, at least one fragment of a non-native compound or any combination thereof, that disrupts the interaction of sclerostin with the LRP5 or LRP6 receptor.

61. A method for the treatment of a bone fracture, bone disease, bone injury, or bone abnormality in a mammalian subject comprising administering at least one non-native compound, at least one fraction of a non-native compound, or any combination thereof, that disrupts the interaction of sclerostin with a homologue of the LRP5 or LRP6 receptor.
62. A method for the treatment of a bone fracture, bone disease, bone injury, or bone abnormality in a mammalian subject comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that disrupts the interaction of sclerostin with at least one domain of the LRP5 or LRP6 receptor.
63. A method for the treatment of a bone fracture, bone disease, bone injury, or bone abnormality in a mammalian subject comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that disrupts the interaction of sclerostin with the first or second domain of the LRP5 or LRP6 receptor.
64. The method of claims 59 to 63 wherein said compound or said fragment of a compound comprises IIC3 or IIC8.
65. The method of claims 59 to 63 wherein said compound or said fragment of a compound comprises IIC3, IIC8 or any derivative or analog thereof.
66. The method of claim 64 or 65 wherein said two or more compounds or said fragments of compounds are directly linked together with cross-linking, or indirectly linked together with a linker arm.
67. The method of claim 66 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on the same binding site, receptor or protein.

68. The method of claim 66 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on different binding sites, receptors or proteins.
69. The method of claims 59 to 63 wherein said compounds, or said fragments of a compound, are linked together with a linker arm or cross-linking.
70. The method of claims 59 to 69 wherein said compound or said fragment of a compound comprises a small molecule, protein, peptide, polypeptide, cyclic molecule, heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, chemical, or a fragment of a compound that comprises a heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, or chemical.
71. The method of claims 59 to 63 wherein said administering step comprises administration by inhalation, oral, intravenous, intraperitoneal, intramuscular, parenteral, transdermal, intravaginal, intranasal, mucosal, sublingual, topical, rectal, or subcutaneous administration, or any combination thereof.
72. The method of claims 59 to 69 wherein said compound or said fragment of a compound comprises at least one agonist, antagonist, partial agonist, or any combination thereof.
73. The method of claims 59 to 72 wherein said non-native compound is identified using a method comprising:
- a. screening for a compound that fits into the cavity on the receptor using the UNITY™ program;
 - b. docking said compound into the cavity using the Flexx™ program; and
 - c. obtaining the compound with the highest binding affinity using the Cscore™ program.

74. A therapeutic composition for the treatment of a bone fracture, bone disease, bone injury or bone abnormality in a mammalian subject comprising at least one non-native compound, at least one fragment of a compound, or any combination thereof, that disrupts the interaction of sclerostin with a receptor or co-receptor involved in bone formation or bone remodeling.
75. A therapeutic composition for the treatment of a bone fracture, bone disease, bone injury or bone abnormality in a mammalian subject comprising at least one non-native compound, at least one fragment of a compound, or any combination thereof, that disrupts the interaction of sclerostin with the LRP5 or LRP6 receptor.
76. A therapeutic composition for the treatment of a bone fracture, bone disease, bone injury or bone abnormality in a mammalian subject comprising at least one non-native compound, at least one fragment of a compound, or any combination thereof, that disrupts the interaction of sclerostin with a homologue of the LRP5 or LRP6 receptor.
77. A therapeutic composition for the treatment of a bone fracture, bone disease, bone injury or bone abnormality in a mammalian subject comprising at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that disrupts the interaction of sclerostin with at least one domain of the LRP5 or LRP6 receptor.
78. A therapeutic composition for the treatment of a bone fracture, bone disease, bone injury or bone abnormality in a mammalian subject comprising at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that disrupts the interaction of sclerostin with the first or second domain of the LRP5 or LRP6 receptor.
79. The composition of claims 74 to 78 wherein said compound comprises IIC3 or IIC8.

