Bone anabolics in osteoporosis: Actuality and perspectives

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Abstract
Vertebral and nonvertebral fractures prevention is the main goal for osteoporosis therapy by inhibiting bone resorption and/or stimulating bone formation. Antiresorptive drugs decrease the activation frequency, thereby determining a secondary decrease in bone formation rate and a low bone turnover. Bisphosphonates are today’s mainstay among antiresorptive treatment of osteoporosis. Also, oral selective estrogen receptor modulators and recently denosumab have a negative effect on bone turnover. Agents active on bone formation are considered a better perspective in the treatment of severe osteoporosis. Recombinant-human parathyroid hormone (rhPTH) decreases vertebral, but not nonvertebral, fractures. On the contrary, antagonists of Wnt-inhibitors, that exert their effects mostly through a bone remodeling-independent mechanism, open new perspectives to improve not only trabecular bone but also cortical bone, with potential positive effect also on nonvertebral fractures incidence. The perspective in osteoporosis treatment should be more effective and better tolerated therapies aimed at minimizing individually fractures risk.

Core tip: The study of agents active on bone formation is the main objective in the treatment of severe osteoporosis. rhparathyroid hormone (rhPTH) decreases vertebral, but not nonvertebral, fractures. On the contrary, antagonists of Wnt-inhibitors, that exert their effects mostly through a bone remodeling-independent mechanism, open new perspectives to improve not only trabecular bone but also cortical bone, with potential positive effect also on nonvertebral fractures incidence. The perspective in osteoporosis treatment should be more effective and better tolerated therapies aimed at minimizing individually fractures risk.

INTRODUCTION
Osteoporosis is an emerging medical and socioeconomic threat characterized by a systemic impairment of bone mass, strength and microarchitecture, which increases the propensity of fragility fractures [1]. Osteoporosis results by a dysfunction of physiological bone turnover and cells in bone by endocrine and/or autocrine/paracrine factors (Figure 1), negatively affecting peak bone mass and/or skeletal homeostasis. Patient with osteoporosis show a higher propensity to spine and femur fractures, even if other bones could be also involved.

Osteoporotic fractures of the hip and spine increase mortality and are related to important medical complications that, such as pneumonia or thromboembolic disease due to chronic immobilization with a negative economic impact on public health [2]. Osteoporosis is considered a global public health concern and result to have great socioeconomic burden [3], worthy to be addressed in an evidence-based and
cost-effective manner\textsuperscript{[6]}, taking into account several risk factors\textsuperscript{[7]}. Taking into account these preliminary considerations is resulting that osteoporosis therapy is considered an important field of study where to converge most of the efforts.

Osteoporosis therapy should prevent both vertebral (mostly dependent on trabecular bone density and architecture) and nonvertebral (mostly dependent on cortical thickness and porosity) fractures. This could be achieved by inhibiting bone resorption and/or by stimulating bone formation.

Bone remodeling or modeling activity is different between cortical and trabecular bone sites and this difference could mostly explain the relative lack of efficacy of antiresorptive drugs on nonvertebral fractures since their effect is higher on trabecular than cortical bone.

Bisphosphonates are the most prescribed drugs for osteoporosis treatment. They have a high affinity for bone and inhibit bone resorption reducing fracture risk. Alendronate, risedronate, and zoledronate were shown to reduce the risk of new vertebral, non-vertebral, and hip fractures\textsuperscript{[8-12]}, showing a prevalent effect on axial with respect to appendicular skeletal site, a relative risk reduction of 50\% for spine \textit{vs} 20\%. Although, long term treatment with bisphosphonate has been associated with a potential risk of osteonecrosis of the jaw and of atypical subtrochanteric femoral fractures, their use for at least 10 years has shown good safety\textsuperscript{[13,14]}. Raloxifene, bazedoxifene and subcutaneous denosumab, a human monoclonal antibody that inhibits RANKL, have showed convincing evidences to reduce osteoporotic fractures. Raloxifene have a positive effect on vertebral fracture and on breast cancer risk worsening the thrombotic risk\textsuperscript{[15,16]}. Denosumab, instead, reduced vertebral, non-vertebral and hip fracture risk in postmenopausal women with osteoporosis by the same order of magnitude as bisphosphonates without significant adverse events\textsuperscript{[17]}. A particular behavior seems to have strontium ranelate (SR), which has a double effect, anabolic, inducing an increase of osteoblast activity, and at the same time antiresorptive, inhibiting osteoclasts activity\textsuperscript{[18]}. In a recent meta-analysis Kanis \textit{et al}\textsuperscript{[19]} reported positive effect on clinical and morphometric vertebral fractures. Since SR has shown to have a reduced safety in patients with venous thromboembolism and ischaemic heart diseases, such a drug should not be administered to patients with a higher risk of atherothrombotic events.

