AAPS National Biotechnology Conference

Advancements and Applications of Multiscale Systems Pharmacology (MSP) Modeling

Systematic Extension of a Physiologic Model of Bone and Calcium Homeostasis

Matthew M. Riggs, Ph.D.

Principal Scientist II
Group Leader, Systems Biology M&S

mattr@metrumrg.com

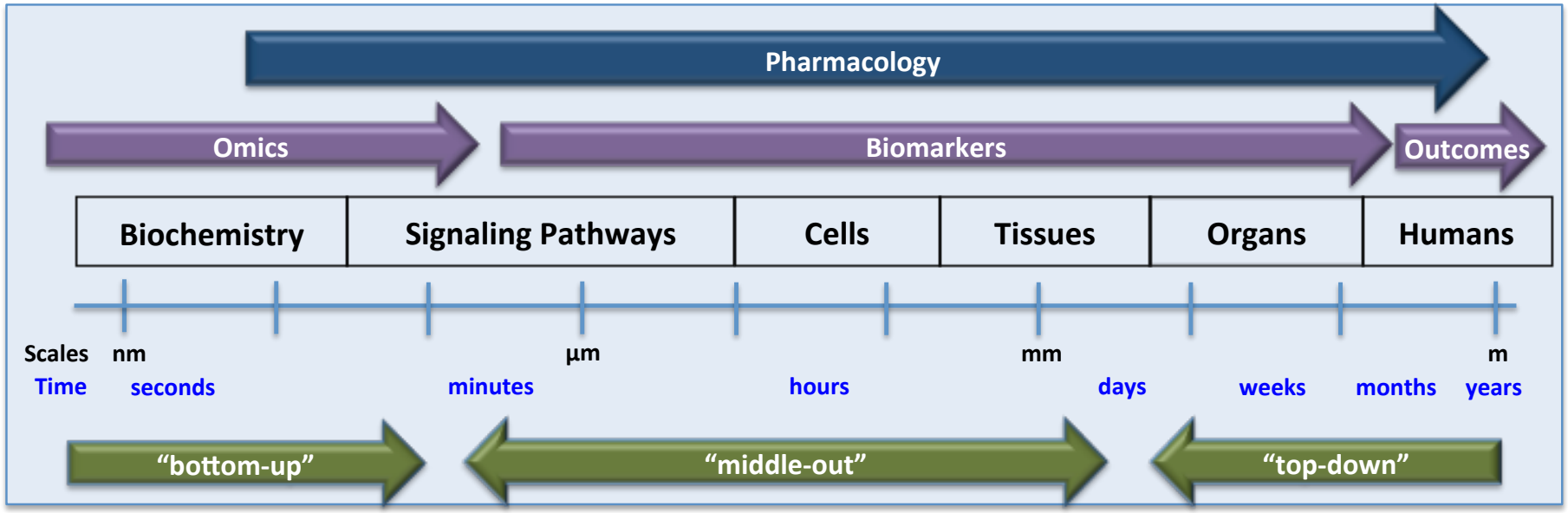
May 22, 2012

METRUM RESEARCH GROUP

Multiscale Modeling

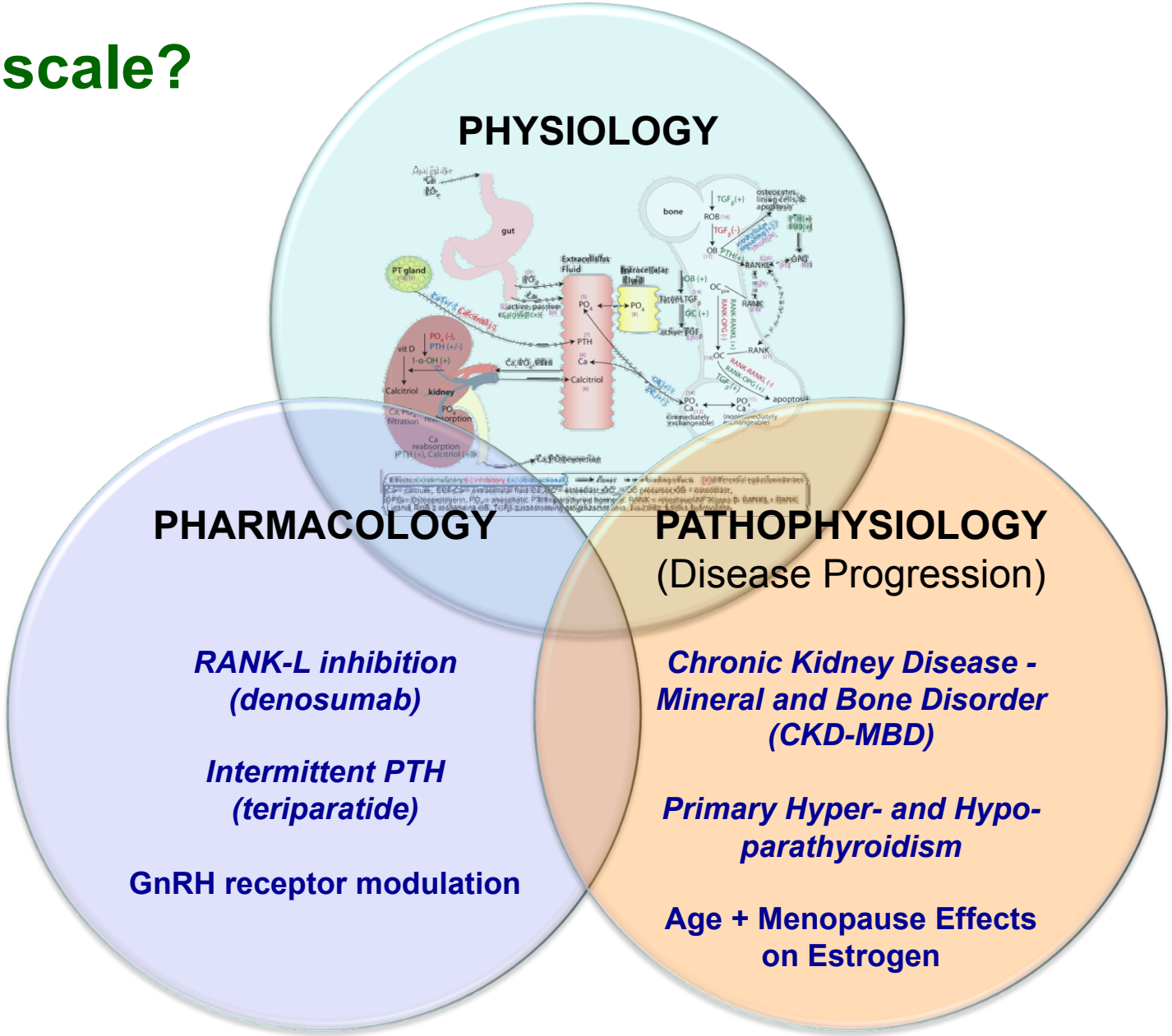
- Introduction
  - Define ‘Scales’
  - Examples:
    - Guyton’s Cardiovascular Model
    - A Calcium/Bone Model
- Extensions of the Calcium/Bone Model
  - Disease Response (example: Chronic Kidney Disease)
  - Therapeutic Response
  - Ongoing R&D
- In Summary
  - Concept: A Research Platform
  - Parting Thoughts

- What is a Multiscale Systems Model?

