The future of osteoporosis treatment – a research update

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Summary

Osteoporosis is characterised by a progressive loss of bone mass and microarchitecture which leads to increased fracture risk. Some of the drugs available to date have shown reductions in vertebral and non-vertebral fracture risk. However, in the ageing population of industrialised countries, still more fractures happen today than are avoided, which highlights the large medical need for new treatment options, models, and strategies. Recent insights into bone biology, have led to a better understanding of bone cell functions and crosstalk between osteoblasts, osteoclasts, and osteocytes at the molecular level. In the future, the armamentarium against osteoporotic fractures will likely be enriched by (1.) new bone anabolic substances such as antibodies directed against the endogenous inhibitors of bone formation sclerostin and dickkopf-1, PTH and PTHrp analogues, and possibly calcilytics; (2.) new inhibitors of bone resorption such as cathepsin K inhibitors which may suppress osteoclast function without impairing osteoclast viability and thus maintain bone formation by preserving the osteoclast-osteoblast crosstalk, and denosumab, an already widely available antibody against RANKL which inhibits osteoclast formation, function, and survival; and (3.) new therapeutic strategies based on an extended understanding of the pathophysiology of osteoporosis which may include sequential therapies with two or more bone active substances aimed at optimising the management of bone capital acquired during adolescence and maintained during adulthood in terms of both quantity and quality. Finally, one of the future challenges will be to identify those patients and patient populations expected to benefit the most from a given drug therapy or regimen. The WHO fracture risk assessment tool FRAX® and improved access to bone mineral density measurements by DXA will play a key role in this regard.

Key words: osteoporosis; pathophysiology; future treatment; fractures; FRAX®; osteoblast; osteoclast; osteocyte; bone resorption; bone formation; sclerostin; dickkopf-1; parathormone; calcilytics; cathepsin K; odanacatib; RANK/RANKL; denosumab

The medical need for new osteoporosis drugs

The World Health Organization (WHO) defined osteoporosis as “a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture” [1]. With the ageing of the population, the complications of osteoporosis, fractures, represent a growing medical and socio-economic threat in industrialised countries. Switzerland belongs to the countries with the highest and still fastest growing life expectancy at birth worldwide (84.6 years for women and 80.2 years for men in 2010, corresponding to +2.0 and +3.3 years gained since 2000) [2]. The recent demographic scenarios projecting the ageing of the population in Switzerland between 2005 and 2050 showed that this increasing trend will not level-off before year 2050, leading to almost a doubling of the population older than 65 years of age by that date [3]. As the incidence of osteoporotic fractures increases exponentially with age, the implementation of measures aimed at reducing fracture risk is needed to preserve quality of life and to ensure adequate control of health care costs. It has been shown that the direct medical costs of hospitalisations for osteoporotic fractures in women and men already exceeded today the costs of hospitalisations of many other chronic diseases, such as major cardiovascular events (stroke, myocardial infarction, heart failure), breast cancer, and chronic obstructive pulmonary diseases [4].

The goal of osteoporosis treatment is to reduce fractures. This can be achieved either by decreasing bone resorption and/or by increasing bone formation. Bisphosphonates are today’s mainstay of osteoporosis treatment. They act as inhibitors of bone resorption with a high affinity for bone and were shown to increase BMD and reduce fracture risk in patients with postmenopausal, male, and glucocorticosteroid-induced osteoporosis. Due to their (very) long terminal half-life in bone, they can be administered either orally (daily, weekly, or monthly tablets) exposing the patient to a risk of esophageal irritation or intravenously (quarterly or yearly infusions), exposing the patient to the risk of an acute-phase reaction. In addition, intravenous bisphosphonates are contra-indicated in...
patients with restricted renal function. The bisphosphonates alendronate, risedronate, and zoledronate were shown to reduce the risk of new vertebral, non-vertebral, and hip fractures [5–9]. However, while relative fracture risk reduction reached 50% for spine and hip fractures, the order of magnitude for non-vertebral fracture risk reduction was around 20%. While long term treatment of osteoporosis with a bisphosphonate up to 10 years has shown excellent safety [10], bisphosphonate therapy has been associated with a potential risk of osteonecrosis of the jaw and atypical subtrochanteric femoral fractures [11–13]. Other available drugs that reduce bone resorption are the oral selective estrogen receptor modulators (SERMs) raloxifene and tamoxifen, and subcutaneous denosumab, a human monoclonal antibody that inhibits RANKL. Raloxifene was shown to reduce vertebral fracture and breast cancer risk in postmenopausal women [14–17]. SERMs increase the risk of venous thromboembolic events, may increase the risk [16] of fatal stroke in postmenopausal women at increased coronary risk, and may trigger or aggravate climacteric symptoms in younger postmenopausal women [15,16]. Finally, SERMs are not indicated in men. In postmenopausal women with osteoporosis, the bone resorption inhibitor denosumab reduced vertebral, non-vertebral and hip fracture risk by the same order of magnitude as bisphosphonates (–68%, –20%, and –40%, respectively) [18]. The incidence of cancers and infections was comparable to that of placebo in controlled trials. However, due to the tight interrelationship with shared signaling pathways between the skeletal and immune systems, potentially associated risks deserve further scrutiny [19,20]. Osteonecrosis of the jaw was not seen in the pivotal trial but was reported in the extension study [21,22] and in studies with patients with metastatic bone disease or myeloma [23,24]. Compared to bisphosphonates, denosumab exhibits a much shorter terminal half-life of several months instead of several years [25].

