METRUM RESEARCH GROUP

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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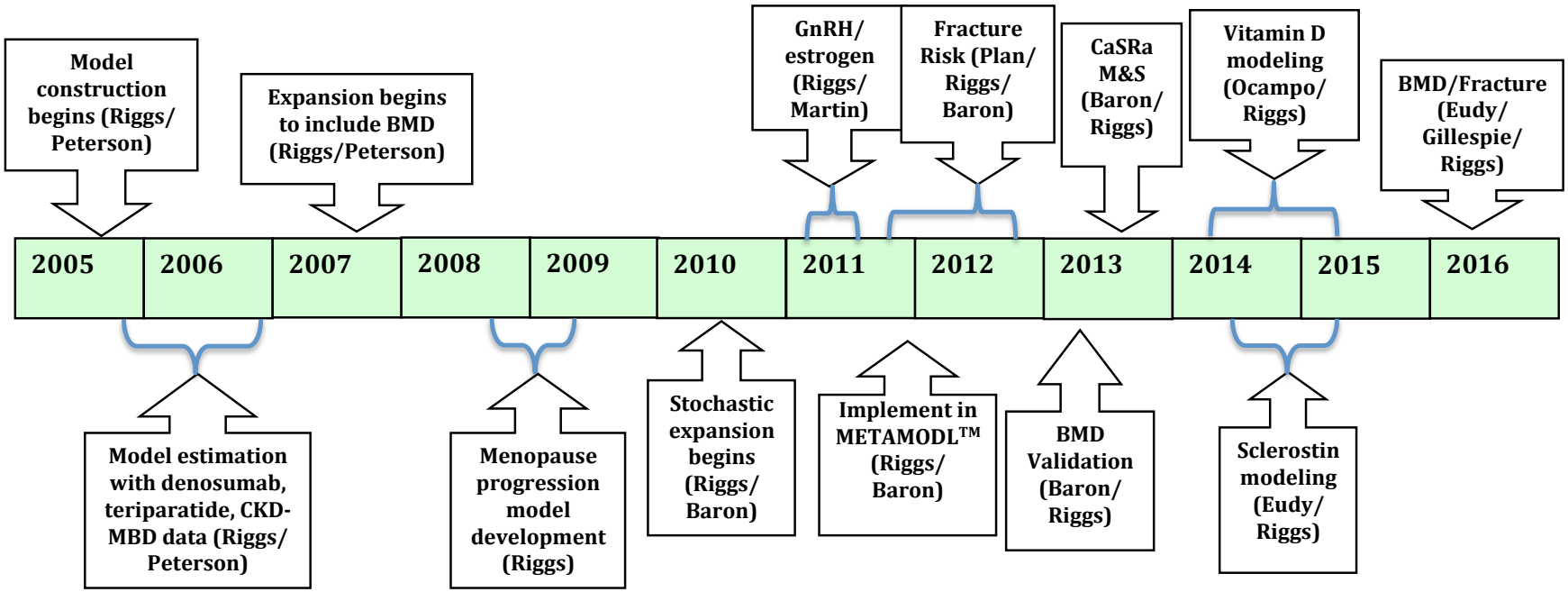
Metrum Research Group LLC

