EMA-EFPIA Workshop
Dose Selection and Dose-Exposure-Response Characterisation
London 4-12-2014

A Systems Pharmacology Perspective on the Clinical Development of Fatty Acid Amide Hydrolase Inhibitors for Pain

Piet van der Graaf

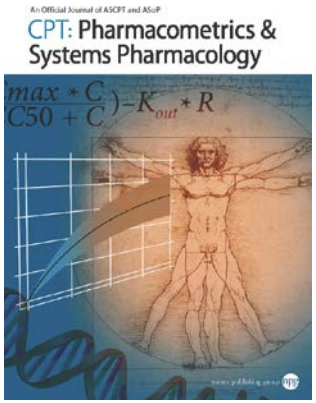
Editor-in-Chief

CPT: Pharmacometrics & Systems Pharmacology

www.nature.com/psp

Leiden Academic Centre for Drug Research (LACDR)

Leiden University, The Netherlands



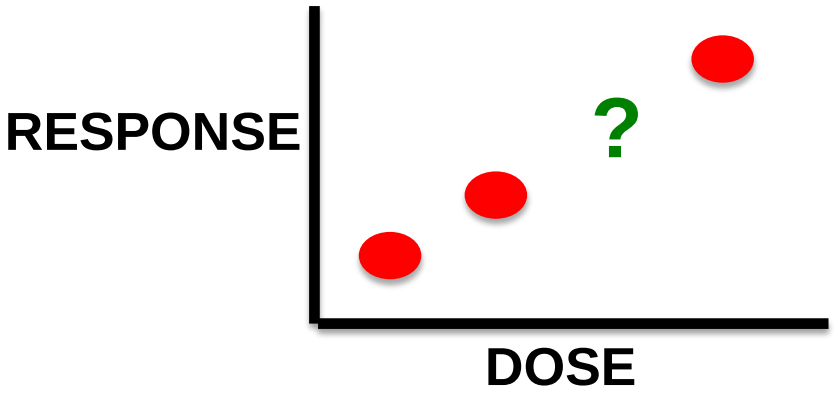
LACDR

XenologiQ

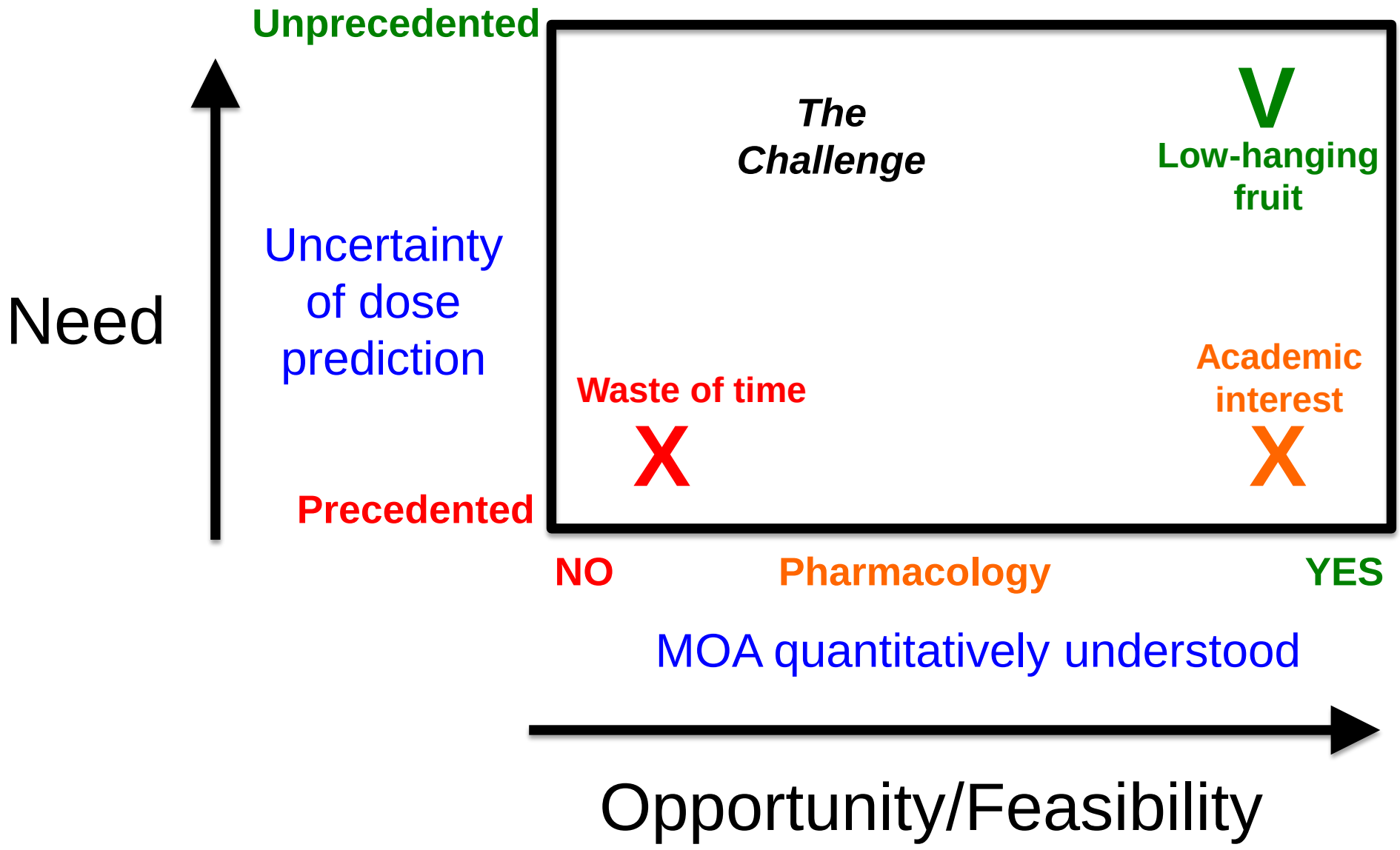
Systems Pharmacology: Picking the right target