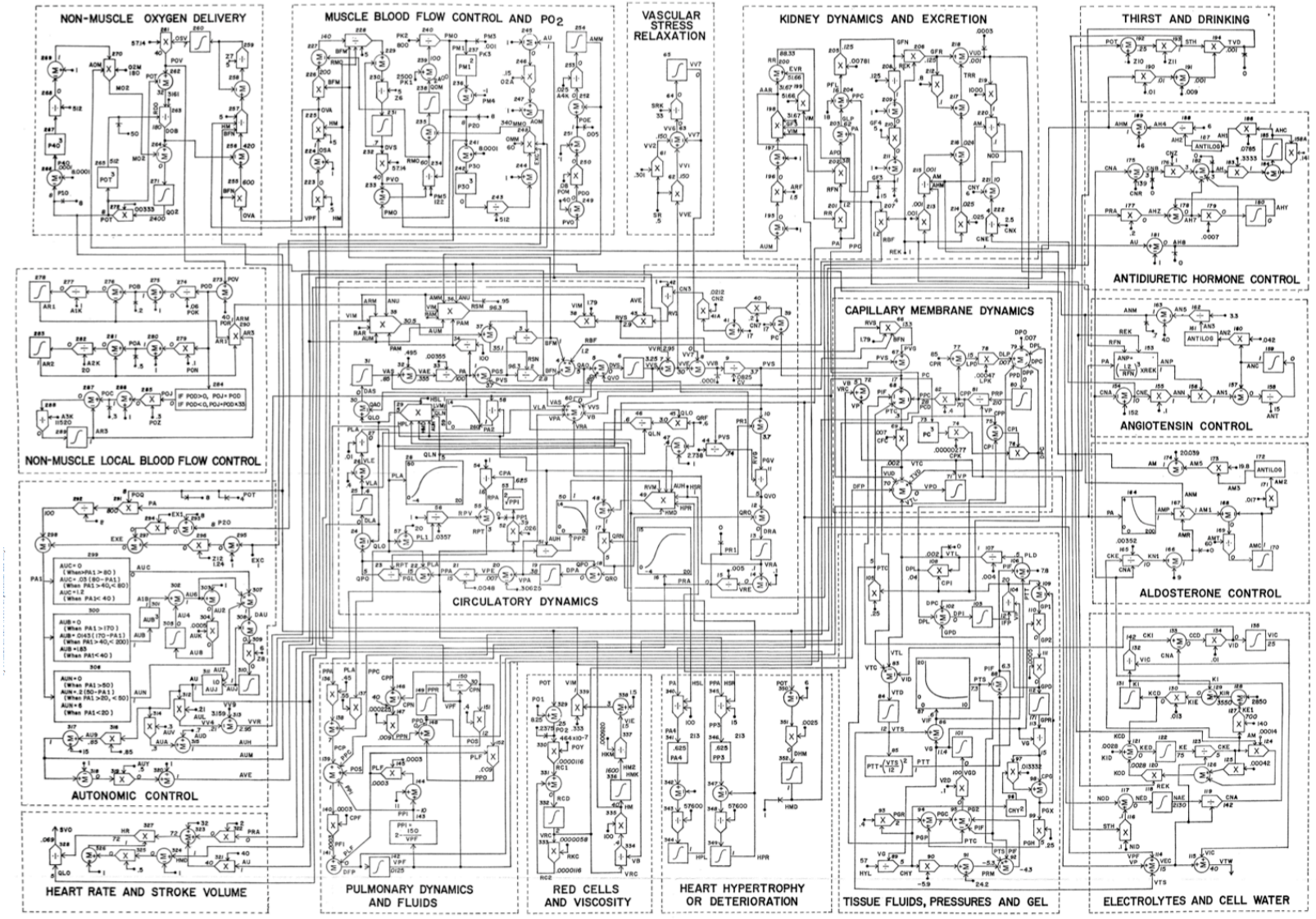


From Figure 1 of Riggs M. Multiscale Systems Models as a Knowledge Bridge Between Biology, Physiology and Pharmacology. *AAPS Newsmagazine (December, 2011)*

- Why Multiscale?



Schematic of Cardiovascular Model



Guyton AC, Coleman TG, Granger HJ 1972. Circulation: overall regulation. Annu Rev Physiol 34:13-46.

Guyton's Cardiovascular Model

"When he first presented his mathematical model of cardiovascular function … in **1968**… responses … (2)… reflected a tone of disbelief and even sarcasm. Dr. Guyton's systems analysis had **predicted a dominant role for the renal pressure natriuresis mechanism in long-term blood pressure regulation**, a concept that seemed **heretical** to most investigators at that time."

2. Guyton AC, Coleman TG. Quantitative analysis of the pathophysiology of hypertension. Circ. Res. 1969, 24 (Suppl I): I1-I19.

http://www.the-aps.org/membership/obituaries/arthur_guyton.htm

Guyton's Cardiovascular Model

"When he first presented his mathematical model of cardiovascular function … in **1968**… responses … (2)… long-term blood pressure regulation, a concept that seemed **heretical** to most investigators at that time."

44 Years Later: Notably Few Multiscale Models of Physiology Exist (Publicly)

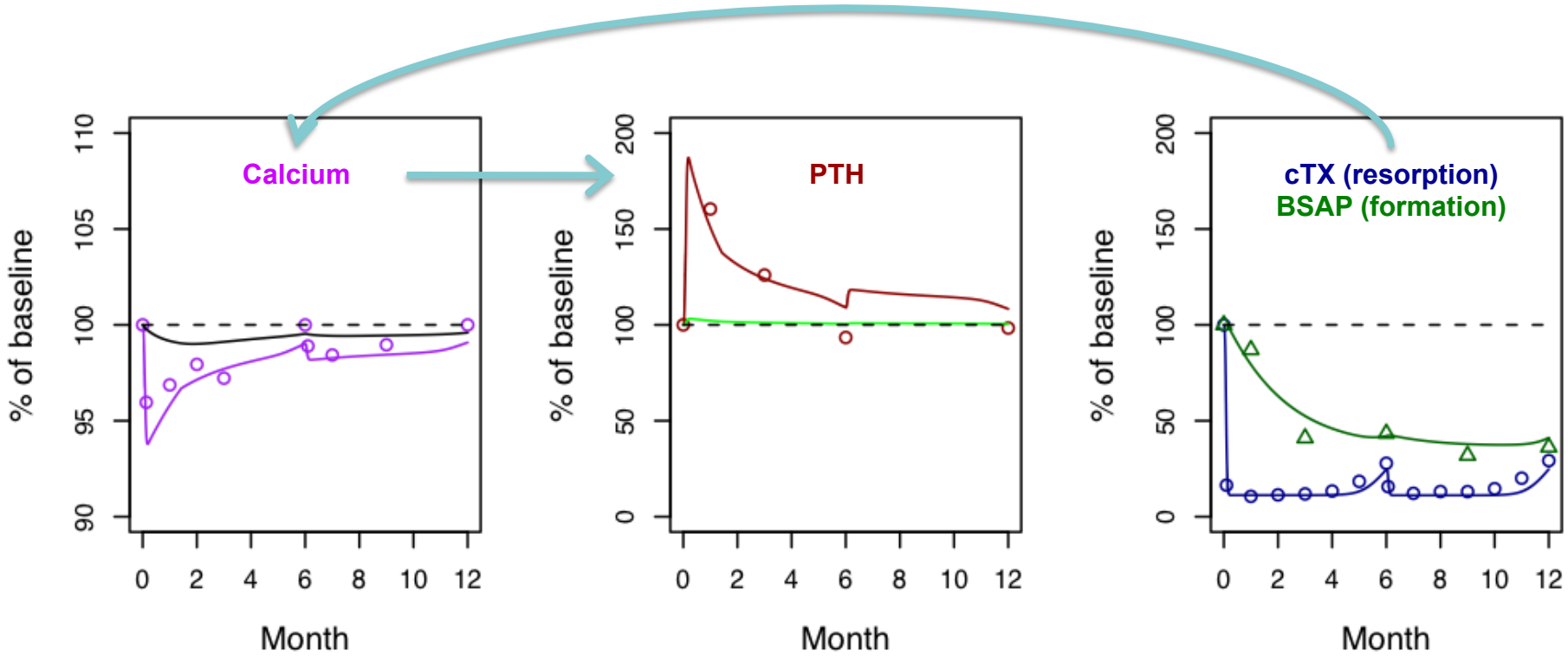
2. Guyton AC, Coleman TG. Quantitative analysis of the pathophysiology of hypertension. Circ. Res. 1969, 24 (Suppl I): I1-I19.

http://www.the-aps.org/membership/obituaries/arthur_guyton.htm

Multiscale Model of Calcium and Bone

- Original Motivation: Denosumab (RANK-L inhibitor)

  ↓ bone resorption = ↓Ca from bone = ↓ plasma Ca = ↑PTH



As reported in: M. R. McClung, E. M. Lewiecki, 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(8):821–31, Feb 2006.*

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. TGF_{beta})
      - 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

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

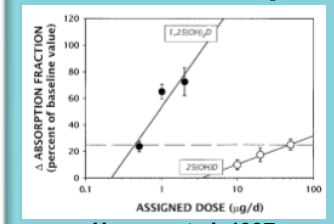
Multiscale Model of Calcium and Bone

- 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?

