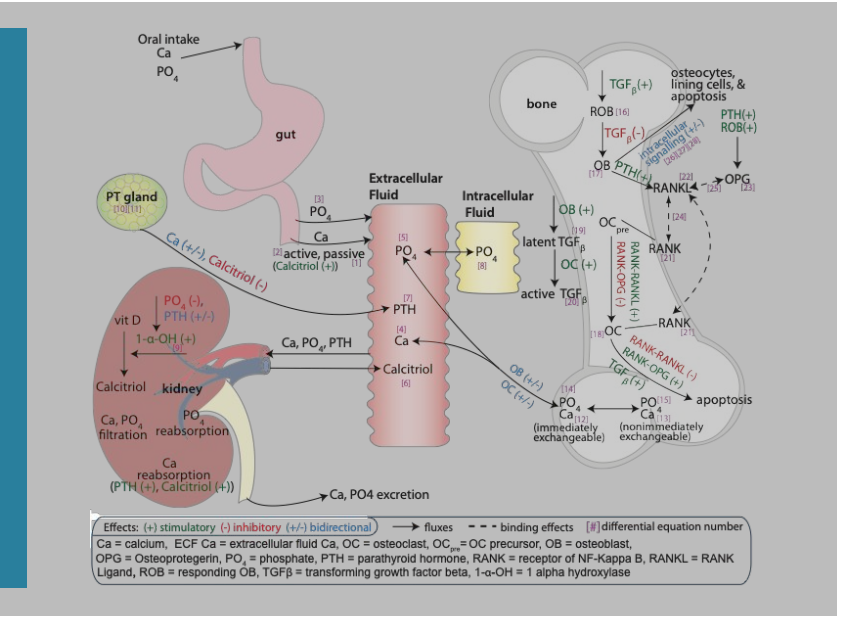


QSP to Link Learn/Confirm with Expand/Understand in Model-Informed Drug Development

Integrating Evidence Across Theory and Observation

28-July-2022

Matthew Riggs, Ph.D.
Chief Science Officer, MetrumRG

METRUM RESEARCH GROUP

Key Points: QSP Models for Integrative Evidence

Expand and Understand: When developed to answer specific questions, models can be used to expand our understanding of clinical observations, thereby guiding further research through informed decision making. This can especially be true when the models represent mechanistic understanding of the system under study.

Models: They come in all forms and sizes. Some are empiric and useful for associative forecasting of events. Others, when focused on theory, can help to integrate theory and data to test our understanding and to probe actual causes of events.

Integrative Evidence: The results from these modeling efforts can provide supportive evidence of the mechanisms related to the disease and of the efficacy and safety of proposed therapies. By providing plausible understandings, they can be used to guide further research (study design, biomarker selection) aimed at confirming, or otherwise learning about, what we expect for clinical responses.

Insight …far beyond the original locus of study

CLINICAL PHARMACOLOGY & THERAPEUTICS
VOLUME 46 NUMBER 6 DECEMBER 1989

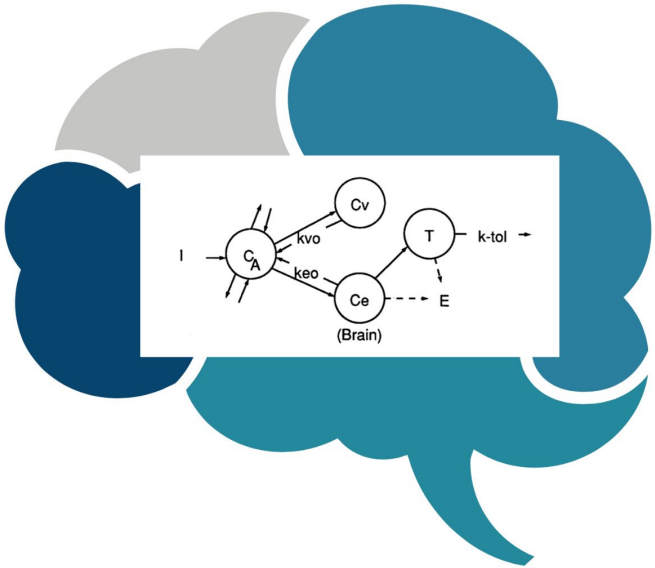
COMMENTARY

Clinical pharmacology and the choice between theory and empiricism

Lewis B. Sheiner, MD *San Francisco, Calif.*

"Thus, by going beyond empiricism and stressing understanding, not data collection, we not only answer our first question, but we also gain far more. For clinical pharmacology,

"…the goal is theory, not data."



LB Sheiner. Clin. Pharmacol. Ther. 46, 605-615, 1989.

LB Sheiner. Clinical Pharmacology and the Choice between Theory and Empiricism. Clin. Pharmacol. Ther. 46, 605-615, 1989.

Application of theory to gain new insights

Why does nicotine gum not help very much with cigarette abstinence?

Model based simulation = applied theory

Explore unstudied conditions and scenarios

Generate insights to drive decisions and hypotheses for future experiments

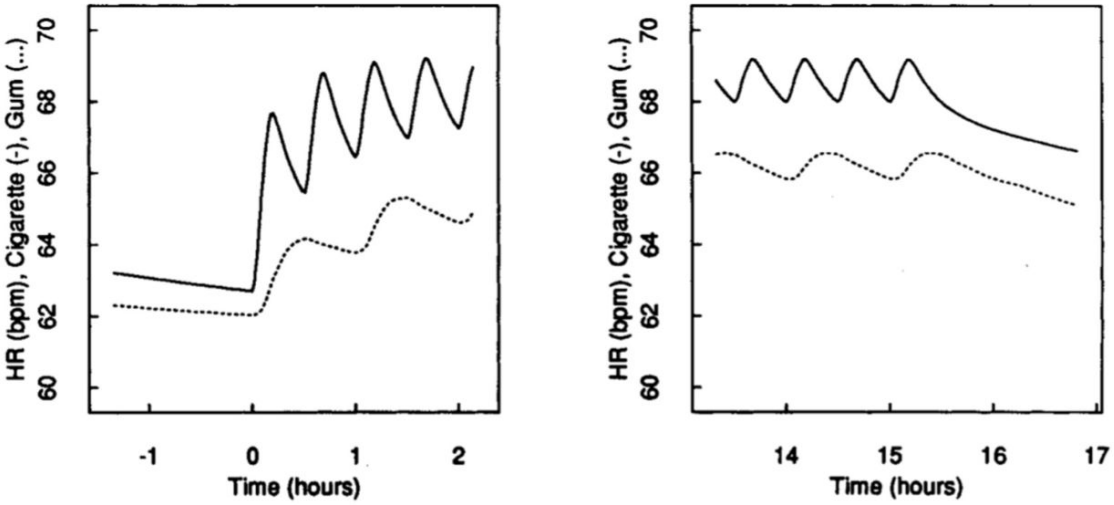
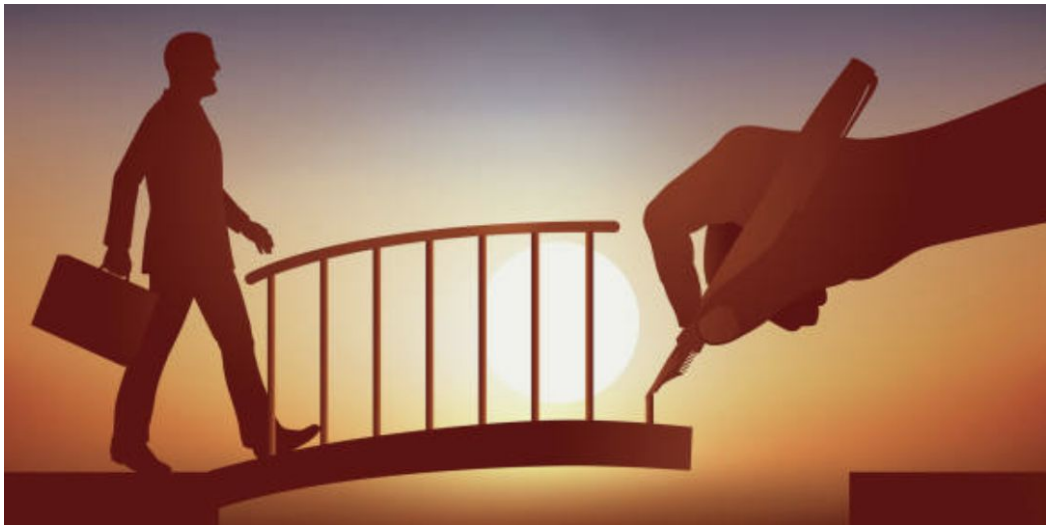