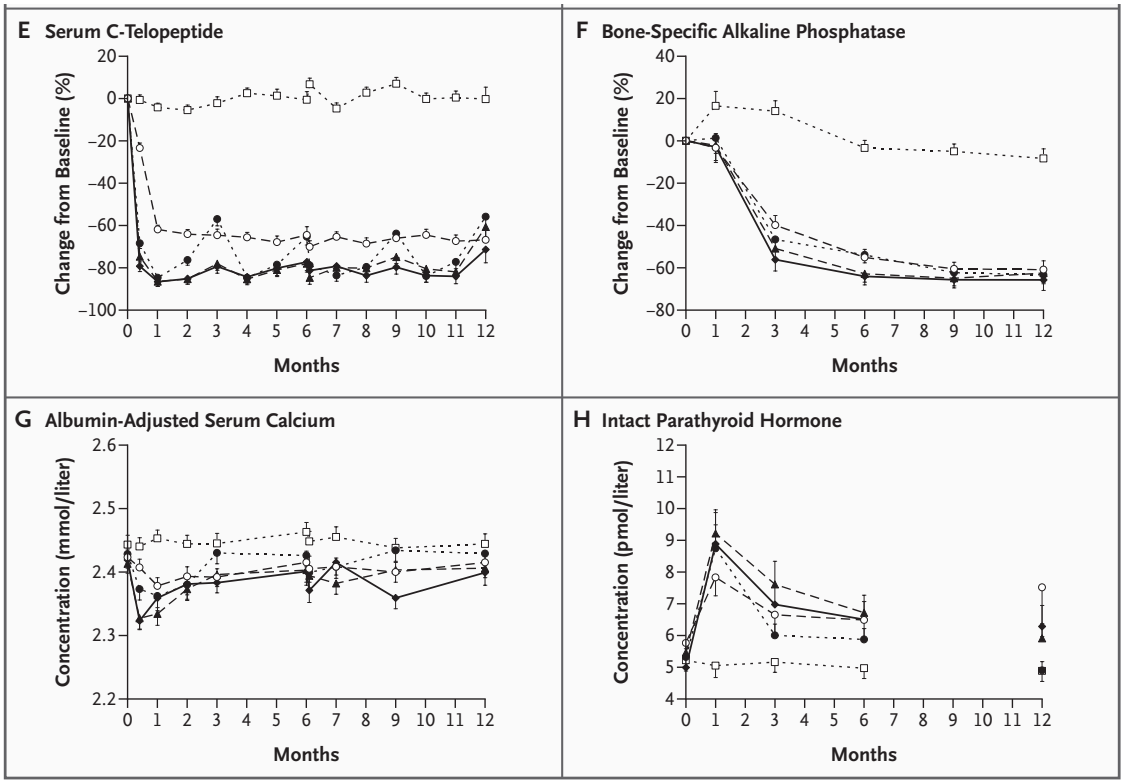
14 Dec 2016

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?

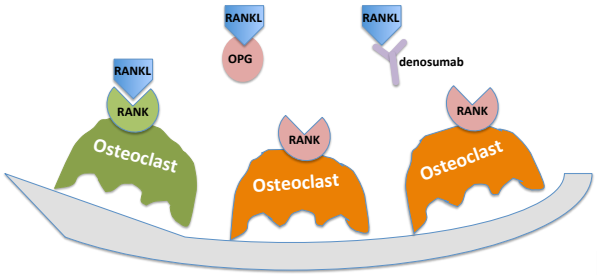


from Figure 3 of McClung et al. N Engl J Med, 354(8):821–31, Feb 2006

The **R**eceptor **A**ctivator of **N**uclear **F**actor-κ B (RANK)-RANK **L**igand (RANKL)-Osteoprotegerin (OPG) system

$\Uparrow$ OC differentiation and $\Uparrow$ OC activation: RANK–RANKL

$\Downarrow$ OC differentiation and $\Uparrow$ 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

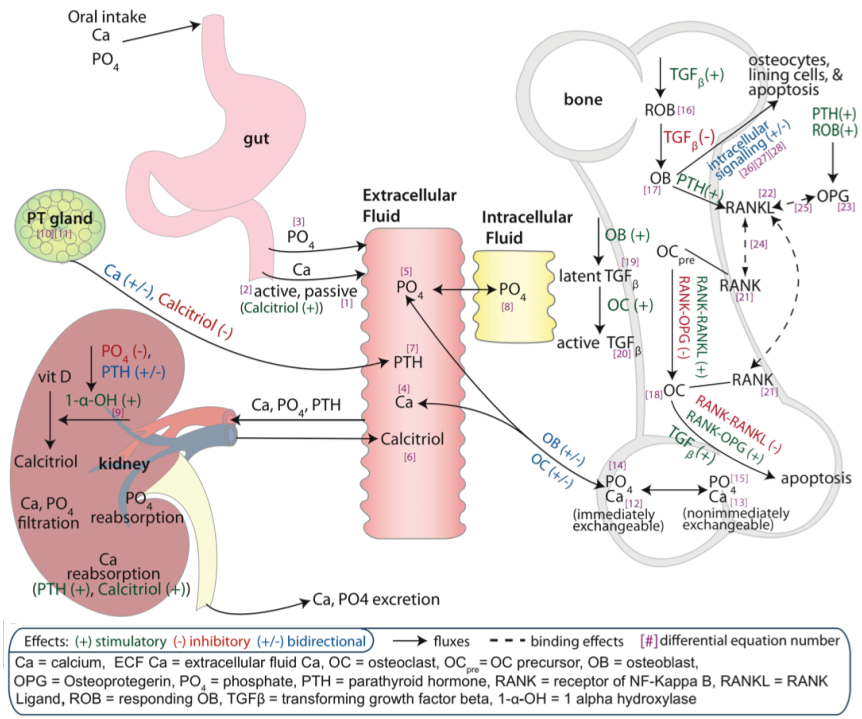
–

McClung et al. N Engl J Med, 354(8):821–31, Feb 2006.

Denosumab–RANKL binding

- $\downarrow$ available RANKL
- $\downarrow$ RANK–RANKL interaction
- $\downarrow$ Osteoclast activity (serum C-telopeptide, CTx)
- $\downarrow$ Activation of TGFβ
- $\downarrow$ Osteoblast activity (bone-specific alkaline phosphatase, BSAP)
- $\uparrow$ bone mineral density (BMD)

