Systems pharmacology model development to provide physiologically based interpretation and drug development decision support in osteoporosis and other bone mineral-related diseases

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Bone Systems Model: A Decade of Active R&D

Examples and citations provided below.
Denosumab Clinical Responses: Can we better understand these changes in bone turnover markers (E and F), calcium (G) and PTH (H) using a single, integrated model?

from Figure 3 of McClung et al. N Engl J Med, 354(8):821–31, Feb 2006
The Receptor Activator of Nuclear Factor-κ B (RANK)-RANK Ligand (RANKL)-Osteoprotegerin (OPG) system

↑ OC differentiation and ↑ OC activation: RANK–RANKL
↓ OC differentiation and ↑ OC apoptosis: RANKL–OPG, RANKL–denosumab

Denosumab

• Fully human monoclonal antibody
• Binds to RANKL with high affinity and specificity
• Blocks interaction of RANKL with RANK
• Mimics endogenous effects of OPG

Denosumab–RANKL binding

• ↓ available RANKL
• ↓ RANK–RANKL interaction
• ↓ Osteoclast activity (serum C-telopeptide, CTx)
• ↓ Activation of TGFβ
• ↓ Osteoblast activity (bone-specific alkaline phosphatase, BSAP)
• ↑ bone mineral density (BMD)
Model Integrates Cellular & Organ-level Interactions

- Cellular apoptosis, cell-cell interactions (RANK-RANKL-OPG)
- Active transporters (Vitamin D, Ca bioavailability)
- Endocrine and paracrine feedback (PTH, calcitriol, TGF-β)
- Organ function: GI, PT gland, kidney, bone

Bone, 46:49;63, Jan 2010
Cross-Functionality is Captured Mathematically

Motivation

Motivation

Bone, 46:49-63, Jan 2010

Bone-Mineral Model

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Applicable Markers & Endpoints

- **Lab indicators:** serum Ca, PTH, urine Ca\(^1,2\)
- **Bone-related biomarkers:** CTx, BSAP, P1NP\(^3,4\)
- **BMD\(^4,5\)**
- **Fracture Risk\(^6\)**


Bone, 46:4963, Jan 2010
Expanded Disease Applications

- Osteoporosis\(^1,2,3,4\)
- Chronic Kidney Disease-Mineral Bone Disorder\(^5\)
- Parathyroid Disorder / Replacement\(^1,3,6\)
- Menopause transition\(^7\)
- Endometriosis: AE from estrogen ablation tx\(^7\)

Estrogen Effects Through GnRH Modulation

Key clinical development questions:

1. What is the optimal range of estrogen levels?
2. Can modulation of the GnRH pathway achieve ideal estrogen levels?
3. Which biomarkers (e.g., estrogen and bone markers), if any, would provide reliable predictions of long-term BMD changes?
4. Can an optimal biomarker range be identified?
5. What is the expected biomarker time course?

Bone markers changes from this mechanism too small, too slow to be useful

An ideal estrogen window was identified

Estrogen Effects Through GnRH Modulation

Key clinical development outcome:

“...this work identified target levels for estrogen that would provide symptomatic pain relief with minimal impact on BMD. ... targeting the GnRH pathway to achieve the desired range of serum estrogen levels would be difficult to achieve; therefore, the research program was halted before any compound entered the clinic.”

Model-Based Decision Support

- Use model-based approach to quantify the physiologic response to calcilytics to support development of DS-9194b, an orally administered investigational calcilytic
- Develop target criteria for PTH response (extent and duration) for first-in-human clinical study of an investigational drug (DS-9194b)
- Assess maximal PTH response and effects of urine Ca excretion using DS-9194b first-in-human clinical data; support development criteria with expectations for maximal BMD changes achievable through CaSR antagonism

PTH-Ca Effects from Ca Sensing Receptor Inhibition

Figure 3: Model of PTH pool within PT gland: PTH release stimulated by CaSR antagonist drug concentration.

**Equations related to PTH release**

\[
\frac{d}{dt} \text{PREPTH} = R_0 - k_i \cdot \text{PREPTH} - k_{\text{inh}} \cdot \text{PREPTH} \cdot \text{INH} \\
\frac{d}{dt} \text{PTH} = k_{\text{inh}} \cdot \text{PREPTH} - \text{INH} - \text{PTH} \cdot k_{\text{inh}} \\
\text{INH} = 1 - \left( 1 - U_{\text{Ca}} \right) \\
I_{\text{Ca}} = \frac{\text{CAT}^+}{E_{\text{IC50, Ca}} + \text{CAT}^+} \\
I_{\text{DRUG}^+} = \frac{\text{DRUG}^+}{E_{\text{IC50, DRUG}} + \text{DRUG}^+} \\
R_0 = \text{PREPTH} + k_i \cdot \text{PTH} + k_{\text{inh}} \cdot \text{inh}
\]

