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

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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 osteoclasts (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 *minqa* [3], minimizing an OLS objective function. Model performance was validated by local sensitivity analysis and predictive performance was evaluated using a *näive* clinical dataset.

Results: PK/PD Model

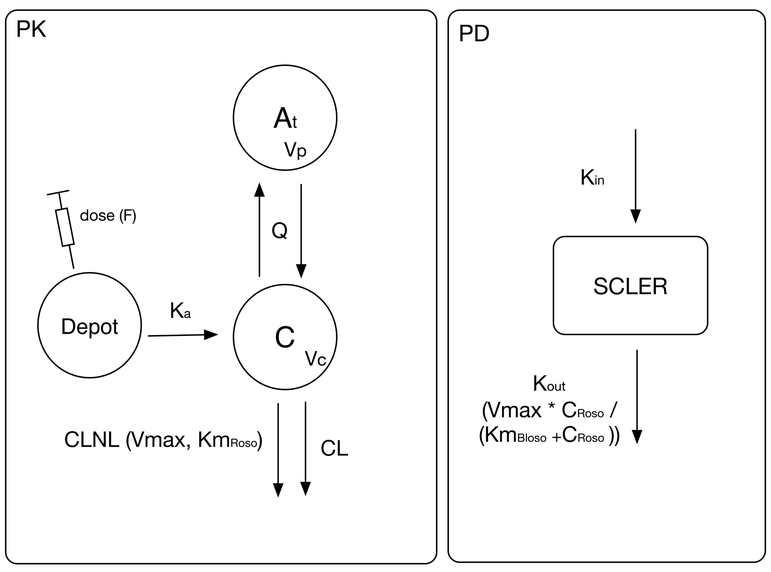

Figure 1: (A) PK model of mAb against sclerostin. (B) PD model of circulating sclerostin, driven by mAb concentration. Vmax parameter is shared between models, but Km is re-estimated in PD model

Parameter estimates

Parameter	Value
Absorption rate constant, k_a	0.187 day^{-1}
Linear clearance, CL	0.254 L/day
Maximum elimination rate, Vmax	5.87 day^{-1}
Michaelis constant, km	0.453 nM for blosozumab 9.93 nM for romosozumab
Volume of the central compartment, Vc	2.90 L
Volume of peripheral compartment, Vp	3.29 L
Intercompartmental clearance, Q	0.467 L/day
Bioavailability, F	0.904 unitless
Synthesis rate of total receptor, k_{in}	3.73 nmol/day
Degradation rate of total receptor, k_{out}	25.0 day^{-1}
Internalization rate of total receptor, k_0	0.197 day^{-1}

References

1. Peterson, M. C., & Riggs, M. M. (2010). A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. Bone, 46(1), 49-63. doi:10.1016/j.bone.2009.08.053.
2. Recker, R., Benson, C., Matsumoto, T., Bolognese, M., Robins, D., Alam, J., ...Myers, S. (2014). A randomized, double-blind phase 2 clinical trial of blosozumab, a sclerostin antibody, in postmenopausal women with low bone mineral density. J Bone Miner Res. doi:10.1002/jbmr.2351.
3. Bates, D. Mullen, K.M., J.C.N. and R.V., 2014. minqa: Derivative-free optimization algorithms by quadratic approximation. URL: http://cran.r-project.org/package=minqa; R package version 1.2.4.
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Results: Bone Model