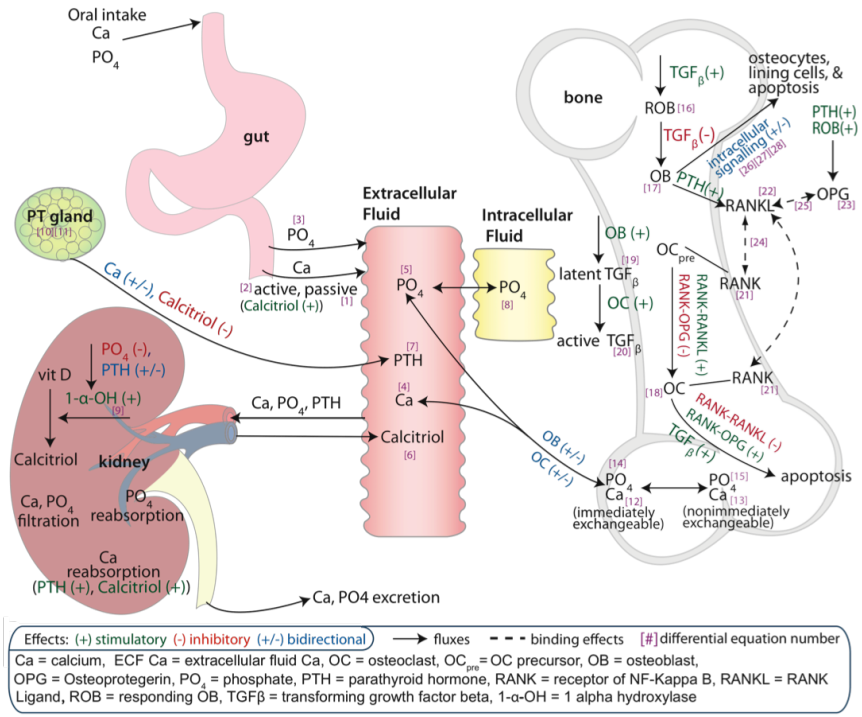
Model Integrates Cellular & Organ-level Interactions



Bone, 46:49;63, Jan 2010

- 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

Cross-Functionality is Captured Mathematically



Bone, 46:49-63, Jan 2010

of Ca and PO4 influenced by plasma Ca, PO4, calcitriol, PTH, and GFR; 5) PT gland—describes PTH production influenced by plasma Ca and calcitriol; 6) bone—describes Ca and PO4 levels via bidirectional diffusion and osteoclast- and osteoblast-promoted exchange with plasma; and (7) osteoblast intracellular component—describes the differential influence of PTH on bone metabolism purported to be controlled by the intracellular Runx2–Bcl-2–CREB system. Within the differential equations, parameters can be identified as either being within hyperbolic functions, or not. To aid identification, rate constants, composite rate constants, and physiologic parameters are listed in Table 2 as non-hyperbolic function parameters. Those embedded in hyperbolic terms are listed in Table 3 as hyperbolic function parameters. The complete model system of differential equations is provided below and descriptions of each component are in the section which follows.

Differential equations

Gut

$$d/dt\,A(1) = D(1)*H_{2,1}^{+} - \nu_{1-4}$$

$$\nu_{1-4} = (H_{1-4}*(A(2)/0.5)/(A(1)+\delta_{2,1}) + k_{1-4})*A(1)$$

$$d/dt\,A(2) = H_{6,2}^{+}*(1-A(2)) - H_{6,2}^{-}*A(2)$$

$$d/dt\,A(3) = D(3)*F_3 - k_{3-5}*A(3)$$

Vasculature

$$d/dt\,A(4) = \nu_{12-4} - \nu_{4-12} - \nu_{4-u} + \nu_{1-4}$$

$$\nu_{12-4} = k_{4-12}*(1-\varphi_{12-4}) + k_{4-12}*\varphi_{12-4}*H_{18,12-4}*[A(24)*A(18)_0/(A(24)_0*A(18))]^{\gamma 24,12-4}$$

$$\nu_{4-12} = k_{4-12}*(A(4)/A(4)_0)*((1-\varphi_{4-12}) + \varphi_{4-12}*(A(17)/A(17)_0))$$

$$\nu_{4-u} = (2-H_{6,4})*(0.3*GFR*A(4) - H_{4-u}*H_{7,4-u})$$

$$d/dt\,A(5) = \nu_{5-14} - \nu_{14-5} - \nu_{5-u} + \nu_{3-5} - \nu_{5-8} + \nu_{8-5}$$

$$\nu_{5-14} = 0.464*\nu_{4-12}$$

$$\nu_{14-5} = 0.464*\nu_{12-4}$$

$$\nu_{5-u} = 0.88*GFR*A(5) - 0.88*GFR*\varphi_{5-u}$$

$$\nu_{3-5} = k_{3-5}*A(3)$$

$$\nu_{5-8} = k_{5-8}*A(5)$$

$$\nu_{8-5} = k_{8-5}*A(8)$$

$$d/dt\,A(6) = A(9) - k_{6D}*A(6)$$

$$d/dt\,A(7) = H_{4,10-7}^{-}*(A(10)/0.5)*A(11) - k_{7D}*A(7)$$

Intracellular phosphate

$$d/dt A(8) = \nu_{5-8} - \nu_{8-5}$$

Kidney

$$d/dt\,A(9) = k_{9S}*H_{7,9}^{+}*H_{5,9}^{-} - k_{9D}*A(9)$$

$$H_{5,9}^{-} = 1 \text{ for } A(5) < A(5)_0$$

Parathyroid gland

$$d/dt\,A(10) = (1-A(10))*\alpha_{10}*(0.85*T_{6'4}^{-} + 0.15) - A(10)*\alpha_{10}*(0.85*T_{6'4}^{+} + 0.15)$$

