Extensions of a Multiscale Systems Pharmacology Model of Bone Mineral Balance and its Regulation of Bone Health

Matthew M. Riggs, Ph.D.
Principal Scientist II
Group Leader, Systems Pharmacology M&S
mattr@metrumrg.com

7 March 2013
Multiscale Systems Pharmacology Modeling (MSPM)

- Introduction
  - MSPM to Integrate Physiology, Pharmacology and Disease
  - Motivation
  - Getting Started

- MSPM of Bone-Related Effects
  - Osteoporosis: Efficacy Response to Denosumab
  - Endometriosis: Balancing Symptom Relief with BMD loss
  - Ongoing R&D

- In Summary
  - Concept: A Research Platform
  - Parting Thoughts
INTRODUCTION

- Integrated Understanding

PHYSIOLOGY

PHARMACOLOGY

PATHOPHYSIOLOGY

(Disease Progression)

RANK-L inhibition (denosumab)

Intermittent PTH (teriparatide)

GnRH receptor modulation

Chronic Kidney Disease - Mineral and Bone Disorder (CKD-MBD)

Primary Hyper- and Hypoparathyroidism

Age + Menopause Effects on Estrogen
INTRODUCTION – ORIGINAL MOTIVATION

Denosumab: RANKL inhibition

- ↓ available RANKL
- ↓ RANK--RANKL interaction
- ↓ Osteoclast activity (sCTx)
- ↓ Activation of TGF-β
- ↓ Osteoblast activity (BSAP)
- ↑ bone mineral density (BMD)

- ↓ Calcium release from bone
- ↓ Serum calcium
- ↓ Ca sensing in PT gland
- ↑ PTH release (calcium-sparing)

- Observed 12 Month Data:
  - ↓ Bone resorption markers (near immediate)
  - ↓ Bone formation markers (delayed, less pronounced)
  - ↓ Serum Ca (transient)
  - ↑ PTH (transient)

- Can these effects be described using a single, physiologically representative model?
INTRODUCTION

Multiscale Model of Calcium and Bone

- Intentions

➢ Represent physiology
  ▶ Include multiscale mechanisms (signaling → organs → outcomes)
  ▶ Incorporate relevant co-factors
    » Phosphate (PO4)
    » Parathyroid hormone (PTH)
    » Calcitriol
    » Cytokines (e.g. TGFβ)
    » Cell Signaling
    » Bone turnover markers (e.g. osteoblast/osteoclast associated)

➢ Predict Ca homeostasis and bone remodeling

➢ Provide a platform for evaluating longitudinal therapeutic and disease state effects
INTRODUCTION

Multiscale Model of Calcium and Bone

- Existing Research / Data
  - 200+ references
  - From 70+ sources (journals, texts, regulatory documents, etc.)
  - Publications: 1959 – present (5+ decades)

- But How to Bring It All Together?
INTRODUCTION

Integrating Existing Data and Models

Calcium Absorption
- e.g., Heaney et al. 1997

PTH Secretion
- e.g., Ramirez et al. 1993

Calcium Excretion
- e.g., Peacock and Nordin 1968

Bone Therapeutics
- Anabolic (teriparatide, 2004)
- Catabolic (denosumab, 2006)

Disease States
- Hyper- and hypo-PTH
- CKD-MBD (Rix et al. 1999)

Calcium Homeostasis
- e.g., Raposo et al. 2002

Bone Remodeling
- e.g., LeMaire et al. 2004

Intracellular Signaling
- e.g., Bellido et al. 2003

- Multiscale Model:

INTRODUCTION

Multiscale Model of Calcium and Bone

Schematic of physiologic system model to describe calcium homeostasis and bone remodeling (reprinted from Figure 1 of (Peterson and Riggs, 2010))
Applications: Therapeutic Response

DENOSUMAB

Rebound in bone metabolism is predictable. BMD can be modeled as a function of bone markers

CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e14; doi:10.1038/psp.2012.15

PHARMAOCOLOGY

TERIPARATIDE

Bone anabolics are predictable. Effects on Ca / other physiology can be evaluated

CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e14; doi:10.1038/psp.2012.15

GnRH RECEPTOR

Estrogen-BMD relationship is predictable. Degree of GnRH modulation targeted

CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e11; doi:10.1038/psp.2012.10

Peterson MC and Riggs MM. Bone 46:49-63; 2010
Example I -- Therapeutic Response

Denosumab: RANKL inhibition

- ↓ available RANKL
- ↓ RANK--RANKL interaction
- ↓ Osteoclast activity (sCTx)
- ↓ Activation of TGF-β
- ↓ Osteoblast activity (BSAP)
- ↑ bone mineral density (BMD)

