FAST MOVING FRONTS - 2008

July 2008

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David Lacey & Scott Simonet talk with *ScienceWatch.com* and answer a few questions about this month's Fast Moving Front in the field of Molecular Biology & Genetics. The authors have also sent along images of their work.

Article: Osteoclast differentiation and activation
Authors: Boyle, WJ;Simonet, WS;Lacey, DL
Journal: NATURE, 423 (6937): 337-342 MAY 15 2003
Addresses: Prot Pathways Inc, Woodland Hills, CA 91367 USA.
Amgen Inc, Thousand Oaks, CA 91320 USA.
Prot Pathways Inc, Woodland Hills, CA 91367 USA.

SW: Why do you think your paper is highly cited?

This paper was an invited review article that summarized, circa 2003, what was known in the field of osteoclast differentiation. There had been an explosion of insights in the field over the previous decade and this article succinctly summarized the current state of knowledge with the focus on the central importance of the RANK Ligand pathway.

Coauthor
Scott Simonet

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

As this was a review article, the publication was a synthesis of knowledge of the field. It was clear by the time that this article was published that the newly characterized signaling pathway, the RANKL (Receptor Activator for Nuclear Factor ? B Ligand) pathway, was essential to all aspects of osteoclast biology. This article was written to integrate the RANKL pathway with the other known pathways, hormones, and cells known to play a role in osteoclast biology.

SW: Would you summarize the significance of your paper in layman's terms?

Excess bone resorption occurs across a spectrum of diseases that affect

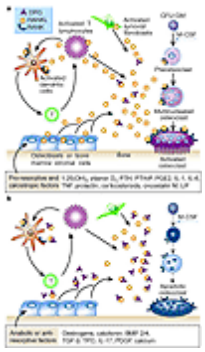
many millions of people worldwide. These would include postmenopausal osteoporosis, cancer-related bone disease, rheumatoid arthritis, and others. The body's cells that actually dissolve the bony tissue are called osteoclasts. The cells develop from immature cells that come from the bone marrow.

This paper describes the factors that govern the development of the bone-resorbing cells from their bone marrow progenitors. The recent discovery of the RANKL pathway represents an important landmark because we now understand a seminal pathway that provides the basis for further research as well as a fundamental rationale for new drug development.

Coauthor
William Boyle

SW: How did you become involved in this research and were there any particular problems encountered along the way?

Figure 1: + details



The authors worked together at Amgen in the mid '90s and discovered osteoprotegerin, the first member of the RANK ligand pathway to be described, and subsequently defined the biology of the other two members (RANK and RANK ligand). The big break in the field for us was the phenotype of the osteoprotegerin (OPG) transgenic mouse that highlighted OPG's central relevance to osteoclast biology. Subsequent efforts were focused on finding the other related members of this pathway. There was intense competition during the latter '90s between the authors and investigators in both industry and academia. The discovery of this pathway and the availability of reagents led to an explosion of knowledge about osteoclast biology.

SW: Where do you see your research leading in the future?

There are two major thrusts that research will lead to in the future. In the area of novel therapeutics for bone loss conditions, Amgen is currently in late-stage clinical trials with a fully human monoclonal antibody directed against RANKL termed "denosumab." And research continues into other aspects of osteoclast biology that are now possible to do given reagent availability.

SW: Do you foresee any social or political implications for your research?

Denosumab has the potential to be a new therapeutic approach for patients with a variety of bone loss conditions. More than 19,000 patients around the world are currently involved in registrational studies necessary to obtain FDA approval for denosumab.

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Keywords: osteoclast differentiation, RANK Ligand pathway, RANKL, Receptor Activator for Nuclear Factor B Ligand, RANKL pathway, osteoclast biology, osteoclasts, bone resorption, postmenopausal osteoporosis, cancer-related bone disease, rheumatoid arthritis, Amgen, osteoprotegerin, OPG, transgenic mouse, Denosumab.