In synthesis, antiresorptive drugs reduce the activation frequency, acting mostly on osteoclast and only indirectly on osteoblast activity, with a final slight gain in trabecular bone mass.

Anabolic therapies, instead, directly stimulate bone formation through activation of bone modeling, independently of resorption activity, suggesting a potential positive effect on non-vertebral other than vertebral fractures.

In Figure 2 are reported the two main bone anabolic pathways: one linked to parathyroid hormone (PTH) signaling and the second dependent on canonical wingless-int (Wnt) signaling (Figure 2). The main difference between this two pathways is that Wnt-signaling acts increasing bone mass independently of bone remodeling, as it does PTH induces an increase of osteoblastic and osteoclastic activity. This could explain why PTH shows a closer therapeutic windows.

**PTH**

The secretion of human PTH, an 84-amino acid peptide, by parathyroid cells is closely controlled by serum calcium levels through the calcium-sensing receptors (CaSR). This hormone plays an important role in calcium homeostasis. PTH determines an increase of serum calcium by mobilization of skeletal stores, increasing intestinal and renal calcium absorption\textsuperscript{[20]}. When PTH is administered by intermittent subcutaneous \textit{via}, it has an anabolic effect on bone, influencing osteoblastic activity directly and indirectly with the regulation of some growth factors\textsuperscript{[21]}. To date, injectable forms of recombinant-human PTH (rhPTH) are the only approved osteoanabolic drugs on the market for the treatment of osteoporosis. It exists an intact form (rhPTH 1-84) and an other bioactive N-terminal 34-amino acid fragment rhPTH 1-34 (teriparatide). rhPTH showed a higher effects on trabecular
bone reducing more the relative risk of vertebral than nonvertebral fractures, confirming that rhPTH has a prevalent effect on trabecular rather than on cortical bone\(^{23}\).

Osteoblasts, activated by rhPTH, produce several paracrine factors, which in turn stimulate osteoclast activity. This, when the rhPTH intermittent treatment is prolonged, could enhance activation frequency and thereby increase bone resorption. Although the initial net effect is positive with a gain of trabecular bone mass, the anabolic effect could show a plateau curve when the treatment is prolonged beyond two years\(^{23}\). Such limit could be overcome by a co-administration of an antiresorptive drug able to limit the rhPTH-activated bone resorption. Some experiences did not report consistent evidence that confirm such hypothesis\(^{24,26}\), however, a recent study has reported that one single administration of zoledronic acid combined with daily sc injections of rhPTH could reduce fracture risk in patients with a high risk profile\(^{28}\). On the other hand, sequential administration of antiresorptive drugs after rhPTH is already an established treatment protocol that limit bone resorption after withdraw of rhPTH treatment\(^{28}\).

Although, rhPTH is usually well tolerated, some adverse effects, such as hypercalcemia, nausea, headache, dizziness, and leg cramps, could be associated to rhPTH treatment with a lower risk of hypercalcemia for the rhPTH 1-84\(^{28}\).

To improve the rhPTH safety profile some attractive options for the alternative delivery have been tested. One is transdermal self-administration using coated microneedle patches\(^{27}\) whereas other are inhaled and oral delivery\(^{28}\). In the first case PTH interestingly showed an increased of trabecular bone to the same extent whereas the gain of total hip BMD was much greater than those obtained with sc administered rhPTH 1-34\(^{27}\). Oral and inhaled administrations are being investigated in phase I studies, showing interesting data.