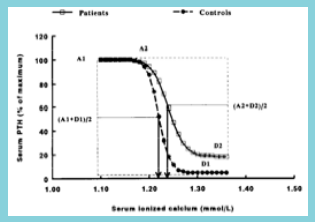
Integrating Existing Data and Models

Calcium Absorption



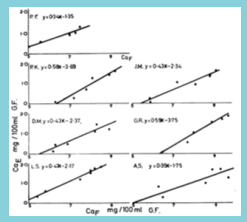
e.g., *Heaney et al. 1997*

PTH Secretion



e.g., *Ramirez et al. 1993*

Calcium Excretion



e.g., *Peacock and Nordin 1968*

Bone Therapeutics

Anabolic (*teriparatide, 2004*)

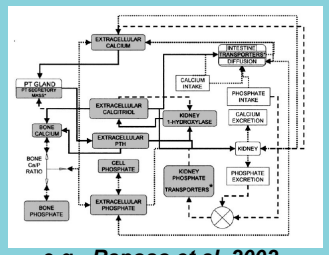
Catabolic (*denosumab, 2006*)

Disease States

Hyper- and hypo-PTH

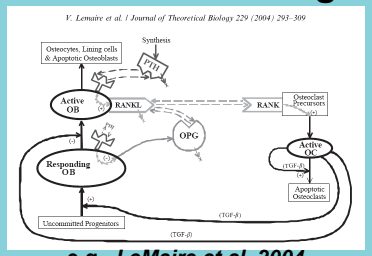
CKD-MBD (*Rix et al. 1999*)

Calcium Homeostasis



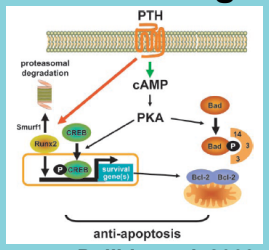
e.g., *Raposo et al. 2002*

Bone Remodeling



e.g., *LeMaire et al. 2004*

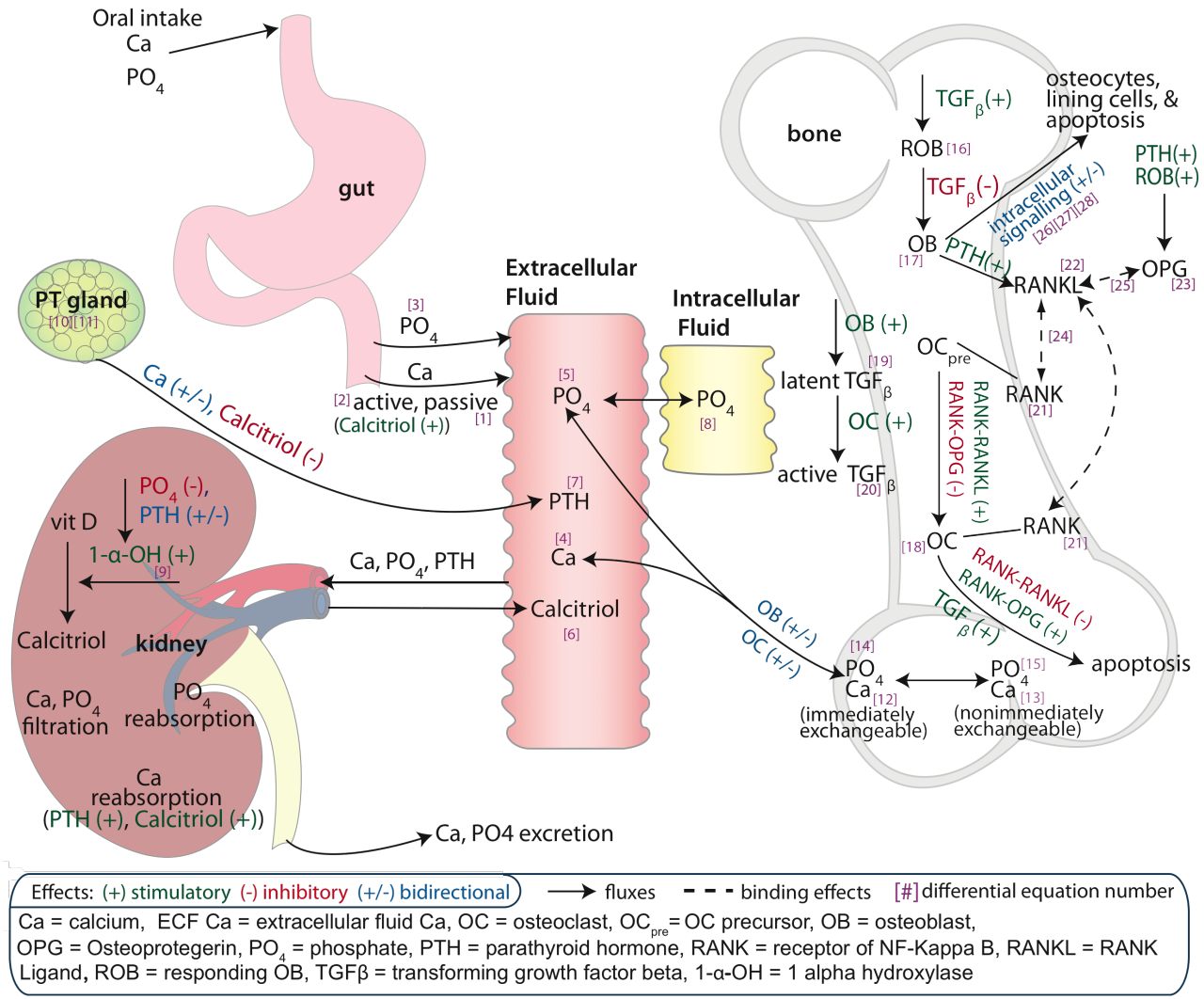
Intracellular Signaling



e.g., *Bellido et al. 2003*

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

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)*)

Chronic Kidney Disease-Mineral Bone Disorder

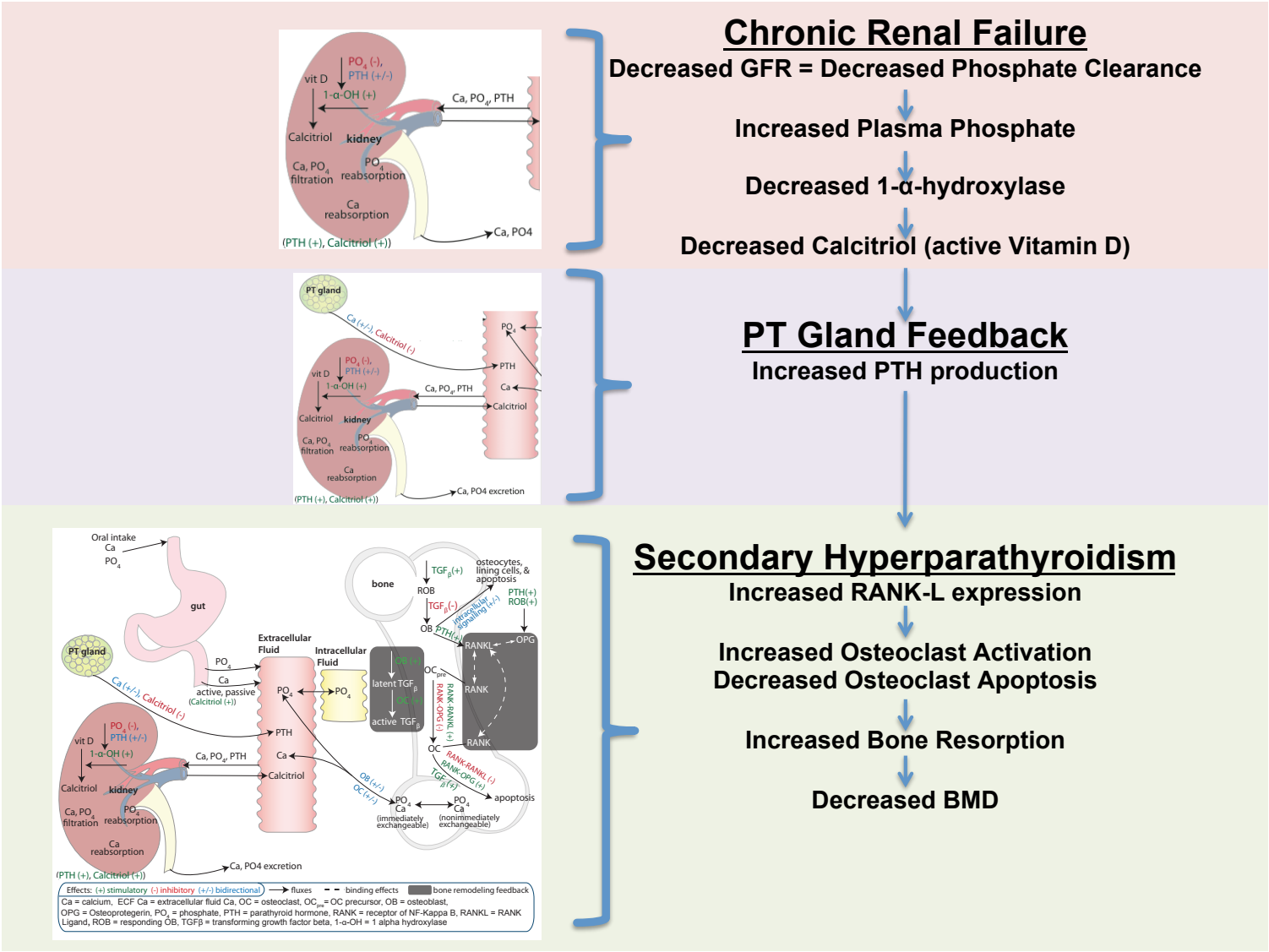
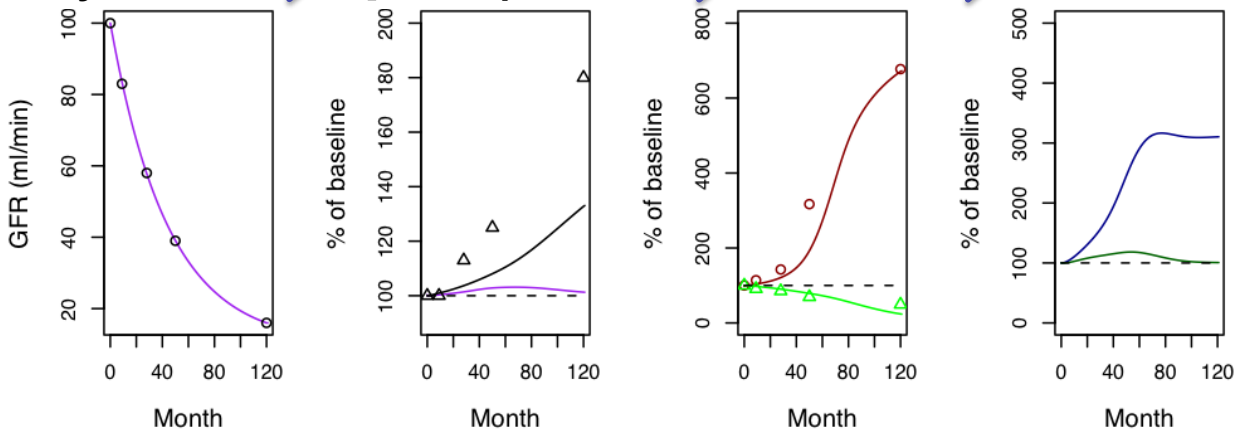


