Can application of quantitative clinical pharmacology improve early clinical development success in neurodegenerative diseases?

Gianluca Nucci,
Early Clinical Development Clinical Pharmacology,
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Pfizer Inc.

Pfizer WORLDWIDE RESEARCH & DEVELOPMENT

SCIENCE FOR LIFE-CHANGING IMPACT

Pfizer: Champions MBDD & MID3 …
… but exits Neuroscience

Model-based Drug Development

RL Lalonde[1], KG Kowalski[2], MM Hutmacher[1], W Ewy[2], DJ Nichols[1], PA Milligan[1], BW Corrigan[1], PA Lockwood[1], SA Marshall[1], LJ Benincosa[1], TG Tensfeldt[1], K Parivar[1], M Amantea[1], P Glue[1], H Koide[1] and R Miller[1]

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Model-Based Drug Development: A Rational Approach to Efficiently Accelerate Drug Development

PA Milligan[1], MJ Brown[2], B Marchant[3,10], SW Martin[1], PH van der Graaf[4,1], N Benson[4,11], G Nucci[5], DJ Nichols[5], RA Boyd[6], JW Mandema[7], S Krishnaswami[6], S Zwillich[8], D Gruben[2], RJ Anziano[2], TC Stock[9] and RL Lalonde[6]

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Understanding Placebo Responses in Alzheimer's Disease Clinical Trials from the Literature Meta-Data and CAMD Database

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Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation

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This document was developed to enable greater consistency in the practice, application, and documentation of Model-Informed Drug Discovery and Development (MID3) across the pharmaceutical industry. A collection of "good practice" recommendations are assembled here in order to minimize the heterogeneity in both the quality and content of MID3 implementation and documentation. The three major objectives of this white paper are to: i) inform company decision makers how the strategic integration of MID3 can benefit R&D efficiency; ii) provide MID3 analysts with sufficient material to enhance the planning, rigor, and consistency of the application of MID3; and iii) provide regulatory authorities with substrate to develop MID3 related and/or MID3 enabled guidelines.

CPT Pharmacometrics Syst. Pharmacol. (2016) **5**, 93–122; doi:10.1002/psp4.12049; published online 14 March 2016.

REUTERS World Business Markets Politics TV

Pfizer ends research for new Alzheimer's, Parkinson's drugs

npr NOW WBUR

the **two-way**

AMERICA

Pfizer Halts Research Into Alzheimer's And Parkinson's Treatments

January 8, 2018 · 12:37 PM ET

LEARN MORE ABOUT OUR NEUROSCIENCE R&D DECISION

NEWS / Learn More About Our Neuroscience R&D Decision

January 11, 2018

Our recent announcement to end our discovery and early clinical development efforts in neuroscience has been an extremely difficult decision and one that we have not taken lightly. We recognize the immense disappointment in the broader community, and we share this; at a personal level, many of us have seen first-hand the devastation of Alzheimer's

to succeed

Pfizer scien
potential th
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that our research efforts were simply not making the

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LE PROSPETTIVE PER MALATI E FAMILIARI

Perché Pfizer abbandona la ricerca su Alzheimer, e quali sono gli sviluppi in corso

di Rossana Magnano

La multinazionale americana Pfizer frena sulla ricerca destinata alle patologie neurodegenerative e dirotta gli investimenti in aree in cui ha già raggiunto una forte leadership scientifica e il massimo impatto sui

Can application of quantitative clinical pharmacology improve early clinical development success in neurodegenerative diseases?

Depends on the meaning of the word “*success*”

What is early clinical development success?

Better Dose Selection?

Better Designs?

Better Decisions?

More Efficient Development?

Higher Proportion of Positive PoC?

GSM & Combo (BACEi) Quantitative Questions

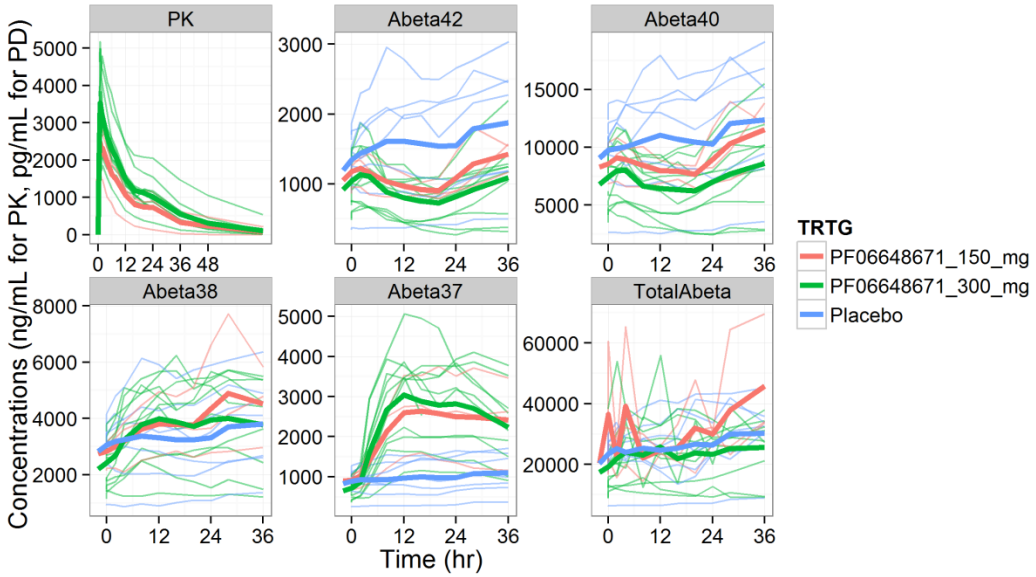
- **Proof of Mechanism**: Exposure-response for CSF biomarkers after single and steady state dosing?
- **Dose selection**: What is the dose to achieve Aβ42 inhibition and optimize shorter Aβ peptides?
- **Combination** : What would be the biomarker response if GSM and BACEi were combined? What would be the optimal combo dose?

