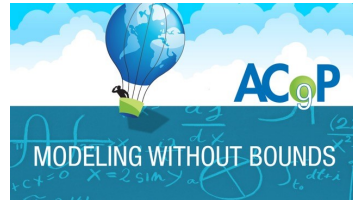


# Multi-scale iPSP Model of Physiologically-based Representations to Describe Bone Mineral Homeostasis and Interrelated Effects

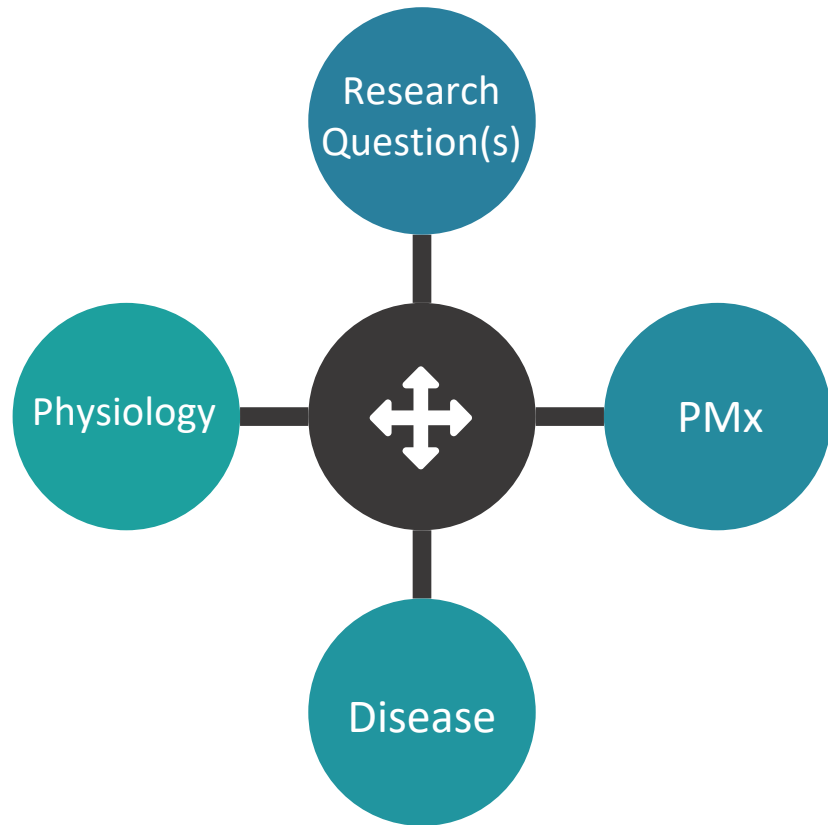
Matthew Riggs, Ph.D.  
Chief Science Officer  
Group Leader, Translational and Systems Pharmacology  
Metrum Research Group LLC  
Tariffville, CT USA



**ACoP9** Loews Coronado Bay Resort, CA  
Monday October 08, 2018

Session 1c: A Perspective on integrating Pharmacometrics and Quantitative Systems Pharmacology characteristics using examples

Peterson MC and Riggs MM (2010) A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. Bone 46:49-63



## Integration with Pharmacometrics

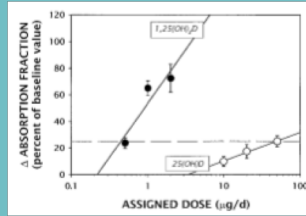
### How Does One Inform the Other?

- 1 Represent physiology (signaling → organs → outcomes)
- 2 Use SP and disease model to interpret and predict drug-related effects
- 3 Use drug-related effects to better understand physiology and disease
- 4 Provide a platform for evaluating longitudinal therapeutic and disease state effects

# SP Development: Integrate Existing Data & Models

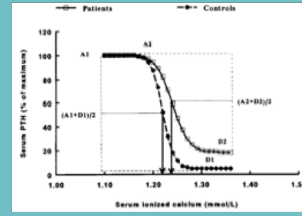
Decades of research available to inform model parameter and disease state effects

## Calcium Absorption



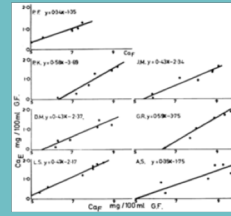
e.g., Heaney et al. 1997

## PTH Secretion



e.g., Ramirez et al. 1993

## Calcium Excretion



e.g., Peacock and Nordin 1968

## Bone Therapeutics

Anabolic  
(teriparatide, 2004)

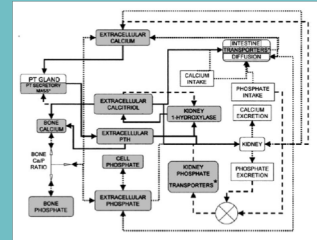
Catabolic  
(denosumab, 2006)

## Disease States

Hyper- and hypo-PTH

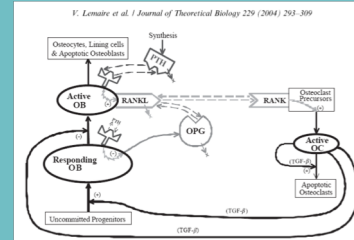
CKD-MBD (Rix et al. 1999)

## Calcium Homeostasis



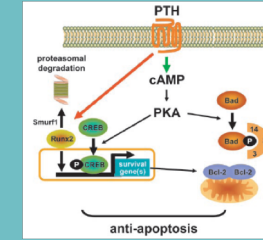
e.g., Raposo et al. 2002

## Bone Remodeling



e.g., LeMaire et al. 2004

## Intracellular Signaling



e.g., Bellido et al. 2003



## Multiscale Model

Peterson MC and Riggs MM (2010) A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. Bone 46:49-63.