**Equations related to renal Ca2+ handling**

\[
\frac{d}{dt} \text{RCA}_{n+1} = k_r \cdot \left( 1 + \frac{\text{SMAX - DRUG}}{E_{\text{IC50, DRUG}} + \text{DRUG}} \right) \cdot \text{RCA}_{n} - k_r \cdot \text{RCA}_{n} \\
\frac{d}{dt} \text{RCA}_{n} = k_r \cdot \left( \text{RCA}_{n-1} - \text{RCA}_{n} \right) \\
m = 2, 3, 4, 5, 6, 7, 8
\]

Figure 4: Schematic of physiologically-based, multiscale systems pharmacology model; modified from figure 1 of Peterson and Riggs, 2010. [1]

Figure 5: System of transit compartments allowing for delay in development of DS-9194b effect on renal Ca2+ reabsorption. In the final model, n=8.

Link to 2013 ASBMR poster
PTH-Ca Effects from Ca Sensing Receptor Inhibition

**RESULTS – MSPM PREDICTION OF PTH RESPONSE**

Quantitative, physiologically-based explanation of observed PTH response to CaSR antagonism:

**RESULTS – PTH EFFECT ON CALCIUM IN URINE (UCA)**

MSPM also provides explanation of observed reduction in Ca\(^{2+}\) excretion due to hypothesized direct CaSR action in the kidney:

**RESULTS – PTH vs. BMD: Maximal PTH predicted 3-, 6- and 12-month lumbar spine BMD**

Simulated maximum PTH on day 1 (pM, difference from baseline)

Link to 2013 ASBMR poster
Key clinical development outcomes:

- Modeling indicated that BMD elevation with calcilytic administration routines evaluated is possible but magnitude of BMD elevation unlikely to match that seen with exogenous PTH.
- The MSPM provided a physiologic explanation of maximal PTH response due to capacity-limited PT gland pool of PTH.
- Results can guide future considerations for calcilytic-related therapies for osteoporosis or other PTH-related disorders.
OPINION: The FDA use of this model (shown next) **COULD NOT** and **WOULD NOT** have happened if this model was a typical ‘black box’ proprietary model.

FOR COLLECTIVE PROGRESSION – WE MUST STRIVE FOR OPEN SHARING OF THESE MODELS

Executable versions of our model are available in:

- R https://github.com/riggsmm/calciumhomeostasis-boneresorption-model

e.g., Waltemath et al. Minimum Information About a Simulation Experiment (MIASE). PLoS Comput Biol. 2011 April; 7(4) http://europepmc.org/articles/PMC3084216
FDA Natpara Review for Hypoparathyroidism

- Natpara clinical program evaluated a once daily dose of up to 100 µg of Natpara in adult patients with hypoparathyroidism
- REPLACE clinical trial designed to demonstrate that maintenance of serum calcium levels using less supplemental calcium and less or no active Vitamin D metabolite/analog
- Long-term complications of low PTH include chronic hypercalciuria can lead to nephrocalcinosis and progressive renal impairment as well as nephrolithiasis

- During the maintenance period, elevated urinary calcium remained an issue in both groups
  - At Week 16, hypercalciuria observed in 30% of placebo group and 47% of Natpara group
  - At Week 24, hypercalciuria observed in 39% of placebo group and 34% of Natpara group

"We wanted to use the model to explain certain things that were seen in the trial. So it’s interesting. It’s thought provoking.” Dr Guettier, FDA

FDA AC Meeting Transcript
FDA Natpara Review: PK Effect on Hypercalciuria

Altering Regimen (QD to BID) or Release Profile Controls Hypercalciuria While Maintaining Normocalcemia

Presented at FDA September 12, 2014 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee

Link to FDA slides
FDA’s application of the model was focused on understanding the effect of Natpara PK on hypercalciuria

“hypothesis generating” results:

“...using a calcium homeostasis model demonstrate that a more frequent dosing regimen or a formulation with slow release profile will provide better control on hypercalciuria compared to the current once daily dosage regimen. ”

FDA Briefing Information for the September 12, 2014 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee

Link to FDA Briefing Information
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System Response to Drug and Disease Effects

References:

**CaSRi**  

**denosumab**  

**GnRH, estrogen**  

**denosumab**  
M. C. Peterson and R. M. M. Predicting nonlinear changes in bone mineral density over time using a multiscale systems pharmacology model. CPT: pharmacomet. syst. pharmacol., 1(e14), 2012/11/14/online.

**BMD-fracture**  

**2nd hyperPTH**  

**dmab, PTH**  
Thank you

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