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Figures and descriptions:

Figure 1:

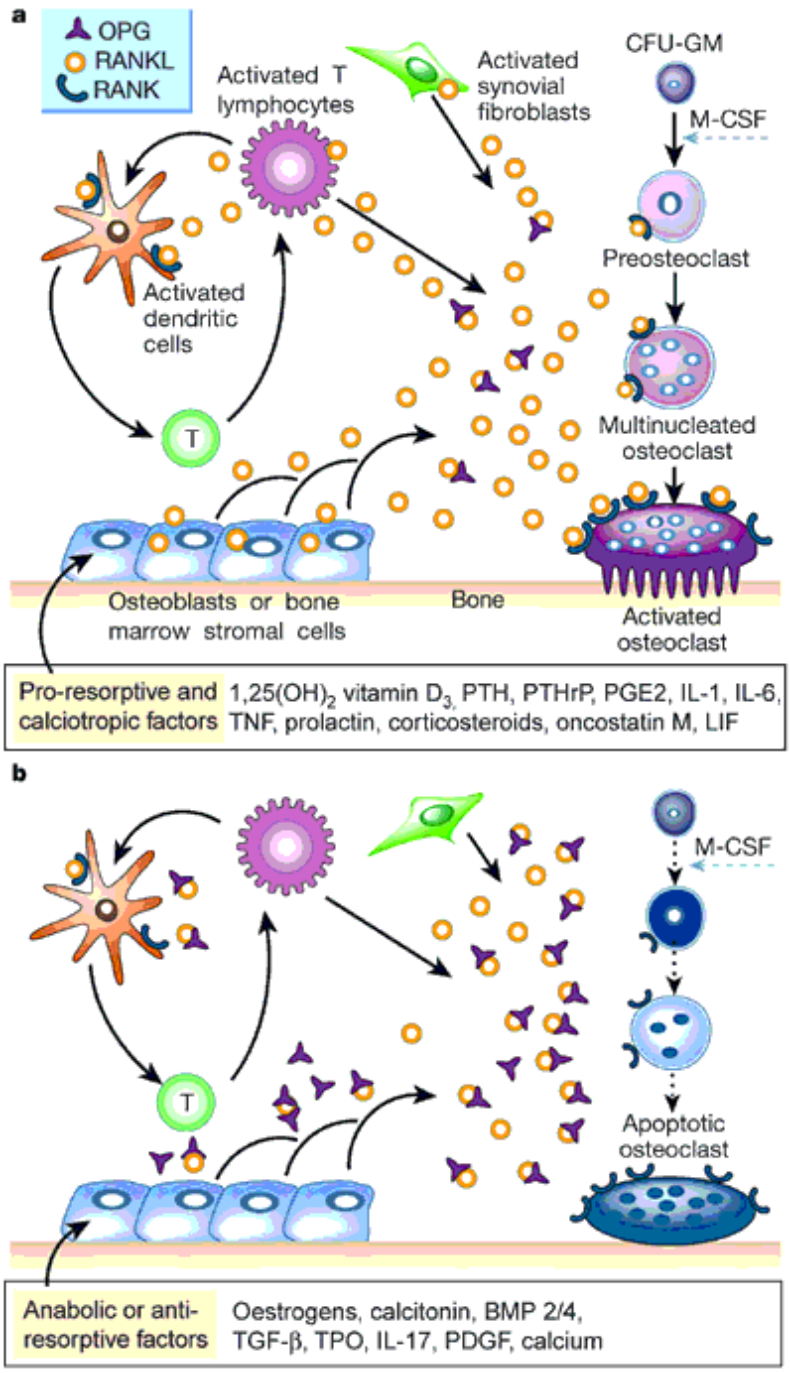

Figure 1: "Hormonal control of bone resorption."

Schematic representation of the mechanism of action of **a**, pro-resorptive and calcitropic factors; and **b**, anabolic and anti-osteoclastic factors. RANKL expression is induced in osteoblasts, activated T cells, synovial fibroblasts and bone marrow stromal cells, and subsequently binds to its specific membrane-bound receptor RANK, thereby triggering a network of TRAF-mediated kinase cascades that promote osteoclast differentiation, activation and survival. Conversely, OPG expression is induced by factors that block bone catabolism and promote anabolic effects. OPG binds and neutralizes RANKL, leading to a block in osteoclastogenesis and decreased survival of pre-existing osteoclasts.

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