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Sclerostin: from bedside to bench, and back to bedside

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The scope and magnitude of medical conditions associated with low bone mass has fueled a great deal of research activity over the past 30 years, aimed at developing compounds, devices, and approaches to improve skeletal properties and reduce fractures. Major advances in approved pharmaceutical therapies for low bone mass began in the early 1990s, with the approval and marketing of calcitonin, etidronate, the first oral nitrogen-containing bisphosphonate—alendronate , and the first selective estrogen receptor modulator (SERM)—raloxifene. While each of these agents has a different mode of action, all function to diminish osteoclast activity in order to prevent further bone loss. The subsequent decades witnessed the debut of additional oral and intravenous bisphosphonates, SERMs and the first bone-targeted monoclonal antibody-based therapy—denosumab. Again, each of these therapies functions to inhibit osteoclast action or osteoclastogenesis. The sole exception to this anti-catabolic trend was the development of parathyroid hormone (PTH) peptides of which teriparatide remains uniquely positioned as the only available skeletal bone-forming compound, i.e., it functions by stimulating osteoblasts to build new bone.

This imbalance in available anti-catabolic versus anabolic agents likely stems, at least in part, from underlying concerns related to patient safety, rather than fundamental issues related to the best approaches to improve skeletal properties particularly in patients with severe osteoporosis. To this point, fears—whether justified or not—over the promotion of skeletal anabolic actions and their potential for driving tumor development and growth either in bone or elsewhere in the body, may explain the delay in pursuing the development of new bone anabolic agents.

Rare genetic diseases, while often debilitating for affected patients, can sometimes provide rare and enlightening insights into human biology that cannot be gleaned through other mechanisms. Within the bone community, such a glimpse has been provided by the rare autosomal recessive condition sclerosteosis, a sclerosing bone disorder that results in abnormally high bone mass. Sclerosteosis was first correctly described in 1967 as a disease distinct from osteopetrosis,[(1)] with affected patients reported to have severe bone overgrowth (hyperostosis) of virtually every skeletal element examined. DXA technology eventually permitted quantitative assessment of the degree of bone overgrowth, and affected patients were found to have Z-scores as high as 14.5 at some skeletal sites (e.g., lumbar spine).[(2)] Further, and perhaps most importantly, studies in human[(3)] and later mouse models of the disease[(4)] revealed that sclerosteosis was primarily a disorder of unrestrained bone formation.

Patients with sclerosteosis present clinically with symptoms related to cranial nerve impingement (e.g., impaired hearing, olfaction, taste, vision) or discomfort due to intracranial pressure, both of which are related to bone overgrowth. Importantly, affected patients do not appear to have increased rates of cancer, though the sample