In women with postmenopausal osteoporosis, daily subcutaneous injections of full length parathormone (1-84 PTH) and teriparatide (the 1-34 N-terminal fragment of PTH) showed the largest increases in BMD reported to date for any treatment of osteoporosis, accompanied by an important reduction of the risk of new vertebral fractures [26,27]. Teriparatide was shown to reduce the risk of vertebral and non-vertebral but not hip fractures in postmenopausal and glucocorticoid-induced osteoporosis [27,28]. Although the safety and efficacy of teriparatide have been studied beyond two years of treatment, the generally approved duration of therapy is limited to two years.

In summary, osteoporosis and its complications, the fragility fractures, belong to the leading chronic diseases in industrialised countries imposing a growing burden to patients, society and healthcare systems. Treatments available to date are imperfect:

– While therapeutic alternatives are available for inhibiting bone resorption, options are much more limited with regard to bone anabolic substances. There is a need for new bone active substances aimed at restoring quantitatively and qualitatively normal bone.
– While the safety profile of most bone active substances is at least partially known, there is considerable potential for improvement (ONJ, atypical fractures, interactions with the immune system). Treatment alternatives are needed for patients exhibiting or at risk of side-effects.
– While a relative fracture risk reduction of up to 20%, 50%, and 70% can be achieved for non-vertebral, hip, and spine fractures, respectively, still 30 to 80% of these fractures cannot be prevented. As osteoporosis is a systemic disease, there is an obvious need for improving the magnitude of the therapeutic effect at all fracture sites.
– While patients included in pivotal randomised controlled trials usually had osteoporosis defined according to the WHO criteria, i.e. a T-score below –2.5 SD and / or prevalent fragility fractures, a large proportion of fractures occurs at T-scores above –2.5 SD and in patients without prior fractures. Thus, therapies with proven fracture risk reduction efficacy in patients at increased fracture risk, e.g. in patients with osteopenia and/or clinical risk factors, might contribute to earlier and more efficient intervention against fractures.
– While fracture risk increases with age, most studies were performed in patients below 80 years of age. Osteoporosis drugs with a good safety profile and proven to reduce fracture risk in the elderly and the very old are lacking.

For all these reasons, there is an urgent need for the development of new bone active substances aimed at treating osteoporosis and preventing fractures.

**New insights in bone biology**

Bone remodeling is the continuous process by which old bone is removed by bone-resorbing cells, the osteoclasts,
and replaced by new bone synthesised by bone forming cells, the osteoblasts. During adult life bone remodeling primarily serves the purposes of regulating calcium homeostasis and repairing bone micro-fractures resulting from mechanical loading. Knowing that the skeleton is completely remodeled every ten years, microfracture repair prevents its excessive ageing by preventing the accumulation of old bone [29]. At their smallest functional level, the bone remodeling unit, osteoblasts and osteoclasts are tightly coupled by paracrine signaling whereby the net balance in new bone built may be positive (during growth), neutral (at peak bone mass) or negative (in osteoporosis and other diseases leading to a net loss of bone mass). Several molecules that either promote or inhibit the activity of bone remodeling and its constituent cells have been recently identified, giving new insights into bone pathophysiology and opening the gateway for possible future therapeutic options.