$$T_{6'4}^{+} = 1 \pm (EXP(b_{T6'4}*(A(6)/V_{vasc} - \delta_{T6'4}*(A(4)_0/A(4))^{\gamma 4,10}) - EXP(-b_{T6'4}*(A(6)/V_{vasc} - \delta_{T6'4}*(A(4)_0/A(4))^{\gamma 4,10}) / (EXP(b_{T6'4}*(A(6)/V_{vasc} - \delta_{T6'4}*(A(4)_0/A(4))^{\gamma 4,10}) + EXP(-b_{T6'4}*(A(6)/V_{vasc} - \delta_{T6'4}*(A(4)_0/A(4))^{\gamma 4,10})$$

$$d/dt\,A(11) = k_{11}*H_{6,11}^{-} - k_{11}*A(11)$$

Bone

$$d/dt\,A(12) = \nu_{4-12} - \nu_{12-4} + k_{13-12}*A(13) - k_{12-13}*A(12)$$

$$d/dt\,A(13) = -k_{13-12}*A(13) + k_{12-13}*A(12)$$

$$d/dt\,A(14) = \nu_{5-14} - \nu_{14-5} + k_{15-14}*A(15) - k_{14-15}*A(14)$$

$$d/dt\,A(15) = k_{14-15}*A(14) - k_{15-14}*A(15)$$

$$d/dt\,A(16) = (k_{17D}*A(17)_0/\pi_0^c)*H_{20,16}^{+} - k_{17D}*A(17)_0*\pi_0^c / (A(16)_0*H_{20,17}^{+})*A(16)$$

$$A(17) = A(17a) + A(17b)$$

$$d/dt\,A(17a) = k_{17D}*A(17)_0*\pi_0^c/(A(16)_0*H_{20,17}^{+})*A(16)*\varphi_{17a}*(k_{17aD}/k_{17D}') - k_{17aD}*A(17a)$$

$$k_{17aD} = (k_{17D}*A(17)_0 + k_{17D}'*\varphi_{k17D}*A(17a)_0*\varphi_{17a} - k_{17D}'*\varphi_{k17D}*A(17)_0)/A(17a)_0$$

$$k_{17D}' = \varphi_{28,k17D}*k_{17D}*H_{20,17D}^{-}/\pi_0^c - H_{28,17D}$$

$$d/dt\,A(17b) = k_{17D}*A(17)_0*\pi_0^c/(A(16)_0*H_{20,17}^{+})*A(16)*(1-\varphi_{17a})*\varphi_{k17D} - k_{17D}'*\varphi_{k17D}*A(17b)$$

$$d/dt\,A(18) = k_{18D}*\pi_0^c*A(18)_0*H_{24,18S}^{+} - k_{18D}*H_{20,18D}^{+}*H_{22,18D}^{-}*A(18)$$

$$d/dt\,A(19) = k_{19-20}*A(19)_0*(A(17)/A(17)_0)^{\gamma 17,19S} - k_{19-20}*(A(19)/A(19)_0)^{\gamma 19-20}*(A(18)/A(18)_0)^{\gamma 18,19-20}*A(19)$$

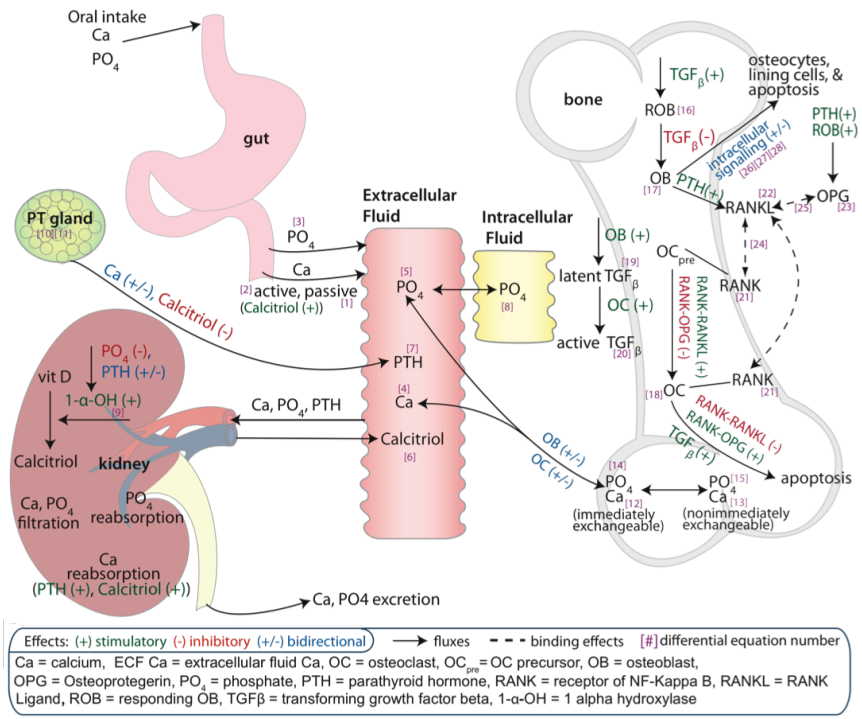
$$d/dt\,A(20) = k_{19-20}*(A(19)/A(19)_0)^{\gamma 19-20}*(A(18)/A(18)_0)^{\gamma 18,19-20}*A(19) - 1000*k_{19-20}*A(20)$$

