

## Cytokine inhibition: a new therapeutic avenue for skeletal diseases ▼

The past four years have witnessed breathtaking progress in our understanding of bone cell biology and an in-depth view of bone metabolism. By elucidating the molecular basis of the function and interactions of bone-forming osteoblasts and bone-resorbing osteoclasts, the pathogenesis of various metabolic bone diseases underwent a substantial paradigmatic change. In addition to providing insights into the cellular basis of metabolic and immunologic bone diseases [1], progress in these research areas has opened promising new avenues for innovative therapeutic strategies.

As described in a recent issue of *Drug Discovery Today* [2], Grimaud and colleagues presented the potential of osteoprotegerin (OPG) as a new drug for bone diseases. OPG was identified in 1997 by Simonet *et al.* [1] as the first soluble member of the tumor necrosis factor receptor superfamily that lacked a transmembrane domain, and was later found to act as an endogenous receptor antagonist for receptor activator of NF- $\kappa$ B ligand (RANKL), the essential cytokine for osteoclast differentiation and activation [3]. By inhibiting the interaction of RANKL with its receptor RANK, which is located on osteoclastic lineage cells, OPG competitively blocks these osteoclast functions *in vitro* [1,3].

Moreover, OPG administration by parenteral injection of a chimeric protein, transgenic overexpression or adenoviral-based gene therapy effectively prevents bone loss in animal models of benign and malignant human diseases that are characterized by an inappropriate increase in osteoclastic bone resorption [4]. These include various forms of osteoporosis (e.g. postmenopausal, glucocorticoid-associated and immobilization-induced),

humoral hypercalcemia of malignancy, osteolytic tumor metastases, tumor pain and multiple myeloma [4]. Moreover, OPG delivery is also effective in counteracting the skeletal changes that are associated with immune-mediated rodent models of skeletal diseases, including rheumatoid arthritis and periodontal disease [5]. Interestingly, OPG administration could also have beneficial effects in immune and vascular disorders [6].

These promising studies have prompted investigators to test this endogenous receptor antagonist in human metabolic bone disease in a randomized, controlled clinical trial [7]. A single injection was effective in reducing enhanced biochemical markers of bone metabolism of postmenopausal women without adverse effects. Other important clinical endpoints in this study cohort (e.g. effects on bone mineral density and reduction of osteoporotic fractures) are currently being investigated. In summary, the discovery and characterization of the molecules responsible for osteoclast function and bone resorption has, for the first time, enabled scientists to design and evaluate cytokine blockade as an innovative form of therapy in skeletal diseases.

## References

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- 7 Bekker, P.J. *et al.* (2001) The effect of a single dose of osteoprotegerin in postmenopausal women. *J. Bone Miner. Res.* 16, 348–360

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## Erratum

Please note a correction to a News in Brief article published in *Drug Discovery Today*, 1st January 2002, Volume 7, No. 1, p. 14.

In the short article entitled *First draft of pufferfish genome published*, it incorrectly states that Myriad Genetics (Salt Lake City, UT, USA) sequenced the genome of the pufferfish (*Fugu rubripes*). However, this genome was actually sequenced by the International Fugu Genome Consortium, which was led by the US Department of Energy's Joint Genome Institute (JGI; Walnut Creek, CA, USA) and the Singapore Biomedical Research Council's Institute for Molecular and Cell Biology (IMCB). Also part of the consortium were the MRC UK Human Genome Mapping Resource Centre (HGMP-RC; Cambridge, UK), the Cambridge University Department of Oncology (Cambridge, UK), and the Institute for Systems Biology (Seattle, WA, USA). The consortium's sequencing efforts were bolstered by two US companies, Celera Genomics (Rockville, MD, USA) and Myriad Genetics (Salt Lake City, UT, USA). For more details, see <http://www.jgi.doe.gov>.

We would like to apologize for this inaccuracy and for any confusion that this might have caused.

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