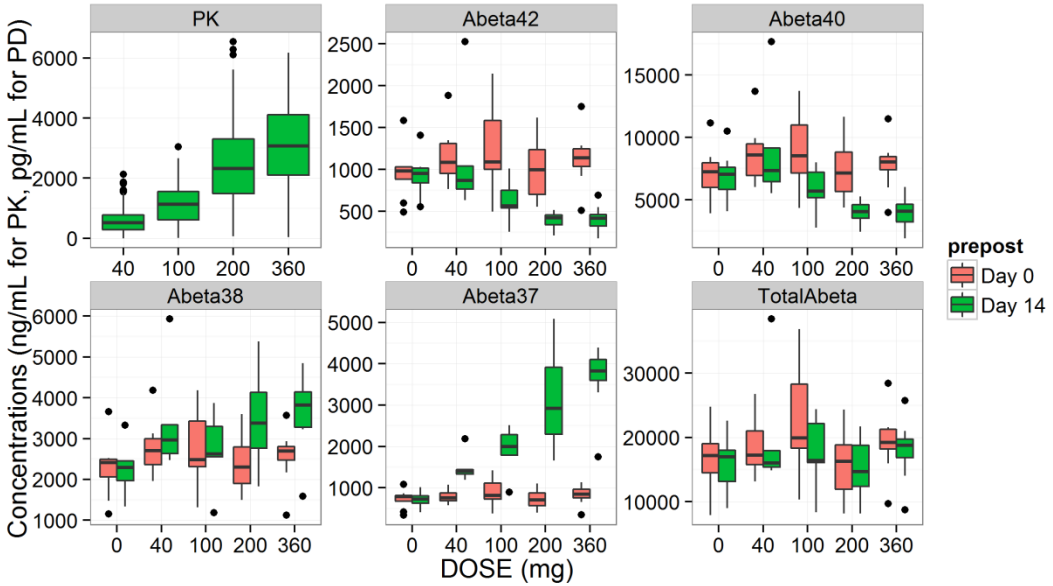
Efficient | Design | Dose

Courtesy
JE Ahn, R Qiu, D Chen

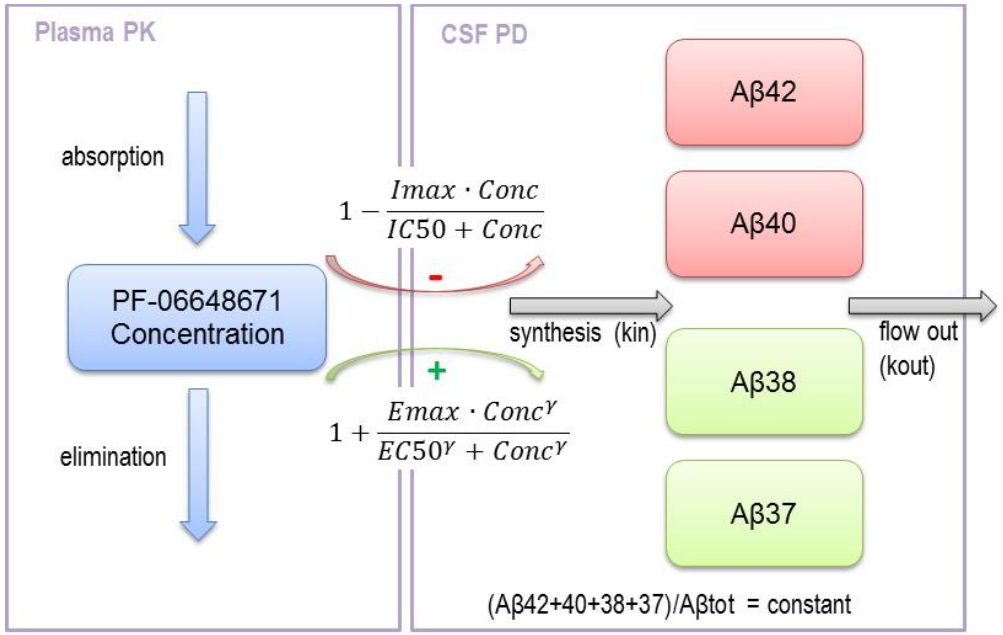
GSM Clinical PK/PD Data

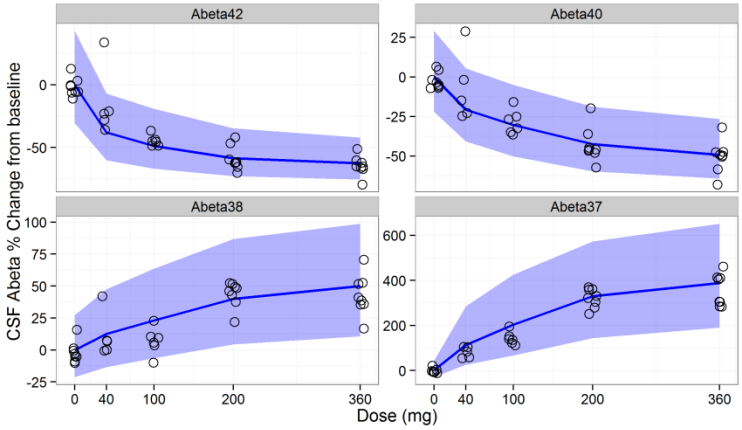
- **Frugal CDP (all CP studies)**
- Dedicated Single Dose PK/CSF
  - Variable, placebo drift, delayed, serial samples
- Multi Dose PK/CSF (part of MAD)
  - Less variable, no placebo drift, dose response, sparse samples