$$d/dt\,A(21) = ((k_{21D}*A(21)_0 + k_{21-24}*A(21)_0*A(22)_0 - k_{24-21}*A(24)_0)/A(20)_0^{\gamma 20,21})*A(20)^{\gamma 20,21} - k_{21D}*A(21) - k_{21-24}*A(21)*A(22) + k_{24-21}*A(24)$$

$$d/dt\,A(22) = k_{22S} - k_{22D}*A(22) - k_{21-24}*(A(23)*A(22) + A(21)*A(22)) + k_{24-21}*(A(24) + A(25))$$

$$k_{22S} = k_{22D}*A(22)_0*(A(17)/A(17)_0)^{\gamma 17,22}*\alpha_{7,22}*(A(7)/V_{vasc}) / (\delta_{7,22}*(A(17)/A(17)_0)^{\gamma 17,22} + (A(7)/V_{vasc}))$$

Applicable Markers & Endpoints

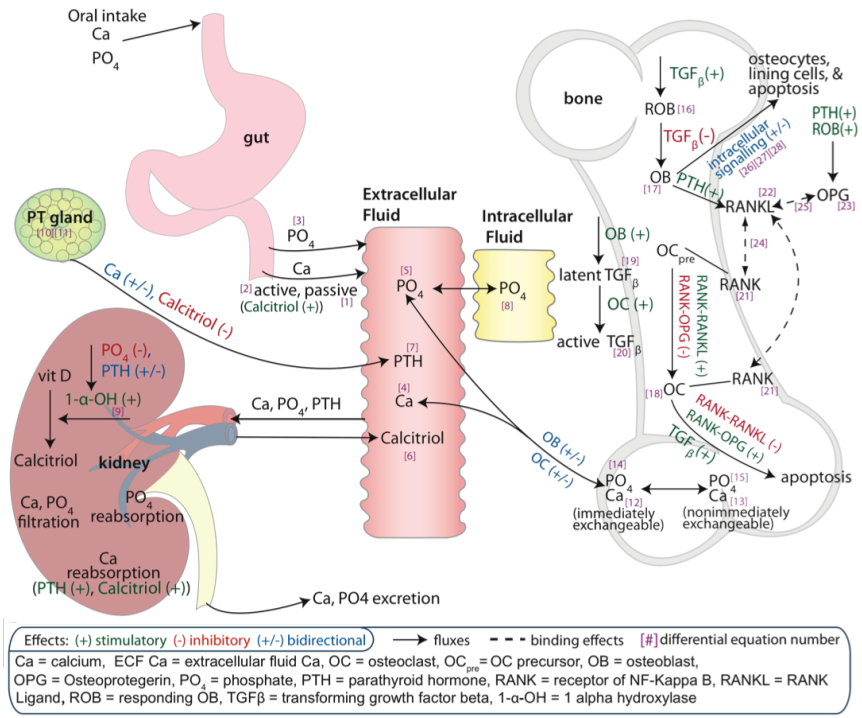


Bone, 46:4963, Jan 2010

- Lab indicators: serum Ca, PTH, urine Ca[1,2]
- Bone-related biomarkers: CTx, BSAP, P1NP[3,4]
- BMD[4,5]
- Fracture Risk[6]

As Published: 1. Bone 2010, 2. JBMR 2013, 3. Bone 2010, 4. CPT: PSP 2012, 5. JBMR 2012, 6. PAGE 2012

Expanded Disease Applications



Bone, 46:4963, Jan 2010

- Osteoporosis[1,2,3,4]
- Chonic Kidney Disease-Mineral Bone Disorder[5]
- Parathyroid Disorder / Replacement[1,3,6]
- Menopause transition[7]
- Endometriosis: AE from estrogen ablation tx[7]

As Published: 1. Bone 2010, 2. JBMR 2012, 3. JBMR 2013, 4. CPT: PSP 2012a, 5. J Clin Pharmacol 2012, 6. FDA Advisory 2014, 7. CPT:PSP 2012b

Estrogen Effects Through GnRH Modulation

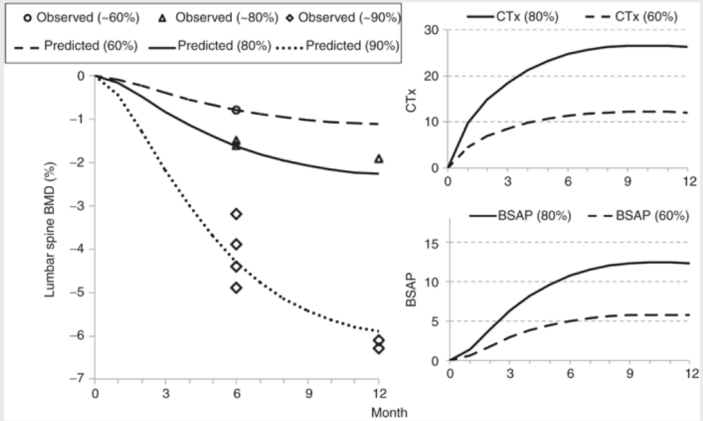
Key clinical development questions:

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?