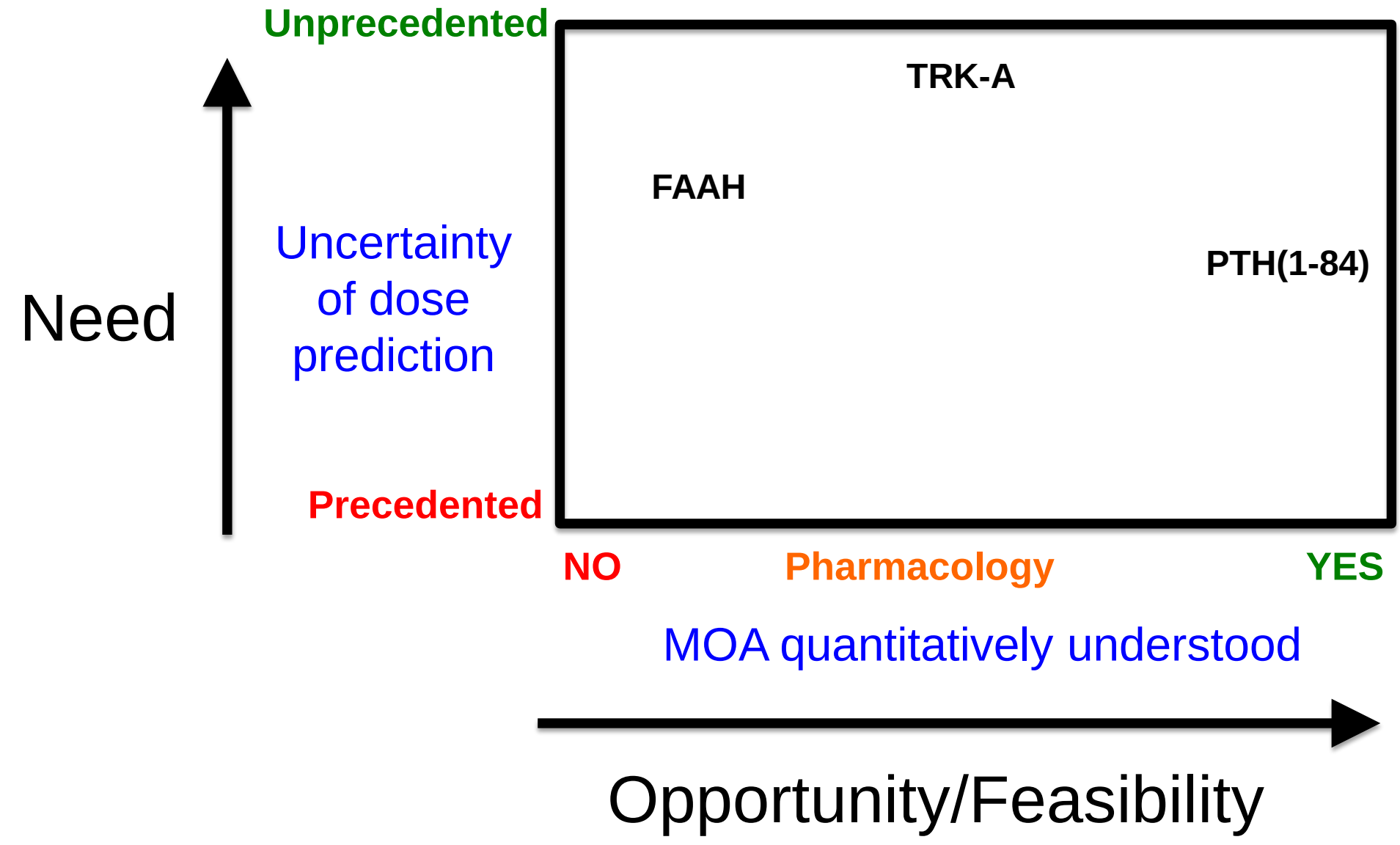
- **Target Selection**
  - ***Generate hypotheses for novel drug targets***
- **Target Validation**
  - ***Further assess the potential of a novel drug target***
- **Target Authorisation**
  - ***Assessment of novel therapeutic intervention against product concept***