Since rhPTH use is limited by a low effect on nonvertebral fractures, by the osteoclasts activation and by the loss of efficacy in a prolonged treatment, it seems to need to search new molecule which show a better profile.

**PTH RELATED PEPTIDE**

PTH related peptide (PTHrP) shows a similar sequence to PTH in its first 36 amino acids and activates PTH1R. In rats and in humans PTHrP has demonstrated similar effect to rhPTH on bone mass, improving mechanical strength of bone tissue in rats\(^{29}\). However, PTHrP appeared to stimulate only bone formation as a pure bone anabolic agent; as showed by bone turnover markers variations with an increase of bone formation markers, such as osteocalcin and P1NP associated to unchanged levels of bone resorption markers\(^{30}\). In a phase 2 study the administration of PTHrP in postmenopausal women determined an 4%-5%/year increase of BMD without serious adverse effects\(^{31}\). On this basis, some phase 3 studies are ongoing and could give further information on efficacy and safety of this interesting molecule, namely in comparison with PTH (www.clinicaltrials.gov).

### CALCILYTIC AGENTS

PTH is synthesized and secreted by parathyroid glands cells expressing on their surface calcium-sensing receptor (CaSR). Serum low levels of Ca\(^{2+}\) determine a low bond with CaSR decreasing its activity, and in turn stimulating PTH release. On the contrary, activation of the CaSR decreases PTH synthesis and secretion\(^{32}\).

Antagonists of the CaSR bind and inhibit the receptor determining a short pulse of PTH secretion. A rapid increase of PTH secretion followed by rapid normalization should cause an anabolic effect in bone. Unfortunately, calcilytics, considered a new class of bone-forming agents, have showed an unfavorable pharmacokinetics\(^{33}\). In fact, a close therapeutic window between the effect on bone and hypercalcemia, the fact that CaSR are also expressed in other organs besides the parathyroid glands and finally, that together to PTH other products, with potential negative effects on PTH secretion itself, represent actual limits to use of these new anabolic drugs\(^{34}\). Although the mechanism of action, calcilytics remain an interesting opportunity for treatment of a reduced bone mass. However, these drugs are worthy of furthers studies to clarify their role in osteoporosis therapy.

### ANTAGONISTS OF WNT-INHIBITORS

In the last decade, some genetic study of the low-density lipoprotein receptor-related protein 5 (Lrp5) associated to low or high bone mass, suggested a potential role of the Wnt pathway as an important player influencing bone mass and as possible target to the PTH signaling pathway (Figure 2).

To date two endogenous inhibitors of the Wnt/β-catenin pathway specific to bone have been known: sclerostin (SOST) and dickkopf-1 (dkk1). These molecule inhibit Wnt signal stopping β-catenin degradation and osteoblast differentiation. When SOST and dkk1 are blocked by specific antibodies bone formation increases with an anabolic effect.

Binding of Wnt to Lrp5/6 prevents the phosphorylation and the proteosomal degradation of β-catenin, stimulates the production of osteoprotegerin (OPG), an osteoblast-derived inhibitor of osteoclast differentiation\(^{35}\) that acts by binding to RANKL and preventing it from binding to its receptor, RANK.

The fact that Wnt signaling pathway is blocked by endogenous inhibitor factors, represents an important opportunity in the field of osteoporosis therapy.

### Sclerostin antibodies

Sclerostin expression is prevalently restricted to late osteoblasts and osteocytes\(^{36}\), and therefore could represent a favorable target of osteoporosis treatment. In studies in animals, SOST antibodies significantly improved the healing of fractures with an increase in bone formation,
ing. Its neutralization by antibodies is still limited to preclinical trials which have showed an inhibited bone loss in a model of rheumatoid and the prevention of the formation of osteolytic lesions with an increased bone formation rate in a myeloma model. These antibodies could also play a role in the treatment of diseases characterized by a low bone mass, first of all osteoporosis. Some concerns may exist about the possibility that Dkk1 is less selective for bone than SOST with possible more off-target effects.