Osteoblasts

The osteoblasts are derived from mesenchymal stem cells, produce the bone matrix which consists of collagenous and non-collagenous proteins (such as type I collagen and osteocalcin, respectively), and control its subsequent mineralisation, that is the deposition of hydroxyapatite. Thus, the rate of bone formation will depend upon individual osteoblast activity, their lifespan and the number of precursor cells recruited. As shown in figure 1, parathormone (PTH) and PTH related protein (PTHrp), the only other known ligand of the PTH receptor, increase the lifespan of mature osteoblasts by reducing their rate of apoptosis, which explains their anabolic effects on bone [30]. The calcium-sensing receptor (CaR) which is located on the surface of the parathyroid gland senses extracellular levels of ionised calcium and controls calcium homeostasis by regulating the release of PTH. Calcimimetics mimic the effects of ionized calcium on the CaR, create a leftward shift in the set point for PTH secretion, i.e. decrease the secretion of PTH [31, 32]. Calcilytics do the opposite, that is mimick low ionised concentrations on the CaR which induces PTH secretion by the parathyroid glands [32].

As recently discovered, osteoblastic differentiation and the number of osteoblast precursor cells recruited is regulated by a core molecular pathway, the canonical Wnt/β-catenin pathway [33]. Wnt, the acronym resulting from a combination of two genes found in Drosophila ("Wingless") and vertebrates ("Int"), stands for a specific family of proteins involved in the Wnt signaling pathway. The latter plays diverse roles ranging from embryology (e.g., during mesoderm, neurectoderm and body axis formation), and bone modeling and remodeling, to causing diseases such as cancer. When activated by Wnt, the pathway ultimately leads to the accumulation of β-catenin in the nucleus and to the subsequent gene transcription, i.e., to signal-dependent cell differentiation. When a cell is not exposed to a Wnt signal, β-catenin is degraded and gene transcription is stopped [34–36]. In bone, the Wnt signaling pathway plays a key role in osteoblast differentiation so that agents directed against endogenous Wnt inhibitors specific to bone, might selectively permit accelerated osteoblast differentiation and thus increase the bone formation rate [33, 36].

Osteoclasts

During the process of matrix building and mineralisation, some osteoblasts remain trapped within lacunae and are named osteocytes, characterised by their dendritic extensions in the bone canaliculi which, in analogy with the dendritic network of the nervous system, allow them to communicate with each other and with cells on the bone surface. Although osteocytes are the most common cell type in bone, they were neglected by research for many years, possibly due to their discrete level of activity. However, osteocytes were shown to play a key role in the regulation of phosphate metabolism (as the source of FGF-23) and to be involved in sensing and transferring information possibly by acting as the not yet fully understood but long sought mechanosensor controlling bone remodeling [37]. As shown in figure 1, Osteocytes were shown to be almost the only source of the endogenous Wnt-inhibitor sclerostin [38] which may be one of the inhibitory signals they use to transmit mechanical load information to the effector cells [39–41].

Osteoclasts

The osteoclasts are issued from haemopoietic stem cells and are formed by the fusion of cells from the monocyte-macrophage cell line. Osteoclastogenesis requires the presence of RANKL (Receptor Activator of Nuclear factor κB Ligand), a member of the TNF (Tumor Necrosis Factor) cytokines, and M-CSF (Macrophage-Colony Stimulating Factor). Once RANKL is expressed by the osteoblasts, it activates its receptor RANK on the cells of the osteoclast lineage leading to their proliferation, maturation, activation, and survival, ultimately resulting into increased bone resorption. Osteoprotegerin (OPG), a soluble decoy receptor of RANKL also produced by the osteoblasts, acts as its natural antagonist [42]. Thus, as shown in figure 2, an antibody directed against RANKL, such as denosumab, will mimic the effects of OPG and reduce the production, maturation, and activity of osteoclasts by reversibly hamper-
New and emerging treatment options of osteoporosis

These recent insights into bone pathophysiology and the better understanding of the core mechanisms involved in the development of osteoporosis have identified new targets for intervention and led to the development of molecules with therapeutic potential.