Fig. 9. Simulation of HR response (ordinate) to usual daily intake of cigarettes (——) or gum (- - -) versus time of day. Simulation with model of Fig. 4, fit of Fig. 5, and individual input functions from Figs. 7 and 8. **Left panel**, morning—intake begins after ovenight abstinence. **Right panel**, evening—input ceases for sleep.

Simulations after model based analysis of nicotine gum PK data

LB Sheiner. Clin. Pharmacol. Ther. 46, 605-615, 1989.

Modeling & Simulation: Moving beyond information



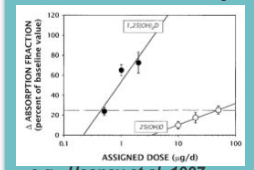
Data | Knowledge | Understanding | Decisions

Modeling and Simulation

Understand: Integrate Existing Data & Models

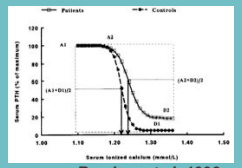
Literature and in-house information is often available to inform model parameter and disease state effects

Calcium Absorption



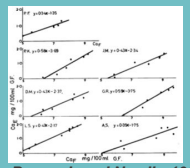
e.g., *Heaney et al. 1997*

PTH Secretion



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

Calcium Excretion



e.g., *Peacock and Nordin 1968*

Bone Therapeutics

Anabolic (*teriparatide, 2004*)

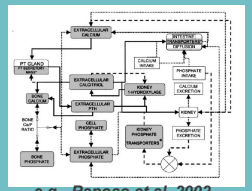
Catabolic (*denosumab, 2006*)

Disease States

Hyper- and hypo-PTH

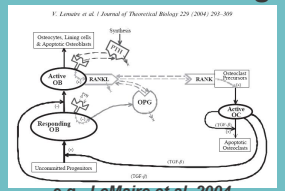
CKD-MBD (*Rix et al. 1999*)

Calcium Homeostasis



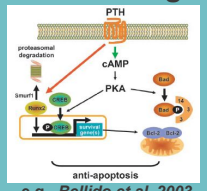
e.g., *Raposo et al. 2002*

Bone Remodeling



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

Intracellular Signaling



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

Multiscale Model

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

Expand/Understand: A Case Study

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

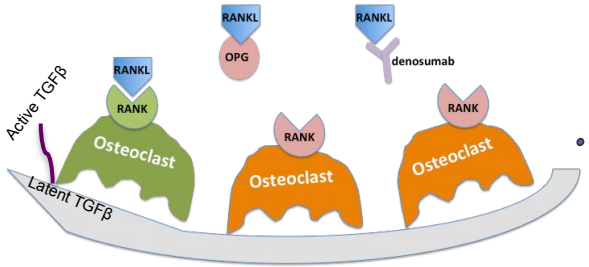
Denosumab: RANKL inhibition

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

Expand/Understand: A Case Study

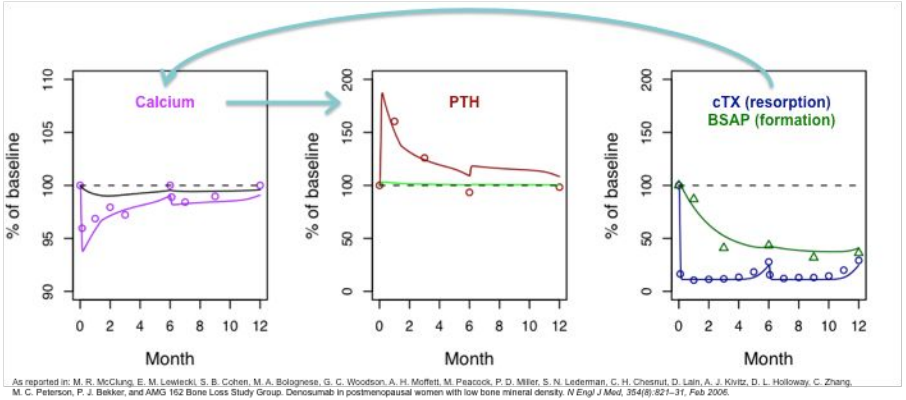
The question: Can we better understand (and predict) the inter-related effects of dmab and the time-courses of on/off tx effects?

Denosumab: RANKL inhibition



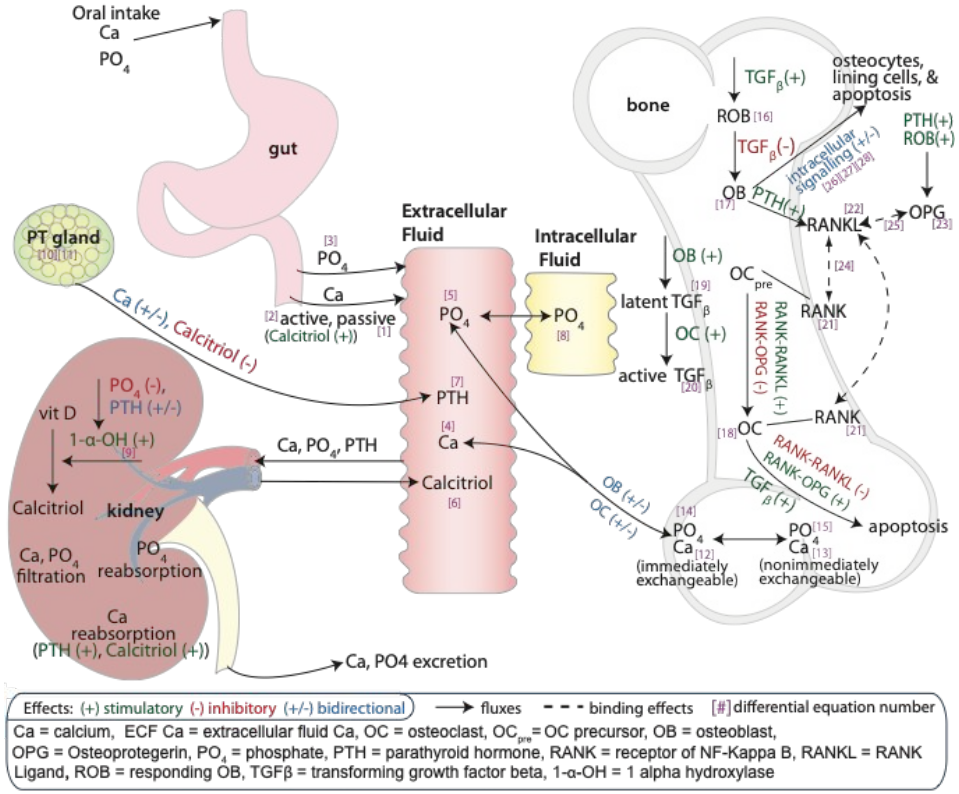
- ↓ available RANKL
- ↓ RANK--RANKL interaction
- ↓ Osteoclast activity (sCTx)
- ↓ Activation of TGF-β
- ↓ Osteoblast activity (BSAP)
- ↑ bone mineral density (BMD)

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



Expand/Understand: A Case Study

One soultion: Understand (and predict) the inter-related effects of dmab and the time-courses of on/off t effects?