**METRUM**

RESEARCH GROUP

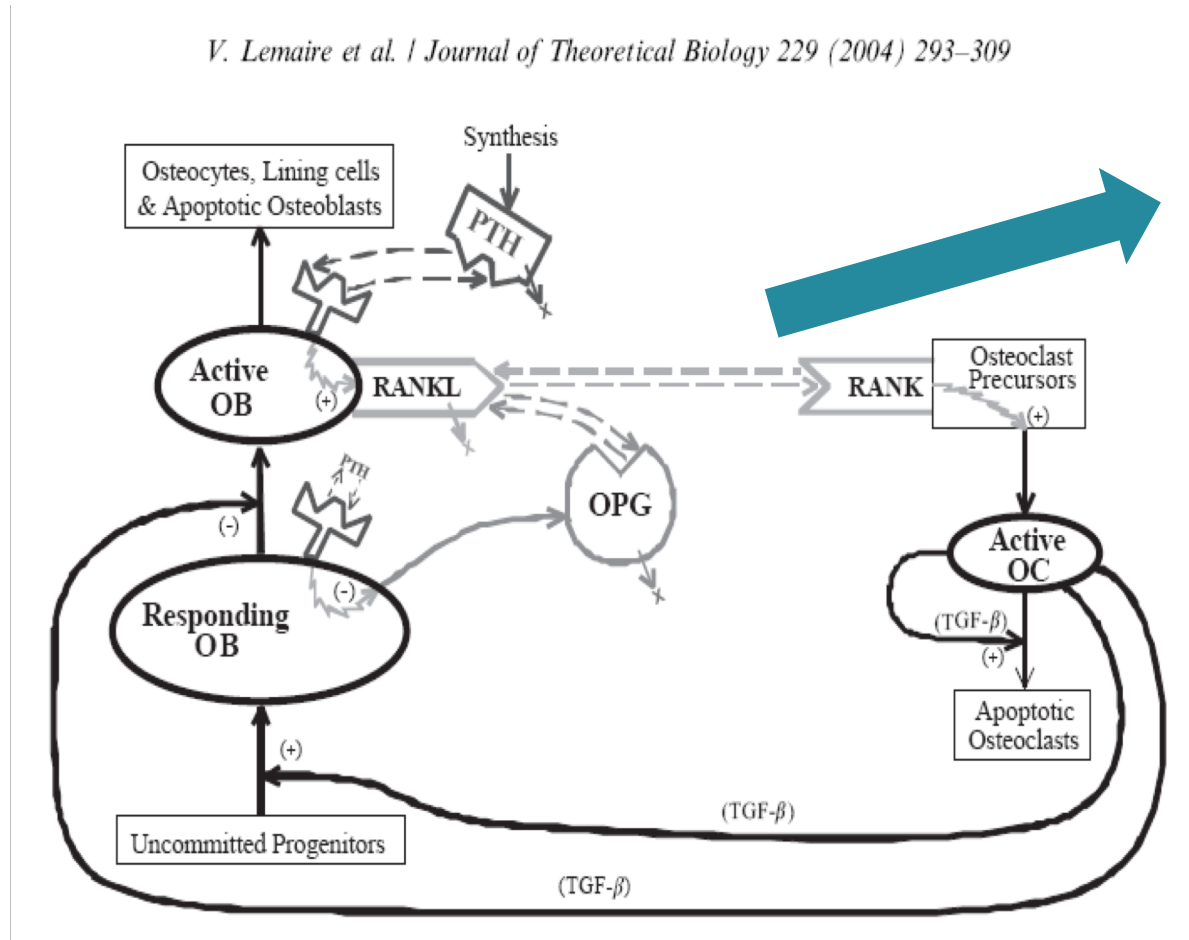


# SP Development: Interrogate Existing Models

What do we know now that we didn't know then?

## Bone Remodeling System Model

V. Lemaire et al. / Journal of Theoretical Biology 229 (2004) 293–309



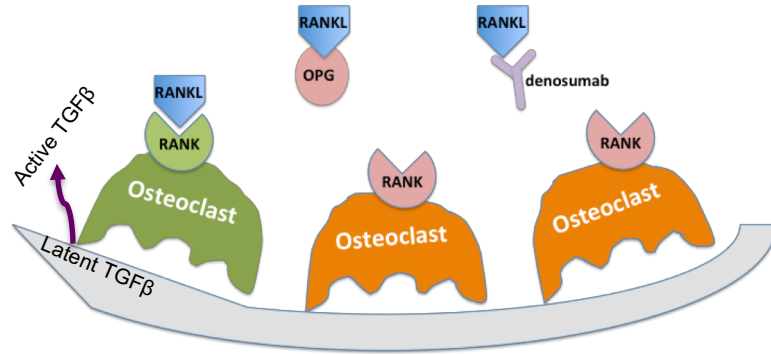
Unlock Steady-State Assumption



# iPSP: Use Drug To Inform SP Estimation

Much like with indirect response models: Maximal inhibition followed by “off” treatment allows for estimation of RANK-RANKL-OPG kinetics

## Denosumab: RANKL inhibition



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

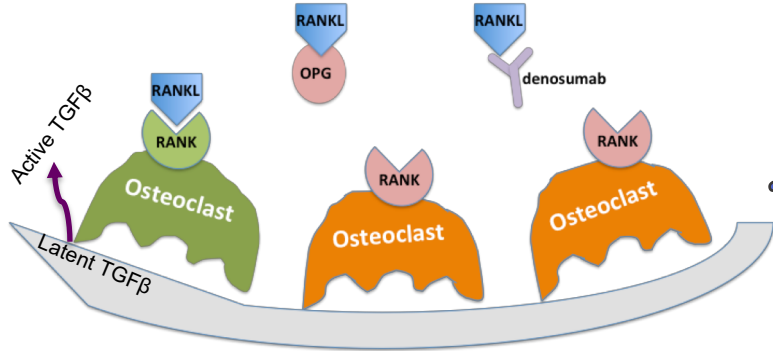
- ↓ Calcium release from bone
- ↓ Serum calcium
- ↓ Ca sensing in PT gland
- ↑ PTH release (calcium-sparing)

- Observed Data:
  - ↓ Bone resorption markers (near immediate)
  - ↓ Bone formation markers (delayed, less pronounced)
  - ↓ Serum Ca (transient)
  - PTH (transient)
- Can these effects be used to develop a single, physiologically representative model?

# iPSP: Use Drug To Inform SP Estimation

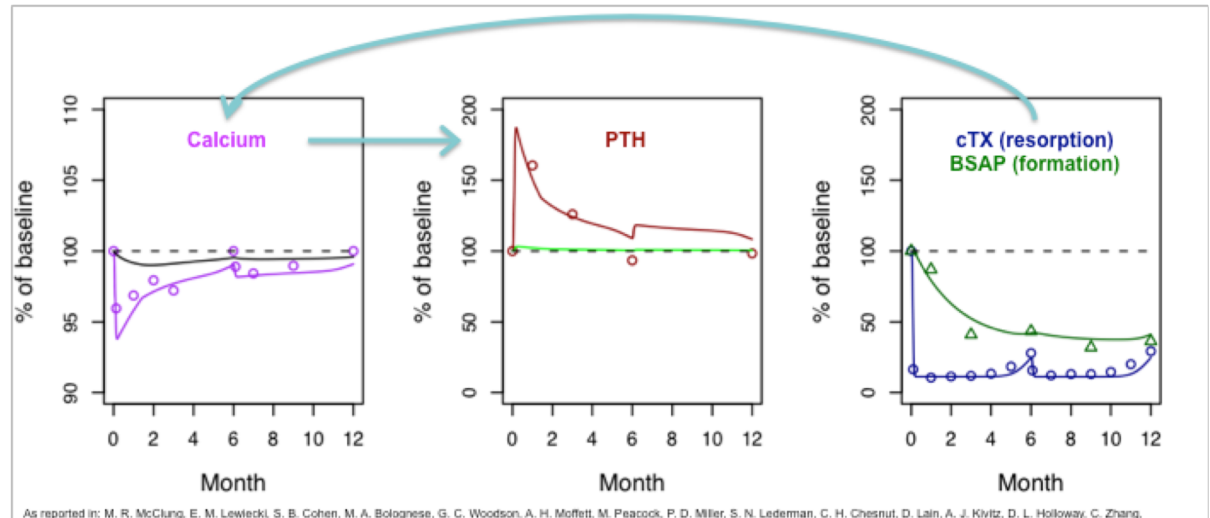
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As reported in: M. R. McClung, E. M. Lewkeck, S. B. Cohen, M. A. Bolognese, G. C. Woodson, A. H. Moffett, M. Peacock, P. D. Miller, S. N. Lederman, C. H. Chesnut, D. Lain, A. J. Kivitz, D. L. Holloway, C. Zhang, M. C. Peterson, P. J. Bekker, and AMG 162 Bone Loss Study Group. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med*, 354(6):827-31, Feb 2006.