Stimulation of bone formation

**PTH and PTHrp analogues**

In many countries, the only available bone anabolic substance is human recombinant N-terminal 1-34 PTH (teriparatide). Full length 1-84 PTH is available in Europe but has not yet been approved in the US and in Switzerland. Due to its unique efficacy profile, a broadened use of teriparatide as a first line treatment for postmenopausal women and for men with severe osteoporosis has been recently advocated [48]. However, there is a need for accessible and more convenient bone anabolic agents. A teriparatide-coated microneedle patch system (ZP-PTH) was developed and the results of a phase II dose-finding study showed an increase in biochemical markers of bone turnover and in lumbar spine BMD [49, 50].

PTHrp is a protein analogue to 1-84 PTH which has physiological functions, such as the stimulation of bone resorption allowing tooth eruption and the control of calcium metabolism in lactating women [51]. PTHrp also plays an important paraneoplastic role in hypercalcaemia of malignancy [52]. While the continuous administration of PTH leads to bone resorption over formation, i.e., to a net loss of bone mass, the continuous administration of PTHrp preferentially stimulates bone formation. It was recently suggested that this apparently discrepant finding may be due to the existence of two activated states of the PTH receptor with continuous cAMP secretion after PTH binding and burst cAMP secretion after PTHrp binding [53], thus mimicking the effects of intermittently administered PTH, such as reduced osteoblast apoptosis [54]. A randomised, placebo- and teriparatide-controlled dose-finding study with the PTHrp analogue BA-058 in 222 women with postmenopausal osteoporosis (mean age 65 years) was completed in 2009, showing a dose-dependent increase in BMD at the spine, the total hip and the femoral neck after 6 months which was comparable to (or at the highest dose (SC 80 µd/d) even numerically higher than) that achieved with teriparatide with comparable tolerability (NCT00542425). A randomised controlled phase III trial comparing the effects of BA-058 80 µd/d SC with teriparatide 20 µd/d SC and SC placebo on the number of new morphometric vertebral fractures after 18 months in postmenopausal women with osteoporosis is currently ongoing (NCT01343004).

**Calcilytics**

Oral CaR-agonists or calcilytics, such as JTT-305/ MK-5442 and SB-423557, were shown to stimulate endogenous transient PTH secretion and bone formation and to prevent bone loss in ovariecotomised rats, thus delivering a proof of concept [55, 56]. However, after two dose-finding studies in women with postmenopausal osteoporosis (NCT00996801 and NCT00960934), the development of...
MK-5442, the most advanced in development, was halted in 2011 for unreported reasons.

**Antagonists of Wnt-inhibitors**

Sclerostin (SOST) and dickkopf-1 (dkk1) are endogenous inhibitors of the canonical Wnt/β-catenin pathway specific to bone. In the presence of these inhibitors, the osteoblast precursors are not exposed to a Wnt signal, so that β-catenin is degraded and osteoblast differentiation and recruitment is stopped. Antibodies directed against sclerostin or dickkopf-1, should therefore have bone anabolic properties.

Sclerosteosis is a rare autosomal recessive craniofacial hyperostosis caused by one of at least six known inactivating mutations of the single gene which encodes for sclerostin [57–59]. Homozygous carriers are exposed to facial palsy and deafness during childhood, as a result of cranial nerve entrapment, and to development of elevated intracranial pressure, as a result of calvarial overgrowth. The complications of the latter are usually the cause of death [60, 61]. Patients with sclerosteosis have bone of normal quality [62]. Heterozygous carriers of sclerosteosis have BMD values consistently higher than the mean of healthy subjects without any of the bone complications encountered in homozygotes [63]. Sclerosteosis and the closely related Van Buchem disease [64–66] represent a natural SOST gene knock-out model in humans, which was seminal for the development of sclerostin antibodies as anabolic bone substances. In preclinical studies, the administration of sclerostin-neutralising monoclonal antibodies was shown to increase bone formation on trabecular, periosteal, endocortical, and intracortical surfaces without increasing bone resorption (as seen with teriparatide or full length PTH), and to increase trabecular thickness, BMD and bone strength [67, 68]. The subcutaneous administration of a single dose of AMG 785, a human recombinant sclerostin antibody, to healthy men and postmenopausal women showed dose-related increases in bone formation markers with a dose-related decrease in one bone resorption marker (serum C-telopeptide, CTX), suggesting a large anabolic window. In addition, BMD increases at the lumbar spine and the hip were reported on day 85 after the single injection. AMG 785 was generally well tolerated. One treatment-related serious adverse event of nonspecific hepatitis was reported and six subjects in the higher-dose groups developed anti-AMG 785 antibodies, 2 of which were neutralising [69]. A dose-finding randomised placebo-, teriparatide- and alendronate-controlled 12-month phase II study in postmenopausal women with low BMD was recently completed (NCT00896532). According to a company press release available under www.amgen.com, “significant increases in lumbar spine bone mineral density at month 12 versus the placebo arm” were demonstrated, and “AMG 785 compared positively with the two active comparators, teriparatide and alendronate.” Furthermore, “the overall incidence of adverse events was generally balanced between groups. Consistent with previous studies, injection site reactions were reported more frequently in those patients receiving AMG 785”.