80. The composition of claims 74 to 78 wherein said compound comprises IIC3, IIC8 or any derivative or analog thereof.
81. The composition of claim 79 or 80 wherein said two or more compounds or said fragments of compounds are directly linked together with cross-linking, or indirectly linked together with a linker arm.
82. The method of claim 81 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on the same binding site, receptor or protein.
83. The method of claim 81 wherein said compounds, said fragments of a compound, or any combination thereof, dock in a first location and a second location on different binding sites, receptors or proteins.
84. The method of claims 74 to 78 wherein said compounds, or said fragments of a compound, are linked together with a linker arm or cross-linking.
85. The composition of claims 74 to 84 wherein said compound or said fragment of a compound comprises a small molecule, protein, peptide, polypeptide, cyclic molecule, heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, chemical, or a fragment of a compound that comprises a heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein, or chemical.
86. The composition of claims 74 to 78 wherein said administering step comprises administration by inhalation, oral, intravenous, intraperitoneal, intramuscular, parenteral, transdermal, intravaginal, intranasal, mucosal, sublingual, topical, rectal, or subcutaneous administration, or any combination thereof.
87. The composition of claims 74 to 86 wherein said non-native compound is identified using a method comprising:

- a. screening for a compound that fits into the cavity on the receptor using the UNITY™ program;
 - b. docking said compound into the cavity using the Flexx™ program; and
 - c. obtaining the compound with the highest binding affinity using the Cscore™ program.
88. The composition of claims 74 to 87 further comprising a pharmaceutically acceptable carrier.
89. The composition of claims 74 to 87 wherein said composition is formulated as a tablet, pill, dragee, liquid, gel, capsule, syrup, slurry or suspension.
90. A method for preventing or blocking bone formation in a mammalian subject by administering sclerostin.
91. A method for the treatment of abnormal bone growth in a mammalian subject comprising administering an antibody for sclerostin, or any other non-native compound or fragment of a compound which decreases or eliminates sclerostin.
92. The method of claim 91 wherein said compound or said fragment of a compound comprises a small molecule, protein, peptide, polypeptide, cyclic molecule, heterocyclic organic molecule, nucleic acid, lipid, charged lipid, polar lipid, non-polar lipid, sugar, glycoprotein, glycolipid, lipoprotein or chemical.
93. The method of claim 91 or 92 wherein said administering step comprises administration by inhalation, oral, intravenous, intraperitoneal, intramuscular, parenteral, transdermal, intravaginal, intranasal, mucosal, sublingual, topical, rectal, or subcutaneous administration, or any combination thereof.
94. The method of claims 90 to 92 wherein said sclerostin comprises a related protein, an unrelated protein with analogous functions, or any homologue or derivative of sclerostin.

95. A therapeutic composition for preventing or blocking bone formation in a mammalian subject comprising sclerostin.
96. A therapeutic composition for preventing or blocking bone formation in a mammalian subject comprising a sclerostin antibody or any other non-native compound or fragment of a compound which decreases or eliminates sclerostin.
97. The method or composition of claims 91 to 96 wherein said non-native compound is identified using a method comprising:
- a. screening for a compound that fits into the cavity on the receptor using the UNITYTM program;
 - b. docking said compound into the cavity using the FlexxTM program; and
 - c. obtaining the compound with the highest binding affinity using the CscoreTM program.
98. A method for identifying a drug candidate or compound which promotes or inhibits a protein-protein interaction comprising:
- a. determining the virtual structure of a receptor protein;
 - b. identifying a particular binding cavity on said receptor protein;
 - c. identifying a specific site within said binding cavity; and
 - d. screening for a compound that fits into said specific site.
99. The method of claim 98 further comprising the step of identifying the compound with the highest binding affinity using the CscoreTM program.
100. The method of claim 98 wherein said step of identifying a particular binding cavity comprises conducting experiments based on the biological functions of the compounds.
101. The method of claim 100 wherein said experiments comprise mutational analyses.

102. The method of claim 98 wherein said receptor protein is non-soluble or membrane bound.
103. A method for identifying a drug candidate or compound which promotes or inhibits a protein-protein interaction comprising:
- a. determining the virtual structure of a receptor protein;
 - b. identifying a particular binding cavity on said receptor protein;
 - c. identifying a specific site within said binding cavity;
 - d. screening for a compound that fits into said specific site using the UNITYTM program;
 - e. docking said compound into the cavity using the FlexxTM program; and
 - f. obtaining the compound with the highest binding affinity using the CscoreTM program.
104. The method of claim 103 wherein said step of identifying a particular binding cavity comprises conducting experiments based on the biological functions of the compounds.
105. The method of claim 104 wherein said experiments comprise mutational analyses.
106. The method of claim 103 wherein said receptor protein is non-soluble or membrane-bound.
107. A method for identifying a drug candidate compound which binds to a receptor protein involved in bone formation or bone remodeling comprising:
- a. determining the virtual or computational structure of a non-soluble receptor protein comprising the use of amino acid sequencing, X-ray crystallography, NMR, analogs or derivatives of said receptor protein, or any combination thereof;
 - b. identifying a particular binding cavity on said receptor protein through the use of experiments based on biological function comprising mutational analysis, chemical modification of amino acids, co-crystallography, NMR, or any combination thereof;