# iPSP: Use Drug To Inform SP Estimation

Much like with indirect response models: Maximal inhibition followed by "off" treatment allows for estimation of RANK-RANKL-OPG kinetics

## Denosumab: RANKL inhibition → Bone Marker Changes

Dose-Ranging: 6 → 210 mg, Q3M and Q6M, d/c, re-Tx

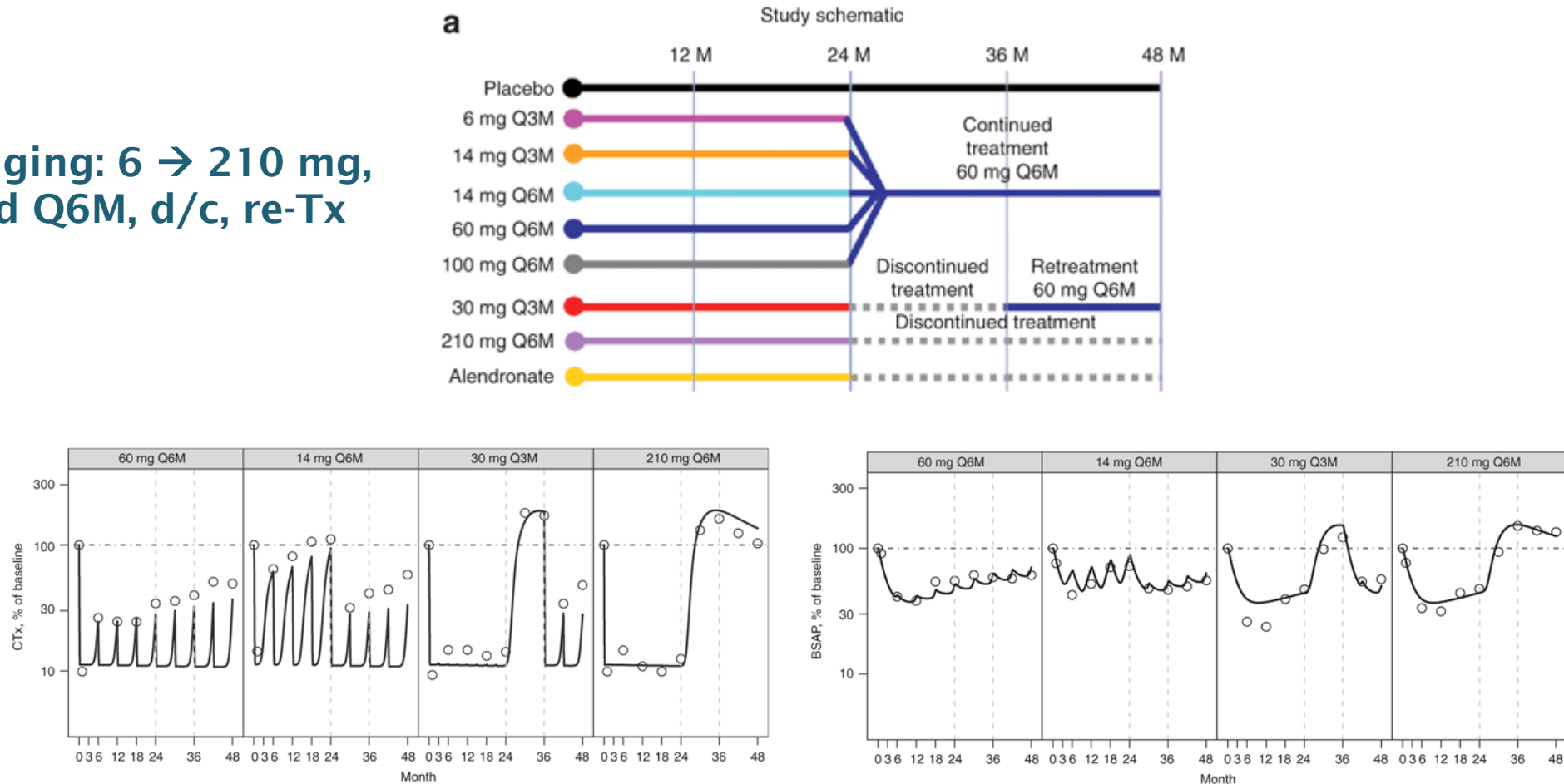


Fig.3 and 4; Peterson MC and Riggs MM., CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e14; doi:10.1038/psp.2012.15

# iPSP: Use SP To Predict Clinical Outcome

SP “middle-out”/ up – Use the model to extend to measured response (BMD)

## Denosumab: RANKL inhibition → Bone Markers → BMD Change

Dose-Ranging: 6 → 210 mg, Q3M and Q6M, d/c, re-Tx

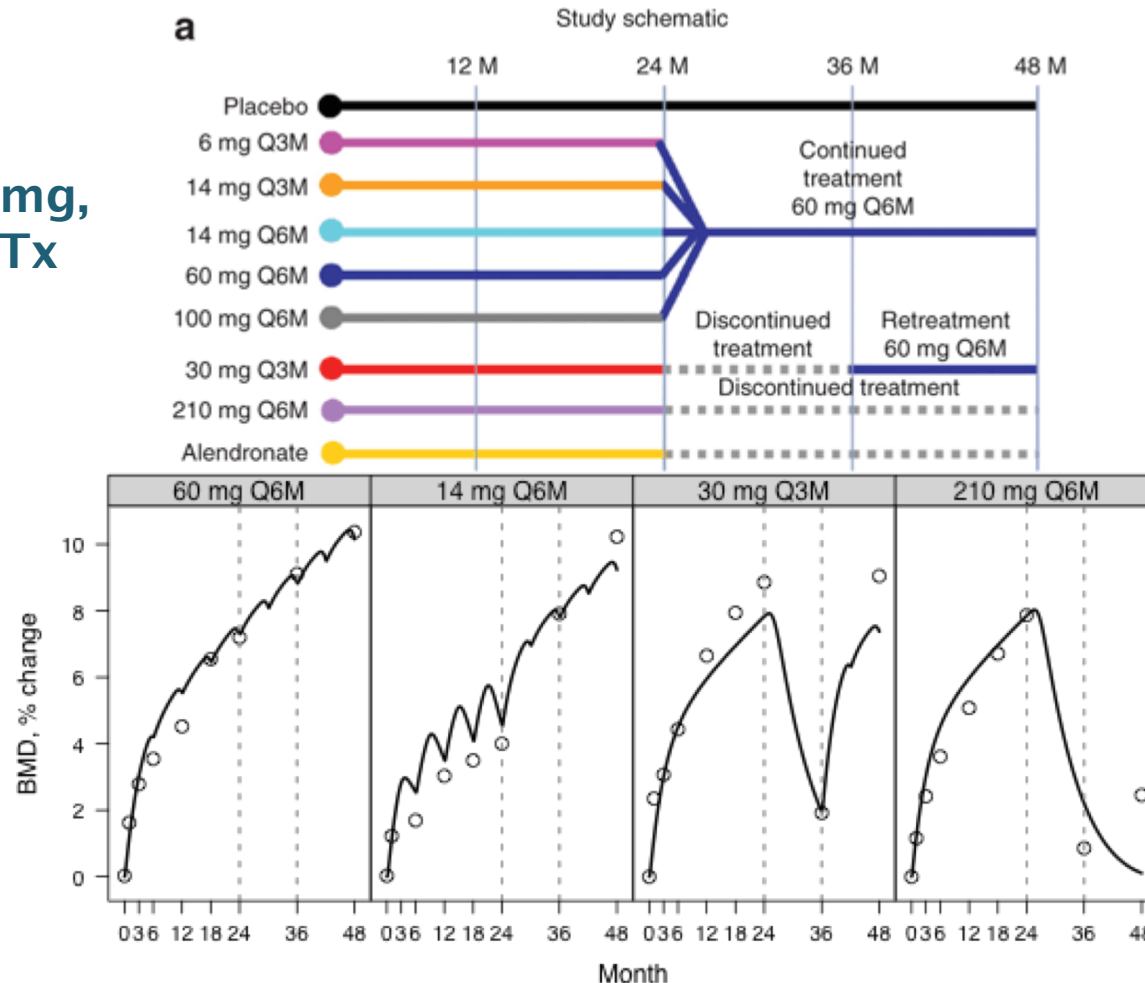


Fig. 5; Peterson MC and Riggs MM, CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e14; doi:10.1038/psp.2012.15

Start with a concept, add clinical data, watch it grow.