When not to use Systems Pharmacology for dose selection?



Compound A with unknown mechanism of action showed a dose-independent efficacy in the rat model of infra-red-light induced schizophrenia


Unprecedented
Need
Uncertainty of dose prediction
Precedented
The Challenge
V
Low-hanging fruit
Waste of time
X
Academic interest
X
NO
Pharmacology
YES
MOA quantitatively understood
Opportunity/Feasibility


Unprecedented
TRK-A
FAAH
PTH(1-84)
Need
Uncertainty of dose prediction
Precedented
NO
Pharmacology
YES
MOA quantitatively understood
Opportunity/Feasibility

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

September 12th 2014

FDA Introductory Remarks

BLA 125511

PTH (1-84) for injection, Natpara

Jean-Marc Guettier, MD

Director

Division of Metabolism and Endocrinology Products (DMEP)

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Natpara

Natpara is recombinant human parathyroid hormone (PTH) identical in primary sequence to the full-length human endogenous hormone (i.e., 84 amino acids)

Indication sought:

- *Natpara for injection is a replacement for endogenous parathyroid hormone (1-84) indicated for the long-term treatment of hypoparathyroidism*

U.S. Food and Drug Administration
Protecting and Promoting Public Health
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Clinical Pharmacology Review of Natpara® (BLA 125511)

Endocrinologic and Metabolic Drugs Advisory Committee Advisory Committee Meeting, September 12, 2014