Two additional phase II fracture healing studies with AMG 785 (in tibial diaphyseal fractures post intramedullary nail-
Inhibition of bone resorption

**RANKL-inhibitors**

Denosumab, the first in class RANKL-inhibitor, is a recombinant human IgG2 antibody with affinity and specificity for RANKL. By binding to RANKL, denosumab prevents the RANKL/RANK interaction on the osteoblast which leads to the inhibition of osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone. The 3-year, randomised, double-blind, placebo-controlled fracture endpoint trial FREEDOM enrolled 7808 women between the ages of 60 and 90 years (mean 72 years) who had a baseline BMD T-score between −2.5 and −4.0 at either the lumbar spine or total hip. The mean baseline lumbar spine BMD T-score was −2.8 SD, and 23% of women had a vertebral fracture at baseline. Women were randomised to receive SC injections of either placebo (N = 3906) or denosumab 60 mg (N = 3902) once every 6 months. All women received at least 1000 mg calcium and 400 IU vitamin D supplementation daily. Denosumab significantly reduced the incidence of new morphometric vertebral fractures (primary endpoint) at 3 years (7.2% vs 2.3%, p = 0.0001). In addition, denosumab significantly reduced the incidence of hip and non-vertebral fractures (secondary endpoints) at 3 years (1.2% vs 0.7%, −40%, p = 0.04 and 8.0% vs 6.5%, −20%, p = 0.01, respectively) [18]. Furthermore, the antifracture efficacy of denosumab was consistent across patients with varying degrees of fracture risk [79]. Denosumab was generally well tolerated. Based on postmarketing and clinical research experience available to date, denosumab exposes patients to a risk of hypocalcaemia, which is significant in patients with severe renal impairment or receiving dialysis, to a potential for adverse outcomes resulting from the induced profound, even if reversible, suppression of bone remodelling such as osteonecrosis of the jaw, atypical fractures and delayed fracture healing, and to a potentially increased risk of severe infections consistent with its osteoimmunological effects. Epidermal and dermal adverse events not specific to the injection site (such as dermatitis, eczema, and rashes) were significantly increased. Finally, cases of pancreatitis and new malignancies of the breast, the reproductive system, and the gastrointestinal system were numerically more frequent with denosumab with no established causal relationship to drug exposure [80]. Denosumab was also proven effective for increasing BMD over 2 years in women receiving adjuvant aromatase inhibitor therapy for breast cancer [81] and for increasing BMD and reducing the incidence of vertebral fractures over 3 years in men with non-metastatic prostate cancer receiving androgen deprivation therapy [82]. The only other RANKL-inhibitor currently under clinical development we are aware of is ALX-0141, a nanobody with Phase I results presented in 2011 [83].

