Open-Source and Open-Science to Progress the Integration of Pharmacometrics and Systems Pharmacology

Matthew Riggs, Ph.D.
Chief Science Officer

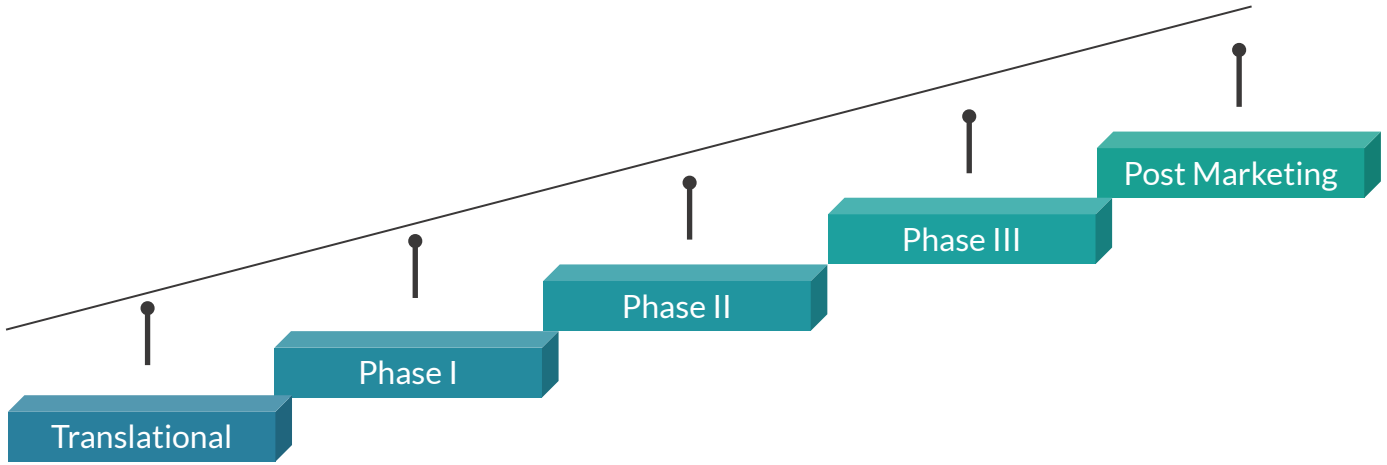
Metrum Research Group

Monday, 26 August 2019

METRUM
RESEARCH GROUP

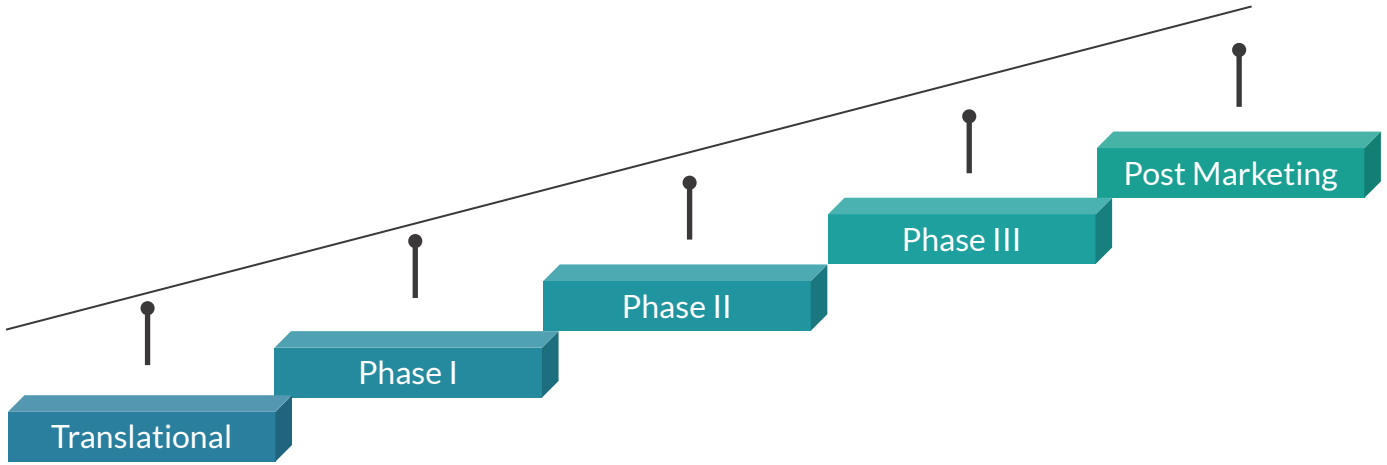
Drug Development

Starts as an idea ... becomes a medicine (if it deserves to be)



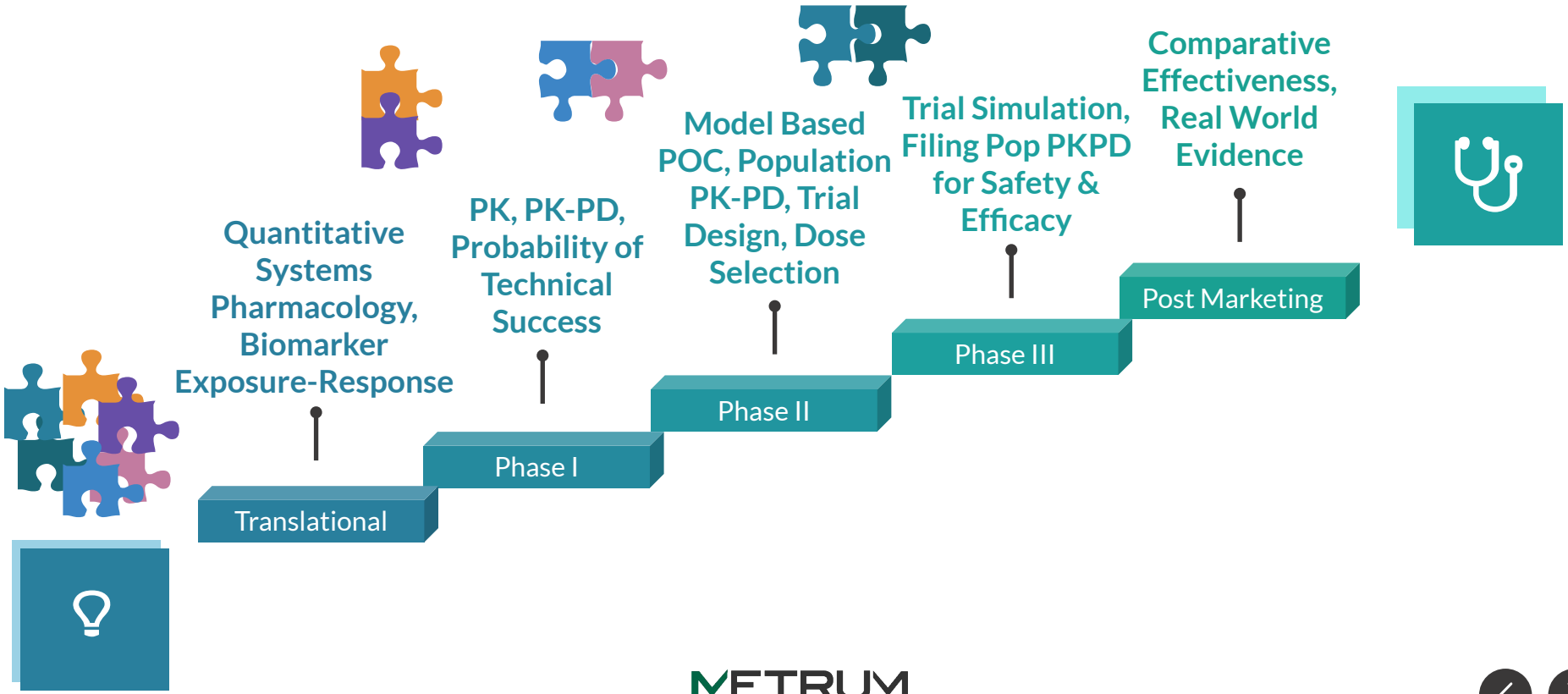
Drug Development

The idea though can be a puzzle at the start



Model-Informed Drug Development

Modeling and Simulation: inform decision support as pieces are fit together

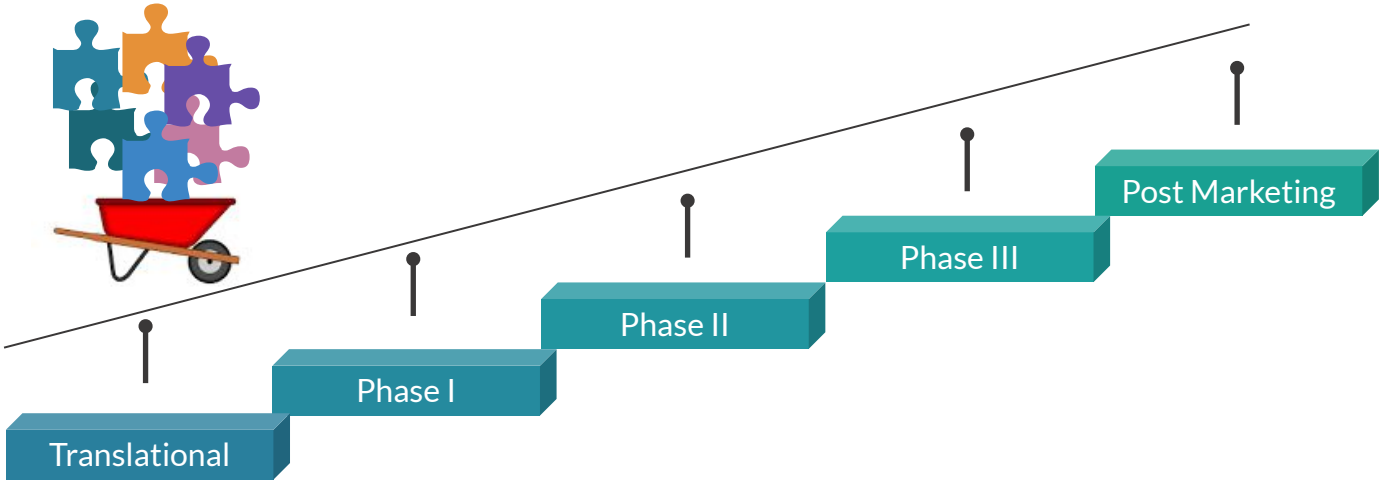


Model-Informed Drug Development

Modeling and Simulation: how do we make our models all the better?

Pretend

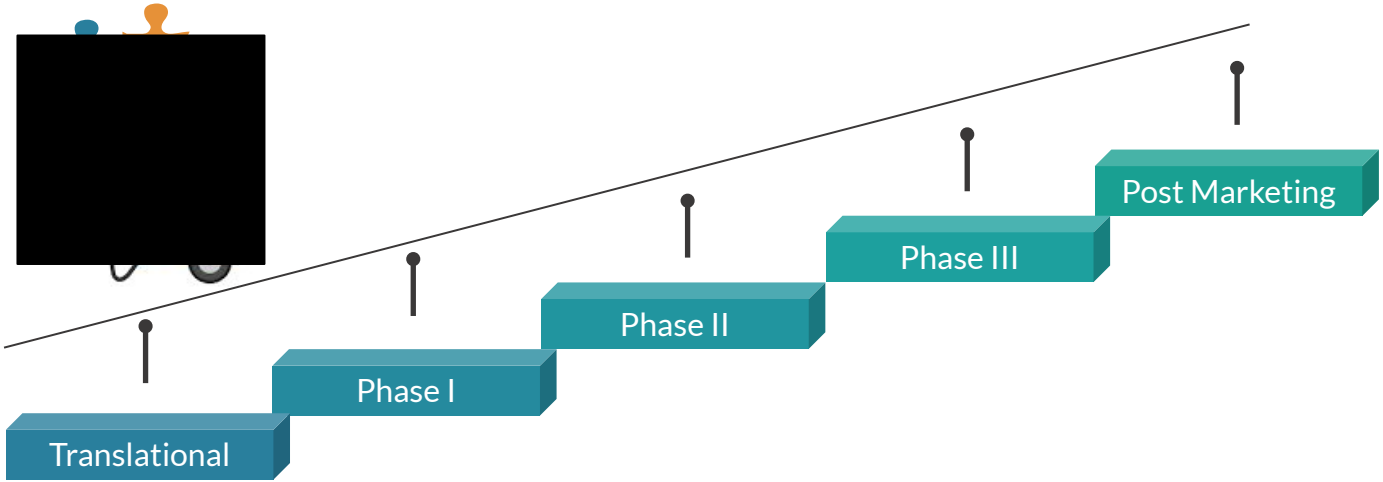
Scenario 1: ***Company A*** **develops a model that helps to carry the pieces more easily through development. They called this a "one-compartment barrow", and boast at ACoP10 that it accelerated development into Phase 1 …**



Model-Informed Drug Development

Modeling and Simulation: how do we make our models all the better?

Scenario 1: … but they hide the model. Because how else can Company A make money off the drug?