The possibility to induce the Wnt signaling pathway is a very promising, however, some doubt exist regarding possible important adverse-effects, namely oncogenic effects and a possible uncontrolled process of bone formation with important neurological consequences at cranial and spine levels. Therefore, a particular attention must be taken in long-term use of Wnt antagonists inhibitors.

OTHER POTENTIAL ANABOLIC AGENTS

Activin antagonists

Activin A, a transforming growth factor-β (TGF-β) superfamily member, has showed to be an antagonist to hu-
man osteoblast differentiation\textsuperscript{[43]} and to induce osteoclast formation and bone resorption\textsuperscript{[44]}. On this basis, an antagonist of activin should shift the balance of bone turnover in favor of bone formation. In fact, as showed by a phase I trial, using an activin antagonist increased markers of bone formation\textsuperscript{[45]} of similar extent determined by rhPTH or antagonists of Wnt signaling inhibitors.

**Agonists of prostaglandin**

Some evidence indicate that prostaglandin E2 (PGE2) play a role in bone metabolism by stimulating bone turnover with a prevalence of bone formation and thereby an increasing bone mass and bone strength\textsuperscript{[46]}. A study in OVX rats animal models has showed that a subcutaneous administration of PGE2 E4 receptor agonist stimulates bone formation by increasing osteoblast recruitment activity on periosteal, endocortical, and trabecular surfaces\textsuperscript{[47]}. The PGE2 effect seems to be present on both smooth and scalloped endocortical and trabecular surface, suggesting an effect both on bone modeling and remodeling-dependent bone formation.

**Statins**

Statins have a well-know hypocholesterolemic effect by reducing 3-hydroxy-3-glutaryl-coenzyme A (HMG-CoA) reductase activity. However, the blocking of such enzyme causes the depletion of farnesyl diphosphate or geranyl diphosphate synthesis and in turn the reduction of protein prenylation, which plays a role in bone cells activity by preventing the post-translational modifications of small GTPases.

However, the main proposed mechanism by which statins stimulate bone formation involves an increase in expression and synthesis of BMP-2\textsuperscript{[48]} and osteocalcin\textsuperscript{[49]}. Evidence regarding the effects of statins on BMD\textsuperscript{[50,51]} and fracture risk are not completely consistent but do suggest the anabolic potential of these drugs. In fact, a meta-analysis conclude that statins reduce hip fracture risk and, to a lesser extent, nonspine fracture risk\textsuperscript{[52]}. Unfortunately, statin shows a high affinity for the liver and only very low concentration reach the bone as potential target. Therefore, to overcome the liver first-pass effect, statins would be administered in a suitable delivery system aimed to allow the major concentration in fracture sites. In such sense, a perspective could be a different copolymerization with ethylene glycol that covalently incorporates into hydrogel networks\textsuperscript{[53]} or a different administration route, as a transdermal application, which bypasses the first-pass liver effect\textsuperscript{[54]}.

**Insulin-growth-factor I and proline-rich tyrosine kinase 2**

Administration of insulin-growth-factor I (IGF-I) determines an increase of bone mass with an anabolic effect by inducing bone remodeling both in healthy and in subjects with GH deficiency or IGF-I deficiency\textsuperscript{[55]}. Although, recombinant human IGF-I is used currently for the treatment of short stature genetic syndromes secondary to caused by mutations of the GH receptor or the IGF1 gene, the long-term efficacy and safety of IGF-I in patients with osteoporosis remain to be determined.

An interesting suggestion to identify a novel future anabolic therapy of osteoporosis seems to come from the study of marrow cultures from the proline-rich tyrosine kinase 2 (PYK2)-null mice, which showed enhanced osteogenesis\textsuperscript{[56]}. Blocking PYK2 activity may be hypothesized to have an osteogenic effect also in humans. However, no evidence for such effect in humans has been reported and therefore up to date, this remains only an interesting field of study.

**CONCLUSION**

All antiresorptive drugs share a minor effect on nonvertebral fracture and this remains the biggest limit of severe osteoporosis therapy inducing an important research to identify an agent able to induce bone formation rather than block resorption\textsuperscript{[57]}.