**Cathepsin K inhibitors**

Odanacatib is the most advanced cathepsin K inhibitor currently under development. Odanacatib was shown to be orally bio-available, highly selective for and reversibly binding to cathepsin K [84]. Cathepsin K selectivity is responsible for the lack of accumulation of undesirable collagen in cutaneous fibroblasts [84]. The development of less selective cathepsin K inhibitors, such as balicatib, was stopped in phase 2 development due to the appearance of sclerodermia-like skin lesions [85]. Based on phase I and II results, the recommended dosage is 50mg once weekly per os [86, 87]. The increases in spine and hip BMD observed with odanacatib were comparable to those observed with the bisphosphate zoledronate and the RANKL-inhibitor denosumab [5, 18, 87]. Interestingly, while there was a smaller reduction in markers of bone resorption in comparison with other powerful antiresorptive agents, the reduction in levels of formation markers was much smaller [88]. Furthermore, histomorphometry of bone biopsies performed in a subset of 32 patients included in the phase II trial showed that the modest reduction in bone formation markers was not accompanied by a suppression of the bone formation rate [87–89]. These findings suggest a decoupling between bone formation and resorption. It was hypothesised that as the inhibition of cathepsin K suppresses osteoclast function but does not impair osteoclast viability, it may preserve the osteoclast-osteoblast crosstalk and maintain bone formation [89]. In addition, unlike conventional antiresorptives, odanacatib displayed site specific effects on trabecular versus cortical bone formation with marked increases in periosteal bone formation and cortical thickness in ovariectomised monkeys [90]. Although their clinical relevance remains to be confirmed, these findings would represent a major advance in the field of bone research. A randomised, placebo-controlled phase III fracture endpoint trial, which has enrolled more than 16000 postmenopausal women with low bone mass, is currently ongoing with expected results during summer 2012 (NCT00529373). Once available, the results of this study will unveil a comprehensive efficacy and safety profile of odanacatib for the treatment of postmenopausal osteoporosis. Another cathepsin K inhibitor currently in phase II of development is ONO-5334 [91].

**Access to therapy – another frontier?**

Several new therapeutic classes against osteoporosis, for which there is an important medical need, will become available in the near future. Based on today’s known or expected profile of drugs such as the cathepsin K inhibitor odanacatib and the sclerostin antibodies, which both may for the first time allow for a decoupling between bone formation and resorption, it should be anticipated that our options for successfully treating osteoporosis, that is for reducing fracture risk, will be considerably enhanced. Whether new and even better drugs alone will suffice to successfully address the socioeconomical challenges ahead is questionable. Keeping in mind that Switzerland, as one of the leading countries with regard to the proportion of elderly and very old in its population, represents a paradigm for the near future of many other industrialised countries, the results of a recent survey conducted at the emergency wards of 8 Swiss hospitals are enlightening: among 3667 patients who presented with a fragility fracture, only 24% of the women and 14% of the men underwent appropriate diagnostic workup (i.e., measurement of...
bone mineral density (BMD) by DXA and were adequately prescribed a treatment with a bone active substance proven to reduce fracture risk [92]. Thus, access to diagnosis and adequate therapy is and will supposedly remain a key challenge in Switzerland as well as in other industrialised countries. The development and calibration of the FRAX® fracture risk calculator to the Swiss setting (available under http://www.shef.ac.uk/FRAX/) represented a critical and important step for simplifying the identification of patients at increased risk of fracture [93, 94]. The FRAX® tool has been developed by World Health Organization to evaluate individual fracture risk. It is based on individual patient models that integrate the risks associated with clinical risk factors as well as bone mineral density (BMD) at the femoral neck. The FRAX® algorithms give the 10-year probabilities of hip fracture and of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture) [76, 95]. Country-specific cost-effective FRAX® intervention thresholds have been established for Switzerland [96] and other industrialised countries [97].

Conclusion

Osteoporosis is a highly prevalent severe disease imposing a heavy burden of suffering on patients and costs to society. Osteoporosis can be diagnosed by DXA and the individual fracture risk can be calculated with FRAX®. FRAX®-based cost-effective intervention thresholds exist and are on their way for implementation in daily practice. Therapies proven to reduce fracture risk, even if imperfect, are already available. More effective and better tolerated therapies will become available soon, which may contribute to increase the currently low treatment rate of even severe osteoporosis by allowing tailor-made approaches aimed at minimising fracture risk at the individual patient level.

