A Multiscale Systems Model for Advancement of a New Line of Therapy for Osteoporosis

By

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The osteocyte is a load-sensing bone cell, which plays a pivotal role in the bone modeling process. This process is highly regulated by feedback control and poorly described by isolated in vivo or in vitro experiments. In silico systems models present a way by which experimental and clinical data can be integrated in a mathematical framework so that signaling networks can be better understood. The Multiscale Systems Model presented here began as an endeavor to link biological markers and clinical endpoints in a mathematical framework. The goal is to be able to make quantitative inferences around bone physiology, disease progression, and therapeutic modulation of biological targets. This underlying framework has now been extended to include the osteocyte as a source of sclerostin protein, signaling effects of this protein on the Wnt pathway and downstream effects on osteoblasts and osteoclasts. A model of sclerostin inhibition by monoclonal antibodies (mAbs) was developed using data from recent clinical trials, describing the unique mechanism of Wnt pathway modulation for a new treatment for osteoporosis. Techniques for parameter identifiability and optimization were compared and contrasted. Parameters describing mAbs exhibiting target-mediated drug disposition (TMDD) pose identifiability problems, and techniques for establishing identifiability of TMDDs were analyzed. A predictive framework for regional changes in bone mineral density was further developed for sclerostin mAbs and marketed therapies teriparatide and denosumab. Finally, a hazard model of fracture was implemented using lumbar spine BMD, patient baseline characteristics and an additional drug effects as covariates in order to compare efficacy of therapies, their dosing regimens and possible combinations that would improve fracture outcomes for patients with osteoporosis. This novel framework is a powerful predictive tool for furthering knowledge of new therapeutic mechanisms in the context of a data-driven, integrated physiological platform.