Manoj Khurana, PhD

Immo Zadezensky, PhD

Nitin Mehrotra, PhD

Office of Clinical Pharmacology

Bone 46 (2010) 49–63

Contents lists available at ScienceDirect

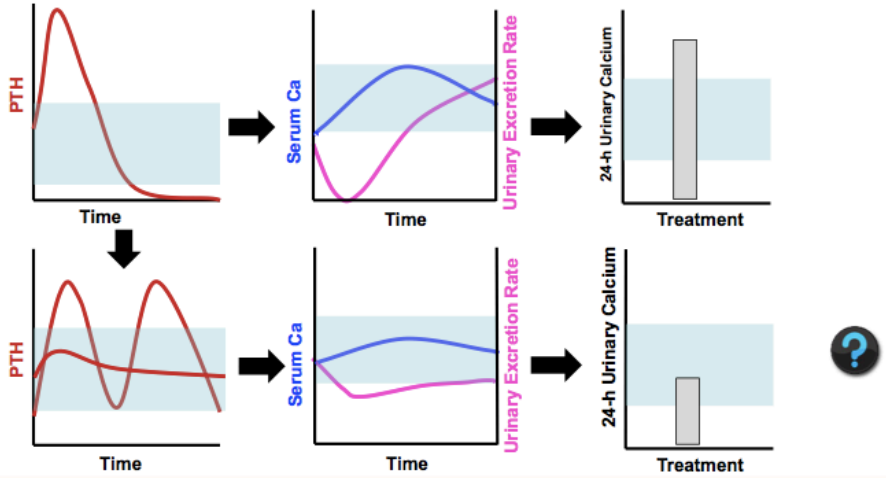
Bone

journal homepage: www.elsevier.com/locate/bone

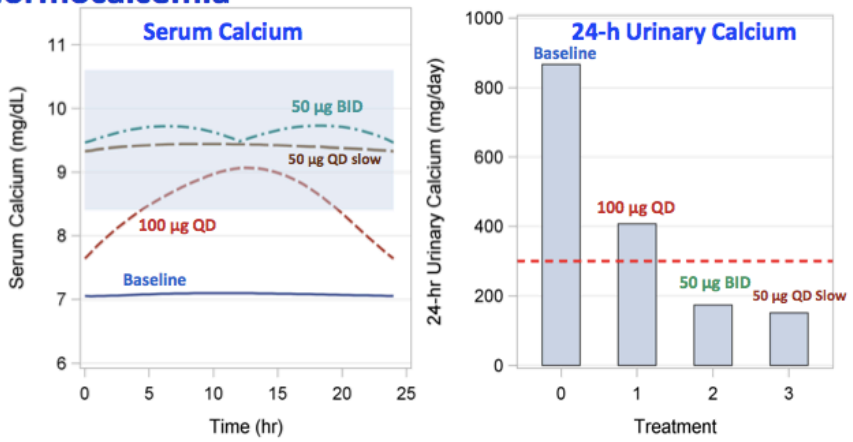
A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling

Mark C. Peterson [a,*,1], Matthew M. Riggs [b]

Optimizing the PKPD – Conceptual Framework



Altering Regimen (QD to BID) or Release Profile Controls Hypercalciuria While Maintaining Normocalcemia



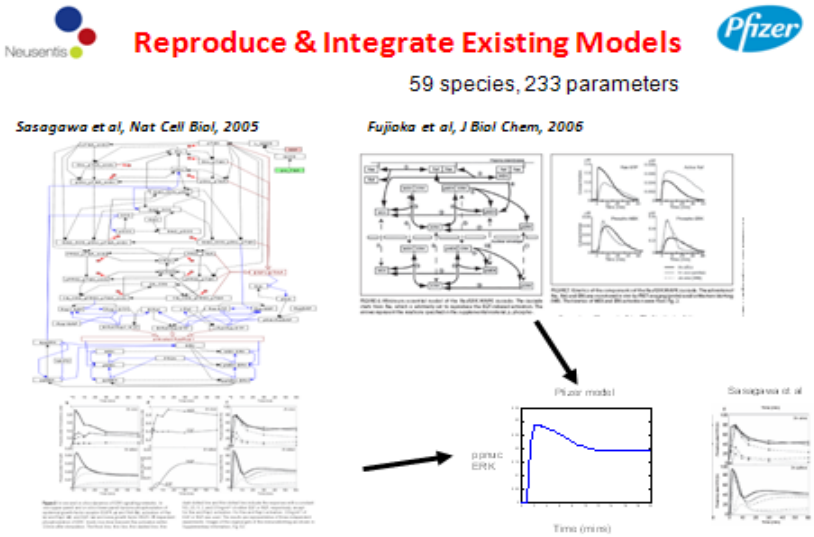
Summary

- Proposed QD regimen was able to control serum calcium, reduce oral calcium and vitamin D requirement
- Proposed QD regimen was not optimal in control on hypercalciuria
- Natpara QD administration does not produce PTH levels to cover the entire 24 hours
- The effect on urinary calcium excretion is short-lived
- Using systems pharmacology model we showed that control on hypercalciuria is feasible with more frequent regimen or a slow release PTH profile at lower systemic exposure than 100 µg QD
- For hormone replacement therapy, applying PKPD data for optimization of dosing regimen is important

Systems pharmacology of the nerve growth factor pathway: use of a systems biology model for the identification of key drug targets using sensitivity analysis and the integration of physiology and pharmacology

Neil Benson, Tomomi Matsuura, Sergey Smirnov, Oleg Demin, Hannah M. Jones, Pinky Dua and Piet H. van der Graaf