To date, only some drugs have demonstrated to have an anabolic effect on bone; one of these, rhPTH, increases bone formation and significantly decreases vertebral fractures in severe patients, but it is less effective on nonvertebral fractures, probably because rhPTH action is mostly based on bone remodeling, that induces an increase both osteoblasts and osteoclasts activity. On the contrary, the agents influencing Wnt signaling pathway, mostly linked to a bone remodeling-independent mechanism (modeling-based), prevalently affect osteoblastic activity, thereby with a major improvement of trabecular than cortical bone. This action may be thought that Antagonists of Wnt-inhibitors may reduce the incidence of nonvertebral other than of vertebral fractures.

In the next years, several clinical trials could give further data making available more effective and better tolerated therapies allowing tailor-made approaches aimed at minimizing individually fractures risk.

**REFERENCES**

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. JAMA 2001; 285: 785-795 [PMID: 11176917 DOI: 10.1001/jama.285.6.785]
2. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet 1999; 353: 878-882 [PMID: 10093980 DOI: 10.1016/S0140-6736(98)09075-8]
3. Harvey N, Dennison E, Cooper C. Osteoporosis: impact on health and economics. Nat Rev Rheumatol 2010; 6: 99-105 [PMID: 20125177 DOI: 10.1038/nrrheum.2009.260]
4. Hodgson SF, Watts NB, Bilezikian JP, Clarke BL, Gray TK, Harris DW, Johnston CC, Kleerekoper M, Lindsay R, Luckey MM, McClung MR, Nankin HR, Petak SM, Roeger RR. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis: 2001 edition, with selected updates for 2003. Endocr Pract 2003; 9: 544-564 [PMID: 14715483 DOI: 10.4158/EP.9.6.544]
5. Compston J, Cooper A, Cooper C, Francis R, Kanis JA,
Marsh D, McCloskey EV, Reid DM, Selby P, Wilkins M. Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. Maturitas 2009; 62: 105-108 [PMID: 19135323 DOI: 10.1016/j.maturitas.2009.11.022]

6 Brown JP, Josse RG. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ 2002; 167: 51-34 [PMID: 12427685]

7 Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet 2002; 359: 1929-1936 [PMID: 12057569 DOI: 10.1016/S0140-6736(02)0767-5]

8 Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Kong T, Rosario-Jansen T, Krasnow J, Yue TF, Sellmeyer D, Eriksen EF, Cummings SR. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007; 356: 1809-1822 [PMID: 17476007 DOI: 10.1056/NEJMoa067312]

9 Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner TA, Josse RG. 2002 clinical practice guidelines for osteoporosis and Osteoarthritis, and International Osteoporosis. Lancet 2002; 359: 1857-1864 [PMID: 12601559 DOI: 10.1016/S0140-6736(02)08761-5]

10 McClung MR, Canalis E, Giustina A, Bilezikian JP. Mechanisms of anabolic therapies for osteoporosis. N Engl J Med 2007; 357: 905-916 [PMID: 17761594 DOI: 10.1056/NEJMoa076685]

11 Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, Prineas RJ, Rosamond W, Criqui MH, Yano K, Dwyer JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Kong T, Rosario-Jansen T, Krasnow J, Yue TF, Sellmeyer D, Eriksen EF, Cummings SR. One-year randomized clinical trial. Multiple Outcomes of Raloxifene for osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 1999; 282: 637-645 [PMID: 10517716 DOI: 10.1001/jama.282.7.637]

12 Martino S, Cauley JA, Barrett-Connor E, Powles TJ, Merzhen J, Disch D, Secrest R, Cummings SR. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. J Natl Cancer Inst 2004; 96: 1751-1761 [PMID: 15527575 DOI: 10.1093/jnci/djh319]