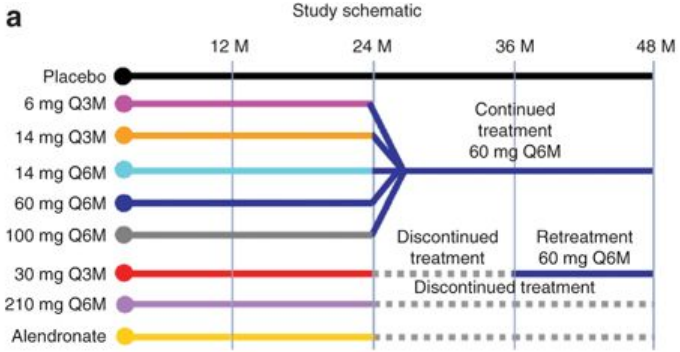
Multiscale QSP Model

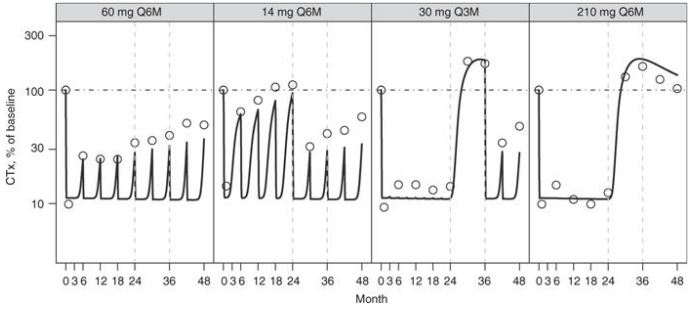
Peterson MC and Riggs MM (2010) A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. Bone 46:49-63.

Understand: On/Off Treatment Effects

Denosumab: RANKL inhibition → Bone Marker Changes

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





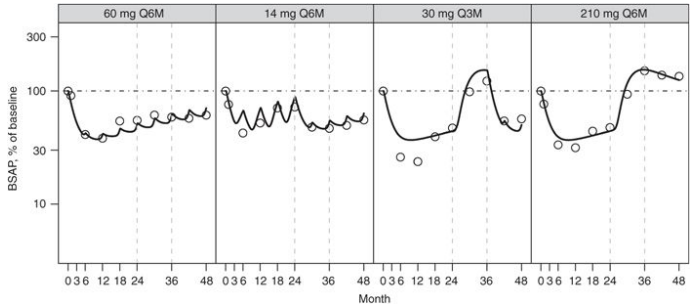
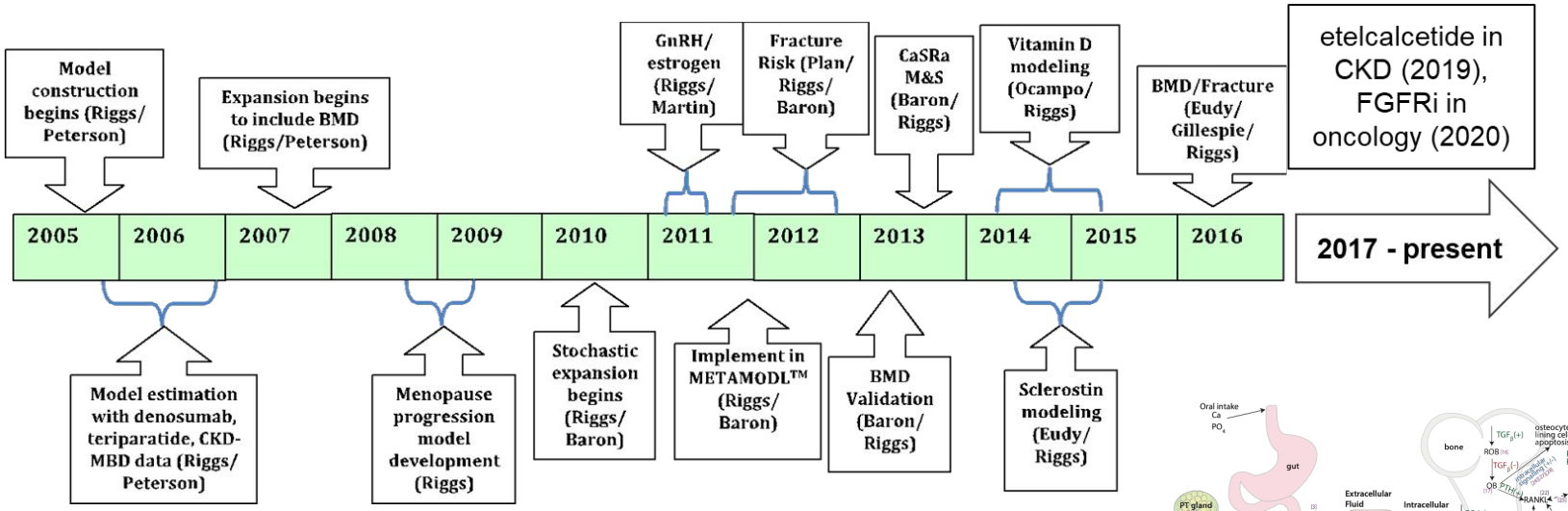


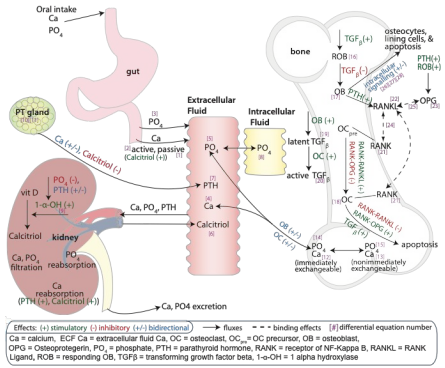
Fig.3 and 4; Peterson MC and Riggs MM,. CPT: Pharmacometrics & Systems Pharmacology (2012) 1, e14; doi:10.1038/psp.2012.15