Interface Focus 2013 **3**, 20120071, published 21 February 2013

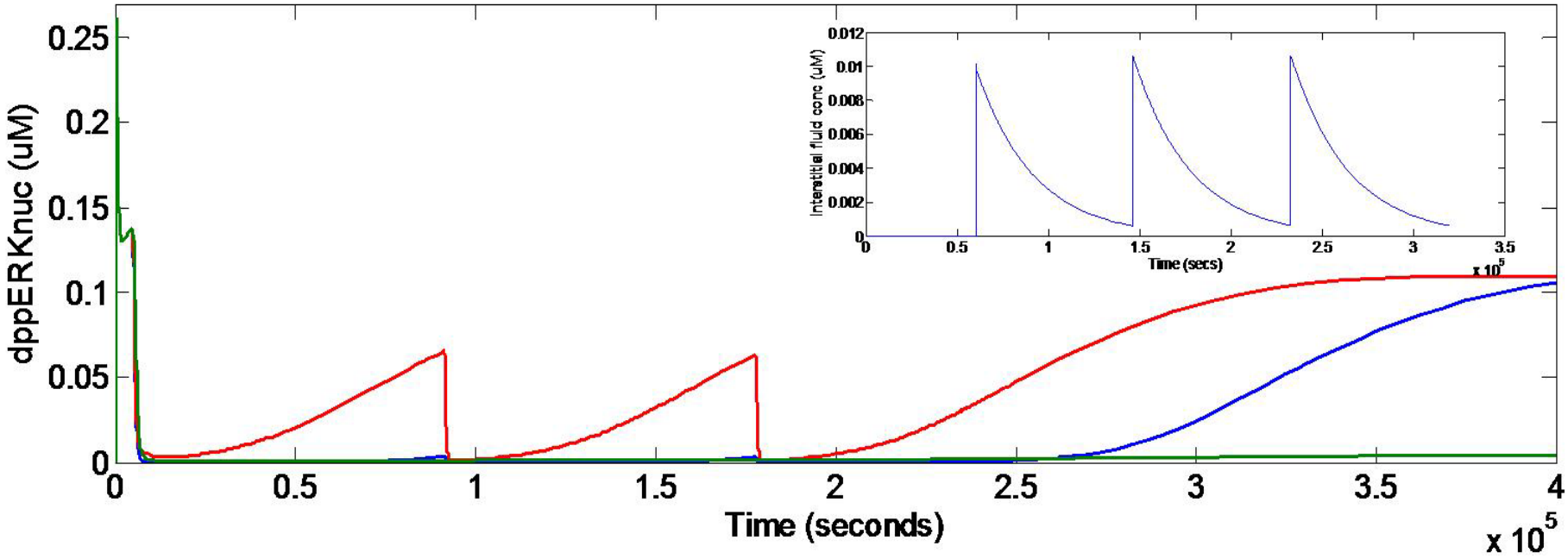


- NGF mAbs clinically-precedented efficacy
- Use Systems Pharmacology model to dose predict for novel targets in NGF pathway (TRK-A)
- High need: balance efficacy – potential CNS side effects TRK-A inhibitors

Known efficacious dose (exposure) NGF mAb → **Predicted Systems Pharmacology pathway response (dpERK)** ← **Equivalent TRK-A dose (exposure)**

Predicted Systems Pharmacology pathway response (dpERK) → **Clinical Efficacy**

Dose Prediction for a TrkA Kinase Inhibitor versus a Compound that Binds NGF



Impact of a compound that binds NGF (green) versus TrkA kinase inhibitor with different pharmacological properties (red and blue) on the dppERK response

Inset panel shows the drug PK in the interstitial fluid compartment

Citation: CPT: Pharmacometrics Systems Pharmacology (2014) 3, e91; doi:10.1038/psp.2013.72

www.nature.com/psp

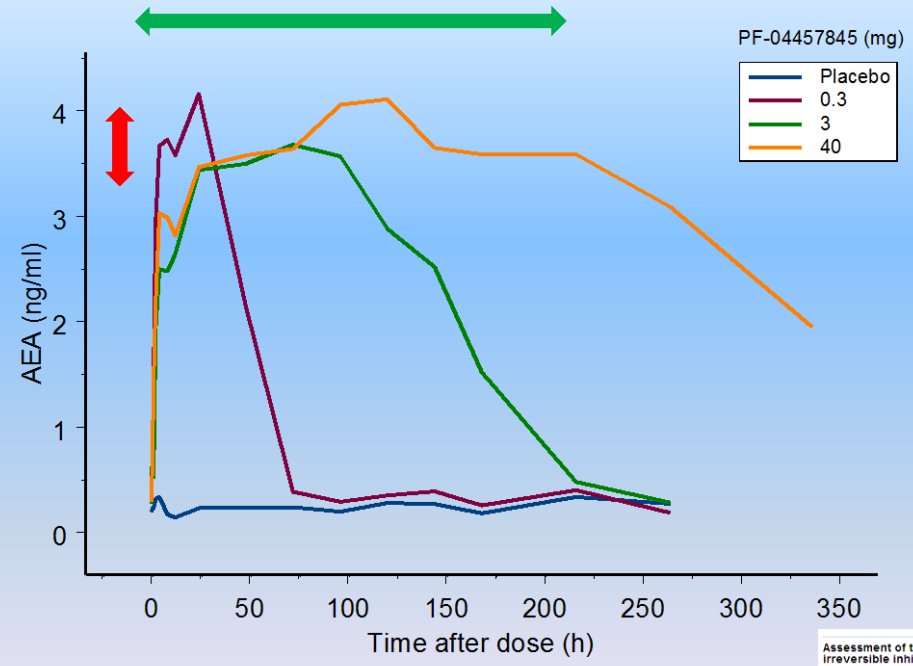
ORIGINAL ARTICLE

A Systems Pharmacology Perspective on the Clinical Development of Fatty Acid Amide Hydrolase Inhibitors for Pain