## Chronic Kidney Disease-Mineral Bone Disorder

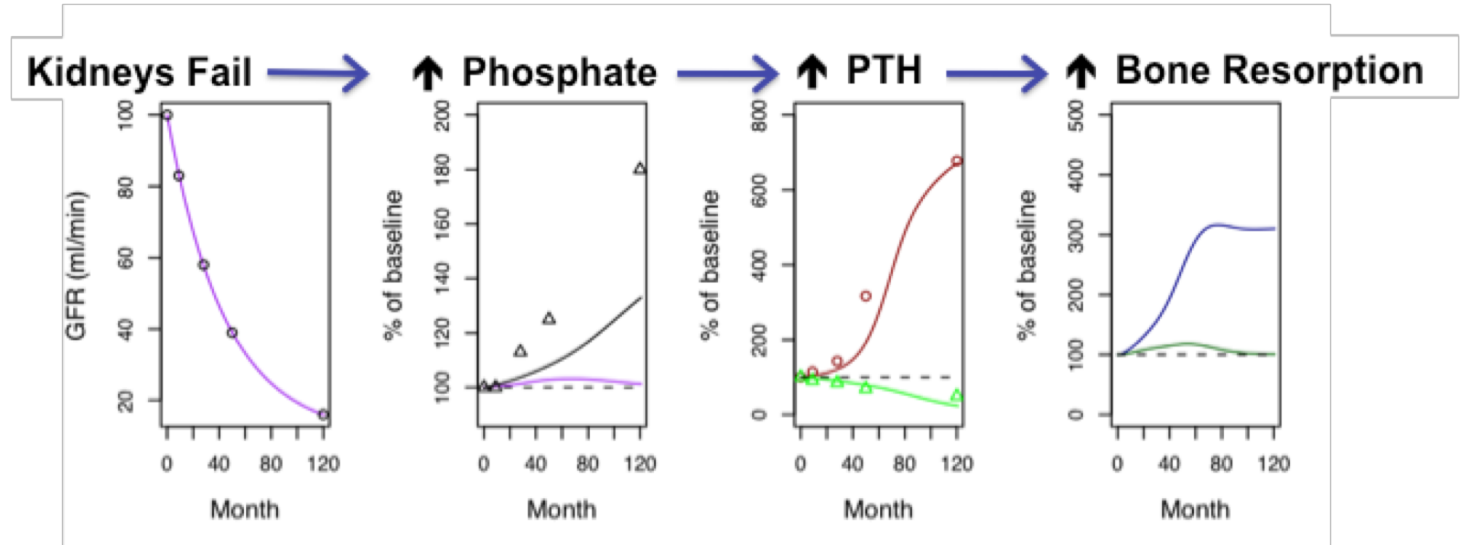
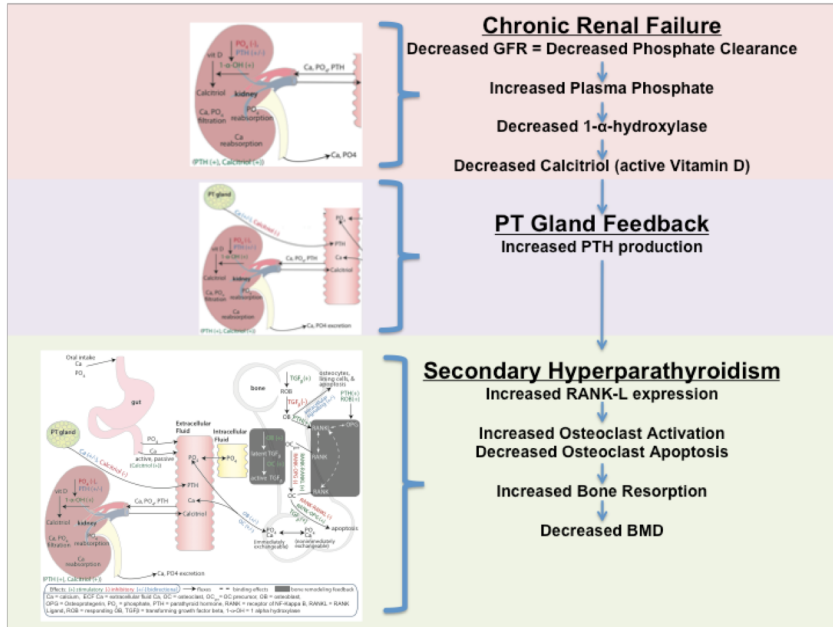


Fig. 1, 2; M. M. Riggs, M. C. Peterson, and M. R. Gastonguay. Multiscale physiology-based modeling of mineral bone disorder in patients with impaired kidney function. *J Clin Pharmacol*, 52(1 Suppl):45S–53S, Jan 2012.

- Can these effects be used to describe PTH and Ca response following long-term etelcalcetide treatment?