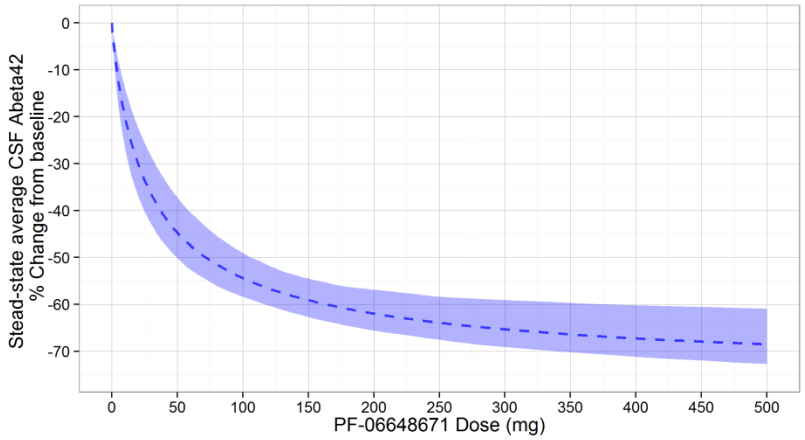


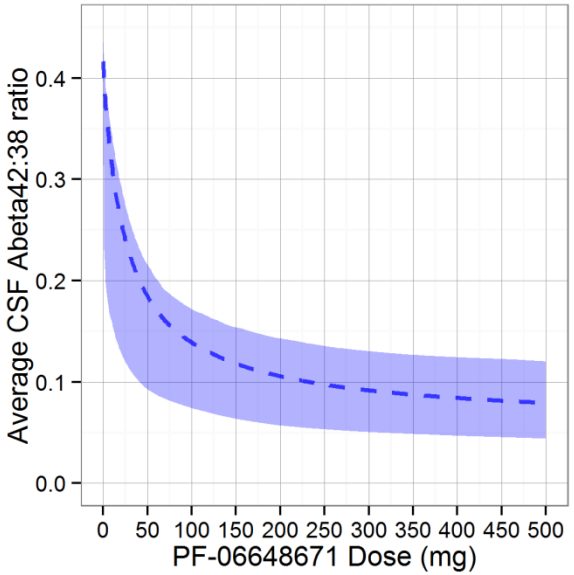


GSM PK/PD Modeling: results & simulations



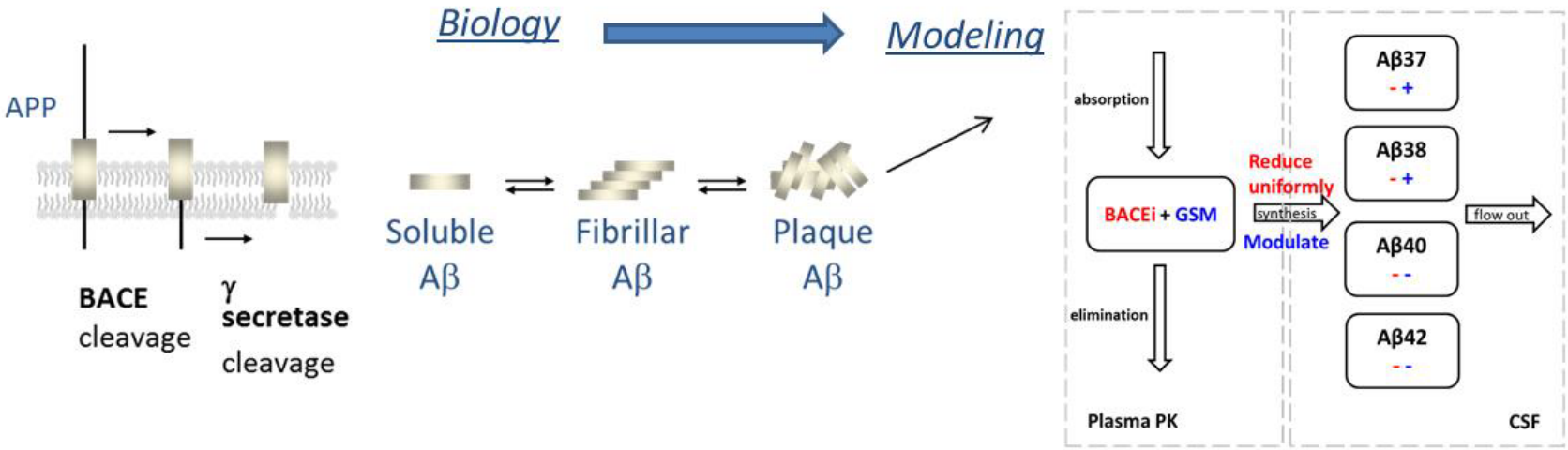






BACEi/GSM combo: Aβ model based dose selection

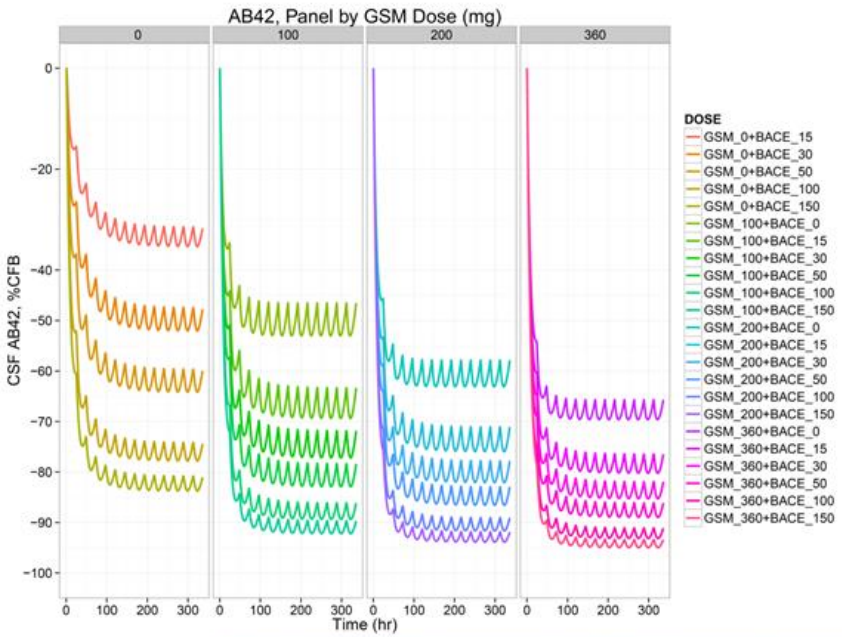
- BACE and GSM while in same pathway, affect amyloid differently

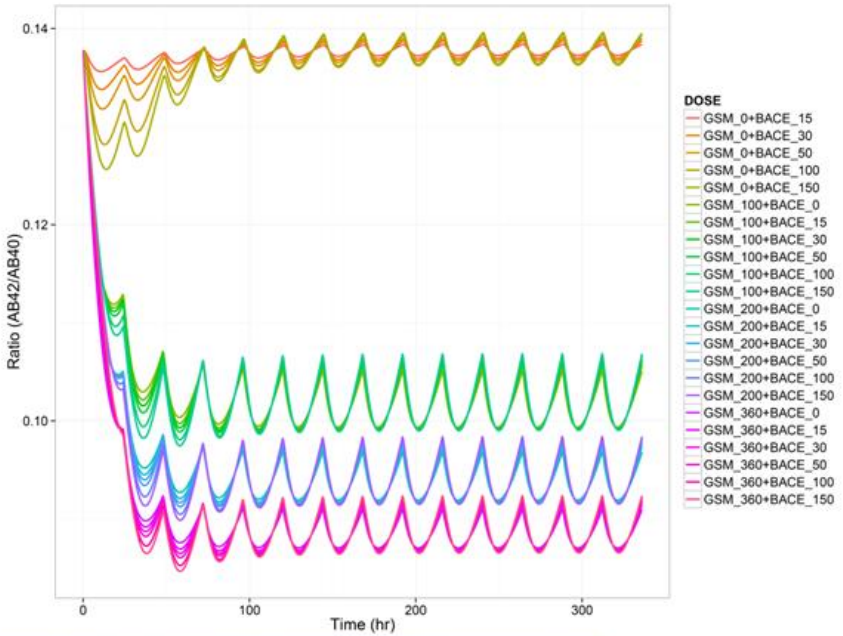


- Model combines Aβ PKPD for GSM and BACEi

- Goal: dose select both agents to maximize Aβ42 lowering maintaining differentiation from BACEi in overall Aβ37-38 and Aβ42/40 ratio

BACEi/GSM combo: M&S to optimize dose selection





GSM dose (mg)	BACE dose (mg)	Aβ42 average reduction (%)	Aβ40 average reduction (%)	Ratio (42/40) at trough	Aβ37 average reduction (%)	Aβ38 average reduction (%)
50	30	-69.3	-61.9	0.115	+16.3	-37.9
	100	-88.1	-85.2	0.115	-55.5	-76.2
100	30	-75.1	-66.9	0.107	+72.9	+33.0
	100	-90.3	-87.1	0.108	-33.7	-49.9
200	30	-80.1	-72	0.101	+128	148
	100	-92.2	-89.1	0.101	-12.3	-4.80

Parkinson's Disease designs: Quantitative Questions

- Do we understand symptomatic motor symptoms scores over time?
- What are appropriate target values for Go/No-Go decisions and study duration?
- Can we answer the same questions for disease modifying treatments in early and late stage PD?