N Benson[1], E Metelkin[2], O Demin[2], GL Li[3], D Nichols[4] and PH van der Graaf[5]

XenologiQ

Elevation of AEA observed in a typical healthy volunteer subject following a single oral dose of PF-04457845




Assessment of the pharmacology and tolerability of PF-04457845, an irreversible inhibitor of fatty acid amide hydrolase-1, in healthy subjects

Gai Ling Li[1], Helen Winter[2], Rosalin Arends[2], Gary W. Jay[2], Vu Le[2], Tim Young[1], John P. Huggins[1]*

Article first published online: 5 APR 2012

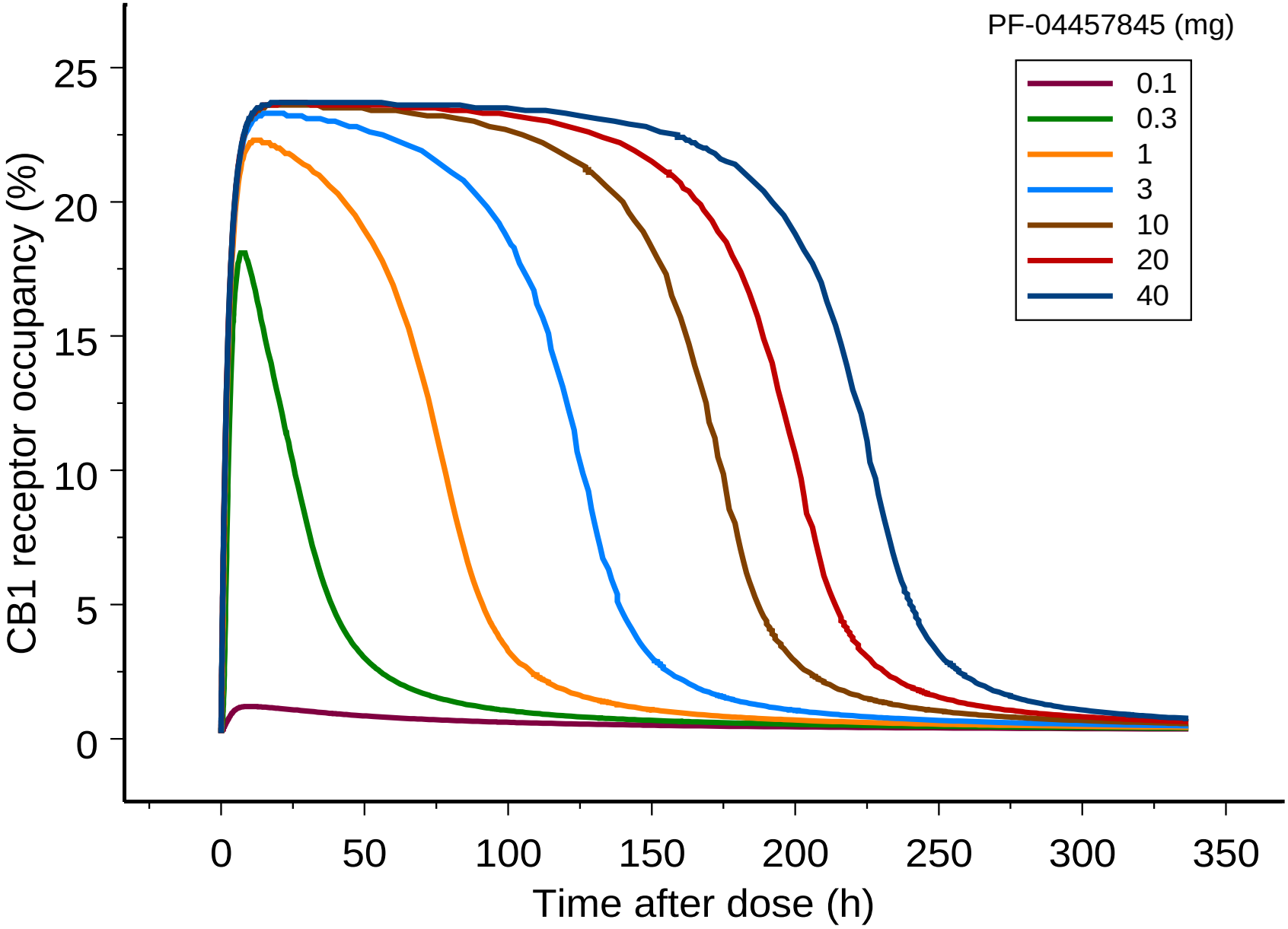
DOI: 10.1111/j.1365-2125.2011.04137.x

Issue

British Journal of Clinical Pharmacology

Volume 73, Issue 5, pages 706–716, May 2012

Systems-pharmacology-model predicted elevations of CNS CB1 receptor occupancy by AEA following a single dose of PF-04457845