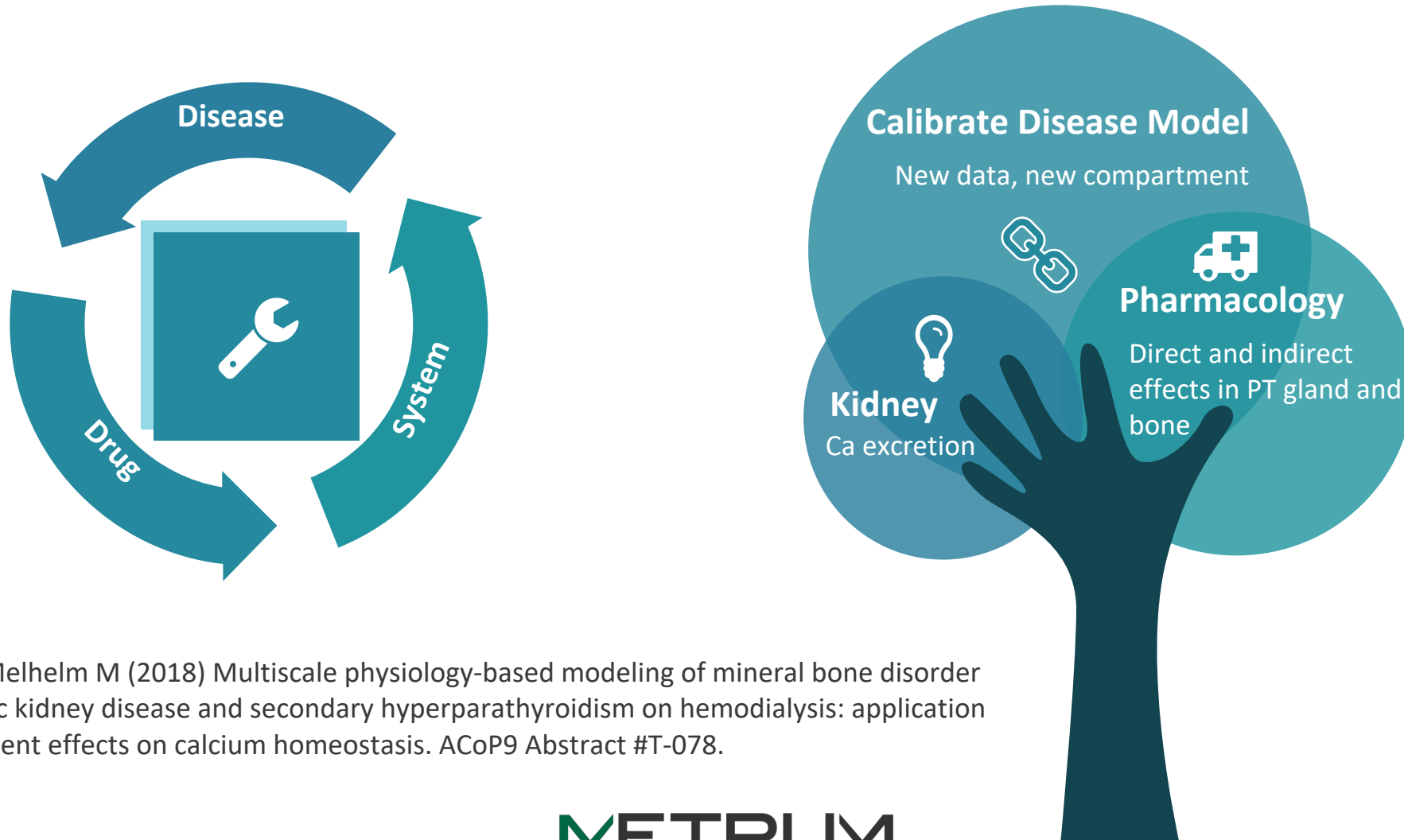
### Multiscale Model

Riggs MM, Baron KT, Melhem M (2018) Multiscale physiology-based modeling of mineral bone disorder in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis: application to etelcalcetide treatment effects on calcium homeostasis. *ACoP9 Abstract #T-078*.

# iPSP: Integrate System, Disease, Drug

Start with a concept, add clinical data, watch it grow.

## Chronic Kidney Disease-Mineral Bone Disorder



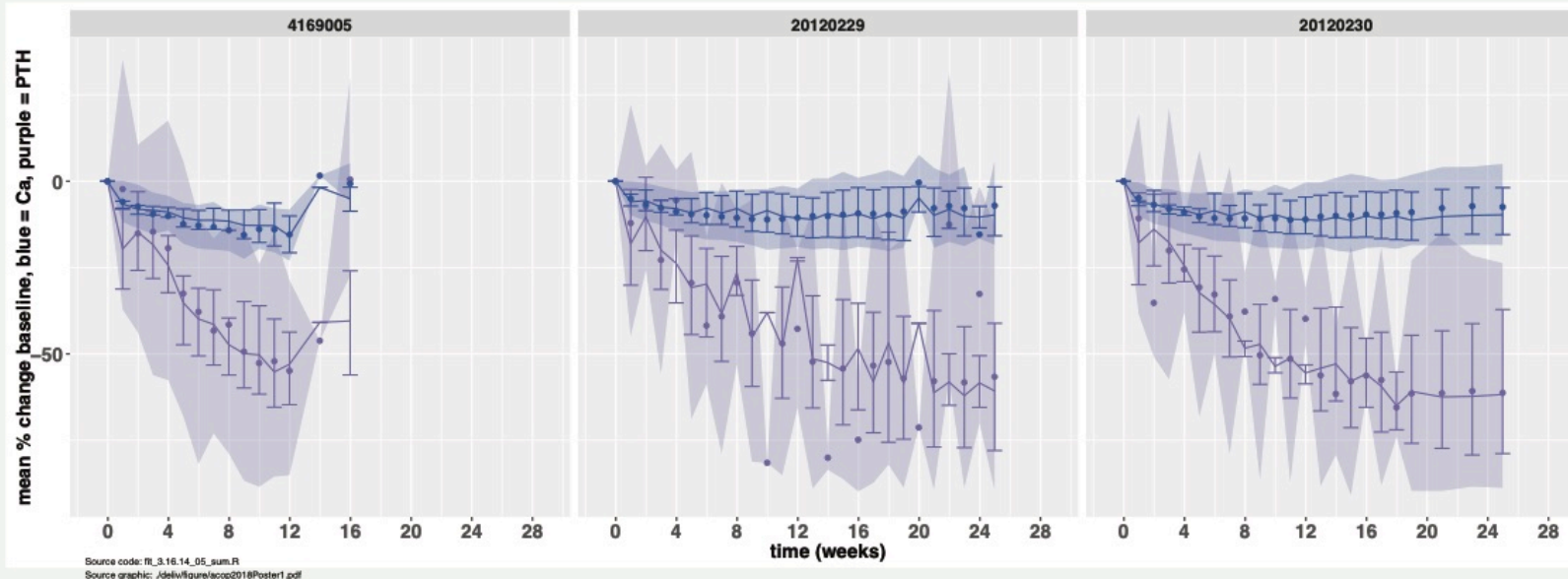
Riggs MM, Baron KT, Melhelm M (2018) Multiscale physiology-based modeling of mineral bone disorder in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis: application to etelcalcetide treatment effects on calcium homeostasis. ACoP9 Abstract #T-078.



Start with a concept, add clinical data, watch it grow.

## Chronic Kidney Disease-Mineral Bone Disorder

### Long-Term Predictive Checks



*Despite continued decline in PTH (e.g., beyond weeks 4-6), feedback controls lead to leveling and partial rebound in Ca.*

Figure 2: *Predictive check: change from baseline (percentage) for serum calcium (blue) and PTH (purple)*

Phase 3 Study 20120229 was included as external validation. Observed data: solid circle (mean) and 10th - 90th percentile range (shaded region); Simulated data: mean (solid line) and 10th - 90th percentile range (error bars).

Riggs MM, Baron KT, Melhelm M (2018) Multiscale physiology-based modeling of mineral bone disorder in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis: application to etelcalcetide treatment effects on calcium homeostasis. ACoP9 Abstract #T-078.

# iPSP: Integrated Outputs

Balancing act: minimized risk for AE (bone loss) while providing therapeutic response