METRUM RESEARCH GROUP

Model-Informed Drug Development

Modeling and Simulation: how do we make our models all the better?

Scenario 1: … the repercussions: Company B, C, D, … Z see the fancy presentation at ACoP10 and want a "one-compartment barrow", too.

From bootlegged photos, they go to work…

"It looked like it had a sled arch on the bottom with some kind of hook; a labmate did a model like that in grad school. I can work with my adviser and we'll have it recreated in no time; shouldn't take more than 2 weeks" Company X

"Let's form an internal working group…" Company H

"There's this private-public consortium, we give them all of our data, then they develop a model that they'll sell back later as a black box" Companies O, M, Y

"Pfft, I'll use machine learning; it can solve anything, even without data…" Company G

Model-Informed Drug Development

Modeling and Simulation: how do we make our models all the better?

Scenario 1: … 6 months later….

We need to show management some progress!

"I know but with the new semester about to start and 3 more NIH grant applications, it's slow but they are making progress (I think?)..." Company X

"Our working group has reached out and engaged key stakeholders, leveraged synergies, and is ensuring with resource utilization that the modeling will be impactful …" Company H

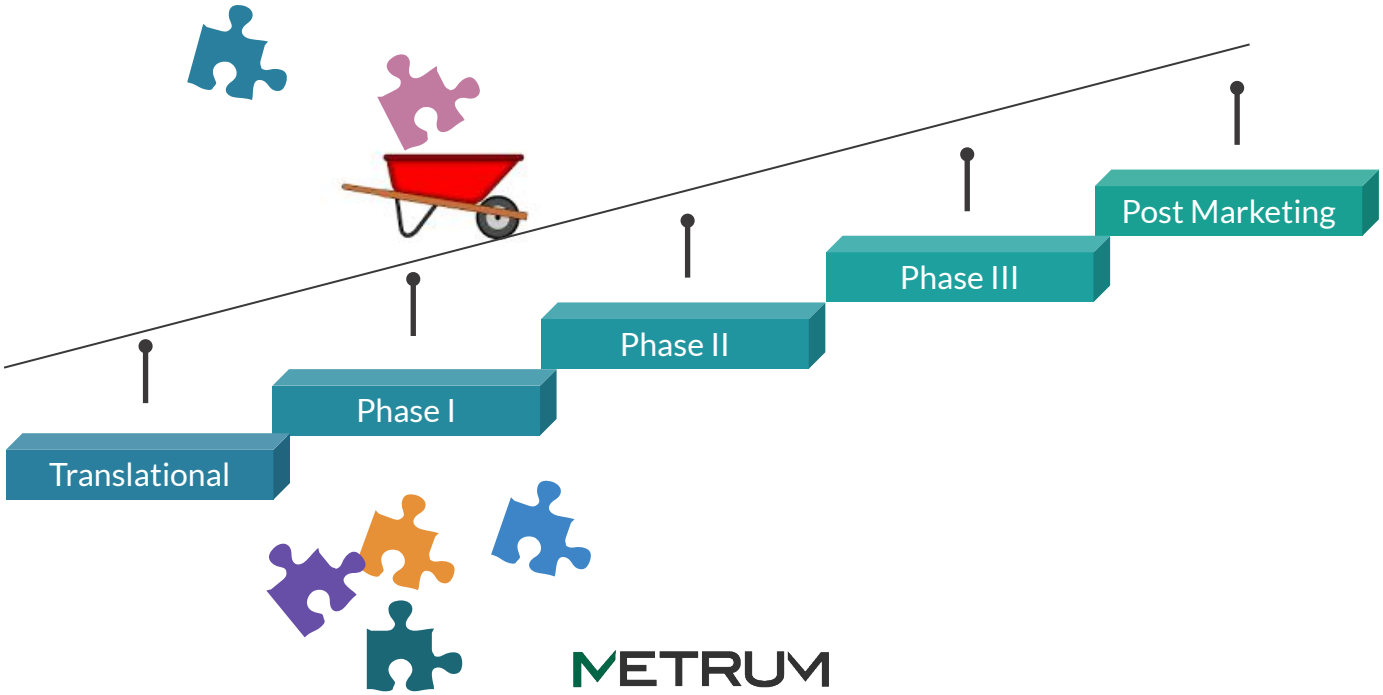
"Legal only let us share summary level placebo data and the goals alignment is, well, complicated... but, we've trademarked the term *'OC barrow'* and assured management that we're streamlining efficiencies." Companies O, M, Y

"I've trained my AI algorithm to perfectly fit both data points…" Company G

Model-Informed Drug Development

Modeling and Simulation: how do we make our models all the better?

Scenario 1: … meanwhile, back at Company A… "well, we didn't see that (AE) coming"



METRUM RESEARCH GROUP

Model-Informed Drug Development

Modeling and Simulation: how do we make our models all the better?

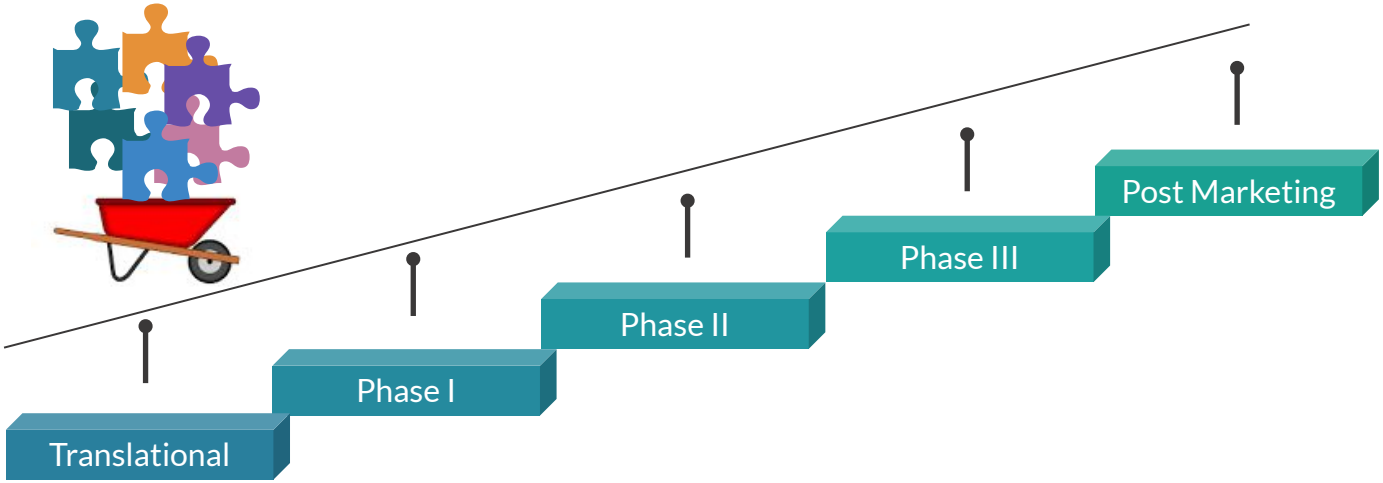
Scenario 1: **… Company A… "we're exiting this therapeutic area, close everything up and send it to archive..."**

Model-Informed Drug Development

Modeling and Simulation: how do we make our models all the better?

Pretend

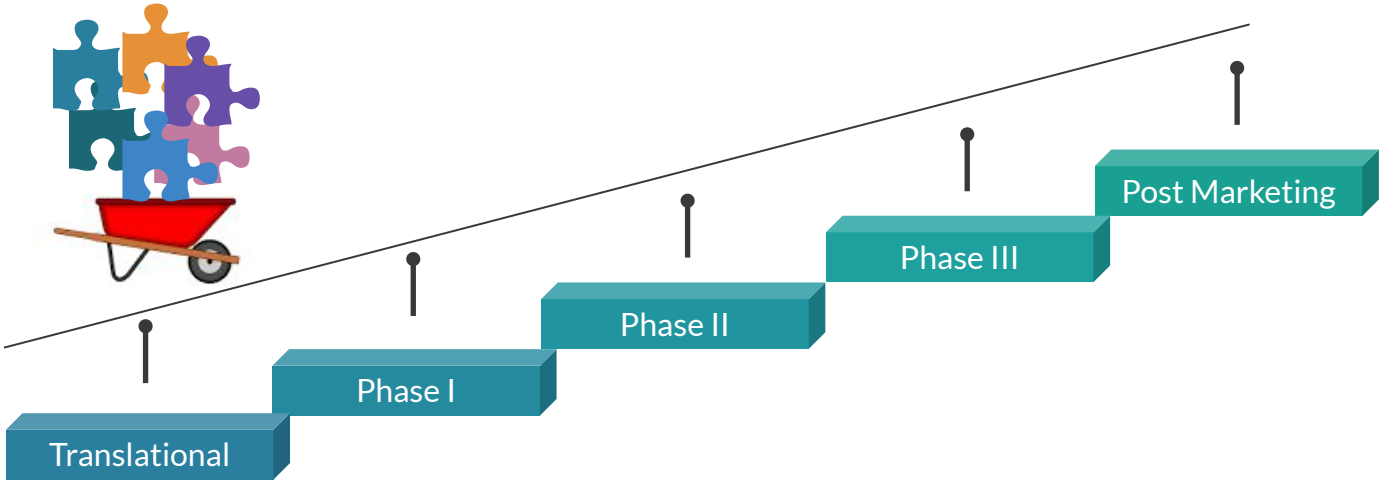
Scenario 2: ***Company A*** **develops a model that helps to carry the pieces more easily through development. They called this a "one-compartment barrow", and boast at ACoP10 that it accelerated development into Phase 1 …**



Model-Informed Drug Development

Modeling and Simulation: how do we make our models all the better?

Scenario 2: **… and they know the model could be made even better, so they share it on (DDMoRe, github, biomodels, …). Because how better can *Company A* multiply their progress from program to program?**



Model-Informed Drug Development

Modeling and Simulation: how do we make our models all the better?

Scenario 2: … the advancement: Company B, C, D, … Z see the fancy presentation at ACoP10 and want a "one-compartment barrow", too.

From the open-source code, they go to work…

"If we add a second wheel up front it will be less likely to tip over..." Company X

"Let's build and add a Shiny app to help visualize the results and path forward…" Company H

"You know, if we share ideas: what do you think about 4 wheels and an engine..." Company O, M, Y

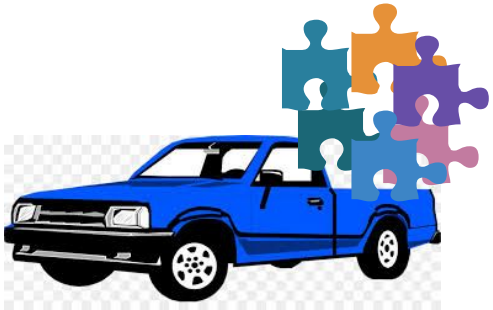
"And we could add an algorithm for better fitting and then use those new verification and validation standards to show its cross-application performance..." Company G

Model-Informed Drug Development

Modeling and Simulation: how do we make our models all the better?

Scenario 2: … 6 months later….

We can't wait to show management the progress!



"This is great, everyone on the team is playing around with the model. That steering wheel Shiny app that H added was great ..." Company X

"We've identified other therapeutic areas that this will work for, too …" Company H

"That VVUQ stuff sounded too complicated but now that the whole community is using the model, we're more confident that (investors, regulators, payers) will be asking for the results, too ... " Company O, M, Y

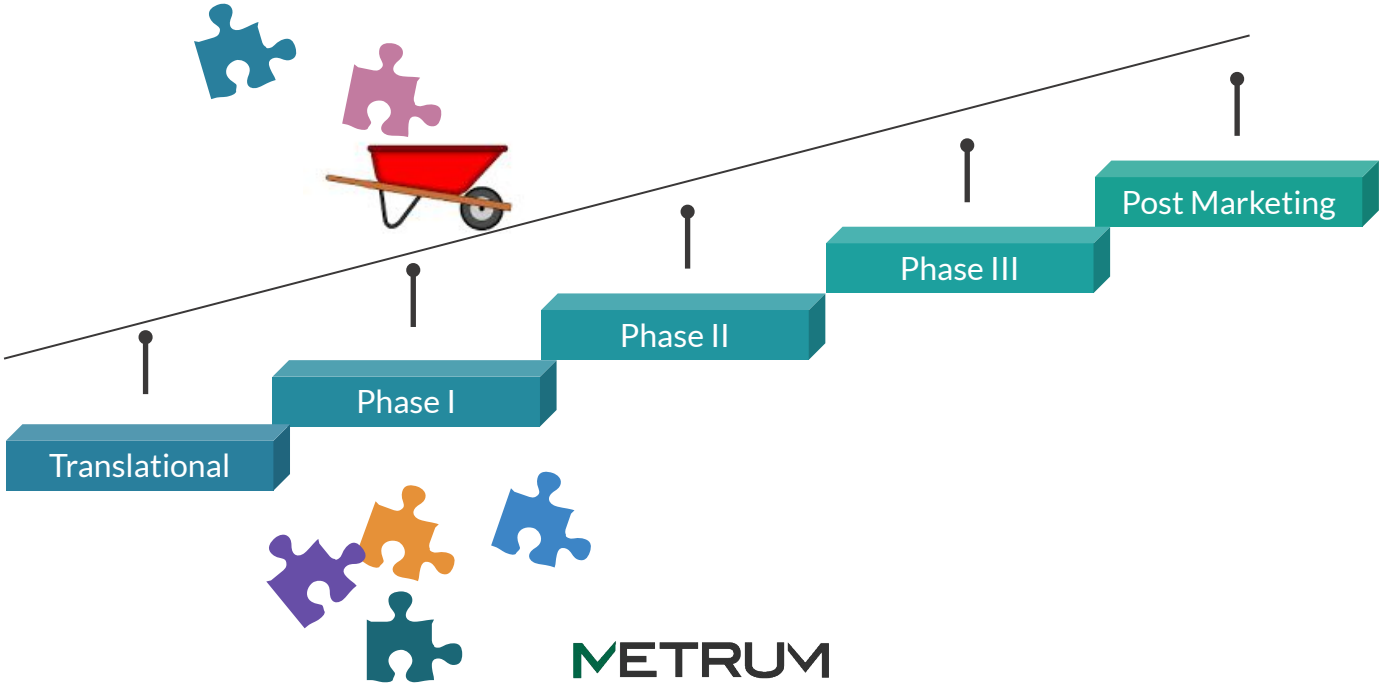
"Oh, that "enhanced barrow", as you're calling it now, is going to like a clunky old pickup truck when you see what we're about to add next …" Company G

METRUM RESEARCH GROUP

Model-Informed Drug Development

Modeling and Simulation: how do we make our models all the better?