QSP Bone Model -- Public Examples

Target	Drug	Disease	Impact	Link
RANKL inhibition	Denosumab (Amgen)	osteoporosis	Understand and predict the impact of dose disruptions, rebound in bone markers, Predict dosing-regimen related BMD responses	Bone 2010 CPT:PSP 2012
Calcium-sensing antagonist	DS-9194b (Daiichi Sankyo)	osteoporosis	Magnitude of BMD elevation is unlikely to meet goal (similar response to exogenous PTH)	ASBMR 2013
PTH replacement	Natpara (NPS)	hypoparathyroidism	A postmarketing trial was recommended to assess pharmacokinetics (PKs) and pharmacodynamics (PDs) of PTH dose and dosing regimen. QSP model-based simulations fulfilled the information gap to support recommendations of this postmarketing trial.	CP&T 2018
Calcium-sensing agonist	etelcalcetide (Amgen)	CKD	Support understanding of the expected contributions of physiologic disease progression, feedback mechanisms and pharmacologic effects of etelcalcetide on Ca homeostasis	ACoP9 (2018)
GnRH antagonism	Preclinical (Pfizer) Linzagolix (ObsEva)	endometriosis	Pfizer dropped program ObsEva used for Phase 3 dose selection	CPT:PSP 2012 ACoP10 (2019)
FGFR inhibition	ASP5878 (Astellas)	oncology	Efficacious response was not obtained by any simulated regimen that minimized to acceptable phosphate; results supported program termination. Also included characterization of phosphate binder effect on serum phosphate	ACoP11 (2020)

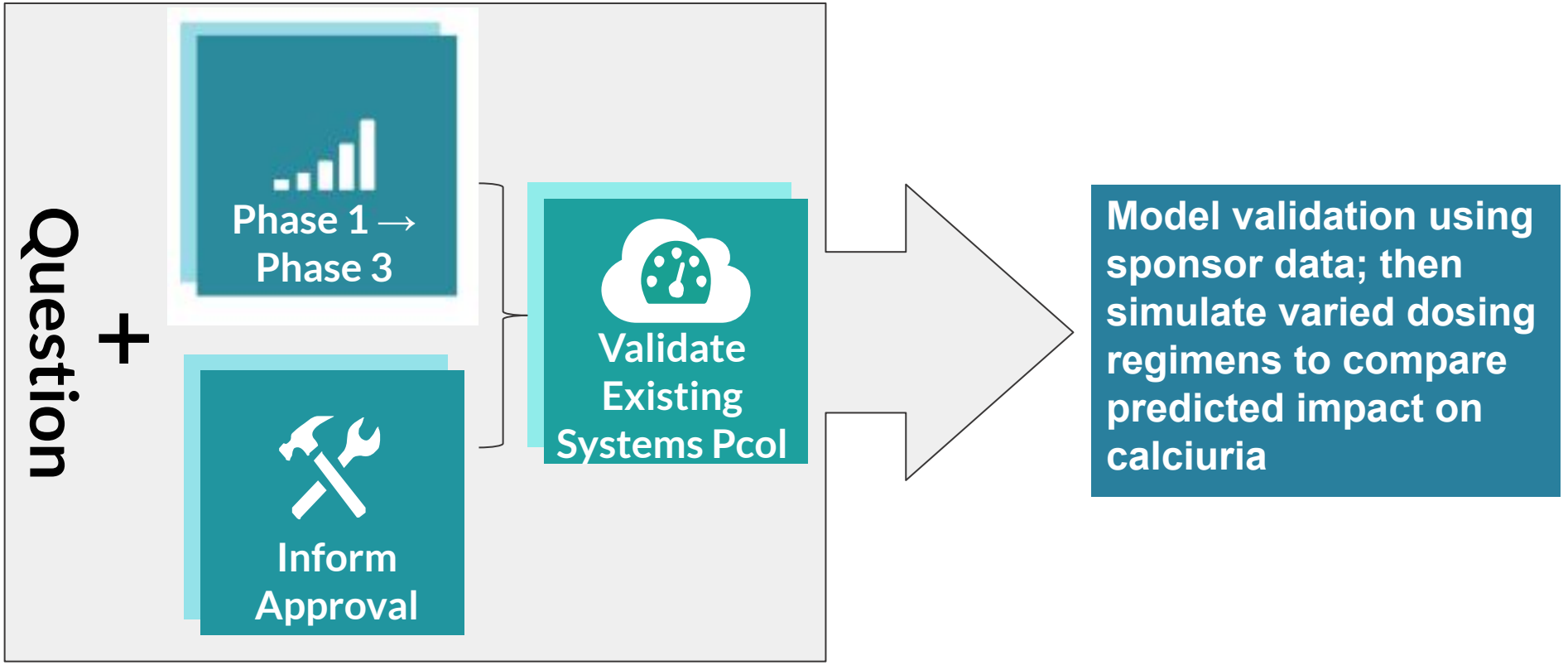
Expand/Understand: Timeline of continued development





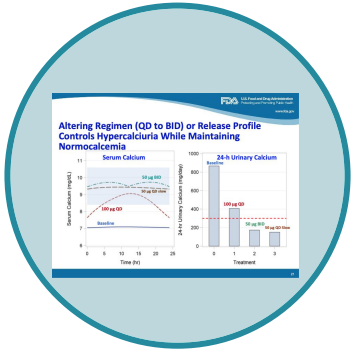
Example: PTH endogenous, replacement tx in hypoPTH