- ↓ Calcium release from bone
- ↓ Serum calcium
- ↓ Ca sensing in PT gland
- ↑ PTH release (calcium-sparing)

Example I -- Therapeutic Response

Denosumab: RANKL inhibition → Bone Markers

Dose-Ranging Bone Marker Responses

Fig. 3 and 4; Peterson MC and Riggs MM., CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e14; doi:10.1038/psp.2012.15
Example I -- Therapeutic Response

Denosumab: RANKL inhibition → Bone Marker → BMD

Dose-Ranging BMD Responses

Fig.5; Peterson MC and Riggs MM,. CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e14; doi:10.1038/psp.2012.15
Example I -- Therapeutic Response

Denosumab Model Evaluation

FREEDOM (Phase 3) Trial Data

Observed (symbols) and simulated (lines) BMD, CTx, and BSAP during during treatment with 60mg Q6M denosumab for 4 years. Observed values from denosumab treatment groups: NCT00089791 (FREEDOM, blue symbols) and NCT00043186 (red symbols); and placebo treatment group: NCT00089791 (grey symbols).

Applications: Disease Response

**AGE + MENOPAUSE**
Includes longitudinal estrogen loss
Predicts Ca & bone estrogen-related effects

- Bone Markers
  - Resorption (dashed)
  - Formation (solid)
- Menopause
- ERT

**DISEASE PROGRESSION**

**1° HYPER- & HYPO-PARATHYROIDISM**
Predicts Ca and bone effects

- Calcium Increases → PTH Increases → Osteoclasts Increase
- Calcium Decreases → PTH Decreases → Osteoclasts Decrease

**CKD-MBD**
Predicts Secondary hyperPTH
Predicts increased bone turnover

- Kidneys Fail → Phosphate ↑ → PTH ↑ → Bone Resorption ↑


Peterson and Riggs (2010)
Bone 46:49-63 (Fig 5 & 7)

Riggs MM, Gastonguay MR, Peterson MC. AAPS Annual Meeting 2010; Poster # W4403
Example II -- Disease Response

Estrogen Loss During Menopause Transition

Peri- through post-menopause transition (FMP: final menstrual period)

Bone Markers: BSAP (solid) and urine NTx (dashed)  Calcium (dashed), TGF-β (dotted); PTH (solid)

Figure 2 of M M Riggs, M Bennetts, P H van der Graaf and S W Martin. Integrated Pharmacometrics and Systems Pharmacology Model-Based Analyses to Guide GnRH Receptor Modulator Development for Management of Endometriosis. CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e11; doi:10.1038/psp.2012.10

http://www.nature.com/psp/journal/v1/n10/fig_tab/psp201210f2.html#figure-title
Example II – Disease Response → Minimize AE Profile

Translate to GnRH Modulation: Estrogen Loss → BMD

Time-course and Magnitude of Responses

Efficacy: Patient-level Data
- Biomarker: Estradiol (E2)
- Response: Endometriosis symptom severity score (ESSS)

Side Effect: Literature Meta Data
- Biomarkers: E2 → Bone Markers
- Response: Bone Mineral Density (BMD)

Logistic Model

Guide Study Design:
- Treatment Duration
- Biomarker Selection
- Target Response

Figure 1 of M M Riggs, M Bennett, P H van der Graaf and S W Martin. Integrated Pharmacometrics and Systems Pharmacology Model-Based Analyses to Guide GnRH Receptor Modulator Development for Management of Endometriosis. CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e11; doi:10.1038/psp.2012.10

http://www.nature.com/psp/journal/v1/n10/fig_tab/psp201210f1.html#figure-title
Example II – Minimize AE Profile

Translate to GnRH Modulation: Estrogen Loss → BMD

External Evaluation of BMD Response


http://www.nature.com/psp/journal/v1/n10/fig_tab/psp201210ft.html
- Ongoing Extensions ("Middle-Out")
  - Bone markers → Bone Mineral Density → Fracture Risk
  - Vitamin D kinetics and biotransformation

- Future Plans
  - WNT/SOST/DKK-1 pathways
  - FGF-23
  - Oncology
  - Glucocorticoid-induced bone loss
- Vitamin D input: diet and sun
- Biotransformation: involves liver and kidney
- Pharmacology: active Vit D = calcitriol
- Applications: disease states evaluations, trial design, supplemental recommendations