Scenario 2: … meanwhile, back at Company A… "well, we didn't see that (AE) coming"

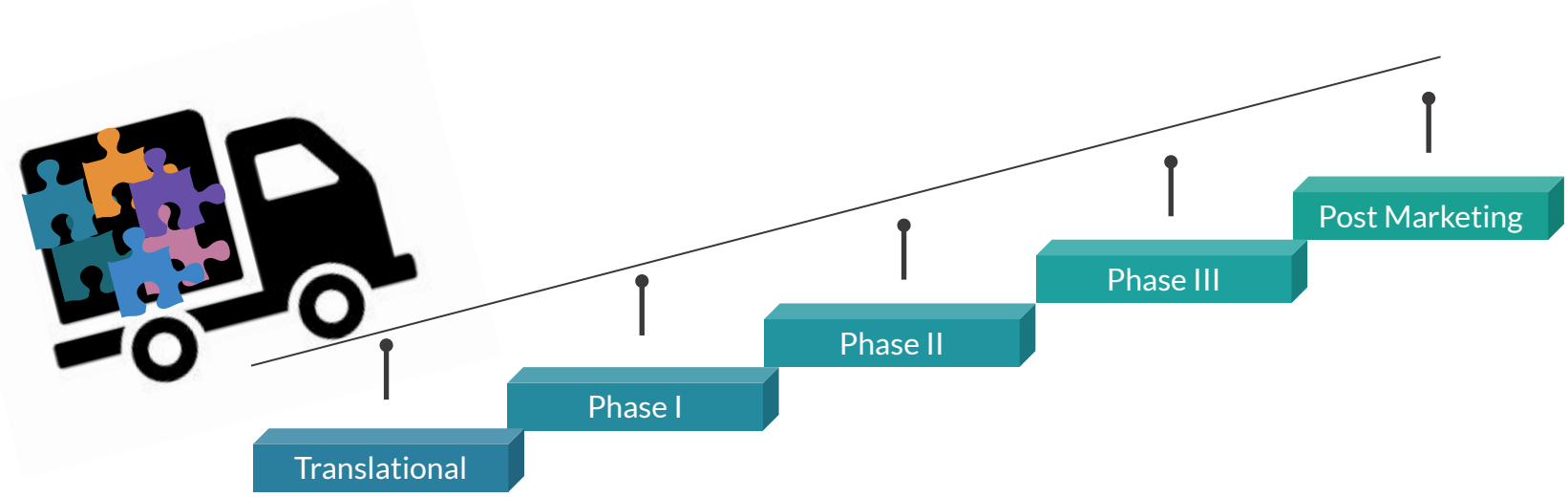


METRUM
RESEARCH GROUP

Model-Informed Drug Development

Modeling and Simulation: how do we make our models all the better?

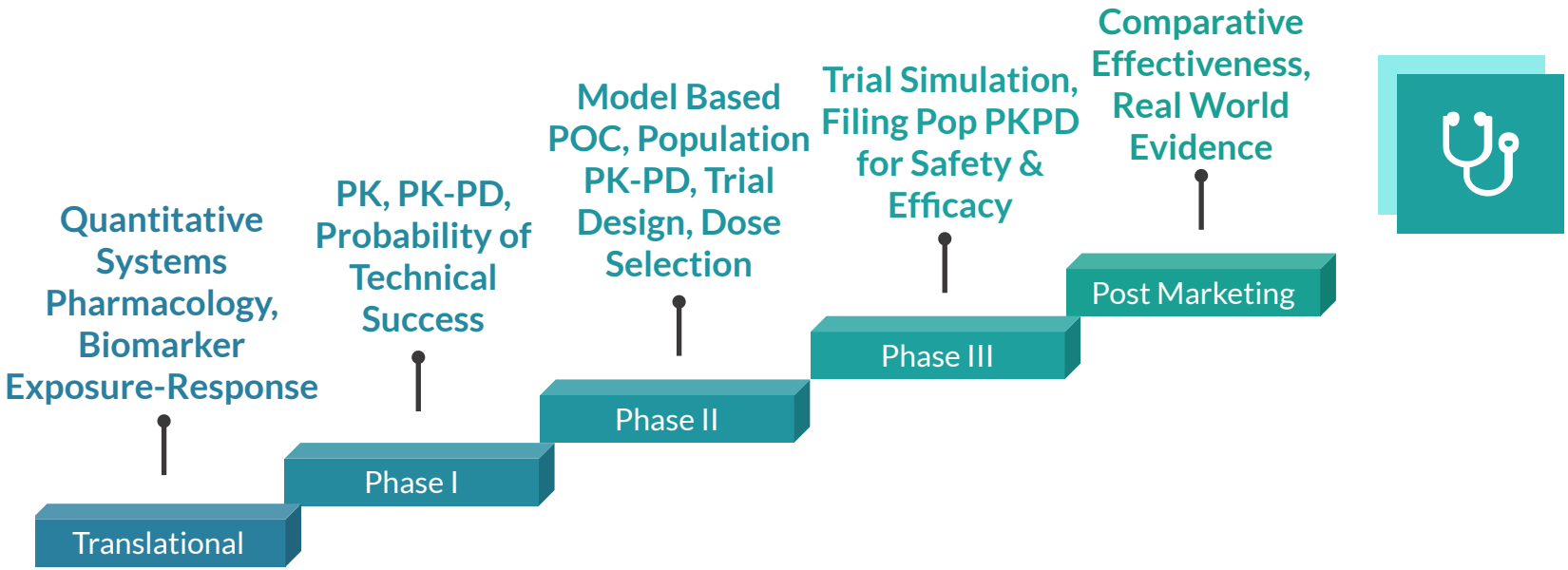
Scenario 2:... Companies A-Z... "we may be exiting this therapeutic, though with improved model-informed decision support we're so much more confident in these next development programs..."



Open Model-Informed Drug Development

Ok sure, it's idealistic, though ... how could it really work?

Open-Source and Open-Science to Progress the Integration of Pharmacometrics and Systems Pharmacology



METRUM RESEARCH GROUP

Open Model-Informed Drug Development

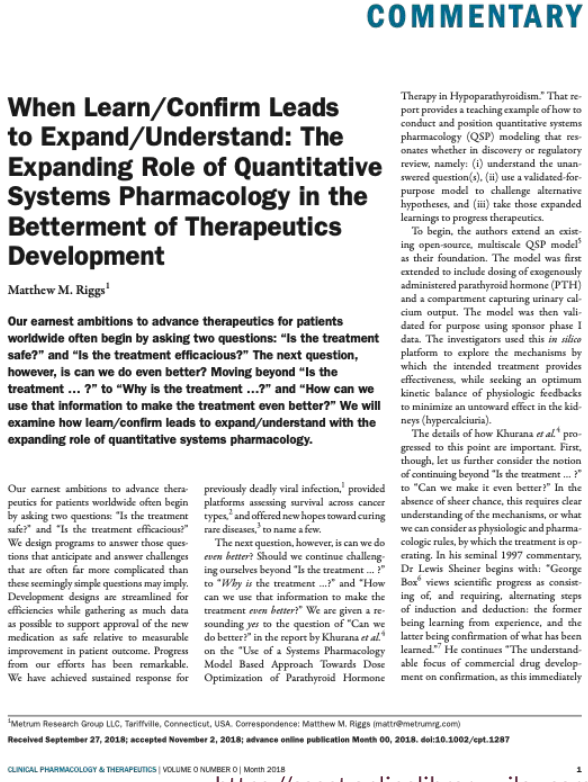
Examples: integrated Pharmacometrics and Systems Pharmacology (iPSP)

Mineral and Bone Health Model

Cardio-Renal Model

ERK Model

OSPSuite



COMMENTARY

When Learn/Confirm Leads to Expand/Understand: The Expanding Role of Quantitative Systems Pharmacology in the Betterment of Therapeutics Development

Matthew M. Riggs[1]

Our earnest ambitions to advance therapeutics for patients worldwide often begin by asking two questions: "Is the treatment safe?" and "Is the treatment efficacious?" The next question, however, is can we do even better? Moving beyond "Is the treatment … ?" to "Why is the treatment …?" and "How can we use that information to make the treatment even better?" We will examine how learn/confirm leads to expand/understand with the expanding role of quantitative systems pharmacology.

Our earnest ambitions to advance therapeutics for patients worldwide often begin by asking two questions: "Is the treatment safe?" and "Is the treatment efficacious?" We design programs to answer those questions that anticipate and answer challenges that are often far more complicated than these seemingly simple questions may imply. Development designs are streamlined for efficiencies while gathering as much data as possible to support approval of the new medication as safe relative to measurable improvement in patient outcome. Progress from our efforts has been remarkable. We have achieved sustained response for previously deadly viral infection,[1] provided platforms assessing survival across cancer types,[2] and offered new hopes toward curing rare diseases,[3] to name a few.

The next question, however, is can we do *even better*? Should we continue challenging ourselves beyond "Is the treatment … ?" to "*Why is* the treatment …?" and "How can we use that information to make the treatment *even better*?" We are given a resounding *yes* to the question of "Can we do better?" in the report by Khurana *et al.*[4] on the "Use of a Systems Pharmacology Model Based Approach Towards Dose Optimization of Parathyroid Hormone Therapy in Hypoparathyroidism." That report provides a teaching example of how to conduct and position quantitative systems pharmacology (QSP) modeling that resonates whether in discovery or regulatory review, namely: (i) understand the unanswered question(s), (ii) use a validated-for-purpose model to challenge alternative hypotheses, and (iii) take those expanded learnings to progress therapeutics.

To begin, the authors extend an existing open-source, multiscale QSP model[5] as their foundation. The model was first extended to include dosing of exogenously administered parathyroid hormone (PTH) and a compartment capturing urinary calcium output. The model was then validated for purpose using sponsor phase I data. The investigators used this *in silico* platform to explore the mechanisms by which the intended treatment provides effectiveness, while seeking an optimum kinetic balance of physiologic feedbacks to minimize an untoward effect in the kidneys (hypercalciuria).