M. Riggs, M. Bennetts, P. van der Graaf, and S. Martin. Integrated pharmacometrics and systems pharmacology model-based analyses to guide GnRH receptor modulator development for management of endometriosis. CPT Pharmacometrics Syst. Pharmacol., 1(e10), 2012.

Estrogen Effects Through GnRH Modulation

- Bone markers changes from this mechanism too small, too slow to be useful
- An ideal estrogen window was identified



Estradiol suppression (%) effect on BMD and bone markers (serum c-telopeptide and bone-specific alkaline phosphatase). Predictions (lines) were from the multiscale model and observations (symbols) from the estimation data set. BMD, bone mineral density; BSAP, bone-specific alkaline phosphatase; CTx, serum c-telopeptide.

M. Riggs, M. Bennetts, P. van der Graaf, and S. Martin. Integrated pharmacometrics and systems pharmacology model-based analyses to guide GnRH receptor modulator development for management of endometriosis. CPT Pharmacometrics Syst. Pharmacol., 1(e10), 2012.

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.****"*

P. A. Milligan et al. Model-based drug development: a rational approach to efficiently accelerate drug development. Clin Pharmacol Ther, 93(6):50214, Jun 2013.

PTH-Ca Effects from Ca Sensing Receptor Inhibition

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

An Evaluation of Calcilytic Effects on Parathyroid Hormone and Bone Mineral Density Response Using a Physiologically-Based, Multiscale Systems Pharmacology Model. Kyle T. Baron, Matthew M. Riggs, Ryoko Sawamura, Takako Shimizu, Fumihiko Okada, Jin Zhou, Takahiro Shibayama, Mendel Jansen. Poster Presentation at ASBMR; October 5th, 2013

PTH-Ca Effects from Ca Sensing Receptor Inhibition

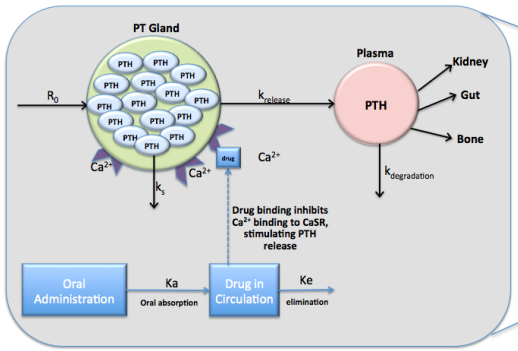


Figure 3: *Model of PTH pool within PT gland: PTH release stimulated by CaSR antagonist drug concentration.*

Equations related to PTH release

$$\frac{d}{dt}PREPTH = R_0 - k_s \cdot PREPTH - k_{release} \cdot PREPTH \cdot INH$$

$$\frac{d}{dt}PTH = k_{release} \cdot PREPTH \cdot INH - PTH \cdot k_{deg}$$

$$INH = 1 - (I_{CA} \cdot (1 - I_{DRUG}))$$

$$I_{CA} = \frac{CA^{\gamma_1}}{EC_{50,CA}^{\gamma_1} + CA^{\gamma_1}} \qquad I_{DRUG} = \frac{DRUG^{\gamma_2}}{EC_{50,DRUG}^{\gamma_2} + DRUG^{\gamma_2}}$$

$$R_0 = PREPTH_{ss} \cdot k_s + PTH_{ss} \cdot k_{deg}$$

Equations related to renal Ca2+ handling

$$REABS_{active} = \frac{Reabs_{max} \cdot CA}{Reabs_{50} + CA} \cdot PTH_{effect} \cdot RCA$$

$$\frac{d}{dt}RCA_1 = ktr \cdot \left[1 + \frac{SMAX \cdot DRUG}{EC_{50,rca} + DRUG}\right] - ktr \cdot RCA_1 \qquad ktr = \frac{n+1}{MTT} \qquad n = 8$$

$$\frac{d}{dt}RCA_m = ktr \cdot [RCA_{(m-1)} - RCA_m] \qquad m = 2, 3, 4, 5, 6, 7, 8$$

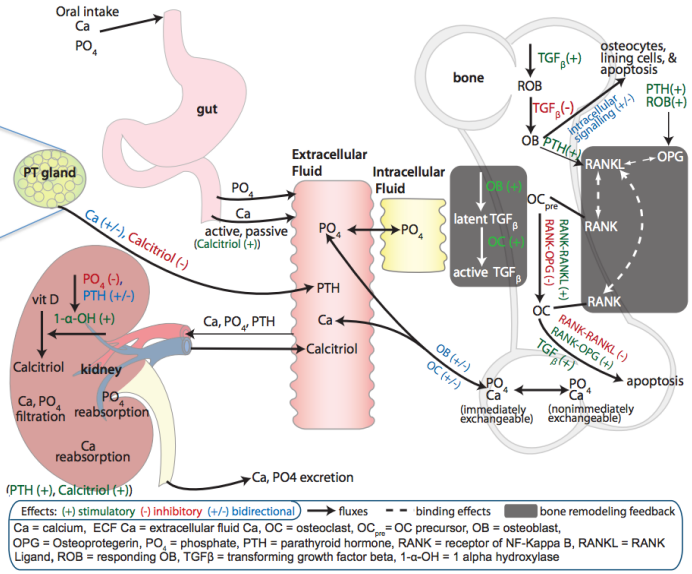


Figure 4: *Schematic of physiologically-based, multiscale systems pharmacology model; modified from figure 1 of Peterson and Riggs, 2010.* [1]

