Sclerostin-Mediated Osteocyte Control in Bone Remodeling: Extension of a Multiscale Systems Model to Consider New Therapies for Osteoporosis

Rena J. Eudy¹, Marc R. Gastonguay¹,², Kyle T. Baron², Matthew M. Riggs²
(1) Department of Biomedical Engineering, University of Connecticut, USA, (2) Metrum Research Group, LLC, Tariffville, Connecticut, USA

Objectives
To extend a mathematical, multiscale systems model of bone metabolism [1] in order to:
1. describe kinetics of mAbs against sclerostin, currently in clinical development [2], and their effects on serum sclerostin, bone turnover markers, and bone mineral density (BMD) within patients with osteoporosis
2. validate and prepare the model to predict the dosing regimen and treatment combination that will result in the greatest increase in BMD
3. further understand the role of the osteocyte (OCY) in bone remodeling

Methods
PK/PD Model. A 2-compartment PK model with first-order absorption and parallel linear and non-linear clearance pathways was built using treatment-arm level data. This was linked to an indirect response model describing circulating sclerostin using NONMEM®(R)v7.2.

Systems Model. Parameters in the bone model were sequentially estimated by first tuning parameters upstream of osteoblasts (OB) and osteocytes (OC), fixing these, and then tuning parameters with greater proximity to OB and OC, fitting to data describing changes in P1NP and CTx (markers of formation and resorption, respectively).

Optimization/Validation. Parameters were optimized using the R package minque [3], minimizing an OLS objective function. Model performance was validated by local sensitivity analysis and predictive performance was evaluated using a naïve clinical dataset.

Results: Bone Model
Systems Model Equations Six points of intersection were identified in the existing systems model where sclerostin has a known effect.

1. The depletion of pre-osteoblasts (ROB)
2. The sclerostin effect on OB propagates though a “translation” (trans) compartment:
3. The osteocyte (OCY) compartment, where apoptosis is proportional to circulating sclerostin:

\[ \frac{d}{dt} \text{OCY} = k_{\text{inj}} - k_{\text{outj}} \cdot \text{SCLER} \]

where \( k_{\text{outj}} \) represents the rate of OB becoming embedded in the bone matrix and

\[ k_{\text{outj}} = \frac{\text{OB}_\text{inj}}{\text{OB}_\text{outj}} \cdot \text{SCLER} \]

4. Osteocyte effect on receptor activator of nuclear factor-kappa-B ligand (RANKL)
5. An osteocyte effect on osteoprotegerin (OPG), with the form:

\[ \text{OSTEoeffect} = \frac{\text{SCLER} \cdot \text{OCY}}{1 + \text{EC}_50 \cdot \text{SCLER} + \text{SCLER}} \]

6. Compartments to describe changes in lumbar spine, femoral neck, and total hip BMD:

\[ \frac{d}{dt} \text{BMD} = k_{\text{inj}} - k_{\text{outj}} \cdot \text{BMD} \]

\[ \text{BMD}_\text{inj} = k_{\text{inj}} \cdot \text{BMD}_\text{outj} \]

\[ \text{BMD}_\text{outj} = \text{BMD}_\text{inj} \]

Simulations
Dose-matched administrations of sclerostin mAb were simulated at several dosing intervals. Larger dosing intervals result in greater increases anabolic activity (top left, fig4), because pre-curser pool (ROB) has more time to replenish (top right, fig4).

Maximum simulated resorption activity, however, is also increased with a large dosing interval (bottom left, fig4). The result is smaller increases in total hip BMD with large dosing intervals (bottom right, fig4).

The model supports the physiologic role of the OCY in the cross-talk between OB and OC by signaling through RANKL and OPG [4].

References

Conclusion
The utility of the model to explore biological implications of Wnt pathway modification and the role of the OCY in bone remodeling has been demonstrated. Findings indicate that choosing an appropriate dosing interval is crucial to achieve sustained increases in BMD, due to differential effects of feedback regulation and depletion of responding osteoblasts.