## Endometriosis: GnRH modulation → Estrogen Loss

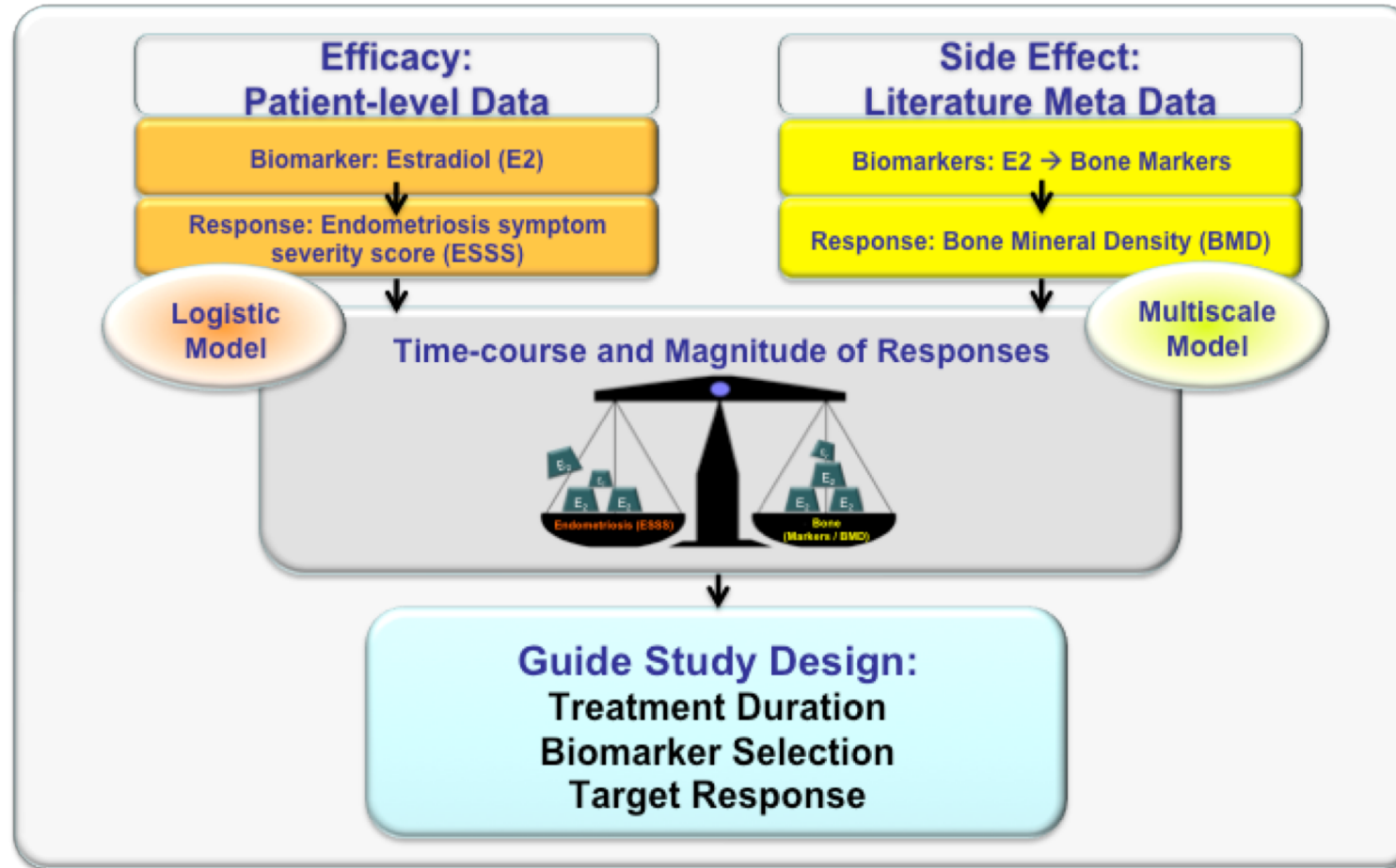


Figure 1 of M M Riggs, M Bennetts, P H van der Graaf and S W Martin. Integrated Pharmacometrics and Systems Pharmacology Model-Based Analyses to Guide GnRH Receptor Modulator Development for Management of Endometriosis. CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e11; doi:10.1038/psp.2012.10

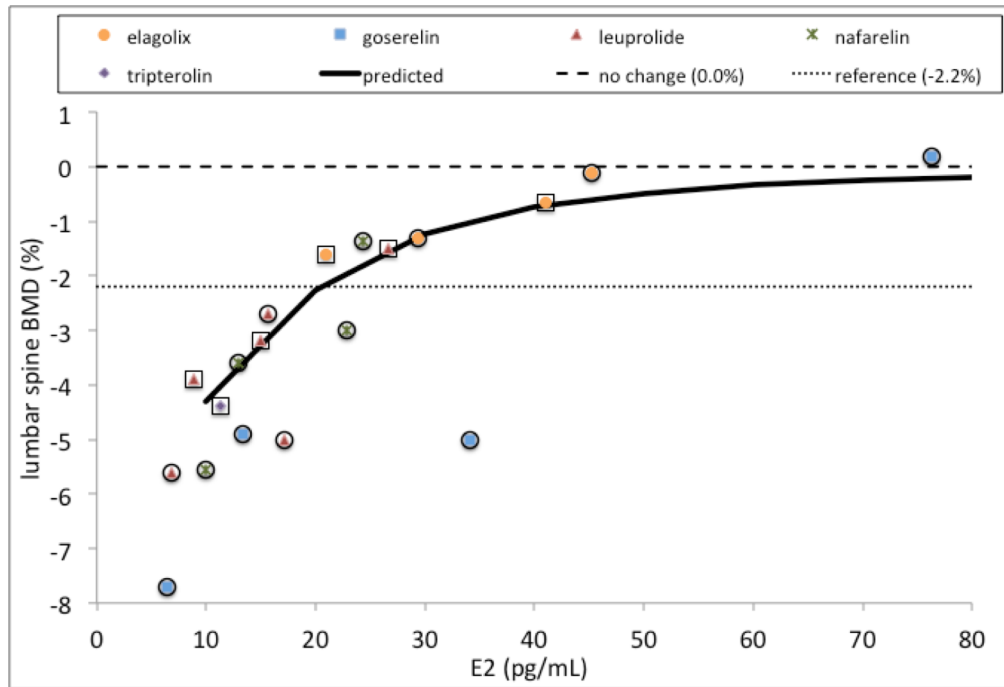
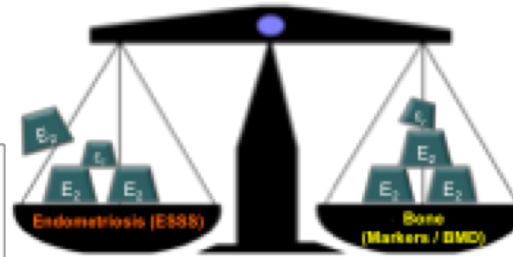
[http://www.nature.com/psp/journal/v1/n10/fig\\_tab/psp201210f1.html#figure-title](http://www.nature.com/psp/journal/v1/n10/fig_tab/psp201210f1.html#figure-title)



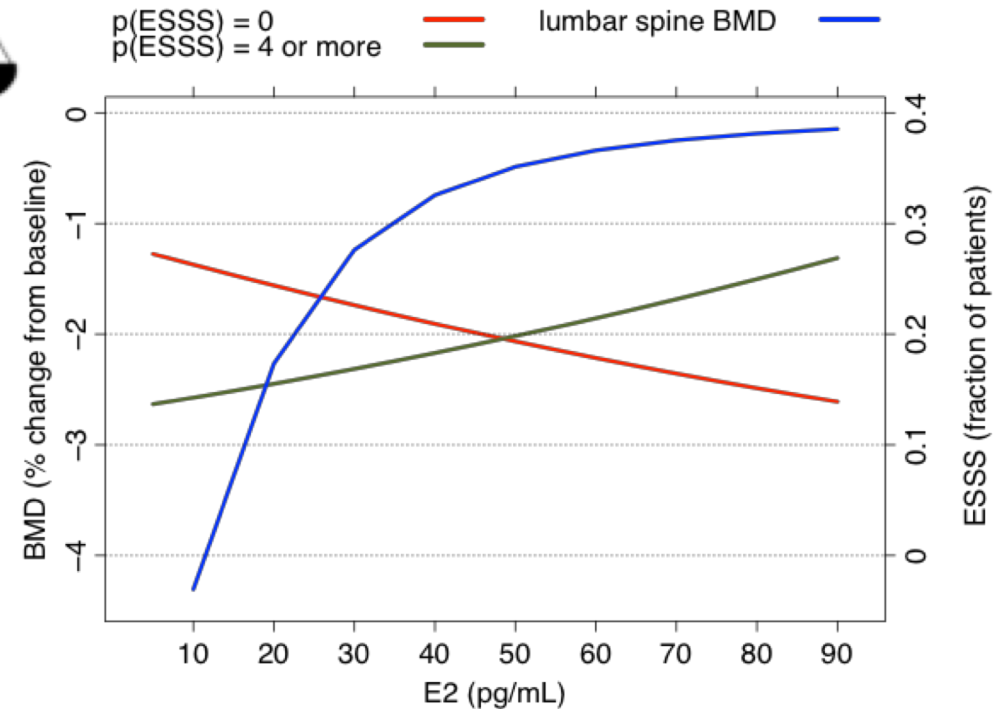
Balancing act: minimized risk for AE (bone loss) while providing therapeutic response