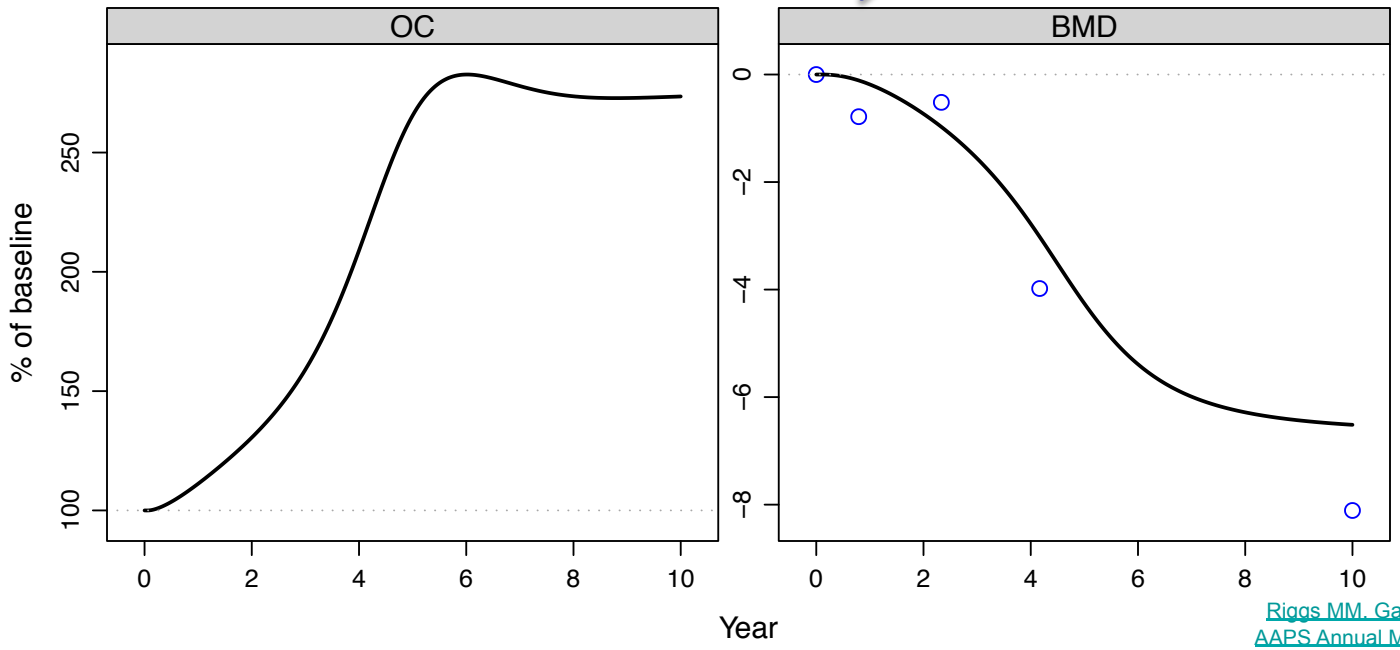
Fig. 1; Riggs MM, Peterson MC, Gastonguay MR. Multiscale Physiology-Based Modeling of Mineral Bone Disorder in Patients With Impaired Kidney Function. J Clin Pharmacol. *In press*.