- c. identifying a specific binding site within said binding cavity based on mutations or chemical modifications;
 - d. screening for a compound that fits into said specific site using the UNITYTM program.; and
 - e. identifying the compound with the highest binding affinity or the lowest energy using the CscoreTM program to find the compound with the best fit
108. A method for identifying a drug candidate compound which binds to a receptor protein involved in bone formation or bone remodeling comprising:
- a. determining the virtual or computational structure of a signal peptide comprising the use of amino acid sequencing, X-ray crystallography, NMR, analogs or derivatives of said signal peptide, or any combination thereof;
 - b. identifying a particular binding cavity on said receptor protein through the use of experiments based on biological function comprising mutational analysis, chemical modification, co-crystallography, NMR or any combination thereof;
 - c. identifying a specific binding site within said binding cavity based on the results obtained from said experiments;
 - d. screening for a compound that fits into said binding cavity or said specific site in said binding cavity using the UNITYTM program;
 - e. docking said compound into said binding cavity or said specific site in said binding cavity using the FlexxTM program; and
 - f. identifying the compound with the highest binding affinity or the lowest energy using the CscoreTM program.
109. A method for identifying a drug candidate or compound which binds to a protein involved in a signal transduction system comprising:
- a. providing or determining the virtual or computational structure of said protein comprising the use of amino acid sequencing, X-ray crystallography, NMR, analogs or derivatives of said receptor protein, or any combination thereof;

- b. identifying a particular binding cavity, site or domain on said protein using various experiments comprising mutational analysis, chemical modification of amino acids, co-crystallography, NMR, or any combination thereof;
- c. identifying a specific binding site within said binding cavity, site or domain based on the results of said experiments; and
- d. screening a library of drug candidate compounds to identify the drug candidate or compound having the best fit with said specific binding site or said binding cavity, site or domain.

110. A method for identifying a drug candidate or compound which binds to a nonsoluble or membrane-bound protein involved in a signal transduction system comprising:

- a. providing or determining the virtual or computational structure of said protein comprising the use of amino acid sequencing, X-ray crystallography, NMR, analogs or derivatives of said receptor protein, or any combination thereof;
- b. identifying a particular binding cavity, site or domain or said protein using various experiments comprising mutational analysis, chemical modification of amino acids, co-crystallography, NMR, or any combination thereof;
- c. identifying a specific binding site within said binding cavity, site or domain based on the results of said experiments; and
- d. screening a library of drug candidate compounds to identify the drug candidate or compound having the best fit with said specific binding site or said binding cavity, site or domain.

111. A method for identifying a drug candidate or compound which binds to a protein involved in a Wnt signaling pathway comprising:

- a. providing or determining the virtual or computational structure of said protein comprising the use of amino acid sequencing, X-ray crystallography, NMR, analogs or derivatives of said receptor protein, or any combination thereof;

- b. identifying a particular binding cavity, site or domain or said protein using various experiments comprising mutational analysis, chemical modification of amino acids, co-crystallography, NMR, or any combination thereof;
- c. identifying a specific binding site within said binding cavity, site or domain based on the results of said experiments; and
- d. screening a library of drug candidate compounds to identify the drug candidate or compound having the best fit with said specific binding site or said binding cavity, site or domain.

112. A method for identifying a drug candidate or compound which binds to a protein involved in a signal transduction system for promoting or inhibiting bone growth comprising:

- a. providing or determining the virtual or computational structure of said protein comprising the use of amino acid sequencing, X-ray crystallography, NMR, analogs or derivatives of said receptor protein, or any combination thereof;
- b. identifying a particular binding cavity, site or domain or said protein using various experiments comprising mutational analysis, chemical modification of amino acids, co-crystallography, NMR, or any combination thereof;
- c. identifying a specific binding site within said binding cavity, site or domain based on the results of said experiments; and
- d. screening a library of drug candidate compounds to identify the drug candidate or compound having the best fit with said specific binding site or said binding cavity, site or domain.