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



Model Evaluation First, Understand the Question

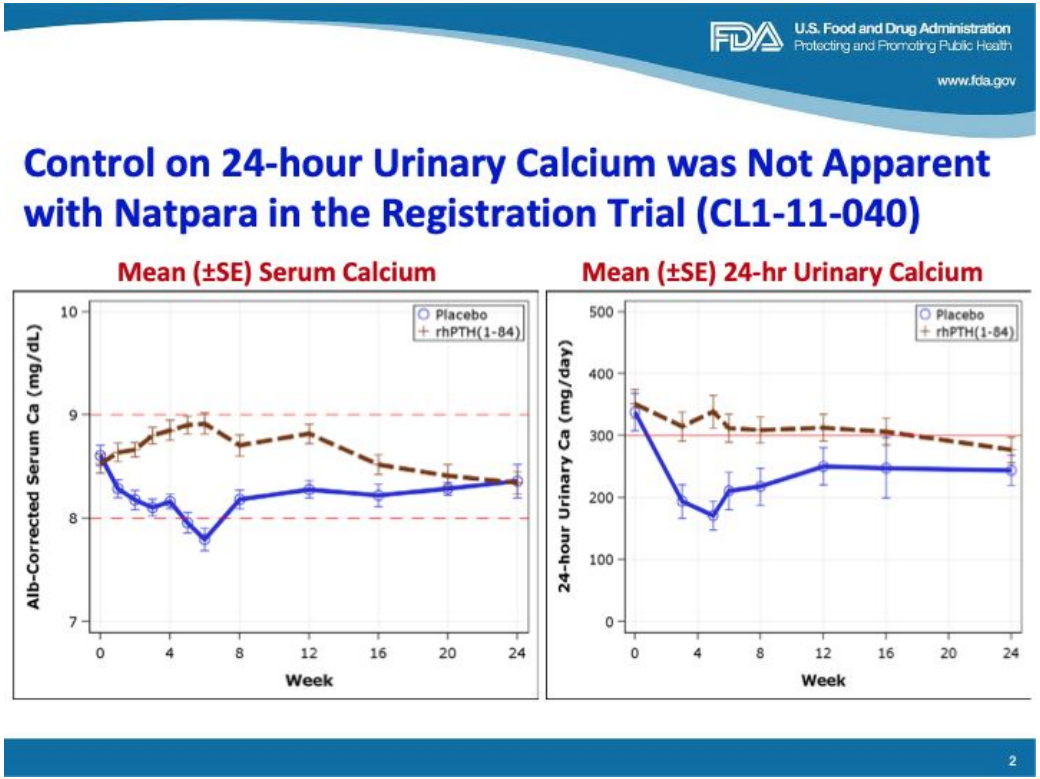
Open science opens doors



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

Expand/Understand: A Case Study

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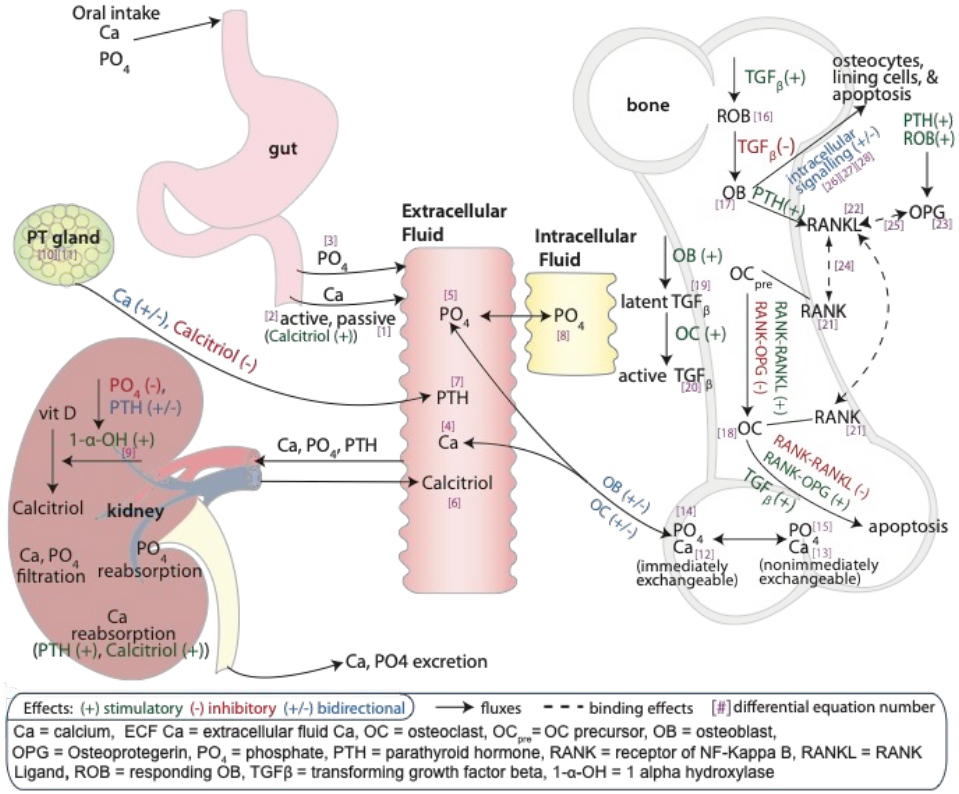

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Model Evaluation First, Understand the Question

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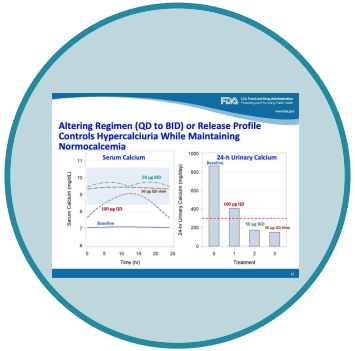

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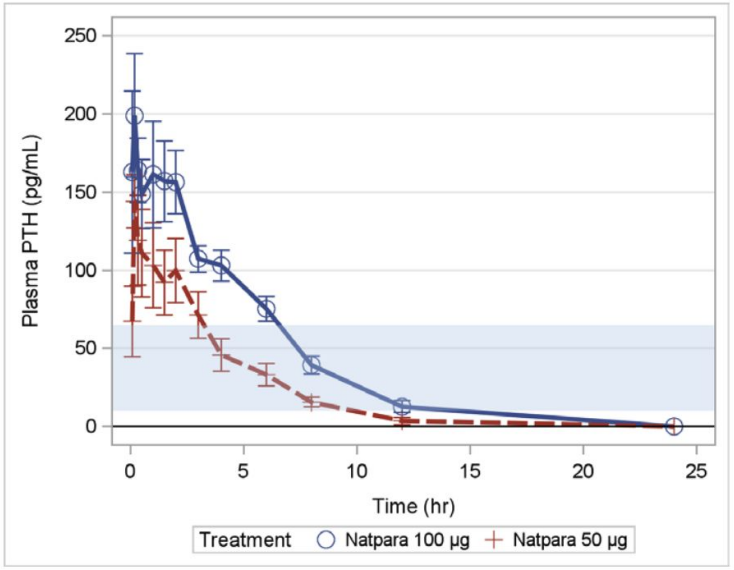
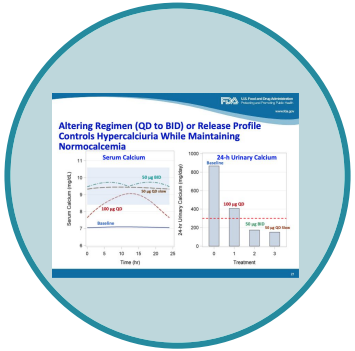


Figure 4 **Mean plasma concentration versus time profile of Natpara (single 50 and 100 µg SC doses in the thigh of same subjects, minimum 7 days washout between 2 periods)**

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

Model Evaluation First, Understand the Question

Open science opens doors



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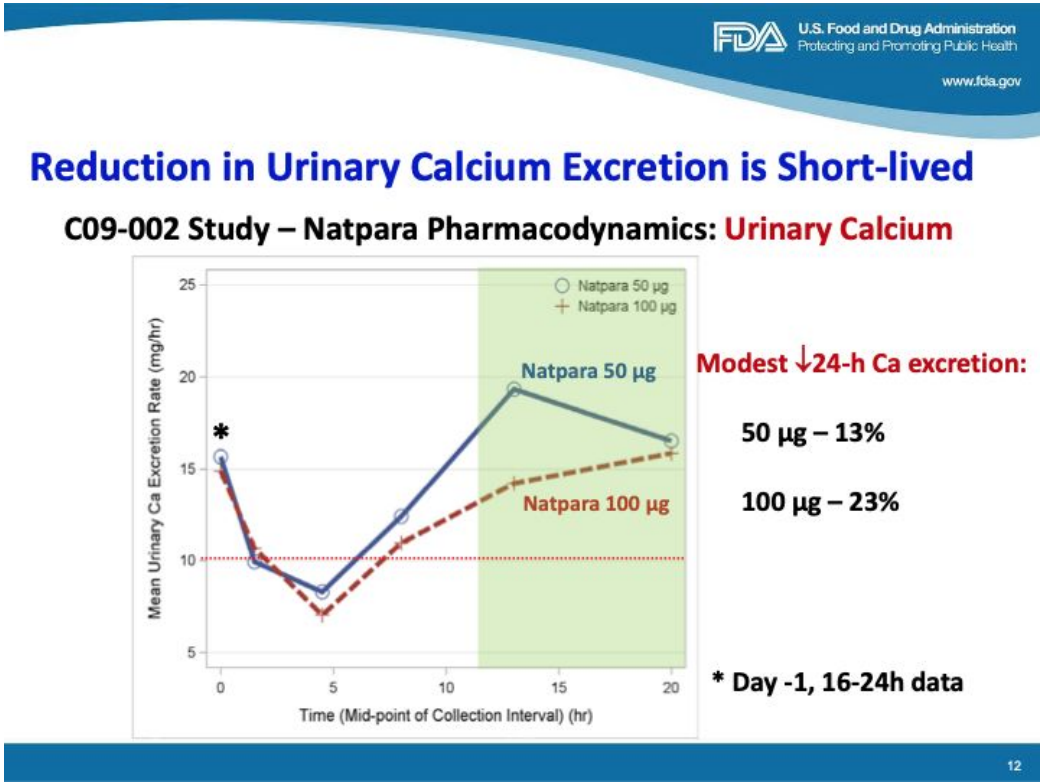