The details of how Khurana *et al.*[4] progressed to this point are important. First, though, let us further consider the notion of continuing beyond "Is the treatment … ?" to "Can we make it even better?" In the absence of sheer chance, this requires clear understanding of the mechanisms, or what we can consider as physiologic and pharmacologic rules, by which the treatment is operating. In his seminal 1997 commentary, Dr Lewis Sheiner begins with: "George Box[6] views scientific progress as consisting of, and requiring, alternating steps of induction and deduction: the former being learning from experience, and the latter being confirmation of what has been learned."[7] He continues "The understandable focus of commercial drug development on confirmation, as this immediately

[1]Metrum Research Group LLC, Tariffville, Connecticut, USA. Correspondence: Matthew M. Riggs (mattr@metrumrg.com)

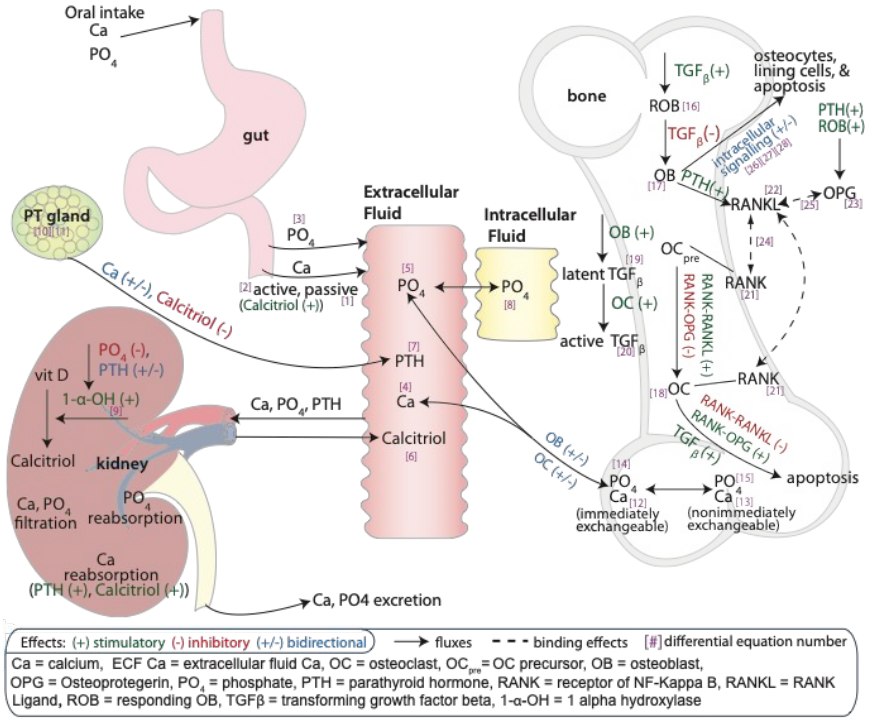
Received September 27, 2018; accepted November 2, 2018; advance online publication Month 00, 2018. doi:10.1002/cpt.1287

https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.1287

METRUM RESEARCH GROUP

Open Model-Informed Drug Development

Mineral and Bone Health Model



Peterson and Riggs. Bone 2010

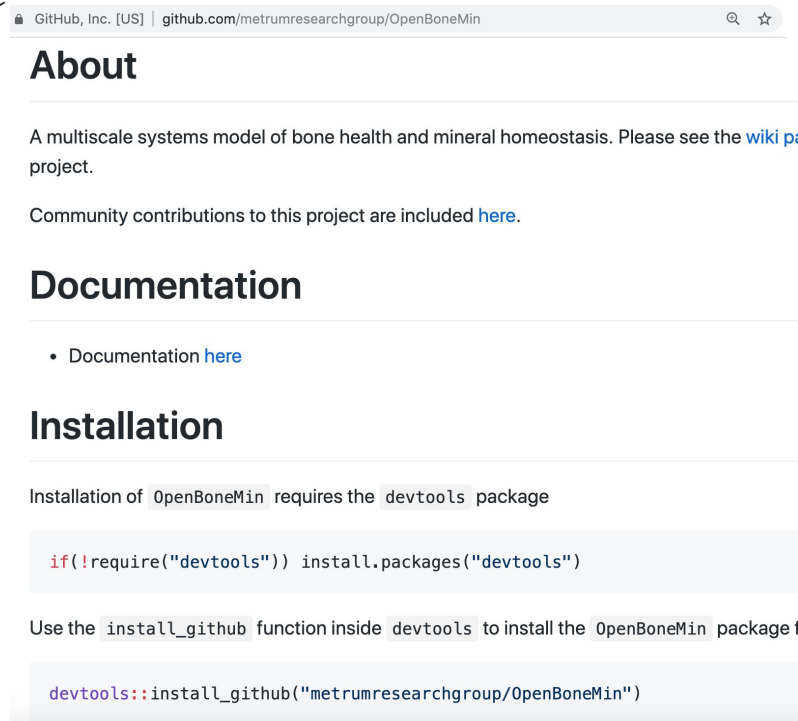
METRUM RESEARCH GROUP

Open Model-Informed Drug Development

Promoting Open-Source, Open Science Community Involvement on GitHub: https://github.com/metrumresearchgroup/OpenBoneMin

Mineral and Bone Health Model

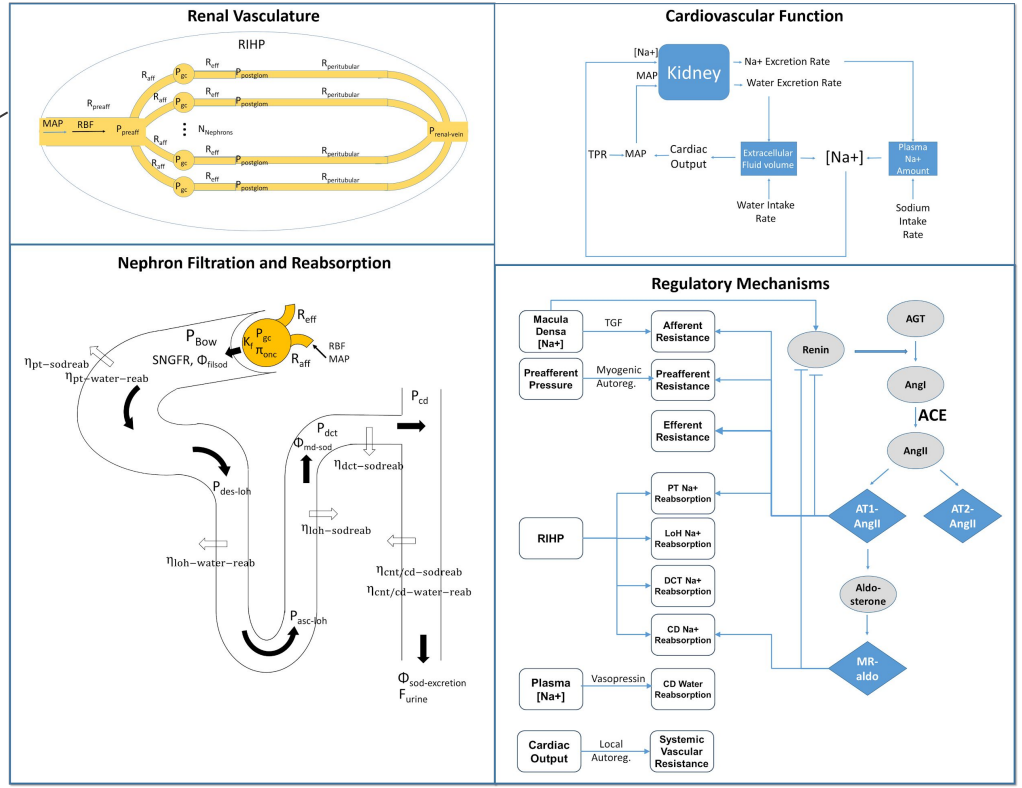
Code: Open-Source R with *mrgsolve*



METRUM RESEARCH GROUP

Open Model-Informed Drug Development

Cardio-Renal Model



Source: https://github.com/hallowkm/RenalModel/blob/master/Schematic.png

METRUM RESEARCH GROUP

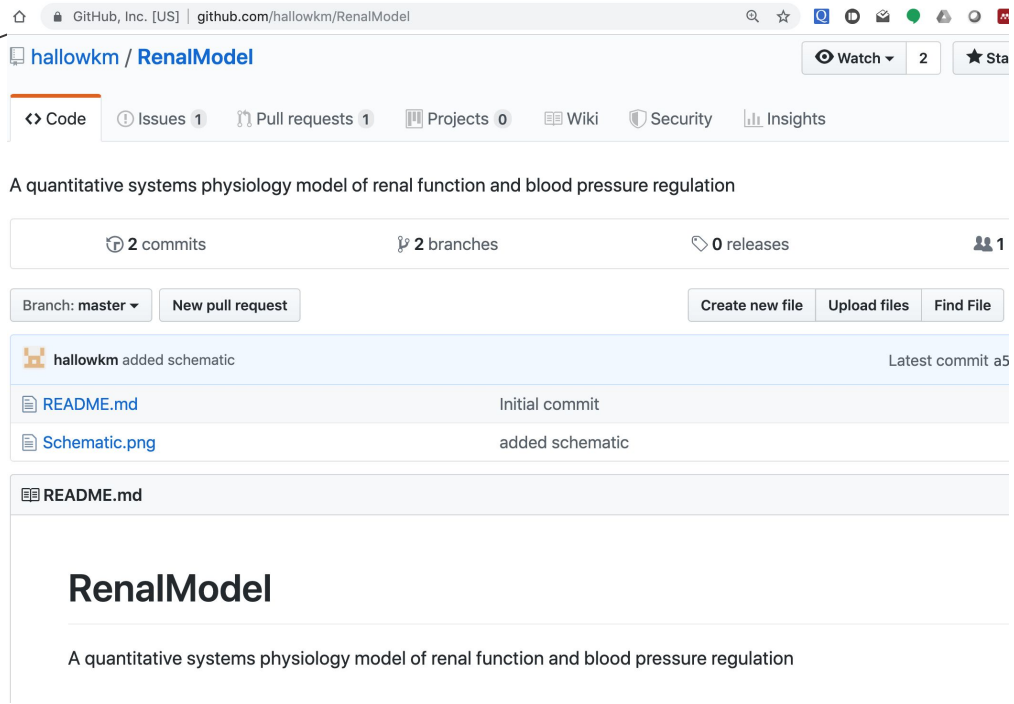
Open Model-Informed Drug Development

Promoting Open-Source, Open Science Community Involvement on GitHub: https://github.com/hallowkm/RenalModel

Cardio-Renal Model

Code: Open-Source R with *RxODE/nlmixR*

Shiny app: http://qsp.engr.uga.edu:3838/CVRmod/



METRUM RESEARCH GROUP

Open iPSP-Informed Drug Development

Cardio-Renal Model

Integrated PK/PD model for direct renin inhibitor: imarikiren

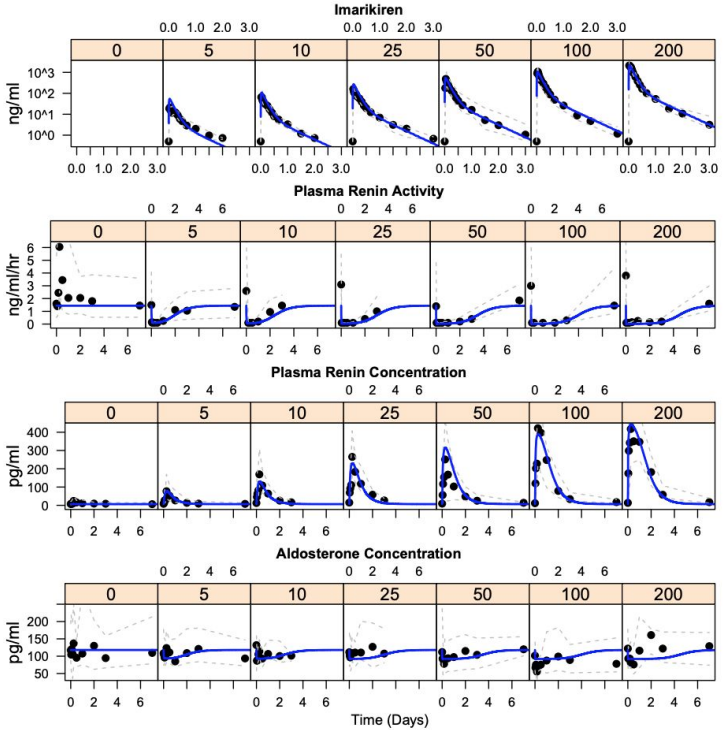


Fig. 2 Plasma concentration–time profile of imarikiren for doses ranging from 5 to 200 mg (top row). Pharmacodynamics response of renin inhibition as shown by PRA (second row), PRC (third row), and aldosterone (fourth row). Panel labels indicate the dose in mg. Solid blue curves represent model fit for the typical individual and filled circles represent clinical data. The dashed gray curves in the figure represent the 5 and 95% quantiles of the clinical data (Color figure online)

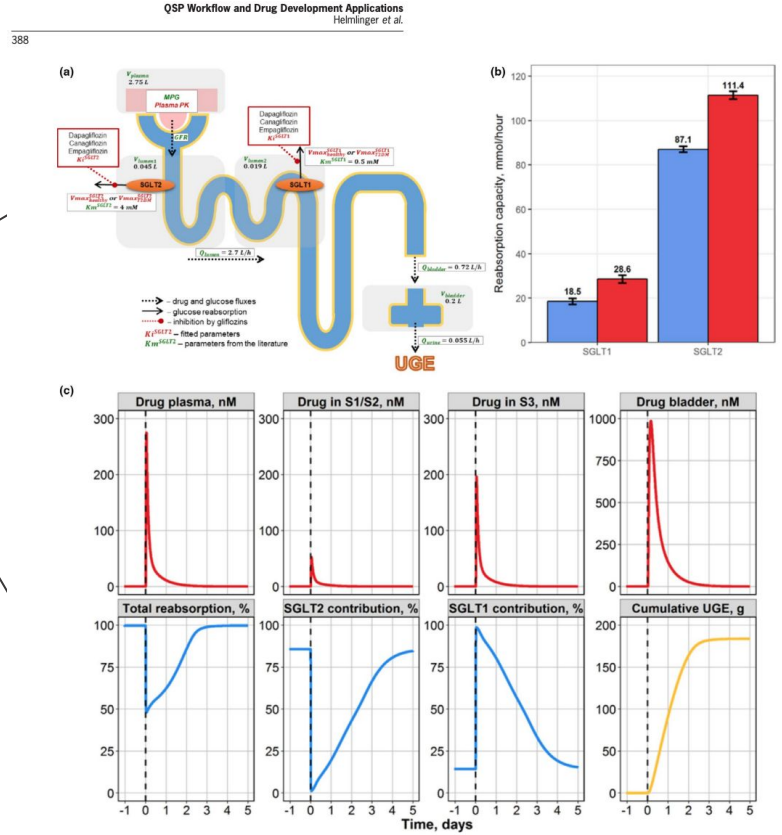
Gebremichael, Y., Lahu, G., Vakilynejad, M., & Hallow, K. M. (2019). J Pharmacokinet Pharmacodyn, 46(1), 15–25.