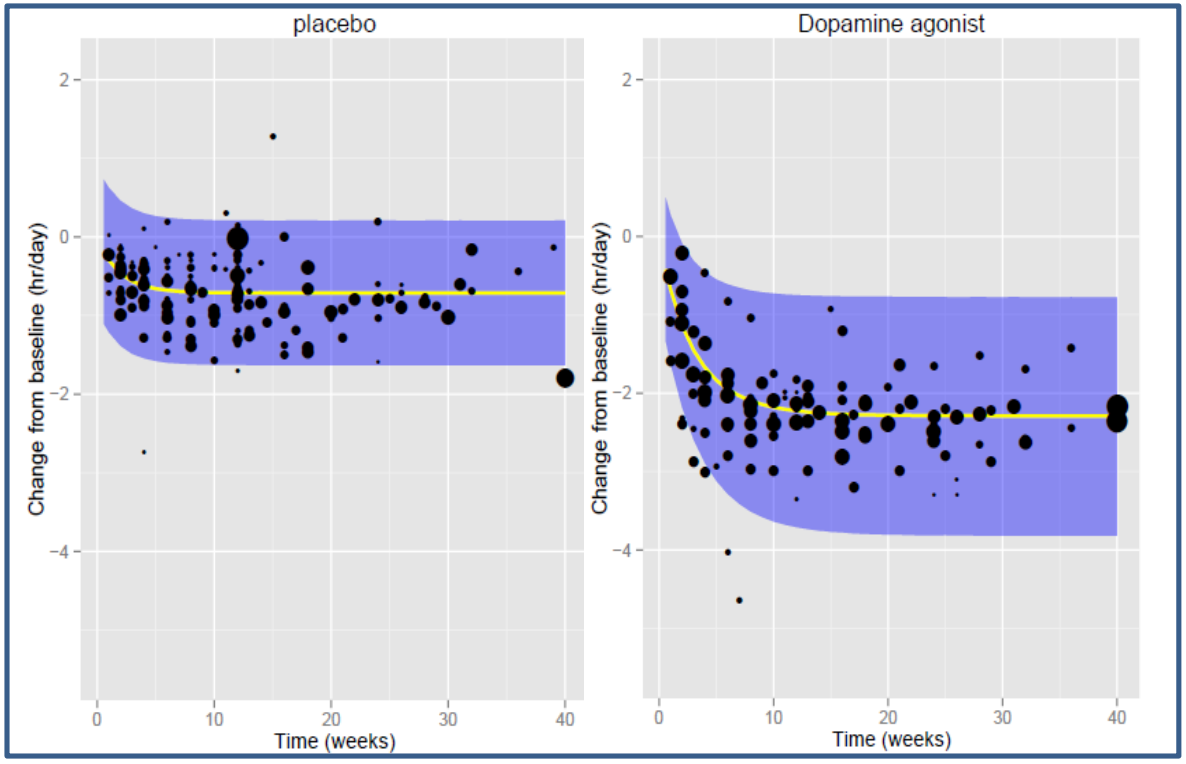
Efficient | Design | Decision

Courtesy

S Duvvuri, T Nicholas, JE Ahn, D Gorman

Symptomatic effect on motor effects with DA: Off Time

Longitudinal Model based meta-analysis of Off Time

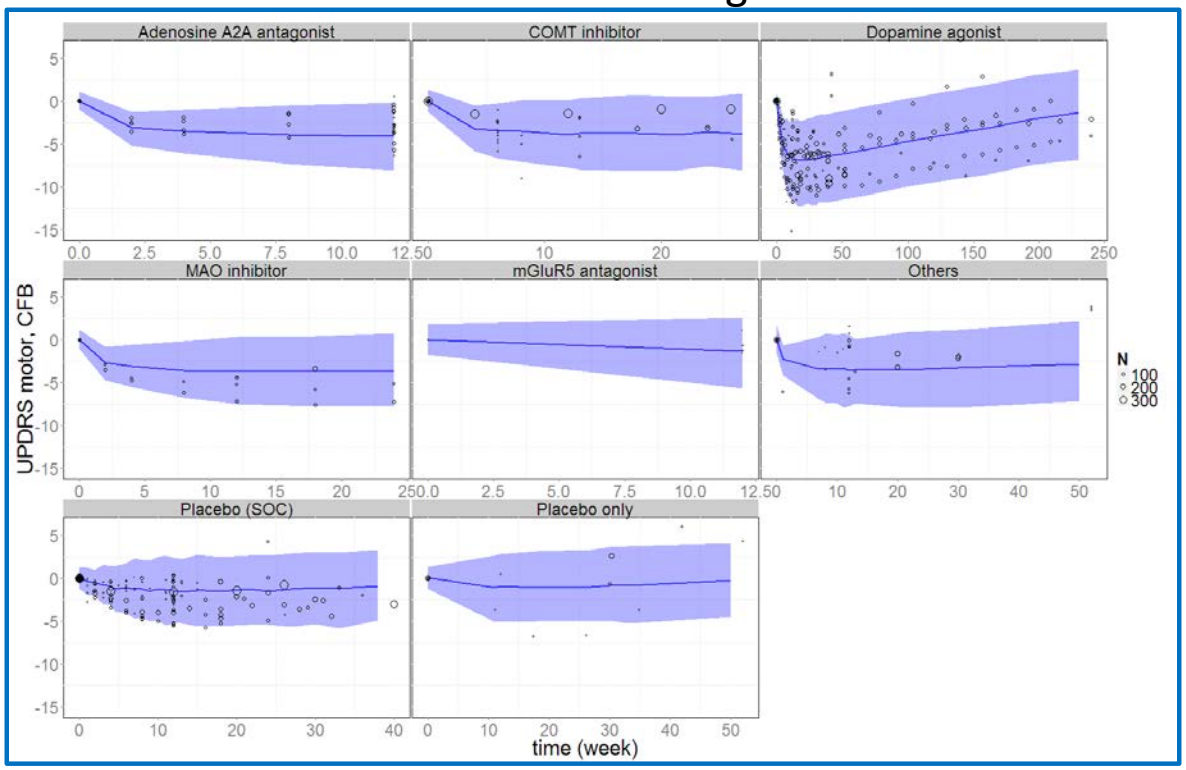


- Mean placebo effect at steady state (~ -0.7 hr).
- Mean DA class effect: (~1.6 hr reduction)
- Steady state achieved by 10 weeks