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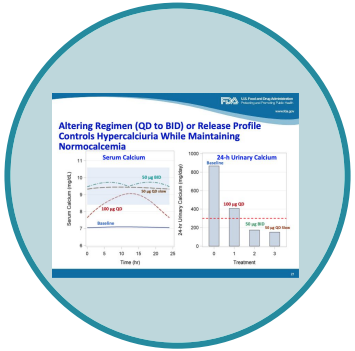
Model Evaluation With added confidence, investigate the question

Open science opens doors



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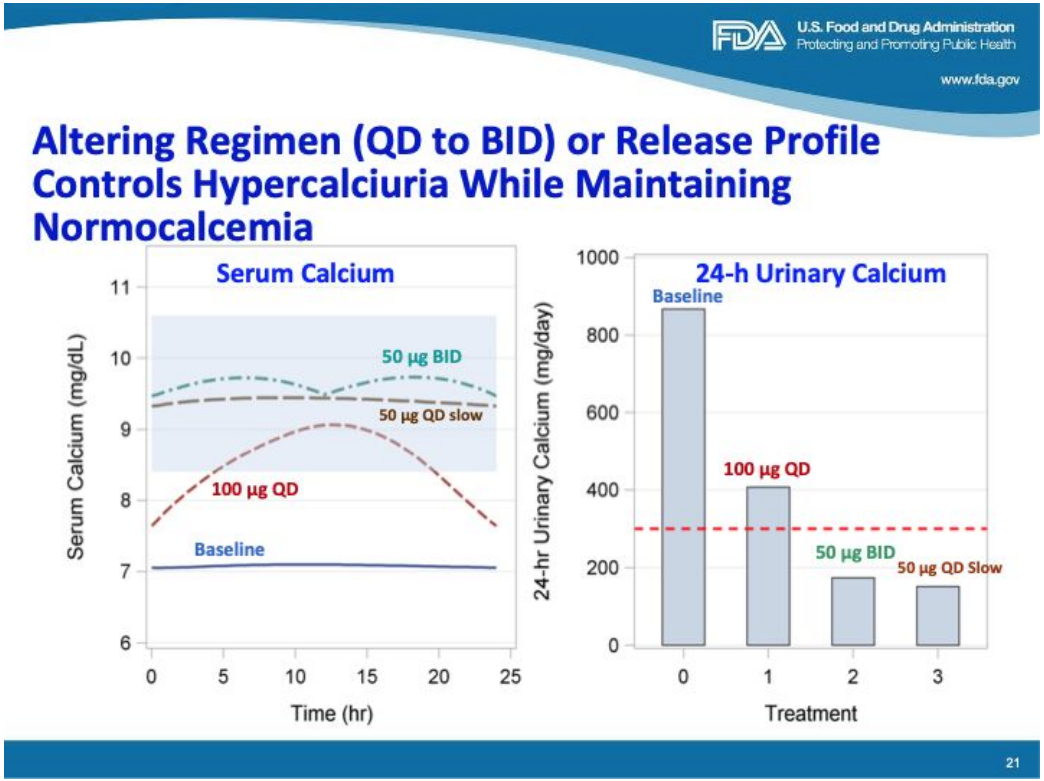

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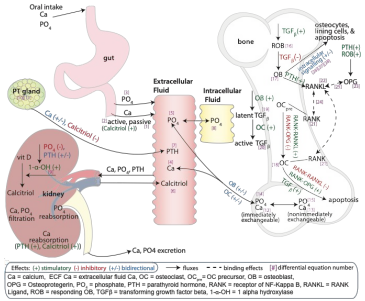
Integrating Evidence Across Theory and Observations



We know a lot about bone, bone minerals, and the mechanisms that control them.

But what if… we are faced with an epic challenge and know very little?

How could prior, shared knowledge of systems (theory) help to solve that challenge?

When there's theory and very few observations?

In March 2020… Covid-19 was happening

There were no treatments, we knew so much less about the virus, treatments were mainly empiric.

Monoclonal antibodies carried hope: but which one(s), how much to give, and how can we develop them (and manufacture them) quickly enough?

Integrating Evidence: 1. Understand the Problem

"**When we have a solution, we want it to be available for as many patients as possible, and the better the antibody, the lower the dose you need. And given manufacturing capacities, the more patients you can help.**" Dan Skovronsky, CSO, Eli Lilly and Company April 30, 2020

From: https://www.insideindianabusiness.com/articles/skovronsky-lilly-aims-to-test-covid19-therapy-by-summer Last accessed 27-July-2022

In another briefing he stated: "**It's good to have two antibodies. The downside is that manufacturing is precious. We have limited manufacturing capacity. If two antibodies are required, half as many people will get treated,**" Skovronsky said. "**So our goal is to see if we can do one antibody at as low a dose as possible.**" June 10, 2020

From: https://www.reuters.com/article/us-health-coronavirus-lilly-exclusive/exclusive-lilly-covid-19-treatment-could-be-authorized-for-use-as-soon-as-september-chief-scientist-idUSKBN23H35S
Last accessed 27-July-2022

Integrating Evidence: 2. Gather What You Know

There will be about 5 candidate mAbs from which to choose

There will be NO *in vivo* data before needing to decide on candidate and its dose for June '20 FIH

We *may* have some *in vitro* experimental neutralization data available just prior to selection

We are NOT the first researchers predicting mAb exposures given limited early info.

We are NOT the first researchers predicting exposure-response impact on viral dynamics.

Integrating Evidence: 3. Gather What Others Know

Enter… Shared Science; and the lives it impacted

J Pharmacokinet Pharmacodyn (2012) 39:67–86
DOI 10.1007/s10928-011-9232-2

ORIGINAL PAPER

Towards a platform PBPK model to characterize the plasma and tissue disposition of monoclonal antibodies in preclinical species and human

Dhaval K. Shah · Alison M. Betts

J Pharmacokinet Pharmacodyn. 2013 October ; 40(5): . doi:10.1007/s10928-013-9332-2.

Second-generation minimal physiologically-based pharmacokinetic model for monoclonal antibodies

Yanguang Cao[1], **Joseph P Balthasar**[1], and **William J Jusko**[1,2]
[1]Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, State University of New York at Buffalo, Buffalo, NY, 14214, USA

Citation: CPT Pharmacometrics Syst. Pharmacol. (2019) 8, 738–747; doi:10.1002/psp4.12461

ARTICLE

A Physiologically-Based Pharmacokinetic Model for the Prediction of Monoclonal Antibody Pharmacokinetics From *In Vitro* Data

Hannah M. Jones[1,*], Zhiwei Zhang[2], Paul Jasper[2], Haobin Luo[2], Lindsay B. Avery[3], Lindsay E. King[4], Hendrik Neubert[4], Hugh A. Barton[5], Alison M. Betts[1] and Robert Webster[1]

Monoclonal antibody (mAb) pharmacokinetics (PK) have largely been predicted via allometric scaling with little consideration for cross-species differences in neonatal Fc receptor (FcRn) affinity or clearance/distribution mechanisms. To address this, we developed a mAb physiologically-based PK model that describes the intracellular trafficking and FcRn recycling of mAbs in a human FcRn transgenic homozygous mouse and human. This model uses mAb-specific *in vitro* data together with species-specific FcRn tissue expression, tissue volume, and blood-flow physiology to predict mAb *in vivo* linear PK *a priori*. The model accurately predicts the terminal half-life of 90% of the mAbs investigated within a twofold error. The mechanistic nature of this model allows us to not only predict linear PK from *in vitro* data but also explore the PK and target binding of mAbs engineered to have pH-dependent binding to its target or FcRn and could aid in the selection of mAbs with optimal PK and pharmacodynamic properties.