Chronic Kidney Disease-Mineral Bone Disorder

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



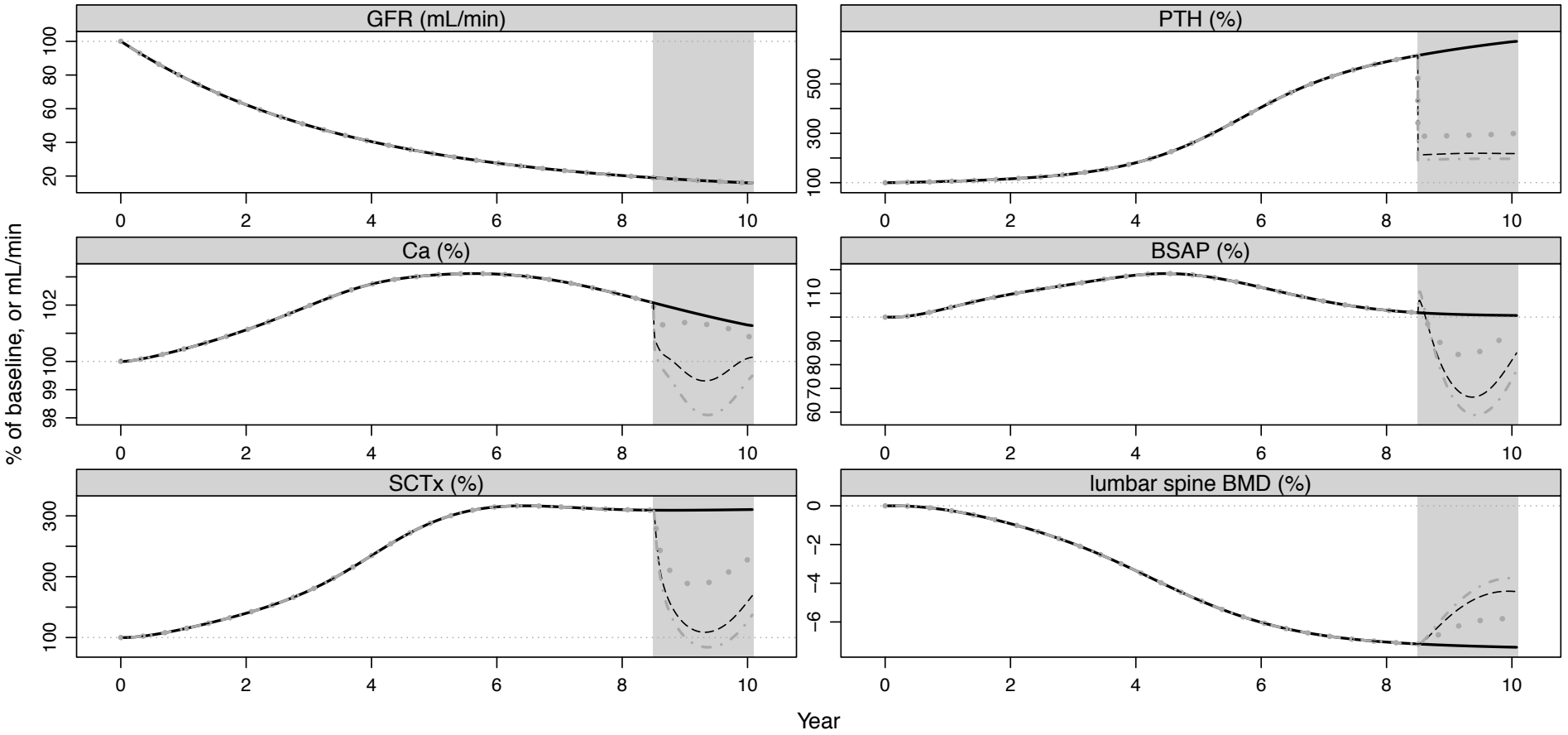
↑ Bone Resorption → ↓ BMD



Riggs MM, Gastonguay MR, Peterson MC. AAPS Annual Meeting 2010; Poster # W4403

Chronic Kidney Disease-Mineral Bone Disorder

Simulated Effects of CaSR agonism

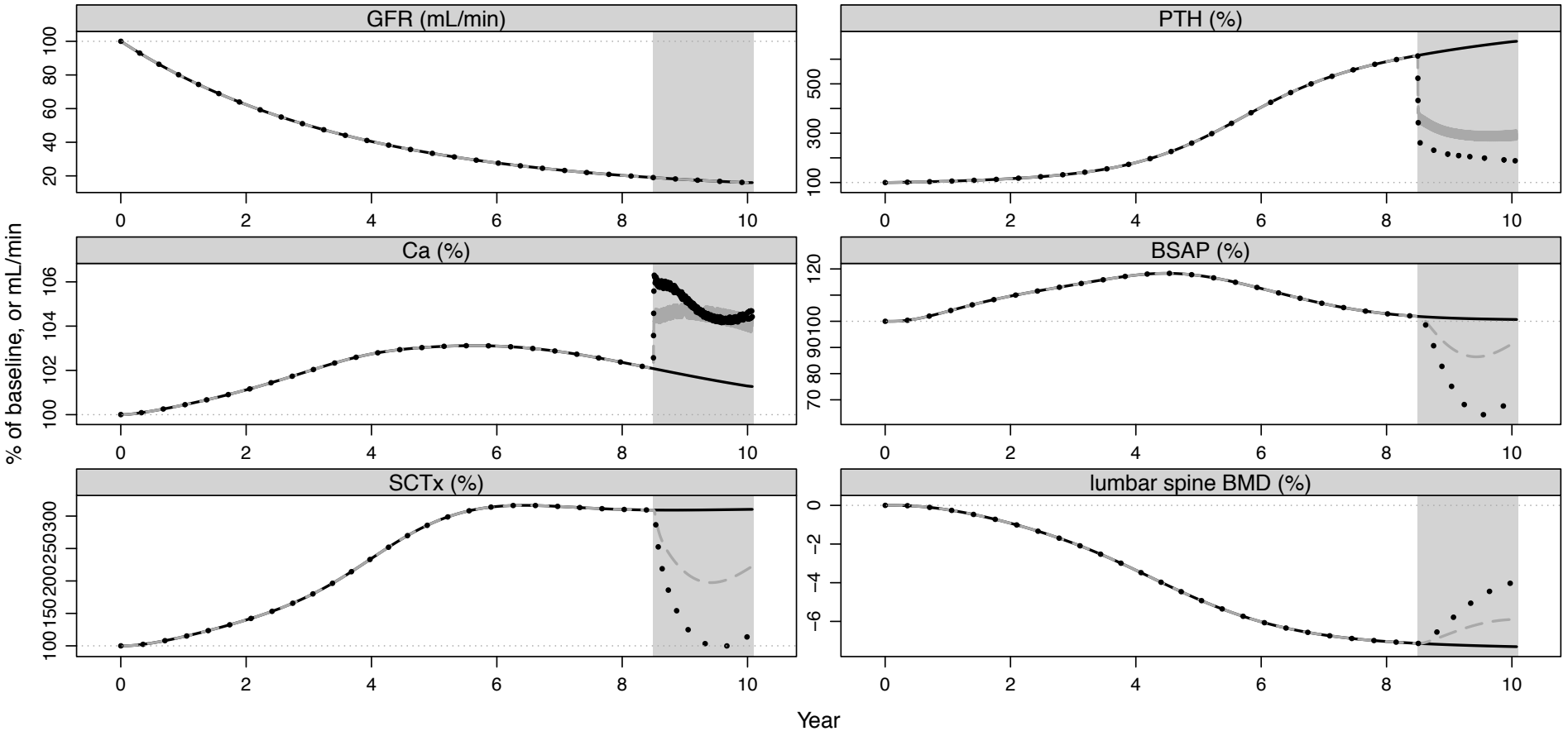


black solid = no intervention; gray dot = 0.33 mmolar Ca Eq; black longdash = 0.67 mmolar Ca Eq; gray dotdash = 1.0 mmolar Ca Eq

Fig.4; Riggs MM, Peterson MC, Gastonguay MR. Multiscale physiology-based modeling of mineral bone disorder in patients with impaired kidney function. J Clin Pharmacol, 52(1 Suppl):45S–53S, Jan 2012.

Chronic Kidney Disease-Mineral Bone Disorder

Simulated Effects of Calcitriol Infusion



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

Fig.5; Riggs MM, Peterson MC, Gastonguay MR. Multiscale Physiology-Based Modeling of Mineral Bone Disorder in Patients With Impaired Kidney Function. J Clin Pharmacol. *In press*.

EXTENSIONS: Disease Response

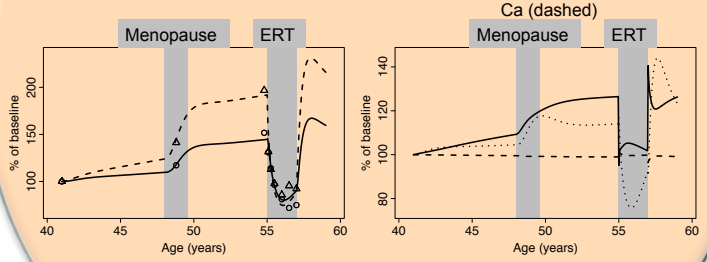
DISEASE PROGRESSION

AGE + MENOPAUSE

Includes longitudinal estrogen loss
Predicts Ca & bone estrogen-related effects

Bone Markers
Resorption (dashed)
Formation (solid)

Maintain Ca Balance
PTH (solid)
Active TGF-beta (dotted)
Ca (dashed)

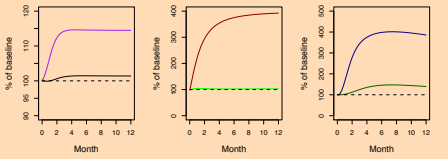


Riggs MM, Gillespie WR, Gastonguay MR, Peterson MC. NIGMS Quantitative Systems Pharmacology Workshop II: September 9, 2010.