- Target values for Go/No-Go (at least 1.5 hr reduction in off-time)
- Optimize the study duration (15 weeks – including titration)
- Informed Bayesian prior reducing sample size and quicker decisions

Symptomatic effect on motor scores: UPDRS Part III

Longitudinal model based meta-analyses of UPDRS part III with L-DOPA back ground



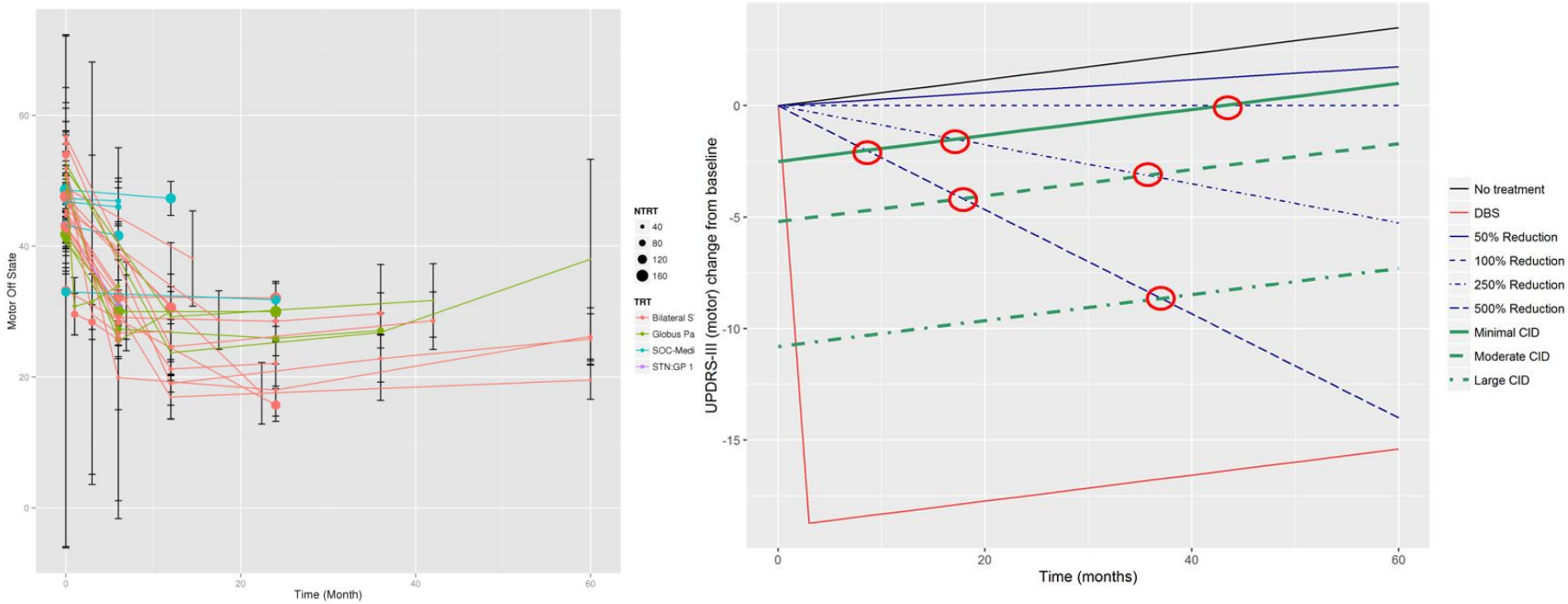
Quantify time course of placebo effect (max ~ 2.1)

Quantify competitor time course

DA effects max (~5.3) with half-life of 2.7 weeks to reach the full effects

- Competitive positioning: max therapeutic effect, study duration
- Interpretation of placebo effects in motor fluctuator studies

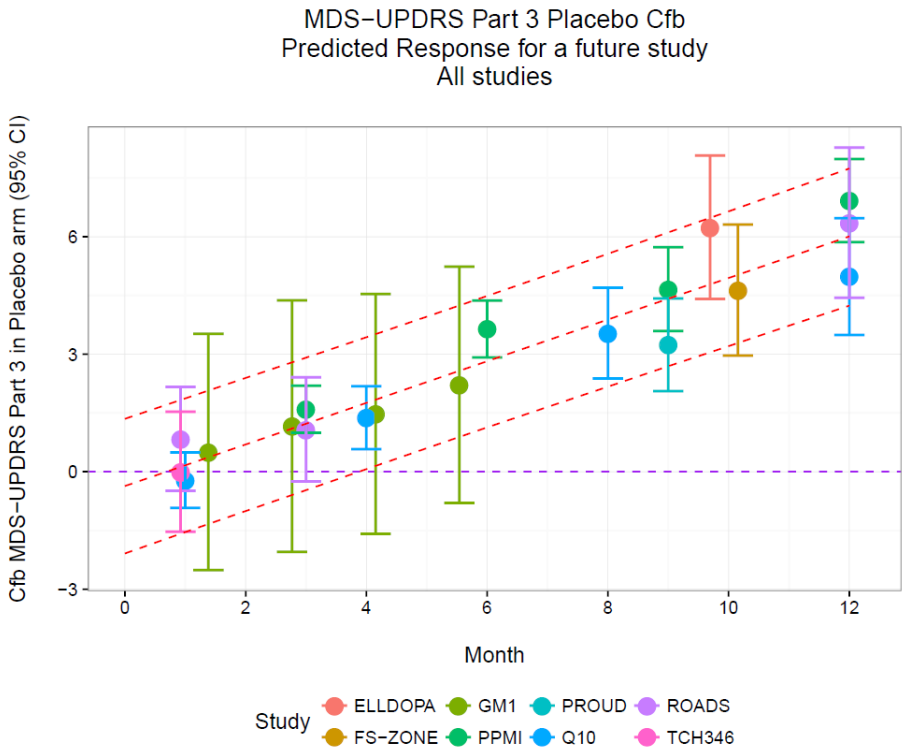
Disease modifying in Late PD: Optimize Designs & Decisions