METRUM RESEARCH GROUP

Open iPSP-Informed Drug Development

Cardio-Renal Model

Integrated PK/PD model for SGLT inhibition



Brady, J. A., & Hallow, K. M. (2017). Model-Based Evaluation of Proximal Sodium Reabsorption Through SGLT2 in Health and Diabetes and the Effect of Inhibition With Canagliflozin. *J Clin Pharmacol*.

Hallow, K. M., Greasley, P. J., Helmlinger, G., Chu, L., Heerspink, H. J., & Boulton, D. W. (2018). Evaluation of renal and cardiovascular protection mechanisms of SGLT2 inhibitors: model-based analysis of clinical data. *Am J Phys. Ren Phys*, *315*(5), F1295–F1306.

Hallow, K. M., Helmlinger, G., Greasley, P. J., McMurray, J. J. V., & Boulton, D. W. (2018). Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. *Diabetes, Obesity & Metabolism*, *20*(3), 479–487.

Helmlinger, G., Sokolov, V., Peskov, K., Hallow, K. M., Kosinsky, Y., Voronova, V., … Penland, R. C. (2019). Quantitative Systems Pharmacology: An Exemplar Model-Building Workflow With Applications in Cardiovascular, Metabolic, and Oncology Drug Development. *CPT: PSP*, *8*(6), 380–395.

METRUM RESEARCH GROUP

Fig 4 of Helmlinger, G., Sokolov, V., Peskov, K., Hallow, K. M., Kosinsky, Y., Voronova, V., … Penland, R. C. (2019). CPT: PSP, 8(6), 380–395.

Open iPSP-Informed Drug Development

Cardio-Renal Model

Integrated PK/PD model for SGLT inhibition

PUBLISHED
20 August 2019

This announcement contains inside information

20 August 2019 07:00 BST

DAPA-HF is the first heart failure outcomes trial with an SGLT2 inhibitor in patients with and without type-2 diabetes

Farxiga significantly reduced the risk of cardiovascular death or worsening of heart failure when added to standard of care

AstraZeneca today announced positive results from the landmark Phase III DAPA-HF trial which showed that *Farxiga* (dapagliflozin) met the primary composite endpoint with a statistically-significant and clinically-meaningful reduction of cardiovascular death or the worsening of heart failure (defined as hospitalisation or an urgent heart failure visit), compared to placebo. The trial was conducted in patients with reduced ejection fraction (HFrEF) on standard of care treatment, including those with and without type-2 diabetes.

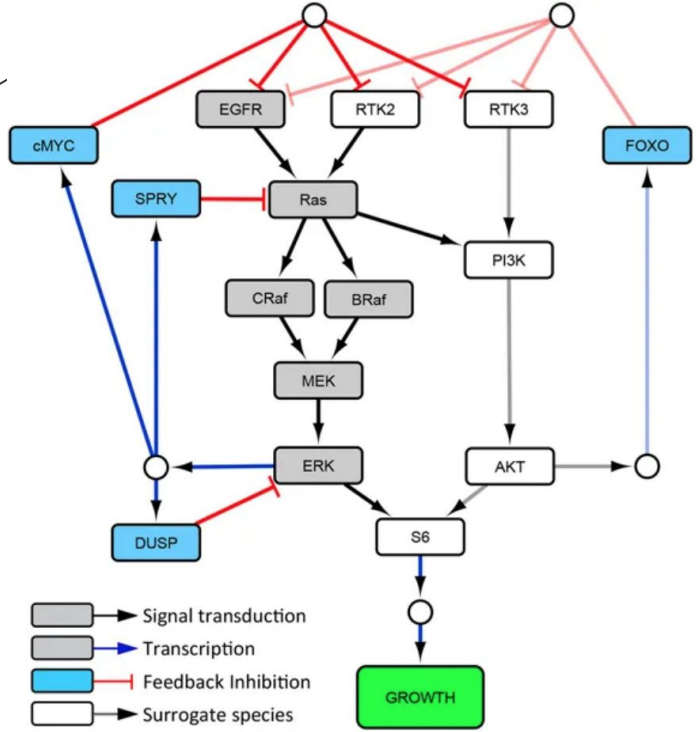
The safety profile of *Farxiga* in the DAPA-HF trial was consistent with the well-established safety profile of the medicine.

METRUM RESEARCH GROUP

Fig 4 of Helmlinger, G., Sokolov, V., Peskov, K., Hallow, K. M., Kosinsky, Y., Voronova, V., … Penland, R. C. (2019). CPT: PSP, 8(6), 380–395.

Open Model-Informed Drug Development

ERK Model



Kirouac, D. C., Schaefer, G., Chan, J., Merchant, M., Orr, C., Huang, S.-M. A., … Ramanujan, S. (2017). *NPJ Systems Biology and Applications*, *3*, 14.

Source: https://www.nature.com/articles/s41540-017-0016-1

METRUM RESEARCH GROUP

Open iPSP-Informed Drug Development

Promoting Open-Source, Open Science through Supplementary Materials (and GitHub)

ERK Model

Code: MatLab files in Supplement

Conversion to R/mrgsolve on GitHub

Kirouac, D. C., Schaefer, G., Chan, J., Merchant, M., Orr, C., Huang, S.-M. A., … Ramanujan, S. (2017). *NPJ Systems Biology and Applications*, *3*, 14.

nature.com/articles/s41540-017-0016-1

MENU Clinical responses to ERK inhibition in BRAF ^{V600E}-mutant c

Electronic supplementary material

Figure S1

Figure S2

Figure S3

Figure S4

Figure S5

HillEQ.m

VPop_Simulator_fixed.m

Supplementary Tables S1-S11

MAPK_model.sbioproj

Supplementary Materials

Supplementary Materials

GitHub, Inc. [US] | github.com/metrumresearchgroup/cic-2017#erki

Clinical responses to ERK inhibition in BRAF{V600E}-mutant colorectal cancer predicted using a computational model

- Daniel C. Kirouac, Gabriele Schaefer, Jocelyn Chan, Mark Merchant, Christine Orr, Shih-Min A. Huang, John Moffat, Lichuan Liu, Kapil Gadkar and Saroja Ramanujan
- npj Systems Biology and Applications (2017) 3:14 ; doi:10.1038/s41540-017-0016-1
- Model, Example, R script, Generate figure 6b

ERK inhibition in CRC (Kirouac et al.) [code]

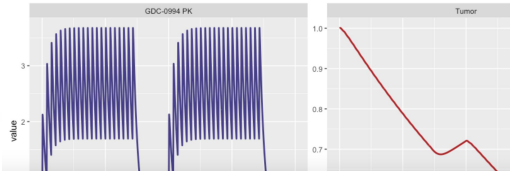
```
mod <- mread("mapk", "content/model")
vp <- read.csv("content/data/s10vpop.csv", header=TRUE) %>% slice(1)
mod <- param(mod,vp) %>% init(vp)
```

Simulate two cycles of `GDC-0994` dosing

```
data <- expand.ev(amt=400, cmt=12, time=c(0,28), ii=1, addl=20) %>% mutate(ID=1)

out <- mrgsim(mod, data=data, end=56, delta=0.1, Req="GDC,TUMOR")
```

Plot (code not shown)

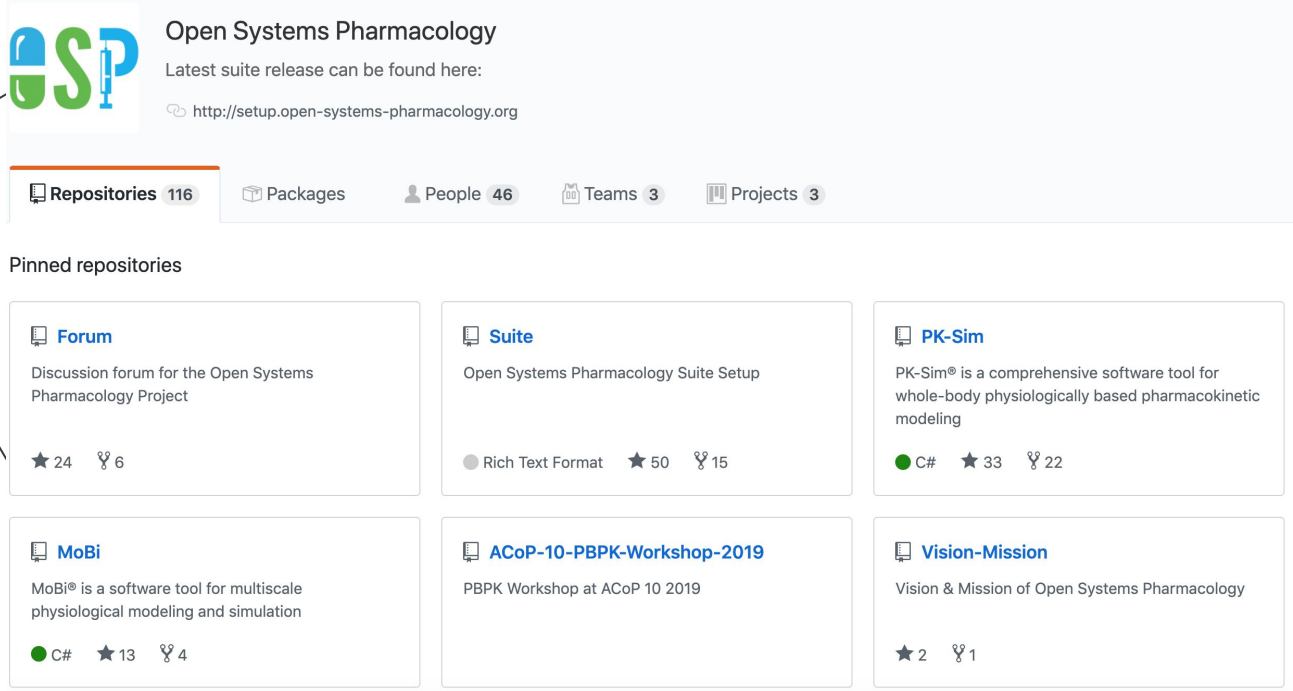


METRUM RESEARCH GROUP

Open Model-Informed Drug Development

Promoting Open-Source, Open Science Community Involvement on GitHub: https://github.com/Open-Systems-Pharmacology

OSPSuite



METRUM RESEARCH GROUP

Open Model-Informed Drug Development

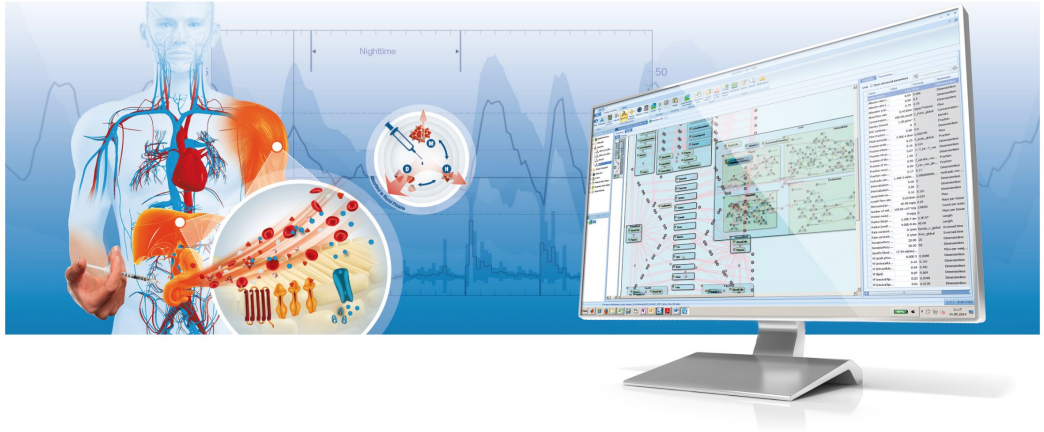
OSPSuite

PBPK Models (PK-Sim)

Bio Models (MoBi)