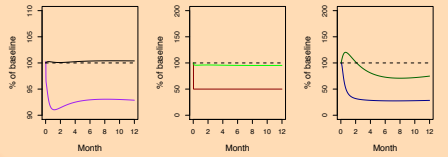
1^0 HYPER- & HYPO-PARATHYROIDISM

Predicts Ca and bone effects

Calcium Increases ← PTH increases → Osteoclasts increase



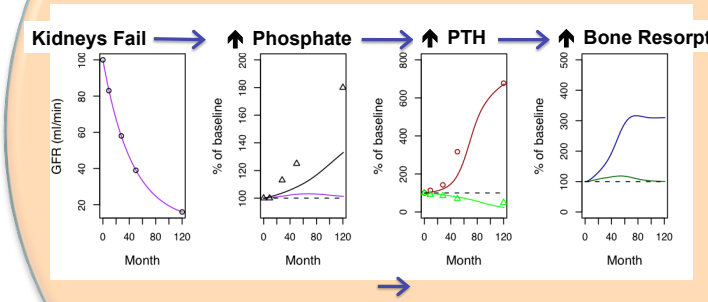
Calcium Decreases ← PTH decreases → Osteoclasts decrease



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

CKD-MBD

Predicts Secondary hyperPTH
Predicts increased bone turnover



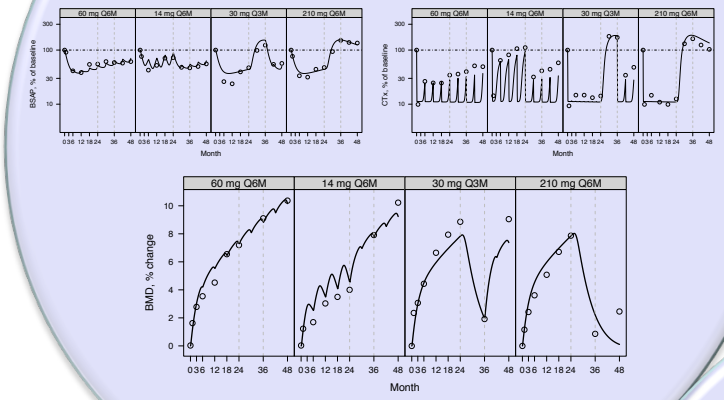
Riggs MM, Gastonguay MR, Peterson MC. AAPS Annual Meeting 2010; Poster # W4403

EXTENSIONS: Therapeutic Response

PHARMACOLOGY

DENOSUMAB

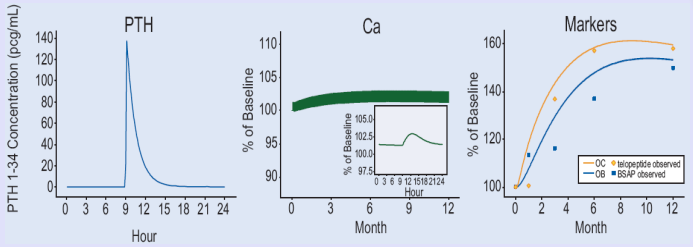
Rebound in bone metabolism is predictable.
BMD can be modeled as a function of bone markers



Peterson MC and Riggs MM.. AAPS-NBC; May 2010.

TERIPARATIDE

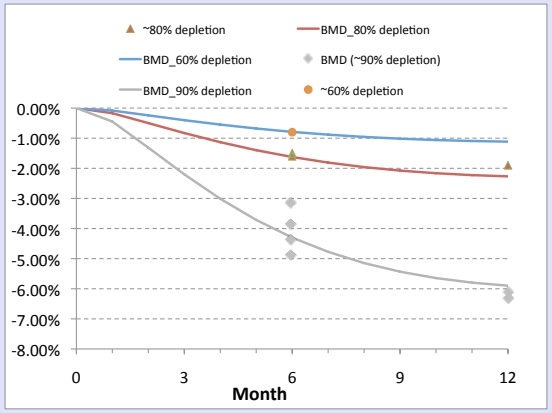
Bone anabolics are predictable.
Effects on Ca / other physiology can be evaluated



Peterson MC and Riggs MM. Bone 46:49-63; 2010

GnRH RECEPTOR

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



ACoP 2011

- Ongoing Extensions

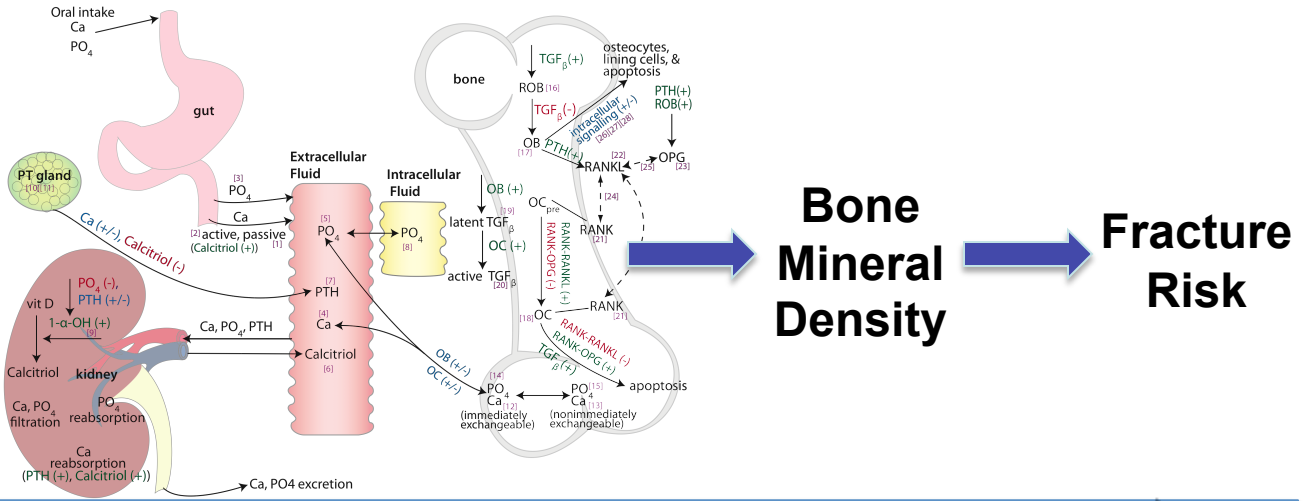
- Bone markers → Bone Mineral Density → Fracture Risk
- Vitamin D kinetics and biotransformation