Integrating Evidence: 3. Gather What Others Know

Enter… Shared Science; and the lives it impacted

Virus Dynamics

Mathematical Principles of Immunology and Virology

By Martin A. Nowak, Martin Andreas Nowak, Robert McCredie May · 2000

J Theor Biol. 2007 July 7; 247(1): 23–35.

Modeling the mechanisms of acute hepatitis B virus infection

Stanca M. Ciupe[*], **Ruy M. Ribeiro**[†], **Patrick W. Nelson**[‡], and **Alan S. Perelson**[*,†,0]

**Santa Fe Institute, 1399 Hyde Park Rd., Santa Fe, NM, 87507*

†Theoretical Biology and Biophysics Group, Theoretical Division, Los Alamos National Laboratory, Los Alamos, NM 87545

‡Dept. of Mathematics, University of Michigan, 5860 E. Hall, Ann Arbor, MI 48109

medRxiv

THE PREPRINT SERVER FOR HEALTH SCIENCES

CSH Cold Spring Harbor Laboratory BMJ Yale

doi: https://doi.org/10.1101/2020.03.23.20040493

History: March 27, 2020.

Modelling SARS-CoV-2 Dynamics: Implications for Therapy

Kwang Su Kim, Keisuke Ejima, Yusuke Ito, Shoya Iwanami, Hirofumi Ohashi, Yoshiki Koizumi, Yusuke Asai, Shinji Nakaoka, Koichi Watashi, Robin N. Thompson, Shingo Iwami

doi: https://doi.org/10.1101/2020.03.23.20040493

Integrating Evidence: 4. Apply to Problem at Hand

Clinical Pharmacology & Therapeutics

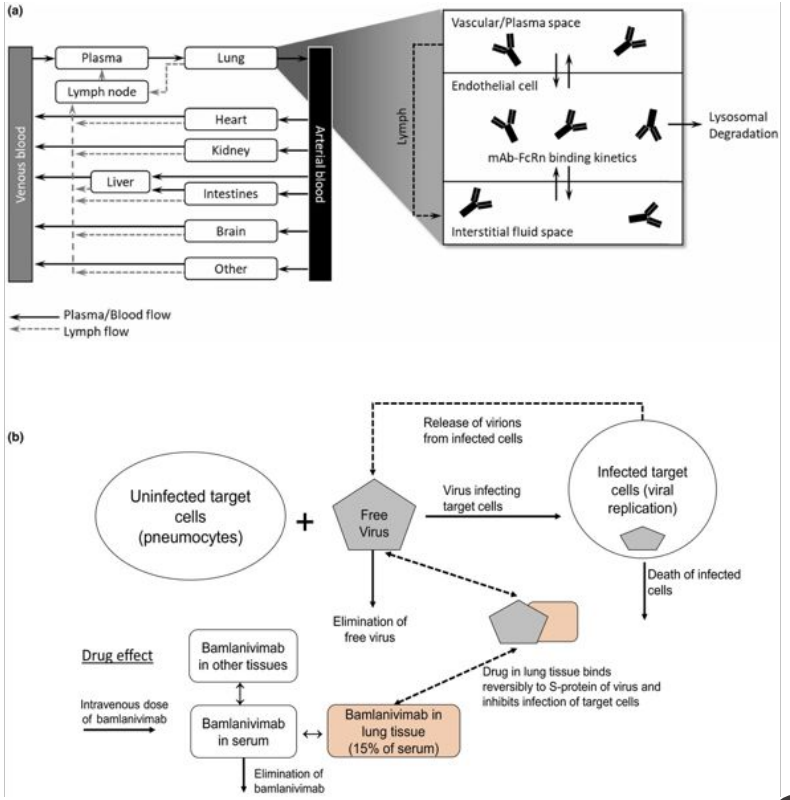
Article | Open Access

A Quantitative Modeling and Simulation Framework to Support Candidate and Dose Selection of Anti-SARS-CoV-2 Monoclonal Antibodies to Advance Bamlanivimab Into a First-in-Human Clinical Trial

Emmanuel Chigutsa, Eric Jordie, Matthew Riggs, Ajay Nirula, Ahmed Elmokadem, Tim Knab, Jenny Y. Chien
... See fewer authors

First published: 22 October 2021 | https://doi.org/10.1002/cpt.2459 | Citations: 1

- The PBPK model-based approach suggested that a clinical dose between 175 and 500 mg of bamlanivimab would maintain target mAb concentrations in the lung tissue over 28 days in 90% of patients.
- The viral dynamic model suggested a 700 mg dose would achieve maximum viral elimination.



Clin Pharma and Therapeutics, Volume: 111, Issue: 3, Pages: 595-604, First published: 22 October 2021, DOI: (10.1002/cpt.2459) https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.2459

Integrating Evidence: 5. Reflect on How We Did…

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

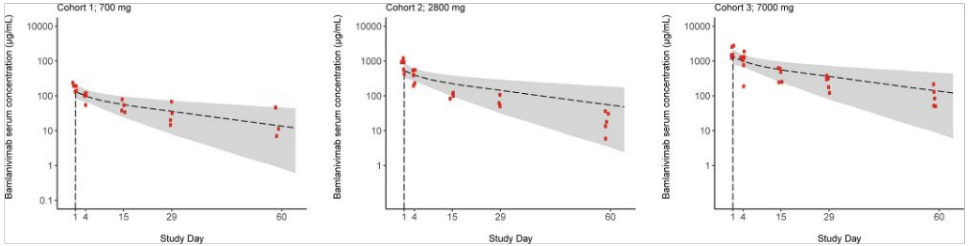
Peter Chen, M.D., Ajay Nirula, M.D., Ph.D., Barry Heller, M.D., Robert L. Gottlieb, M.D., Ph.D., Joseph Boscia, M.D., Jason Morris, M.D., Gregory Huhn, M.D., M.P.H.T.M., Jose Cardona, M.D., Bharat Mocherla, M.D., Valentina Stosor, M.D., Imad Shawa, M.D., Andrew C. Adams, Ph.D., Jacob Van Naarden, B.S., Kenneth L. Custer, Ph.D., Lei Shen, Ph.D., Michael Durante, M.S., Gerard Oakley, M.D., Andrew E. Schade, M.D., Ph.D., Janelle Sabo, Pharm.D., Dipak R. Patel, M.D., Ph.D., Paul Klekotka, M.D., Ph.D., and Daniel M. Skovronsky, M.D., Ph.D., for the BLAZE-1 Investigators*

"The doses of LY-CoV555 that were evaluated in this trial were based on pharmacologic modeling that predicted that the 700-mg dose would be efficacious. (Details about dose selection are provided in the Supplementary Appendix, available at NEJM.org.)"