GitHub, Inc. [US] | github.com/Open-Systems-Pharmacology/Glucose-Insulin-Model

Welcome to the Glucose Insulin model



The physiologically-based whole-body model of the glucose-insulin-glucagon regulatory system

Within this repository, we distribute the physiologically-based whole-body model of glucose-insulin-glucagon regulation based

METRUM RESEARCH GROUP

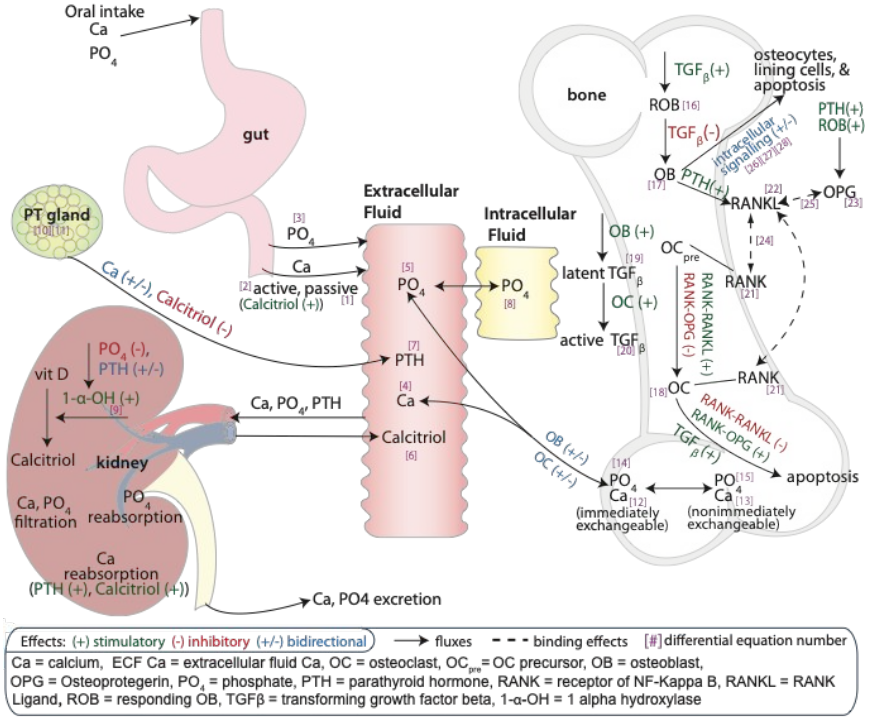
Open Model-Informed Drug Development

Taking a Deeper Dive

How did this model come to be?

How has it expanded?

How did it come back years later (with extra wheels) to help Sponsor again?



Peterson and Riggs. Bone 2010

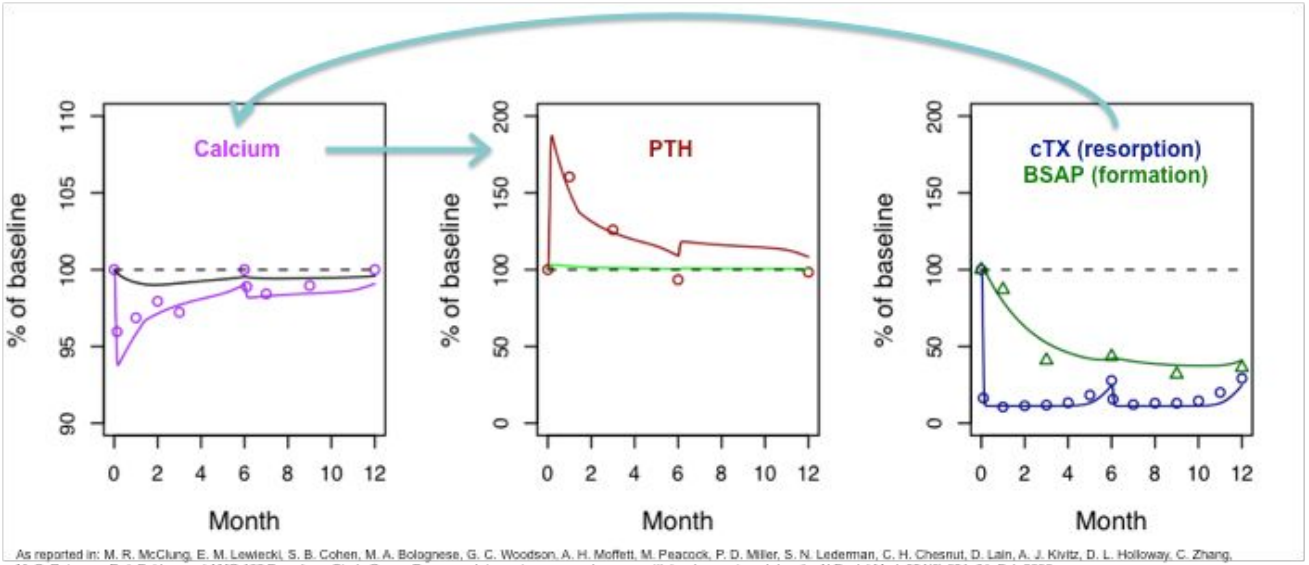
METRUM RESEARCH GROUP

iPSP: A Case Study

The question: Can we better understand (and predict) the inter-rational effects of dmab and the time-courses of on/off t effects?

Denosumab: RANKL inhibition

- ↓ Bone Resorption
- Can we better understand the other changes (e.g., bone formation marker, serum calcium and PTH)? Should we be concerned?



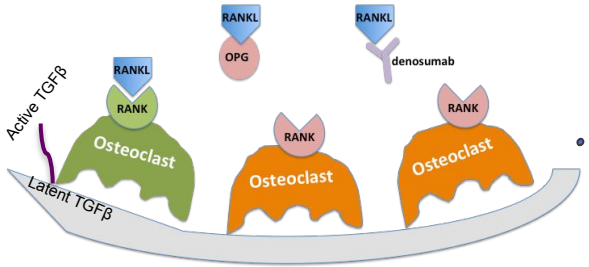
As reported in: M. R. McClung, E. M. Lewiecki, S. B. Cohen, M. A. Bolognese, G. C. Woodson, A. H. Moffett, M. Peacock, P. D. Miller, S. N. Lederman, C. H. Chesnut, D. Lain, A. J. Kivitz, D. L. Holloway, C. Zhang, M. C. Peterson, P. J. Bekker, and AMG 162 Bone Loss Study Group. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med, 354(8):821–31, Feb 2006.*

METRUM RESEARCH GROUP

iPSP: A Case Study

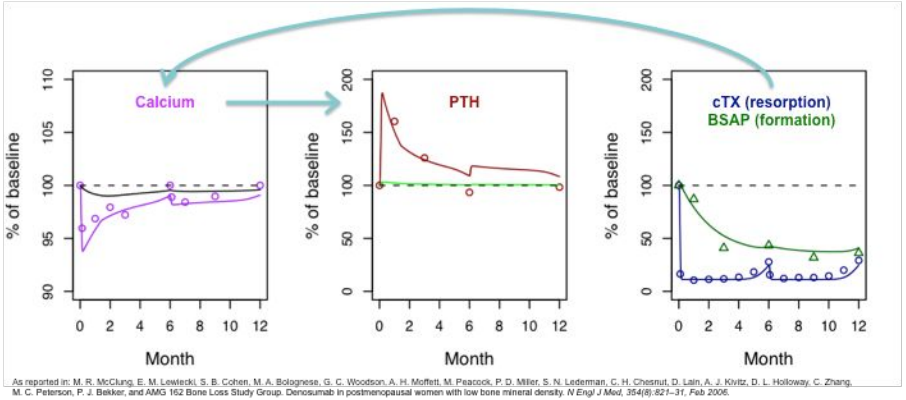
The question: Can we better understand (and predict) the inter-rational effects of dmab and the time-courses of on/off t effects?

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)

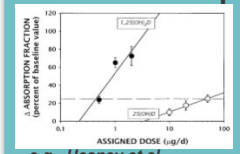


METRUM RESEARCH GROUP

iPSP: Integrate Existing Data & Models

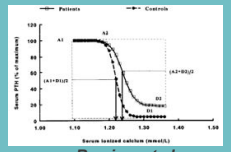
Literature and in-house information is often available to inform model parameter and disease state effects

Calcium Absorption



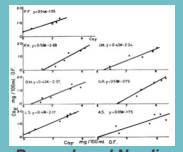
e.g., *Heaney et al. 1997*

PTH Secretion



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

Calcium Excretion



e.g., *Peacock and Nordin 1968*

Bone Therapeutics

Anabolic (*teriparatide, 2004*)

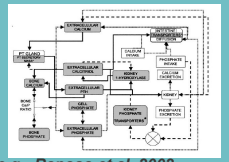
Catabolic (*denosumab, 2006*)

Disease States

Hyper- and hypo-PTH

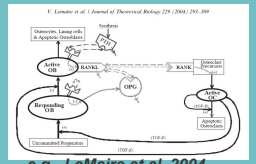
CKD-MBD (*Rix et al. 1999*)

Calcium Homeostasis



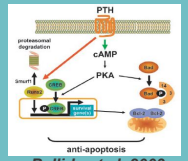
e.g., *Raposo et al. 2002*

Bone Remodeling



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

Intracellular Signaling

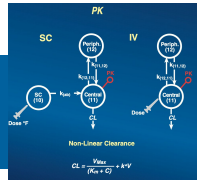


e.g., *Bellido et al. 2003*

A Population PK/PD Model Describes the Rapid, and Sustained Suppression of Urinary N-telopeptide Following Administration of AMG 162, a Fully Human Monoclonal Antibody Against RANKL, to Healthy Postmenopausal Women

M. C. Peterson[1], B. J. Stouch[1], D. Chen[1], S. Baughman[1], D. L. Holloway[2], P. J. Bekker[2], S. W. Martin[1]

[1]Pharmacokinetics and Drug Metabolism, [2]Clinical Research, Amgen Inc., Thousand Oaks, CA, USA



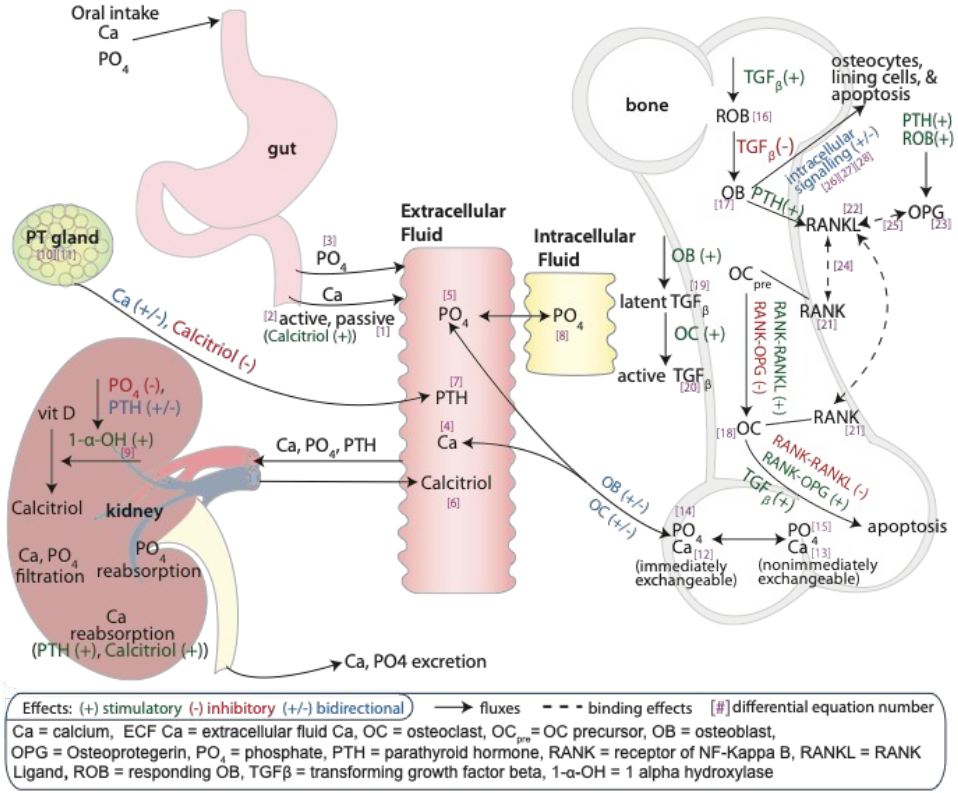
Multiscale Model

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

iPSP: A Case Study

The question: Can we better understand (and predict) the inter-rational effects of dmab and the time-courses of on/off effects?



Multiscale Model

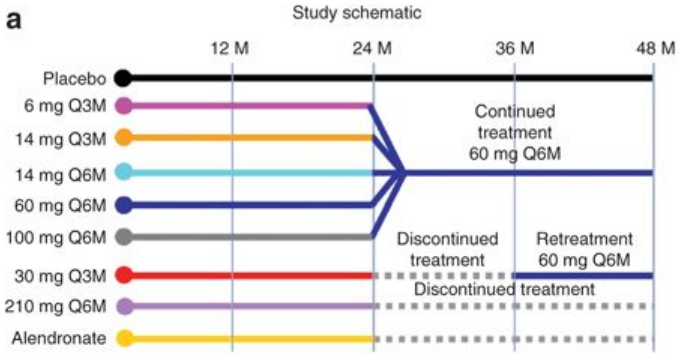
Peterson MC and Riggs MM (2010) A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. Bone 46:49-63.