13 Cummings SR, Baranowski T, Martin J, McClung MR, Siris ES, Eastell R, Reid IR, Delmas P, Zoog HB, Austin M, Wang A, Kutilek S, Adams S, Zanchetta J, Libanati C, Siddhant S, Christiansen C. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009; 361: 756-765 [PMID: 19671655 DOI: 10.1056/NEJMoa080493]
and parathyroid hormone-related peptide to adult ovariectomized rats markedly enhances bone mass and biomechanical properties: a comparison of human parathyroid hormone 1-34, parathyroid hormone-related protein 1-36, and SDZ-parathyroid hormone 893. J Bone Miner Res 2000; 15: 1517-1525 [PMID: 10936450 DOI: 10.1359/jbmr.2000.15.8.1517]

Horwitz MJ, Tedesco MB, Garcia-Ocaña A, Sereika SM, Prebhalia L, Bisello A, Hollis BW, Gundberg CM, Stewart AF. Parathyroid hormone-related protein for the treatment of postmenopausal osteoporosis: defining the maximal tolerable dose. J Clin Endocrinol Metab 2010; 95: 1279-1287 [PMID: 20614142 DOI: 10.1210/jc.2009-0223]

Horwitz MJ, Tedesco MB, Gundberg C, Garcia-Ocaña A, Stewart AF. Short-term, high-dose parathyroid hormone-related protein as a skeletal anabolic agent for the treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab 2003; 88: 569-575 [PMID: 12574182 DOI: 10.1210/jc.2002-021122]

John MR, Widler LG, Gamse R, Buhl T, Seuwen K, Breitenstein W, Bruin GJ, Bellieri R, Klickstein LB, Neeensel M. ATFP956, a novel oral calciylic, increases bone mineral density in rats and transiently releases parathyroid hormone in humans. Bone 2011; 49: 233-241 [PMID: 21514409 DOI: 10.1016/j.bone.2011.04.007]

Fukumoto S. [Antagonist for calcium-sensing receptor. JTT-305/MK-5442]. Clin Calcium 2011; 21: 89-93 [PMID: 21815799 DOI: CliCa11018993]

Cohn DV, Fasciottio BH, Reese BK, Zhang JX. Chromogranin A: a novel regulator of parathyroid gland secretion. J Nutr 1995; 125: 2015S-2019S [PMID: 7602385]

MacDonald BT, Tamai K, He X. Wnt/beta-catenin signaling: components, mechanisms, and diseases. Dev Cell 2009; 17: 9-26 [PMID: 19619488 DOI: 10.1016/j.devcel]

van Beuzooin RL, ten Dijke P, Papapoulo SE, Łowić CW. SOST/sclerostin, an osteocyte-derived negative regulator of bone formation. Cytokine Growth Factor Rev 2005; 16: 319-327 [PMID: 15869900 DOI: 10.1016/j.cytogfr.2005.02.005]

Ominsky MS, Li C, Li X, Tan HL, Lee E, Barrero M, Asuncion FJ, Dwyer D, Han CY, Vlassiuros F, Samadfam R, Jolette J, Simonsen S, Franci MB, Lucani B, Gennari C. Effect of simvastatin treatment on bone mineral density and bone turnover in hypercholesterolemic postmenopausal women: a 1-year longitudinal study. J Bone Miner Res 2003; 18: 2218-2219 [PMID: 12154204 DOI: 10.1002/jbmr.307]

Li X, Wattson KF, Niu QT, Asuncion FJ, Barrero M, Grisanti M, Dwyer D, Stouch B, Thway TM, Li X, Ge HZ. Inhibition of sclerostin by monoclonal antibody enhances bone healing and improves bone tissue quality and strength of nonfractured bones. J Bone Miner Res 2010; 25: 2647-2656 [PMID: 20641040 DOI: 10.1002/jbmr.182]

Padhi D, Jang G, Stouch B, Fang L, Posvar E. Single-dose, placebo-controlled, randomized study of AMG 785, a calcilytic, increases bone mineral density and bone strength in aged male rats. J Bone Miner Res 2010; 26: 19-26 [PMID: 20743411 DOI: 10.1002/jbmr.173]

Baron R, Hassel E. Update on bone anabolics in osteoporosis treatment: rationale, current status, and perspectives. J Clin Endocrinol Metab 2012; 97: 311-325 [PMID: 22238383 DOI: 10.1210/jc.2011-2332]