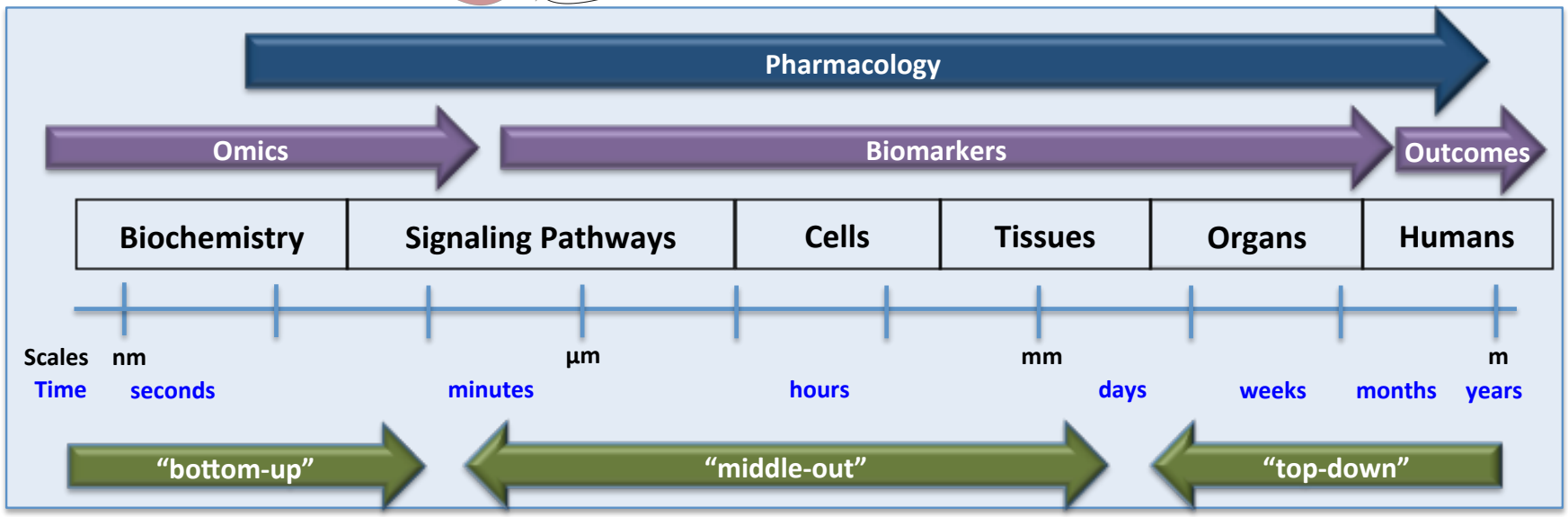
- Future Plans

- WNT/SOST/DKK-1 pathways
- FGF-23
- Oncology
- Glucocorticoid-induced bone loss

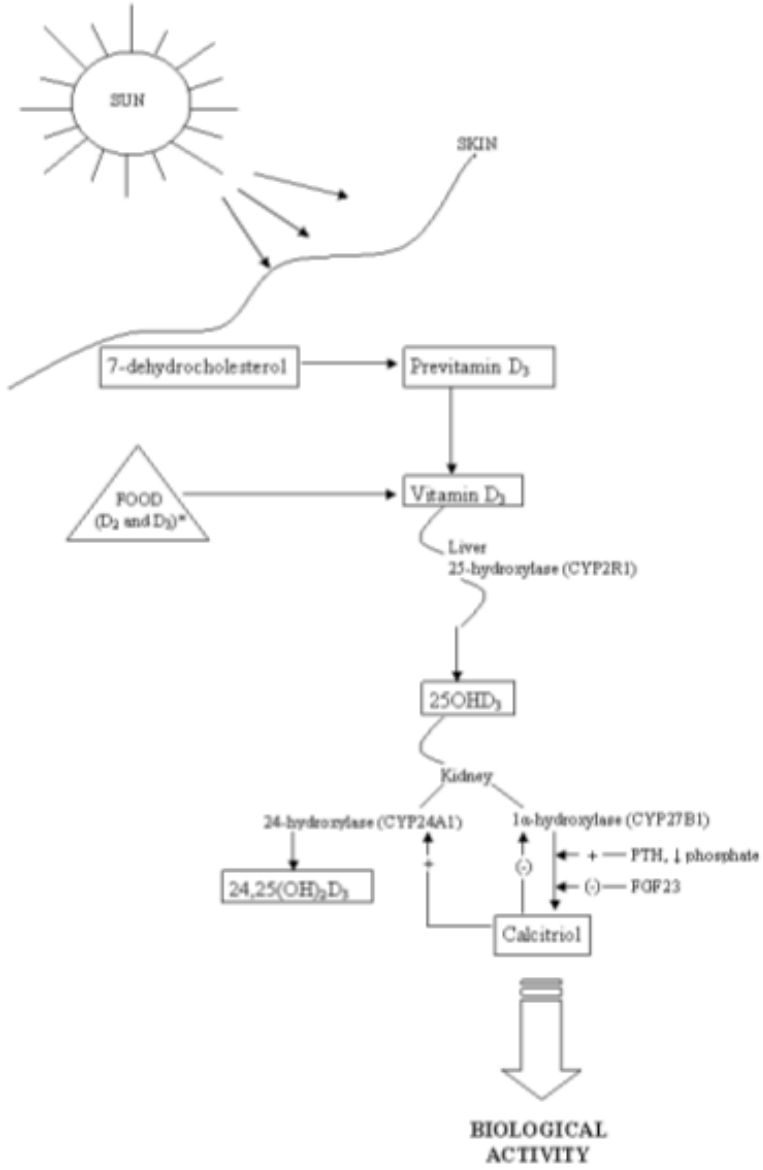
R&D – Fracture Risk Modeling

- **Bayesian Joint Modeling of Bone Mineral Density and Repeated Time-To-Fracture Event for Multiscale Bone Systems Model Extension.**
  Elodie L. Plan. PAGE 21 (2012) Abstr 2592 [www.page-meeting.org/?abstract=2592]





R&D -- Vitamin D kinetics and biotransformation



*Vitamin D can also be in the diet as vitamin D_2, which undergoes the same metabolic steps shown here for vitamin D_3.

- Vitamin D input: diet and sun
- Biotransformation: involves liver and kidney
- Pharmacology: active Vit D = calcitriol
- Applications: disease states & trial design

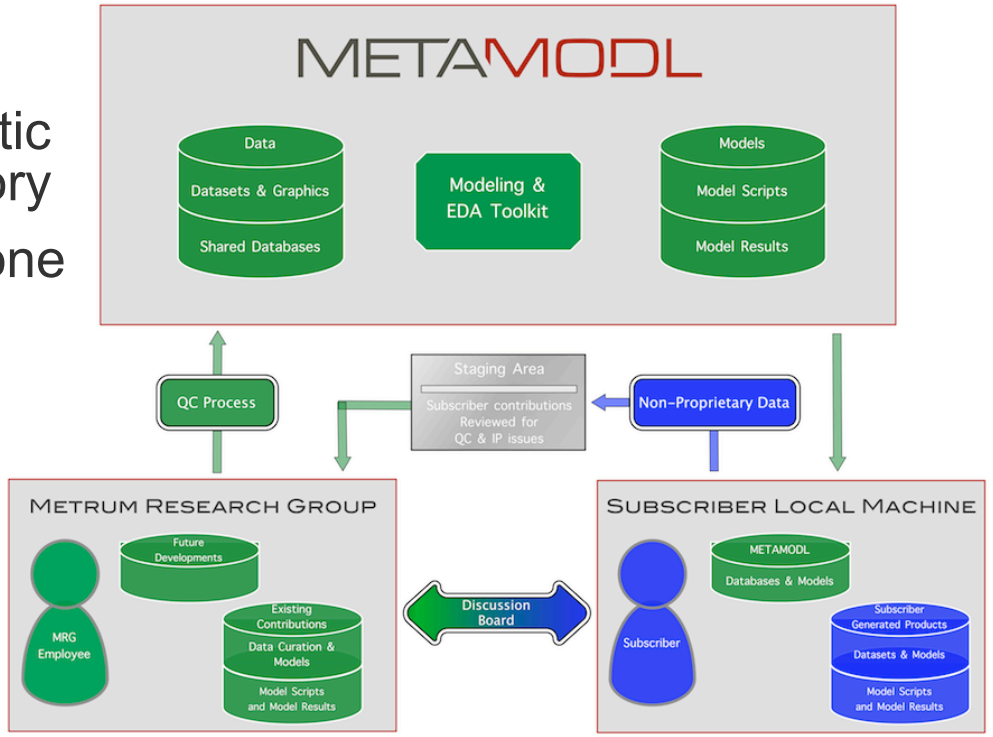
Figure 3-1 of Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. *Dietary Reference Intakes for Calcium and Vitamin D. National Academies Press, 500 Fifth Street, N.W. Wasington, DC 20001, 2011.*

- Public Source

- Opendiseasemodels.org
- Extensions available from individual papers and posters: see www.metrumrg.com/publications

- METAMODL™

- Subscription-Based, Therapeutic Area Model and Data Repository
- Incorporates All Current Ca-Bone Model Extensions

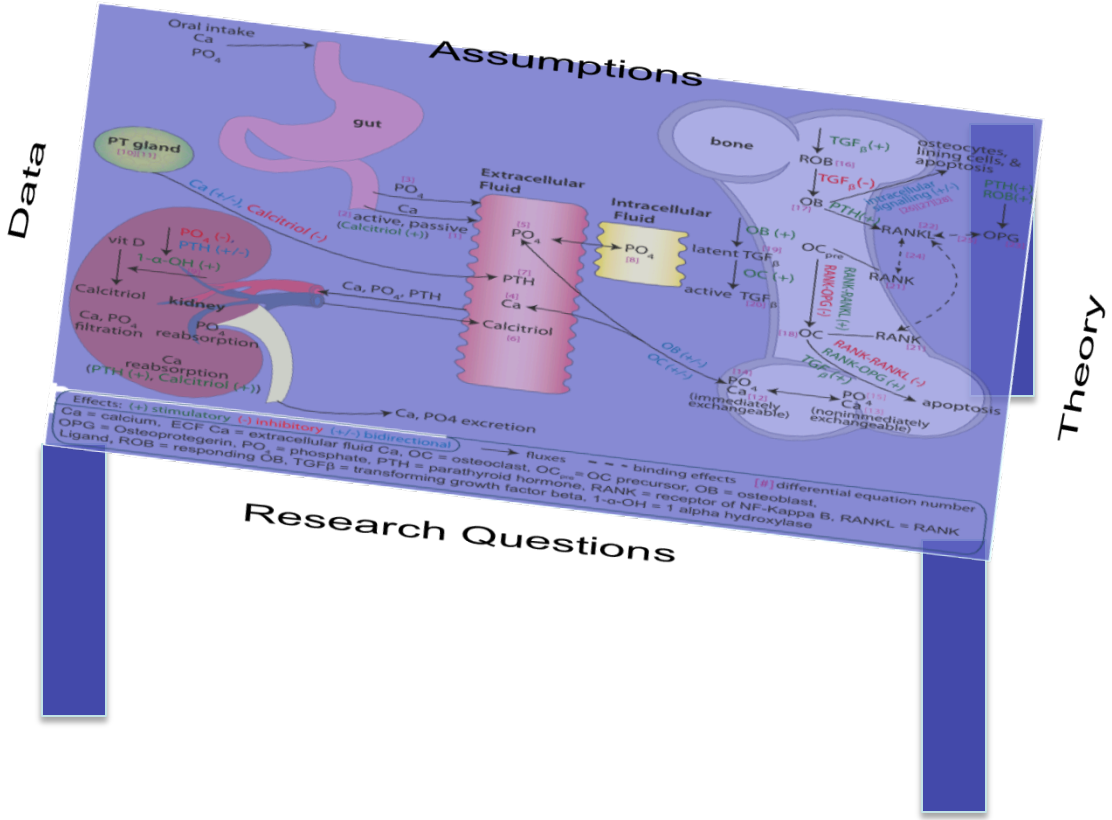


- Multiscale Models as a Knowledge Platform

- A repository of known mechanisms, hypotheses (theory), and assumptions
- 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