Figure 3-1 of Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. Dietary Reference Intakes for Calcium and Vitamin D. National Academies Press, 500 Fifth Street, N.W. Washington, DC 20001, 2011.
**SUMMARY**

- **Multiscale Models as a Knowledge Platform / Repository**

  - Include supporting data
  - Input emerging research
    - New data = learn/confirm hypotheses and assumptions
    - Information becomes knowledge (translational, model-based R&D)
  - Sharing within and across R&D teams
    - Portable across drug and disease states
    - Expandable to new drug and disease states
MSPM as an expandable R&D platform

- Construct in adaptable framework: address broad research questions
- Offer efficient, timely extension and application
- Repository of known mechanisms, hypotheses (theory), assumptions, and ongoing R&D goals
- Acknowledgements

- Metrum RG
  - Kyle Baron, Ph.D.
  - Marc Gastonguay, Ph.D.
  - Alanna Ocampo-Pelland, M.S., Ph.D. Student
  - Elodie Plan, Ph.D. (now @ Uppsala U)

- Mark Peterson, Ph.D., Pfizer (formerly Amgen)

- Pfizer (GnRH modulation modeling)
  - Steve Martin, Ph.D.
  - Piet van der Graaf, Ph.D. (now @ Leiden U)
- Parting Thoughts

- The scales do not need to be all inclusive…
  - but should match the question(s) at hand

- Model validation/evaluation?
  - Consider model validation at different scales

- Team ownership: biologists, pharmacologists, clinicians
  - Shared consensus on assumptions
  - Appropriate representations
    - the known
    - the unknown
    - the ‘to be determined’

- These models are complicated, but…
  - biology, pathphysiology and pharmacology are even more complicated
- Benefits: What’s to be Gained?

- selection of therapeutic modality
- hypothesis driven experimentation
- holistic drug design
- selection of target pathways and patient populations
- dose / regimen selection
- broad scale understanding of intended (and unintended) effects associated with disease, genetic variants and drug intervention,
- trial (experiment) simulation/optimization
- simultaneous predictions of all involved co-factors -- potential for biomarker identification
- can serve as repository of known, suspected, and assumed effects with supporting data ... information sharing within and across R&D teams
- ...
- Challenges/Barriers: What's holding us back?

- differing role(s) on R&D teams
- sufficient resources (time, people and/or $)
- training -- broad skill set required
- leadership investment in defining opportunities for real impact
- intellectual inertia (differing discipline nomenclatures, perspectives, and motivations to develop models),
- data (formatting, availability, quality)
- …
-What is a Multiscale Systems Model?

From Figure 1 of Riggs M. Multiscale Systems Models as a Knowledge Bridge Between Biology, Physiology and Pharmacology. AAPS Newsmagazine (December, 2011)
- **Public Source**
  - Opendiseasemodels.org
  - Extensions available from individual papers and posters: see www.metrumrg.com/publications

- **META\textsuperscript{MODL} \textsuperscript{TM}**
  - Subscription-Based, Therapeutic Area Model and Data Repository
  - Incorporates All Current Ca-Bone Model Extensions
Chronic Kidney Disease-Mineral Bone Disorder

**Chronic Renal Failure**
- Decreased GFR = Decreased Phosphate Clearance
- Increased Plasma Phosphate
- Decreased 1-α-hydroxylase
- Decreased Calcitriol (active Vitamin D)

**PT Gland Feedback**
- Increased PTH production

**Secondary Hyperparathyroidism**
- Increased RANK-L expression
- Increased Osteoclast Activation
- Decreased Osteoclast Apoptosis
- Increased Bone Resorption
- Decreased BMD

Example II -- Disease Response

Chronic Kidney Disease-Mineral Bone Disorder

Kidneys Fail ➔ Phosphate ➔ PTH ➔ Bone Resorption

Example II -- Disease Response

Chronic Kidney Disease-Mineral Bone Disorder

Example II -- Disease Response

Chronic Kidney Disease-Mineral Bone Disorder

Simulated Effects of CaSR agonism

black solid = no intervention; gray dot = 0.33 mmolar Ca Eq; black longdash = 0.67 mmolar Ca Eq; gray dotdash = 1.0 mmolar Ca Eq

Example II -- Disease Response

Chronic Kidney Disease-Mineral Bone Disorder

Simulated Effects of Calcitriol Infusion

- **GFR (mL/min)**
- **PTH (%)**
- **Ca (%)**
- **BSAP (%)**
- **SCTx (%)**
- **lumbar spine BMD (%)**

- **Year**
- **black solid = no intervention; gray dash = 1.25 mcg QOD; black dot = 2.5 mcg QOD**