IASP

PAIN® 153 (2012) 1837–1846

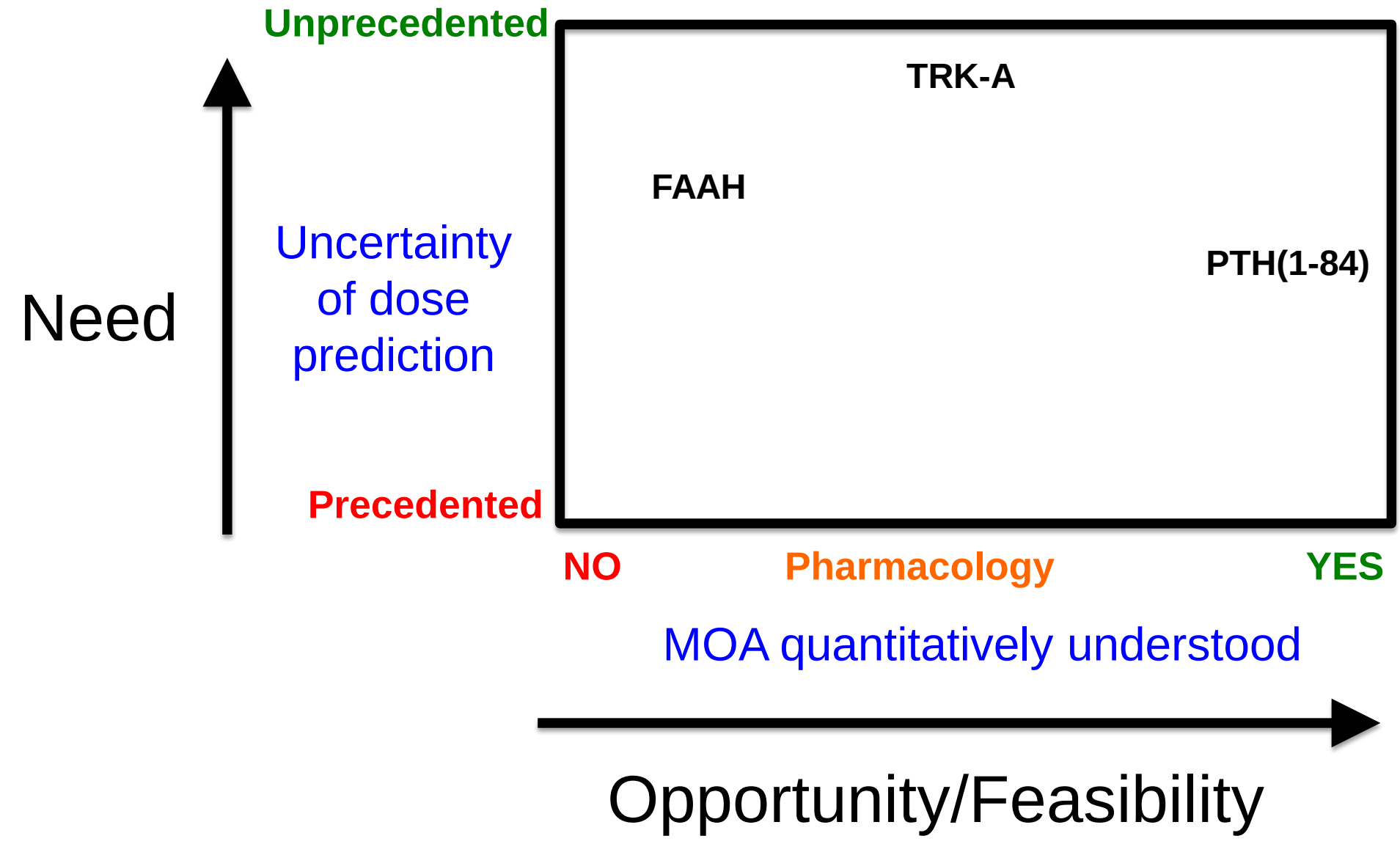
PAIN®

www.elsevier.com/locate/pain

An efficient randomised, placebo-controlled clinical trial with the irreversible fatty acid amide hydrolase-1 inhibitor PF-04457845, which modulates endocannabinoids but fails to induce effective analgesia in patients with pain due to osteoarthritis of the knee

John P. Huggins *, Trevor S. Smart, Stephen Langman, Louise Taylor, Tim Young

Pfizer Global Research and Development, Sandwich, UK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An Official Journal of ASCPT and ASoP

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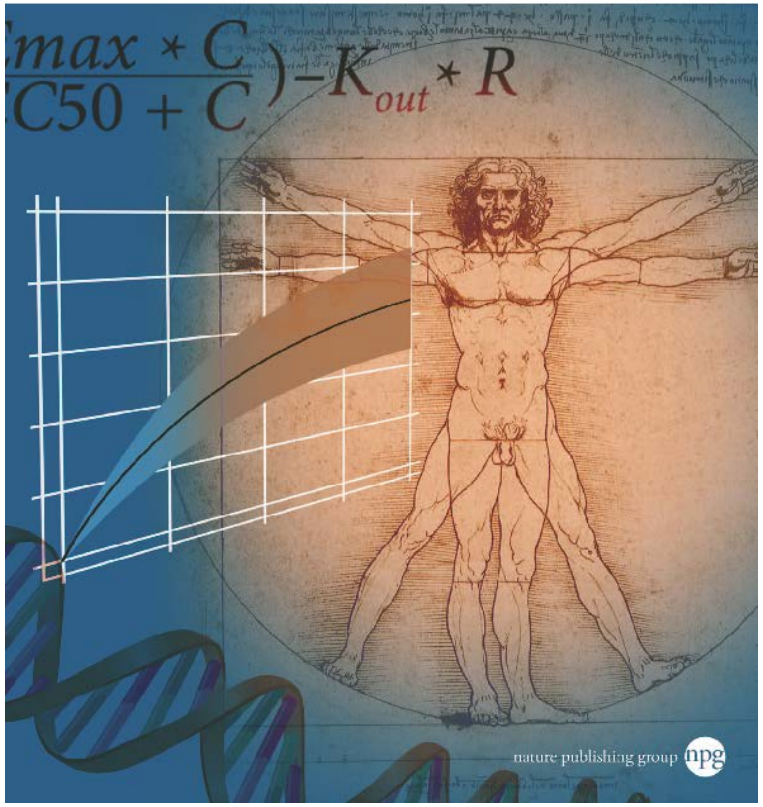

www.nature.com/psp

Citation: CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e149; doi:10.1038/psp.2014.47

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ORIGINAL ARTICLE

A Mechanistic Systems Pharmacology Model for Prediction of LDL Cholesterol Lowering by PCSK9 Antagonism in Human Dyslipidemic Populations

K Gadkar[1], N Budha[1], A Baruch[1], JD Davis[1], P Fielder[1] and S Ramanujan[1]

Citation: CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e142; doi:10.1038/psp.2014.40

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REVIEW

Implementation of Quantitative and Systems Pharmacology in Large Pharma

SAG Visser[1], DP de Alwis[1], T Kerbusch[2], JA Stone[1] and SRB Allerheiligen[1]

Citation: CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e133; doi:10.1038/psp.2014.30

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ORIGINAL ARTICLE

A Mechanistic, Multiscale Mathematical Model of Immunogenicity for Therapeutic Proteins: Part 1—Theoretical Model

X Chen[1], TP Hickling[2] and P Vicini[3]

Citation: CPT Pharmacometrics Syst. Pharmacol. (2014) 3, e118; doi:10.1038/psp.2014.16

www.nature.com/psp

ORIGINAL ARTICLE

Effects of IL-1β–Blocking Therapies in Type 2 Diabetes Mellitus: A Quantitative Systems Pharmacology Modeling Approach to Explore Underlying Mechanisms

R Palmér[1], E Nyman[1,2], M Penney[3], A Marley[4], G Cedersund[2,5] and B Agoram[3]