Diarra D, Stolina M, Polzer K, Zwerina J, Ominsky MS, Dwyer D, Korb A, Amdelen J, Hoffmann M, Schneeche C, van der Heide D, Landewe R, Lacey D, Richards WG, Schett G. Dickkopf-1 is a master regulator of joint remodeling, Nat Med 2007; 13: 156-163 [PMID: 17273793 DOI: 10.1038/nm1538]

Heath DJ, Chandry AD, Buckle CH, Coulton L, Shaugnessy JD, Evans HR, Snowden JA, Stover DR, Vanderkerken K, Croucher PJ. Inhibiting Dickkopf-1 (Dkk1) removes suppression of bone formation and prevents the development of osteolytic bone disease in multiple myeloma. J Bone Miner Res 2009; 24: 425-436 [PMID: 19016584 DOI: 10.1359/jbmr.081104]

Eijken M, Swagemakers S, Koedam M, Steenbergen C, Derks P, Uitterlinden AG, van der Spek PJ, Visser JA, de Jong FH, Pols HA, van Leeuwen JP. The activin A-lissfollistatin system: potent regulator of human extracellular matrix mineralization. FASEB J 2007; 21: 2949-2960 [PMID: 17449718 DOI: 10.1096/fj.07-0808ocm]

Suganati T, Alvarez UM, Hruska KA. Activin A stimulates IkappaB-alpha/NFkappaB and RANK expression for osteoclast differentiation, but not AKT survival pathway in osteoclast precursors. J Cell Biochem 2009; 109: 59-67 [PMID: 19293156 DOI: 10.1002/jcb.10613]

Ruckle J, Jacobs M, Kramer W, Pearsall AE, Kumar R, Underwood KW, Ssehra J, Yang Y, Condon CH, Sherman ML. Single-dose, randomized, double-blind, placebo-controlled study of ACE-011 (ActRIIA-IgG1) in postmenopausal women. J Bone Miner Res 2004; 29: 744-752 [PMID: 15049830 DOI: 10.1093/jbmr/081208]

Jee WS, Ma YF. The in vivo anabolic actions of prostaglandins in bone. Bone 1997; 21: 297-304 [PMID: 9315332 DOI: 10.1016/s8766-3929(97)00147-6]

Ke HZ, Crawford DT, Qi H, Simmons HA, Owen TA, Parakkal VM, Li M, Lu B, Grassner WA, Cameron KO, Lefker BA, DaSilva-Jardine P, Scott DO, Zhang Q, Tian XY, Jee WS, Brown TA, Thompson DD. A nonprostanoic EP4 receptor selective prostaglandin E2 agonist restores bone mass and strength in aged, ovariectomized rats. J Bone Miner Res 2006; 21: 565-575 [PMID: 16598377]

Mundy G, Garrett R, Harris S, Chan J, Chen D, Rossini G, Boyce B, Zhao M, Gutierrez G. Stimulation of bone formation in vitro and in rodents by statins. Science 1999; 286: 1946-1949 [PMID: 10583956 DOI: 10.1126/science.286.5446.1946]
Buckbinder L, Crawford DT, Qi H, Ke HZ, Olson LM, Long KR, Bonnette PC, Baumann AP, Hambor JE, Grasser WA, Pan LC, Owen TA, Luzzio MJ, Hulford CA, Gebhard DF, Paralkar VM, Simmons HA, Kath JC, Roberts WG, Smock SL, Guzman-Perez A, Brown TA, Li M. Proline-rich tyrosine kinase 2 regulates osteoprogenitor cells and bone formation, and offers an anabolic treatment approach for osteoporosis. Proc Natl Acad Sci USA 2007; 104: 10619-10624 [PMID: 17537919 DOI: 10.1073/pnas.0701421104]

Rachner TD, Khosla S, Hofbauer LC. Osteoporosis: now and the future. Lancet 2011; 377: 1276-1287 [PMID: 21450337 DOI: 10.1016/S0140-6736(10)62349-5]