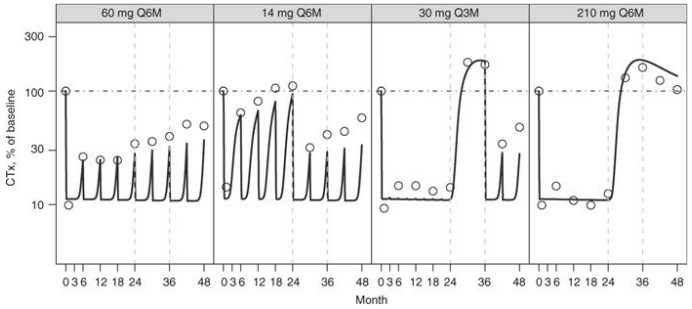
METRUM RESEARCH GROUP

iPSP: On/Off Treatment Effects

Denosumab: RANKL inhibition → Bone Marker Changes

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





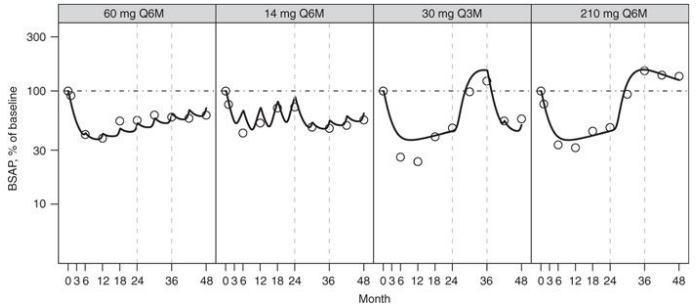


Fig.3 and 4; Peterson MC and Riggs MM,. CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e14; doi:10.1038/psp.2012.15

METRUM RESEARCH GROUP

iPSP: Expand to Predict Clinical Outcome

Denosumab: RANKL inhibition → Bone Markers → BMD Change

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

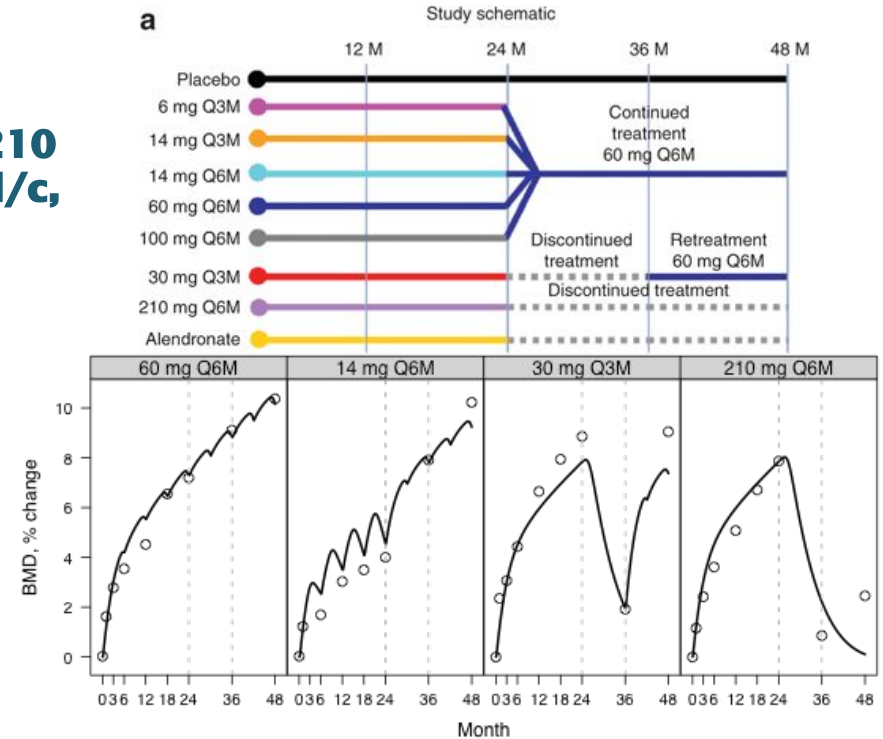


Fig. 5; Peterson MC and Riggs MM,. CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e14; doi:10.1038/psp.2012.15

METRUM RESEARCH GROUP

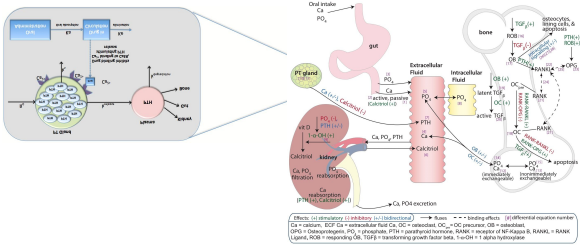
Open iPSP Calcilytic, target for osteoporosis?

Question: Were prior results a “class effect” or was this still a viable target?

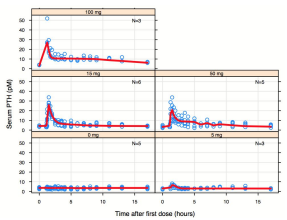
Updated Existing Systems Pcol

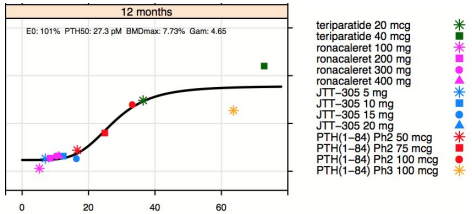
Evaluate prior tests’ persistent hyperPTH and minimal BMD changes. Can PK / binding improve target

PT gland capacity limits maximal PTH response



Limited maximal PTH response (confirmed in Ph 1) = would likely limit BMD response



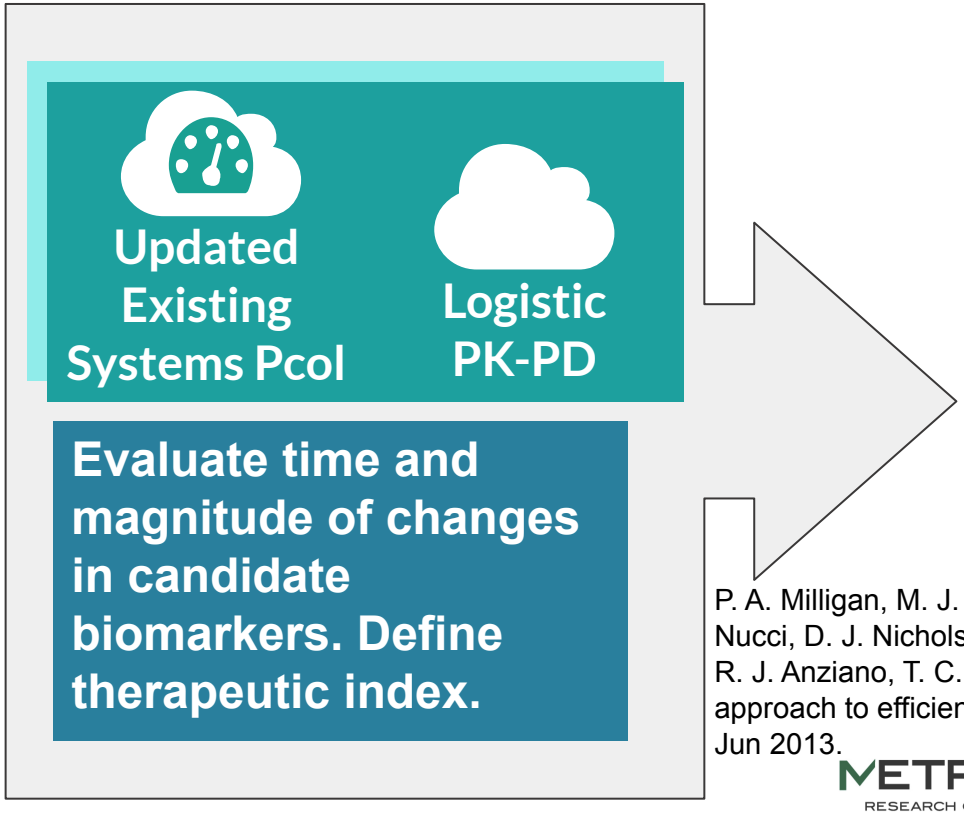


K. Baron, M. Riggs, R. Sawamura, T. Shimizu, F. Okada, J. Zhou, T. Shibayama, and M. Jansen. An evaluation of calcilytic effects on parathyroid hormone and bone mineral density response using a physiologically-based, multiscale systems pharmacology model. J. Bone Miner. Res. 28, (Suppl 1, 2013).

METRUM RESEARCH GROUP

Open iPSP GnRH modulation for endometriosis?

Question: Can we design a shorter trial? Which biomarker(s) to target response to optimize efficacy while staying below a threshold for BMD loss?



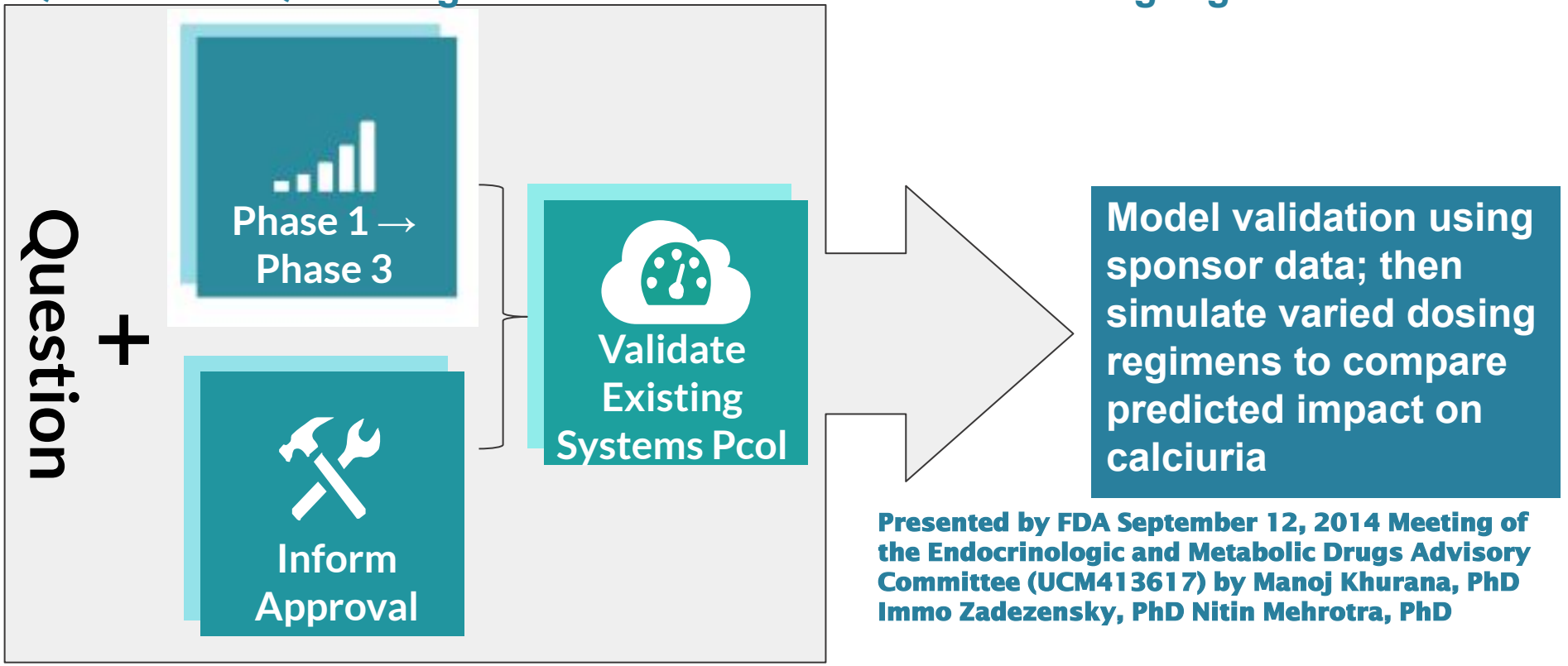
" ... targeting the GnRH pathway to achieve the desired range of serum estrogen levels would be difficult to achieve; therefore, **the research program was halted before any compound entered the clinic.**"

P. A. Milligan, M. J. Brown, B. Marchant, S. W. Martin, P. H. van der Graaf, N. Benson, G. Nucci, D. J. Nichols, R. A. Boyd, J. W. Mandema, S. Krishnaswami, S. Zwillich, D. Gruben, R. J. Anziano, T. C. Stock, and R. L. Lalonde. Model-based drug development: a rational approach to efficiently accelerate drug development. Clin Pharmacol Ther, 93(6):502–14, Jun 2013.