$$RCA1,ss = RCA2,ss = \ldots = RCAn,ss = 1$$

$$\text{with :} \quad kin = ktr \cdot \left[1 + \frac{SMAX \cdot DRUG}{EC_{50,rca} + DRUG}\right]$$

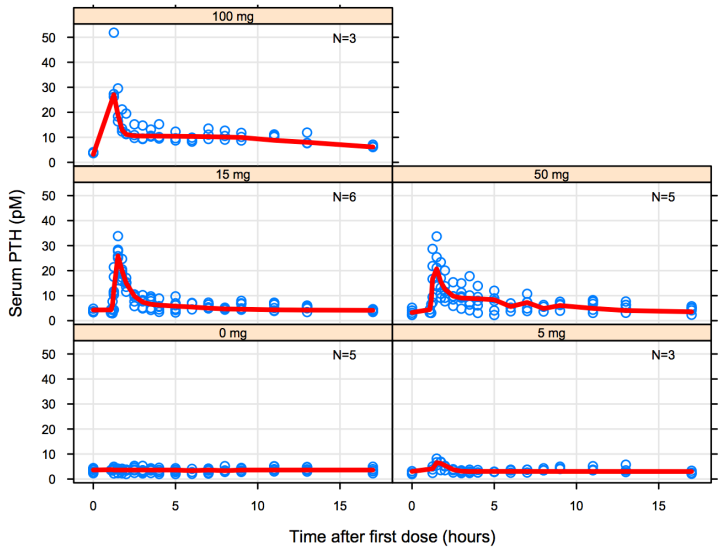
Figure 5: *System of transit compartments allowing for delay in development of DS-9194b effect on renal Ca^{2+} reabsorption. In the final model, n=8.*

Link to 2013 ASBMR poster

PTH-Ca Effects from Ca Sensing Receptor Inhibition

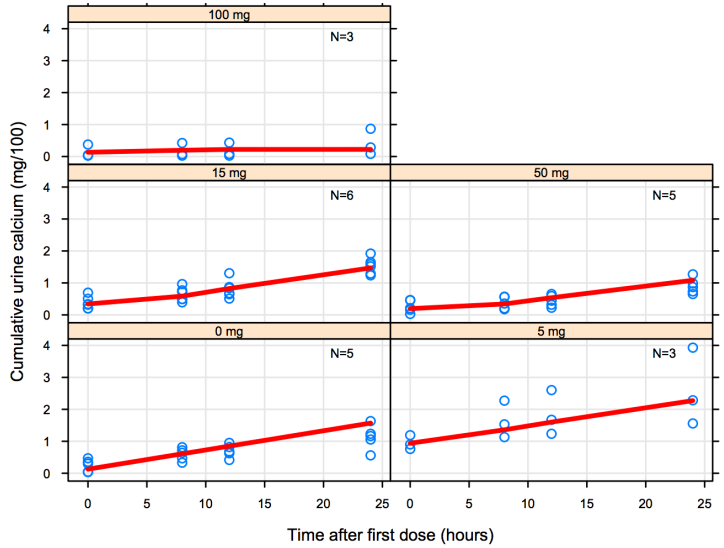
RESULTS – MSPM PREDICTION OF PTH RESPONSE

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

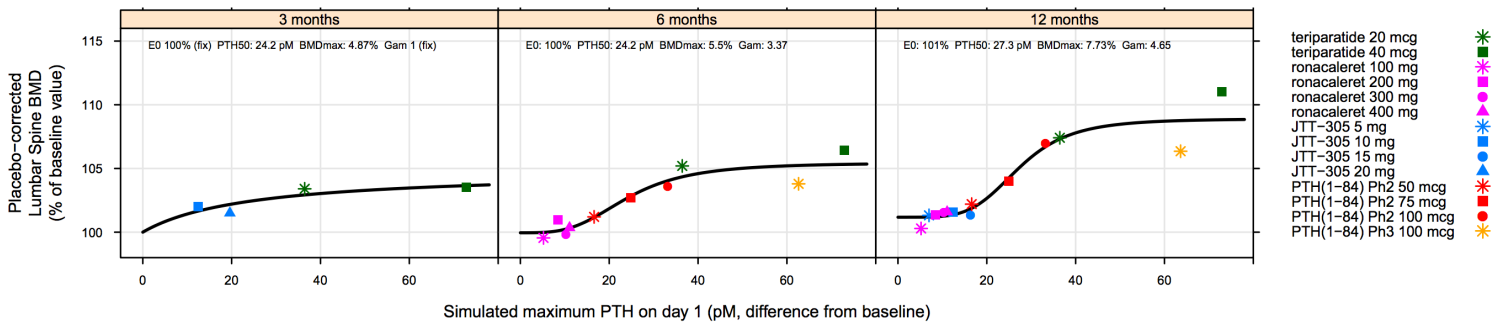


RESULTS – PTH EFFECT ON CALCIUM IN URINE (UCA)