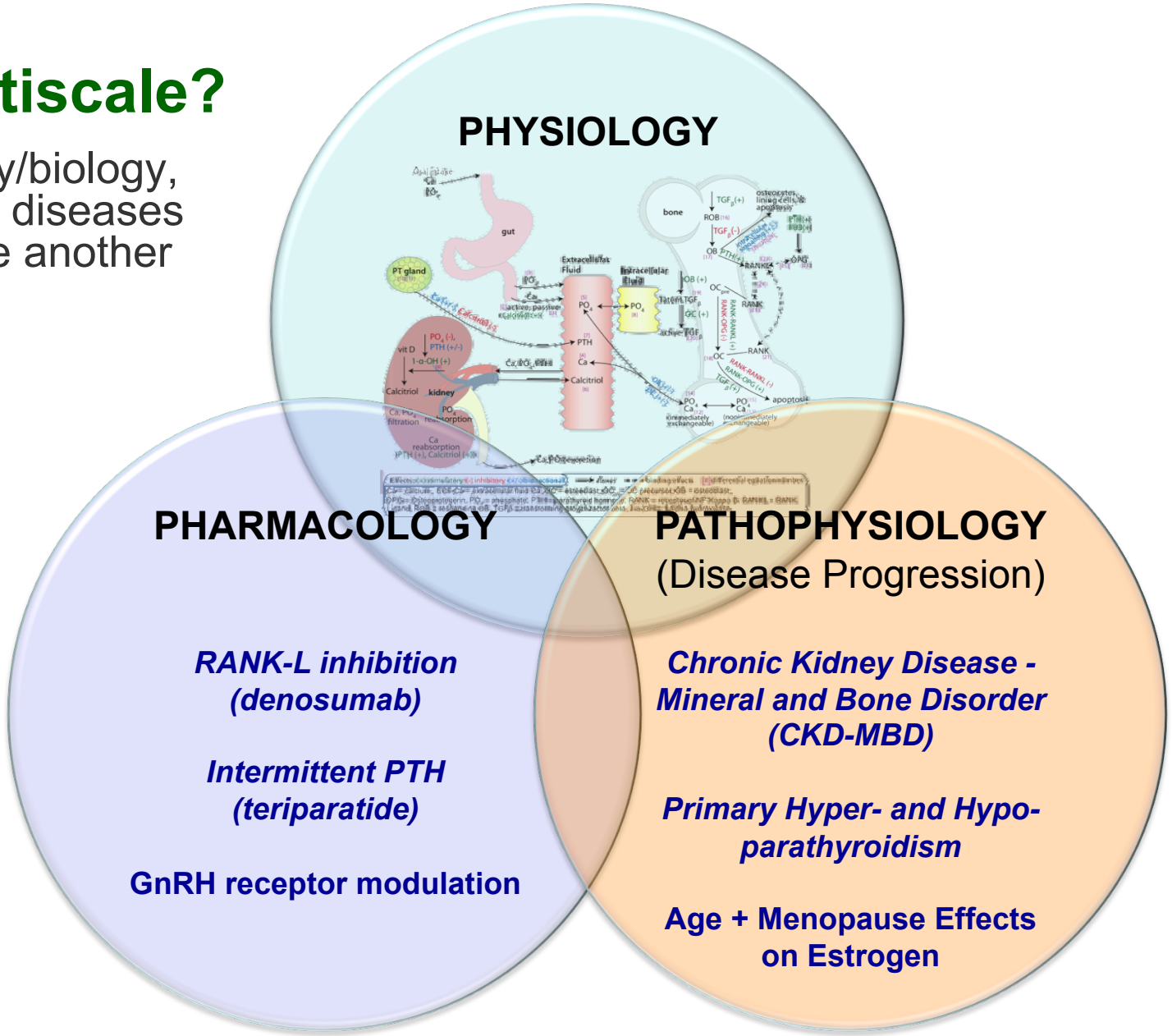
- Multiscale Models as a Knowledge Platform

- A repository of known mechanisms, hypotheses (theory), and assumptions

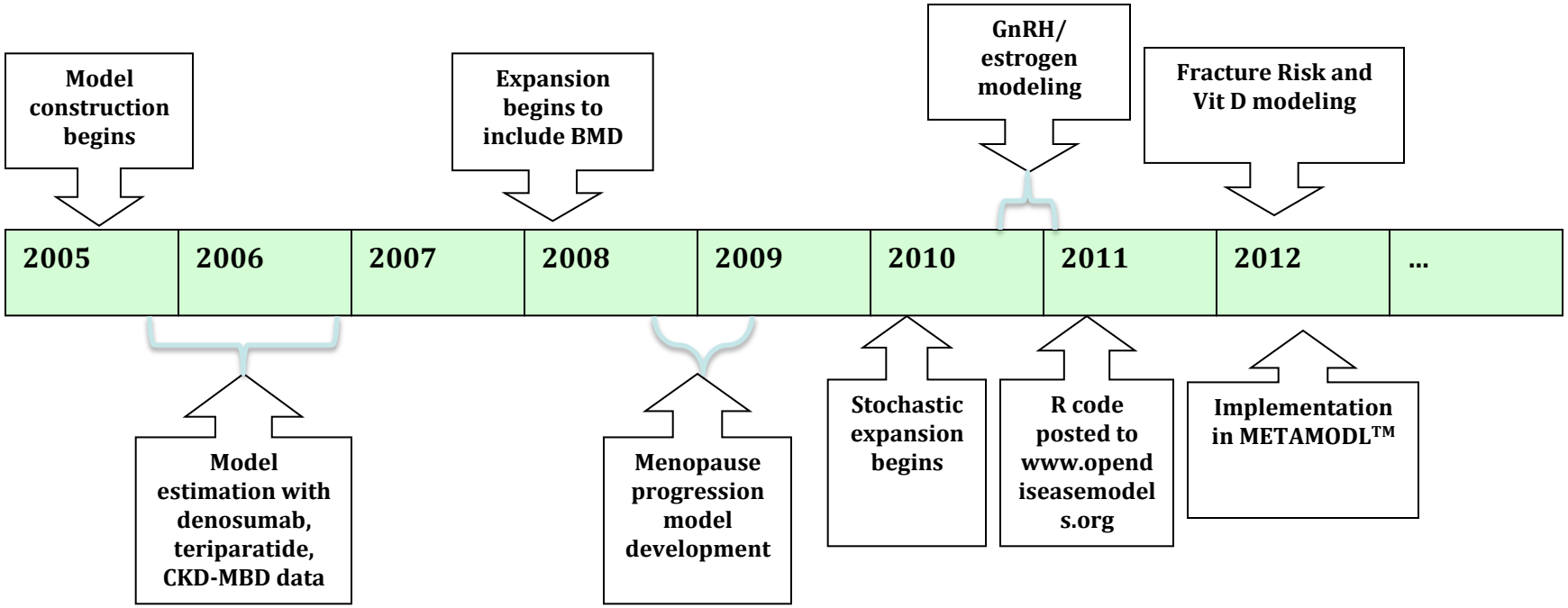


- Why Multiscale?

- Physiology/biology, drugs and diseases inform one another



TIMELINE


Model construction begins
Expansion begins to include BMD
GnRH/ estrogen modeling
Fracture Risk and Vit D modeling
2005
2006
2007
2008
2009
2010
2011
2012
...
Model estimation with denosumab, teriparatide, CKD-MBD data
Menopause progression model development
Stochastic expansion begins
R code posted to www.opendiseasemodels.org
Implementation in METAMODL™

- 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

- Acknowledgements

- Metrum RG
  - Kyle Baron, Ph.D.
  - Marc Gastonguay, Ph.D.
  - Alanna Ocampo, M.S., Ph.D. Student
  - Elodie Plan, Ph.D.
- Mark Peterson, Ph.D., Pfizer (formerly Amgen)
- Pfizer (GnRH modulation modeling)
  - Steve Martin, Ph.D.
  - Piet van der Graaf, Ph.D.

Metrum Research Group LLC
2 Tunxis Road, Suite 112
Tariffville, CT

- 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)
- …