METRUM RESEARCH GROUP

Open iPSP PTH, replacement in hypoPTH

Question: Is QD dosing the safest and most effective dosing regimen?

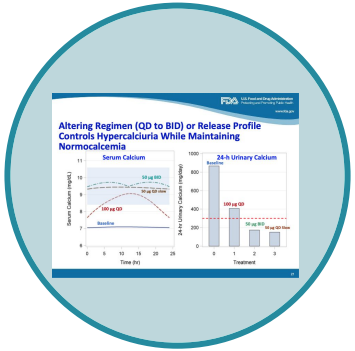


Presented by FDA September 12, 2014 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (UCM413617) by Manoj Khurana, PhD Immo Zadezensky, PhD Nitin Mehrotra, PhD

METRUM RESEARCH GROUP

Model Evaluation With added confidence, investigate the question

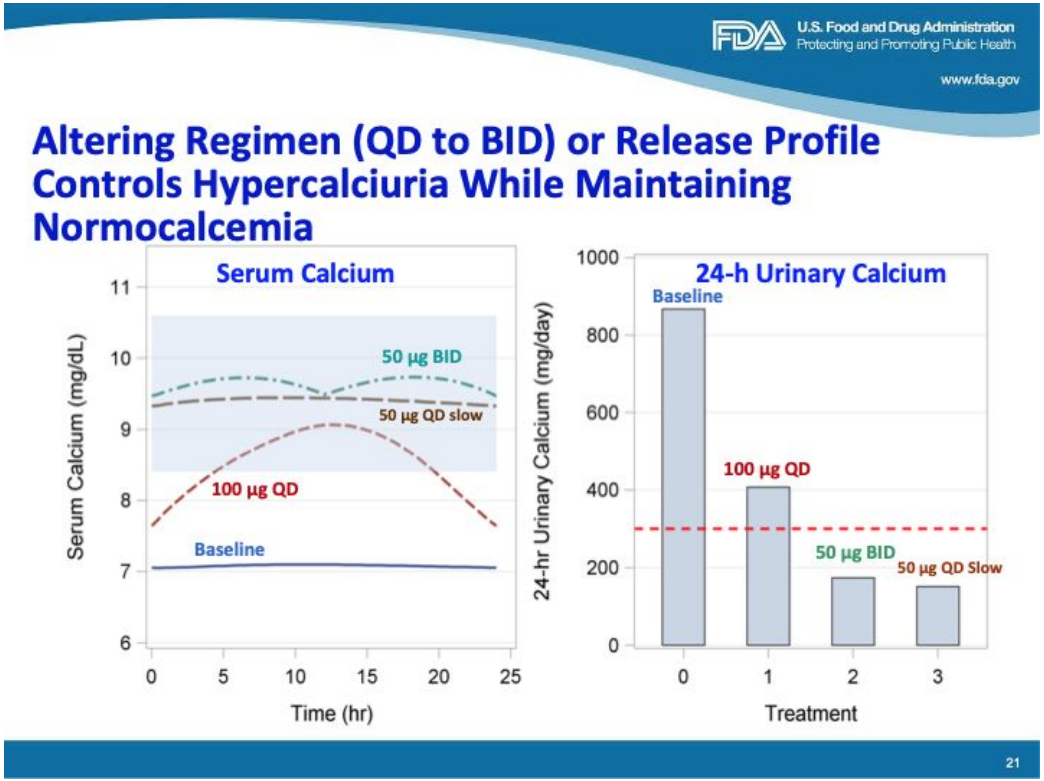
Open science opens doors



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 (UCM413617) by Manoj Khurana, PhD Immo Zadezensky, PhD Nitin Mehrotra, PhD

METRUM RESEARCH GROUP

Open iPSP PTH, replacement in hypoPTH

Question: Is QD dosing the safest and most effective dosing regimen?

II-75 **Development of a Quantitative Systems Pharmacology Model to Support Dosing of rhPTH(1-84), a Recombinant Human Parathyroid Hormone, in Adult Patients with Hypoparathyroidism**

Thomas Peyret,[1] Benjamin Rich,[1] JF Marier,[1] Nicole Sherry,[2] Richard Finkelman,[2] Ivy Song[2]

[1]Certara Strategic Consulting, Princeton, NJ; [2]Shire Human Genetic Therapies, Inc., Lexington, MA, USA, a member of the Takeda group of companies

Model Customization #2: Calcium Reabsorption

Various publications have reported a lower renal reabsorption of calcium in patients with hypoPT.[2] The effect is believed to be due to lower number of sites of hormone action in renal tubules, where it promotes calcium reabsorption. Based on this mechanism of action, the QSP model was customized as follows:

$$\text{CaReabsActive} = \frac{CaReabs_{max} \times Ca_{serum}}{CaReabs_{50} + Ca_{serum}} \times PTHeffect$$

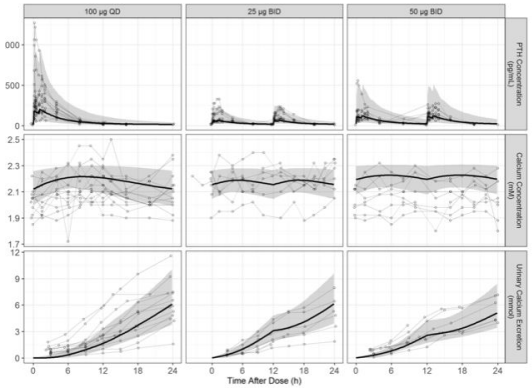
$$PTHeffect = \frac{PTHeffect_{max} \times PTH_{plasma}}{PTHeffect_{50} + PTH_{plasma}}$$

Where CaReabs50 = Caserum needed to achieve 50% of CaReabsmax; CaReabsActive = rate of calcium active renal reabsorption (mmol/h); CaReabsmax = maximum CaReabsActive; Caserum = Calcium serum concentration (mM) (T16 in model code); PTHplasma = PTH plasma concentration (pM); PTHeffect = effect of PTH on Calcium renal active reabsorption (unitless); PTHeffect50 = PTHplasma needed to achieve 50% of PTHeffectmax (T17 in model code); PTHeffectmax = maximum PTHeffect.

In the original QSP model, the maximum effect of PTH on calcium renal active reabsorption, PTHeffectmax, was fixed to 1.06147 (106% of reference reabsorption) and the PTH concentration needed to achieve 50% PTHeffectmax was scaled. In the current QSP model, the following values were used:

$$PTHeffect_{50} = 3.85 \times T16 - 3.85 = 0.2366595$$

Figure 1. QSP Model Qualification - Study SHP634-101[3]



PAGE 28 (2019) Abstr 9002
[www.page-meeting.org/?abstract=9002]

CONCLUSIONS

Both QD and BID dosing regimens of rhPTH(1-84) at daily doses from 25 µg to 100 µg markedly reduced urinary calcium excretion and the possibility of hypercalciuria while maintaining serum calcium level in target range as compared to the SOC.

Although these modeling simulations appear to show that rhPTH(1-84) BID dosing regimens may predict a lower likelihood of hypercalciuria than the QD dosing regimens, clinical data are needed, and a clinical study is planned to confirm these findings.

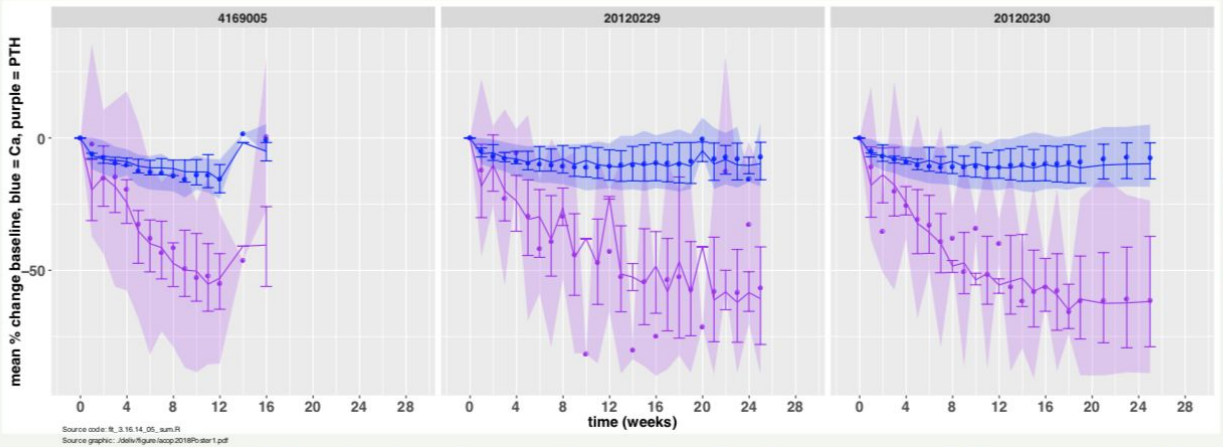
METRUM RESEARCH GROUP

Open iPSP: Integrate System, Disease, Drug

Model comes full circle, applied now to another Amgen-Sponsored Program

Chronic Kidney Disease-Mineral Bone Disorder

Long-Term Predictive Checks

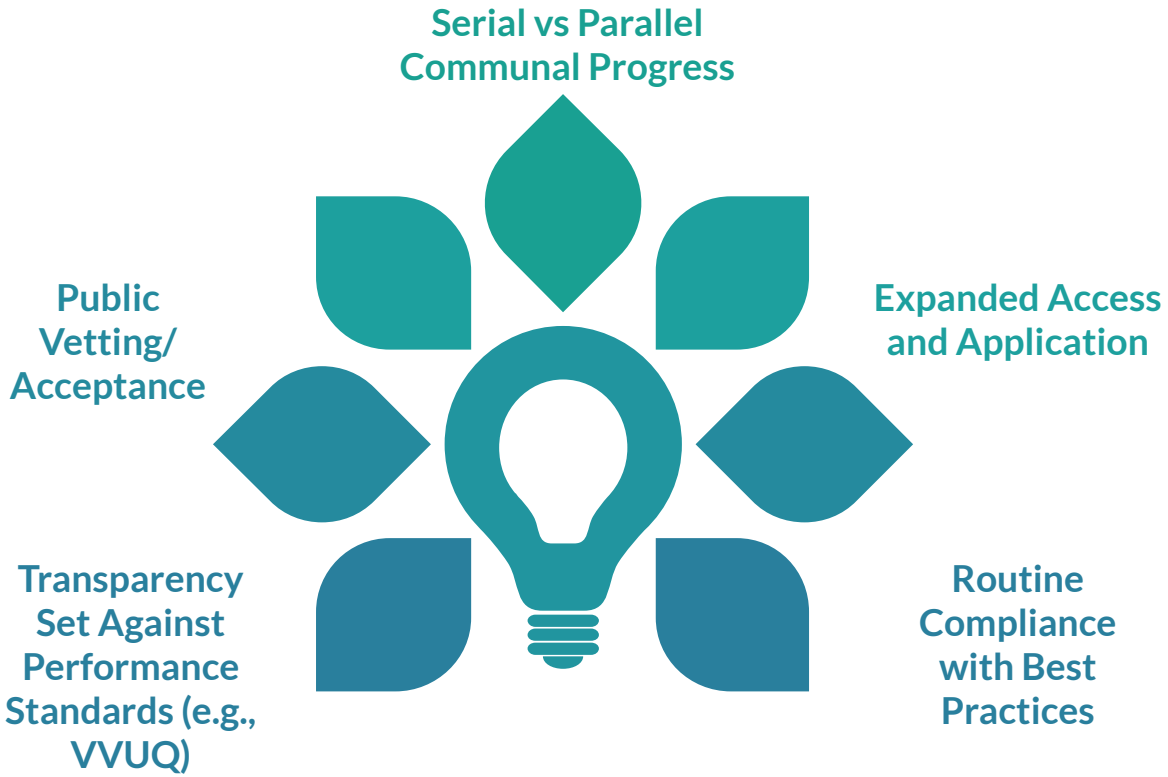


Despite continued decline in PTH (e.g., beyond weeks 4-6), feedback controls lead to leveling and partial rebound in Ca.

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).

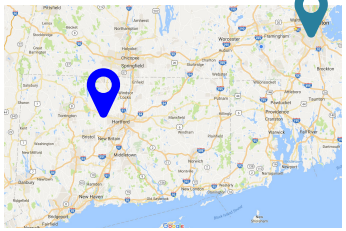
Riggs MM, Baron KT, Melhelm M (2018) Multiscale physiology-based modeling of mineral bone disorder in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis: application to etelcalcetide treatment effects on calcium homeostasis. ACoP9 Abstract #T-078.

iPSP Open-Source and Open-Science



METRUM
RESEARCH GROUP

Questions?



Headquarters:
2 Tunxis Rd. Suite 112 Tariffville, CT 06081

Cambridge Innovation Center (CIC)
1 Broadway, Cambridge, MA 02142

+1 860 735 7043

info@metrumrg.com

www.metrumrg.com

Matthew Riggs, Ph.D.
mattr@metrumrg.com