January 21, 2021 N Engl J Med 2021; 384:229-237 DOI: 10.1056/NEJMoa2029849

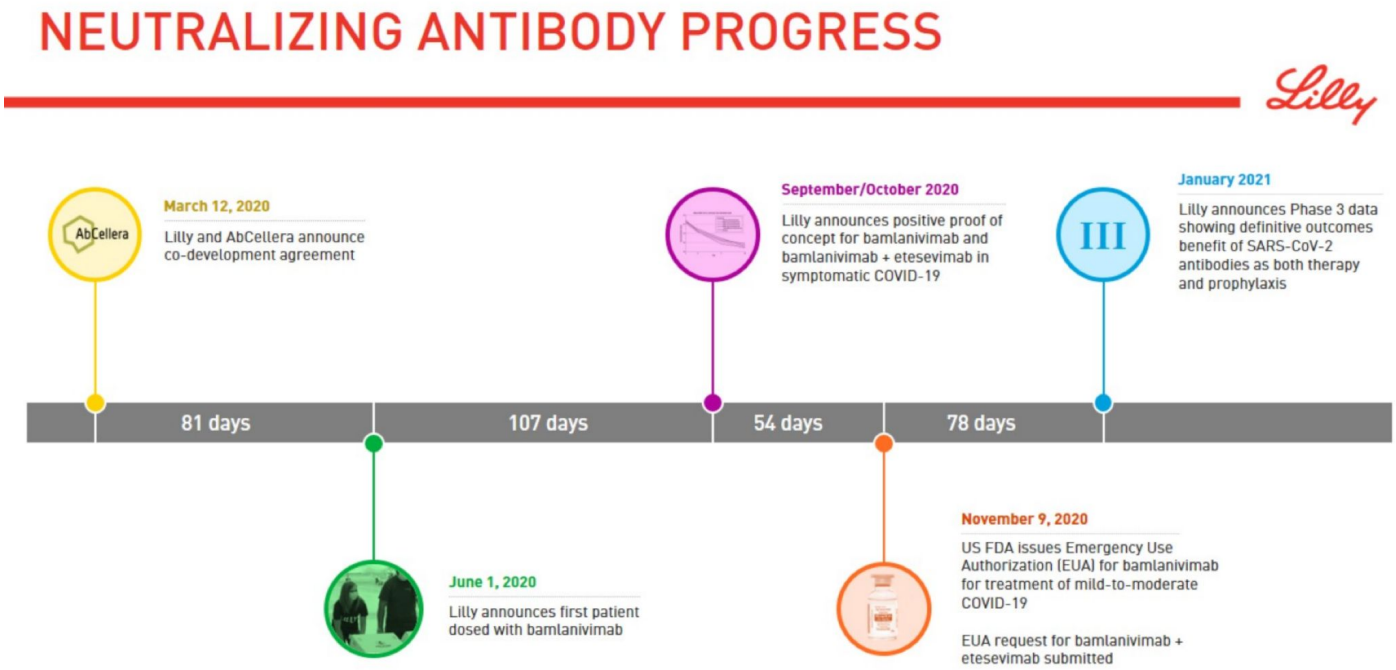
https://github.com/metrumresearchgroup/bioPBPK/tree/main/mAb_bamlanivimab

Overlay of pharmacokinetic (PK) profiles as predicted a priori using the physiologically-based pharmacokinetic (PBPK) model with observed data from the first-in-human trial. Bamlanivimab serum concentrations from cohorts of patients receiving 700, 2,800, or 7,000 mg of bamlanivimab. Red data points are the observed clinical data from each of the respective three cohorts. The grey shaded area represents the 90% prediction interval from PBPK modeling with the black dotted line representing the median.



Clin Pharma and Therapeutics, Volume: 111, Issue: 3, Pages: 595-604, First published: 22 October 2021, DOI: (10.1002/cpt.2459)

Integrating Evidence: 6. How Quickly Did Lilly Do It



From: https://investor.lilly.com/static-files/081a5ef7-f5d6-4acc-b0d2-7ae4daf9e953 accessed 26-July-2022

Integrating Evidence: 7. Impact on patient outcome

Figure 1. Frequency of 28-day study outcomes among propensity-matched patients receiving and not receiving bamlanivimab ...

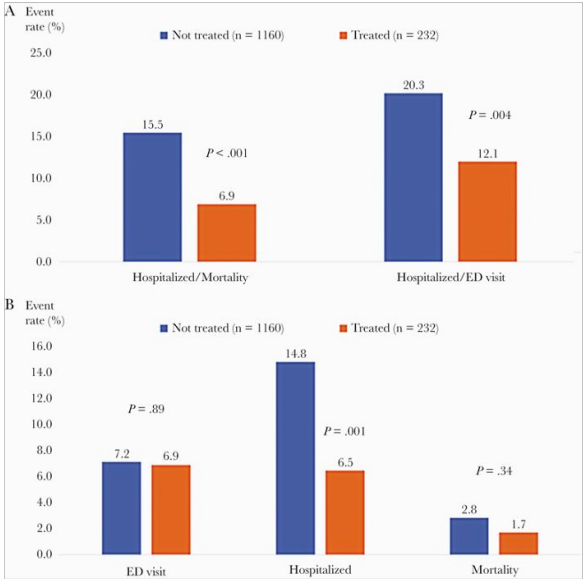


Table 2. Primary and Secondary Outcomes From Propensity-Matched Models Stratified by Age

Outcome All Patients	Number of Events		28-Day Event Rate (%)		Odds Ratio Estimates		
	Treated (n = 232)	Not Treated (n = 1160)	Treated	Not Treated	Odds Ratio	(95% CI)	*P* Value
Hospitalization or mortality	16	180	6.9	15.5	0.40	(0.24–0.69)	<.001
Hospitalization or ED visit without hospitalization	28	235	12.1	20.3	0.54	(0.35–0.82)	.004
ED visit without hospitalization	16	83	6.9	7.2	0.96	(0.55–1.67)	.89
Hospitalization	15	172	6.5	14.8	0.40	(0.23–0.69)	.001
Mortality	4	33	1.7	2.8	0.60	(0.21–1.71)	.34

Open Forum Infect Dis, Volume 8, Issue 7, July 2021, ofab254, https://doi.org/10.1093/ofid/ofab254

Key Points: QSP Models for Integrative Evidence

Expand and Understand: When developed to answer specific questions, models can be used to expand our understanding of clinical observations, thereby guiding further research through informed decision making. This can especially be true when the models represent mechanistic understanding of the system under study.

Models: They come in all forms and sizes. Some are empiric and useful for associative forecasting of events. Others, when focused on theory, can help to integrate theory and data to test our understanding and to probe actual causes of events.

Integrative Evidence: The results from these modeling efforts can provide supportive evidence of the mechanisms related to the disease and of the efficacy and safety of proposed therapies. By providing plausible understandings, they can be used to guide further research (study design, biomarker selection) aimed at confirming, or otherwise learning about, what we expect for clinical responses.

Questions: QSP Models for Integrative Evidence

Our turn to Expand and Understand…

Matthew Riggs, PhD

- Experienced and passionate developer of therapeutics for rare and metabolic diseases.
- 20+ years of experience applying modeling and simulation methods to clinical and drug development decision support
- 4.5 years in Clinical Pharmacology at Pfizer Global R&D
- 17 years at Metrum Research Group
- Founded MetrumRG's Systems Pharmacology group
- As CSO, works closely with our PKPD, Systems Pharmacology, Statistics, Data Science, and HPC (Metworx™) teams to continually advance our quantitative decision support