- MBMA to quantify the rate of disease progression in moderate to severe PD (based on DBS)
- Simulate magnitude of effect and trial duration to detect a meaningful clinical change
- Slowing or even halting disease progression is not sufficient to detect a clinically important signal within a reasonable trial duration in moderate/severe PD (will take >3 years halting progression)

Disease modifying in Early PD: Optimize Designs & Decisions

- Early PD: Disease progression combining randomized studies and natural disease progression database



- Early disease progression slope makes for more reasonable design for a treatment offering 50% reduction in disease progression (9 months and 270 patients randomized 2:1 with Bayesian prior)

- Enrich populations, set appropriate inclusion criteria
- Identification of sub/composite scores for better signal detection

CK1i (sundowning syndrome in AD): Quantitative Questions

- Therapeutic Hypothesis:
  - AD patients have sleep fragmentation, circadian phase delay, may develop sundowning.
  - CK1 is critical for the circadian clock. Circadian correction will normalize behavior in AD
- Can we bridge circadian rhythm changes from nonclinical (nocturnal) to human (diurnal)?
- Can we inform design of Phase 1 and Proof of mechanism study?

Design | Dose

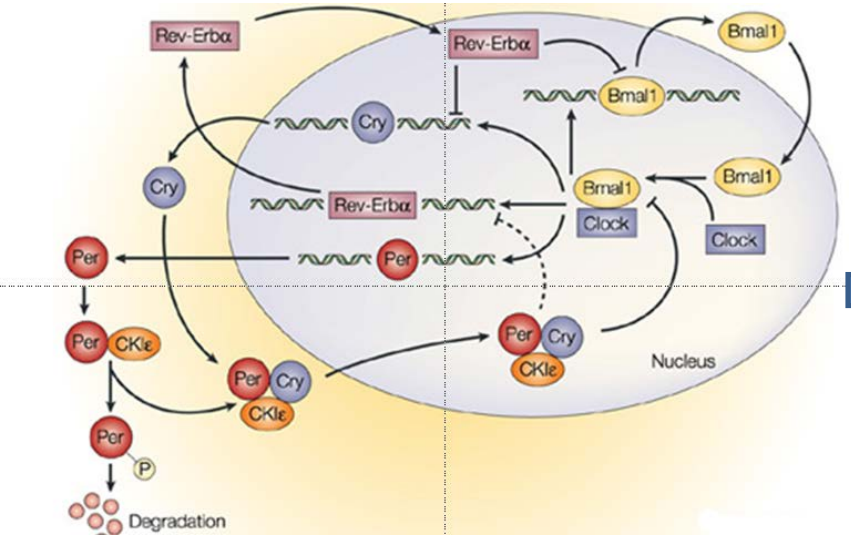
Courtesy
Cheng Chang & Francois Gaudreault

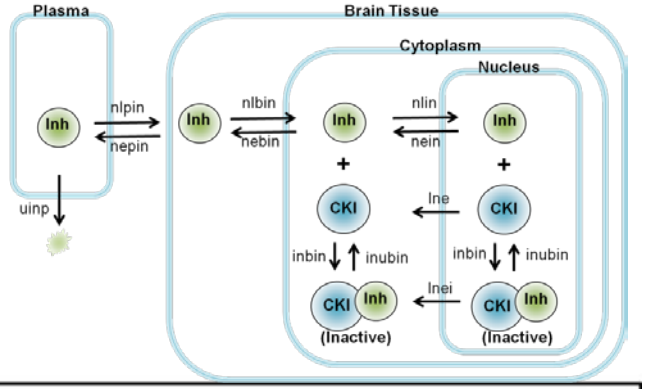
Enabling Translation with QSP model of CK1 Inhibition

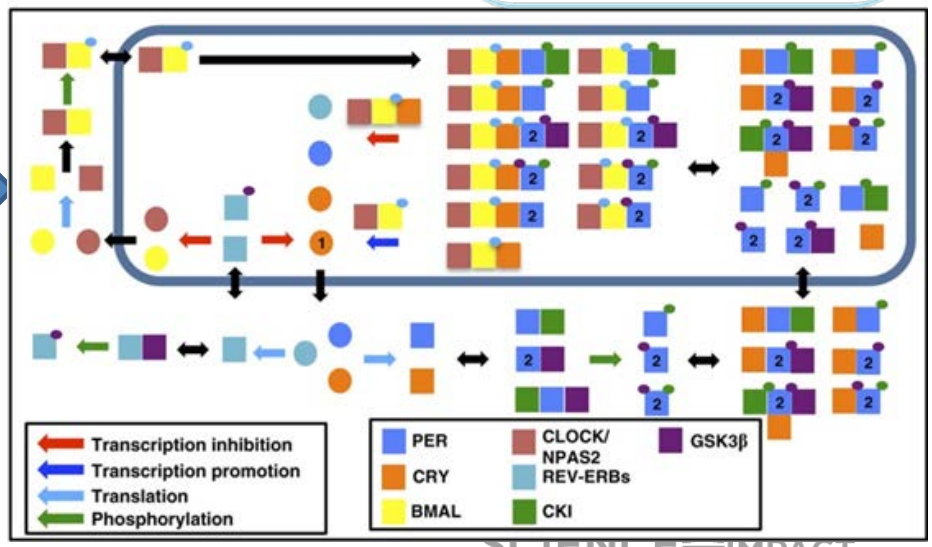
Challenge: Translate from rodent to human pharmacology. Accounting for the effect of light and time of CK1i dosing on the magnitude and time course of circadian rhythm modulation

Approach: Development of a systems model to account for the pharmacological effect of CK1 inhibition in the context of circadian biology

