Published in final edited form as:

Nat Med. 2009 February ; 15(2): 144–145. doi:10.1038/nm0209-144.

Breaking into bone biology: Target practice

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Bone strength in adults is maintained through the proper balance of continuous bone formation and resorption¹. An imbalance favoring resorption over formation results in osteoporosis—loss of bone mass—a condition that increases the risk for fractures and is predicted to affect half of Americans over the age of 50 by the year 2020 (ref. ²).

Two cell types have pivotal roles in bone biology: osteoblasts, which build bone up, and osteoclasts, which resorb bone. Although some current treatments result in building of new bone, most of them, such as bisphosphonates, employ an antiresorptive approach aimed at blocking bone loss³. There are downsides to these treatments, such as esophagitis associated with bisphosphonates. But they have been used quite effectively for more than ten years³, and so the bar for improved treatments is high.

At least three elements for improving antiresorptive drug development should be considered: efficacy, specificity and dosing, meaning the agent should be convenient to administer for both the doctor and the patient as infrequently as possible.

Recent clinical findings, reported this January by Brown *et al.*⁴, have bolstered the reputation of one potential osteoporosis drug target—the receptor activator of nuclear factor- κ B (RANK)—RANK ligand (RANKL) pathway, which is central to osteoclast differentiation and activation. These clinical findings emerge against a backdrop of new basic research findings that have probed the value of other drug targets, including pathways that bump up osteoclast formation or activity^{5–7}. These basic findings should cause researchers to think carefully about how to manage the issue of specificity—for some bone-related conditions, a drug target that regulates more than one pathway might be worth pursuing.

Since the discovery of RANKL more than a decade ago, the major pathways leading to differentiation of hematopoietic progenitor cells into osteoclasts and their subsequent activation have been defined (Fig. 1). The RANKL-RANK [AU: **Before you listed RANK first. Please choose one way to be consistent.**] pathway directs terminal differentiation of osteoclast precursor cells and stimulates bone resorption by mature osteoclasts. Preclinical characterization of the RANKL-RANK pathway has led to the development of drugs that specifically block the terminal differentiation of osteoclasts.

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Osteoporosis researchers do not suffer from a lack of potential drug targets—so one challenge is to decide which ones to focus on. Yongwon Choi, Matthew C. Walsh and Joseph R. Arron now examine several molecules involved in bone biology and assess their prospects. In a second commentary, Cliff Rosen analyzes findings that serotonin, derived from the gut, regulates bone formation. The findings not only could lead to new drug targets, they also could help explain clinical data that serotonin reuptake inhibitors—widely prescribed as antidepressants—widen bones.

Brown *et al.*⁴ tested a humanized antibody against RANKL. They found that the antibody effectively prevents bone decay associated with postmenopausal osteoporosis⁴, and that it seems to be at least as effective as bisphosphonates. Although long-term safety and efficacy remain to be determined, anti-RANKL therapy may have fewer adverse effects, because it is so specifically targeted to osteoclast biology. In addition, the antibody can be dosed as infrequently as once every six months, which is particularly attractive as a preventive therapy for osteoporosis in which the affected individual feels and appears outwardly healthy despite inherent fracture risks.

As osteoclasts are derived from hematopoietic precursors, many molecules previously associated with functional regulation of cells of the immune system also control terminal differentiation of osteoclast precursor cells^{8,9}. For instance, recent reports show that Bruton's tyrosine kinase (Btk), a factor essential for B cell development, and its relative Tec kinase regulate terminal differentiation of osteoclasts⁵. Another study shows that a molecule thought to function specifically in the osteoclast to degrade bone, cathepsin K, also has a role in the function of Toll-like receptor 9, a molecular sensor of infection⁶.

Although it is logical to expand the scope of potential molecular targets for osteoporosis treatment to include the growing list of factors associated with osteoclast differentiation and function, many of these factors, such as Btk and cathepsin K, may lack the degree of functional specificity that RANKL has for osteoclasts and in many cases may contribute to other aspects of human physiology. Decreased specificity is associated with obvious drawbacks, particularly given the low tolerance [AU: of who or what?] for adverse effects in a preventive therapeutic.

However, in some contexts, broader target expression could be advantageous. For example, small molecule inhibitors of Btk can be used to prevent bone loss and are also likely to induce immunosuppression—a dual effect that could be an advantage in some settings, such as rheumatoid arthritis, an inflammatory disease in the joints associated with bone erosion and systemic osteoporosis. B cell depletion via rituximab is successfully used to treat rheumatoid arthritis, and so the combined immunosuppressive and antiresorptive effects of Btk inhibition may be particularly beneficial to individuals with rheumatoid arthritis with considerable bone erosions. In a similar fashion, inhibitors of cathepsin K may also be considered for treatment of inflammatory disease in addition to blocking pathogenic osteoclast activity.

Considering the opposing effects of osteoclasts and osteoblasts on bone homeostasis, an ideal therapeutic might decrease the function of the former while simultaneously increasing the function of the latter. A recent report shows that mice lacking the protein thought to regulate osteoclast maturation, dendritic cell–specific transmembrane protein [AU: OK?], are of particular interest in this regard because they both [AU: unclear who 'they both' refers to— if to the processes described next, the word is not necessary] show lower osteoclast activity in the presence of increased new bone formation⁷.

It is generally believed that, in addition to resorbing bone, osteoclasts can enhance osteoblast differentiation and function through a loosely defined process called 'coupling'¹⁰. Identifying the molecular pathways that regulate this [au: cut out 'presumed' because it sounds dismissive. If that is your intent, should be framed with more explanation] coupling process may lead to the development of therapeutics capable of simultaneously preventing bone loss and inducing new bone formation.

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Figure 1.

Targeting the osteoclast. When RANKL binds to its receptor RANK, a signaling adaptor tumor necrosis factor receptor-associated factor-6 (TRAF6) is activated, which eventually leads to induction of the transcription factor nuclear factor of activated T cells, cytoplasmic, calcineurin-dependent-1 (NFATc1). Co-stimulatory receptor ligation stimulates Btk and calcium signaling that amplifies the magnitude of NFATc1 activity, which then induces gene expression profiles required for osteoclast differentiation and activation. DC-STAMP, dendritic cell-specific transmembrane protein.