## Endometriosis: GnRH modulation → Estrogen Loss

### External Evaluation of BMD Response



### Overlay of BMD and Symptom Severity



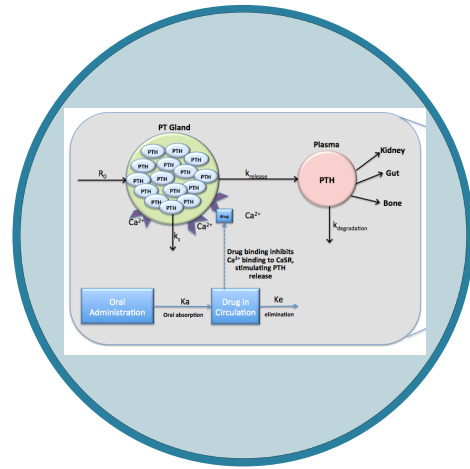
Figs 4, 6 of M M Riggs, M Bennetts, P H van der Graaf and S W Martin. Integrated Pharmacometrics and Systems Pharmacology Model-Based Analyses to Guide GnRH Receptor Modulator Development for Management of Endometriosis. CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e11; doi:10.1038/psp.2012.10

[http://www.nature.com/psp/journal/v1/n10/fig\\_tab/psp201210f1.html#figure-title](http://www.nature.com/psp/journal/v1/n10/fig_tab/psp201210f1.html#figure-title)



# iPSP Same SP Model, More iPSP Examples

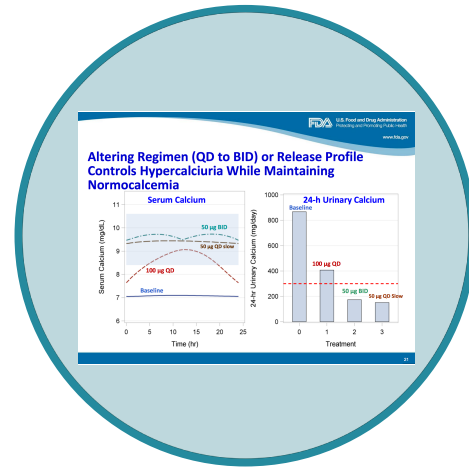
Open science opens doors



## Calcilytic Translational, clinical, literature data

Threshold / Maximum Release of PTH from PT gland: ceiling effect for BMD response well below teriparatide clinical data

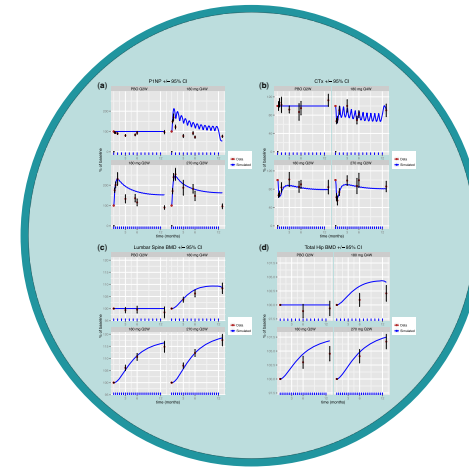
Presented at American Society of Bone Mineral Research (ASBMR) Annual Meeting, Baltimore, MD; October 6, 2013 (Abstract# SU0407)



## PTH for Hypoparathyroidism Clinical data

FDA suggested BID or sustained release likely to retain efficacy while minimizing risk of hypercalciuria

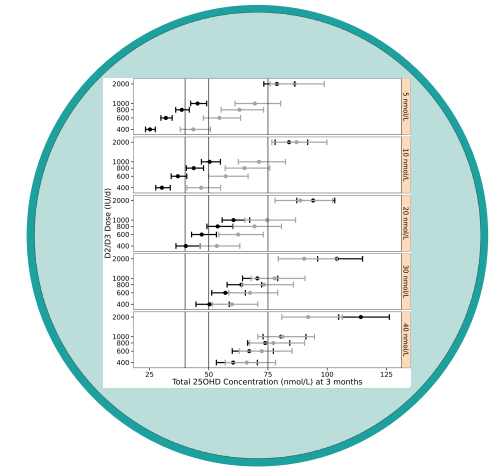
Presented at FDA September 12, 2014 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee



## Sclerostin Inhibition Clinical literature data

Explored dose and dosing interval responses and provided descriptive responses of bone markers changes over time

Eudy R, Gastonguay M, Baron K, and Riggs M. Connecting the dots. CPT: Pharmacometrics Syst Pharmacol, 2015



## Vitamin D Clinical literature data

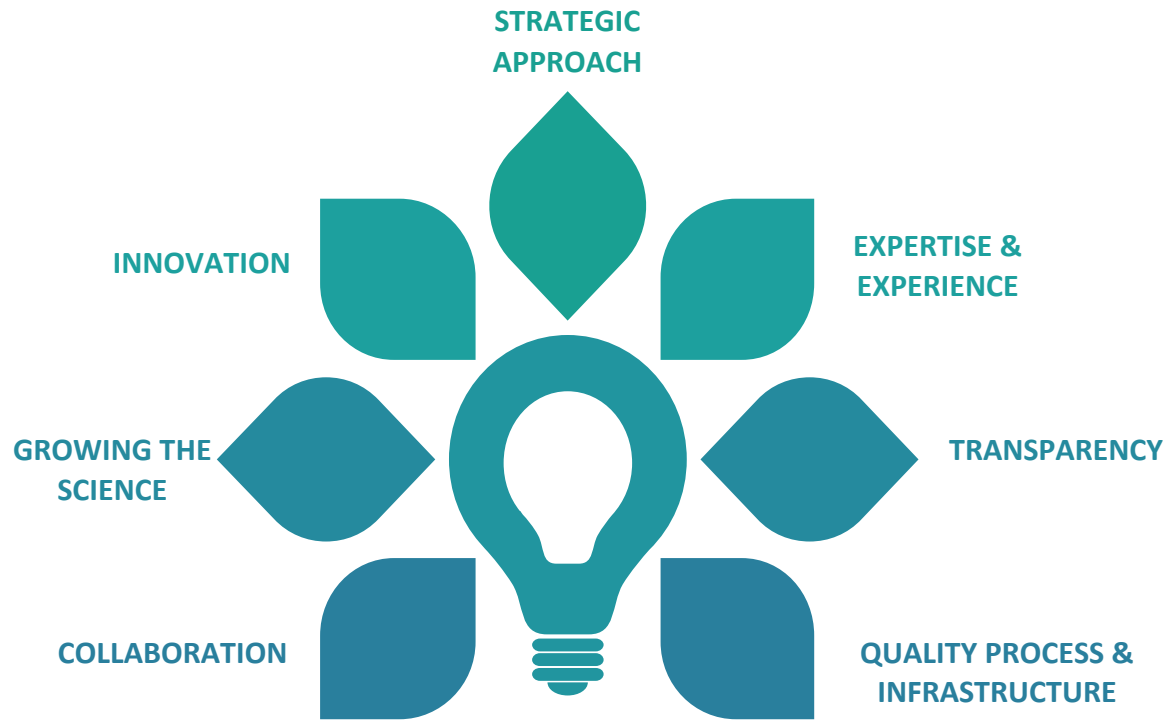
Included pharmacokinetic conversion of Vitamin D in liver (calcidiol) and kidney (calitriol) with link into system model to evaluate dose-response on Ca and BMD response