113. A method for the regulation of bone formation or bone remodeling comprising administering at least one non-native compound, at least one fragment of a non-native compound, or any combination thereof, that decreases or eliminates the affinity of sclerostin to a receptor or co-receptor involved in bone formation or bone remodeling.

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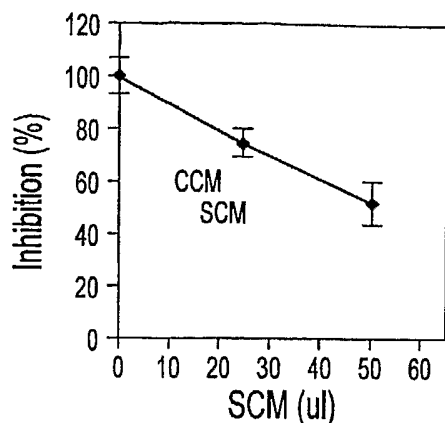


FIG. 1A

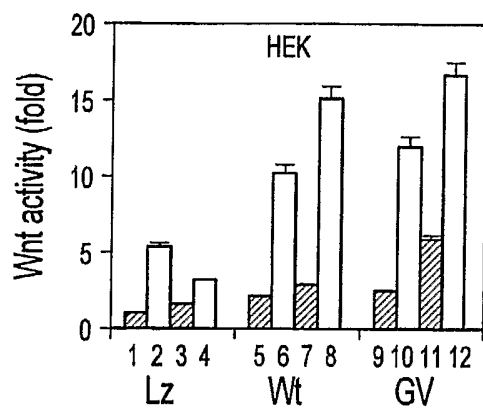


FIG. 1B

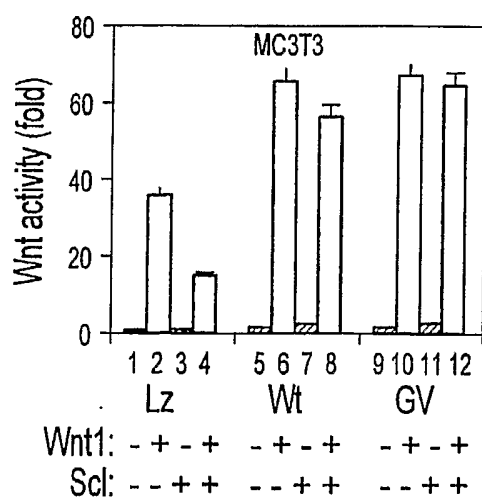


FIG. 1C

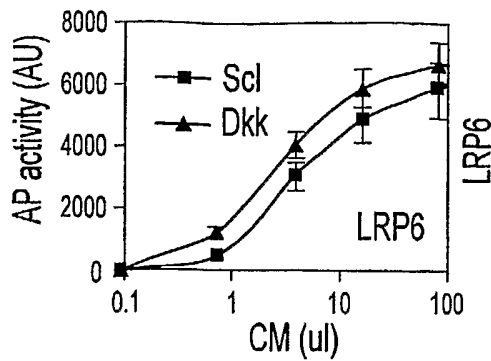


FIG. 2A

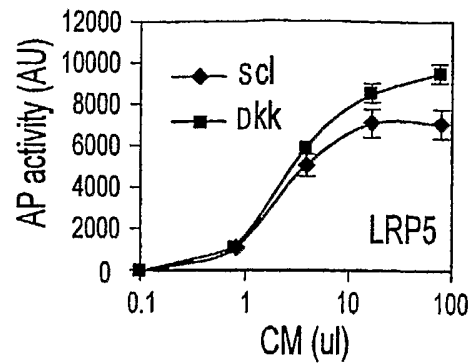


FIG. 2B

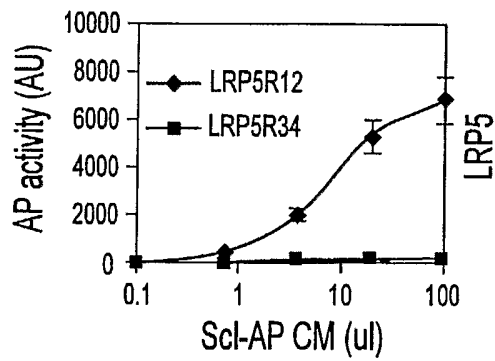


FIG. 2C

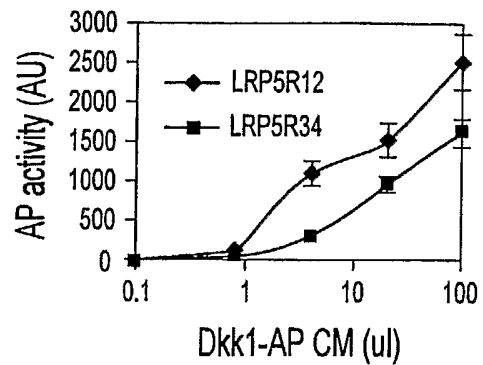


FIG. 2D

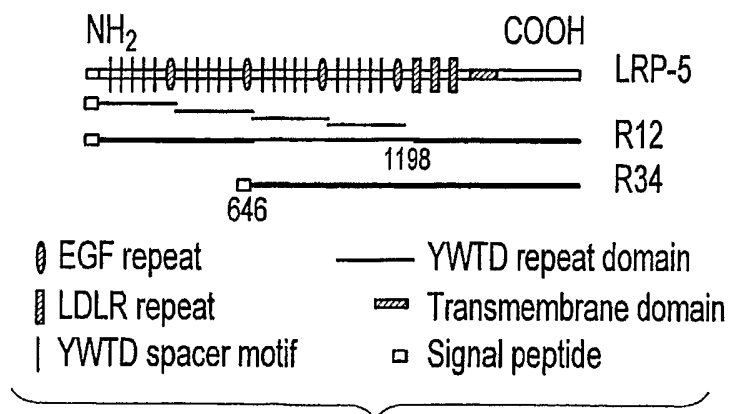


FIG. 2E

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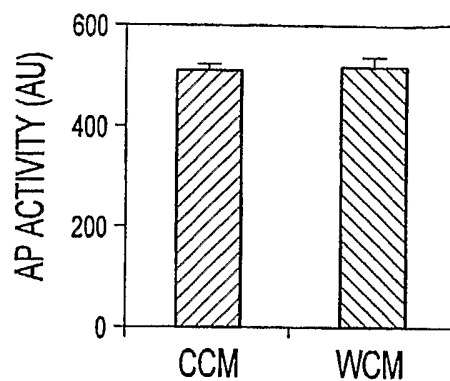