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

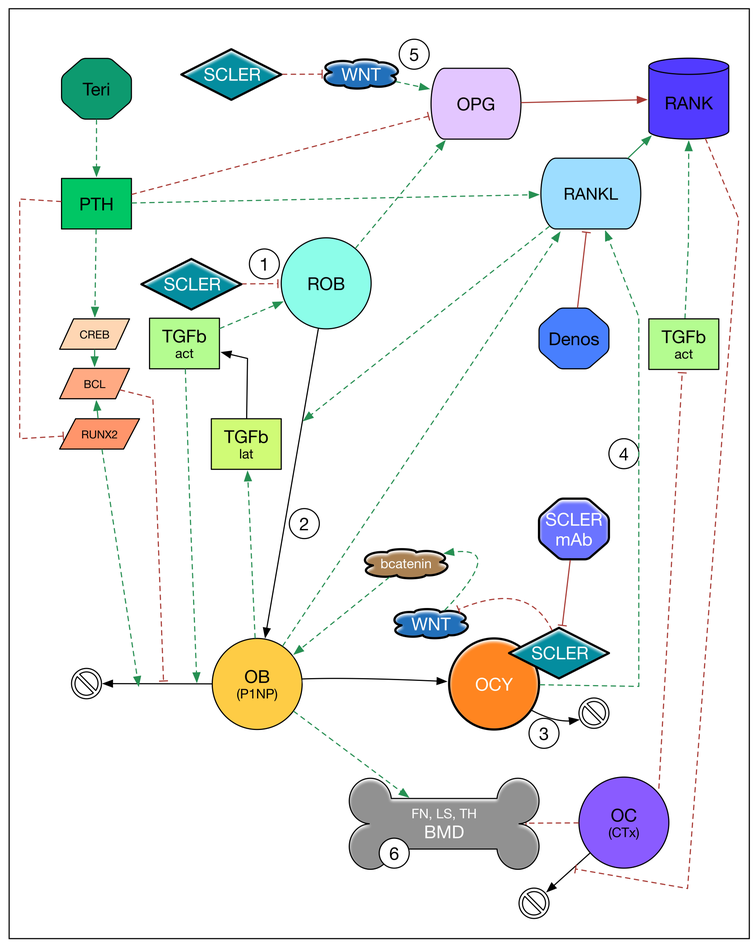

Figure 2: Bone model schematic showing intersection points where sclerostin has an effect

1. The depletion of pre-osteoblasts (ROB)
2. The sclerostin effect on OB propagates though a "translation" (*trans*) compartment:

$$\frac{\mathrm{d}}{\mathrm{dt}} trans = kin_{trans} \cdot \left(1 + \frac{EMAX_{\mathrm{SCLER}} \cdot \mathrm{SCLER}^{\gamma OB}}{EC_{50,\mathrm{SCLER}}^{\gamma OB} + \mathrm{SCLER}^{\gamma OB}}\right) - kout_{trans} \cdot trans, \quad (1)$$

where

$$OB = OBfast \cdot trans + OBslow \qquad \& \qquad kin_{trans} = kout_{trans} \quad (2)$$

3. The osteocyte (*OCY*) compartment, where apoptosis is proportional to circulating sclerostin:

$$\frac{\mathrm{d}}{\mathrm{dt}} OCY = OB \cdot \mathrm{FRACTION}_{OCY} - kout_{OCY} \cdot OCY \quad (3)$$

where $\mathrm{FRACTION}_{OCY}$ represents the rate of OB becoming embedded in the bone matrix and

$$kout_{OCY} = OB_{\mathrm{baseline}} \cdot \mathrm{FRACTION}_{OCY} \cdot \mathrm{SCLER}^{\gamma OCY} \quad (4)$$

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

$$\mathrm{OSTEOEFFECT} = \left(\frac{OCY}{OCY_{\mathrm{baseline}}}\right)^{\delta} \quad (5)$$

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

$$\frac{\mathrm{d}}{\mathrm{dt}} BMD = kin_{BMD} \cdot \left(\frac{OB}{OB_{\mathrm{baseline}}}\right)^{\lambda_{OB}} - \left(\frac{OC}{OC_{\mathrm{baseline}}}\right)^{\lambda_{OC}} \cdot kout_{BMD} \cdot BMD \quad (6)$$