Highly nonlinear and time dependent system





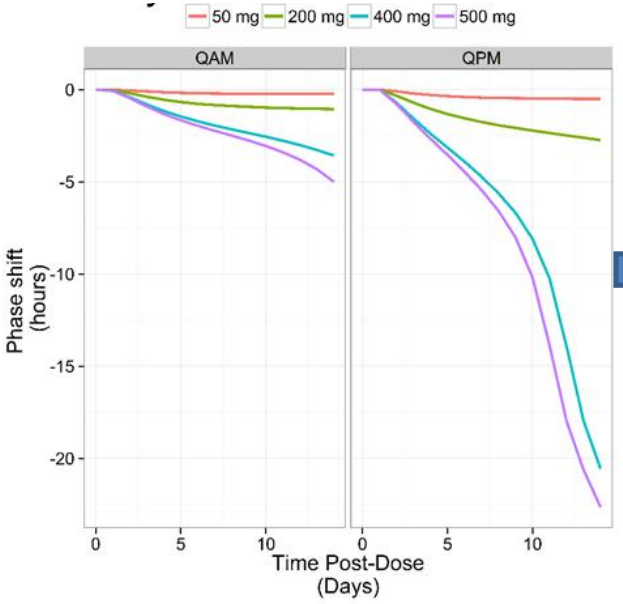


POM Design & Interpretation with QSP Model of CK1 Inhibition

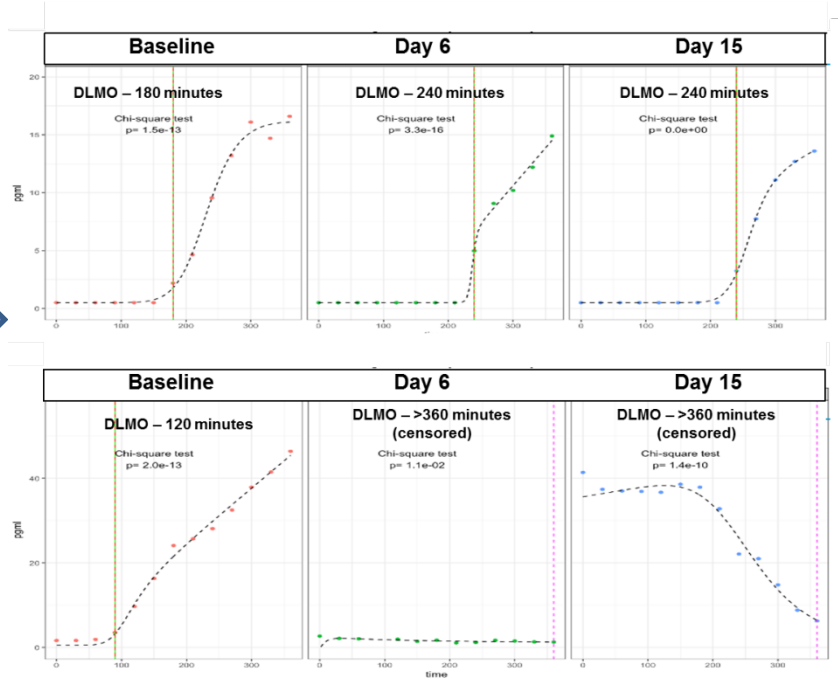
Model informed Proof of Mechanism Design

- Efficient study design (POM as part of MAD, also inclusion of active comparator)
- Dosing regimen and time of dosing (AM vs PM) PM dose escalation scheme (slower than typical study due to predicted super-pharmacology)
- Time of PD sampling (day 7 and 14 PD observations based on simulated time course)
- Study cohort design (parallel instead of cross-over due to simulated PD washout)

Model-based translation (Preclinical to clinical Simulation)



Clinical study results



Observed biomarker modulation

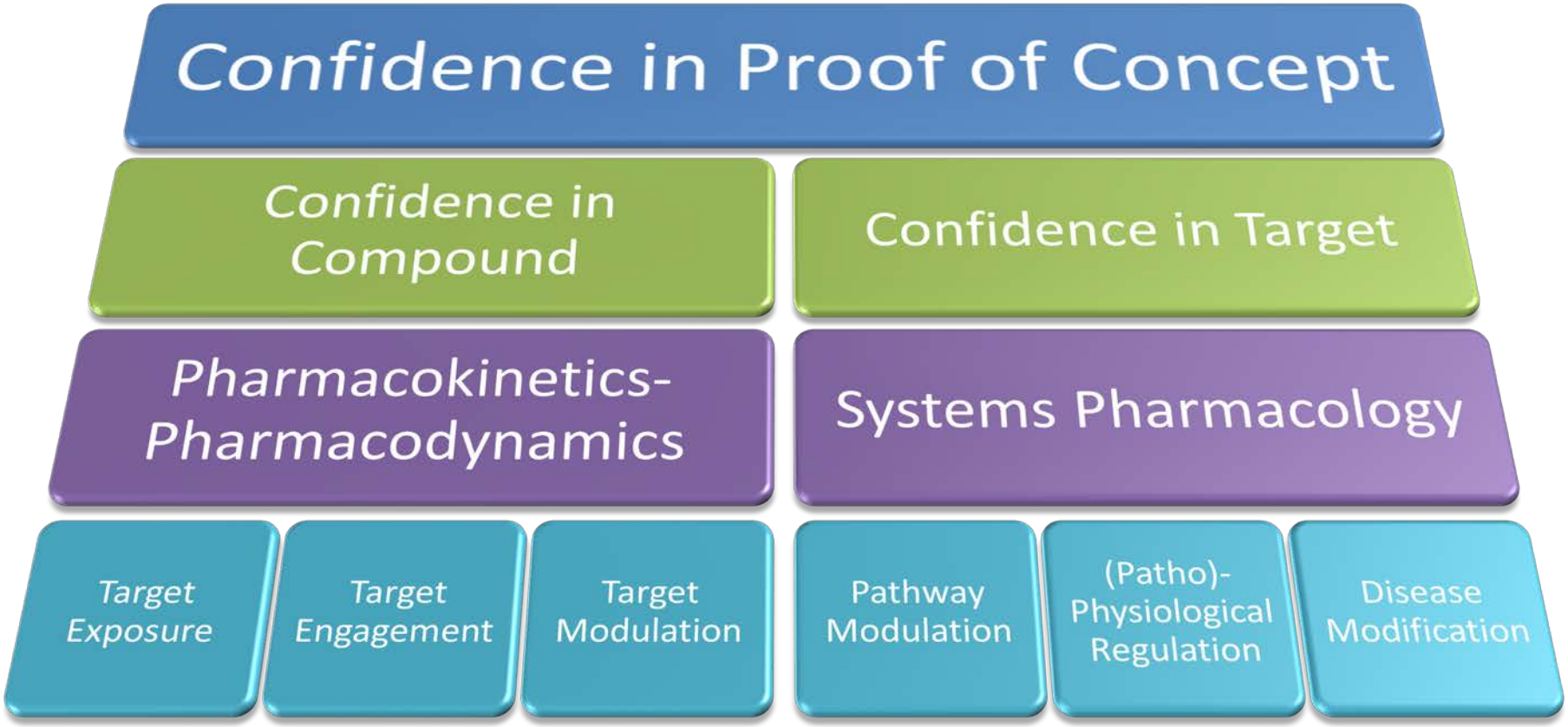
1 hr

> 12 hrs

Can MID3 improve ECD success in neuro diseases?