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References


three blinded active-controlled phase III trials in cancer patients with bone metastases. Ann Oncol
29 Manolagas SC. Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosi-
36 Rey JP, Ellis D. Wnt modulators in the biotech pipeline. Develop-
minal dynamics: an official publication of the American Association of Anato-
ates bone response to mechanical unloading through antagonizing Wnt/beta-
42 Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and ac-
45 Bromme D, Lecaille F. Cathepsin K inhibitors for osteoporosis and poten-
46 Gell BD, Shi GP, Chapman HA, Desnick RJ. Pycnodysostosis, a lyso-
49 Daddona PE, Matriano JA, Mandema J, Mao YF. Parathyroid hormone (1–34)-coated microneedle patch system: clinical pharmacokinetics and pharmacodynamics for treatment of osteoporosis. Pharmaceutical re-
51 Lippuner K, Zehnder HJ, Casez JP, Takkenen R, Jaeger P. PTH-related protein is released into the mother’s bloodstream during location: evi-
52 Casez J, Pfannmutter R, Nguyen Q, Lippuner K, Jaeger P. Diagnostic ap-
proach to hypercalcemia: relevance of parathyroid hormone and para-
53 Rosenblatt M. When two keys ﬁt one lock, surprises follow. Nat Chem 
55 Kimura S, Nakagawa T, Matsuo Y, Ishida Y, Okamoto Y, Hayashi M. JTT-305, an orally active calcium-sensing receptor antagonist, stimu-
56 Kumar S, Matheny CJ, Hoffman SJ, et al. An orally active calcium-sensing receptor antagonist that transiently increases plasma concentra-
57 Brunkow ME, Gardner JC, Van Ness J, et al. Bone dysplasia sclero-
58 Balemans W, Ebeling M, Patel N, et al. Increased bone density in scler-
59 Papapoulos SE. Targeting sclerostin as potential treatment of osteo-
61 Hamersma H, Gardner J, Beighton P. The natural history of sclero-
63 Gardner JC, van Bezooyen RL, Mervis B, Handy NA, Lowik CW, Hamersma H, et al. Bone mineral density in sclerosteosis; affected in-
64 Vanhoenacker FM, Balemans W, Tan GJ, Dikkers FG, De Schepper AM, Mathysen DG, et al. Van Buchem disease: lifetime evolution of ra-
67 Ominsky MS, Vlassores F, Joette J, et al. Two doses of sclerostin anti-
68 Li X, Warnimming KS, Niu QT, et al. Inhibition of sclerostin by mono-
69 Padhi D, Jang G, Stouch B, Fang L, Posvar E. Single-dose, placebo-
controlled, randomized study of AMG 785, a sclerostin monoclonal anti-
70 Tian E, Zhan F, Walker R, Rasmussen E, Ma Y, Barlogie B, et al. The role of the Wnt-signaling antagonist DKK1 in the development
Targeting osteoblasts to stimulate bone formation.
Recombinant human full length parathormone, rhPTH (1-84), its N-terminal segment rhPTH (1-34) and PTH related protein (PTHrp) analogues exert their bone anabolic after binding to the PTH receptor present on the osteoblasts. Calcilytics modulate PTH secretion by shifting the setpoint of the calcium-receptor (CaR) found on parathyroid cells. Sclerostin and Dickkopf-1 (dkk1) are endogenous inhibitors of the canonical Wnt-β-catenin signaling pathway. Monoclonal antibodies directed against sclerostin or dkk1 induce an intracellular accumulation of β-catenin followed by increased gene transcription which ultimately results into stimulation of osteoblastic bone formation.

Figure 1

Targeting osteoclasts to inhibit bone resorption.
By binding to the RANK-ligand (RANKL), the recombinant human IgG2-antibody denosumab prevents the interaction of RANKL with its receptor RANK, which leads to the inhibition of osteoclast formation, function, and survival, and to decreasing bone resorption. Odanacatib is an inhibitor of cathepsin K, a lysosomal cysteine protease with high collagenase activity expressed predominantly in osteoclasts, which may suppress osteoclast function without impairing osteoclast viability, thus preserving the osteoclast-osteoblast crosstalk and bone formation.

Figure 2
Current and future treatment paradigm of osteoporotic bone loss of bone mass and microarchitecture.

According to the current treatment paradigm, antiresorptive drugs are the mainstay first-line therapy for reducing fracture risk in patients with osteoporosis, and anabolic substances are usually recommended in patients with severe osteoporosis only. As lost bone microarchitecture cannot be recovered, a future treatment paradigm may aim at reversing osteoporosis by maximising bone mass and preserving bone microarchitecture during the early phase of disease progression, the achieved gains being preserved by an inhibitor of bone resorption used in a second step.