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SESSION TIME: 1115 – 1245, Thursday 26 Oct 2006

Invited Plenary Abstracts
Plenary Lectures 7 - Therapeutics

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New treatments for postmenopausal osteoporosis

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Bisphosphonates are, by far, the most commonly used antiresorptive treatments. In addition to alendronate, risedronate and ibandronate, zoledronate given by yearly injection is likely to be available in a near future. There is room, however, for new antiresorptive therapies. Selective estrogen receptor modulators have the potential to provide beneficial effects on other target organs than bone, and large phase III trials are ongoing with lasofoxifene, bazedoxifene and arzoxifene. Denosumab is a monoclonal antibody blocking RANK-ligand and subcutaneous injections have been shown to induce a profound and sustained suppression of bone turnover over 6 months. A fracture trial in postmenopausal osteoporosis is ongoing, but the drug has also a potential role in the management of malignant bone diseases and rhumatoid arthritis.

The fact that cathepsin K is the major osteoclast-derived enzyme responsible for the degradation of type I collagen in bone has led to the ongoing development of specific inhibitors of that enzyme (currently under phase II trials). Finally, there is growing interest in the development of selective antiresorptive agents that would inhibit bone resorption without subsequent inhibition of bone formation, in contrast to other antiresorptive therapy. The development of these "uncoupling" agents, such as chloride channel-7 inhibitors, is based on several recent experimental observations.

The development of anabolic agents specific for bone tissue is a challenge. Non-injectable parathyroid hormone fragments/analogs are likely to be available soon. An alternative strategy is to inhibit the calcium sensing receptor with a specific and short-acting antagonist. Another alternative is to develop parathyroid hormone analogs, with the goal to dissociate the anabolic and resorptive effects, based on interesting preclinical studies. Finally, the recent discovery of the role of sclerostin on the BMP/Wnt pathway and on the expression of osteocytes has led to the development of antisclerostin monoclonal antibodies, that have the potential in animal models to induce a marked stimulation of bone formation.

In conclusion, although currently available treatments are able to reduce the risk of vertebral, and to some extent non vertebral fractures, there is room for improvement. The availability of new agents, especially those stimulating bone formation, alone or in sequential combination with antiresorptives, will improve significantly our management of postmenopausal osteoporosis.

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Anabolic agents – approaches to The Holy Grail for Bone

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We have spent some years attempting to find stimulators of bone formation that could be used in the common diseases of bone loss. One of the observations that we have made is that the bone remodeling cycle shares a number of characteristics in common with the hair follicle cycle. In both, there are phases of growth, resorption or regression, and rest. Moreover, the regulatory controls of both hair follicle and bone remodeling cycles involve many of the same extracellular and intracellular factors. For example, both anagen (the growth phase of the hair cycle) and the bone formation phase of the bone remodeling cycle are controlled by the BMP-2 ligand-signal transduction pathway and downstream molecules such as Wnt and beta-catenin. We have gathered evidence for this notion using a number of small molecules that stimulate BMP2 transcription and determining their effects both on anagen induction in the hair follicle and on bone formation. There has been perfect concordance. This suggests that there are common molecular mechanisms that control cycling tissues in the hair follicle and in the bone remodeling unit, and that manipulation of this pathway therapeutically may have multiple unexpected effects.

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Future of new Vitamin D analogs

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The vitamin D hormone [1α,25$(OH)_2D_3$] exerts pleiotropic effects through the nuclear vitamin D receptor (VDR). The connection between vitamin D and bone resorption started in 1972, when it was reported that 1α,25$(OH)_2D_3$ stimulates bone resorption in fetal long bone cultures. In 1997-98, 2 important cytokines were discovered, osteoprotegerin (OPG), which protects bone by negatively regulating osteoclast formation, and OPGL or RANKL (receptor activator of nuclear factor-κB ligand) as an essential cytokine for osteoclast formation. The demonstration that 1α,25$(OH)_2D_3$ induces RANKL in ostoblastic/stromal cells provided the molecular proof that 1α,25$(OH)_2D_3$ is a bone-resorbing hormone that acts on osteoblasts to stimulate osteoclastogenesis indirectly.

Unexpectedly, through a series of experiments in osteoporosis models with accelerated bone resorption, we found that pharmacological doses of active vitamin D drugs inhibit bone resorption *in vivo*. I will summarize what has been learned from these pharmacology experiments, and present data on the anti-osteoclastogenic action of VDR, direct action of VDR on bone marrow macrophages, c-Fos protein as a target of VDR, and synthesis of mechanism-based, new vitamin D analogs.