Better Dose Selection?	√
Better Designs?	√
Better Decisions?	√
More Efficient Development?	√
Higher Proportion of Positive PoC?	✗

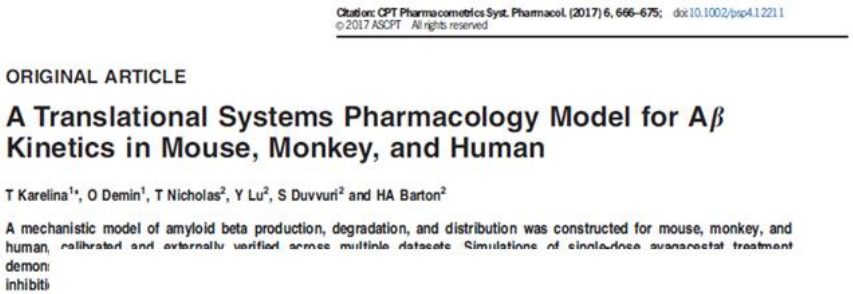
Confidence in Target & Compound → Confidence in PoC



Paolo Vicini and Piet van der Graaf
Clinical Pharmacology & Therapeutics (2013); 93 5, 379–381;

What is the story at Pfizer (in Neuro)?

- Few QSP examples in neuro



Citation: CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 666–675; doi:10.1002/psp4.12211
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ORIGINAL ARTICLE

A Translational Systems Pharmacology Model for Aβ Kinetics in Mouse, Monkey, and Human

T Karelina[1]*, O Demin[1], T Nicholas[2], Y Lu[2], S Duvvuri[2] and HA Barton[2]

A mechanistic model of amyloid beta production, degradation, and distribution was constructed for mouse, monkey, and human, calibrated and externally verified across multiple datasets. Simulations of single-dose avagacestat treatment demon
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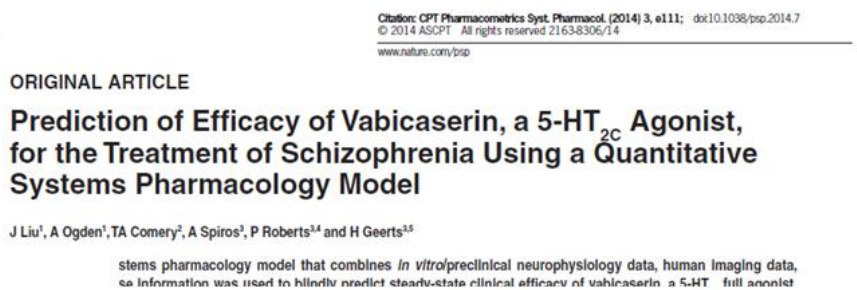


Citation: CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e111; doi:10.1038/psp.2014.7
© 2014 ASCPT All rights reserved 2163-8306/14
www.nature.com/psp

ORIGINAL ARTICLE

Prediction of Efficacy of Vabicaserin, a 5-HT$_{2C}$ Agonist, for the Treatment of Schizophrenia Using a Quantitative Systems Pharmacology Model

J Liu[1], A Ogden[1], TA Comery[2], A Spiros[3], P Roberts[3,4] and H Geerts[3,5]

stems pharmacology model that combines *in vitro*/preclinical neurophysiology data, human imaging data, se information was used to blindly predict steady-state clinical efficacy of vabicaserin, a 5-HT full agonist

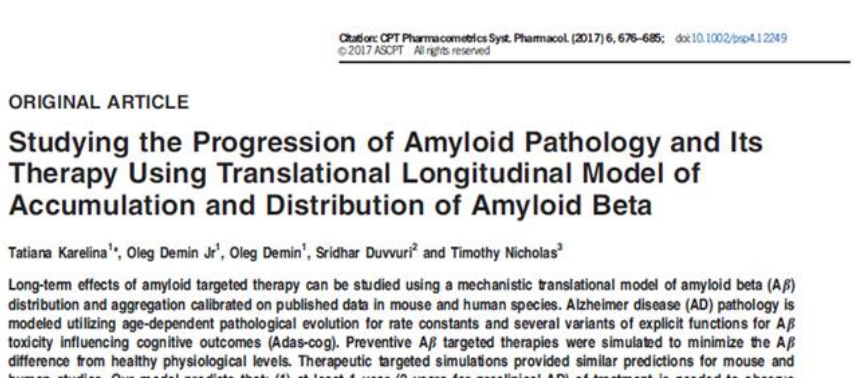
Vol.2, No.3, 83-98 (2013)
http://dx.doi.org/10.4236/aad.2013.23012

Advances in Alzheimer's Disease

Systems pharmacology modeling in neuroscience: Prediction and outcome of PF-04995274, a 5-HT$_4$ partial agonist, in a clinical scopolamine impairment trial

Timothy Nicholas[1*], Sridhar Duvvuri[1], Claire Leurent[1], David Raunig[1,3], Tracey Rapp[1], Phil Iredale[1], Carolyn Rowinski[1], Robert Carr[2], Patrick Roberts[2], Athan Spiros[2], Hugo Geerts[2]

[1]Pfizer Global Research and Development, Groton, USA; *Corresponding Author: timothy.nicholas@pfizer.com
[2]In Silico Biosciences, Lexington, USA
[3]ICON, North Wales, USA



Citation: CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 676–685; doi:10.1002/psp4.12249
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ORIGINAL ARTICLE

Studying the Progression of Amyloid Pathology and Its Therapy Using Translational Longitudinal Model of Accumulation and Distribution of Amyloid Beta

Tatiana Karelina[1]*, Oleg Demin Jr[1], Oleg Demin[1], Sridhar Duvvuri[2] and Timothy Nicholas[3]

Long-term effects of amyloid targeted therapy can be studied using a mechanistic translational model of amyloid beta (Aβ) distribution and aggregation calibrated on published data in mouse and human species. Alzheimer disease (AD) pathology is modeled utilizing age-dependent pathological evolution for rate constants and several variants of explicit functions for Aβ toxicity influencing cognitive outcomes (Adas-cog). Preventive Aβ targeted therapies were simulated to minimize the Aβ difference from healthy physiological levels. Therapeutic targeted simulations provided similar predictions for mouse and

- However were too late to impact target selection, and efforts were too isolated

Conclusions

- Quantitative pharmacology integrates all available data to improve the probability of making the right decision in an efficient manner in early clinical development in neurodegenerative diseases

- However to improve probability of successful PoC it requires for us to be able to inform better target selection & validation through earlier and broader use of QSP to help
  - Prioritize targets
  - Select more appropriate patient populations
  - Link nonclinical observations to clinical predictions
  - With combination drug strategies

Acknowledgments

Many Pfizer colleagues and collaborators that influenced the NPRU discovery and development

Particular THANKS to the authors of the examples presented:

Danny Chen, Sridhar Duvvuri, Jae Eun Ahn, Ruolun Qiu, Cheng Chang, Francois Gaudreault, Donal Gorman, Jing Liu, Brian Corrigan, David Stiles and Tim Nicholas