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



Link to 2013 ASBMR poster

PTH-Ca Effects from Ca Sensing Receptor Inhibition

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:

- Berkeley-Madonna – electronic supplement in http://onlinelibrary.wiley.com/doi/10.1038/psp.2012.10/abstract
- *R* https://github.com/riggsmm/calciumhomeostasis-boneresorption-model
- SBML – **BioModels Model of the Month, July 2016** – http://www.ebi.ac.uk/biomodels-main/static-pages.do?page=ModelMonth%2F2016-07 added by Vincent Knight-Schrijver

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

FDA AC Meeting Slides

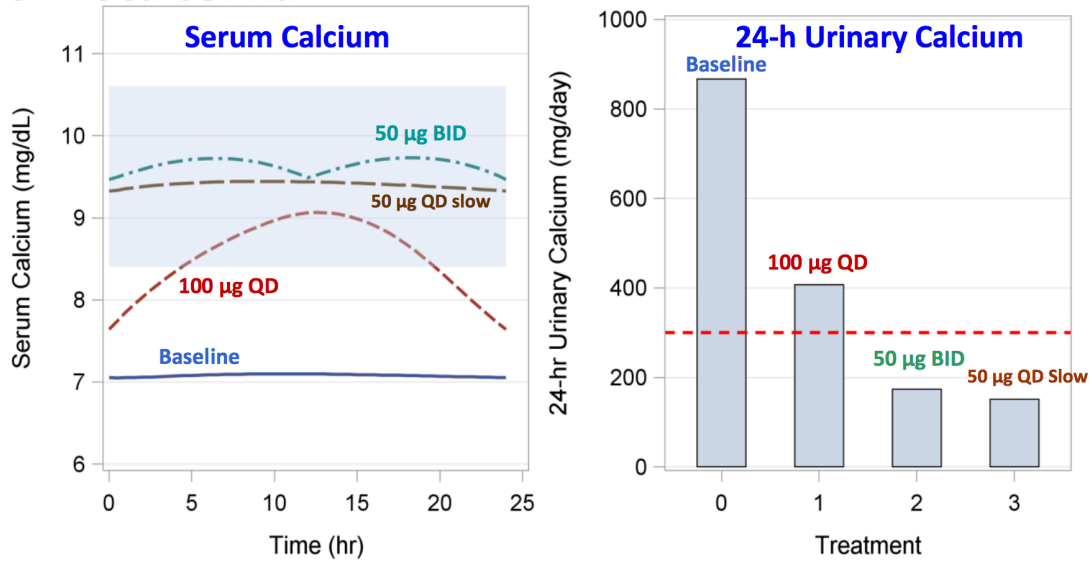
"We wanted to use the model to explain certain things that were seen in the trial. So it's interesting. It's thought provoking." *Dr Guettier, FDA*

FDA AC Meeting Transcript

FDA Natpara Review: PK Effect on Hypercalciuria

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

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



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

Link to FDA slides

FDA Natpara Review: Model Applications

- 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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- Executable in *R* https://github.com/riggsmm/calciumhomeostasis-boneresorption-model
- Executable in SBML – **BioModels Model of the Month, July 2016** – http://www.ebi.ac.uk/biomodels-main/static-pages.do?page=ModelMonth%2F2016-07 added by Vincent Knight-Schrijver

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

System Response to Drug and Disease Effects

References:

CaSRi K. Baron, M. Riggs, R. Sawamura, T. Shimizu, F. Okada, J. Zhou, T. Shibayama, and M. Jansen. An evaluation of calcilytic effects on parathyroid hormone and bone mineral density response using a physiologically-based, multiscale systems pharmacology model. Presented at American Society of Bone Mineral Research (ASBMR) Annual Meeting, Abstract SU0407; Baltimore, MD; 06-October 2013. J Bone Miner Res, 28(Suppl 1), 2013.

denosumab M. M. Riggs, K. T. Baron, E. L. Plan, and M. R. Gastonguay. Qualification of a physiologically-based model for predicted bone marker and bone mineral density changes associated with denosumab treatment. Presented at American Society of Bone Mineral Research (ASBMR) Annual Meeting, Abstract SU0363, Minneapolis, MN, October 2012. J Bone Miner Res, 27 (Suppl 1), 2012

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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.

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dmab, PTH M. C. Peterson and M. M. Riggs. A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. Bone, 46:4963, Jan 2010.

Thank you

- British Pharmacology Society (BPS) and American Society of Clinical Pharmacology and Therapeutics (ASCPT)
- Many collaborators (as referenced above) including:
  - Mark Peterson
  - Steve Martin
  - Mendel Jansen
- Metrum colleagues: Marc Gastonguay, Kyle Baron, Rena Eudy-Byrne, Alanna Ocampo

Questions / Contact

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