FIG. 3A

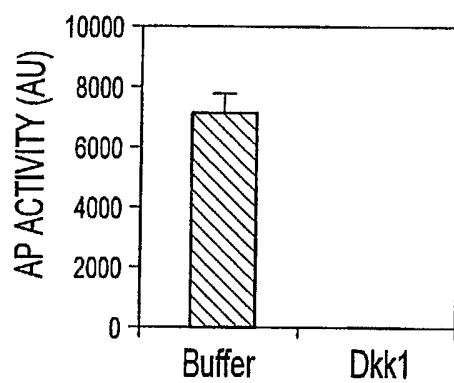


FIG. 3B

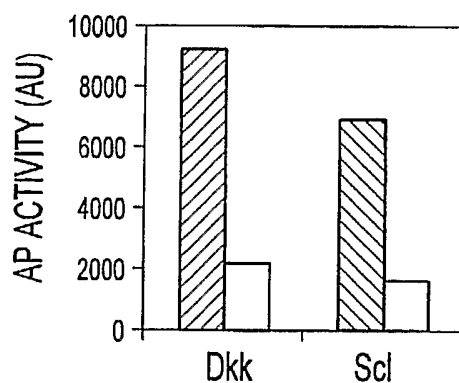


FIG. 3C

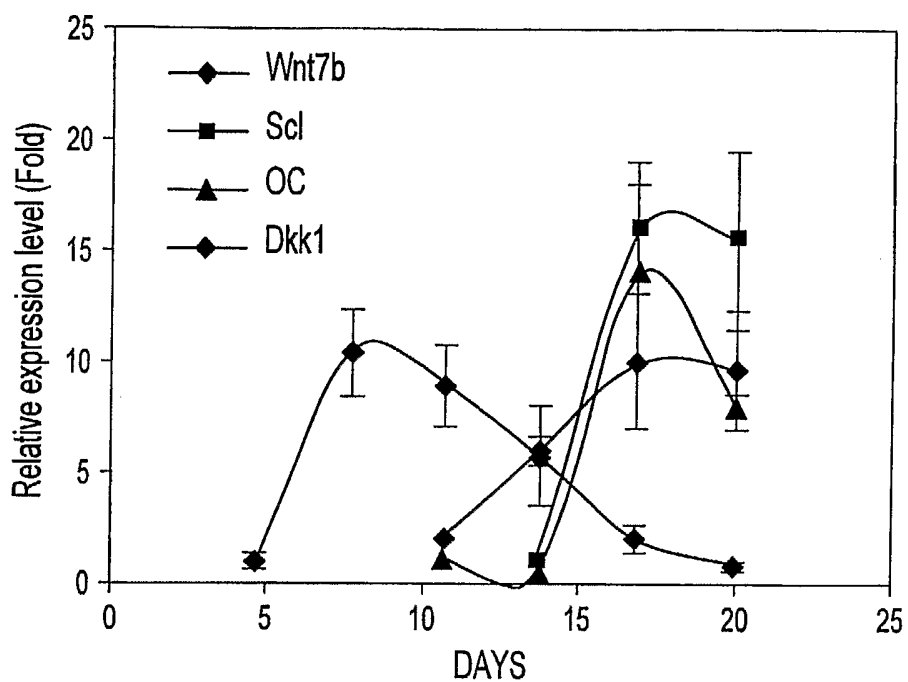


FIG. 4A



FIG. 4B

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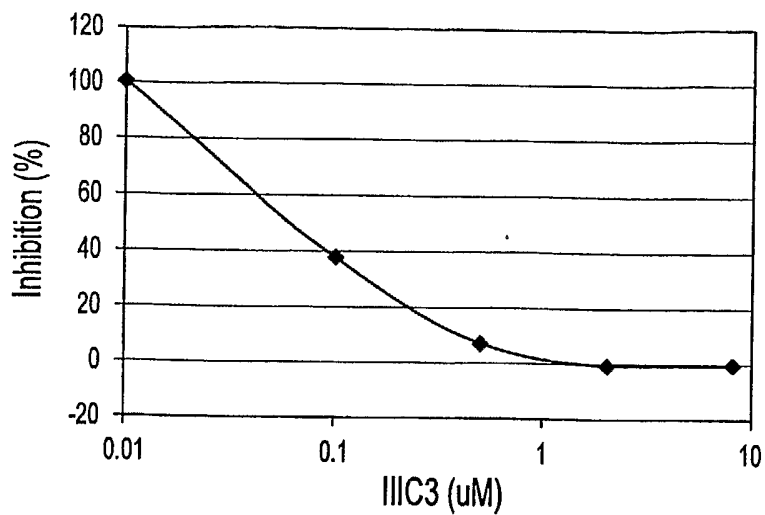


FIG. 5A

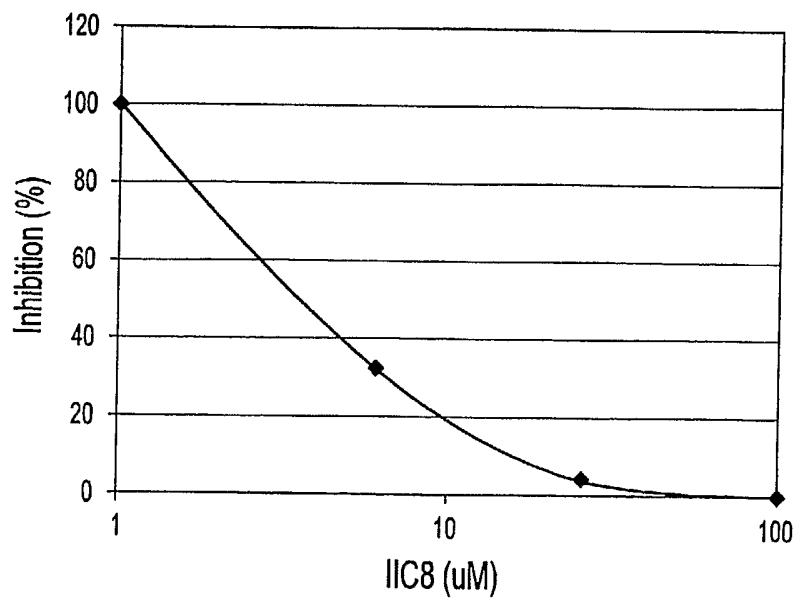


FIG. 5B