Ocampo-Pelland, Gastonguay, and Riggs. J Pharmacokinet Pharmacodyn, 44(4):375-388, Aug 2017.

# iPSP An ODE to Open Science

Without open science , none of this would have been possible... be open, make it possible!!

<https://github.com/metrumresearchgroup/OpenBoneMin>



https://github.com/metrumresearchgroup/OpenBoneMin

## README.md

### About

A multiscale systems model of bone health and mineral homeostasis. Please see the [wiki page](#) for more information on this project.

Community contributions to this project are included [here](#).

### Documentation

- Documentation [here](#)

### Installation

Installation of `OpenBoneMin` requires the `devtools` package

```
if(!require("devtools")) install.packages("devtools")
```

Use the `install_github` function inside `devtools` to install the `OpenBoneMin` package from GitHub to your local machine

```
devtools::install_github("metrumresearchgroup/OpenBoneMin")
```

You can test the installation by trying an example

```
example("sim_teri", package = "OpenBoneMin")
```

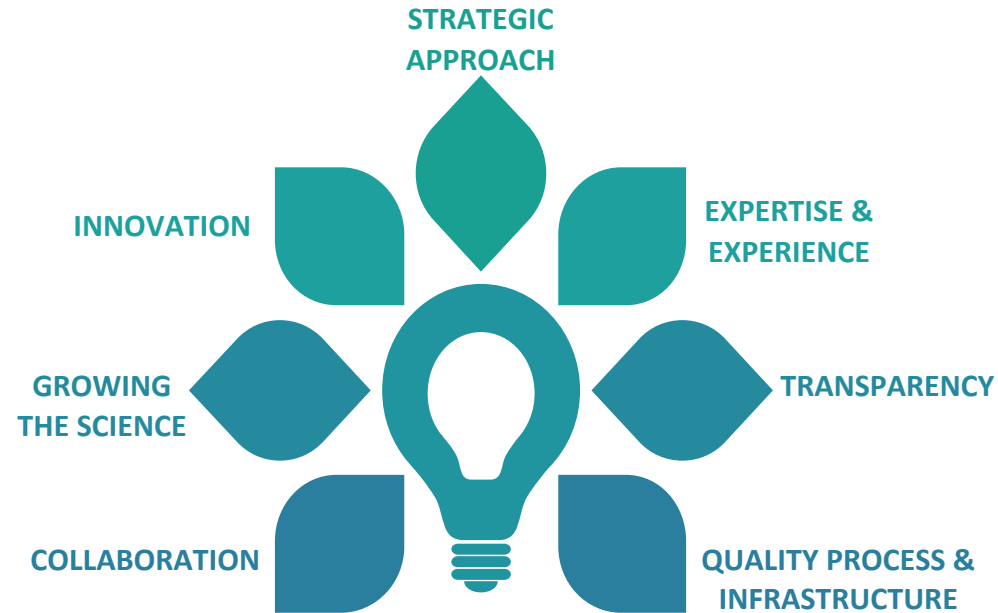
### Usage

- Simulate teriparatide data

# iPSP An ODE to Open Science

Without open science , none of this would have been possible... be open, make it possible!!

<https://github.com/metrumresearchgroup/OpenBoneMin>



19 lines (9 sloc) | 434 Bytes

Raw Blame History

## Community Contributions

This folder contains community contributions to the OpenBoneMin repo.

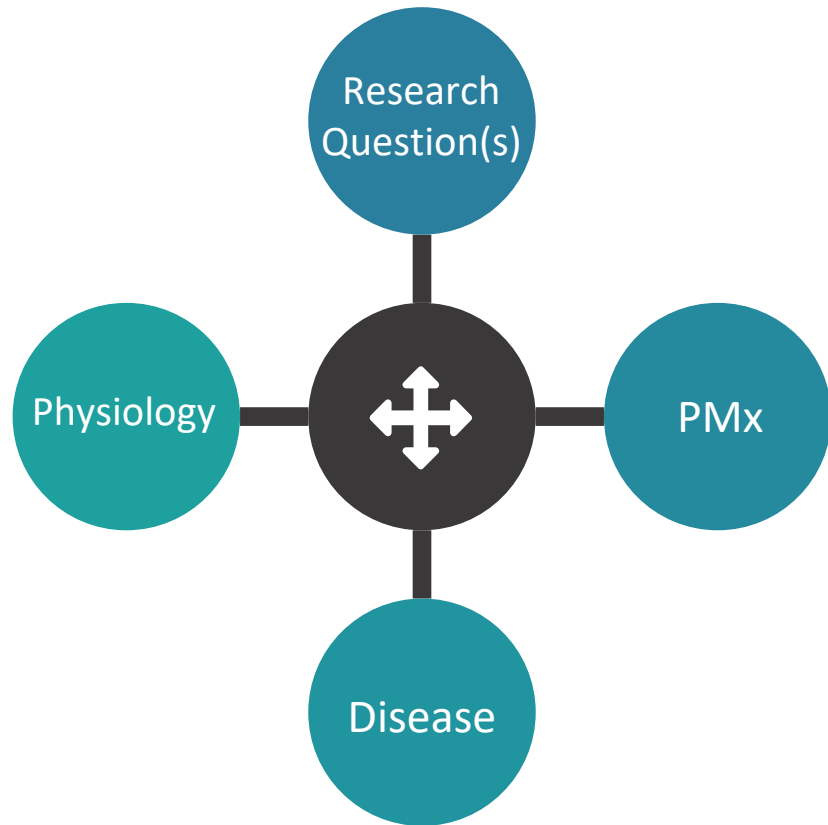
### Contents

[lump](#)

Supplementary code from:

Hasegawa C, Duffull SB. Automated Scale Reduction of Nonlinear QSP Models With an Illustrative Application to a Bone Biology System. CPT Pharmacometrics Syst Pharmacol. 2018 Jul 24. doi: 10.1002/psp4.12324. PMID 30043496

Peterson MC and Riggs MM (2010) A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. Bone 46:49-63



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- 4 Provide a platform for evaluating longitudinal therapeutic and disease state effects

# Acknowledgements Collaborating Authors/Researchers

It has been my privilege to work with so many brilliant researchers



Thank you!!!



Eudy-Byrne  
Baron Plan  
Shibayama French Shimizu  
Okada Jansen  
Gastonguay  
Ocampo-Pelland Melhem  
vanderGraaf Martin Zhou Bennetts  
Sawamura  
Peterson  
Gillespie

WordItOut