where

$$kin_{BMD} = kout_{BMD} \cdot BMD_{\mathrm{baseline}} \quad (7)$$

Validation

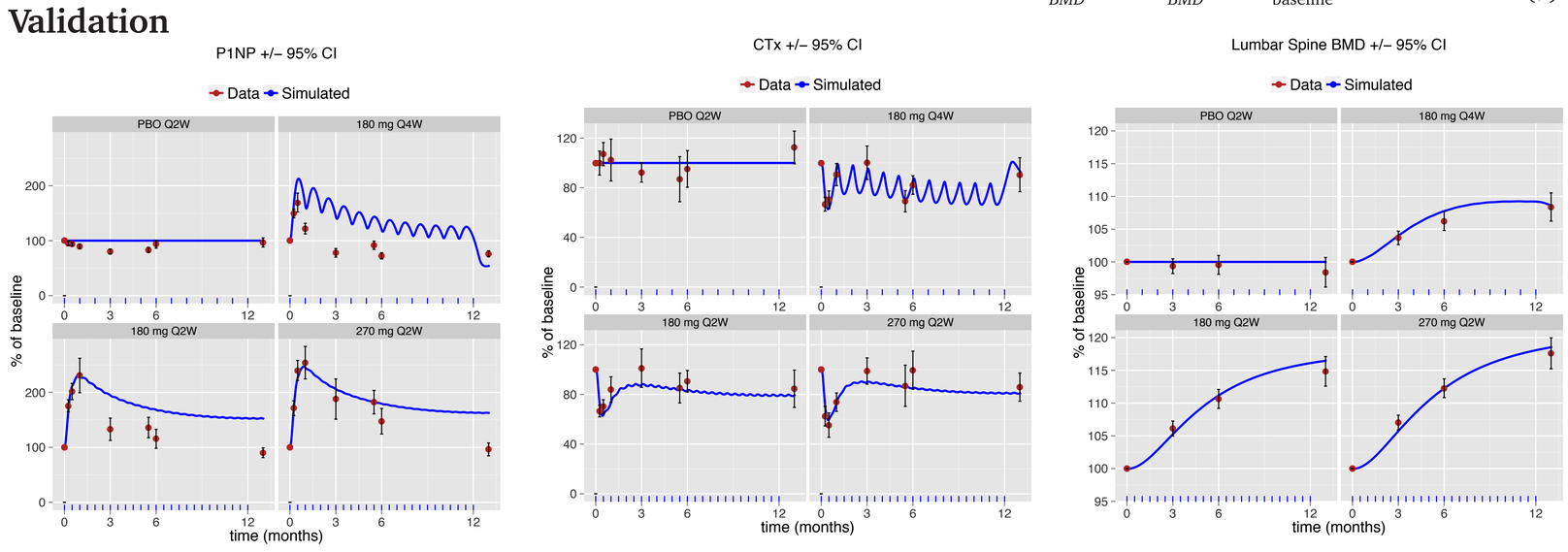

Figure 3: Predictive performance for turnover markers and regional changes in BMD. Tick marks indicate dose administration

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-cursor 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].

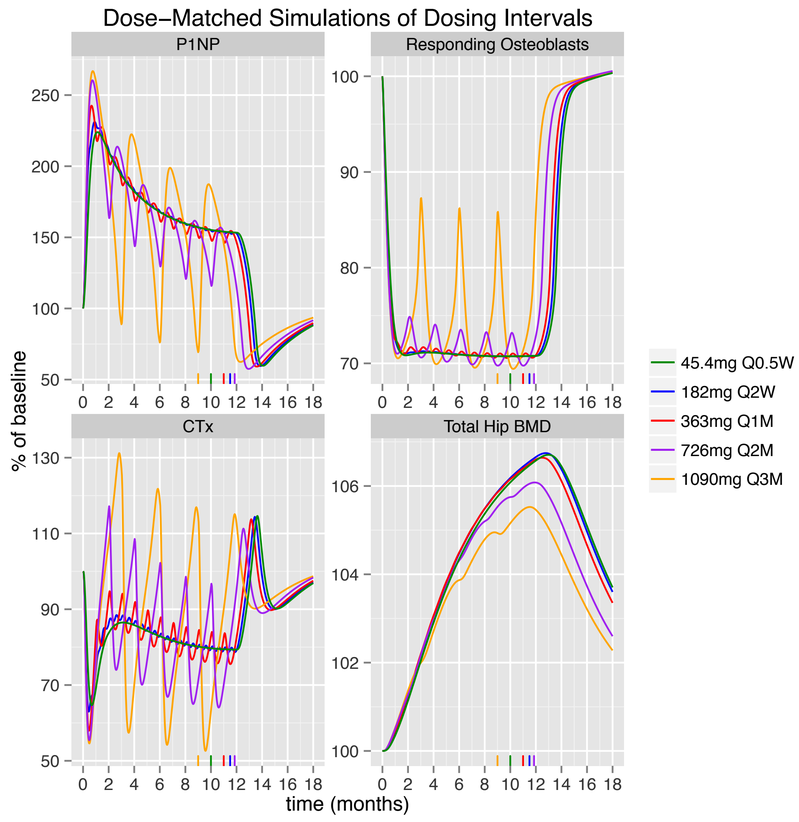

Figure 4: Dose-equivalent simulations show how dosing intervals affect P1NP, ROB, CTx and total hip BMD. Tick marks indicate final dose administration

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.